Quality of care and clinical outcomes following Acute Myocardial Infarction: High resolution investigation using electronic health record data.

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Publications

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Abstract

Introduction:

Despite substantial improvements in treatment, adherence to guideline indicated treatment for acute myocardial infarction (AMI) patients remains sub-optimal. Therefore, the purpose of this research project was to investigate the quality of care and associated outcomes of patients hospitalised with AMI using electronic health record data.

Methods:

This thesis was based on prospective cohort data from the nationwide population-based clinical registry: Myocardial Ischaemia National Audit Project (MINAP) (2003-13). MINAP records all AMI admissions from 247 hospitals in England and Wales. The research conducted in this thesis consisted of four research strands all in the framework of assessing quality of care and outcomes for AMI patients which included: 1) determining the excess mortality associated with sub-optimal management of AMI (restricted to Non-ST-elevation myocardial infarction phenotype (NSTEMI)), 2) assessing variation in receipt of NSTEMI care, 3) investigating the association of temporal changes in clinical factors and therapeutic strategies with improvements in survival following ST-elevation myocardial infarction (STEMI) and 4) determining the efficacy of β blockers in treating AMI patients without heart failure or left ventricular systolic dysfunction (LVSD).

Results:

The majority (86.9% (n=337,881)) of the NSTEMI patients evaluated did not receive one or more guideline-indicated care interventions for which they were eligible and the identified sub-optimal care was found to be associated with 32,765 potentially avoidable deaths (95% CI 30,531 to 33,509). Most of the excess variation (99.6%) in receipt of care was due to between hospital differences (median 64.7%, IQR 57.4% to 70.0%; between hospital variance: 1.92, 95% CI 1.51 to 2.44; ICC 0.996, 0.976 to 0.999). For the STEMI phenotype the temporal improvements in six months and one year survival that have been noted between 2004 and 2013 were associated with the introduction of reperfusion (PPCI) and temporal improvements in $P2Y_{12}$

inhibitors prescription at hospital discharge. No significant differences in average time to death were found if all the AMI patients without heart failure or LVSD in the population had received β blockers compared with if no patients had received β blockers.

Conclusion:

The thesis provides evidence of important care deficits in an otherwise modern and efficient national health care system. The deficits in receipt care identified were found to be associated with avoidable deaths and most of the variation in receipt of care was explained by hospital differences in provision of care. The thesis also provides evidence that the introduction of PPCI and increased prescription of $P2Y_{12}$ inhibitors at discharge was associated with improved survival improvements that have been noted for STEMI patients admitted between 2004 and 2013. However, among survivors of hospitalisation with AMI without heart failure or LVSD as recorded in hospital, the use of β blockers was not associated with a lower risk of death at up to one year. Only through higher resolution investigations using whole healthcare system clinical registries can modifiable deficits of care be identified and, therefore, addressed.

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List of abbreviations

ACACIA	Acute Coronary Syndrome Prospective Audit
ACC	American College of Cardiology
ACEi	Angiotensin-Converting Enzyme Inhibitors
ACOS	Acute Coronary Syndromes Registry
ACS	Acute Coronary Syndrome
ACME	Average Causal Mediation Effects
ADE	Average Direct Effects
AFT	Accelerated Failure Time
AHA	American Heart Association
AMI	Acute Myocardial Infarction
ARBs	Angiotensin-Receptor Blockers
ATE	Average Treatment Effect
ATET	Average Treatment Effect on the Treated
AUBMC	American University of Beirut Medical Centre
AUROC	Area Under the Receiver Operator Curve
AIC	Akaike's Information Criteria
ASA	Acetylsalicyclic Acid
A & E	Accidents and Emergencies
BCIS	British Cardiovascular Intervention Society
BHF	British Heart Foundation
BIC	Bayesian Information Criterion
CABG	Coronary Artery Bypass Grafting
CASP	Critical Appraisal Skills Programme
CCGs	Clinical Commissioning Groups
CCAD	Central Cardiac Audit Database
CHD	Coronary Heart Disease
CI	Confidence Interval
CPACS	Clinical Pathways for Acute Coronary Syndromes in China
CPRD	Clinical Practice Research Datalink
COPD	Chronic Obstructive Pulmonary Disease
CRUSADE	Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the ACC/AHA Guidelines
CVD	Cardiovascular disease
DAGs	Directed Acyclic Graphs
ECG	Electrocardiogram
EHRs	Electronic Health Records
EHS-ACS	Euro Heart Survey of Acute Coronary Syndromes
ESC	European Society of Cardiology
EUROASPIRE	European Action on Secondary and Primary Prevention by Intervention to Reduce Events
FCE	Finished Consultant Episodes
GBD	Global Burden of Disease
GRACE	Global Registry of Acute Coronary Events
GWTG–CAD	Get with the Guidelines–Coronary Artery Disease registry
GPRD	General Practice Research Database
GP	General Practitioner

