Improving cardiovascular care and outcomes: cross-boundary clinical registries and quality indicators

Suleman Aktaa

Student ID Number: 201456560

Submitted in accordance with the requirements for the degree of Doctor of Philosophy (PhD)

The University of Leeds

School of Medicine

March 2022

Primary Supervisor: Professor Chris P. Gale

Secondary Supervisors: Dr Theresa Munyombwe, Dr Tatendashe Bernadette Dondo

UNIVERSITY OF LEEDS

Intellectual property statement

The candidate confirms that the work submitted is his own, except where work which has formed part of jointly authored publications has been included. The contribution of the candidate and the other authors to this work has been explicitly indicated. The candidate confirms that appropriate credit has been given within the thesis where reference has been made to the work of others.

Publications

Part II of this thesis comprises the following publications by the candidate:

1. **Aktaa S**, Batra G, Wallentin L, Baigent C, Erlinge D, James S, Ludman P, Maggioni AP, Price S, Weston C, Casadei B, Gale CP. European Society of Cardiology methodology for the development of quality indicators for the quantification of cardiovascular care and outcomes. Eur Heart J Qual Care Clin Outcomes. 2020 Aug 26:qcaa069. doi: 10.1093/ehjqcco/qcaa069.

2. Batra G, **Aktaa S**, Wallentin L, Maggioni AP, Wilkinson C, Casadei B, Gale CP. Methodology for the development of international clinical data standards for common cardiovascular conditions: European Unified Registries for Heart Care Evaluation and Randomised Trials (EuroHeart). Eur Heart J Qual Care Clin Outcomes. 2021 Aug 5:qcab052. doi: 10.1093/ehjqcco/qcab052.

3. Schiele F, **Aktaa S**, Rossello X, Ahrens I, Claeys MJ, Collet JP, Fox KAA, Gale CP, Huber K, Iakobishvili Z, Keys A, Lambrinou E, Leonardi S, Lettino M, Masoudi FA, Price S, Quinn T, Swahn E, Thiele H, Timmis A, Tubaro M, Vrints CJM, Walker D, Bueno H; ESC Scientific Document Group, Halvorsen S, Jernberg T, Jortveit J, Blöndal M, Ibanez B, Hassager C. 2020 Update of the quality indicators for AMI: a position paper of the Association for Acute Cardiovascular Care: the study group for quality indicators from the ACVC and the NSTE-ACS guideline group. Eur Heart J Acute Cardiovasc Care. 2021 Apr 8;10(2):224-233. doi: 10.1093/ehjacc/zuaa037.

4. **Aktaa S**, Yadegarfar ME, Wu J, Rashid M, de Belder M, Deanfield J, Schiele F, Minchin M, Mamas M, Gale CP. Quality of AMI care in England and Wales during the COVID-19 pandemic: linked nationwide cohort study. BMJ Qual Saf. 2021 Jun 22:bmjqs-2021-013040. doi: 10.1136/bmjqs-2021-013040.

5. Arbelo E, **Aktaa S**, Bollmann A, D'Avila A, Drossart I, Dwight J, Hills MT, Hindricks G, Kusumoto FM, Lane DA, Lau DH, Lettino M, Lip GYH, Lobban T, Pak HN, Potpara T, Saenz LC, Van Gelder IC, Varosy P, Gale CP, Dagres N. Quality indicators for the care and outcomes of adults with atrial fibrillation. Europace. 2021 Apr 6;23(4):494-495. doi: 10.1093/europace/euaa253.

6. **Aktaa S**, Abdin A, Arbelo E, Burri H, Vernooy K, Blomström-Lundqvist C, Boriani G, Defaye P, Deharo JC, Drossart I, Foldager D, Gold MR, Johansen JB, Leyva F, Linde C, Michowitz Y, Kronborg MD, Slotwiner D, Steen T, Tolosana JM, Tzeis S, Varma N, Glikson M, Nielsen JC, Gale CP. European Society of Cardiology Quality Indicators for the care and outcomes of cardiac pacing: developed by the Working Group for Cardiac Pacing Quality Indicators in collaboration with the European Heart Rhythm Association of the European Society of Cardiology. Europace. 2021 Aug 29:euab193. doi: 10.1093/europace/euab193

7. **Aktaa S**, Polovina M, Rosano G, Abdin A, Anguita M, Lainscak M, Lund LH, McDonagh T, Metra M, Mindham R, Piepoli M, Störk S, Tokmakova MP, Seferovic´ P, Gale CP, and Coats AJS. European Society of Cardiology Quality Indicators for heart failure: developed by the Working Group for Heart Failure Quality Indicators in collaboration with the Heart Failure Association of the European Society of Cardiology. Eur J Heart Fail. 2022 Jan;24(1):132-142. doi: 10.1002/ejhf.2371.

8. **Aktaa S**, Gencer B, Arbelo E, Davos CH, Désormais I, Hollander M, Abreu A, Ambrosetti M, Bäck M, Carballo D, Crawford C, Deaton C Dendale P, Eijsvogels TMH, Galbraith M, Piepoli MF, Salzwedel A, Smulders Y, Wilhelm M, Biondi-Zoccai G, Mach F, Visseren FLJ, Gale CP. European Society of Cardiology Quality Indicators for preventive cardiology: developed by the Working Group for Preventive Cardiology Quality Indicators in collaboration with the European Association of Preventive Cardiology of the European Society of Cardiology. Eur J Prev Cardiol. 2021 Oct 23:zwab160. doi: 10.1093/eurjpc/zwab160.

9. **Aktaa S**, Batra G, Cleland JGF, Coats A, Lund LH, McDonagh T, Rosano G, Seferovic P, Vasko P, Wallentin L, Maggioni AP, Barbara Casadei B, Gale CP. Data standards for heart failure: The European Unified Registries for Heart Care Evaluation and Randomised Trials (EuroHeart). Developed in collaboration with the Heart Failure Association of the European Society of Cardiology. Accepted for publication in the European Heart Journal.

10. Batra G, **Aktaa S**, Wallentin L, Maggioni AP, Ludman P, Erlinge D, Casadei B, Gale CP. Data standards for acute coronary syndrome and percutaneous coronary intervention: The European Unified Registries for Heart Care Evaluation and Randomised Trials (EuroHeart). In collaboration with the Association of Cardiovascular Nursing and Allied Professions (ACNAP), Association for Acute Cardiovascular Care (ACVC), European Association of Percutaneous Cardiovascular Interventions (EAPCI), EURObservational Research Programme (EORP), ESC Patient Forum, ESC Working Group on Thrombosis and ESC Committee for Young Cardiovascular Professionals. Accepted for publication in the European Heart Journal.

11. Book chapter: **Aktaa S**, Baumbach A, Ludman PF. Administration and data collection. May 2021. The PCR - EAPCI textbook of percutaneous interventional cardiovascular medicine. Edited by William Wijns, Patrick W. Serruys, Alec Vahanian, Eric Eeckhout, Rodney De Palma, Marc van Sambeek.

Dedication

This thesis is dedicated to the people who have lost their lives during the two crises that shaped my professional career: the Syrian war, and the COVID-19 pandemic.

Acknowledgment

Abstract

Cardiovascular registries have provided infrastructures for the conduction of observational and, in recent years, randomised research using routinely collected data. Clinical registries help identify gaps in care deliver, disparities in practice and stimulate quality improvement. However, the lack of integration between related registries increases the burden of data collection and limits the ability to combine data from different sources. Thus, there is a need to standardise the methods by which clinical data pertinent to cardiovascular disease (CVD) are defined and the quality of cardiovascular care is measured across various settings.

The aim of this PhD is to harmonise the clinical definitions of the data variables for common cardiovascular conditions and interventions. Such a harmonisation is a prerequisite for the integration between cardiovascular registries and their interoperability with electronic health records. Thus, routinely collected data may be efficiently utilised for conducting quality improvement projects, high-quality clinical research and post-marketing surveillance of new drugs and devices.

Under the auspice of the European Unified Registries On Heart Care Evaluation and Randomized Trials (EuroHeart) initiative of the European Society of Cardiology (ESC), I led the establishment of a methodological process for the development of data standards for CVD. In addition, I applied this process and developed standardised clinical definitions for several cardiovascular domains, including acute coronary syndrome, percutaneous coronary intervention, heart failure, atrial fibrillation and transcatheter aortic valve implantation. I then participated in the implementation of the developed standards into the EuroHeart IT platform which has been adopted by a number of European countries.

Furthermore, I led the construction of a standardised methodology for the development of quality indicators (QIs) for CVD. This methodology was used for the development of QIs for a variety of cardiovascular conditions, including acute myocardial infarction (AMI), atrial fibrillation, heart failure, CVD prevention and cardiac pacing. I then carried out external

validation processes to evaluate the performance of some these QIs, such as AMI and heart failure, using data from national registries in Sweden and the UK.

In conclusion, my PhD has been centred around the development, application and validation of methodological approaches for the construction of data standards and QIs for CVD. Such an endeavour not only addresses an unmet need in Europe, but also enables the conduction of international comparative analyses and clinical trials across the continent. The results of my PhD will provide a means for the generation of high-quality evidence that may help reduce the burden of CVD and improve patient outcomes.

Table of Contents

PART I

Chapter 7. 2020 Update of the quality indicators for acute myocardial infarction: a position paper of the Association for Acute Cardiovascular Care: the study group for quality indicators from the ACVC and the NSTE-ACS guideline group.. ………...……145

Chapter 8. Quality of acute myocardial infarction care in England and Wales during the COVID-19 pandemic: linked nationwide cohort study…………………..………175

Chapter 11. European Society of Cardiology Quality Indicators for the care and outcomes of cardiac pacing …………………..………..………….…..………………………265

Chapter 12. European Society of Cardiology Quality Indicators for Cardiovascular Disease Prevention……...…………………………………….…..……………286

Chapter 13. European Society of Cardiology Quality Indicators for the care and outcomes of adults with heart failure. ………………..………………………317

List of tables

PART I

PART II
- **Chapter 3**

- **Chapter 4**

List of figures

PART I

PART II

- **Chapter 5**

- **Chapter 6**

- **Chapter 7**

- **Chapter 8**

- **Chapter 9**

PART III

Glossary

Abbreviations	Definition
ACS	Acute coronary syndrome
ACC	American College of Cardiology
ACEI	Angiotensin converting enzyme inhibitors
ACNAP	Association of Cardiovascular Nursing and Allied Professions
ACVC	Association for Acute Cardiovascular Care
AF	Atrial fibrillation
AHA	American Heart Association
AMI	AMI
APHRS	Asian Pacific Heart Rhythm Society
ARB	Angiotensin receptor blockers

BCIS	British Cardiovascular Intervention Society
CA	Catheter ablation
CABG	Coronary artery bypass surgery
CARDS	Cardiology Audit and Registration Data Standards
CCS	Canadian Cardiovascular Society
CIED	Cardiac implantable electronic devices
CPG	Committee of Practice Guidelines
CPRD	Clinical Practice Research Datalink
CRFs	Case report forms
CRM	Cardiac Rhythm Management
CVD	Cardiovascular disease
DALYs	Disability-adjusted life years
DAPT	Dual anti-platelet therapy
DCG	Data Science Group
DQI	Data quality indicator
EAPCI	European Association of Percutaneous Cardiovascular Interventions
EHRs	Electronic healthcare records
EHRA	European Heart Rhythm Association
EMA	European Medicine Agency
EORP	EURObservational Research Programme
ESC	European Society of Cardiology
ESRD	End-stage renal disease
EuroHeart	European Unified Registries On Heart Care Evaluation and Randomized Trials
GDPR	General Data Protection Regulations
GRACE	Global Registry of Acute Coronary Events
GWTG	Get With the Guidelines
HES	Hospital Episodes Statistics
HF	Heart Failure
HQIP	Healthcare Quality Improvement Partnership
HRS	Heart Rhythm Society
HRQoL	Health-related quality of life

Hs-cTn	high-sensitivity cardiac troponin
ICD	International Classification of Diseases
IHD	Ischaemic heart disease
ICA	Invasive coronary angiography
ICHOM	International Consortium for Health Outcomes Measurement
LAHRS	Latin-American Heart Rhythm Society
LDL-C	Low-density lipoprotein cholesterol
LVSD	Left ventricular systolic dysfunction
MHRA	Medicines and Healthcare products Regulatory Agency
MINAP	Myocardial Ischaemia National Audit Project
NACSA	National Adult Cardiac Surgery Audit
NCAP	National Cardiac Audit Programme
NCDR	National Cardiovascular Data Registry
NCHDA	National Congenital Heart Disease Audit
NHFA	National Heart Failure Audit
NHS	National Health Service
NICE	National Institute for Care and Health Excellence
NICOR	National Institute for Cardiovascular Outcomes Research
NSTE-ACS	Non-ST segment elevation acute coronary syndrome
NOAC	Non-vitamin K antagonist oral anticoagulant
OAC	Oral anticoagulant
OECD	Organization for Economic Co-Operation and Development
ONS	Office of National Statistics
PCI	Percutaneous coronary intervention
PMs	Performance measures
PROMs	Patient-reported outcome measures
PRISMA	Preferred Reporting Items for Systematic reviews and Meta-Analysis
QIs	Quality indicators
QRCG	Quality Registry Coordinating Group
QoL	Quality of life

RCTs	Randomised controlled trials
R-RCT	Registry-based randomised controlled trials
RTG	Registry Technology Group
SAP	Statistical analysis plan
SCAAR	Swedish Coronary Angiography and Angioplasty Registry
STEMI	ST-segment elevation myocardial infarction
SWEDEHEART	Swedish Web-system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies
TIA	Transient ischaemic attack
TTR	Time in therapeutic range
TAVI	Transcatheter aortic valve implantation
UCLA	University of California–Los Angeles
UCL	University College London
WHO	World Health Organisations

xxx

PART I

Chapter 1. Introduction

In this thesis, I will develop a standardised methodology for the construction of clinical registries for cardiovascular disease (CVD). Such a methodology enables the harmonisation of the various efforts that aim to improve the quality of cardiovascular care and patient outcomes. The thesis is structured and presented in accordance with the format of an alternative style of doctoral thesis including published material of the University of Leeds.

In Part I, I highlight the limitations of existing cardiovascular registries and the need for a unified infrastructure for data acquisition, analysis and reporting. Then, I introduce the EuroHeart (European Unified Registries On Heart Care Evaluation and Randomized Trials) initiative which aims to harmonise the clinical definitions and the collection methods of cardiovascular data. In Part II, I outline the accomplishments of my PhD studies by presenting the published papers that are pertinent to the development of a pan-European system for cardiovascular data capture and quality improvement. PART III comprises a critical discussion of the presented material in the context of the literature, with an overview of potential future directions and challenges. Figure 1 provides a central illustration of my PhD studies and accomplishments.

Figure 1. Central illustration of this PhD studies and accomplishments.
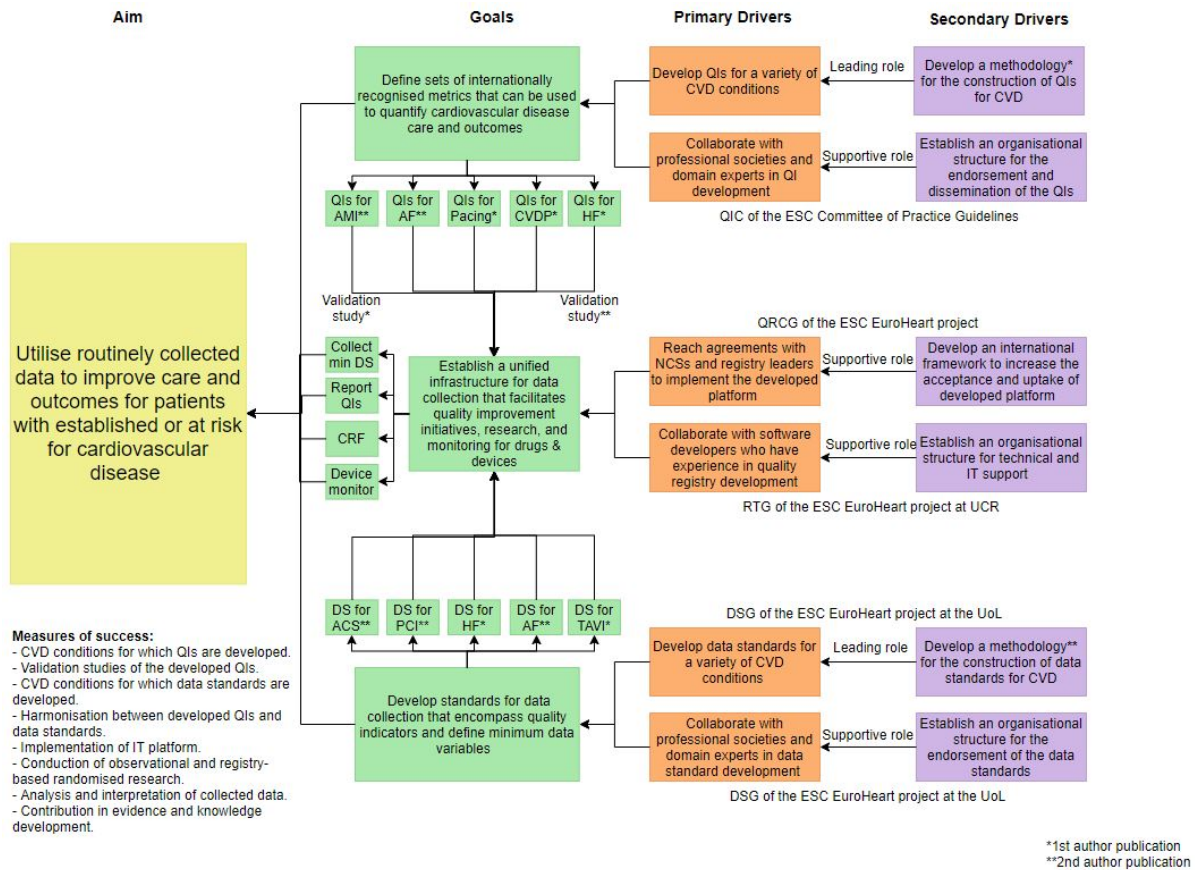
ACS=acute coronary syndrome, AF=atrial fibrillation, AMI=AMI, CRF=case report form, CVD=cardiovascular disease, CVDP=CVD prevention, DS=data standards, DSG=Data Science Group, ESC=European Society of Cardiology, HF=heart failure, NCSs=National Cardiac Societies, PCI=percutaneous coronary intervention, QI=quality indicators, QRCG=Quality Registry coordinating Group, RTG=Registry Technology Group, TAVI=transcatheter aortic valve implantation, UCR=Uppsala Centre of Research, UoL=University of Leeds.

1.1 Burden of cardiovascular disease

This section aims to highlight the burden of CVD in Europe and the unwanted variations in the delivery of care and patient outcomes within and between countries. In addition, it presents comparisons of the expenditure on cardiovascular care between different European countries based on published data from international registries and surveys.

1.1.1 Morbidly and mortality from cardiovascular disease

Despite the advances in CVD treatment and preventive technologies, it remains the most common cause of morbidity and mortality worldwide.[1] According to the 2019 European Society of Cardiology (ESC) Cardiovascular Disease Statistics, there were 108.7 million

people living with CVD in the ESC member countries in 2017, with 19.9 million new CVD cases in the same year.[2] Without standardising for age, both the prevalence (55.7 million vs. 52.9 million) and the incidence (10.3 million vs. 9.6 million) of CVD were higher in women compared with men, with a reversed trend in the median rates per 100 000 people for prevalence (6190 vs. 7250) and incidence (1006 vs. 1291) after age-standardisation.[2] Furthermore, the median number of age-standardised disability-adjusted life years (DALYs) from CVD in 2017 was 4530 per 100 000 inhabitants in the ESC member countries.[2]

The annual death toll from CVD globally is around 17 million deaths.[1] In Europe, a substantial decline has been observed in the age-standardised mortality rates from CVD, with a particular improvement in survival following ischaemic heart disease (IHD) and stroke.[2] However, CVD remains the most common cause of death in Europe with over 60 million potential years of life lost annually to CVD.[2] In addition, it is estimated that around 4 million people die from CVD in Europe each year accounting for 44% of all deaths.[3, 4] Of those, 44% deaths are attributed to IHD and 25% to stroke.[3, 4]

1.1.2 Economic burden of cardiovascular disease

In addition to its morbidity and mortality, CVD has a substantial economic and financial burden. In 2016, the Eurostat and Organization for Economic Co-Operation and Development (OECD) reported that CVD was responsible for the largest proportion of hospitalisation and pharmaceuticals spending accounting for over 10% of all health expenditure in Europe.[5] In the UK, it is estimated that CVD costs the National Health Service (NHS) around £7.4 billion per year accounting for around 6% of the total budget of the NHS.[6] This estimation rises to £15.8 billion per annum with the addition of the broader and indirect costs of CVD.[6] Of note, the estimated annual cost of CVD in France and Germany is €15.1 billion and €34.7 billion, respectively.[7, 8] In 2016, spending on IHD and hypertension in the US was estimated at $80 billion and $71 billion, respectively.[9]

Whilst the economic burden of CVD has increased over the years,[2, 9] it is expected to rise further with the aging population and the advances in CVD therapeutic strategies.[9] The World Heart Federation predicts that the global cost of CVD is set to rise to around $1044 billion in 2030, which is a 20% increase from that of 2010.[10] Thus, CVD is a major healthcare and economic challenge that affects patients, authorities and healthcare professionals around the world.

1.1.3 Variations in cardiovascular disease

1.1.3.1 Variation in cardiovascular disease care and outcomes

Data from observational studies and clinical registries show suboptimal attainment for guideline-directed therapies for CVD,[11-13] with large variations and inequalities in care delivery within and between countries.[14-16] Consequently, the outcomes of CVD vary across regions highlighting the missed opportunity to reduce premature deaths and standardise the processes of care for CVD.[17, 18] Such a variation is evident in the substantial differences in the outcomes of CVD across the ESC members countries, with DALYs ranging from less than 1600 to more than 10,000 and observed disparities in the rates of premature deaths from CVD between high- and middle-income countries.[2]

1.1.3.2 Variation in cardiovascular disease health expenditure

The variation in cardiovascular care and outcomes across the ESC member countries is paralleled with substantial differences in healthcare expenditure on CVD.[2] The proportion of spending on CVD ranged from 10% to over 24% of the total healthcare expenditure,[2] with large variations in the availability of resources, such as percutaneous coronary intervention (PCI) and transcatheter aortic valve implantation (TAVI).[2] The rates of PCI ranged from less than 500 to over 3500 procedures per million people across the ESC member, while the rates of TAVI ranged from less than one procedure to over 200 procedures per million people.[2]

1.1.3.3 Variations in cardiovascular disease data collection systems

International surveys and prospective registries illuminated patterns of CVD and variations in its management across different regions. However, the heterogeneity in the methods by which cardiovascular data are coded, captured and analysed between participating countries restricts the validity of the comparison and hampers the interpretation of the results.[2] Such a heterogeneity may result in misclassification bias and large missingness of relevant data due to the differences in the clinical definitions of the variables within and between countries.[19]

Furthermore, the lack of harmonisation in the definitions of cardiovascular data creates a disintegration between quality indicators (QIs) and clinical registries.[19] Whilst QIs are tools that be used to standardise the measurement of cardiovascular care quality and promote the adherence to guideline recommended therapies,[20, 21] clinical registries serve as the mechanism that allows the operationalisation of QIs and their implementation in practice.[22-24]

Hence, there is a need to develop standardised strategies for defining, collecting and reporting cardiovascular data on an international level such that a unified infrastructure may be established for the monitoring and improvement cardiovascular care and outcomes.[25-27]

1.1.4   Summary

- CVD is a major healthcare and economic challenge for patients, authorities and healthcare professional around the world.
- Systematic collection of prospectively defined cardiovascular data allows the monitoring of the patterns of care delivery and subsequent outcomes for CVD.
- Substantial variation exists in the quality of care for CVD across the ESC member countries.
- There is a need to harmonise the methods by which CVD data are defined, captured and analysed and quality of CVD care is measured.

1.2 Aims and objectives

In this thesis, I will investigate the methods that are needed to establish a unified system for collecting cardiovascular data for quality improvement, clinical research and post-marketing surveillance of new drugs and devices.

1.2.1 Objectives

1. To establish a standardised methodologies for the development of data standards and QIs for CVD.
2. To apply these methodologies in establishing data standards and QIs for common CVD conditions.
3. To investigate the feasibility and validity of the developed data standards and QIs in 'real-world' settings.
4. To implement the developed data standards and QIs into a user-friendly interface that allows the seamless collection, analysis and reporting of data.

1.2.2 Research questions

1. What is the extent of variation in the existing data collection systems for CVD?
2. What are the key methodological steps that are needed to develop a unified system for collecting cardiovascular data in a valid and feasible fashion?
3. What is the applicability of such a methodology in different domains of CVD?
4. How can the definitions of data variables for CVD be harmonised across different settings including quality improvement initiatives, clinical registry and trials?
5. What is the role of a methodologically developed set of data standards or QIs in highlighting gapes in care delivering or addressing the existing 'evidence-practice' gap?

1.3 Translational gaps:

In 2006, Sir David Cooksey described two gaps in the translation of science into practice.[28] The first is transforming the knowledge accumulated from basic and clinical research into defined products, approaches and interventions. This is the gap that traditional Clinical Practice Guidelines from various societies aim to address by providing hierarchical recommendations based on the validity and generalisability of available evidence. The second gap involves implementing these recommendations into clinical practice (Figure 2).[28] In his report, A review of UK health research funding, Sir Cooksey recommended the establishment of strategies to monitor the delivery of health research and the identification of measurable performance indicators that can provide the infrastructure for public reporting and accountability.[28]

Sir David Cooksey's call to develop integrated strategies for the monitoring and improvement of care delivery is valid beyond the UK and more than a decade later, particularly for CVD.[29-31] The availability of a high-quality body of evidence supporting different preventive, diagnostic and therapeutic measures for CVD demands the utilisation of these measures which have a strong association with favourable patient outcomes.[32-35]

Figure 2. Gaps in science translation into clinical practice
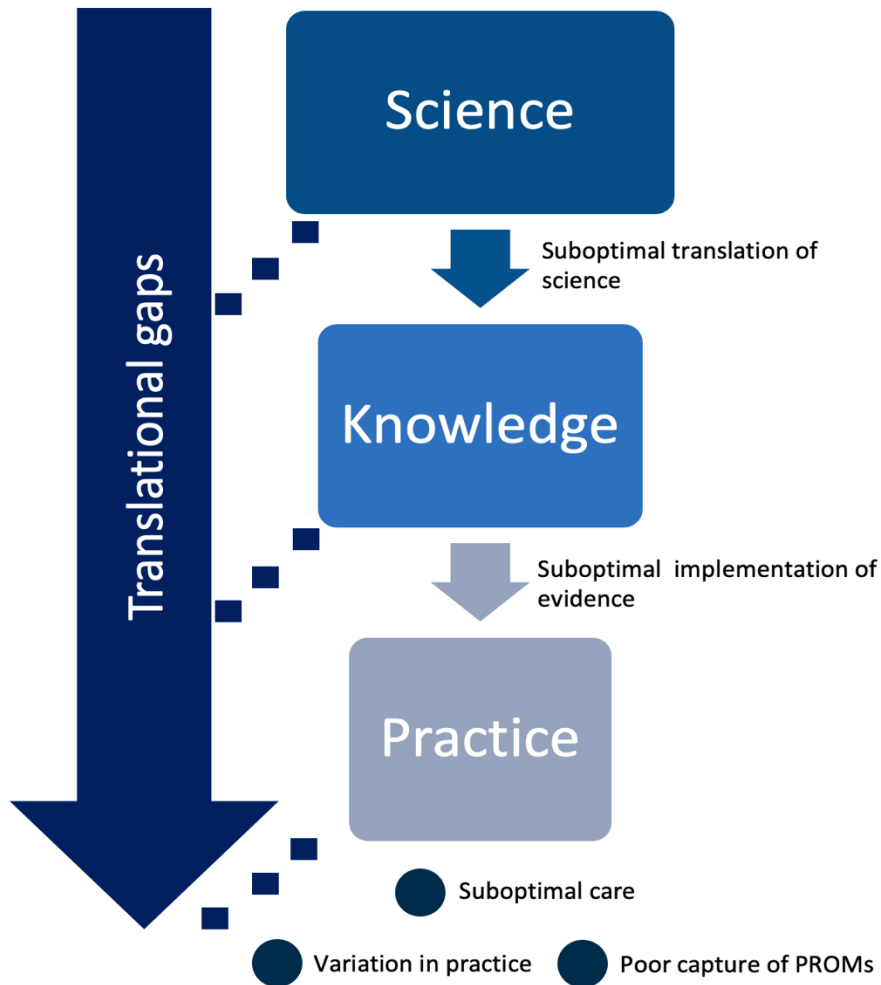
Adopted from: Best care at lower cost: the path to continuously learning health care in America, 2013, ISBN:0-309-26074-4[36]

PROM= patient-reported outcome measures.

In the next section, I will explore the hypotheses that have been suggested in the literature to explain the emergence and/or the persistence of the transitional gaps in healthcare in general and in cardiovascular medicine in particular. Afterwards, I will explore various methods that may help address these gaps and stimulate the implementation of known evidence into practice.

1.3.1 Emergence and persistence of the translational gaps

Several reasons can be attributed to the emergence and/or persistence of the translational gaps in healthcare. First, the disintegration between the gaps in evidence and the needs in clinical practice on the one hand and the research activities that are meant to address these needs on the other hand. One explanation for this disintegration may be the disconnection between researchers and healthcare providers who may have different perspective or understanding on the areas in which clinical research is mostly needed.[37] Whilst the ideal research questions are these that address pivotal needs in clinical practice and aim to improve effectiveness and/or efficiency, some research efforts may be redundant or even harmful. For instance, a recent article in the British Medical Journal identified more than 2000 redundant clinical trials on statins in patients who are eligible for statin therapy resulting in an excess of around 600 deaths from participation in these trials.[38]

Second, the efforts that are needed to create a structural framework and training schemes to adopt emerging procedural technologies. Examples of such technologies include the implementation of a regional network for primary PCI for patients presenting with ST-segment elevation myocardial infarction (STEMI) and the use of radial access, as opposed to femoral, for PCI procedures.[39] The adherence to such important evidence-based aspects of cardiovascular care requires the development of infrastructures and training programs as well as regulatory approvals and funding.[39]

Third, the mismatch between the educational activities that aim to keep healthcare professionals up to speed with contemporary knowledge and the exponential advances in healthcare technologies over a short space of time.[36] Healthcare professionals, particularly those with a broad area of clinical practice may find it challenging to comprehend all mandatory therapies in each and every domain of their practice.[36] This explains the recommendations from regulators to refer patients with certain conditions (e.g. heart failure) to a specialist within a specified timeframe.[36]

Fourth, the controversial beliefs on medical scenarios for which no consensus exists between healthcare professionals. This may arise from the lack of robust evidence for a given process of care, contradicting results from different studies or substantial limitations in available studies.[40] For instance, the Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment (ISAR-REACT) 5 trial showed that prasugrel was superior to ticagrelor in the management of patients with acute coronary syndrome (ACS) for whom an invasive strategy was planned.[41] However, several observational studies showed contradicting results,[42] creating a state of uncertainty as to which agent should be prioritised in this group of patients.[43]

Finally, the lack of integration between clinical care and the tools by which care quality is measured.[44] This disintegration may be exaggerated by the administrative, organizational and regulatory complexities of modern healthcare systems.[36] Therefore, the creation of a reliable infrastructure that enables the monitoring of clinical care, provides timely feedback to guide the implementation of prognostic measures and participates in evidence development is needed.[45] Such an infrastructure helps address the transitional gaps identified by Sir Cooksey and allows the capture of patients' perspective through the inclusion of patient-reported outcome measures (PROMs) as shown in figure 2.

1.3.2 Time lag assessment

The time that is needed to translate science into practice is known as the time lag in translational research.[46] Whilst the measurement of this time lag may help address the translational gaps (figure 2), the time points at which the measurement should be conducted vary substantially.[46] For instance, one definition used the time between the ethical approval of a given study and the first publication of the results of this study, while another used the time between the first publication of the results and the incorporation of these results into Clinical Practice Guidelines.[46] Furthermore, one method proposed to assess the lag retrospectively from the time of implementation to the time of evidence emrgence.[46]

The solely use of time as a measurement of the translational gap abstracts quality assessment from its broader and multifaceted context. In addition, this method restricts the opportunity to understand the factors which may have contributed to the time lag and does not evaluate the quality of the implementation process.[37]

1.3.3 Quality assessment

Given the limitations of the time lag assessment method in addressing the translational gaps (figure 2), an alternative approach has been proposed in the literature. This approach defines key domains (or 'proximities') which serve as the goals of the quality assessment process and then identifies a step-wise pathway for the accomplishments of these goals.[37] Here, the translational gaps are addressed by identifying an important set of feasible goals rather than measuring the time to implement these goals.[37]

However, this approach requires the development of a framework by which the assessment process is carried out across various settings.[37] As such, there is a need to establish a framework that uses standardised tools to evaluate the implementation of emerging knowledge. In the next section, I will investigate the methods by which evidence is developed and used as a 'gold-standard' measure for practice (figure 2).

1.4 Evidence development

Clinical research aims to narrow the range of uncertainties in clinical practice by illuminating potential harm and benefits of available interventions and identifying those with the highest effectiveness.[47] Robust safety and efficacy data are usually needed to derive the evidence that controls the approval of medical therapies and the development of new indications, approaches or strategies for medical practice.[48] To that end, the Food and Drug Administration (FDA) in the United States, the European Medicine Agency (EMA) in Europe and the Medicines and Healthcare products Regulatory Agency (MHRA) in the UK mandate the availability of a valid scientific evidence for the pre-market approval of medical drugs and devices to ensure their safety, appropriateness and effectiveness.[49, 50] In addition, post-

marketing surveillance of new technologies have been increasingly emphasised by healthcare regulators.[51, 52]

When designing, conducting and analysing trials for clinical effectiveness, two threats may affect the study's internal validity: bias and confounders. Bias is a variation due to a systematic error and may lead to different results to that of the actual truth. Examples of biases include selection bias (systematic differences in responsiveness to an intervention between study groups), misclassification bias (inappropriate categorisations of patients in relation to exposure or outcome) and recall bias (variation in the likelihood to recall adverse events between study groups). Confounders, however, are the factors that may influence the studied exposure(s) and the measured outcome(s), and thus affect the direction and the amplitude of any potential association.[53]

1.4.1 Clinical Practice Guidelines

Clinical Practice Guidelines from different professional societies aim to provide evidence-based recommendations that can help practicing physicians in everyday clinical decision-making, but also address areas where there is a lack of strong evidence. The periodic updates of the Clinical Practice Guidelines, their translation to other languages and presentation in various forms (e.g. handbooks, mobile applications), help facilitate the education of practicing healthcare professional around the world.[54]

1.4.2 Randomised clinical trials

Randomised clinical trial (RCTs) are the 'gold-standard' method for the assessment of treatment effect.[55] Randomisation balances out potential confounders between study groups and thus causation can be inferred from RCTs with good sample size.[56] In addition, bias in the assessment of treatment effects is minimised in RCTs by the non-differential outcome ascertainment between the study arms, which can be further augmented by blinding.[57]

However, RCTs are costly, and the strict eligibility criteria for enrolment in some RCTs limit their generalisability and the applicability of their findings in daily practice.[58-60] For patients with CVD, only a very small proportion of patients are enrolled in RCTs, with enrolled patients having better care quality, higher adherence to guideline-recommendations and better outcomes compared with those who have not been enrolled.[60]

Such limitations have led in recent years the New England Journal of Medicine (NEJM) to establish a policy to safeguard the sufficient representation of disease population in trials,[61] and to encourage healthcare professionals and researchers to utilise existing resources to conduct efficient and cost-effective clinical research.[62, 63]

1.4.3 Clinical registries

Registries are organised systems that collect structured data into a common database to serve a pre-determined and specific purpose.[64] Clinical registry is an observational database of a particular condition (or procedure), with no mandated intervention for enrolment and few exclusion criteria.[65] As such, clinical registries aim to capture data that represent the overall cohort with this condition.[57] Clinical registries for CVD (hereafter referred to as clinical registries) are those that collect data pertinent to patients with a particular condition (e.g. heart failure) or those undergoing a given intervention (e.g. heart valve replacement).[66]

Historically, clinical registries started as components of RCTs.[67] In 1984, the Coronary Artery Surgery Study (CASS) was an RCT that compared coronary artery bypass surgery (CABG) with optimal medical therapy at the time.[68] The subsequent CASS registry validated the results of the study and illustrated the generalisability of its findings. Professional specialist societies and academic institutions then began to develop local, regional and national registries to address particular research questions.[69-71] One of the first clinical registries that aimed to measure and improve patients' care (quality registries) was the Cooperative Cardiovascular Project in 1994 for patients with acute myocardial infarction (AMI).[67, 72]

Clinical registries provide generalisable data reflecting routine clinical practice and are an important source for evidence development.[44] In addition, clinical registries have a role in evaluating the burden of diseases,[73] assessing the implementation of guideline-directed therapy,[13] estimating the consequences of substandard care,[12] and guiding quality improvement initiatives.[74] Furthermore, clinical registries allow the systematic collection of allcomers for a medical procedure,[66] monitor the safety of new medical technologies,[75] assess the response to, and care quality during, natural crises (e.g. COVID-19)[76, 77] and improve the understanding of rare diseases.[78]

Clinical registries can complement RCTs in addressing gaps in knowledge, especially in clinical areas in which RCTs may be difficult (e.g. long follow up) or less cost-effective.[79] In addition, clinical registries may assess the feasibility of a future RCT, guide the identification of potential sites (e.g. based on the prevalence of a given disease) and help develop the inclusion criteria for a study.[57] Furthermore, clinical registries may have a role in the evaluation of the eligibility of emerging therapies in real-world settings.[80]

Despite their strengths and various uses, clinical registries have limitations. First, participation in a registry, particularly those with a national or international representation, is dependent on the willingness of patients, the engagement of healthcare professionals and the continuous financial support from regulators.[57] These dependencies create barriers against the creation and/or maintenance of full populace registries for long periods of time.[57]

Second, the observational nature of clinical registries limits their ability to infer causation, given the lack of randomisation which increases the risk of confounders effect on the direction and magnitude of an exposure-outcome association.[57] Third, clinical registries enrol heterogeneous population which in turn may mask small or variable treatment effects on subgroups of patients. Fourth, clinical registries are prone to data missingness which may hamper the validity of the analysis.[57]

All in all, clinical registries are fundamental to evidence development and quality improvement.[81] However, and despite statistical adjustments,[82] data from traditional clinical registries remain prone to confounders. Thus, their assessment of treatment effects should be interpreted with caution and considered on the basis of hypothesis generating.[83]

In recent years, registry-based RCTs (R-RCT) have emerged as a pragmatic alternative to RCT. Patients are randomly enrolled to a prospective registry which combines the features of a traditional RCT with those of a large clinical registry.[83] Platforms of clinical registries can be used for R-RCTs to enable fast and non-selective enrolment of patients, with long follow up and relatively low cost.[84] In CVD, R-RCTs have been widely accepted by healthcare professionals,[85] impacting on Clinical Practice Guidelines[86] and highlighting the trustworthiness of such an alternative approach for evidence development.

Figure 3. The characteristics of clinical registry with the encompassed data standards and quality indicators
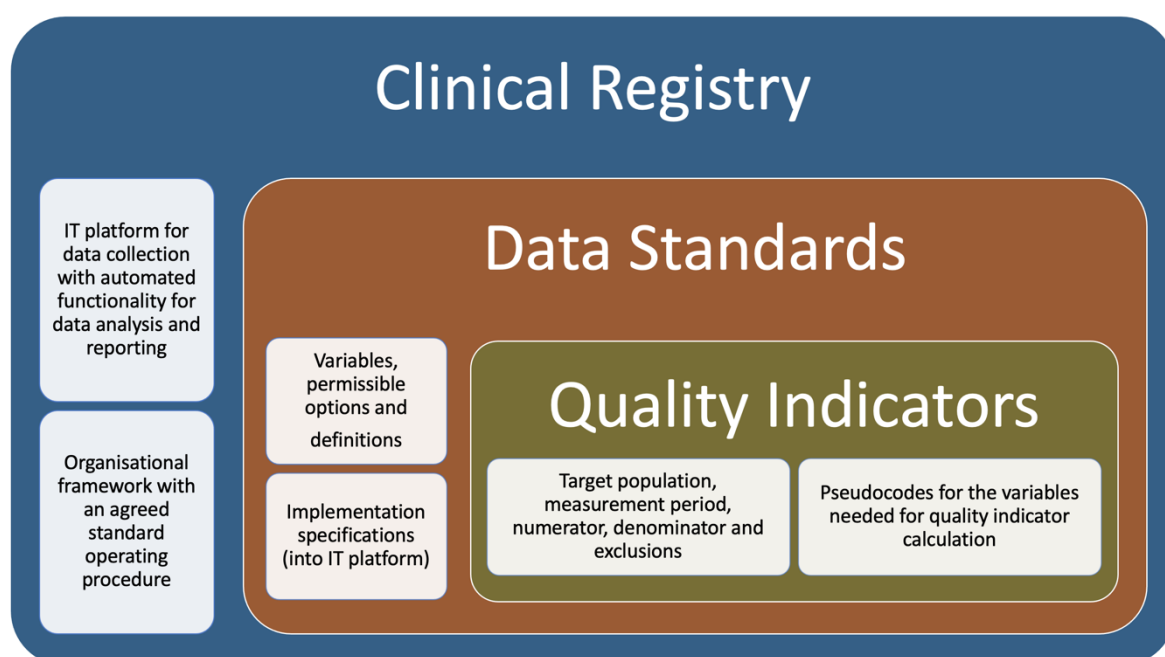
Clinical registry encapsulates a number of technical (e.g. IT platform with an electronic case report form [eCRF]), organisational (e.g. oversight committee) and clinical (e.g. data standards and QIs) specifications. Developing an IT platform for data collection that enables seamless analysis and reporting of data is an important component of a clinical registry. Such a platform may enhance the uptake of the registry in clinical practice, particularly if incorporated with electronic healthcare records.[64] In addition, there is a need to establish a committee that oversees the legal (e.g. authorisation, ethical approval, and confidentiality) and operational (e.g. data acquisition, storage and security) requirements of the registry and standardise the definitions of data variables by developing harmonised data standards and QIs (Figure 3).[64]

While different types of registries exist,[64] in this thesis I will focus on quality registries that aim to improve the quality of care for CVD. Such registries may also provide a means for the conduction of observational and randomised research as well as the port-marketing surveillance for new drugs and devices. In the following section, I will present the characteristics of a selection of large existing cardiovascular registries and expand on the core components of a quality registry: the data standards and QIs (Figure 3).

1.4.3.1 Characteristics of the existing national CVD registries

A recent systematic review of the literature showed the proliferation and the exponential growth of cardiovascular registries around the world, with over 73 million patients enrolled.[87] The review identified 155 registries across six subspeciality domains, namely coronary artery disease (45 registries), cardiac rhythm disturbance and management (28 registries), heart failure/cardiomyopathies (24 registries), structural heart disease (21 registries), congenital heart disease (21 registries) and cardiac surgery (16 registries).[87]

The review found substantial variations in the: (1) number of patients enrolled into these registries between countries, (2) cardiovascular domains covered, with only four countries (Denmark, Sweden, UK, and USA) having registries for all the 6 subspecialty domains, (3)

outcomes reported, with 43 registries reporting only in-hospital outcomes while 12 registries not reporting any outcome measures and (4) quality scores of these registries using an established data quality grading system for clinical databases.[87, 88]

Notably, the review reported that only a minority of the countries with national registries for more than one cardiovascular domain have a degree of integration between these registries.[87] Amongst these countries were Sweden, the UK and the USA which are known for their well-established national registries for CVD.[89]

Thus, in the following section, I will explore the characteristics of the national registries in these countries as well as some international registries and highlight areas for improvement based on the findings of a series of systematic reviews presented in Part II of this thesis.

1.4.3.1.1 National Institute for Cardiovascular Outcomes Research

The National Institute for Cardiovascular Outcomes Research (NICOR) is the framework that encapsulates cardiovascular registries in the UK.[90] In 2006, Professor Sir Bruce Keogh established NICOR which used to be based at University College London (UCL).[90] However, following a European Union tender in 2017, NICOR has been hosted at Barts Health NHS Trust with a 3-year contract that has been extended until June 2022.[91] NICOR is funded by the Department of Health through the Healthcare Quality Improvement Partnership (HQIP), and manages the National Cardiac Audit Programme (NCAP) which comprises the following national registries: (1) Myocardial Ischaemia audit, (2) Adult Percutaneous Coronary Interventions audit, (3) Transcatheter Aortic Valve Implantation registry, (4) Adult Cardiac Surgery audit, (5) Heart Failure audit, (6) Cardiac Rhythm Management audit and (7) Congenital Heart Disease in Children and Adults audit.[91, 92]

In addition to playing an important role in managing the cardiovascular registries in the UK, NICOR publishes regular reports of relevance to the public, NHS hospitals and regulators. In addition, NICOR facilitates the use of collected data for research, quality improvement and policy-making purposes.[90] This is achieved through the collaboration with healthcare providers, as well as data analysts, researchers and patients to generate reports and publications on various aspects of cardiovascular care delivered.[90] Furthermore, NICOR offers a linkage between the national audits and other data sources (e.g. Clinical Practice Research Datalink [CPRD], Office of National Statistics [ONS] and Hospital Episodes Statistics [HES]) to capture outcome measures (e.g. mortality and hospitalisation) and allow the continuous monitoring of patients' care across various settings.[91]

1.4.3.1.1.1 Myocardial Ischaemia National Audit Project

The Myocardial Ischaemia National Audit Project (MINAP) is the UK national registry for AMI, which collects data from 247 NHS hospitals in England and Wales.[93] Since 2000, MINAP aims to assess the quality of AMI care against the standards of the National Service Framework for Coronary Heart Disease.[94] MINAP comprises around 130 data variables that span across the multifaceted journey for patient with AMI including pre-hospital care, admission details, past medical history, in-patient diagnostic and therapeutic management, and in-hospital events. Outcomes are obtained from a linkage with other databases such as HES or ONS.[93]

1.4.3.1.1.2 British Cardiovascular Intervention Society

The British Cardiovascular Intervention Society (BCIS) registry is the UK national registry for PCI, which was initiated in 1988.[71] BCIS aims to capture all-comer data for patients undergoing PCI for the purpose of quality improvement, accountability and observational research. Over 113 data variables are collected in BCIS including information on patient demographics and comorbidities, clinical context of the PCI, procedural data and in-hospital events. Linkage with other databases (e.g. ONS) is obtained using each patient's unique NHS number.[66]

1.4.3.1.1.3 Transcatheter Aortic Valve Implantation

The development of the TAVI registry in the UK started in 2008 following the first TAVI procedure in the country in 2007.[92] Representatives from relevant professional societies were invited to form a Steering Committee for the registry which laid out the governance structure and the characteristics of the registry.[92] The TAVI registry comprises 110 data variables (101 in the initial version) across several key domains of TAVI care including patient demographics, indications for procedure, risk factors, operators identifiers, procedural details, in-hospital events and follow-up variables.[91, 92]

1.4.3.1.1.4 National Adult Cardiac Surgery Audit

The National Adult Cardiac Surgery Audit (NACSA) is the UK's national registry for adult cardiac surgery with data entry from all NHS hospitals and some private centres in the UK.[95] NACSA was established in 1977 and aims to improve the quality of cardiac surgery care through monitoring and benchmarking, with regular reports on the patterns of risk-adjusted outcomes across regions and over time.[91] NACSA comprises over 170 data variables that span the breadth of cardiac surgery with a set of outcome measures (e.g. wound infection, post-operative stroke) and provides a means for the conduction of real-world observational research relevant to coronary,[96] aortic,[97] and valvular[98] surgeries.

1.4.3.1.1.5 National Heart Failure Audit

The National Heart Failure Audit (NHFA) was established in 2007, with compulsory participation in England and Wales since 2011 and 2012, respectively.[91] The audit aims to capture data that are relevant to the quality of heart failure care and have an association with patient outcomes.[91] Such data include the attainment for evidence-based diagnostic and therapeutic strategies for heart failure. These data are shared with hospitals and regulators to drive improvement and address missed opportunities.[99] The NHFA dataset comprises 233

data variables, of which 21 are mandatory and supports the conduction of observational research to highlight the variation in practice.[100]

1.4.3.1.1.6 Cardiac Rhythm Management

The National Audit of Cardiac Rhythm Management (CRM) collects data relevant to cardiac implantable electronic devices (CIED) in the UK. The aim of the audit is to monitor and improve care and outcomes in the NHS.[91] Besides CIED, CRM captures information about cardiac ablation procedures including thermal and cryo-ablation, and comprises 115 initial and 34 follow-up data variables. Additionally, CRM reports QIs relevant to cardiac rhythm management care, which includes: (1) hospital activity volumes, (2) operator volumes for CIED implants and ablation procedures, (3) data completeness, (4) data validity, (5) adherence to the National Institute for Care and Health Excellence (NICE) guidance for CIED, (6) re-interventions within the first year following CIED implantation and (7) re-interventions in the first two years following ablations therapy.[101]

1.4.3.1.1.7 National Congenital Heart Disease Audit

In 2000, the National Congenital Heart Disease Audit (NCHDA) was initiated in the UK, with the aim to assess the quality and outcomes of care following 72 therapeutic interventions for paediatric and congenital cardiovascular conditions including both surgical and transcatheter procedures.[91] NCHDA is one of the largest registries for congenital heart disease in the world, with mandatory participation from all hospitals that perform such procedures. The main focus of NCHDA is to monitor and improve the quality and the outcomes of congenital heart disease care on a national level and it publishes risk-adjusted outcomes reports that may be used for benchmarking and quality assurance.[102]

The NCHDA has a robust method for monitoring the reliability of the data collection process. This process does not only involve local verification step, but also regular visits to the participating hospitals by an independent team to evaluate case attainment and the quality of

data acquisition.[102] During these visits, a number of random cases may be selected from each centre for an in-depth evaluation of the accuracy of data submission and for the calculation of a data quality indicator (DQI), which is expected to be over 90%. In addition, NCHDA mandates an independent review of all deaths to examine the correctness and completeness of the collected data.[102]

The process by which the NCHDA assesses the quality of data entry into the audit involves the evaluation of 7 data management and 3 data output criteria (Table 1).[102] The DQI is calculated on the basis of the independent team's evaluation to each of the following four domains: demographics, pre-procedure, procedure and outcomes.[102] Each domain is scored according to its proportion of completed records, with the DQI being the average of all the domains.[102]

Table 4. National Congenital Heart Disease Audit data management and output criteria

Criterion	Definition
Data Management Quality Criteria	
1. Security and Confidentiality	Regulations are in place to safeguard the adherence to regulatory and legal requirements regarding confidentiality and data security.
2. Coverage	Data collection covers all activity within the centre.
3. Validation and Quality Assurance	The availability of strategies for data validation with the source(s) from which data were originally extracted.
4. Training	Training staff involved in data collection and management with available resources for continues support and education.
5. Communications	The existence of policies to ensure that information collected is shared with the

	relevant stakeholders who need to have access to the data.
6. Accountability	The identification of an accountable personnel for the quality of data collected.
7. Health Records Management	The availability of functional and efficient health records.
Data Output Quality criteria	
1. Timeliness	The availability of data that are verified locally.
2. Completeness and Validity	The completeness of all core data variables within in a case record according to the agreed standards.
3. Accuracy	The presence of sufficient correlation between collected data and the actual clinical events.

1.4.3.1.1.8 Harmonisation between NICOR registries

While Dawson et al. reported a degree of 'integration' between the cardiovascular registries in the UK.[87] This integration is facilitated by the ability to track patients across various databases including hospitalisation records (HES) and death data (ONS) using each patient's unique NHS number.[90] However, the overriding aim of national (and ideally international) 'integration' between cardiovascular registries is to enable 'data integration',[19] which is defined as "*combining data residing in different sources and providing users with a unified view of them*".[103] In other words, integrated registries are those that compile data from diverse sources and allow the performance of quality assurance activities, comparative analyses and meaningful research with minimal assumptions and reasonable effort.[19]

Conversely, the cardiovascular registries in the UK function as separate entities and each has its own data standards and definitions.[91] In addition, there is a substantial overlap between the registries that capture intersecting conditions (e.g. MINAP and BCIS) with different

definitions and collection methods for the common variables between these registries. This overlap increases the burden of data collection whilst creating an unwanted duplication that may decrease the quality of the data entered.[19] As such, a fully 'integrated' registries are those that share harmonised <u>data standards</u> and are designed in an efficient way that minimises data entry duplication ([Figure 4](#)).

Figure 4. Models of management of common variables in intersecting registries.
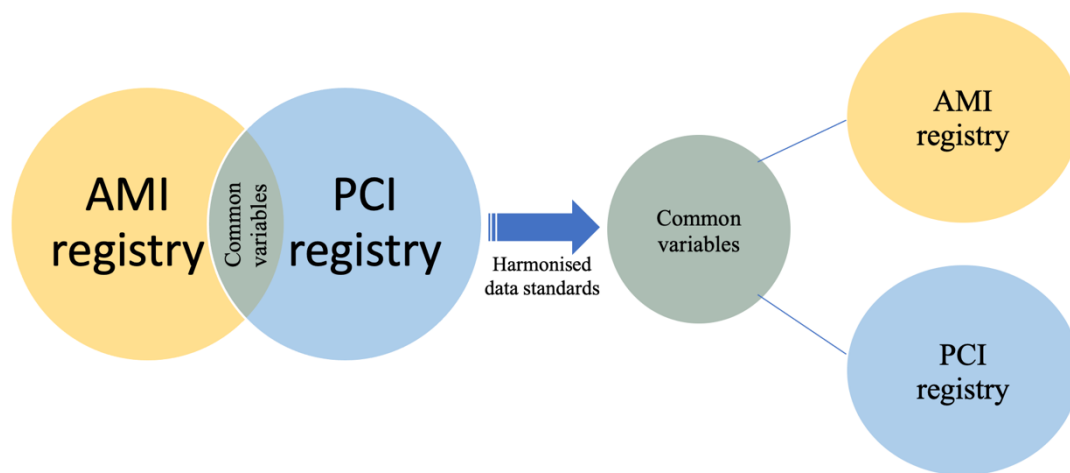
AMI= AMI, PCI= percutaneous coronary intervention.

<u>NICOR</u> registries have other limitations which may affect the collection, analysis and interpretation of their results. First, <u>NICOR</u> registries rely on external sources (e.g. HES or ONS) to obtain outcome measures. Such sources may not have the level of granularity that is needed in registry-based trials or effectiveness analyses. For instance, all-cause mortality rather than cardiovascular mortality is the information that can be obtained from ONS. Additionally, while HES has high sensitivity and specificity in capturing clinical events, HES coding for specific event rates mismatches those of an adjudicated events.[104]

Second, NICOR registries underestimate the total number of events for a given condition because a proportion of events may not be recorded into the registry. However, this underestimation may not be substantial. For example, case ascertainment of non-STEMI (NSTEMI) in MINAP was between 89.7% and 93.8% (depending on the International Classification of Diseases [ICD] codes used for the comparison) in England (68.3% and 87.7% in Wales) when compared to the HES records according to the 2021 MINAP annual report.[105]

Third, data missingness in some of NICOR registries may limit the ability to evaluate patient care.[106] Data completeness in a registry enables this registry to reliability draw firm conclusions with greater confidence, facilitate subsequent analyses and validate the interpretation of the results.[105] However, multiple imputation methods (e.g. by chained equations) have been used to minimise any potential bias created by data missingness and allowed the inclusion higher number of patients in the analysis.[15]

1.4.3.1.2 Swedish Web-system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies

In 2009, the Swedish registry for acute coronary syndrome (the Register of Information and Knowledge About Swedish Heart Intensive Care Admissions [RIKSeHIA]), PCI (the Swedish Coronary Angiography and Angioplasty Registry [SCAAR]), cardiac surgery (the Swedish Heart Surgery Registry) and secondary prevention (the National Registry of Secondary Prevention [SEPHIA]) were merged to form the Swedish Web-system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies (SWEDEHEART) registry.[107] In 2010, the Swedish Transcatheter Cardiac Intervention Registry (SWENTRY) was added to capture all TAVI procedures across the eight centers in Sweden.[108]

Like the NHS number in the UK, data linkage between SWEDEHEART and other databases is enabled by the use of the Swedish personal identification number.[107] These databases include the National Cause of Death Register (i.e. equivalent to ONS in the UK) and the National Patient Registry (i.e equivalent to HES in the UK). Such a linkage help track important outcomes of care including mortality and hospitalisation. Like the UK, SWEDEHEART linkage with the National Cause of Death Register and the National Patient Registry allows the identification of limited information based on ICD codes limiting the ability to obtain granular data about patient outcomes.[108]

Additionally, SWEDEHEART performs visits to random participating centres to evaluate the completeness and the accuracy of the data entered into the registry by checking with patients' records.[107] The registry has high case ascertainment which is 100% in SCAAR, SWENTRY and the Swedish Heart Surgery Registry, but mush lower (around 60%) in RIKSeHIA (given the variation in the admission locations (e.g. general medical wards) and the managing specialty (e.g. care of elderly) for patients with acute coronary syndrome.[107]

There are registries in Sweden that are separate to SWEADHEART and capture various domains of CVD. These include the National Quality Registry for Atrial Fibrillation (AuriculA), which was established in 2006,[109] the Swedish Heart Failure Registry (SwedeHF) which was established in 2000 (implemented throughout Sweden in 2003),[110] and other registries such as the Swedish Registry for Hereditary Heart Diseases, the Swedish Registry for Pulmonary Hypertension and the Swedish Acute Care Registry.[111] Notably, case ascertainment for SwedeHF is much lower compared with SCAAR and RIKSeHIA, with coverage of around 54% in the in-patient setting and 10% in the community.[110]

Over the last decade, SWEDEHEART has emerged as a successful example of a national registry that plays an important role in the conduction of high-calibre research activities. Not only the studies that were conducted using SWEDEHEART registry,[84, 112, 113] impacted clinical practice,[85] but also changed the Clinical Practice Guidelines.[86] Furthermore,

SWEDEHEART had a major role in improving care and outcomes for a number of CVD conditions, with continuous monitoring to the geographic and temporal trends in care delivery.[11, 114]

However, variations in care persistent across Sweden resulting in missed opportunities and a room for improvement.[115] Furthermore, the differences in the characteristics of various registries within SWEDEHEART and with other registries around the world (e.g. NICOR) limits the opportunity to conduct harmonised registry-based comparative analyses or multinational trials.[116]

1.4.3.1.3 National Cardiovascular Data Registry and Society of Thoracic Surgeons registries

In 1987, the National Cardiovascular Data Registry (NCDR) was established in the US by the American College of Cardiology (ACC) to evaluate the quality of care and outcomes for patients receiving cardiac interventions.[117, 118] Currently, NCDR comprises ten cardiac registries, of which eight collect in-hospital or procedural data: (1) Chest Pain - MI registry for patients with acute coronary syndrome, (2) AFib Ablation registry for patients with atrial fibrillation, (3) CathPCI registry for patients undergoing percutaneous coronary intervention (PCI), (4) EP Device Implant registry for patients undergoing cardiac ablation and/or cardiac devices implantation, (5) IMPACT registry for paediatric and adult patients with congenital heart disease, (6) LAAO registry for patients undergoing left atrial appendage occlusion, (7) PVI registry for patient undergoing peripheral vascular interventions and (8) Transcatheter Valve Therapy (TVT) registry (in collaborating with Society of Thoracic Surgeons [STS]) for patients undergoing transcatheter aortic and/or mitral valve interventions.[119] The out-patient registries are the Diabetes Collaborative registry for patients with diabetes and cardiometabolic disorders and the PINNACLE registry for patients with coronary artery disease, hypertension, heart failure and atrial fibrillation.[67, 119]

On the other hand, the American Heart Association (AHA) established a separate set of registries to monitor patterns and outcomes of care for patients with a number of CVD conditions.[120, 121] The AHA's Get With the Guidelines (GWTG) program initially comprised three domains of CVD care including coronary artery disease (GWTG-CAD), stroke (GWTG-Stroke) and heart failure (GWTG-HF).[120] Subsequently, the National Registry of Cardiopulmonary Resuscitation (NRCPR) of the AHA joined the GWTG initiative (GWTG-Resuscitation), and more recently the AHA established an atrial fibrillation registry (GWTG-AFib).[121-123]

In 1989, the STS established several registries for cardiac surgery.[19, 67] These registries are now ones of the largest and most efficient registries, with over 90% case ascertainment nationally.[67] It is estimated that the STS registries comprise data from around 7 million surgical cases across the following five domains: (1) Adult Cardiac Surgery Database (ACSD), (2) General Thoracic Surgery Database (GTSD), (3) Congenital Heart Surgery Database (CHSD), (4) Mechanical Circulatory Support (Intermacs) Database and (5) TVT Registry (in collaboration with the ACC).[67, 124, 125]

These efforts from various professional societies played a vital role in monitoring and improving the quality of cardiovascular care,[67, 126-128] and in serving as a vehicle for the conduction of pragmatic trials.[129] However, the heterogeneity in the data standards between these registries limits the opportunity to combine data from various resources to obtain a comprehensive and full evaluation of patient care across different settings.[67] In addition, the variations between intersecting registries (e.g. Chest Pain - MI of the ACC and GWTG-CAD of the AHA)[130]creates a need for an integration between the efforts for different cardiovascular domain.[67]

1.4.3.1.4 EURObservational Research Programme

In 2009, the EURObservational Research Programme (EORP) was launched by the ESC with the aim to understand the patterns of cardiovascular care across Europe. The program

comprises 20 different registries with participation from around 2500 centres across the ESC-member countries. It provided a means for the conduction of high-quality studies in a number of cardiovascular domains, including heart failure (EORP Heart Failure Long-Term registry),[131] cardiovascular prevention (European survey of CVD prevention and diabetes [EUROASPIRE]),[132] atrial fibrillation (EORP-AF),[133] infective endocarditis (EURO-ENDO),[134] ACS (EORP-ACS),[135] cardiomyopathy,[136] and implantable cardiac devices lead extraction (EORP ELECTRa registry).[137]

In addition, EOPR has recently launched the spontaneous coronary artery dissection (SCAD) registry to better understand the clinical characteristics and pathophysiology of SCAD and obtain international data on the demographics of patients presenting with SCAD, as well as on the diagnostic methods, treatment patterns and outcomes for this group of patients.[138]

However, the integration between different EORP registries is restricted by the variations in the data standards between registries, the variability in the methods by the registry-based studies are performed and the lack of a unified platform to harmonise the data collection process within and between different EORP registries.

1.4.3.2 The need for a unified longitudinal pan-European registry

The limitations of, and the heterogeneity between, existing registries, creates a need for a unified infrastructure that leads the development of pan-European registry for common CVD conditions. Such an infrastructure may encapsulate various registries that are developed using standardised methodology and provide the tools that are needed for the analysis and reporting of the data collected.

1.4.3.3 Summary

- Translational gaps persist in the implementation of science into practice.

- Clinical registries play a major role in addressing translational gaps and improving adherence to guidelines recommendations.

- Existing registries form an important component of evidence development and quality improvement cycle.

- Within and between country variations in the characteristics of clinical registries limit the scale of the activities that may be conducted using these registries.

- There is a need to develop a unified infrastructure that encapsulates harmonised registries for common cardiovascular conditions and interventions.

1.4.4 Data standards

Data standards are the data variables (also called data fields or data elements) with their definitions and collection specifications.[139] Firstly, the variable definition which describes the clinical meaning of the variable is important to facilitate its identification in practice. For example, 'stable angina' is a commonly used variable in cardiovascular care. The clinical definition of 'stable angina' may be derived from the 2019 ESC guidelines for the diagnosis and management of chronic coronary syndromes as a: (1) constricting discomfort in the front of the chest (or in the neck, jaw, shoulder, or arm), that is (2) precipitated by physical exertion and (3) relieved by rest or nitrates within 5 minutes.[140]

Secondly, the permissible options (also called permissible values) for the variable and the clinical definition for each option. In the example above, these can also be specified according to the ESC guidelines which distinguish between typical angina, atypical angina and non-anginal chest pain.[140] Typical angina is defined as the presentation that meets all the above three criteria, atypical angina meets two out of the three and non-anginal chest pain meets one or none of the above characteristics.[140] As such, the permissible options for the 'stable angina' variable would be: (1) typical angina, (2) atypical angina, and (3) non-anginal chest pain using the definitions above for each of these three permissible options. Further

permissible options may be needed, such as (4) no angina (or not applicable) and (5) unknown depending on the clinical scenario(s) in which the variables will be collected.

Another method of collecting information about the 'stable angina' variable is to determine the severity (or grade) of the condition according to the Canadian Cardiovascular Society (CCS) grading. Here, the variable definition is this of typical angina according to the ESC guidelines,[140] but the permissible options are the grades of the CCS classification. The clinical definitions for these permissible options are the clinical characteristics of each of the CCS grades as shown in Table 2.[141, 142] As illustrated in Table 2, the purpose of the data collection determines the methods by which certain permissible options are defined ('no angina (a)', 'no angina (b)', 'unknown (a) and 'unknown (b)').

Table 5. Specifications and variations in the collection of data for stable angina according to the Canadian Cardiovascular Society.

Data variable	Stable angina
Data variable definition	Clinical presentation that meets all the following characteristics: (i) Constricting discomfort in the front of the chest or in the neck, jaw, shoulder, or arm; (ii) precipitated by physical exertion; (iii) relieved by rest or nitrates within 5 minutes.
Permissible options	No angina, Grade I, Grade II, Grade III, Grade IV, Unknown
Permissible options definitions	• **No angina (a):** two or less of the above three criteria are met (i.e. atypical angina and non-anginal chest pain). • **No angina (b):** less than two of the above three criteria are met (e.g. non-anginal chest pain but not atypical angina). • **Grade I:** Ordinary physical activity (i.e. walking and climbing stairs) does not cause angina. Angina with strenuous or rapid or prolonged exertion at work or recreation. • **Grade II:** Slight limitation of ordinary activity. Walking or climbing stairs rapidly, walking uphill, walking or stair climbing

after meals, or in cold, or in wind, or under emotional stress, or only during the few hours after awakening. Walking more than two blocks on the level and climbing more than one flight of ordinary stairs at a normal pace and in normal conditions.

- **Grade III:** Marked limitation of ordinary physical activity. Walking one or two blocks on the level and climbing one flight of stairs in normal conditions and at normal pace.

- **Grade IV:** Inability to carry on any physical activity without discomfort, anginal syndrome may be present at rest.

- **Unknown (a):** Inability to ascertain whether the patient has angina.

- **Unknown (b):** Inability to ascertain the Canadian Cardiovascular Society grade of the patient's angina.

Data standards are fundamental component of a clinical registry (Figure 3).[64] However, specifications are needed for the implementation of the data standards within the registry, such as the potential sources for data acquisition (e.g. electronic healthcare records), the clinical setting(s) during which the variables are applicable (e.g. patients undergoing percutaneous coronary intervention) and the time point for collection (e.g. before procedure and at 30-day follow up).[143]

Beyond their use in registries, data standards may be used for the design of the data collection (e.g. eCRF) for RCTs, quality improvement projects and electronic healthcare records.[130] However, and as highlighted in the example above, the standards for a given data variable can vary on a number of levels even when a widely agreed clinical definition exists for this variable. Another example for such a variation and its implications on the interpretation of landmark clinical trial results have been recently debated in relation to the EXCEL (Evaluation of XIENCE versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization) trial in which the rates of myocardial infarction events following coronary artery bypass graft or percutaneous coronary intervention varied substantially with

the use of different definitions for peri-procedural myocardial infarction,[144] despite the presence of a universal definition for myocardial infarction.[145]

Hence, the development of data standards for CVD that are harmonised across various settings is much needed. Such standards help unify the definitions of data variables as well as their collection specifications and thus allow the seamless exchange of information between different systems. Additionally, harmonised data standards enable the integration between clinical care, research and quality improvement endeavours using routinely collected data to conduct traditional[62, 63] and registry-based[84] studies that is both generalisable, cost-effective[58] and help address the growing burden of cardiovascular disease.[2, 58, 146]

1.4.4.1 Characteristics of the existing data standards

In the following section, I will present some of the efforts that have been undertaken by professional societies around the world to create data standards for CVD and highlight some characteristics to their development methodology and/or implementation process based on the findings of a series of systematic reviews of the literature presented in PART II.

1.4.4.1.1   Cardiology Audit and Registration Data Standards

In 2004, the Cardiology Audit and Registration Data Standards (CARDS) project was launched in collaboration with the ESC, the Department of Health and Children in Ireland and the Irish Cardiac Society with funding and endorsement from the European Commission.[147] By way of expert consensus and through reviewing relevant registries and Clinical Practice Guidelines, CARDS defined a set of variables for ACS, PCI and electrophysiology.[147] Table 3 shows a sample of the CARDS data variables for ACS with the names, codes and definitions for each of these variables (fields).

Table 3. A sample of the CARDS data variables for acute coronary syndrome.

ID	Field name/prompt	Short code		Definition
Working Diagnosis				
ACS 5.01	Predominant presenting symptom	1	Asymptomatic	Indicate the predominant symptom/reason why patient presented for medical attention.
		2	Chest pain	
		3	Dyspnoea	
		4	Fatigue	
		5	Syncope	
		6	Cardiac arrest/aborted sudden death	
		88	Other symptoms	
		99	Unknown	
ACS 5.02	Symptom onset date and time			Indicate the date and time of onset of symptoms/reason that prompted the patient's presentation for medical attention.
ACS 5.03	Heart rate			Indicate the patient's heart rate (beats per minute) reading. This should be the first heart rate recorded by a health care provider (GP/ambulance staff/A&E staff) AND when the patient is in stable cardiac rhythm.

| ACS 5.04 | Systolic blood pressure | Indicate the patient's blood pressure reading (mmHg). This should be the first heart rate recorded by a health care provider (GP/ambulance staff/A&E staff) AND when the patient is in stable cardiac rhythm. |
| ACS 5.06 | Date and time of admission/arrival at hospital | Indicate the date and time the patient first presented to the hospital for this admission. |

ACS= acute coronary syndrome, CARDS= Cardiology Audit and Registration Data Standards

The CARDS initiative was one of the first steps towards the harmonisation of data definitions for CVD in Europe. It provided clinically relevant variables that have been used for collecting patients' data in various settings.[148, 149] However, a number of issues may have attributed to the limited adoption of the CARDS standards. First, the lack of an accompanying IT infrastructure that may facilitate the collection , analysis and reporting of data. Second, the underrepresentation of common CVD conditions such as heart failure in the developed data standards. Third, the absence of regular updates to the standards in line with the changes in evidence. Fourth, the development methodology of the CARDS standards which comprised reviewing relevant registries and Clinical Practice Guidelines (as opposed to conducting a systematic review of the literature) and inviting a central working group for the development of the data standards for different clinical domains (as opposed to inviting a separate working group of experts for each of the domains).[147]

1.4.4.1.2 American College of Cardiology/American Heart Association Data Standards

The American College of Cardiology (ACC) and the American Heart Association (AHA) have a track records in the development of data standards for CVD[150] using an established methodological approach.[130] Unlike CARDS, the ACC/AHA data standards are updated over time to incorporate the developments in the diagnostic and management strategies,[151, 152] are developed by different Task Forces,[153 154] and some have a specific focus (e.g. clinical trials).[155]

The development methodology of the ACC/AHA data standards comprises the selection of the data elements, their permissible values and definitions through a comprehensive review of the literature and collaboration with various stakeholders. As such, the ACC/AHA data standards provide a medical nomenclature that is in line with contemporary knowledge and relevant to clinical practice.[130] Table 4 shows a sample of the 2021 ACC/AHA data standards for heart failure, with the data element, data element definition, permissible values, permissible value definitions and the source of definition.[152]

Table 4. Sample of the data elements and their specifications from the 2021 ACC/AHA Data Standards for heart failure.

Data Element	Data Element Definition	Permissible Values	Permissible Value Definitions
Oral diabetes medications	Types of oral therapeutic medications for diabetes	(multi-select) • Metformin • Sulfonylurea • Thiazolidinediones • GLP-1 agonists • DPP-4 inhibitors	

	• SGLT-2 inhibitors • Other • None • Unknown	
	Metformin	An agent belonging to the biguanide class of antidiabetics with antihyperglycemic activity
	Sulfonylurea	Sulfonamide urea derivatives with antihyperglycemic activity that induce secretion of insulin to increase glucose uptake from the blood
	Thiazolidinediones	Insulin-sensitizing agent that overcome insulin resistance by activation of the PPAR-gamma.
	GLP-1 agonist	Chemical agents that stimulate insulin release and inhibit glucagon release
	DDP-4 inhibitors	Chemical agents that prevent inactivation of GLP-1 levels and

		stimulate insulin release
	SGLT-2 inhibitors	Chemical agents that reduce renal glucose reabsorption, therapy increasing urinary glucose
	Other	
	None	No oral agent for diabetes treatment
	Unknown	Unknown oral agent for diabetes treatment

ACC= American College of Cardiology, AHA= American Heart Association, DPP-4=
dipeptidyl peptidase-4, GLP-1= glucagon-like peptide-1, PPAR= peroxisome proliferator-
activated receptor, SGLT2= sodium-glucose cotransporter-2,

However, there are limitations to the ACC/AHA data standards restricting their implementation even within the clinical registries in the US.[19] This results in variations in the definitions of key data variables (e.g. diabetes mellitus and hyperlipidaemia) in different cardiovascular registries in the US.[130] One of the limitation is that the collection of the ACC/AHA data standards involves substantial effort given the number of variables within each of the standard domains. For instance, the ACC/AHA data standards for heart failure comprise over 290 variables.[152] Another limitation is that unlike CARDS, the ACC/AHA data standards have no hierarchical ranking according to their importance to guide the prioritization of data aqcuisition.[130] Third, the ACC/AHA standards are developed according to the American Clinical Practice Guidelines, medical practice and healthcare system characteristics, which are different from those in Europe. Finally, these standards are not centrally implemented into a dedicated IT platform- potentially limiting their widespread uptake in practice.

1.4.4.1.3   Canadian Cardiovascular Society Data Standards

In 2012, the CCS developed a suite of data definitions for a number of conditions including heart failure and atrial fibrillation,[156] which were predominantly based on the respective ACC/AHA data standards.[157] However, like the CARDS initiative, the CCS data standards have not been updated to align with the developments in CVD diagnostic and therapeutic strategies. Additionally, whilst the CCS data standards have core and non-core variables to highlight the variables with a particular importance, they are not integrated into an IT platform to facilitate their adoption in practice.[156]

1.4.4.2 The need for Pan-European Data Standards

There is a need to establish an infrastructure that leads the development and implementation of pan-European data standards for CVD. Such an infrastructure may use a standardised methodology and collaborate with relevant stakeholders and professional societies to construct widely accepted standards for cardiovascular data collection, analysis and reporting.

1.4.4.3 Summary

- Data standards define the specifications and characteristics of clinical registries and determine the breadth and depth of data collection.
- Lack of harmonisation in the existing data standards for cardiovascular registries creates a need for pan-European standards that are developed according to a structured methodology.

1.4.5   Quality indicators

In addition to <u>data standards</u>, <u>QIs</u> are an important element of a clinical registry. They allow the measurement and reporting of the quality and outcomes of cardiovascular care (<u>Figure 3</u>).[19] Given that quality registries primarily focus on driving quality improvement, the identification of the indicators of quality is fundamental to the design and functionality of these registries. In addition, the identification of QIs help minimise the amount of collected data and ensures that the registry is meeting its primary goal(s).[19]

Performance evaluation using well-defined <u>QIs</u> provides valid information for several parties. First, reports from QIs help healthcare professionals identify areas for improvement in their own practice. Second, healthcare regulators use such reports in planning policies and commissioning services. Third, the public may choose their care provider (if possible) according to these reports which may improve the trustworthiness of healthcare systems and show accountability.[158] Therefore, reports about performance measurement need to be developed in a scientific, yet simple way to enable the derivation of actionable information that may stimulate behaviour change and improve patient care.[64, 90]

1.4.5.1 Characteristics of the existing quality indicators

In the following section, I will present some of the efforts that have been undertaken by professional societies around the world to create indicators of care quality for patients with CVD and highlight some characteristics to their development methodology and/or implementation process.

1.4.5.1.1   ACC/AHA Performance and Quality Measures

The Strategic Framework Board and the National Quality Forum in the US established frameworks for the development,[159] evaluation[160] and implementation[161] of national goals that aim to monitor and improve the quality and outcomes of health care in various settings. These goals are meant to meet certain characteristics including achievability (i.e. interventions performed by healthcare providers or systems can drive quality improvement),

importance (i.e. the goals are pertinent to clinical area which is known to cause substantial morbidity or mortality and is of importance to patients), evidence-base (i.e. data exist supporting the goals proposed), representativeness (i.e. the goals relates to conditions that affect populations of various ages, races and socioeconomic groups).[159]

Additionally, the Strategic Framework Board established criteria for the evaluation of potential national goals. These criteria include: (1) defining the clinical setting(s) during which the performance measurement may occur, (2) identifying the 'agents' within the healthcare system who may be held accountable for the measurement, (3) illustrating the burden of the disease including the incidence and the prevalence, (4) describing the cohort of patients suffering (or at risk) from the condition in addition to those who may be at risk for care inequalities and (5) providing evidence-based data to support a framework that aims to help ameliorate substandard quality and improve outcomes.[159]

Based on the Strategic Framework Board and the National Quality Forum criteria, the ACC and the AHA have established Task Forces for the development of performance and quality measures for CVD,[162] using a standardised methodology for the selection of these measures.[163] These Task Forces developed a suite of performance and quality measures for a number of CVD conditions and interventions, including for AMI,[164] atrial fibrillation,[165] heart failure,[166] high blood pressure,[167] sudden cardiac death,[168] secondary prevention,[169] and cardiac rehabilitation.[170]

Whilst the terms QIs and performance (or quality) measures are used interchangeably, there are differences in the aspects of care that are evaluated by each of these terms.[171] A QI describes a particular clinical scenario in which an intervention is (or is not) recommended for a particular group of patients. For instance, a QI intended to evaluate the prescription of beta-blockers for patients with heart failure with reduced ejection fraction may be used to develop different performance (or quality) measures depending on the specifications that are

used to operationalise this QI.[171] Figure 5 illustrates four potential performance measurements for the same QI based on various data collection sources.

Figure 5. An example of different performance measures derived from the same quality indicator depending on data collection source.

PM 1 (EHR)	PM 2 (clinical registry)
Numerator: patients prescribed beta-blockers.	Numerator: patients recorded to be on beta-blockers.
Denominator: patients with an ICD code of HFrEF on their EHR.	Denominator: patients with HFrEF who have been enrolled in the registry.

QI
Prescribtion of beta-blockers for patients with HFrEF

PM 3 (patient survey)	PM 4 (drug dispensing register)
Numerator: patients report taking beta-blockers.	Numerator: patients collecting prescription for beta-blockers.
Denominator: patients identify themselves as having HFrEF.	Denominator: patients identified as having HFrEF as the indication for beta-blockers.

EHR= electronic healthcare records, HFrEF= heart failure with reduced ejection fraction, ICD= International Classification of Diseases, PM= performance measure, QI= quality indicator,

As shown in figure 5, four different performance measures have been derived from the same QI. Here, the 'clinical context' is identical in all the performance measures, but the cohort of patients included in each of the assessments is different. Thus, ensuring that the same specifications are used when comparing quality-of-care between centres is of paramount importance.[171] In addition, providing an infrastructure (e.g. IT platform) with unified methods for the collection, measurement and reporting of the clinically defined QIs help standardise the specifications of these indicators and ensure that the measurement is homogeneous across participating centres.

The ACC/AHA methodology for performance (and quality) measure development lacks the integration of these measures with a standardised platform for data variables. In addition, whilst the ACC/AHA methodology recommends the conduction of a literature review for the development of performance (and quality) measures, it does not mandates following a systematic method for the design, undertaking and reporting of this literature review.[171] Systematic reviews have been increasingly used as a standardised method for the identification of gaps in knowledge, and are recommended for the development of indicators of healthcare quality.[171] Widely agreed frameworks for systematic reviews have been established,[172] and used in Clinical Practice Guidelines,[40] creating an opportunity to integrate these frameworks in the development of QIs for health care and outcomes.[171]

1.4.5.1.2   NICE Quality Standards

In the UK, the National Institute for Health and Care Excellence (NICE) has for some time developed standards for healthcare quality and established a methodological process for their development.[23] NICE engages a wide range of stakeholders in the development of the NICE quality standards. However, its methodology lacks the emphasis on conducting a systematic review of the literature.[23] Besides, the NICE quality standards are limited to a small number of recommendations that do not span the breadth of the condition of interest.[173] Whilst, this limited layout of the NICE quality standards may be explained by legal considerations,[174] it creates a need for the development of comprehensive sets of QIs using systematic reviews of the literature and covering wide aspects of various CVD conditions and interventions.

1.4.5.1.3   Canadian Cardiovascular Society Quality Indicators

In Canada, the Appraisal of Guidelines for Research and Evaluation II (AGREE II) initiative was launched in 2003 to improve the quality, applicability and thus the uptake of Clinical Practice Guidelines in cardiovascular medicine.[175, 176] One of the tools by which the AGREE II initiative sought to improve the adherence to guideline recommendations was the development of well-defined and specific QIs. As such, suites of QIs for a number of CVD

conditions including heart failure and atrial fibrillation were developed.[156] Subsequently, further sets were developed such as these for cardiac rehabilitation and secondary prevention, PCI and TAVI.[156] However, these QIs were developed in accordance with the CCS Clinical Practice Guidelines with a primary focus on the characteristics of the Canadian healthcare system, limiting their generalisability to other regions around the world.

1.4.5.2 The need for Pan-European Quality Indicators

There is a need for an infrastructure that leads the establishment and implementation of a methodological process for the development of pan-European QIs for CVD. Such an infrastructure should collaborate with relevant stakeholders and professional societies to ensure that the developed QIs are valid measures of care quality and widely applicable in clinical practice.

1.4.5.3 Summary

- Quality indicators are tools that enable the systematic evaluation of the quality-of-care.
- The lack of harmonisation between existing quality indicators for CVD limits the opportunity to measure patterns of care delivery across regions.
- The disintegration between quality indicators and clinical registries restricts the ability to used routinely collected data for quality monitoring and improvement.
- The standardisation of the methods by which cardiovascular quality indicators are developed allows creating a unified system for performance evaluation and quality improvement.

1.5 The virtuous circle

The integration between best practice guidelines, clinical registries and quality indicators creates a continuous patient-centred model for evidence development and quality

improvement ([Figure 6]).[44] The so called 'virtuous (or great) circle', is a concept that was first described by Arthur Garson in 1999 and uses the knowledge derived from clinical and basic research about effective and safe interventions to develop indicators of care quality (QIs) that are measurable, specific and feasible.[177] The fundamental part of such a circle is the availability of a system for constant data acquisition (e.g. clinical registries) which uses harmonised data standards across Clinical Practice Guidelines, QIs and educational activities (e.g. national report cards).[177] Such a unified lexicon across various settings facilitates the communication between healthcare professionals and allows the conduction of 'pragmatic' observational and randomised clinical research.[178]

Figure 6. The virtuous circle for the integration of quality monitoring into evidence development.
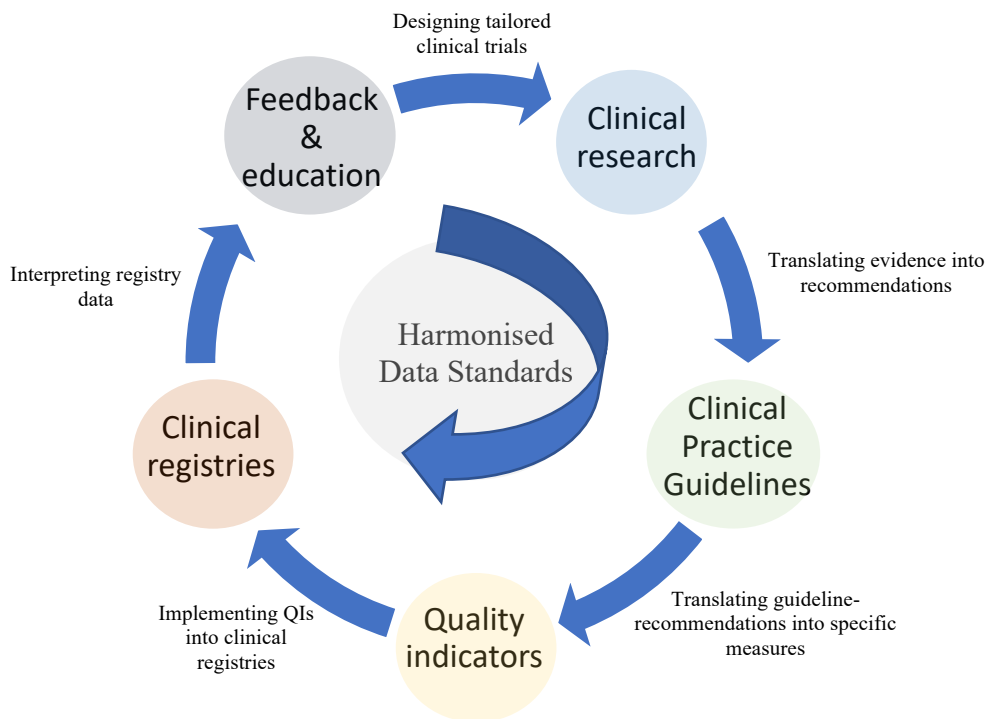
Adopted from Califf, et al.[44] PROMS= patient-reported outcome measures, QIs= quality indicators.

Healthcare authorities and regulators around the world have developed strategies to achieve the virtuous circle in health care, particularly for conditions contributing to substantial

morbidity and mortality such as CVD. In the following Chapter, I will present an international collaborative effort that aims to address the 'evidence-practice gap' and create a unified system for the collection, analysis and reporting of defined data variables for a number of CVD conditions and intervention.

Chapter 2. Integrating data standards and QIs in a pan-European registry: the European Unified Registries On Heart Care Evaluation and Randomized Trials (EuroHeart) initiative

The growing economic and healthcare burden of CVD,[2, 146] coupled with the increasing number of segregated activities that aim to collect patient data (as presented in Chapter 1), created a need to harmonise the standards by which CVD data are defined and quality measured.[45] Such a harmonisation facilitates the integrations between routine clinical care, quality improvement activities and clinical research ([Figure 6]).[58]

Providing unified definitions for CVD conditions, such as the universal definitions of AMI and heart failure, help standardise the criteria by which these conditions are identified across various settings.[145, 179] However, there remain variations in the definitions of the data standards within and between the different data collection platforms that capture information pertinent to these conditions. Such information includes patients' baseline and case-mix characteristics, QIs and outcomes of care. Not only these variations limit the opportunity to combine and compare data from different sources or between conditions, but also increase the cost and effort needed for data collection.

As presented in Chapter 1, efforts have been invested to establish tools for the collection of 'real-world' data for CVD and constantly monitor the patterns and the outcomes of care delivery. However, the lack of harmonisation between these efforts and the lack of agreed standards for data collection, analysis and interpretation restricts the opportunity to

proliferate such initiatives on the international level. The need for such standards is imminent given the advances in prognostic CVD therapies and the growing realisation of the role of clinical registries in facilitating the implementation of such therapies.

In this chapter, I will present an international collaboration that aims to address the gaps in evidence development and quality improvement circle that have been illustrated in chapter 1. In addition, I will describe my personal involvement in this international collaboration which aims primarily to standardise and facilitate the continuous collection and reporting of structured, well-defined data standards and QIs for CVD. As such, the heterogeneity in the definitions of data within[144] and between studies[180, 181] may be minimised and burden of data collection reduced.

2.1 Aims and objectives

The European Unified Registries On Heart Care Evaluation and Randomized Trials (EuroHeart) is an initiative by the European Society of Cardiology (ESC) that aims to provide a means for centre- and country-level quality improvement, as well as an infrastructure for post-marketing surveillance of drugs and devices.[45] Furthermore, EuroHeart provides a platform for the conduction of international registry-based observational and RCTs through the collaboration with a wide variety of stakeholders including National Cardiac Societies and registry leaders.[45]

2.1.1 Aims

The EuroHeart initiative aims to harmonise the definitions of data standards and QIs across various CVD conditions and interventions to:
-   enable continuous quality improvement on the local, national and international level,
-   facilitate the conduction of registry-based randomised and observational research,
-   help integrate the post-marketing surveillance of new drugs and devices for CVD into clinical registries and

- minimise the burden of data collection for CVD by utilising routinely collected data.

2.1.2   Objectives

The objectives by which the EuroHeart strives to achieve its aim include:
- the establishment of and collaboration with various Working Groups and domain experts,
- engage with relevant ESC Associations and national registry leaders for each of the clinical domains of EuroHeart,
- develop a standardised methodology for data standard development,
- apply this methodology in the construction of valid and feasible <u>data standards</u> for ACS, PCI, heart failure, atrial fibrillation, TAVI and cardiovascular outcomes,
- integrate these standards into a web-based IT platform and
- collaborate with National Cardiac Societies and registry leaders to implement the EuroHeart <u>data standards</u>.

2.2 Organisational structure

During its pilot phase (January 2020 to December 2021), EuroHeart was funded by the ESC, with complementary funding from industry partners and national research foundations. The organisational structure of EuroHeart comprises five Working Groups, an Executive Committee and an Oversight Committee. The relationship between the EuroHeart structural components and with national leaders is illustrated in Figure 7.

Figure 7. Organisational structure of EuroHeart
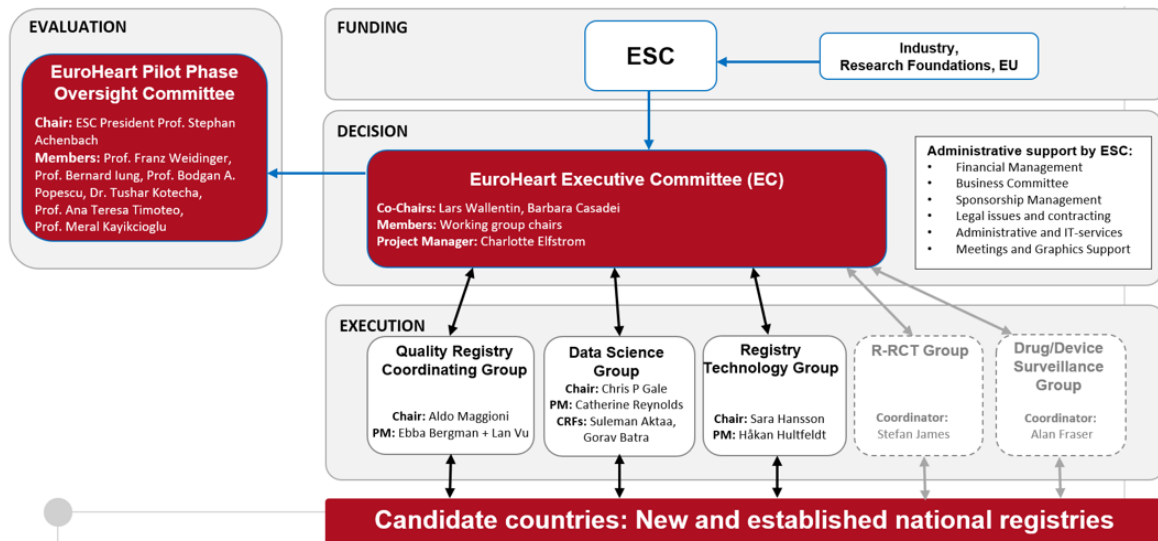
CRF= Clinical Research Fellows, EC= Executive Committee, EU= European Union, EuroHeart= European Unified Registries On Heart Care Evaluation and Randomized Trials, ESC= European Society of Cardiology, PM= project manager, R-RCT= registry-based randomised controlled trial.

2.2.1 Quality Registry Coordinating Group

The Quality Registry Coordinating Group (QRCG) presents EuroHeart to the national registry leaders in the countries that are interested in participating in EuroHeart. The group evaluates the existing infrastructure in this country and explores various methods with the national leaders to overcome the obstacles that may prevent the establishment (or the update) of national registries. The QRCG offers introductory meetings to highlight the role of registries in improving the quality of cardiovascular care and the opportunities it may provide through the participation in international clinical trials.

In addition, the QRCG presents the criteria by which countries are selected to participate in the EuroHeart initiative. First, the QRCG evaluates whether the country can capture full (or near full) populace data for the condition of interest. This is important given the mission of EuroHeart is to provide generalisable data that provide sufficient representation of the

incidence and patterns of care delivery for CVD. Second, the QRCG assesses the feasibility of obtaining outcome data and whether this can be performed through a deterministic linkage of data with other databases (e.g. national death registry). Third, the QRCG explores the existing infrastructure in the countries that are interested in participating in EuroHeart and accordingly decide whether the country meets the criteria for Tier 1 participation (i.e. adopting the EuroHeart data standards and the EuroHeart IT platform), Tier 2 participation (i.e. adopting the EuroHeart data standards but using own IT platform) or Tier 3 participation (i.e. adopting the EuroHeart data standards but using own paper-based CRF) (Figure 8).

2.2.2 Data Science Group

The Data Science Group (DSG) of EuroHeart is responsible for the creation of the EuroHeart data standards and for the establishment of data sharing arrangements with the participating countries. The activities of the DSG include:

- developing a standardised methodology for the creation of the EuroHeart data standards (including QIs) for CVD
- applying this methodology in the development of data standards for a number of CVD conditions and interventions. That is (during the pilot phase): ACS, PCI, heart failure, atrial fibrillation, TAVI and CVD outcomes,
- ensuring the availability of methodologically developed QIs for the EuroHeart domains,
- supporting the QRCG in their interaction with national leaders by presenting the data standards and their development process,
- providing an advisory role to the participating countries in EuroHeart to implement the data standards,
- collaborating with the EuroHeart Registry Technology Group (RTG) to implement the developed data standards into the EuroHeart IT platform and
- establishing the statistical analysis plan (SAP) for the aggregated data that will be shared with the DSG.

2.2.2.1 Data sharing

Data collected using the EuroHeart platform are owned, managed and analysed by a dedicated local team as any traditional national registry. Only aggregated data may be shared with the DSG following agreements from all parties and the fulfilment of the General Data Protection Regulations (GDPR) in each of the involved countries. In addition, data sharing arrangements will take into considerations the legal framework for healthcare data exchange of the European Union.[182] Such aggregated data may be used by the DSG to perform high-level analyses according to the SAP (Appendix - Part I) and in collaboration with the national leaders of the participating countries (Figure 8).

Figure 8. Tiers of participating countries in EuroHeart and mode of data sharing
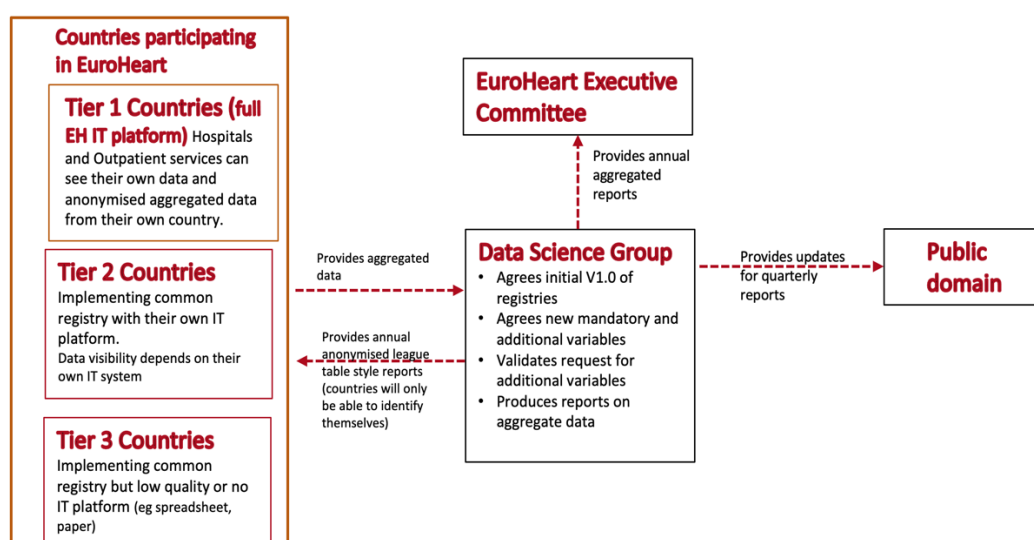
2.2.3 Registry Technology Group

The RTG is the team responsible for the development and implementation of the EuroHeart IT platform in the participating countries. An agreement has been reached between the ESC and the Uppsala Clinical Research (UCR) centre in Sweden to apply the experience accumulated from the SWEDEHEART registry into EuroHeart. The RTG uses the data standards that are developed by the DSG to create a web-based interface for patient-level data collection. This interface provides an automatic calculation and simultaneous reporting of the

QIs to support the continuous quality evaluation of care quality against internationally agreed standards (Figure 9).

Figure 9. The EuroHeart reporting page
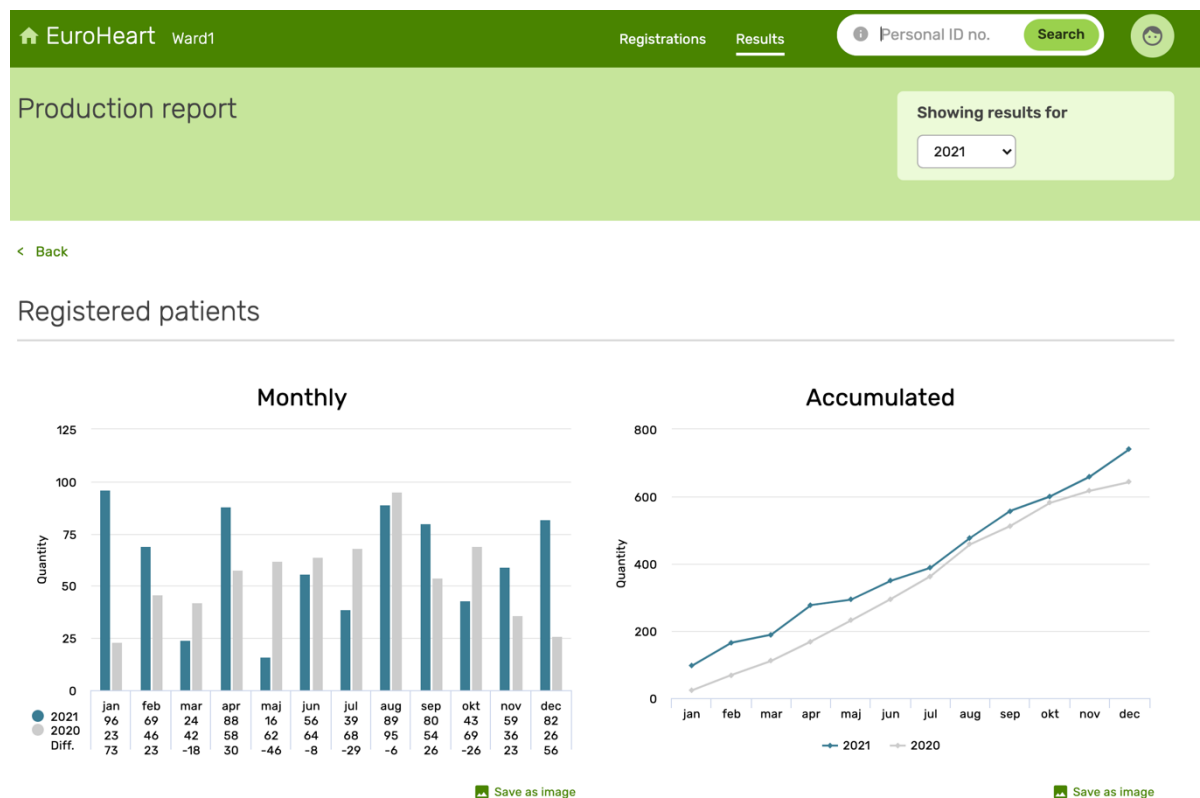
In addition to the above Groups, the EuroHeart comprises the R-RCT Group and the Drugs and Devices Surveillance Group. The former regulates the conduction of randomised trials using the EuroHeart data standards and IT platform, whilst the latter ensures that EuroHeart data standards capture the information that is needed for regulators in relation to the post-marketing surveillance of new cardiovascular drugs and devices.

2.3 Contribution to EuroHeart

As a Clinical Research Fellow within the DSG of EuroHeart, I have been primarily involved in the Group's activities and responsibilities (Central illustration). I led the development of

standardised methodologies for the selection of <u>data standards</u> and <u>QIs</u> for CVD as presented in <u>PART II</u>. In addition, I applied these methodologies in constructing <u>data standards</u> and <u>QIs</u> for a variety of CVD conditions (<u>PART II</u>). Furthermore, I evaluated the clinical use of the developed <u>QIs</u> for AMI in a naturistic study that assessed the quality of care for AMI in England and Wales during compared with before the COVID-19 pandemic (<u>PART II</u>).

2.3.1 Involvement in data standard development

Under the auspice of the <u>DSG</u> of <u>EuroHeart,</u> I examined the existing methodologies for the development of <u>data standards</u> for CVD and established a stepwise approach for this endeavor. This approach was adopted as the standardised methodology for the development of <u>data standards</u> for EuroHeart (<u>PART II</u>). In addition, I led the implementation of this methodological process in developing and <u>data standards</u> for several CVD conditions by performing systematic reviews of the literature, inviting domain experts to form wide Working Groups and reaching consensus through a modified Delphi method for each of the <u>EuroHeart</u> domain. These systematic reviews have been conducted in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guidelines,[183] and are presented in the respective publications in <u>PART II</u>. Figure 10 shows the different groups that are involved in the development of the <u>data standards</u> for each of the <u>EuroHeart</u> domains with their responsibilities.

Figure 10. Structure and role of the Working and Reference Groups in the development of the EuroHeart Data Standards
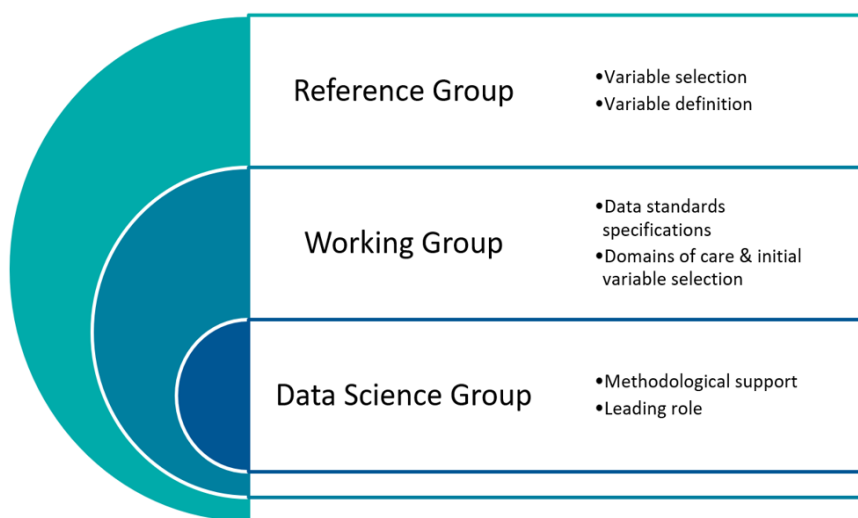
2.3.1.1 Methodology development

The development and publication of a methodological approach for EuroHeart aimed to: (1) standardise the selection of the EuroHeart data standards, (2) ensure the process is transparent and evidence-based and (3) disseminate the methodology such that it can be used by various healthcare professionals for other cardiovascular and non-cardiovascular conditions. My role involved reviewing existing forms of data standards and their development processes in collaboration with the DSG and reach consensus with the wider EuroHeart team on the key methodological steps that are needed to established the EuroHeart methodology for the development of data standards for CVD (PART II).[184]

2.3.1.2 Data standard development

In addition to the development of the methodological process, I led the application of this methodology in various areas within CVD. As such, the EuroHeart data standards for ACS and PCI, heart failure, atrial fibrillation and TAVI (PART II) were developed using the standardised methodology. In addition, the same methodology was used for the development

of an outcome domain for EuroHeart, which is an overarching domain that defines and captures the outcomes of care in relation to various CVD conditions and interventions.

My role during the development of the EuroHeart data standards involved conducting systematic reviews of the literature by developing search strategies, screening retrieved articles and extracting potential data variables for final selection. In addition, I presented the results of these reviews and used modified Delphi method to reach consensus on the data standards between the Working and the Reference Groups (Figure 10). Once developed, I sought endorsement from relevant professional Association(s) and National Cardiac Societies and supported the RTG in implementing these standards into the IT platform (Figure 11).

Figure 11. Steps of the development of the EuroHeart Data Standards for CVD.
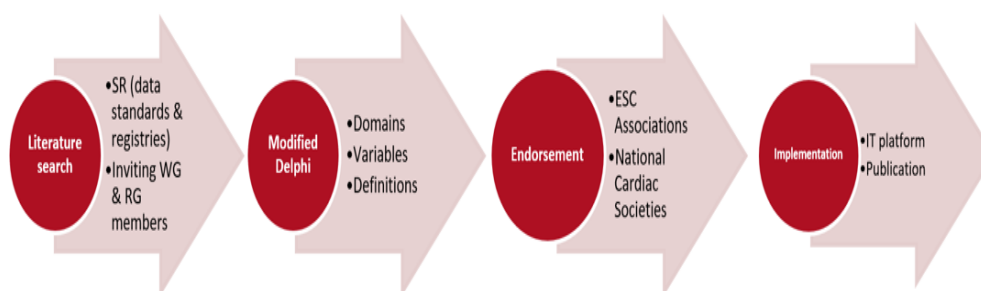
CVD= cardiovascular disease, ESC= European Society of Cardiology, IT= information technology, RG= Reference Group, SR= systematic review, WG= Working Group.

My support to the RTG comprised conducting a series of virtual and face-to-face meetings with the IT developed to transform the data standards from clinically defined variables into electronically collected fields in an interactive and consistent way. Such a transformation required constructing a prototype for each of the data standards and test this prototype to identify areas for improvement. Simultaneously, I had a major role in the writing process of the data standards and their development stages. This effort resulted in a number of scientific manuscripts in high-impact journals illustrating the need of such knowledge and the appropriateness of the used methodology (PART II).

2.3.1.3 Support with queries

Following the implementation of the <u>data standards</u> in the countries participating in <u>EuroHeart</u> (e.g. Estonia), I helped address the queries that have risen from those countries and were related to the <u>data standards</u>. As such, a framework was established within the <u>DSG</u> in collaboration with the <u>RTG</u> to answer questions and provide support whilst and after the implementation of the <u>EuroHeart</u> <u>data standards</u>. An example of these queries is the methods by which the data variables are linked between the registries to ensure internal validity of the data entry (e.g. between the ACS and PCI registries).

2.3.2 Involvement in QI development

Given the importance of <u>QIs</u> for the <u>EuroHeart</u> initiative, parallel efforts aimed to ensure the availability of methodologically developed <u>QIs</u> for the <u>EuroHeart</u> domains. As such, the Quality Indicator Committee (QIC) was established under the auspice of the Committee of Practice Guidelines (CPG) of the ESC (<u>Figure 12</u>). This Committee aims to serve as the framework that safeguards the development of the ESC QIs for a variety of CVD conditions in alignment with pertinent activities including the Clinical Practice Guideline and clinical registries (<u>Figure 6</u>). I have played a leading role in developing a methodological process for the creation of <u>QIs</u> for CVD. This was achieved through the critical examination of existing methodologies and the evaluation of alternative methods to develop parameters that can be valid and feasible in practice (<u>PART II</u>). Furthermore, I applied this methodology in several CVD conditions and interventions through a first-hand involvement in the conduction of systematic reviews of the literature to identify key aspects (structural, process and outcome) of care delivery that may be used as indicators of care quality. In addition, I collaborated with domain experts, specialist society representatives and patients to reach consensus on the selection of sets of <u>QIs</u> using a modified Delphi method (<u>PART II</u>).

Figure 12. Organisational structure of the QI Committee of the ESC CPG
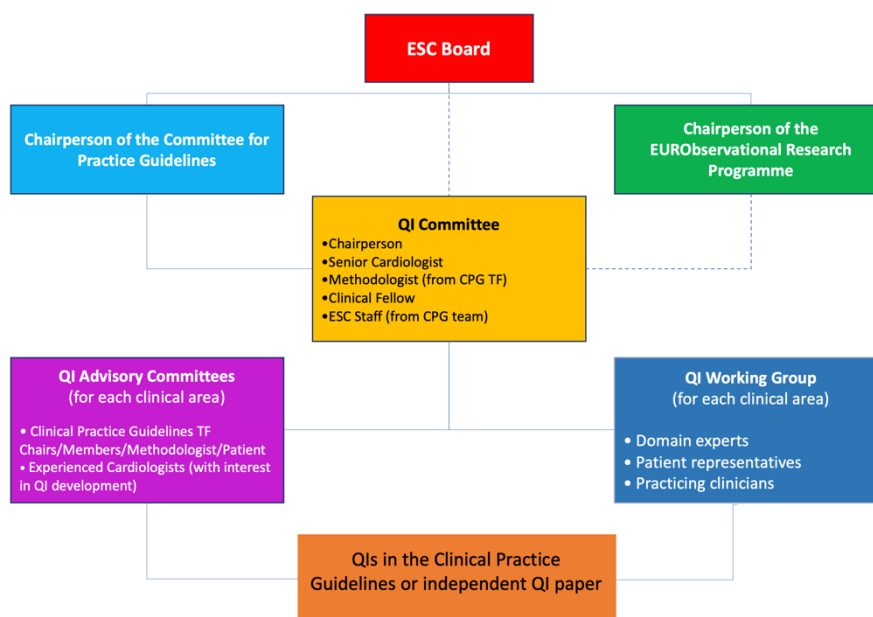
CPG= Committee of Practice Guidelines, TF= Task Force, QI= quality indicator,

2.3.2.1 Methodology development

The development and publication of a standardised methodology for the selection of QIs for CVD (2.3.1.1) was a result of an international collaboration which I had the privilege of leading. The group involved in the development comprised clinical experts in CVD, as well as researchers, registry leaders and methodologists.[185] I performed the literature search that laid the foundations for the development process and liaised with the writing group members to ensure that the developed methodology is valid and practical. The resulted methodology was endorsed and adopted by the ESC and published in a peer-reviewed journal highlighting the need for such knowledge and its acceptability in practice.[185]

2.3.2.2 QI development and validation

In addition to the development of the methodology for QI selection, I applied this methodology in different CVD areas and published the ESC QIs for AMI,[186] atrial fibrillation,[187] cardiac pacing,[188] heart failure[189] and CVD prevention (PART II).[190]

My role included leading the conduction of the systematic review for each of the domains (accordance with the PRISMA guidelines),[183] and collaborating with wider groups (i.e. Advisory Committee and the Working Groups) of domain experts to reach consensus on the final selection of QIs (PART II). For the cardiac pacing domain, I co-led and published a meta-analysis evaluating the various methods of cardiac pacing in patients with normal left ventricular ejection fraction,[191] and for AMI, I led the external validation of the respective QIs to determine their applicability in evaluating care quality during the COVID-19 pandemic.[192]

PART II

Chapter 3. Methodology for the development of international clinical data standards for common cardiovascular conditions: European Unified Registries for Heart Care Evaluation and Randomised Trials (EuroHeart)

Gorav Batra, Suleman Aktaa, Lars Wallentin, Aldo P Maggioni, Chris Wilkinson, Barbara Casadei, Chris P Gale

3.1 Summary of the publication:

- This paper presents the standardised approach that has been used for the development of data standards during my PhD studies.
- The approach comprises four methodological steps:
    1. identification of clinical domains for data standard development by evaluating specific cardiovascular conditions with high prevalence and opportunities for quality improvement,
    2. construction of data standard specifications by systematic review of the literature
    3. selection of variables by a domain-specific Working Group using a modified Delphi method
    4. validation of data standards by a domain-specific Reference Group, and
    5. implementation of the developed data standards into an IT platform

3.2 Publication status:

Published: 05 August 2021

European Heart Journal - Quality of Care and Clinical Outcomes, qcab052,

https://doi.org/10.1093/ehjqcco/qcab052

3.3 Abstracts

3.3.1 Aims

Data standards are consensual specifications for the representation of data arising from different sources. If provided with internationally harmonized variables, permissible values, and clinical definitions, they have the potential to enable reliable between- and within-country analysis of care and outcomes. The European Unified Registries for Heart Care Evaluation and Randomised Trials (EuroHeart) is a European Society of Cardiology project that allows participating countries to collect patient data to undertake quality improvement, observational studies, drug and device surveillance, and registry-based randomized controlled trials for cardiovascular conditions. This paper describes the methodology for development of harmonized data standards for EuroHeart.