HES	Hospital Episodes Statistics
HRA	Health Research Association
ICCS	Interclass Correlation Coefficient
ICD-10	International Classification of Diseases Tenth Revision
IHD	Ischaemia Heart Disease
IQR	Interquartile Range
LCA	Latent Class Analysis
LDL	Low Density Lipoprotein
LVEF	Left Ventricular Ejection Fraction
LVSD	Left Ventricular Systolic Dysfunction
LIDA	Leeds Institute for Data Analytics
MAR	Missing At Random
MACCE	Major Adverse Cerebrovascular or Cardiovascular Events
MCAR	Missing Completely at Random
MCE	Monte Carlo Errors
MRIS	Medical Research Information System
MICE	Multiple Imputation by Chained Equations
MINAP	Myocardial Ischaemia National Audit Project
MNAR	Missing Not At Random
NICOR	National Institute for Cardiovascular Outcomes
NHFA	National Heart Failure National Audit
NHS	National Health Service
NSTEMI	non-ST Elevation Myocardial Infarction
NICOR	National Institute for Cardiovascular Outcomes Research
OASIS	Organisation to Assess Strategies for Ischaemic Syndromes
OLS	Ordinary Least Squares
OR	Odds Ratio
OMT	Optimal Medical Therapy
ONS	Office for National Statistics
OPCS-4	Office of Population, Census and Surveys Classification of Interventions and Procedures Fourth Revision
PCI	Percutaneous Coronary Intervention
PDC	Proportion of Days Covered Metric
PH	Proportional Hazard
POM	Potential Outcome Mean
PPCI	Primary Percutaneous Coronary Intervention
PPP	Physician Prescribing Preferences
PROMs	Patient Reported Outcome Measures
PTCA	Percutaneous Transluminal Coronary Angioplasty
RCT	Randomised Clinical Trials
REC	Research Ethics Committee
RON	Registration Online
SCNs	Strategic Clinical Networks
SEM	Structural Equation Modelling
STEMI	ST-elevation Myocardial Infarction

SUS	Secondary Uses Service
SSNAP	Sentinel Stroke National Audit Project
SWEDEHEART	Swedish We-System for Enhancement and Development of Evidence-Based Care in Heart Disease Evaluated According to Recommended Therapies
UA	Unstable Angina Pectoris
UK	United Kingdom
WHO	World Health Organisation

Chapter 1

1.1 Introduction

In Europe cardiovascular disease (CVD) is the leading cause of mortality, causing approximately 4.1 million (46%) deaths annually, with 20% (1.8 million) of these deaths being attributed to coronary heart disease (CHD)(1). Of the 4.1 million deaths, 1.4 million have been reported to be pre-mature deaths (deaths before the age of 75 years)(2). Globally, the Global Burden of Disease (GBD) report has reported that CVD has caused approximately 17.3 million deaths(2).

The purpose of this research project was to explore the association between quality of care and outcomes for AMI, the most common manifestation of CHD. The research investigated both sub-types of AMI, ST-elevation Myocardial Infarction (STEMI) and Non-ST-elevation Myocardial Infarction (NSTEMI), and for each subtype selected a particular theme based on literature reviews which assessed the knowledge gaps. The thesis will be in the area of cardiovascular epidemiology. Advanced statistical techniques such as latent class analysis, multilevel accelerated failure time models, multilevel Poisson regression, survival-time inverse-probability weighting, flexible parametric survival modelling, instrumental variable analysis, and mediation analysis were explored.

1.2 Thesis outline

A detailed description of the background of AMI is provided within this chapter. The description includes information on the definition of AMI, burden, care pathway and available data sources for validation of mortality, morbidity and treatment of AMI patients. This will be followed by Chapter 2, which explored the available literature on adherence to guideline-indicated

care for AMI patients and associated outcomes. The review aimed to explore AMI adherence to guideline-indicated care interventions prevalence, identify key components in determinants of poor adherence as well as investigate outcomes associated with non-adherence to guideline-indicated care for AMI patients. This knowledge base was then used to build the rationale for this current research and develop the research questions used to achieve the research aim.

Chapter 3 gives a detailed description of the study design, data source, and statistical methods that were used throughout the thesis. The main results of the research are presented in four chapters focusing on: quantifying the excess mortality associated with sub-optimal care of NSTEMI patients and determining the predictors of sub-optimal care (chapter 4), assessing geographic variation in receipt of care for NSTEMI patients (chapter 5), investigating the association of clinical factors and therapeutic strategies with improvements in survival following STEMI (chapter 6), and estimating the efficacy of β-blockers in treating AMI patients without heart failure or left ventricular systolic dysfunction (LVSD) (chapter 7). Each result chapter included: interpretation of the descriptive, analytical and sensitivity analysis results, as well as a summary and conclusion of the main findings.

Chapter 8 provides a detailed and critical discussion of the thesis, highlighting the main contributions of this work in the context of previous research and policy as well as a discussion of the strengths and limitations, and recommendations for future work.

1.3 Background of acute myocardial infarction

Acute coronary syndromes (ACS) consist of three main conditions which include STEMI, NSTEMI and unstable angina (UA)(3). These conditions result from reduced or terminated blood flow to the heart due to blockage of

the arteries that supply the heart muscle with blood (oxygen), which in turn causes myocardial cell death(4, 5). Blockage is mainly caused by atherosclerosis with thrombus(4, 5). STEMI is characterised by complete total blockage of the coronary artery, NSTEMI by partial blockage of the coronary artery and UA by restricted blood supply to the heart but with no permanent damage to the heart(6). Of the three ACS types UA is considered the least serious, with STEMI being considered the most serious(6). However, if NSTEMI is left untreated it can cause severe heart damage and even progress to being a STEMI(6). The leading symptom that starts the diagnostic and therapeutic cascade in ACS patients is chest pain(4). Severity of damage as a result of the ACS depends on size and location of infarction. The extent of infarction being determined by the level of blockage of arteries, severity and duration of ischaemia with no residual flow(7). The work of this research will focus on the two phenotypes considered most serious of the three ACS conditions, which are STEMI and NSTEMI, and collectively known as AMI.

1.3.1 Universal definition of myocardial infarction

The most recent (2015/2016) universal definition of AMI defines the condition as the rise or fall of cardiac biomarkers (high-sensitivity cardiac troponin) together with either presenting features; 1) symptoms of ischaemia, 2) new or presumed new significant ST-T wave changes or left bundle branch block on 12-lead ECG, 3) development of pathological Q wave on ECG, 4) imaging evidence of new or presumed new loss of viable myocardium or regional wall motion abnormality and 5) intracoronary thrombus detected on angiography or autopsy(4). The definition was further stratified to five sub-categories, that is type 1: spontaneous AMI (usually related to coronary artery blockage and ceased or decreased blood flow), type 2: an AMI secondary to an ischaemic imbalance, type 3: AMI resulting in death, type 4: AMI related to stent thrombosis and type 5: AMI related to coronary artery bypass grafting (CABG)(5). For this thesis, the research work was based on AMI of type 1 (spontaneous myocardial infarction) as the data source used (Myocardial Ischaemia National Audit Project

(MINAP)) records only information on AMI type 1(8), thus assessments of quality of care and outcomes could only be possible for this type.