3.3.2 Methods and results

We adopted a five-step process for the development of harmonized data standards. The process includes (i) identification of clinical domains for data standard development by evaluating specific cardiovascular conditions with high prevalence and opportunities for quality improvement; (ii) construction of data standard specifications by systematic review of the literature; (iii) selection of variables by a domain-specific Working Group using a modified Delphi method; (iv) validation of data standards by a domain-specific Reference Group; and (v) implementation of the developed data standards into an IT platform.

3.3.3 Conclusion

This paper describes the approach adopted by EuroHeart for the development of clinical data standards for cardiovascular disease. The methodology has been developed and is used by EuroHeart to create a suite of international data standards for cardiovascular diseases. The EuroHeart data standards may be used to systematically capture individual patient data about clinical care and for research

3.3.4 Keywords

EuroHeart, Methodology, Data standards, Data variables, Data definitions

3.3.5 Topic

cardiovascular diseases, randomization, heart, surveillance, medical, medical devices, quality improvement, European Society of Cardiology

Graphical Abstract
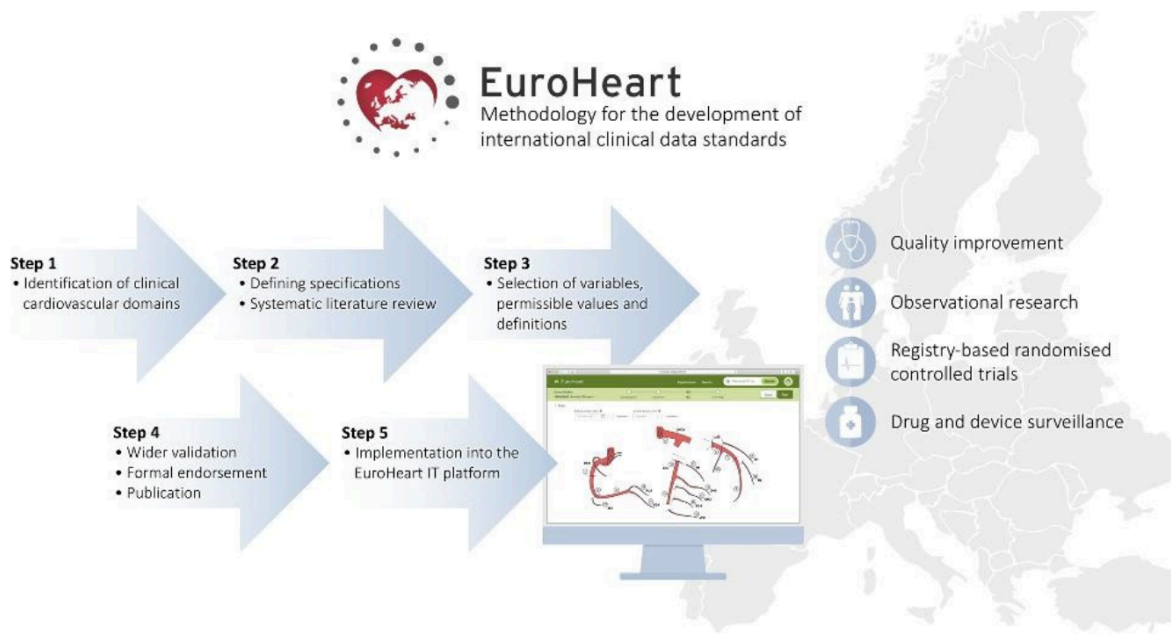
3.4 Introduction

Advances in cardiovascular innovations and technologies have led to improvement in patient outcomes.[1] Alongside these developments, vast quantities of heterogeneous patient data have been collected in clinical trials, registries, and electronic healthcare records (EHRs).[2–6] Standardization of data definitions across various clinical and research settings allows the seamless transfer of data,[7] as such enhancing the efficiency and the cost-effectiveness of initiatives that aim to improve care and outcomes.[8,9]

Defining data standards for a cardiovascular disease involves the identification and definition of variables pertinent to the individual, the disease, and its diagnosis, treatment, and outcomes. While data standards for several cardiovascular diseases have been established, there are variations in the methodology by which the data standards are developed.[10–12] The American College of Cardiology (ACC) and the American Heart Association (AHA) have established a Task Force for data standards, which in addition to creating high-quality data standards for a number of cardiovascular condition has laid out a structured approach for data standard development.[10] Such recommendations, however, are designed to meet the specifications of the American healthcare system.

The European Unified Registries for Heart Care Evaluation and Randomised Trials (EuroHeart) initiative, supported by the European Society of Cardiology (ESC), aims to facilitate the continuous collection of patient data across Europe to improve the quality of care and outcomes of people with cardiovascular disease.[13] To achieve this mission, EuroHeart defines data variables for cardiovascular conditions and integrates these into a bespoke IT platform to enable real-time data collection. This will enable the online analysis and direct reporting of patient characteristics, processes of care, and pre-defined quality indicators, as well as observational research, registry-based randomized controlled trials (R-RCTs), and post-marketing drug and device monitoring.[13]

This paper outlines the methodology for the development of the EuroHeart data standards for cardiovascular disease.

3.5 Methods

Herein, we use the term data standards as consensual specifications for the representation of data from different sources or settings.[14] They include the specifications for data variables, permissible values, and definitions (*Table*1). In this paper, the term data is reserved for individual observations (e.g. 180 cm) and the term variables for data items (e.g. height).[9] Permissible values are the type of information captured by the variables, which may, for example, be numeric, binary (no, yes), dates, or free text for qualitative variables. Data variables may also be classified according to how critical their collection is for the

meaningful interpretation of the dataset. Definitions are the explicit description of the factual meaning of the information captured by the variable (e.g. height on admission in centimetres).[9]

Table 1. Terminologies and definitions

Terminology	Definition
Data standards	Consensual specifications for the representation of data arising from different sources.
Cardiovascular domain	A distinct category of cardiovascular disease or treatment.
Variable	Data field that is to be collected.
Candidate variable	Variable that has been extracted from the literature but that has not been agreed upon.
Permissible value	Format and structure of the information that is allowed to be captured within a variable.
Variable definition	Explicit description of the factual meaning of the information captured by a variable.

3.5.1 Operational framework

3.5.1.1 Data Science Group

Under the auspice of EuroHeart, the Data Science Group comprises a chair, medical experts, and project managers (*Figure* 1). The Data Science Group is responsible for

- Developing a standardized methodology for the construction of data standards.
- Identifying potential domain areas for data standard development. Potential clinical domains for creation of data standards are based on the importance of the cardiovascular condition/procedure and the purpose of the data standards. The identified clinical areas may include, but are not limited to, the ESC Clinical Practice Guidelines.

- Ensuring that the developed methodology is applied across all domains and according to the agreed timelines with other stakeholders.
- Providing supporting research, such as systematic literature reviews, and the evaluation of any ongoing national data efforts.
- Translating the research findings into a candidate set of variables, permissible values, and definitions.
- Supporting the consistent development and refinement of different cardiovascular data standards together with the Working Group and the Reference Group.
- Co-ordinating with national registry leaders of countries participating in the EuroHeart project to facilitate the transition to, or the harmonization with, the developed data standards.
- Supporting the transparent publication of the developed data standards in scientific documents alongside their development process.
- Undertaking the periodic evaluation, revision, and update of the EuroHeart data standards.

Figure 1. Operational framework during the development of the EuroHeart data standards
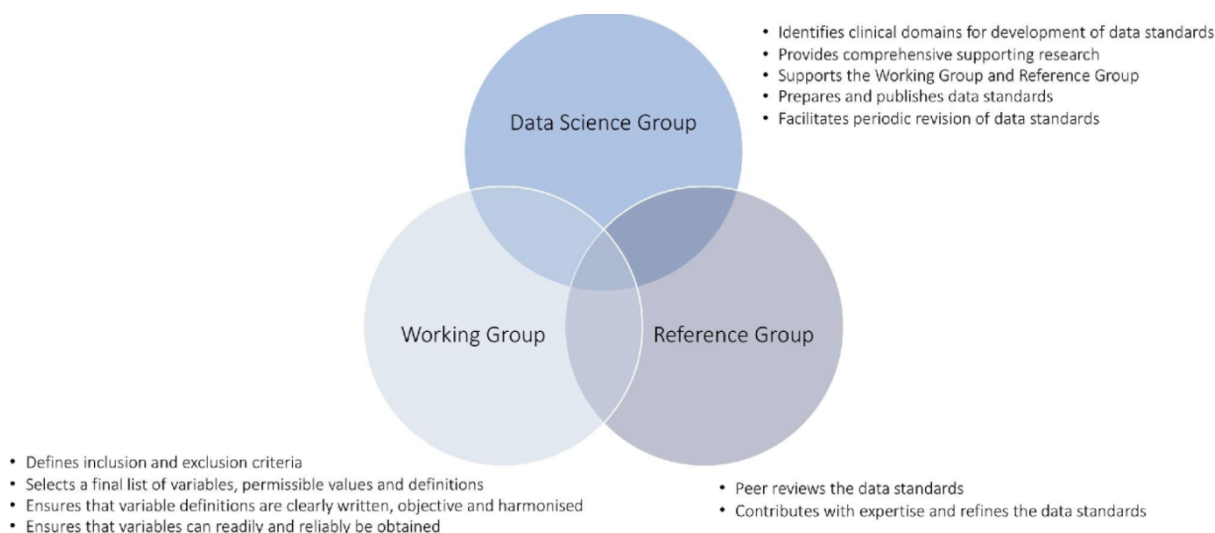
3.5.1.2 Working Group

A Working Group is established for each cardiovascular domain (*Figure* 1). The nomination of members for the Working Group is solicited by relevant ESC Associations and Working Groups, and other ESC member country National Cardiac Societies. Ideally, the Working Group should include approximately 10–20 cardiovascular domain experts and members with

experience in developing and maintaining national quality registries. This group forms the 'core' team for the data standard development and aims to

- Define the inclusion and exclusion criteria for the data standards in development.
- Identify the clinical setting(s) for which the data standards are applicable.
- Specify the data standard characteristics and anticipated number of variables.
- Develop a proposal of the subcategories within the data standards by constructing a conceptual framework of the patient journey.
- Provide a final list of variables, permissible values, and definitions to be included in the data standards.
- Ensure that variable definitions are clearly written, objective, and harmonized against current Clinical Practice Guidelines. Close attention is paid to definitions regarding the timing of events and procedures, device and drug names, and consistency with respect to other variables.
- Ensure that variables may be readily and reliably obtained in real-life clinical settings.

3.5.1.3 Reference Group

The Reference Group defines a team whose members are nominated by the relevant ESC Associations and Working Groups (*Figure* 1). It may also include representatives from the ESC National Cardiac Societies, the ESC Patient Forum, the ESC Association of Cardiovascular Nursing and Allied Professions, and the ESC Committee for Young Cardiovascular Professionals. The involvement of these professional bodies provides broader insights and a more generalizable perspective. Ideally, the Reference Group should include approximately 20–30 representatives from as many ESC member countries as possible to increase the acceptance and uptake of the developed standards. The objective of the Reference Group is to

- Provide feedback on the data standard characteristics and inclusion and exclusion criteria.
- Review and provide feedback on the proposed data standards.

- Assess the applicability of the data standards in different patient groups and across different countries.
- Critically appraise the proposed data standards.

3.5.2 **The five-step process**

The EuroHeart data standards are developed through a five-step process (*Figure* 2): (i) identification of clinical domains for data standard development by evaluating specific cardiovascular conditions with high prevalence and opportunities for quality improvement; (ii) construction of data standard specifications by systematic review of the literature; (iii) selection of variables by a domain-specific Working Group using a modified Delphi method; (iv) validation of data standards by a domain-specific Reference Group; and (v) implementation of the developed data standards into an online IT platform.

Figure 2. Process for development of the EuroHeart data standards.

Step 1

Data Science Group: Identifying clinical domains based on disease burden and clinical need for data collection

Step 2 ↓

Data Science Group and Working Group: Constructing data standard specifications

↓

Data Science Group: Constructing candidate variables, permissible values and definitions based on literature review and qualitative comparisons between identified registries

Step 3 ↓

Working Group: Selection of the variables, permissible values and definitions from a candidate list using the modified Delphi process

↓

Data Science Group: Revision based on feedback

Step 4 ↓

Reference Group: Peer review and refinement of the data standards

↓

Data Science Group and Working Group: Revision based on feedback

↓

Endorsement by relevant professional cardiovascular associations and publication

Step 5 ↓

Implementation into the EuroHeart IT platform

3.5.2.1 Step 1: identifying the clinical domains

Potential clinical domains, for which data standards are to be developed, are identified by the Data Science Group in collaboration with, and on approval by, the EuroHeart Executive Committee.[13] The identified domains are based on the disease burden and clinical need for data collection. The latter point may be driven by paucity of registries, heterogeneity of existing registries, recognized gaps, or variation in care and outcomes. During the pilot phase of EuroHeart, four cardiovascular conditions were selected: acute coronary syndrome and percutaneous coronary intervention; heart failure; atrial fibrillation; and valvular heart disease.[13]

3.5.2.2 Step 2: evidence synthesis and constructing data standard specifications

The specifications of the data standards are determined by the inclusion and exclusion criteria and the clinical setting(s) for which the data standards are applicable. Such specifications are defined by the Working Group members and developed from a conceptual framework of the patient journey. This facilitates the selection of variables and ensures that the registry captures information relevant to the continuum of the patient care. This step is achieved by close working between the Data Science Group and members of the Working Group through the following steps:

- Identifying the target population, which is the cohort of patients for whom the data standards are intended to be used (e.g. patients with acute coronary syndrome).
- Determining the clinical setting(s) for the data standards in development (e.g. in-hospital care for patients with acute coronary syndrome).
- Conducting a systematic literature review to identify existing registries and data standard documents pertinent to the clinical area.

A systematic review of the literature, required for the construction of the candidate data variables, is undertaken by the Data Science Group. The review aims to identify data variables relevant to the proposed clinical domain and assess their importance, evidence base, validity, reliability, feasibility, and applicability in relation to contemporary knowledge (*Table*2).[9,15] Data variables may be adopted from clinical trials, registries, or published data standard documents. The search strategy involves the use of medical online databases including, but not limited to, PubMed®, MEDLINE®, and Embase®, using MeSH (medical subject headings) terms. In addition, Clinical Practice Guidelines from the ESC and other professional organizations, as well as other statements such as consensus documents and quality indicators, are important sources for the candidate data variables.[16] The latter provide tools for measuring processes of care that can be captured in registries and thus form an essential source for candidate variables. Of note, the ESC quality indicators applicable to the domain in development are automatically selected as candidate variables.

Table 2. Criteria for the selection of the EuroHeart data variables

Domain	Criteria
Importance	Variables related to quality indicators which are important for monitoring and benchmarking of quality of care.
	Variables related to areas where there are disparities or suboptimal care.
	Variables addressing appropriateness of medical interventions.
Evidence base	Variables based on evidence consistent with current medical knowledge and ESC Clinical Practice Guidelines.
Validity	Variables that can correctly assess what they are designed to measure.
Reliability	Variables that can be collected and assessed in a reproducible manner, including when collected by different people.
Feasibility	Variables can be collected and assessed readily and easily within acceptable time frames.
Applicability	Variables that support the purpose of the registry, e.g. quality improvement, observational and randomised research, drug and device monitoring.

ESC, European Society of Cardiology

In addition to systematic reviews, qualitative comparisons between identified registries help evaluate the feasibility of the candidate data variables within their respective registries. Case report forms and published articles from the identified registries are reviewed, and information mapped to a single tabular form and qualitatively assessed in relation to the quality of data reported.

3.5.2.3 Step 3: selection of variables, permissible values, and definitions

The third step aims to build consensus on the candidate variables extracted from the systematic literature review. When selecting the variables, careful attention is paid towards

balancing completeness vs. complexity, so that variables may be readily and reliably obtained in naturalistic clinical settings. The main goal is to focus on variables that capture the patient, treatment, and outcome characteristics.

The selection of variables from a pool of candidate variables is determined using a modified Delphi process. As such, the Data Science Group presents the results of the systematic literature review to the Working Group members who are also informed with the voting criteria.[17,18] Each variable is voted upon by each member of the Working Group. This process is anonymous, iterative, and interposed with a series of web conference meetings, along with extensive correspondence by e-mail. To facilitate the selection process, preliminary permissible values and definitions may be provided for each variable before the Delphi voting. Variable definitions include a concise description of the component of care being captured with all relevant information. For instance, the collection of data about the measurement of cardiac troponin in an acute coronary syndrome registry requires the specification of the time of the measurement (e.g. within 24 h from hospital admission), the type of assay used (e.g. high-sensitivity troponin T), the units of measurement (e.g. ng/L), and the permissible value data type and format [e.g. numerical value vs. binary (elevated, non-elevated)].

Based on the voting results, the EuroHeart variables may be classified into three levels (*Table*3). Level 1 variables are considered essential and mandatory by the Working Groups and are consequently both defined and pre-programmed into the EuroHeart IT platform. Many of the level 1 variables include key patient and disease characteristics, guideline recommended treatments, pre-defined quality indicators, and other variables pertinent to accountability and public reporting of quality of care. Level 2 variables are optional but relevant to clinical practice. Standardized definitions are provided for level 2 variables, but they are not pre-programmed into the EuroHeart IT platform. Country-specific level 3 variables, which may address regulatory or administrative requirements, can be integrated into the EuroHeart IT platform locally.

Table 3. Level of variables in the EuroHeart data standards

Level	Definition
Level 1	Variables that are mandatory to collect and that are clinically defined and pre-programed into the EuroHeart IT platform.
Level 2	Variables for which standardised definitions are provided, but the collection of these variables is not mandatory, and the variables are not pre-programed into the EuroHeart IT platform.
Level 3	Variables which are locally defined and 'country-specific' and that e.g. addresses local regulatory or administrative requirements. These variables are not provided in the data standards and are not pre-programed into the EuroHeart IT platform.

Following the selection of variables, the permissible values and definitions for variables are finalized based on the data available from the literature review as well as the comments and feedback obtained during the modified Delphi process by members of the Working Group. The proceedings of the Working Group are then assembled by the Data Science Group and a draft of the data standards is compiled.

3.5.2.4 Step 4: wider validation of the developed data standards

The developed data standards are reviewed independently by the members of the Reference Group, by online surveys, web conference meetings, or e-mail correspondence. This validation process aims to assess the suitability of the proposed variable for application in various registries and across different countries. Furthermore, this step aims to assess the external generalizability of the data standards and their suitability to be used for different purposes such as benchmarking, quality improvement, observational and randomized clinical trials, and drug and device safety surveillance. The Data Science Group collates input from members of the Reference Group, and prepares a document with the final data variables, permissible values, and definitions that is then circulated among the members of the Working Group for final approval. Once approved, the data standard document is sent to relevant

professional cardiovascular associations for formal endorsement before being submitted for publication. Revised data standards are periodically published online as a supplement and on the EuroHeart website (www.escardio.org/euroheart).

3.5.2.5 Step 5: implementation of the developed data standards into the EuroHeart IT platform

The EuroHeart data standards are pre-programmed into the EuroHeart IT platform that is delivered to interested countries based on their existing infrastructure and their willingness to adopt the EuroHeart IT platform that is periodically updated. In addition, this platform collects and automatically calculates and reports many of the ESC quality indicators for the respective clinical domain area with a comparison between the centre's performance and the national average being presented. For instance, the EuroHeart IT platform for acute coronary syndrome and percutaneous coronary intervention allows the automatic calculation and feedback on the majority of the ESC quality indicators for acute myocardial infarction.[19] Alternatively, countries may implement the EuroHeart data standards into their existing data collection platforms, or use the data standards without an IT infrastructure.

3.6 Discussion

This paper describes the EuroHeart methodology for the development of data standards for cardiovascular disease. During recent years, the adoption of clinical registries, administrative databases, and EHRs has opened up major opportunities for cost-efficient observational and randomized clinical studies.[20–23] However, comparison and collaboration between different data sources remain complex, mostly due to varying data variables and definitions with non-standardized vocabulary for presenting clinical concepts. Standardized data variables, permissible values, and definitions would provide opportunities to overcome this ambiguity and enable collaboration between various data sources and facilitate efficient exchange of data and delivery of international observational and randomized research and quality improvement. The framework in this paper provides a structured methodology for developing clinical data standards, underpinned by an approach that encompasses scientific evidence and expert opinion.

Today, cardiovascular disease accounts for a substantial health and economic burden in Europe and globally, with an increasing burden especially in developing countries.[24] Data from national registries, health surveys, and administrative records show persisting geographic and social variation in cardiovascular morbidity, mortality, and treatment.[24,25] By implementing a common lexicon with data standards into national registries in Europe, pooled data from multiple geographical locations might be used for quality improvement, benchmarking of care providers, and research. Existing national cardiovascular registries, clinical trial case report forms, and EHRs are distinct entities with varying data variables, permissible values, and definitions. This limits the possibilities of linkage between large datasets and collaborative initiatives. To address these limitations, initiatives such as the Cardiology Audit and Registration Data Standards (CARDS) and the ACC/AHA have established Task Forces for developing data standards.[10,12] However, the data standards presented by CARDS were established in 2004 and are now outdated.[12] In contrast, data standards presented by ACC/AHA have recently been updated using a similar methodology to the one presented in this paper, but are designed for the American healthcare system and are not implemented into a bespoke IT platform.[10,26,27] In addition, the ACC/AHA data standards often include over 300 variables that are challenging to capture in real-life clinical settings.[26,27]

EuroHeart is an international collaboration that aims to improve the quality of cardiovascular care and facilitate observation and randomized research through continuous and longitudinal capture of individual patient data.[13] To achieve this aim, a purpose-built IT platform enabling real-time data collection and monitoring of standards of care is delivered in parallel with cardiovascular data standards. Once fully adopted, the IT infrastructure will facilitate pragmatic R-RCTs, surveillance of device therapies, and observation research with pooled data from several European countries.[13] Nonetheless, the success of this type of research using linked datasets from several geographical locations is dependent on the harmonization of clinical data variables, permissible values, and definitions.

We believe the methodology described in this paper provides a transparent and organized approach for the development of clinical data standards. Not only does this ensure consistency across the various cardiovascular domains that EuroHeart is planning to capture, but it also provides a scientific base, validity, and hopefully wide acceptance of the developed data standards. The completion of a systematic review of the literature enables the collection of data variables that are contemporary and relevant to current practice. In addition, the use of a modified Delphi method to build consensus and the obtaining of feedback and endorsement from various stakeholders provide a wide representation and perspective to the developed variables. The proposed methodology has now been, and is being, used for the development of data standards for several cardiovascular domains, including acute coronary syndrome, heart failure, atrial fibrillation, and valvular heart disease.

The methodology for development of clinical data standards is inclusive of clinical 'content' and 'patient' experts from a range of geographic, experiential, and specialist backgrounds. Still, the method is not without limitations. Given the nature of the topic, the selection of data variables by content experts may be prone to biases, subjectivities, and/or conflicts of interest.[9,28] Members of the Data Science Group and Working Groups are required to disclose all relevant relationships with industry; however, as the data standards do not include any recommendations for clinical care, the potential for conflict of interest is likely to be negligible.

Furthermore, the proposed methodology encompasses scientific evidence (e.g. systematic literature review, qualitative comparison between existing registries) and the use of the modified Delphi process and involves a Reference Group including patients, young cardiologists, and representatives from the nursing and allied healthcare professional community. However, we recognize that there may have been pressure for experts to provide results within a timeline and this may have 'forced decisions'. Despite efforts to select variables based on pre-specified criteria (*Table*2), future updates will have to re-evaluate the selected variables based on accumulated data on their reliability and feasibility. Translation of these data standards into computational phenotypes to enable syntactic interoperability (i.e.

the ability for systems to communicate and exchange data) and semantic interoperability (i.e. the ability for systems to communicate, effectively exchange, interpret, and use data) is also relevant but beyond the scope of the EuroHeart project at present.[29]

3.7 Conclusion

This paper provides a methodology for development of clinical data standards based on scientific evidence and expert consensus. It is anticipated that data standards developed using the proposed framework will have a wide applicability in various settings, including registries, clinical trials, EHRs, and public reporting programmes. As a part of the EuroHeart project, the developed data standards, and their implementation into a functioning IT platform, will facilitate standardized pan-European data collection, reporting of quality indicators, observational and registry-based randomized research, and post-marketing surveillance of devices and pharmacotherapies. The anticipation is that the proposed methodology may also be adopted by other initiatives when developing clinical data standards.

3.8 References for Chapter 3

1. Benjamin EJ, Blaha MJ, Chiuve SE, Cushman M, Das SR, Deo R et al. Heart disease and stroke statistics—2017 update: a report from the American Heart Association. Circulation 2017;135:e146–e603.
2. Chung S-C, Gedeborg R, Nicholas O, James S, Jeppsson A, Wolfe C et al. Acute myocardial infarction: a comparison of short-term survival in national outcome registries in Sweden and the UK. Lancet 2014;383:1305–1312.
3. Szummer K, Wallentin L, Lindhagen L, Alfredsson J, Erlinge D, Held C et al. Improved outcomes in patients with ST-elevation myocardial infarction during the last 20 years are related to implementation of evidence-based treatments: experiences from the SWEDEHEART registry 1995–2014. Eur Heart J 2017;38: 3056–3065.
4. Szummer K, Wallentin L, Lindhagen L, Alfredsson J, Erlinge D, Held C et al. Relations between implementation of new treatments and improved outcomes in patients with non-ST-elevation myocardial infarction during the last 20 years: experiences from SWEDEHEART registry 1995 to 2014. Eur Heart J 2018;39: 3766–3776.

5. Bebb O, Hall M, Fox KAA, Dondo TB, Timmis A, Bueno H et al. Performance of hospitals according to the ESC ACCA quality indicators and 30-day mortality for acute myocardial infarction: national cohort study using the United Kingdom Myocardial Ischaemia National Audit Project (MINAP) register. Eur Heart J 2017;38: 974–982.

6. Jernberg T, Attebring MF, Hambraeus K, Ivert T, James S, Jeppsson A et al. The Swedish Web-system for Enhancement and Development of Evidencebased care in Heart disease Evaluated According to Recommended Therapies (SWEDEHEART). Heart 2010;96:1617–1621.

7. Dudeck J. Aspects of implementing and harmonizing healthcare communication standards. Int J Med Inform 1998;48:163–171.

8. Gregson J, Stone GW, Ben-Yehuda O, Redfors B, Kandzari DE, Morice M-C et al. Implications of alternative definitions of peri-procedural myocardial infarction after coronary revascularization. J Am Coll Cardiol 2020;76:1609–1621.

9. Gliklich RE, Dreyer NA, Leavy MB. Registries for Evaluating Patient Outcomes: A User's Guide. 3rd ed. Rockville, MD: Agency for Healthcare Research and Quality, 2014.

10. Hendel RC, Bozkurt B, Fonarow GC, Jacobs JP, Lichtman JH, Smith EE et al. ACC/AHA 2013 methodology for developing clinical data standards: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Data Standards. J Am Coll Cardiol 2014;63:2323–2334.

11. Burns DJP, Arora J, Okunade O, Beltrame JF, Bernardez-Pereira S, Crespo-Leiro MG et al. International Consortium for Health Outcomes Measurement (ICHOM): standardized patient-centered outcomes measurement set for heart failure patients. JACC Heart Fail 2020;8:212–222.

12. Flynn MR, Barrett C, Cosío FG, Gitt AK, Wallentin L, Kearney P et al. The Cardiology Audit and Registration Data Standards (CARDS), European data standards for clinical cardiology practice. Eur Heart J 2005;26:308–313.

13. Wallentin L, Gale CP, Maggioni A, Bardinet I, Casadei B. EuroHeart: European Unified Registries on Heart Care Evaluation and Randomized Trials—an ESC project to develop a new IT registry system which will encompass multiple features of cardiovascular medicine. Eur Heart J 2019;40:2745–2749.

14. Richesson RL, Krischer J. Data standards in clinical research: gaps, overlaps, challenges and future directions. J Am Med Inform Assoc 2007;14:687–696.

15. MacLean CH, Kerr EA, Qaseem A. Time out—charting a path for improving performance measurement. N Engl J Med 2018;378:1757–1761.

16. Aktaa S, Batra G, Wallentin L, Baigent C, Erlinge D, James S et al. European Society of Cardiology methodology for the development of quality indicators for the quantification of cardiovascular care and outcomes. Eur Heart J Qual Care Clin Outcomes 2020; https://doi.org/10.1093/ehjqcco/qcaa069.

17. Jones J, Hunter D. Qualitative research: consensus methods for medical and health services research. BMJ 1995;311:376–380.

18. Normand S-LT, McNeil BJ, Peterson LE, Palmer RH. Eliciting expert opinion using the Delphi technique: identifying performance indicators for cardiovascular disease. Int J Qual Health Care 1998;10:247–260.

19. Schiele F, Aktaa S, Rossello X, Ahrens I, Claeys MJ, Collet J-P et al. 2020 Update of the quality indicators for acute myocardial infarction: a position paper of the Association for Acute Cardiovascular Care: the study group for quality indicators from the ACVC and the NSTE-ACS guideline group. Eur Heart J Acute Cardiovasc Care 2021;10:224–233.

20. Fröbert O, Lagerqvist B, Olivecrona GK, Omerovic E, Gudnason T, Maeng M et al. Thrombus aspiration during ST-segment elevation myocardial infarction. N Engl J Med 2013;369:1587–1597.

21. Hofmann R, James SK, Jernberg T, Lindahl B, Erlinge D, Witt N et al. Oxygen therapy in suspected acute myocardial infarction. N Engl J Med 2017;377:1240–1249.

22. Erlinge D, Omerovic E, Fröbert O, Linder R, Danielewicz M, Hamid M et al. Bivalirudin versus heparin monotherapy in myocardial infarction. N Engl J Med 2017;377:1132–1142.

23. Bowman L, Baras A, Bombien R, Califf RM, Chen Z, Gale CP et al. Understanding the use of observational and randomized data in cardiovascular medicine. Eur Heart J 2020;41:2571–2578.

24. Timmis A, Townsend N, Gale CP, Torbica A, Lettino M, Petersen SE et al. European Society of Cardiology: cardiovascular disease statistics 2019. Eur Heart J 2020;41:12–85.

25. Wang H, Naghavi M, Allen C, Barber RM, Bhutta ZA, Carter A et al. Global, regional, and national life expectancy, all-cause mortality, and cause-specific mortality for 249 causes of death, 1980–2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet 2016;388:1459–1544.

26. Dehmer GJ, Badhwar V, Bermudez EA, Cleveland JC, Cohen MG, D'Agostino RS et al. 2020 AHA/ACC key data elements and definitions for coronary revascularization: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Data Standards (Writing Committee to Develop Clinical Data Standards for Corona). Circ Cardiovasc Qual Outcomes 2020;13: e000059.

27. Bozkurt B, Hershberger RE, Butler J, Grady KL, Heidenreich PA, Isler ML et al. 2021 ACC/AHA key data elements and definitions for heart failure: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Data Standards (Writing Committee to Develop Clinical Data Standards for Heart Failure). Circ Cardiovasc Qual Outcomes 2021;14:e000102.

28. Neuman J, Korenstein D, Ross JS, Keyhani S. Prevalence of financial conflicts of interest among panel members producing clinical practice guidelines in Canada and United States: cross sectional study. BMJ 2011;343:d5621.

29. Liyanage H, Krause P, de Lusignan, S. Using ontologies to improve semantic interoperability in health data. BMJ Health Care Informatics 2015;22:309–315.

Chapter 4. European Society of Cardiology methodology for the development of quality indicators for the quantification of cardiovascular care and outcomes

Suleman Aktaa, Gorav Batra, Lars Wallentin, Colin Baigent , David Erlinge, Stefan James, Peter Ludman, Aldo P. Maggioni, Susanna Price, Clive Weston, Barbara Casadei, and Chris P. Gale

4.1 Summary of the publication:

- This paper presents the standardised approach that has been used for the development of QIs during my PhD studies.
- The approach comprises four methodological steps:
  1. the identification of key domains of care by constructing a conceptual framework of care,
  2. the construction of candidate QIs by conducting a systematic review of the literature,
  3. the selection of a final set of QIs by obtaining expert opinions using the modified Delphi method, and
  4. the undertaking of a feasibility assessment.

4.2 Publication status:
- Published: 26 August 2020
- European Heart Journal - Quality of Care and Clinical Outcomes, qcaa069, https://doi.org/10.1093/ehjqcco/qcaa069.

4.3 Abstract

4.3.1 Aims

It is increasingly recognized that tools are required for assessing and benchmarking quality of care in order to improve it. The European Society of Cardiology (ESC) is developing a suite of quality indicators (QIs) to evaluate cardiovascular care and support the delivery of evidence-based care. This paper describes the methodology used for their development.

4.3.2 Methods and results

We propose a four-step process for the development of the ESC QIs. For a specific clinical area with a gap in care delivery, the QI development process includes: (i) the identification of key domains of care by constructing a conceptual framework of care; (ii) the construction of candidate QIs by conducting a systematic review of the literature; (iii) the selection of a final set of QIs by obtaining expert opinions using the modified Delphi method; and (iv) the undertaking of a feasibility assessment by evaluating different ways of defining the QI specifications for the proposed data collection source. For each of the four steps, key methodological areas need to be addressed to inform the implementation process and avoid misinterpretation of the measurement results.

4.3.3 Conclusion

Detailing the methodology for the ESC QIs construction enables healthcare providers to develop valid and feasible metrics to measure and improve the quality of cardiovascular care. As such, high-quality evidence may be translated into clinical practice and the 'evidence-practice' gap closed.

4.3.4 Keywords

Quality indicators • Cardiovascular disease • Quality improvement • Clinical practice guidelines

4.4 Introduction

There is substantial variation in the delivery of care for cardiovascular disease (CVD) which is reflected in variation in disease outcomes. Data from health surveys, administrative records, cohort studies, and registries show persisting geographic and social variation in CVD treatments and mortality across Europe.[1,2] Moreover, the potential to reduce premature cardiovascular death has not been fully realized.[3] The European Society of Cardiology (ESC) recognizes the variation in CVD burden and delivery of care across its 57 member countries, as well as the need to invest in closing the 'evidence-practice gap'.[2]

There is an increasing emphasis on the need for measuring and reporting both processes and outcomes of care and for a better understanding of how analytical tools can facilitate quality improvement initiatives.[4,5]. For example, the quantification and public reporting of hospital times to reperfusion for the management of patients with ST-segment elevation myocardial infarction has been associated with improvements in patient outcomes.[6] Similar successes have been achieved in the surgical management of congenital heart disease, where the implementation of structural measures, such as regionalization of care and setting standards for minimum surgical volume, has been associated with reductions in perioperative mortality.[7]

It has been proposed that quality indicators (QIs) may serve as a mechanism for stimulating the delivery of evidence-based medicine, through quality improvement, benchmarking of care providers, accountability, and pay-for-performance programs.[8] Consequently, the use of indicators of quality is expanding and is of interest to a range of stakeholders including health authorities, professional organizations, payers, and the public.[9]

In the UK, the National Institute for Health and Care Excellence (NICE) has, for some time, endorsed certain NICE quality indicators, which are typically used by commissioners to ensure that that the services they commission are driving up quality. The introduction of such indicators has been shown to improve outcomes[10] and their withdrawal to negatively influence quality of care.[11] Notably, the production of NICE indicators follows a structured

process, which includes the identification of a topic for indicator development, and the evaluation of a proposed set of indicators by an 'indicator advisory committee' that contains patient representatives.[12] Other organizations such as the American College of Cardiology (ACC) and the American Heart Association (AHA) have developed Performance Measures for a variety of cardiovascular conditions, also using a structured process for their development.[13,14] However, the approach by which QIs are developed is heterogeneous and establishing a uniform framework for the construction of QIs for healthcare should increase their acceptance and perceived trustworthiness.[15]

In addition, the lack of widely agreed definitions for data variables hampers the development of QIs and their integration with clinical registries.[16] Initiatives, such as the European Unified Registries On Heart Care Evaluation and Randomized Trials (EuroHeart), are fundamental to QI development and implementation.[17] EuroHeart aims to harmonize data standards for CVD and establish a platform for continuous data collection. Moreover, EuroHeart will provide the means to evaluate cardiovascular care through QIs which are underpinned by standardized data collection and definitions.

This document outlines the process by which the ESC develops its QIs for CVD and provides a standardized methodology which may be used by all stakeholders to ensure the QIs are clinically relevant, scientifically justified, feasible, and usable.[18] The ESC anticipates that this process will enable the prioritization of areas for QI development and improve the utility of the developed QIs. Thus, the ESC QIs may be implemented with reasonable cost and effort, interpreted in a context of quality improvement, and reported in a scientifically credible, yet user-friendly format.

4.5 Methods

4.5.1 Definition of quality indicators

The ESC uses the term QI to describe, in a specific clinical situation, aspects of the process of care that are recommended (or not recommended) to be performed. Although used interchangeably, a distinction between QIs and performance (or quality) measures has been drawn.[15] QIs can be illustrated in an *'if-then'* format, meaning that *'if'* a patient has had a given condition and satisfies relevant criteria, *'then'* he or she should (or should not) be offered a given intervention. Different performance (or quality) measurements may then be derived from the same QI depending on several factors, including the definition of the respective data variables and the sources of data.[15] The ESC QIs include main and secondary indicators according to whether they represent a major and complementary component of an aspect of health care. Secondary QIs may be used instead of the main ones in situation where missing data and/or limited resources preclude the measurement of the main QIs.

4.5.2 Types of quality indicators

The ESC QIs are expressed as structural, process, and outcome indicators. Structural QIs describe organizational aspects of care, such as physical facilities, human resources, and available protocols or networks. Process QIs capture actions taken by healthcare providers or patients, such as adherence to established guidelines or recommended therapies. On the other hand, outcome QIs concern the effects of health care on patients, populations, or societies. Outcome QIs may also include patient-reported outcome measures (PROMs), such as health-related quality of life.[19]

High-quality evidence tends to be available to support process QIs rather than structural or outcome indicators.[14] However, the inclusion of outcome indicators provides a more comprehensive performance evaluation,[20] even though adjustment for differences in patient characteristics is necessary to evaluate whether or not variation in outcomes is due to true differences in quality of care.[21] Thus, risk-adjusted outcome QIs form one element of the ESC QIs. For this document, we do not consider the statistical methods for interpreting outcome measurement results and acknowledge that different methods may provide differing results regarding quality of care assessment.[22]

PROMs have a complementary role to other outcome measures, such as mortality and re-hospitalization rates. Notwithstanding the fact that many PROMs may not yet be based on strong recommendations within guidelines, they provide a patient's perspective of health outcomes and, thus, allow patient-centred ill-health to be captured.[23] Given that many patients value their quality of life and survival equally following an illness,[24] improving perceived health and well-being should be the aim of all contemporary cardiovascular interventions, in addition to the reducing major cardiovascular events and mortality.[25]

4.5.3 Operational framework
4.5.3.1 Quality indicators committee

The ESC established a QI Committee (QIC) whose members have a range of clinical, statistical, and quality improvement expertise. The aim of the QIC is to develop QIs for ESC Clinical Practice Guidelines by working collaboratively with:

- small groups of specialists in the topic of interest (Advisory Committees). Ideally, Advisory Committees would include members (or chairs) of the respective ESC Clinical Practice Guideline Task Forces and
- wider teams of domain experts, practising clinicians and patient representatives (Working Groups) for each clinical area.

The major objectives of the ESC QIC are to:

- build an explicit, standardized, and transparent methodology for QI development, and ensure that the methodology is followed within agreed timelines and standards of quality,
- identify clinical areas for QI development on the basis of prevalence, association with morbidity, mortality and/or healthcare utilization, and availability of effective interventions. These clinical areas may include, but are not limited to, the ESC Clinical Practice Guidelines,

- support the process of translating evidence or Practice Guideline recommendations into explicitly defined, specific QI,

- determine the specifications needed for operationalizing the developed QIs, according to potential data sources,

- support the development and maintenance of means to measure QIs, such as the EurObservational Research Programme, and

- facilitate the periodic evaluation, revision, and update the ESC QIs as more data and/or new recommendations become available.

4.5.3.2 Advisory committees

The main role of a QI Advisory Committee is to identify the domains of health care that would have an impact on the quality of care and subsequent outcomes. This is achieved by drawing upon evidence and construct a conceptual framework articulating the dimensions for the measurement and the pathways by which processes of care are linked to desired outcomes. The structure-process-outcome model illustrated in *Figure 1* is a simple and commonly used framework.[19] It helps identify the interplay between different aspects of health care, and allows the inclusion of patient and environmental factors.[26] This framework was used by the ESC previously to develop QIs for acute myocardial infarction (AMI),[27] and, thus, is recommended over other available methods.[28]

Figure 1. Conceptual framework of the dimensions of health care based on the Donabedian model.
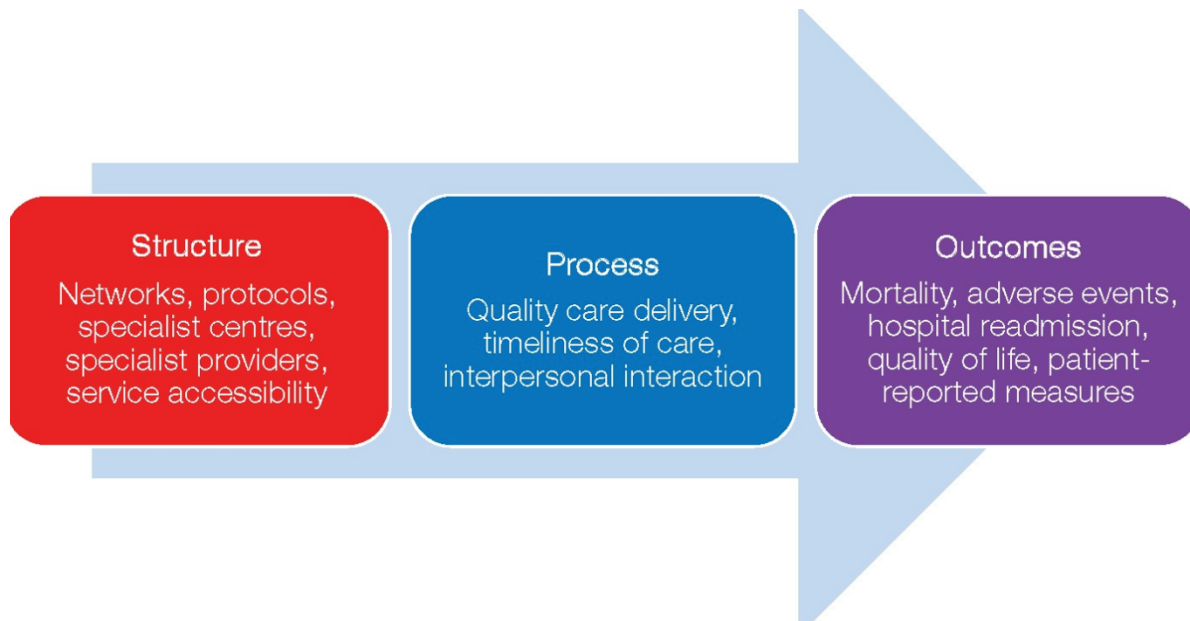
4.5.3.3 Working groups

Working Groups are the wider teams responsible for selecting the final set of QIs. Ideally, Working Groups should comprise a wide range of stakeholders including domain experts, practising clinicians, researchers and commissioners as well as members of the public, healthcare consumers, and patients.

Patient engagement is important so that professional scientific knowledge is complemented by the patient perspective on receiving care and on meaningful outcomes. This may be achieved by a 'co-productive partnership'[29] with patients and seeking their insights into quality assessment and improvement. The ESC has an established the ESC Patient Forum whose members are involved in the development of the ESC Clinical Practice Guidelines and the accompanying educational products.[30]

4.5.3.4 Clinical practice guideline task forces

Close working with members of the ESC Clinical Practice Guidelines Task Force is integral to the development of QIs. Not only does this ensure that QIs are comprehensive and cover

broad aspects of care, but also that they are harmonized with the corresponding Clinical Practice Guideline recommendations. Furthermore, simultaneous writing and/or updating of QIs and ESC Clinical Practice Guidelines facilitates seamless incorporation of QIs within the respective documents, enhance their dissemination and, therefore, uptake into clinical practice.

4.6 The four-step process

We propose that the development of the ESC QIs follows a four-step process consisting of: identification of the key domains of health care; construction of candidate indicators; selection of a final QI set; and undertaking of a feasibility assessment (*Figure 2*). For each step, published evidence and consensus expert opinion are used to inform the development, implementation, and interpretation of QIs (*Table 1*).

Figure 2. Process for the development of the ESC quality indicators for cardiovascular disease. ESC, European Society of Cardiology; QIs, quality indicators.

Identification of the key domains of health care

Defining target population with inclusion and exclusion criteria

Specifying measurement period and measurement duration

Construction of candidate indicators

Conducting literature review including relevant Clinical Practice Guidelines and existing QIs

Defining numerator, denominator, and exclusion

Selection of the final QI set

Obtaining expert opinion using modified Delphi process

Considering composite QIs

Conducting a feasibility assessment

Assessing the availability of the data needed to identify the numerator and denominator

Evaluating the relaibility of data extraction for the potential data collection source(s)

4.6.1   Step 1: identifying domains of care

It is important to define the domains of care for which the QIs are being developed. Through comprehending the journey of a patient with a given condition, the QI Advisory Committee may identify important aspects of care process. For example, the ESC Association for Acute Cardiovascular Care (ACVC), formerly the Acute Cardiovascular Care Association, suite of QIs for the management of AMI comprises the following seven domains: centre organization, reperfusion/invasive strategy, in-hospital risk assessment, antithrombotic treatment during hospitalization, secondary prevention discharge treatments, patient satisfaction, and risk adjusted 30-day mortality.[27] Identifying the domains of care entails the following four tasks:

Table 1. Process for the development of the ESC quality indicators for cardiovascular disease.

Step 1. Identifying domains of care	
Defining the target population	Define the cohort of patients for whom the set of QIs is intended. This may include age, sex, ethnicity bounds, or any other relevant patients' characteristics which may help in identifying the sample of interest.
Specifying the measurement period	Specify the period during which the process of care being measured would be anticipated to occur. The measurement period should be chosen carefully so that data needed for measurement is readily available and reliably extractable. with reasonable cost and effort.
Specifying the measurement duration	Specify the time frame during which a sufficient sample size can be collected to provide good assessment of care quality.
Specifying the inclusion and exclusion criteria	Specify subgroups of the target population that should be excluded from the measurement when clinically appropriate and/or when data cannot be reliably obtained.
Step 2: Constructing candidate indicators	
Conducting a literature review	Conduct a systematic review of the literature, to include the relevant Clinical Practice Guidelines and existing QIs.

	Candidate QIs synthesized from the literature review should meet the ESC attributes of QIs (Table 2).
Defining candidate QIs	Define the numerator, which is the subset of the patients that has had the indicator met.
	Define the denominator, which is the proportion of patients within the target population eligible for the measurement.
	Define the exclusion, which is a comprehensive list of potential medical-, patient-, or system-related reasons for not meeting the measurement.
Step 3: Selecting the final QIs set	
Obtaining expert opinion	Use RAND/UCLA appropriateness method and modified Delphi process. Conduct at least two rating rounds, with interposed meeting. Ratings should be structured, anonymous and categorical, with instructions provided to voting panellists detailing the selection criteria.
Considering composite QIs	Combine two or more of the QIs into a single measure to form a single score. Selection the individual QIs according to the intention, development and scoring method of the composite QI.
Step 4: Conducting feasibility assessment	
Identifying the numerator and denominator	Assess whether identifying the numerator and denominator can be (or should be) achieved using data that is readily available in the average medical records.
Assessing burden of data collection	Assess whether identifying the numerator and denominator can be extracted with reasonable time and effort.
Evaluating data completeness and reliability	Evaluate inter-rater reliability, response rate, frequency of assessments and timeliness of reporting.

QI=quality indicator; ESC=European Society of Cardiology; UCLA=university of California–Los Angeles

4.6.1.1 Defining the target population

The target population is the cohort of patients for whom the set of QIs is intended. An unambiguous and concise definition of the target population allows simple inclusion and exclusion criteria and facilitates QI development.[13] Target population definitions may include, but not be limited to age, sex, and ethnicity of patients for whom the set of QIs applies. Other characteristics might specify, for instance, patients with a given disease (e.g. heart failure), patients undergoing a particular treatment (e.g. percutaneous coronary intervention [PCI]), or patients at risk of developing a certain condition (e.g. sudden cardiac death).

4.6.1.2 Specifying the measurement period

The 'measurement period' is that interval during which the component of care of interest is measured. For instance, the prescription of angiotensin converting enzyme inhibitors or angiotensin receptor blockers (ACEI/ARB) for patients with left ventricular systolic dysfunction (LVSD) immediately after AMI, can be conducted at the time of hospital discharge, which is, in this example, the 'measurement period'. In other cases, continuous monitoring of the target population may be needed, such as when assessing the adherence to guideline recommended therapies up to 6 months after AMI.[13]

It is necessary to consider data sources when specifying the measurement period, as they have implications on what components of care can be assessed. In the example above, relevant data may be obtained from hospital records, national registries, or patient surveys. Not only will these potential sources have different degrees of reliability, but they will also provide different samples of patients.[15] Defining a measurement period during which an important component of care delivery can be captured reliably with minimal effort is fundamental to developing QIs.

4.6.1.3 Specifying measurement duration

Measurement duration is the time frame during which sufficient data may be collected to provide a reliable assessment of care. For example, a measurement duration of 12 months for

a given QI implies that cases occurring during this time frame will be used in the assessment of quality. The measurement duration determines the number of cases obtained and, as for the measurement period, will determine the components of care that can be assessed. The number of cases may vary between providers according to workload and/or resources. Too short a measurement duration may disallow the collection of sufficient cases,[31] while too long duration may affect the relevance of the data collected.[13]

4.6.1.4 Specifying inclusion and exclusion criteria

Certain subgroups of the target population may need to be excluded from the measurement when clinically appropriate. Additionally, a comprehensive list of the alternative therapies which may be considered equivalent to the intervention of interest should be specified. Returning to the example above (prescribing ACEI/ARB for patients with LVSD), exclusion criteria may include low blood pressure, intolerance, or a contraindication to ACEI and ARB, while alternative therapies may include sacubitril/valsartan combination. Other reasons for exclusion may be patient-related (e.g. patient preference) or system-related (e.g. limited resources).[14]

4.6.2 Step 2: constructing candidate quality indicators

The goal of this step is to construct a preliminary list of QIs (candidate QIs) for the domains of care identified in Step 1. This is accomplished by systematically reviewing the literature, including relevant Clinical Practice Guidelines and existing QIs already in use. Since adherence to QIs imply the delivery of optimal care for patients, an extensive review of the medical literature is an important part of their development process. When conducting the literature review, and to ensure candidate QIs are directly associated with improving quality of care and outcomes, one should consider:

- The applicability (and relevance) of the data to the target population for which the indicator is being developed.
- The strength of evidence supporting the indicator based on the assigned level of evidence (LOE).

- The degree to which adherence to the indicator is associated with clinically meaningful benefit (or harm) based on the assigned class of recommendation.
- The clinical significance of the outcome most likely to be achieved by adherence to the indicator, as opposed to a statistical significance with little clinical value (see below).

4.6.2.1 Literature review

Conducting a systematic review of the literature according to a standardized methodology is needed. This ensures that QIs are both clinically meaningful and evidence-based. Initially, a scoping search may be performed to map the literature and identify existing QIs from professional organizations. This preliminary search aims to guide the development of a more comprehensive systematic search strategy focused on addressing gaps in care delivery. It is recommended that a range of medical subject heading (MeSH) terms and online databases (e.g. Embase, Ovid MEDLINE, and PubMed) are used to capture published, peer-reviewed randomized controlled trials. The search should provide clinically important outcomes for a given condition and identify processes of care that correlate with improvements in these outcomes. As such, large observational studies may be included in the search to support the identification of clinically meaningful outcomes.

Defining 'clinically important' outcomes may be challenging, and involves the consideration of the magnitude of the treatment effect, as well as the importance, and frequency of the outcome. In contrast to established guidance for statistical significance thresholds in clinical trials, no rigorous standards exist to define a "clinically significant" difference.[32]High-quality evidence is usually derived from large randomized studies with large treatment effects or from individual-patient meta-analyses.[32] However, such evidence may be lacking for certain aspects of care delivery, adherence to which implies a reflection of optimal care.[9] For example, patient preference and shared decision making (e.g. the heart team) may not be underpinned by strong guideline recommendations, yet from a philosophical viewpoint are important aspects of optimal care.[33]

4.6.2.2 Clinical Practice Guidelines

The ESC Clinical Practice Guidelines should serve as a basis for the development of QIs. However, the ESC QIs are not simply a reflection of the strongest Guideline recommendations. They should also consider areas where there are gaps in care, room for improvement and where there may be longitudinal outcomes data from existing registries. In addition, clinical recommendations for care by other professional organizations may also be considered as a potential source for QIs. Reviewing Clinical Practice Guidelines to develop QIs involves identifying the recommendations with the strongest association of benefit and harm, and evaluating these recommendations against predetermined criteria to assess their suitability for quality measurement.

The ESC has developed criteria to aid the development and evaluation of its QIs. These criteria (*Table 2*) aim to assess the clinical importance of a given set of QIs, their evidence base, validity, reliability, and feasibility.[34,35] Moreover, the criteria aim to ensure that developed QIs can be clearly defined, easily interpreted by healthcare providers, and that the result of the assessment may positively influence current practice. The ESC criteria for QIs will be complemented by expert clinical advice and should form the foundation for the ESC QI development.

Table 2. Criteria for the development and evaluation of the ESC quality indicators for cardiovascular disease.

Domain	Criteria
Importance	QI reflects a clinical area that is of high importance (e.g., common, major cause for morbidity, mortality, and/or health-related quality of life).
	QI relates to an area where there is gap in care delivery and/or variation in practice.

	QI implementation will lead to a meaningful improvement in patient outcomes.
	QI may address under- and/or over-use of a test or treatment.
Evidence base	QI is derived from a clearly defined, acceptable evidence consistent with contemporary knowledge.
	QI aligns with the respective ESC Clinical Practice Guideline recommendations.
Specification	QI has clearly defined patient group to whom the measurement applies (denominator), including explicit eligibility criteria.
	QI has clearly defined patient group for whom the QI is met (numerator), including explicit definition of QI meeting criteria.
	QI has a minimum population level.
Validity	QI is able to correctly assess what it is intended to, adequately distinguishes between good and poor quality care, and compliance with the indicator would confer health benefits.
Reliability	QI is reproducible even when data is extracted by different people and estimates of performance on the basis of available data are likely to be reliable and unbiased.
Feasibility	QI may be identified and implemented with reasonable cost and effort
	Data needed for the assessment is (or should be) readily available and easily extracted within an acceptable time frame.
Interpretability	QI is interpretable by healthcare providers, so that practitioners can understand the results of the assessment and take actions accordingly.
Actionability	QI is influential to the current practice where a large proportion of the determinants of adherence to the QI are under the control of healthcare providers being assessed.
	This influence of QIs on behaviour will likely improve care delivery.
	QI is unlikely to cause negative unintended consequences.

ESC=European Society of Cardiology; QI=quality indicator

4.6.2.3 Existing quality indicators

The goal of this step is to avoid duplication of reporting and to incorporate available information about existing indicators' validity and/or feasibility. Conceptual issues underlying the endorsement and validation of existing QIs have been developed.[12,18] As with Clinical Practice Guidelines, reviewing existing QIs involves identifying pertinent indicators, and evaluating them against the ESC criteria for QIs (*Table 2*). Two considerations are whether existing QIs are endorsed by other professional societies, and whether any validation and/or feasibility data are available as this information may influence the utilization (or adaptation) of the existing QIs.

4.6.2.4 Defining candidate quality indicators

Following candidate QI synthesis from the literature search, the numerator and denominator for each candidate QI should be defined. By providing an explicit definition to each indicator, the Working Group will be able to evaluate this indicator against the ESC criteria (*Table 2*) and specify appropriate exclusions from the measurement.

4.6.2.5 Defining the numerator

The numerator of a QI is the group of patients who have fulfilled the QI. *Table 3* provides an example in which a QI to assess the prescription of an ACEI/ARB to patients with LVSD following AMI is developed.[27] In this example, the numerator definition determines what 'counts' as being prescribed an ACEI/ARB and at which time point in relation to the AMI event.

Table 3. Target population characteristics, measurement period and definition of an example quality indicator for the use of an ACEI or ARB for patients with hospitalised acute myocardial infarction.

Quality indicator	Proportion of patients with LVEF < 0.40 who are discharged from hospital on ACEI (or ARB if intolerant of ACEI)	
Target population	**Age**	≥18 years
	Sex	Any
	Primary diagnosis	Survivors of hospitalised acute myocardial infarction
	Subgroup	Patients with left ventricular ejection fraction < 0.40
Measurement period	At the time of hospital discharge	
Numerator	Patients with acute myocardial infarction who have a LVEF < 0.40 and are prescribed an ACEI or ARB* at the time of hospital discharge *Patient prescribed medications that contain ACEI or ARB as part of a combination therapy, such as sacubitril/valsartan, meet the numerator criteria.	
Denominator	Patients with acute myocardial infarction who have a LVEF < 0.40, alive at the time of hospital discharge and are eligible** for an ACEI or ARB	
Exclusion	Contraindications to ACEI and ARB, such as, allergy, intolerance, angioedema, hyperkalaemia, hypotension, renal artery stenosis, worsening renal function.	

ACEI=angiotensin converting enzyme inhibitor; ARB= angiotensin receptor blocker; LVEF=left ventricular ejection fraction

4.6.2.6 Defining the denominator

Patients within the target population who are eligible for the assessment of each QI form the denominator. In the example provided in *Table 3*, the denominator represents the subset of the target population eligible for an ACEI/ARB. Here, the eligibility criteria include, being clinically appropriate, without contraindications or intolerance to both ACEI and ARB, and being willing to take an ACEI/ARB. Providing specifications on how to identify (or validate) the target condition (AMI in the example above), and potential data sources for the assessment enhances indicators implementation and feasibility.

For some structural QIs, no denominator is needed because the assessment is binary. In such cases, the numerator may be the healthcare centre and the assessment may be whether or not a given measure is available at the centre.

4.6.2.7 Defining the exclusions

It is important to provide an extensive list of potential exclusions for each candidate QI. Using exclusions enables fairer assessment, particularly when the QI is intended for accountability, pay-for-performance, and public reporting.[33,36] Considering the ACEI/ARB example provided in *Table 3*, patients with low blood pressure, hyperkalaemia, or severe renal impairment should not be prescribed an ACEI/ARB, and, thus, they are excluded from the assessment (see Step 1.4).

4.6.3 Step 3: selecting the final quality indicator set

To derive the final set of QIs from amongst the candidate indicators menu, a structured selection process is recommended. This process is based on, and underpinned by, the ESC criteria for QIs (*Table 2*) combined with consensus expert opinion. The composition of consensus panels (Working Groups) should include a wide range of stakeholders, such as domain experts, practising clinicians, researches, commissioners, and patients to provide breadth and depth of expertise to address aspects of care quality. To reduce difficulties with implementation, efforts should be made to select the minimum number of QIs for each domain.

Consensus methods for obtaining and combining group judgement exist.[37] These provide reliable and valid means for assessment and improvement of quality of care.[34] The ESC QIC recommends the use of the RAND/University of California–Los Angeles (UCLA) appropriateness method and modified Delphi process,[38,39] which are reliable and have content, construct and predictive validity for QI development.[40] The modified Delphi technique involves conducting structured, anonymous, iterative and categorical surveys, with

interposed face-to-face (or video/teleconference) meetings to reach consensus. An example on how to obtain, combine, and analyse expert opinion is provided in <u>Supplementary material online</u>.[40]

4.6.4 Step 4: feasibility assessment

The feasibility assessment aims to determine whether translating each developed QI into an actual measure of care quality is (or should be) achievable using available data sources. It also entails assessment of the cost and effort required for data extraction, as well as the reliability of this data. When the data used for quality assessment include patient perspectives, such as health-related quality of life, an evaluation of the response rates and the time of these responses in relation to the index event is needed.[13] Thus, a feasible set of QIs is one in which data needed for estimating performance are available in the medical records, likely be unbiased, and can be obtained with no significant recording and/or reporting delays.[13]

The feasibility assessment may require a different skill set to that required for QI development (such as clinical coding experts, clinical informaticians). Feasibility assessment is an iterative process that involves operationalizing the QI for the potential data source,[15] and involves the evaluation of: (i) the different methods of defining the numerator and denominator for the data source to be used (e.g. national registry), and (ii) the interrater reliability in extracting the necessary data. If defining these parameters cannot be achieved with reasonable effort and acceptable reliability, excluding the QI from the final set should be considered.

4.6.5 Defining composite quality indicators

Composite QIs (CQIs) are derived by combining two or more individual indicators in a single measure that results in a single score. Such CQIs may encapsulate broader aspects of care delivery (such as overall quality) or have a focused perspective (such as adherence to a

specific set of guidelines). They serve as a tool for benchmarking providers, reducing data collection burden, and providing a more comprehensive assessment of performance.[41] When developed according to a structured methodology, CQI for AMI have been shown to have an inverse association with mortality.[42,43] The intention of, and the methodology used to develop, the CQIs determine the selection of the individual QIs within the composite and should be stated alongside the proposed scoring method (e.g. all-or-none, opportunity-based, or empirically weighted).

4.7 Discussion

This document describes ESC methodology for the development of QIs for the quantification of cardiovascular care and outcomes. Cardiovascular disease is one of the major causes of morbidity and mortality worldwide[1] and although Clinical Practice Guidelines exist, gaps in care remain a major challenge. The recommended approach should bring together scientific evidence, Clinical Practice Guidelines, consensus expert opinion, and patient involvement in a structured manner to inform the construction of QIs. By developing the domain specific QIs relating to ESC Clinical Practice Guidelines, it is hoped that the local, regional, national, and international quality improvement initiatives may be promoted so that geographic variation in care delivery and outcomes is addressed and premature death from cardiovascular disease is reduced.

The ESC recognizes the need to improve the quality of care across its member countries to reduce the burden of CVD. As such, and in addition to the publication of its Clinical Practice Guidelines, the ESC delivers a suite of international registries of cardiovascular disease and treatments under the auspice of the EurObservational Research Programme. Furthermore, the ESC recently launched the EuroHeart project, which provides the means for quality improvement, observational research and randomized trials.[17] Healthcare centres may implement QIs developed using this methodology into their local quality assessment systems to evaluate clinical practice or to participate in wider quality assurance programs aiming to improve quality of care and clinical outcomes for our patients.

Quality assessment provides the mechanisms to identify areas where improvements in care are most needed and evaluates the effectiveness of implemented interventions and initiatives.[44] Quantifying measures of healthcare performance and implementing measures to improve them was associated with improved prognosis.[8,10] Notwithstanding that adherence to therapies recommended by guidelines for the management of cardiovascular disease improves outcomes,[45] substantial variation in care across countries suggests there is room for improvement.[3]

The ESC QIs are tools which may be used to assess and improve cardiovascular care quality in light of ESC Clinical Practice Guideline recommendations and therefore considered as a step to help determine the degree to which these recommendations are being implemented. The QIs will serve as specific, quantifiable, and actionable measures that facilitate the rapid incorporation of the best evidence into practice. They are not intended for ranking or pay-for-performance, but rather for quality improvement and performance measurement through meaningful surveillance, as well as for integration within registries, cohort studies, and clinical audits.

Clinical Practice Guidelines are also written with expert consensus using best available evidence to standardize care. There are important differences between the ESC Clinical Practice Guidelines and ESC QIs. First, guidelines tend to be comprehensive and cover almost all aspects of care, whereas QIs are targeted to specific clinical circumstances. Second, the ESC Clinical Practice Guidelines are usually prescriptive recommendations intended to influence subsequent behaviour. On the other hand, QIs are generally applied retrospectively to distinguish between good- and poor-quality care (although they may improve guideline implementation). Third, guidelines provide flexible recommendations that intentionally leave room for clinical judgement, while QIs are precise measures that can be applied systematically to available data to ensure comparability.[40] Finally, QIs are intended for a more narrowly defined population than Clinical Practice Guidelines. The target population for a QI should only include patients (or subset of patients) for whom good

evidence supporting the intervention exists taking into account patient preference and health status.[33]

A number of unintended consequences to QIs have been described in the literature.[36] These consequences may arise from the fact that performance measurement itself is not capable of improving quality. Performance measurement may miss areas where evidence is not available. Furthermore, important aspects of care quality may not be readily and/or reliably quantifiable.[9] Thus, by providing this methodology statement, the ESC anticipates that the developed QIs are associated with favourable outcomes and seen as a tool within a broader quality improvement strategy that encompasses multiple dimensions of quality, follows its own 'learn-adapt' cycle, and adjusts both the QIs themselves and how they are used.[9]

This approach to the development of QIs is not without limitations. Since the QIs are developed on condition-specific basis, this may lead to condition-specific assessment at the provider-level, and thus, may impact on the care in other areas not captured by the assessment. This challenge may be solved by combining broad sets of QIs that are integrated into a system of quality assessment. Furthermore, when assessed in national and international registries, QIs for AMI that have been developed using similar approach,[27] were inversely associated with mortality.[46] This proposed methodology has now been, and is being, used for the development of QIs for other cardiovascular domains, including atrial fibrillation and heart failure.

Another limitation is the reliance on expert panel opinion. Although different panels may select different QIs, the proposed QIs development process is based on robust literature review, explicit selection criteria, and the use of the modified Delphi technique. Previous QIs developed in relatively similar methodology were found to be highly valid, feasible, and inversely related with mortality.[46] In addition, having a wide range of stakeholders, including practitioners, researchers, members of the respective Clinical Practice Guidelines Task Force, commissioners, and patients in the rating rounds would ensure reasonable representation of important aspect of care delivery.

4.8 Conclusion

The provision of tools for the measurement of care quality is a necessary next step to reducing the burden of cardiovascular disease and close the 'evidence-practice gap'. By means of a transparent methodological approach for the construction of valid and feasible QIs, a suite of ESC QIs will be developed for a wide range of cardiovascular conditions and interventions. These will provide the underpinning framework that enables healthcare professionals and their organizations systematically to improve care and, therefore, clinical outcomes.

4.9 References for Chapter 4

1. Wang H, Naghavi M, Allen C, Barber RM, Bhutta ZA, Carter A et al. Global, regional, and national life expectancy, all-cause mortality, and cause-specific mortality for 249 causes of death, 1980–2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet 2016;388:1459–1544.

2. Timmis A, Townsend N, Gale CP, Torbica A, Lettino M, Petersen SE, European Society of Cardiology et al. European Society of Cardiology: cardiovascular disease statistics 2019. Eur Heart J 2020;41:12–85.

3. Chung SC, Sundstrom J, Gale CP, James S, Deanfield J, Wallentin L, et al. Comparison of hospital variation in acute myocardial infarction care and outcome between Sweden and United Kingdom: population based cohort study using nationwide clinical registries. BMJ 2015;351:h3913.

4. Pronovost PJ, Nolan T, Zeger S, Miller M, Rubin H. How can clinicians measure safety and quality in acute care? Lancet 2004;363:1061–1067.

5. Randell R, Alvarado N, McVey L, Greenhalgh J, West RM, Farrin A et al. How, in what contexts, and why do quality dashboards lead to improvements in care quality in acute hospitals? Protocol for a realist feasibility evaluation. BMJ Open 2020;10:e033208.

6. Park J, Choi KH, Lee JM, Kim HK, Hwang D, Rhee TM et al.; The KAMIR-NIH (Korea Acute Myocardial Infarction Registry–National Institutes of Health) Investigators. Prognostic implications of door-to-balloon time and onset-to-door time on mortality in patients with ST-

segment-elevation myocardial infarction treated with primary percutaneous coronary intervention. J Am Heart Assoc 2019;8:e012188.

7. Backer CL, Pasquali SK, Dearani JA. Improving national outcomes in congenital heart surgery. Circulation 2020;141:943–945.

8. Song Z, Ji Y, Safran DG, Chernew ME. Health care spending, utilization, and quality 8 years into global payment. N Engl J Med 2019;381:252–263.

9. Raleigh VS, Foot C. Getting the Measure of Quality: Opportunities and Challenges. London: King's Fund; 2010.

10. Sutton M, Nikolova S, Boaden R, Lester H, McDonald R, Roland M. Reduced mortality with hospital pay for performance in England. N Engl J Med 2012;367: 1821–1828.

11. Minchin M, Roland M, Richardson J, Rowark S, Guthrie B. Quality of care in the United Kingdom after removal of financial incentives. N Engl J Med 2018;379: 948–957.

12. NICE indicator process guide, 2019. https://wwwniceorguk/media/default/Getinvolved/Meetings-In-Public/indicator-advisory-committee/ioc-process-guidepdf (24 March 2020).

13. Spertus JA, Eagle KA, Krumholz HM, Mitchell KR, Normand S-LT. American College of Cardiology and American Heart Association methodology for the selection and creation of performance measures for quantifying the quality of cardiovascular care. Circulation 2005;111:1703–1712.

14. Spertus JA, Chan P, Diamond GA, Drozda JP, Kaul S, Krumholz HM et al.; Writing Committee Members. ACCF/AHA new insights into the methodology of performance measurement. Circulation 2010;122:2091–2106.

15. Shekelle PG. Quality indicators and performance measures: methods for development need more standardization. J Clin Epidemiol 2013;66:1338–1339.

16. Bhatt DL, Drozda JP, Shahian DM, Chan PS, Fonarow GC, Heidenreich PA et al. ACC/AHA/STS statement on the future of registries and the performance measurement enterprise. J Am Coll Cardiol 2015;66:2230–2245.

17. Wallentin L, Gale CP, Maggioni A, Bardinet I, Casadei B. EuroHeart: European Unified Registries on heart care evaluation and randomized trials. Eur Heart J 2019;40:2745–2749.

18. National Quality Forum. Measure evaluation criteria. http://www.qualityforum.org/Measuring_Performance/Submitting_Standards/Measure_Evaluation_Criteria.aspx#comparison (25 March 2020).

19. Donabedian A. An Introduction to Quality Assurance in Health Care, 1st ed., Vol. 1. New York, NY: Oxford University Press; 2003.

20. Krumholz HM, Normand S-LT, Spertus JA, Shahian DM, Bradley EH. Measuring performance for treating heart attacks and heart failure: the case for outcomes measurement. Health Aff 2007;26:75–85.

21. National Quality Forum. Risk adjustment for sociodemographic factors. https://www.qualityforum.org/Publications/2014/08/Risk_Adjustment_for_Socioeconomic_Status_or_Other_Sociodemographic_Factors.aspx (28 April 2020).

22. Shahian DM, Wolf RE, Iezzoni LI, Kirle L, Normand S-LT. Variability in the measurement of hospital-wide mortality rates. N Engl J Med 2010;363:2530–2539.

23. Sajobi TT, Wang M, Awosoga O, Santana M, Southern D, Liang Z et al. Trajectories of health-related quality of life in coronary artery disease. Circ Cardiovasc Qual Outcomes 2018;11:e003661.

24. Thompson DR, Yu C-M. Quality of life in patients with coronary heart disease-I: assessment tools. Health Qual Life Outcomes 2003;1:42.

25. Lewis E, Zile MR, Swedberg K, Rouleau JL, Claggett B, Lefkowitz MP et al. Health-related quality of life outcomes in paradigm-hf. Circulation 2015; 132(Suppl_3):A17912.

26. Coyle YM, Battles JB. Using antecedents of medical care to develop valid quality of care measures. Int J Qual Health Care 1999;11:5–12.

27. Schiele F, Gale CP, Bonnefoy E, Capuano F, Claeys MJ, Danchin N et al. Quality indicators for acute myocardial infarction: a position paper of the Acute Cardiovascular Care Association. Eur Heart J Acute Cardiovasc Care 2017;6:34–59.

28. Klassen A, Miller A, Anderson N, Shen J, Schiariti V, O'Donnell M. Performance measurement and improvement frameworks in health, education and social services systems: a systematic review. Int J Qual Health Care 2010; 22:44–69.

29. Batalden M, Batalden P, Margolis P, Seid M, Armstrong G, Opipari-Arrigan L et al. Coproduction of healthcare service. BMJ Qual Saf 2016;25:509–517.

30. Fitzsimons D. Patient engagement at the heart of all European Society of Cardiology activities. Cardiovasc Res 2019;115:e99–e101.

31. Dimick JB, Welch HG, Birkmeyer JD. Surgical mortality as an indicator of hospital quality: the problem with small sample size. JAMA 2004;292:847–851.

32. Kaul S, Diamond GA. Trial and error. How to avoid commonly encountered limitations of published clinical trials. J Am Coll Cardiol 2010;55:415–427.

33. Walter LC, Davidowitz NP, Heineken PA, Covinsky KE. Pitfalls of converting practice guidelines into quality measures: lessons learned from a VA performance measure. JAMA 2004;291:2466–2470.

34. Normand S-LT, McNeil BJ, Peterson LE, Palmer RH. Eliciting expert opinion using the Delphi technique: identifying performance indicators for cardiovascular disease. Int J Qual Health Care 1998;10:247–260.

35. MacLean CH, Kerr EA, Qaseem A. Time out—charting a path for improving performance measurement. N Engl J Med 2018;378:1757–1761.

36. Werner RM, Asch DA. The unintended consequences of publicly reporting quality information. JAMA 2005;293:1239–1244.

37. Jones J, Hunter D. Consensus methods for medical and health services research. BMJ 1995;311:376–380.

38. Brook RH, McGlynn EA, Cleary PD. Quality of health care. Part 2: measuring quality of care. N Engl J Med 1996;335:966–970.

39. Brook RH, The RAND/UCLA appropriateness method. In: KA McCormack, SR Moore, RA Siegel, eds. Clinical Practice Guideline Development: Methodology Perspectives. Rockville, MD: Agency for Healthcare Research and Policy; 1994.

40. Mangione-Smith R, DeCristofaro AH, Setodji CM, Keesey J, Klein DJ, Adams JL et al. The Quality of ambulatory care delivered to children in the United States. N Engl J Med 2007;357:1515–1523.

41. Peterson ED, Delong ER, Masoudi FA, O'Brien SM, Peterson PN, Rumsfeld JS et al. ACCF/AHA 2010 Position Statement on Composite Measures for Healthcare Performance Assessment: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Performance Measures (Writing Committee to develop a position statement on composite measures). Circulation 2010;121:1780–1791.

42. Zusman O, Bebb O, Hall M, Dondo TB, Timmis A, Schiele F et al. International comparison of acute myocardial infarction care and outcomes using quality indicators. Heart 2019;105:820–825.

43. Rossello X, Medina J, Pocock S, Van de Werf F, Chin CT, Danchin N et al. Assessment of quality indicators for acute myocardial infarction management in 28 countries and use of composite quality indicators for benchmarking. Eur Heart J Acute Cardiovasc Care 2020;2048872620911853. doi: 10.1177/2048872620911853.

44. Berwick DM. Era 3 for medicine and health care. JAMA 2016;315:1329–1330.

45. Hall M, Dondo TB, Yan AT, Goodman SG, Bueno H, Chew DP et al. Association of clinical factors and therapeutic strategies with improvements in survival following non-ST-elevation myocardial infarction, 2003–2013. JAMA 2016;316: 1073–1082.

46. Bebb O, Hall M, Fox KAA, Dondo TB, Timmis A, Bueno H et al. Performance of hospitals according to the ESC ACCA quality indicators and 30-day mortality for acute myocardial infarction: National Cohort Study using the United Kingdom Myocardial Ischaemia National Audit Project (MINAP) register. Eur Heart J 2017; 38:974–982.

Chapter 5. Data standards for acute coronary syndrome and percutaneous coronary intervention: The European Unified Registries for Heart Care Evaluation and Randomised Trials (EuroHeart)

In collaboration with the Association of Cardiovascular Nursing and Allied Professions (ACNAP), Association for Acute Cardiovascular Care (ACVC), European Association of Percutaneous Cardiovascular Interventions (EAPCI), EURObservational Research Programme (EORP), ESC Patient Forum, ESC Working Group on Thrombosis and ESC Committee for Young Cardiovascular Professionals

Gorav Batra, Suleman Aktaa, Lars Wallentin, Aldo P Maggioni, Peter Ludman, David Erlinge, Barbara Casadei, Chris P Gale

5.1 Summary of the publication:

- Using the methodology outlined in Chapter 3, this document presents the EuroHeart data standards for acute coronary syndrome and percutaneous coronary interventions.
- These data standards have been implemented in the EuroHeart IT platform and are currently in use collecting real-world data in a number of countries.

5.2 Publication status:

Accepted for publication in the European Heart Journal.

5.3 Abstract and Keywords

5.3.1 Aims

Standardised data definitions are essential for monitoring and benchmarking quality of care and patient outcomes in observational studies and randomised controlled trials (RCTs). There are no contemporary pan-European data standards for acute coronary syndrome (ACS) and percutaneous coronary intervention (PCI). The European Unified Registries for Heart Care

Evaluation and Randomised Trials (EuroHeart) project of the European Society of Cardiology (ESC) aimed to develop such data standards for ACS and PCI.

5.3.2 Methods and Results

Following a systematic review of the literature on ACS and PCI data standards and evaluation of contemporary ACS and PCI registries, we undertook a modified Delphi process involving clinical and registry experts from 11 European countries, as well as representatives from relevant ESC Associations, including the European Association for Percutaneous Coronary Intervention (EAPCI) and Acute CardioVascular Care (ACVC). This resulted in final sets of 68 and 84 'mandatory' variables and several catalogues of optional variables for ACS and PCI, respectively. Data definitions were provided for these variables, which have been programmed as the basis for continuous registration of individual patient data in the online EuroHeart IT platform.

5.3.3 Conclusion

By means of a structured process and the interaction with major stakeholders, internationally harmonised data standards for ACS and PCI have been developed. In the context of the EuroHeart project, this will facilitate country-level quality of care improvement, international observational research, registry-based randomised trials and post-marketing surveillance of devices and pharmacotherapies.

5.3.4 Keywords

Data standards. Data variables. Data definitions. Acute coronary syndrome. Percutaneous coronary intervention. EuroHeart.

5.4 One-sentence summary

The EuroHeart data standards for acute coronary syndrome and percutaneous coronary intervention are a suite of standardised data variables and definitions that once implemented will enable reliable monitoring of quality of care and outcomes.

Central illustration. Domains of the 2021 EuroHeart acute coronary syndrome and percutaneous coronary intervention data standards with number of level 1 (mandatory) variables
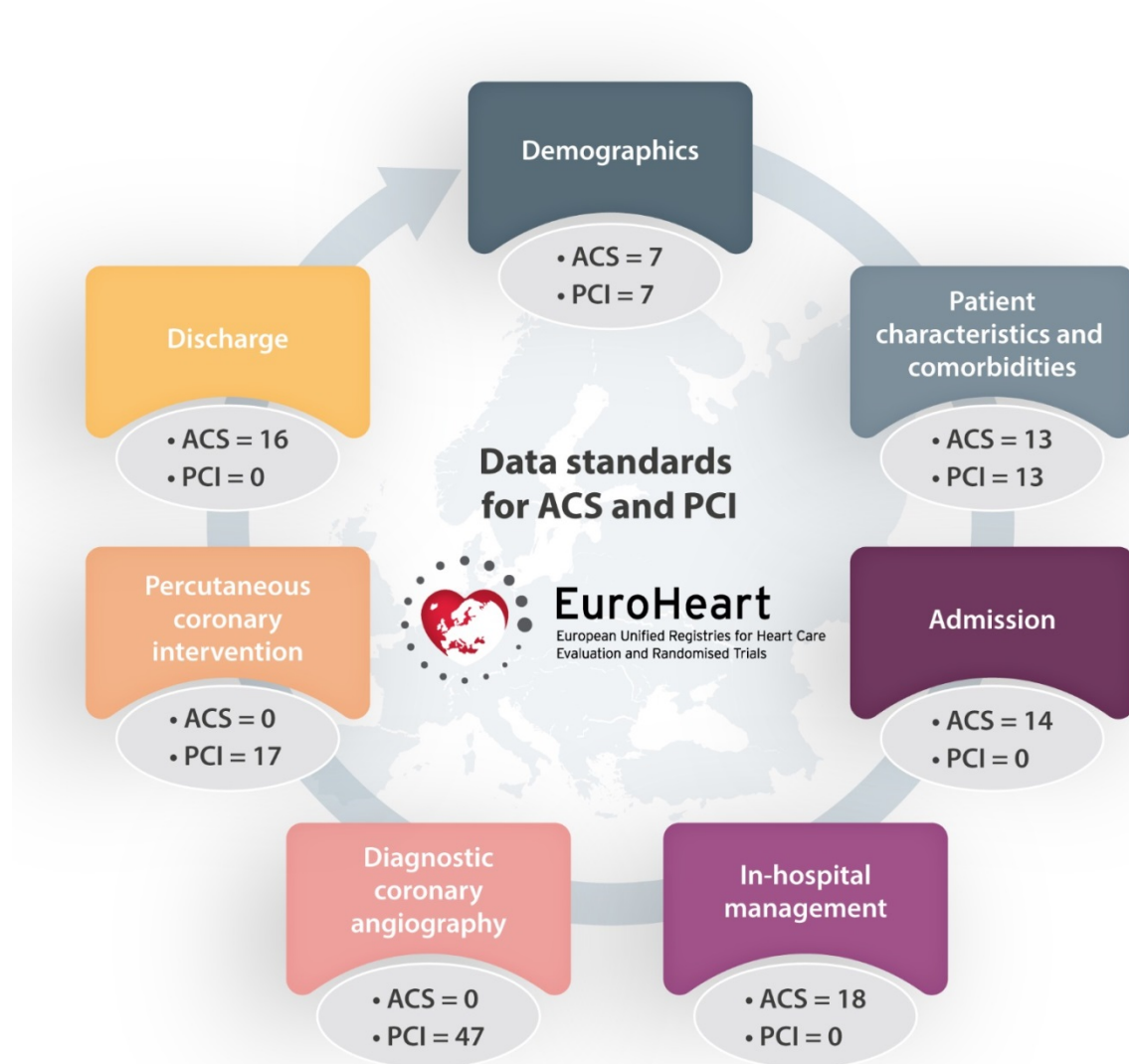
5.5 Introduction

Standardised data definitions are essential for the reliable investigation of quality of care and outcomes in observational studies and randomised controlled trials. Heterogeneity in such definitions impedes benchmarking and leads to inconsistencies that directly impact the interpretation of clinical studies and the implementation of their findings.[1]

With the advent of large-scale registries, administrative databases, and the widespread use of electronic health records (EHRs) in routine clinical practice, opportunities to deliver cost efficient investigator-initiated observational and randomised studies of both devices and pharmacological treatments have been realised.[2–4] Yet, between-country comparisons remain challenging. This is often driven by a variation in the variables and their definitions.[5] This restricts the ability to combine and efficiently compare data across databases. In countries where registry-based randomised controlled trials (R-RCTs) are feasible, country-specific definitions of outcomes or disease states that inform patient recruitment can limit the international generalisability of the study findings.[6] Standardised data variables and definitions would provide means to overcome these limitations and enable international R-RCTs and the evaluation of quality of care according to guideline-recommended quality indicators in multi-country observational cohorts.[7–10]

Currently, there are no contemporary pan-European data standards for cardiovascular disease. The Cardiology Audit and Registration Data Standards (CARDS) was developed in 2004 and was the first European initiative to address this gap in knowledge.[11] The European Unified Registries for Heart Care Evaluation and Randomised Trials (EuroHeart) is an international collaboration initiated and supported by the European Society of Cardiology (ESC) that aims to improve the quality of cardiovascular care through continuous capture of individual patient data.[12] EuroHeart is underpinned by a purpose-built IT platform enabling real-time data recording, monitoring of standards of care, data linkages and the delivery of R-RCTs and observational studies. During the pilot phase, EuroHeart will focus on four clinical domains, the first of which is acute coronary syndrome (ACS) and percutaneous coronary intervention (PCI). Here we describe the development process and the resultant standardised data

variables and definitions for ACS and PCI based on the EuroHeart methodology for development of data standards[13].

5.6 Methods

5.6.1 Working Group composition

A Data Science Group under the auspice of EuroHeart was established in August 2019. This comprised a project chair (C.G.), two medical experts (G.B. and S.A.) and a project manager. An international ACS/PCI Working Group was established and included 22 ACS/PCI and registry experts, representing 11 European countries. The selection of the Working Group members was based on ACS and/or PCI expertise and experience of national registries.

Figure 1. EuroHeart data standards structure
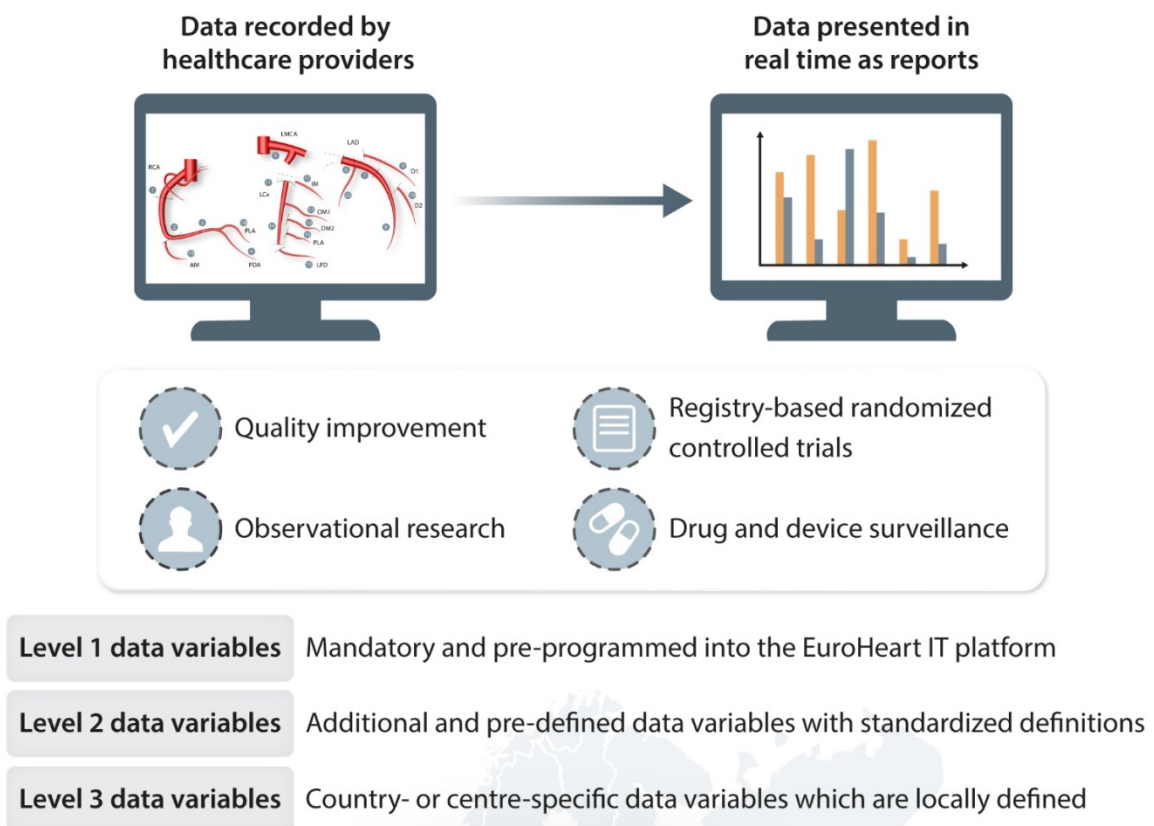
5.6.2 Defining data standards

The goal of the development process was to select and define a catalogue of ACS/PCI variables, the extent of which was balanced between all-encompassing and parsimonious. For instance, whereas some registries collect up to 370 variables,[14,15] the Data Science Group opted to limit the number of 'mandatory' variables to between 50 and 100. Three levels of variables were proposed (Figure 1). Level 1: 'mandatory' variables that also are pre-programed into the EuroHeart IT platform and include quality indicators and variables pertinent to accountability and public reporting of quality of care. Level 2: 'additional' variables that are provided together with definitions, but collection not being mandatory and not pre-programed into the IT platform. Level 3: country- or centre-specific variables that address local regulatory and/or administrative requirements and that are not defined or programmed into the IT platform.

5.6.3 Literature search and evaluation of registries

A systematic review of the published literature (1st January 2004 – 4th August 2020) identified 554 ACS/PCI variables with accompanying definitions. Evaluation of contemporary national registries in Sweden (Swedish Web-system for Enhancement and Development of Evidence-based care in Heart Disease Evaluated according to Recommended Therapies [SWEDEHEART]), United Kingdom (Myocardial Ischaemia National Audit Project [MINAP], National Audit of Percutaneous Coronary Intervention [NAPCI]) and United States (National Cardiovascular Data Registry [NCDR]) was performed.[14–17] Variables defined as quality indicators for ACS were automatically selected as candidate variables.[10] Other variables were assessed according to their evidence-base, validity, reliability, feasibility and applicability. Candidate variables were classified according to timepoint of care delivery and, where possible, reconciled with Clinical Practice Guidelines and quality indicators.[7,8,18,19]

5.6.4 Consensus development

The modified Delphi method was used to draw from the candidate variables a final set of ACS/PCI variables. To achieve this, candidate variables were shared with the Working Group, who were asked to assess them for inclusion against the pre-defined criteria and to

evaluate the associated definitions. Responses and feedback were evaluated by the Data Science Group and the candidate variable catalogue updated accordingly. In total, 11 peer-to-peer meetings were held during 2020. The developed variables were thereafter reviewed by the Association for Acute Cardiovascular Care (ACVC), European Association of Percutaneous Cardiovascular Interventions (EAPCI), ESC Working Group on Thrombosis, Association of Cardiovascular Nursing and Allied Professions (ACNAP), ESC Patient Forum and ESC Committee for Young Cardiovascular Professionals.

5.7 Results

In total, 302 variables were included in the EuroHeart ACS/PCI catalogue: 152 Level 1 'mandatory' variables (68 for ACS and 84 for PCI) with 20 variables common to both datasets, and 150 Level 2 'additional' variables. Tables 1-7 show the 'mandatory' variables, with condensed definitions. Detailed information about the 'mandatory' variables are provided in Supplementary Tables s1-s7, whereas 'additional' variables are provided in Supplementary Tables s8-s14.

5.7.1 Demographics

There are 7 'mandatory' variables in this section, all of which are common between the ACS and PCI data standards (Table 1). The section will be replicated in the other EuroHeart clinical domains so that time-independent patient information (e.g. date of birth) may be collected once and applied to all subsequent episodes of care. This section allows the use of permanent unique personal identification numbers to identify patients.[20] When matching the identification number with other data sources, information such as forename, surname, sex and postal code may be extracted automatically. The EuroHeart IT platform will generate unique patient identifiers for those countries that do not use them, which once assigned may not be changed or reassigned to other patients. Each patient's geolocation is collected as their current residential postal code.

5.7.2 Patient characteristics and comorbidities

The patient characteristics and comorbidities section contains 13 'mandatory' variables collecting comorbidities relevant to ACS and/or PCI (Table 2). The choice of comorbidities was prioritised according to what the Working Group perceived to be information available in an average medical case record. Many of the variables are also relevant when characterising the patient's risk and are essential when reporting underlying medical history in observational and randomised trials, when understanding trends in quality improvement and when assessing treatment strategies.

5.7.3 Admission

Table 3 depicts the 'mandatory' variables for the admission section. Information about care timepoints can be difficult to collect, but is important given it is used for the derivation of quality indicators.[7,8] Medications at the time of admission form 'additional' variables and are defined in Supplementary Table s10.

5.7.4 In-hospital management

This section collects information concerning investigations, treatments and events occurring in-hospital (Table 4). Laboratory results for diagnosis (e.g. cardiac biomarkers), risk stratification (e.g. serum creatinine) and risk factors modification (e.g. low-density lipoprotein cholesterol) are 'mandatory' variables.[7,8,18] Laboratory results for specific situations or subgroups (e.g. N-terminal prohormone of brain natriuretic peptide, C-reactive protein, cholesterol, glucose and haemoglobin A1c) are 'additional' variables and are detailed in Supplementary Table s11. The 2020 ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation recommends the assessment of the left ventricular ejection fraction (LVEF) during the hospital stay, and thus forms a 'mandatory' variable.[7] Categorisation of LVEF aligns with the 2021 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure.[21] Given that reperfusion is the cornerstone for the management of patients with ACS, five 'mandatory' variables are dedicated to the evaluation of the coronary artery anatomy and reperfusion strategy.[7,8]

Figure 2. Conceptual image of the EuroHeart IT platform and the EuroHeart-PCI coronary artery segments
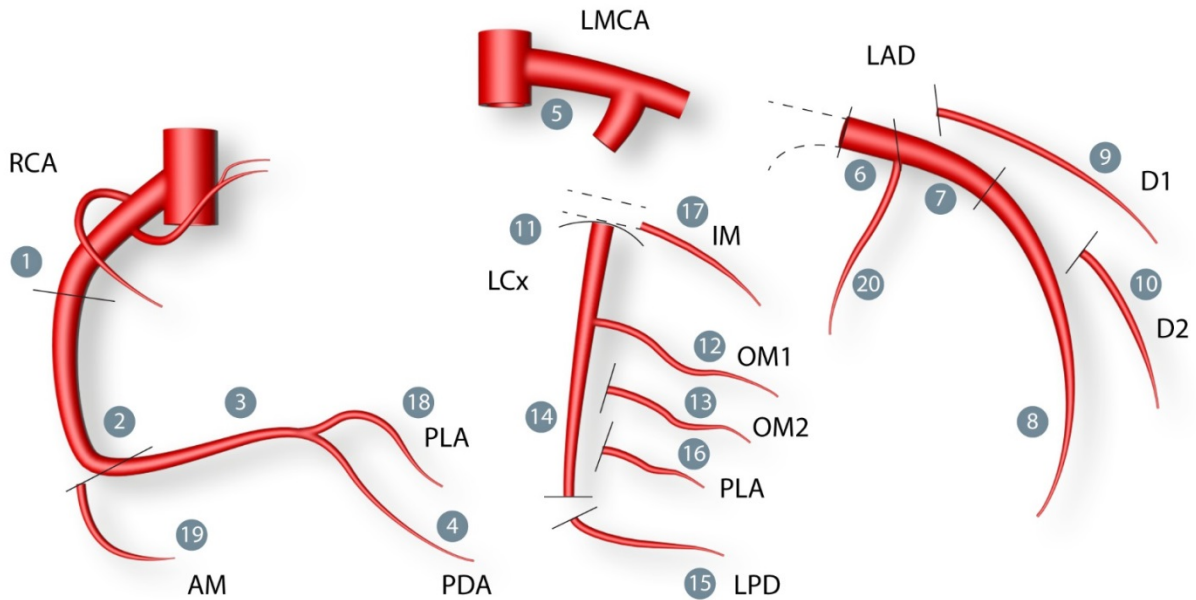
AM= acute marginal, D= diagonal, LAD= left anterior descending artery, LCx= left circumflex artery, LMCA= left main coronary artery, LPD= left posterior descending artery, OM= obtuse marginal, PLA= posterior left artery, RCA= right coronary artery, IM= intermediate artery.

5.7.5 Diagnostic coronary angiography and percutaneous coronary intervention

This section has two parts. The first part captures information about invasive coronary angiography (ICA) (Table 5) and includes an interactive diagram of the coronary tree (Figure 2). It provides a solution for the fact that there are international differences in the extent of information recorded in registries (e.g. all ICA procedures in Sweden[14] vs. all PCI procedures in the United Kingdom[16]). Equally, the Data Science Group reviewed coronary anatomy visualisation tools including the Bypass Angioplasty Revascularisation Investigation (BARI) and the Coronary Artery Surgery Study (CASS) schemes describing coronary anatomy.[22,23] The consensus of the Working Group was to adopt a simplified 20-segment system adapted from the SWEDEHEART registry, which enables interactive reporting of stenoses found in major coronary arteries (Figure 2).[14]

The second part captures information about the procedural indication, urgency, findings and complications (Table 6). It collects information such as date, time and type of the arterial access, given the use of radial access is recommended as a quality indicator in the 2020 ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation.[7] In addition, thrombolysis with myocardial infarction (TIMI) grades before and following the procedure, and intracoronary equipment and devices used are captured in this section.

5.7.6 Discharge

This section collects information about the final ACS diagnosis and medications prescribed at the time of discharge from hospital (Table 7). The final diagnosis includes ST-elevation myocardial infarction, non-ST-elevation myocardial infarction and unstable angina (with accompanying World Health Organisations (WHO) standardised International Classification of Diseases (ICD-10) codes). Medication information includes Anatomical Therapeutic Chemical codes and drug dosages as 'additional' variables (Supplementary Material, Table s14).

5.8 Discussion

Adoption of harmonised data collections are central for continuous improvement of cardiovascular care.[24] The lack of internationally recognised data standards has led to large inequalities in monitoring and standards of care within and between European countries and also resulted in expensive and inefficiently coordinated and delivered studies of cardiovascular treatments.[25] Currently, there are no contemporary pan-European data standards for ACS and PCI. The EuroHeart project of the ESC, by means of a structured methodology, has defined a catalogue of data standards for ACS and PCI, which will be implemented into a bespoke IT platform to facilitate harmonised country-level quality improvement, international observational and registry-based randomised research and post-marketing surveillance of devices and pharmacotherapies.

Existing European national cardiovascular registries comprise distinct and discordant entities with differing data variables and definitions.[26] This substantially limits their usability in collaborative large-scale studies. Data standards and case report forms presented by CARDS, the EURObservational Research Programme (EORP) and the American College of Cardiology (ACC) and the American Heart Association (AHA) have been used in national registries and in clinical trials,[11,27,28] but differ in their data variables and definitions. Furthermore, no previous international cardiovascular data standards initiative has provided the means by which data may be efficiently collected in 'real-world' settings. Moreover, the ACC/AHA data standards for coronary artery disease and PCI contain over 300 variables that make it difficult to implement in a pragmatic registry.[28,29] By contrast, the EuroHeart data standards presented in this article have a restricted number of mandatory ACS/PCI variables, bolted onto an IT platform for effective data collection.

After years of steady decline, the reduction of mortality rates post-MI has plateaued in many countries; CVD remains the main cause of death worldwide and the burden of CVD is increasing in low- to middle-income economies.[30] The standardised collection of cardiovascular data and the understanding of how to use observational and randomised data in cardiovascular medicine is a clear unmet need and an important next step towards defining variation in cardiovascular care and facilitating continuous quality improvement.[4] The emergence of new devices and drugs for the management of CVD provide opportunities for improved outcomes but require post-marketing surveillance. In addition, the growing complexity and financial burden of traditional RCTs create a need to develop innovative ways to conduct high-quality, yet cost-effective research. National registries which implement uniform data standards will facilitate rapid and efficient post-marketing surveillance of device therapies and pragmatic R-RCT with pooled data from multiple geographical locations.[6] Starting in 2021, the EuroHeart IT platform will collect all 'mandatory' variables and support the development of 'additional' variables in participating countries. Once fully adopted, the IT infrastructure will include applications for clinical reporting in the local health care system, and provide tools for observational research, R-RCTs and post-marketing surveillance of drugs and devices. Importantly, no individual patient-level data will be transferred outside the local country/region, and thus a signed

informed consent will not be required for the standard data collection in most countries. For future reports on standards of care in different countries, aggregated and anonymised data might be shared by the individual countries. However, for prospective research projects, such as R-RCTs or drug and device monitoring, informed consent from participants' will be required as in any clinical trials. In these cases, selected anonymised individual study data may be transferred for analysis to a central repository according to clinical trial protocols. Finally, as part of mutually agreed international epidemiological research projects and based on ethical and regulatory approval, anonymised retrospective registry cohorts may be transferred to a central repository for predefined statistical analysis. In all cases, the national/regional registry parties are responsible for defining the legal framework applicable to their participation in EuroHeart and its various features and for ensuring that they do not violate either local or international law.

We recognise the limitations of the EuroHeart data standards development process. This includes the use of expert opinion (which may be biased) for the selection of the final data variables and definitions from those identified in the literature review. However, the EuroHeart ACS and PCI data standards were developed using a structured and recognised methodology for selecting the expert panel and for obtaining their opining and feedback. Likewise, the inclusiveness of the Working Group, which comprised experts from many European countries, provided a robustness and transparent framework for the development of the variables and definitions. Of note, the data standards proposed in this document are based on the evidence available at the time of development. Accordingly, updates may be required as more and new knowledge becomes available.

5.9 Conclusions

This document presents the first set of data standards, developed as part of the EuroHeart project, which aims to harmonise data variables and definitions across common cardiovascular domains. In total, 68 and 84 'mandatory' variables for ACS and PCI domains have been proposed. Also, several 'additional' variables have been defined. Once fully adopted into the EuroHeart IT platform, the data standards will facilitate country-level quality

improvement, observational and registry-based randomised research and post-marketing surveillance of new devices and pharmacotherapies.

5.10 References for Chapter 5

1. Gregson J, Stone GW, Ben-Yehuda O, Redfors B, Kandzari DE, Morice M-C, Leon MB, Kosmidou I, Lembo NJ, Brown WM, Karmpaliotis D, Banning AP, Pomar J, Sabaté M, Simonton CA, Dressler O, Kappetein AP, Sabik JF, Serruys PW, Pocock SJ. Implications of alternative definitions of peri-procedural myocardial infarction after coronary revascularization. *J Am Coll Cardiol* 2020;76:1609–1621.

2. Fröbert O, Lagerqvist B, Olivecrona GK, Omerovic E, Gudnason T, Maeng M, Aasa M, Angerås O, Calais F, Danielewicz M, Erlinge D, Hellsten L, Jensen U, Johansson AC, Kåregren A, Nilsson J, Robertson L, Sandhall L, Sjögren I, Ostlund O, Harnek J, James SK. Thrombus aspiration during ST-segment elevation myocardial infarction. *N Engl J Med* 2013;369:1587–1597.

3. Erlinge D, Omerovic E, Fröbert O, Linder R, Danielewicz M, Hamid M, Swahn E, Henareh L, Wagner H, Hårdhammar P, Sjögren I, Stewart J, Grimfjärd P, Jensen J, Aasa M, Robertsson L, Lindroos P, Haupt J, Wikström H, Ulvenstam A, Bhiladvala P, Lindvall B, Lundin A, Tödt T, Ioanes D, Råmunddal T, Kellerth T, Zagozdzon L, Götberg M, Andersson J, et al. Bivalirudin versus heparin monotherapy in myocardial infarction. *N Engl J Med* 2017;377:1132–1142.

4. Bowman L, Baras A, Bombien R, Califf RM, Chen Z, Gale CP, Gaziano JM, Grobbee DE, Maggioni AP, Muse ED, Roden DM, Schroeder S, Wallentin L, Casadei B. Understanding the use of observational and randomized data in cardiovascular medicine. *Eur Heart J* 2020;41:2571–2578.

5. Rapsomaniki E, Thuresson M, Yang E, Blin P, Hunt P, Chung S-C, Stogiannis D, Pujades-Rodriguez M, Timmis A, Denaxas SC, Danchin N, Stokes M, Thomas-Delecourt F, Emmas C, Hasvold P, Jennings E, Johansson S, Cohen DJ, Jernberg T, Moore N, Janzon M, Hemingway H. Using big data from health records from four countries to evaluate chronic disease outcomes: a study in 114 364 survivors of myocardial infarction. *Eur Hear J - Qual Care Clin Outcomes* 2016;2:172–183.

6. James S, Rao S V, Granger CB. Registry-based randomized clinical trials - a new clinical trial paradigm. *Nat Rev Cardiol* 2015;12:312–316.

7. Collet J-P, Thiele H, Barbato E, Barthélémy O, Bauersachs J, Bhatt DL, Dendale P,

Dorobantu M, Edvardsen T, Folliguet T, Gale CP, Gilard M, Jobs A, Jüni P, Lambrinou E, Lewis BS, Mehilli J, Meliga E, Merkely B, Mueller C, Roffi M, Rutten FH, Sibbing D, Siontis GCM, Group ESCSD. 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: The Task Force for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. *Eur Heart J* 2020;42:1289–1367.

8. Ibanez B, James S, Agewall S, Antunes MJ, Bucciarelli-Ducci C, Bueno H, Caforio ALP, Crea F, Goudevenos JA, Halvorsen S, Hindricks G, Kastrati A, Lenzen MJ, Prescott E, Roffi M, Valgimigli M, Varenhorst C, Vranckx P, Widimský P, Group ESCSD. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. *Eur Heart J* 2017;39:119–177.

9. Aktaa S, Batra G, Wallentin L, Baigent C, Erlinge D, James S, Ludman P, Maggioni AP, Price S, Weston C, Casadei B, Gale CP. European Society of Cardiology methodology for the development of quality indicators for the quantification of cardiovascular care and outcomes. *Eur Hear J - Qual Care Clin Outcomes* 2020;

10. Schiele F, Aktaa S, Rossello X, Ahrens I, Claeys MJ, Collet J-P, Fox KAA, Gale CP, Huber K, Iakobishvili Z, Keys A, Lambrinou E, Leonardi S, Lettino M, Masoudi FA, Price S, Quinn T, Swahn E, Thiele H, Timmis A, Tubaro M, Vrints CJM, Walker D, Bueno H, Group ESCSD, Halvorsen S, Jernberg T, Jortveit J, Blöndal M, Ibanez B, et al. 2020 Update of the quality indicators for acute myocardial infarction: a position paper of the Association for Acute Cardiovascular Care: the study group for quality indicators from the ACVC and the NSTE-ACS guideline group. *Eur Hear Journal Acute Cardiovasc Care* 2021;10:224–233.

11. Flynn MR, Barrett C, Cosío FG, Gitt AK, Wallentin L, Kearney P, Lonergan M, Shelley E, Simoons ML. The Cardiology Audit and Registration Data Standards (CARDS), European data standards for clinical cardiology practice. *Eur Heart J* 2005;26:308–313.

12. Wallentin L, Gale CP, Maggioni A, Bardinet I, Casadei B. EuroHeart: European unified registries on heart care evaluation and randomized trials - An ESC project to develop a new it registry system which will encompass multiple features of cardiovascular medicine. *Eur Heart J* 2019;40:2745–2749.

13. Batra G, Aktaa S, Wallentin L, Maggioni AP, Wilkinson C, Casadei B, Gale CP. Methodology for the development of international clinical data standards for common cardiovascular conditions: European Unified Registries for Heart Care Evaluation and Randomised Trials (EuroHeart). *Eur Hear J - Qual Care Clin Outcomes* 2021;qcab052.

14. Jernberg T, Attebring MF, Hambraeus K, Ivert T, James S, Jeppsson A, Lagerqvist B, Lindahl B, Stenestrand U, Wallentin L. The Swedish Web-system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies (SWEDEHEART). *Heart* 2010;96:1617–1621.

15. Wilkinson C, Weston C, Timmis A, Quinn T, Keys A, Gale CP. The Myocardial Ischaemia National Audit Project (MINAP). *Eur Hear J - Qual Care Clin Outcomes* 2020;6:19–22.

16. Ludman PF. British Cardiovascular Intervention Society Registry for audit and quality assessment of percutaneous coronary interventions in the United Kingdom. *Heart* 2011;97:1293–1297.

17. Messenger JC, Ho KKL, Young CH, Slattery LE, Draoui JC, Curtis JP, Dehmer GJ, Grover FL, Mirro MJ, Reynolds MR, Rokos IC, Spertus JA, Wang TY, Winston SA, Rumsfeld JS, Masoudi FA. The National Cardiovascular Data Registry (NCDR) Data Quality Brief: The NCDR Data Quality Program in 2012. *J Am Coll Cardiol* 2012;60:1484–1488.

18. Thygesen K, Alpert JS, Jaffe AS, Chaitman BR, Bax JJ, Morrow DA, White HD, Group ESCSD. Fourth universal definition of myocardial infarction. *Eur Heart J* 2018;40:237–269.

19. Kastrati A, Banning AP, Koller A, Ahlsson A, Richter DJ, Sibbing D, Alfonso F, Stefanini GG, Collet J-P, Niebauer J, Zembala MO, Seferović PM, Jüni P, Yadav R, Byrne RA, Kristensen SD, Windecker S, Head SJ, Benedetto U, Falk V, Neumann F-J, Sousa-Uva M, Ahlsson A, Alfonso F, Banning AP, Benedetto U, Byrne RA, Collet J-P, Falk V, Head SJ, et al. 2018 ESC/EACTS Guidelines on myocardial revascularization. *Eur Heart J* 2018;40:87–165.

20. Mills S, Lee JK, Rassekh BM, Zorko Kodelja M, Bae G, Kang M, Pannarunothai S, Kijsanayotin B. Unique health identifiers for universal health coverage. *J Heal Popul Nutr* 2019;38:22.

21. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, Burri H, Butler J, Čelutkienė J, Chioncel O, Cleland JGF, Coats AJS, Crespo-Leiro MG, Farmakis D, Gilard M, Heymans S, Hoes AW, Jaarsma T, Jankowska EA, Lainscak M, Lam CSP, Lyon AR, McMurray JJ V, Mebazaa A, Mindham R, Muneretto C, Francesco Piepoli M, Price S, Rosano GMC, Ruschitzka F, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: Developed by the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society

of Cardiology (ESC) With the special contributio. *Eur Heart J* 2021;ehab368.

22. Rogers WJ, Alderman EL, Chaitman BR, DiSciascio G, Horan M, Lytle B, Mock MB, Rosen AD, Sutton-Tyrrell K, Weiner BH, Whitlow PL. Bypass angioplasty revascularization investigation (BARI): Baseline clinical and angiographic data. *Am J Cardiol* 1995;75:9C-17C.

23. CASS principal investigators and their associates. Coronary artery surgery study (CASS): A randomized trial of coronary artery bypass surgery. *Circulation* 1983;68:939–950.

24. Benjamin EJ, Blaha MJ, Chiuve SE, Cushman M, Das SR, Deo R, Ferranti SD de, Floyd J, Fornage M, Gillespie C, Isasi CR, Jiménez MC, Chaffin JL, E JS, Daniel L, H LJ, Lynda L, Simin L, T LC, H MR, Kunihiro M, Dariush M, E MM, Khurram N, W NR, Latha P, K PD, R TR, J RM, Matthew R, et al. Heart disease and stroke statistics — 2017 update: a report from the American Heart Association. *Circulation* American Heart Association; 2017;135:e146–e603.

25. Scherer FM. The Pharmaceutical Industry — Prices and Progress. *N Engl J Med* Massachusetts Medical Society; 2004;351:927–932.

26. Widimsky P, Wijns W, Fajadet J, Belder M de, Knot J, Aaberge L, Andrikopoulos G, Baz JA, Betriu A, Claeys M, Danchin N, Djambazov S, Erne P, Hartikainen J, Huber K, Kala P, Klinčeva M, Kristensen SD, Ludman P, Ferre JM, Merkely B, Miličić D, Morais J, Noč M, Opolski G, Ostojić M, Radovanovič D, Servi S De, Stenestrand U, Studenčan M, et al. Reperfusion therapy for ST elevation acute myocardial infarction in Europe: description of the current situation in 30 countries. *Eur Heart J* 2010;31:943–957.

27. Zeymer U, Ludman P, Danchin N, Kala P, Maggioni AP, Weidinger F. Background and design of the ACCA–EAPCI registry on ST-segment elevation myocardial infarction of the European Society of Cardiology. *Eur Hear J Acute Cardiovasc Care* SAGE Publications; 2018;8:63–67.

28. Cannon CP, Brindis RG, Chaitman BR, Cohen DJ, Cross JT, Drozda JP, Fesmire FM, Fintel DJ, Fonarow GC, Fox KA, Gray DT, Harrington RA, Hicks KA, Hollander JE, Krumholz H, Labarthe DR, Long JB, Mascette AM, Meyer C, Peterson ED, Radford MJ, Roe MT, Richmann JB, Selker HP, Shahian DM, Shaw RE, Sprenger S, Swor R, Underberg JA, Werf F Van de, et al. 2013 ACCF/AHA Key Data Elements and Definitions for Measuring the Clinical Management and Outcomes of Patients With Acute Coronary Syndromes and Coronary Artery Disease. *Circulation* 2013;127:1052–1089.

29. Dehmer GJ, Badhwar V, Bermudez EA, Cleveland JC, Cohen MG, D'Agostino RS, Ferguson TB, Hendel RC, Isler ML, Jacobs JP, Jneid H, Katz AS, Maddox TM, Shahian DM. 2020 AHA/ACC Key Data Elements and Definitions for Coronary Revascularization: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Data Standards (Writing Committee to Develop Clinical Data Standards for Corona. *Circ Cardiovasc Qual Outcomes* American Heart Association; 2020;13:e000059.

30. Timmis A, Townsend N, Gale CP, Torbica A, Lettino M, Petersen SE, Mossialos EA, Maggioni AP, Kazakiewicz D, May HT, Smedt D De, Flather M, Zuhlke L, Beltrame JF, Huculeci R, Tavazzi L, Hindricks G, Bax J, Casadei B, Achenbach S, Wright L, Vardas P. European Society of Cardiology: Cardiovascular disease statistics 2019. *Eur Heart J* 2020;41:12–85.

Chapter 6. Data standards for heart failure: The European Unified Registries for Heart Care Evaluation and Randomised Trials (EuroHeart)

Developed in collaboration with the Heart Failure Association of the European Society of Cardiology.

Suleman Aktaa, Gorav Batra, John G. F. Cleland, Andrew Coats, Lars H. Lund, Theresa McDonagh, Giuseppe Rosano, Petar Seferovic, Peter Vasko, Lars Wallentin, Aldo P Maggioni, Barbara Casadei, Chris P Gale

6.1 Summary of the publication:

- Using the methodology outlined in Chapter 3, this document presents the EuroHeart data standards for heart failure.

6.2 Publication status:

6.3 Abstract

6.3.1 Aims

Standardised data definitions are essential for assessing quality of care and patient outcomes in observational studies and randomised controlled trials (RCTs). The European Unified Registries for Heart Care Evaluation and Randomised Trials (EuroHeart) project of the European Society of Cardiology (ESC) aims to create contemporary pan-European data-standards for cardiovascular diseases, including heart failure.

6.3.2 Methods and Results

We followed the EuroHeart methodology for cardiovascular data standard development. A Working Group including experts in heart failure registries, representatives from the Heart Failure Association of the ESC and EuroHeart was formed. Using Embase and Medline

(2016 to 2021), we conducted a systematic review of the literature on data standards, registries and trials to identify variables pertinent to heart failure. A modified Delphi method was used to reach consensus on the final set of variables. For each variable, the Working Group developed data definitions and agreed on whether it was a mandatory (Level 1) or additional (Level 2). In total, 84 Level 1 and 79 Level 2 variables were selected for 9 domains of heart failure care. These variables were reviewed by an international reference group with the level 1 variables providing the dataset for registration of patients with heart failure on the EuroHeart IT platform.

6.3.3 Conclusion

By means of a structured process and interaction with international stakeholders, harmonised data standards for heart failure have been developed. In the context of the EuroHeart, this will facilitate quality improvement, international observational research, registry-based randomised trials and post-marketing surveillance of devices and pharmacotherapies across Europe.

6.3.4 Keywords

Data standards. Variables. Data definitions. Heart failure. Quality of Care. EuroHeart.

6.4 One-sentence summary

The EuroHeart data standards for heart failure are a suite of internationally standardised data variables and definitions that, once implemented, will facilitate monitoring and improving the quality of care and outcomes for patients with heart failure.

Central illustration. 2021 ESC EuroHeart Data Standards for heart failure
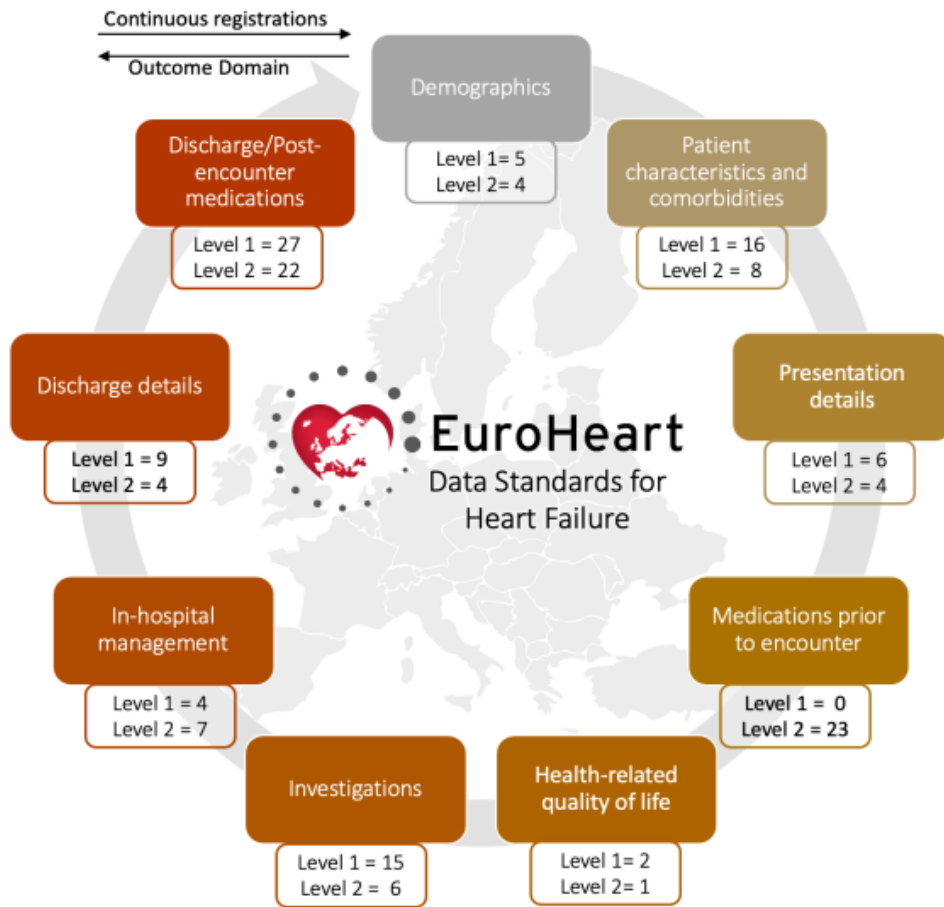
EuroHeart=European Unified Registries for Heart Care Evaluation and Randomised Trials.

6.5 Introduction

Standardised data definitions are essential for the reliable monitoring and comparison of quality of care and outcomes in observational studies and form the basis for data management in randomised controlled trials (RCT). There is lack of international consensus about the use and description of heart failure (HF) variables for patient characteristics, care delivery and outcomes.[1] As such, heterogeneity exists in the selection and definitions of data which impedes benchmarking and leads to inconsistencies that impair the interpretation of clinical studies and the acceptance of their findings.[1,2]

The 2021 American College of Cardiology (ACC) / American Heart Association (AHA) Key Data Elements and Definitions for HF provides a comprehensive list of data variables relevant to the HF care process.[3] It comprises 295 data variables, but with no hierarchical specification as to which are of a greater importance - potentially limiting their uptake in clinical practice.[3] Also, the dataset was developed in accordance with North American Clinical Practice Guidelines and healthcare system characteristics and, unlike the European Society of Cardiology (ESC) recommendations, uses a locally proposed staging system for HF that has not been adopted widely outside North America. For Europe, the Cardiology Audit and Registration Data Standards (CARDS) project in 2004 defined a set of variables for acute coronary syndrome, percutaneous coronary intervention and clinical electrophysiology, but not HF.[4] The ESC EuroHeart project is a new initiative to develop contemporary data standards for a range of cardiovascular diseases and interventions, and has to date developed international data standards for acute coronary syndrome, percutaneous coronary intervention and atrial fibrillation, with plans for the same for transcatheter aortic valve implementation and cardiovascular outcomes among other cardiovascular areas.[55,6] This document specifically presents the EuroHeart data standards for HF, which have been developed in collaboration with the Heart Failure Association (HFA) of the ESC.

6.6 Methods

A Data Science Group under the auspice of the EuroHeart project was established in August 2019. This comprised a project chair (C.G.), two medical experts (G.B. and S.A.) and a project manager.

Figure 1. EuroHeart registry structure
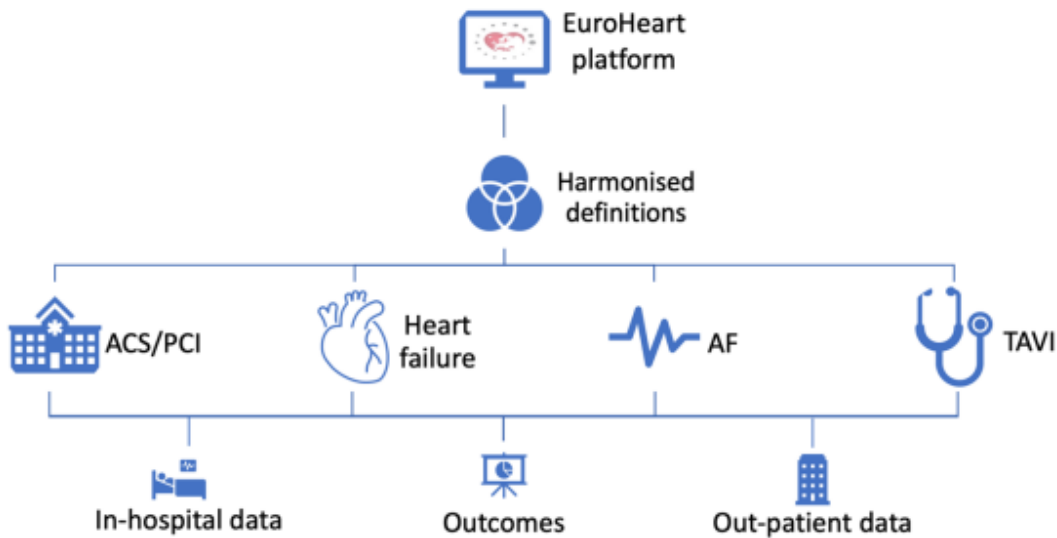
ACS=acute coronary syndrome, AF=atrial fibrillation, HCP=healthcare professional,
PCI=percutaneous coronary intervention, TAVI=transcatheter aortic valve implantation

6.6.1 Working and Reference groups

A Working Group for the development of the 2021 EuroHeart data standards for HF was
formed from members of the EuroHeart Data Science Group, HFA representatives and
selected HF experts who have experience in national or international HF registries. Names
and affiliations of the Working Group members are provided in the Appendix (Table A1).

In addition, a Reference Group comprising 44 international HF experts from 34 countries was
convened to review and provide feedback on the final set of variables, permissible values,
and definitions.

6.6.2 EuroHeart methodology

We followed the EuroHeart methodology for cardiovascular data standard development.[7] In
brief, this methodology involves: (1) identification of a cardiovascular domain for
development of data standards; (2) conduction systematic review of the literature to
synthesise a list of 'candidate' variables; (3) selection and prioritisation of variables by

domain experts using a modified Delphi method; (4) Reference Group feedback and (5) programming the final data variables into the EuroHeart IT platform.[7]

6.6.3 Scope

From the outset, the Data Science Group consulted with the Working Group to decide upon the extent of the HF registry for EuroHeart. It was agreed that the registry should capture information relating to both in-hospital and out-patient care because, unlike acute coronary syndrome for instance, HF is a chronic disease spanning multiple clinical settings, where treatment is often optimised and adjusted in response to disease progression, the development of co-morbid disease and the side-effects of therapy.

6.6.4 Systematic literature review

The EuroHeart Data Science Group conducted a systematic review of the literature on data definitions in HF (Appendix table A2). The search included studies that defined variables relevant to HF published between 01 January 2016 and 10 January 2021. These dates were chosen to capture contemporary HF management and data-collection. We included peer-reviewed randomised trials or prospective observational studies that provided definitions for at least one variable relevant to HF diagnosis, management, or outcomes. We also reviewed data dictionaries from HF registries, as well as HF quality indicators and HF Guidelines.[8-10] Following the literature search, a 'long-list' of candidate HF variables was identified for potential inclusion in the EuroHeart dataset.

6.6.5 Variable level

In EuroHeart, variables are classified as Level 1 variables if they are needed for the assessment of the quality of HF care (quality indicators), important for risk stratification, case-mix adjustment and outcome evaluation. EuroHeart provides clinical definitions for the Level 1 variables and implements them on the EuroHeart IT platform to facilitate their collection. Level 2 variables are further measures which may prove useful in selected areas or circumstances, but which are not universally available or useful. They complement quality

assessment and may have a role in observational or randomised research. Level 2 variables are defined in the EuroHeart data standard documents, but are not implemented on the EuroHeart IT platform. Given that the end users of EuroHeart will be healthcare providers, the EuroHeart platform allows for the addition of a third set of variables (Level 3) that can be centre- or country-specific, and may be needed for a national or local study or a quality improvement project (Figure 1).[7] Level 3 variables are not defined or programmed by EuroHeart.

6.6.6 Selection of the final set of variables

Using a modified Delphi method, the Working Group reviewed the list of candidate variables identified from the systematic literature review to select the final set, to decide whether they were Level 1 or Level 2, and to create permissible values and definitions. The EuroHeart criteria for data standard development (importance, evidence base, validity, reliability, feasibility and applicability) was used to guide the selection process.[7] In total, six virtual meetings were conducted between January 2021 and April 2021, with a large volume of e-mail correspondence between meetings.

6.6.7 Implementation

After arriving at the final set of variables, the Data Science Group worked with the Registry Technology groups of the EuroHeart project to programme the Level 1 variables into the EuroHeart IT platform. For each variable, details were provided to the IT team regarding the clinical setting(s) in which the variable is applicable, the permissible ranges for the numerical response options, and the inter-relationships between the chosen variables to facilitate the design of a logical prototype for data entry.

6.7 Results

The systematic review retrieved 1,715 articles. Of these, 372 met the inclusion criteria and were used to extract candidate variables (Appendix, figure A1). Of the 189 candidate variables considered for inclusion, 107 (57%) were obtained from the systematic review and

82 (43%) from Clinical Practice Guidelines and quality indicators. Following the modified Delphi method, 84 Level 1 variables (Supplementary table S1), and 79 Level 2 variables (Supplementary table S2) were selected across 9 domains of HF care.

These key domains of HF care in the EuroHeart-HF registry are: (1) Demographics, (2) Patient characteristics and comorbidities, (3) Presentation details, (4) Medications prior to encounter, (5) Health-related quality of life, (6) tests, (7) In-hospital management, (8) Discharge details and (9) Medications at discharge. With the exception of the 'In-hospital management' domain, all other domains comprise variables for the inpatient and outpatient settings as shown in Supplementary tables S1 and S2.

6.7.1 Domain 1: Demographics

This domain was aligned with the EuroHeart acute coronary syndrome and percutaneous coronary intervention registries[5] to minimise the burden of data collection when patients are enrolled in more than one EuroHeart registry (Figure 1). Some of the Level 1 variables within this domain capture patient-identifiable information to allow multi-source data linkage (Supplementary table S1).[11] Patient-identifiable data are stored and managed locally in line with each country's data-sharing regulations. Anonymised data that are aggregated at the centre- or the country-level may be shared centrally with the EuroHeart Data Centre following an agreement from both parties.

Figure 2. Sample of the variables in patient characteristics and comorbidities domain

6.7.2 Domain 2: Patient characteristics and comorbidities

This domain contains data about the patient's characteristics at the time of registration (e.g. weight), lifestyle habits (e.g. smoking), and past medical history at the time of encounter with a healthcare professional (Supplementary table S1). In addition, this domain captures information about comorbidities that may influence the decisions for patient care, improve the prediction of outcomes,[12] or allow risk adjustments when variations in performance are evaluated (Figure 2).[13] A wider list of characteristics (e.g. frailty) and comorbidities have also been selected as Level 2 variables and are presented in Supplementary table S2.

6.7.3 Domain 3: Presentation details

Many patients are likely to have received a diagnosis of HF many months or years prior to initial registration. Clinically stable patients may be enrolled in clinics. Patients with

worsening chronic HF or new-onset HF may be enrolled in a variety of settings. This domain may be completed serially for each patient encounter if resources to do so exist.

 The 'Presentation details' domain, includes the type of the clinical encounter (in-patient / out-patient) as well as the patient's clinical status at the time of assessment (initial or recurrent). Such information may be easily captured and is of a prognostic value for risk stratification and for determining the best treatment strategy (Appendix, figure A2).[14] Examples of the variables in this domain include the New York Heart Association (NYHA) class prior to encounter, as well as heart rate, systolic blood, and Killip class at the time of initial assessment (Supplementary table S1).[12, 15]

Figure 3. Sample of the variables in the Tests domain

LVEF=left ventricular ejection fraction.

6.7.4 Domain 4: Prescribed medication prior to encounter

Whilst a patient's pharmacotherapy prior to registration may provide insight about the changes in treatment which have taken place during the episode of care, the Working Group

raised concerns about the feasibility of collecting such information. Therefore, pre-registration medications were included as Level 2 variables (Supplementary table S2), unlike medications at discharge (Domain 9).

6.7.5 Domain 5: Health-related quality of life

Patient reported outcome measures, particularly health-related quality of life (HRQoL) are of importance.[16] A number of validated HF-specific measurement tools exist for HRQoL.[17] The Kansas City Cardiomyopathy Questionnaire and the Minnesota Living with Heart Failure Questionnaire are commonly used HF-specific tools to measure HRQoL.[18] Other generic tool, such as the EuroQol 5-dimensions and the short-form survey have also been used to evaluate HRQoL in patients with HF.[19] For the EuroHeart HF registry, information about whether HRQoL was assessed at each encounter and which tool was used as Level 1 category variables (Supplementary table S1) is collected. The results of the measurement are developed as Level 2 variables (Supplementary table S2). Notably, the EuroHeart IT platform allows the implementation of HRQoL questionnaires as Level 3 variables for those who have the desire, resources and appropriate licensing permissions.

Figure 4. Sample of the variables in the Discharge medications domain

6.7.6 Domain 6: Investigations

Tests such as the measurement of the left ventricular ejection fraction and plasma concentration of natriuretic peptides are important for the diagnosis of HF, assessing the effect of interventions, and evaluating prognosis.[20] Other results including renal function, serum electrolytes,[21, 22] and ECG characteristics influence decisions about treatment[23] and have a role in risk stratification (Figure 3).[24, 25] As such, these variables are included as Level 1 variables (Supplementary table S1), with other investigations (e.g. C-reactive protein) placed as Level 2 variables (Supplementary table S2).

6.7.7 Domain 7: In-hospital management

This relates to the processes of care that are delivered during episodes of hospitalisation with HF (Appendix, figure A3). That is, the prescription of loop diuretics, the implantation of cardiac therapeutic or monitoring devices, heart transplantation and the performance of

interventions such as percutaneous coronary intervention or transcatheter aortic valve implantation (Supplementary table S1). Here, there are also a number of Level 2 variables capturing information about the use of circulatory support (mechanical and pharmacological), respiratory support and renal replacement therapy during the hospital stay (Supplementary table S2).[26]

6.7.8 Domain 8: Discharge details

The 'Discharge details' domain includes information about length of hospital stay, in-hospital deaths and discharge information, such as weight and plasma concentration of natriuretic peptides at the time of discharge (Supplementary table S1). Such data are important for the evaluation of outcomes of care, but also may have a role in risk stratification.[27] Moreover, an accumulating body of evidence supports the involvement of a multidisciplinary team (e.g., cardiac rehabilitation, heart failure clinics) in the management of HF and, after hospital discharge, early follow-up with a healthcare professional.[23, 28] Recently, these aspects of care have been proposed as ESC quality indicators for HF[9] and are thus included as Level 1 variables (Supplementary table S1). Less well-established assessments (e.g., NYHA class at discharge) or highly-specialised interventions (e.g., referral to heart transplantation) are classified as Level 2 variables (Supplementary table S2).

6.7.9 Domain 9: Discharge medications

This domain forms the basis for the evaluation of performance and the assessment of adherence to the 2021 ESC Clinical Practice Guidelines and 2021 ESC quality indicators for HF (Figure 4).[9, 23] As such, for medications known to improve outcomes in patients with HF of any clinical type, data are collected not only about the class of the drug prescribed, but also about the generic name and the dose, recognising that titration of medication may be incomplete at the time of discharge (from clinic or hospital) (Supplementary table S1).[9, 23] These variables may also be of an importance for evaluating changes in care and outcomes over time.[29]

Whilst capturing information about existing contraindications to guideline recommended therapy for HF may provide a more meaningful assessment of care quality,[30] it does increase the burden of data collection and can be difficult to obtain from routine medical records. Hence, variables that address the reason for not using guideline-recommended treatments for HF when apparently indicated are Level 2 (Supplementary table S2).

6.8 Discussion

Adoption of harmonised data-collection is central to improving cardiovascular care.[25] The lack of internationally recognised standardised data definitions has led to variability and inefficiencies in the monitoring of HF epidemiology and standards of care within and between countries.[31, 32] The EuroHeart project of the ESC, by means of a structured methodology and in collaboration with the HFA has defined 84 Level 1 and 79 Level 2 variables for HF, which will be implemented on a bespoke IT platform to facilitate harmonised country-level quality improvement, international observational and registry-based randomised trials and post-marketing surveillance of devices and pharmacotherapies.

The prevalence of HF and the healthcare resources required to manage it is increasing worldwide,[33] including Europe.[34-36] The emergence of novel therapies for HF in recent years[23] and the emphasis on integrating these therapies with established care[37] has shaped the need to develop systems that ensure a continuous supply of data to monitor and improve quality of care. Clinical registries for HF highlight gaps in care-delivery and geographical variation in practice.[38-41] However, the lack of harmonised data standards for HF limits the scalability of such registries, makes international comparisons less reliable and hinders the development of registry-based randomised trials that could improve the efficiency and cost-effectiveness of both research and healthcare.[42-44]

EuroHeart provides a unique opportunity to develop an infrastructure for data-capture through which generalisable evidence can be derived to manage the growing burden of cardiovascular disease.[6] EuroHeart aims to collect longitudinal patient data such that the

patterns of care delivery over time can be captured. As opposed to a cross-sectional assessment, this model allows the continuous identification of the changes in the characteristics and type of HF, as well as in the symptoms and treatment strategy.

The EuroHeart data standards for HF have been developed in collaboration with the HFA and with involvement of experts in European HF registries and a panel of HF experts from 34 countries who have provided their feedback, taking the resources available in their own countries into consideration. Furthermore, these standards have been formally endorsed by the National Cardiac Societies from 13 ESC member countries, the ESC Patient Forum, and the ESC Committee for Young Cardiovascular Professional, highlighting the level of acceptance (and need) for the EuroHeart Data Standards for HF amongst the HF community.

The developed data standards for HF extends the existing literature by providing the European perspective to other HF quality registries, such as Get With the Guidelines (GWTG) in the United States.[45] Although EuroHeart-HF and GWTG have similar mandatory variables, some differences exist. EuroHeart-HF records information about whether patient-reported outcome measures were collected, which GWTG does not. On the other hand, GWTG mandates collection of variables capturing the rationale for not prescribing guidelines-recommended therapies for HF (e.g., beta-blockers), while these are Levels 2 variables in EuroHeart-HF.

The EuroHeart variables have been implemented on the EuroHeart IT platform to facilitate their integration with routine care. However, providing the computational phenotyping and coding details for these variables is beyond the scope of this project.[46] The Working Group acknowledges that standardised data-ontologies are needed to achieve semantic interoperability between registries, clinical trials and routinely collected electronic healthcare records (EHR).[47] Whilst individual centres can integrate the EuroHeart registry with their EHR to allow the seamless transfer of data from one system to another, this integration needs to be performed on the local level because of the substantial variation in the EHR systems

that are being used in different centres. Furthermore, we recognise the limitations of the EuroHeart methodology for data-standard development. Despite the conduct of a systematic review of the literature, we relied on expert opinion for the selection of the final set of variables and this selection may be biased. Nonetheless, we believe that a working collaboration with experts who have experience in national and international registries and quality improvement projects, and the wide representation of the Reference Group has enabled a degree of robustness to the selection process. Future Working Groups may benefit from the inclusion of patients and wider members of the multidisciplinary team for HF such as nurses, pharmacists and primary care physicians.

6.9 Conclusions

This document presents the first EuroHeart international data standards for HF which have been developed in collaboration with the HFA using a standardised methodology. The 84 Level 1 and variables have been implemented on the EuroHeart IT platform and can be adopted by HF registries around the world to harmonise the method by which HF data are captured.

6.10 References for Chapter 6

1.   Bozkurt B, Coats AJS, Tsutsui H, Abdelhamid CM, Adamopoulos S, Albert N, Anker SD, Atherton J, Böhm M, Butler J, Drazner MH, Michael Felker G, Filippatos G, Fiuzat M, Fonarow GC, Gomez-Mesa J-E, Heidenreich P, Imamura T, Jankowska EA, Januzzi J, Khazanie P, Kinugawa K, Lam CSP, Matsue Y, Metra M, Ohtani T, Francesco Piepoli M, Ponikowski P, Rosano GMC, Sakata Y, Seferović P, Starling RC, Teerlink JR, Vardeny O, Yamamoto K, Yancy C, Zhang J, Zieroth S. Universal definition and classification of heart failure: a report of the Heart Failure Society of America, Heart Failure Association of the European Society of Cardiology, Japanese Heart Failure Society and Writing Committee of the Universal Definition of Heart Failure. European Journal of Heart Failure 2021;**23**(3):352-380.

2.   Seferović PM, Vardas P, Jankowska EA, Maggioni AP, Timmis A, Milinković I, Polovina M, Gale CP, Lund LH, Lopatin Y, Lainscak M, Savarese G, Huculeci R,

Kazakiewicz D, Coats AJS. The Heart Failure Association Atlas: Heart Failure Epidemiology and Management Statistics 2019. Eur J Heart Fail 2021;**23**(6):906-914.

3.   Bozkurt B, Hershberger RE, Butler J, Grady KL, Heidenreich PA, Isler ML, Kirklin JK, Weintraub WS. 2021 ACC/AHA Key Data Elements and Definitions for Heart Failure: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Data Standards (Writing Committee to Develop Clinical Data Standards for Heart Failure). Circulation: Cardiovascular Quality and Outcomes 2021;**14**(4):e000102.

4.   Flynn MR, Barrett C, Cosio FG, Gitt AK, Wallentin L, Kearney P, Lonergan M, Shelley E, Simoons ML. The Cardiology Audit and Registration Data Standards (CARDS), European data standards for clinical cardiology practice. European Heart Journal 2005;**26**(3):308-313.

5.   Batra G, Aktaa S, Gale CP. ESC EH Data Standards for ACS and PCI Eur Heart J 2021.

6.   Wallentin L, Gale CP, Maggioni A, Bardinet I, Casadei B. EuroHeart: European Unified Registries On Heart Care Evaluation and Randomized Trials. European Heart Journal 2019;**40**(33):2745-2749.

7.   Batra G, Aktaa S, Wallentin L, Maggioni AP, Wilkinson C, Casadei B, Gale CP. Methodology for the development of international clinical data standards for common cardiovascular conditions: European Unified Registries for Heart Care Evaluation and Randomised Trials (EuroHeart). Eur Heart J Qual Care Clin Outcomes 2021.

8.   McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, Burri H, Butler J, Čelutkienė J, Chioncel O, Cleland JGF, Coats AJS, Crespo-Leiro MG, Farmakis D, Gilard M, Heymans S, Hoes AW, Jaarsma T, Jankowska EA, Lainscak M, Lam CSP, Lyon AR, McMurray JJV, Mebazaa A, Mindham R, Muneretto C, Francesco Piepoli M, Price S, Rosano GMC, Ruschitzka F, Kathrine Skibelund A, Group ESD. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: Developed by the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) With the special contribution of the Heart Failure Association (HFA) of the ESC. European Heart Journal 2021.

9.   Aktaa S, Polovina M, …, Gale CP, Coates A. European Society of Cardiology Quality indicators for the care and outcomes of adults with heart failure.

Developed by the Working Group for Heart Failure Quality Indicators in collaboration with the Heart Failure Association of the European Society of Cardiology. European Journal of Heart Failure 2021.

10.   Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, Falk V, González-Juanatey JR, Harjola V-P, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GMC, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P, Group ESD. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. European Heart Journal 2016;**37**(27):2129-2200.

11.   Mills S, Lee JK, Rassekh BM, Zorko Kodelja M, Bae G, Kang M, Pannarunothai S, Kijsanayotin B. Unique health identifiers for universal health coverage. Journal of Health, Population and Nutrition 2019;**38**(1):22.

12.   Pocock SJ, Ariti CA, McMurray JJV, Maggioni A, Køber L, Squire IB, Swedberg K, Dobson J, Poppe KK, Whalley GA, Doughty RN, Failure obotM-AGGiCH. Predicting survival in heart failure: a risk score based on 39 372 patients from 30 studies. European Heart Journal 2012;**34**(19):1404-1413.

13.   Emdin CA, Conrad N, Kiran A, Salimi-Khorshidi G, Woodward M, Anderson SG, Mohseni H, Dargie HJ, Hardman SM, McDonagh T, McMurray JJ, Cleland JG, Rahimi K. Variation in hospital performance for heart failure management in the National Heart Failure Audit for England and Wales. Heart 2017;**103**(1):55-62.

14.   Chioncel O, Mebazaa A, Maggioni AP, Harjola V-P, Rosano G, Laroche C, Piepoli MF, Crespo-Leiro MG, Lainscak M, Ponikowski P, Filippatos G, Ruschitzka F, Seferovic P, Coats AJS, Lund LH, Investigators E-E-HHFL-TR. Acute heart failure congestion and perfusion status – impact of the clinical classification on in-hospital and long-term outcomes; insights from the ESC-EORP-HFA Heart Failure Long-Term Registry. European Journal of Heart Failure 2019;**21**(11):1338-1352.

15.   The survival of patients with heart failure with preserved or reduced left ventricular ejection fraction: an individual patient data meta-analysis. Eur Heart J 2012;**33**(14):1750-7.

16.   Johansson I, Joseph P, Balasubramanian K, McMurray JJV, Lund LH, Ezekowitz JA, Kamath D, Alhabib K, Bayes-Genis A, Budaj A, Dans ALL, Dzudie A, Probstfield JL, Fox KAA, Karaye KM, Makubi A, Fukakusa B, Teo K, Temizhan A, Wittlinger T, Maggioni AP, Lanas F, Lopez-Jaramillo P, Silva-Cardoso J, Sliwa K, Dokainish H, Grinvalds A, McCready T, Yusuf S. Health-Related Quality of Life and Mortality in Heart Failure: The Global Congestive Heart Failure Study of 23 000 Patients From 40 Countries. Circulation 2021;**143**(22):2129-2142.

17.   Mackintosh A, Gibbons E, Fitzpatrick R, editors.
A Structured Review of Patient-Reported Outcome
Measures for People With Heart Failure: An Update 2009. University of Oxford, Oxford, United
Kingdom, 2009.

18.   Burns DJP, Arora J, Okunade O, Beltrame JF, Bernardez-Pereira S, Crespo-Leiro MG, Filippatos GS, Hardman S, Hoes AW, Hutchison S, Jessup M, Kinsella T, Knapton M, Lam CSP, Masoudi FA, McIntyre H, Mindham R, Morgan L, Otterspoor L, Parker V, Persson HE, Pinnock C, Reid CM, Riley J, Stevenson LW, McDonagh TA. International Consortium for Health Outcomes Measurement (ICHOM): Standardized Patient-Centered Outcomes Measurement Set for Heart Failure Patients. JACC: Heart Failure 2020;**8**(3):212-222.

19.   Moradi M, Daneshi F, Behzadmehr R, Rafiemanesh H, Bouya S, Raeisi M. Quality of life of chronic heart failure patients: a systematic review and meta-analysis. Heart Failure Reviews 2020;**25**(6):993-1006.

20.   Roberts E, Ludman AJ, Dworzynski K, Al-Mohammad A, Cowie MR, McMurray JJV, Mant J. The diagnostic accuracy of the natriuretic peptides in heart failure: systematic review and diagnostic meta-analysis in the acute care setting. BMJ : British Medical Journal 2015;**350**:h910.

21.   Rossignol P, Lainscak M, Crespo-Leiro MG, Laroche C, Piepoli MF, Filippatos G, Rosano GMC, Savarese G, Anker SD, Seferovic PM, Ruschitzka F, Coats AJS, Mebazaa A, McDonagh T, Sahuquillo A, Penco M, Maggioni AP, Lund LH. Unravelling the interplay between hyperkalaemia, renin-angiotensin-aldosterone inhibitor use and clinical outcomes. Data from 9222 chronic heart failure patients of the ESC-HFA-EORP Heart Failure Long-Term Registry. Eur J Heart Fail 2020;**22**(8):1378-1389.

22.   Ponikowski P, Kirwan BA, Anker SD, McDonagh T, Dorobantu M, Drozdz J, Fabien V, Filippatos G, Göhring UM, Keren A, Khintibidze I, Kragten H, Martinez FA, Metra M, Milicic D, Nicolau JC, Ohlsson M, Parkhomenko A, Pascual-Figal DA, Ruschitzka F, Sim D, Skouri H, van der Meer P, Lewis BS, Comin-Colet J, von Haehling S, Cohen-Solal A, Danchin N, Doehner W, Dargie HJ, Motro M, Butler J, Friede T, Jensen KH, Pocock S, Jankowska EA. Ferric carboxymaltose for iron deficiency at discharge after acute heart failure: a multicentre, double-blind, randomised, controlled trial. Lancet 2020;**396**(10266):1895-1904.

23.   McDonagh T MM, et al. 2021 ESC Guidelines for Heart Failure

24.   Collins SP, Pang PS. ACUTE Heart Failure Risk Stratification. Circulation 2019;**139**(9):1157-1161.

25.   Mosterd A, Hoes AW. Clinical epidemiology of heart failure. Heart 2007;**93**(9):1137-46.

26.   Collins SP, Jenkins CA, Harrell FE, Liu D, Miller KF, Lindsell CJ, Naftilan AJ, McPherson JA, Maron DJ, Sawyer DB, Weintraub NL, Fermann GJ, Roll SK, Sperling M, Storrow AB. Identification of Emergency Department Patients With Acute Heart Failure at Low Risk for 30-Day Adverse Events. JACC: Heart Failure 2015;**3**(10):737-747.

27.   Sawano M, Shiraishi Y, Kohsaka S, Nagai T, Goda A, Mizuno A, Sujino Y, Nagatomo Y, Kohno T, Anzai T, Fukuda K, Yoshikawa T. Performance of the MAGGIC heart failure risk score and its modification with the addition of discharge natriuretic peptides. ESC Heart Failure 2018;**5**(4):610-619.

28.   Van Spall HGC, Rahman T, Mytton O, Ramasundarahettige C, Ibrahim Q, Kabali C, Coppens M, Brian Haynes R, Connolly S. Comparative effectiveness of transitional care services in patients discharged from the hospital with heart failure: a systematic review and network meta-analysis. European Journal of Heart Failure 2017;**19**(11):1427-1443.

29.   Kapelios CJ, Laroche C, Crespo-Leiro MG, Anker SD, Coats AJS, Díaz-Molina B, Filippatos G, Lainscak M, Maggioni AP, McDonagh T, Mebazaa A, Metra M, Moura B, Mullens W, Piepoli MF, Rosano GMC, Ruschitzka F, Seferovic PM, Lund LH. Association between loop diuretic dose changes and outcomes in chronic heart failure: observations from the ESC-EORP Heart Failure Long-Term Registry. Eur J Heart Fail 2020;**22**(8):1424-1437.

30.   Aktaa S, Batra G, Wallentin L, Baigent C, Erlinge D, James S, Ludman P, Maggioni A, Price S, Weston C, Casadei B, Gale CP. European Society of Cardiology methodology for the development of quality indicators for the quantification of cardiovascular care and outcomes. 2020.

31.   Timmis A, Townsend N, Gale CP, Torbica A, Lettino M, Petersen SE, Mossialos EA, Maggioni AP, Kazakiewicz D, May HT, De Smedt D, Flather M, Zuhlke L, Beltrame JF, Huculeci R, Tavazzi L, Hindricks G, Bax J, Casadei B, Achenbach S, Wright L, Vardas P. European Society of Cardiology: Cardiovascular Disease Statistics 2019. European heart journal 2020;**41**(1):12-85.

32.   Seferović PM, Vardas P, Jankowska EA, Maggioni AP, Timmis A, Milinković I, Polovina M, Gale CP, Lund LH, Lopatin Y, Lainscak M, Savarese G, Huculeci R, Kazakiewicz D, Coats AJS, countries icwtNHFSotEm. The Heart Failure Association Atlas:

Heart Failure Epidemiology and Management Statistics 2019. European Journal of Heart Failure;**n/a**(n/a).

33.   Tromp J, Bamadhaj S, Cleland JGF, Angermann CE, Dahlstrom U, Ouwerkerk W, Tay WT, Dickstein K, Ertl G, Hassanein M, Perrone SV, Ghadanfar M, Schweizer A, Obergfell A, Lam CSP, Filippatos G, Collins SP. Post-discharge prognosis of patients admitted to hospital for heart failure by world region, and national level of income and income disparity (REPORT-HF): a cohort study. Lancet Glob Health 2020;**8**(3):e411-e422.

34.   Conrad N, Judge A, Tran J, Mohseni H, Hedgecott D, Crespillo AP, Allison M, Hemingway H, Cleland JG, McMurray JJV, Rahimi K. Temporal trends and patterns in heart failure incidence: a population-based study of 4 million individuals. Lancet 2018;**391**(10120):572-580.

35.   Lawson CA, Zaccardi F, Squire I, Ling S, Davies MJ, Lam CSP, Mamas MA, Khunti K, Kadam UT. 20-year trends in cause-specific heart failure outcomes by sex, socioeconomic status, and place of diagnosis: a population-based study. Lancet Public Health 2019;**4**(8):e406-e420.

36.   Savarese G, Lund LH. Global Public Health Burden of Heart Failure. Card Fail Rev 2017;**3**(1):7-11.

37.   Vaduganathan M, Claggett BL, Jhund PS, Cunningham JW, Pedro Ferreira J, Zannad F, Packer M, Fonarow GC, McMurray JJV, Solomon SD. Estimating lifetime benefits of comprehensive disease-modifying pharmacological therapies in patients with heart failure with reduced ejection fraction: a comparative analysis of three randomised controlled trials. Lancet 2020;**396**(10244):121-128.

38.   Chioncel O, Mebazaa A, Harjola V-P, Coats AJ, Piepoli MF, Crespo-Leiro MG, Laroche C, Seferovic PM, Anker SD, Ferrari R, Ruschitzka F, Lopez-Fernandez S, Miani D, Filippatos G, Maggioni AP, Investigators obotEHFL-TR. Clinical phenotypes and outcome of patients hospitalized for acute heart failure: the ESC Heart Failure Long-Term Registry. European Journal of Heart Failure 2017;**19**(10):1242-1254.

39.   Fu M, Vedin O, Svennblad B, Lampa E, Johansson D, Dahlström U, Lindmark K, Vasko P, Lundberg A, Costa-Scharplatz M, Lund LH. Implementation of sacubitril/valsartan in Sweden: clinical characteristics, titration patterns, and determinants. ESC Heart Fail 2020;**7**(6):3633-43.

40.   Kapelios CJ, Laroche C, Crespo-Leiro MG, Anker SD, Coats AJS, Díaz-Molina B, Filippatos G, Lainscak M, Maggioni AP, McDonagh T, Mebazaa A, Metra M, Moura B, Mullens W, Piepoli MF, Rosano GMC, Ruschitzka F, Seferovic PM, Lund LH, Group HFL-

TRI. Association between loop diuretic dose changes and outcomes in chronic heart failure: observations from the ESC-EORP Heart Failure Long-Term Registry. European Journal of Heart Failure 2020;**22**(8):1424-1437.

41.   Emdin CA, Conrad N, Kiran A, Salimi-Khorshidi G, Woodward M, Anderson SG, Mohseni H, Dargie HJ, Hardman SMC, McDonagh T, McMurray JJV, Cleland JGF, Rahimi K. Variation in hospital performance for heart failure management in the National Heart Failure Audit for England and Wales. Heart 2017;**103**(1):55-62.

42.   Parissis J, Farmakis D, Triposkiadis F. Heart failure registries: how far can we go? European Journal of Heart Failure 2016;**18**(6):626-628.

43.   Bowman L, Baras A, Bombien R, Califf RM, Chen Z, Gale CP, Gaziano JM, Grobbee DE, Maggioni AP, Muse ED, Roden DM, Schroeder S, Wallentin L, Casadei B. Understanding the use of observational and randomized data in cardiovascular medicine. European heart journal 2020;**41**(27):2571-2578.

44.   Lund LH, Oldgren J, James S. Registry-Based Pragmatic Trials in Heart Failure: Current Experience and Future Directions. Current heart failure reports 2017;**14**(2):59-70.

45.   Get With The Guidelines Heart Failure. https://www.heart.org/-/media/files/professional/quality-improvement/get-with-the-guidelines/get-with-the-guidelines-hf/clinical-tools/gwtghffullcrfjuly2018ucm_457483.pdf?la=en.

46.   Liyanage H, Krause P, de Lusignan S. Using ontologies to improve semantic interoperability in health data. BMJ Health & Care Informatics 2015;**22**(2):309-315.

47.   Fitzpatrick T, Perrier L, Shakik S, Cairncross Z, Tricco AC, Lix L, Zwarenstein M, Rosella L, Henry D. Assessment of Long-term Follow-up of Randomized Trial Participants by Linkage to Routinely Collected Data: A Scoping Review and Analysis. JAMA Network Open 2018;**1**(8):e186019-e186019.

Chapter 7. 2020 Update of the quality indicators for acute myocardial infarction: a position paper of the Association for Acute Cardiovascular Care: the study group for quality indicators from the ACVC and the NSTE-ACS guideline group

François Schiele, Suleman Aktaa, Xavier Rossello, Ingo Ahrens, Marc J Claeys, Jean-Philippe Collet, Keith A A Fox, Chris P Gale, Kurt Huber, Zaza Iakobishvili, Alan Keys, Ekaterini Lambrinou, Sergio Leonardi, Maddalena Lettino, Frederick A Masoudi, Susanna Price, Tom Quinn, Eva Swahn, Holger Thiele, Adam Timmis, Marco Tubaro, Christiaan J M Vrints, David Walker, Hector Bueno, ESC Scientific Document Group, Sigrun Halvorsen, Tomas Jernberg, Jarle Jortveit, Mai Blöndal, Borja Ibanez, Christian Hassager

7.1 Summary of the publication:

- This paper describes an international collaboration to develop quality indicators for acute myocardial infarction (AMI) using the methodology presented in Chapter 4.
- Overall, 26 quality indicators were developed across 7 domains of AMI care and are provided here with their collection specifications.

7.2 Publication status:

7.3 Abstract

7.3.1 Aims

Quality indicators (QIs) are tools to improve the delivery of evidence-base medicine. In 2017, the European Society of Cardiology (ESC) Association for Acute Cardiovascular Care (ACVC) developed a set of QIs for acute myocardial infarction (AMI), which have been

evaluated at national and international levels and across different populations. However, an update of these QIs is needed in light of the accumulated experience and the changes in the supporting evidence.

7.3.2 Methods and results

The ESC methodology for the QI development was used to update the 2017 ACVC QIs. We identified key domains of AMI care, conducted a literature review, developed a list of candidate QIs, and used a modified Delphi method to select the final set of indicators. The same seven domains of AMI care identified by the 2017 Study Group were retained for this update. For each domain, main and secondary QIs were developed reflecting the essential and complementary aspects of care, respectively. Overall, 26 QIs are proposed in this document, compared to 20 in the 2017 set. New QIs are proposed in this document (e.g. the centre use of high-sensitivity troponin), some were retained or modified (e.g. the in-hospital risk assessment), and others were retired in accordance with the changes in evidence [e.g. the proportion of patients with non-ST segment elevation myocardial infarction (NSTEMI) treated with fondaparinux] and the feasibility assessments (e.g. the proportion of patients with NSTEMI whom risk assessment is performed using the GRACE and CRUSADE risk scores).

7.3.3 Conclusion

Updated QIs for the management of AMI were developed according to contemporary knowledge and accumulated experience. These QIs may be applied to evaluate and improve the quality of AMI care.

7.3.4 Keywords

Quality indicators, Quality improvement, Myocardial infarction

7.4 Backgrounds

Assessing the quality of care has become mandatory in many healthcare systems and is an intrinsic component of quality improvement. In 2017, the European Society of Cardiology (ESC) Association for Acute Cardiovascular Care (ACVC) published a position paper defining quality indicators (QIs) for acute myocardial infarction (AMI)[1] with the aim of supporting quality improvement, and based on the assumption that rigorous measurement is fundamental. This was the first QI initiative undertaken within the ESC by one of its constituent associations, concordant with the mission statement of the ACVC to 'improve the quality of care of patients with acute cardiovascular disease'. The ACVC Study Group on QIs decided that QIs should not only reflect high-grade recommendations in ESC guidelines but also should consider the domains of care for which there is potential room for improvement, and where measurement can be performed using existing registries or databases. As a result, the ACVC QIs covered seven domains of care, including centre organization, reperfusion/invasive strategies, risk assessment, antithrombotic selection, secondary prevention, and patient experience. Lastly, two composite indicators and one outcome were defined.

7.5 Objectives

The 2017 ESC ACVC QIs were used to support quality assessment and improvement at national[2–7] and international levels,[8] and across different populations.[9] Various studies evaluating the ESC ACVC QIs using existing registries have shown that most QIs can be captured, and, thus can guide the development of future cardiovascular registries.[10] In addition, the ESC ACVC QIs identified gaps in care delivery within and between countries, highlighting missed opportunities to improve clinical outcomes.[2,3,5,9]

Three years after the publication of the initial set of QIs, the ACVC study group on QI considered that an update was timely, because the ESC has updated its Clinical Practice Guidelines for the management of patients with AMI (with and without ST-segment elevation), and published the methodology by which the ESC QIs should be developed.[11] Hence, the QI update was driven by the experience accumulated from assessment of previous QIs in existing registries (Supplementary material online, Table S1),

the ESC methodology for QI development[11] as well as other methodologies,[12,13] and to ensure the validity of the measurements.[14]

7.6 Methods

The 2017 ESC ACVC QIs were updated using the RAND/University of California–Los Angeles (UCLA) appropriateness method,[15,16] which is recommended by the ESC methodology for QI development,[11] and combines best scientific evidence with the collective judgement of experts using the modified Delphi process.[17]

7.7 The 2020 ESC ACVC QIs for AMI

The seven domains of AMI care identified by the 2017 Study Group were retained. The list of the main and secondary QIs for each domain are presented in *Figure 1* and Supplementary material online, Table S2, with the definitions of numerators and denominators, and the corresponding ESC guidelines recommendations.

Main and secondary Quality Indicators for each domain. Timely reperfusion is defined as time from ST-segment elevation myocardial infarction diagnosis to (i) infarct-related artery wire crossing: <60 min for patients presenting at a primary percutaneous coronary intervention hospital, or (ii) <90 min for patients diagnosed either in a non-percutaneous coronary intervention hospital or in the out-of-hospital setting, or (iii) injection of the bolus of fibrinolysis <10 min for patients reperfused with fibrinolysis.

Figure 1. Main and secondary Quality Indicators for each domain.

Timely reperfusion is defined as time from ST-segment elevation myocardial infarction diagnosis to (i) infarct-related artery wire crossing: <60 min for patients presenting at a primary percutaneous coronary intervention hospital, or (ii) <90 min for patients diagnosed either in a non-percutaneous coronary intervention hospital or in the out-of-hospital setting, or (iii) injection of the bolus of fibrinolysis <10 min for patients reperfused with fibrinolysis.

7.7.1 Domain 1: centre organization
7.7.1.1 Network organization
7.7.1.1.1 Clinical relevance

In the setting of acute coronary syndrome (ACS), a network organization has a beneficial impact through the availability of different capacities, such as the use of a single telephone emergency number, early identification of ACS, transportation with ambulances with basic or advanced life support capability, direct access to catheterization laboratory, and delivery of care following written protocols.[18] This organization facilitates the selection of the appropriate reperfusion strategy, and reduces times to reperfusion in ST-segment elevation myocardial infarction (STEMI) patients.[19–21] Furthermore, local, regional, or national written protocols can help to reduce delays, reduce variations in the quality of care,[22] and improve the quality of secondary prevention in post-discharge settings.[23]

7.7.1.1.2 Specific aspects for selection

Two QIs are related to participation in a regional network: the main QI (1) as a measure of network organization for the management of ACS, including written protocols; and the assessment of essential components of effective systems of STEMI care.[18] Similar QIs were already included in the 2017 ACVC QI list, are supported by class IC recommendations and also feature in the list of QIs in the 2017 STEMI[24] and 2020 non-ST segment elevation ACS (NSTE-ACS) ESC guidelines.[25]

7.7.1.2 Availability of high-sensitivity troponin assay
7.7.1.2.1 Clinical relevance

Cardiac troponin (cTn) elevation is a key diagnostic and prognostic feature in NSTE-ACS. Only 'high-sensitivity' cardiac troponin (hs-cTn) assays have imprecision of <10% at the 99th percentile of the upper reference limit and have the ability to quantify cTn levels in >50% of apparently healthy individuals. Data have shown that more sensitive cardiac troponin assays, such as hs-troponin assay increase diagnostic accuracy with greater and more rapid ability to 'rule-in' or 'rule-out' myocardial infarction.[26]

7.7.1.2.2 Specific aspects for selection

Main QI (2) relates to the availability of hs-cTn assay measured at centre level. The use of hs-cTn over less sensitive assays is recommended by guidelines.[25] This QI is also included in the QIs list of the 2020 ESC Guidelines for NSTE-ACS.[25]

7.7.1.3 Pre-hospital interpretation of Electrocardiogram (ECG)

7.7.1.3.1 Clinical relevance

Timely diagnosis for patients with STEMI is determinant for clinical outcomes. The ESC guidelines for STEMI recommend acquiring and interpreting a 12-lead ECG as soon as possible following first medical contact (FMC) to facilitate early diagnosis and risk stratification.[23,24]

7.7.1.3.2 Specific aspects for selection

Main QI (3) captures the availability of systems of care in which STEMI diagnosis can be performed in the pre-hospital settings, with the initiation of appropriate treatment pathways.

7.7.1.4 Participation in a regular registry or quality assessment programme

7.7.1.4.1 Clinical relevance

Participation in a registry for quality assessment improves adherence to guidelines.[27] Major improvements in hospital performance and mortality rates have been reported over short periods of time, narrowing the gap between the quality of care delivered between hospitals[28,29] and the association between the participation in a quality programme for timely reperfusion therapy and clinical improvement has been shown.[23] In addition, the assessment of reperfusion times for STEMI patients is an important and measurable component of STEMI care.

7.7.1.4.2 Specific aspects for selection

The two secondary QIs cover the quality improvement programme: participation in a regular registry, and regular monitoring of times to reperfusion. These QIs were already included in the 2017 ESC STEMI guidelines.[24]

7.7.2 Domain 2: invasive strategy

7.7.2.1 Reperfusion for ST segment elevation myocardial infarction patients

7.7.2.1.1 Clinical relevance

Reperfusion therapy should be administered to all eligible patients presenting with STEMI. Primary percutaneous coronary intervention (PCI) is the preferred option, provided it can be performed expeditiously. Based on considerable evidence, the ESC guidelines recommend time targets for reperfusion therapy based on the strategy used and the initial healthcare facility to which the STEMI patient was admitted. As such, time from STEMI diagnosis to wire crossing is recommended to be <60 min for patients presenting at a primary PCI hospital, whereas it should be <90 min for patients diagnosed either in a non-PCI hospital or in the out-of-hospital setting. For patients treated by fibrinolysis, the recommended time between STEMI diagnosis and initiation of fibrinolysis is <10 min.[24]

7.7.2.1.2 Specific aspects for selection

Both reperfusion and time to reperfusion have been used as key indicators of quality in patients with STEMI in most sets of QIs or performance measures (PMs).[1,30,31] Main QI (1) assesses the proportion of patients with STEMI admitted within 12 h of the onset of symptoms and treated with reperfusion (irrespective of the timing). Main QI (2) assesses 'timely' reperfusion, defined for reperfusion strategy, by primary PCI or fibrinolysis.[32] The time targets correspond to those recommended by the ESC Guidelines.[24] From a practical viewpoint, the measure of the proportion of patients with STEMI reperfused among those eligible has been measured in all publications reporting ESC-ACVC QIs assessment and ranged from 57% to 98%.

7.7.2.2 Early invasive strategy in non-ST segment elevation myocardial infarction patients

7.7.2.2.1 Clinical relevance

Patients with non-ST segment elevation myocardial infarction (NSTEMI) are on the spectrum of high-risk NSTE-ACS and, therefore, eligible for an invasive approach. The benefit of a routine over a selective invasive approach has been shown in high-risk patients and the timing of the strategy is split into immediate (for patients with very high-risk features such as persistent chest pain), early (<24 h after admission for patients with high-risk features, including those with diagnosis of NSTEMI) or <72 h.

7.7.2.2.2 Specific aspects for selection

Main QI (3) measures the use of an early invasive strategy and is therefore suitable for use in patients with NSTEMI. Compared with the previous QI list, the timing has been set at <24 h (instead of <72 h), in line with the ESC Guidelines.[25,33]

7.7.2.3 The use of radial access

7.7.2.3.1 Clinical relevance

The use of radial access is a new QI in this domain. It is justified by the reduction in bleeding and vascular complications achieved with the radial approach,[34,35] especially in ACS.[36]

7.7.2.3.2 Specific aspects for selection

This new QI is likely to be easy to assess and will be applicable in the majority of patients, both STEMI and NSTE-ACS. Supported by ESC Guidelines, the 'radial-first strategy' has been referred to as 'best practice' in a position paper from the American Heart Association (AHA).[37]

7.7.3 Domain 3: in-hospital risk assessment

7.7.3.1 Assessment of left ventricular ejection fraction

7.7.3.1.1 Clinical relevance

Left ventricular ejection fraction (LVEF) assessment is important for both prognostic and therapeutic reasons.

7.7.3.1.2 Specific aspects for selection

This QI was already in the previous ESC ACVC QIs set.

7.7.3.2 Assessment of LDL-cholesterol

7.7.3.2.1 Clinical relevance

LDL-cholesterol (LDL-c) is considered a causal factor for atherosclerosis.[38] Early and intense reduction of LDL-c as soon as possible after admission has been shown to be effective. The utility of LDL-c assessment is therefore not for the prescription of statins, but rather to have an initial reference value (called 'baseline', i.e. without the effect of LDL-C lowering therapy) and to estimate the potential likelihood of reaching the 2019 ESC guidelines target,[39] with a view to using additional therapies such as the combination with ezetimibe[40] or the early (within 4–6 weeks after discharge) introduction of a proprotein convertase subtilisin–kexin type 9 (PCSK9) inhibitor.[39]

7.7.3.2.2 Specific aspects for selection

This QI is new and applicable in all patients.

7.7.3.3 Risk assessment using a validated score

7.7.3.3.1 Clinical relevance

Patient stratification using validated scores is important, both for ischaemic and haemorrhagic risks. Thus, the use of a validated risk score is recommended by the ESC Guidelines (Class IA) for prognosis.

7.7.3.3.2 Specific aspects for selection

In the 2017 ESC ACVC QIs, two specific validated scores were included as independent QIs (i.e. the GRACE risk score for ischaemic risk, and the CRUSADE score for haemorrhagic risk). The Study Group decided to retire the specification of the tool used, but to keep the recommendation to perform risk assessment using a validated method.

7.7.4 Domain 4: antithrombotic treatment during hospitalization

7.7.4.1 Proportion of patients with 'adequate P2Y12 inhibition'

7.7.4.1.1 Clinical relevance

In patients with AMI, dual antiplatelet therapy (DAPT) is recommended as soon as possible when ACS is suspected. Among patients eligible for DAPT, the choice between clopidogrel, prasugrel, and ticagrelor is mainly driven by the results of randomized studies comparing clopidogrel to prasugrel[41,42] and to ticagrelor,[43,44] and the bleeding risk. 'Adequate P2Y$_{12}$ inhibition' is defined as the appropriate selection of the P2Y$_{12}$ inhibitor in accordance with the 2020 ESC Guidelines:

- the use of ticagrelor in patients without a contraindication (e.g. previous haemorrhagic stroke, high bleeding risk, treatment with fibrinolysis, or concomitant use of oral anticoagulation).
- the use of prasugrel in PCI-treated AMI patients without previous haemorrhagic or ischaemic stroke, high bleeding risk (patients $\geqslant$ 75 years of age and/or with body weight < 60 kg), fibrinolysis or oral anticoagulation
- the use of clopidogrel when there is no indication for prasugrel or ticagrelor.

7.7.4.1.2 Specific aspects for selection

Given the importance of selecting the most appropriate P2Y$_{12}$ inhibitor in patients with coronary artery disease (i.e. tailored to the patient's ischaemic and bleeding risks), a Task Force of the ESC and European Association for Cardio-Thoracic Surgery published a focused update on DAPT,[45] in line with the STEMI and NSTE-ACS Guidelines, all supporting the concept of 'adequate P2Y$_{12}$ inhibition'. This QI already featured in the previous ACVC QIs set, and is included in the list of QIs of the 2020 ESC Guidelines for NSTE-ACS. Experience with the assessment of the ACVC QIs shows that this QI may be measured from many, but not all, existing registries, depending on the quality of the variables recorded (Supplementary material online, Table S1).

7.7.4.2 Parenteral anticoagulant at (or before) admission

7.7.4.2.1 Clinical relevance

Parenteral anticoagulation is recommended in AMI from the time of diagnosis up to PCI unless otherwise indicated. Different anticoagulant agents (unfractionated heparin, enoxaparin, fondaparinux, or bivalirudin) may be used in this setting. Parenteral anticoagulation is recommended for all patients, in addition to antiplatelet therapy, at the time of diagnosis.

7.7.4.2.2 Specific aspects for selection

This QI replaces the previous QI relating to fondaparinux because the ESC Guidelines no longer express a strong preference for any particular drug.

7.7.4.3 Patients discharged on dual antiplatelet therapy

7.7.4.3.1 Clinical relevance

The need for DAPT is a cornerstone of AMI management at the time of hospital admission and discharge, unless the patient is deemed to be at high bleeding risk.[45]

7.7.4.3.2 Specific aspects for selection

This QI is a complement to main QI (1), with the particular interest of being more straightforward, easier to assess, and including the prescription of aspirin. Contrary to 'adequate $P2Y_{12}$ inhibition', this QI is reported in all published assessments. Notably, patients treated with oral anticoagulation are excluded because several alternative strategies are available, including some without aspirin.

7.7.4.4 Mention the duration of dual antiplatelet therapy in the discharge letter

7.7.4.4.1 Clinical relevance

Although the standard duration of DAPT after AMI is 12 months, it must be determined according to the patient's risk and ischaemic profile, and may range from 1 to 48 months.[45] At discharge, a shortening or prolongation of the DAPT duration may be proposed according to specific tools, depending on the patient's characteristics, coronary anatomy, the extent of coronary artery disease, or PCI procedure.

7.7.4.4.2 Specific aspects for selection

Poor quality discharge letters represent a deficit in communication between hospital specialists and primary care physicians.[46] The post-AMI discharge document is a crucial element to ensuring transmission of medical information to the corresponding physician or the patient, including the ischaemic and haemorragic risk as perceived during the acute hospitalization. Standardization of the discharge document, including insights about the type and duration of the anti-thrombotic treatment has been highlighted by the recent ESC guidelines[25] and its routine application has been accepted by a national group in France.[47]

7.7.5 Domain 5: secondary prevention discharge treatments

After AMI, patients remain at very high-risk and secondary prevention treatment is crucial for reducing mortality and further cardiovascular events. The QIs in this domain cover the prescription of three therapeutic classes, in addition to the anti-thrombotic treatment.

7.7.5.1 High-intensity statins

7.7.5.1.1 Clinical relevance

Statins are fundamental to the treatment of atherosclerosis. In the setting of AMI, high intensity statins are safe and provide better prevention as compared to moderate intensity,[48] irrespective of admission LDL-c. Despite the body of evidence regarding the beneficial effects of lowering LDL-c[38] by statins (alone or in combination with ezetimibe or PCSK9 inhibitors), their use in current registries remains sub-optimal and the proportion of patients at LDL-c target is low: 32% in men and 23% in women in the EuroAspire V registry.[49]

7.7.5.1.2 Specific aspects for the selection

This QI was already in the 2017 ESC-ACVC list. Experience of assessment suggests that this QI cannot be assessed from some registries, because the type and dose of statins prescribed at discharge were not recorded. In addition, it is likely that intolerance to high-intensity statins was also not recorded. In registries reporting this QI, the rate of prescription of statins (any intensity) is high, but at high intensity in only about half of the patients.[49]

7.7.5.2 Patients with left ventricular ejection fraction <40% who are discharged from hospital on angiotensin-converting enzyme

inhibitors (or angiotensin receptor antagonists if intolerant of ACEI)

7.7.5.2.1 Clinical relevance

Angiotensin-converting enzyme inhibitors (ACEIs) improve survival in patients with impaired LV systolic function, defined by an LVEF <40%. Initiation of ACEI [or angiotensin receptor antagonists (ARBs) in patients intolerant to ACEI] and prescription at the time of hospital discharge is beneficial among patients with an LVEF <40%.

7.7.5.2.2 Specific aspects for the selection

This QI was already in the 2017 ESC ACVC list, supported by a Class IIA recommendation. In practice, the proportion of patients with LVEF ≤40% is 15–20% in current registries; therefore, the QI applies only to a subset of high-risk patients.

7.7.5.3 Patients with left ventricular ejection fraction <40% who are discharged from hospital on beta-blockers

7.7.5.3.1 Clinical relevance

Beta-blockers remain a standard of care following AMI, however, the evidence was based on studies performed before the era of reperfusion.[50] In a recent large-scale observational study, a benefit with beta-blockade in post-AMI patients was shown, but only among patients with LV dysfunction.[51]

7.7.5.3.2 Specific aspects for the selection

This QI was already in the 2017 ESC-ACVC list. The exact type of beta-blocker indicated for patients with LV systolic dysfunction was not specified for the QI, given the complexity of the measure.

7.7.6 Domain 6: patient satisfaction

7.7.6.1 Feedback regarding the patient's experience and systematic assessment of health-related quality of life

7.7.6.1.1 Clinical relevance

The concept of 'patient-centred care' is based on focusing care on the patient rather than on the disease. In this approach, patients are actively involved in their own care, congruent with the principle of shared-decision making. Patient-reported outcomes (PRO, which can be seen as an assessment of the perceived level of impairment, disability, and quality of life) and patient-reported experience (PRE, which gather information on the care)[52] can be considered as QIs. To this end, PRO and PRE can be measured through patient satisfaction questionnaires.[53] In the setting of AMI, patient satisfaction PRO and PRE are associated with other indices of quality of care.[54,55]

7.7.6.1.2 Specific aspects for selection

This QI was already included in the 2017 ESC-ACVC QI list, but only partial assessment has been reported, except for 'referral to rehabilitation programmes' and 'pain control'. The use of a health-related quality of life questionnaire at discharge is reported in the long-tErm follow-up of antithrombotic management patterns In acute CORonary syndrome patients (EPICOR) and the Evaluation of the Methods and Management of Acute Coronary Events (EMMACE)-3 and -4 registries.[8] The Study Group has defined the main QI as a 4-item composite indicator including referral to a rehabilitation programme, patient information about the disease, treatment, and pain control. The secondary QI is the assessment of the health-related quality of life in all patients using a validated instrument.

7.7.6.2 Discharge letter sent to the patient

7.7.6.2.1 Clinical relevance

Copying the hospital discharge letter to the patient is an essential part of communication. The UK Academy of Medical Royal Colleges has published guidance on this topic, considering that excellent written communication is essential to good quality of care and that the letter would be better addressed to the patient and not to the corresponding physician ('Write to, not about').[56] This practice of writing to the patient, compared with writing to the clinician, increases patient satisfaction, improves both the doctor-patient relationship and trust, and reduces anxiety.[57]

7.7.6.2.2 Specific aspects for selection

To date, no similar QI or PM has been defined, but it appears to be feasible even if this currently remains undetermined.

7.7.7 Domain 7: outcome and composite quality indicator

7.7.7.1 Outcomes quality indicator

Thirty-day mortality rate adjusted for a validated risk score is unchanged.

7.7.7.1.1 Clinical relevance

All-cause mortality is a self-evident assessment of quality of care and the most easily interpretable, objective and unambiguous indicator. While the accuracy of mortality as a direct measure of quality of care is controversial,[58] the association between the ESC ACVC composite QI and the risk-adjusted outcomes is important.

7.7.7.1.2 Specific aspects for the selection

All-cause mortality is easy to assess and this measure provides essential information at broad-level (i.e. region-, country-, or continent-levels). At centre-level, the interpretation may be more challenging and less generalizable, depending on the size of the denominator.

7.7.7.2 Composite quality indicator

Composite quality indicators (CQIs) summarize information from different domains into a single measure. Thus, it is possible to expand the scope of the measure by including a broad range of individual indicators, to provide a single metric that enables temporal comparisons, classification of centres, and demonstration of the association between the CQI and outcomes, a way of reassuring clinicians about the validity of process instead of clinical outcome assessment.[13]

7.7.7.2.1 Clinical relevance

By reducing the information from all domains into a single CQI, the areas for specific improvement may be obscured. Among the different types of composites, the opportunity-based and the all-or-none are the most frequently recommended for the quality of care assessment.[59,60] Since the two methods, while associated,[61] provide different approaches, both types of CQI have been maintained in the updated version. The main CQI is an opportunity-based score, where all domains are represented and have the same weight (except in patients with LVEF ≤40% in whom two additional items are required, giving more weight to the secondary prevention domain). This design has the advantage of increasing the number of items, which may vary according to the patient characteristics and the database used. The secondary CQI has an all-or-none design with only three individual QIs, but all three are deemed clinically relevant: the timely reperfusion or invasive strategy, the prescription of the 'appropriate' $P2Y_{12}$ inhibition and high-intensity statins. With this CQI, only patients who received all three processes are considered as a success and therefore, this method best reflects the patient's interest and tracks excellence.

7.7.7.2.2 Specific aspects for the selection

In the previous experience of assessment of the 2017 ESC ACVC QIs, the opportunity-based CQI was reported in most cases and, after transformation into categories, was associated with

mortality.[2,3,5,7,8] The Study Group decided that the opportunity-based CQI should contain one item per domain, namely the most adequate to capture quality, despite the challenges for assessment, and considering that this was more an issue related to the design of current registries than the definition of the CQI.

7.8 Comparison with previous quality metrics definitions and future developments

The comparison of QI selection between the ESC ACVC 2020 and ESC-ACCA 2017, the American College of Cardiology (ACC) and AHA 2017[62] and Canadian Cardiovascular Society (CCS) 2008 is presented in *Table 1*.

Table 1. Quality metrics selected by ESC-ACVC 2020, ESC ACCA 2017, ACC/AHA 2017, and CCS 2008

Domain	Indicators	ACCA 2020	ACCA 2017	ACC/ AHA	CCS 2008
Center organization	Network	🟩	🟩	🟩	
	Availability hs-Tn	🟩		🟧	
	Pre-hospital interpretation of ECG	🟩	🟩		🟧
	Registry/quality programme	🟩	🟩	🟩	
	Assessment times for reperfusion	🟩	🟩	🟩	
Reperfusion – invasive coronary strategy	STEMI with reperfusion	🟩	🟩	🟩	🟩
	Timely reperfusion by PCI	🟩	🟧	🟩	🟧
	Time for fibrinolytic therapy	🟥	🟩	🟩	🟩
	Door to needle time	🟥	🟩	🟩	
	Door in Door out time	🟥	🟩	🟩	
	Time to PCI transferred patient	🟩	🟩	🟩	
	Invasive strategy <24h	🟩	🟧	🟩	
	Radial access	🟩			
	FMC to arterial access (STEMI)	🟩	🟩	🟩	🟧

Category	Indicator	Col1	Col2	Col3	Col4
Risk assessment	LVEF assessment	Green	Green	Green	White
	LDL-c assessment	Green	Green	Red	White
	Risk assessment with a score	Green	Green	Green	Green
Antithrombotics	Adequate P2Y12	Green	Green	Orange	White
	Aspirin admission	White	White	Green	Green
	Parenteral anticoagulation	Green	Orange	Red	White
	DAPT at discharge	Green	Green	Green	White
	Mention about DAPT duration	Green	White	White	White
Secondary Prevention	High intensity statins	Green	Green	Green	Orange
	Aspirin discharge	White	White	Green	Green
	ACEI/ARB if LVEF≤0.40	Green	Green	Green	White
	Aldosterone antagonist at discharge	White	White	Green	White
	Beta-blockers if LVEF≤0.40	Green	Green	Orange	Orange
Patient satisfaction	Feedback	Green	Orange	White	White
	Cardiac rehabilitation	Green	Green	Green	White
	Smoking cessation advice	White	White	Red	Green
	Quality of life	Green	White	White	White
	Discharge letter	Green	White	White	White
Cardiac arrest	Immediate angiography	White	White	Green	White
	Hypothermia	White	White	Green	White
Composite Indicator	Opportunity-based	Green	Orange	White	White
	All or none	Green	Orange	White	White
Outcomes	30 day adjusted mortality	Green	Green	White	Orange

In bold, the Main QIs in 2020. Green indicates quality metric with comparable definition to ESC ACVC 2020; in orange, quality metric selected items with a different definition, in white, no corresponding quality metric. In red, withdrawn indicators

- *Centre organization*: compared to the 2017 selection, the QI on availability of hs-cTn in the centre is new.
- *Reperfusion/invasive strategy*: the number of QIs has been reduced and the indicators related to the time for reperfusion have been aligned with the 2017 ESC GL and

simplified as compared to the 2017 definition. As compared to the ACC/AHA measure set, the starting time is the initial diagnosis of STEMI (vs. first medical contact for ACC/AHA) and the thresholds are different: <60 min to wire crossing the lesion for patients presenting at a primary PCI hospital, or <90 min for patients diagnosed either in a non-PCI hospital or in the out-of-hospital setting who were then transferred to a PCI-capable centre, and <10 min in case of reperfusion with fibrinolysis. The radial access QI is new and has not been presented in other selections. The reduction of the time to invasive approach to 24 h in NSTEMI is in line with comparable PM from the ACC/AHA.

- *Risk assessment*: the main change is the simplification of the overall risk assessment, without specifying specific risk scores. The assessment of LDL-c has been added as a Main QI. The ESC Guidelines recommend this measure because available evidence supports the addition of ezetimibe and PCSK9 inhibitors on top of high-intensity statins in selected patients.

- *Antithrombotic treatment during hospitalization*: the prescription of 'adequate $P2Y_{12}$ inhibition', already in the 2017 list, has been confirmed, despite the complexity of the assessment. The selection of an 'adequate' $P2Y_{12}$ inhibitor is also in the ACC/AHA PM list with two different definitions, both focusing on the safety side, without considering the potential benefit of using a more potent $P2Y_{12}$ inhibitor in eligible patients. The use of fondaparinux (for NSTE-ACS in the ACVC 2017 selection) has been replaced by the use of a parenteral agent at admission. The mention of the duration of DAPT in the discharge letter is a new indicator, never seen in previous selections. As in 2017, aspirin at admission and at discharge are not included in the list of QIs, reflecting the fact that although this treatment is of paramount importance, the Study Group considers it to be widely applied, with limited room for improvement.[30]

- *Secondary prevention:* there has been no change to this section, compared to the 2017 selection. The prescription of high-intensity statins at discharge was also adopted by ACC/AHA, while aspirin at discharge (and at admission) is considered to be 'topped out' and not included in the ESC ACVC list.

- *Patient satisfaction:* with the exception of cardiac rehabilitation, no comparable indicators have been defined by the ACC/AHA or CCS. The Study Group consider these QI to be important, and there is a compelling need to include the necessary variables in future registries to render assessment possible.

- *Mortality:* risk-adjusted 30-day all-cause mortality has been maintained in the updated QI list, despite significant limitations for interpretation. In contrast, no outcome measure has been selected by ACC/AHA, because the outcomes are only partially dependent on the quality of care, risk adjustment is challenging and, used as PM and not a QI, inclusion of outcome measures could have potentially negative consequences.[12]

7.9 Perspectives

The first set of QIs was developed to improve quality through self-assessment. This has been possible in different countries, not carried out by health agencies or insurance companies, but by cardiologists themselves at low cost through existing registries. To facilitate such use of QIs, the Study Group considered the results of these assessments in revising the QIs. Thus, some QIs that were found to be challenging to report have been retired or modified. Conversely, despite not being measured in all registries, certain QIs have been maintained, considering that they capture important aspects of quality care. The next step will be the standardization of the main registries in Europe in order to include the specific variables needed for quality assessment according to the revised set of QIs. In most existing registries and surveys, this would correspond to the addition of a limited number of variables, which should be reliable and straightforward to assess.

7.10 References for Chapter 7

1. Schiele F, Gale CP, Bonnefoy E, Capuano F, Claeys MJ, Danchin N, Fox KA, Huber K, Iakobishvili Z, Lettino M, Quinn T, Rubini Gimenez M, Botker HE, Swahn E, Timmis A, Tubaro M, Vrints C, Walker D, Zahger D, Zeymer U, Bueno H. Quality indicators for acute myocardial infarction: a position paper of the acute cardiovascular care association. Eur Heart J Acute Cardiovasc Care 2017; 6:34–59.

2. Arau´jo C, Laszczynska O, Viana M, Dias P, Maciel MJ, Moreira I, Azevedo A. Quality of care and 30-day mortality of women and men with acute myocardial infarction. Rev Esp Cardiol (Engl Ed) 2019;72:543–552.

3. Bebb O, Hall M, Fox KAA, Dondo TB, Timmis A, Bueno H, Schiele F, Gale CP. Performance of hospitals according to the ESC ACCA quality indicators and 30- day mortality for acute myocardial infarction: national cohort study using the United Kingdom Myocardial Ischaemia National Audit Project (MINAP) register. Eur Heart J 2017;38:974–982.

4. Hudzik B, Budaj A, Gierlotka M, Witkowski A, Wojakowski W, Zdrojewski T, Gil R, Legutko J, Bartus S, Buszman P, Dudek D, Gasior M. Assessment of quality of care of patients with ST-segment elevation myocardial infarction. Eur Heart J Acute Cardiovasc Care 2019;2048872619882360.

5. Schiele F, Gale CP, Simon T, Fox KAA, Bueno H, Lettino M, Tubaro M, Puymirat E, Ferrieres J, Meneveau N, Danchin N. Assessment of quality indicators for acute myocardial infarction in the FAST-MI (French Registry of Acute STElevation or Non-ST-Elevation Myocardial Infarction) Registries. Circ Cardiovasc Qual Outcomes 2017;10:e003336.

6. Timoteo AT, Mimoso J, Pro ACSI, on behalf of the ProACS Investigators. Assessment of quality performance measures in patients with acute coronary syndromes: data from the Portuguese Registry of Acute Coronary Syndromes (ProACS), a nationwide registry. J Eval Clin Pract 2018;24:439–446.

7. Zusman O, Bebb O, Hall M, Dondo TB, Timmis A, Schiele F, Fox KA, Kornowski R, Gale CP, Iakobishvili Z. International comparison of acute myocardial infarction care and outcomes using quality indicators. Heart 2019;105:820–825.

8. Rossello X, Medina J, Pocock S, Van de Werf F, Chin CT, Danchin N, Lee SW, Huo Y, Bueno H. Assessment of quality indicators for acute myocardial infarction management in 28 countries and use of composite quality indicators for benchmarking. Eur Heart J Acute Cardiovasc Care 2020;9:911–922.

9. Wilkinson C, Bebb O, Dondo TB, Munyombwe T, Casadei B, Clarke S, Schiele F, Timmis A, Hall M, Gale CP. Sex differences in quality indicator attainment for myocardial infarction: a nationwide cohort study. Heart 2019;105:516–523.

10. Wallentin L, Gale CP, Maggioni A, Bardinet I, Casadei B. EuroHeart: European unified registries on heart care evaluation and randomized trials. Eur Heart J 2019;40:2745–2749.

11. Aktaa S, Batra G, Wallentin L, Baigent C, Erlinge D, James S, Ludman P, Maggioni AP, Price S, Weston C, Casadei B, Gale CP. European Society of Cardiology methodology for the development of quality indicators for the quantification of cardiovascular care and outcomes. Eur Heart J Qual Care Clin Outcomes 2020.

12. Spertus JA, Bonow RO, Chan P, Diamond GA, Drozda JP Jr, Kaul S, Krumholz HM, Masoudi FA, Normand SL, Peterson ED, Radford MJ, Rumsfeld JS; Writing Committee Members. ACCF/AHA new insights into the methodology of performance measurement: a report of the American College of Cardiology Foundation/American Heart Association Task Force on performance measures. Circulation 2010;122:2091–2106.

13. Peterson ED, DeLong ER, Masoudi FA, O'Brien SM, Peterson PN, Rumsfeld JS, Shahian DM, Shaw RE. ACCF/AHA 2010 Position Statement on Composite Measures for Healthcare Performance Assessment: a report of American College of Cardiology Foundation/American Heart Association Task Force on Performance Measures (Writing Committee to Develop a Position Statement on Composite Measures). J Am Coll Cardiol 2010;55:1755–1766.

14. MacLean CH, Kerr EA, Qaseem A. Time out—charting a path for improving performance measurement. N Engl J Med 2018;378:1757–1761.

15. Brook RH, McGlynn EA, Cleary PD. Quality of health care. Part 2: measuring quality of care. N Engl J Med 1996;335:966–970.

16. Brook RH. Clinical Practice Guideline Development: Methodology Perspectives. Rockville, MD: Agency for Healthcare Research and Policy, 1994.The RAND/UCLA appropriateness method. In: KA McCormack, SR Moore, RA Siegel, (eds):;

17. Normand SL, McNeil BJ, Peterson LE, Palmer RH. Eliciting expert opinion using the Delphi technique: identifying performance indicators for cardiovascular disease. Int J Qual Health Care 1998;10:247–260.

18. Huber K, Gersh BJ, Goldstein P, Granger CB, Armstrong PW. The organization, function, and outcomes of ST-elevation myocardial infarction networks worldwide: current state, unmet needs and future directions. Eur Heart J 2014;35: 1526–1532.

19. Alexander T, Mullasari AS, Joseph G, Kannan K, Veerasekar G, Victor SM, Ayers C, Thomson VS, Subban V, Gnanaraj JP, Narula J, Kumbhani DJ, Nallamothu BK. A system of care for patients with ST-segment elevation myocardial infarction in India: the Tamil Nadu-ST-segment elevation myocardial infarction program. JAMA Cardiol 2017;2:498–505.

20. Henry TD, Sharkey SW, Burke MN, Chavez IJ, Graham KJ, Henry CR, Lips DL, Madison JD, Menssen KM, Mooney MR, Newell MC, Pedersen WR, Poulose AK, Traverse JH, Unger BT, Wang YL, Larson DM. A regional system to provide timely access to percutaneous coronary intervention for ST-elevation myocardial infarction. Circulation 2007;116:721–728.

21. Le May MR, So DY, Dionne R, Glover CA, Froeschl MP, Wells GA, Davies RF, Sherrard HL, Maloney J, Marquis JF, O'Brien ER, Trickett J, Poirier P, Ryan SC, Ha A, Joseph PG, Labinaz M, Citywide A. protocol for primary PCI in STsegment elevation myocardial infarction. N Engl J Med 2008;358:231–240.

22. Saia M, Mantoan D, Fonzo M, Bertoncello C, Soattin M, Sperotto M, Baldovin T, Furlan P, Scapellato ML, Viel G, Baldo V, Cocchio S, Buja A. Impact of the regional network for AMI in the management of STEMI on care processes, outcomes and health inequities in the veneto region. Italy. Int J Environ Res Public Health 2018;15:1980.

23. Scholz KH, Lengenfelder B, Jacobshagen C, Fleischmann C, Moehlis H, Olbrich HG, Jung J, Maier LS, Maier SK, Bestehorn K, Friede T, Meyer T. Long-term effects of a standardized feedback-driven quality improvement program for timely reperfusion therapy in regional STEMI care networks. Eur Heart J Acute Cardiovasc Care 2020;2048872620907323.

24. Ibanez B, James S, Agewall S, Antunes MJ, Bucciarelli-Ducci C, Bueno H, Caforio ALP, Crea F, Goudevenos JA, Halvorsen S, Hindricks G, Kastrati A, Lenzen MJ, Prescott E, Roffi M, Valgimigli M, Varenhorst C, Vranckx P, Widimsky P. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: the Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). Eur Heart J 2018;39:119–177.

25. Collet JP, Thiele H, Barbato E, Barthelemy O, Bauersachs J, Bhatt DL, Dendale P, Dorobantu M, Edvardsen T, Folliguet T, Gale CP, Gilard M, Jobs A, Juni P, Lambrinou E, Lewis BS, Mehilli J, Meliga E, Merkely B, Mueller C, Roffi M, Rutten FH, Sibbing D, Siontis GCM. 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. Eur Heart J 2020;29:ehaa575.

26. Mueller C. Biomarkers and acute coronary syndromes: an update. Eur Heart J 2014;35:552–556.

27. Lewis WR, Peterson ED, Cannon CP, Super DM, LaBresh KA, Quealy K, Liang L, Fonarow GC. An organized approach to improvement in guideline adherence for acute myocardial infarction: results with the get with the guidelines quality improvement program. Arch Intern Med 2008;168:1813–1819.

28. Boulkedid R, Abdoul H, Loustau M, Sibony O, Alberti C. Using and reporting the Delphi method for selecting healthcare quality indicators: a systematic review. PLoS One 2011;6:e20476.

29. Gitt AK, Bueno H, Danchin N, Fox K, Hochadel M, Kearney P, Maggioni AP, Opolski G, Seabra-Gomes R, Weidinger F. The role of cardiac registries in evidence-based medicine. Eur Heart J 2010;31:525–529.

30. Jneid H, Addison D, Bhatt DL, Fonarow GC, Gokak S, Grady KL, Green LA, Heidenreich PA, Ho PM, Jurgens CY, King ML, Kumbhani DJ, Pancholy S. 2017 AHA/ACC clinical performance and quality measures for adults with STelevation and non-ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Performance Measures. J Am Coll Cardiol 2017;70:2048–2090.

31. Anderson HV, Jacob R. Assessing performance and quality after non-ST segment elevation acute coronary syndromes. Curr Cardiol Rep 2018;20:133.

32. Cenko E, Ricci B, Kedev S, Vasiljevic Z, Dorobantu M, Gustiene O, Knezevic B, Milicic D, Dilic M, Trninic D, Smith F, Manfrini O, Badimon L, Bugiardini R. Reperfusion therapy for ST-elevation acute myocardial infarction in Eastern Europe: the ISACS-TC registry. Eur Heart J Qual Care Clin Outcomes 2016;2: 45–51.

33. Roffi M, Patrono C, Collet JP, Mueller C, Valgimigli M, Andreotti F, Bax JJ, Borger MA, Brotons C, Chew DP, Gencer B, Hasenfuss G, Kjeldsen K, Lancellotti P, Landmesser U, Mehilli J, Mukherjee D, Storey RF, Windecker S. Group ESCSD. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). Eur Heart J 2016;37:267–315.

34. Jolly SS, Yusuf S, Cairns J, Niemela K, Xavier D, Widimsky P, Budaj A, Niemela M, Valentin V, Lewis BS, Avezum A, Steg PG, Rao SV, Gao P, Afzal R, Joyner CD, Chrolavicius S, Mehta SR; RIVAL group. Radial versus femoral access for coronary angiography and intervention in patients with acute coronary syndromes (RIVAL): a randomised, parallel group, multicentre trial. Lancet 2011;377: 1409–1420.

35. Valgimigli M, Gargiulo G, Juni P. Radial versus femoral access for cardiac catheterization—Authors' reply. Lancet 2015;386:2394.

36. Romagnoli E, Biondi-Zoccai G, Sciahbasi A, Politi L, Rigattieri S, Pendenza G, Summaria F, Patrizi R, Borghi A, Di Russo C, Moretti C, Agostoni P, Loschiavo P, Lioy E, Sheiban I, Sangiorgi G. Radial versus femoral randomized investigation in ST-segment elevation acute coronary syndrome: the RIFLE-STEACS (Radial Versus Femoral

Randomized Investigation in ST-Elevation Acute Coronary Syndrome) study. J Am Coll Cardiol 2012;60:2481–2489.

37. Mason PJ, Shah B, Tamis-Holland JE, Bittl JA, Cohen MG, Safirstein J, Drachman DE, Valle JA, Rhodes D, Gilchrist IC; American Heart Association Interventional Cardiovascular Care Committee of the Council on Clinical Cardiology; Council on Cardiovascular and Stroke Nursing; Council on Peripheral Vascular Disease; and Council on Genomic and Precision Medicine. An update on radial artery access and best practices for transradial coronary angiography and intervention in acute coronary syndrome: a scientific statement from the American Heart Association. Circ Cardiovasc Interv 2018;11:e000035.

38. Ference BA, Ginsberg HN, Graham I, Ray KK, Packard CJ, Bruckert E, Hegele RA, Krauss RM, Raal FJ, Schunkert H, Watts GF, Bore´n J, Fazio S, Horton JD, Masana L, Nicholls SJ, Nordestgaard BG, van de Sluis B, Taskinen M-R, Tokgo¨zoglu L, Landmesser U, Laufs U, Wiklund O, Stock JK, Chapman MJ, Catapano AL. Low-density lipoproteins cause atherosclerotic cardiovascular disease. 1. Evidence from genetic, epidemiologic, and clinical studies. A consensus statement from the European Atherosclerosis Society Consensus Panel. Eur Heart J 2017;38:2459–2472.

39. Mach F, Baigent C, Catapano AL, Koskinas KC, Casula M, Badimon L, Chapman MJ, De Backer GG, Delgado V, Ference BA, Graham IM, Halliday A, Landmesser U, Mihaylova B, Pedersen TR, Riccardi G, Richter DJ, Sabatine MS, Taskinen M-R, Tokgozoglu L, Wiklund O; ESC Scientific Document Group. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. Eur Heart J 2020;41:111–188.

40. Cannon CP, Blazing MA, Giugliano RP, McCagg A, White JA, Theroux P, Darius H, Lewis BS, Ophuis TO, Jukema JW, De Ferrari GM, Ruzyllo W, De Lucca P, Im K, Bohula EA, Reist C, Wiviott SD, Tershakovec AM, Musliner TA, Braunwald E, Califf RM; for the IMPROVE-IT Investigators. Ezetimibe added to statin therapy after acute coronary syndromes. N Engl J Med 2015;372:2387–2397.

41. Montalescot G, Wiviott SD, Braunwald E, Murphy SA, Gibson CM, McCabe CH, Antman EM; for the TRITON-TIMI 38 investigators. Prasugrel compared with clopidogrel in patients undergoing percutaneous coronary intervention for STelevation myocardial infarction (TRITON-TIMI 38): double-blind, randomised controlled trial. Lancet 2009;373:723–731.

42. Wiviott SD, Braunwald E, McCabe CH, Montalescot G, Ruzyllo W, Gottlieb S, Neumann FJ, Ardissino D, De Servi S, Murphy SA, Riesmeyer J, Weerakkody G, Gibson

CM, Antman EM. Prasugrel versus clopidogrel in patients with acute coronary syndromes. N Engl J Med 2007;357:2001–2015.

43. Steg PG, James S, Harrington RA, Ardissino D, Becker RC, Cannon CP, Emanuelsson H, Finkelstein A, Husted S, Katus H, Kilhamn J, Olofsson S, Storey RF, Weaver WD, Wallentin L, Group PS; for the PLATO Study Group. Ticagrelor versus clopidogrel in patients with ST-elevation acute coronary syndromes intended for reperfusion with primary percutaneous coronary intervention: a Platelet Inhibition and Patient Outcomes (PLATO) trial subgroup analysis. Circulation 2010;122:2131–2141.

44. Wallentin L, Becker RC, Budaj A, Cannon CP, Emanuelsson H, Held C, Horrow J, Husted S, James S, Katus H, Mahaffey KW, Scirica BM, Skene A, Steg PG, Storey RF, Harrington RA, Freij A, Thorsen M. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. N Engl J Med 2009;361:1045–1057.

45. Valgimigli M, Bueno H, Byrne RA, Collet JP, Costa F, Jeppsson A, Juni P, Kastrati A, Kolh P, Mauri L, Montalescot G, Neumann FJ, Petricevic M, Roffi M, Steg PG, Windecker S, Zamorano JL, Levine GN; Guidelines ESCCfP, Societies ESCNC. 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS: The Task Force for dual antiplatelet therapy in coronary artery disease of the European Society of Cardiology (ESC) and of the European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J 2018;39:213–260.

46. Bado W, Williams CJ. Usefulness of letters from hospitals to general practitioners. Br Med J (Clin Res Ed) 1984;288:1813–1814.

47. Schiele F, Lemesle G, Angoulvant D, Krempf M, Kownator S, Cheggour S, Belle L, Ferrieres J. Proposal for a standardized discharge letter after hospital stay for acute myocardial infarction. Eur Heart J Acute Cardiovasc Care 2019; 2048872619844444.

48. Cannon CP, Braunwald E, McCabe CH, Rader DJ, Rouleau JL, Belder R, Joyal SV, Hill KA, Pfeffer MA, Skene AM; Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis in Myocardial Infarction 22 Investigators. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. N Engl J Med 2004;350:1495–1504.

49. De Backer G, Jankowski P, Kotseva K, Mirrakhimov E, Reiner Z, Ryden L, Tokgozoglu L, Wood D, De Bacquer D; EUROASPIRE V collaborators; Writing Committee. Management of dyslipidaemia in patients with coronary heart disease: Results from the ESC-EORP EUROASPIRE V survey in 27 countries. Atherosclerosis 2019;285:135–146.

50. Poole-Wilson PA, Swedberg K, Cleland JG, Di Lenarda A, Hanrath P, Komajda M, Lubsen J, Lutiger B, Metra M, Remme WJ, Torp-Pedersen C, Scherhag A, Skene A;

Carvedilol Or Metoprolol European Trial I. Comparison of carvedilol and metoprolol on clinical outcomes in patients with chronic heart failure in the Carvedilol Or Metoprolol European Trial (COMET): randomised controlled trial. Lancet 2003;362:7–13.

51. Bangalore S, Steg G, Deedwania P, Crowley K, Eagle KA, Goto S, Ohman EM, Cannon CP, Smith SC, Zeymer U, Hoffman EB, Messerli FH, Bhatt DL; Reach Registry Investigators. beta-Blocker use and clinical outcomes in stable outpatients with and without coronary artery disease. JAMA 2012;308:1340–1349.

52. Anker SD, Agewall S, Borggrefe M, Calvert M, Jaime Caro J, Cowie MR, Ford I, Paty JA, Riley JP, Swedberg K, Tavazzi L, Wiklund I, Kirchhof P. The importance of patient-reported outcomes: a call for their comprehensive integration in cardiovascular clinical trials. Eur Heart J 2014;35:2001–2009.

53. Ware JE Jr, Davies-Avery A, Stewart AL. The measurement and meaning of patient satisfaction. Health Med Care Serv Rev 1978;1:3–15.

54. Lee DS, Tu JV, Chong A, Alter DA. Patient satisfaction and its relationship with quality and outcomes of care after acute myocardial infarction. Circulation 2008; 118:1938–1945.

55. Doyle F, Rohde D, Rutkowska A, Morgan K, Cousins G, McGee H. Systematic review and meta-analysis of the impact of depression on subsequent smoking cessation in patients with coronary heart disease: 1990 to 2013. Psychosom Med 2014;76:44–57.

56. National Health Service England: ROAN information sheet 23: Quality improvement: best practice for clinical letters. 2018. https://www.england.nhs.uk/medicalrevalidation/ro/info-docs/roan-information-sheets/quality-improvement-best-prac tice-for-clinical-letters/ (31 December 2020).

57. Weetman K, Wong G, Scott E, MacKenzie E, Schnurr S, Dale J. Improving best practice for patients receiving hospital discharge letters: a realist review. BMJ Open 2019;9:e027588.

58. Shahian DM, Wolf RE, Iezzoni LI, Kirle L, Normand SL. Variability in the measurement of hospital-wide mortality rates. N Engl J Med 2010;363: 2530–2539.

59. Weston CF. Performance indicators in acute myocardial infarction: a proposal for the future assessment of good quality care. Heart 2008;94: 1397–1401.

60. Simms AD, Batin PD, Weston CF, Fox KA, Timmis A, Long WR, Hall AS, Gale CP. An evaluation of composite indicators of hospital acute myocardial infarction care: a study of 136,392 patients from the Myocardial Ischaemia National Audit Project. Int J Cardiol 2013;170:81–87.

61. Eapen ZJ, Fonarow GC, Dai D, O'Brien SM, Schwamm LH, Cannon CP, Heidenreich PA, Bhatt DL, Peterson ED, Hernandez AF; Get With The Guidelines Steering Committee

and Hospitals. Comparison of composite measure methodologies for rewarding quality of care: an analysis from the American Heart Association's Get With The Guidelines program. Circ Cardiovasc Qual Outcomes 2011;4:610–618.

62. Tu JV, Khalid L, Donovan LR, Ko DT. Indicators of quality of care for patients with acute myocardial infarction. Canadian Medical Association Journal 2008;179: 909–915. 10.1503/cmaj.080749

Chapter 8. Quality of acute myocardial infarction care in England and Wales during the COVID-19 pandemic: linked nationwide cohort study

Suleman Aktaa, Mohammad E Yadegarfar, Jianhua Wu, Muhammad Rashid, Mark de Belder, John Deanfield, Francois Schiele, Mark Minchin, Mamas Mamas, Chris P Gale

8.1 Summary about the publication:

- This analysis has been performed using the quality indicators developed in Chapter 7 to assess the quality of acute myocardial infarction (AMI) on a national level in England and Wales.
- Data from the national cardiovascular registries for AMI and percutaneous coronary intervention were linked and the quality indicators were used a measurement of care quality during compared with before the COVID-19 pandemic.
- The study found a modest improvement in the quality of AMI care during the COVID-19 pandemic.

8.2 Publication status:

- Published 21 June 2021
- BMJ Qual Saf. 2021 Jun : bmjqs-2021-013040.

8.3 Abstract

8.3.1 Background and objective

The impact of the COVID-19 pandemic on the quality of care for patients with acute myocardial infarction (AMI) is uncertain. We aimed to compare quality of AMI care in England and Wales during and before the COVID-19 pandemic using the 2020 European Society of Cardiology Association for Acute Cardiovascular Care quality indicators (QIs) for AMI.

8.3.2 Methods

Cohort study of linked data from the AMI and the percutaneous coronary intervention registries in England and Wales between 1 January 2017 and 27 May 2020 (representing 236 743 patients from 186 hospitals). At the patient level, the likelihood of attainment for each QI compared with pre COVID-19 was calculated using logistic regression. The date of the first national lockdown in England and Wales (23 March 2020) was chosen for time series comparisons.

8.3.3 Results

There were 10 749 admissions with AMI after 23 March 2020. Compared with before the lockdown, patients admitted with AMI during the first wave had similar age (mean 68.0 vs 69.0 years), with no major differences in baseline characteristics (history of diabetes (25% vs 26%), renal failure (6.4% vs 6.9%), heart failure (5.8% vs 6.4%) and previous myocardial infarction (22.9% vs 23.7%)), and less frequently had high Global Registry of Acute Coronary Events risk scores (43.6% vs 48.6%). There was an improvement in attainment for 10 (62.5%) of the 16 measured QIs including a composite QI (43.8% to 45.2%, OR 1.06, 95% CI 1.02 to 1.10) during, compared with before, the lockdown.

8.3.4 Conclusion

During the first wave of the COVID-19 pandemic in England and Wales, quality of care for AMI as measured against international standards did not worsen, but improved modestly.

8.3.5 Keywords: COVID-19, quality improvement, performance measures

8.4 Introduction

The COVID-19 pandemic has impacted on the structure and organisation of services delivered through the National Health Service (NHS) with knock-on effects on the management of a number of acute cardiovascular conditions including acute myocardial infarction (AMI) in the UK.[1–4] For patients admitted to hospital with AMI, guideline-indicated therapies such as invasive coronary angiography, timely reperfusion and secondary prevention medications improve survival,[5] and professional organisations in the UK recommended the perpetuation of these therapies during the pandemic.[6 7] Yet, an earlier study found an increase in 30-day mortality and a reduction in the proportion of invasive coronary angiography during the national lockdown for patients with non-ST segment elevation myocardial infarction (NSTEMI).[8] There has been, however, no comprehensive evaluation of the quality of AMI care during the first national lockdown and no study has used recognised standards for such an investigation.

Quality indicators (QIs) have been increasingly used as a mechanism to measure broad aspects of care,[9] identify unwanted variation[10 11] and drive quality improvement.[12] For AMI, a suite of QIs exist which are valid,[13] internationally recognised[14] and have built on earlier indicators that have an inverse association with mortality.[15–19] We used the UK national cardiovascular registries to investigate the quality of AMI care according to these indicators during the first national lockdown in the COVID-19 pandemic. This may help understand changes in the processes of AMI care during the time of national crisis and identify areas for improvement.

8.5 Methods

8.5.1 Data and population

We used linked data from the UK national AMI and percutaneous coronary intervention (PCI) registries, namely the Myocardial Ischaemia National Audit Project (MINAP)[20 21] and the National Audit of Percutaneous Coronary Intervention (NAPCI), championed by the British Cardiovascular Intervention Society.[22] MINAP and NAPCI registries have been described previously.[20 23] The National Institute for Cardiovascular Outcomes Research

(NICOR), commissioned through the Healthcare Quality Improvement Partnership, manages MINAP, NAPCI and other registries.

NICOR has support under section 251 of the NHS Act 2006 (Ref: NIGB: ECC 1-06 (d)/2011) to use patient information for medical research without consent. Thus, ethical approval was not required under NHS research governance arrangements. We conducted our study in compliance with the Declaration of Helsinki using the MINAP and NAPCI databases.

8.5.2 Sample selection

We included all adult patients (⩾18 years of age), discharged alive with ST-segment elevation myocardial infarction (STEMI) or NSTEMI from MINAP between 1 January 2017 and 27 May 2020. Data related to PCI were obtained from the NAPCI registry using each patient's unique NHS number to deterministically link patients between the two registries. Where multiple admissions for the same patient were recorded, the earlier admission was used to reduce potential bias from previous treatments. Patients with no valid NHS number were excluded.

8.5.3 Quality indicators

We used the 2020 European Society of Cardiology (ESC) Association for Acute Cardiovascular Care (ACVC) QIs for AMI, which comprise 26 indicators. The eligibility criteria for each QI was determined according to the specifications provided in the ESC ACVC document.14

8.5.4 Outcomes

The outcome was quality of AMI care. Care quality was quantified according to the degree to which eligible patients received the care outlined in the QIs prior to, compared with after, 23

March 2020 (up to 27 May 2020). This date was chosen for the time series comparison because it corresponded with the first national lockdown in England and Wales.

8.5.5 Statistical analysis

Patient baseline characteristics, comorbidities and treatments were reported according to the study period and type of AMI as percentages and numbers for categorical variables, means and SDs for parametric continuous variables, and medians and IQRs for non-parametric variables. Baseline differences between each diagnosis were tested using χ^2 test for categorical variables, t-test for continuous parametric and the Mann-Whitney U test for non-parametric variables. At the patient level, the likelihood of attainment for each QI compared with that before the COVID-19 pandemic was estimated using logistic regression.

All analyses were performed on complete cases. All tests were two-sided, and statistical significance was considered as p value <0.05. Statistical analyses were performed in Stata IC V.14.2 and R V.3.4.3.

8.6 Results

8.6.1 Study population

Data for 236 743 patients admitted with AMI to one of 186 NHS hospitals were included. Of those, 152 109 (64.3%) patients had NSTEMI, and the median age was 69.0 (58–79) years with 75 918 (32.2%) patients being women. The cohort following lockdown (10 749) were compared with the period chosen before lockdown (225 994). Table 1 shows the demographics, comorbidities, in-hospital treatment and discharge details according to the study period. Data are presented according to the type of AMI in online supplemental table 1. Compared with before the lockdown, patients admitted with AMI during the first wave had similar age (mean 68.0 vs 69.0 years), similar baseline characteristics (history of diabetes (25% vs 26%), renal failure (6.4% vs 6.9%), heart failure (5.8% vs 6.4%) and previous myocardial infarction (22.9% vs 23.7%)) and less frequently had high Global Registry of Acute Coronary Events (GRACE) risk scores (43.6% vs 48.6%) (table 1).

Table 1. Baseline characteristics for patients with AMI, by AMI type

	STEMI	NSTEMI	AMI	Missing Data % (n)
Patients, n	84,634	152,109	236,743	
Hospitals, n	183	186	186	
Demographics				
Female, % (n)	27.9 (23,484)	34.5 (52,434)	32.2 (75,918)	0.3 (621)
Age (years), median (IQR)	65 (56 - 75)	71 (60 - 81)	69 (58 - 79)	0 (0)
Since lockdown, % (n)	4.8 (4,070)	4.4 (6,679)	4.5 (10,749)	0 (0)
Baseline characteristics				
Heart rate at hospitalisation (bpm), median (IQR)	77 (65 - 90)	77 (66 - 90)	77 (66 - 90)	3.4 (7960)
Systolic blood pressure (mmHg), median (IQR)	130 (112 - 150)	140 (123 - 160)	137 (120 - 157)	3.3 (7826)
Initial creatinine, μmol/L, median (IQR)	81 (69 - 98)	86 (72 - 108)	85 (71 - 104)	4.6 (10824)
GRACE				
Score, median (IQR)	125 (103 - 156)	118 (95 - 148)	121 (96 - 151)	18.4 (43566)
Low, % (n)	22.3 (14,662)	17.9 (22,829)	19.4 (37,491)	
Intermediate, % (n)	29.5 (19,367)	33.7 (42,960)	32.3 (62,327)	
High, % (n)	48.3 (31,722)	48.4 (61,637)	48.3 (93,359)	
Killip Class				
I, % (n)	84.0 (62,435)	81.6 (112,510)	82.4 (174,945)	10.4 (24511)
II, % (n)	8.3 (6,138)	13.0 (17,863)	11.3 (24,001)	
III, % (n)	3.7 (2,776)	5.0 (6,892)	4.6 (9,668)	
IV, % (n)	4.0 (2,982)	0.5 (636)	1.7 (3,618)	
Comorbidities				
Diabetes, % (n)	19.0 (16,603)	29.8 (45,389)	26.0 (61,452)	0 (0)
COPD, % (n)	10.8 (9,115)	17.1 (25,992)	14.8 (35,107)	0 (0)

Chronic heart failure, % (n)	2.7 (2,316)	8.4 (12,760)	6.4 (15,076)	0 (0)
Chronic renal failure, % (n)	3.0 (2,493)	9.1 (13,837)	6.9 (16,330)	0 (0)
Cerebrovascular disease, % (n)	4.6 (3,878)	8.7 (13,254)	7.2 (17,132)	0 (0)
Peripheral vascular disease, % (n)	2.4 (2,057)	4.9 (7,461)	4.0 (9,518)	0 (0)
Hypertension, % (n)	38.4 (32,491)	52.6 (80,057)	47.5 (112,548)	0 (0)
Previous MI, % (n)	13.2 (9,489)	29.1 (40,303)	23.7 (49,792)	11.3 (26692)
Previous Angina, % (n)	9.8 (6,907)	26.2 (35,695)	20.6 (42,602)	12.7 (30083)
Previous PCI, % (n)	10.2 (7,224)	18.2 (24,758)	15.5 (31,982)	12.6 (29742)
Previous CABG, % (n)	2.7 (1,924)	9.5 (13,010)	7.2 (14,934)	12.5 (29565)
In-hospital procedures				
Invasive coronary angiography, % (n)	78.3 (66,024)	67.5 (102,612)	71.3 (168,636)	0.15 (354)
PCI, % (n)	78.1 (66,093)	37.0 (56,203)	51.7 (122,296)	0 (0)
CABG, % (n)	0.1 (45)	3.1 (4,661)	2.0 (4,706)	0 (0)
Medications at discharge				
Aspirin, % (n)	98.7 (68,467)	97.4 (106,813)	97.9 (175,280)	24.4 (57682)
P2Y$_{12}$ inhibitor, % (n)	98.2 (68,704)	95.6 (105,081)	96.6 (173,785)	24.0 (56849)
β-blocker, % (n)	97.7 (65,189)	95.1 (99,311)	96.1 (164,500)	27.7 (65590)
ACEi or ARB, % (n)	97.1 (64,597)	92.3 (90,962)	94.2 (155,559)	30.3 (71643)
Statins, % (n)	98.6 (68,459)	96.5 (108,061)	97.3 (176,520)	23.5 (55639)
Lifestyle advice				

Cardiac rehabilitation, % (n)	91.7 (64,686)	87.1 (102,965)	88.8 (167,651)	20.2 (47903)
Smoking cessation advice, % (n)	80.4 (24,272)	70.3 (26,869)	74.6 (51,141)	71.1 (168331)
Dietary advice, % (n)	92.7 (57,507)	88.2 (98,519)	89.8 (156,026)	26.6 (63013)

ACEi; angiotensin converting enzyme inhibitors, ARB; angiotensin receptor blockers, CABG; coronary artery bypass graft, COPD; chronic obstructive pulmonary disease, GRACE; Global Registry of Acute Coronary Events, IQR, interquartile range, MI; myocardial infarction, NSTEMI; non-ST segment elevation myocardial infarction, STEMI; PCI; percutaneous coronary intervention, ST-segment elevation myocardial infarction.

8.6.2 Quality of care assessment

Data from the national registries enabled the direct measurement of 16 (61.5%) of the 26 ESC ACVC QIs. The QIs that could not be assessed included the planned duration of dual anti-platelet therapy, the QIs within the patient satisfaction domain and the objective risk-stratification using validated tools. GRACE risk scores, however, were indirectly derived for 193 177 (81.6%) patients. In addition, while participating in a network for STEMI management, taking part in a registry and routine monitoring to reperfusion times in STEMI could not be directly measured, these form part of routine practice in the UK. The outcome QI (30-day mortality) may be obtained from data linkage with the Civil Registration of Deaths Register, but was not evaluated for this work because mortality had been previously investigated[8] and this study concerned processes of care.

8.6.3 Quality of care during the COVID-19 pandemic

During, compared with before, the national lockdown, in England and Wales there was an improvement in attainment for 10 (62.5%) QIs, with evidence for a slight reduction in attainment for the other QIs that could be measured using the datasets (table 2). Figure 1 shows the OR for QI attainment during the lockdown referenced to the pre-COVID period.

Overall, there was a slight increase in attainment for the composite QI after the first national lockdown (43.8% to 45.2%, OR 1.06, 95% CI 1.02 to 1.10) suggesting good overall adherence to guidelines-indicated therapies for AMI during the COVID-19 pandemic.