1.4 Epidemiology of acute myocardial infarction

Acute myocardial infarction is a major cause of death and disability world-wide(5), with ischaemic heart disease being named as one of the top 10 causes of death, accounting for 15 million deaths in 2015 combined with stroke(9). The World Health Organisation (WHO) fact sheet has reported that these diseases have continued to be the principal cause of death globally for the last 15 years(9). In Europe it has been approximated that every sixth man and every seventh woman will die from myocardial infarction(4).

In the United Kingdom (UK) CVD has been related to more than 1.6 million NHS hospital episodes in 2012/13, accounting for 10% of all inpatient episodes among men and 6.2% among women(10, 11). Of the 10% male inpatient episodes 3.5% were attributed to coronary heart disease (CHD) and of the 6.2% female inpatient episodes, 1.5% were attributed to CHD (10, 11), with the most common manifestation of CHD being an AMI. Specifically, focusing on AMI, approximately 200,000 hospital visits annually have been attributed to AMI(12). Also 26% of all deaths in the UK have been attributed to CVD, i.e. approximately 160,000 deaths annually (435 per day and approximately one death every three minutes)(12). Annually, approximately 42,000 premature deaths have been reported in the UK(12).

The 2012 British Heart Foundation (BHF) coronary heart disease compendium of health statistics reported that although there have been decreased incidence rates of AMI in England, some regional differences were still evident with the highest incidences noted in the North and lowest in the South. It is estimated that there are around 50,000 heart attacks in

men, 32,000 heart attacks in women in England, and 8,000 heart attacks in men, 5,000 heart attacks in women in Scotland(13). Assuming that the rates of heart attacks in England were comparable to Wales and Northern Ireland, the compendium of health statistics reported that annually the UK would have approximately have 103,000 heart attacks cases(13). The most recent MINAP audit report (2015/2016) reported over 85,123 AMI cases in England, Wales and Isle of Man(8). Of these reported AMI cases, 39% (33,797) were diagnosed as STEMI and 60.3% (51,326) were diagnosed as NSTEMI(8). For England alone, 67% of the patients who suffered a heart attack were male and the majority of the STEMI patients (71%) were male. The females tended to be older than males for both AMI phenotypes(8). However, for both sexes the median age was greater for those who had suffered an NSTEMI compared to the STEMI, with most of the NSTEMIs being aged 70 years old or older(8). The associated production losses due to mortality and morbidity as a result of CHD amount to over £3 billion for the UK(14). Across Europe CHD accounts for 20% (1.8 million) of all deaths annually(1). Associated productivity losses, direct health care costs and informal care, due to mortality and morbidity, cost the European Union economy approximately €60 billion a year(15).

In 2014 the National Institute for Health and Care Excellence (NICE) estimated the population prevalence in the UK of STEMI patients to range between 750-1250 per million people and due to NSTEMI's difficult diagnosis thus harder to estimate, the annual incidence of hospitalisation is 3 per 1000 people (16). The incidence of AMI in the UK has been approximated to be around 200-220 per 100,000 men and 80-90 per 100,000 women, corresponding to an annual rate of 124,000 cases(17). The incidence data are usually derived from annual records of inpatient episodes from NHS hospitals (18). However using hospital records as a source of incidence data can result to overestimation of the number of new cases if an individual has multiple hospital episodes, the true number of new cases maybe overestimated. Also the incidence data can be underestimated in situations where a patient suffers a condition and does

not attend hospital. Usually this is quite common for conditions with high mortality rates, for example if a patient dies after a heart attack before reaching hospital their episode may not be recorded in the hospital records. Collecting accurate incidence rate data can prove difficult because unlike death, the presence and onset of disease is not absolute for example accurate case ascertainment for NSTEMI phenotype of AMI can be challenging due to the heterogeneous nature of symptoms which makes it harder to diagnose. As such availability of sources of robust incidence rates data for AMI in the UK are limited(18).

1.5 The management of acute myocardial infarction

The care pathway for AMI patients is characterised by five stages namely;

- Pre-hospital care (characterised by performance of an electrocardiogram (ECG) and receipt of aspirin before hospital admission, usually done by the attending paramedic or ambulance staff)
- Early hospital care (characterised by recording of an ECG and receipt of cardio-protective drugs)
- In hospital care (characterised by receipt of an invasive strategy angioplasty/ thrombolysis)
- Hospital discharge care (characterised by prescription of cardio-protective drugs and education on smoking cessation and dietary advice)
- Post hospital discharge care (characterised by comprehensive cardiac rehabilitation and long term drug therapy)

The five stages are preceded by a patient seeking medical help after suffering AMI symptoms which comprise of pain, pressure or discomfort in the chest, shortness of breath, sweating or feeling sick to the stomach and pain in the neck, jaw or shoulders(19).

The care pathways for the two phenotypes of AMI are quite different, with the major difference being that STEMI patients care encompasses prompt

diagnosis and timely treatment (through Primary Percutaneous Coronary Intervention (PPCI) or thrombolysis) to revive the obstructed coronary artery (20) whilst for NSTEMI patients performance of an angiogram and coronary intervention within 2-4 days is essential depending on the risk profile of the NSTEMI patient(21).

The European Society of Cardiology (ESC) and American College of Cardiology/American Heart Association (ACC/AHA) have published consensus guidelines to define the ACS care pathway and promote the use of the evidence-based therapies(4, 20-24).

The main categories of diagnosis and treatment of AMI are described briefly in §1.5.1 and §1.5.2 below, respectively.

1.5.1 Acute myocardial infarction: Diagnostics

The guidelines recommend that an ECG be taken within 10 minutes of the patient's arrival in the emergency room or at first contact with the emergency medical services, as the first line diagnostic tool in the assessment of the patient(4, 22). STEMI diagnosis is characterised by persistent ST elevation with suggestive signs and symptoms(4). For NSTEMIs the ECG maybe normal, however some characteristic abnormalities maybe observed for some of the patients that is ST depression, transient ST elevation and T-wave changes(4).

1.5.1.1 Biomarkers

Due to the fact that for NSTEMI patients a normal ECG maybe observed, diagnosis should be complemented by measurement of a biomarker of cardiomyocyte injury. Preferably cardiac troponins as they are more sensitive and specific than creatinine kinase, its isoenzyme CK-MB and myoglobin(4). An elevation of cardiac troponin above the 99th percentile of healthy individuals indicates AMI(4).

1.5.2 Acute myocardial infarction: Treatment

1.5.2.1 Pharmacological treatment of ischaemia

The goal of pharmacological anti-ischaemic therapy is to change how the heart or blood circulation works i.e. to decrease myocardial oxygen demand or to increase myocardial oxygen supply(4, 25). Details on the main categories of pharmacological drugs used to treat AMI and how they work are given below.

1.5.2.1.1 Antiplatelet therapy

Antiplatelet therapy is the cornerstone in the management of AMI patients. The three types of drugs that constitute antiplatelet therapy for AMI patients include; acetylsalicylic acid (aspirin), $P2Y_{12}$ receptor inhibitors and GP IIb/IIIa antagonists(4, 22). These cardio-protective drugs work by preventing blood clotting, which is achieved by inhibiting platelets from sticking together to form a thrombus (clot)(19, 25). This reduces the risk of re-infarction(26).

1.5.2.1.2 Anticoagulants

Anticoagulants are used in the treatment of AMI to prevent harmful blood clots from forming(4, 14, 22). They work by inhibiting thrombin generation and are more effective if used in conjunction with platelet inhibitors (antiplatelet therapy)(4, 25). Examples include enoxaparin, fondaparinux, warfarin and unfractionated heparin. Use of this pharmacotherapy does come with a side effect of increased risk of bleeding(25).