Figure 1. Attainment for the quality indicators for patients with AMI during the first national lockdown
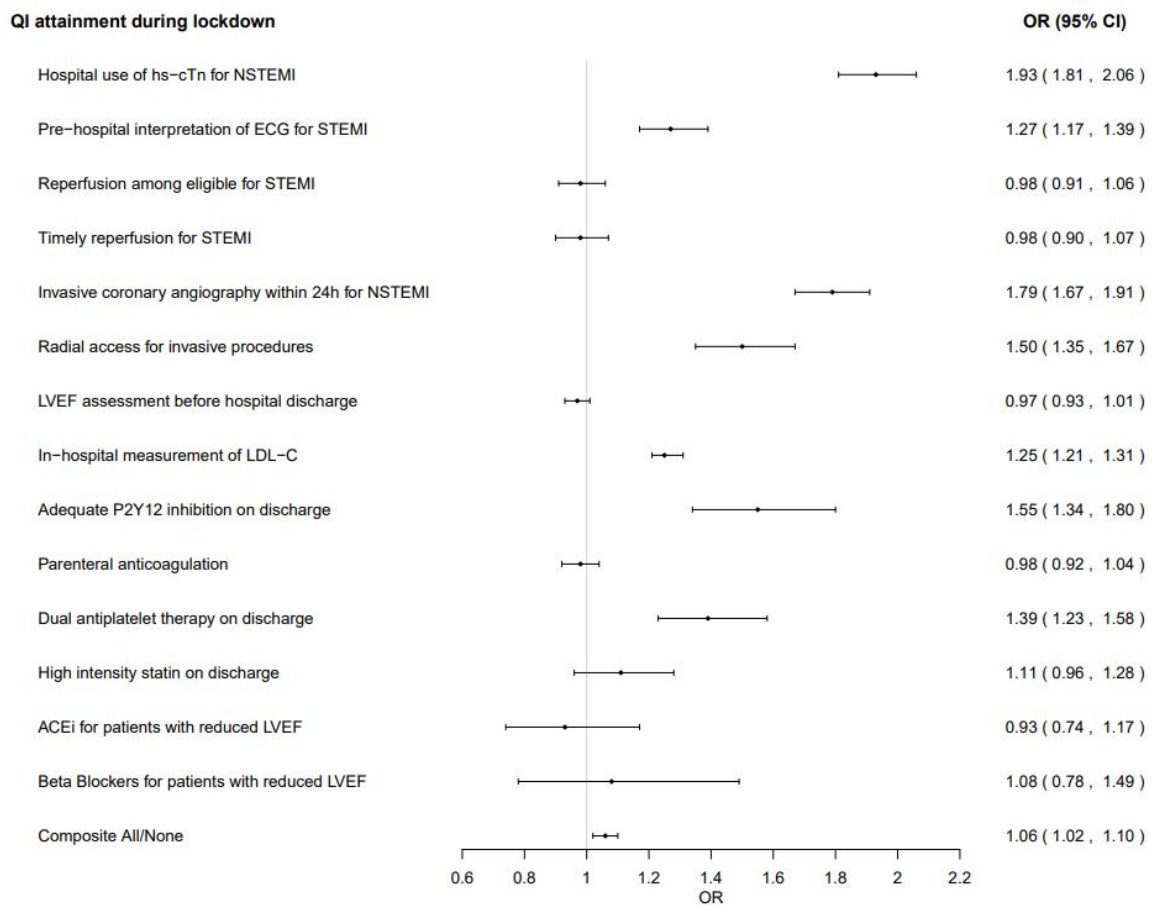
ACEi; angiotensin converting enzyme inhibitor, AMI; acute myocardial infarction, DAPT; dual anti-platelet therapy, ECG; electrocardiogram, hs-cTn; high-sensitivity cardiac troponin, ICA; invasive coronary angiography, LDL-C; low-density lipoprotein cholesterol, LVEF; left ventricular ejection fraction, NSTEMI; non-ST elevation myocardial infarction, STEMI; ST elevation myocardial infarction

*Door-to-Balloon time
**Serum cholesterol measurement
***Discharged on statin

8.7 Discussion

This real-world naturalistic study evaluated the quality of AMI care in England and Wales before and during the COVID-19 pandemic using routinely collected nationwide registry data. We found that the NHS provided high-quality AMI care during the pandemic as measured against international standards. In particular, we found that early detection and timely invasive investigation for NSTEMI were delivered at much higher rates, while STEMI reperfusion was slightly delayed than prior to the UK lockdown. Such insights were gained by means of routinely collected cardiovascular data. These findings highlight the role that the UK national cardiovascular registries may play in the evaluation of processes of AMI care in times of need.

Others have described changes in the patterns of treatment for patients with AMI during the COVID-19 pandemic,[1–3 8] but no study has quantified the breadth or depth of AMI care on a national level using validated QIs. Similar findings of an overall improvement in the quality of care have recently been reported for patients with stroke in the UK.[24] Taken together, this emphasises the consequences of a national crisis on the delivery of processes of care for acute cardiovascular conditions and may help identify areas for improvement.

One may only speculate as to the reasons for improved care quality for AMI following the national lockdown. Given that there was a reported decline of between 16% and 40% in admissions with AMI to hospitals following the first UK lockdown, the modest improvement in attainment of the majority of the QIs during the pandemic could be explained by a relative increase in availability of cardiology staff and resources.[1 2 8 25] That is, a reduction in admissions for AMI, with the maintenance of a specialist emergency heart attack service, would provide greater opportunities for specialist staff to deliver higher quality care.[3] Indeed, at the time, the British Cardiovascular Society recommended the UK national heart attack service to continue as previously and not to revert to historical treatments for AMI such as thrombolysis.[6 7] This was in contrast to recommendations during the early stages of the pandemic to adopt a 'thrombolysis-first' approach.[26] Given the decline in admissions with

AMI, our findings suggest that care quality could be further improved with appropriate staffing and resources.

However, it is possible that other factors were at play. This includes the preparedness of dedicated services (and with this additional staff availability and attention) and the prioritisation of hospital discharges (and therefore greater attention to the provision of care prior to leaving hospital).[27] Moreover, the 'shut down' of normal elective activity,[28] [29] which spanned all services, would have enabled the NHS to be better equipped to receive and treat patients with AMI. It is also plausible that the recording of data into the national registries was more selective, with a bias towards patients who were lower risk, had better care and who were more likely to be discharged alive (previous work has suggested that missing data is associated with 30-day mortality for STEMI and NSTEMI).[30]

The delay in STEMI reperfusion observed in our study is consistent with other UK[3] and international[31] studies, and may be related to the changes to STEMI service during the pandemic including the redeployment of catheter laboratory staff to other intensive care environments.[27] Furthermore, the slight reduction in the prescription of angiotensin converting enzyme inhibitors or angiotensin receptor blockers for those with a reduced ejection fraction, as well as the increase in radial access use after the lockdown, may be due to the fact that there was an imperative to make available hospital beds and therefore enable the early hospital discharge of stable patients following AMI.

Our study does emphasise an opportunity to integrate local efforts with those wider afield that aim to evaluate and improve the quality of AMI care. The ESC QIs have been designed to enable the assessment of care quality for AMI, according to international clinical practice guidelines.[32] Equally, MINAP and NAPCI are used as tools for audit and evaluation of NHS heart attack services.[33] Hitherto, we were only able to measure 61.5% of the ESC AMI QIs against these two national registers. We propose that routine national data collection aligns to and harmonises with national and international standards for the measurement of quality of care.[34] Equally, we recognise that while information such as health-related quality of life

may be difficult to capture via national registries,[35] greater alliance may help enhance the comprehensiveness of data collection systems in the UK.[36] [37]

Our study has limitations. MINAP does not collect information pertaining to all admissions with AMI across the NHS.[38] It is possible that care quality for those admissions recorded were systematically different from those not in the registry. Nonetheless, MINAP does collect detailed clinical information pertaining to the majority of admissions in England and Wales with AMI, and is the largest single healthcare system AMI registry.[20] We substituted statin therapy for high-intensity statin, serum cholesterol for low-density lipoprotein cholesterol, and balloon inflation time for arterial access time. While these are slightly different aspects of care to the ones proposed in the ESC ACVC QIs, they provide insights into current practice of pharmacotherapy following AMI. This was a retrospective cohort study which has bias inherent to its observational design.

8.8 Conclusion

The COVID-19 pandemic created a natural experiment for the NHS. During this period, quality of care for AMI as measured against international standards did not worsen, but improved modestly. Give the decline in admissions with AMI, our findings could suggest that care quality may be further improved with appropriate staffing and resources. Implicit in the study is the notion that routinely collected data in concert with standardised measures of care quality allow appropriate evaluation of care quality.

8.9 References for Chapter 8

1 Mafham MM, Spata E, Goldacre R, et al. COVID-19 pandemic and admission rates for and management of acute coronary syndromes in England. Lancet 2020;396:381–9.

2 Pessoa-Amorim G, Camm CF, Gajendragadkar P, et al. Admission of patients with STEMI since the outbreak of the COVID-19 pandemic: a survey by the European Society of Cardiology. Eur Heart J Qual Care Clin Outcomes 2020;6:210–6.

3 Kwok CS, Gale CP, Kinnaird T, et al. Impact of COVID-19 on percutaneous coronary intervention for ST-elevation myocardial infarction. Heart 2020;106:1805–11.

4 Rashid Hons M, Gale Hons CP, Curzen Hons N, et al. Impact of coronavirus disease 2019 pandemic on the incidence and management of out-of-hospital cardiac arrest in patients presenting with acute myocardial infarction in England. J Am Heart Assoc 2020;9:e018379.

5 Collet J-P, Thiele H, Barbato E, et al. 2020 ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. Eur Heart J 2021;42:1289–367.

6 Curzen N. An extended statement by the British Cardiovascular Intervention Society president regarding the COVID-19 pandemic. Interv Cardiol 2020;15:e01.

7 Speciality guides for patient management during the coronavirus pandemic. Clinical guide for the management of cardiology patients during the coronavirus pandemic. Available: https://www.nice.org.uk/Media/Default/About/ COVID-19/Specialty-guides/specialty-guide-cardiolgycoronavirus.pdf

8 Wu J, Mamas M, Rashid M, et al. Patient response, treatments, and mortality for acute myocardial infarction during the COVID-19 pandemic. Eur Heart J Qual Care Clin Outcomes 2021;7:238–46.

9 Duclos A, Chollet F, Pascal L, et al. Effect of monitoring surgical outcomes using control charts to reduce major adverse events in patients: cluster randomised trial. BMJ 2020;371:m3840.

10 Hofstede SN, Ceyisakar IE, Lingsma HF, et al. Ranking hospitals: do we gain reliability by using composite rather than individual indicators? BMJ Qual Saf 2019;28:94–102.

11 Mulley AG. Improving productivity in the NHS. BMJ 2010;341:c3965.

12 Friebel R, Steventon A. Composite measures of healthcare quality: sensible in theory, problematic in practice. BMJ Qual Saf 2019;28:85–8.

13 Schiele F, Gale CP, Simon T, et al. The 2020 ESC-ACVC quality indicators for the management of acute myocardial infarction applied to the FAST-MI registries. Eur Heart J Acute Cardiovasc Care 2021;10:207–15.

14 Schiele F, Aktaa S, Rossello X, et al. 2020 Update of the quality indicators for acute myocardial infarction: a position paper of the Association for Acute Cardiovascular Care: the study group for quality indicators from the ACVC and the NSTE-ACS guideline group. Eur Heart J Acute Cardiovasc Care 2021;10:224–33.

15 Schiele F, Gale CP, Bonnefoy E, et al. Quality indicators for acute myocardial infarction: a position paper of the Acute Cardiovascular Care Association. Eur Heart J Acute Cardiovasc Care 2017;6:34–59.

16 Zusman O, Bebb O, Hall M, et al. International comparison of acute myocardial infarction care and outcomes using quality indicators. Heart 2019;105:820–5.

17 Rossello X, Medina J, Pocock S, et al. Assessment of quality indicators for acute myocardial infarction management in 28 countries and use of composite quality indicators for benchmarking. Eur Heart J Acute Cardiovasc Care 2020;9:911–22.

18 Schiele F, Gale CP, Simon T, et al. Assessment of quality indicators for acute myocardial infarction in the FAST-MI (French registry of acute ST-elevation or non-ST-elevation myocardial infarction) registries. Circ Cardiovasc Qual Outcomes 2017;10.

19 Bebb O, Hall M, Fox KAA, et al. Performance of hospitals according to the ESC ACCA quality indicators and 30-day mortality for acute myocardial infarction: national cohort study using the United Kingdom Myocardial Ischaemia National Audit Project (MINAP) register. Eur Heart J 2017;38:974–82.

20 Wilkinson C, Weston C, Timmis A, et al. Cohort profile: the Myocardial Ischaemia National Audit Project (MINAP). European Heart Journal - Quality of Care and Clinical Outcomes 2019;39:19–22.

21 Simms AD, Weston CF, West RM, et al. Mortality and missed opportunities along the pathway of care for ST-elevation myocardial infarction: a national cohort study. Eur Heart J Acute Cardiovasc Care 2015;4:241–53.

22 Ludman PF, British Cardiovascular Intervention Society. British Cardiovascular Intervention Society Registry for audit and quality assessment of percutaneous coronary interventions in the United Kingdom. Heart 2011;97:1293–7.

23 Ludman P. British Cardiovascular Intervention Society database: insights into interventional cardiology in the United Kingdom. Heart 2019;105:1289.

24 Douiri A, Muruet W, Bhalla A, et al. Stroke care in the United Kingdom during the COVID-19 pandemic. Stroke 2021;52:2125–33.

25 Wu J, Mamas MA, Mohamed MO, et al. Place and causes of acute cardiovascular mortality during the COVID-19 pandemic. Heart 2021;107:113–9.

26 Zhang L, Fan Y, Lu Z. Experiences and lesson strategies for cardiology from the COVID-19 outbreak in Wuhan, China, by 'on the scene' cardiologists. Eur Heart J 2020;41:1788–90.

27 Kwok CS, Gale CP, Curzen N, et al. Impact of the COVID-19 pandemic on percutaneous coronary intervention in England: insights from the British Cardiovascular Intervention Society PCI database cohort. Circ Cardiovasc Interv 2020;13:e009654.

28 Iacobucci G. Covid-19: all non-urgent elective surgery is suspended for at least three months in England. BMJ 2020;368:m1106.

29 Morris EJA, Goldacre R, Spata E, et al. Impact of the COVID-19 pandemic on the detection and management of colorectal cancer in England: a population-based study. Lancet Gastroenterol Hepatol 2021;6:199–208.

30 Gale CP, Cattle BA, Moore J, et al. Impact of missing data on standardised mortality ratios for acute myocardial infarction: evidence from the myocardial ischaemia national audit project (MINAP) 2004–7. Heart 2011;97:1926–31.

31 Rattka M, Dreyhaupt J, Winsauer C, et al. Effect of the COVID-19 pandemic on mortality of patients with STEMI: a systematic review and meta-analysis. Heart 2021;107:482–7.

32 Aktaa S, Batra G, Wallentin L. European Society of Cardiology methodology for the development of quality indicators for the quantification of cardiovascular care and outcomes. Eur Heart J Qual Care Clin Outcomes 2020;388.

33 Ludman P. British Cardiovascular Intervention Society database: insights into interventional cardiology in the United Kingdom. Heart 2019;105:1289–89.

34 Wallentin L, Gale CP, Maggioni A, et al. EuroHeart: European Unified Registries On Heart Care Evaluation and Randomized Trials. Eur Heart J 2019;40:2745–9.

35 Bhatt DL, Drozda JP, Shahian DM, et al. ACC/AHA/STS statement on the future of registries and the performance measurement enterprise. J Am Coll Cardiol 2015;66:2230–45.

36 Elshehaly M, Randell R, Brehmer M. QualDash: Adaptable Generation of Visualisation Dashboards for Healthcare Quality Improvement. IEEE Trans Vis Comput Graph 2020;PP(99).

37 Alabas OA, West RM, Gillott RG, et al. Evaluation of the Methods and Management of Acute Coronary Events (EMMACE)-3: protocol for a longitudinal study. BMJ Open 2015;5:e006256.

38 Herrett E, Shah AD, Boggon R, et al. Completeness and diagnostic validity of recording acute myocardial infarction events in primary care, hospital care, disease registry, and national mortality records: cohort study. BMJ 2013;346:f2350.

Chapter 9. Association of quality indicators for acute myocardial infarction and mortality: feasibility and validation study using linked nationwide registry data

Suleman Aktaa, Mohammad E Yadegarfar, Jianhua Wu, Muhammad Rashid, Mark de Belder, John Deanfield, Francois Schiele, Mark Minchin, Mamas Mamas, Chris P Gale

9.1 Summary of this publication:
- The data included in this Chapter was conducted as part of the analysis performed in Chapter 8, but was not included in the above publication.
- These data present the association between the attainment for the quality indicators for acute myocardial infarction (AMI) presented in Chapter 7 with mortality at different time points.
- Overall, there was an inverse association between adherence to the majority of the AMI quality indicators and mortality.
- The magnitude of this association attenuated over time, with greater long-term survival gains in the high GRACE risk patients.

9.2 Publication status:
- Not published
- Abstract presentation at the ESC Congress 2021

9.3 Abstract

9.3.1 Background

Quality indicators (QIs) have been increasingly used as tools to assess and improve the quality of care for acute myocardial infarction (AMI). However, it is not known if it is feasible to use the 2020 iteration of international AMI QIs using routinely collected data and, if so, whether better care is associated with improved outcomes.

9.3.2 Objective

To investigate if nationwide cardiovascular registry data captures data variables relating to the 2020 European Society of Cardiology association for Acute Cardiovascular Care QIs for AMI, quantify their association with all-cause mortality.

9.3.3 Methods

Cohort study of linked data from the United Kingdom AMI and percutaneous coronary intervention (PCI) registries and Civil Registration of Deaths Register between 2017 and 2020 (representing 236 743 patients from 186 hospitals). The Global Registry of Acute Coronary Events (GRACE) risk score was used to estimate baseline ischaemic risk. The likelihood of attainment for each QI based on GRACE risk was estimated using logistic regression and the risk-adjusted QI effect on mortality at 30 days, 6 months, 1 year and long-term (maximum 1243 days) was obtained from Cox proportional hazard models.

9.3.4 Results

Of 26 QIs, 17 (65.3%) could be directly measured and were each inversely associated with risk-adjusted mortality for 1-year and long-term survival, which was also true for 30-day and 6-months survival with exception of early invasive angiography for non-ST elevation myocardial infarction. The QI with the greatest magnitude for the reduction in long-term mortality was for the prescription of high-intensity statin at discharge (HR 0.32 [95% CI 0.31-0.34]), follow by reperfusion therapy (0.34 [0.32-0.35]) and adequate $P2Y_{12}$ inhibition at discharge (0.38 [0.36-0.40]). The magnitude of association between the composite QI and survival attenuated over time, with greater long-term survival gains in the high GRACE risk patients.

9.3.5 Conclusion

Care quality for AMI may be evaluated using routinely collected clinical data from the UK, whereby increasing hospital performance is associated with reduced mortality.

9.3.6 Keywords

Quality indicators. Acute myocardial infarction. GRACE. Mortality

9.4 Introduction

Quality indicators (QIs) provide the mechanism to evaluate medical care and guide the decision making for healthcare professionals, policy makers and patients alike.[193] They may help identify gaps in care delivery and enable the implementation of quality improvement interventions, but also assess the effectiveness of these interventions.[194] The systematic collection of QIs through registries,[19] and the public reporting of their results allow commissioners to monitor performance, and institutes to evaluate care quality.[23, 194, 195] Previously published international QIs for the management of acute myocardial infarction (AMI)[196] aligned with AMI care as recommended in international guidelines at the time, and were significantly associated with favourable patient outcomes.[13, 16, 197, 198] However, the recommended management of AMI has since changed,[199] and updated QIs have been developed.[200] Notably, it is not known whether it is feasible to use the 2020 iteration of international AMI QIs using routinely collected data and, if so, whether better care is associated with improved outcomes.

9.5 Methods

    9.5.1 Data and population

We used linked data from the UK national AMI and percutaneous coronary intervention (PCI) registries, namely the Myocardial Ischaemia National Audit Project (MINAP)[201, 202] and the British Cardiovascular Intervention Society (BCIS).[71] MINAP is a national registry representing all acute hospitals in England and Wales and prospectively collects information about patients hospitalized with AMI, including demographics, cardiovascular risk factors, co-morbidities, clinical characteristics at the time of hospitalization, and treatment delivered.[201] Data are encrypted and submitted electronically at each hospital site and securely transferred to a central database, where they are anonymized and then shared with research units upon request.

The BCIS registry is a national registry that prospectively collects data around the clinical, procedural, and outcome of over 95% of PCI procedures undertaken in the UK.[203] The National Institute for Cardiovascular Outcomes Research (NICOR), which encapsulates

BCIS and MINAP, has support under section 251 of the National Health Service (NHS) Act 2006 (Ref: NIGB: ECC 1-06 (d)/2011) to use patient information for medical research without consent. Thus, ethical approval was not required under NHS research governance arrangements.

9.5.2 Sample selection

We conducted our study in compliance with the Declaration of Helsinki using the MINAP and BCIS databases. We included all adult patients ($\geqslant$18 years of age), discharged alive with ST-segment elevation myocardial infarction (STEMI) or non-STEMI (NSTEMI) from MINAP between 2017 and 2020. Data related to PCI were obtained from the BCIS registry using each patient's unique NHS number to deterministically link patients between MINAP and BCIS registries. Where multiple admissions for the same patient were recorded, the earlier admission was used to reduce potential bias from previous treatments. Patients with no available survival data were excluded.

9.5.3 Ischaemic risk assessment

The QI attainment was evaluated across the different Global Registry of Acute Coronary Events (GRACE)[204, 205] risk scores for 6-month mortality.[206] The GRACE risk assessment tool has been validated using UK registry data for different phenotypes of AMI,[207, 208] and uses a number of prognostic information including age, cardiac arrest, Killip class, systolic blood pressure, heart rate, electrocardiographic ST-segment deviation, elevated cardiac enzyme and serum creatinine levels. Scores were calculated separately for STEMI and NSTEMI as low (<=88), intermediate (100 - 127) and high (128 - 263), and low (>=88), intermediate (89 – 118) and high (119 – 263), respectively.[206]

9.5.4 Outcome data

Mortality data were obtained from deterministic data linkage with the Civil Registration of Deaths Register from the Office for National Statistics using each patient's NHS number, thus providing vital status or date of death at 30 days, 6 months,1 year and long term.

9.5.5 Statistical analysis

Patient baseline characteristics, co-morbidities, and treatments were reported according to the phenotype of AMI as percentages and numbers for categorical variables, means and standard deviations (SD) for parametric continuous variables, and medians and interquartile ranges for non-parametric variables. Baseline differences between each diagnosis were tested using Chi-square test for categorical variables, t-test for continuous parametric and the Mann-Whitney test for non-parametric variables.

The distribution of QI attainment across different GRACE risk categories was reported as percentages and numbers. The likelihood of attainment for each QI at the patient level was calculated using logistic regression based on each patient's GRACE score risk category, with the low-risk group used as the reference group, and reporting odds ratio and accompanying confidence intervals (CI) for intermediate and high-risk groups.

Survival times were calculated from the time of admission to hospital until the date of death or censorship, with the maximum survival/censor time being 1243 days. Those with survival time of less than zero (n=37) were excluded from the analysis. Cox proportional-hazards were used to analyse the effect of each QI on patients' survival at 30-days, 6 months, 1 year and long-term. Univariate and GRACE risk-adjusted models survival models were performed for each survival time-point. The proportional hazards assumption was upheld when tested using Schoenfeld residuals.

All analyses were performed on complete cases. All tests were 2-sided, and statistical significance was considered as $P < 0.05$. Statistical analyses were performed in Stata IC version 14.2 and R version 3.4.3.

9.6 Results

9.6.1 Population

Data for 236 743 patients admitted with AMI to one of 186 NHS hospitals were included. Table 1 shows the baseline characteristics, co-morbidities, in-hospital treatment and discharge details according to the AMI diagnosis. Overall, 152 109 (64.3%) patients had NSTEMI, and the median age was 69 (58 – 79) years with 75 918 (32.2%) patients being women. Survival data were available for 234 556 patients and equated to 677 276 person years follow-up. After 23rd March 2020 (start of the first lockdown in England and Wales), there were 10 749 (4.5%) admissions with AMI, of which 6 679 (4.4%) and 4 070 (4.8%) were NSTEMI and STEMI, respectively (Table 1).

9.6.2 GRACE risk scores

Sufficient data were available to calculate GRACE risk scores for 193 177 (81.8%) patients (65 751[77.6%] for STEMI and 127 462 [83.8%] for NSTEMI), with an overall median GRACE score of 121 (96 – 151). Supplement Table S1 shows the proportion of patients in each of the GRACE risk groups for both STEMI and NSTEMI. There were more high-risk patients than intermediate- and low-risk for both STEMI (31 722 [48.25%], 19 367 [29.46%], 14 662 [22.30%]) and NSTEMI (61 637 [48.37%], 42 960 [33.71%], 22 829 [17.92%]). Most patients (82.4%), however, had Killip class I at the time of presentation with AMI, suggesting that GRACE scores were driven by factors other than Killip class in our cohort.

9.6.3 Deaths

In total, there were 15 555 (6.6%) deaths at 30 days, 26 422 (11.3%) at 6 months, 32 811 (14.0%) at 1 year and 43 335 (18.5%) long-term (at censor 1243 days). Mortality rates at all time points varied according to the baseline GRACE risk scores, with significantly higher mortality observed in the high-GRACE risk group compared with the intermediate- and low-risk (Supplement Table S2).

9.6.4 Quality indicator feasibility

Data from MINAP and BICIS registries enabled the direct measurement of 17 (65.3%) out of the 26 ESC ACVC QIs, including 2 (7.6%) structural, 13 (50%) process, and 2 (7.6%) composites. Another three (11.5%) QIs, albeit not directly measured, formed part of the routine practice in the UK. These include the participation in national registries, the involvement in networks for STEMI management and the monitoring of STEMI reperfusion times. The time between STEMI diagnosis and balloon inflation time (substituted for arterial access) was only measurable in 7 836 (9.3%) patients because of missing data, highlighting the difficulty in the capture of timing variables.

On the other hand, the planned duration of dual anti-platelets therapy (DAPT) and the three QIs within the patient satisfaction domain [evaluating patient feedback, assessing health-related quality of life (HRQoL), and providing discharge letters] could not be assessed because of the lack of data to support the measurement of these aspects of care. In addition, and while data were available to indirectly derive GRACE risk scores for 193 177 (81.8%) patients, objective risk-stratification for patients presenting with AMI using validated tools is not part of routine practice in the UK, nor captured in its national registries.

Figure 1. Performance variation across hospitals according to all-or-none composite quality indicator
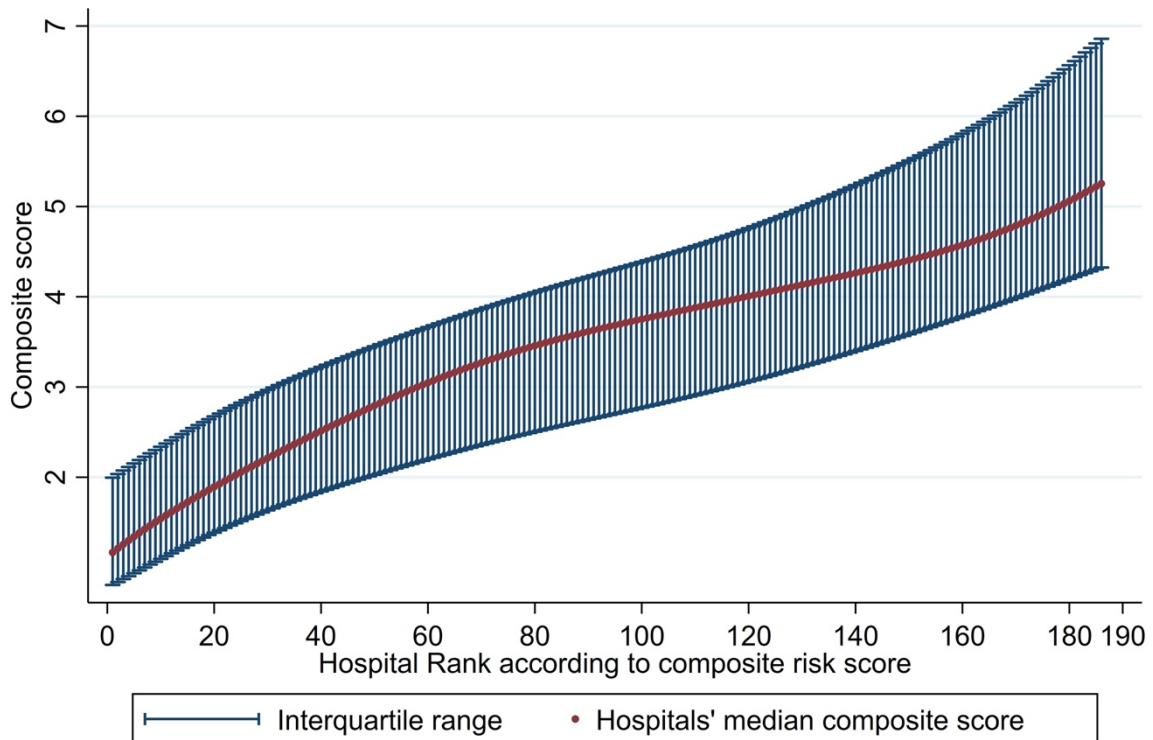
9.6.5 Quality indicator attainment

The quality of AMI care in the UK defined as the degree of attainment to the 2020 ESC ACVC QIs varied across hospitals in England and Wales (Figure 1) and by GRACE risk group (Table 1). The attainment for 13 (76.5%) of the 17 measured QIs inversely proportional to GRACE risk scores (Figure 2). The largest variation was noted in the adherence to secondary prevention medications at the time of hospital discharge, the use of radial access for PCI, and reperfusion therapy for eligible STEMI patient, with lower attainment in the high-risk group, compared with the intermediate- and low-risk. Structural QIs, however, as well as the assessment of left ventricular function during the hospital stay showed little discrimination to the quality of care across different GRACE risk groups.

Table 1. Quality indicator attainment across different GRACE categories

QI (Receipt or availability)	GRACE

	Low (n=37,491)	Intermediate (n=62,327)	High (n=93,359)	All (n=193,177)	p-value
Hospital use of hs-cTn for NSTEMI	73.0 (16,562)	74.0 (31,576)	73.4 (44,994)	73.5 (93,132)	0.007
Pre-hospital interpretation of ECG for STEMI	73.4 (9,679)	74.1 (12,967)	78.5 (22,437)	76.1 (45,083	<0.001
Reperfusion among eligible for STEMI	86.5 (12,675)	86.4 (16,729)	74.7 (23,679)	80.7 (53,083)	<0.001
Timely reperfusion for STEMI	83.7 (10,605)	83.2 (13,912)	81.6 (19,317)	82.6 (43,834)	<0.001
Invasive coronary angiography within 24h for NSTEMI	39.9 (5,740)	36.6 (9,384)	30.1 (7,070)	34.9 (22,194)	<0.001
Radial access for invasive procedures	92.1 (19,405)	90.9 (28,667)	83.4 (28,413)	88.2 (76,485)	<0.001
Median time from ECG to arterial access* for STEMI	87.4 (65.5 - 120.1)	85.2 (65.5 - 118.0)	89.6 (67.7 - 122.3)	87.4 (65.5 - 120.1)	<0.001
LVEF assessment before hospital discharge	65.4 (24,525)	65.4 (40,788)	63.6 (59,406)	64.6 (124,719	<0.001
In-hospital measurement of LDL-C**	67.9 (25,444)	62.9 (39,196)	53.3 (49,711)	59.2 (114,351)	<0.001
Adequate P2Y$_{12}$ inhibition on discharge	98.4 (30,638)	97.8 (49,646)	95.5 (65,320)	96.9 (145,604)	<0.001
Parenteral anticoagulation	87.8 (26,132)	87.7 (43,715)	82.8 (63,056)	85.3 (132,903)	<0.001
Dual antiplatelet therapy on discharge	98.0 (30,120)	97.2 (47,968)	93.8 (59,218)	95.9 (137,306)	<0.001
High intensity statin on discharge**	99.0 (31,006)	98.6 (50,412)	95.9 (66,295)	97.5 (147,713)	<0.001
ACEi for patients with reduced LVEF	98.6 (6,971)	98.1 (12,270)	96.0 (21,373)	97.0 (40,614)	<0.001
Beta Blockers for patients with reduced LVEF	99.0 (6,939)	98.8 (12,382)	98.0 (23,659)	98.4 (42,980)	<0.001
Composite All/None	46.5 (17,437)	44.0 (27,439)	45.6 (42,571)	45.3 (87,447)	<0.001

Composite Score				
Denominator (median/IQR)	5 (4 - 5)	5 (4 - 5)	5 (3 - 5)	5 (4 - 5)
Numerator (median/IQR)	4 (3 - 5)	4 (3 - 5)	4 (2 - 5)	4 (3 - 5)
Ratio (median/IQR)	0.8 (0.8 - 1)	0.8 (0.8 - 1)	0.8 (0.8 - 1)	0.8 (0.8 - 1)

ACEi; angiotensin converting enzyme inhibitors, GRACE; Global Registry of Acute Coronary Events, hscTn; high-sensitivity cardiac troponin, LDL-C; low density lipoprotein cholesterol, LVEF; left ventricular ejection fraction, NSTEMI; non-ST segment elevation myocardial infarction, STEMI; ST-segment elevation myocardial infarction, QI; quality indicator

9.6.6 Survival trajectories

Of the 17 measured QIs, the attainment for 16 (94%) was associated with improved long-term survival (Figure 2). There was also an inverse association between the median time from STEMI diagnosis to balloon inflation (substituted for arterial access) and mortality (Supplementary Table S2). At all time-points, mortality was reduced by the attainment for 16 (94%) QIs, with the early invasive angiography within 24 hours from NSTEMI diagnosis associating with a reduction in 6-month, 1-year, and long-term, and an increase in 30-day mortality.

Figure 2. Risk-adjusted survival estimates for each of the quality indicators
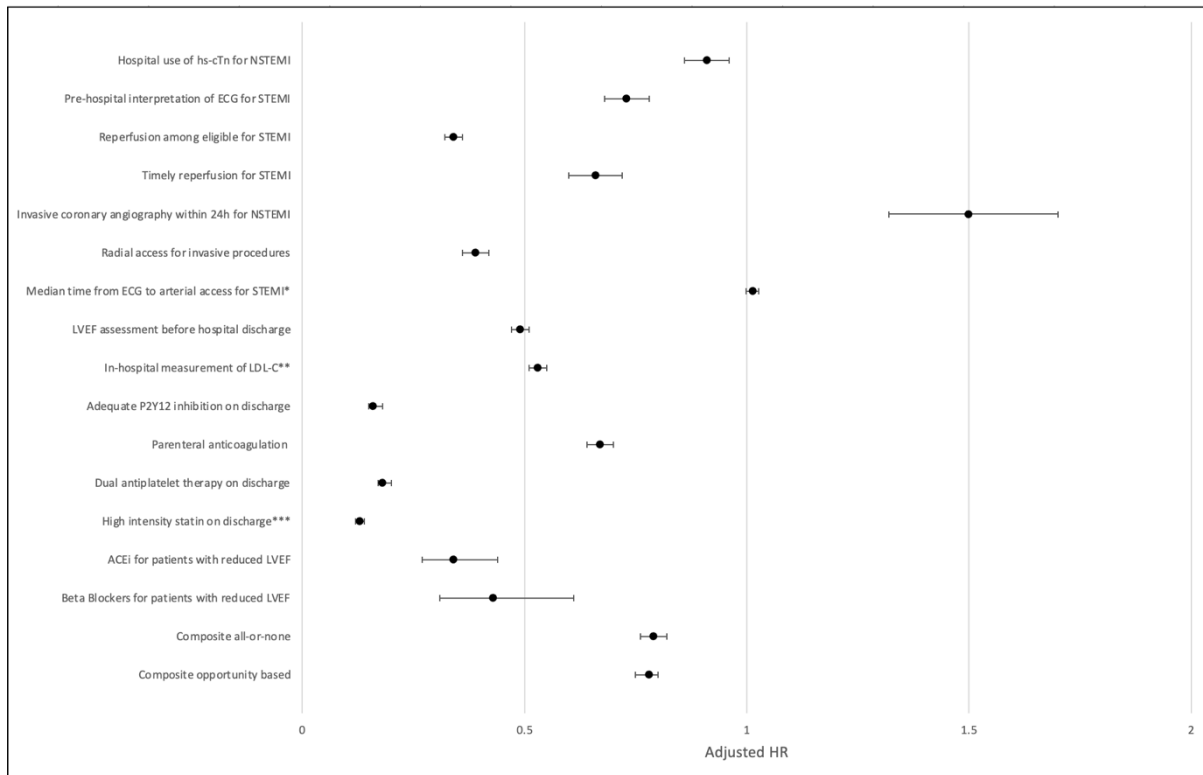
ACEi; angiotensin converting enzyme inhibitors, GRACE; Global Registry of Acute Coronary Events, hscTn; high-sensitivity cardiac troponin, LDL-C; low density lipoprotein cholesterol, LVEF; left ventricular ejection fraction, NSTEMI; non-ST segment elevation myocardial infarction, STEMI; ST-segment elevation myocardial infarction, QI; quality indicator

The QI with the greatest magnitude for the reduction in long-term mortality was the prescription of statins (substituted for high-intensity statin) at discharge (HR 0.32 [95% CI 0.31-0.34]), follow by reperfusion therapy (0.34 [0.32-0.35]) and adequate P2Y$_{12}$ inhibition at discharge (0.38 [0.36-0.40]). While the QI with the least reduction in long-term mortality was the median time between STEMI diagnosis and arterial access (1.02 [1.01-1.03] per 10 minutes), hospital use of high-sensitive cardiac troponin (0.88 [0.86-0.91]), and invasive coronary angiography within 24 hours for patients with NSTEMI (0.85 [0.80-0.90]). Over time, the magnitude of the association between the composite QI and survival attenuated, and

greater long-term survival gains were observed in the high GRACE risk group compared with the intermediate and low risk patients (Figure 3).

Figure 3. Long-term survival of patients with AMI according to composite quality indicator attainment, by GRACE risk category
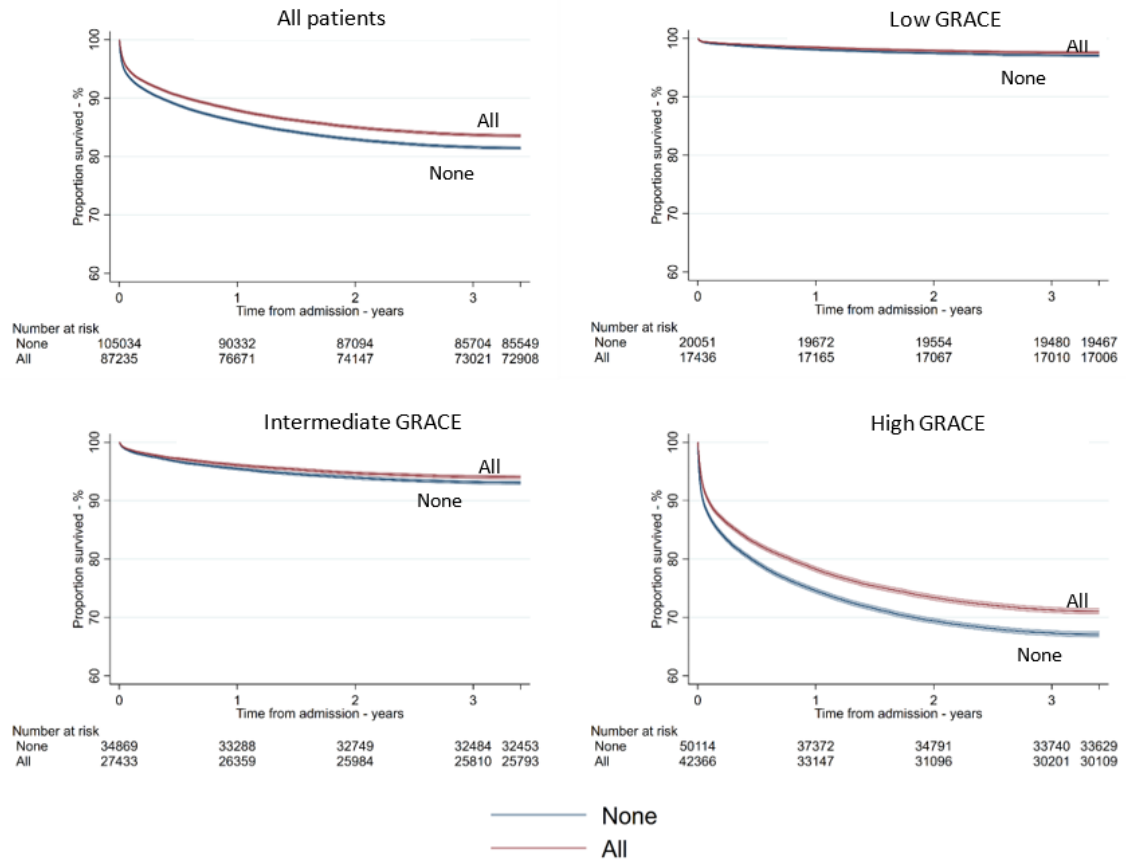
AMI- acute myocardial infarction, GRACE= Global Registry of Acute Coronary Events.

9.6.7 The composite quality indicators scores

The opportunity-based composite QI (CQI) had a mean value of 3.94 (+/- 1.70) for all AMI patients in whom a GRACE risk score could be calculated, 4.11 (+/- 1.63), 4.03 (+/- 1.63), and 3.81 (+/- 1.75) for the high, intermediate, and low GRACE risk score groups. The all-or-none CQI had was 45.6% (42 571), 44.0% (27 439), and 46.5% (17 437) for the high, intermediate and low GRACE risk score groups. For patients with LVEF $\geq$0.40, the all-or-

none CQI was achieved (calculated at 1) in 66.6% (n= 45,819) of all AMI patients, in 67.2% (n= 11,090), 64.0% (n= 16,496), and 68.8% (n= 18,233) for the high, intermediate, and low GRACE categories, while it was achieved in 74.5% (n= 41,628) of all AMI patients, in 79.1% (n= 6,347), 73.0% (n= 10,943), and 74.0% (n= 24,338) for high, intermediate, and low GRACE categories for patients with LVEF <0.40.

9.7 Discussion

This study investigated whether UK national cardiovascular registries enabled the evaluation of AMI care quality using internationally developed QIs,[200] and assessed their association with survival. It shows that the 2020 ESC ACVC QIs for AMI are feasible metrics that have a meaningful association with patient outcomes and that they may be used to report quality of care for AMI. Furthermore, this study highlights the role of secondary prevention medications in reducing long-term mortality following an AMI, and identifies, using 'real-world' data, areas for improvement in contemporary practice. As such, strategies to enhance the adherence to guideline-indicated care and continuously evaluate AMI care processes may be implemented.

The use of a suite of QIs as opposed to a single measure provides multi-faceted assessment of the quality of medical care.[185, 193] While various sets of QIs for the management of AMI exist,[164, 196, 209], the ESC ACVC QIs are aimed for the European healthcare systems, and the 2017 version was validated in a number of national and international registries.[13, 197, 198] However, only 6 QIs remained unchanged in the 2020 iteration, compared with the 2017 set, and no other study has evaluated their feasibility using existing registry data. Thus, the findings of our study may enhance the dissemination and implementation of the 2020 ESC ACVC QIs and, consequently, drive quality assessment and improvement.

We have shown that while adherence to QIs was associated with a reduction in mortality over time, its use decreased with increasing GRACE risk scores. Risk stratifying patients with

AMI using GRACE module has been found to be superior to subjective assessment of healthcare providers for the estimation of prognosis.[210, 211] We found that patients with high GRACE risk scores have higher mortality at all time points, as well as greater and persistent survival gains from QI attainment, compared with patients in the intermediate and low categories. This highlights the importance of validated tools, such as GRACE to estimate risk and enable the timely activation of care interventions.

It is evident that there are missed opportunities in the management of patients with high GRACE risk scores.[212 213 199] Our study shows, using contemporary data, the persistence of the so called 'risk-treatment paradox'.[76, 77, 214, 215] As such, efforts to understand the factors contributing to the persistence of the existing gaps in care delivery, and whether pressure on resources contribute to the sub-optimal adherence to guideline-indicated care are needed.

Clinical Practice Guidelines recommend performing an invasive coronary angiography (ICA) within 24 hours for patients with NSTEMI.[199] While our study demonstrated an improvement in long-term survival with the attainment of this QI, it was associated with an increase in mortality at 30 days. This may be explained by survivorship bias given that NSTEMI patients with features of haemodynamic instability may be prioritized for an early invasive treatment.

Our study emphasises the importance of the integration of clinical registries design with QIs.[185] Notwithstanding that 17 out of the 26 ESC ACVC QIs were measured using UK registry data, the 'patient satisfaction' domain requires data about HRQoL, which are not captured in MINAP or BCIS. Patient reported outcome measures (PROMs), such as HRQoL are increasingly recognised as important indicators of performance,[199 185] and, thus, PROMs should be integrated within quality assessment systems. The Evaluation of the Methods and Management of Acute Coronary Events (EMMACE) study[216] collects HRQoL for AMI survivors, but data from EMMACE were not available for our study cohort.

In addition, our study identified other areas for improvement within the existing UK registries. These include information regarding the time of arterial access for invasive strategy, whether statin prescribed at discharge was high intensity, the planned duration of DAPT following AMI, and the assessment of risk using validated tools. The implementation of such information may facilitate the adherence to these evidence-based aspects of AMI care, and the capture of data when measuring performance.

While our study has a number of strengths, it has limitations. First, the observational nature of the study increases the risks of confounding factors in determining survival and limits the ability to infer causation. However, the use of one of the largest, whole-country databases for AMI patients (MINAP) and adjusting mortality using a validated risk score (GRACE) allowed drawing meaningful conclusions regarding the quality of care and gaps in care delivery. Second, because evaluating long-term survival was one of the objectives of the study, patient who died during the hospital stay were excluded from the study, which may have resulted in survival bias. Third, missing data could have biased the estimates. Fourth, all-cause mortality, rather than cardiovascular mortality was evaluated due to the unavailability of cause-specific mortality. Non-cardiovascular deaths may not be attributable to AMI care, and, thus, mortality rates could be overestimated in our study[217]. Fifth, the 'risk-treatment paradox' may be an indicator of higher ischaemic risk itself, which may explain the lower attainment of QIs observed in high-risk patients.

9.8 Conclusion

Quality of care for the management of AMI may be evaluated using routinely collected clinical data from the UK registries. The ESC ACVC QIs for AMI could be applied to UK data to measured care quality and were inversely associated with survival.

9.9 References for Chapter 9

1. Friebel R, Steventon A. Composite measures of healthcare quality: sensible in theory, problematic in practice. *BMJ Quality & Safety* 2019;28(2):85-88. doi: 10.1136/bmjqs-2018-008280

2. Duclos A, Chollet F, Pascal L, et al. Effect of monitoring surgical outcomes using control charts to reduce major adverse events in patients: cluster randomised trial. *BMJ* 2020;371:m3840. doi: 10.1136/bmj.m3840

3. Bhatt DL, Drozda JP, Shahian DM, et al. ACC/AHA/STS Statement on the Future of Registries and the Performance Measurement Enterprise. *Journal of the American College of Cardiology* 2015;66(20):2230-45. doi: 10.1016/j.jacc.2015.07.010

4. Hofstede SN, Ceyisakar IE, Lingsma HF, et al. Ranking hospitals: do we gain reliability by using composite rather than individual indicators? *BMJ Quality & Safety* 2019;28(2):94-102. doi: 10.1136/bmjqs-2017-007669

5. NICE indicator process guide. December 2019. *Available at: https://wwwniceorguk/media/default/Get-involved/Meetings-In-Public/indicator-advisory-committee/ioc-process-guidepdf Accessed 24 March 2020* 2019:26.

6. Schiele F, Gale CP, Bonnefoy E, et al. Quality indicators for acute myocardial infarction: A position paper of the Acute Cardiovascular Care Association. *Eur Heart J Acute Cardiovasc Care* 2017;6(1):34-59. doi: 10.1177/2048872616643053

7. Zusman O, Bebb O, Hall M, et al. International comparison of acute myocardial infarction care and outcomes using quality indicators. *Heart* 2019;105(11):820-25. doi: 10.1136/heartjnl-2018-314197 [published Online First: 2019/02/01]

8. Rossello X, Medina J, Pocock S, et al. Assessment of quality indicators for acute myocardial infarction management in 28 countries and use of composite quality indicators for benchmarking. *Eur Heart J Acute Cardiovasc Care* 2020:2048872620911853. doi: 10.1177/2048872620911853 [published Online First: 2020/03/12]

9. Schiele F, Gale CP, Simon T, et al. Assessment of Quality Indicators for Acute Myocardial Infarction in the FAST-MI (French Registry of Acute ST-Elevation or Non-ST-Elevation Myocardial Infarction) Registries. *Circulation Cardiovascular quality and outcomes* 2017;10(6) doi: 10.1161/CIRCOUTCOMES.116.003336

10. Bebb O, Hall M, Fox KAA, et al. Performance of hospitals according to the ESC ACCA quality indicators and 30-day mortality for acute myocardial infarction: national cohort study using the United Kingdom Myocardial Ischaemia National Audit Project

(MINAP) register. *European Heart Journal* 2017;38(13):974-82. doi: 10.1093/eurheartj/ehx008

11. Collet J-P, Thiele H, Barbato E, et al. 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: The Task Force for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J* 2020 doi: 10.1093/eurheartj/ehaa575

12. Schiele F, Aktaa S, Rossello X, Collet JP, Gale CP, Huber K, Keys A, Lambrinou E, Leonardi S, Masoudi FA, Tubaro M, Bueno H. 2020 update of the quality indicators for acute myocardial infarction: A position paper of the association for acute cardiovascular care Eur Heart J Acute Cardiovasc Care. 2020;In press.

13. Mafham MM, Spata E, Goldacre R, et al. COVID-19 pandemic and admission rates for and management of acute coronary syndromes in England. *The Lancet* 2020;396(10248):381-89. doi: 10.1016/S0140-6736(20)31356-8

14. Wu J, Mamas MA, Mohamed MO, et al. Place and causes of acute cardiovascular mortality during the COVID-19 pandemic. *Heart* 2020:heartjnl-2020-317912. doi: 10.1136/heartjnl-2020-317912

15. Pessoa-Amorim G, Camm CF, Gajendragadkar P, et al. Admission of patients with STEMI since the outbreak of the COVID-19 pandemic: a survey by the European Society of Cardiology. *Eur Heart J Qual Care Clin Outcomes* 2020;6(3):210-16. doi: 10.1093/ehjqcco/qcaa046

16. Wu J, Mamas M, Rashid M, et al. Patient response, treatments, and mortality for acute myocardial infarction during the COVID-19 pandemic. *Eur Heart J Qual Care Clin Outcomes* 2020 doi: 10.1093/ehjqcco/qcaa062

17. Wilkinson C, Weston C, Timmis A, et al. The Myocardial Ischaemia National Audit Project (MINAP). *European Heart Journal - Quality of Care and Clinical Outcomes* 2019;6(1):19-22. doi: 10.1093/ehjqcco/qcz052

18. Simms AD, Weston CF, West RM, et al. Mortality and missed opportunities along the pathway of care for ST-elevation myocardial infarction: a national cohort study. *European heart journal Acute cardiovascular care* 2015;4(3):241-53. doi: 10.1177/2048872614548602

19. Ludman PF. British Cardiovascular Intervention Society Registry for audit and quality assessment of percutaneous coronary interventions in the United Kingdom. *Heart* 2011;97(16):1293-97. doi: 10.1136/heartjnl-2011-300299

20. Ludman P. British Cardiovascular Intervention Society database: insights into interventional cardiology in the United Kingdom. *Heart* 2019;105(16):1289. doi: 10.1136/heartjnl-2018-314533

21. Granger CB, Goldberg RJ, Dabbous O, et al. Predictors of hospital mortality in the global registry of acute coronary events. *Arch Intern Med* 2003;163(19):2345-53. doi: 10.1001/archinte.163.19.2345 [published Online First: 2003/10/29]

22. Fox KA, Dabbous OH, Goldberg RJ, et al. Prediction of risk of death and myocardial infarction in the six months after presentation with acute coronary syndrome: prospective multinational observational study (GRACE). *Bmj* 2006;333(7578):1091. doi: 10.1136/bmj.38985.646481.55 [published Online First: 2006/10/13]

23. https://www.outcomes-umassmed.org/grace/grace_risk_table.aspx. Accessed 27 September 2020.

24. Simms AD, Reynolds S, Pieper K, et al. Evaluation of the NICE mini-GRACE risk scores for acute myocardial infarction using the Myocardial Ischaemia National Audit Project (MINAP) 2003-2009: National Institute for Cardiovascular Outcomes Research (NICOR). *Heart* 2013;99(1):35-40. doi: 10.1136/heartjnl-2012-302632 [published Online First: 2012/09/25]

25. Gale CP, Manda SOM, Weston CF, et al. Evaluation of risk scores for risk stratification of acute coronary syndromes in the Myocardial Infarction National Audit Project (MINAP) database. *Heart* 2009;95(3):221-27. doi: 10.1136/hrt.2008.144022

26. Aktaa S, Batra G, Wallentin L, et al. European Society of Cardiology methodology for the development of quality indicators for the quantification of cardiovascular care and outcomes. 2020

27. Jneid H, Addison D, Bhatt DL, et al. 2017 AHA/ACC Clinical Performance and Quality Measures for Adults With ST-Elevation and Non-ST-Elevation Myocardial Infarction: A Report of the American College of Cardiology/American Heart Association Task Force on Performance Measures. *Journal of the American College of Cardiology* 2017;70(16):2048-90. doi: 10.1016/j.jacc.2017.06.032

28. Tu JV, Khalid L, Donovan LR, et al. Indicators of quality of care for patients with acute myocardial infarction. *Cmaj* 2008;179(9):909-15. doi: 10.1503/cmaj.080749 [published Online First: 2008/10/22]

29. Bing R, Goodman SG, Yan AT, et al. Use of clinical risk stratification in non-ST elevation acute coronary syndromes: an analysis from the CONCORDANCE registry.

European heart journal Quality of care & clinical outcomes 2018;4(4):309-17. doi: 10.1093/ehjqcco/qcy002

30. Chew DP, Junbo G, Parsonage W, et al. Perceived risk of ischemic and bleeding events in acute coronary syndromes. *Circ Cardiovasc Qual Outcomes* 2013;6(3):299-308. doi: 10.1161/CIRCOUTCOMES.111.000072

31. Fox KAA, Anderson FA, Dabbous OH, et al. Intervention in acute coronary syndromes: do patients undergo intervention on the basis of their risk characteristics? The Global Registry of Acute Coronary Events (GRACE). *Heart* 2007;93(2):177-82. doi: 10.1136/hrt.2005.084830

32. Saar A, Marandi T, Ainla T, et al. The risk-treatment paradox in non-ST-elevation myocardial infarction patients according to their estimated GRACE risk. *International Journal of Cardiology* 2018;272:26-32. doi: 10.1016/j.ijcard.2018.08.015

33. Alabas OA, West RM, Gillott RG, et al. Evaluation of the Methods and Management of Acute Coronary Events (EMMACE)-3: protocol for a longitudinal study. *BMJ Open* 2015;5(6):e006256. doi: 10.1136/bmjopen-2014-006256 [published Online First: 2015/06/25]

34. Hall M, Alabas OA, Dondo TB, et al. Use of relative survival to evaluate non-ST-elevation myocardial infarction quality of care and clinical outcomes. *Eur Heart J Qual Care Clin Outcomes* 2015;1(2):85-91. doi: 10.1093/ehjqcco/qcv011

Chapter 10. Quality indicators for the care and outcomes of adults with atrial fibrillation

Task Force for the development of quality indicators in atrial fibrillation of the European Heart Rhythm Association (EHRA) of the European Society of Cardiology (ESC): Developed in collaboration with the Heart Rhythm Society (HRS), the Asia Pacific Heart Rhythm Society (APHRS), and the Latin-American Heart Rhythm Society (LAHRS)

Elena Arbelo, Suleman Aktaa, Andreas Bollmann, André D'Avila, Inga Drossart, Jeremy Dwight, Mellanie True Hills, Gerhard Hindricks, Fred M Kusumoto, Deirdre A Lane, Dennis H Lau, Maddalena Lettino, Gregory Y H Lip, Trudie Lobban, Hui-Nam Pak, Tatjana Potpara, Luis C Saenz, Isabelle C Van Gelder, Paul Varosy, Chris P Gale, Nikolaos Dagres

10.1 Summary of the publication:

- Using the methodology described in Chapter 4, this paper presents the quality indicators for atrial fibrillation (AF).
- Six domains of AF care have been defined: (1) Patient assessment (baseline and follow-up), (2) Anticoagulation therapy, (3) Rate control strategy, (4) Rhythm control strategy, (5) Risk factor management, and (6) Outcomes measures, including patient-reported outcome measures (PROMs).
- In total, 17 main and 17 secondary quality indicators for AF across the six domains of care were defined.

10.2 Publication status:

- Published 29 August 2020
- EP Europace, Volume 23, Issue 4, April 2021, Pages 494–495, https://doi.org/10.1093/europace/euaa253

10.3 Abstract

10.3.1 Aims

To develop quality indicators (QIs) that may be used to evaluate the quality of care and outcomes for adults with atrial fibrillation (AF).

10.3.2 Methods and results

We followed the ESC methodology for QI development. This methodology involved (i) the identification of the domains of AF care for the diagnosis and management of AF (by a group of experts including members of the ESC Clinical Practice Guidelines Task Force for AF); (ii) the construction of candidate QIs (including a systematic review of the literature); and (iii) the selection of the final set of QIs (using a modified Delphi method). Six domains of care for the diagnosis and management of AF were identified: (i) Patient assessment (baseline and follow-up), (ii) Anticoagulation therapy, (iii) Rate control strategy, (iv) Rhythm control strategy, (v) Risk factor management, and (vi) Outcomes measures, including patient-reported outcome measures (PROMs). In total, 17 main and 17 secondary QIs, which covered all six domains of care for the diagnosis and management of AF, were selected. The outcome domain included measures on the consequences and treatment of AF, as well as PROMs.

10.3.3 Conclusion

This document defines six domains of AF care (patient assessment, anticoagulation, rate control, rhythm control, risk factor management, and outcomes), and provides 17 main and 17 secondary QIs for the diagnosis and management of AF. It is anticipated that implementation of these QIs will improve the quality of AF care.

10.3.4 Keywords

Atrial fibrillation, Quality indicators, Outcome measures

10.4 Introduction

Atrial fibrillation (AF) is a key public health challenge and major source of morbidity, mortality and economic burden for governments worldwide[218]. Despite progress in the management of patients with AF, this arrhythmia is still a major cause of stroke, heart failure, and cardiovascular morbidity and mortality globally[219]. Additionally, AF is associated with cognitive impairment[220-222], reduced quality of life (QoL)[223, 224], depression[225], and frequent hospital admissions[226-228]. The magnitude of the economic burden of AF is increasing, mainly driven by AF-related complications and management costs, particularly those associated with hospitalizations[219, 229, 230].

Data from the EURObservational Research Programme in AF (EORP-AF) found that adherence to guideline recommended therapies in the treatment of AF is associated with lower mortality[231], yet large variability persists in the delivery of such therapies across Europe[232, 233]. To improve the implementation of evidence-based medicine[234], some professional organisations have developed quality standards, clinical indicators and quality measures to evaluate and improve the quality of AF care[235-237,238, 239]. However, no AF quality indicators (QIs) have been specifically designed for the wider international community.

Hence, the European Heart Rhythm Association (EHRA), in collaboration with the Asian Pacific Heart Rhythm Society (APHRS), the Heart Rhythm Society (HRS) and the Latin-American Heart Rhythm Society (LAHRS), established the AF QI Working Group, which was tasked with the development of QIs for the diagnosis and management of adults with AF. It is hoped that these QIs can serve as a mechanism to improve the quality of AF care, and be used by healthcare providers to evaluate care delivery at the patient, centre, and national levels.

To enhance the translation of guideline recommendations into clinical practice and provide healthcare providers with tools to identify opportunities for improvement, a summary of the

AF QIs has been embedded in the 2020 ESC Clinical Practice Guidelines for AF[240]. Efforts were made to ensure alignment between the developed QIs and the ESC Guidelines for AF, which may differ from recommendations developed by other professional organisations.

10.5 Methods

The detailed methodology for the development of QIs for the quantification of cardiovascular care and outcomes for the ESC Clinical Practice Guidelines is published separately[241]. This methodology consists of a four-step process: identification of the key domains of care; construction of candidate indicators; selection of a final QI set; and undertaking of a feasibility assessment. In this document, we have identified important domains of AF care, and developed QIs for each domain. The development process involved conducting a systematic review of the literature, and using a modified Delphi method[242] to derive the final set of QIs and divide them into main and secondary QIs. The next step would be to conduct a feasibility assessment of the developed QIs using existing AF registries[241].

Quality indicators may be divided into structural, process, and outcome indicators[243]. For each proposed QI, we provided relevant specifications, including numerator, denominator, measurement period, and measurement duration. However, no care settings were suggested, because the proposed QIs are applicable in both the inpatient and outpatient care. It is, thus, important to determine locally the clinical setting during which QIs are applied in order to ensure the same processes of care are evaluated between healthcare providers.

10.5.1 Members of the Working Group

The Working Group comprised of members of the ECG Clinical Practice Guidelines Task Force, as well as international experts in AF management, patients with AF, and representatives from patient organisations. Six domains of AF care were defined: 1) Patient assessment (baseline and follow-up), 2) Anticoagulation therapy, 3) Rate control strategy, 4) Rhythm control strategy, 5) Risk factor management, and 6) Outcomes measures, including patient-

reported outcome measures (PROMs). The names, affiliations, and conflicts of interest of the AF QIs Working Group is provided in APPENDIX 1.

10.5.2 Systematic review

10.5.2.1 Search strategy

We conducted a systematic review of the published literature in accordance with the Preferred Reporting Items for Systematic Review and Meta-analyses statement[244, 245] (APPENDIX 2). We searched two online bibliographic databases; MEDLINE and Embase via OVID®. The initial search strategy was developed in MEDLINE using keywords and, when available, medical subject headings (MesH) terms based on three main terms: "atrial fibrillation", "quality indicators", and "outcome measures", (APPENDIX 3). The final search strategies were, then, developed using an iterative process, which also included citations search, grey literature, and hand search of the reference lists of the selected studies.

We included randomised controlled trials (RCTs) and observational studies, including local, national, and international registries. We excluded systematic reviews, meta-analyses, editorial letters and conference proceedings. We only included the main publications of major trials and registries from which our search obtained only their sub-studies. The search was restricted to those full-text articles published in English language and publication date between 01 January 2014 and 05 October 2019, to capture QIs and outcome measures for AF from contemporary practice.

10.5.2.2 Eligibility criteria

We included articles which fulfilled the following criteria: 1) the study population was adult patients (≥18 years old) with AF, 2) the study explicitly stated at least one QI or outcome measure to define best practice for AF diagnosis and/or management, 3) the study provided specifications for the QI or outcome measure (e.g., definition, data collection source, method of reporting), 4) RCT or registry, and 5) full-text publication. No restrictions were applied to the presence of, or the type of, intervention or comparison in the study.

10.5.2.3 Study selection

A reference manager software (Zotero) was used for duplicates removal and data management. Two authors (Suleman Aktaa and Elena Arbelo) independently examined the abstracts of the studies retrieved from the search against the inclusion criteria. Disagreements were resolved through discussion and review of the full text of the article when required.

10.5.2.4 Data extraction

The full texts of the included studies were independently reviewed by two authors (Suleman Aktaa and Elena Arbelo). All QIs relevant to the agreed 6 domains of AF care, namely: 1) Patient assessment (baseline and follow-up), 2) Anticoagulation therapy, 3) Rate control strategy, 4) Rhythm control strategy, 5) Risk factor management, and 6) Outcomes measures (including PROMs) were extracted and listed on an Excel spreadsheet. When available, the following information was obtained for the extracted QIs: definition (including numerator, denominator, and exclusions), objective, type of QI (structural, process, outcome, or PROM), domain of application, and potential data collection source.

10.5.2.5 Clinical Practice Guidelines and Existing QIs

In addition to the systematic review outlined above, we reviewed relevant Clinical Practice Guidelines and existing QIs from different professional organizations (Table 1). The goal of the Clinical Practice Guidelines review was to identify the recommendations with the strongest association with benefit or harm and to assess these recommendations against the ESC criteria for QIs (Table 2)[241]. Additionally, existing publications on QIs for patients with AF were also reviewed and, when applicable, information about the feasibility and/or validity of these measures was obtained.

Table 1. Existing Clinical Practice Guidelines and QIs used during the development process

Organisation	Type	Year	Country/Region

ESC Guideline for the Management of Patients with Atrial Fibrillation[240]	Clinical Practice Guidelines	2020	Europe
ICHOM International Standard Set of Outcome Measures for patients with Atrial Fibrillation[246]	QIs	2020	Worldwide
AHA/ACC/HRS Focused Update of the 2014 AHA/ACC/HRS Guideline for the Management of Patients with Atrial Fibrillation[247]	Clinical Practice Guidelines	2019	United States
Canadian Quality Indicators for Atrial Fibrillation and Atrial Flutter[237]	QIs	2019	Canada
Harmonized outcome measures for use in atrial fibrillation patient registries and clinical practice[248]	QIs	2019	United States
ACC/AHA Clinical Performance and Quality Measures for Adults with Atrial	QIs	2016	United States

Fibrillation or Atrial Flutter[249]			
ESC Guidelines for the management of atrial fibrillation developed[250]	Clinical Practice Guidelines	2016	Europe
NICE Atrial Fibrillation Quality standard [QS93][173]	QIs	2015	United Kingdom
AHA/ACC/HRS Guidelines for the Management of Patients with Atrial Fibrillation[251]	Clinical Practice Guidelines	2014	United States

QI=quality indicators; AHA=American Heart Association; ACC=American College of Cardiology; ESC=European Society of Cardiology; ICHOM=International Consortium for Health Outcomes Measurement; NICE=National Institute of Clinical Excellence;

10.5.2.6 Data synthesis

10.5.2.6.1 Candidate QIs

A list of candidate QIs was derived from the aforementioned systematic review and classified into structural, process, or outcome measures depending on the aspect of care being measured[243]. For each QI, a detailed definition was provided in order to facilitate the evaluation process.

10.5.2.6.2 Modified Delphi process

We used the modified Delphi process[242, 252] to evaluate the candidate QIs and arrive at the final set of QIs. Instructions on the voting process, including QIs criteria (Table 2) were sent to the Working Group before the vote. All measures were independently graded by each member of the Group using the SurveyMonkey platform. Three rounds of voting were conducted, with a teleconference after each round to discuss the results of the vote. In the first voting round, we

used a 9-point ordinal scale, where ratings of 1 to 3 signified that the QI was not valid; ratings of 4 to 6 meant that the QI was of uncertain validity; and ratings of 7 to 9 indicated that the QI was valid. Candidate QIs were included if ≥75% of the Working Group members ranked them between 7 and 9, and were excluded if ≥75% of the Working Group members ranked them between 1 and 3. Indicators that did not fall in the two categories above where carried forward to the second voting round, where a 3-point scale (should not be included, maybe, and should be included) was implemented, but same percentage agreement (≥75% of the Working Group members) cut-off was used. The final round comprised a binary, 'yes' or 'no' questionnaire to obtain the Working Group members' agreement on the proposed final set of QIs.

Table 2. Criteria for the development and evaluation of the ESC quality indicators for cardiovascular disease[241].

Domain	Criteria
Importance	QI reflects a clinical area that is of high importance (e.g., common, major cause for morbidity, mortality, and/or health-related quality of life impairment).
	QI relates to an area where there are disparities or suboptimal care.
	QI implementation will result in an improvement in patient outcomes.
	QI may address appropriateness of medical interventions.
Evidence base	QI is derived from an acceptable evidence consistent with contemporary knowledge.
	QI aligns with the respective ESC Clinical Practice Guideline recommendations.
Specification	QI has a clearly defined patient group to whom the measurement applies (denominator), including explicit exclusions.
	QI has clearly accomplishment criteria (numerator).
Validity	QI is able to correctly assess what it is intended to, adequately distinguishes between good and poor quality of care, and compliance with the indicator would confer health benefits.

Reliability	QI is reproducible even when data is extracted by different people and estimates of performance on the basis of available data are likely to be reliable and unbiased.
Feasibility	QI may be identified and implemented with reasonable cost and effort.
	Data needed for the assessment is (or should be) readily available and easily extracted within an acceptable time frame.
Interpretability	QI is interpretable by healthcare providers, so that practitioners can understand the results of the assessment and take actions accordingly.
Actionability	QI is influential to the current practice, where a large proportion of the determinants of adherence to the QI are under the control of healthcare providers.
	This influence of QI on behaviour will likely improve care delivery.
	QI is unlikely to cause negative unintended consequences.

QI=quality indicator

10.6 RESULTS

10.6.1 Search results

The literature search retrieved 2954 articles, of which 441 met the inclusion criteria (Figure 1). These articles were used to extract a total of 352 candidate QIs (17 related to structure, 162 to process and 173 related to outcomes) before the first voting round. Of these 34 QIs (19 related to process and 15 related to outcomes) were selected by the end of the second round (Table 3). Over 93% of the Working Group members agreed on this final set of QIs in the third voting round.

Figure 1. PRISMA flow diagram for selection of included studies
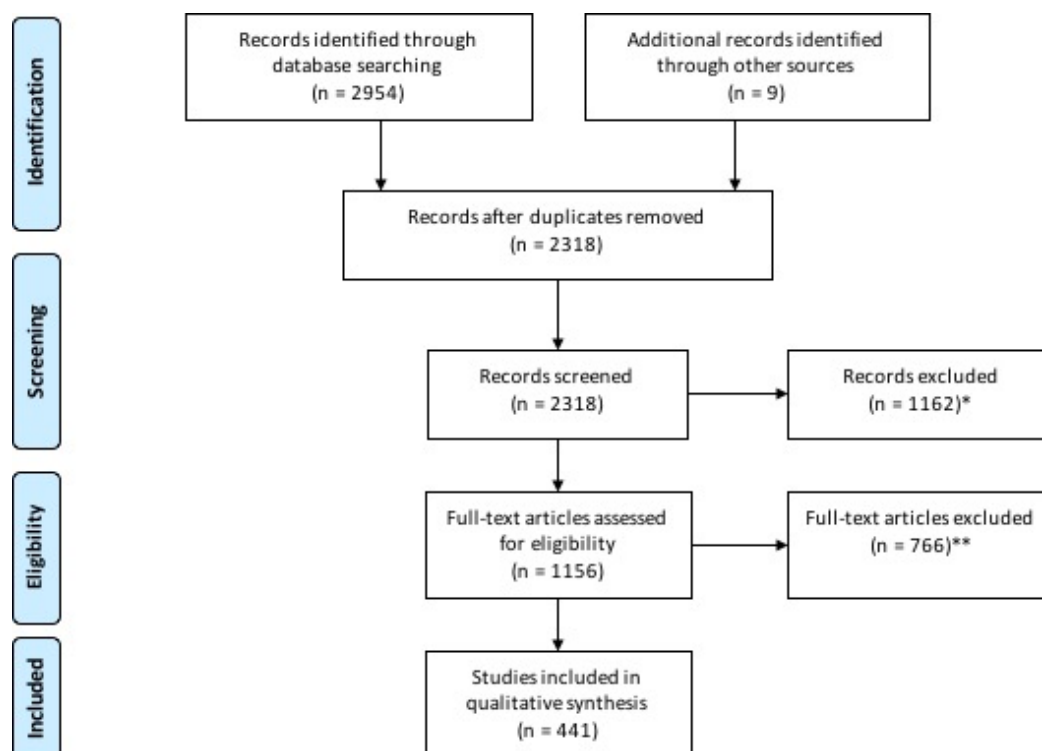
*Records excluded:
- *Not population of interest* (825): unrelated to cardiovascular disease (266), stroke (113), heart failure/congenital (81), cardiovascular surgery (69), other arrhythmias (55), coronary artery disease (50), cardiovascular risk factors (35), valvular heart disease (29), cardiovascular disease general (20), other (107)
- *Study type* (274): abstract (201), study protocol (22), non-systematic review (20), systematic-review/meta-analysis (7), letter/note/survey (11), cost-effectiveness analysis (5), editorial (4), basic research (4),
- *Sub-studies of main publications* (53)
- *Other* (10)
**Full text articles excluded due the lack of clear definitions and/or specifications of the quality indicators and/or outcome measures.

Table 3. Primary (green) and secondary (yellow) quality indicators for the diagnosis and management of AF.

Code	Quality Indicators
Domain 01: Patient assessment (at baseline and follow-up)	
01MQI1	Proportion of patients with cardioembolic risk assessment using CHA_2DS_2-VASc score
01MQI2	Proportion of patients with bleeding risk assessment using a validated method, such as the HAS-BLED score

01MQI3	Proportion of patients with a measurement of their serum creatinine (or creatinine clearance)
01SQI1	Proportion of people ≥65 years of age with risk factors for AF who have pulse check
01SQI2	Proportion of patients with atrial high-rate episodes (AHREs) detected on implantable cardiac devices who undergo further cardiovascular evaluation
01SQI3	Proportion of cryptogenic stroke patients who have been screened for AF
01SQI4	Proportion of patients with an ECG documentation of AF
01SQI5	Proportion of patients who have been engaged in shared decision-making when deciding treatment strategy
	Domain 02: Anticoagulation
02MQI1	Proportion of patients who are appropriately prescribed anticoagulation according to CHA_2DS_2-VASc score*
02MQI2	Proportion of patients with a CHA_2DS_2-VASc score of 0 for men and 1 for women who are inappropriately prescribed long-term anticoagulation
02MQI3	Proportion of patients with 'appropriate anticoagulation' at every follow-up visit, defined as: a. Time in therapeutic range TTR** ≥70% for vitamin-K antagonist. b. Appropriate dose for NOAC according to manufacturer recommendations.
	Domain 03: Rate control
03MQI1	Proportion of patients with permanent AF (i.e. where no attempt to restore sinus rhythm is planned), who are inappropriately prescribed antiarrhythmic drugs
03SQI1	Proportion of patients with LVEF <40% who are inappropriately prescribed non-dihydropyridine calcium channel blockers
	Domain 04: Rhythm control
04MQI1	Proportion of patients with structural heart disease who are inappropriately prescribed class IC antiarrhythmic drugs

04MQI2	Proportion of patients with end-stage kidney disease who are inappropriately prescribed dofetilide or sotalol
04MQI3	Proportion of patients with symptomatic paroxysmal or persistent AF who are offered AF catheter ablation after failure of, or intolerance to, one class I or class III antiarrhythmic drug
04SQI1	Proportion of patients with complete electrical isolation of the PVs during AF catheter ablation procedures
04SQI2	Proportion of patients with new onset persistent AF who are offered cardioversion
Domain 05: Risk factor management	
05MQI1	Proportion of patients who have their modifiable risk factors identified
Domain 06: Outcomes	
Sub-domain 06.1: Consequences of the disease	
06.1MQI1	Annual rate of all-cause mortality***
06.1MQI2	Annual rate of ischaemic stroke or transient ischaemic attack***
06.1SQI1	Annual rate of cardiovascular mortality***
06.1SQI2	Annual rate of cardiovascular hospitalization ***
06.1SQI3	Annual rate of overall thromboembolic event ***
06.1SQI4	Annual rate of clinician-reported symptom status assessment
Sub-domain 06.2: Consequences of treatment	
06.2MQI1	Annual rate of life-threatening or major bleeding events
06.2MQI2	Annual rate of procedure-related 30-day mortality
06.2MQI3	Annual rate of procedure-related major complications or drug-related serious adverse events
06.2SQI1	Annual rate of haemorrhagic stroke
Sub-domain 06.3: Patient-reported outcomes	
06.3MQI1	Proportion of patients with health-related quality of life assessment

06.3SQI1	Proportion of patients with patient-reported symptom status assessment
06.3SQI2	Proportion of patients with physical function assessment
06.3SQI3	Proportion of patients with emotional wellbeing (including anxiety and depression) assessment
06.3SQI4	Proportion of patients with cognitive function assessment

*Appropriateness of anticoagulation prescription is defined as CHA_2DS_2-VASc score of ≥ 1 for men and ≥ 2 for women in the 2020 ESC Guidelines (REF). The 2014 ACC/AHA Guidelines (and 2019 focused update) define anticoagulation prescription appropriateness and CHA_2DS_2-VASc score of ≥ 2 for men and ≥ 3 for women[247, 251].

**TTR calculated using Rosendaal method.

***Crude and risk-adjusted rates (risk-adjustment should, as a minimum, consider age, sex, and comorbidities.

The domains for AF care identified by the Working Group were: 1) Patient assessment (baseline and follow-up), 2) Anticoagulation therapy, 3) Rate control strategy, 4) Rhythm control strategy, 5) Risk factor management, and 6) Outcome measures (including PROMs). For each domain main, and for some secondary, QIs have been developed. Figure 2 shows the main QIs according to their respective domain of care. The full set of main and secondary QIs, alongside their definitions, proposed measurement period (the timepoint at which the assessment is performed), proposed measurement duration (the time frame needed for enough cases to be collected), and when applicable, the corresponding ESC Clinical Practice Guidelines recommendations are illustrated in APPENDIX 4. For each QI, a unique code was developed using the domain number and indicating whether the QI is main or secondary.

Figure 2. Domains of AF care with their respective main quality indicators

AAD, antiarrhythmic drug; AF, atrial fibrillation; CA, catheter ablation; ESRD, end-stage renal disease; HRQoL, health-related quality of life; NOAC, non-vitamin K antagonist oral anticoagulant; OAC, oral anticoagulants; TTR, time in therapeutic range; TIA, transient ischaemic attack

10.6.2 Quality Indicators

10.6.2.1 Domain 1: Patient assessment (baseline and follow-up)

Stroke prevention is the cornerstone of the AF patient management pathway, and 'Avoid Stroke/Anticoagulation' is the 'A' of the ABC pathway[253], within the 2020 ESC guidelines[240].

01MQI1: **Proportion of patients with cardioembolic risk assessment using CHA$_2$DS$_2$-VASc score**

Numerator: Number of patients with AF who have their CHA$_2$DS$_2$-VASc score documented at the time of diagnosis and at every follow up appointment.

Denominator: Number of patients with AF.

01MQI2: **Proportion of patients with bleeding risk assessment using a validated method, such as the HAS-BLED score**

Numerator: Number of patients with AF who have their bleeding risk assessment documented at the time of diagnosis and at every follow up appointment using a validated bleeding risk score.

Denominator: Number of patients with AF.

01MQI3: **Proportion of patients with a measurement of their serum creatinine (or creatinine clearance)**

Numerator: Number of patients with AF who have their serum creatinine checked at the time of diagnosis and at every follow up appointment.

Denominator: Number of patients with AF.

Stroke risk in AF is not homogeneous and depends on the presence of various stroke risk factors[254]. The CHA$_2$DS$_2$-VASc score is recommended to assess stroke risk where the default should be to offer stroke prevention, unless the patient is low risk; hence use the CHA$_2$DS$_2$-VASc score to initially define low risk patients (CHA$_2$DS$_2$-VASc score 0 in males, 1 in females) who do not need antithrombotic therapy (indicator 01MQI1). The subsequent step is to offer stroke prevention in those with 1 or more risk factors (CHA$_2$DS$_2$-VASc score ≥ 1 in males, ≥ 2 in females). Since stroke risk is dynamic, and influenced by ageing and incident risk factors, risk reassessment should occur at every follow-up visit[255].

Bleeding risk also changes over time and should also be assessed at every patient contact, initially to identify modifiable bleeding risks that should be mitigated, and to identify the 'high bleeding risk' patient who should be scheduled for early follow-up[256] (indicator 01MQI2). Based on a Patient-Centered Outcomes Research Institute (PCORI) systematic review and

evidence appraisal, the best validated bleeding risk score is the HAS-BLED score[257]. While stroke and bleeding risks track each other, the evidence shows that a formal bleeding risk score (HAS-BLED) is superior to stroke risk scores (e.g. CHADS$_2$, CHA$_2$DS$_2$-VASc) for assessing bleeding risk[258, 259]. A strategy for dynamic bleeding risk assessment using the HAS-BLED score has been shown to reduce bleeding risk and to increase oral anticoagulation (OAC) use[260].

Given that renal function has implications for both stroke and bleeding risk[261], as well as prescriptions of OAC (choice of agent and dose), regular measurements of serum creatinine or creatinine clearance (based on the Cockroft-Gault formula) are needed, the frequency of which is determined by the renal function at baseline[262] (indicator 01MQI3).

01SQI1: Proportion of people ≥65 years of age with risk factors for AF who have pulse check

Numerator: Number of people ≥65 years of age with risk factors for AF who have a documentation of pulse check (or ECG) to identify rhythm.

Denominator: Number of people ≥65 years of age with risk factors for AF.

01SQI2: Proportion of patients with atrial high-rate episodes (AHREs) detected on implantable cardiac devices who undergo further cardiovascular evaluation

Numerator: Number of patients with AHREs detected on implantable cardiac devices who have documentation of complete cardiovascular evaluation.

Denominator: Number of patients with atrial high-rate episodes detected on implantable cardiac devices.

01SQI3: Proportion of cryptogenic stroke patients who have been screened for AF

Numerator: Number of patients with cryptogenic stroke* who have documentation of AF screening using continuous ECG recording.

Denominator: Number of patients with cryptogenic stroke with no previous history of AF

01SQI4: Proportion of patients with an ECG documentation of AF

Numerator: Number of patients with AF who have a documentation of an ECG confirming AF diagnosis.

Denominator: Number of patients with AF.

01SQI5: Proportion of patients who have been engaged in shared decision-making when deciding treatment strategy

Numerator: Number of patients with AF who have a documentation of patient engagement when deciding treatment strategy.

Denominator: Number of patients with AF.

Asymptomatic AF is associated with a higher risk of stroke and mortality compared to symptomatic AF[263-266]. An observational study indicated that the application of standard care treatments for subclinical AF detected on screening improves outcomes[266] and a systematic review and economic analysis suggested that screening programmes for AF are likely to represent a cost-effective use of resources[267]. Thus, screening for AF amongst people ≥65 years

of age by checking their pulse may have therapeutic implications as these individuals need to be considered for thromboprophylaxis (indicator 01SQI1).

To that end, atrial high rate episodes (AHRE) detected by implanted cardiac devices, which may represent asymptomatic AF, should be investigated[268, 269]. Ideally, AHRE detection should be performed at every device interrogation, including home monitoring transmission as it determines whether or not subclinical AF is confirmed and whether anticoagulation and/or regular follow-up is warranted[240], indicator 01SQI2. Furthermore, the detection of previously unknown AF following a stroke has relevant implications for secondary prevention[270, 271]. Thus, it is recommended to screen for AF following a cryptogenic stroke[240, 272-274] (indicator 01SQI3).

However, screening for AF should be accompanied by confirming the diagnosis by traditional means, such as by 12-lead ECG or >30 seconds recording of a single-lead ECG, Holter monitor, or event recorder (indicator 01SQI4). Following the diagnosis, a dialogue between treating physician and patient to ensure patient involvement in decision-making is recommended[240, 275]. Thus, the indicator 01SQI5 captures shared decision-making when deciding on the treatment strategy.

10.6.2.2 Domain 2: Anticoagulation

Oral anticoagulation is an essential part of AF management and the ESC 2020 guidelines recommend oral anticoagulation for stroke prevention in males with CHA_2DS_2-VASc scores of ≥ 1, and females with scores ≥ 2[240]. Accordingly, it is important that a set of QIs to regularly assesses the proportion of patients with CHA_2DS_2-VASc score ≥ 1 in males, ≥ 2 in females who are offered stroke prevention (indicator 02MQI1), as well as the inappropriate use of long-term antithrombotic therapy in low risk patients (CHA_2DS_2-VASc score 0 in males, and 1 in females) (indicator 02MQI2).

02MQI1: Proportion of patients who are appropriately prescribed anticoagulation according to CHA2DS2-VASc score**

Numerator: Number of patients with AF who have CHA_2DS_2-VASc score of ≥ 1 for men or ≥ 2 for women and are prescribed anticoagulation for AF**.

Denominator: Number of patients with AF who have CHA_2DS_2-VASc score of ≥ 1 for men or ≥ 2 for women and are eligible for anticoagulation with no contraindication or refusal**.

02MQI2: Proportion of patients with a CHA2DS2-VASc score of 0 for men and 1 for women who are inappropriately prescribed long-term anticoagulation

Numerator: Number of patients with AF who have CHA_2DS_2-VASc score of 0 for men or 1 for women and are inappropriately prescribed long-term anticoagulation for AF.

Denominator: Number of patients with AF who have CHA_2DS_2-VASc score of 0 for men and 1 for women and do not have other indication for anticoagulation.

02MQI3: Proportion of patients with 'appropriate anticoagulation' at every follow-up visit, defined as:
  - **c.   Time in therapeutic range TTR $\geq 70\%$ for vitamin-K antagonist.**
  - **d.   Appropriate dose for NOAC according to manufacturer recommendations***.**

Numerator: Number of patients with AF who are appropriate anticoagulation defined as TTR $\geq 70\%$ for vitamin-K antagonist, or appropriate dose for NOAC according to manufacturer recommendations***.

Denominator: Number of patients with AF on anticoagulation.

**Appropriateness of anticoagulation prescription is defined as CHA_2DS_2-VASc score of ≥ 1 for men and ≥ 2 for women in the 2020 ESC Guidelines[240]. The 2014 ACC/AHA Guidelines (and 2019 focused update) define anticoagulation prescription appropriateness and CHA_2DS_2-VASc score of ≥ 2 for men and ≥ 3 for women[247, 251].

***Manufacturer recommendations are defined in APPENDIX 5.

Assessment of the quality of anticoagulation is also important. If patients are taking a non-vitamin K antagonist oral anticoagulant (NOAC), the label-adherent dose of the respective NOAC should be prescribed and the proportion appropriately dosed is indicative of quality of care. Regular audits should be performed to ensure that under- or over-dosing of the respective

NOAC does not occur, given the association with worse outcomes[276-278] (indicator 02MQI3). Oral anticoagulation can also be offered as well-managed vitamin K antagonist (VKA) (e.g., warfarin, acenocoumarol, phenprocoumon etc.), with a high (≥70%) time in therapeutic range (TTR) calculated using Rosendaal method, with INR 2.0-3.0. High TTR has been associated with low rates of stroke and bleeding, as well as reduced mortality[279-281]. Thus, the proportion of patients with TTR ≥70% is a good QI of anticoagulation control for patients on VKA.

10.6.2.3 Domain 3: Rate control

Rate control is an integral part of AF management, and may be sufficient to improve AF-related symptoms[282]. In patients for whom a decision has been made not to restore or maintain sinus rhythm (permanent AF), rate control can be achieved by rate-limiting medications (e.g., beta-blockers, digoxin, diltiazem, or verapamil). The use of antiarrhythmic drugs, such as amiodarone, dronedarone, or sotalol for rate-control is not recommended when no attempts to restore sinus rhythm is planned[283-286] (indicator 03MQI1).

03MQI1: Proportion of patients with permanent AF (i.e. where no attempt to restore sinus rhythm is planned), who are inappropriately prescribed antiarrhythmic drugs$

Numerator: Number of patients with permanent AF who are prescribed one or more antiarrhythmic drugs$ for rhythm control.

Denominator: Number of patients with permanent AF.

03SQI1: Proportion of patients with LVEF <40% who are inappropriately prescribed non-dihydropyridine calcium channel blockers

Numerator: Number of patients with AF who have LVEF <40% and/or decompensated heart failure, and are inappropriate prescription of non-dihydropyridine calcium channel blockers.

Denominator: Number of patients with AF who have LVEF <40% and/or decompensated heart failure.

The use of certain types of rate control drugs, such as non-dihydropyridine calcium channel blockers can influence outcomes in patients with heart failure and/or left ventricular ejection

fraction (LVEF) of ≤40%[226, 287]. Thus the indicator 03SQI1, evaluates the inappropriate use of non-dihydropyridine calcium channel blockers in AF patients with concomitant reduced LVEF[288].

10.6.2.4 Domain 4: Rhythm control

Rhythm control therapy is central for the reduction and/or relief of AF symptoms and improvement of patients' quality of life (QoL)[289-291]. Given that the safety profile of an antiarrhythmic agent is a major determinant of treatment choice, the Working Group selected QIs based on this notion. Certain antiarrhythmic drugs have major contraindications that increase the likelihood of adverse events, such as the presence of structural heart disease (for instance ischemic heart disease, LV dysfunction and/or significant cardiomyopathy) for class IC antiarrhythmic drugs (indicator 04MQI1), and advanced chronic kidney disease for dofetilide and sotalol (indicator 04MQI2)[240].

04MQI1: Proportion of patients with structural heart disease who are inappropriately prescribed class IC antiarrhythmic drugs

Numerator: Number of patients with AF who have structural heart disease and are inappropriately prescribed class IC antiarrhythmic drugs.

Denominator: Number of patients with AF who have structural heart disease

---

04MQI2: Proportion of patients with end-stage kidney disease who are inappropriately prescribed dofetilide or sotalol

Numerator: Number of patients with AF who have end-stage kidney disease and/or on dialysis[$$] and are inappropriately prescribed dofetilide or sotalol.

Denominator: Number of patients with AF who have end-stage kidney disease, including patients on dialysis.

04MQI3: Proportion of patients with symptomatic paroxysmal or persistent AF who are offered AF catheter ablation after failure of, or intolerance to, one class I or class III antiarrhythmic drug

Numerator: Number of patients with paroxysmal or persistent AF who are offered catheter ablation after the failure of, or intolerance to, one class I or class III antiarrhythmic drug.

Denominator: Number of patients with paroxysmal or persistent AF with no contraindications (or refusal) to catheter ablation who remain symptomatic on, or intolerant to, one class I or class III antiarrhythmic drug.

Catheter ablation is effective in maintaining sinus rhythm and improving symptoms in patients with AF[292-303]. Ablation is generally recommended in symptomatic patients after failure or intolerance to one class I or class III antiarrhythmic drugs (indicator 04MQI3). Several factors may influence the decision between conservative and invasive treatment for AF, including age, AF duration, left atrial size, co-morbidities, and substrate visualization by cardiac magnetic resonance[304-310]. Ultimately, patient preference supported by treating physician recommendation are the main determinants of the type of rhythm control strategy employed[240, 275].

04SQI1: Proportion of patients with complete electrical isolation of the PVs during AF catheter ablation procedures

Numerator: Number of patients with AF who have complete electrical isolation (entrance and exit block) of the PVs during AF catheter ablation procedures.

Denominator: Number of patients with AF treated with catheter ablation procedures.

04SQI2: Proportion of patients with new onset persistent AF who are offered cardioversion

Numerator: Number of patients with new onset persistent AF who are haemodynamically stable and are offered cardioversion.

Denominator: Number of patients with new onset persistent AF who are haemodynamically stable and in whom attempts to restore sinus rhythm were deemed appropriate.

A QI to assess the complete electrical isolation (entrance and exit block) of the pulmonary veins during AF catheter ablation procedures (indicator 04SQI1) was developed given that this is the desired outcome of AF ablation[292, 296, 297, 311-322]. In addition, the indicator 04SQI2 assesses the consideration of cardioversion for patients with new onset persistent AF.

10.6.2.5 Domain 5: Risk factor management

The Working Group considered the role of risk factors in AF and developed a QI accordingly (indicator 05MQI1). Recent research has highlighted the potential benefits of risk factor management as upstream non-invasive therapy to lower the risk of AF progression and recurrence[323-329]. A large proportion of these risk factors are lifestyle related and, therefore, are amenable to be targeted and modified[330]. It is recommended that in the assessment of AF patients, practitioners actively evaluate and document these modifiable risk factors, such as smoking, obesity[323, 325, 331], physical inactivity[332-334], alcohol intake[328, 335-337], sleep[338] apnea[339, 340], hypertension[338, 341, 342] and poor glycaemic control[343]. Where necessary, appropriate education, support, and intervention (e.g., smoking cessation options, continuous positive airway pressure (CPAP), exercise prescription, etc.) can be provided to the patient to address the risk factors that may improve health outcomes.

05MQI1: Proportion of patients who have their modifiable risk factors identified

Numerator: Number of patients with AF who have their modifiable risk factors (e.g., blood pressure, obesity, obstructive sleep apnoea, alcohol excess, lack of exercise, poor glycaemic control and smoking) identified.

Denominator: Number of patients with AF.

10.6.2.6 Domain 6: Outcome measures
10.6.2.6.1 Consequences of the disease

Reducing the risk of death is one of the primary aims of AF management, and healthcare in general[240]. As such, annual assessment of crude and risk-adjusted rates of all-cause mortality is recommended (indicator 06.1MQI1). Risk-adjustment should, as a minimum, consider age, sex, and comorbidities. In addition, the inclusion of lifestyle factors (e.g., smoking status, body mass index, physical activity, and alcohol intake) provides a better insight to the adjustment process. Given that ischaemic stroke is a major complication of AF and, that most AF patients (CHA$_2$DS$_2$-VASc score of ≥1 in men and ≥2 in women) will be eligible for stroke prevention, the overall and risk-adjusted annual incidence of stroke and, separately, transient ischaemic attack should be recorded as QI (indicator 06.1MQI2). Other outcomes measures, which may provide an illustration of the quality of AF care include, the rate of cardiovascular mortality (indicator 06.1SQI1), cardiovascular hospitalization (indicator 06.1SQI2), overall thromboembolic events (indicator 06.1SQI3), and clinician-reported AF symptom status (indicator 06.1SQI4).

06.1MQI1: Annual rate of all-cause mortality*

Numerator: Number of patients with AF who died during the measurement duration.
Denominator: Number of patients with AF.

06.1MQI2: Annual rate of ischaemic stroke or transient ischaemic attack*

Numerator: Number of patients with AF who had documented ischaemic stroke or transient ischaemic attack during the measurement duration.
Denominator: Number of patients with AF.

---

*Crude and risk-adjusted rates (risk-adjustment should, as a minimum, consider age, sex, and comorbidities.

In the ABC pathway of AF management mentioned above, the 'B' component pertains to 'better' symptom management[253]. Many AF patients may not be overtly symptomatic. However, assessment of AF-related symptoms can be a useful subjective measure of both the clinical consequences of AF and the success of rate- and rhythm-control treatment from the patients' perspective. Using a validated method, such as the modified European Heart

Rhythm Association (EHRA) score[344] is recommended to assess symptom status (indicator 06.1SQI4).

06.1SQI1: Annual rate of cardiovascular mortality*

Numerator: Number of patients with AF who died from cardiovascular cause during the measurement duration.

Denominator: Number of patients with AF.

06.1SQI2: Annual rate of cardiovascular hospitalization*

Numerator: Number of patients with AF who had unplanned hospitalization for a cardiovascular cause during the measurement duration.

*Denominator***:** Number of patients with AF.

06.1SQI3: Annual rate of overall thromboembolic events*

Numerator: Number of documented AF-related thromboembolic events during the measurement duration.

*Denominator***:** Number of AF patients.

06.1SQI4: Annual rate of clinician-reported symptom status assessment

Numerator: Number of patients with AF who had their clinician-reported symptom status assessed using a validated tool (e.g., EHRA symptom score) during the measurement duration.

*Denominator***:** Number of patients with AF.

*Crude and risk-adjusted rates (risk-adjustment should, as a minimum, consider age, sex, and comorbidities.

10.6.2.6.2 Complications of treatment

OAC treatment conveys an increased risk of major bleeding. However, bleeding complications can also occur in the absence of OAC treatment[345]. The incidence of life-threatening or major bleeding events, defined by the International Society of Thrombosis and

Haemostasis criteria,[346, 347] should be reported annually as a QI (indicator 06.2MQI1). The annual rate of haemorrhagic stroke is of particular importance (indicator 06.2SQI1) and should be documented as a QI.

06.2MQI1: Annual rate of life-threatening or major bleeding events[&]

Numerator: Number of patients with AF who are on anticoagulation and had documented life-threatening or major bleeding events during the measurement duration.

Denominator: Number of patients with AF on anticoagulation.

06.2MQI2: Annual rate of procedure-related[&&] 30-day mortality

Numerator: Number of patients with AF who died due to an invasive procedure for AF management during the measurement duration.

Denominator: Number of patients with AF treated with invasive procedures.

06.2MQI3: Annual rate of procedure-related[&&] major complications or drug-related serious adverse events[$]

Numerator: Number of patients with AF who had documented major procedural complications and/or drug-related serious adverse events during the measurement duration.

Denominator: Number of patients with AF.

06.2SQI1: Annual rate of haemorrhagic stroke

Numerator: Number of patients with AF who had documented haemorrhagic stroke during the measurement duration.

Denominator: Number of patients with AF on anticoagulation.

AF procedure-related deaths occurring within the first 30 days following catheter-based ablation, surgical ablation procedure, hybrid catheter and surgical ablation, left atrial appendage closure/occlusion (device), left atrial appendage ligation/excision (surgical), electrical cardioversion, or pacemaker implantation, should be reported annually as a QI (indicator 06.2MQI2). Furthermore, any procedure-related major complication or drug-related serious adverse event, defined as any untoward medical occurrence that results in death, life-

threatening outcomes, hospitalization (initial inpatient hospitalization or prolongation of existing hospitalization for ≥24h), or permanent injury, should be reported in real-time according to local or national policy, and annually as a marker of quality (indicator 06.2MQI3). Although a single QI is suggested for procedural complications (e.g., atrio-oesophageal fistula, cardiac tamponade, PV stenosis, phrenic nerve palsy, etc.), and drug-related adverse events (e.g., arrhythmias, sudden cardiac death, etc.), individual events may be collected in each centre for local monitoring and between centre comparisons.

10.6.2.6.3 Patient-reported outcomes

PROMs are important determinants of the patients' perceived quality and success of treatment[348-350]. The 2020 ESC guidelines recommend that patient-reported outcomes should be routinely collected to measure treatment success and improve patient care[240]. Health-related quality of life (HRQoL) is considered the main QI and should be assessed at baseline and at follow-up visits (indicator 06.3MQI1).

Several validated tools are available to measure general HRQoL[351] (e.g., the Short-Form 12 [SF-12])[352], while others specifically measure AF-specific HRQoL[353] (e.g., the Atrial Fibrillation Effect on QualiTy of life [AFEQT] or the Atrial Fibrillation Severity Scale [AFSS])[354-357]. Both the SF-12 and the AFEQT are validated, psychometrically robust assessments of HRQoL, and are recommended by the International Consortium of Healthcare Outcome Measures (ICHOM) for AF [358]. Regardless of which validated tool is employed, it is important that the same PROM is used consecutively to assess HRQoL to permit temporal comparison of scores and allow the determination of response to treatment.

06.3MQI1: Proportion of patients with health-related quality of life assessment

Numerator: Number of patients with AF who have their health-related quality of life assessed at the time of diagnosis and least annually afterwards using a validated instrument.

Denominator: Number of patients with AF.

06.3SQI1: Proportion of patients with patient-reported symptom status assessment

Numerator: Number of patients with AF who have their patient-reported symptom status assessed at the time of diagnosis and least annually afterwards using a validated instrument.

Denominator: Number of patients with AF.

06.3SQI2: Proportion of patients with physical function assessment

Numerator: Number of AF patients who have their physical function assessed at the time of diagnosis and at every follow up appointment using a validated instrument.

Denominator: Number of AF patients.

06.3SQI3: Proportion of patients with emotional wellbeing (including anxiety and depression) assessment

Numerator: Number of patients with AF who have their emotional wellbeing (including anxiety and depression) assessed at the time of diagnosis and at every follow up appointment using a validated instrument.

Denominator: Number of patients with AF.

06.3SQI4: Proportion of patients with cognitive function assessment

Numerator: Number of patients with AF who have their cognitive function assessed at the time of diagnosis and at least annually afterwards using a validated instrument.

Denominator: Number of patients with AF.

Determining the impact of AF and its treatment on the patient are important considerations in the management of AF and may contribute to patient and healthcare provider decisions regarding continuation/cessation of certain treatments and/or initiating alternatives. In addition to HRQoL, the assessment of other PROMs, such patient reported symptom status (indicator 06.3SQI1), physical functioning (indicator 06.3SQI2), emotional wellbeing (indicator 06.3SQI3), and cognitive function (indicator 06.3SQI4), could also be considered. The assessment of HRQoL, patient-reported symptom status, physical functioning and emotional wellbeing is recommended at baseline and once to twice annually, while the assessment of cognitive function is recommended at baseline and annually thereafter, given that it may show little variation over a shorter period of time. Validated tools, such as the ones recommended by

the ICHOM for AF[358] (PROMIS Global Health for physical and emotional wellbeing, and PROMIS for cognitive function) can be used.

10.7 Comparison with other quality metrics

Table 4 shows a comparison between the 2020 ESC QIs for AF and quality metrics from other professional organisations, such as the American College of Cardiology and the American Heart Association (ACC/AHA), the National Institute for Clinical Excellence (NICE), the Canadian Cardiovascular Society (CCS), and ICHOM. There are major differences between the process QIs proposed here, and those developed by ACC/AHA, NICE and CCS. These differences may be explained by the variation in Clinical Practice Guidelines endorsed by different societies and/or local needs to address certain gaps in AF care. Outcome QIs were relatively similar compared to those proposed by ICHOM.

Table 4. Comparison between the 2020 ESC AF QIs, and the ACC/AHA, NICE, CCS, and ICHOM indicators for AF.

Green colour represent measures with similar definition; orange represent measures with different definitions, and white represent no corresponding measure.

Domain	2020 ESC QIs	2016 ACC/AHA	2017 NICE	2019 CCS	2020 ICHOM
Patient assessment (at baseline and follow-up)	CHA_2DS_2-VASc score risk assessment	■		■	
	Bleeding risk assessment		■		
	Serum creatinine		■		
	Screening people ≥65 years of age with risk factors for AF		■		
	Evaluating AHREs detected on implantable cardiac devices				

	Screening for AF after cryptogenic stroke		
	ECG documentation of AF diagnosis		
	Shared decision-making when deciding treatment strategy		
Anticoagulation	Anticoagulation with CHA_2DS_2-VASc score ≥ 1 for men and ≥ 2 for women		
	Inappropriate anticoagulation with CHA_2DS_2-VASc score 0 for men and 1 for women		
	Appropriate anticoagulation (TTR $\geq 70\%$ or appropriate NOAC dose)		
Rate control	Inappropriate AAD use for patients with permanent AF		
	Inappropriate non-dihydropyridine CCBs use for patients with LVEF <40%		
Rhythm control	Inappropriate class IC AAD use for patients with structural heart disease		
	Inappropriate dofetilide or sotalol use for patients with end-stage kidney disease		
	Offering CA for symptomatic paroxysmal or persistent AF after single AAD failure		
	Complete PVs electrical isolation during all AF CA procedures		

	Cardioversion for patients with new onset AF			
Risk factor management	Identifying modifiable risk factors for AF patients			
Outcomes: Consequences of the disease	Rate of all-cause mortality			🟩
	Rate of ischaemic stroke or TIA		🟩	
	Rate of CV mortality			🟩
	Rate of CV hospitalization			🟩
	Rate of overall thromboembolic event			🟩
	Rate of clinician-reported symptom status assessment			
Outcome: Consequences of treatment	Rate of life-threatening or major bleeding events			🟩
	Rate of procedure-related 30-day mortality		🟩	
	Rate of procedure-related major complications or drug-related serious adverse events		🟧	🟩
	Rate of haemorrhagic stroke		🟩	🟩
Outcome: Patient-reported outcomes	Assessment of health-related quality of life assessed			🟩
	Assessment of patient-reported symptom status			🟩
	Assessment of physical function			🟩
	Assessment of emotional wellbeing (including anxiety and depression)			🟩
	Assessment of cognitive function			🟩

AAD=anti-arrhythmic drug; ACC=American College of Cardiology; AF=atrial fibrillation; AHA=American Heart Association; AHRE=atrial high-rate episodes; CA=catheter ablaton; CCB=calcium-channel blockers; CCS=Canadian Cardiovascular Society; CV=cardiovascular; ECG=electrocardiogram; ESC=European Society of Cardiology; ICHOM= International Consortium of Healthcare Outcome Measures, LVEF=left ventricular ejection fraction; NICE=National Institute for National Excellence, NOAC=Non-vitamin k oral anti-coagulant; PVs=pulmonary veins; QI=quality indicator; TIA=transient ischaemic attack; TTR-time in therapeutic range;

10.8 Discussion

Evaluating the quality of care delivered and measuring meaningful outcomes of both the condition and its treatment have become an essential element of modern health care[359]. AF is the most common cardiac arrhythmia, affecting 2-4% of the population, and is a major cause of significant morbidity[360]. Although evidence suggests that adherence to guideline recommended therapies for AF is associated with improved outcomes[361, 362], data from AF registries continue to show room for improvement and significant geographical variation in AF quality of care and outcomes[277, 278, 363-376]. QIs have been developed to evaluate the quality of AF care[235, 237, 239, 248, 377]. Furthermore, QIs provide the mechanism to assess the effectiveness of quality improvement initiatives[161]. However, standardized measures to facilitate ongoing efforts to quantify the adherence to guidelines are needed.

The present document is the first effort undertaken by the ESC to develop a set of QIs to assess the quality of care for patients with AF. Using the ESC methodology for QIs development[241], we have established a comprehensive set of QIs for AF care, which are supported by evidence and underpinned by expert consensus. Thus, they provide tools to quantify the quality of AF care and can be used as a basis for quality improvement. The simultaneous development of the ESC AF QIs and the ESC Clinical Practice Guidelines for AF facilitated seamless incorporation of QIs within the guidelines document. As such, a summary form of the developed QIs is embedded within the ESC Clinical Practice Guidelines for AF, with the hope to enhance their dissemination and, therefore, uptake into clinical practice[240].

This document is the result of an international collaboration (12 countries) from seven professional societies/associations with a Working Group consisting of a wide range of stakeholders, including patients. In addition, the application of ESC criteria ensured that developed QIs are not only based on evidence, but also cover broad aspects of AF care where there is gap in care delivery, potential for quality improvement, and the availability of reliable data collection sources. To that end, different types of QIs including structural, process and outcome indicators[243] were included in the initial set of candidate QIs.

The Working Group, however, considered structural QIs, such as the volume of catheter ablation cases for centres and individual operators not to be directly under the control of healthcare providers. Thus, structural QIs, although important, were given less priority compared to other process ones which may influence providers' behaviour and practice and were not included in the final set of indicators. Other QIs, such as the reintroduction of OAC after a severe bleeding event, once the condition leading to the bleeding event has been appropriately addressed[279, 378], and the use of strict versus lenient rate-control treatment[379] were proposed in the initial set of candidate QIs, but were deemed difficult to operationalise, and, thus, were not included.

On the other hand, and to emphasise that improving outcomes is the ultimate aim of quality of care assessment (Figure 1), particular attention was given to outcome QIs. The term 'outcome measures' was used separately and in different variations in the systematic review search strategy (APPENDIX 3). The outcome QIs selected are applicable to all domains of AF care, and are in line with the recent ICHOM recommendations[380].

One important type of outcome QIs are PROMs, which are increasingly used in everyday practice. Although a structured methodology for developing and reporting PROMs exist[381], there is uncertainty around the best instruments to collect such measures. By defining specific PROMs and recommending tools for their measurement, the Working Group hopes to promote

PROMs use in a systematic manner. However, developing outcome QIs to measure the results of PROMs assessment, as well as its temporal trends may not be feasible in contemporary practice. Thus, process QIs to measure and encourage PROMs assessment were developed instead.

The Working Group acknowledges that high-quality evidence supporting PROMs use is limited, widely accepted tools to collect them are lacking, and little experience exist on how PROMs can guide AF treatment decisions. The same argument can be levelled at shared-decision making in AF management. However, these aspects of AF care were deemed essential by the Working Group, thus QIs for PROMs and shared-decision making were developed.

The patient's perspective is a fundamental element of optimal AF care given that most therapies are aimed at improving patients' symptoms, wellbeing, and overall quality of life. Measuring patient-centred outcomes in a standardized way may allow comparison of performance, allow clinicians to learn from each other, and improve the care we provide to our patients. However, further validation of the tools and methods used to collect patient's perspective in routine clinical practice is needed. As such, these tools may be used to guide the development of, and the effect of, treatment strategies for AF patients.

The methodology used for the selection of QIs has limitations. We relied on expert opinion to arrive at the final set of QIs following the comprehensive systematic review of the literature. A different panel of experts may have selected different QIs. We addressed this challenge by using the modified Delphi method, and involving AF specialists with different areas of expertise, as well as patients and representatives from AF patient associations.

Another challenge is that, if considered in isolation, QIs may cause some unintended consequences, such as anticoagulation prescription for patients with very high bleeding risk or recommending catheter ablation for frail patients with major risk factors for AF recurrence.

We have sought to circumvent this issue by clearly defining eligible patients for each QI and specifying relevant exclusions. The suggested QIs are intended to drive a holistic patient assessments and tailor treatments to individual patient to improve patient care. More refinement of these QIs and/or their definitions may be needed in the future when more 'real-world' and feasibility data become available.

It is hoped that the developed set of QIs can be used in a wider quality assessment and improvement initiatives. As such, integration between different efforts (e.g., the ESC Clinical Practice Guidelines and registries), can be achieved and performance gaps addressed. Ongoing projects, such as the European Unified Registries on Heart care Evaluation and Randomized Trials (EuroHeart) of the ESC[382] or the Stroke prevention and rhythm control Therapy: Evaluation of an Educational Programme of the European society of cardiology in a cluster-Randomised trial in patients with Atrial Fibrillation (STEEER-AF) Study[383] may favour the use of systematically developed QIs for future AF registries in Europe, which this statement uniquely provides.

10.9 Conclusion

This document defines 6 domains of AF care (patient assessment, anticoagulation, rate control, rhythm control, risk factor management and outcomes), and provides 17 main and 17 secondary QIs for AF diagnosis and management. For each QI, relevant specifications were described to enhance their use in practice. The recommended set of QIs may facilitate the implementation of, and assess the adherence to, Clinical Practice Guidelines and enable institutions to monitor, compare and improve quality of care in patients with AF.

10.10 References for Chapter 10

1.   Chugh SS, Havmoeller R, Narayanan K, et al. Worldwide Epidemiology of Atrial Fibrillation. A Global Burden of Disease 2010 Study. *Circulation*. 2014;129(8):837-847. doi:10.1161/circulationaha.113.005119

2.   Kirchhof P, Benussi S, Kotecha D, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *European Heart Journal*. 2016;37(38):2893-2962. doi:10.1093/eurheartj/ehw210

3.   Ott A, Breteler MMB, de Bruyne MC, van Harskamp F, Grobbee DE, Hofman A. Atrial Fibrillation and Dementia in a Population-Based Study. The Rotterdam Study. *Stroke*. 1997;28(2):316-321. doi:10.1161/01.str.28.2.316

4.   Knecht S, Oelschläger C, Duning T, et al. Atrial fibrillation in stroke-free patients is associated with memory impairment and hippocampal atrophy. *European Heart Journal*. September 1, 2008 2008;29(17):2125-2132. doi:10.1093/eurheartj/ehn341

5.   Ball J, Carrington MJ, Stewart S, investigators obotS. Mild cognitive impairment in high-risk patients with chronic atrial fibrillation: a forgotten component of clinical management? *Heart*. April 15, 2013 2013;99(8):542-547. doi:10.1136/heartjnl-2012-303182

6.   Marzona I, O'Donnell M, Teo K, et al. Increased risk of cognitive and functional decline in patients with atrial fibrillation: results of the ONTARGET and TRANSCEND studies. *Canadian Medical Association Journal*. April 3, 2012 2012;184(6):E329-E336. doi:10.1503/cmaj.111173

7.   Thrall G, Lane D, Carroll D, Lip GYH. Quality of Life in Patients with Atrial Fibrillation: A Systematic Review. *American Journal of Medicine*. 2006;119(5):448.e1-448.e19.

8.   von Eisenhart Rothe A, Hutt F, Baumert J, et al. Depressed mood amplifies heart-related symptoms in persistent and paroxysmal atrial fibrillation patients: a longitudinal analysis—data from the German Competence Network on Atrial Fibrillation. *EP Europace*. 2015;17(9):1354-1362. doi:10.1093/europace/euv018

9.   Kotecha D, Holmes J, Krum H, et al. Efficacy of β blockers in patients with heart failure plus atrial fibrillation: an individual-patient data meta-analysis. *Lancet*. 2014;384(9961):2235-2243. doi:http://dx.doi.org/10.1016/S0140-6736(14)61373-8

10.   Steinberg BA, Kim S, Fonarow GC, et al. Drivers of hospitalization for patients with atrial fibrillation: Results from the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF). *American Heart Journal*. 5// 2014;167(5):735-742.e2. doi:http://dx.doi.org/10.1016/j.ahj.2014.02.003

11.   Kirchhof P, Schmalowsky J, Pittrow D, et al. Management of Patients With Atrial Fibrillation by Primary-Care Physicians in Germany: 1-Year Results of the ATRIUM Registry. *Clinical Cardiology*. 2014;37(5):277-284. doi:10.1002/clc.22272

12.   Wattigney WA, Mensah GA, Croft JB. Increased atrial fibrillation mortality: United States, 1980-1998. *Am J Epidemiol*. May 1 2002;155(9):819-26.

13.   Wattigney WA, Mensah GA, Croft JB. Increasing Trends in Hospitalization for Atrial Fibrillation in the United States, 1985 Through 1999: Implications for Primary Prevention. *Circulation*. August 12, 2003 2003;108(6):711-716. doi:10.1161/01.cir.0000083722.42033.0a

14.   Boriani G, Proietti M, Laroche C, et al. Association between antithrombotic treatment and outcomes at 1-year follow-up in patients with atrial fibrillation: the EORP-AF General Long-Term Registry. *EP Europace*. 2019;doi:10.1093/europace/euz032

15.   Boriani G, Proietti M, Laroche C, et al. Contemporary stroke prevention strategies in 11 096 European patients with atrial fibrillation: a report from the EURObservational Research Programme on Atrial Fibrillation (EORP-AF) Long-Term General Registry. *Europace*. 2018 2018;20(5):747-757. doi:10.1093/europace/eux301

16.   Wu J, Alsaeed ES, Barrett J, Hall M, Cowan C, Gale CP. Prescription of oral anticoagulants and antiplatelets for stroke prophylaxis in atrial fibrillation: nationwide time series ecological analysis. *EP Europace*. 2020;doi:10.1093/europace/euaa126

17.   Trivedi AN, Nsa W, Hausmann LRM, et al. Quality and Equity of Care in U.S. Hospitals. *New England Journal of Medicine*. 2014;371(24):2298-2308. doi:10.1056/NEJMsa1405003

18.   Heidenreich PA, Solis P, Estes NAM, et al. 2016 ACC/AHA Clinical Performance and Quality Measures for Adults With Atrial Fibrillation or Atrial Flutter. 10.1016/j.jacc.2016.03.521. *Journal of the American College of Cardiology*. 2016;68(5):525.

19.   Cox JL, Dai S, Gong Y, et al. The Development and Feasibility Assessment of Canadian Quality Indicators for Atrial Fibrillation. *Canadian Journal of Cardiology*. 2016;32(12):1566-1569. doi:10.1016/j.cjca.2016.02.059

20.   Sandhu RK, Wilton SB, Cruz J, et al. An Update on the Development and Feasibility Assessment of Canadian Quality Indicators for Atrial Fibrillation and Atrial Flutter. *CJC Open*. 2019/07/01/ 2019;1(4):198-205. doi:https://doi.org/10.1016/j.cjco.2019.05.007

21.   Inohara T, Kimura T, Ueda I, et al. Effect of Compliance to Updated AHA/ACC Performance and Quality Measures Among Patients With Atrial Fibrillation on Outcome

(from Japanese Multicenter Registry). *The American Journal of Cardiology*. 2017/08/15/ 2017;120(4):595-600. doi:https://doi.org/10.1016/j.amjcard.2017.05.029

22.   The National Institute for Health and Care Excellence (NICE). NICE Atrial fibrillation Quality standard [QS93]. https://www.nice.org.uk/guidance/qs93. Updated July 2015. https://www.nice.org.uk/guidance/qs93

23.   Hindricks G et al. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association of Cardio-Thoracic Surgery (EACTS). European Heart Journal (2020) doi:10.1093/eurheartj/ehaa612.

24.   Aktaa S, Batra G, Wallentin L, et al. European Society of Cardiology methodology for the development of quality indicators for the quantification of cardiovascular care and outcomes. *Eur Heart J Qual Care Clin Outcomes*. 2020;doi:10.1093/ehjqcco/qcaa069

25.   Hsu C, Sandford B. The Delphi Technique: Making Sense Of Consensus. . *Practical Assessment, Research & Evaluation*. 2007;Vol 12, No 10:1-8

26.   Donabedian A. Evaluating the Quality of Medical Care. *The Milbank Memorial Fund Quarterly*. 1966;44(3):166-206. doi:10.2307/3348969

27.   Moher D, Shamseer L, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. journal article. *Systematic Reviews*. 2015;4(1):1-9. doi:10.1186/2046-4053-4-1

28.   Shamseer L, Moher D, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. *BMJ : British Medical Journal*. 2015;349:g7647. doi:10.1136/bmj.g7647

29.   Seligman WH, Das-Gupta Z, Jobi-Odeneye AO, et al. Development of an international standard set of outcome measures for patients with atrial fibrillation: a report of the International Consortium for Health Outcomes Measurement (ICHOM) atrial fibrillation working group. *European Heart Journal*. 2020;41(10):1132-1140. doi:10.1093/eurheartj/ehz871

30.   January CT, Wann LS, Calkins H, et al. 2019 AHA/ACC/HRS Focused Update of the 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society in Collaboration With the Society of Thoracic Surgeons. *Circulation*. 2019;140(2):e125-e151. doi:doi:10.1161/CIR.0000000000000665

31.   Calkins H, Gliklich RE, Leavy MB, et al. Harmonized outcome measures for use in atrial fibrillation patient registries and clinical practice: Endorsed by the Heart Rhythm

Society Board of Trustees. *Heart Rhythm*. 2019/01/01/ 2019;16(1):e3-e16. doi:https://doi.org/10.1016/j.hrthm.2018.09.021

32.   Heidenreich PA, Solis P, Estes NAM, et al. 2016 ACC/AHA Clinical Performance and Quality Measures for Adults With Atrial Fibrillation or Atrial Flutter: A Report of the American College of Cardiology/American Heart Association Task Force on Performance Measures. *Journal of the American College of Cardiology*. 2016/08/02/ 2016;68(5):525-568. doi:https://doi.org/10.1016/j.jacc.2016.03.521

33.   Kirchhof P, Benussi S, Kotecha D, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *European Heart Journal*. 2016;37(38):2893-2962. doi:10.1093/eurheartj/ehw210

34.   The National Institute for H, Care E. NICE Atrial fibrillation Quality standard [QS93]. *https://wwwniceorguk/guidance/qs93*. 2015/07//Published date: Last updated: February 2018 2015;

35.   January CT, Wann LS, Alpert JS, et al. 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation. *Circulation*. 2014;130(23):e199-e267. doi:doi:10.1161/CIR.0000000000000041

36.   Brook RH, McGlynn EA, Cleary PD. Measuring Quality of Care. *New England Journal of Medicine*. 1996;335(13):966-970. doi:doi:10.1056/NEJM199609263351311

37.   Lip GYH. The ABC pathway: an integrated approach to improve AF management. *Nat Rev Cardiol*. 2017/11/01 2017;14(11):627-628. doi:10.1038/nrcardio.2017.153

38.   Lip GYH, Banerjee A, Boriani G, et al. Antithrombotic Therapy for Atrial Fibrillation: CHEST Guideline and Expert Panel Report. *Chest*. Nov 2018;154(5):1121-1201. doi:10.1016/j.chest.2018.07.040

39.   Chao TF, Lip GYH, Liu CJ, et al. Relationship of Aging and Incident Comorbidities to Stroke Risk in Patients With Atrial Fibrillation. *Journal of the American College of Cardiology*. Jan 16 2018;71(2):122-132. doi:10.1016/j.jacc.2017.10.085

40.   Chao TF, Lip GYH, Lin YJ, et al. Incident Risk Factors and Major Bleeding in Patients with Atrial Fibrillation Treated with Oral Anticoagulants: A Comparison of Baseline, Follow-up and Delta HAS-BLED Scores with an Approach Focused on Modifiable Bleeding Risk Factors. *Thrombosis and haemostasis*. Apr 2018;118(4):768-777. doi:10.1055/s-0038-1636534

41.   Borre ED, Goode A, Raitz G, et al. Predicting Thromboembolic and Bleeding Event Risk in Patients with Non-Valvular Atrial Fibrillation: A Systematic Review. *Thrombosis and haemostasis*. Dec 2018;118(12):2171-2187. doi:10.1055/s-0038-1675400

42.   Roldan V, Marin F, Manzano-Fernandez S, et al. The HAS-BLED score has better prediction accuracy for major bleeding than CHADS2 or CHA2DS2-VASc scores in anticoagulated patients with atrial fibrillation. *Journal of the American College of Cardiology*. Dec 10 2013;62(23):2199-204. doi:10.1016/j.jacc.2013.08.1623

43.   Apostolakis S, Lane DA, Buller H, Lip GY. Comparison of the CHADS2, CHA2DS2-VASc and HAS-BLED scores for the prediction of clinically relevant bleeding in anticoagulated patients with atrial fibrillation: the AMADEUS trial. *Thrombosis and haemostasis*. Nov 2013;110(5):1074-9. doi:10.1160/TH13-07-0552

44.   Guo Y, Lane DA, Chen Y, Lip GYH, m AFAIITi. Regular bleeding risk assessment associated with reduction in bleeding outcomes: The mAFA II randomised trial. *The American journal of medicine*. Apr 11 2020;doi:10.1016/j.amjmed.2020.03.019

45.   Kumar S, Lim E, Covic A, et al. Anticoagulation in Concomitant Chronic Kidney Disease and Atrial Fibrillation: JACC Review Topic of the Week. *Journal of the American College of Cardiology*. 2019/10/29/ 2019;74(17):2204-2215. doi:https://doi.org/10.1016/j.jacc.2019.08.1031

46.   Steffel J, Verhamme P, Potpara TS, et al. The 2018 European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation: executive summary. *EP Europace*. 2018;20(8):1231-1242. doi:10.1093/europace/euy054

47.   Potpara TS, Polovina MM, Marinkovic JM, Lip GY. A comparison of clinical characteristics and long-term prognosis in asymptomatic and symptomatic patients with first-diagnosed atrial fibrillation: the Belgrade Atrial Fibrillation Study. *Int J Cardiol*. Oct 12 2013;168(5):4744-9. doi:10.1016/j.ijcard.2013.07.234

48.   Boriani G, Laroche C, Diemberger I, et al. Asymptomatic atrial fibrillation: clinical correlates, management, and outcomes in the EORP-AF Pilot General Registry. *Am J Med*. May 2015;128(5):509-18 e2. doi:10.1016/j.amjmed.2014.11.026

49.   Siontis KC, Gersh BJ, Killian JM, et al. Typical, atypical, and asymptomatic presentations of new-onset atrial fibrillation in the community: Characteristics and prognostic implications. *Heart Rhythm*. Jul 2016;13(7):1418-24. doi:10.1016/j.hrthm.2016.03.003

50.   Martinez C, Katholing A, Freedman SB. Adverse prognosis of incidentally detected ambulatory atrial fibrillation. A cohort study. *Thrombosis and haemostasis*. Aug 2014;112(2):276-86. doi:10.1160/TH4-04-0383

51.   Welton NJ, McAleenan A, Thom HH, et al. Screening strategies for atrial fibrillation: a systematic review and cost-effectiveness analysis. *Health Technol Assess*. May 2017;21(29):1-236. doi:10.3310/hta21290

52.   Pollak WM, Simmons JD, Interian Jr. A, et al. Clinical Utility of Intraatrial Pacemaker Stored Electrograms to Diagnose Atrial Fibrillation and Flutter. *Pacing and Clinical Electrophysiology*. 2001;24(4):424-429. doi:10.1046/j.1460-9592.2001.00424.x

53.   Kaufman ES, Israel CW, Nair GM, et al. Positive predictive value of device-detected atrial high-rate episodes at different rates and durations: An analysis from ASSERT. *Heart Rhythm*. 2012/08/01/ 2012;9(8):1241-1246. doi:https://doi.org/10.1016/j.hrthm.2012.03.017

54.   Kishore A, Vail A, Majid A, et al. Detection of atrial fibrillation after ischemic stroke or transient ischemic attack: a systematic review and meta-analysis. *Stroke*. Feb 2014;45(2):520-6. doi:10.1161/STROKEAHA.113.003433

55.   Sposato LA, Cipriano LE, Saposnik G, Ruiz Vargas E, Riccio PM, Hachinski V. Diagnosis of atrial fibrillation after stroke and transient ischaemic attack: a systematic review and meta-analysis. *Lancet Neurol*. Apr 2015;14(4):377-87. doi:10.1016/S1474-4422(15)70027-X

56.   Gladstone DJ, Spring M, Dorian P, et al. Atrial Fibrillation in Patients with Cryptogenic Stroke. *New England Journal of Medicine*. 2014;370(26):2467-2477. doi:10.1056/NEJMoa1311376

57.   Sanna T, Diener H-C, Passman RS, et al. Cryptogenic Stroke and Underlying Atrial Fibrillation. *New England Journal of Medicine*. 2014;370(26):2478-2486. doi:doi:10.1056/NEJMoa1313600

58.   Thijs VN, Brachmann J, Morillo CA, et al. Predictors for atrial fibrillation detection after cryptogenic stroke. *Results from CRYSTAL AF*. 2016;86(3):261-269. doi:10.1212/wnl.0000000000002282

59.   Piccini JP, Sr., Allred J, Bunch TJ, et al. HRS white paper on atrial fibrillation centers of excellence: Rationale, considerations, and goals. *Heart Rhythm*. May 5 2020;doi:10.1016/j.hrthm.2020.04.033

60.   Steinberg BA, Kim S, Fonarow GC, et al. Drivers of hospitalization for patients with atrial fibrillation: Results from the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF). *Am Heart J*. May 2014;167(5):735-42.e2. doi:10.1016/j.ahj.2014.02.003

61.   Steinberg BA, Gao H, Shrader P, et al. International trends in clinical characteristics and oral anticoagulation treatment for patients with atrial fibrillation: Results from the

GARFIELD-AF, ORBIT-AF I, and ORBIT-AF II registries. *American Heart Journal*. 2017/12/01/ 2017;194:132-140. doi:https://doi.org/10.1016/j.ahj.2017.08.011

62.   Steinberg BA, Shrader P, Pieper K, et al. Frequency and Outcomes of Reduced Dose Non-Vitamin K Antagonist Anticoagulants: Results From ORBIT-AF II (The Outcomes Registry for Better Informed Treatment of Atrial Fibrillation II). *Journal of the American Heart Association*. 2018;7(4):e007633. doi:doi:10.1161/JAHA.117.007633

63.   Wan Y, Heneghan C, Perera R, et al. Anticoagulation control and prediction of adverse events in patients with atrial fibrillation: a systematic review. *Circulation Cardiovascular quality and outcomes*. Nov 2008;1(2):84-91. doi:10.1161/CIRCOUTCOMES.108.796185

64.   Sjalander S, Sjogren V, Renlund H, Norrving B, Sjalander A. Dabigatran, rivaroxaban and apixaban vs. high TTR warfarin in atrial fibrillation. *Thrombosis research*. Jul 2018;167:113-118. doi:10.1016/j.thromres.2018.05.022

65.   Amin A, Deitelzweig S, Jing Y, et al. Estimation of the impact of warfarin's time-in-therapeutic range on stroke and major bleeding rates and its influence on the medical cost avoidance associated with novel oral anticoagulant use-learnings from ARISTOTLE, ROCKET-AF, and RE-LY trials. *J Thromb Thrombolysis*. 2014;38(2):150-9. doi:10.1007/s11239-013-1048-z

66.   Al-Khatib SM, Allen LaPointe NM, Chatterjee R, et al. Rate- and rhythm-control therapies in patients with atrial fibrillation: a systematic review. *Ann Intern Med*. Jun 3 2014;160(11):760-73. doi:10.7326/M13-1467

67.   Camm AJ. Hopes and disappointments with antiarrhythmic drugs. *Int J Cardiol*. Jun 15 2017;237:71-74. doi:10.1016/j.ijcard.2017.03.056

68.   De Vecchis R. Long-term antiarrhythmic drug treatment after atrial fibrillation ablation: does a too obstinate rhythm control strategy bring serious risk of proarrhythmia to ablated patients? *Eur Heart J Cardiovasc Pharmacother*. Apr 1 2019;5(2):117-118. doi:10.1093/ehjcvp/pvy043

69.   Fabritz L, Kirchhof P. Predictable and less predictable unwanted cardiac drugs effects: individual pre-disposition and transient precipitating factors. *Basic Clin Pharmacol Toxicol*. Mar 2010;106(3):263-8. doi:10.1111/j.1742-7843.2010.00547.x

70.   Reimold FR, Reynolds MR. Proarrhythmia and death with antiarrhythmic drugs for atrial fibrillation, and the unfulfilled promise of comparative effectiveness research. *American heart journal*. Nov 2018;205:128-130. doi:10.1016/j.ahj.2018.08.011

71.   Darby AE, DiMarco JP. Management of Atrial Fibrillation in Patients With Structural Heart Disease. *Circulation*. 2012;125(7):945-957. doi:doi:10.1161/CIRCULATIONAHA.111.019935

72.   Goldstein RE, Boccuzzi SJ, Cruess D, Nattel S. Diltiazem increases late-onset congestive heart failure in postinfarction patients with early reduction in ejection fraction. The Adverse Experience Committee; and the Multicenter Diltiazem Postinfarction Research Group. *Circulation*. 1991;83(1):52-60. doi:10.1161/01.cir.83.1.52

73.   Singh BN, Singh SN, Reda DJ, et al. Amiodarone versus sotalol for atrial fibrillation. *The New England journal of medicine*. May 5 2005;352(18):1861-72. doi:10.1056/NEJMoa041705

74.   Capucci A, Piangerelli L, Ricciotti J, Gabrielli D, Guerra F. Flecainide-metoprolol combination reduces atrial fibrillation clinical recurrences and improves tolerability at 1-year follow-up in persistent symptomatic atrial fibrillation. *Europace*. Nov 2016;18(11):1698-1704. doi:10.1093/europace/euv462

75.   Shiga T, Yoshioka K, Watanabe E, et al. Paroxysmal atrial fibrillation recurrences and quality of life in symptomatic patients: A crossover study of flecainide and pilsicainide. *J Arrhythm*. Aug 2017;33(4):310-317. doi:10.1016/j.joa.2017.03.005

76.   Mont L, Bisbal F, Hernandez-Madrid A, et al. Catheter ablation vs. antiarrhythmic drug treatment of persistent atrial fibrillation: a multicentre, randomized, controlled trial (SARA study). *Eur Heart J*. Feb 2014;35(8):501-7. doi:10.1093/eurheartj/eht457

77.   Morillo CA, Verma A, Connolly SJ, et al. Radiofrequency ablation vs antiarrhythmic drugs as first-line treatment of paroxysmal atrial fibrillation (RAAFT-2): a randomized trial. *JAMA*. Feb 19 2014;311(7):692-700. doi:10.1001/jama.2014.467

78.   Hakalahti A, Biancari F, Nielsen JC, Raatikainen MJ. Radiofrequency ablation vs. antiarrhythmic drug therapy as first line treatment of symptomatic atrial fibrillation: systematic review and meta-analysis. Journal Article. *Europace*. Mar 2015;17(3):370-8. doi:10.1093/europace/euu376

79.   Di Biase L, Mohanty P, Mohanty S, et al. Ablation Versus Amiodarone for Treatment of Persistent Atrial Fibrillation in Patients With Congestive Heart Failure and an Implanted Device: Results From the AATAC Multicenter Randomized Trial. *Circulation*. Apr 26 2016;133(17):1637-44. doi:10.1161/CIRCULATIONAHA.115.019406

80.   Kuck KH, Brugada J, Furnkranz A, et al. Cryoballoon or Radiofrequency Ablation for Paroxysmal Atrial Fibrillation. *The New England journal of medicine*. Jun 9 2016;374(23):2235-45. doi:10.1056/NEJMoa1602014

81.   Sohara H, Ohe T, Okumura K, et al. HotBalloon Ablation of the Pulmonary Veins for Paroxysmal AF: A Multicenter Randomized Trial in Japan. *J Am Coll Cardiol*. Dec 27 2016;68(25):2747-2757. doi:10.1016/j.jacc.2016.10.037

82.   Nyong J, Amit G, Adler AJ, et al. Efficacy and safety of ablation for people with non-paroxysmal atrial fibrillation. *Cochrane Database Syst Rev*. Nov 22 2016;11(11):CD012088. doi:10.1002/14651858.CD012088.pub2

83.   Nielsen JC, Johannessen A, Raatikainen P, et al. Long-term efficacy of catheter ablation as first-line therapy for paroxysmal atrial fibrillation: 5-year outcome in a randomised clinical trial. *Heart*. Mar 2017;103(5):368-376. doi:10.1136/heartjnl-2016-309781

84.   Chen C, Zhou X, Zhu M, et al. Catheter ablation versus medical therapy for patients with persistent atrial fibrillation: a systematic review and meta-analysis of evidence from randomized controlled trials. journal article. *Journal of interventional cardiac electrophysiology : an international journal of arrhythmias and pacing*. Jun 2018;52(1):9-18. doi:10.1007/s10840-018-0349-8

85.   Packer DL, Mark DB, Robb RA, et al. Effect of Catheter Ablation vs Antiarrhythmic Drug Therapy on Mortality, Stroke, Bleeding, and Cardiac Arrest Among Patients With Atrial Fibrillation: The CABANA Randomized Clinical Trial. *JAMA*. 2019;321(13):1261-1274. doi:10.1001/jama.2019.0693

86.   Mark DB, Anstrom KJ, Sheng S, et al. Effect of Catheter Ablation vs Medical Therapy on Quality of Life Among Patients With Atrial Fibrillation: The CABANA Randomized Clinical Trial. *JAMA*. 2019;321(13):1275-1285. doi:10.1001/jama.2019.0692

87.   Blomstrom-Lundqvist C, Gizurarson S, Schwieler J, et al. Effect of Catheter Ablation vs Antiarrhythmic Medication on Quality of Life in Patients With Atrial Fibrillation: The CAPTAF Randomized Clinical Trial. *JAMA*. Mar 19 2019;321(11):1059-1068. doi:10.1001/jama.2019.0335

88.   Teh AW, Kistler PM, Lee G, et al. Electroanatomic remodeling of the left atrium in paroxysmal and persistent atrial fibrillation patients without structural heart disease. *Journal of cardiovascular electrophysiology*. Mar 2012;23(3):232-8. doi:10.1111/j.1540-8167.2011.02178.x

89.   D'Ascenzo F, Corleto A, Biondi-Zoccai G, et al. Which are the most reliable predictors of recurrence of atrial fibrillation after transcatheter ablation?: a meta-analysis. *Int J Cardiol*. Sep 1 2013;167(5):1984-9. doi:10.1016/j.ijcard.2012.05.008

90. Berruezo A, Tamborero D, Mont L, et al. Pre-procedural predictors of atrial fibrillation recurrence after circumferential pulmonary vein ablation. *Eur Heart J*. Apr 2007;28(7):836-41. doi:10.1093/eurheartj/ehm027

91. Nedios S, Kosiuk J, Koutalas E, et al. Comparison of left atrial dimensions in CT and echocardiography as predictors of long-term success after catheter ablation of atrial fibrillation. journal article. *Journal of interventional cardiac electrophysiology : an international journal of arrhythmias and pacing*. Sep 2015;43(3):237-44. doi:10.1007/s10840-015-0010-8

92. Njoku A, Kannabhiran M, Arora R, et al. Left atrial volume predicts atrial fibrillation recurrence after radiofrequency ablation: a meta-analysis. *Europace*. Jan 1 2018;20(1):33-42. doi:10.1093/europace/eux013

93. Costa FM, Ferreira AM, Oliveira S, et al. Left atrial volume is more important than the type of atrial fibrillation in predicting the long-term success of catheter ablation. *Int J Cardiol*. Apr 1 2015;184:56-61. doi:10.1016/j.ijcard.2015.01.060

94. Marrouche NF, Wilber D, Hindricks G, et al. Association of atrial tissue fibrosis identified by delayed enhancement MRI and atrial fibrillation catheter ablation: the DECAAF study. *JAMA*. Feb 5 2014;311(5):498-506. doi:10.1001/jama.2014.3

95. Natale A, Reddy VY, Monir G, et al. Paroxysmal AF catheter ablation with a contact force sensing catheter: results of the prospective, multicenter SMART-AF trial. *J Am Coll Cardiol*. Aug 19 2014;64(7):647-56. doi:10.1016/j.jacc.2014.04.072

96. Arbelo E, Guiu E, Ramos P, et al. Benefit of left atrial roof linear ablation in paroxysmal atrial fibrillation: a prospective, randomized study. *J Am Heart Assoc*. Sep 5 2014;3(5):e000877. doi:10.1161/JAHA.114.000877

97. McLellan AJ, Ling LH, Azzopardi S, et al. A minimal or maximal ablation strategy to achieve pulmonary vein isolation for paroxysmal atrial fibrillation: a prospective multi-centre randomized controlled trial (the Minimax study). *Eur Heart J*. Jul 21 2015;36(28):1812-21. doi:10.1093/eurheartj/ehv139

98. Verma A, Jiang CY, Betts TR, et al. Approaches to catheter ablation for persistent atrial fibrillation. *The New England journal of medicine*. May 7 2015;372(19):1812-22. doi:10.1056/NEJMoa1408288

99. Luik A, Radzewitz A, Kieser M, et al. Cryoballoon Versus Open Irrigated Radiofrequency Ablation in Patients With Paroxysmal Atrial Fibrillation: The Prospective, Randomized, Controlled, Noninferiority FreezeAF Study. *Circulation*. Oct 6 2015;132(14):1311-9. doi:10.1161/CIRCULATIONAHA.115.016871

100.   Dukkipati SR, Cuoco F, Kutinsky I, et al. Pulmonary Vein Isolation Using the Visually Guided Laser Balloon: A Prospective, Multicenter, and Randomized Comparison to Standard Radiofrequency Ablation. *J Am Coll Cardiol*. Sep 22 2015;66(12):1350-60. doi:10.1016/j.jacc.2015.07.036

101.   Reddy VY, Dukkipati SR, Neuzil P, et al. Randomized, Controlled Trial of the Safety and Effectiveness of a Contact Force-Sensing Irrigated Catheter for Ablation of Paroxysmal Atrial Fibrillation: Results of the TactiCath Contact Force Ablation Catheter Study for Atrial Fibrillation (TOCCASTAR) Study. *Circulation*. Sep 8 2015;132(10):907-15. doi:10.1161/CIRCULATIONAHA.114.014092

102.   Scherr D, Khairy P, Miyazaki S, et al. Five-year outcome of catheter ablation of persistent atrial fibrillation using termination of atrial fibrillation as a procedural endpoint. *Circ Arrhythm Electrophysiol*. Feb 2015;8(1):18-24. doi:10.1161/CIRCEP.114.001943

103.   Kuck KH, Hoffmann BA, Ernst S, et al. Impact of Complete Versus Incomplete Circumferential Lines Around the Pulmonary Veins During Catheter Ablation of Paroxysmal Atrial Fibrillation: Results From the Gap-Atrial Fibrillation-German Atrial Fibrillation Competence Network 1 Trial. *Circ Arrhythm Electrophysiol*. Jan 2016;9(1):e003337. doi:10.1161/CIRCEP.115.003337

104.   Nery PB, Belliveau D, Nair GM, et al. Relationship Between Pulmonary Vein Reconnection and Atrial Fibrillation Recurrence: A Systematic Review and Meta-Analysis. *JACC Clin Electrophysiol*. Aug 2016;2(4):474-483. doi:10.1016/j.jacep.2016.02.003

105.   Bassiouny M, Saliba W, Hussein A, et al. Randomized Study of Persistent Atrial Fibrillation Ablation: Ablate in Sinus Rhythm Versus Ablate Complex-Fractionated Atrial Electrograms in Atrial Fibrillation. *Circ Arrhythm Electrophysiol*. Feb 2016;9(2):e003596. doi:10.1161/CIRCEP.115.003596

106.   Hindricks G, Sepehri Shamloo A, Lenarczyk R, et al. Catheter ablation of atrial fibrillation: current status, techniques, outcomes and challengesCatheter ablation of atrial fibrillation: current status, techniques, outcomes, and challenges. *Kardiologia polska*. 2018;76(12):1680-1686. doi:10.5603/KP.a2018.0216

107.   Pathak RK, Middeldorp ME, Lau DH, et al. Aggressive risk factor reduction study for atrial fibrillation and implications for the outcome of ablation: the ARREST-AF cohort study. *J Am Coll Cardiol*. Dec 2 2014;64(21):2222-31. doi:10.1016/j.jacc.2014.09.028

108.   Pathak RK, Elliott A, Middeldorp ME, et al. Impact of CARDIOrespiratory FITness on Arrhythmia Recurrence in Obese Individuals With Atrial Fibrillation: The CARDIO-FIT Study. *J Am Coll Cardiol*. Sep 01 2015;66(9):985-96. doi:10.1016/j.jacc.2015.06.488

109.	Pathak RK, Middeldorp ME, Meredith M, et al. Long-Term Effect of Goal-Directed Weight Management in an Atrial Fibrillation Cohort: A Long-Term Follow-Up Study (LEGACY). *J Am Coll Cardiol*. May 26 2015;65(20):2159-69. doi:10.1016/j.jacc.2015.03.002

110.	Donnellan E, Wazni OM, Kanj M, et al. Association between pre-ablation bariatric surgery and atrial fibrillation recurrence in morbidly obese patients undergoing atrial fibrillation ablation. *Europace*. Oct 1 2019;21(10):1476-1483. doi:10.1093/europace/euz183

111.	Donnellan E, Aagaard P, Kanj M, et al. Association Between Pre-Ablation Glycemic Control and Outcomes Among Patients With Diabetes Undergoing Atrial Fibrillation Ablation. *JACC Clin Electrophysiol*. Aug 2019;5(8):897-903. doi:10.1016/j.jacep.2019.05.018

112.	Voskoboinik A, Kalman JM, De Silva A, et al. Alcohol Abstinence in Drinkers with Atrial Fibrillation. *N Engl J Med*. Jan 2 2020;382(1):20-28. doi:10.1056/NEJMoa1817591

113.	Elliott AD, Linz D, Mishima R, et al. Association between physical activity and risk of incident arrhythmias in 402 406 individuals: evidence from the UK Biobank cohort. *Eur Heart J*. Apr 14 2020;41(15):1479-1486. doi:10.1093/eurheartj/ehz897

114.	Lau DH, Nattel S, Kalman JM, Sanders P. Modifiable Risk Factors and Atrial Fibrillation. *Circulation*. Aug 8 2017;136(6):583-596. doi:10.1161/CIRCULATIONAHA.116.023163

115.	Abed HS, Wittert GA, Leong DP, et al. Effect of weight reduction and cardiometabolic risk factor management on symptom burden and severity in patients with atrial fibrillation: a randomized clinical trial. *JAMA*. Nov 20 2013;310(19):2050-60. doi:10.1001/jama.2013.280521

116.	Lavie CJ, Thomas RJ, Squires RW, Allison TG, Milani RV. Exercise training and cardiac rehabilitation in primary and secondary prevention of coronary heart disease. *Mayo Clin Proc*. Apr 2009;84(4):373-83. doi:10.1016/S0025-6196(11)60548-X

117.	Mont L. Arrhythmias and sport practice. *Heart*. Mar 2010;96(5):398-405. doi:10.1136/hrt.2008.160903

118.	Menezes AR, Lavie CJ, De Schutter A, et al. Lifestyle modification in the prevention and treatment of atrial fibrillation. *Progress in cardiovascular diseases*. Sep-Oct 2015;58(2):117-25. doi:10.1016/j.pcad.2015.07.001

119.	Conen D, Albert CM. Alcohol consumption and risk of atrial fibrillation: how much is too much? *J Am Coll Cardiol*. Jul 22 2014;64(3):290-2. doi:10.1016/j.jacc.2014.04.038

120. Larsson SC, Drca N, Wolk A. Alcohol consumption and risk of atrial fibrillation: a prospective study and dose-response meta-analysis. *J Am Coll Cardiol*. Jul 22 2014;64(3):281-9. doi:10.1016/j.jacc.2014.03.048

121. Pisters R, Lane DA, Marin F, Camm AJ, Lip GY. Stroke and thromboembolism in atrial fibrillation. *Circ J*. 2012;76(10):2289-304.

122. Freedman B, Camm J, Calkins H, et al. Screening for Atrial Fibrillation: A Report of the AF-SCREEN International Collaboration. *Circulation*. May 9 2017;135(19):1851-1867. doi:10.1161/CIRCULATIONAHA.116.026693

123. Epstein LJ, Kristo D, Strollo PJ, Jr., et al. Clinical guideline for the evaluation, management and long-term care of obstructive sleep apnea in adults. *Journal of clinical sleep medicine : JCSM : official publication of the American Academy of Sleep Medicine*. Jun 15 2009;5(3):263-76.

124. Linz D, McEvoy RD, Cowie MR, et al. Associations of Obstructive Sleep Apnea With Atrial Fibrillation and Continuous Positive Airway Pressure Treatment: A Review. *JAMA cardiology*. Jun 1 2018;3(6):532-540. doi:10.1001/jamacardio.2018.0095

125. Lip GYH, Coca A, Kahan T, et al. Hypertension and cardiac arrhythmias: a consensus document from the European Heart Rhythm Association (EHRA) and ESC Council on Hypertension, endorsed by the Heart Rhythm Society (HRS), Asia-Pacific Heart Rhythm Society (APHRS) and Sociedad Latinoamericana de Estimulacion Cardiaca y Electrofisiologia (SOLEACE). *Europace*. Jun 1 2017;19(6):891-911. doi:10.1093/europace/eux091

126. Hobbs FD, Fitzmaurice DA, Mant J, et al. A randomised controlled trial and cost-effectiveness study of systematic screening (targeted and total population screening) versus routine practice for the detection of atrial fibrillation in people aged 65 and over. The SAFE study. *Health Technol Assess*. Oct 2005;9(40):iii-iv, ix-x, 1-74.

127. Pallisgaard JL, Schjerning AM, Lindhardt TB, et al. Risk of atrial fibrillation in diabetes mellitus: A nationwide cohort study. *Eur J Prev Cardiol*. Apr 2016;23(6):621-7. doi:10.1177/2047487315599892

128. Wynn GJ, Todd DM, Webber M, et al. The European Heart Rhythm Association symptom classification for atrial fibrillation: validation and improvement through a simple modification. *Europace : European pacing, arrhythmias, and cardiac electrophysiology : journal of the working groups on cardiac pacing, arrhythmias, and cardiac cellular electrophysiology of the European Society of Cardiology*. Jul 2014;16(7):965-72. doi:10.1093/europace/eut395

129.   Friberg L, Rosenqvist M, Lip GYH. Evaluation of risk stratification schemes for ischaemic stroke and bleeding in 182 678 patients with atrial fibrillation: the Swedish Atrial Fibrillation cohort study. *European Heart Journal*. 2012;33(12):1500-1510. doi:10.1093/eurheartj/ehr488

130.   Schulman S, Kearon C. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. *Journal of thrombosis and haemostasis : JTH*. Apr 2005;3(4):692-4. doi:10.1111/j.1538-7836.2005.01204.x

131.   Schulman S, Angeras U, Bergqvist D, et al. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in surgical patients. *Journal of Thrombosis and Haemostasis*. 2010;8(1):202-204. doi:10.1111/j.1538-7836.2009.03678.x

132.   Calvert M, Kyte D, Price G, Valderas JM, Hjollund NH. Maximising the impact of patient reported outcome assessment for patients and society. *BMJ (Clinical research ed)*. Jan 24 2019;364:k5267. doi:10.1136/bmj.k5267

133.   Rotenstein LS, Huckman RS, Wagle NW. Making Patients and Doctors Happier - The Potential of Patient-Reported Outcomes. *The New England journal of medicine*. Oct 5 2017;377(14):1309-1312. doi:10.1056/NEJMp1707537

134.   Steinberg BA, Dorian P, Anstrom KJ, et al. Patient-Reported Outcomes in Atrial Fibrillation Research: Results of a Clinicaltrials.gov Analysis. *JACC Clinical electrophysiology*. May 2019;5(5):599-605. doi:10.1016/j.jacep.2019.03.008

135.   Aliot E, Botto GL, Crijns HJ, Kirchhof P. Quality of life in patients with atrial fibrillation: how to assess it and how to improve it. *Europace : European pacing, arrhythmias, and cardiac electrophysiology : journal of the working groups on cardiac pacing, arrhythmias, and cardiac cellular electrophysiology of the European Society of Cardiology*. Jun 2014;16(6):787-96. doi:10.1093/europace/eut369

136.   Ware J, Jr., Kosinski M, Keller SD. A 12-Item Short-Form Health Survey: construction of scales and preliminary tests of reliability and validity. *Medical care*. Mar 1996;34(3):220-33. doi:10.1097/00005650-199603000-00003

137.   Kotecha D, Ahmed A, Calvert M, Lencioni M, Terwee CB, Lane DA. Patient-Reported Outcomes for Quality of Life Assessment in Atrial Fibrillation: A Systematic Review of Measurement Properties. *PloS one*. 2016;11(11):e0165790. doi:10.1371/journal.pone.0165790

138.   Spertus J, Dorian P, Bubien R, et al. Development and validation of the Atrial Fibrillation Effect on QualiTy-of-Life (AFEQT) Questionnaire in patients with atrial

fibrillation. *Circulation Arrhythmia and electrophysiology*. Feb 2011;4(1):15-25. doi:10.1161/circep.110.958033

139.   Singh SN, Tang XC, Singh BN, et al. Quality of Life and Exercise Performance in Patients in Sinus Rhythm Versus Persistent Atrial Fibrillation: A Veterans Affairs Cooperative Studies Program Substudy. *Journal of the American College of Cardiology*. 2006/08/15/ 2006;48(4):721-730. doi:https://doi.org/10.1016/j.jacc.2006.03.051

140.   Dorian P, Guerra PG, Kerr CR, et al. Validation of a New Simple Scale to Measure Symptoms in Atrial Fibrillation. *Circulation: Arrhythmia and Electrophysiology*. 2009;2(3):218-224. doi:doi:10.1161/CIRCEP.108.812347

141.   Dorian P, Jung W, Newman D, et al. The impairment of health-related quality of life in patients with intermittent atrial fibrillation: implications for the assessment of investigational therapy. *Journal of the American College of Cardiology*. 2000/10/01/ 2000;36(4):1303-1309. doi:https://doi.org/10.1016/S0735-1097(00)00886-X

142.   Seligman WH, Das-Gupta Z, Jobi-Odeneye AO, et al. Development of an international standard set of outcome measures for patients with atrial fibrillation: a report of the International Consortium for Health Outcomes Measurement (ICHOM) atrial fibrillation working group. *European heart journal*. Mar 7 2020;41(10):1132-1140. doi:10.1093/eurheartj/ehz871

143.   *Crossing the Quality Chasm: A New Health System for the 21st Century*. National Academies Press (US); 2001.

144.   Benjamin EJ, Muntner P, Alonso A, et al. Heart Disease and Stroke Statistics-2019 Update: A Report From the American Heart Association. *Circulation*. Mar 5 2019;139(10):e56-e528. doi:10.1161/CIR.0000000000000659

145.   Gorin L, Fauchier L, Nonin E, Charbonnier B, Babuty D, Lip GYH. Prognosis and Guideline-Adherent Antithrombotic Treatment in Patients With Atrial Fibrillation and Atrial Flutter: Implications of Undertreatment and Overtreatment in Real-life Clinical Practice; the Loire Valley Atrial Fibrillation Project. *Chest*. 2011/10/01/ 2011;140(4):911-917. doi:https://doi.org/10.1378/chest.10-2436

146.   Nielsen PB, Larsen TB, Skjøth F, Overvad TF, Lip GYH. Stroke and thromboembolic event rates in atrial fibrillation according to different guideline treatment thresholds: A nationwide cohort study. *Scientific Reports*. 2016/06/06 2016;6(1):27410. doi:10.1038/srep27410

147.   Lip GYH, Laroche C, Dan G-A, et al. A prospective survey in European Society of Cardiology member countries of atrial fibrillation management: baseline results of

EURObservational Research Programme Atrial Fibrillation (EORP-AF) Pilot General Registry. Journal Article. *Europace*. 2014-03-01 00:00:00 2014;16(3):308-319. doi:10.1093/europace/eut373

148.   Lip GYH, Laroche C, Dan G-A, et al. 'Real-World' Antithrombotic Treatment in Atrial Fibrillation: The EORP-AF Pilot Survey. *American Journal of Medicine*. 2014;127(6):519-529.e1. doi:http://dx.doi.org/10.1016/j.amjmed.2013.12.022

149.   Lip GYH, Laroche C, Popescu MI, et al. Improved outcomes with European Society of Cardiology guideline-adherent antithrombotic treatment in high-risk patients with atrial fibrillation: a report from the EORP-AF General Pilot Registry. *EP Europace*. 2015;17(12):1777-1786. doi:10.1093/europace/euv269

150.   Lip GYH, Laroche C, Boriani G, et al. Regional differences in presentation and treatment of patients with atrial fibrillation in Europe: a report from the EURObservational Research Programme Atrial Fibrillation (EORP-AF) Pilot General Registry. *Europace*. 2015-02-01 00:00:00 2015;17(2):194-206. doi:10.1093/europace/euu201

151.   Fumagalli S, Said SAM, Laroche C, et al. Age-Related Differences in Presentation, Treatment, and Outcome of Patients With Atrial Fibrillation in Europe: The EORP-AF General Pilot Registry (EURObservational Research Programme-Atrial Fibrillation). *JACC: Clinical Electrophysiology*. 2015/08/01/ 2015;1(4):326-334. doi:https://doi.org/10.1016/j.jacep.2015.02.019

152.   Boriani G, Laroche C, Diemberger I, et al. Asymptomatic Atrial Fibrillation: Clinical Correlates, Management, and Outcomes in the EORP-AF Pilot General Registry. *American Journal of Medicine*. 2015/05/01/ 2015;128(5):509-518.e2. doi:http://dx.doi.org/10.1016/j.amjmed.2014.11.026

153.   Boriani G, Laroche C, Diemberger I, et al. 'Real-world' management and outcomes of patients with paroxysmal vs. non-paroxysmal atrial fibrillation in Europe: the EURObservational Research Programme–Atrial Fibrillation (EORP-AF) General Pilot Registry. *EP Europace*. 2016;18(5):648-657. doi:10.1093/europace/euv390

154.   Proietti M, Laroche C, Opolski G, Maggioni AP, Boriani G, Lip GYH. 'Real-world' atrial fibrillation management in Europe: observations from the 2-year follow-up of the EURObservational Research Programme-Atrial Fibrillation General Registry Pilot Phase. *Europace*. 2016-05-18 00:00:00 2016;doi:10.1093/europace/euw112

155.   Boriani G, Glotzer TV, Ziegler PD, et al. Detection of new atrial fibrillation in patients with cardiac implanted electronic devices and factors associated with transition to

higher device-detected atrial fibrillation burden. *Heart Rhythm*. 2018;15(3):376-383. doi:10.1016/j.hrthm.2017.11.007

156.   Arbelo E, Brugada J, Hindricks G, et al. The Atrial Fibrillation Ablation Pilot Study: an European Survey on Methodology and results of catheter ablation for atrial fibrillation conducted by the European Heart Rhythm Association. *European Heart Journal*. June 7, 2014 2014;35(22):1466-1478. doi:10.1093/eurheartj/ehu001

157.   Arbelo E, Brugada J, Lundqvist CB, et al. Contemporary management of patients undergoing atrial fibrillation ablation: in-hospital and 1-year follow-up findings from the ESC-EHRA atrial fibrillation ablation long-term registry. 10.1093/eurheartj/ehw564. *European Heart Journal*. 2017;

158.   Riahi S, Arbelo E, Brugada J, et al. Regional differences in referral, procedures, and outcome after ablation for atrial fibrillation in Europe: a report from the Atrial Fibrillation Ablation Pilot Registry of the European Society of Cardiology. *Europace*. 2016-02-01 00:00:00 2016;18(2):191-200. doi:10.1093/europace/euv386

159.   Barnett AS, Kim S, Fonarow GC, et al. Treatment of Atrial Fibrillation and Concordance With the American Heart Association/American College of Cardiology/Heart Rhythm Society Guidelines. *Circulation: Arrhythmia and Electrophysiology*. 2017;10(11):e005051. doi:doi:10.1161/CIRCEP.117.005051

160.   Potpara TS, Lip GYH, Dagres N, et al. Cohort profile The ESC EURObservational Research Programme Atrial Fibrillation III (AF III) Registry. *European Heart Journal - Quality of Care and Clinical Outcomes*. 2020;doi:10.1093/ehjqcco/qcaa050

161.   McNamara RL, Brass LM, Drozda JP, et al. ACC/AHA key data elements and definitions for measuring the clinical management and outcomes of patients with atrial fibrillation. A report of the American College of Cardiology/American Heart Association Task Force on clinical data standards (writing commitee to develop data standards on atrial fibrillation). *Journal of the American College of Cardiology*. 2004;44(2):475-495. doi:10.1016/j.jacc.2004.06.041

162.   McGlynn EA. Introduction and overview of the conceptual framework for a national quality measurement and reporting system. *Med Care*. Jan 2003;41(1 Suppl):I1-7. doi:10.1097/00005650-200301001-00001

163.   Staerk L, Lip GY, Olesen JB, et al. Stroke and recurrent haemorrhage associated with antithrombotic treatment after gastrointestinal bleeding in patients with atrial fibrillation: nationwide cohort study. *BMJ (Clinical research ed)*. Nov 16 2015;351:h5876. doi:10.1136/bmj.h5876

164.	Van Gelder IC, Groenveld HF, Crijns HJGM, et al. Lenient versus Strict Rate Control in Patients with Atrial Fibrillation. *New England Journal of Medicine*. 2010;362(15):1363-1373. doi:doi:10.1056/NEJMoa1001337

165.	Seligman WH, Das-Gupta Z, Jobi-Odeneye AO, et al. Development of an international standard set of outcome measures for patients with atrial fibrillation: a report of the International Consortium for Health Outcomes Measurement (ICHOM) atrial fibrillation working group. *European Heart Journal*. 2020;doi:10.1093/eurheartj/ehz871

166.	Calvert M, Blazeby J, Altman DG, et al. Reporting of patient-reported outcomes in randomized trials: The consort pro extension. *JAMA*. 2013;309(8):814-822. doi:10.1001/jama.2013.879

167.	Wallentin L, Gale CP, Maggioni A, Bardinet I, Casadei B. EuroHeart: European Unified Registries On Heart Care Evaluation and Randomized Trials: An ESC project to develop a new IT registry system which will encompass multiple features of cardiovascular medicine. *European Heart Journal*. 2019;40(33):2745-2749. doi:10.1093/eurheartj/ehz599

168.	Bunting KV, Van Gelder IC, Kotecha D. STEEER-AF: a cluster-randomized education trial from the ESC: The STEEER-AF trial is designed by the European Society of Cardiology (ESC) to see if better education for healthcare professionals can improve how patients are treated and how AF is managed. *European Heart Journal*. 2020;41(21):1952-1954. doi:10.1093/eurheartj/ehaa421

Chapter 11. European Society of Cardiology Quality Indicators for the care and outcomes of cardiac pacing

Developed by the Working Group for Cardiac Pacing Quality Indicators in collaboration with the European Heart Rhythm Association of the European Society of Cardiology.

Suleman Aktaa*, Amr Abdin*, Elena Arbelo, Harran Burri, Kevin Vernooy, Carina Blomström-Lundqvist, Giuseppe Boriani, Pascal Defaye, Jean-Claude Deharo, Inga Drossart, Dan Foldager, Michael R Gold, Jens Brock Johansen, Francisco Leyva, Cecilia Linde, Yoav Michowitz, Mads Brix Kronborg[21], David Slotwiner[22], Torkel Steen[23], José Maria Tolosana, Stylianos Tzeis, Niraj Varma, Michael Glikson, Jens Cosedis Nielsen, Chris P Gale

*Contributed equally

11.1 Summary of the publication:

- Using the methodology described in Chapter 4, this paper presents the developed quality indicators for cardiac pacing.
- Four domains of care were identified for cardiac pacing: (1) Structural framework, (2) Patient assessment, (3) Pacing strategy, and (4) Outcomes.
- In total, 7 main and 4 secondary quality indicators were developed across these domains, and were included within the 2021 ESC Guidelines on cardiac pacing and cardiac resynchronisation therapy.

11.2 Publication status

- Published 29 August 2021
- EP Europace, euab193, https://doi.org/10.1093/europace/euab193

11.3 Abstract

11.3.1 Aims

To develop a suite of quality indicators (QIs) for the evaluation of the care and outcomes for adults undergoing cardiac pacing.

11.3.2 Methods and results

Under the auspice of the Clinical Practice Guideline Quality Indicator Committee of the European Society of Cardiology (ESC), the Working Group for cardiac pacing QIs was formed. The Group comprised Task Force members of the 2021 ESC Clinical Practice Guidelines on cardiac pacing and cardiac resynchronisation therapy, members of the European Heart Rhythm Association (EHRA), international cardiac device experts, and patient representatives. We followed the ESC methodology for QI development, which involved 1) the identification of the key domains of care by constructing a conceptual framework of the management of patients receiving cardiac pacing, 2) the development of candidate QIs by conducting a systematic review of the literature, 3) the selection of the final set of QIs using a modified-Delphi method, and 4) the evaluation of the feasibility of the developed QIs. Four domains of care were identified: 1) structural framework, 2) patient assessment, 3) pacing strategy, and 4) outcomes. In total, seven main and four secondary QIs were selected across these domains, and were within the 2021 ESC Guidelines on cardiac pacing and cardiac resynchronisation therapy.

11.3.3 Conclusion

By way of a standardized process, 11 QIs for cardiac pacing have been developed. These indicators may be used to quantify adherence to guideline-recommended clinical practice and have the potential to improve the care and outcomes of patients receiving cardiac pacemakers.

11.3.4 Keywords

Cardiac pacemaker. Quality indicators. Clinical Practice Guidelines

11.4 Introduction

Cardiac pacing is commonly used to reduce morbidity and mortality in patients with cardiac rhythm disturbances.[384] Expanding pacing indications, aging population, and increased life expectancy have led to an increase in pacemaker implantation rates in recent years.[385, 386] However, large variations in the rates of implantation and associated complications has been observed within and between countries.[386, 387] According to the European Society of Cardiology (ESC) Cardiovascular Disease Statistics, in 2018/19 age and sex standardized implantation rates ranged from <60 to >1000 pacemakers per million people across the ESC member countries.[2] Clinical registries provide an opportunity to capture real world naturalistic data on cardiac pacing to better understand variations and gaps in practice.[387, 388] However, there is a need to develop and standardize the tools by which the quality of care for cardiac pacing is evaluated and resultant outcomes monitored and reported. Such tools may integrate with and provide the means to develop clinical registries for cardiac pacing, as well as have the potential to improve patient outcomes.

Quality indicators (QIs) are increasingly used to measure quality of medical care. They provide an opportunity to quantify geographic variation, and identify areas where quality improvement interventions are needed.[13] The multifaceted nature of cardiac pacing care necessitates the adoption of a broad set of QIs that conceptualises the patient journey and enables the interpretation of the results of quality assessment. Furthermore, QIs may serve as a means of closing the second translational gap between evidence and practice and facilitate a unified approach to the appraisal of care using clinical registries.[389]

While a few individual indicators for cardiac devices have been developed by the Centres for Medicare and Medicaid Services,[390-392] we are not aware of any published set of QIs for cardiac pacing. This is in contrast with the established sets of QIs for other cardiovascular conditions, such as acute myocardial infarction,[186] atrial fibrillation,[187] and heart failure[393], by various professional societies.[162, 394] Therefore, the ESC established the Working Group for cardiac pacing QIs to work on the development of indicators of care quality for cardiac pacing in collaboration with the European Heart Rhythm Association (EHRA) and in parallel with the writing of the 2021 ESC Guidelines on cardiac pacing and cardiac resynchronisation therapy.

This was undertaken under the auspice of the Clinical Practice Guideline Quality Indicator Committee of the ESC. This article describes the process by which the ESC QIs for cardiac pacing have been developed and their measurement specifications.

11.5 Methods

The methodology by which the ESC develops QIs for the quantification of cardiovascular care and outcomes has been published.[185] In brief, the methodology involves 1) the identification of the key domains of care by constructing a conceptual framework of the patients' management, 2) the development of candidate QIs by conducting a systematic review of the literature, 3) the selection of the final set of QIs using a modified-Delphi method, and 4) the evaluation of the feasibility of the developed QIs.[185]

The term QI is used here to describe a discreet clinical situation in which a process of care is or is not recommended. Thus, a distinction between QIs and 'performance measures' is drawn given that different measurements of performance may be performed from the same QI depending on a specifications such as source of data collection and the development methodology employed.[171] We propose that QIs include main and secondary indicators which can relate to the structure, process and outcomes of care.[243]

11.5.1 Members of the Working Group

The Working Group comprised members of the Task Force of the 2021 ESC Guidelines on cardiac pacing and cardiac resynchronisation therapy, members of the ESC Quality Indicator Committee, nominees from EHRA and the ESC Patient Forum, as well as international experts in cardiac devices. In total, 25 members from 13 countries participated in the Working Group, and attended a series of virtual meetings between November 2020 and March 2021.

11.5.2 Target population

The Working Group defined the 'target population' for the developed QIs as patients for whom a decision has been made to implant a cardiac pacemaker for bradyarrhythmia indication in accordance with the 2021 ESC Guidelines on cardiac pacing and cardiac resynchronisation therapy.[384] As such, patients with an indication for an implantable defibrillators and those undergoing device therapy for heart failure have been excluded. In addition, the definition used for the 'target population' excluded patients with undiagnosed bradyarrhythmia to facilitate the identification of a cohort of patients for whom the QIs may be applicable – thereby simplifying the operationalization of quality assessment when the QIs have been established.

The Working Group defined, for each *process* QI, a denominator which describes the patient group eligible for the measurement, a numerator which outlines the criteria by which the QI is accomplished, a measurement period which specifies the time point at which the quality assessment is taking place, and a measurement duration which is the time frame needed for enough cases to be collected in order to accumulate meaningful data. For *structural* QIs, only numerator definitions were provided because these are binary (yes, no) measurements.[186]

11.5.3 Literature review

During the initial phases of the development process, the specifications for the literature review were agreed between the members of the Working Group. In addition, the members identified the key domains of cardiac pacing care by constructing a conceptual illustration of the care provision pathway, which formed the framework for the development of the QIs (Figure 1).[185]

Figure 1. Conceptual framework of cardiac pacing patient journey
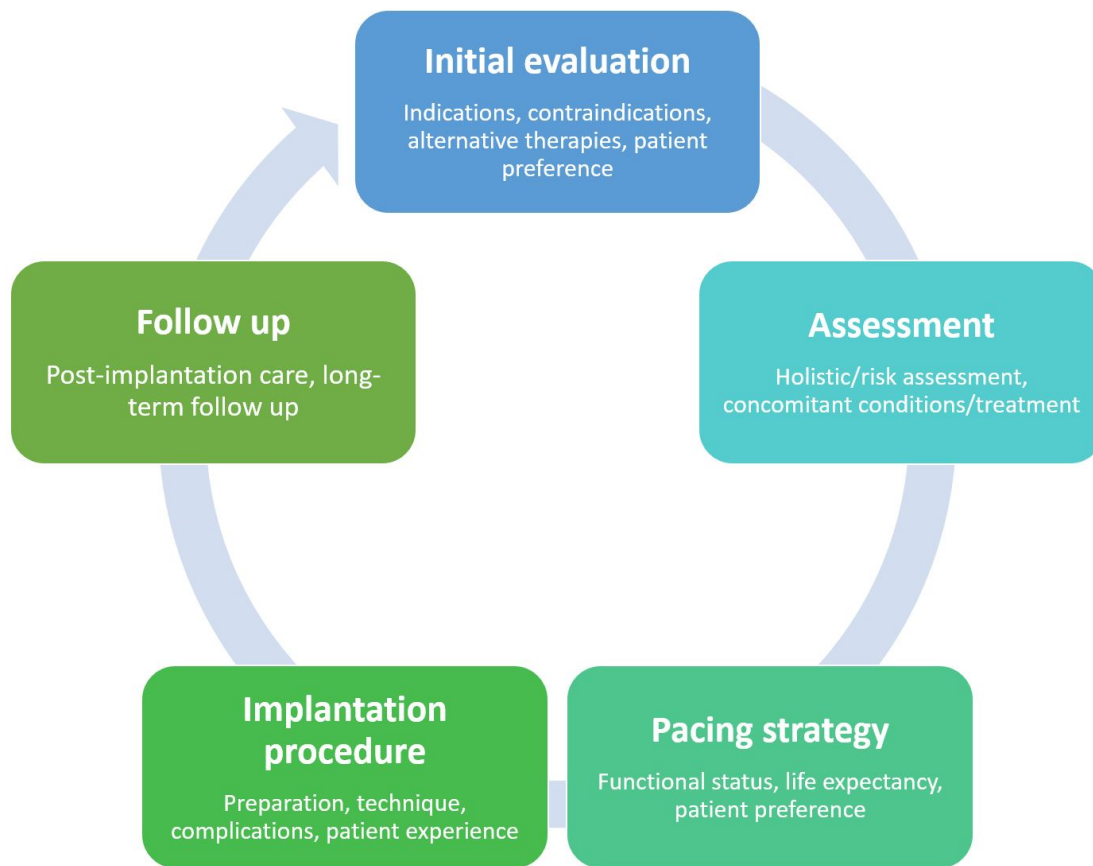
We conducted a literature search of articles pertinent to cardiac pacing including publications from clinical registries,[386, 395] international guidelines,[396, 397] as well as the Centres for Medicare and Medicaid Services indicators[390-392] and societal recommendations.[398] The literature review aimed to identify structural components, or processes, of cardiac pacing care that have a strong association with favourable patients' outcomes, while the goal of the Clinical Practice Guidelines review was to assess the suitability of the class I and class III recommendations against the ESC criteria for QIs (Supplementary Table S1).

Furthermore, and to help identify the optimal pacing strategy for patients requiring a de novo permeant pacemaker for bradyarrhythmia, a systematic review and meta-analysis was conducted simultaneously with the development of this document.[399] This review highlighted that whilst novel pacing modalities such as His bundle pacing and left bundle branch area pacing maintain physiological ventricular activation, the published studies to date are limited

by their observational design or sample size and that comparative studies are needed to understand the impact of such pacing strategies on clinical outcomes.[399]

11.5.4 Consensus development

11.5.4.1 Modified Delphi process

The candidate QIs derived from the aforementioned process were evaluated using the modified Delphi method.[252, 400] The ESC criteria for QI development (Supplementary Table S1) were shared with the Working Group members prior to the voting in order to standardize the selection process. All candidate QIs were graded for validity and feasibility by each panellist via an online questionnaire using a 9-point ordinal scale.[185, 401] Two rounds in total were conducted, with teleconferences in between to discuss the results of the vote and address any concerns or ambiguities.

11.5.4.2 Analysing voting results

A 9-point ordinal scale was used in the Delphi rounds. Ratings of 1 to 3 from the were interpreted as the QI was not valid/feasible, with ratings of 4 to 6 meaning that the QI was of an uncertain validity/feasibility and ratings of 7 to 9 that the QI was valid/feasible. For each candidate QI, the median and the mean deviation from the median were calculated to provide the central tendency and dispersion of votes. Cut offs for inclusion were similar to those reported in the literature.[402] Thus, candidate QIs with median scores ≥ 7 for validity, ≥ 4 for feasibility, and with minimal inter-rater variation were included in the final set of QIs. We defined those QIs fulfilling the above numerical threshold for inclusion following the first voting round as the main QIs, while those fulfilling the numerical threshold for inclusion after a second round of voting as secondary QIs (Supplementary material).

11.6 Results

11.6.1 Domains of care

Four domains of cardiac pacing care were identified by the Working Group. These included: 1) structural framework domain, which evaluates the characteristics of the centres providing a cardiac pacing service, 2) patient assessment domain, which evaluates the appropriateness of the investigations performed prior to cardiac pacing implantation, 3) pacing strategy domain, which evaluates the selection of the pacing method and 4) outcomes domain, which evaluates the clinical outcomes of cardiac pacing (Figure 2).

Figure 2. The domains of cardiac pacing care, with the corresponding QIs for each domain
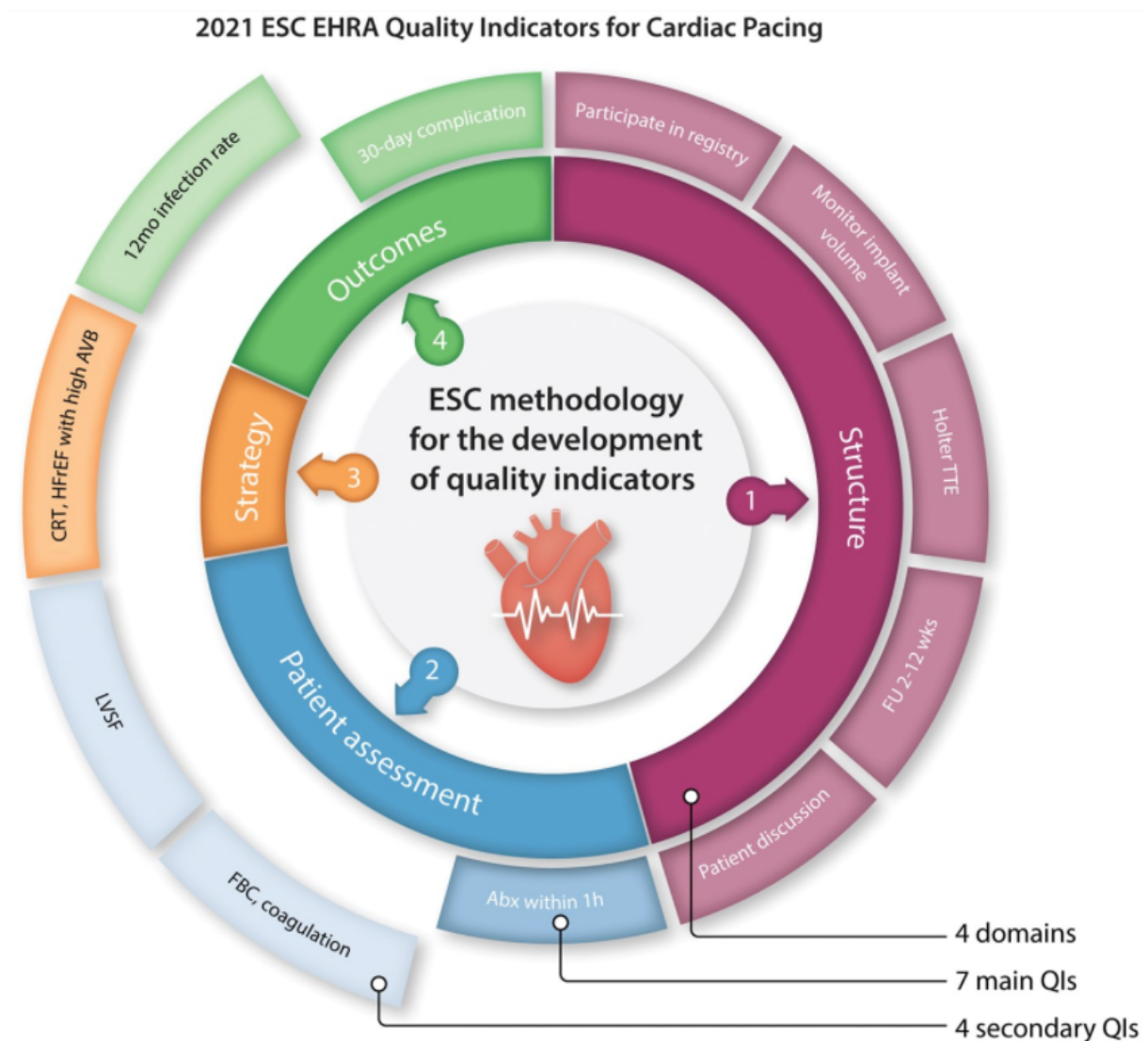
Abx=antibiotics; AVB=atrioventricular block; CRT=cardiac resynchronisation therapy; ECG=electrocardiogram; FBC=full blood count; HFrEF=heart failure with reduced ejection fraction; LV=left ventricle; QIs=quality indicators; TTE=transthoracic echocardiography.

Procedural complications are defined as pacemaker-related bleeding, pneumothorax, cardiac perforation, tamponade, pocket haematoma, lead displacement (all requiring intervention), or infection.

In addition, there was an agreement between the Working Group members on patient-related outcome measures as an important domain of care for cardiac pacing. As such, patient-related outcome measures, including the assessment of health-related quality of life using various tools (generic [e.g., EuroQol] and disease-specific [e.g., KCCQ]) were obtained from the literature search and included in the Delphi voting.

11.6.2 Quality Indicators

The literature search retrieved a total of 25 candidate QIs, which were included in the first round of the voting process. Of those, 12 (48%) were excluded and 7 (28%) were included as main QIs. The remaining 6 QIs were deemed inconclusive and were, therefore, carried to a second voting round following which 4 (66%) were included as secondary QIs. Of the 11 selected QIs, 5 (46%) related to the structural domain, 3 (27%) to the patient assessment domain, 1 (9%) to the pacing strategy domain, and 2 (18%) to the outcome domain (Figure 2). According to the voting results, the proposed patient-related outcome measures did not meet the inclusion criteria and so none were selected for the final set of indicators.

11.6.2.1 Domain 1: Structural framework

Structural QIs evaluate the characteristics of the centres providing cardiac pacing service, and play a major role in quality assessment at the institutional level. The association between certain aspects of cardiac devices patient care and outcomes has been facilitated by well-conducted registries at the national level.[387] As such, the participation in at least one registry for cardiac pacing is an indicator of care quality (**Main 1.1**). In addition, data from observational studies have shown an inverse association between the centre procedural volume

and complication rates and thus the monitoring and reporting of the centre-specific annual rate of cardiac pacing implantation has been recommended (**Main 1.2**).[387, 403]

Table 1. The 2021 ESC QIs for patients undergoing cardiac pacemaker implantation

Domain 1. Structural Framework
Main (1.1): Centres providing CIED service should participate in at least one CIED[&] registry*.
Numerator: Number of centres participating in at least one CIED registry.
Main (1.2): Centres providing CIED service should monitor and report the volume of procedures performed by individual operators on annual basis*.
Numerator: Number of centres monitoring and reporting the volume of procedures performed by individual operators.
Main (1.3): Centres providing CIED service should have available resources (ambulatory ECG monitoring, echocardiogram) to stratify patients according to their risk for ventricular arrhythmias*.
Numerator: Number of centres with an available ambulatory ECG and echocardiogram service.
Main (1.4): Centres providing CIED service should have established protocols to follow up patients within 2-12 weeks following implantation*.
Numerator: Number of centres that have an established protocols to follow up patients within 2-12 weeks following CIED implantation.
Main (1.5): Centres providing CIED service should have a pre-procedural checklist to ensure discussion with patient regarding risks, benefits, and alternative treatment options*.
Numerator: Number of centres that have a checklist to ensure discussion with patient regarding risks, benefits, and alternative treatment options prior to CIED implantation.
Domain 2. Patient Assessment
Main (2): Proportion of patients considered for CIED implantation who receive prophylactic antibiotics 1 hour before their procedure**.
Numerator: Number of patients who receive antibiotics 1 hour before their CIED implantation. *Denominator:* Number of patients who have CIED implantation.

Secondary (2.1): Proportion of patients considered for CIED implantation who have their full blood count and coagulation profile checked prior to the procedure**.

Numerator: Number of patients who have their full blood count and coagulation profile checked prior to CIED implantation.

Denominator: Number of patients who have CIED implantation.

Secondary (2.2): Proportion of patients considered for CIED implantation who have an imaging evaluation of their LV structure and systolic function prior to the procedure**.

Numerator: Number of patients who have an imaging evaluation of their LV structure and systolic function prior to CIED implantation.

Denominator: Number of patients who have CIED implantation.

Domain 3. Pacing Strategy

Secondary (3): Proportion of patients with an indication for ventricular pacing and high degree AV block who have HFrEF and undergo CRT**.

Numerator: Number of patients with an indication for ventricular pacing and high degree AV block who have HFrEF and undergo CRT implantation.

Denominator: Number of patients with an indication for ventricular pacing and high degree AV block who have HFrEF and undergo CIED implantation.

Domain 4. Outcomes

Main (4): Annual rate of procedural complications 30 days following CIED implantation^.

Numerator: Number of patients who develop one or more of the procedural complications[§] within 30 days from their CIED implantations

Denominator: Number of patients who have CIED implantation.

Secondary (4): Annual rates of CIED-related infections up to 1 year following CIED implantation, replacement, or revision^.

Numerator: Number of patients who develop CIED-related infections up to 1 year following CIED implantation, replacement, or revision.

Denominator: Number of patients who have CIED implantation, replacement, or revision.

AV=atrioventricular, CRT=Cardiac resynchronisation therapy, CIED= cardiovascular

implantable electronic device, LV=left ventricular, QIs= quality indicators,

The other 3 indicators in the structural domain include the availability of resources for the risk-stratification and clinical characterization of patients undergoing cardiac pacing, such as ambulatory rhythm monitoring and echocardiography (**Main 1.3**),[398] of follow up protocols within 2-12 weeks after device implantation (**Main 1.4**), and the presence of pre-procedural checklists documenting a discussion with patients regarding the risks benefits of device implantation and alternative treatment options prior to implantation (**Main 1.5**).

11.6.2.2 Domain 2: Patient assessment

Patient evaluation and preparation prior to cardiac pacing implantation reduces the risks of complications associated with the procedure and guides the selection of an appropriate pacing strategy.[404, 405] Evidence favours the efficacy of prophylactic antibiotics in reducing the rates of cardiac device-related infections (**Main 2**).[406, 407] The performance of basic blood tests, such as full blood count and coagulation profile may help identify patients with high risk of periprocedural complications (**Secondary 2.1**),[405] while the evaluation of the left ventricular structure and function prior to cardiac pacing helps determine the most appropriate device for the patient (**Secondary 2.2**).[404]

11.6.2.3 Domain 3: Pacing strategy

For patients with heart failure with a reduced ejection fraction who have an indication for ventricular pacing and a high degree atrioventricular block, biventricular pacing with cardiac synchronization therapy has been shown to improve clinical outcomes over right ventricular

pacing. Thus, the proportion of patients who receive cardiac synchronization therapy among those eligible has been selected as a QI (**Secondary 3**).[404]

11.6.2.4 Domain 4: Outcomes

The measurement of outcomes following cardiac pacing helps benchmark performance, monitor temporal trends of adverse events and study the efficacy of quality improvement interventions. As such, complications occurring within 30 days following device implantation is delegated an indicator of care quality (**Main 4**). However, infections related to cardiac pacing may be delayed beyond the first month following implantation.[388] Accordingly, infections up to one year after device insertion is also regarded as a measure of care quality (**Secondary 4**).

11.6.3 Patient perspective

Patient reported outcome measures reflect the patients' perspective of the impact of the condition and its treatment on their lives, and are important determinants of the patients' perceived quality and outcomes of care. Among the different categories of patient reported outcome measures, patients' health-related quality of life is of interest because it is multi-dimensional and allows the exploration of patients' physical, emotional, and social well-being.[408] While disease-specific tools exist for a number of cardiovascular disease conditions, including atrial fibrillation, arrhythmia, and heart failure, these capture limited data specific to cardiac devices implantation.[409] As such, the Delphi voting reached no consensus as to the inclusion of patient reported outcome measures in the final set of QIs with reason being lack of specificity and limited evidence to support their use.

Whereas there are common outcomes that matter to the majority of patients, individual patients may have specific outcomes of a higher importance to them based on a number of factors, such as their age or sex. For instance, a physically active patient might be concerned about restrictions of their arm and shoulder movement which may affect the ability to perform certain activities. The appearance of the scar and/or the implanted device may be more of a worry for women than men, and elderly patients might have concerns about complications related to

device implantation and therapies. As such, attention is needed when designing patient reported outcome measures to capture not only what matters to the 'average' patient, but also to individual patient's values.

Furthermore, it should be noted that patients' perceptions, particularly in cardiac pacing, may change over time. For example, the implanted device implications on patients' lives may differ according to changes in patient's overall health, their underlying condition, and their response to treatment and repeated procedures.[410] Therefore, the patient representatives within the Working Group felt that it was important to capture the trajectories of patients health-related quality of life following cardiac device implantation, and proposed a non-exhaustive list of potential areas for pacing QIs based on personal experience and exchanges with other patients (Supplementary Table S2).

11.7 Discussion

In this document, we provide a suite of 7 main and 4 secondary QIs covering 4 patient journey domains that may be used in the evaluation of cardiac pacing care and outcomes. The QIs were developed though a standardized methodology,[185] which has been used for the development of feasible and valid QIs for other cardiovascular conditions,[186, 411, 412] and as a joint effort between the Task Force of the 2021 ESC Guidelines on Cardiac Pacing and Cardiac Resynchronization Therapy, EHRA, the ESC Patient Forum, and international experts in cardiac devices under the remit of the ESC Clinical Practice Guideline Quality Indicator Committee. The participation of stakeholders from 13 countries, including patients, and the co-development of these QIs with the 2021 ESC Guidelines on Cardiac Pacing and Cardiac Resynchronization Therapy, have enabled the provision of specific, measurable, and relevant QIs for cardiac pacing care.

The increasing implantation rates of cardiac pacemakers across Europe, and the variation in practice observed in clinical registries, creates a need to develop standardized indicators for cardiac pacing quality of care and outcomes. Notwithstanding that the Centres for Medicare

and Medicaid Services have developed individual measures for cardiac devices, those were limited to specific domains of patients care, such as follow up following implantation,[391] infection rates,[390] and complications after defibrillator implantation.[392] Here we propose a suite of QIs that provides a framework encompassing the various multilayers of cardiac pacing care and, thus, help identify areas for quality improvement initiatives.

It is hoped that by providing QIs for cardiac pacing that are endorsed by professional societies and co-developed with patients, a standardized system for the assessment of care and outcomes for patients undergoing cardiac pacemakers may be established. Such a system may be used by the professional societies, healthcare authorities or hospitals to identify and address unwanted variation and monitor patterns of care. Consequently, policies and quality improvement activities may be developed to facilitate continuous benchmarking of performance over time and across regions, and the subsequent behaviour change needed to improve care delivery. The set of QIs that have been developed may be the basis for applying the process of Health Technology Assessment also to the setting of cardiac pacing.[413]

Notwithstanding that the Working Group acknowledges the importance of patient reported outcome measures and the assessment of health-related quality of life in patients undergoing cardiac pacemaker implantation, no such measures were selected in the final set of QIs. However, the Working Group envisages that there is a need to develop and validate patient reported measures which are specific to the implant of cardiac pacemakers. As such, potential areas patient reported outcome measures pertinent to cardiac pacing have been proposed and co-developed with patients to ensure highlight the need for evidence-based and validated tools to capture these aspects of pacing care.

The methodology used for the development of these QIs has limitations. We relied on expert opinion to arrive at the final set of QIs. Different panel of experts may have selected a different set of QIs, but the use of the modified Delphi method to obtain group opinion, and the involvement of patients and registry experts have provided wide perspective and

standardization to the selection process. Furthermore, the application of a structured criteria, namely the ESC criteria for QI development, in selecting the QIs and guiding the voting process improved the objectivity in building consensus amongst the Working Group members.

The developed QIs are intended to drive comprehensive patient assessments and drive quality improvement, and, thus, should not be considered in isolation. Furthermore, regular updates are needed for the these QIs and/or to their specifications when 'real-world' and feasibility data become available. It is hoped that the developed set of QIs would be implemented in, and facilitate the development of, data collection efforts aiming to assess and improve the quality of cardiac pacing care. For instance, the European Unified Registries on Heart care Evaluation and Randomized Trials (EuroHeart) project[45] may favour the implementation of methodologically developed QIs for future cardiac device registries in Europe, which this statement uniquely provides.

11.8 Conclusion

Using the ESC methodology for QI development, a set of QIs for cardiac pacing have been developed across 4 key domains of care. These QIs provide the means to systematically measure the quality of care for patients undergoing cardiac pacemakers and capture care outcomes through their implementation in daily practice and clinical registries.

11.9 References for Chapter 11

1.   Nielsen JC GM, et al. ESC Guidelines on cardiac pacing and CRT. 2021.

2.   Bradshaw PJ, Stobie P, Knuiman MW, Briffa TG and Hobbs MS. Trends in the incidence and prevalence of cardiac pacemaker insertions in an ageing population. *Open Heart*. 2014;1:e000177.

3.   Raatikainen MJP, Arnar DO, Merkely B, Nielsen JC, Hindricks G, Heidbuchel H and Camm J. A Decade of Information on the Use of Cardiac Implantable Electronic Devices and Interventional Electrophysiological Procedures in the European Society of Cardiology Countries: 2017 Report from the European Heart Rhythm Association. *EP Europace*. 2017;19:ii1-ii90.

4.   Kirkfeldt RE, Johansen JB, Nohr EA, Jørgensen OD and Nielsen JC. Complications after cardiac implantable electronic device implantations: an analysis of a complete, nationwide cohort in Denmark. *Eur Heart J*. 2014;35:1186-94.

5.   Timmis A, Townsend N, Gale CP, Torbica A, Lettino M, Petersen SE, Mossialos EA, Maggioni AP, Kazakiewicz D, May HT, De Smedt D, Flather M, Zuhlke L, Beltrame JF, Huculeci R, Tavazzi L, Hindricks G, Bax J, Casadei B, Achenbach S, Wright L and Vardas P. European Society of Cardiology: Cardiovascular Disease Statistics 2019. *European heart journal*. 2020;41:12-85.

6.   Olsen T, Jørgensen OD, Nielsen JC, Thøgersen AM, Philbert BT and Johansen JB. Incidence of device-related infection in 97 750 patients: clinical data from the complete Danish device-cohort (1982-2018). *Eur Heart J*. 2019;40:1862-1869.

7.   Bebb O, Hall M, Fox KAA, Dondo TB, Timmis A, Bueno H, Schiele F and Gale CP. Performance of hospitals according to the ESC ACCA quality indicators and 30-day mortality for acute myocardial infarction: national cohort study using the United Kingdom Myocardial Ischaemia National Audit Project (MINAP) register. *European Heart Journal*. 2017;38:974-982.

8.   Medicine Io. *Best Care at Lower Cost: The Path to Continuously Learning Health Care in America*. Washington, DC: The National Academies Press; 2013.

9.   Centers for Medicare and Medicaide Services Measures Inventory Tool. Available at: https://cmit.cms.gov/CMIT_public/ViewMeasure?MeasureId=2389. Accessed 17 December 2020.

10.   Centers for Medicare and Medicaide Services Measures Inventory Tool. Available at: https://cmit.cms.gov/CMIT_public/ViewMeasure?MeasureId=3218. Accessed 17 December 2020.

11.   Centers for Medicare and Medicaide Services Measures Inventory Tool. Available at: https://cmit.cms.gov/CMIT_public/ViewMeasure?MeasureId=1979. Accessed 17 December 2020.

12.   Schiele F, Aktaa S, Rossello X, Ahrens I, Claeys MJ, Collet J-P, Fox KAA, Gale CP, Huber K, Iakobishvili Z, Keys A, Lambrinou E, Leonardi S, Lettino M, Masoudi FA, Price S, Quinn T, Swahn E, Thiele H, Timmis A, Tubaro M, Vrints CJM, Walker D, Bueno H and reviewers D. 2020 Update of the quality indicators for acute myocardial infarction: a position paper of the Association for Acute Cardiovascular Care: the study group for quality indicators from the ACVC and the NSTE-ACS guideline group. *Eur Heart J Acute Cardiovasc Care*. 2021.

13.   Arbelo E, Aktaa S, Bollmann A, D'Avila A, Drossart I, Dwight J, Hills MT, Hindricks G, Kusumoto FM, Lane DA, Lau DH, Lettino M, Lip GYH, Lobban T, Pak HN, Potpara T, Saenz LC, Van Gelder IC, Varosy P, Gale CP and Dagres N. Quality indicators for the care and outcomes of adults with atrial fibrillation. *Europace*. 2020.

14.   Aktaa S, Polovina M, …, Gale CP and Coats A. Quality indicators for the care and outcomes of adults with heart failure.
The Working Group for Heart Failure Quality Indicators of the Heart Failure Association of the European Society of Cardiology
. 2021.

15.   ACC/AHA Clinical Performance and Quality Measures. Available at: https://www.onlinejacc.org/collection/performance-measures. Accessed 04 April 2021

16.   Heidenreich PA, Solis P, Estes NAM, Fonarow GC, Jurgens CY, Marine JE, McManus DD and McNamara RL. 2016 ACC/AHA Clinical Performance and Quality Measures for Adults With Atrial Fibrillation or Atrial Flutter. *A Report of the American College of Cardiology/American Heart Association Task Force on Performance Measures*. 2016;68:525-568.

17.   Aktaa S, Batra G, Wallentin L, Baigent C, Erlinge D, James S, Ludman P, Maggioni A, Price S, Weston C, Casadei B and Gale CP. European Society of Cardiology methodology for the development of quality indicators for the quantification of cardiovascular care and outcomes. 2020.

18.   Shekelle PG. Quality indicators and performance measures: Methods for development need more standardization. *Journal of Clinical Epidemiology*. 2013;66:1338-1339.

19.   Donabedian A. Evaluating the Quality of Medical Care. *The Milbank Memorial Fund Quarterly*. 1966;44:166-206.

20.   Zhang S, Gaiser S and Kolominsky-Rabas PL. Cardiac implant registries 2006-2016: A systematic review and summary of global experiences. *BMJ Open*. 2018;8:e019039.

21.   Kusumoto FM, Schoenfeld MH, Barrett C, Edgerton JR, Ellenbogen KA, Gold MR, Goldschlager NF, Hamilton RM, Joglar JA, Kim RJ, Lee R, Marine JE, McLeod CJ, Oken KR, Patton KK, Pellegrini CN, Selzman KA, Thompson A and Varosy PD. 2018 ACC/AHA/HRS Guideline on the Evaluation and Management of Patients With Bradycardia and Cardiac Conduction Delay: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. *Circulation*. 2019;140:e382-e482.

22.   Brignole M, Auricchio A, Baron-Esquivias G, Bordachar P, Boriani G, Breithardt OA, Cleland J, Deharo JC, Delgado V, Elliott PM, Gorenek B, Israel CW, Leclercq C, Linde C, Mont L, Padeletti L, Sutton R, Vardas PE, Zamorano JL, Achenbach S, Baumgartner H, Bax JJ, Bueno H, Dean V, Deaton C, Erol C, Fagard R, Ferrari R, Hasdai D, Hoes AW, Kirchhof P, Knuuti J, Kolh P, Lancellotti P, Linhart A, Nihoyannopoulos P, Piepoli MF, Ponikowski P, Sirnes PA, Tamargo JL, Tendera M, Torbicki A, Wijns W, Windecker S, Kirchhof P, Blomstrom-Lundqvist C, Badano LP, Aliyev F, Bänsch D, Baumgartner H, Bsata W, Buser P, Charron P, Daubert JC, Dobreanu D, Faerestrand S, Hasdai D, Hoes AW, Le Heuzey JY, Mavrakis H, McDonagh T, Merino JL, Nawar MM, Nielsen JC, Pieske B, Poposka L, Ruschitzka F, Tendera M, Van Gelder IC and Wilson CM. 2013 ESC Guidelines on cardiac pacing and cardiac resynchronization therapy: the Task Force on cardiac pacing and resynchronization therapy of the European Society of Cardiology (ESC). Developed in collaboration with the European Heart Rhythm Association (EHRA). *Eur Heart J*. 2013;34:2281-329.

23.   Haines DE, Beheiry S, Akar JG, Baker JL, Beinborn D, Beshai JF, Brysiewicz N, Chiu-Man C, Collins KK, Dare M, Fetterly K, Fisher JD, Hongo R, Irefin S, Lopez J, Miller JM, Perry JC, Slotwiner DJ, Tomassoni GF and Weiss E. Heart Rythm Society expert consensus statement on electrophysiology laboratory standards: process, protocols, equipment, personnel, and safety. *Heart Rhythm*. 2014;11:e9-51.

24.   Abdin A and Aktaa S. Outcomes of conduction system pacingcompared to right ventricular pacing as a primary strategy for treating bradyarrhythmia: Systematic review and meta-analysis. *Eur Heart J QCCO*. 2021.

25.   Brook RH, McGlynn EA and Cleary PD. Measuring Quality of Care. *New England Journal of Medicine*. 1996;335:966-970.

26.   Brook RH. The RAND/UCLA appropriateness method. . In: K. A. McCormack, S. R. Moore and R. A. Siegel, eds. *Clinical Practice Guideline Development: Methodology Perspectives* Rockville, MD: Agency for Healthcare Research and Policy; 1994.

27.   Gurvitz M, Marelli A, Mangione-Smith R and Jenkins K. Building quality indicators to improve care for adults with congenital heart disease. *Journal of the American College of Cardiology*. 2013;62:2244-2253.

28.   Mangione-Smith R, DeCristofaro AH, Setodji CM, Keesey J, Klein DJ, Adams JL, Schuster MA and McGlynn EA. The Quality of Ambulatory Care Delivered to Children in the United States. *New England Journal of Medicine*. 2007;357:1515-1523.

29.   Nowak B, Tasche K, Barnewold L, Heller G, Schmidt B, Bordignon S, Chun KR, Fürnkranz A and Mehta RH. Association between hospital procedure volume and early complications after pacemaker implantation: results from a large, unselected, contemporary cohort of the German nationwide obligatory external quality assurance programme. *Europace*. 2015;17:787-93.

30.   Curtis AB, Worley SJ, Adamson PB, Chung ES, Niazi I, Sherfesee L, Shinn T and St. John Sutton M. Biventricular Pacing for Atrioventricular Block and Systolic Dysfunction. *New England Journal of Medicine*. 2013;368:1585-1593.

31.   Klug D, Balde M, Pavin D, Hidden-Lucet F, Clementy J, Sadoul N, Rey JL, Lande G, Lazarus A, Victor J, Barnay C, Grandbastien B and Kacet S. Risk factors related to infections of implanted pacemakers and cardioverter-defibrillators: results of a large prospective study. *Circulation*. 2007;116:1349-55.

32.   Polyzos KA, Konstantelias AA and Falagas ME. Risk factors for cardiac implantable electronic device infection: a systematic review and meta-analysis. *Europace*. 2015;17:767-77.

33.   Blomström-Lundqvist C, Traykov V, Erba PA, Burri H, Nielsen JC, Bongiorni MG, Poole J, Boriani G, Costa R, Deharo JC, Epstein LM, Saghy L, Snygg-Martin U, Starck C, Tascini C and Strathmore N. European Heart Rhythm Association (EHRA) international consensus document on how to prevent, diagnose, and treat cardiac implantable electronic device infections-endorsed by the Heart Rhythm Society (HRS), the Asia Pacific Heart Rhythm Society (APHRS), the Latin American Heart Rhythm Society (LAHRS), International Society for Cardiovascular Infectious Diseases (ISCVID) and the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS). *Europace*. 2020;22:515-549.

34.   Cella D HE, Jensen SE, et al. Patient-Reported Outcomes in Performance Measurement. Research Triangle Park (NC): RTI Press; 2015 Sep. Types of Patient-Reported Outcomes. Available from: https://www.ncbi.nlm.nih.gov/books/NBK424381/.

35.   Algurén B, Coenen M, Malm D, Fridlund B, Mårtensson J, Årestedt K, on behalf of the C and Exchange in Swedish cardiovascular caring Academic Research g. A scoping review and mapping exercise comparing the content of patient-reported outcome measures (PROMs) across heart disease-specific scales. *Journal of Patient-Reported Outcomes*. 2020;4:7.

36.   Udo EO, van Hemel NM, Zuithoff NPA, Nijboer H, Taks W, Doevendans PA and Moons KGM. Long term quality-of-life in patients with bradycardia pacemaker implantation. *International Journal of Cardiology*. 2013;168:2159-2163.

37.   Aktaa S, Yadegarfar M, Wu J, Rashid M and al. e. Quality of acute myocardial infarction care in England and Wales during the COVID-19 pandemic: linked nationwide cohort study. 2021.

38.   Schiele F, Gale CP, Simon T, Fox KAA, Bueno H, Lettino M, Tubaro M, Puymirat E, Ferrières J, Ecarnot F, Danchin N and Meneveau N. The 2020 ESC-ACVC quality indicators for the management of acute myocardial infarction applied to the FAST-MI registries. *Eur Heart J Acute Cardiovasc Care*. 2021.

39.   Boriani G, Maniadakis N, Auricchio A, Müller-Riemenschneider F, Fattore G, Leyva F, Mantovani L, Siebert M, Willich SN, Vardas P and Kirchhof P. Health technology assessment in interventional electrophysiology and device therapy: a position paper of the European Heart Rhythm Association. *European heart journal*. 2013;34:1869-1874.

40.   Wallentin L, Gale CP, Maggioni A, Bardinet I and Casadei B. EuroHeart: European Unified Registries On Heart Care Evaluation and Randomized Trials. *European Heart Journal*. 2019;40:2745-2749.

Chapter 12. European Society of Cardiology Quality Indicators for Cardiovascular Disease Prevention.

Developed by the Working Group for Cardiovascular Disease Prevention Quality Indicators in collaboration with the European Association for Preventive Cardiology of the European Society of Cardiology.

Suleman Aktaa, Baris Gencer, Elena Arbelo, Constantinos H. Davos, Ileana Désormais, Monika Hollander, Ana Abreu, Marco Ambrosetti, Maria Bäck, David Carballo, Carolyn Crawford, Christi Deaton, Paul Dendale, Thijs M. H. Eijsvogels, Mary Galbraith, Massimo Francesco Piepoli, Annett Salzwedel, Yvo Smulders, Matthias Wilhelm, Giuseppe Biondi-Zoccai, François Mach, Frank L J Visseren, Chris P Gale

12.1 Summary of the publication:

- Using the methodology described in Chapter 4, this paper presents the quality indicators for atherosclerosis CVD prevention.
- six domains of care for ASCVD prevention: 1) Structural framework, 2) Risk assessment, 3) Care for people at risk for ASCVD, 4) Care for patients with established ASCVD and/or diabetes mellitus, 5) Patient education and experience, and 6) Outcomes
- In total, 17 main and 14 secondary QIs were selected across

12.2 Publication status

- Published 23 October 2021
- European Journal of Preventive Cardiology, zwab160, https://doi.org/10.1093/eurjpc/zwab160

12.3 Abstract

12.3.1 Aims

To develop a set of quality indicators (QIs) for the evaluation of the care and outcomes for atherosclerotic cardiovascular disease (ASCVD) prevention.

12.3.2 Methods and results

The Quality Indicator Committee of the European Society of Cardiology (ESC) formed the Working Group for Cardiovascular Disease Prevention Quality Indicators in collaboration with Task Force members of the 2021 ESC Guidelines on Cardiovascular Disease Prevention in Clinical Practice and the European Association of Preventive Cardiology (EAPC). We followed the ESC methodology for QI development, which involved 1) the identification of the key domains of care for ASCVD prevention by constructing a conceptual framework of care, 2) the development of candidate QIs by conducting a systematic review of the literature, 3) the selection of the final set of QIs using a modified Delphi method and 4) the evaluation of the feasibility of the developed QIs. In total, 17 main and 14 secondary QIs were selected across six domains of care for ASCVD prevention: 1) Structural framework, 2) Risk assessment, 3) Care for people at risk for ASCVD, 4) Care for patients with established ASCVD and/or diabetes mellitus, 5) Patient education and experience, and 6) Outcomes.

12.3.3 Conclusion

We present the 2021 ESC QIs for Cardiovascular Disease Prevention, which have been co-constructed with EAPC using the ESC methodology for QI development. These indicators are supported by evidence from the literature, underpinned by expert consensus and aligned with the 2021 ESC Guidelines on Cardiovascular Disease Prevention in Clinical Practice to offer a mechanism for the evaluation of ASCVD prevention care and outcomes.

12.3.4 Keywords

Cardiovascular Disease. Atherosclerosis. Preventive Cardiology. Quality Indicators. Clinical Practice Guidelines.

12.4 Introduction

Atherosclerotic cardiovascular disease (ASCVD) is a leading cause of mortality globally.[414] Evidence suggests that large proportions of individuals at high cardiovascular disease risk have unhealthy lifestyles and inadequate control of blood pressure, lipids and diabetes.[132, 415] Although the advent of effective treatments for ASCVD has led to a reduction in morbidity and mortality,[2] future challenges involve improving adherence to guideline-recommended therapies, optimizing patients' risk factors and modifying lifestyle behaviours to prevent the development and progression of ASCVD.[416] To that end, international registries such as the European Action on Secondary and Primary Prevention by Intervention to Reduce Events (EUROASPIRE) have demonstrated gaps in care delivery and geographic variation in clinical practice.[417]

Quality indicators (QIs) are tools that may provide a means to evaluate the implementation of guideline-recommended therapies.[185] The US federal Agency for Healthcare Research and Quality (AHRQ) has developed prevention QIs for a range of clinical conditions, some of which are relevant to ASCVD.[418] These indicators have been used to describe temporal and spatial patterns of the outcomes of preventive care.[419, 420] However, they do not include structural and process components of care, which are known to be more relevant to the delivery of care.[421] Professional Societies including the European Association for Preventive Cardiology (EAPC) have also developed quality measures for aspects of ASCVD.[167, 170, 422-428] Each focus on particular elements of ASCVD prevention (primary prevention,[425] hypertension,[167] dyslipidaemia,[426] and cardiac rehabilitation,[170, 422, 424, 428]) or are directed to a particular clinical setting, such as primary care.[423, 427] However, there is no single contemporary set of QIs that encapsulates the wider aspect of cardiovascular prevention to allow a holistic evaluation of care.

Therefore, in parallel with the development of the 2021 European Society of Cardiology (ESC) Guidelines on Cardiovascular Disease Prevention in Clinical Practice, the ESC Quality Indicator Committee formed the Working Group for Cardiovascular Disease Prevention QIs in collaboration with EAPC to develop a comprehensive set of QIs for the prevention of ASCVD.

This document presents the 2021 ESC QIs for ASCVD prevention in line with other ESC Clinical Practice Guidelines.[33, 34] The ESC and EAPC anticipate that such QIs may facilitate the standardised evaluation of ASCVD prevention care and outcomes, and therefore identify where improvement initiatives may be used to reduce the burden of cardiovascular disease.

12.5 Methods

We followed the ESC methodology for the development of QIs for the quantification of cardiovascular care and outcomes.[185] In brief, this involves 1) the identification of the key domains of ASCVD preventive care by constructing a conceptual framework of care delivery, 2) the development of candidate QIs by conducting a systematic review of the literature, 3) the selection of the final set of QIs using a modified Delphi method, and 4) the evaluation of the feasibility of the developed QIs.[185] The ESC QIs include main and secondary indicators. The main indicators are those that have higher validity and feasibility by the Working Group members and thus may be used for measurement across regions and over time. Both the main and secondary QIs may be used for local quality improvement activities.[185]

12.5.1 Members of the Working Group

The Working Group comprised Task Force members of the 2021 Guidelines on Cardiovascular Disease Prevention in Clinical Practice, EAPC representatives, patients, and international experts in ASCVD prevention, as well as members of the ESC Quality Indicator Committee. A series of virtual meetings were convened between the members of the Working Group from December 2020 until June 2021.

12.5.2 Target population and domains of care

The initial phase of the development process involved the identification of the 'target population' and the key domains of ASCVD preventive care. The 'target population' for whom the QIs are intended was defined as patients with established or high risk for ASCVD, and the key domains of care were established accordingly by constructing a conceptual illustration of

the multi-layered care pathway for this group of patients.[185] To facilitate the operationalization of the developed QIs, ASCVD was defined as 'atherosclerotic clinical conditions, including acute/chronic coronary syndrome, coronary artery disease documented by computed tomography/invasive coronary angiography, coronary or other arterial revascularization, stroke, transient ischaemic attack, documented carotid, aortic, peripheral artery disease or atherosclerotic renovascular disease', while patients at high risk for ASCVD were defined as those with no documented ASCVD diagnosis, but with diabetes mellitus, hypertension, moderate-severe renal disease, smoking, familial hyperlipidaemia or other lipid disorder and deemed at high or very high risk for ASCVD according to the 2021 ESC Guidelines on Cardiovascular Disease Prevention in Clinical Practice.[32]

Definitions were developed for each of the QIs. This included a numerator, which is the group of patients for whom the QI is delivered, and, with the exception of the structural QIs, a denominator, which is the group of patients eligible for the measurement. We also defined a measurement period (the time point at which the assessment is performed) and a measurement duration (the time frame needed for enough cases to be collected).[185] Structural QIs are designed as binary measurements evaluating the availability of services in healthcare centres or units involved in the management of patients with established or high risk for ASCVD.

12.5.3 Systematic review
12.5.3.1 Search strategy

We conducted a systematic review of the published literature in accordance with the Preferred Reporting Items for Systematic Review and Meta-analyses statement (Appendix Table A1).[172] We searched two online bibliographic databases; MEDLINE and Embase via OVID (Wolters Kluwer, Alphen aan den Rijn, Netherlands). The initial search strategy was developed in MEDLINE using keywords and medical subject headings (MeSH) terms, such as "primary prevention", "secondary prevention", "cardiac rehabilitation", "health education", "smoking cessation", and "exercise" (for full list see Appendix Table A2). Further potential articles were identified using citation-searching and hand-searching of the references of identified articles.

We only included the primary publication of randomized controlled trials, and included the main publications of major trials from which our search obtained only sub-studies. We excluded systematic reviews, meta-analyses, editorials, letters, and conference proceedings. The search was restricted to English language reports and publication dates between 01 January 2016 and 08 March 2021. The search was restricted to the period after 2016 because this year corresponds to the publication of the previous ESC Guidelines on Cardiovascular Disease Prevention in Clinical Practice, thus ensuring current validity and applicability.[429]

12.5.3.2 Eligibility criteria

We included articles fulfilling the following criteria: 1) the study population was adult patients (≥18 years old) with established or with risk factors for ASCVD, 2) the study defined an intervention (structural or process aspect of preventive care) for which at least one outcome measure was reported, 3) the outcome measures were hard endpoints (e.g. mortality, re-admission) or patient reported outcomes (e.g. quality of life), 4) the study provided definitions for the intervention and outcome measure(s) evaluated and 5) the study was a peer-reviewed randomized controlled trial. No restriction was placed on sample sizes, but studies which reported surrogate outcomes (e.g. biomarkers) as the main endpoints were excluded.

12.5.3.3 Study selection

EndNote X9 (Clarivate Analytics, London, UK) was used for reference management and for duplicate removal. Each retrieved study was independent evaluated by two reviewers (SA and CD, BG and ID, or EA and MH) against prespecified inclusion criteria. Disagreements were resolved through discussions and full text review of the article.

12.5.3.4 Quality assessment and Data extraction

Studies that met the eligibility criteria were included in the initial phase of the review. The broad inclusion was important to ensure that a list of initial (candidate) QIs was representative of a wide range of preventive care. For each included study both the intervention studied and the outcome measure(s) that were evaluated were extracted. The variables were then classified

according to their domain of care and to the type of the measurement (structural, process, or outcome).[185] Definitions of the data items extracted were also obtained when provided in the studies.

12.5.3.5 Clinical Practice Guidelines and existing QIs

In addition to the systematic review, Clinical Practice Guidelines pertinent to the prevention of ASCVD were reviewed.[429-435] The goal of the Clinical Practice Guidelines review was to assess the suitability of their recommendations with the strongest association with benefit and harm (Class I and III, respectively) against the ESC criteria for QIs (Appendix Table A3).[185] Existing QIs and 'performance measures' relevant to ASCVD prevention[167, 170, 421-428] were considered as candidate QIs using the same criteria.

12.5.4 Data synthesis

12.5.4.1 Modified Delphi process

The modified Delphi approach was used to evaluate the candidate QIs derived from the literature review.[185] The Working Group members were made aware of the ESC criteria for QI development (Appendix Table A3) to standardise the voting process, and each candidate QI was ranked by each panellist on a 9-point ordinal scale for both validity and feasibility using an online questionnaire.[185] In total, two rounds of voting were conducted, with a number of teleconferences after each round to discuss the results of the vote and address any concerns, questions or ambiguities.

12.5.4.2 Analysing voting results

The 9-point ordinal scale used for voting implied that ratings of 1 to 3 meant that the QI is not valid/feasible; ratings of 4 to 6 meant that the QI is of an uncertain validity/feasible; and ratings of 7 to 9 meant that the QI is valid/feasible. For each candidate QI, the median and the mean deviation from the median were calculated to evaluate the central tendency and the dispersion of the votes. Indicators, with median scores ≥ 7 for validity, ≥ 4 for feasibility, and with minimal dispersion, were included in the final set of QIs.[185] The candidate QIs that met the inclusion

criteria in the first voting round were defined as main QIs, whilst those that met the inclusion criteria after the second round of voting were defined as secondary indicators.

12.6 Results

12.6.1 Domains of ASCVD prevention

The Working Group identified 6 domains of preventive care for ASCVD during the early phases of the development process. These domains aim to capture the spectrum of ASCVD prevention care and outcomes irrespective of the healthcare institution at which the performance measurement is taking place, and in line with the EAPC Core Curriculum for Preventive Cardiology.[436] The domains are: 1) Structural framework, 2) Risk assessment, 3) Care for people at risk for ASCVD, 4) Care for patients with established ASCVD and/or diabetes mellitus, 5) Patient education and experience, and 6) Outcomes.

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart of systematic review.
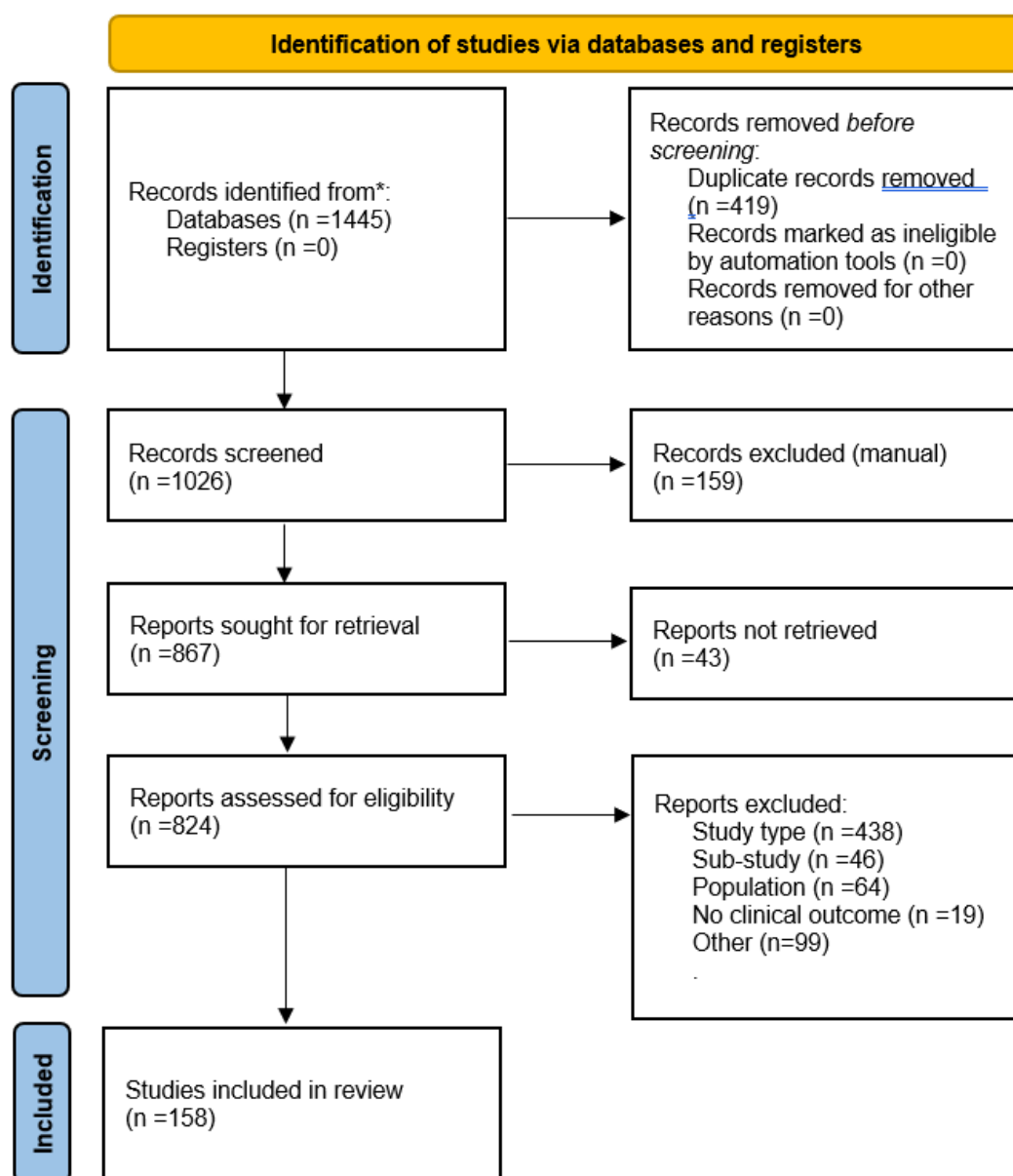
12.6.2 Systematic review results

The literature search retrieved 1026 articles, of which 158 met the inclusion criteria (Figure 1). In total, 75 potential QIs were extracted from the included studies. Of those, 51 candidate QIs were included in the first Delphi round. The remaining 24 indicators overlapped with other

ESC QIs, such as those for acute myocardial infarction,[186] atrial fibrillation,[187] heart failure,[189] or cardiac pacing,[437] and were, thus, removed.

Figure 2. 2021 ESC EAPC Quality Indicators for ASCVD Prevention across key domains of care
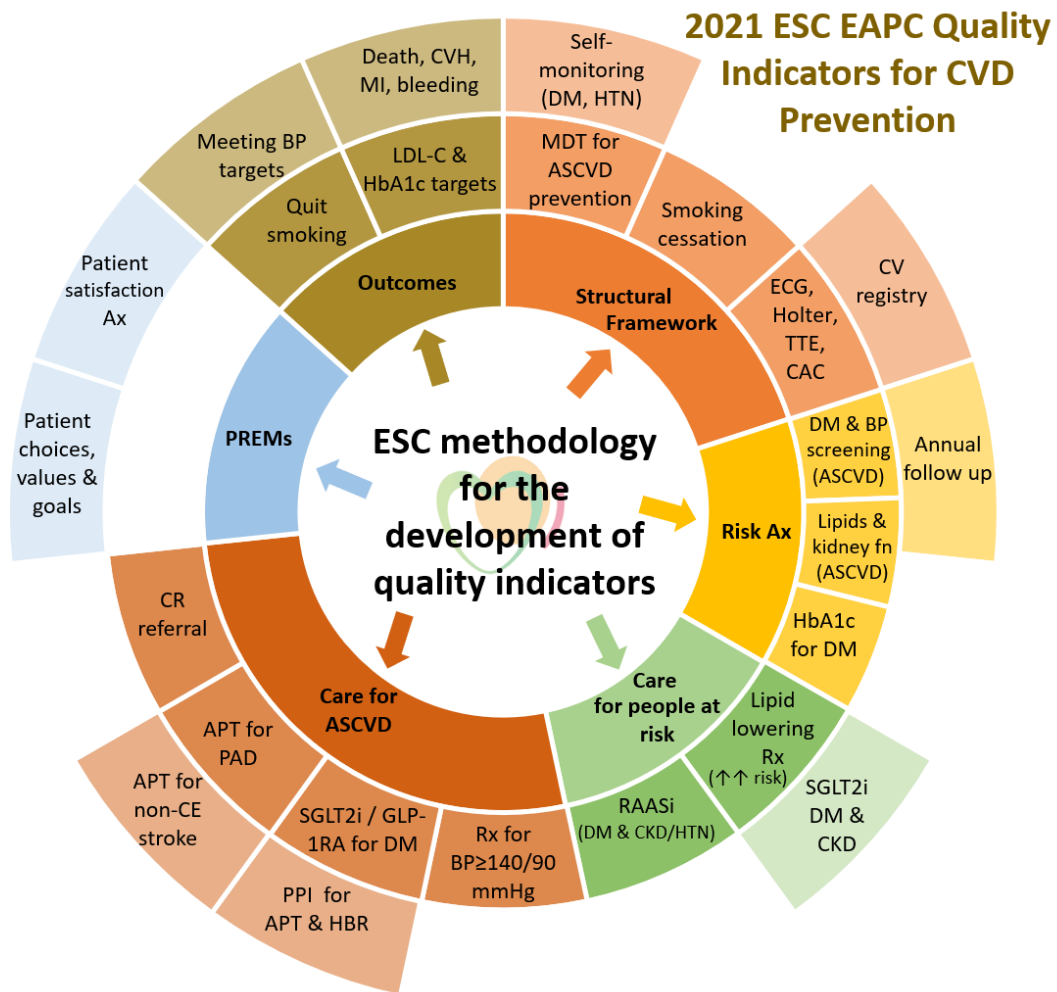
Ax=assessment, ASCVD=atherosclerosis cardiovascular disease, ACR=albumin creatinine ratio, APT=antiplatelet therapy, BP=blood pressure, CE=cardio-embolic, CKD-chronic kidney disease, CR=cardiac rehabilitation, CV= cardiovascular, CVH=cardiovascular hospitalisation, CAC=coronary calcium scoring, DM=diabetes mellitus, ECG=electrocardiogram, eGFR=estimated glomerular filtration rate, GLP-1 RA=glucagon-like peptide-1 receptor agonists, HTN=hypertension, HbA1c= glycated haemoglobin, HBR=high bleeding risk, LDL-C=low-density lipoprotein cholesterol,

MDT=multidisciplinary team, MI=myocardial infarction, PPI=proton pump inhibitors,
PREMs=patient reported experience measures, RAAS=renin-angiotensin-aldosterone system
inhibitors, Rx=treatment, SGLT2i=sodium/glucose cotransporter-2 inhibitors,
TTE=transthoracic echocardiogram.

12.6.3 Modified Delphi results

Following the first round of voting, 23/51 (45%) candidate QIs were excluded; 17/51 (33%) met the inclusion threshold and thus were included as main QIs. The remaining 11/51 (22%) were deemed inconclusive and carried to the second voting round. The excluded QIs (N=23) were reviewed by the Working Group in subsequent meetings and agreement reached to reconsider modified versions of 16/23 (70%) in the second round of voting. As such, a total of 27 QIs (11 inconclusive and 16 modified) were included in the second Delphi round, following which 14 (52%) were included as secondary QIs. Figure 2 shows the main and the secondary indicators of the 2021 ESC EAPC Quality Indicators for ASCVD Prevention across six domains of care.