1.5.2.1.3 Angiotensin-converting enzyme (ACE) inhibitors

Angiotensin-converting enzyme (ACE) inhibitors are used to regulate high blood pressure in the management of AMI(25). They work by making the blood vessels relax and widen by preventing the body from making the hormone that makes the blood vessels tighten, angiotensin II(19, 25). The lowering of the blood pressure ensures that the heart does not have to work so hard to pump blood through the vessels thus making the heart more efficient(19). Examples of ACE inhibitors include Ramipril and perindopril(25).

1.5.2.1.4 Angiotensin-II antagonists / Angiotensin receptor blockers (ARBs)

Angiotensin receptor blockers (ARBs) are also used for regulating high blood pressure like ACE inhibitors but less likely to cause some side effects that can be experienced when taking ACE inhibitors(19). Examples of ARBs include losartan and candesartan(25). They are usually given to patients who cannot take ACE inhibitors.

1.5.2.1.5 β blockers

Beta blockers act by slowing the heart rate and lowering the blood pressure(4, 22, 25). This is achieved by supressing the hormone adrenaline(19). When adrenaline is stopped the heart slows down, making blood flow through the vessels slow thus the pressure inside the vessels drops and the heart works less(19, 25). β blockers use reduces the risk of re-infarction(25).

1.5.2.1.6 Statins

Statins are lipid lowering drugs that lower blood low density lipoprotein (LDL) cholesterol (bad type of cholesterol)(19, 25). They act in several ways, that is: some change the way the liver processes cholesterol and fat, others affect the way the body digests nutrients whilst others prevent cholesterol from flowing though the blood vessels(19). The most commonly prescribed lipid lowering drug in the UK are Statins and they work by reducing the amount of cholesterol produced by the liver(25).

1.5.2.2 Invasive strategy

In order to restore or improve blood flow to the heart, coronary angioplasty is implemented(4, 22). Coronary angioplasty is sometimes called Percutaneous Coronary Intervention (PCI), Percutaneous Transluminal Coronary Angioplasty (PTCA), balloon angioplasty or coronary stent implantation(27). If the coronary angioplasty is done as an emergency treatment, it is called Primary Percutaneous Coronary Intervention (PPCI). Coronary angioplasty involves the insertion of a deflated balloon by aid of a catheter through the groin or wrist of the AMI patient to look for thickening and hardening of the coronary artery. To aid visibility by X-ray, a dye is

injected into the catheter. After identification of the affected area the balloon is then lined up next to the plaque and then inflated resulting in flattening of the plaque within the walls of the artery. This will reopen the artery and blood flow will be restored. To keep the artery re-opened a stent (short tube of stainless steel mesh) can be inserted, usually same time as the balloon. Different types of stents can be used, with the main type being the drug-eluting stents and bare-metal stents. If the narrowed region of the vessel is not responsive to this approach then bypass surgery is implemented, that is CABG. CABG surgery involves bypassing the narrowings in the coronary arteries(27).

As described in §1.5 for STEMI patients' prompt diagnosis and timely treatment is required thus they receive PPCI (performed within 12 hours from symptom onset)(22). However if this is not possible immediate fibrinolysis or thrombolysis should be performed. Both procedures involve the enzymatic dissolution of blood clots.

1.5.2.3 Invasive vs. conservative strategy for NSTEMI

NSTEMI patients can be treated by two approaches that is the invasive care (plus cardio-protective drugs) approach or the conservative strategy(4). The conservative strategy patients are initially treated with the drugs only and only those that persist with ischemic symptoms or ongoing artery narrowing (noted via stress testing or imaging) undergo coronary angiography and revascularisation(4). NSTEMI patients in whom invasive care is withheld as indicated by the guidelines include the very elderly/frail patients, patients with comorbidities such as dementia, severe chronic renal insufficiency or cancer and those at high risk of bleeding complications(4).

1.5.3 Risk assessment

Accurate risk assessment is essential in the treatment of AMI patients; especially for NSTEMI patients where after diagnosis further treatment is based on responsiveness to anti-anginal treatment and risk of mortality(4).

The Global Registry of Acute Coronary Events (GRACE) risk score is the most commonly used risk score as it is derived from an international registry (approximately 100,000 patients in 30 countries) of “real world” patients and is applicable to all types of ACS types predicting short and long-term mortality(28). Timely risk stratification is vital as the benefits of aggressive treatment are mainly observed in those at higher risk of adverse clinical events(21, 29, 30). Use of the risk score allows for easier identification of the high risk patients by clinicians at time of presentation(28). The GRACE risk score prediction model includes eight predictors namely: age, heart rate, systolic blood pressure, renal function, congestive heart failure, ST-segment deviation, cardiac arrest and elevated biomarkers(28). The risk score is recommended for use by both the ESC and National Institute for Health and Clinical Excellence (NICE)(4, 16). However, NICE utilises a modified version of the GRACE risk score in which the model uses “prescription of a loop diuretic during admission” as a surrogate for Killip class and creatinine concentration re-coded as a categorical variable. This version of the score was termed adjusted mini-GRACE risk score(31).

1.5.4 Cardiac rehabilitation

Following an AMI, hospital stay is usually a few days and the patient can usually go back to normal daily life within a few weeks. However to prevent hospital readmissions the patients are enrolled into cardiac rehabilitation as indicated by the guidelines(4, 22). Cardiac rehabilitation is characterised by detailed and evidence-based plan of care that promotes medication adherence, timely follow-up with the healthcare team, appropriate dietary and physical activities. Patients are also educated on the importance of stopping smoking as well as avoiding second-hand smoke.

1.6 Data sources for validation of mortality, morbidity and treatment of AMI

There are several data sources that provide information on mortality, morbidity and treatment of AMI namely: Office for National Statistics (ONS) (mainly mortality data), Clinical Practice Research Datalink (CPRD), Hospital Episode Statistics (HES), British Cardiovascular Intervention Society (BCIS), ResearchOne database, and Myocardial Ischaemia National Audit Project (MINAP) (Table 1.1). The use of these data sources for research is governed by several factors which include: representativeness, relevance, quality and accessibility of the data.

Table 1.1 Characteristics of the data sources commonly used in the evaluation of mortality, morbidity and treatment of AMI.

	Data source					
Characteristic	**MINAP**	**CPRD***	**ONS (mortality statistics)**	**ResearchOne**	**HES**	**BCIS**
Type of data source	Nationwide register for acute coronary syndrome	Primary healthcare database	National death data	Pseudo-anonymous clinical research database	National hospital episodes database	Nationwide registry of all percutaneous coronary intervention (PCI) procedures.
Who is included	Patients admitted with ACS in 247 NHS hospitals	Patients registered with participating GP practices in the UK	All deaths	Patient data from primary and secondary healthcare providers which include: • General practice • Child health • Community care • Palliative hospital • Out of Hours • Urgent care • Accident & Emergency • Acute hospital • Social services	Hospitalisation data of all admitted patients in NHS trusts.	All patients admitted to all hospitals performing PCI in the UK.
Year start of data collection	2000	1987	2001	2013	1989	1994
Area covered	England and Wales	England, Wales, Northern Ireland and Scotland	England and Wales	England	England	UK

	Data source					
Characteristic	**MINAP**	**CPRD***	**ONS (mortality statistics)**	**ResearchOne**	**HES**	**BCIS**
Data description	• Patient demographics • Admission method • Clinical features and investigations • Medical history • Drug treatment in-hospital and at discharge • Clinical complications • Interventional treatments Collected across 130 fields.	• Patient demographics • Prescriptions details • Preventive care provided • Specialist referrals • Immunisations • Behavioural factors • Tests • lifestyle factors • Clinical events (symptoms, diagnoses)	Date and cause of death.	• Diagnostic codes • Procedure codes • Pathology test data • Prescribing data • Deprivation indices • Care pathways	All admissions, outpatient appointments, patient reported outcome measures, adult critical care, A&E attendances and mortality data.	• Patient demographics • Indications for PCI • Procedural details • Outcomes Collected across 113 fields.
Representativeness of the data	MINAP records most of the STEMI cases, however fewer NSTEMI cases in England and Wales.	Approximately 6.9% of the UK population.	All death records for England and Wales	A representative sample of the English population (~26 million patients)	Representative of all the hospitalised population as it covers all NHS trusts in England, including acute hospitals, primary care trusts and mental health trusts.	All hospitals performing PCI in the UK. (>97% of PCI cases are included in the audit).