12.6.4 Quality Indicators

12.6.4.1 Domain 1: Structural framework

This domain evaluates the characteristics of the centres that provide preventive care for patients with established or high risk for ASCVD. While the association between structural QIs and favourable patient outcomes is less established compared with process QIs, they may provide a qualitative assessment of the allocations of resources which are needed for the delivery of optimal care.[185] As such, three main and two secondary QIs were selected. The main QIs captures the availability of a multidisciplinary team that is dedicated for the delivery of lifestyle modification advice and medication adherence counselling (**Main 1.1**), smoking cessation programs (**Main 1.2**) and investigations such as a 12-lead ECG, Holter monitoring, transthoracic echocardiography and CT calcium scoring (**Main 1.3**) for patients with established or high risk for ASCVD, which are fundamental aspects of cardiovascular disease protection (Table 1).[32-34]

Table 6. 2021 European Society of Cardiology Quality Indicators for Cardiovascular Disease Prevention

Domain 1. Structural Framework
Main 1.1 Healthcare centres should have access to a multidisciplinary team dedicated to CVD prevention who deliver lifestyle modification (including diet, exercise, and alcohol consumption) advice and medication adherence counselling for patients with risk factors for, or established, ASCVD.
Numerator: Healthcare centres or units involved in the management of patients with established or high risk for ASCVD that have a dedicated multidisciplinary team.
Main 1.2 Healthcare centres should have access to smoking cessation program for patients with risk factors for or established ASCVD.
Numerator: Healthcare centres or units involved in the management of patients with established or high risk for ASCVD that have access to smoking cessation program.
Main 1.3 Healthcare centres should have access to 12-lead ECG, ambulatory ECG Holter monitoring, and transthoracic echocardiogram, and CT calcium scoring to facilitate the assessment of patients with established or high risk for ASCVD.
Numerator: Healthcare centres or units involved in the management of patients with established or high risk for ASCVD that have access to 12-lead ECG, ambulatory ECG Holter monitoring, and transthoracic echocardiogram, and CT calcium scoring.
Secondary 1.1 Healthcare centres should participate in a registry or common database to record clinical data relevant to cardiovascular risk (body mass index [BMI], blood pressure [BP], LDL-C, HbA1c, and renal function) for patients with established or high risk for ASCVD.
Numerator: Healthcare centres or units involved in the management of patients with established or high risk for ASCVD that participate in a registry or common database to record patients' BMI, BP, LDL-C, HbA1c, and renal function.
Secondary 1.2 Healthcare centres should have available written protocols that encourage and facilitate disease self-measurement for patients with hypertension and diabetes.

Numerator: Healthcare centres or units involved in the management of patients with established or high risk for ASCVD that have available written protocols to encourage and facilitate disease self-measurement for patients with hypertension and diabetes.

Domain 2. Risk Assessment

Main 2.1 Proportion of patients with established ASCVD who have their kidney function (eGFR and albuminuria) checked at least once and if had new treatment or event.

Numerator: Patients with established ASCVD who have their eGFR and albuminuria checked at least once and if had new treatment or event.
Denominator: Patients with established ASCVD.

Main 2.2 Proportion of patients with established ASCVD who have their lipid profile checked at least once and if had new treatment or event.

Numerator: Patients with established ASCVD who have their lipid profile checked at least once and if had new treatment or event.
Denominator: Patients with established ASCVD.

Main 2.3 Proportion of patients with established ASCVD who are screened for diabetes (with fasting blood glucose and/or HbA1c) at least annually.

Numerator: Patients with established ASCVD who are not known to have diabetes and have their fasting blood glucose and/or HbA1c checked at least annually.
Denominator: Patients with established ASCVD who are not known to have diabetes.

Main 2.4 Proportion of patients with established ASCVD who are screened for hypertension at least annually.

Numerator: Patients with established ASCVD who are not known to have hypertension and have their BP measured[a] at least annually.
Denominator: Patients with established ASCVD who are not known to have hypertension.

Main 2.5 Proportion of patients with diabetes who have their HbA1c checked at least annually.

Numerator: Patients with diabetes who have their HbA1c checked at least annually.
Denominator: Patients with diabetes.

Secondary 2.1 Proportion of patients with established or high risk for ASCVD who have follow up at least annually to assess and address cardiovascular risk factors.

Numerator: Patients who have follow up at least annually to assess and address cardiovascular risk factors.

Denominator: Patients with established or high risk for ASCVD.

Domain 3. Care for people at risk for ASCVD

Main 3.1 Proportion of patients 40 to 70 years of age with very high risk for ASCVD and a baseline LDL-C ≥ 1.8 mmol/L (≥70 mg/dL) who are offered lipid lowering therapy.

Numerator: Patients between 40 and 70 years of age with very high risk for ASCVD and a baseline LDL-C ≥ 1.8 mmol/L (≥70 mg/dL) who are prescribed lipid lowering therapy.

Denominator: Patients between 40 and 70 years of age with very high risk for ASCVD and a baseline LDL-C ≥ 1.8 mmol/L (≥70 mg/dL) who have no contraindication, refusal, or history of intolerance to lipid lowering therapy.

Main 3.2 Proportion of patients with diabetes and chronic kidney disease or hypertension who are prescribed renin-angiotensin-aldosterone system inhibitors.

Numerator: Patients with diabetes and chronic kidney disease or hypertension who are prescribed renin-angiotensin-aldosterone system inhibitors.

Denominator: Patients with diabetes and chronic kidney disease or hypertension who have no contraindication, refusal, or history of intolerance to renin-angiotensin-aldosterone system inhibitors.

Secondary 3.1 Proportion of patients with type 2 diabetes and chronic kidney disease who are prescribed SGLT2 inhibitors.

Numerator: Patients with type 2 diabetes and chronic kidney disease who are prescribed SGLT2 inhibitors.

Denominator: Patients with type 2 diabetes and chronic kidney disease who have no contraindication, refusal, or history of intolerance to SGLT2 inhibitors.

Domain 4. Care for patients with established ASCVD

Main 4.1 Proportion of patients with established ASCVD and type 2 diabetes who are prescribed SGLT2 inhibitor or GLP-1RA.

Numerator: Patients with established ASCVD and type 2 diabetes who are prescribed SGLT2 inhibitor or GLP-1RA.

Denominator: Patients with established ASCVD and type 2 diabetes who have no contraindication, refusal, or history of intolerance to SGLT2 inhibitor and GLP-1RA.

Main 4.2 Proportion of patients with symptomatic peripheral artery disease who are prescribed appropriate antiplatelet therapy.

Numerator: Patients with symptomatic peripheral artery disease who are prescribed appropriate antiplatelet therapy[b].

Denominator: Patients with symptomatic peripheral artery disease who have no contraindication, refusal, or history of intolerance to antiplatelet therapy, no indication for anticoagulation, and have not undergone revascularisation procedure within 1 month.

Main 4.3 Proportion of patients with established ASCVD and BP ≥ 140/90mmHg who are prescribed BP lowering treatment.

Numerator: Patients with established ASCVD and documented BP ≥ 140/90mmHg who are prescribed BP lowering treatment[c].

Denominator: Patients with established ASCVD and documented BP ≥ 140/90mmHg who have no contraindication, refusal, or history of intolerance to BP lowering treatment[c].

Main 4.4 Proportion of patients with established ASCVD who participate in a cardiac rehabilitation program following an acute cardiovascular event or an elective revascularisation procedure.

Numerator: Patients with established ASCVD who are referred to cardiac rehabilitation program at the time of hospital discharge following an acute cardiovascular event or an elective revascularisation procedure.

Denominator: Patients with established ASCVD following an acute cardiovascular event or an elective revascularisation procedure who have not refused referral to cardiac rehabilitation program.

Secondary 4.1 Proportion of patients with non-cardioembolic ischaemic (or embolic of undetermined source) stroke or TIA who are prescribed appropriate antiplatelet therapy.

Numerator: Patients with non-cardioembolic ischaemic (or embolic of undetermined source) stroke or TIA who are prescribed appropriate antiplatelet therapy[d].

Denominator: Patients with non-cardioembolic ischaemic (or embolic of undetermined source) stroke or TIA who have no contraindication, refusal, or history of intolerance to antiplatelet therapy, have no indication for anticoagulation, and have not undergone revascularisation procedure within 1 month.

Secondary 4.2 Proportion of patients with established ASCVD, on antiplatelets therapy, and have high bleeding risk who are prescribed a proton-pump inhibitor

Numerator: Patients on antiplatelets therapy for ASCVD and have high bleeding risk[e] who are prescribed a proton-pump inhibitor.

Denominator: Patients who are on antiplatelets therapy for ASCVD and have high bleeding risk[e] with no contraindication, refusal, or history of intolerance to proton-pump inhibitor.

Domain 5. Patient Education & Experience

Secondary 5.1 Proportion of patients with established, or high risk for, ASCVD who have a documented discussion with a member of the multidisciplinary team about their treatment goals, preference, and values at least annually.

Numerator: Patients who have a documented discussion about their treatment goals, preference, and values at least annually.

Denominator: Patients with established or high risk for ASCVD.

Secondary 5.2 Proportion of patients with established or high risk for ASCVD who have their satisfaction about risk factor control captured at least annually.

Numerator: Patients who have their satisfaction about risk factor control captured at least annually.

Denominator: Patients with established or high risk for ASCVD.

Domain 6. Outcomes

Treatment Outcomes

Main 6.1 Proportion of patients with established or high risk for ASCVD who have LDL-C levels at or below that recommended for their estimated cardiovascular risk.

Numerator: Patients with established or high risk for ASCVD who have LDL-C levels at or below that recommended for their estimated cardiovascular risk[f].

Denominator: Patients with established or high risk for ASCVD who have no contraindication, refusal, or history of intolerance to statins, ezetimibe and proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors..

Main 6.2 Proportion of patients with established ASCVD and diabetes, who have HbA1c levels <7.0% (53 mmol/mol).

Numerator: Patients with established ASCVD and diabetes who have their HbA1c levels <7.0% (53 mmol/mol).

Denominator: Patients with established ASCVD and diabetes who have no contraindication, refusal, or history of intolerance to optimal glycaemic control.

Main 6.3 Proportion of patients with established, or high risk for, ASCVD who stop smoking.

Numerator: Patients with established, or high risk for, ASCVD who self-identify as non-smokers.

Denominator: Patients with established, or high risk for, ASCVD who previously self-identified as 'current smokers'.

Secondary 6.1 Proportion of patients with established ASCVD who have their BP well-controlled.

Numerator: Patients with established ASCVD and hypertension who achieve their target BP levels[g].

Denominator: Patients with established ASCVD who have hypertension and no contraindication, refusal, or history of intolerance to optimal BP control.

Disease Outcomes

Secondary 6.2 Annual rate of all-cause mortality.

Secondary 6.3 Annual rate of cardiovascular mortality.

Secondary 6.4 Annual rate of cardiovascular hospitalisation.

Secondary 6.5 Annual rate of non-fatal myocardial infarction.

Treatment complications

Secondary 6.6 Annual rate of bleeding resulting in hospital admission.

[a]*Screening for hypertension involves office BP measurement, ambulatory BP monitor, and/or home-measurements using a validated device.*

[b]*Peripheral artery disease is defined as carotid artery stenosis irrespective of clinical symptoms, carotid/lower extremity artery revascularization, or symptomatic lower extremity artery disease. Appropriate antiplatelet therapy is defined as aspirin 75-100mg daily or Clopidogrel 75mg daily in case of aspirin intolerance.*

[c]*Appendix Table A4. Blood pressure lowering drugs, with absolute and relative contraindications.*

[d]*Appropriate antiplatelet therapy for non-cardioembolic ischaemic (or embolic of undetermined source) stroke or TIA is defined as aspirin 75-100mg daily or Clopidogrel 75mg daily in case of aspirin intolerance.*

[e]*According to the Academic Research Consortium criteria for high bleeding risk.*

[f]*LDL_C targets for patients with established ASCVD is <1.4 mmol/L (55 mg/dl) and >50% reduction from baseline. LDL_C targets for patients with high risk for ASCVD <1.8 mmol/L (70 mg/dl) and >50% reduction from baseline.*

[g]*Controlled BP is defined as home-measured/mean ambulatory BP between 120-129/70-80 mmHg for those < 65 years of age, and between 130-139/70-80 mmHg for those ≥ 65 years of age.*

ASCVD=atherosclerosis cardiovascular disease, BP=blood pressure, HbA1c= glycated haemoglobin, LDL-C=low-density lipoprotein cholesterol, SGLT2i=sodium/glucose cotransporter-2 inhibitors

The **Secondary 1.1** QI within the Structural framework domain evaluates the healthcare centre's participation in a registry that allows the capture of data relevant to ASCVD given the vital role longitudinal databases have in monitoring patterns of ASCVD risk factors[415] and outcomes.[438] Moreover, disease self-monitoring for patients with diabetes and hypertension has a role in improving treatment adherence and control (**Secondary 1.2**) (Table 1).[433, 434]

12.6.4.2 Domain 2: Risk assessment

The estimation of risk is the cornerstone of the ASCVD prevention because it determines the appropriateness of the preventive interventions needed.[32] For patients with established ASCVD, the annual measurement of kidney function (**Main 2.1**),[439, 440] lipid profile (**Main 2.2**),[432] fasting blood glucose and/or glycated haemoglobin (HbA1c) (**Main 2.3**),[433] and blood pressure (**Main 2.4**)[434] can help identify those with suboptimal risk factor modification and requiring treatment optimization.[441] Furthermore, glycaemic control in patients with diabetes mellitus who have no history of established ASCVD has prognostic implications on the development of cardiovascular complications, and thus regular monitoring to HbA1c in this group of patients may be used as an indicator of care quality (**Main 2.5**).[433] The provision of systems that allow the follow up of patients with established and those with high risk for

ASCVD facilitates the implementation of these monitoring/screening measures, but may not be feasible in all healthcare systems (**Secondary 2.1**) (Table 1).

12.6.4.3 Domain 3: Care for people at risk for ASCVD

A number of primary preventive measures have a role in delaying the onset of cardiovascular events and in improving clinical outcomes in individuals at high or very high risk for ASCVD.[32] For patients at very high risk for the development of ASCVD, such as those over the age of 40 years old who have diabetes, lipid lowering therapy has shown effective in reducing major vascular events (**Main 3.1**).[432, 442] In addition, the prescription of renin-angiotensin-aldosterone system inhibitors for patients with diabetes who have a concomitant chronic kidney disease and/or hypertension has been shown to improve cardiovascular outcomes (**Main 3.2**).[433, 434] Furthermore, sodium–glucose cotransporter 2 (SGLT2) inhibitors have recently emerged as cardioprotective agents for patient with diabetes who have chronic kidney disease (**Secondary 3.1**) (Table 1).[433, 443, 444]

12.6.4.4 Domain 4: Care for patients with established ASCVD

For patients with established ASCVD, intensive measures are needed to prevent further cardiovascular events.[32] Whilst these measures are initially based on lifestyle modification such as smoking cessation, pharmacotherapies play a role in slowing and/or delaying disease progression and preventing unfavourable outcomes. As such, the QIs within the 'Secondary prevention' domain focus on medical interventions for patients with established ASCVD, including the prescription of: I) SGLT2 inhibitors or glucagon like peptide-1 receptor agonist (GLP-1RA) for patients with diabetes (**Main 4.1**),[21] II) appropriate antiplatelet therapy for patients with symptomatic peripheral artery disease (**Main 4.2**),[435] III) blood pressure lowering treatment for patients with readings $\geq$ 140/90mmHg (**Main 4.3**),[434] IV) appropriate antiplatelet therapy following a non-cardioembolic ischaemic (or embolic of undetermined source) stroke (**Secondary 4.1**),[445] and V) proton pump inhibitors for those on antiplatelet therapy and have high risk for gastrointestinal bleeding (**Secondary 4.2**).[140] Furthermore, cardiac rehabilitation has an important role in secondary prevention following an acute cardiovascular event and elective coronary revascularization (**Main 4.4**) (Table 1).[422]

12.6.4.5 Domain 5: Patient education and experience

Shared decision-making about treatment benefit, risk modifiers, and lifestyle changes in accordance to patient preferences is an essential element of ASCVD prevention.[32] Thus, recording the delivery of patient education for those with established or high risk for ASCVD about their treatment goals, preference is a QI (**Secondary 5.1**). In addition, the assessment of patient satisfaction with care quality has also been proposed as a QI (**Secondary 5.2**) (Table 1).

12.6.4.6 Domain 6: Outcomes

The collection of outcome measures pertinent to ASCVD or its treatment provides information about the effectiveness and the safety of management strategy. For patients with established ASCVD, achieving the target levels of low-density lipoprotein (LDL) cholesterol (**Main 6.1**),[432] the target level of HbA1c in the presence of diabetes (**Main 6.2**),[446] the cessation of smoking (**Main 6.3**)[32] and controlling blood pressure (**Secondary 6.1**)[434] have a role in determining the success of treatment and in improving clinical outcomes (Table 1). Achieving blood pressure control (**Secondary 6.1**) has been proposed as a secondary QI given concerns from the Working Group members on the feasibility of the measurement of this QI which carries the same level of clinical relevance as the other main QIs within this domain.

Furthermore, recording annual rates of all-cause mortality (**Secondary 6.2**), cardiovascular mortality (**Secondary 6.3**), cardiovascular hospitalization (**Secondary 6.4**), non-fatal myocardial infarction (**Secondary 6.5**) and hospitalised major bleeding events (**Secondary 6.6**) provides information about the outcome of care (Table 1). However, adjustments for baseline risk and other patient characteristics may be needed when interpreting the results of such outcome QIs.[447] Furthermore, whilst the measurement duration for these QIs is 12 months, longer follow up may be needed to capture sufficient events, especially in lower risk population.

12.7 Discussion

By way of a joint working group between the EAPC, members of the Task Force of the 2021 ESC Guidelines on Cardiovascular Disease Prevention in Clinical Practice and the ESC Patient Forum, 17 main and 14 secondary QIs for ASCVD prevention have been developed across 6 key domains of care. This work has been conducted under the auspice of the ESC Quality Indicator Committee using the ESC standardized methodology of QI development.[185] The QIs presented in this document align with recommendations of the 2021 ESC Guidelines on Cardiovascular Disease Prevention in Clinical Practice and do not overlap or conflict with published ESC QIs.[186, 187, 189, 437] It is hoped that by developing such QIs and providing the specifications needed for their implementation, local, regional, national, or international initiatives aiming to improve the quality of ASCVD care can be created in accordance to the specific needs of individual centers or countries.

Monitoring and reporting the structure, process and / or outcome of care has become a mandatory requirement for modern healthcare systems.[448] QIs provide a means by which this may be undertaken and performance evidenced.[19] QIs also help evaluate the effectiveness of quality improvement initiatives and may be used to ascertain if patient's perceptions of their care have been considered.[185] Additionally, QIs can be used as an advocacy tool to demonstrate to health politicians the gaps of ASCVD prevention in different regions or countries. Although the literature describes a range of quality measures for ASCVD,[167, 170, 418, 422-427] until now there has been no set of QIs that span the breadth of cardiovascular prevention. We believe this document describes a QI set that covers the key domains of ASCVD prevention care.

We believe that our approach to the development of the ESC QIs for cardiovascular disease prevention will facilitate their implementation in clinical practice. First, the achievement of a systematic review of the literature ensured that the developed QIs are derived from, and supported by, evidence. Second, the inclusiveness of our Working Group provided far-reaching representation through the close working with patients, Task Force members of the 2021 ESC Guidelines on Cardiovascular Disease Prevention in Clinical Practice, and EAPC experts who have a track records in the field of preventive cardiology.[424, 436] As such, our work integrates,

and complements, current ESC and EAPC activities that aim to improve the quality of ASCVD prevention care across Europe. Third, the methodological approach used to develop these QIs enhances their incorporation into international registries that aim to capture key aspects of care delivery across a number of cardiovascular disease conditions, such as the ESC European Unified Registries On Heart Care Evaluation and Randomized Trials (EuroHeart) project.[184]

While our work has a number of strengths, it does, however, have several evident limitations. First, we acknowledge that it may be difficult for a healthcare centre to adopt all the QIs given that fact that they cover many aspects of care, which may be delivered in different settings. Therefore, the Working Group opted not to design a composite QI because such an indicator could disadvantage centres that rely on community or smaller hospital services. Also, the Working Group believes that efforts should be made to ensure that performance is measured along the continuum of patient care pathway. This may be achieved through the integration of systems used across various clinical settings, such as electronic healthcare records, clinical registries and quality improvement projects.[19] Evaluating the quality of care based on data that do not span the full breadth of cardiovascular prevention may result in unintended consequences and system 'gaming' to improve the scores rather than the actual care quality.[185] Second, the methodology used for the development relied on expert opinion. One may argue that this approach created subjectivity in the selection process. However, the use of the modified Delphi method, the involvement of patient representatives, and the application of the ESC criteria to guide the voting provided a level of standardization to the process. Third, the developed QIs will require continuous update and revision as new evidence arises, and feasibility data become available.

12.8 Conclusion

This document defines the 2021 ESC QIs for Cardiovascular Disease prevention, which have been co-developed by the members of the Task Force of the 2021 ESC Guidelines on Cardiovascular Disease Prevention in Clinical Practice, the ESC Patient Forum, the Quality Indicator Committee, and EAPC. In total, 17 main and 14 secondary QIs have been defined across six key domains of ASCVD preventive care. These indicators cover the breadth pf

ASCVD prevention care, including: 1) Structural framework, 2) Risk assessment, 3) Care for people at risk for ASCVD, 4) Care for patients with established ASCVD and/or diabetes mellitus, 5) Patient education and experience, and 6) Outcomes. Their implementation in clinical practice will standardize the evaluation of cardiovascular preventive care.

12.9 References for Chapter 12

1.	Vos T, Lim SS, Abbafati C, et al. Global burden of 369 diseases and injuries in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. The Lancet 2020;**396**(10258):1204-1222.

2.	Fang M, Wang D, Coresh J, Selvin E. Trends in Diabetes Treatment and Control in U.S. Adults, 1999–2018. New England Journal of Medicine 2021;**384**(23):2219-2228.

3.	Kotseva K, Wood D, De Bacquer D. Determinants of participation and risk factor control according to attendance in cardiac rehabilitation programmes in coronary patients in Europe: EUROASPIRE IV survey. European Journal of Preventive Cardiology 2018;**25**(12):1242-1251.

4.	Timmis A, Townsend N, Gale CP, Torbica A, Lettino M, Petersen SE, Mossialos EA, Maggioni AP, Kazakiewicz D, May HT, De Smedt D, Flather M, Zuhlke L, Beltrame JF, Huculeci R, Tavazzi L, Hindricks G, Bax J, Casadei B, Achenbach S, Wright L, Vardas P. European Society of Cardiology: Cardiovascular Disease Statistics 2019. European heart journal 2020;**41**(1):12-85.

5.	2021 ESC Guidelines on Cardiovascular Disease Prevenrtion in Clinical Practice

6.	De Smedt D, De Backer T, Petrovic M, De Backer G, Wood D, Kotseva K, De Bacquer D. Chronic medication intake in patients with stable coronary heart disease across Europe: Evidence from the daily clinical practice. Results from the ESC EORP European Survey of Cardiovascular Disease Prevention and Diabetes (EUROASPIRE IV) Registry. International Journal of Cardiology 2020;**300**:7-13.

7.	Aktaa S, Batra G, Wallentin L, Baigent C, Erlinge D, James S, Ludman P, Maggioni A, Price S, Weston C, Casadei B, Gale CP. European Society of Cardiology methodology for the development of quality indicators for the quantification of cardiovascular care and outcomes. 2020.

8.	Department of Health and Human Services Agency for Healthcare Researchand Quality, Guide to Prevention Quality Indicators: Hospital Admission forAmbulatory Care Sensitive Conditions, April 2002. Available online: https://www.ahrq.gov/downloads/pub/ahrqqi/pqiguide.pdf. (Accessed 09 June 2021), 2002.

9.	Ramalho A, Lobo M, Duarte L, Souza J, Santos P, Freitas A. Landscapes on Prevention Quality Indicators: A Spatial Analysis of Diabetes Preventable Hospitalizations in Portugal (2016-2017). Int J Environ Res Public Health 2020;**17**(22).

10.	Ramalho A, Castro P, Lobo M, Souza J, Santos P, Freitas A. Integrated quality assessment for diabetes care in Portuguese primary health care using prevention quality indicators. Prim Care Diabetes 2021;**15**(3):507-512.

11.	Spertus John A, Chan P, Diamond George A, Drozda Joseph P, Kaul S, Krumholz Harlan M, Masoudi Frederick A, Normand Sharon-Lise T, Peterson Eric D, Radford Martha J, Rumsfeld John S. ACCF/AHA New Insights Into the Methodology of Performance Measurement. Circulation 2010;**122**(20):2091-2106.

12.	Ambrosetti M, Abreu A, Corrà U, Davos CH, Hansen D, Frederix I, Iliou MC, Pedretti RF, Schmid JP, Vigorito C, Voller H, Wilhelm M, Piepoli MF, Bjarnason-Wehrens B, Berger T, Cohen-Solal A, Cornelissen V, Dendale P, Doehner W, Gaita D, Gevaert AB, Kemps H, Kraenkel N, Laukkanen J, Mendes M, Niebauer J, Simonenko M, Zwisler AO. Secondary prevention through comprehensive cardiovascular rehabilitation: From knowledge to implementation. 2020 update. A position paper from the Secondary Prevention and Rehabilitation Section of the European Association of Preventive Cardiology. Eur J Prev Cardiol 2020:2047487320913379.

13.	Campbell SM, Ludt S, Lieshout JV, Boffin N, Wensing M, Petek D, Grol R, Roland MO. Quality indicators for the prevention and management of cardiovascular disease in primary care in nine European countries. European Journal of Cardiovascular Prevention & Rehabilitation 2008;**15**(5):509-515.

14.	Abreu A, Frederix I, Dendale P, Janssen A, Doherty P, Piepoli MF, Völler H, Davos CH. Standardization and quality improvement of secondary prevention through cardiovascular rehabilitation programmes in Europe: The avenue towards EAPC accreditation programme: A position statement of the Secondary Prevention and Rehabilitation Section of the European Association of Preventive Cardiology (EAPC). Eur J Prev Cardiol 2020:2047487320924912.

15.	Casey DE, Jr., Thomas RJ, Bhalla V, Commodore-Mensah Y, Heidenreich PA, Kolte D, Muntner P, Smith SC, Jr., Spertus JA, Windle JR, Wozniak GD, Ziaeian B. 2019 AHA/ACC Clinical Performance and Quality Measures for Adults With High Blood Pressure: A Report of the American College of Cardiology/American Heart Association Task Force on Performance Measures. Circ Cardiovasc Qual Outcomes 2019;**12**(11):e000057.

16.	Redberg RF, Benjamin EJ, Bittner V, Braun LT, Goff DC, Jr., Havas S, Labarthe DR, Limacher MC, Lloyd-Jones DM, Mora S, Pearson TA, Radford MJ, Smetana GW, Spertus JA, Swegler EW. AHA/ACCF [corrected] 2009 performance measures for primary prevention of cardiovascular disease in adults: a report of the American College of

Cardiology Foundation/American Heart Association task force on performance measures (writing committee to develop performance measures for primary prevention of cardiovascular disease): developed in collaboration with the American Academy of Family Physicians; American Association of Cardiovascular and Pulmonary Rehabilitation; and Preventive Cardiovascular Nurses Association: endorsed by the American College of Preventive Medicine, American College of Sports Medicine, and Society for Women's Health Research. Circulation 2009;**120**(13):1296-336.

17.   Drozda JP, Jr., Ferguson TB, Jr., Jneid H, Krumholz HM, Nallamothu BK, Olin JW, Ting HH. 2015 ACC/AHA Focused Update of Secondary Prevention Lipid Performance Measures: A Report of the American College of Cardiology/American Heart Association Task Force on Performance Measures. J Am Coll Cardiol 2016;**67**(5):558-87.

18.   Thomas RJ, Balady G, Banka G, Beckie TM, Chiu J, Gokak S, Ho PM, Keteyian SJ, King M, Lui K, Pack Q, Sanderson BK, Wang TY. 2018 ACC/AHA Clinical Performance and Quality Measures for Cardiac Rehabilitation: A Report of the American College of Cardiology/American Heart Association Task Force on Performance Measures. Circulation: Cardiovascular Quality and Outcomes 2018;**11**(4):e000037.

19.   Burge FI, Bower K, Putnam W, Cox JL. Quality indicators for cardiovascular primary care. Can J Cardiol 2007;**23**(5):383-8.

20.   Grace SL, Poirier P, Norris CM, Oakes GH, Somanader DS, Suskin N. Pan-Canadian development of cardiac rehabilitation and secondary prevention quality indicators. Can J Cardiol 2014;**30**(8):945-8.

21.   McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, Burri H, Butler J, Čelutkienė J, Chioncel O, Cleland JGF, Coats AJS, Crespo-Leiro MG, Farmakis D, Gilard M, Heymans S, Hoes AW, Jaarsma T, Jankowska EA, Lainscak M, Lam CSP, Lyon AR, McMurray JJV, Mebazaa A, Mindham R, Muneretto C, Francesco Piepoli M, Price S, Rosano GMC, Ruschitzka F, Kathrine Skibelund A, Group ESD. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: Developed by the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) With the special contribution of the Heart Failure Association (HFA) of the ESC. European Heart Journal 2021.

22.   Glikson M, Nielsen JC, Kronborg MB, Michowitz Y, Auricchio A, Barbash IM, Barrabés JA, Boriani G, Braunschweig F, Brignole M, Burri H, Coats AJS, Deharo J-C, Delgado V, Diller G-P, Israel CW, Keren A, Knops RE, Kotecha D, Leclercq C, Merkely B, Starck C, Thylén I, Tolosana JM, Group ESD. 2021 ESC Guidelines on cardiac pacing and

cardiac resynchronization therapy: Developed by the Task Force on cardiac pacing and cardiac resynchronization therapy of the European Society of Cardiology (ESC) With the special contribution of the European Heart Rhythm Association (EHRA). European Heart Journal 2021.

23.   Visseren FLJ, Mach F, Smulders YM, Carballo D, Koskinas KC, Bäck M, Benetos A, Biffi A, Boavida J-M, Capodanno D, Cosyns B, Crawford C, Davos CH, Desormais I, Di Angelantonio E, Franco OH, Halvorsen S, Hobbs FDR, Hollander M, Jankowska EA, Michal M, Sacco S, Sattar N, Tokgozoglu L, Tonstad S, Tsioufis KP, van Dis I, van Gelder IC, Wanner C, Williams B, Group ESD. 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice: Developed by the Task Force for cardiovascular disease prevention in clinical practice with representatives of the European Society of Cardiology and 12 medical societies With the special contribution of the European Association of Preventive Cardiology (EAPC). European Heart Journal 2021.

24.   Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, Shamseer L, Tetzlaff JM, Akl EA, Brennan SE, Chou R, Glanville J, Grimshaw JM, Hróbjartsson A, Lalu MM, Li T, Loder EW, Mayo-Wilson E, McDonald S, McGuinness LA, Stewart LA, Thomas J, Tricco AC, Welch VA, Whiting P, Moher D. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;**372**:n71.

25.   Piepoli MF, Hoes AW, Agewall S, Albus C, Brotons C, Catapano AL, Cooney M-T, Corrà U, Cosyns B, Deaton C, Graham I, Hall MS, Hobbs FDR, Løchen M-L, Löllgen H, Marques-Vidal P, Perk J, Prescott E, Redon J, Richter DJ, Sattar N, Smulders Y, Tiberi M, van der Worp HB, van Dis I, Verschuren WMM, Binno S, Group ESD. 2016 European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts)Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). European Heart Journal 2016;**37**(29):2315-2381.

26.   Pearson GJ, Thanassoulis G, Anderson TJ, Barry AR, Couture P, Dayan N, Francis GA, Genest J, Grégoire J, Grover SA, Gupta M, Hegele RA, Lau D, Leiter LA, Leung AA, Lonn E, Mancini GBJ, Manjoo P, McPherson R, Ngui D, Piché M-E, Poirier P, Sievenpiper J, Stone J, Ward R, Wray W. 2021 Canadian Cardiovascular Society Guidelines for the Management of Dyslipidemia for the Prevention of Cardiovascular Disease in the Adult. Canadian Journal of Cardiology.

27.   Arnett DK, Blumenthal RS, Albert MA, Buroker AB, Goldberger ZD, Hahn EJ, Himmelfarb CD, Khera A, Lloyd-Jones D, McEvoy JW, Michos ED, Miedema MD, Muñoz D, Smith SC, Virani SS, Williams KA, Yeboah J, Ziaeian B. 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation 2019;**140**(11):e596-e646.

28.   Mach F, Baigent C, Catapano AL, Koskinas KC, Casula M, Badimon L, Chapman MJ, De Backer GG, Delgado V, Ference BA, Graham IM, Halliday A, Landmesser U, Mihaylova B, Pedersen TR, Riccardi G, Richter DJ, Sabatine MS, Taskinen M-R, Tokgozoglu L, Wiklund O, Group ESD. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk: The Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS). European Heart Journal 2019;**41**(1):111-188.

29.   Cosentino F, Grant PJ, Aboyans V, Bailey CJ, Ceriello A, Delgado V, Federici M, Filippatos G, Grobbee DE, Hansen TB, Huikuri HV, Johansson I, Jüni P, Lettino M, Marx N, Mellbin LG, Östgren CJ, Rocca B, Roffi M, Sattar N, Seferović PM, Sousa-Uva M, Valensi P, Wheeler DC, Group ESD. 2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD: The Task Force for diabetes, pre-diabetes, and cardiovascular diseases of the European Society of Cardiology (ESC) and the European Association for the Study of Diabetes (EASD). European Heart Journal 2019;**41**(2):255-323.

30.   Williams B, Mancia G, Spiering W, Agabiti Rosei E, Azizi M, Burnier M, Clement DL, Coca A, de Simone G, Dominiczak A, Kahan T, Mahfoud F, Redon J, Ruilope L, Zanchetti A, Kerins M, Kjeldsen SE, Kreutz R, Laurent S, Lip GYH, McManus R, Narkiewicz K, Ruschitzka F, Schmieder RE, Shlyakhto E, Tsioufis C, Aboyans V, Desormais I, Group ESD. 2018 ESC/ESH Guidelines for the management of arterial hypertension: The Task Force for the management of arterial hypertension of the European Society of Cardiology (ESC) and the European Society of Hypertension (ESH). European Heart Journal 2018;**39**(33):3021-3104.

31.   Aboyans V, Ricco J-B, Bartelink M-LEL, Björck M, Brodmann M, Cohnert T, Collet J-P, Czerny M, De Carlo M, Debus S, Espinola-Klein C, Kahan T, Kownator S, Mazzolai L, Naylor AR, Roffi M, Röther J, Sprynger M, Tendera M, Tepe G, Venermo M, Vlachopoulos C, Desormais I, Group ESD. 2017 ESC Guidelines on the Diagnosis and Treatment of Peripheral Arterial Diseases, in collaboration with the European Society for Vascular Surgery

(ESVS): Document covering atherosclerotic disease of extracranial carotid and vertebral, mesenteric, renal, upper and lower extremity arteriesEndorsed by: the European Stroke Organization (ESO)The Task Force for the Diagnosis and Treatment of Peripheral Arterial Diseases of the European Society of Cardiology (ESC) and of the European Society for Vascular Surgery (ESVS). European Heart Journal 2017;**39**(9):763-816.

32.   Wilhelm M, Abreu A, Adami PE, Ambrosetti M, Antonopoulou M, Biffi A, Cavarretta E, D'Ascenzi F, Gibson I, Grobbee DE, Iliou M-C, Koskinas K, Marques-Vidal P, Nixdorff U, Papadakis M, Piepoli MF, Vassiliou V, Wood D, Dendale P, Halle M. EAPC Core Curriculum for Preventive Cardiology. European Journal of Preventive Cardiology 2021.

33.   Schiele F, Aktaa S, Rossello X, Ahrens I, Claeys MJ, Collet J-P, Fox KAA, Gale CP, Huber K, Iakobishvili Z, Keys A, Lambrinou E, Leonardi S, Lettino M, Masoudi FA, Price S, Quinn T, Swahn E, Thiele H, Timmis A, Tubaro M, Vrints CJM, Walker D, Bueno H, reviewers D. 2020 Update of the quality indicators for acute myocardial infarction: a position paper of the Association for Acute Cardiovascular Care: the study group for quality indicators from the ACVC and the NSTE-ACS guideline group. European Heart Journal. Acute Cardiovascular Care 2021.

34.   Arbelo E, Aktaa S, Bollmann A, D'Avila A, Drossart I, Dwight J, Hills MT, Hindricks G, Kusumoto FM, Lane DA, Lau DH, Lettino M, Lip GYH, Lobban T, Pak HN, Potpara T, Saenz LC, Van Gelder IC, Varosy P, Gale CP, Dagres N. Quality indicators for the care and outcomes of adults with atrial fibrillation. Europace 2020.

35.   Aktaa S, Polovina M, …, Gale CP, Coates A. European Society of Cardiology Quality indicators for the care and outcomes of adults with heart failure.

Developed by the Working Group for Heart Failure Quality Indicators in collaboration with the Heart Failure Association of the European Society of Cardiology. European Journal of Heart Failure 2021.

36.   Aktaa S, Abdin A, …, Gale CP. European Society of Cardiology Quality Indicators for the care and outcomes of cardiac pacing

Developed by the Working Group for Cardiac Pacing Quality Indicators in collaboration with the European Heart Rhythm Association of the European Society of Cardiology.
. EP Europace 2021.

37.   Figtree GA, Vernon ST, Hadziosmanovic N, Sundström J, Alfredsson J, Arnott C, Delatour V, Leósdóttir M, Hagström E. Mortality in STEMI patients without standard

modifiable risk factors: a sex-disaggregated analysis of SWEDEHEART registry data. The Lancet 2021;**397**(10279):1085-1094.

38.   Chang AR, Grams ME, Ballew SH, Bilo H, Correa A, Evans M, Gutierrez OM, Hosseinpanah F, Iseki K, Kenealy T, Klein B, Kronenberg F, Lee BJ, Li Y, Miura K, Navaneethan SD, Roderick PJ, Valdivielso JM, Visseren FLJ, Zhang L, Gansevoort RT, Hallan SI, Levey AS, Matsushita K, Shalev V, Woodward M. Adiposity and risk of decline in glomerular filtration rate: meta-analysis of individual participant data in a global consortium. Bmj 2019;**364**:k5301.

39.   Global, regional, and national burden of chronic kidney disease, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet 2020;**395**(10225):709-733.

40.   Si S, Moss JR, Sullivan TR, Newton SS, Stocks NP. Effectiveness of general practice-based health checks: a systematic review and meta-analysis. Br J Gen Pract 2014;**64**(618):e47-53.

41.   Kearney PM, Blackwell L, Collins R, Keech A, Simes J, Peto R, Armitage J, Baigent C. Efficacy of cholesterol-lowering therapy in 18,686 people with diabetes in 14 randomised trials of statins: a meta-analysis. Lancet 2008;**371**(9607):117-25.

42.   Neal B, Perkovic V, Mahaffey KW, de Zeeuw D, Fulcher G, Erondu N, Shaw W, Law G, Desai M, Matthews DR. Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes. New England Journal of Medicine 2017;**377**(7):644-657.

43.   Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, Mattheus M, Devins T, Johansen OE, Woerle HJ, Broedl UC, Inzucchi SE. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. New England Journal of Medicine 2015;**373**(22):2117-2128.

44.   Chiarito M, Sanz-Sánchez J, Cannata F, Cao D, Sturla M, Panico C, Godino C, Regazzoli D, Reimers B, De Caterina R, Condorelli G, Ferrante G, Stefanini GG. Monotherapy with a P2Y(12) inhibitor or aspirin for secondary prevention in patients with established atherosclerosis: a systematic review and meta-analysis. Lancet 2020;**395**(10235):1487-1495.

45.   Knuuti J, Wijns W, Saraste A, Capodanno D, Barbato E, Funck-Brentano C, Prescott E, Storey RF, Deaton C, Cuisset T, Agewall S, Dickstein K, Edvardsen T, Escaned J, Gersh BJ, Svitil P, Gilard M, Hasdai D, Hatala R, Mahfoud F, Masip J, Muneretto C, Valgimigli M, Achenbach S, Bax JJ, Group ESD. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes: The Task Force for the diagnosis and management of chronic

coronary syndromes of the European Society of Cardiology (ESC). European Heart Journal 2019;**41**(3):407-477.

46.   Perkovic V, Jardine MJ, Neal B, Bompoint S, Heerspink HJL, Charytan DM, Edwards R, Agarwal R, Bakris G, Bull S, Cannon CP, Capuano G, Chu P-L, de Zeeuw D, Greene T, Levin A, Pollock C, Wheeler DC, Yavin Y, Zhang H, Zinman B, Meininger G, Brenner BM, Mahaffey KW. Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy. New England Journal of Medicine 2019;**380**(24):2295-2306.

47.   National Quality Forum. Risk adjustment for sociodemographic factors. https://www.qualityforum.org/Publications/2014/08/Risk_Adjustment_for_Socioeconomic_Status_or_Other_Sociodemographic_Factors.aspx. Accessed 20 April 2021.

48.   National Library of Quality Indicators. National Institute for Health and Care Excellence. Availiable at https://www.nice.org.uk/standards-and-indicators/index/All/All/7. Accessed 15 December 2020.

49.   Bhatt DL, Drozda JP, Shahian DM, Chan PS, Fonarow GC, Heidenreich PA, Jacobs JP, Masoudi FA, Peterson ED, Welke KF. ACC/AHA/STS Statement on the Future of Registries and the Performance Measurement Enterprise. Journal of the American College of Cardiology 2015;**66**(20):2230-2245.

50.   Batra G, Aktaa S, Wallentin L, Maggioni AP, Wilkinson C, Casadei B, Gale CP. Methodology for the development of international clinical data standards for common cardiovascular conditions: European Unified Registries for Heart Care Evaluation and Randomised Trials (EuroHeart). Eur Heart J Qual Care Clin Outcomes 2021.

Chapter 13. European Society of Cardiology Quality Indicators for the care and outcomes of adults with heart failure.

Developed by the Working Group for Heart Failure Quality Indicators in collaboration with the Heart Failure Association of the European Society of Cardiology.

Suleman Aktaa, Marija Polovina, Giuseppe Rosano, Amr Abdin, Manuel Anguita, Mitja Lainscak, Lars H. Lund, Theresa McDonagh, Marco Metra, Richard Mindham, Massimo Piepoli, Stefan Stöerk, Mariya P Tokmakova, Petar Seferović, Chris P Gale*, Andrew JS Coats*.

*Contributed equally

13.1 Summary of the publication:

- Using the methodology described in Chapter 4, this paper presents the developed quality indicators for heart failure (HF).
- Five domains of care for the management of HF were identified: (1) Structural framework, (2) Patient assessment, (3) Initial treatment, (4) Therapy optimization, and (5) Assessment of patient health-related quality of life.
- In total, 12 main and 4 secondary QIs were selected across these domains.

13.2 Publication status:

- Published: 24 January 2022
- Eur J Heart Fail. 2022 Jan;24(1):132-142. doi: 10.1002/ejhf.2371.

13.3 Abstract

14.3.1 Aims

To develop a suite of quality indicators (QIs) for the evaluation of the care and outcomes for adults with heart failure (HF).

13.3.2 Methods and results

The Working Group comprised experts in HF management including Task Force members of the 2021 European Society of Cardiology (ESC) Clinical Practice Guidelines for HF, members of the Heart Failure Association (HFA), Quality Indicator Committee and a patient representative. We followed the ESC methodology for QI development, which involved 1) the identification of the key domains of care for the management of HF by constructing a conceptual framework of HF care, 2) the development of candidate QIs by conducting a systematic review of the literature, 3) the selection of the final set of QIs using a modified-Delphi method, and 4) the evaluation of the feasibility of the developed QIs. In total, 12 main and 4 secondary QIs were selected across five domains of care for the management of HF: 1) Structural framework, 2) Patient assessment, 3) Initial treatment, 4) Therapy optimization, and 5) Assessment of patient health-related quality of life.

13.3.3 Conclusion

We present the ESC HFA QIs for HF, describe their development process and provide the scientific rationale for their selection. The indicators may be used to quantify and improve adherence to guideline-recommended clinical practice and thus improve patient outcomes.

13.3.4 Keywords

Heart Failure. Quality Indicators. Treatment. Accountability. Clinical Practice Guidelines. Outcomes.

13.4 Introduction

The emergence of new therapies for heart failure (HF)[449] and a focus on integrating these with established care,[450] has created a need to develop systems in which HF management may be systematically monitored and optimized. Guideline-recommended therapy for HF, particularly HF with reduced ejection fraction, reduces morbidity and mortality.[449] Yet data from clinical registries show substantial variation in practice and room for improved implementation of guideline recommendations.[100, 451-453] Furthermore, the burden of polypharmacy for patients with HF,[454] who are often comorbid and frail,[455] coupled with the logistical, financial and safety concerns for initiating and/or up-titrating guideline-recommended therapies,[456] call for the development of mechanisms to minimise missed opportunities to deliver optimal medical care.

Quality indicators (QIs) have been increasingly used as means to measure the adherence to, and the outcomes associated with, guideline-recommended therapy.[100] Given that QIs define a set of 'exclusions' for discrete processes of care, they allow informed interpretation of 'real-world' data.[185] The American College of Cardiology (ACC) and the American Heart Association (AHA)[166] as well as other societies[166, 448, 457-459] and initiatives[460, 461] developed 'performance measures' or QIs for HF. However, there is a need for QIs that are specifically designed for and applicable to the European healthcare systems, endorsed by major European cardiovascular and HF societies, and incorporate recent developments in HF therapy.

In collaboration with the Heart Failure Association (HFA) of the European Society of Cardiology (ESC), the Working Group for HF QIs was established to develop a set of indicators for the management of adults with HF. Work was undertaken in parallel with the writing of the 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure, and in collaboration with Task Force members of the Guidelines. A summary form of these indicators have been embedded within the Guidelines document.[449] The ESC anticipates that developing a suite of QIs relevant to the contemporary management of adults with HF will facilitate the evaluation of adherence to guideline-recommended clinical practice and therefore improve the care and outcomes of patients with HF.

13.5 Methods

The ESC methodology for the development of QIs for the quantification of cardiovascular care and outcomes was used.[185] In brief, the methodology involves 1) the identification of the key domains of care for the management of HF by constructing a conceptual framework of HF care, 2) the development of candidate QIs by conducting a systematic review of the literature, 3) the selection of the final set of QIs using a modified-Delphi method, and 4) the evaluation of the feasibility of the developed QIs.[185]

The ESC QIs may be classified into structural, process or outcomes indicators.[185] Structural QIs are those measures that assess the quality of care at the institutional level, while process QIs evaluate care quality at the individual patient's level. Outcome QIs capture those outcomes that are believed to be relevant to the condition itself (such as disease complications), its treatment (such as adverse events to a therapy) or patient reported outcome measures (such as health-related quality of life). Furthermore, the ESC QIs comprise main and secondary indicators, whereby the main QIs were deemed to have higher validity and feasibility by the Working Group members and thus may be used for measurement across regions and over time.[185] Both the main and secondary QIs may be used for local quality improvement activities.

13.5.1 Members of the Working Group

The Working Group comprised of Task Force members of the 2021 ESC Clinical Practice Guidelines for HF, members of the HFA, members of the ESC Clinical Practice Guidelines Quality Indicator Committee, experts in the management of patients with HF and a patient representative. A number of virtual meetings were convened between the members of the Working Group between February 2020 and March 2021.

13.5.2 Domains of HF care

During the initial phases of the development process, the Working Group defined the target population as those for whom the QIs are applicable, and identified the key domains for HF care. The target population was defined as patients with an established diagnosis of HF of any

type (heart failure with preserved ejection fraction, heart failure with mildly reduced ejection fraction, and heart failure with reduced ejection fraction). QIs that are only relevant to a particular HF type were defined accordingly. The key domains of care were established by constructing a conceptual illustration of the multi-faceted journey for patients with HF (Figure 1).[185]

Figure 1. Conceptual framework for the management of patients with Heart Failure
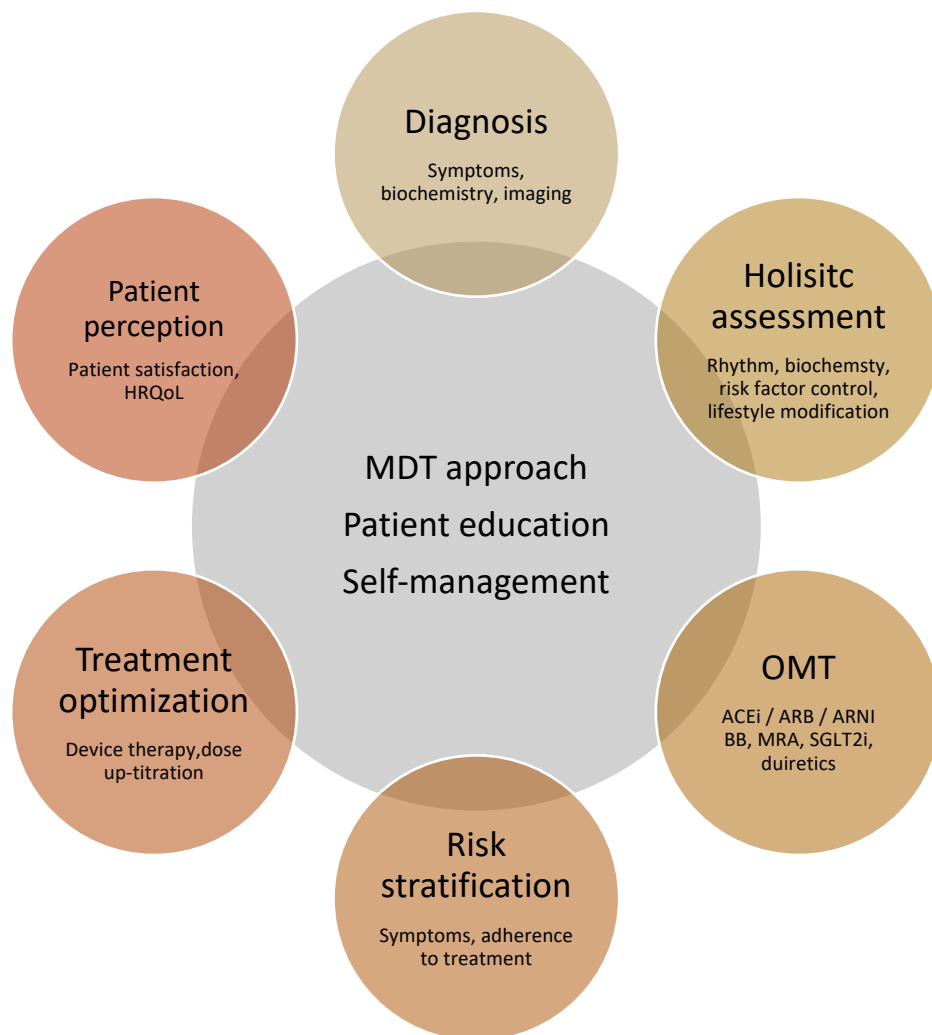
ACE= angiotensin converting enzymes; ARB=angiotensin receptor blocker;

ARNI=angiotensin-receptor neprilysin inhibitor; HRQoL=health-related quality of life;

MRA= Mineralocorticoid receptor antagonists; OMT=optimal medical therapy;

SGLT2=sodium-glucose transport protein 2, TSH=thyroid stimulating hormone;

U&Es=urea and electrolytes.

We excluded patients with suspected HF from the target population to allow better identification of patients eligible for the aspects of care being measured.[185] In addition, the Working Group defined for each process QI a numerator (patients who received the aspect of care being measured), a denominator (patients eligible for the aspect of care being measured), measurement period (the timepoint at which the assessment is performed) and measurement duration (the time frame needed for enough cases to be collected). For the structural QIs, only numerator definitions were provided given these are binary measurements (yes, no) which capture information about the availability of resources and infrastructure.[185]

13.5.3 Systematic review
13.5.3.1 Search strategy

We conducted a systematic review of the published literature in accordance with the Preferred Reporting Items for Systematic Review and Meta-analyses statement (Appendix Table A1).[172] We searched two online bibliographic databases; MEDLINE and Embase via OVID®. The initial search strategy was developed in MEDLINE using keywords and, when available, medical subject headings (MeSH) terms based on three main terms: "heart failure", "quality indicators" and "outcome measures" with a variety of other terms (Appendix Table A2). The final search strategies were then developed using an iterative process which included citation search and hand search of the references of the identified articles.

We included two types of studies: randomized controlled trials and controlled observational studies, including publications from clinical registries. We included the main publications of the major trials and registries from which our search obtained only sub-studies, and reviewed the studies included in the retrieved systematic reviews and meta-analyses against our inclusion criteria. The search was restricted to English language and publication dates between 01 January 2016 and 30 July 2020 given the year 2016 corresponds to the publication of the ESC Clinical Practice Guidelines for HF.[462]

13.5.3.2 Eligibility criteria

We included articles fulfilling the following criteria: 1) the study population was adult patients (≥18 years old) with HF , 2) the study explicitly defined an intervention (structural or process aspect of HF care) for which at least one outcome measure was evaluated, 3) the outcome measures were hard endpoints (e.g., mortality, re-admission) or patient reported outcomes (e.g., quality of life), 5) the study provided definitions for the intervention and outcome measure(s) evaluated and 6) the study was a peer-reviewed randomized controlled trial or controlled observational study.

13.5.3.3 Study selection

EndNote X9 was used for reference management and for duplicate removal. Two reviewers (SA and MP) independently examined the abstracts of the studies retrieved from the search against the inclusion criteria. Disagreements were resolved through a full text review of the article or by consulting a senior author (CPG).

13.5.3.4 Quality assessment and Data extraction

Studies that met the eligibility criteria were included in the initial phase of the review. This broad inclusion was important to ensure that the list of initial (candidate) QIs was representative of a wide range of HF care. The full texts of the included articles were reviewed by two authors (SA and MP) and for each study both the intervention studied and the outcome measure(s) evaluated were extracted to an Excel spreadsheet. Definitions of the data items extracted were also obtained when provided in the study.

13.5.3.5 Clinical Practice Guidelines and existing QIs

In addition to the systematic review, Clinical Practice Guidelines and existing QIs pertinent to HF management from selected professional organizations were reviewed.[462-466] The goal of the Clinical Practice Guidelines review was to assess the suitability of their recommendations with the strongest association with benefit and harm (Class I and III, respectively) against the ESC criteria for QIs (Appendix Table A3).[185] We also reviewed existing QIs and 'performance

measures' for patients with HF including that from the National Institute for Health and Care Excellence (NICE), Canadian Cardiovascular Society and Get With The Guidlelines.[166, 448, 457-459]

13.5.3.6 Data synthesis

13.5.3.6.1 Modified Delphi process

The candidate QIs which were derived from the aforementioned process were evaluated by the Working Group members using the modified Delphi method.[185] The ESC criteria for QI development (Appendix Table A3) were shared with the Working Group members prior to voting in order to standardize the selection process. All proposed QIs were individually graded by each panellist via online questionnaires using a 9-point ordinal scale for both validity and feasibility.[185] Two rounds in total were conducted, with a number of teleconferences after each round to discuss the results of the vote and address any concerns or ambiguities.

13.5.3.6.2 Analysing voting results

The 9-point ordinal scale used for voting implied that ratings of 1 to 3 meant that the QI is not valid/feasible; ratings of 4 to 6 meant that the QI is of an uncertain validity/feasible; and ratings of 7 to 9 meant that the QI is valid/feasible. For each candidate QI, the median and the mean deviation from the median were calculated to evaluate the central tendency and the dispersion of the votes. Indicators, with median scores ≥ 7 for validity, ≥ 4 for feasibility, and with minimal dispersion, were included in the final set of QIs.[185] The candidate QIs that met the inclusion criteria in the first voting round, with those that have the same strength of recommendations in the 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure, were defined as main QIs. The QIs which met the inclusion criteria after the second round of voting were defined as secondary indicators.

13.6 Results

13.6.1 Domains of HF Care

Five domains of care for the management of HF were identified by the Working Group. These domains included: 1) Structural framework, 2) Patient assessment, 3) Initial treatment, 4) Therapy optimization, and 5) Assessment of patients' health-related quality of life (Figure 2).

Figure 2. ESC HFA quality indicators for the management of patients with heart failure.
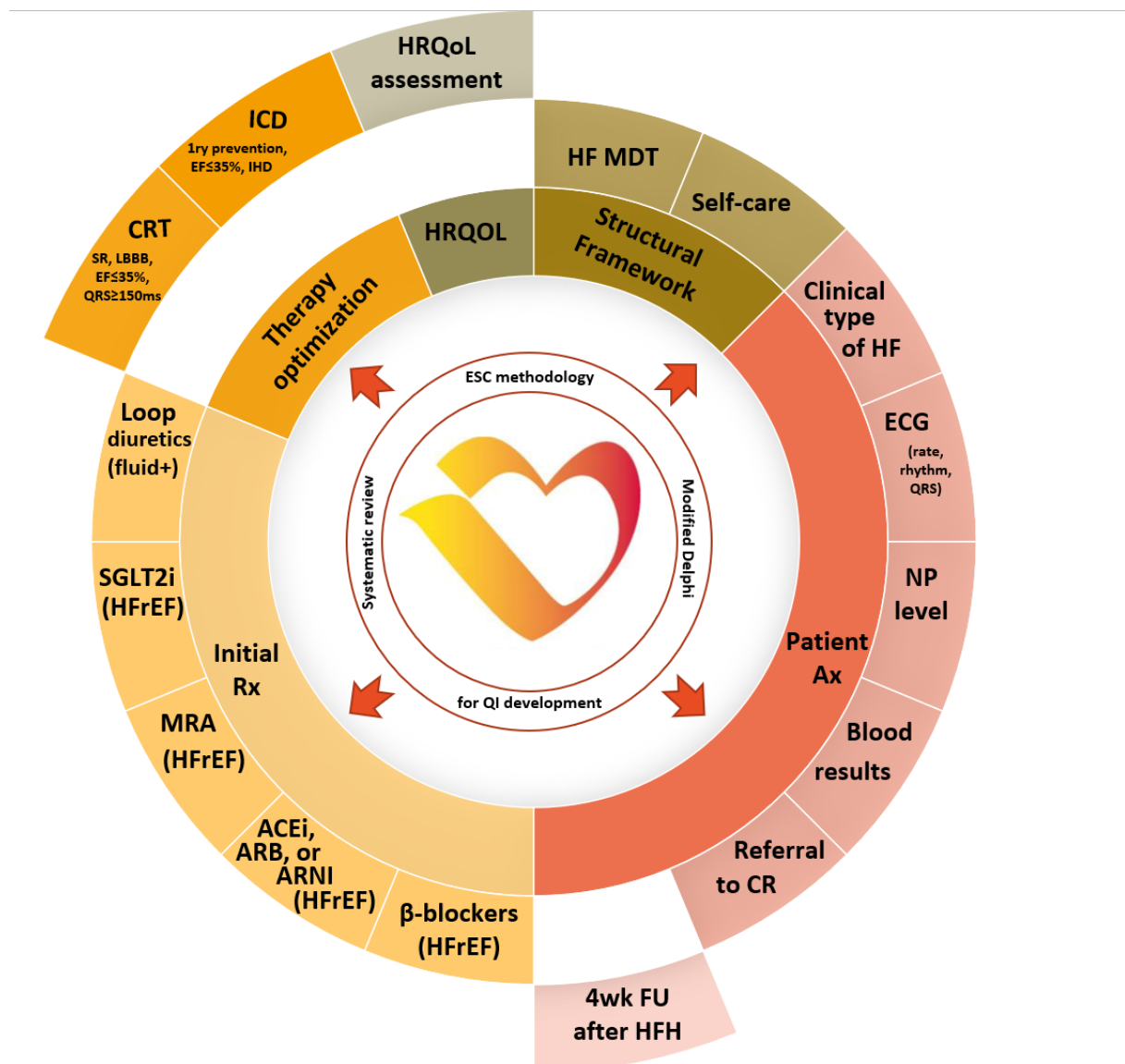
Ax=assessment; ACE= angiotensin converting enzymes; ARB=angiotensin receptor blocker; ARNI=angiotensin-receptor neprilysin inhibitor; CR= Cardiac rehabilitation; CRT= cardiac resynchronization therapy; ECG= electrocardiogram; EF= ejection fraction; ESC=European Society of Cardiology; FU= follow up; HF=heart failure; HFA= Heart Failure Association, HFrEF=heart failure with reduced ejection fraction; HRQoL=health-

*related quality of life; ICD= implantable cardioverter-defibrillators, MDT=
multidisciplinary team; MRA= mineralocorticoid receptor antagonists, NP=natriuretic
peptides; QIs=quality indicators, Rx= treatment; SGLT2i= sodium-glucose cotransporter 2
inhibitors*

Blood results include: urea, creatinine, electrolytes, full blood count, glucose, HbA1c, TSH,
liver function test, lipids and iron profile. *B-blockers are bisoprolol, carvedilol, sustained-
release metoprolol succinate or nebivolol.*

13.6.2 Systematic review results

The literature search retrieved 6556 articles, of which 237 met the inclusion criteria (Figure 3).
These articles were used to extract 71 'candidate' QIs (Appendix Table A4), which were voted
upon in the first Delphi round. Of those, 10 (14%) QIs met the inclusion criteria, and were,
thus included as main indicators, 49 (69%) QIs were excluded, and 12 (17%) QIs were carried
to the second round. Following the second Delphi round 6 (50%) QIs met the criteria for
inclusion, 2 (33%) of which were upgraded to main QIs to align with the level of
recommendation in the 2021 ESC HF Guidelines, and 4 (67%) were included as secondary
indicators. As such, a total of 12 main and 4 secondary QIs were included in the final set of the
2021 ESC HFA QIs for HF (Figure 2).

Figure 3. PRISMA flowchart for the studies included in the systematic review.

.
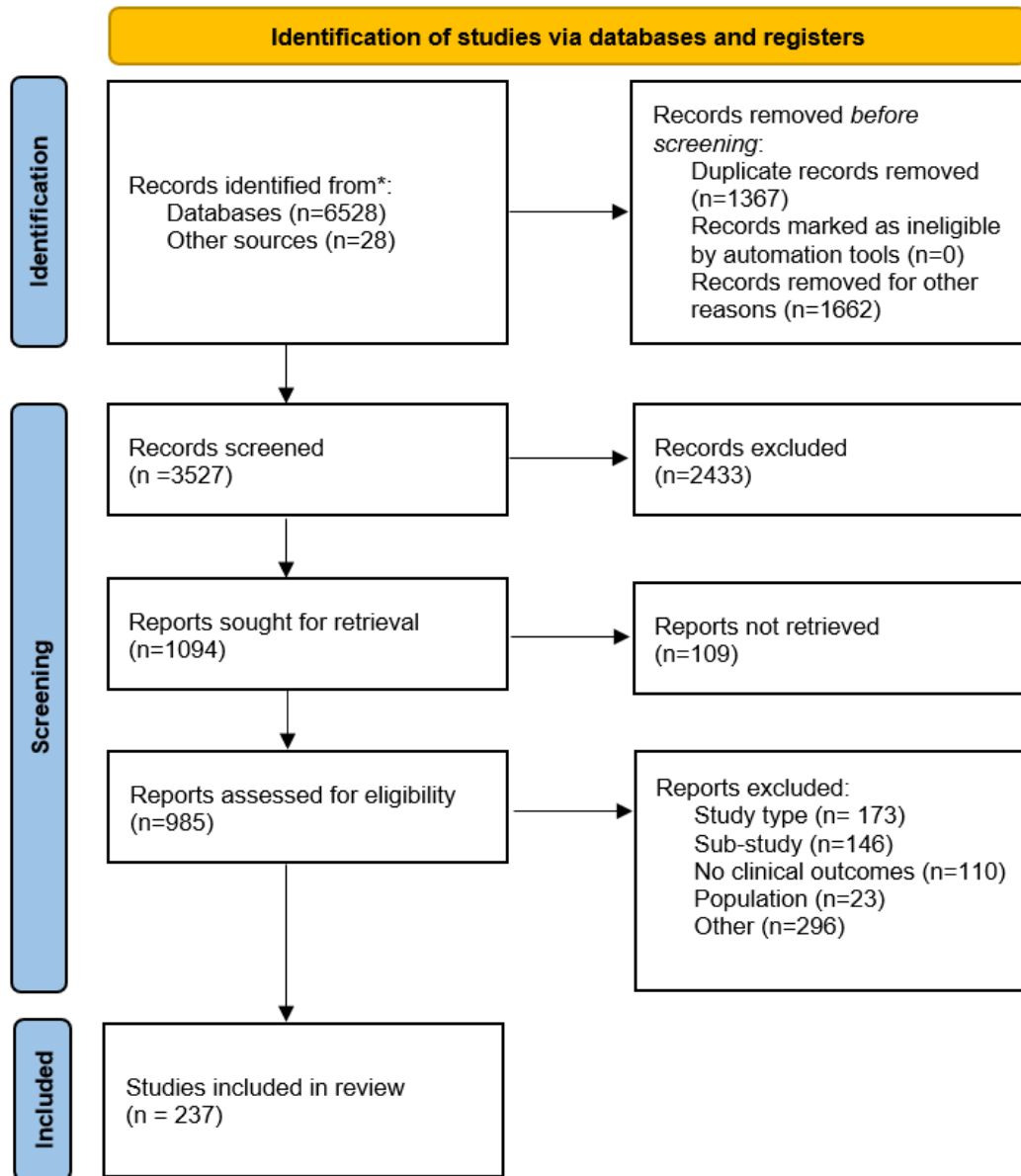
Preferred Reporting Items for Systematic Reviews and Meta-Analyses

*Search dates 01 January 2016 to 30 July 2020 including the 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure.

13.6.3 Quality Indicators

13.6.3.1 Domain 1: Structural framework

Structural QIs allow the measurement of aspects of care that may be difficult to capture on the individual patient level.[185] While such a measurement may be an indirect assessment of care quality, it has a role in the implementation of evidence based interventions for HF and an association with outcomes.[467, 468] Furthermore, structural QIs address aspects of HF care that are under the influence of healthcare authorities.[469]

Table 1. ESC HFA quality indicators for the management of patients with heart failure.

Domain 1. Structural framework
Main (1.1)[P]: Centre should have a dedicated multidisciplinary team to manage patients with HF
Numerator: Availability of a dedicated multidisciplinary team to manage patients with HF.
Main (1.2)[P]: Centres should have dedicated trained healthcare professionals to deliver HF specific education to facilitate patient self-care
Numerator: Availability of dedicated trained healthcare professionals to deliver HF specific education to facilitate patient self-care.
Domain 2. Patient assessment
Main (2.1)*: Proportion of patients with HF who have a documentation of their HF clinical type (HFrEF, HFmrEF, HFpEF)
Numerator: Number of patients with HF who have a documentation of their HF clinical type (HFrEF, HFmrEF, HFpEF).
Denominator: Number of patients with HF.
Main (2.2)*: Proportion of patients with HF who have a documentation of their ECG findings
Numerator: Number of patients with HF who have a documentation of their ECG findings[$].
Denominator: Number of patients with HF.
Main (2.3)*: Proportion of patients with HF who have their NPs measured
Numerator: Number of patients with HF who have a documentation of their NP levels[&].
Denominator: Number of patients with HF.
Main (2.4)*: Proportion of patients with HF who have their blood tests documented
Numerator: Number of patients with HF who have a documentation of their creatinine, U&Es, FBC, glucose, HbA1c, TSH, LFTs, lipids, and iron profile results documented[^].

Denominator: Number of patients with HF.

Main (2.5)*: Proportion of patients hospitalized with HF who have been referred for a cardiac rehabilitation program

Numerator: Number of patients with HF who have been referred for a cardiac rehabilitation program following HF hospitalization.

Denominator: Number of patients hospitalized with HF.

Secondary (2.1)*: Proportion of patients hospitalized with HF who have a follow up review by a healthcare professional within 4 weeks from their hospital discharge

Numerator: Number of patients with HF who have a follow up review by a healthcare professional within 4 weeks following HF hospitalization.

Denominator: Number of patients hospitalized with HF.

Domain 3. Initial treatment

Main (3.1)*: Proportion of patients with HFrEF who are prescribed the beta-blocker bisoprolol, carvedilol, sustained-release metoprolol succinate, or nebivolol in the absence of any contraindications

Numerator: Number of patients with HFrEF who are prescribed the beta-blocker bisoprolol, carvedilol, sustained-release metoprolol succinate, or nebivolol.

Denominator: Number of patients with HFrEF without any contraindications for the beta-blocker bisoprolol, carvedilol, sustained-release metoprolol succinate, and nebivolol.

Main (3.2)*: Proportion of patients with HFrEF who are prescribed ACE inhibitor, ARB or ARNI in the absence of any contraindications

Numerator: Number of patients with HFrEF who are prescribed an ACE inhibitor, ARB or ARNI.

Denominator: Number of patients with HFrEF without any contraindications for ACE inhibitors, ARBs and ARNI.

Main (3.3)*: Proportion of patients with HFrEF who are prescribed an MRA in the absence of any contraindications

Numerator: Number of patients with HFrEF who are prescribed an MRA.

Denominator: Number of patients with HFrEF without any contraindications for MRA.

Main (3.4)*: Proportion of patients with HFrEF who are prescribed a SGLT2 inhibitor in the absence of any contraindications

Numerator: Number of patients with HFrEF who are prescribed a SGLT2 inhibitor.

Denominator: Number of patients with HFrEF without any contraindications for SGLT2 inhibitor.

Main (3.5)*: Proportion of patients with HF who are prescribed loop diuretic therapy if they have evidence of fluid retention

Numerator: Number of patients with HF, with evidence of fluid retention who are prescribed loop diuretic therapy.

Denominator: Number of patients with HF who have evidence of fluid retention and no contraindications diuretic therapy.

Domain 4. Therapy optimization

Secondary (4.1)*: Proportion of symptomatic patients with HFrEF in sinus rhythm with a QRS duration ≥150 msec and LBBB QRS morphology and with LVEF ≤35% despite ≥3 months OMT who are offered CRT

Numerator: Number of symptomatic (NYHA II–III) patients with HFrEF in sinus rhythm with a QRS duration ≥150 msec and LBBB QRS morphology and with LVEF ≤35% despite ≥3 months OMT who are offered CRT.

Denominator: Number of symptomatic (NYHA II–III) patients with HF in sinus rhythm with a QRS duration ≥150 msec and LBBB QRS morphology and with LVEF ≤35% despite ≥3 months OMT.

Secondary (4.2)*: Proportion of symptomatic patients with HF, LVEF ≤35% despite ≥3 months of OMT, and IHD who are offered primary prevention ICD

Numerator: Number of symptomatic (NYHA II–III) patients with HF, LVEF ≤35% despite ≥3 months of OMT, and IHD who are offered primary prevention ICD.

Denominator: Number of symptomatic (NYHA II–III) patients with HF, LVEF ≤35% despite ≥3 months of OMT, and IHD who are expected to survive substantially longer than one year with good functional status.

Domain 5. Assessment of patient HRQoL

Secondary (5.1)*: Proportion of patients with HF who have an assessment of their HRQoL using a validated tool

Numerator: Number of patients with HF who have an assessment of their HRQoL using a validated tool

Denominator: Number of patients with HF.

ACE= angiotensin converting enzymes; ARB=angiotensin receptor blocker;

ARNI=angiotensin-receptor neprilysin inhibitor; CRT=cardiac resynchronization therapy;

ECG=electrocardiogram; ESC=European Society of Cardiology; FBC=full blood count;

HbA1c=glycated haemoglobin; HF=heart failure; HFA=Heart Failure Association;

HRQoL=health-related quality of life; HFmrEF=heart failure with mildly reduced ejection fraction; HFpEF=heart failure with preserved ejection fraction; HFrEF=heart failure with reduced ejection fraction; ICD=implantable cardioverter defibrillator; IHD-ischaemic heart disease; LFTs=liver function tests, LVEF=left ventricular ejection fraction; MRA= Mineralocorticoid receptor antagonists; NP=natriuretic peptides; NYHA= New York Heart Association; OMT=optimal medical therapy; QIs=quality indicators; SGLT2=sodium-glucose transport protein 2, TSH=thyroid stimulating hormone; U&Es=urea and electrolytes.

ᵖMeasurement period=the time of enrolment in a registry or quality improvement program, and annually thereafter.
*Measurement period= the time of outpatient visit or hospital discharge, measurement duration=12 months, exclusion criteria=patients with advanced heart failure who are not considered for heart transplant and/or mechanical circulatory support.
$ECG findings must include rhythm, rate, and QRS complexes that are recorded within a 12-month period from the time of outpatient visit or hospital discharge.
&Natriuretic peptide (NP) measurement is defined as recorded levels of B-type NP (BNP) or NT-proBNP within a 3-monht period from the time of heart failure diagnosis.
^Blood test measurement must be performed within a 6-months period from the time of outpatient visit or hospital discharge.

Thus, two main QIs were proposed in this domain; the availability of a dedicated multidisciplinary team for the management of patients with HF (**Main 1.1**) and the availability of dedicated healthcare professional(s) who may be able to deliver HF specific education to facilitate patient self-care (**Main 1.2**). These are key aspects of HF care, and have been shown to be associated with improved outcomes (Table 1).[470-472] Multidisciplinary HF management is defined as a holistic assessment for patients with HF that do not solely focus on HF treatment, but extends to risk factor control and lifestyle modification, as well as to the patient's overall physical and mental wellbeing.[449]

13.6.3.2 Domain 2: Patient assessment

The clinical type of HF determines the appropriateness and the eligibility for certain guideline-recommended interventions, such as novel medications or device therapy.[449] Accordingly, the evaluation and the documentation of the clinical type of HF (heart failure with preserved ejection fraction, heart failure with mildly reduced ejection fraction, and heart failure with reduced ejection fraction) (**Main 2.1**) and patient's ECG findings (**Main 2.2**) are indicators of care quality for patients with HF (Table 1).[449] Moreover, natriuretic peptide concentrations (**Main 2.3**), which may guide the diagnosis and the prognostication of HF, and other relevant blood tests (**Main 2.4**) are important variables to enable holistic assessment of patient's health.

Given the importance of extended patient assessment following a hospitalization with HF, post-discharge interventions, such as cardiac rehabilitation (**Main 2.5**) and early follow up (**Secondary 2.1**), have been associated with improved patients' outcomes(Table 1).[472, 473]

13.6.3.3 Domain 3: Initial treatment

Pharmacotherapy forms the cornerstone of the management of patients with HF. For those with heart failure with reduced ejection fraction in particular, there are a number of guideline-recommended therapies that improve prognosis, and recent studies have both consolidated the existing evidence on established therapies and provided additional options that should be considered.[449] Such therapies for patients with heart failure with reduced ejection fraction include 1) the beta-blocker bisoprolol, carvedilol, sustained-release metoprolol succinate or nebivolol (**Main 3.1**), 2) angiotensin converting enzyme (ACE) inhibitor, angiotensin receptor blockers (ARB) or angiotensin receptor neprilysin inhibitor (ARNI) (**Main 3.2**), 3) mineralocorticoid receptor antagonists (**Main 3.3**), and 4) sodium-glucose cotransporter 2 (SGLT2) inhibitors (**Main 3.4**) (Table 1).[449] **Main 3.5** captures the prescription of loop diuretics for patients with HF who have evidence of fluid retention (Table 1).[449] The contraindications for the medications captured in this domain are provided in the supplement (Appendix Table A5).

13.6.3.4 Domain 4: Therapy optimization

Clinical outcomes can be improved with cardiac resynchronization therapy for patients in sinus rhythm with left ventricular ejection fraction ≤35%, a QRS duration ≥150 msec, and a left bundle branch block morphology on their ECG who remain symptomatic despite at least three months of optimal medical therapy (**Secondary 4.1**), and with primary prevention implantable cardioverter-defibrillators for those who are symptomatic with a left ventricular ejection fraction ≤35% despite at least three months of optimal medical therapy and have a history of ischaemic heart disease, with life expectancy greater than 1 year (**Secondary 4.2**) (Table 1).[449]

13.6.3.5 Domain 5: Assessment of patient health-related quality of life

Despite an existing methodology for the development and patients reported outcome measures,[381] their implementation in clinical practice is limited by the burden of data collection. The International Consortium for Health Outcomes Measurement (ICHOM) recommends the use of the shortened Kansas City Cardiomyopathy Questionnaire (KCCQ-12) to assess patients' health-related quality of life.[457] However, generic measurement tools, such as the EuroQoL Group Quality of Life Questionnaire, have also been used in the literature.[473] As such, the Working Group agreed to recommend the use of a 'validated tool' for the assessment of patients' health-related quality of life (**Secondary 5.1**). Furthermore, given the concerns about the feasibility of capturing health-related quality of life in clinical practice, this QI has been designed as a process QI, rather than an outcome measure. Thus, the assessment of the patient's health-related quality of life would constitute an accomplishment of the QI without setting certain scores as targets for therapy (Table 1).[166]

Other outcome QIs pertinent to HF (Appendix Table A4), such as mortality and rehospitalization rates were included in the list of candidate QIs, but none met the inclusion criteria in either of the voting rounds and were excluded.

13.6.3.6 Composite QIs

The composite QIs is a combination of two or more indicators into a single score, and serve to condense a number of individual QIs into a comprehensive assessment of care quality.[185] Composite QIs provide more reliable information about benchmarking compared with individual indicators.[474] Whilst a number of methods exist for the development of composite

QIs, the Working Group opted for the opportunity-based and the all-or-none.[475] The opportunity-based is calculated by counting the total number of *opportunities* in which the individual component QIs were indicated and the total number of *times* in which these QIs were successfully accomplished. Whereas, one patient may contribute to a number of opportunities in the opportunity-based composite QI, the all-or-none counts the proportion of patients who attain all components of the composite QIs for which they were eligible.[475] Table 2 shows the individual component QIs for both the opportunity-based (**Composite main**) and the all-or-none (**Composite secondary**) composite QIs in the 2021 ESC HFA QIs for HF.

Table 2. Composite QIs

Composite QIs
Composite main: Opportunity-based
Calculated on 6 individual QIs in patients with LVEF > 40%:
1. Proportion of patients with HF who have a documentation of their HF clinical type (HFrEF, HFmrEF, HFpEF).
2. Proportion of patients with HF who have a documentation of their ECG findings.
3. Proportion of patients with HF who have their NPs measured.
4. Proportion of patients with HF who have their blood tests checked.
5. Proportion of patients hospitalized with HF who have been referred for a cardiac rehabilitation program.
6. Proportion of patients hospitalized with HF who have a follow up review by a healthcare professional within 4 weeks from their hospital discharge.
Calculated on 12 individual QIs in patients with LVEF ≤ 40%:
1. Proportion of patients with HF who have a documentation of their HF clinical type (HFrEF, HFmrEF, HFpEF).
2. Proportion of patients with HF who have a documentation of their ECG findings.
3. Proportion of patients with HF who have their NPs measured.
4. Proportion of patients with HF who have their blood tests checked.
5. Proportion of patients hospitalized with HF who have been referred for a cardiac rehabilitation program.

6. Proportion of patients hospitalized with HF who have a follow up review by a healthcare professional within 4 weeks from their hospital discharge.

7. Proportion of patients with HFrEF who are prescribed the beta-blocker bisoprolol, carvedilol, sustained-release metoprolol succinate, or nebivolol in the absence of any contraindications.

8. Proportion of patients with HFrEF who are prescribed ACE inhibitor, ARB or ARNI in the absence of any contraindications.

9. Proportion of patients with HFrEF who are prescribed an MRA in the absence of any contraindications.

10. Proportion of patients with HFrEF who are prescribed a SGLT2 inhibitor in the absence of any contraindications.

11. Proportion of symptomatic patients with HFrEF in sinus rhythm with a QRS duration ≥150 msec and LBBB QRS morphology and with LVEF ≤35% despite OMT who are offered CRT.

12. Proportion of symptomatic patients with HF, LVEF ≤35% despite ≥3 months of OMT, and IHD who are offered primary prevention ICD.

Numerator: Number of times each of the above individual QIs were accomplished correctly*.

Denominator: Number of chances existed to deliver individual QIs based on the inclusion criteria of each QI (Table 1).

Composite secondary: All-or-none

1. Proportion of patients with HFrEF who are prescribed the beta blocker bisoprolol, carvedilol, sustained-release metoprolol succinate, or nebivolol in the absence of any contraindications.

2. Proportion of patients with HFrEF who are prescribed ACE inhibitor, ARB or ARNI in the absence of any contraindications.

3. Proportion of patients with HFrEF who are prescribed an MRA in the absence of any contraindications.

4. Proportion of patients with HFrEF who are prescribed a SGLT2 inhibitor in the absence of any contraindications.

Numerator: Number of patients who are eligible for and have accomplished all the above individual QIs.

Denominator: Number of patients who are eligible for all the above individual QIs based on the inclusion criteria of each QI (Table 1).

ACE= angiotensin converting enzymes; ARB=angiotensin receptor blocker; ARNI=angiotensin-receptor neprilysin inhibitor; CRT=cardiac resynchronization therapy; CQI=composite quality indicator; ECG=electrocardiogram; ESC=European Society of Cardiology; HF=heart failure; HFA=Heart Failure Association; HRQoL=health-related quality of life; HFmrEF=heart failure with mildly reduced ejection fraction; HFpEF=heart failure with preserved ejection fraction; HFrEF=heart failure with reduced ejection fraction; ICD=implantable cardioverter defibrillator; LVEF=left ventricular ejection fraction; MRA= Mineralocorticoid receptor antagonists; NP=natriuretic peptides; OMT=optimal medical therapy; QIs=quality indicators; SGLT2=sodium-glucose transport protein 2.

*Weighting for the individual component QIs within the composite is not provided here as this needs to be determined according to the volume of opportunities for these QIs for a particular hospital (e.g., a hospital that frequently has patients eligible for pharmacotherapies for HF but rarely performs implantable cardioverter defibrillator (ICD) implantation would be scored in a manner that weights pharmacotherapy QIs more heavily).

13.7 Discussion

This document presents the first ESC suite of QIs for the evaluation of HF care. These QIs are derived from evidence, underpinned by expert consensus and provide the means for quality improvement initiatives. The simultaneous development of these QIs and the 2021 ESC Clinical Practice Guidelines for HF has facilitated a seamless incorporation of these indicators within the Guideline document, and provided translation for some Guideline recommendations into specific and measurable indicators.[449] Furthermore, the a priori identification of key domains which span the continuum of HF care, as well as the engagement of Working Group members from diverse backgrounds and expertise has ensured that the QIs presented in this document are relevant to clinical practice and cover the breadth of HF care.

In 2011, the ACC/AHA developed a set of 'performance measures' for HF.[476] However, they may not be generalizable to European clinical practice and mechanisms by which information may be captured.[477] Furthermore, the 2020 update of the ACC/AHA 'performance measures'

set did not include indicators for SGLT2 inhibitors or composite QIs.[166] A comparison between the 2021 ESC QIs for HF and the 2020 ACC/AHA Clinical Performance and Quality Measures for Adults with HF is presented in Appendix Table A6. For example, the ESC QIs recommend follow up after hospitalization with HF within four weeks and compares a recommendation of seven days in the ACC/AHA set – the ESC Working Group deemed a 4-week follow up more feasible for the European healthcare systems.

The QIs presented in this document were developed using a standardized methodology.[185] They may facilitate the monitoring and reporting of the quality of HF care, which is a mandatory component of accountable healthcare systems.[448] HF is a major cause of hospital admissions of adult patients worldwide,[478] with substantial rates of re-hospitalization, high mortality and a growing economic burden.[479] Establishing a set of measurable indicators for HF care quality provides a mechanism to improve adherence to guideline-recommended therapies[449] and help reduce the burden of HF through an integration with international quality improvement collaborations, such as the European Unified Registries on Heart care Evaluation and Randomized Trials (EuroHeart) project.[45]

Healthcare quality assessment is determined by the methods by which the QIs are developed, the clinical setting(s) in which the indicators are implemented and the interpretation of the measurement results.[185] While the association between quality measurement in HF and improvement in clinical outcomes may be difficult to illustrate,[480, 481] this challenge creates a need to establish an integrated quality improvement programs that capture longitudinal data relevant to the care for patients with HF across various settings.[456, 482] It is anticipated that the ESC QIs will serve as a catalyst for HF quality improvement by highlighting areas with suboptimal attainment for guideline-recommended therapies, and evaluating the temporal and geographical patterns of HF care.

Whilst our study has a number of strengths, we acknowledge its limitations. First, we relied on expert opinion to arrive at the final set of QIs following the systematic review of the literature.

However, we used a modified Delphi method that independently involved experts' votes to select main and secondary QIs and applied the ESC criteria to standardize the voting process. Second, whilst the Working Group agreed on the importance of outcome QIs, these were not included in the final set of QIs given the concerns about the feasibility of capturing these data across various healthcare systems in Europe. Third, reflecting the current gaps in knowledge base, we have not developed QIs that are specific for HF with preserved ejection fraction.[449] Fourth, the opportunity-based method is influenced by the frequency, rather than the importance, of the individual component QIs.[483] Fifth, the all-or-none method does not distinguish between providers that achieve some of the individual component QIs from those who achieve none of the indicators.[483] Sixth, only process QIs were included in the composites because no outcome QIs were included in the developed set. However, composite scores tend to be predominantly influenced by their process components.[484] Seventh, more refinement of the QIs (including the composites) and/or their definitions may be needed in the future when more feasibility data become available. Finally, we recommend that future Working Groups include other members of the HF multidisciplinary team, such as nurses and pharmacists.

13.8 Conclusion

This document defines 12 main and 4 secondary QIs across five domains of care for the management of HF: 1) Structural framework, 2) Patient assessment, 3) Initial treatment, 4) Therapy optimization, and 5) Assessment of patient health-related quality of life. For each QI, relevant specifications were described to enhance their use in practice. The recommended set of QIs may facilitate the implementation of, and assess the adherence to, Clinical Practice Guidelines and enable institutions to monitor, compare, and improve quality of care in patients with HF.

13.9 References for Chapter 13

1. McDonagh T MM, et al. 2021 ESC Guidelines for Heart Failure

2. Vaduganathan M, Claggett BL, Jhund PS, Cunningham JW, Pedro Ferreira J, Zannad F, Packer M, Fonarow GC, McMurray JJV, Solomon SD. Estimating lifetime benefits of comprehensive disease-modifying pharmacological therapies in patients with heart failure with reduced ejection fraction: a comparative analysis of three randomised controlled trials. Lancet 2020;**396**(10244):121-128.

3. Kapelios CJ, Laroche C, Crespo-Leiro MG, Anker SD, Coats AJS, Díaz-Molina B, Filippatos G, Lainscak M, Maggioni AP, McDonagh T, Mebazaa A, Metra M, Moura B, Mullens W, Piepoli MF, Rosano GMC, Ruschitzka F, Seferovic PM, Lund LH, Group HFL-TRI. Association between loop diuretic dose changes and outcomes in chronic heart failure: observations from the ESC-EORP Heart Failure Long-Term Registry. European Journal of Heart Failure 2020;**22**(8):1424-1437.

4. Emdin CA, Conrad N, Kiran A, Salimi-Khorshidi G, Woodward M, Anderson SG, Mohseni H, Dargie HJ, Hardman SMC, McDonagh T, McMurray JJV, Cleland JGF, Rahimi K. Variation in hospital performance for heart failure management in the National Heart Failure Audit for England and Wales. Heart 2017;**103**(1):55-62.

5. Crespo-Leiro MG, Anker SD, Maggioni AP, Coats AJ, Filippatos G, Ruschitzka F, Ferrari R, Piepoli MF, Delgado Jimenez JF, Metra M, Fonseca C, Hradec J, Amir O, Logeart D, Dahlström U, Merkely B, Drozdz J, Goncalvesova E, Hassanein M, Chioncel O, Lainscak M, Seferovic PM, Tousoulis D, Kavoliuniene A, Fruhwald F, Fazlibegovic E, Temizhan A, Gatzov P, Erglis A, Laroche C, Mebazaa A, Cardiology obotHFAotESo. European Society of Cardiology Heart Failure Long-Term Registry (ESC-HF-LT): 1-year follow-up outcomes and differences across regions. European Journal of Heart Failure 2016;**18**(6):613-625.

6. Chioncel O, Mebazaa A, Harjola V-P, Coats AJ, Piepoli MF, Crespo-Leiro MG, Laroche C, Seferovic PM, Anker SD, Ferrari R, Ruschitzka F, Lopez-Fernandez S, Miani D, Filippatos G, Maggioni AP, Investigators obotEHFL-TR. Clinical phenotypes and outcome of patients hospitalized for acute heart failure: the ESC Heart Failure Long-Term Registry. European Journal of Heart Failure 2017;**19**(10):1242-1254.

7. Allen LA, Fonarow GC, Liang L, Schulte PJ, Masoudi FA, Rumsfeld JS, Ho PM, Eapen ZJ, Hernandez AF, Heidenreich PA, Bhatt DL, Peterson ED, Krumholz HM. Medication Initiation Burden Required to Comply With Heart Failure Guideline Recommendations and Hospital Quality Measures. Circulation 2015;**132**(14):1347-53.

8.   Chioncel O, Mebazaa A, Harjola VP, Coats AJ, Piepoli MF, Crespo-Leiro MG, Laroche C, Seferovic PM, Anker SD, Ferrari R, Ruschitzka F, Lopez-Fernandez S, Miani D, Filippatos G, Maggioni AP. Clinical phenotypes and outcome of patients hospitalized for acute heart failure: the ESC Heart Failure Long-Term Registry. European Journal of Heart Failure 2017;**19**(10):1242-1254.

9.   Grandin EW, Jessup M. Rethinking the Focus of Heart Failure Quality Measures. Circulation 2015;**132**(14):1307-1310.

10.   Aktaa S, Batra G, Wallentin L, Baigent C, Erlinge D, James S, Ludman P, Maggioni A, Price S, Weston C, Casadei B, Gale CP. European Society of Cardiology methodology for the development of quality indicators for the quantification of cardiovascular care and outcomes. 2020.

11.   Heidenreich PA, Fonarow GC, Breathett K, Jurgens CY, Pisani BA, Pozehl BJ, Spertus JA, Taylor KG, Thibodeau JT, Yancy CW, Ziaeian B. 2020 ACC/AHA Clinical Performance and Quality Measures for Adults With Heart Failure. Circulation: Cardiovascular Quality and Outcomes 2020;**13**(11):e000099.

12.   Burns DJP, Arora J, Okunade O, Beltrame JF, Bernardez-Pereira S, Crespo-Leiro MG, Filippatos GS, Hardman S, Hoes AW, Hutchison S, Jessup M, Kinsella T, Knapton M, Lam CSP, Masoudi FA, McIntyre H, Mindham R, Morgan L, Otterspoor L, Parker V, Persson HE, Pinnock C, Reid CM, Riley J, Stevenson LW, McDonagh TA. International Consortium for Health Outcomes Measurement (ICHOM): Standardized Patient-Centered Outcomes Measurement Set for Heart Failure Patients. JACC: Heart Failure 2020;**8**(3):212-222.

13.   McKelvie RS, Heckman GA, Blais C, Cox JL, Ezekowitz JA, Gong Y, Harkness K, Moe G, Dai S, Dorian P, Johnstone DE, McGeachie EC, Tu JV, Lambert LJ. Canadian Cardiovascular Society Quality Indicators for Heart Failure. Can J Cardiol 2016;**32**(8):1038.e5-9.

14.   Get With The Guidelines®- Heart Failure. Febrruary 2016. https://www.heart.org/-/media/files/professional/quality-improvement/get-with-the-guidelines/get-with-the-guidelines-hf/educational-materials/hf-fact-sheet_updated-011119_v2.pdf?la=en. Accessed 12 December 2020.

15.   National Library of Quality Indicators. National Institute for Health and Care Excellence. Availiable at https://www.nice.org.uk/standards-and-indicators/index/All/All/7. Accessed 15 December 2020.

16.   Lambie L, Mattke S and the Members of the OECD Cardiac Care Panel. Selecting indicators for the quality of cardiac care at the health system level in the OECD countries: https://www.oecd.org/els/health-systems/33865450.pdf. 2004.

17.   Smets M, Smeets M, Van den Bulck S, Janssens S, Aertgeerts B, Vaes B. Defining quality indicators for heart failure in general practice. Acta Cardiologica 2019;**74**(4):291-298.

18.   Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, Shamseer L, Tetzlaff JM, Akl EA, Brennan SE, Chou R, Glanville J, Grimshaw JM, Hróbjartsson A, Lalu MM, Li T, Loder EW, Mayo-Wilson E, McDonald S, McGuinness LA, Stewart LA, Thomas J, Tricco AC, Welch VA, Whiting P, Moher D. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;**372**:n71.

19.   Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, Falk V, González-Juanatey JR, Harjola V-P, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GMC, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P, Group ESD. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. European Heart Journal 2016;**37**(27):2129-2200.

20.   https://www.nice.org.uk/guidance/ng106/resources. Accessed 13 December 2020 NIfHaCENgNChfiadamPdS.

21.   Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE, Drazner MH, Fonarow GC, Geraci SA, Horwich T, Januzzi JL, Johnson MR, Kasper EK, Levy WC, Masoudi FA, McBride PE, McMurray JJV, Mitchell JE, Peterson PN, Riegel B, Sam F, Stevenson LW, Tang WHW, Tsai EJ, Wilkoff BL. 2013 ACCF/AHA Guideline for the Management of Heart Failure. Journal of the American College of Cardiology 2013;**62**(16):e147-e239.

22.   Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE, Colvin MM, Drazner MH, Filippatos GS, Fonarow GC, Givertz MM, Hollenberg SM, Lindenfeld J, Masoudi FA, McBride PE, Peterson PN, Stevenson LW, Westlake C. 2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure. Journal of the American College of Cardiology 2017;**70**(6):776-803.

23.   McDonald M, Virani S, Chan M, Ducharme A, Ezekowitz JA, Giannetti N, Heckman GA, Howlett JG, Koshman SL, Lepage S, Mielniczuk L, Moe GW, O'Meara E, Swiggum E, Toma M, Zieroth S, Anderson K, Bray SA, Clarke B, Cohen-Solal A, D'Astous M, Davis M, De S, Grant ADM, Grzeslo A, Heshka J, Keen S, Kouz S, Lee D, Masoudi FA, McKelvie R,

Parent M-C, Poon S, Rajda M, Sharma A, Siatecki K, Storm K, Sussex B, Van Spall H, Yip AMC. CCS/CHFS Heart Failure Guidelines Update: Defining a New Pharmacologic Standard of Care for Heart Failure With Reduced Ejection Fraction. Canadian Journal of Cardiology 2021;**37**(4):531-546.

24. Lund LH, Carrero JJ, Farahmand B, Henriksson KM, Jonsson Å, Jernberg T, Dahlström U. Association between enrolment in a heart failure quality registry and subsequent mortality-a nationwide cohort study. Eur J Heart Fail 2017;**19**(9):1107-1116.

25. McAlister FA, Youngson E, van Diepen S, Ezekowitz JA, Kaul P. Influence of hospital volume on outcomes for patients with heart failure: Evidence from a Canadian national cohort study. American Heart Journal 2018;**202**:148-150.

26. Seferovic PM, Piepoli MF, Lopatin Y, Jankowska E, Polovina M, Anguita-Sanchez M, Stork S, Lainscak M, Milicic D, Milinkovic I, Filippatos G, Coats AJS. Heart Failure Association of the European Society of Cardiology Quality of Care Centres Programme: design and accreditation document. European Journal of Heart Failure 2020;**22**(5):763-774.

27. Horne BD, Roberts CA, Rasmusson KD, Buckway J, Alharethi R, Cruz J, Evans RS, Lloyd JF, Bair TL, Kfoury AG, Lappe DL. Risk score-guided multidisciplinary team-based Care for Heart Failure Inpatients is associated with lower 30-day readmission and lower 30-day mortality. American Heart Journal 2020;**219**:78-88.

28. Pedraza LL, Pokorski SCS, MacHado BB, Ferro EB, Souza RH, Caetano FS, Rabelo-Silva ER. Health literacy, knowledge, treatment adhesion and self-care in heart failure in a middle income country. European Journal of Heart Failure 2019;**21**(Supplement 1):298.

29. Van Spall HGC, Rahman T, Mytton O, Ramasundarahettige C, Ibrahim Q, Kabali C, Coppens M, Brian Haynes R, Connolly S. Comparative effectiveness of transitional care services in patients discharged from the hospital with heart failure: a systematic review and network meta-analysis. European Journal of Heart Failure 2017;**19**(11):1427-1443.

30. Long L, Mordi IR, Bridges C, Sagar VA, Davies EJ, Coats AJ, Dalal H, Rees K, Singh SJ, Taylor RS. Exercise-based cardiac rehabilitation for adults with heart failure. Cochrane Database Syst Rev 2019;**1**(1):Cd003331.

31. Calvert M, Blazeby J, Altman DG, et al. Reporting of patient-reported outcomes in randomized trials: The consort pro extension. JAMA 2013;**309**(8):814-822.

32. Hofstede SN, Ceyisakar IE, Lingsma HF, Kringos DS, Marang-Van De Mheen PJ. Ranking hospitals: Do we gain reliability by using composite rather than individual indicators? BMJ Quality and Safety 2019;**28**(2):94-102.

33.   CMS Measure Management System Blueprint. Version 16.0. September 2020. https://www.cms.gov/Medicare/Quality-Initiatives-Patient-Assessment-Instruments/MMS/Downloads/Blueprint.pdf. Accessed 19 February 2021.

34.   Bonow RO, Ganiats TG, Beam CT, Blake K, Casey DE, Goodlin SJ, Grady KL, Hundley RF, Jessup M, Lynn TE, Masoudi FA, Nilasena D, Piña IL, Rockswold PD, Sadwin LB, Sikkema JD, Sincak CA, Spertus J, Torcson PJ, Torres E, Williams MV, Wong JB. ACCF/AHA/AMA-PCPI 2011 Performance Measures for Adults With Heart Failure. Circulation 2012;**125**(19):2382-2401.

35.   Blecker S, Agarwal SK, Chang PP, Rosamond WD, Casey DE, Kucharska-Newton A, Radford MJ, Coresh J, Katz S. Quality of Care for Heart Failure Patients Hospitalized for Any Cause. Journal of the American College of Cardiology 2014;**63**(2):123-130.

36.   Savarese G, Lund LH. Global Public Health Burden of Heart Failure. Cardiac failure review 2017;**3**(1):7-11.

37.   Smith SC, Jr, Fonarow GC, Zhao D. Measuring and Improving the Quality of Heart Failure Care Globally. JAMA Network Open 2020;**3**(1):e1918642-e1918642.

38.   Wallentin L, Gale CP, Maggioni A, Bardinet I, Casadei B. EuroHeart: European Unified Registries On Heart Care Evaluation and Randomized Trials. European Heart Journal 2019;**40**(33):2745-2749.

39.   Fonarow GC, Abraham WT, Albert NM, Stough WG, Gheorghiade M, Greenberg BH, O'Connor CM, Pieper K, Sun JL, Yancy C, Young JB. Association between performance measures and clinical outcomes for patients hospitalized with heart failure. Jama 2007;**297**(1):61-70.

40.   Polanczyk CA, Ruschel KB, Castilho FM, Ribeiro AL. Quality Measures in Heart Failure: the Past, the Present, and the Future. Curr Heart Fail Rep 2019;**16**(1):1-6.

41.   Fonarow GC, Albert NM, Curtis AB, Gheorghiade M, Heywood JT, Liu Y, Mehra MR, O'Connor CM, Reynolds D, Walsh MN, Yancy CW. Associations Between Outpatient Heart Failure Process-of-Care Measures and Mortality. Circulation 2011;**123**(15):1601-1610.

42.   Peterson ED, Delong ER, Masoudi FA, O'Brien SM, Peterson PN, Rumsfeld JS, Shahian DM, Shaw RE, Goff DC, Jr., Grady K, Green LA, Jenkins KJ, Loth A, Radford MJ. ACCF/AHA 2010 Position Statement on Composite Measures for Healthcare Performance Assessment: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Performance Measures (Writing Committee to develop a position statement on composite measures). Circulation 2010;**121**(15):1780-91.

43.   O'Brien SM, DeLong ER, Dokholyan RS, Edwards FH, Peterson ED. Exploring the Behavior of Hospital Composite Performance Measures. Circulation 2007;**116**(25):2969-2975.

PART III

Chapter 14. Discussion

In this Chapter, I will present the accomplishments of my PhD studies and critically discuss the strengths and weaknesses of the methodology used. Then I will discuss my individual role and suggest a future direction based on the findings of this PhD studies.

14.1 Accomplishments of the PhD studies

This thesis presents my involvement in an international collaboration that aims to develop the standards by which the collection of CVD data is defined and the methods by which the quality of CVD care is measured. The overarching aim of my PhD studies is to harmonise the clinical definitions for data standards and QIs (hereafter collectively referred to as data variables) for common CVD conditions, such that quality improvement initiatives and research activities can be integrated with routine clinical care.

I have developed a methodological approach and established an operational framework for the construction of data variables for CVD. As such, consistency in the development of data variables for CVD can be achieved across different domains and regions. The endorsement of major cardiovascular societies for the developed data variables highlights the need for such tools to reduce the burden of data collection for CVD,[34, 35, 485] but also illustrates the appropriateness of the methods used and the applicability of the developed data variables in practice.

The publication of the methodology by which the data variables were developed allows healthcare professional around the world to use this stepwise approach to establish data variables that are relevant to their local practice. In addition, the implementation of the developed methodology in constructing data variables for various CVD conditions and

interventions illuminates the feasibility of the process and provide methodologically defined sets of data variables that may be adopted by healthcare organisations to facilitate data collection and quality improvement endeavours in cardiovascular medicine.

The reliance on existing knowledge and high-quality evidence to developed data variables for CVD, besides the involvement of a wide range of key stakeholders including patient representatives creates a balance between clinical validity and feasibility.[184] Furthermore, the diversity of the clinical topics for which data variables were developed during this PhD studies, including AMI and heart failure, illustrates the prioritisation of common cardiovascular conditions that are of importance to patients and society.

Furthermore, I have not only developed data variables for various CVD conditions, but also applied these variables to show their clinical uses in practice. For instance, I measured the AMI QIs using national databases to evaluate the quality of care for patients presenting with AMI in England and Wales during the COVID-19 pandemic.[192] In addition, the EuroHeart data standards were programmed into a dedicated IT platform, which has been implemented in a number of European countries.

The accomplishments of this PhD studies serve as a catalyst for the establishment of a unified system for quality assurance that reduces the burden of CVD and improve patient outcomes. Standardising the methods by which cardiovascular data are defined, collected and interpreted, facilitates evidence development and creates generalisable knowledge that can be used to better understand the patterns of CVD and illuminate disparities, inequalities and areas for improvement.

14.2 The gap that this PhD studies address

The systematic collection of structured healthcare data has been increasingly recognised in cardiovascular medicine.[486] This recognition has been exponentially emphasised during the COVID-19 pandemic, which has placed healthcare systems around the world under unprecedented pressure.[31, 487] The pandemic illustrated the importance of unifying the medical lexicon and harmonising the data definitions across countries given the crucial role that the cardiovascular registries played in understanding the changes in the patterns of CVD care and its outcomes during compared with before the pandemic.[76, 77, 192]

Thus, the efforts that aim to harmonise the definitions of cardiovascular data variables across different settings, including clinical care and research, as well as across regions need to be prioritised such that redundancy in data collection can be reduced.[67] Such a harmonisation facilitates the integration between segregated initiatives that aim to improve the quality of CVD care and capture patient outcomes efficiently and cost-effectively.

The successes of national registries such as NICOR and SWEDEHEART provide a proof of the concept that clinical registries have a role in improving quality, addressing disparities and conducting high-quality observational and randomised research. However, there remains a need for a unified international collaboration that uses a federated approach in which national registries for CVD across Europe are harmonised. As such, comparative analyses and large clinical trials can be performed using routinely collected data.[45] Furthermore, the establishment of a pan-European system for harmonised data collection for CVD allows the post-marketing surveillance for new drugs and devices. Such a system is mostly needed considering the exponential advances in the development of new technologies for CVD.[2, 488]

In addition to creating systems that are enabled to continuously capture harmonised data for CVD, developing well-defined parameters that are selected methodologically and according to contemporary evidence allows the structured assessment of quality-of-care and outcomes. Thus, the construction of sets of QIs for various CVD conditions and implementing these QIs

into the EuroHeart registries provides an integrated system in which data are utilised to measure and improve patient care across different settings.

Thus, the accomplishments of my PhD studies which are presented in this thesis help address the transitional gaps between science and practice and aim to reduce the burden of CVD (Figure 2).[36, 44]

14.3 Addition to existing knowledge

Despite the efforts that have been undertaken by professional organisations around the world to standardise the nomenclature for CVD,[143, 147, 151, 153, 489-501] variation in the definitions of CVD data variables persists. This thesis presents a comprehensive system that enables the integration of various initiatives that aim to improve CVD care and outcomes by defining scientifically valid, yet feasible standards for the collection of cardiovascular data across various settings.[502]

My PhD is the first step in achieving complete semantic interoperability for CVD across different systems.[503] Whether extracting data from EHRs or clinical registries, developing phenotyping algorithms to identify patients with certain traits using machine learning and natural language processing require standardised ontologies for each of the clinical terminology.[504] However, an essential prerequisite for such ontologies is the availability of clinical definitions for a methodologically selected set of data variables for each of the conditions or interventions (15.7 Future direction).[504]

In my PhD, I have developed a framework for the selection of data variables to CVD and identified the specifications needed for data standards and these for QIs. Such an identification allows end users to implement the variables that best suites the goal(s) for which data are collected and then map these definitions to their respective ontologies. Hence, data are exchanged seamlessly across settings, diseases and regions with a preservation of the conceptual meaning of the exchanged data.[505]

14.4 Appraisal of the used methodology

Underpinning the development of the <u>data standards</u> and <u>QIs</u> is a common methodology that shares key features with this of the Clinical Practice Guidelines (<u>Figure 1</u>).[40] However, each of these processes has its unique specifications and development strategies that I described separately for <u>data standards</u>[184] and <u>QIs</u> (<u>PART II</u>).[506] In this section, I will discuss the common steps in these methodologies and explore alternative approaches that could have been adopted, with an illustration of the strengths and weaknesses for each approach.

Figure 1. Common methodological components of the development of QIs, data standards and Clinical Practice Guidelines
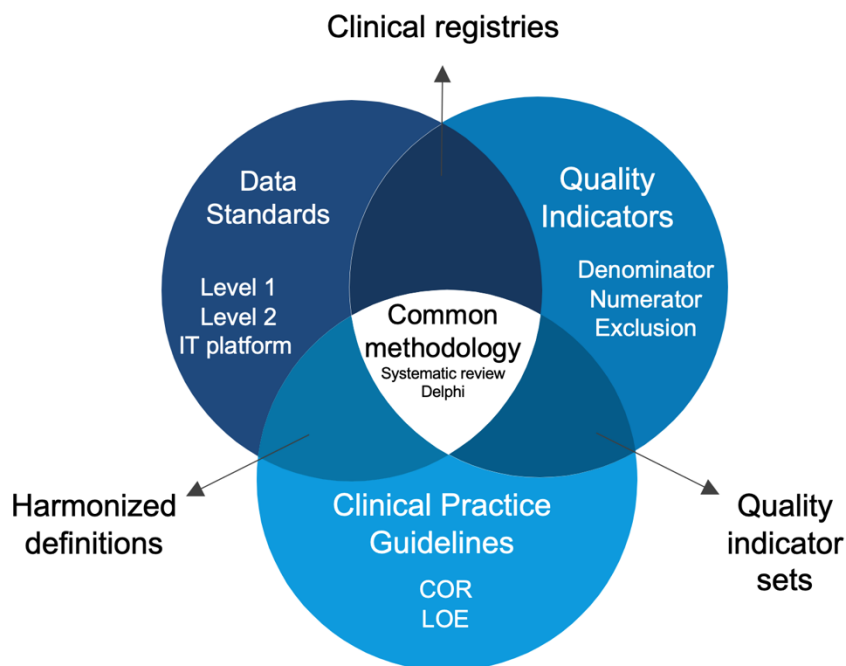
COR=class of recommendations, LOE=level of evidence, QI= quality indicators

14.4.1 Alternative methodologies

There are two major methods that have been adopted in the literature to develop data variables for the collection and measurement of the processes and outcomes of health care. First, the inductive approach which involves the derivation of data variables from the information that is available within a particular data source(s), such as a registry or EHR.[507, 508] This approach ensures the feasibility of the selected data variables, but not necessarily their alignment with contemporary knowledge. Besides, this approach may miss measuring key concepts of care delivery that are not captured in the data sources from which the data variables are derived.[509]

Second, the direct derivation of data variables from strong guideline recommendations, typically class of recommendations I and III. That is rephrasing these recommendations into specific measures of care quality with a defined target population, eligibility (denominator) and accomplishment (numerator) criteria. This approach is called the deductive approach and is by far the most commonly used method to develop data variables, particularly QIs in health care.[509] This method ensures the validity of the data variables given the strong evidence the underpins their selection, but lacks the capture of important aspects of care for which strong guideline recommendations are difficult to develop. For example, structural aspects of care (e.g. availability of certain services) and its outcomes (e.g. quality of life) may not be assigned a strong recommendations in Clinical Practice Guidelines.[509]

14.4.1.1 ACC/AHA methodology

In 2005, the ACC/AHA Task Force on Performance Measures published their methodology for the development of performance and quality measures for CVD,[163] and updated some key methodological aspects 5 years later.[421] The Task Force adopted the deductive approach and recommended conducting a literature review to guide the development of performance and quality measures. In addition, it combined available evidence with expert opinion and used a systematic method (Delphi approach) to obtain experts' opinion.[421] This methodology has been widely adopted for the development of performance and quality measures for CVD in the US.[162] However, its applicability in a healthcare system other than the North American one may be limited for a number of reasons.

First, the lack of an update to the ACC/AHA methodology to incorporate new approaches in data variable development. Second, whilst the methodology recommends the conduction of a literature review as part of the development process, it does not define the specifications of this review. Third, the tendency to promote the ACC/AHA Performance Measures as tools to guide pay-for-performance and re-imbursement initiatives may be associated with several unintended consequences as discussed in the next section.[185]

14.4.2 Linkage of performance measurement with payment

Linking QIs with payment incentives in pay-for-performance programs may leads healthcare centres to shift their focus towards improving the quality scores rather than improving the quality-of-care.[510, 511] Moreover, performance measurement may only identify the consequences, but not the underlying cause(s) of a certain gap in care delivery. This may result in the implementation of ineffective interventions that primarily aim to address the symptoms of a problem rather its actual roots and causes (e.g. change the coding strategy of certain condition).[512]

Another issue which may arise from linking performance measurement with payment incentives is that healthcare regulators often prioritise outcomes (e.g. mortality) as the main indicatory of care quality. However, these outcomes are substantially determined by factors other than the quality-of-care (e.g. baseline risk and comorbidities), even when risk-adjustment methods are applied.[447] As such, linking performance measurement with payment may result in 'cherry-picking' patients with the lowest perceived risk of unfavourable outcomes which my disadvantage patients with higher baseline risk who may be eligible, but not offered, particular processes of care.[513]

For instance, during the COVID-19 pandemic, the quality of AMI care in England did not worsen when measured against an internationally recognised set of QIs.[192] Yet, in-hospital

mortality rates from AMI during the pandemic were higher compared with the rates during the same period in previous years.[77] This increase has been attributed, at least partially, to the public reluctance to seek timely medical attention, particularly in the early stages of the pandemic resulting in late presentations with complications of AMI (e.g. cardiogenic shock) which are known to be associated with worse outcomes.[214]

14.4.3 Strengths of the adopted methodology

The methodology that I adopted for the development of QIs for CVD recommends the conduction of a systematic review of the literature using a recognised framework such as the preferred reporting items for systematic reviews and meta-analyses.[172, 183] In addition, the methodology discourages linking the quality assessment with payment incentives or reimbursement and proposes creating a comprehensive system for quality assurance and improvement to minimise the potential unintended consequences.

Another strength of the used methodology is the establishment of a framework and organisational structure for development of QIs for CVD. This framework serves as a centralised infrastructure for the various activities and provides a consistent methodological support to domain experts and Working Group members. As such, the development of data variables across different clinical areas is conducted according to the agreed standards and timelines.

In addition, the use of a comparative methodology for the development of data standards for CVD shows the consistency across the various component of this PhD studies and illustrates the feasibility of the process and its acceptance by the involved stakeholders. Besides, the adopted methodology outlines a far-reaching engagement of members with a wide variety of background and expertise, including domain experts, registry leaders and patients. Another strength of the used methodology is the representation of specialist Associations in the development process and the endorsement of professional societies.

14.4.4 Weaknesses of the adopted methodology

14.4.4.1 Limitations of systematic reviews

Despite the rigorousness of the methods by which systematic reviews are conducted, the reproducibility of the systematic reviews that are addressing the same research question may be limited due to substantial variations in the planning, design and/or undertaking of these reviews.[359] The variation within and between reviews may involve one or more of the following steps which form key parts of a systematic review: (1) conducting a comprehensive search of the literature using a pre-specified search strategy, (2) critically appraising the identified evidence, (3) synthesising data and (4) interpreting results.[359]

For the purpose of the development of data variables for CVD during this PhD studies, structured methods were used to review relevant literature. However, one may argue that the reproducibility and the consistency of the reviews undertaken during this PhD may be limited by a variation in the development of the search strategies, the appraisal of the retrieved studies and the methods by which the data were extracted and/or the subsequently knowledge was generated.

Whilst it is difficult to eliminate the subjectivity of the research team conducting any systematic review, two considerations may help minimise the impact of this subjectivity on the quality of the selected data variables during my PhD. First, the establishment of frameworks that were involved in different clinical areas (Data Science Group for EuroHeart and Quality Indicator Committee for QIs) ensured the standardisation of the process across these areas. Second, the collaboration with domain experts for each of the clinical domains during the early stages of the development process (i.e. designing the search strategy for the systematic review). This collaboration helped formulate the appropriate research question for the systematic reviews and construct clear inclusion and exclusion criteria for these reviews.

14.4.4.2 Limitations of censuses development

As discussed in Chapter 4, the Delphi method which is used to obtain expert opinion has limitations. Experts vote according to their interpretation of the available evidence which may vary between panellists. However, the establishment of criteria for voting helps guide the voting process and minimise interrater variability. In addition, the conduction of more than one voting round and the discussions amongst the Working Group members in-between these rounds allow appraising existing evidence and reaching consensus.

Another issue with the Delphi method is the selection of the panellists who participate in the voting process. One may argue that the composition of the developing group of a set of data variables determines the selection of the variables, but also the societies which endorse them. Similar concerns have been raised about the selection of the writing committees of the Clinical Practice Guidelines,[514] resulting in conflicts and disagreements between different societies.[515]

For the data variables that have developed during my PhD studies, a standardised criteria were followed to select the members of the Working Group for each of the clinical domains. The criteria involved a far-reaching engagement of pertinent stakeholders including experts with a wide variety of backgrounds, as well as representatives from professional Associations and patient groups. For the development of QIs, the process has been embedded with the writing of the Clinical Practice Guidelines to ensure alignment between the recommendations from the two processes.

14.5 Challenges of an international registry

The participation in a clinical registry entails an administrative and financial burden resulting from the efforts that are needed to collect, manage and transfer data.[19] In addition, substantial redundancy may arise from participating in different registries that capture intersecting conditions (PART I).[67] Whilst creating a unified infrastructure that encapsulates various CVD

registries (e.g. <u>EuroHeart</u>) help minimise the burden data collection and eliminate redundancy, it entails a number of challenges. Some of these challenges may be similar in other types of local or national registries, but other are specific to the all-encompassing nature of such an infrastructure. In the following section, I will explore some of these challenges, particularly those that are relevant to the aspects of <u>EuroHeart</u> initiative that I was involved in.

14.5.1 Funding

The design, implementation and management of registries require constant funding to maintain the sustainability of this registry. Unlike RCT where selected centres are provided with a logistical support to participate in the study, funding for clinical registries is less well defined and varies between different registries. In particular, registries that aim to enrol all-comers with a given condition to obtain real-world and generalisable data, have a constant need to identify and maintain sources for funding which may be challenging.[19]

In addition, the longer time that is needed to conduct registry activities compared with RCT, and the focus on quality assurance rather, increases the pressure on payers as well as on participating centres and limits the sustainability of this registry and. As such, funding sources for a given registry may change over time resulting in the need to re-evaluate the primary goal(s) of this registry which may lead to a need to modify the data collection process accordingly.[64]

The Get-with-The-Guidelines registries of the AHA use a public-private partnership in which a common aim is agreed between stakeholders. Here, the aim is to improve the quality of CVD care and thus hospitals pay to participate in the registry, and in return, the registry uses the submitted data to publish reports that are used for accountability and performance measurement. Such reports are of an interest to regulators with a responsibility to monitor the quality of care and benchmarking centres partnered with the AHA. The Association may in

turn support those centres financially in order to facilitate their participation in the Get-With-The-Guidelines programme.[64]

14.5.1.1 EuroHeart funding

The EuroHeart initiative has been funded primarily by the ESC during its pilot phase with educational grants from the industry and national heart foundations (PART I). However, the activities undertaken by the different groups within EuroHeart have been conducted independently of the sponsors. This has been important to ensure transparency in the key decisions which are related to the cardiovascular domains for which the data variables were developed, the methodology used and the compositions of the developing groups. More importantly, the final selection of the data variables for each clinical area has been solely performed by the domain experts involved in the development process with no interference from the ESC or the industry partners.

However, the long-term funding of EuroHeart and the specifications of the potential clinical trials which may be conducted using the EuroHeart platform need to be determined. It is recognised that industry sponsorship may result in a number of methodological biases.[516] That is, the research question of the trial, the methods by which this research question is addressed and the data presented in the final report of the trial.[516] As such, EuroHeart has established the RRCT group to regulate the partnership between EuroHeart and interested stakeholders to ensure high standards and transparency (PART I).

14.5.2 Information governance

Another challenge is the variation in the regulations that govern the collection, management and exchange of healthcare data within and between countries. For instance, this variation includes the legal requirement in some countries to obtain an informed consent from patients before enrolment in a clinical registry, which is not needed in the UK.[91] In addition, data

sharing between countries needs to be regulated according to the established criteria and guidelines that ensure data protection and confidentiality.

In 2016, the European Union (EU) updated their 1995 Data Protection Directive which regulates the transfer and processing of data within the EU. The Directive permits, with certain conditions, sharing personal data from a Member State to a third country or an international organisation for scientific or research purposes.[517] In this context, personal data were defined as any information that may result in the identification of an individual based on their name, unique number, geographical location or their physical, physiological, genetic, mental, economic, cultural or social factors.[517]

In the UK, a number of legislations exist to safeguard the use of healthcare data in medical research including the 2020 Caldicott Principles,[518] the 2018 Data Protection Act,[519] and the 2006 NHS Act.[520] These legislations aim to ensure that confidential data are collected, used and reported within the legal frameworks and in accordance with a clear, open and transparent process. As such, any international registry should have a defined data-sharing agreement that is designed by a dedicated legal team to ensure that all the activities undertaken using the registry platform are aligned with the existing regulations across all involves countries.

14.5.2.1 EuroHeart information governance

The flow of data between EuroHeart and participating countries is characterised by sharing aggregated data with the Data Science Centre. In 2004, Gliklich et al. described three layers of identification when exchanging healthcare data: fully identifiable data, limited dataset and de-identified data.[64] EuroHeart aims to collect fully identifiable data at the healthcare centre-level, but share de-identifiable data with the EuroHeart Data Science Centre in accordance with a predefined data-sharing agreement. The de-identification of the individual patient data is undertaken at the healthcare centre level, with support from local clinical and statistical

experts, while the EuroHeart Data Science Centre receives aggregated data that can be used to produce high level reports.

14.5.3 Data ownership

The ownership of the data entered into a registry and the intellectual property of the documents produced are critical considerations in the development of an international registry.[521] On a national-level, the sponsor of a registry may be the owner of its data and intellectual property, but on an international level, an agreement has to be made as to whether pooled data are owned by any stakeholder or an independent organisations.[521] For instance, in the UK, the data collected through NICOR are owned by the Secretary of State for Health, while the intellectual property of the registry outputs lays within the professional cardiac societies and the sponsor (HQIP).[521]

14.5.3.1 EuroHeart data ownership

The ownership of the data that are collected using the EuroHeart platform belongs to the country in which the data were collected. For instance, should the UK joins EuroHeart, the same arrangements that currently govern NICOR data would be applicable to the data collected using the EuroHeart platform. The intellectual property of any documents produced by EuroHeart will be determined for each document according to a clear and pre-defined publication plan that is agreed with all the stakeholders participating in the data collection, analysis and reporting process.

14.6 Role of clinical registries in the era of EHRs

Whilst the automatic extraction of healthcare data from EHRs to perform quality improvement projects and conduct clinical research may be the intuitive 'gold-standard' method for seamless utilisation of routinely collected data,[62, 63] EHRs have their own limitations. First, EHRs may not provide sufficient granular information to determine the

eligibility of a patient for enrolment in clinical study or quality improvement initiative.[19, 67] This limitation is because EHRs are primarily designed to serve an administrative role rather than a scientific or research purpose.[522]

Second, and despite their ability to capture endpoints of a trial with reasonable sensitivity and specificity,[104] EHRs may fall short in collecting reliable data relevant to patient characteristics and baseline comorbidities.[523] Such data may be of paramount importance in clinical studies and performance measurement given the crucial role of patient characteristics and baseline comorbidities in risk adjustment methods.[523] Inaccuracies in risk adjustment may lead to false conclusions about the effectiveness of a particular therapy or to unfair assessments of performance at different levels.[523]

Third, there are challenges in implementing structured (as opposed to free-text) data variables in routine EHRs.[524] Clinical registries tend to capture structured data to facilitate the analysis and the reporting of collected data. However, the multi-dimensional and complex nature of clinical care limits the opportunity to capture pre-defined data variables in routine daily practice in which healthcare professionals prefer submitting unstructured data into EHRs.

Fourth, the intellectual property of the data that are collected in EHRs may be ambiguous. As such, there is a need to establish a framework to safeguard the authorship attribution of the research projects that are undertaken using EHR data, as well as the integrity of the data and the legal (and/or ethical) framework under which the research is conducted.[525] Clinical registries as discussed in PART I have a designated Steering Committee and Working Groups that regulate the structural and technical aspects of the registry and ensure the attainment of the required approvals for all the activities conducted through the registry platform.[64]

14.7 Future direction

Whilst the overarching aim is to unify the computational nomenclature of healthcare data, this can only be achieved on the basis of harmonised <u>data standards</u>.[139, 526] Such standards enable databases to have common data models, and therefore, homogeneously understand the exchanged data at the level of medical concepts.[64] Translating these variables into a computational language provides a syntactic representation of information and thus allows <u>semantic interoperability</u>. That is, the seamless transfer of data between various settings including EHR, registries and clinical trials (Figure 2).[62, 526]

Figure 2. The layers of healthcare data standards and the pathway for harmonisation
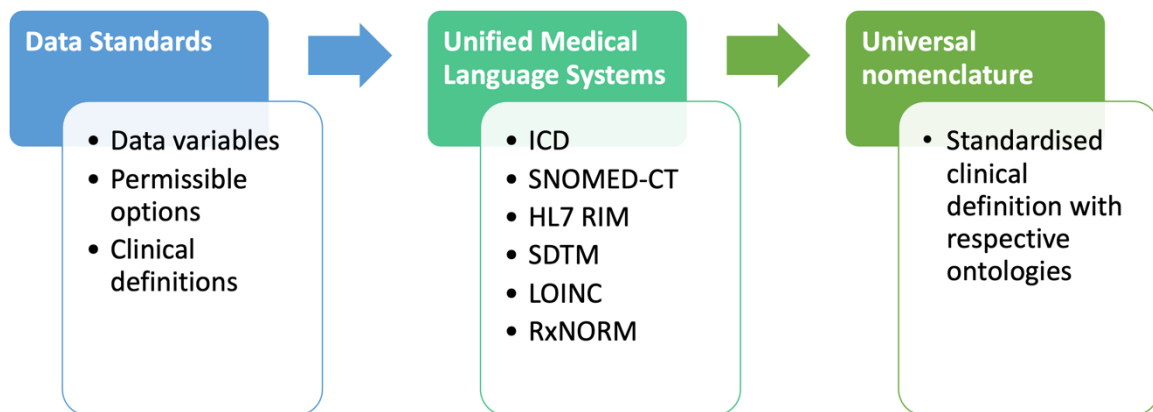
ACS= acute coronary syndrome, AF= atrial fibrillation, EHRs= electronic healthcare records, HF= heart failure, HL7= Health Level Seven International, ICD= International Classification of Diseases, LOINC= Logical Observation Identifiers Names and Codes, PCI= percutaneous coronary intervention, QIs= quality indicators, RCTs= randomised clinical trials, RIM= Reference Information Model, TAVI= transcatheter aortic valve implantation,

For instance, the data variable 'stable angina' may be defined clinically according to the specifications of the <u>Canadian Cardiovascular Society</u>. However, a number of computational phenotypes may be used to define this same 'stable angina' data variables using different unified medical language systems. For 'stable angina', that is *I20.9* using the International Classifications of Diseases (ICD) coding system and *194828000* using the SNOMED-CT (Figure 2).

Unified medical language systems differ from each other in several ways. First, the domain which encapsulates the data variables within this system. For instance, the logical observation identifiers names and codes (LOINC) provides standardised coding for medical laboratory tests, while systems like ICD and SNOMED-CT define clinical entities as shown in the example above.

Second, the granularity of the coding system and the extent to which it provides detailed categories and subcategories. For instance, LOINC allocates a unique code to a laboratory result name which is independent to, and share the same hierarchical level with, all other codes.[527] As such, laboratory tests that are performed at various locations may be aggregated regardless of the local assigned name for this test at different healthcare centres.[527]

On the other hand, some unified medical language systems, such as SNOMED CT and ICD, use hierarchical coding structure to identify disease subtypes which allows the identification of granular information about the concept of interest.[527] All different types of unified medical language systems aim to provide computational representation of a clinical (or biochemical) concepts to facilitate seamless data exchange between healthcare systems. This seamless data exchange is known as *interoperability* which has two different levels.

Semantic interoperability refers to the transfer not only of the computational phenotype of the exchanged data, but also the meaning of these data. The term process interoperability is sometimes used to describe semantic interoperability in which machine learning algorithms may be implemented to guide the decision making in determining eligibility for enrolment (e.g. in a registry or a trial) or for a care intervention (e.g. revascularisation).[505] Syntactic (or structural) interoperability on the other hand refers to the exchange of healthcare data at a raw-level. As such, receiving centres can access these data, but without being granted conceptual meaning of these data.[505]

In this thesis, I only focused on the development of the clinical definitions of data variables for a number of CVD conditions and interventions without specifying the respective ontologies. Such an endeavour may be conducted as a separate follow-on effort using the same methodology used for the development of <u>data standards</u>.

Chapter 15. Conclusion

This PhD has established a framework for the development and adoption of standardised <u>data standards</u> and <u>QIs</u> for CVD. The success of this PhD is evident not only by the ability to publish the accomplished work in peer-reviewed journals, but also in the role these accomplishments played in improving patient care. The developed registries for various cardiovascular domains are being used to collect real-world patient data in a number of European countries. Some of these countries had no established cardiovascular registries which is a major development towards monitoring the quality-of-care of CVD and capturing its outcomes. In addition, the developed QIs have been used to evaluate the quality of AMI care in England and Wales and endorsed by regulatory bodies, such as NICE in the UK. Thus, these QIs have already illustrated an integration with CVD care and a potential role in driving quality improvement and addressing the unwanted variations.

All in all, I have presented in this thesis a system that utilises routinely collected data to improve patient care through the structured collection, analysis and interpretation of the patterns of medical practice. As discussed in Chapter 14, EHRs provide a wealth of healthcare data that may play a major role in the assessment of care quality and the conduction of clinical research. However, clinical registries remain an essential component of the quality improvement circle given the fact that clinical registries are usually designed to address a particular clinical question. Besides, clinical registries provide a level of granularity that EHRs may not be able to capture.

Furthermore, the disintegration between clinical registries and QIs creates an unnecessary need for segregated efforts increasing the burden of data collection.[19] This thesis provides a means to harmonise QIs with quality registries such that routinely collected data through registries provide detailed variables that are tailored towards both addressing the clinical question for the registry, but also assessing care quality and allow risk adjustments.[421] Such an endeavour is only feasible when clinical registries are designed in parallel with the development of QIs given each indicator of care quality has unique eligibility and exclusion criteria.[506]

Whilst the methodology I developed and used to select QIs is based on conducting systematic reviews of the literature to identify key aspects of care delivery, these QIs may share the same limitations of the evidence they were derived from. For instance, it is recognised that certain subgroup of patients may be under-represented in the majority of the clinical trials which may be used to developed QIs.[61] Yet, these QIs are applied to evaluate the quality-of-care for different patient groups regardless of their representation in the available evidence. As such, it is of a paramount importance to use clinical acumen and clinical context when adopting QIs and interpreting their results.

Another limitation of the methodologies that I adopted to develop QIs and data standards for CVD involves the characteristic of the systematic review of the literature. Whilst some of these limitations may be inherent to the nature of systematic reviews,[528] others are specific to the specifications of the systematic reviews that aim to develop QIs and/or data standards. For the latter, broad spectrum of relevant aspects of care necessitates the use of multiple terms whist developing the search strategies for the systematic reviews resulting in a high number of retrieved articles. Thus, these terms were combined with others relevant to the standardisation of cardiovascular data standards or QIs to narrow the search down to a manageable and feasible level.

The accomplishments of this PhD studies were made possible by the successes of the existing national registries such as those in the UK and Sweden which proofed the concept of clinical registries as platforms for quality improvement, research and post-marketing surveillance of new technologies. In addition, this PhD form the basis for a fully interoperable healthcare system in CVD. A system in which data are collected, transferred and analysed efficiently and cost-effectively. A system in which quality improvement is an integrated element of routine healthcare delivery rather than a separate enterprise with its own cost and resources.

It is important, however, to align international registries, such as EuroHeart with existing or new national registries in order to avoid duplicating the burden of data collection. In my PhD studies, I have therefore emphasised on the importance of harmonising the definitions of the data variables such that data may be transferred between different systems without the need to submit disconnected CRFs to various databases. By harmonising the data standards for CVD, comparative analyses can be conducted across regions and over time allowing for the continuous monitoring of the quality-of-care using unified definitions.

Another fundamental issue is the need to evaluate and update QIs in line with the changes in knowledge. Quality assessment and improvement is a continuous endeavour which cannot be achieved by the exclusive development of a valid and feasible system for data collection, analysis and reporting. This system needs to be constantly evaluated to ensure that it captures relevant information to address the question for which the data are being collected. In addition, the results of the quality assessment need to be evaluated on regular basis to determine the validity of these results and, thus, guide the interpretation of the findings.

Concerns have been raised recently about the validity of performance measurement activities and whether they actually measure or improve quality.[529] Quality assessment depends on the availability of coding resources and efforts are needed to ensure that the quality of care delivery rather than the quality of coding is being measured. Besides, the cost and effort involved in quality measurement need to be justified by identifying a correlation between such measures and an improvement in outcomes. For instance, setting standards for minimum surgical volume for congenital heart disease was associated with a reduction in perioperative mortality.[530] In addition, on a regional level in the UK, the introduction of QIs has been shown to improve outcomes[531] and their withdrawal to negatively influence quality of care.[532]

Another concern is the use of outcome measures (e.g. mortality after acute myocardial infarction) as a reflection of care quality which may be misleading. Outcomes are determined by the severity of the disease, the baseline risk of the patients, as well as their pre-hospital and post-discharge care. Therefore, the evaluation of quality-of-care solely from outcome measures may discourage individual clinicians or centres to offer high-risk patients treatment interventions when indicated. Whilst risk-adjustment models exist, they largely lack sufficient granularity to distinguish suboptimal from appropriate care.[529]

In this thesis, I have identified and addressed potential unintended consequences to QIs through key methodological steps.[510] I acknowledge that there remain important components of the care delivery pathway that may not be readily measurable and that those measured components may not be directly capturing the quality of health care.[533] However, I established a framework that adopts its own 'learn-adapt' cycle and adjusts the QIs according

to continuous feedback and evaluation.[533] Therefore, the developed systems during this PhD studies need to be updated to accommodate changes in evidence and data collection methods.

References for Part I & Part III:

1.   Roth GAea. Global, regional, and national age-sex-specific mortality for 282 causes of death in 195 countries and territories, 1980–2017: a systematic analysis for the Global Burden of Disease Study 2017. *The Lancet*. 2018;392:1736-1788.
2.   Timmis A, Townsend N, Gale CP, Torbica A, Lettino M, Petersen SE, Mossialos EA, Maggioni AP, Kazakiewicz D, May HT, De Smedt D, Flather M, Zuhlke L, Beltrame JF, Huculeci R, Tavazzi L, Hindricks G, Bax J, Casadei B, Achenbach S, Wright L and Vardas P. European Society of Cardiology: Cardiovascular Disease Statistics 2019. *European heart journal*. 2020;41:12-85.
3.   Timmis A, Townsend N, Gale C, Grobbee R, Maniadakis N, Flather M, Wilkins E, Wright L, Vos R, Bax J, Blum M, Pinto F and Vardas P. European Society of Cardiology: Cardiovascular Disease Statistics 2017. *European heart journal*. 2018;39:508-579.
4.   Townsend N, Wilson L, Bhatnagar P, Wickramasinghe K, Rayner M and Nichols M. Cardiovascular disease in Europe: epidemiological update 2016. *Eur Heart J*. 2016;37:3232-3245.
5.   Eurostat. HEDIC: Health Expenditures by Diseases and Conditions. 2016. Avaliable at: https://ec.europa.eu/eurostat/documents/3888793/7605571/KS-TC-16-008-EN-N.pdf/6cb33aa4-2e65-4df7-9b2b-1ff171eb1fba. Accessed 27 December 2021. .
6.   Health matters: preventing cardiovascular disease—GOV.UK. Available at: https://www.gov.uk/government/publications/health-matters-preventing-cardiovascular-disease/health-matters-preventing-cardiovascular-disease. Accessed 27 December 2021. .
7.   Tuppin P, Rivière S, Rigault A, Tala S, Drouin J, Pestel L, Denis P, Gastaldi-Ménager C, Gissot C, Juillière Y and Fagot-Campagna A. Prevalence and economic burden of cardiovascular diseases in France in 2013 according to the national health insurance scheme database. *Arch Cardiovasc Dis*. 2016;109:399-411.
8.   Centre for Economics and Business Research. The economic cost of cardiovascular disease from 2014 2020 in six European economies; 2014. Available at: https://www.cebr.com/wp-content/uploads/2015/08/Short-Report-18.08.14.pdf. Accessed 27 December 2021.
9.   Birger M, Kaldjian AS, Roth GA, Moran AE, Dieleman JL and Bellows BK. Spending on Cardiovascular Disease and Cardiovascular Risk Factors in the United States: 1996 to 2016. *Circulation*. 2021;144:271-282.
10.   World Heart Federation: Champion Advocates Programme. The costs of CVD. Available at: http://www.championadvocates.org/en/champion-advocates-programme/thecosts-

of-CVD. Accessed 27 December 2021.

11.   Szummer K, Wallentin L, Lindhagen L, Alfredsson J, Erlinge D, Held C, James S, Kellerth T, Lindahl B, Ravn-Fischer A, Rydberg E, Yndigegn T and Jernberg T. Relations between implementation of new treatments and improved outcomes in patients with non-ST-elevation myocardial infarction during the last 20 years: Experiences from SWEDEHEART registry 1995 to 2014. *European Heart Journal*. 2018;39:3766-3776.

12.   Dondo TB, Hall M, Timmis AD, Gilthorpe MS, Alabas OA, Batin PD, Deanfield JE, Hemingway H and Gale CP. Excess mortality and guideline-indicated care following non-ST-elevation myocardial infarction. *Eur Heart J Acute Cardiovasc Care*. 2017;6:412-420.

13.   Bebb O, Hall M, Fox KAA, Dondo TB, Timmis A, Bueno H, Schiele F and Gale CP. Performance of hospitals according to the ESC ACCA quality indicators and 30-day mortality for acute myocardial infarction: national cohort study using the United Kingdom Myocardial Ischaemia National Audit Project (MINAP) register. *European Heart Journal*. 2017;38:974-982.

14.   Wilkinson C, Bebb O, Dondo TB, Munyombwe T, Casadei B, Clarke S, Schiele F, Timmis A, Hall M and Gale CP. Sex differences in quality indicator attainment for myocardial infarction: a nationwide cohort study. *Heart*. 2019;105:516-523.

15.   Hall M, Bebb OJ, Dondo TB, Yan AT, Goodman SG, Bueno H, Chew DP, Brieger D, Batin PD, Farkouh ME, Hemingway H, Timmis A, Fox KAA and Gale CP. Guideline-indicated treatments and diagnostics, GRACE risk score, and survival for non-ST elevation myocardial infarction. *European Heart Journal*. 2018;39:3798-3806.

16.   Zusman O, Bebb O, Hall M, Dondo TB, Timmis A, Schiele F, Fox KA, Kornowski R, Gale CP and Iakobishvili Z. International comparison of acute myocardial infarction care and outcomes using quality indicators. *Heart*. 2019;105:820-825.

17.   Greene SJ, Butler J, Albert NM, DeVore AD, Sharma PP, Duffy CI, Hill CL, McCague K, Mi X, Patterson JH, Spertus JA, Thomas L, Williams FB, Hernandez AF and Fonarow GC. Medical Therapy for Heart Failure With Reduced Ejection Fraction: The CHAMP-HF Registry. *J Am Coll Cardiol*. 2018;72:351-366.

18.   Vaduganathan M, Fonarow GC, Greene SJ, DeVore AD, Kavati A, Sikirica S, Albert NM, Duffy CI, Hill CL, Patterson JH, Spertus JA, Thomas LE, Williams FB, Hernandez AF and Butler J. Contemporary Treatment Patterns and Clinical Outcomes of Comorbid Diabetes Mellitus and HFrEF: The CHAMP-HF Registry. *JACC: Heart Failure*. 2020;8:469-480.

19.   Bhatt DL, Drozda JP, Shahian DM, Chan PS, Fonarow GC, Heidenreich PA, Jacobs JP, Masoudi FA, Peterson ED and Welke KF. ACC/AHA/STS Statement on the Future of Registries and the Performance Measurement Enterprise. *Journal of the American College of Cardiology*. 2015;66:2230-2245.

20.   Minchin M, Roland M, Richardson J, Rowark S and Guthrie B. Quality of Care in the United Kingdom after Removal of Financial Incentives. *N Engl J Med*. 2018;379:948-957.

21.   Song Z, Ji Y, Safran DG and Chernew ME. Health Care Spending, Utilization, and Quality 8 Years into Global Payment. *New England Journal of Medicine*. 2019;381:252-263.

22.   MacLean CH, Kerr EA and Qaseem A. Time Out — Charting a Path for Improving Performance Measurement. *New England Journal of Medicine*. 2018;378:1757-1761.

23.   NICE indicator process guide. December 2019. *Available at:* *https://wwwniceorguk/media/default/Get-involved/Meetings-In-Public/indicator-advisory-committee/ioc-process-guidepdf Accessed 24 March 2020*. 2019:26.

24.   Berwick DM. Era 3 for Medicine and Health Care. *JAMA*. 2016;315:1329-1330.

25.   Townsend N, Kazakiewicz D, Lucy Wright F, Timmis A, Huculeci R, Torbica A, Gale CP, Achenbach S, Weidinger F and Vardas P. Epidemiology of cardiovascular disease in Europe. *Nat Rev Cardiol*. 2021.

26.   Kahn M, Grayson AD, Chaggar PS, Ng Kam Chuen MJ, Scott A, Hughes C and Campbell NG. Primary care heart failure service identifies a missed cohort of heart failure patients with reduced ejection fraction. *European Heart Journal*. 2021.

27.   Barbato E, Dudek D, Baumbach A, Windecker S and Haude M. EAPCI registries: A first step towards systematic monitoring of European interventional cardiology practice. *EuroIntervention*. 2017;13:Z6-Z7.

28.   Sir David Cooksey. A review of UK health research funding. HM Treasury report, 2006. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/228984/0118404881.pdf. Accessed 29 June 2021.

29.   McGlynn EA, Asch SM, Adams J, Keesey J, Hicks J, DeCristofaro A and Kerr EA. The quality of health care delivered to adults in the United States. *N Engl J Med*. 2003;348:2635-45.

30.   Sarkies MN, Jones LK, Gidding SS and Watts GF. Improving clinical practice guidelines with implementation science. *Nature Reviews Cardiology*. 2021.

31.   McGlynn EA. Improving the Quality of U.S. Health Care — What Will It Take? *New England Journal of Medicine*. 2020;383:801-803.

32.   Visseren FLJ, Mach F, Smulders YM, Carballo D, Koskinas KC, Bäck M, Benetos A, Biffi A, Boavida J-M, Capodanno D, Cosyns B, Crawford C, Davos CH, Desormais I, Di Angelantonio E, Franco OH, Halvorsen S, Hobbs FDR, Hollander M, Jankowska EA, Michal M, Sacco S, Sattar N, Tokgozoglu L, Tonstad S, Tsioufis KP, van Dis I, van Gelder IC, Wanner C, Williams B and Group ESD. 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice: Developed by the Task Force for cardiovascular disease prevention in clinical practice with representatives of the European Society of Cardiology and 12 medical societies With the special contribution of the European Association of Preventive Cardiology (EAPC). *European Heart Journal*. 2021.

33.   McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, Burri H, Butler J, Čelutkienė J, Chioncel O, Cleland JGF, Coats AJS, Crespo-Leiro MG, Farmakis D, Gilard M, Heymans S, Hoes AW, Jaarsma T, Jankowska EA, Lainscak M, Lam CSP, Lyon AR, McMurray JJV, Mebazaa A, Mindham R, Muneretto C, Francesco Piepoli M, Price S, Rosano GMC, Ruschitzka F, Kathrine Skibelund A and Group ESD. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: Developed by the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) With the special contribution of the Heart Failure Association (HFA) of the ESC. *European Heart Journal*. 2021.

34.   Glikson M, Nielsen JC, Kronborg MB, Michowitz Y, Auricchio A, Barbash IM, Barrabés JA, Boriani G, Braunschweig F, Brignole M, Burri H, Coats AJS, Deharo J-C, Delgado V, Diller G-P, Israel CW, Keren A, Knops RE, Kotecha D, Leclercq C, Merkely B, Starck C, Thylén I, Tolosana JM and Group ESD. 2021 ESC Guidelines on cardiac pacing and cardiac resynchronization therapy: Developed by the Task Force on cardiac pacing and cardiac resynchronization therapy of the European Society of Cardiology (ESC) With the special contribution of the European Heart Rhythm Association (EHRA). *European Heart Journal*. 2021.

35.   Collet JP, Thiele H, Barbato E, Barthélémy O, Bauersachs J, Bhatt DL, Dendale P, Dorobantu M, Edvardsen T, Folliguet T, Gale CP, Gilard M, Jobs A, Jüni P, Lambrinou E, Lewis BS, Mehilli J, Meliga E, Merkely B, Mueller C, Roffi M, Rutten FH, Sibbing D and Siontis GCM. 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. *Eur Heart J*. 2020.

36.   Institute of Medicine 2013. Best Care at Lower Cost: The Path to Continuously Learning Health Care in America. Washington, DC: The National Academies Press. https://doi.org/10.17226/13444.

37.   Molas-Gallart J, D'Este P, Llopis O and Rafols I. Towards an alternative framework for the evaluation of translational research initiatives. *Research Evaluation*. 2015;25:235-243.

38.   Jia Y, Wen J, Qureshi R, Ehrhardt S, Celentano DD, Wei X, Rosman L, Wen Y and Robinson KA. Effect of redundant clinical trials from mainland China evaluating statins in patients with coronary artery disease: cross sectional study. *BMJ*. 2021;372:n48.

39.   Mason PJ, Shah B, Tamis-Holland JE, Bittl JA, Cohen MG, Safirstein J, Drachman DE, Valle JA, Rhodes D and Gilchrist IC. An Update on Radial Artery Access and Best Practices for Transradial Coronary Angiography and Intervention in Acute Coronary Syndrome: A Scientific Statement From the American Heart Association. *Circulation: Cardiovascular Interventions*. 2018;11:e000035.

40.   ACCF/AHA Task Force on Practice Guidelines Methodology Manual and Policies From the ACCF/AHA Task Force on Practice Guidelines. Available at: http://my.americanheart.org/idc/groups/ahamah-public/@wcm/@sop/documents/downloadable/ucm_319826.pdf. Accessed 25 March 2020.

41.   Schüpke S, Neumann FJ, Menichelli M, Mayer K, Bernlochner I, Wöhrle J, Richardt G, Liebetrau C, Witzenbichler B, Antoniucci D, Akin I, Bott-Flügel L, Fischer M, Landmesser U, Katus HA, Sibbing D, Seyfarth M, Janisch M, Boncompagni D, Hilz R, Rottbauer W, Okrojek R, Möllmann H, Hochholzer W, Migliorini A, Cassese S, Mollo P, Xhepa E, Kufner S, Strehle A, Leggewie S, Allali A, Ndrepepa G, Schühlen H, Angiolillo DJ, Hamm CW, Hapfelmeier A, Tölg R, Trenk D, Schunkert H, Laugwitz KL and Kastrati A. Ticagrelor or Prasugrel in Patients with Acute Coronary Syndromes. *N Engl J Med*. 2019;381:1524-1534.

42.   Venetsanos D, Träff E, Erlinge D, Hagström E, Nilsson J, Desta L, Lindahl B, Mellbin L, Omerovic E, Szummer KE, Zwackman S, Jernberg T and Alfredsson J. Prasugrel versus ticagrelor in patients with myocardial infarction undergoing percutaneous coronary intervention. *Heart*. 2021;107:1145-1151.

43.   Debating ISAR-REACT 5: Ticagrelor vs Prasugrel in ACS. Available at: https://www.medscape.com/viewarticle/917980. Accessed 28 December 2021. .

44.   Califf RM, Peterson ED, Gibbons RJ, Garson A, Brindis RG, Beller GA and Smith SC. Integrating quality into the cycle of therapeutic development. *Journal of the American College of Cardiology*. 2002;40:1895-1901.

45.   Wallentin L, Gale CP, Maggioni A, Bardinet I and Casadei B. EuroHeart: European Unified Registries On Heart Care Evaluation and Randomized Trials. *European Heart Journal*. 2019;40:2745-2749.

46.   Morris ZS, Wooding S and Grant J. The answer is 17 years, what is the question: understanding time lags in translational research. *Journal of the Royal Society of Medicine*. 2011;104:510-520.

47.   Reith C, Landray M and Califf RM. Randomized clinical trials--removing obstacles. *N Engl J Med*. 2013;369:2269.

48.	Fanaroff AC, Califf RM and Lopes RD. New Approaches to Conducting Randomized Controlled Trials. *J Am Coll Cardiol*. 2020;75:556-559.

49.	Chen E, Sapirstein W, Ahn C, Swain J and Zuckerman B. FDA perspective on clinical trial design for cardiovascular devices. *Ann Thorac Surg*. 2006;82:773-5.

50.	Szymanski P, Leggeri I, Kautzner J and Fraser AG. The new European regulatory framework for medical devices: opportunities for engagement by electrophysiologists. *Europace*. 2018;20:902-905.

51.	Strengthening our national system for medical device postmarket surveillance. Center For Devices and Radiological Health U.S. Food And Drug Adminstration. April 2013. Update and Next Steps. Available at: https://www.fda.gov/files/about%20fda/published/Strengthening-Our-National-System-for-Medical-Device-Postmarket-Surveillance.pdf. Accessed 15 November 2021.

52.	Fraser AG, Byrne RA, Kautzner J, Butchart EG, Szymański P, Leggeri I, de Boer RA, Caiani EG, Van de Werf F, Vardas PE and Badimon L. Implementing the new European Regulations on medical devices-clinical responsibilities for evidence-based practice: a report from the Regulatory Affairs Committee of the European Society of Cardiology. *Eur Heart J*. 2020;41:2589-2596.

53.	Garg P, Kastrati A and Mauri L. Clinical trial design. The PCR - EAPCI Textbook of percutaneous interventional cardiovascular medicine. Available at: https://www.pcronline.com/eurointervention/textbook/pcr-textbook/chapter/?chapter_id=150. Accessed on 19 November 2021. 2017.

54.	Windecker S. ESC Committee for Practice Guidelines: providing knowledge to everyday clinical practice. *Cardiovascular Research*. 2020;116:e146-e148.

55.	McMurray JJV. Only Trials Tell the Truth About Treatment Effects. *J Am Coll Cardiol*. 2018;71:2640-2642.

56.	Hennekens CH, Buring JE and Hebert PR. Implications of overviews of randomized trials. *Statistics in Medicine*. 1987;6:397-402.

57.	Bowman L, Baras A, Bombien R, Califf RM, Chen Z, Gale CP, Gaziano JM, Grobbee DE, Maggioni AP, Muse ED, Roden DM, Schroeder S, Wallentin L and Casadei B. Understanding the use of observational and randomized data in cardiovascular medicine. *European heart journal*. 2020;41:2571-2578.

58.	Bothwell LE, Greene JA, Podolsky SH and Jones DS. Assessing the Gold Standard — Lessons from the History of RCTs. *New England Journal of Medicine*. 2016;374:2175-2181.

59.	Ford I and Norrie J. Pragmatic Trials. *New England Journal of Medicine*. 2016;375:454-463.

60.	Fanaroff AC, Vora AN, Chen AY, Mathews R, Udell JA, Roe MT, Thomas LE and Wang TY. Hospital participation in clinical trials for patients with acute myocardial infarction: Results from the National Cardiovascular Data Registry. *Am Heart J*. 2019;214:184-193.

61.	Striving for Diversity in Research Studies. *New England Journal of Medicine*. 2021;385:1429-1430.

62.	Fitzpatrick T, Perrier L, Shakik S, Cairncross Z, Tricco AC, Lix L, Zwarenstein M, Rosella L and Henry D. Assessment of Long-term Follow-up of Randomized Trial Participants by Linkage to Routinely Collected Data: A Scoping Review and Analysis. *JAMA Network Open*. 2018;1:e186019-e186019.

63.	Shah ASV, Anand A, Strachan FE, Ferry AV, Lee KK, Chapman AR, Sandeman D, Stables CL, Adamson PD, Andrews JPM, Anwar MS, Hung J, Moss AJ, O'Brien R, Berry C, Findlay I, Walker S, Cruickshank A, Reid A, Gray A, Collinson PO, Apple FS, McAllister DA,

Maguire D, Fox KAA, Newby DE, Tuck C, Harkess R, Parker RA, Keerie C, Weir CJ, Mills NL, Marshall L, Stewart SD, Fujisawa T, Vallejos CA, Tsanas A, Hautvast M, McPherson J, McKinlay L, Malo J, Fischbacher CM, Croal BL, Leslie SJ, Walker A, Wackett T, Armstrong R, Stirling L, MacDonald C, Sadat I, Finlay F, Charles H, Linksted P, Young S, Alexander B and Duncan C. High-sensitivity troponin in the evaluation of patients with suspected acute coronary syndrome: a stepped-wedge, cluster-randomised controlled trial. *The Lancet*. 2018;392:919-928.

64.   Gliklich R, Dreyer N, Leavy M, eds. Registries for Evaluating Patient Outcomes: A User's Guide. Third edition. Two volumes. (Prepared by the Outcome DEcIDE Center [Outcome Sciences, Inc., a Quintiles company] under Contract No. 290 2005 00351 TO7.) AHRQ Publication No. 13(14)-EHC111. Rockville, MD: Agency for Healthcare Research and Quality. April 2014. http://www.effectivehealthcare.ahrq.gov/ registries-guide-3.cfm.

65.   Bufalino VJ, Masoudi FA, Stranne SK, Horton K, Albert NM, Beam C, Bonow RO, Davenport RL, Girgus M, Fonarow GC, Krumholz HM, Legnini MW, Lewis WR, Nichol G, Peterson ED, Rosamond W, Rumsfeld JS, Schwamm LH, Shahian DM, Spertus JA, Woodard PK and Yancy CW. The American Heart Association's Recommendations for Expanding the Applications of Existing and Future Clinical Registries. *Circulation*. 2011;123:2167-2179.

66.   Rashid M, Ludman PF and Mamas MA. British Cardiovascular Intervention Society registry framework: a quality improvement initiative on behalf of the National Institute of Cardiovascular Outcomes Research (NICOR). *European heart journal Quality of care & clinical outcomes*. 2019;5:292-297.

67.   Meltzer SN and Weintraub WS. The Role of National Registries in Improving Quality of Care and Outcomes for Cardiovascular Disease. *Methodist Debakey Cardiovasc J*. 2020;16:205-211.

68.   Coronary artery surgery study (CASS): a randomized trial of coronary artery bypass surgery. Comparability of entry characteristics and survival in randomized patients and nonrandomized patients meeting randomization criteria. *J Am Coll Cardiol*. 1984;3:114-28.

69.   Velazquez EJ, Francis GS, Armstrong PW, Aylward PE, Diaz R, O'Connor CM, White HD, Henis M, Rittenhouse LM, Kilaru R, van Gilst W, Ertl G, Maggioni AP, Spac J, Weaver WD, Rouleau JL, McMurray JJ, Pfeffer MA and Califf RM. An international perspective on heart failure and left ventricular systolic dysfunction complicating myocardial infarction: the VALIANT registry. *Eur Heart J*. 2004;25:1911-9.

70.   Venkitachalam L, Kip KE, Selzer F, Wilensky RL, Slater J, Mulukutla SR, Marroquin OC, Block PC, Williams DO and Kelsey SF. Twenty-year evolution of percutaneous coronary intervention and its impact on clinical outcomes: a report from the National Heart, Lung, and Blood Institute-sponsored, multicenter 1985-1986 PTCA and 1997-2006 Dynamic Registries. *Circ Cardiovasc Interv*. 2009;2:6-13.

71.   Ludman PF. British Cardiovascular Intervention Society Registry for audit and quality assessment of percutaneous coronary interventions in the United Kingdom. *Heart*. 2011;97:1293-1297.

72.   Vogel RA. HCFA's Cooperative Cardiovascular Project: a nationwide quality assessment of acute myocardial infarction. *Clin Cardiol*. 1994;17:354-6.

73.   Seferović PM, Vardas P, Jankowska EA, Maggioni AP, Timmis A, Milinković I, Polovina M, Gale CP, Lund LH, Lopatin Y, Lainscak M, Savarese G, Huculeci R, Kazakiewicz D, Coats AJS and countries icwtNHFSotEm. The Heart Failure Association Atlas: Heart Failure Epidemiology and Management Statistics 2019. *European Journal of Heart Failure*. n/a.

74.   Peterson ED, Roe MT, Chen AY, Fonarow GC, Lytle BL, Cannon CP and Rumsfeld JS. The NCDR ACTION Registry - GWTG: Transforming contemporary acute myocardial infarction clinical care. *Heart*. 2010;96:1798-1802.

75.   Resnic FS, Majithia A, Marinac-Dabic D, Robbins S, Ssemaganda H, Hewitt K, Ponirakis A, Loyo-Berrios N, Moussa I, Drozda J, Normand S-L and Matheny ME. Registry-Based Prospective, Active Surveillance of Medical-Device Safety. *New England Journal of Medicine*. 2017;376:526-535.

76.   Mafham MM, Spata E, Goldacre R, Gair D, Curnow P, Bray M, Hollings S, Roebuck C, Gale CP, Mamas MA, Deanfield JE, de Belder MA, Luescher TF, Denwood T, Landray MJ, Emberson JR, Collins R, Morris EJA, Casadei B and Baigent C. COVID-19 pandemic and admission rates for and management of acute coronary syndromes in England. *The Lancet*. 2020;396:381-389.

77.   Wu J, Mamas M, Rashid M, Weston C, Hains J, Luescher T, de Belder MA, Deanfield JE and Gale CP. Patient response, treatments, and mortality for acute myocardial infarction during the COVID-19 pandemic. *Eur Heart J Qual Care Clin Outcomes*. 2020.

78.   Douwes JM, Humpl T, Bonnet D, Beghetti M, Ivy DD and Berger RMF. Acute Vasodilator Response in Pediatric Pulmonary Arterial Hypertension. *Journal of the American College of Cardiology*. 2016;67:1312-1323.

79.   Dondo TB, Hall M, West RM, Jernberg T, Lindahl B, Bueno H, Danchin N, Deanfield JE, Hemingway H, Fox KAA, Timmis AD and Gale CP. β-Blockers and Mortality After Acute Myocardial Infarction in Patients Without Heart Failure or Ventricular Dysfunction. *Journal of the American College of Cardiology*. 2017;69:2710-2720.

80.   Simpson J, Benson L, Jhund PS, Dahlström U, McMurray JJV and Lund LH. "Real World" Eligibility for Sacubitril/Valsartan in Unselected Heart Failure Patients: Data from the Swedish Heart Failure Registry. *Cardiovascular drugs and therapy*. 2019;33:315-322.

81.   Yndigegn T, Hofmann R, Jernberg T and Gale CP. Registry-based randomised clinical trial: efficient evaluation of generic pharmacotherapies in the contemporary era. *Heart*. 2018;104:1562-1567.

82.   Hripcsak G, Duke JD, Shah NH, Reich CG, Huser V, Schuemie MJ, Suchard MA, Park RW, Wong IC, Rijnbeek PR, van der Lei J, Pratt N, Norén GN, Li YC, Stang PE, Madigan D and Ryan PB. Observational Health Data Sciences and Informatics (OHDSI): Opportunities for Observational Researchers. *Stud Health Technol Inform*. 2015;216:574-8.

83.   James S, Rao SV and Granger CB. Registry-based randomized clinical trials--a new clinical trial paradigm. *Nature Reviews Cardiology*. 2015;12:312+.

84.   Götberg M, Christiansen EH, Gudmundsdottir IJ, Sandhall L, Danielewicz M, Jakobsen L, Olsson S-E, Öhagen P, Olsson H, Omerovic E, Calais F, Lindroos P, Maeng M, Tödt T, Venetsanos D, James SK, Kåregren A, Nilsson M, Carlsson J, Hauer D, Jensen J, Karlsson A-C, Panayi G, Erlinge D and Fröbert O. Instantaneous Wave-free Ratio versus Fractional Flow Reserve to Guide PCI. *New England Journal of Medicine*. 2017;376:1813-1823.

85.   Buccheri S, Sarno G, Frobert O, Gudnason T, Lagerqvist B, Lindholm D, Maeng M, Olivecrona G and James S. Assessing the Nationwide Impact of a Registry-Based Randomized Clinical Trial on Cardiovascular Practice. *Circulation Cardiovascular interventions*. 2019;12:e007381.

86.   Ibanez B, James S, Agewall S, Antunes MJ, Bucciarelli-Ducci C, Bueno H, Caforio ALP, Crea F, Goudevenos JA, Halvorsen S, Hindricks G, Kastrati A, Lenzen MJ, Prescott E, Roffi M, Valgimigli M, Varenhorst C, Vranckx P, Widimský P and Group ESCSD. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment

elevation: The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). *European Heart Journal*. 2017;39:119-177.

87.   Dawson LP, Biswas S, Lefkovits J, Stub D, Burchill L, Evans SM, Reid C and Eccleston D. Characteristics and Quality of National Cardiac Registries: A Systematic Review. *Circ Cardiovasc Qual Outcomes*. 2021;14:e007963.

88.   Md Emdadul Hoque D, Ruseckaite R, Lorgelly P, McNeil JJ and Evans SM. Cross-sectional study of characteristics of clinical registries in Australia: a resource for clinicians and policy makers. *Int J Qual Health Care*. 2018;30:192-199.

89.   !!! INVALID CITATION !!! 11, 13, 89.

90.   Gale CP, Weston C, Denaxas S, Cunningham D, de Belder MA, Gray HH, Boyle R and Deanfield JE. Engaging with the clinical data transparency initiative: a view from the National Institute for Cardiovascular Outcomes Research (NICOR). *Heart*. 2012;98:1040-1043.

91.   National Institute for Cardiovascular Outcomes Research. Available at: https://www.nicor.org.uk/about-nicor/. Accessed on 06 December 2021.

92.   Ludman PF. The UK transcatheter aortic valve implantation registry; one of the suite of registries hosted by the National Institute for Cardiovascular Outcomes Research (NICOR). *Heart*. 2012;98:1787-9.

93.   Wilkinson C, Weston C, Timmis A, Quinn T, Keys A and Gale CP. Cohort profile: The Myocardial Ischaemia National Audit Project (MINAP). *European heart journal Quality of care & clinical outcomes*. 2019.

94.   National Service Framework for Coronary Heart Disease. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment data/file/198931/National_Service_Framework_for_Coronary_Heart_Disease.pdf. Accessed 05 December 2021.

95.   Hickey GL, Cosgriff R, Grant SW, Cooper G, Deanfield J, Roxburgh J and Bridgewater B. A technical review of the United Kingdom National Adult Cardiac Surgery Governance Analysis 2008-11. *Eur J Cardiothorac Surg*. 2014;45:225-33.

96.   Hickey GL, Pullan M, Oo A, Mediratta N, Chalmers J, Bridgewater B and Poullis M. A comparison of survival between on-pump and off-pump left internal mammary artery bypass graft surgery for isolated left anterior descending coronary artery disease: an analysis of the UK National Adult Cardiac Surgery Audit Registry. *Eur J Cardiothorac Surg*. 2016;49:1441-9.

97.   Benedetto U, Dimagli A, Kaura A, Sinha S, Mariscalco G, Krasopoulos G, Moorjani N, Field M, Uday T, Kendal S, Cooper G, Uppal R, Bilal H, Mascaro J, Goodwin A, Angelini G, Tsang G and Akowuah E. Determinants of outcomes following surgery for type A acute aortic dissection: the UK National Adult Cardiac Surgical Audit. *Eur Heart J*. 2021.

98.   Baghai M, Wendler O, Grant SW, Goodwin AT, Trivedi U, Kendall S and Jenkins DP. Aortic valve surgery in the UK, trends in activity and outcomes from a 15-year complete national series. *Eur J Cardiothorac Surg*. 2021;60:1353-1357.

99.   Cleland JGF, McDonagh T, Rigby AS, Yassin A, Whittaker T and Dargie HJ. The national heart failure audit for England and Wales 2008–2009. *Heart*. 2011;97:876-886.

100.   Emdin CA, Conrad N, Kiran A, Salimi-Khorshidi G, Woodward M, Anderson SG, Mohseni H, Dargie HJ, Hardman SMC, McDonagh T, McMurray JJV, Cleland JGF and Rahimi K. Variation in hospital performance for heart failure management in the National Heart Failure Audit for England and Wales. *Heart*. 2017;103:55-62.

101.	NATIONAL AUDIT OF CARDIAC RHYTHM MANAGEMENT (NACRM). Available at: https://www.nicor.org.uk/wp-content/uploads/2021/10/NACRM-Domain-Report_2021_FINAL.pdf. Accessed 06 December 2021. 2021.

102.	National Congenital Heart Disease Audit (NCHDA). Available at: http://www.bcca-uk.org/pages/page_box_contents.asp?pageid=932&navcatid=244. Accessed 06 December 2021

103.	Maurizio Lenzerini (2002). "Data Integration: A Theoretical Perspective". PODS 2002. pp. 233–246. Available at: http://www.diag.uniroma1.it//~lenzerin/homepagine/talks/TutorialPODS02.pdf. Accessed 07 December 2021.

104.	Blake SR, Roome C, Shahzad A, Kemp I, Mars C, Wilson K and Stables RH. A comparison of hospital episode statistics and traditional methods to identify outcomes in a randomized trial; a sub-study of HEAT-PPCI. *J Public Health (Oxf)*. 2020;42:175-182.

105.	National Cardiac Audit Programme. Myocardial Ischaemia National Audit Project (MINAP). 2021 Summary Report. Available at: https://www.nicor.org.uk/wp-content/uploads/2021/10/MINAP-Domain-Report_2021_FINAL.pdf. Accessed 07 December 2021.

106.	Cattle BA, Baxter PD, Greenwood DC, Gale CP and West RM. Multiple imputation for completion of a national clinical audit dataset. *Statistics in Medicine*. 2011;30:2736-2753.

107.	Jernberg T, Attebring MF, Hambraeus K, Ivert T, James S, Jeppsson A, Lagerqvist B, Lindahl B, Stenestrand U and Wallentin L. The Swedish Web-system for enhancement and development of evidence-based care in heart disease evaluated according to recommended therapies (SWEDEHEART). *Heart*. 2010;96:1617-21.

108.	Nilsson K, Buccheri S, Christersson C, Koul S, Nilsson J, Pétursson P, Renlund H, Rück A and James S. Causes, Pattern, Predictors and Prognostic Implications of New Hospitalizations after TAVI: A Long-Term Nationwide Observational Study. *Eur Heart J Qual Care Clin Outcomes*. 2021.

109.	Wieloch M, Själander A, Frykman V, Rosenqvist M, Eriksson N and Svensson PJ. Anticoagulation control in Sweden: reports of time in therapeutic range, major bleeding, and thrombo-embolic complications from the national quality registry AuriculA. *European Heart Journal*. 2011;32:2282-2289.

110.	Savarese G, Vasko P, Jonsson Å, Edner M, Dahlström U and Lund LH. The Swedish Heart Failure Registry: a living, ongoing quality assurance and research in heart failure. *Ups J Med Sci*. 2019;124:65-69.

111.	National quality registries. Uppsala Clinical Research Centre (UCR). Available at: https://www.ucr.uu.se/en/services/quality-registry-center/national-quality-registries. Accessed 07 December 2021. .

112.	Fröbert O, Lagerqvist B, Olivecrona GK, Omerovic E, Gudnason T, Maeng M, Aasa M, Angerås O, Calais F, Danielewicz M, Erlinge D, Hellsten L, Jensen U, Johansson AC, Kåregren A, Nilsson J, Robertson L, Sandhall L, Sjögren I, Östlund O, Harnek J and James SK. Thrombus Aspiration during ST-Segment Elevation Myocardial Infarction. *New England Journal of Medicine*. 2013;369:1587-1597.

113.	Hofmann R, James SK, Jernberg T, Lindahl B, Erlinge D, Witt N, Arefalk G, Frick M, Alfredsson J, Nilsson L, Ravn-Fischer A, Omerovic E, Kellerth T, Sparv D, Ekelund U, Linder R, Ekstrom M, Lauermann J, Haaga U, Pernow J, Ostlund O, Herlitz J and Svensson L. Oxygen Therapy in Suspected Acute Myocardial Infarction. *The New England journal of medicine*. 2017;377:1240-1249.

114.   Szummer K, Wallentin L, Lindhagen L, Alfredsson J, Erlinge D, Held C, James S, Kellerth T, Lindahl B, Ravn-Fischer A, Rydberg E, Yndigegn T and Jernberg T. Improved outcomes in patients with ST-elevation myocardial infarction during the last 20 years are related to implementation of evidence-based treatments: Experiences from the SWEDEHEART registry 1995-2014. *European Heart Journal*. 2017;38:3056-3065.

115.   Baron T, Beskow A, James S and Lindahl B. Biobank linked to SWEDEHEART quality registry-routine blood sample collection opens new opportunities for cardiovascular research. *Upsala journal of medical sciences*. 2019;124:12-15.

116.   Chung SC, Sundstrom J, Gale CP, James S, Deanfield J, Wallentin L, Timmis A, Jernberg T and Hemingway H. Comparison of hospital variation in acute myocardial infarction care and outcome between Sweden and United Kingdom: population based cohort study using nationwide clinical registries. *Bmj*. 2015;351:h3913.

117.   Moussa I, Hermann A, Messenger JC, Dehmer GJ, Weaver WD, Rumsfeld JS and Masoudi FA. The NCDR CathPCI Registry: a US national perspective on care and outcomes for percutaneous coronary intervention. *Heart*. 2013;99:297-303.

118.   Masoudi FA, Ponirakis A, Yeh RW, Maddox TM, Beachy J, Casale PN, Curtis JP, De Lemos J, Fonarow G, Heidenreich P, Koutras C, Kremers M, Messenger J, Moussa I, Oetgen WJ, Roe MT, Rosenfield K, Shields TP, Jr., Spertus JA, Wei J, White C, Young CH and Rumsfeld JS. Cardiovascular care facts: a report from the national cardiovascular data registry: 2011. *J Am Coll Cardiol*. 2013;62:1931-1947.

119.   American College of Cardiology (ACC) National Cardiovascular Data Registries (NCDR). Available at: https://cvquality.acc.org/NCDR-Home/registries. Accessed 07 December 2021. https://cvquality.acc.org/NCDR-Home/registries.

120.   Hong Y and LaBresh KA. Overview of the American Heart Association "Get With the Guidelines" Programs: Coronary Heart Disease, Stroke, and Heart Failure. *Critical Pathways in Cardiology*. 2006;5:179-186.

121.   American Heart Association. Get With The Guideline registries. Available at: https://www.heart.org/en/professional/quality-improvement. Accessed 07 December 2021. .

122.   Ambardekar AV, Fonarow GC, Hernandez AF, Pan W, Yancy CW and Krantz MJ. Characteristics and in-hospital outcomes for nonadherent patients with heart failure: Findings from Get With The Guidelines-Heart Failure (GWTG-HF). *American Heart Journal*. 2009;158:644-652.

123.   Curtis AB, Piccini JP, Fonarow GC, Butler J, Desai N, Fang M, McCabe P, Page RL, Turakhia M and Lewis W. Improvement in quality of care for atrial fibrillation in get with the guidelines-atrial fibrillation (GWTG-AFIB). *Cardiology (Switzerland)*. 2017;137:156.

124.   The Society of Thoracic Surgery (STS) National Database. Available at: https://www.sts.org/registries/sts-national-database. Accessed 07 December 2021.

125.   Jacobs JP, Mayer JE, Jr., Pasquali SK, Hill KD, Overman DM, St Louis JD, Kumar SR, Backer CL, Tweddell JS, Dearani JA and Jacobs ML. The Society of Thoracic Surgeons Congenital Heart Surgery Database: 2019 Update on Outcomes and Quality. *Ann Thorac Surg*. 2019;107:691-704.

126.   Lowenstern A, Wu J, Bradley SM, Fanaroff AC, Tcheng JE and Wang TY. Current landscape of hybrid revascularization: A report from the NCDR CathPCI Registry. *American Heart Journal*. 2019;215:167-177.

127.	Freeman JV, Varosy P, Price MJ, Slotwiner D, Kusumoto FM, Rammohan C, Kavinsky CJ, Turi ZG, Akar J, Koutras C, Curtis JP and Masoudi FA. The NCDR Left Atrial Appendage Occlusion Registry. *Journal of the American College of Cardiology*. 2020;75:1503-1518.

128.	Jayaram N, Spertus JA, Kennedy KF, Vincent R, Martin GR, Curtis JP, Nykanen D, Moore PM and Bergersen L. Modeling major adverse outcomes of pediatric and adult patients with congenital heart disease undergoing cardiac catheterization: Observations from the NCDR IMPACT registry (National Cardiovascular Data Registry Improving Pediatric and Adult Congenital Treatment). *Circulation*. 2017;136:2009-2019.

129.	Rao SV, Hess CN, Barham B, Aberle LH, Anstrom KJ, Patel TB, Jorgensen JP, Mazzaferri EL, Jr., Jolly SS, Jacobs A, Newby LK, Gibson CM, Kong DF, Mehran R, Waksman R, Gilchrist IC, McCourt BJ, Messenger JC, Peterson ED, Harrington RA and Krucoff MW. A registry-based randomized trial comparing radial and femoral approaches in women undergoing percutaneous coronary intervention: the SAFE-PCI for Women (Study of Access Site for Enhancement of PCI for Women) trial. *JACC Cardiovasc Interv*. 2014;7:857-67.

130.	Hendel RC, Bozkurt B, Fonarow GC, Jacobs JP, Lichtman JH, Smith EE, Tcheng JE, Wang TY and Weintraub WS. ACC/AHA 2013 Methodology for Developing Clinical Data Standards: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Data Standards. *Circulation*. 2014;129:2346-2357.

131.	Rossignol P, Lainscak M, Crespo-Leiro MG, Laroche C, Piepoli MF, Filippatos G, Rosano GMC, Savarese G, Anker SD, Seferovic PM, Ruschitzka F, Coats AJS, Mebazaa A, McDonagh T, Sahuquillo A, Penco M, Maggioni AP and Lund LH. Unravelling the interplay between hyperkalaemia, renin-angiotensin-aldosterone inhibitor use and clinical outcomes. Data from 9222 chronic heart failure patients of the ESC-HFA-EORP Heart Failure Long-Term Registry. *Eur J Heart Fail*. 2020;22:1378-1389.

132.	Kotseva K, Wood D and De Bacquer D. Determinants of participation and risk factor control according to attendance in cardiac rehabilitation programmes in coronary patients in Europe: EUROASPIRE IV survey. *European Journal of Preventive Cardiology*. 2018;25:1242-1251.

133.	Boriani G, Proietti M, Laroche C, Fauchier L, Marin F, Nabauer M, Potpara T, Dan G-A, Kalarus Z, Tavazzi L, Maggioni AP, Lip GYH and Investigators E-AL-TGR. Association between antithrombotic treatment and outcomes at 1-year follow-up in patients with atrial fibrillation: the EORP-AF General Long-Term Registry. *EP Europace*. 2019;21:1013-1022.

134.	Habib G, Lancellotti P, Erba PA, Sadeghpour A, Meshaal M, Sambola A, Furnaz S, Citro R, Ternacle J, Donal E, Cosyns B, Popescu B, Iung B, Prendergast B, Laroche C, Tornos P, Pazdernik M, Maggioni A and Gale CP. The ESC-EORP EURO-ENDO (European Infective Endocarditis) registry. *Eur Heart J Qual Care Clin Outcomes*. 2019;5:202-207.

135.	Zeymer U, Ludman P, Danchin N, Kala P, Maggioni AP and Weidinger F. The ESC ACCA EAPCI EORP acute coronary syndrome ST-elevation myocardial infarction registry. *Eur Heart J Qual Care Clin Outcomes*. 2020;6:100-104.

136.	Heliö T, Elliott P, Koskenvuo JW, Gimeno JR, Tavazzi L, Tendera M, Kaski JP, Mansencal N, Bilińska Z, Carr-White G, Damy T, Frustaci A, Kindermann I, Ripoll-Vera T, Čelutkienė J, Axelsson A, Lorenzini M, Saad A, Maggioni AP, Laroche C, Caforio ALP and Charron P. ESC EORP Cardiomyopathy Registry: real-life practice of genetic counselling and testing in adult cardiomyopathy patients. *ESC Heart Fail*. 2020;7:3013-3021.

137.	Polewczyk A, Rinaldi CA, Sohal M, Golzio PG, Claridge S, Cano O, Laroche C, Kennergren C, Deharo JC, Kutarski A, Butter C, Blomström-Lundqvist C, Romano SL, Maggioni AP, Auricchio A, Diemberger I, Pisano ECL, Rossillo A, Kuck KH, Forster T and

Bongiorni MG. Transvenous lead extraction procedures in women based on ESC-EHRA EORP European Lead Extraction ConTRolled ELECTRa registry: is female sex a predictor of complications? *Europace*. 2019;21:1890-1899.

138.   Adlam D, Alfonso F, Maas A, Vrints C and Committee W. European Society of Cardiology, acute cardiovascular care association, SCAD study group: a position paper on spontaneous coronary artery dissection. *European Heart Journal*. 2018;39:3353-3368.

139.   Hendel RC, Bozkurt B, Fonarow GC, Jacobs JP, Lichtman JH, Smith EE, Tcheng JE, Wang TY and Weintraub WS. ACC/AHA 2013 Methodology for Developing Clinical Data Standards. *A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Data Standards*. 2014;63:2323-2334.

140.   Knuuti J, Wijns W, Saraste A, Capodanno D, Barbato E, Funck-Brentano C, Prescott E, Storey RF, Deaton C, Cuisset T, Agewall S, Dickstein K, Edvardsen T, Escaned J, Gersh BJ, Svitil P, Gilard M, Hasdai D, Hatala R, Mahfoud F, Masip J, Muneretto C, Valgimigli M, Achenbach S, Bax JJ and Group ESD. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes: The Task Force for the diagnosis and management of chronic coronary syndromes of the European Society of Cardiology (ESC). *European Heart Journal*. 2019;41:407-477.

141.   Campeau L. Letter: Grading of angina pectoris. *Circulation*. 1976;54:522-523.

142.   Knuuti J, Wijns W, Saraste A, Capodanno D, Barbato E, Funck-Brentano C, Prescott E, Storey RF, Deaton C, Cuisset T, Agewall S, Dickstein K, Edvardsen T, Escaned J, Gersh BJ, Svitil P, Gilard M, Hasdai D, Hatala R, Mahfoud F, Masip J, Muneretto C, Valgimigli M, Achenbach S, Bax JJ and Group ESCSD. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes: The Task Force for the diagnosis and management of chronic coronary syndromes of the European Society of Cardiology (ESC). *Eur Heart J*. 2020;41:407-477.

143.   Dehmer GJ, Badhwar V, Bermudez EA, Cleveland JC, Cohen MG, D'Agostino RS, Ferguson TB, Hendel RC, Isler ML, Jacobs JP, Jneid H, Katz AS, Maddox TM and Shahian DM. 2020 AHA/ACC Key Data Elements and Definitions for Coronary Revascularization: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Data Standards (Writing Committee to Develop Clinical Data Standards for Coronary Revascularization). *Circulation: Cardiovascular Quality and Outcomes*. 2020;13:e000059.

144.   Gregson J, Stone GW, Ben-Yehuda O, Redfors B, Kandzari DE, Morice M-C, Leon MB, Kosmidou I, Lembo NJ, Brown WM, Karmpaliotis D, Banning AP, Pomar J, Sabaté M, Simonton CA, Dressler O, Kappetein AP, Sabik JF, Serruys PW and Pocock SJ. Implications of Alternative Definitions of Peri-Procedural Myocardial Infarction After Coronary Revascularization. *Journal of the American College of Cardiology*. 2020;76:1609-1621.

145.   Thygesen K, Alpert JS, Jaffe AS, Chaitman BR, Bax JJ, Morrow DA, White HD and Group ESD. Fourth universal definition of myocardial infarction (2018). *European Heart Journal*. 2018;40:237-269.

146.   McClellan M, Brown N, Califf RM and Warner JJ. Call to Action: Urgent Challenges in Cardiovascular Disease: A Presidential Advisory From the American Heart Association. *Circulation*. 2019;139:e44-e54.

147.   Flynn MR, Barrett C, Cosio FG, Gitt AK, Wallentin L, Kearney P, Lonergan M, Shelley E and Simoons ML. The Cardiology Audit and Registration Data Standards (CARDS), European data standards for clinical cardiology practice. *European Heart Journal*. 2005;26:308-313.

148.   van der Putten N, van der Velde ET, Dijk WA, Maikoe T and Hoekema R. Implementation of the CARDS data standards in five Dutch University Medical Centres *Computers in Cardiology 2005, Vol 32*; 2005(32): 327-330.

149.   Hanssen M, Martinez OGC and Legrand V. Using the cardiology audit and Registration Data Standards (CARDS) to predict short- and long-term mortality from ST-elevation myocardial infarction treated by PCI. *Acta Cardiologica*. 2010;65:127-128.

150.   ACC/AHA Clinical Data Standards. Available at: https://www.jacc.org/guidelines/data-standards. Accessed 01 December 2021.

151.   Radford MJ, Arnold JMO, Bennett SJ, Cinquegrani MP, Cleland JGF, Havranek EP, Heidenreich PA, Rutherford JD, Spertus JA and Stevenson LW. ACC/AHA key data elements and definitions for measuring the clinical management and outcomes of patients with chronic heart failure: A report of the American College of Cardiology/American Heart Association Task Force on Clinical Data Standards (Writing Committee to Develop Heart Failure Clinical Data Standards). *Circulation*. 2005;112:1888-1916.

152.   Bozkurt B, Hershberger RE, Butler J, Grady KL, Heidenreich PA, Isler ML, Kirklin JK and Weintraub WS. 2021 ACC/AHA Key Data Elements and Definitions for Heart Failure: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Data Standards (Writing Committee to Develop Clinical Data Standards for Heart Failure). *Circulation: Cardiovascular Quality and Outcomes*. 2021;14:e000102.

153.   Cannon CP, Brindis RG, Chaitman BR, Cohen DJ, Cross JT, Drozda JP, Fesmire FM, Fintel DJ, Fonarow GC, Fox KA, Gray DT, Harrington RA, Hicks KA, Hollander JE, Krumholz H, Labarthe DR, Long JB, Mascette AM, Meyer C, Peterson ED, Radford MJ, Roe MT, Richmann JB, Selker HP, Shahian DM, Shaw RE, Sprenger S, Swor R, Underberg JA, Van De Werf F, Weiner BH and Weintraub WS. 2013 ACCF/AHA Key data elements and definitions for measuring the clinical management and outcomes of patients with acute coronary syndromes and coronary artery disease: A report of the American college of cardiology foundation/American Heart Association Task force on Clinical Data Standards (Writing committee to develop acute coronary syndromes and coronary artery disease clinical data standards). *Circulation*. 2013;127:1052-1089.

154.   Douglas PS, Carabello BA, Lang RM, Lopez L, Pellikka PA, Picard MH, Thomas JD, Varghese P, Wang TY, Weissman NJ and Wilgus R. 2019 ACC/AHA/ASE Key Data Elements and Definitions for Transthoracic Echocardiography: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Data Standards (Writing Committee to Develop Cardiovascular Endpoints Data Standards) and the American Society of Echocardiography. *Circ Cardiovasc Imaging*. 2019;12:e000027.

155.   Hicks KA, Tcheng JE, Bozkurt B, Chaitman BR, Cutlip DE, Farb A, Fonarow GC, Jacobs JP, Jaff MR, Lichtman JH, Limacher MC, Mahaffey KW, Mehran R, Nissen SE, Smith EE, Targum SL, Weintraub WS, Hendel RC, Jneid HH, Kutcher MA, Wang TY, Writing Comm M and Data AATFC. 2014 ACC/AHA Key Data Elements and Definitions for Cardiovascular Endpoint Events in Clinical Trials A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Data Standards (Writing Committee to Develop Cardiovascular Endpoints Data Standards). *Circulation*. 2015;132:302-361.

156.   Canadian Cardiovascualr Society Data Definitions and quality indicators. Available at: https://ccs.ca/ccs-data-definitions-quality-indicators/. Accessed 03 December 2021.

157.   Johnstone DE, Buller CE, National Steering Committees on Quality I and Data Definitions CCS. Pan-Canadian cardiovascular data definitions and quality indicators: a status update. *The Canadian journal of cardiology*. 2012;28:599-601.

158.   Raleigh VS and Foot C. Getting the Measure of Quality. Opportunities and challenges. London: The King's Fund. 2010.

159.   McGlynn EA, Cassel CK, Leatherman ST, DeCristofaro A and Smits HL. Establishing national goals for quality improvement. *Med Care*. 2003;41:I16-29.

160.   National Quality Forum. Measure evaluation criteria. Available at: http://www.qualityforum.org/Measuring_Performance/Submitting_Standards/Measure_Evaluation_Criteria.aspx#comparison. Accessed 25 March 2020.

161.   McGlynn EA. Introduction and overview of the conceptual framework for a national quality measurement and reporting system. *Med Care*. 2003;41:I1-7.

162.   ACC/AHA Clinical Performance and Quality Measures. Available at: https://www.onlinejacc.org/collection/performance-measures. Accessed 04 April 2021

163.   Spertus JA, Eagle KA, Krumholz HM, Mitchell KR and Normand S-LT. American College of Cardiology and American Heart Association methodology for the selection and creation of performance measures for quantifying the quality of cardiovascular care. *Circulation*. 2005;111:1703-1712.

164.   Jneid H, Addison D, Bhatt DL, Fonarow GC, Gokak S, Grady KL, Green LA, Heidenreich PA, Ho PM, Jurgens CY, King ML, Kumbhani DJ and Pancholy S. 2017 AHA/ACC Clinical Performance and Quality Measures for Adults With ST-Elevation and Non-ST-Elevation Myocardial Infarction: A Report of the American College of Cardiology/American Heart Association Task Force on Performance Measures. *Journal of the American College of Cardiology*. 2017;70:2048-2090.

165.   2016 ACC/AHA Clinical Performance and Quality Measures for Adults With Atrial Fibrillation or Atrial Flutter.46.

166.   Heidenreich PA, Fonarow GC, Breathett K, Jurgens CY, Pisani BA, Pozehl BJ, Spertus JA, Taylor KG, Thibodeau JT, Yancy CW and Ziaeian B. 2020 ACC/AHA Clinical Performance and Quality Measures for Adults With Heart Failure. *Circulation: Cardiovascular Quality and Outcomes*. 2020;13:e000099.

167.   Casey DE, Jr., Thomas RJ, Bhalla V, Commodore-Mensah Y, Heidenreich PA, Kolte D, Muntner P, Smith SC, Jr., Spertus JA, Windle JR, Wozniak GD and Ziaeian B. 2019 AHA/ACC Clinical Performance and Quality Measures for Adults With High Blood Pressure: A Report of the American College of Cardiology/American Heart Association Task Force on Performance Measures. *Circ Cardiovasc Qual Outcomes*. 2019;12:e000057.

168.   Al-Khatib SM, Yancy CW, Solis P, Becker L, Benjamin EJ, Carrillo RG, Ezekowitz JA, Fonarow GC, Kantharia BK, Kleinman M, Nichol G and Varosy PD. 2016 AHA/ACC Clinical Performance and Quality Measures for Prevention of Sudden Cardiac Death. *A Report of the American College of Cardiology/American Heart Association Task Force on Performance Measures*. 2017;69:712-744.

169.   Drozda JP, Ferguson TB, Jneid H, Krumholz HM, Nallamothu BK, Olin JW, Ting HH, Heidenreich PA, Albert NM, Chan PS, Curtis LH, Fonarow GC, Ho PM, O'Brien S, Russo AM, Thomas RJ and Varosy PD. 2015 ACC/AHA Focused Update of Secondary Prevention Lipid Performance Measures: A Report of the American College of Cardiology/American Heart Association Task Force on Performance Measures. *Circulation: Cardiovascular Quality and Outcomes*. 2016;9:68-95.

170.   Thomas RJ, Balady G, Banka G, Beckie TM, Chiu J, Gokak S, Ho PM, Keteyian SJ, King M, Lui K, Pack Q, Sanderson BK and Wang TY. 2018 ACC/AHA Clinical Performance and Quality Measures for Cardiac Rehabilitation: A Report of the American College of

Cardiology/American Heart Association Task Force on Performance Measures. *Circulation: Cardiovascular Quality and Outcomes*. 2018;11:e000037.

171.   Shekelle PG. Quality indicators and performance measures: Methods for development need more standardization. *Journal of Clinical Epidemiology*. 2013;66:1338-1339.

172.   Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, Shamseer L, Tetzlaff JM, Akl EA, Brennan SE, Chou R, Glanville J, Grimshaw JM, Hróbjartsson A, Lalu MM, Li T, Loder EW, Mayo-Wilson E, McDonald S, McGuinness LA, Stewart LA, Thomas J, Tricco AC, Welch VA, Whiting P and Moher D. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. 2021;372:n71.

173.   The National Institute for H and Care E. NICE Atrial fibrillation Quality standard [QS93]. *https://wwwniceorguk/guidance/qs93*. 2015.

174.   Samanta A, Samanta J and Gunn M. Legal considerations of clinical guidelines: will NICE make a difference? *Journal of the Royal Society of Medicine*. 2003;96:133-138.

175.   Appraisal of Guidelines for Research & Evaluation II (AGREE II). Available at: https://www.agreetrust.org/wp-content/uploads/2013/10/AGREE-II-Users-Manual-and-23-item-Instrument_2009_UPDATE_2013.pdf. Accessed 08 December 2021.

176.   Brouwers MC, Kho ME, Browman GP, Burgers JS, Cluzeau F, Feder G, Fervers B, Graham ID, Grimshaw J, Hanna SE, Littlejohns P, Makarski J and Zitzelsberger L. AGREE II: advancing guideline development, reporting and evaluation in health care. *Cmaj*. 2010;182:E839-42.

177.   Garson A. President's page: The Great Circle: a target for better patient care. *J Am Coll Cardiol*. 1999;34:294-5.

178.   Hicks KA, Tcheng JE, Bozkurt B, Chaitman BR, Cutlip DE, Farb A, Fonarow GC, Jacobs JP, Jaff MR, Lichtman JH, Limacher MC, Mahaffey KW, Mehran R, Nissen SE, Smith EE and Targum SL. 2014 ACC/AHA key data elements and definitions for cardiovascular endpoint events in clinical trials: A report of the American College of Cardiology/American Heart Association task force on clinical data standards (Writing Committee to Develop Cardiovascular Endpoints Data Standards). *Circulation*. 2015;132:302-361.

179.   Bozkurt B, Coats AJS, Tsutsui H, Abdelhamid CM, Adamopoulos S, Albert N, Anker SD, Atherton J, Böhm M, Butler J, Drazner MH, Michael Felker G, Filippatos G, Fiuzat M, Fonarow GC, Gomez-Mesa J-E, Heidenreich P, Imamura T, Jankowska EA, Januzzi J, Khazanie P, Kinugawa K, Lam CSP, Matsue Y, Metra M, Ohtani T, Francesco Piepoli M, Ponikowski P, Rosano GMC, Sakata Y, Seferović P, Starling RC, Teerlink JR, Vardeny O, Yamamoto K, Yancy C, Zhang J and Zieroth S. Universal definition and classification of heart failure: a report of the Heart Failure Society of America, Heart Failure Association of the European Society of Cardiology, Japanese Heart Failure Society and Writing Committee of the Universal Definition of Heart Failure. *European Journal of Heart Failure*. 2021;23:352-380.

180.   Xaplanteris P, Fournier S, Pijls NHJ, Fearon WF, Barbato E, Tonino PAL, Engstrøm T, Kääb S, Dambrink J-H, Rioufol G, Toth GG, Piroth Z, Witt N, Fröbert O, Kala P, Linke A, Jagic N, Mates M, Mavromatis K, Samady H, Irimpen A, Oldroyd K, Campo G, Rothenbühler M, Jüni P and De Bruyne B. Five-Year Outcomes with PCI Guided by Fractional Flow Reserve. *New England Journal of Medicine*. 2018;379:250-259.

181.   Maron DJ, Hochman JS, Reynolds HR, Bangalore S, O'Brien SM, Boden WE, Chaitman BR, Senior R, López-Sendón J, Alexander KP, Lopes RD, Shaw LJ, Berger JS, Newman JD, Sidhu MS, Goodman SG, Ruzyllo W, Gosselin G, Maggioni AP, White HD, Bhargava B, Min JK, Mancini GBJ, Berman DS, Picard MH, Kwong RY, Ali ZA, Mark DB, Spertus JA, Krishnan MN,

Elghamaz A, Moorthy N, Hueb WA, Demkow M, Mavromatis K, Bockeria O, Peteiro J, Miller TD, Szwed H, Doerr R, Keltai M, Selvanayagam JB, Steg PG, Held C, Kohsaka S, Mavromichalis S, Kirby R, Jeffries NO, Harrell FE, Rockhold FW, Broderick S, Ferguson TB, Williams DO, Harrington RA, Stone GW and Rosenberg Y. Initial Invasive or Conservative Strategy for Stable Coronary Disease. *New England Journal of Medicine*. 2020;382:1395-1407.

182. Complete guide to GDPR compliance. Available at: https://gdpr.eu. Accessed on 14 December 2021.

183. Moher D, Liberati A, Tetzlaff J and Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ*. 2009;339:b2535.

184. Batra G, Aktaa S, Wallentin L, Maggioni AP, Wilkinson C, Casadei B and Gale CP. Methodology for the development of international clinical data standards for common cardiovascular conditions: European Unified Registries for Heart Care Evaluation and Randomised Trials (EuroHeart). *Eur Heart J Qual Care Clin Outcomes*. 2021.

185. Aktaa S, Batra G, Wallentin L, Baigent C, Erlinge D, James S, Ludman P, Maggioni A, Price S, Weston C, Casadei B and Gale CP. European Society of Cardiology methodology for the development of quality indicators for the quantification of cardiovascular care and outcomes. 2020.

186. Schiele F, Aktaa S, Rossello X, Ahrens I, Claeys MJ, Collet J-P, Fox KAA, Gale CP, Huber K, Iakobishvili Z, Keys A, Lambrinou E, Leonardi S, Lettino M, Masoudi FA, Price S, Quinn T, Swahn E, Thiele H, Timmis A, Tubaro M, Vrints CJM, Walker D, Bueno H and reviewers D. 2020 Update of the quality indicators for acute myocardial infarction: a position paper of the Association for Acute Cardiovascular Care: the study group for quality indicators from the ACVC and the NSTE-ACS guideline group. *Eur Heart J Acute Cardiovasc Care*. 2021.

187. Arbelo E, Aktaa S, Bollmann A, D'Avila A, Drossart I, Dwight J, Hills MT, Hindricks G, Kusumoto FM, Lane DA, Lau DH, Lettino M, Lip GYH, Lobban T, Pak HN, Potpara T, Saenz LC, Van Gelder IC, Varosy P, Gale CP and Dagres N. Quality indicators for the care and outcomes of adults with atrial fibrillation. *Europace*. 2020.

188. Aktaa S, Abdin A, Arbelo E, Burri H, Vernooy K, Blomström-Lundqvist C, Boriani G, Defaye P, Deharo JC, Drossart I, Foldager D, Gold MR, Johansen JB, Leyva F, Linde C, Michowitz Y, Kronborg MB, Slotwiner D, Steen T, Tolosana JM, Tzeis S, Varma N, Glikson M, Nielsen JC and Gale CP. European Society of Cardiology Quality Indicators for the care and outcomes of cardiac pacing: developed by the Working Group for Cardiac Pacing Quality Indicators in collaboration with the European Heart Rhythm Association of the European Society of Cardiology. *Europace*. 2021.

189. Aktaa S, Polovina M, Rosano G, Abdin A, Anguita M, Lainscak M, Lund L, McDonagh T, Metra M, Mindham R, Piepoli M, Stork S, Tokmakova M, Seferovic P, Gale C and Coats A. European Society of Cardiology Quality indicators for the care and outcomes of adults with heart failure. Developed by the Working Group for Heart Failure Quality Indicators in collaboration with the Heart Failure Association of the European Society of Cardiology. *European Journal of Heart Failure*. 2021.

190. Aktaa S, Gencer B, Arbelo E, Davos CH, Désormais I, Hollander M, Abreu A, Ambrosetti M, Bäck M, Carballo D, Crawford C, Deaton C, Dendale P, Eijsvogels TMH, Galbraith M, Piepoli MF, Salzwedel A, Smulders Y, Wilhelm M, Biondi-Zoccai G, Mach F, Visseren FLJ and Gale CP. European Society of Cardiology Quality Indicators for Cardiovascular Disease Prevention: developed by the Working Group for Cardiovascular Disease Prevention Quality Indicators in collaboration with the European Association for Preventive Cardiology of the European Society of Cardiology. *Eur J Prev Cardiol*. 2021.

191.   Abdin A, Aktaa S, Vukadinović D, Arbelo E, Burri H, Glikson M, Meyer C, Munyombwe T, Nielsen JC, Ukena C, Vernooy K and Gale CP. Outcomes of conduction system pacing compared to right ventricular pacing as a primary strategy for treating bradyarrhythmia: systematic review and meta-analysis. *Clin Res Cardiol*. 2021.

192.   Aktaa S, Yadegarfar ME, Wu J, Rashid M, de Belder M, Deanfield J, Schiele F, Minchin M, Mamas M and Gale CP. Quality of acute myocardial infarction care in England and Wales during the COVID-19 pandemic: linked nationwide cohort study. *BMJ Qual Saf*. 2021.

193.   Friebel R and Steventon A. Composite measures of healthcare quality: sensible in theory, problematic in practice. *BMJ Quality & Safety*. 2019;28:85-88.

194.   Duclos A, Chollet F, Pascal L, Ormando H, Carty MJ, Polazzi S and Lifante J-C. Effect of monitoring surgical outcomes using control charts to reduce major adverse events in patients: cluster randomised trial. *BMJ*. 2020;371:m3840.

195.   Hofstede SN, Ceyisakar IE, Lingsma HF, Kringos DS and Marang-van de Mheen PJ. Ranking hospitals: do we gain reliability by using composite rather than individual indicators? *BMJ Quality & Safety*. 2019;28:94-102.

196.   Schiele F, Gale CP, Bonnefoy E, Capuano F, Claeys MJ, Danchin N, Fox KA, Huber K, Iakobishvili Z, Lettino M, Quinn T, Rubini Gimenez M, Botker HE, Swahn E, Timmis A, Tubaro M, Vrints C, Walker D, Zahger D, Zeymer U and Bueno H. Quality indicators for acute myocardial infarction: A position paper of the Acute Cardiovascular Care Association. *Eur Heart J Acute Cardiovasc Care*. 2017;6:34-59.

197.   Rossello X, Medina J, Pocock S, Van de Werf F, Chin CT, Danchin N, Lee SW, Huo Y and Bueno H. Assessment of quality indicators for acute myocardial infarction management in 28 countries and use of composite quality indicators for benchmarking. *Eur Heart J Acute Cardiovasc Care*. 2020:2048872620911853.

198.   Schiele F, Gale CP, Simon T, Fox KAA, Bueno H, Lettino M, Tubaro M, Puymirat E, Ferrieres J, Meneveau N and Danchin N. Assessment of Quality Indicators for Acute Myocardial Infarction in the FAST-MI (French Registry of Acute ST-Elevation or Non-ST-Elevation Myocardial Infarction) Registries. *Circulation Cardiovascular quality and outcomes*. 2017;10.

199.   Collet J-P, Thiele H, Barbato E, Barthélémy O, Bauersachs J, Bhatt DL, Dendale P, Dorobantu M, Edvardsen T, Folliguet T, Gale CP, Gilard M, Jobs A, Jüni P, Lambrinou E, Lewis BS, Mehilli J, Meliga E, Merkely B, Mueller C, Roffi M, Rutten FH, Sibbing D, Siontis GCM and Group ESD. 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: The Task Force for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J*. 2020.

200.   Schiele F, Aktaa S, Rossello X, Collet JP, Gale CP, Huber K, Keys A, Lambrinou E, Leonardi S, Masoudi FA, Tubaro M, Bueno H. 2020 update of the quality indicators for acute myocardial infarction: A position paper of the association for acute cardiovascular care Eur Heart J Acute Cardiovasc Care. 2020;In press.

201.   Wilkinson C, Weston C, Timmis A, Quinn T, Keys A and Gale CP. The Myocardial Ischaemia National Audit Project (MINAP). *European Heart Journal - Quality of Care and Clinical Outcomes*. 2019;6:19-22.

202.   Simms AD, Weston CF, West RM, Hall AS, Batin PD, Timmis A, Hemingway H, Fox K and Gale CP. Mortality and missed opportunities along the pathway of care for ST-elevation myocardial infarction: a national cohort study. *European heart journal Acute cardiovascular care*. 2015;4:241-53.

203.   Ludman P. British Cardiovascular Intervention Society database: insights into interventional cardiology in the United Kingdom. *Heart*. 2019;105:1289.

204.   Granger CB, Goldberg RJ, Dabbous O, Pieper KS, Eagle KA, Cannon CP, Van De Werf F, Avezum A, Goodman SG, Flather MD and Fox KA. Predictors of hospital mortality in the global registry of acute coronary events. *Arch Intern Med*. 2003;163:2345-53.

205.   Fox KA, Dabbous OH, Goldberg RJ, Pieper KS, Eagle KA, Van de Werf F, Avezum A, Goodman SG, Flather MD, Anderson FA, Jr. and Granger CB. Prediction of risk of death and myocardial infarction in the six months after presentation with acute coronary syndrome: prospective multinational observational study (GRACE). *Bmj*. 2006;333:1091.

206.   https://www.outcomes-umassmed.org/grace/grace_risk_table.aspx. Accessed 27 September 2020.

207.   Simms AD, Reynolds S, Pieper K, Baxter PD, Cattle BA, Batin PD, Wilson JI, Deanfield JE, West RM, Fox KA, Hall AS and Gale CP. Evaluation of the NICE mini-GRACE risk scores for acute myocardial infarction using the Myocardial Ischaemia National Audit Project (MINAP) 2003-2009: National Institute for Cardiovascular Outcomes Research (NICOR). *Heart*. 2013;99:35-40.

208.   Gale CP, Manda SOM, Weston CF, Birkhead JS, Batin PD and Hall AS. Evaluation of risk scores for risk stratification of acute coronary syndromes in the Myocardial Infarction National Audit Project (MINAP) database. *Heart*. 2009;95:221-227.

209.   Tu JV, Khalid L, Donovan LR and Ko DT. Indicators of quality of care for patients with acute myocardial infarction. *Cmaj*. 2008;179:909-15.

210.   Bing R, Goodman SG, Yan AT, Fox K, Gale CP, Hyun K, D'Souza M, Shetty P, Atherton J, Hammett C, Chew D and Brieger D. Use of clinical risk stratification in non-ST elevation acute coronary syndromes: an analysis from the CONCORDANCE registry. *European heart journal Quality of care & clinical outcomes*. 2018;4:309-317.

211.   Chew DP, Junbo G, Parsonage W, Kerkar P, Sulimov VA, Horsfall M, Mattchoss S, Perceived Risk of I and Bleeding Events in Acute Coronary Syndrome Patients Study I. Perceived risk of ischemic and bleeding events in acute coronary syndromes. *Circ Cardiovasc Qual Outcomes*. 2013;6:299-308.

212.   Fox KAA, Anderson FA, Dabbous OH, Steg PG, López-Sendón J, Van de Werf F, Budaj A, Gurfinkel EP, Goodman SG and Brieger D. Intervention in acute coronary syndromes: do patients undergo intervention on the basis of their risk characteristics? The Global Registry of Acute Coronary Events (GRACE). *Heart*. 2007;93:177-182.

213.   Saar A, Marandi T, Ainla T, Fischer K, Blöndal M and Eha J. The risk-treatment paradox in non-ST-elevation myocardial infarction patients according to their estimated GRACE risk. *International Journal of Cardiology*. 2018;272:26-32.

214.   Wu J, Mamas MA, Mohamed MO, Kwok CS, Roebuck C, Humberstone B, Denwood T, Luescher T, de Belder MA, Deanfield JE and Gale CP. Place and causes of acute cardiovascular mortality during the COVID-19 pandemic. *Heart*. 2020:heartjnl-2020-317912.

215.   Pessoa-Amorim G, Camm CF, Gajendragadkar P, De Maria GL, Arsac C, Laroche C, Zamorano JL, Weidinger F, Achenbach S, Maggioni AP, Gale CP, Poppas A and Casadei B. Admission of patients with STEMI since the outbreak of the COVID-19 pandemic: a survey by the European Society of Cardiology. *Eur Heart J Qual Care Clin Outcomes*. 2020;6:210-216.

216.   Alabas OA, West RM, Gillott RG, Khatib R, Hall AS and Gale CP. Evaluation of the Methods and Management of Acute Coronary Events (EMMACE)-3: protocol for a longitudinal study. *BMJ Open*. 2015;5:e006256.

217. Hall M, Alabas OA, Dondo TB, Jernberg T and Gale CP. Use of relative survival to evaluate non-ST-elevation myocardial infarction quality of care and clinical outcomes. *Eur Heart J Qual Care Clin Outcomes*. 2015;1:85-91.

218. Chugh SS, Havmoeller R, Narayanan K, Singh D, Rienstra M, Benjamin EJ, Gillum RF, Kim Y-H, McAnulty JH, Zheng Z-J, Forouzanfar MH, Naghavi M, Mensah GA, Ezzati M and Murray CJL. Worldwide Epidemiology of Atrial Fibrillation. A Global Burden of Disease 2010 Study. *Circulation*. 2014;129:837-847.

219. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, Castella M, Diener H-C, Heidbuchel H, Hendriks J, Hindricks G, Manolis AS, Oldgren J, Popescu BA, Schotten U, Van Putte B, Vardas P, Agewall S, Camm J, Baron Esquivias G, Budts W, Carerj S, Casselman F, Coca A, De Caterina R, Deftereos S, Dobrev D, Ferro JM, Filippatos G, Fitzsimons D, Gorenek B, Guenoun M, Hohnloser SH, Kolh P, Lip GYH, Manolis A, McMurray J, Ponikowski P, Rosenhek R, Ruschitzka F, Savelieva I, Sharma S, Suwalski P, Tamargo JL, Taylor CJ, Van Gelder IC, Voors AA, Windecker S, Zamorano JL and Zeppenfeld K. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *European Heart Journal*. 2016;37:2893-2962.

220. Ott A, Breteler MMB, de Bruyne MC, van Harskamp F, Grobbee DE and Hofman A. Atrial Fibrillation and Dementia in a Population-Based Study. The Rotterdam Study. *Stroke*. 1997;28:316-321.

221. Knecht S, Oelschläger C, Duning T, Lohmann H, Albers J, Stehling C, Heindel W, Breithardt Gn, Berger K, Ringelstein EB, Kirchhof P and Wersching H. Atrial fibrillation in stroke-free patients is associated with memory impairment and hippocampal atrophy. *European Heart Journal*. 2008;29:2125-2132.

222. Ball J, Carrington MJ, Stewart S and investigators obotS. Mild cognitive impairment in high-risk patients with chronic atrial fibrillation: a forgotten component of clinical management? *Heart*. 2013;99:542-547.

223. Marzona I, O'Donnell M, Teo K, Gao P, Anderson C, Bosch J and Yusuf S. Increased risk of cognitive and functional decline in patients with atrial fibrillation: results of the ONTARGET and TRANSCEND studies. *Canadian Medical Association Journal*. 2012;184:E329-E336.

224. Thrall G, Lane D, Carroll D and Lip GYH. Quality of Life in Patients with Atrial Fibrillation: A Systematic Review. *American Journal of Medicine*. 2006;119:448.e1-448.e19.

225. von Eisenhart Rothe A, Hutt F, Baumert J, Breithardt G, Goette A, Kirchhof P and Ladwig K-H. Depressed mood amplifies heart-related symptoms in persistent and paroxysmal atrial fibrillation patients: a longitudinal analysis—data from the German Competence Network on Atrial Fibrillation. *EP Europace*. 2015;17:1354-1362.

226. Kotecha D, Holmes J, Krum H, Altman DG, Manzano L, Cleland JGF, Lip GYH, Coats AJS, Andersson B, Kirchhof P, von Lueder TG, Wedel H, Rosano G, Shibata MC, Rigby A and Flather MD. Efficacy of β blockers in patients with heart failure plus atrial fibrillation: an individual-patient data meta-analysis. *Lancet*. 2014;384:2235-2243.

227. Steinberg BA, Kim S, Fonarow GC, Thomas L, Ansell J, Kowey PR, Mahaffey KW, Gersh BJ, Hylek E, Naccarelli G, Go AS, Reiffel J, Chang P, Peterson ED and Piccini JP. Drivers of hospitalization for patients with atrial fibrillation: Results from the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF). *American Heart Journal*. 2014;167:735-742.e2.

228.   Kirchhof P, Schmalowsky J, Pittrow D, Rosin L, Kirch W, Wegscheider K, Meinertz T and for the ASG. Management of Patients With Atrial Fibrillation by Primary-Care Physicians in Germany: 1-Year Results of the ATRIUM Registry. *Clinical Cardiology*. 2014;37:277-284.

229.   Wattigney WA, Mensah GA and Croft JB. Increased atrial fibrillation mortality: United States, 1980-1998. *Am J Epidemiol*. 2002;155:819-26.

230.   Wattigney WA, Mensah GA and Croft JB. Increasing Trends in Hospitalization for Atrial Fibrillation in the United States, 1985 Through 1999: Implications for Primary Prevention. *Circulation*. 2003;108:711-716.

231.   Boriani G, Proietti M, Laroche C, Fauchier L, Marin F, Nabauer M, Potpara T, Dan G-A, Kalarus Z, Tavazzi L, Maggioni AP and Lip GYH. Association between antithrombotic treatment and outcomes at 1-year follow-up in patients with atrial fibrillation: the EORP-AF General Long-Term Registry. *EP Europace*. 2019.

232.   Boriani G, Proietti M, Laroche C, Fauchier L, Marin F, Nabauer M, Potpara T, Dan G-A, Kalarus Z, Diemberger I, Tavazzi L, Maggioni AP, Lip GYH, Investigators E-AL-TGR and Steering C. Contemporary stroke prevention strategies in 11 096 European patients with atrial fibrillation: a report from the EURObservational Research Programme on Atrial Fibrillation (EORP-AF) Long-Term General Registry. *Europace : European pacing, arrhythmias, and cardiac electrophysiology : journal of the working groups on cardiac pacing, arrhythmias, and cardiac cellular electrophysiology of the European Society of Cardiology*. 2018;20:747-757.

233.   Wu J, Alsaeed ES, Barrett J, Hall M, Cowan C and Gale CP. Prescription of oral anticoagulants and antiplatelets for stroke prophylaxis in atrial fibrillation: nationwide time series ecological analysis. *EP Europace*. 2020.

234.   Trivedi AN, Nsa W, Hausmann LRM, Lee JS, Ma A, Bratzler DW, Mor MK, Baus K, Larbi F and Fine MJ. Quality and Equity of Care in U.S. Hospitals. *New England Journal of Medicine*. 2014;371:2298-2308.

235.   Heidenreich PA, Solis P, Estes NAM, Fonarow GC, Jurgens CY, Marine JE, McManus DD and McNamara RL. 2016 ACC/AHA Clinical Performance and Quality Measures for Adults With Atrial Fibrillation or Atrial Flutter. *Journal of the American College of Cardiology*. 2016;68:525.

236.   Cox JL, Dai S, Gong Y, McKelvie R, McMurtry MS, Oakes GH, Skanes A, Verma A, Wilton SB and Wyse DG. The Development and Feasibility Assessment of Canadian Quality Indicators for Atrial Fibrillation. *Canadian Journal of Cardiology*. 2016;32:1566-1569.

237.   Sandhu RK, Wilton SB, Cruz J, Aztema CL, MacFarlane K, McKelvie R, Lambert L, Rush K, Zimmerman R, Oakes G, Deyell M, Wyse DG, Cox JL and Skanes A. An Update on the Development and Feasibility Assessment of Canadian Quality Indicators for Atrial Fibrillation and Atrial Flutter. *CJC Open*. 2019;1:198-205.

238.   Inohara T, Kimura T, Ueda I, Ikemura N, Tanimoto K, Nishiyama N, Aizawa Y, Nishiyama T, Katsumata Y, Fukuda K, Takatsuki S and Kohsaka S. Effect of Compliance to Updated AHA/ACC Performance and Quality Measures Among Patients With Atrial Fibrillation on Outcome (from Japanese Multicenter Registry). *The American Journal of Cardiology*. 2017;120:595-600.

239.   The National Institute for Health and Care Excellence (NICE). NICE Atrial fibrillation Quality standard [QS93]. https://www.nice.org.uk/guidance/qs93. 2015.

240.   Hindricks G et al. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association of Cardio-Thoracic Surgery (EACTS). European Heart Journal (2020) doi:10.1093/eurheartj/ehaa612.

241.   Aktaa S, Batra G, Wallentin L, Baigent C, Erlinge D, James S, Ludman P, Maggioni A, Price S, Weston C, Casadei B and Gale CP. European Society of Cardiology methodology for the development of quality indicators for the quantification of cardiovascular care and outcomes. *Eur Heart J Qual Care Clin Outcomes*. 2020.

242.   Hsu C and Sandford B. The Delphi Technique: Making Sense Of Consensus. . *Practical Assessment, Research & Evaluation*. 2007;Vol 12, No 10:1-8.

243.   Donabedian A. Evaluating the Quality of Medical Care. *The Milbank Memorial Fund Quarterly*. 1966;44:166-206.

244.   Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P and Stewart LA. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews*. 2015;4:1-9.

245.   Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P and Stewart LA. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. *BMJ : British Medical Journal*. 2015;349:g7647.

246.   Seligman WH, Das-Gupta Z, Jobi-Odeneye AO, Arbelo E, Banerjee A, Bollmann A, Caffrey-Armstrong B, Cehic DA, Corbalan R, Collins M, Dandamudi G, Dorairaj P, Fay M, Van Gelder IC, Goto S, Granger CB, Gyorgy B, Healey JS, Hendriks JM, Hills MT, Hobbs FDR, Huisman MV, Koplan KE, Lane DA, Lewis WR, Lobban T, Steinberg BA, McLeod CJ, Moseley S, Timmis A, Yutao G and Camm AJ. Development of an international standard set of outcome measures for patients with atrial fibrillation: a report of the International Consortium for Health Outcomes Measurement (ICHOM) atrial fibrillation working group. *European Heart Journal*. 2020;41:1132-1140.

247.   January CT, Wann LS, Calkins H, Chen LY, Cigarroa JE, Cleveland JC, Ellinor PT, Ezekowitz MD, Field ME, Furie KL, Heidenreich PA, Murray KT, Shea JB, Tracy CM and Yancy CW. 2019 AHA/ACC/HRS Focused Update of the 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society in Collaboration With the Society of Thoracic Surgeons. *Circulation*. 2019;140:e125-e151.

248.   Calkins H, Gliklich RE, Leavy MB, Piccini JP, Hsu JC, Mohanty S, Lewis W, Nazarian S and Turakhia MP. Harmonized outcome measures for use in atrial fibrillation patient registries and clinical practice: Endorsed by the Heart Rhythm Society Board of Trustees. *Heart Rhythm*. 2019;16:e3-e16.

249.   Heidenreich PA, Solis P, Estes NAM, Fonarow GC, Jurgens CY, Marine JE, McManus DD and McNamara RL. 2016 ACC/AHA Clinical Performance and Quality Measures for Adults With Atrial Fibrillation or Atrial Flutter: A Report of the American College of Cardiology/American Heart Association Task Force on Performance Measures. *Journal of the American College of Cardiology*. 2016;68:525-568.

250.   Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, Castella M, Diener H-C, Heidbuchel H, Hendriks J, Hindricks G, Manolis AS, Oldgren J, Popescu BA, Schotten U, Van Putte B, Vardas P and Group ESD. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *European Heart Journal*. 2016;37:2893-2962.

251.   January CT, Wann LS, Alpert JS, Calkins H, Cigarroa JE, Cleveland JC, Conti JB, Ellinor PT, Ezekowitz MD, Field ME, Murray KT, Sacco RL, Stevenson WG, Tchou PJ, Tracy CM and

Yancy CW. 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation. *Circulation*. 2014;130:e199-e267.

252.   Brook RH, McGlynn EA and Cleary PD. Measuring Quality of Care. *New England Journal of Medicine*. 1996;335:966-970.

253.   Lip GYH. The ABC pathway: an integrated approach to improve AF management. *Nature Reviews Cardiology*. 2017;14:627-628.

254.   Lip GYH, Banerjee A, Boriani G, Chiang CE, Fargo R, Freedman B, Lane DA, Ruff CT, Turakhia M, Werring D, Patel S and Moores L. Antithrombotic Therapy for Atrial Fibrillation: CHEST Guideline and Expert Panel Report. *Chest*. 2018;154:1121-1201.

255.   Chao TF, Lip GYH, Liu CJ, Lin YJ, Chang SL, Lo LW, Hu YF, Tuan TC, Liao JN, Chung FP, Chen TJ and Chen SA. Relationship of Aging and Incident Comorbidities to Stroke Risk in Patients With Atrial Fibrillation. *Journal of the American College of Cardiology*. 2018;71:122-132.

256.   Chao TF, Lip GYH, Lin YJ, Chang SL, Lo LW, Hu YF, Tuan TC, Liao JN, Chung FP, Chen TJ and Chen SA. Incident Risk Factors and Major Bleeding in Patients with Atrial Fibrillation Treated with Oral Anticoagulants: A Comparison of Baseline, Follow-up and Delta HAS-BLED Scores with an Approach Focused on Modifiable Bleeding Risk Factors. *Thrombosis and haemostasis*. 2018;118:768-777.

257.   Borre ED, Goode A, Raitz G, Shah B, Lowenstern A, Chatterjee R, Sharan L, Allen LaPointe NM, Yapa R, Davis JK, Lallinger K, Schmidt R, Kosinski A, Al-Khatib SM and Sanders GD. Predicting Thromboembolic and Bleeding Event Risk in Patients with Non-Valvular Atrial Fibrillation: A Systematic Review. *Thrombosis and haemostasis*. 2018;118:2171-2187.

258.   Roldan V, Marin F, Manzano-Fernandez S, Gallego P, Vilchez JA, Valdes M, Vicente V and Lip GY. The HAS-BLED score has better prediction accuracy for major bleeding than CHADS2 or CHA2DS2-VASc scores in anticoagulated patients with atrial fibrillation. *Journal of the American College of Cardiology*. 2013;62:2199-204.

259.   Apostolakis S, Lane DA, Buller H and Lip GY. Comparison of the CHADS2, CHA2DS2-VASc and HAS-BLED scores for the prediction of clinically relevant bleeding in anticoagulated patients with atrial fibrillation: the AMADEUS trial. *Thrombosis and haemostasis*. 2013;110:1074-9.

260.   Guo Y, Lane DA, Chen Y, Lip GYH and m AFAIITi. Regular bleeding risk assessment associated with reduction in bleeding outcomes: The mAFA II randomised trial. *The American journal of medicine*. 2020.

261.   Kumar S, Lim E, Covic A, Verhamme P, Gale CP, Camm AJ and Goldsmith D. Anticoagulation in Concomitant Chronic Kidney Disease and Atrial Fibrillation: JACC Review Topic of the Week. *Journal of the American College of Cardiology*. 2019;74:2204-2215.

262.   Steffel J, Verhamme P, Potpara TS, Albaladejo P, Antz M, Desteghe L, Georg Haeusler K, Oldgren J, Reinecke H, Roldan-Schilling V, Rowell N, Sinnaeve P, Collins R, Camm AJ, Heidbüchel H and Group ESD. The 2018 European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation: executive summary. *EP Europace*. 2018;20:1231-1242.

263.   Potpara TS, Polovina MM, Marinkovic JM and Lip GY. A comparison of clinical characteristics and long-term prognosis in asymptomatic and symptomatic patients with first-diagnosed atrial fibrillation: the Belgrade Atrial Fibrillation Study. *Int J Cardiol*. 2013;168:4744-9.

264.   Boriani G, Laroche C, Diemberger I, Fantecchi E, Popescu MI, Rasmussen LH, Sinagra G, Petrescu L, Tavazzi L, Maggioni AP and Lip GY. Asymptomatic atrial fibrillation: clinical

correlates, management, and outcomes in the EORP-AF Pilot General Registry. *Am J Med*. 2015;128:509-18 e2.

265.	Siontis KC, Gersh BJ, Killian JM, Noseworthy PA, McCabe P, Weston SA, Roger VL and Chamberlain AM. Typical, atypical, and asymptomatic presentations of new-onset atrial fibrillation in the community: Characteristics and prognostic implications. *Heart Rhythm*. 2016;13:1418-24.

266.	Martinez C, Katholing A and Freedman SB. Adverse prognosis of incidentally detected ambulatory atrial fibrillation. A cohort study. *Thrombosis and haemostasis*. 2014;112:276-86.

267.	Welton NJ, McAleenan A, Thom HH, Davies P, Hollingworth W, Higgins JP, Okoli G, Sterne JA, Feder G, Eaton D, Hingorani A, Fawsitt C, Lobban T, Bryden P, Richards A and Sofat R. Screening strategies for atrial fibrillation: a systematic review and cost-effectiveness analysis. *Health Technol Assess*. 2017;21:1-236.

268.	Pollak WM, Simmons JD, Interian Jr. A, Atapattu SA, Castellanos A, Myeburg RJ and Mitrani RD. Clinical Utility of Intraatrial Pacemaker Stored Electrograms to Diagnose Atrial Fibrillation and Flutter. *Pacing and Clinical Electrophysiology*. 2001;24:424-429.

269.	Kaufman ES, Israel CW, Nair GM, Armaganijan L, Divakaramenon S, Mairesse GH, Brandes A, Crystal E, Costantini O, Sandhu RK, Parkash R, Connolly SJ, Hohnloser SH and Healey JS. Positive predictive value of device-detected atrial high-rate episodes at different rates and durations: An analysis from ASSERT. *Heart Rhythm*. 2012;9:1241-1246.

270.	Kishore A, Vail A, Majid A, Dawson J, Lees KR, Tyrrell PJ and Smith CJ. Detection of atrial fibrillation after ischemic stroke or transient ischemic attack: a systematic review and meta-analysis. *Stroke*. 2014;45:520-6.

271.	Sposato LA, Cipriano LE, Saposnik G, Ruiz Vargas E, Riccio PM and Hachinski V. Diagnosis of atrial fibrillation after stroke and transient ischaemic attack: a systematic review and meta-analysis. *Lancet Neurol*. 2015;14:377-87.

272.	Gladstone DJ, Spring M, Dorian P, Panzov V, Thorpe KE, Hall J, Vaid H, O'Donnell M, Laupacis A, Côté R, Sharma M, Blakely JA, Shuaib A, Hachinski V, Coutts SB, Sahlas DJ, Teal P, Yip S, Spence JD, Buck B, Verreault S, Casaubon LK, Penn A, Selchen D, Jin A, Howse D, Mehdiratta M, Boyle K, Aviv R, Kapral MK and Mamdani M. Atrial Fibrillation in Patients with Cryptogenic Stroke. *New England Journal of Medicine*. 2014;370:2467-2477.

273.	Sanna T, Diener H-C, Passman RS, Di Lazzaro V, Bernstein RA, Morillo CA, Rymer MM, Thijs V, Rogers T, Beckers F, Lindborg K and Brachmann J. Cryptogenic Stroke and Underlying Atrial Fibrillation. *New England Journal of Medicine*. 2014;370:2478-2486.

274.	Thijs VN, Brachmann J, Morillo CA, Passman RS, Sanna T, Bernstein RA, Diener H-C, Di Lazzaro V, Rymer MM, Hogge L, Rogers TB, Ziegler PD and Assar MD. Predictors for atrial fibrillation detection after cryptogenic stroke. *Results from CRYSTAL AF*. 2016;86:261-269.

275.	Piccini JP, Sr., Allred J, Bunch TJ, Deering TF, Di Biase L, Hussein AA, Lewis WR, Mittal S, Natale A, Osorio J, Packer DL, Ruff C, Russo AM, Sanders P, Seiler A, Slotwiner D, Hills MT, Turakhia MP, Van Gelder IC, Varosy PD, Verma A, Volgman AS, Wood KA and Deneke T. HRS white paper on atrial fibrillation centers of excellence: Rationale, considerations, and goals. *Heart Rhythm*. 2020.

276.	Steinberg BA, Kim S, Fonarow GC, Thomas L, Ansell J, Kowey PR, Mahaffey KW, Gersh BJ, Hylek E, Naccarelli G, Go AS, Reiffel J, Chang P, Peterson ED and Piccini JP. Drivers of hospitalization for patients with atrial fibrillation: Results from the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF). *Am Heart J*. 2014;167:735-42.e2.

277.   Steinberg BA, Gao H, Shrader P, Pieper K, Thomas L, Camm AJ, Ezekowitz MD, Fonarow GC, Gersh BJ, Goldhaber S, Haas S, Hacke W, Kowey PR, Ansell J, Mahaffey KW, Naccarelli G, Reiffel JA, Turpie A, Verheugt F, Piccini JP, Kakkar A, Peterson ED and Fox KAA. International trends in clinical characteristics and oral anticoagulation treatment for patients with atrial fibrillation: Results from the GARFIELD-AF, ORBIT-AF I, and ORBIT-AF II registries. *American Heart Journal*. 2017;194:132-140.

278.   Steinberg BA, Shrader P, Pieper K, Thomas L, Allen LA, Ansell J, Chan PS, Ezekowitz MD, Fonarow GC, Freeman JV, Gersh BJ, Kowey PR, Mahaffey KW, Naccarelli GV, Reiffel JA, Singer DE, Peterson ED and Piccini JP. Frequency and Outcomes of Reduced Dose Non-Vitamin K Antagonist Anticoagulants: Results From ORBIT-AF II (The Outcomes Registry for Better Informed Treatment of Atrial Fibrillation II). *Journal of the American Heart Association*. 2018;7:e007633.

279.   Wan Y, Heneghan C, Perera R, Roberts N, Hollowell J, Glasziou P, Bankhead C and Xu Y. Anticoagulation control and prediction of adverse events in patients with atrial fibrillation: a systematic review. *Circulation Cardiovascular quality and outcomes*. 2008;1:84-91.

280.   Sjalander S, Sjogren V, Renlund H, Norrving B and Sjalander A. Dabigatran, rivaroxaban and apixaban vs. high TTR warfarin in atrial fibrillation. *Thrombosis research*. 2018;167:113-118.

281.   Amin A, Deitelzweig S, Jing Y, Makenbaeva D, Wiederkehr D, Lin J and Graham J. Estimation of the impact of warfarin's time-in-therapeutic range on stroke and major bleeding rates and its influence on the medical cost avoidance associated with novel oral anticoagulant use-learnings from ARISTOTLE, ROCKET-AF, and RE-LY trials. *J Thromb Thrombolysis*. 2014;38:150-9.

282.   Al-Khatib SM, Allen LaPointe NM, Chatterjee R, Crowley MJ, Dupre ME, Kong DF, Lopes RD, Povsic TJ, Raju SS, Shah B, Kosinski AS, McBroom AJ and Sanders GD. Rate- and rhythm-control therapies in patients with atrial fibrillation: a systematic review. *Ann Intern Med*. 2014;160:760-73.

283.   Camm AJ. Hopes and disappointments with antiarrhythmic drugs. *Int J Cardiol*. 2017;237:71-74.

284.   De Vecchis R. Long-term antiarrhythmic drug treatment after atrial fibrillation ablation: does a too obstinate rhythm control strategy bring serious risk of proarrhythmia to ablated patients? *Eur Heart J Cardiovasc Pharmacother*. 2019;5:117-118.

285.   Fabritz L and Kirchhof P. Predictable and less predictable unwanted cardiac drugs effects: individual pre-disposition and transient precipitating factors. *Basic Clin Pharmacol Toxicol*. 2010;106:263-8.

286.   Reimold FR and Reynolds MR. Proarrhythmia and death with antiarrhythmic drugs for atrial fibrillation, and the unfulfilled promise of comparative effectiveness research. *American heart journal*. 2018;205:128-130.

287.   Darby AE and DiMarco JP. Management of Atrial Fibrillation in Patients With Structural Heart Disease. *Circulation*. 2012;125:945-957.

288.   Goldstein RE, Boccuzzi SJ, Cruess D and Nattel S. Diltiazem increases late-onset congestive heart failure in postinfarction patients with early reduction in ejection fraction. The Adverse Experience Committee; and the Multicenter Diltiazem Postinfarction Research Group. *Circulation*. 1991;83:52-60.

289.   Singh BN, Singh SN, Reda DJ, Tang XC, Lopez B, Harris CL, Fletcher RD, Sharma SC, Atwood JE, Jacobson AK, Lewis HD, Jr., Raisch DW, Ezekowitz MD and Sotalol Amiodarone

Atrial Fibrillation Efficacy Trial I. Amiodarone versus sotalol for atrial fibrillation. *The New England journal of medicine*. 2005;352:1861-72.

290.   Capucci A, Piangerelli L, Ricciotti J, Gabrielli D and Guerra F. Flecainide-metoprolol combination reduces atrial fibrillation clinical recurrences and improves tolerability at 1-year follow-up in persistent symptomatic atrial fibrillation. *Europace*. 2016;18:1698-1704.

291.   Shiga T, Yoshioka K, Watanabe E, Omori H, Yagi M, Okumura Y, Matsumoto N, Kusano K, Oshiro C, Ikeda T, Takahashi N, Komatsu T, Suzuki A, Suzuki T, Sato Y, Yamashita T and investigators A-Qs. Paroxysmal atrial fibrillation recurrences and quality of life in symptomatic patients: A crossover study of flecainide and pilsicainide. *J Arrhythm*. 2017;33:310-317.

292.   Mont L, Bisbal F, Hernandez-Madrid A, Perez-Castellano N, Vinolas X, Arenal A, Arribas F, Fernandez-Lozano I, Bodegas A, Cobos A, Matia R, Perez-Villacastin J, Guerra JM, Avila P, Lopez-Gil M, Castro V, Arana JI, Brugada J and investigators S. Catheter ablation vs. antiarrhythmic drug treatment of persistent atrial fibrillation: a multicentre, randomized, controlled trial (SARA study). *Eur Heart J*. 2014;35:501-7.

293.   Morillo CA, Verma A, Connolly SJ, Kuck KH, Nair GM, Champagne J, Sterns LD, Beresh H, Healey JS, Natale A and Investigators R-. Radiofrequency ablation vs antiarrhythmic drugs as first-line treatment of paroxysmal atrial fibrillation (RAAFT-2): a randomized trial. *JAMA*. 2014;311:692-700.

294.   Hakalahti A, Biancari F, Nielsen JC and Raatikainen MJ. Radiofrequency ablation vs. antiarrhythmic drug therapy as first line treatment of symptomatic atrial fibrillation: systematic review and meta-analysis. *Europace*. 2015;17:370-8.

295.   Di Biase L, Mohanty P, Mohanty S, Santangeli P, Trivedi C, Lakkireddy D, Reddy M, Jais P, Themistoclakis S, Dello Russo A, Casella M, Pelargonio G, Narducci ML, Schweikert R, Neuzil P, Sanchez J, Horton R, Beheiry S, Hongo R, Hao S, Rossillo A, Forleo G, Tondo C, Burkhardt JD, Haissaguerre M and Natale A. Ablation Versus Amiodarone for Treatment of Persistent Atrial Fibrillation in Patients With Congestive Heart Failure and an Implanted Device: Results From the AATAC Multicenter Randomized Trial. *Circulation*. 2016;133:1637-44.

296.   Kuck KH, Brugada J, Furnkranz A, Metzner A, Ouyang F, Chun KR, Elvan A, Arentz T, Bestehorn K, Pocock SJ, Albenque JP, Tondo C, Fire and Investigators ICE. Cryoballoon or Radiofrequency Ablation for Paroxysmal Atrial Fibrillation. *The New England journal of medicine*. 2016;374:2235-45.

297.   Sohara H, Ohe T, Okumura K, Naito S, Hirao K, Shoda M, Kobayashi Y, Yamauchi Y, Yamaguchi Y, Kuwahara T, Hirayama H, YeongHwa C, Kusano K, Kaitani K, Banba K, Fujii S, Kumagai K, Yoshida H, Matsushita M, Satake S and Aonuma K. HotBalloon Ablation of the Pulmonary Veins for Paroxysmal AF: A Multicenter Randomized Trial in Japan. *J Am Coll Cardiol*. 2016;68:2747-2757.

298.   Nyong J, Amit G, Adler AJ, Owolabi OO, Perel P, Prieto-Merino D, Lambiase P, Casas JP and Morillo CA. Efficacy and safety of ablation for people with non-paroxysmal atrial fibrillation. *Cochrane Database Syst Rev*. 2016;11:CD012088.

299.   Nielsen JC, Johannessen A, Raatikainen P, Hindricks G, Walfridsson H, Pehrson SM, Englund A, Hartikainen J, Mortensen LS, Hansen PS and Investigators M-P. Long-term efficacy of catheter ablation as first-line therapy for paroxysmal atrial fibrillation: 5-year outcome in a randomised clinical trial. *Heart*. 2017;103:368-376.

300.   Chen C, Zhou X, Zhu M, Chen S, Chen J, Cai H, Dai J, Xu X and Mao W. Catheter ablation versus medical therapy for patients with persistent atrial fibrillation: a systematic

review and meta-analysis of evidence from randomized controlled trials. *Journal of interventional cardiac electrophysiology : an international journal of arrhythmias and pacing*. 2018;52:9-18.

301.   Packer DL, Mark DB, Robb RA, Monahan KH, Bahnson TD, Poole JE, Noseworthy PA, Rosenberg YD, Jeffries N, Mitchell LB, Flaker GC, Pokushalov E, Romanov A, Bunch TJ, Noelker G, Ardashev A, Revishvili A, Wilber DJ, Cappato R, Kuck K-H, Hindricks G, Davies DW, Kowey PR, Naccarelli GV, Reiffel JA, Piccini JP, Silverstein AP, Al-Khalidi HR, Lee KL and Investigators ftC. Effect of Catheter Ablation vs Antiarrhythmic Drug Therapy on Mortality, Stroke, Bleeding, and Cardiac Arrest Among Patients With Atrial Fibrillation: The CABANA Randomized Clinical Trial. *JAMA*. 2019;321:1261-1274.

302.   Mark DB, Anstrom KJ, Sheng S, Piccini JP, Baloch KN, Monahan KH, Daniels MR, Bahnson TD, Poole JE, Rosenberg Y, Lee KL, Packer DL and Investigators ftC. Effect of Catheter Ablation vs Medical Therapy on Quality of Life Among Patients With Atrial Fibrillation: The CABANA Randomized Clinical Trial. *JAMA*. 2019;321:1275-1285.

303.   Blomstrom-Lundqvist C, Gizurarson S, Schwieler J, Jensen SM, Bergfeldt L, Kenneback G, Rubulis A, Malmborg H, Raatikainen P, Lonnerholm S, Hoglund N and Mortsell D. Effect of Catheter Ablation vs Antiarrhythmic Medication on Quality of Life in Patients With Atrial Fibrillation: The CAPTAF Randomized Clinical Trial. *JAMA*. 2019;321:1059-1068.

304.   Teh AW, Kistler PM, Lee G, Medi C, Heck PM, Spence SJ, Sparks PB, Morton JB and Kalman JM. Electroanatomic remodeling of the left atrium in paroxysmal and persistent atrial fibrillation patients without structural heart disease. *Journal of cardiovascular electrophysiology*. 2012;23:232-8.

305.   D'Ascenzo F, Corleto A, Biondi-Zoccai G, Anselmino M, Ferraris F, di Biase L, Natale A, Hunter RJ, Schilling RJ, Miyazaki S, Tada H, Aonuma K, Yenn-Jiang L, Tao H, Ma C, Packer D, Hammill S and Gaita F. Which are the most reliable predictors of recurrence of atrial fibrillation after transcatheter ablation?: a meta-analysis. *Int J Cardiol*. 2013;167:1984-9.

306.   Berruezo A, Tamborero D, Mont L, Benito B, Tolosana JM, Sitges M, Vidal B, Arriagada G, Mendez F, Matiello M, Molina I and Brugada J. Pre-procedural predictors of atrial fibrillation recurrence after circumferential pulmonary vein ablation. *Eur Heart J*. 2007;28:836-41.

307.   Nedios S, Kosiuk J, Koutalas E, Kornej J, Sommer P, Arya A, Richter S, Rolf S, Husser D, Hindricks G and Bollmann A. Comparison of left atrial dimensions in CT and echocardiography as predictors of long-term success after catheter ablation of atrial fibrillation. *Journal of interventional cardiac electrophysiology : an international journal of arrhythmias and pacing*. 2015;43:237-44.

308.   Njoku A, Kannabhiran M, Arora R, Reddy P, Gopinathannair R, Lakkireddy D and Dominic P. Left atrial volume predicts atrial fibrillation recurrence after radiofrequency ablation: a meta-analysis. *Europace*. 2018;20:33-42.

309.   Costa FM, Ferreira AM, Oliveira S, Santos PG, Durazzo A, Carmo P, Santos KR, Cavaco D, Parreira L, Morgado F and Adragao P. Left atrial volume is more important than the type of atrial fibrillation in predicting the long-term success of catheter ablation. *Int J Cardiol*. 2015;184:56-61.

310.   Marrouche NF, Wilber D, Hindricks G, Jais P, Akoum N, Marchlinski F, Kholmovski E, Burgon N, Hu N, Mont L, Deneke T, Duytschaever M, Neumann T, Mansour M, Mahnkopf C, Herweg B, Daoud E, Wissner E, Bansmann P and Brachmann J. Association of atrial tissue fibrosis identified by delayed enhancement MRI and atrial fibrillation catheter ablation: the DECAAF study. *JAMA*. 2014;311:498-506.

311.   Natale A, Reddy VY, Monir G, Wilber DJ, Lindsay BD, McElderry HT, Kantipudi C, Mansour MC, Melby DP, Packer DL, Nakagawa H, Zhang B, Stagg RB, Boo LM and Marchlinski FE. Paroxysmal AF catheter ablation with a contact force sensing catheter: results of the prospective, multicenter SMART-AF trial. *J Am Coll Cardiol*. 2014;64:647-56.
312.   Arbelo E, Guiu E, Ramos P, Bisbal F, Borras R, Andreu D, Tolosana JM, Berruezo A, Brugada J and Mont L. Benefit of left atrial roof linear ablation in paroxysmal atrial fibrillation: a prospective, randomized study. *J Am Heart Assoc*. 2014;3:e000877.
313.   McLellan AJ, Ling LH, Azzopardi S, Lee GA, Lee G, Kumar S, Wong MC, Walters TE, Lee JM, Looi KL, Halloran K, Stiles MK, Lever NA, Fynn SP, Heck PM, Sanders P, Morton JB, Kalman JM and Kistler PM. A minimal or maximal ablation strategy to achieve pulmonary vein isolation for paroxysmal atrial fibrillation: a prospective multi-centre randomized controlled trial (the Minimax study). *Eur Heart J*. 2015;36:1812-21.
314.   Verma A, Jiang CY, Betts TR, Chen J, Deisenhofer I, Mantovan R, Macle L, Morillo CA, Haverkamp W, Weerasooriya R, Albenque JP, Nardi S, Menardi E, Novak P, Sanders P and Investigators SAI. Approaches to catheter ablation for persistent atrial fibrillation. *The New England journal of medicine*. 2015;372:1812-22.
315.   Luik A, Radzewitz A, Kieser M, Walter M, Bramlage P, Hormann P, Schmidt K, Horn N, Brinkmeier-Theofanopoulou M, Kunzmann K, Riexinger T, Schymik G, Merkel M and Schmitt C. Cryoballoon Versus Open Irrigated Radiofrequency Ablation in Patients With Paroxysmal Atrial Fibrillation: The Prospective, Randomized, Controlled, Noninferiority FreezeAF Study. *Circulation*. 2015;132:1311-9.
316.   Dukkipati SR, Cuoco F, Kutinsky I, Aryana A, Bahnson TD, Lakkireddy D, Woollett I, Issa ZF, Natale A, Reddy VY and HeartLight Study I. Pulmonary Vein Isolation Using the Visually Guided Laser Balloon: A Prospective, Multicenter, and Randomized Comparison to Standard Radiofrequency Ablation. *J Am Coll Cardiol*. 2015;66:1350-60.
317.   Reddy VY, Dukkipati SR, Neuzil P, Natale A, Albenque JP, Kautzner J, Shah D, Michaud G, Wharton M, Harari D, Mahapatra S, Lambert H and Mansour M. Randomized, Controlled Trial of the Safety and Effectiveness of a Contact Force-Sensing Irrigated Catheter for Ablation of Paroxysmal Atrial Fibrillation: Results of the TactiCath Contact Force Ablation Catheter Study for Atrial Fibrillation (TOCCASTAR) Study. *Circulation*. 2015;132:907-15.
318.   Scherr D, Khairy P, Miyazaki S, Aurillac-Lavignolle V, Pascale P, Wilton SB, Ramoul K, Komatsu Y, Roten L, Jadidi A, Linton N, Pedersen M, Daly M, O'Neill M, Knecht S, Weerasooriya R, Rostock T, Manninger M, Cochet H, Shah AJ, Yeim S, Denis A, Derval N, Hocini M, Sacher F, Haissaguerre M and Jais P. Five-year outcome of catheter ablation of persistent atrial fibrillation using termination of atrial fibrillation as a procedural endpoint. *Circ Arrhythm Electrophysiol*. 2015;8:18-24.
319.   Kuck KH, Hoffmann BA, Ernst S, Wegscheider K, Treszl A, Metzner A, Eckardt L, Lewalter T, Breithardt G, Willems S and Gap AFAI. Impact of Complete Versus Incomplete Circumferential Lines Around the Pulmonary Veins During Catheter Ablation of Paroxysmal Atrial Fibrillation: Results From the Gap-Atrial Fibrillation-German Atrial Fibrillation Competence Network 1 Trial. *Circ Arrhythm Electrophysiol*. 2016;9:e003337.
320.   Nery PB, Belliveau D, Nair GM, Bernick J, Redpath CJ, Szczotka A, Sadek MM, Green MS, Wells G and Birnie DH. Relationship Between Pulmonary Vein Reconnection and Atrial Fibrillation Recurrence: A Systematic Review and Meta-Analysis. *JACC Clin Electrophysiol*. 2016;2:474-483.
321.   Bassiouny M, Saliba W, Hussein A, Rickard J, Diab M, Aman W, Dresing T, Callahan Tt, Bhargava M, Martin DO, Shao M, Baranowski B, Tarakji K, Tchou PJ, Hakim A, Kanj M,

Lindsay B and Wazni O. Randomized Study of Persistent Atrial Fibrillation Ablation: Ablate in Sinus Rhythm Versus Ablate Complex-Fractionated Atrial Electrograms in Atrial Fibrillation. *Circ Arrhythm Electrophysiol*. 2016;9:e003596.

322.   Hindricks G, Sepehri Shamloo A, Lenarczyk R, Kalarus Z, Arya A, Kircher S, Darma A and Dagres N. Catheter ablation of atrial fibrillation: current status, techniques, outcomes and challengesCatheter ablation of atrial fibrillation: current status, techniques, outcomes, and challenges. *Kardiologia polska*. 2018;76:1680-1686.

323.   Pathak RK, Middeldorp ME, Lau DH, Mehta AB, Mahajan R, Twomey D, Alasady M, Hanley L, Antic NA, McEvoy RD, Kalman JM, Abhayaratna WP and Sanders P. Aggressive risk factor reduction study for atrial fibrillation and implications for the outcome of ablation: the ARREST-AF cohort study. *J Am Coll Cardiol*. 2014;64:2222-31.

324.   Pathak RK, Elliott A, Middeldorp ME, Meredith M, Mehta AB, Mahajan R, Hendriks JM, Twomey D, Kalman JM, Abhayaratna WP, Lau DH and Sanders P. Impact of CARDIOrespiratory FITness on Arrhythmia Recurrence in Obese Individuals With Atrial Fibrillation: The CARDIO-FIT Study. *J Am Coll Cardiol*. 2015;66:985-96.

325.   Pathak RK, Middeldorp ME, Meredith M, Mehta AB, Mahajan R, Wong CX, Twomey D, Elliott AD, Kalman JM, Abhayaratna WP, Lau DH and Sanders P. Long-Term Effect of Goal-Directed Weight Management in an Atrial Fibrillation Cohort: A Long-Term Follow-Up Study (LEGACY). *J Am Coll Cardiol*. 2015;65:2159-69.

326.   Donnellan E, Wazni OM, Kanj M, Baranowski B, Cremer P, Harb S, McCarthy CP, McEvoy JW, Elshazly MB, Aagaard P, Tarakji KG, Jaber WA, Schauer PR and Saliba WI. Association between pre-ablation bariatric surgery and atrial fibrillation recurrence in morbidly obese patients undergoing atrial fibrillation ablation. *Europace*. 2019;21:1476-1483.

327.   Donnellan E, Aagaard P, Kanj M, Jaber W, Elshazly M, Hoosien M, Baranowski B, Hussein A, Saliba W and Wazni O. Association Between Pre-Ablation Glycemic Control and Outcomes Among Patients With Diabetes Undergoing Atrial Fibrillation Ablation. *JACC Clin Electrophysiol*. 2019;5:897-903.

328.   Voskoboinik A, Kalman JM, De Silva A, Nicholls T, Costello B, Nanayakkara S, Prabhu S, Stub D, Azzopardi S, Vizi D, Wong G, Nalliah C, Sugumar H, Wong M, Kotschet E, Kaye D, Taylor AJ and Kistler PM. Alcohol Abstinence in Drinkers with Atrial Fibrillation. *The New England journal of medicine*. 2020;382:20-28.

329.   Elliott AD, Linz D, Mishima R, Kadhim K, Gallagher C, Middeldorp ME, Verdicchio CV, Hendriks JML, Lau DH, La Gerche A and Sanders P. Association between physical activity and risk of incident arrhythmias in 402 406 individuals: evidence from the UK Biobank cohort. *Eur Heart J*. 2020;41:1479-1486.

330.   Lau DH, Nattel S, Kalman JM and Sanders P. Modifiable Risk Factors and Atrial Fibrillation. *Circulation*. 2017;136:583-596.

331.   Abed HS, Wittert GA, Leong DP, Shirazi MG, Bahrami B, Middeldorp ME, Lorimer MF, Lau DH, Antic NA, Brooks AG, Abhayaratna WP, Kalman JM and Sanders P. Effect of weight reduction and cardiometabolic risk factor management on symptom burden and severity in patients with atrial fibrillation: a randomized clinical trial. *JAMA*. 2013;310:2050-60.

332.   Lavie CJ, Thomas RJ, Squires RW, Allison TG and Milani RV. Exercise training and cardiac rehabilitation in primary and secondary prevention of coronary heart disease. *Mayo Clin Proc*. 2009;84:373-83.

333.   Mont L. Arrhythmias and sport practice. *Heart*. 2010;96:398-405.

334.   Menezes AR, Lavie CJ, De Schutter A, Milani RV, O'Keefe J, DiNicolantonio JJ, Morin DP and Abi-Samra FM. Lifestyle modification in the prevention and treatment of atrial fibrillation. *Progress in cardiovascular diseases*. 2015;58:117-25.

335.   Conen D and Albert CM. Alcohol consumption and risk of atrial fibrillation: how much is too much? *J Am Coll Cardiol*. 2014;64:290-2.

336.   Larsson SC, Drca N and Wolk A. Alcohol consumption and risk of atrial fibrillation: a prospective study and dose-response meta-analysis. *J Am Coll Cardiol*. 2014;64:281-9.

337.   Pisters R, Lane DA, Marin F, Camm AJ and Lip GY. Stroke and thromboembolism in atrial fibrillation. *Circ J*. 2012;76:2289-304.

338.   Freedman B, Camm J, Calkins H, Healey JS, Rosenqvist M, Wang J, Albert CM, Anderson CS, Antoniou S, Benjamin EJ, Boriani G, Brachmann J, Brandes A, Chao TF, Conen D, Engdahl J, Fauchier L, Fitzmaurice DA, Friberg L, Gersh BJ, Gladstone DJ, Glotzer TV, Gwynne K, Hankey GJ, Harbison J, Hillis GS, Hills MT, Kamel H, Kirchhof P, Kowey PR, Krieger D, Lee VWY, Levin LA, Lip GYH, Lobban T, Lowres N, Mairesse GH, Martinez C, Neubeck L, Orchard J, Piccini JP, Poppe K, Potpara TS, Puererfellner H, Rienstra M, Sandhu RK, Schnabel RB, Siu CW, Steinhubl S, Svendsen JH, Svennberg E, Themistoclakis S, Tieleman RG, Turakhia MP, Tveit A, Uittenbogaart SB, Van Gelder IC, Verma A, Wachter R, Yan BP and AF-SCREEN Collaborators. Screening for Atrial Fibrillation: A Report of the AF-SCREEN International Collaboration. *Circulation*. 2017;135:1851-1867.

339.   Epstein LJ, Kristo D, Strollo PJ, Jr., Friedman N, Malhotra A, Patil SP, Ramar K, Rogers R, Schwab RJ, Weaver EM, Weinstein MD and Adult Obstructive Sleep Apnea Task Force of the American Academy of Sleep M. Clinical guideline for the evaluation, management and long-term care of obstructive sleep apnea in adults. *Journal of clinical sleep medicine : JCSM : official publication of the American Academy of Sleep Medicine*. 2009;5:263-76.

340.   Linz D, McEvoy RD, Cowie MR, Somers VK, Nattel S, Levy P, Kalman JM and Sanders P. Associations of Obstructive Sleep Apnea With Atrial Fibrillation and Continuous Positive Airway Pressure Treatment: A Review. *JAMA cardiology*. 2018;3:532-540.

341.   Lip GYH, Coca A, Kahan T, Boriani G, Manolis AS, Olsen MH, Oto A, Potpara TS, Steffel J, Marin F, de Oliveira Figueiredo MJ, de Simone G, Tzou WS, Chiang CE, Williams B, Reviewers, Dan GA, Gorenek B, Fauchier L, Savelieva I, Hatala R, van Gelder I, Brguljan-Hitij J, Erdine S, Lovic D, Kim YH, Salinas-Arce J and Field M. Hypertension and cardiac arrhythmias: a consensus document from the European Heart Rhythm Association (EHRA) and ESC Council on Hypertension, endorsed by the Heart Rhythm Society (HRS), Asia-Pacific Heart Rhythm Society (APHRS) and Sociedad Latinoamericana de Estimulacion Cardiaca y Electrofisiologia (SOLEACE). *Europace*. 2017;19:891-911.

342.   Hobbs FD, Fitzmaurice DA, Mant J, Murray E, Jowett S, Bryan S, Raftery J, Davies M and Lip G. A randomised controlled trial and cost-effectiveness study of systematic screening (targeted and total population screening) versus routine practice for the detection of atrial fibrillation in people aged 65 and over. The SAFE study. *Health Technol Assess*. 2005;9:iii-iv, ix-x, 1-74.

343.   Pallisgaard JL, Schjerning AM, Lindhardt TB, Procida K, Hansen ML, Torp-Pedersen C and Gislason GH. Risk of atrial fibrillation in diabetes mellitus: A nationwide cohort study. *Eur J Prev Cardiol*. 2016;23:621-7.

344.   Wynn GJ, Todd DM, Webber M, Bonnett L, McShane J, Kirchhof P and Gupta D. The European Heart Rhythm Association symptom classification for atrial fibrillation: validation and improvement through a simple modification. *Europace : European pacing, arrhythmias, and cardiac electrophysiology : journal of the working groups on cardiac pacing,*

arrhythmias, and cardiac cellular electrophysiology of the European Society of Cardiology. 2014;16:965-72.

345.   Friberg L, Rosenqvist M and Lip GYH. Evaluation of risk stratification schemes for ischaemic stroke and bleeding in 182 678 patients with atrial fibrillation: the Swedish Atrial Fibrillation cohort study. *European Heart Journal*. 2012;33:1500-1510.

346.   Schulman S and Kearon C. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. *Journal of thrombosis and haemostasis : JTH*. 2005;3:692-4.

347.   Schulman S, Angeras U, Bergqvist D, Eriksson B, Lassen MR, Fisher W, SCIENTIFIC OBOTSOCOAOT, THROMBOSIS SCOTISO and HAEMOSTASIS. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in surgical patients. *Journal of Thrombosis and Haemostasis*. 2010;8:202-204.

348.   Calvert M, Kyte D, Price G, Valderas JM and Hjollund NH. Maximising the impact of patient reported outcome assessment for patients and society. *BMJ (Clinical research ed)*. 2019;364:k5267.

349.   Rotenstein LS, Huckman RS and Wagle NW. Making Patients and Doctors Happier - The Potential of Patient-Reported Outcomes. *The New England journal of medicine*. 2017;377:1309-1312.

350.   Steinberg BA, Dorian P, Anstrom KJ, Hess R, Mark DB, Noseworthy PA, Spertus JA and Piccini JP. Patient-Reported Outcomes in Atrial Fibrillation Research: Results of a Clinicaltrials.gov Analysis. *JACC Clinical electrophysiology*. 2019;5:599-605.

351.   Aliot E, Botto GL, Crijns HJ and Kirchhof P. Quality of life in patients with atrial fibrillation: how to assess it and how to improve it. *Europace : European pacing, arrhythmias, and cardiac electrophysiology : journal of the working groups on cardiac pacing, arrhythmias, and cardiac cellular electrophysiology of the European Society of Cardiology*. 2014;16:787-96.

352.   Ware J, Jr., Kosinski M and Keller SD. A 12-Item Short-Form Health Survey: construction of scales and preliminary tests of reliability and validity. *Medical care*. 1996;34:220-33.

353.   Kotecha D, Ahmed A, Calvert M, Lencioni M, Terwee CB and Lane DA. Patient-Reported Outcomes for Quality of Life Assessment in Atrial Fibrillation: A Systematic Review of Measurement Properties. *PloS one*. 2016;11:e0165790.

354.   Spertus J, Dorian P, Bubien R, Lewis S, Godejohn D, Reynolds MR, Lakkireddy DR, Wimmer AP, Bhandari A and Burk C. Development and validation of the Atrial Fibrillation Effect on QualiTy-of-Life (AFEQT) Questionnaire in patients with atrial fibrillation. *Circulation Arrhythmia and electrophysiology*. 2011;4:15-25.

355.   Singh SN, Tang XC, Singh BN, Dorian P, Reda DJ, Harris CL, Fletcher RD, Sharma SC, Atwood JE, Jacobson AK, Lewis HD, Lopez B, Raisch DW and Ezekowitz MD. Quality of Life and Exercise Performance in Patients in Sinus Rhythm Versus Persistent Atrial Fibrillation: A Veterans Affairs Cooperative Studies Program Substudy. *Journal of the American College of Cardiology*. 2006;48:721-730.

356.   Dorian P, Guerra PG, Kerr CR, O'Donnell SS, Crystal E, Gillis AM, Mitchell LB, Roy D, Skanes AC, Rose MS and Wyse DG. Validation of a New Simple Scale to Measure Symptoms in Atrial Fibrillation. *Circulation: Arrhythmia and Electrophysiology*. 2009;2:218-224.

357.   Dorian P, Jung W, Newman D, Paquette M, Wood K, Ayers GM, Camm J, Akhtar M and Luderitz B. The impairment of health-related quality of life in patients with intermittent

atrial fibrillation: implications for the assessment of investigational therapy. *Journal of the American College of Cardiology*. 2000;36:1303-1309.

358.   Seligman WH, Das-Gupta Z, Jobi-Odeneye AO, Arbelo E, Banerjee A, Bollmann A, Caffrey-Armstrong B, Cehic DA, Corbalan R, Collins M, Dandamudi G, Dorairaj P, Fay M, Van Gelder IC, Goto S, Granger CB, Gyorgy B, Healey JS, Hendriks JM, Hills MT, Hobbs FDR, Huisman MV, Koplan KE, Lane DA, Lewis WR, Lobban T, Steinberg BA, McLeod CJ, Moseley S, Timmis A, Yutao G and Camm AJ. Development of an international standard set of outcome measures for patients with atrial fibrillation: a report of the International Consortium for Health Outcomes Measurement (ICHOM) atrial fibrillation working group. *European heart journal*. 2020;41:1132-1140.

359.   *Crossing the Quality Chasm: A New Health System for the 21st Century*. Washington (DC): National Academies Press (US); 2001.

360.   Benjamin EJ, Muntner P, Alonso A, Bittencourt MS, Callaway CW, Carson AP, Chamberlain AM, Chang AR, Cheng S, Das SR, Delling FN, Djousse L, Elkind MSV, Ferguson JF, Fornage M, Jordan LC, Khan SS, Kissela BM, Knutson KL, Kwan TW, Lackland DT, Lewis TT, Lichtman JH, Longenecker CT, Loop MS, Lutsey PL, Martin SS, Matsushita K, Moran AE, Mussolino ME, O'Flaherty M, Pandey A, Perak AM, Rosamond WD, Roth GA, Sampson UKA, Satou GM, Schroeder EB, Shah SH, Spartano NL, Stokes A, Tirschwell DL, Tsao CW, Turakhia MP, VanWagner LB, Wilkins JT, Wong SS, Virani SS, American Heart Association Council on E, Prevention Statistics C and Stroke Statistics S. Heart Disease and Stroke Statistics-2019 Update: A Report From the American Heart Association. *Circulation*. 2019;139:e56-e528.

361.   Gorin L, Fauchier L, Nonin E, Charbonnier B, Babuty D and Lip GYH. Prognosis and Guideline-Adherent Antithrombotic Treatment in Patients With Atrial Fibrillation and Atrial Flutter: Implications of Undertreatment and Overtreatment in Real-life Clinical Practice; the Loire Valley Atrial Fibrillation Project. *Chest*. 2011;140:911-917.

362.   Nielsen PB, Larsen TB, Skjøth F, Overvad TF and Lip GYH. Stroke and thromboembolic event rates in atrial fibrillation according to different guideline treatment thresholds: A nationwide cohort study. *Scientific Reports*. 2016;6:27410.

363.   Lip GYH, Laroche C, Dan G-A, Santini M, Kalarus Z, Rasmussen LH, Oliveira MM, Mairesse G, Crijns HJGM, Simantirakis E, Atar D, Kirchhof P, Vardas P, Tavazzi L and Maggioni AP. A prospective survey in European Society of Cardiology member countries of atrial fibrillation management: baseline results of EURObservational Research Programme Atrial Fibrillation (EORP-AF) Pilot General Registry. *Europace*. 2014;16:308-319.

364.   Lip GYH, Laroche C, Dan G-A, Santini M, Kalarus Z, Rasmussen LH, Ioachim PM, Tica O, Boriani G, Cimaglia P, Diemberger I, Hellum CF, Mortensen B and Maggioni AP. 'Real-World' Antithrombotic Treatment in Atrial Fibrillation: The EORP-AF Pilot Survey. *American Journal of Medicine*. 2014;127:519-529.e1.

365.   Lip GYH, Laroche C, Popescu MI, Rasmussen LH, Vitali-Serdoz L, Dan G-A, Kalarus Z, Crijns HJGM, Oliveira MM, Tavazzi L, Maggioni AP and Boriani G. Improved outcomes with European Society of Cardiology guideline-adherent antithrombotic treatment in high-risk patients with atrial fibrillation: a report from the EORP-AF General Pilot Registry. *EP Europace*. 2015;17:1777-1786.

366.   Lip GYH, Laroche C, Boriani G, Dan G-A, Santini M, Kalarus Z, Rasmussen LH, Oliveira MM, Mairesse G, Crijns HJGM, Simantirakis E, Atar D, Maggioni AP and Tavazzi L. Regional differences in presentation and treatment of patients with atrial fibrillation in Europe: a report from the EURObservational Research Programme Atrial Fibrillation (EORP-AF) Pilot General Registry. *Europace*. 2015;17:194-206.

367.	Fumagalli S, Said SAM, Laroche C, Gabbai D, Marchionni N, Boriani G, Maggioni AP, Popescu MI, Rasmussen LH, Crijns HJGM and Lip GYH. Age-Related Differences in Presentation, Treatment, and Outcome of Patients With Atrial Fibrillation in Europe: The EORP-AF General Pilot Registry (EURObservational Research Programme-Atrial Fibrillation). *JACC: Clinical Electrophysiology*. 2015;1:326-334.

368.	Boriani G, Laroche C, Diemberger I, Fantecchi E, Popescu MI, Rasmussen LH, Sinagra G, Petrescu L, Tavazzi L, Maggioni AP and Lip GYH. Asymptomatic Atrial Fibrillation: Clinical Correlates, Management, and Outcomes in the EORP-AF Pilot General Registry. *American Journal of Medicine*. 2015;128:509-518.e2.

369.	Boriani G, Laroche C, Diemberger I, Fantecchi E, Popescu MI, Rasmussen LH, Dan G-A, Kalarus Z, Tavazzi L, Maggioni AP and Lip GYH. 'Real-world' management and outcomes of patients with paroxysmal vs. non-paroxysmal atrial fibrillation in Europe: the EURObservational Research Programme–Atrial Fibrillation (EORP-AF) General Pilot Registry. *EP Europace*. 2016;18:648-657.

370.	Proietti M, Laroche C, Opolski G, Maggioni AP, Boriani G and Lip GYH. 'Real-world' atrial fibrillation management in Europe: observations from the 2-year follow-up of the EURObservational Research Programme-Atrial Fibrillation General Registry Pilot Phase. *Europace*. 2016.

371.	Boriani G, Glotzer TV, Ziegler PD, De Melis M, Mangoni di S. Stefano L, Sepsi M, Landolina M, Lunati M, Lewalter T and Camm AJ. Detection of new atrial fibrillation in patients with cardiac implanted electronic devices and factors associated with transition to higher device-detected atrial fibrillation burden. *Heart Rhythm*. 2018;15:376-383.

372.	Arbelo E, Brugada J, Hindricks G, Maggioni AP, Tavazzi L, Vardas P, Laroche C, Anselme F, Inama G, Jais P, Kalarus Z, Kautzner J, Lewalter T, Mairesse GH, Perez-Villacastin J, Riahi S, Taborsky M, Theodorakis G, Trines SA and Investigators otbotAFAPS. The Atrial Fibrillation Ablation Pilot Study: an European Survey on Methodology and results of catheter ablation for atrial fibrillation conducted by the European Heart Rhythm Association. *European Heart Journal*. 2014;35:1466-1478.

373.	Arbelo E, Brugada J, Lundqvist CB, Laroche C, Kautzner J, Pokushalov E, Raatikainen P, Efremidis M, Hindricks G, Barrera A, Maggioni A, Tavazzi L and Dagres N. Contemporary management of patients undergoing atrial fibrillation ablation: in-hospital and 1-year follow-up findings from the ESC-EHRA atrial fibrillation ablation long-term registry. *European Heart Journal*. 2017.

374.	Riahi S, Arbelo E, Brugada J, Maggioni AP, Tavazzi L, Vardas P, Laroche C, Efremidis M, Xhaet O, Woźniak A, Van Gelder IC and Hjortshoj S. Regional differences in referral, procedures, and outcome after ablation for atrial fibrillation in Europe: a report from the Atrial Fibrillation Ablation Pilot Registry of the European Society of Cardiology. *Europace*. 2016;18:191-200.

375.	Barnett AS, Kim S, Fonarow GC, Thomas LE, Reiffel JA, Allen LA, Freeman JV, Naccarelli G, Mahaffey KW, Go AS, Kowey PR, Ansell JE, Gersh BJ, Hylek EM, Peterson ED and Piccini JP. Treatment of Atrial Fibrillation and Concordance With the American Heart Association/American College of Cardiology/Heart Rhythm Society Guidelines. *Circulation: Arrhythmia and Electrophysiology*. 2017;10:e005051.

376.	Potpara TS, Lip GYH, Dagres N, Crijns HJMG, Boriani G, Kirchhof P, Arbelo E, Savelieva I, Lenarczyk R, Fauchier L, Maggioni AP, Gale CP and Group tE-AII. Cohort profile The ESC EURObservational Research Programme Atrial Fibrillation III (AF III) Registry. *European Heart Journal - Quality of Care and Clinical Outcomes*. 2020.

377. McNamara RL, Brass LM, Drozda JP, Go AS, Halperin JL, Kerr CR, Lévy S, Malenka DJ, Mittal S, Pelosi F, Rosenberg Y, Stryer D, Wyse DG, Radford MJ, Goff DC, Grover FL, Heidenreich PA, Malenka DJ, Peterson ED and Redberg RF. ACC/AHA key data elements and definitions for measuring the clinical management and outcomes of patients with atrial fibrillation. A report of the American College of Cardiology/American Heart Association Task Force on clinical data standards (writing commitee to develop data standards on atrial fibrillation). *Journal of the American College of Cardiology*. 2004;44:475-495.

378. Staerk L, Lip GY, Olesen JB, Fosbol EL, Pallisgaard JL, Bonde AN, Gundlund A, Lindhardt TB, Hansen ML, Torp-Pedersen C and Gislason GH. Stroke and recurrent haemorrhage associated with antithrombotic treatment after gastrointestinal bleeding in patients with atrial fibrillation: nationwide cohort study. *BMJ (Clinical research ed)*. 2015;351:h5876.

379. Van Gelder IC, Groenveld HF, Crijns HJGM, Tuininga YS, Tijssen JGP, Alings AM, Hillege HL, Bergsma-Kadijk JA, Cornel JH, Kamp O, Tukkie R, Bosker HA, Van Veldhuisen DJ and Van den Berg MP. Lenient versus Strict Rate Control in Patients with Atrial Fibrillation. *New England Journal of Medicine*. 2010;362:1363-1373.

380. Seligman WH, Das-Gupta Z, Jobi-Odeneye AO, Arbelo E, Banerjee A, Bollmann A, Caffrey-Armstrong B, Cehic DA, Corbalan R, Collins M, Dandamudi G, Dorairaj P, Fay M, Van Gelder IC, Goto S, Granger CB, Gyorgy B, Healey JS, Hendriks JM, Hills MT, Hobbs FDR, Huisman MV, Koplan KE, Lane DA, Lewis WR, Lobban T, Steinberg BA, McLeod CJ, Moseley S, Timmis A, Yutao G and Camm AJ. Development of an international standard set of outcome measures for patients with atrial fibrillation: a report of the International Consortium for Health Outcomes Measurement (ICHOM) atrial fibrillation working group. *European Heart Journal*. 2020.

381. Calvert M, Blazeby J, Altman DG and et al. Reporting of patient-reported outcomes in randomized trials: The consort pro extension. *JAMA*. 2013;309:814-822.

382. Wallentin L, Gale CP, Maggioni A, Bardinet I and Casadei B. EuroHeart: European Unified Registries On Heart Care Evaluation and Randomized Trials: An ESC project to develop a new IT registry system which will encompass multiple features of cardiovascular medicine. *European Heart Journal*. 2019;40:2745-2749.

383. Bunting KV, Van Gelder IC and Kotecha D. STEEER-AF: a cluster-randomized education trial from the ESC: The STEEER-AF trial is designed by the European Society of Cardiology (ESC) to see if better education for healthcare professionals can improve how patients are treated and how AF is managed. *European Heart Journal*. 2020;41:1952-1954.

384. Nielsen JC GM, et al. ESC Guidelines on cardiac pacing and CRT. 2021.

385. Bradshaw PJ, Stobie P, Knuiman MW, Briffa TG and Hobbs MS. Trends in the incidence and prevalence of cardiac pacemaker insertions in an ageing population. *Open Heart*. 2014;1:e000177.

386. Raatikainen MJP, Arnar DO, Merkely B, Nielsen JC, Hindricks G, Heidbuchel H and Camm J. A Decade of Information on the Use of Cardiac Implantable Electronic Devices and Interventional Electrophysiological Procedures in the European Society of Cardiology Countries: 2017 Report from the European Heart Rhythm Association. *EP Europace*. 2017;19:ii1-ii90.

387. Kirkfeldt RE, Johansen JB, Nohr EA, Jørgensen OD and Nielsen JC. Complications after cardiac implantable electronic device implantations: an analysis of a complete, nationwide cohort in Denmark. *Eur Heart J*. 2014;35:1186-94.

388.   Olsen T, Jørgensen OD, Nielsen JC, Thøgersen AM, Philbert BT and Johansen JB. Incidence of device-related infection in 97 750 patients: clinical data from the complete Danish device-cohort (1982-2018). *Eur Heart J*. 2019;40:1862-1869.

389.   Medicine Io. *Best Care at Lower Cost: The Path to Continuously Learning Health Care in America*. Washington, DC: The National Academies Press; 2013.

390.   Centers for Medicare and Medicaide Services Measures Inventory Tool. Available at: https://cmit.cms.gov/CMIT_public/ViewMeasure?MeasureId=2389. Accessed 17 December 2020.

391.   Centers for Medicare and Medicaide Services Measures Inventory Tool. Available at: https://cmit.cms.gov/CMIT_public/ViewMeasure?MeasureId=3218. Accessed 17 December 2020.

392.   Centers for Medicare and Medicaide Services Measures Inventory Tool. Available at: https://cmit.cms.gov/CMIT_public/ViewMeasure?MeasureId=1979. Accessed 17 December 2020.

393.   Aktaa S, Polovina M, …, Gale CP and Coats A. Quality indicators for the care and outcomes of adults with heart failure.
The Working Group for Heart Failure Quality Indicators of the Heart Failure Association of the European Society of Cardiology
. 2021.

394.   Heidenreich PA, Solis P, Estes NAM, Fonarow GC, Jurgens CY, Marine JE, McManus DD and McNamara RL. 2016 ACC/AHA Clinical Performance and Quality Measures for Adults With Atrial Fibrillation or Atrial Flutter. *A Report of the American College of Cardiology/American Heart Association Task Force on Performance Measures*. 2016;68:525-568.

395.   Zhang S, Gaiser S and Kolominsky-Rabas PL. Cardiac implant registries 2006-2016: A systematic review and summary of global experiences. *BMJ Open*. 2018;8:e019039.

396.   Kusumoto FM, Schoenfeld MH, Barrett C, Edgerton JR, Ellenbogen KA, Gold MR, Goldschlager NF, Hamilton RM, Joglar JA, Kim RJ, Lee R, Marine JE, McLeod CJ, Oken KR, Patton KK, Pellegrini CN, Selzman KA, Thompson A and Varosy PD. 2018 ACC/AHA/HRS Guideline on the Evaluation and Management of Patients With Bradycardia and Cardiac Conduction Delay: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. *Circulation*. 2019;140:e382-e482.

397.   Brignole M, Auricchio A, Baron-Esquivias G, Bordachar P, Boriani G, Breithardt OA, Cleland J, Deharo JC, Delgado V, Elliott PM, Gorenek B, Israel CW, Leclercq C, Linde C, Mont L, Padeletti L, Sutton R, Vardas PE, Zamorano JL, Achenbach S, Baumgartner H, Bax JJ, Bueno H, Dean V, Deaton C, Erol C, Fagard R, Ferrari R, Hasdai D, Hoes AW, Kirchhof P, Knuuti J, Kolh P, Lancellotti P, Linhart A, Nihoyannopoulos P, Piepoli MF, Ponikowski P, Sirnes PA, Tamargo JL, Tendera M, Torbicki A, Wijns W, Windecker S, Kirchhof P, Blomstrom-Lundqvist C, Badano LP, Aliyev F, Bänsch D, Baumgartner H, Bsata W, Buser P, Charron P, Daubert JC, Dobreanu D, Faerestrand S, Hasdai D, Hoes AW, Le Heuzey JY, Mavrakis H, McDonagh T, Merino JL, Nawar MM, Nielsen JC, Pieske B, Poposka L, Ruschitzka F, Tendera M, Van Gelder IC and Wilson CM. 2013 ESC Guidelines on cardiac pacing and cardiac resynchronization therapy: the Task Force on cardiac pacing and resynchronization therapy of the European Society of Cardiology (ESC). Developed in collaboration with the European Heart Rhythm Association (EHRA). *Eur Heart J*. 2013;34:2281-329.

398. Haines DE, Beheiry S, Akar JG, Baker JL, Beinborn D, Beshai JF, Brysiewicz N, Chiu-Man C, Collins KK, Dare M, Fetterly K, Fisher JD, Hongo R, Irefin S, Lopez J, Miller JM, Perry JC, Slotwiner DJ, Tomassoni GF and Weiss E. Heart Rythm Society expert consensus statement on electrophysiology laboratory standards: process, protocols, equipment, personnel, and safety. *Heart Rhythm*. 2014;11:e9-51.

399. Abdin A and Aktaa S. Outcomes of conduction system pacingcompared to right ventricular pacing as a primary strategy for treating bradyarrhythmia: Systematic review and meta-analysis. *Clinical Research in Cardiology In Press* 2021.

400. Brook RH. The RAND/UCLA appropriateness method. . In: K. A. McCormack, S. R. Moore and R. A. Siegel, eds. *Clinical Practice Guideline Development: Methodology Perspectives* Rockville, MD: Agency for Healthcare Research and Policy; 1994.

401. Gurvitz M, Marelli A, Mangione-Smith R and Jenkins K. Building quality indicators to improve care for adults with congenital heart disease. *Journal of the American College of Cardiology*. 2013;62:2244-2253.

402. Mangione-Smith R, DeCristofaro AH, Setodji CM, Keesey J, Klein DJ, Adams JL, Schuster MA and McGlynn EA. The Quality of Ambulatory Care Delivered to Children in the United States. *New England Journal of Medicine*. 2007;357:1515-1523.

403. Nowak B, Tasche K, Barnewold L, Heller G, Schmidt B, Bordignon S, Chun KR, Fürnkranz A and Mehta RH. Association between hospital procedure volume and early complications after pacemaker implantation: results from a large, unselected, contemporary cohort of the German nationwide obligatory external quality assurance programme. *Europace*. 2015;17:787-93.

404. Curtis AB, Worley SJ, Adamson PB, Chung ES, Niazi I, Sherfesee L, Shinn T and St. John Sutton M. Biventricular Pacing for Atrioventricular Block and Systolic Dysfunction. *New England Journal of Medicine*. 2013;368:1585-1593.

405. Klug D, Balde M, Pavin D, Hidden-Lucet F, Clementy J, Sadoul N, Rey JL, Lande G, Lazarus A, Victor J, Barnay C, Grandbastien B and Kacet S. Risk factors related to infections of implanted pacemakers and cardioverter-defibrillators: results of a large prospective study. *Circulation*. 2007;116:1349-55.

406. Polyzos KA, Konstantelias AA and Falagas ME. Risk factors for cardiac implantable electronic device infection: a systematic review and meta-analysis. *Europace*. 2015;17:767-77.

407. Blomström-Lundqvist C, Traykov V, Erba PA, Burri H, Nielsen JC, Bongiorni MG, Poole J, Boriani G, Costa R, Deharo JC, Epstein LM, Saghy L, Snygg-Martin U, Starck C, Tascini C and Strathmore N. European Heart Rhythm Association (EHRA) international consensus document on how to prevent, diagnose, and treat cardiac implantable electronic device infections-endorsed by the Heart Rhythm Society (HRS), the Asia Pacific Heart Rhythm Society (APHRS), the Latin American Heart Rhythm Society (LAHRS), International Society for Cardiovascular Infectious Diseases (ISCVID) and the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS). *Europace*. 2020;22:515-549.

408. Cella D HE, Jensen SE, et al. Patient-Reported Outcomes in Performance Measurement. Research Triangle Park (NC): RTI Press; 2015 Sep. Types of Patient-Reported Outcomes. Available from: https://www.ncbi.nlm.nih.gov/books/NBK424381/.

409. Algurén B, Coenen M, Malm D, Fridlund B, Mårtensson J, Årestedt K, on behalf of the C and Exchange in Swedish cardiovascular caring Academic Research g. A scoping review and mapping exercise comparing the content of patient-reported outcome measures

(PROMs) across heart disease-specific scales. *Journal of Patient-Reported Outcomes*. 2020;4:7.

410.   Udo EO, van Hemel NM, Zuithoff NPA, Nijboer H, Taks W, Doevendans PA and Moons KGM. Long term quality-of-life in patients with bradycardia pacemaker implantation. *International Journal of Cardiology*. 2013;168:2159-2163.

411.   Aktaa S, Yadegarfar M, Wu J, Rashid M and al. e. Quality of acute myocardial infarction care in England and Wales during the COVID-19 pandemic: linked nationwide cohort study. 2021.

412.   Schiele F, Gale CP, Simon T, Fox KAA, Bueno H, Lettino M, Tubaro M, Puymirat E, Ferrières J, Ecarnot F, Danchin N and Meneveau N. The 2020 ESC-ACVC quality indicators for the management of acute myocardial infarction applied to the FAST-MI registries. *Eur Heart J Acute Cardiovasc Care*. 2021.

413.   Boriani G, Maniadakis N, Auricchio A, Müller-Riemenschneider F, Fattore G, Leyva F, Mantovani L, Siebert M, Willich SN, Vardas P and Kirchhof P. Health technology assessment in interventional electrophysiology and device therapy: a position paper of the European Heart Rhythm Association. *European heart journal*. 2013;34:1869-1874.

414.   Vos T, Lim SS, Abbafati C, Abbas KM, Abbasi M, Abbasifard M, Abbasi-Kangevari M, Abbastabar H, Abd-Allah F, Abdelalim A, Abdollahi M, Abdollahpour I, Abolhassani H, Aboyans V, Abrams EM, Abreu LG, Abrigo MRM, Abu-Raddad LJ, Abushouk AI, Acebedo A, Ackerman IN, Adabi M, Adamu AA, Adebayo OM, Adekanmbi V, Adelson JD, Adetokunboh OO, Adham D, Afshari M, Afshin A, Agardh EE, Agarwal G, Agesa KM, Aghaali M, Aghamir SMK, Agrawal A, Ahmad T, Ahmadi A, Ahmadi M, Ahmadieh H, Ahmadpour E, Akalu TY, Akinyemi RO, Akinyemiju T, Akombi B, Al-Aly Z, Alam K, Alam N, Alam S, Alam T, Alanzi TM, Albertson SB, Alcalde-Rabanal JE, Alema NM, Ali M, Ali S, Alicandro G, Alijanzadeh M, Alinia C, Alipour V, Aljunid SM, Alla F, Allebeck P, Almasi-Hashiani A, Alonso J, Al-Raddadi RM, Altirkawi KA, Alvis-Guzman N, Alvis-Zakzuk NJ, Amini S, Amini-Rarani M, Aminorroaya A, Amiri F, Amit AML, Amugsi DA, Amul GGH, Anderlini D, Andrei CL, Andrei T, Anjomshoa M, Ansari F, Ansari I, Ansari-Moghaddam A, Antonio CAT, Antony CM, Antriyandarti E, Anvari D, Anwer R, Arabloo J, Arab-Zozani M, Aravkin AY, Ariani F, Ärnlöv J, Aryal KK, Arzani A, Asadi-Aliabadi M, Asadi-Pooya AA, Asghari B, Ashbaugh C, Atnafu DD, Atre SR, Ausloos F, Ausloos M, Ayala Quintanilla BP, Ayano G, Ayanore MA, Aynalem YA, Azari S, Azarian G, Azene ZN, Babaee E, Badawi A, Bagherzadeh M, Bakhshaei MH, Bakhtiari A, Balakrishnan S, Balalla S, Balassyano S, Banach M, Banik PC, Bannick MS, Bante AB, Baraki AG, Barboza MA, Barker-Collo SL, Barthelemy CM, Barua L, Barzegar A, Basu S, Baune BT, Bayati M, Bazmandegan G, Bedi N, Beghi E, Béjot Y, Bello AK, Bender RG, Bennett DA, Bennitt FB, Bensenor IM, Benziger CP, Berhe K, Bernabe E, Bertolacci GJ, Bhageerathy R, Bhala N, Bhandari D, Bhardwaj P, Bhattacharyya K, Bhutta ZA, Bibi S, Biehl MH, Bikbov B, Bin Sayeed MS, Biondi A, Birihane BM, Bisanzio D, Bisignano C, Biswas RK, Bohlouli S, Bohluli M, Bolla SRR, Boloor A, Boon-Dooley AS, Borges G, Borzì AM, Bourne R, Brady OJ, Brauer M, Brayne C, Breitborde NJK, Brenner H, Briant PS, Briggs AM, Briko NI, Britton GB, Bryazka D, Buchbinder R, Bumgarner BR, Busse R, Butt ZA, Caetano dos Santos FL, Cámera LLAA, Campos-Nonato IR, Car J, Cárdenas R, Carreras G, Carrero JJ, Carvalho F, Castaldelli-Maia JM, Castañeda-Orjuela CA, Castelpietra G, Castle CD, Castro F, Catalá-López F, Causey K, Cederroth CR, Cercy KM, Cerin E, Chandan JS, Chang AR, Charlson FJ, Chattu VK, Chaturvedi S, Chimed-Ochir O, Chin KL, Cho DY, Christensen H, Chu D-T, Chung MT, Cicuttini FM, Ciobanu LG, Cirillo M, Collins EL, Compton K, Conti S, Cortesi PA, Costa VM, Cousin E, Cowden RG, Cowie BC, Cromwell EA, Cross DH, Crowe CS, Cruz JA, Cunningham M, Dahlawi SMA, Damiani G, Dandona L, Dandona

R, Darwesh AM, Daryani A, Das JK, Das Gupta R, das Neves J, Dávila-Cervantes CA, Davletov K, De Leo D, Dean FE, DeCleene NK, Deen A, Degenhardt L, Dellavalle RP, Demeke FM, Demsie DG, Denova-Gutiérrez E, Dereje ND, Dervenis N, Desai R, Desalew A, Dessie GA, Dharmaratne SD, Dhungana GP, Dianatinasab M, Diaz D, Dibaji Forooshani ZS, Dingels ZV, Dirac MA, Djalalinia S, Do HT, Dokova K, Dorostkar F, Doshi CP, Doshmangir L, Douiri A, Doxey MC, Driscoll TR, Dunachie SJ, Duncan BB, Duraes AR, Eagan AW, Ebrahimi Kalan M, Edvardsson D, Ehrlich JR, El Nahas N, El Sayed I, El Tantawi M, Elbarazi I, Elgendy IY, Elhabashy HR, El-Jaafary SI, Elyazar IRF, Emamian MH, Emmons-Bell S, Erskine HE, Eshrati B, Eskandarieh S, Esmaeilnejad S, Esmaeilzadeh F, Esteghamati A, Estep K, Etemadi A, Etisso AE, Farahmand M, Faraj A, Fareed M, Faridnia R, Farinha CSeS, Farioli A, Faro A, Faruque M, Farzadfar F, Fattahi N, Fazlzadeh M, Feigin VL, Feldman R, Fereshtehnejad S-M, Fernandes E, Ferrari AJ, Ferreira ML, Filip I, Fischer F, Fisher JL, Fitzgerald R, Flohr C, Flor LS, Foigt NA, Folayan MO, Force LM, Fornari C, Foroutan M, Fox JT, Freitas M, Fu W, Fukumoto T, Furtado JM, Gad MM, Gakidou E, Galles NC, Gallus S, Gamkrelidze A, Garcia-Basteiro AL, Gardner WM, Geberemariyam BS, Gebrehiwot AM, Gebremedhin KB, Gebreslassie AAAA, Gershberg Hayoon A, Gething PW, Ghadimi M, Ghadiri K, Ghafourifard M, Ghajar A, Ghamari F, Ghashghaee A, Ghiasvand H, Ghith N, Gholamian A, Gilani SA, Gill PS, Gitimoghaddam M, Giussani G, Goli S, Gomez RS, Gopalani SV, Gorini G, Gorman TM, Gottlich HC, Goudarzi H, Goulart AC, Goulart BNG, Grada A, Grivna M, Grosso G, Gubari MIM, Gugnani HC, Guimaraes ALS, Guimarães RA, Guled RA, Guo G, Guo Y, Gupta R, Haagsma JA, Haddock B, Hafezi-Nejad N, Hafiz A, Hagins H, Haile LM, Hall BJ, Halvaei I, Hamadeh RR, Hamagharib Abdullah K, Hamilton EB, Han C, Han H, Hankey GJ, Haro JM, Harvey JD, Hasaballah AI, Hasanzadeh A, Hashemian M, Hassanipour S, Hassankhani H, Havmoeller RJ, Hay RJ, Hay SI, Hayat K, Heidari B, Heidari G, Heidari-Soureshjani R, Hendrie D, Henrikson HJ, Henry NJ, Herteliu C, Heydarpour F, Hird TR, Hoek HW, Hole MK, Holla R, Hoogar P, Hosgood HD, Hosseinzadeh M, Hostiuc M, Hostiuc S, Househ M, Hoy DG, Hsairi M, Hsieh VC-r, Hu G, Huda TM, Hugo FN, Huynh CK, Hwang B-F, Iannucci VC, Ibitoye SE, Ikuta KS, Ilesanmi OS, Ilic IM, Ilic MD, Inbaraj LR, Ippolito H, Irvani SSN, Islam MM, Islam M, Islam SMS, Islami F, Iso H, Ivers RQ, Iwu CCD, Iyamu IO, Jaafari J, Jacobsen KH, Jadidi-Niaragh F, Jafari H, Jafarinia M, Jahagirdar D, Jahani MA, Jahanmehr N, Jakovljevic M, Jalali A, Jalilian F, James SL, Janjani H, Janodia MD, Jayatilleke AU, Jeemon P, Jenabi E, Jha RP, Jha V, Ji JS, Jia P, John O, John-Akinola YO, Johnson CO, Johnson SC, Jonas JB, Joo T, Joshi A, Jozwiak JJ, Jürisson M, Kabir A, Kabir Z, Kalani H, Kalani R, Kalankesh LR, Kalhor R, Kamiab Z, Kanchan T, Karami Matin B, Karch A, Karim MA, Karimi SE, Kassa GM, Kassebaum NJ, Katikireddi SV, Kawakami N, Kayode GA, Keddie SH, Keller C, Kereselidze M, Khafaie MA, Khalid N, Khan M, Khatab K, Khater MM, Khatib MN, Khayamzadeh M, Khodayari MT, Khundkar R, Kianipour N, Kieling C, Kim D, Kim Y-E, Kim YJ, Kimokoti RW, Kisa A, Kisa S, Kissimova-Skarbek K, Kivimäki M, Kneib CJ, Knudsen AKS, Kocarnik JM, Kolola T, Kopec JA, Kosen S, Koul PA, Koyanagi A, Kravchenko MA, Krishan K, Krohn KJ, Kuate Defo B, Kucuk Bicer B, Kumar GA, Kumar M, Kumar P, Kumar V, Kumaresh G, Kurmi OP, Kusuma D, Kyu HH, La Vecchia C, Lacey B, Lal DK, Lalloo R, Lam JO, Lami FH, Landires I, Lang JJ, Lansingh VC, Larson SL, Larsson AO, Lasrado S, Lassi ZS, Lau KM-M, Lavados PM, Lazarus JV, Ledesma JR, Lee PH, Lee SWH, LeGrand KE, Leigh J, Leonardi M, Lescinsky H, Leung J, Levi M, Lewington S, Li S, Lim L-L, Lin C, Lin R-T, Linehan C, Linn S, Liu H-C, Liu S, Liu Z, Looker KJ, Lopez AD, Lopukhov PD, Lorkowski S, Lotufo PA, Lucas TCD, Lugo A, Lunevicius R, Lyons RA, Ma J, MacLachlan JH, Maddison ER, Maddison R, Madotto F, Mahasha PW, Mai HT, Majeed A, Maled V, Maleki S, Malekzadeh R, Malta DC, Mamun AA, Manafi A, Manafi N, Manguerra H, Mansouri B, Mansournia MA, Mantilla Herrera AM,

Maravilla JC, Marks A, Martins-Melo FR, Martopullo I, Masoumi SZ, Massano J, Massenburg BB, Mathur MR, Maulik PK, McAlinden C, McGrath JJ, McKee M, Mehndiratta MM, Mehri F, Mehta KM, Meitei WB, Memiah PTN, Mendoza W, Menezes RG, Mengesha EW, Mengesha MB, Mereke A, Meretoja A, Meretoja TJ, Mestrovic T, Miazgowski B, Miazgowski T, Michalek IM, Mihretie KM, Miller TR, Mills EJ, Mirica A, Mirrakhimov EM, Mirzaei H, Mirzaei M, Mirzaei-Alavijeh M, Misganaw AT, Mithra P, Moazen B, Moghadaszadeh M, Mohamadi E, Mohammad DK, Mohammad Y, Mohammad Gholi Mezerji N, Mohammadian-Hafshejani A, Mohammadifard N, Mohammadpourhodki R, Mohammed S, Mokdad AH, Molokhia M, Momen NC, Monasta L, Mondello S, Mooney MD, Moosazadeh M, Moradi G, Moradi M, Moradi-Lakeh M, Moradzadeh R, Moraga P, Morales L, Morawska L, Moreno Velásquez I, Morgado-da-Costa J, Morrison SD, Mosser JF, Mouodi S, Mousavi SM, Mousavi Khaneghah A, Mueller UO, Munro SB, Muriithi MK, Musa KI, Muthupandian S, Naderi M, Nagarajan AJ, Nagel G, Naghshtabrizi B, Nair S, Nandi AK, Nangia V, Nansseu JR, Nayak VC, Nazari J, Negoi I, Negoi RI, Netsere HBN, Ngunjiri JW, Nguyen CT, Nguyen J, Nguyen M, Nguyen M, Nichols E, Nigatu D, Nigatu YT, Nikbakhsh R, Nixon MR, Nnaji CA, Nomura S, Norrving B, Noubiap JJ, Nowak C, Nunez-Samudio V, Oţoiu A, Oancea B, Odell CM, Ogbo FA, Oh I-H, Okunga EW, Oladnabi M, Olagunju AT, Olusanya BO, Olusanya JO, Oluwasanu MM, Omar Bali A, Omer MO, Ong KL, Onwujekwe OE, Orji AU, Orpana HM, Ortiz A, Ostroff SM, Otstavnov N, Otstavnov SS, Øverland S, Owolabi MO, P A M, Padubidri JR, Pakhare AP, Palladino R, Pana A, Panda-Jonas S, Pandey A, Park E-K, Parmar PGK, Pasupula DK, Patel SK, Paternina-Caicedo AJ, Pathak A, Pathak M, Patten SB, Patton GC, Paudel D, Pazoki Toroudi H, Peden AE, Pennini A, Pepito VCF, Peprah EK, Pereira A, Pereira DM, Perico N, Pham HQ, Phillips MR, Pigott DM, Pilgrim T, Pilz TM, Pirsaheb M, Plana-Ripoll O, Plass D, Pokhrel KN, Polibin RV, Polinder S, Polkinghorne KR, Postma MJ, Pourjafar H, Pourmalek F, Pourmirza Kalhori R, Pourshams A, Poznańska A, Prada SI, Prakash V, Pribadi DRA, Pupillo E, Quazi Syed Z, Rabiee M, Rabiee N, Radfar A, Rafiee A, Rafiei A, Raggi A, Rahimi-Movaghar A, Rahman MA, Rajabpour-Sanati A, Rajati F, Ramezanzadeh K, Ranabhat CL, Rao PC, Rao SJ, Rasella D, Rastogi P, Rathi P, Rawaf DL, Rawaf S, Rawal L, Razo C, Redford SB, Reiner RC, Jr., Reinig N, Reitsma MB, Remuzzi G, Renjith V, Renzaho AMN, Resnikoff S, Rezaei N, Rezai Ms, Rezapour A, Rhinehart P-A, Riahi SM, Ribeiro ALP, Ribeiro DC, Ribeiro D, Rickard J, Roberts NLS, Roberts S, Robinson SR, Roever L, Rolfe S, Ronfani L, Roshandel G, Roth GA, Rubagotti E, Rumisha SF, Sabour S, Sachdev PS, Saddik B, Sadeghi E, Sadeghi M, Saeidi S, Safi S, Safiri S, Sagar R, Sahebkar A, Sahraian MA, Sajadi SM, Salahshoor MR, Salamati P, Salehi Zahabi S, Salem H, Salem MRR, Salimzadeh H, Salomon JA, Salz I, Samad Z, Samy AM, Sanabria J, Santomauro DF, Santos IS, Santos JV, Santric-Milicevic MM, Saraswathy SYI, Sarmiento-Suárez R, Sarrafzadegan N, Sartorius B, Sarveazad A, Sathian B, Sathish T, Sattin D, Sbarra AN, Schaeffer LE, Schiavolin S, Schmidt MI, Schutte AE, Schwebel DC, Schwendicke F, Senbeta AM, Senthilkumaran S, Sepanlou SG, Shackelford KA, Shadid J, Shahabi S, Shaheen AA, Shaikh MA, Shalash AS, Shams-Beyranvand M, Shamsizadeh M, Shannawaz M, Sharafi K, Sharara F, Sheena BS, Sheikhtaheri A, Shetty RS, Shibuya K, Shiferaw WS, Shigematsu M, Shin JI, Shiri R, Shirkoohi R, Shrime MG, Shuval K, Siabani S, Sigfusdottir ID, Sigurvinsdottir R, Silva JP, Simpson KE, Singh A, Singh JA, Skiadaresi E, Skou STS, Skryabin VY, Sobngwi E, Sokhan A, Soltani S, Sorensen RJD, Soriano JB, Sorrie MB, Soyiri IN, Sreeramareddy CT, Stanaway JD, Stark BA, Ştefan SC, Stein C, Steiner C, Steiner TJ, Stokes MA, Stovner LJ, Stubbs JL, Sudaryanto A, Sufiyan MaB, Sulo G, Sultan I, Sykes BL, Sylte DO, Szócska M, Tabarés-Seisdedos R, Tabb KM, Tadakamadla SK, Taherkhani A, Tajdini M, Takahashi K, Taveira N, Teagle WL, Teame H, Tehrani-Banihashemi A, Teklehaimanot BF, Terrason S, Tessema ZT, Thankappan KR,

Thomson AM, Tohidinik HR, Tonelli M, Topor-Madry R, Torre AE, Touvier M, Tovani-Palone MRR, Tran BX, Travillian R, Troeger CE, Truelsen TC, Tsai AC, Tsatsakis A, Tudor Car L, Tyrovolas S, Uddin R, Ullah S, Undurraga EA, Unnikrishnan B, Vacante M, Vakilian A, Valdez PR, Varughese S, Vasankari TJ, Vasseghian Y, Venketasubramanian N, Violante FS, Vlassov V, Vollset SE, Vongpradith A, Vukovic A, Vukovic R, Waheed Y, Walters MK, Wang J, Wang Y, Wang Y-P, Ward JL, Watson A, Wei J, Weintraub RG, Weiss DJ, Weiss J, Westerman R, Whisnant JL, Whiteford HA, Wiangkham T, Wiens KE, Wijeratne T, Wilner LB, Wilson S, Wojtyniak B, Wolfe CDA, Wool EE, Wu A-M, Wulf Hanson S, Wunrow HY, Xu G, Xu R, Yadgir S, Yahyazadeh Jabbari SH, Yamagishi K, Yaminfirooz M, Yano Y, Yaya S, Yazdi-Feyzabadi V, Yearwood JA, Yeheyis TY, Yeshitila YG, Yip P, Yonemoto N, Yoon S-J, Yoosefi Lebni J, Younis MZ, Younker TP, Yousefi Z, Yousefifard M, Yousefinezhadi T, Yousuf AY, Yu C, Yusefzadeh H, Zahirian Moghadam T, Zaki L, Zaman SB, Zamani M, Zamanian M, Zandian H, Zangeneh A, Zastrozhin MS, Zewdie KA, Zhang Y, Zhang Z-J, Zhao JT, Zhao Y, Zheng P, Zhou M, Ziapour A, Zimsen SRM, Naghavi M and Murray CJL. Global burden of 369 diseases and injuries in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. *The Lancet*. 2020;396:1204-1222.

415.   Fang M, Wang D, Coresh J and Selvin E. Trends in Diabetes Treatment and Control in U.S. Adults, 1999–2018. *New England Journal of Medicine*. 2021;384:2219-2228.

416.   2021 ESC Guidelines on Cardiovascular Disease Prevenrtion in Clinical Practice

417.   De Smedt D, De Backer T, Petrovic M, De Backer G, Wood D, Kotseva K and De Bacquer D. Chronic medication intake in patients with stable coronary heart disease across Europe: Evidence from the daily clinical practice. Results from the ESC EORP European Survey of Cardiovascular Disease Prevention and Diabetes (EUROASPIRE IV) Registry. *International Journal of Cardiology*. 2020;300:7-13.

418.   Department of Health and Human Services Agency for Healthcare Researchand Quality, Guide to Prevention Quality Indicators: Hospital Admission forAmbulatory Care Sensitive Conditions, April 2002. Available online: https://www.ahrq.gov/downloads/pub/ahrqqi/pqiguide.pdf. (Accessed 09 June 2021), 2002.

419.   Ramalho A, Lobo M, Duarte L, Souza J, Santos P and Freitas A. Landscapes on Prevention Quality Indicators: A Spatial Analysis of Diabetes Preventable Hospitalizations in Portugal (2016-2017). *Int J Environ Res Public Health*. 2020;17.

420.   Ramalho A, Castro P, Lobo M, Souza J, Santos P and Freitas A. Integrated quality assessment for diabetes care in Portuguese primary health care using prevention quality indicators. *Prim Care Diabetes*. 2021;15:507-512.

421.   Spertus John A, Chan P, Diamond George A, Drozda Joseph P, Kaul S, Krumholz Harlan M, Masoudi Frederick A, Normand Sharon-Lise T, Peterson Eric D, Radford Martha J and Rumsfeld John S. ACCF/AHA New Insights Into the Methodology of Performance Measurement. *Circulation*. 2010;122:2091-2106.

422.   Ambrosetti M, Abreu A, Corrà U, Davos CH, Hansen D, Frederix I, Iliou MC, Pedretti RF, Schmid JP, Vigorito C, Voller H, Wilhelm M, Piepoli MF, Bjarnason-Wehrens B, Berger T, Cohen-Solal A, Cornelissen V, Dendale P, Doehner W, Gaita D, Gevaert AB, Kemps H, Kraenkel N, Laukkanen J, Mendes M, Niebauer J, Simonenko M and Zwisler AO. Secondary prevention through comprehensive cardiovascular rehabilitation: From knowledge to implementation. 2020 update. A position paper from the Secondary Prevention and Rehabilitation Section of the European Association of Preventive Cardiology. *Eur J Prev Cardiol*. 2020:2047487320913379.

423.   Campbell SM, Ludt S, Lieshout JV, Boffin N, Wensing M, Petek D, Grol R and Roland MO. Quality indicators for the prevention and management of cardiovascular disease in primary care in nine European countries. *European Journal of Cardiovascular Prevention & Rehabilitation*. 2008;15:509-515.

424.   Abreu A, Frederix I, Dendale P, Janssen A, Doherty P, Piepoli MF, Völler H and Davos CH. Standardization and quality improvement of secondary prevention through cardiovascular rehabilitation programmes in Europe: The avenue towards EAPC accreditation programme: A position statement of the Secondary Prevention and Rehabilitation Section of the European Association of Preventive Cardiology (EAPC). *Eur J Prev Cardiol*. 2020:2047487320924912.

425.   Redberg RF, Benjamin EJ, Bittner V, Braun LT, Goff DC, Jr., Havas S, Labarthe DR, Limacher MC, Lloyd-Jones DM, Mora S, Pearson TA, Radford MJ, Smetana GW, Spertus JA and Swegler EW. AHA/ACCF [corrected] 2009 performance measures for primary prevention of cardiovascular disease in adults: a report of the American College of Cardiology Foundation/American Heart Association task force on performance measures (writing committee to develop performance measures for primary prevention of cardiovascular disease): developed in collaboration with the American Academy of Family Physicians; American Association of Cardiovascular and Pulmonary Rehabilitation; and Preventive Cardiovascular Nurses Association: endorsed by the American College of Preventive Medicine, American College of Sports Medicine, and Society for Women's Health Research. *Circulation*. 2009;120:1296-336.

426.   Drozda JP, Jr., Ferguson TB, Jr., Jneid H, Krumholz HM, Nallamothu BK, Olin JW and Ting HH. 2015 ACC/AHA Focused Update of Secondary Prevention Lipid Performance Measures: A Report of the American College of Cardiology/American Heart Association Task Force on Performance Measures. *J Am Coll Cardiol*. 2016;67:558-87.

427.   Burge FI, Bower K, Putnam W and Cox JL. Quality indicators for cardiovascular primary care. *Can J Cardiol*. 2007;23:383-8.

428.   Grace SL, Poirier P, Norris CM, Oakes GH, Somanader DS and Suskin N. Pan-Canadian development of cardiac rehabilitation and secondary prevention quality indicators. *Can J Cardiol*. 2014;30:945-8.

429.   Piepoli MF, Hoes AW, Agewall S, Albus C, Brotons C, Catapano AL, Cooney M-T, Corrà U, Cosyns B, Deaton C, Graham I, Hall MS, Hobbs FDR, Løchen M-L, Löllgen H, Marques-Vidal P, Perk J, Prescott E, Redon J, Richter DJ, Sattar N, Smulders Y, Tiberi M, van der Worp HB, van Dis I, Verschuren WMM, Binno S and Group ESD. 2016 European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts)Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). *European Heart Journal*. 2016;37:2315-2381.

430.   Pearson GJ, Thanassoulis G, Anderson TJ, Barry AR, Couture P, Dayan N, Francis GA, Genest J, Grégoire J, Grover SA, Gupta M, Hegele RA, Lau D, Leiter LA, Leung AA, Lonn E, Mancini GBJ, Manjoo P, McPherson R, Ngui D, Piché M-E, Poirier P, Sievenpiper J, Stone J, Ward R and Wray W. 2021 Canadian Cardiovascular Society Guidelines for the Management of Dyslipidemia for the Prevention of Cardiovascular Disease in the Adult. *Canadian Journal of Cardiology*.

431.   Arnett DK, Blumenthal RS, Albert MA, Buroker AB, Goldberger ZD, Hahn EJ, Himmelfarb CD, Khera A, Lloyd-Jones D, McEvoy JW, Michos ED, Miedema MD, Muñoz D, Smith SC, Virani SS, Williams KA, Yeboah J and Ziaeian B. 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation*. 2019;140:e596-e646.

432.   Mach F, Baigent C, Catapano AL, Koskinas KC, Casula M, Badimon L, Chapman MJ, De Backer GG, Delgado V, Ference BA, Graham IM, Halliday A, Landmesser U, Mihaylova B, Pedersen TR, Riccardi G, Richter DJ, Sabatine MS, Taskinen M-R, Tokgozoglu L, Wiklund O and Group ESD. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk: The Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS). *European Heart Journal*. 2019;41:111-188.

433.   Cosentino F, Grant PJ, Aboyans V, Bailey CJ, Ceriello A, Delgado V, Federici M, Filippatos G, Grobbee DE, Hansen TB, Huikuri HV, Johansson I, Jüni P, Lettino M, Marx N, Mellbin LG, Östgren CJ, Rocca B, Roffi M, Sattar N, Seferović PM, Sousa-Uva M, Valensi P, Wheeler DC and Group ESD. 2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD: The Task Force for diabetes, pre-diabetes, and cardiovascular diseases of the European Society of Cardiology (ESC) and the European Association for the Study of Diabetes (EASD). *European Heart Journal*. 2019;41:255-323.

434.   Williams B, Mancia G, Spiering W, Agabiti Rosei E, Azizi M, Burnier M, Clement DL, Coca A, de Simone G, Dominiczak A, Kahan T, Mahfoud F, Redon J, Ruilope L, Zanchetti A, Kerins M, Kjeldsen SE, Kreutz R, Laurent S, Lip GYH, McManus R, Narkiewicz K, Ruschitzka F, Schmieder RE, Shlyakhto E, Tsioufis C, Aboyans V, Desormais I and Group ESD. 2018 ESC/ESH Guidelines for the management of arterial hypertension: The Task Force for the management of arterial hypertension of the European Society of Cardiology (ESC) and the European Society of Hypertension (ESH). *European Heart Journal*. 2018;39:3021-3104.

435.   Aboyans V, Ricco J-B, Bartelink M-LEL, Björck M, Brodmann M, Cohnert T, Collet J-P, Czerny M, De Carlo M, Debus S, Espinola-Klein C, Kahan T, Kownator S, Mazzolai L, Naylor AR, Roffi M, Röther J, Sprynger M, Tendera M, Tepe G, Venermo M, Vlachopoulos C, Desormais I and Group ESD. 2017 ESC Guidelines on the Diagnosis and Treatment of Peripheral Arterial Diseases, in collaboration with the European Society for Vascular Surgery (ESVS): Document covering atherosclerotic disease of extracranial carotid and vertebral, mesenteric, renal, upper and lower extremity arteriesEndorsed by: the European Stroke Organization (ESO)The Task Force for the Diagnosis and Treatment of Peripheral Arterial Diseases of the European Society of Cardiology (ESC) and of the European Society for Vascular Surgery (ESVS). *European Heart Journal*. 2017;39:763-816.

436.   Wilhelm M, Abreu A, Adami PE, Ambrosetti M, Antonopoulou M, Biffi A, Cavarretta E, D'Ascenzi F, Gibson I, Grobbee DE, Iliou M-C, Koskinas K, Marques-Vidal P, Nixdorff U, Papadakis M, Piepoli MF, Vassiliou V, Wood D, Dendale P and Halle M. EAPC Core Curriculum for Preventive Cardiology. *European Journal of Preventive Cardiology*. 2021.

437.   Aktaa S, Abdin A, … and Gale CP. European Society of Cardiology Quality Indicators for the care and outcomes of cardiac pacing
Developed by the Working Group for Cardiac Pacing Quality Indicators in collaboration with the European Heart Rhythm Association of the European Society of Cardiology.
. *EP Europace*. 2021.

438.   Figtree GA, Vernon ST, Hadziosmanovic N, Sundström J, Alfredsson J, Arnott C, Delatour V, Leósdóttir M and Hagström E. Mortality in STEMI patients without standard modifiable risk factors: a sex-disaggregated analysis of SWEDEHEART registry data. *The Lancet*. 2021;397:1085-1094.

439.   Chang AR, Grams ME, Ballew SH, Bilo H, Correa A, Evans M, Gutierrez OM, Hosseinpanah F, Iseki K, Kenealy T, Klein B, Kronenberg F, Lee BJ, Li Y, Miura K, Navaneethan SD, Roderick PJ, Valdivielso JM, Visseren FLJ, Zhang L, Gansevoort RT, Hallan SI, Levey AS, Matsushita K, Shalev V and Woodward M. Adiposity and risk of decline in glomerular filtration rate: meta-analysis of individual participant data in a global consortium. *Bmj*. 2019;364:k5301.

440.   Global, regional, and national burden of chronic kidney disease, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet*. 2020;395:709-733.

441.   Si S, Moss JR, Sullivan TR, Newton SS and Stocks NP. Effectiveness of general practice-based health checks: a systematic review and meta-analysis. *Br J Gen Pract*. 2014;64:e47-53.

442.   Kearney PM, Blackwell L, Collins R, Keech A, Simes J, Peto R, Armitage J and Baigent C. Efficacy of cholesterol-lowering therapy in 18,686 people with diabetes in 14 randomised trials of statins: a meta-analysis. *Lancet*. 2008;371:117-25.

443.   Neal B, Perkovic V, Mahaffey KW, de Zeeuw D, Fulcher G, Erondu N, Shaw W, Law G, Desai M and Matthews DR. Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes. *New England Journal of Medicine*. 2017;377:644-657.

444.   Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, Mattheus M, Devins T, Johansen OE, Woerle HJ, Broedl UC and Inzucchi SE. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. *New England Journal of Medicine*. 2015;373:2117-2128.

445.   Chiarito M, Sanz-Sánchez J, Cannata F, Cao D, Sturla M, Panico C, Godino C, Regazzoli D, Reimers B, De Caterina R, Condorelli G, Ferrante G and Stefanini GG. Monotherapy with a P2Y(12) inhibitor or aspirin for secondary prevention in patients with established atherosclerosis: a systematic review and meta-analysis. *Lancet*. 2020;395:1487-1495.

446.   Perkovic V, Jardine MJ, Neal B, Bompoint S, Heerspink HJL, Charytan DM, Edwards R, Agarwal R, Bakris G, Bull S, Cannon CP, Capuano G, Chu P-L, de Zeeuw D, Greene T, Levin A, Pollock C, Wheeler DC, Yavin Y, Zhang H, Zinman B, Meininger G, Brenner BM and Mahaffey KW. Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy. *New England Journal of Medicine*. 2019;380:2295-2306.

447.   National Quality Forum. Risk adjustment for sociodemographic factors. https://www.qualityforum.org/Publications/2014/08/Risk_Adjustment_for_Socioeconomic_Status_or_Other_Sociodemographic_Factors.aspx. Accessed 20 April 2021.

448.   National Library of Quality Indicators. National Institute for Health and Care Excellence. Availiable at https://www.nice.org.uk/standards-and-indicators/index/All/All/7. Accessed 15 December 2020.

449.   McDonagh T MM, et al. 2021 ESC Guidelines for Heart Failure

450.   Vaduganathan M, Claggett BL, Jhund PS, Cunningham JW, Pedro Ferreira J, Zannad F, Packer M, Fonarow GC, McMurray JJV and Solomon SD. Estimating lifetime benefits of comprehensive disease-modifying pharmacological therapies in patients with heart failure with reduced ejection fraction: a comparative analysis of three randomised controlled trials. *Lancet*. 2020;396:121-128.

451. Kapelios CJ, Laroche C, Crespo-Leiro MG, Anker SD, Coats AJS, Díaz-Molina B, Filippatos G, Lainscak M, Maggioni AP, McDonagh T, Mebazaa A, Metra M, Moura B, Mullens W, Piepoli MF, Rosano GMC, Ruschitzka F, Seferovic PM, Lund LH and Group HFL-TRI. Association between loop diuretic dose changes and outcomes in chronic heart failure: observations from the ESC-EORP Heart Failure Long-Term Registry. *European Journal of Heart Failure*. 2020;22:1424-1437.

452. Crespo-Leiro MG, Anker SD, Maggioni AP, Coats AJ, Filippatos G, Ruschitzka F, Ferrari R, Piepoli MF, Delgado Jimenez JF, Metra M, Fonseca C, Hradec J, Amir O, Logeart D, Dahlström U, Merkely B, Drozdz J, Goncalvesova E, Hassanein M, Chioncel O, Lainscak M, Seferovic PM, Tousoulis D, Kavoliuniene A, Fruhwald F, Fazlibegovic E, Temizhan A, Gatzov P, Erglis A, Laroche C, Mebazaa A and Cardiology obotHFAotESo. European Society of Cardiology Heart Failure Long-Term Registry (ESC-HF-LT): 1-year follow-up outcomes and differences across regions. *European Journal of Heart Failure*. 2016;18:613-625.

453. Chioncel O, Mebazaa A, Harjola V-P, Coats AJ, Piepoli MF, Crespo-Leiro MG, Laroche C, Seferovic PM, Anker SD, Ferrari R, Ruschitzka F, Lopez-Fernandez S, Miani D, Filippatos G, Maggioni AP and Investigators obotEHFL-TR. Clinical phenotypes and outcome of patients hospitalized for acute heart failure: the ESC Heart Failure Long-Term Registry. *European Journal of Heart Failure*. 2017;19:1242-1254.

454. Allen LA, Fonarow GC, Liang L, Schulte PJ, Masoudi FA, Rumsfeld JS, Ho PM, Eapen ZJ, Hernandez AF, Heidenreich PA, Bhatt DL, Peterson ED and Krumholz HM. Medication Initiation Burden Required to Comply With Heart Failure Guideline Recommendations and Hospital Quality Measures. *Circulation*. 2015;132:1347-53.

455. Chioncel O, Mebazaa A, Harjola VP, Coats AJ, Piepoli MF, Crespo-Leiro MG, Laroche C, Seferovic PM, Anker SD, Ferrari R, Ruschitzka F, Lopez-Fernandez S, Miani D, Filippatos G and Maggioni AP. Clinical phenotypes and outcome of patients hospitalized for acute heart failure: the ESC Heart Failure Long-Term Registry. *European Journal of Heart Failure*. 2017;19:1242-1254.

456. Grandin EW and Jessup M. Rethinking the Focus of Heart Failure Quality Measures. *Circulation*. 2015;132:1307-1310.

457. Burns DJP, Arora J, Okunade O, Beltrame JF, Bernardez-Pereira S, Crespo-Leiro MG, Filippatos GS, Hardman S, Hoes AW, Hutchison S, Jessup M, Kinsella T, Knapton M, Lam CSP, Masoudi FA, McIntyre H, Mindham R, Morgan L, Otterspoor L, Parker V, Persson HE, Pinnock C, Reid CM, Riley J, Stevenson LW and McDonagh TA. International Consortium for Health Outcomes Measurement (ICHOM): Standardized Patient-Centered Outcomes Measurement Set for Heart Failure Patients. *JACC: Heart Failure*. 2020;8:212-222.

458. McKelvie RS, Heckman GA, Blais C, Cox JL, Ezekowitz JA, Gong Y, Harkness K, Moe G, Dai S, Dorian P, Johnstone DE, McGeachie EC, Tu JV and Lambert LJ. Canadian Cardiovascular Society Quality Indicators for Heart Failure. *Can J Cardiol*. 2016;32:1038.e5-9.

459. Get With The Guidelines®- Heart Failure. Febrruary 2016. https://www.heart.org/-/media/files/professional/quality-improvement/get-with-the-guidelines/get-with-the-guidelines-hf/educational-materials/hf-fact-sheet_updated-011119_v2.pdf?la=en. Accessed 12 December 2020.

460. Lambie L, Mattke S and the Members of the OECD Cardiac Care Panel. Selecting indicators for the quality of cardiac care at the health system level in the OECD countries: https://www.oecd.org/els/health-systems/33865450.pdf. 2004.

461. Smets M, Smeets M, Van den Bulck S, Janssens S, Aertgeerts B and Vaes B. Defining quality indicators for heart failure in general practice. *Acta Cardiologica*. 2019;74:291-298.

462.	Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, Falk V, González-Juanatey JR, Harjola V-P, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GMC, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P and Group ESD. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *European Heart Journal*. 2016;37:2129-2200.

463.	https://www.nice.org.uk/guidance/ng106/resources. Accessed 13 December 2020 NIfHaCENgNChfiadamPdS.

464.	Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE, Drazner MH, Fonarow GC, Geraci SA, Horwich T, Januzzi JL, Johnson MR, Kasper EK, Levy WC, Masoudi FA, McBride PE, McMurray JJV, Mitchell JE, Peterson PN, Riegel B, Sam F, Stevenson LW, Tang WHW, Tsai EJ and Wilkoff BL. 2013 ACCF/AHA Guideline for the Management of Heart Failure. *Journal of the American College of Cardiology*. 2013;62:e147-e239.

465.	Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE, Colvin MM, Drazner MH, Filippatos GS, Fonarow GC, Givertz MM, Hollenberg SM, Lindenfeld J, Masoudi FA, McBride PE, Peterson PN, Stevenson LW and Westlake C. 2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure. *Journal of the American College of Cardiology*. 2017;70:776-803.

466.	McDonald M, Virani S, Chan M, Ducharme A, Ezekowitz JA, Giannetti N, Heckman GA, Howlett JG, Koshman SL, Lepage S, Mielniczuk L, Moe GW, O'Meara E, Swiggum E, Toma M, Zieroth S, Anderson K, Bray SA, Clarke B, Cohen-Solal A, D'Astous M, Davis M, De S, Grant ADM, Grzeslo A, Heshka J, Keen S, Kouz S, Lee D, Masoudi FA, McKelvie R, Parent M-C, Poon S, Rajda M, Sharma A, Siatecki K, Storm K, Sussex B, Van Spall H and Yip AMC. CCS/CHFS Heart Failure Guidelines Update: Defining a New Pharmacologic Standard of Care for Heart Failure With Reduced Ejection Fraction. *Canadian Journal of Cardiology*. 2021;37:531-546.

467.	Lund LH, Carrero JJ, Farahmand B, Henriksson KM, Jonsson Å, Jernberg T and Dahlström U. Association between enrolment in a heart failure quality registry and subsequent mortality-a nationwide cohort study. *Eur J Heart Fail*. 2017;19:1107-1116.

468.	McAlister FA, Youngson E, van Diepen S, Ezekowitz JA and Kaul P. Influence of hospital volume on outcomes for patients with heart failure: Evidence from a Canadian national cohort study. *American Heart Journal*. 2018;202:148-150.

469.	Seferovic PM, Piepoli MF, Lopatin Y, Jankowska E, Polovina M, Anguita-Sanchez M, Stork S, Lainscak M, Milicic D, Milinkovic I, Filippatos G and Coats AJS. Heart Failure Association of the European Society of Cardiology Quality of Care Centres Programme: design and accreditation document. *European Journal of Heart Failure*. 2020;22:763-774.

470.	Horne BD, Roberts CA, Rasmusson KD, Buckway J, Alharethi R, Cruz J, Evans RS, Lloyd JF, Bair TL, Kfoury AG and Lappe DL. Risk score-guided multidisciplinary team-based Care for Heart Failure Inpatients is associated with lower 30-day readmission and lower 30-day mortality. *American Heart Journal*. 2020;219:78-88.

471.	Pedraza LL, Pokorski SCS, MacHado BB, Ferro EB, Souza RH, Caetano FS and Rabelo-Silva ER. Health literacy, knowledge, treatment adhesion and self-care in heart failure in a middle income country. *European Journal of Heart Failure*. 2019;21:298.

472.	Van Spall HGC, Rahman T, Mytton O, Ramasundarahettige C, Ibrahim Q, Kabali C, Coppens M, Brian Haynes R and Connolly S. Comparative effectiveness of transitional care services in patients discharged from the hospital with heart failure: a systematic review and network meta-analysis. *European Journal of Heart Failure*. 2017;19:1427-1443.

473. Long L, Mordi IR, Bridges C, Sagar VA, Davies EJ, Coats AJ, Dalal H, Rees K, Singh SJ and Taylor RS. Exercise-based cardiac rehabilitation for adults with heart failure. *Cochrane Database Syst Rev*. 2019;1:Cd003331.

474. Hofstede SN, Ceyisakar IE, Lingsma HF, Kringos DS and Marang-Van De Mheen PJ. Ranking hospitals: Do we gain reliability by using composite rather than individual indicators? *BMJ Quality and Safety*. 2019;28:94-102.

475. CMS Measure Management System Blueprint. Version 16.0. September 2020. https://www.cms.gov/Medicare/Quality-Initiatives-Patient-Assessment-Instruments/MMS/Downloads/Blueprint.pdf. Accessed 19 February 2021.

476. Bonow RO, Ganiats TG, Beam CT, Blake K, Casey DE, Goodlin SJ, Grady KL, Hundley RF, Jessup M, Lynn TE, Masoudi FA, Nilasena D, Piña IL, Rockswold PD, Sadwin LB, Sikkema JD, Sincak CA, Spertus J, Torcson PJ, Torres E, Williams MV and Wong JB. ACCF/AHA/AMA-PCPI 2011 Performance Measures for Adults With Heart Failure. *Circulation*. 2012;125:2382-2401.

477. Blecker S, Agarwal SK, Chang PP, Rosamond WD, Casey DE, Kucharska-Newton A, Radford MJ, Coresh J and Katz S. Quality of Care for Heart Failure Patients Hospitalized for Any Cause. *Journal of the American College of Cardiology*. 2014;63:123-130.

478. Savarese G and Lund LH. Global Public Health Burden of Heart Failure. *Card Fail Rev*. 2017;3:7-11.

479. Smith SC, Jr, Fonarow GC and Zhao D. Measuring and Improving the Quality of Heart Failure Care Globally. *JAMA Network Open*. 2020;3:e1918642-e1918642.

480. Fonarow GC, Abraham WT, Albert NM, Stough WG, Gheorghiade M, Greenberg BH, O'Connor CM, Pieper K, Sun JL, Yancy C and Young JB. Association between performance measures and clinical outcomes for patients hospitalized with heart failure. *Jama*. 2007;297:61-70.

481. Polanczyk CA, Ruschel KB, Castilho FM and Ribeiro AL. Quality Measures in Heart Failure: the Past, the Present, and the Future. *Curr Heart Fail Rep*. 2019;16:1-6.

482. Fonarow GC, Albert NM, Curtis AB, Gheorghiade M, Heywood JT, Liu Y, Mehra MR, O'Connor CM, Reynolds D, Walsh MN and Yancy CW. Associations Between Outpatient Heart Failure Process-of-Care Measures and Mortality. *Circulation*. 2011;123:1601-1610.

483. Peterson ED, Delong ER, Masoudi FA, O'Brien SM, Peterson PN, Rumsfeld JS, Shahian DM, Shaw RE, Goff DC, Jr., Grady K, Green LA, Jenkins KJ, Loth A and Radford MJ. ACCF/AHA 2010 Position Statement on Composite Measures for Healthcare Performance Assessment: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Performance Measures (Writing Committee to develop a position statement on composite measures). *Circulation*. 2010;121:1780-91.

484. O'Brien SM, DeLong ER, Dokholyan RS, Edwards FH and Peterson ED. Exploring the Behavior of Hospital Composite Performance Measures. *Circulation*. 2007;116:2969-2975.

485. Hindricks G, Potpara T, Dagres N, Arbelo E, Bax JJ, Blomström-Lundqvist C, Boriani G, Castella M, Dan GA, Dilaveris PE, Fauchier L, Filippatos G, Kalman JM, La Meir M, Lane DA, Lebeau JP, Lettino M, Lip GYH, Pinto FJ, Thomas GN, Valgimigli M, Van Gelder IC, Van Putte BP and Watkins CL. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association of Cardio-Thoracic Surgery (EACTS). *Eur Heart J*. 2020.

486. Faxon David P and Burgess A. Cardiovascular Registries. *Circulation: Cardiovascular Interventions*. 2016;9:e003866.

487.   Pessoa-Amorim G, Campbell M, Fletcher L, Horby P, Landray M, Mafham M and Haynes R. Making trials part of good clinical care: lessons from the RECOVERY trial. *Future Healthc J*. 2021;8:e243-e250.

488.   Seferović PM, Vardas P, Jankowska EA, Maggioni AP, Timmis A, Milinković I, Polovina M, Gale CP, Lund LH, Lopatin Y, Lainscak M, Savarese G, Huculeci R, Kazakiewicz D and Coats AJS. The Heart Failure Association Atlas: Heart Failure Epidemiology and Management Statistics 2019. *Eur J Heart Fail*. 2021;23:906-914.

489.   Johnstone DE and Buller CE. Pan-Canadian Cardiovascular Data Definitions and Quality Indicators: A Status Update. *Canadian Journal of Cardiology*. 2012;28:599-601.

490.   Chew DPB, Allan RM, Aroney CN and Sheerin NJ. National data elements for the clinical management of acute coronary syndromes. *Medical Journal of Australia*. 2005;182:S5-S14.

491.   Douglas PS, Carabello BA, Lang RM, Lopez L, Pellikka PA, Picard MH, Thomas JD, Varghese P, Wang TY, Weissman NJ and Wilgus R. 2019 ACC/AHA/ASE Key Data Elements and Definitions for Transthoracic Echocardiography: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Data Standards (Writing Committee to Develop Cardiovascular Endpoints Data Standards) and the American Society of Echocardiography. *Circulation Cardiovascular imaging*. 2019;12:e000027.

492.   Hendel RC, Budoff MJ, Cardella JF, Chambers CE, Dent JM, Fitzgerald DM, Hodgson JM, Klodas E, Kramer CM, Stillman AE, Tilkemeier PL, Ward RP, Weigold WG, White RD and Woodard PK. ACC/AHA/ACR/ASE/ASNC/HRS/NASCI/RSNA/SAIP/SCAI/ SCCT/SCMR/SIR 2008 Key Data Elements and Definitions for Cardiac Imaging: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Data Standards (Writing Committee to Develop Clinical Data Standards for Cardiac Imaging). *Circulation*. 2009;119:154-86.

493.   Buxton AE, Calkins H, Callans DJ, DiMarco JP, Fisher JD, Leon Greene H, Haines DE, Hayes DL, Heidenreich PA, Miller JM, Poppas A, Prystowsky EN, Schoenfeld MH, Zimetbaum PJ, Heidenreich PA, Goff DC, Grover FL, Malenka DJ, Peterson ED, Radford MJ and Redberg RF. ACC/AHA/HRS 2006 Key Data Elements and Definitions for Electrophysiological Studies and Procedures. *A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Data Standards (ACC/AHA/HRS Writing Committee to Develop Data Standards on Electrophysiology)*. 2006;48:2360-2396.

494.   Hicks KA, Tcheng JE, Bozkurt B, Chaitman BR, Cutlip DE, Farb A, Fonarow GC, Jacobs JP, Jaff MR, Lichtman JH, Limacher MC, Mahaffey KW, Mehran R, Nissen SE, Smith EE, Targum SL, American College of C and American Heart A. 2014 ACC/AHA Key Data Elements and Definitions for Cardiovascular Endpoint Events in Clinical Trials: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Data Standards (Writing Committee to Develop Cardiovascular Endpoints Data Standards). *Circulation*. 2015;132:302-61.

495.   Weintraub WS, Karlsberg RP, Tcheng JE, Boris JR, Buxton AE, Dove JT, Fonarow GC, Goldberg LR, Heidenreich P, Hendel RC, Jacobs AK, Lewis W, Mirro MJ and Shahian DM. ACCF/AHA 2011 key data elements and definitions of a base cardiovascular vocabulary for electronic health records: A report of the American College of Cardiology Foundation/American Heart Association Task Force on clinical data standards. *Journal of the American College of Cardiology*. 2011;58:202-222.

496.   Mehran R, Rao SV, Bhatt DL, Gibson CM, Caixeta A, Eikelboom J, Kaul S, Wiviott SD, Menon V, Nikolsky E, Serebruany V, Valgimigli M, Vranckx P, Taggart D, Sabik JF, Cutlip DE,

Krucoff MW, Ohman EM, Steg PG and White H. Standardized Bleeding Definitions for Cardiovascular Clinical Trials. *Circulation*. 2011;123:2736-2747.

497.   Garcia-Garcia HM, McFadden EP, Farb A, Mehran R, Stone GW, Spertus J, Onuma Y, Morel M-a, Es G-Av, Zuckerman B, Fearon WF, Taggart D, Kappetein A-P, Krucoff MW, Vranckx P, Windecker S, Cutlip D and Serruys PW. Standardized End Point Definitions for Coronary Intervention Trials: The Academic Research Consortium-2 Consensus Document. *Circulation*. 2018;137:2635-2650.

498.   Cutlip DE, Windecker S, Mehran R, Boam A, Cohen DJ, Es G-Av, Steg PG, Morel M-a, Mauri L, Vranckx P, McFadden E, Lansky A, Hamon M, Krucoff MW and Serruys PW. Clinical End Points in Coronary Stent Trials. *Circulation*. 2007;115:2344-2351.

499.   Thygesen K, Alpert JS, Jaffe AS, Chaitman BR, Bax JJ, Morrow DA and White HD. Fourth Universal Definition of Myocardial Infarction (2018). *Journal of the American College of Cardiology*. 2018;72:2231-2264.

500.   Hicks KA, Mahaffey KW, Mehran R, Nissen SE, Wiviott SD, Dunn B, Solomon SD, Marler JR, Teerlink JR, Farb A, Morrow DA, Targum SL, Sila CA, Thanh Hai MT, Jaff MR, Joffe HV, Cutlip DE, Desai AS, Lewis EF, Gibson CM, Landray MJ, Lincoff AM, White CJ, Brooks SS, Rosenfield K, Domanski MJ, Lansky AJ, McMurray JJV, Tcheng JE, Steinhubl SR, Burton P, Mauri L, O'Connor CM, Pfeffer MA, Hung HMJ, Stockbridge NL, Chaitman BR, Temple RJ, Fitter HD, Illoh K, Cavanaugh KJ, Scirica BM, Irony I, Brown Kichline RE, Levine JG, Park A, Sacks L, Szarfman A, Unger EF, Wachter LA, Zuckerman B, Mitchel Y, Peddicord D, Shook T, Kisler B, Jaffe C, Bartley R, DeMets DL, Mencini M, Janning C, Bai S, Lawrence J, D'Agostino RB and Pocock SJ. 2017 Cardiovascular and Stroke Endpoint Definitions for Clinical Trials. *Journal of the American College of Cardiology*. 2018;71:1021-1034.

501.   McNamara RL, Spatz ES, Kelley TA, Stowell CJ, Beltrame J, Heidenreich P, Tresserras R, Jernberg T, Chua T, Morgan L, Panigrahi B, Ruiz AR, Rumsfeld JS, Sadwin L, Schoeberl M, Shahian D, Weston C, Yeh R and Lewin J. Standardized Outcome Measurement for Patients With Coronary Artery Disease: Consensus From the International Consortium for Health Outcomes Measurement (ICHOM). *Journal of the American Heart Association*. 2015;4:e001767.

502.   Eapen ZJ, Vavalle JP, Granger CB, Harrington RA, Peterson ED and Califf RM. Rescuing clinical trials in the United States and beyond: A call for action. *American Heart Journal*. 2013;165:837-847.

503.   !!! INVALID CITATION !!! 502.

504.   Chapman M, Mumtaz S, Rasmussen LV, Karwath A, Gkoutos GV, Gao C, Thayer D, Pacheco JA, Parkinson H, Richesson RL, Jefferson E, Denaxas S and Curcin V. Desiderata for the development of next-generation electronic health record phenotype libraries. *GigaScience*. 2021;10.

505.   Blumenthal S. Improving Interoperability between Registries and EHRs. *AMIA Jt Summits Transl Sci Proc*. 2018;2017:20-25.

506.   Aktaa S, Batra G, Wallentin L, Baigent C, Erlinge D, James S, Ludman P, Maggioni AP, Price S, Weston C, Casadei B and Gale CP. European Society of Cardiology methodology for the development of quality indicators for the quantification of cardiovascular care and outcomes. *European Heart Journal - Quality of Care and Clinical Outcomes*. 2020.

507.   Kentgen M, Varghese J, Samol A, Waltenberger J and Dugas M. Common Data Elements for Acute Coronary Syndrome: Analysis Based on the Unified Medical Language System. *JMIR Med Inform*. 2019;7:e14107.

508.   Holz C, Kessler T, Dugas M and Varghese J. Core Data Elements in Acute Myeloid Leukemia: A Unified Medical Language System-Based Semantic Analysis and Experts' Review. *JMIR Med Inform*. 2019;7:e13554.

509.   Stelfox HT and Straus SE. Measuring quality of care: considering conceptual approaches to quality indicator development and evaluation. *J Clin Epidemiol*. 2013;66:1328-37.

510.   Werner RM and Asch DA. The unintended consequences of publicly reporting quality information. *Jama*. 2005;293:1239-44.

511.   Khot UN. Exploring the risk of unintended consequences of quality improvement efforts. *Journal of the American College of Cardiology*. 2012;60:812-813.

512.   McWilliams JM. Professionalism Revealed: Rethinking Quality Improvement in the Wake of a Pandemic. *NEJM Catalyst*. 2020;1.

513.   Dimick JB, Welch HG and Birkmeyer JD. Surgical mortality as an indicator of hospital quality: the problem with small sample size. *Jama*. 2004;292:847-51.

514.   Trust and Transparency: From Ancient Rome to Guideline Committees. Available at: https://www.tctmd.com/news/trust-and-transparency-ancient-rome-guideline-committees. Accessed 06 January 2021.

515.   Sabik JF, 3rd, Bakaeen FG, Ruel M, Moon MR, Malaisrie SC, Calhoon JH, Girardi LN and Guyton R. The American Association for Thoracic Surgery and Society of Thoracic Surgeons Reasoning for Not Endorsing the 2021 ACC/AHA/SCAI Coronary Revascularization Guidelines. *Ann Thorac Surg*. 2021.

516.   Chopra SS. Industry Funding of Clinical Trials: Benefit or Bias? *JAMA*. 2003;290:113-114.

517.   Regulation (EU) 2016/679 of the European Parliament and of the Council. Available at: https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:02016R0679-20160504&from=EN. Accessed 31 December 2021.

518.   Caldicott Principles. Available at: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/942217/Eight_Caldicott_Principles_08.12.20.pdf. Accessed 31 December 2021.

519.   Data Protection Act 2018. Available at: https://www.legislation.gov.uk/ukpga/2018/12/contents/enacted. Accessed 31 December 2021. .

520.   National Health Service Act 2006. Available at: https://www.legislation.gov.uk/ukpga/2006/41/contents. Accessed 31 December 2021.

521.   Hickey GL, Grant SW, Cosgriff R, Dimarakis I, Pagano D, Kappetein AP and Bridgewater B. Clinical registries: governance, management, analysis and applications. *European Journal of Cardio-Thoracic Surgery*. 2013;44:605-614.

522.   Weintraub WS. Role of Big Data in Cardiovascular Research. *Journal of the American Heart Association*. 2019;8:e012791-e012791.

523.   Daskivich TJ, Abedi G, Kaplan SH, Skarecky D, Ahlering T, Spiegel B, Litwin MS and Greenfield S. Electronic Health Record Problem Lists: Accurate Enough for Risk Adjustment? *American Journal of Managed Care*. 2018;24:e24-e29.

524.   Sanborn TA, Tcheng JE, Anderson HV, Chambers CE, Cheatham SL, DeCaro MV, Durack JC, Everett AD, Gordon JB, Hammond WE, Hijazi ZM, Kashyap VS, Knudtson M, Landzberg MJ, Martinez-Rios MA, Riggs LA, Sim KH, Slotwiner DJ, Solomon H, Szeto WY, Weiner BH, Weintraub WS and Windle JR. ACC/AHA/SCAI 2014 Health Policy Statement on

Structured Reporting for the Cardiac Catheterization Laboratory. *Journal of the American College of Cardiology*. 2014;63:2591-2623.

525.   Weis JM and Levy PC. Copy, paste, and cloned notes in electronic health records: prevalence, benefits, risks, and best practice recommendations. *Chest*. 2014;145:632-8.

526.   Liyanage H, Krause P and de Lusignan S. Using ontologies to improve semantic interoperability in health data. *BMJ Health & Care Informatics*. 2015;22:309-315.

527.   Carter AB, de Baca ME, Luu HS, Campbell WS and Stram MN. Use of LOINC for interoperability between organisations poses a risk to safety. *Lancet Digit Health*. 2020;2:e569.

528.   Xu C, Yu T, Furuya-Kanamori L, Lin L, Zorzela L, Zhou X, Dai H, Loke Y and Vohra S. Validity of data extraction in evidence synthesis practice of adverse events: reproducibility study. *BMJ*. 2022;377:e069155.

529.   Rosenbaum L. Reassessing Quality Assessment — The Flawed System for Fixing a Flawed System. *New England Journal of Medicine*. 2022;386:1663-1667.

530.   Backer CL, Pasquali SK and Dearani JA. Improving National Outcomes in Congenital Heart Surgery. *Circulation*. 2020;141:943-945.

531.   Sutton M, Nikolova S, Boaden R, Lester H, McDonald R and Roland M. Reduced Mortality with Hospital Pay for Performance in England. *New England Journal of Medicine*. 2012;367:1821-1828.

532.   Minchin M, Roland M, Richardson J, Rowark S and Guthrie B. Quality of Care in the United Kingdom after Removal of Financial Incentives. *New England Journal of Medicine*. 2018;379:948-957.

533.   Raleigh VS and Foot C. *Getting the measure of quality: opportunities and challenges*. London: King's Fund; 2010.