*Clinical Practice Research Datalink (CPRD)(32) has taken on the original work of GPRD since 2012.

1.6.1 CPRD

1.6.1.1 Overview

The CPRD is a primary care database that was set up from the General Practice Research Database (GPRD) in 2012, with GPRD having been started in 1987(32). Data from this database is collected (on-going) from 674 practices in the UK (approximately 11.3 million coverage), to date with 4.4 million of the recorded patients being considered as active(32). Patient information collected includes: demographics, symptoms, tests, diagnoses, therapies, health-related behaviours and referrals to secondary care(32). Data is collected in participating GP practices during normal clinical care and the data is then transferred to the CPRD servers monthly(32).

1.6.1.2 Strengths

Key strengths of CPRD data include:

- Breadth of coverage, i.e. CPRD database is one of the few large databases that collect data including morbidity and life-style data with linkage to secondary care and mortality data.
- Size, i.e. to date CPRD database has information on approximately 11 million patients, with 4.4 million of them being active (alive, currently registered).
- Long term follow-up, i.e. the median follow-up time for the active patients is 9.4 years (interquartile range (IQR) 3.4-13.9) and for the overall patient population in CPRD (including the inactive ones) is 5.1 years (IQR 1.8-11.1years).
- Representativeness, i.e. the patients recorded in CPRD were found to be representative of the UK population in terms of age and sex when compared to the UK census carried out in 2011.
- Data quality, i.e. the Quality and Outcomes Framework (33) launched in 2004 has prompted an improvement in recording of data in the English general practice and also CPRD data is maintained by high standard validation checks supported by independent studies(34).

1.6.1.3 Weaknesses

As with other sources of data arising from electronic health records (EHRs), the major weakness that CPRD database has is missing data and dealing with the missing data for researchers can prove challenging as missing data patterns are complex(32). The missing data include, data from over the counter prescriptions and morbidities in which the patient does not require GP consultation. Another weakness of the CPRD data is misclassification, i.e. the absence of a read code for disease is interpreted as an absence of the disease(34). This usually arises as a result of either patients failing to present to the GP with the disease or variation between GPs in coding diagnoses of the diseases(34).

1.6.2 BCIS

1.6.2.1 Overview

The British Cardiovascular Intervention Society (BCIS) registry is a nationwide registry for all PCI procedures performed in the UK(35). The registry was initiated when the BCIS was started in 1988(35). The main aims of society included creating an all-encompassing and accurate registry of all PCI procedures done in the UK, in order to allow for audit by assessing quality of care and driving improvements, and also to provide data for research(35, 36). Data collection at time of commencement was for descriptive survey purposes which developed over time with the aid of the electronic methods for data collection developed by the Central Cardiac Audit Database (CCAD) group(35). Full UK-wide involvement was reached in 2005(35). In March 2010 it was reported that BCIS-CCAD database had approximately 460,000 patient records, with an estimated annual addition of 80,000 new patient records(35).

Patient information is collected across 113 fields in the BCIS registry and it includes information on: patient demographic features and identification information, indication for PCI, details of the PCI operators, technical aspects of the PCI procedure and adverse outcomes/complications(35). Data entry is done by healthcare professionals and data entry clerks(35). The data is uploaded into local software systems (e.g. the Lotus Notes

software and Microsoft Access database), encrypted and transferred to CCAD data servers(35). Mortality data is added through linkage with ONS by the Medical Research Information System (MRIS) using the patients' unique NHS numbers(35).

1.6.2.2 Strengths

Key strengths of BCIS data include:

- Size and population coverage, i.e. BCIS database contains all PCI procedures performed UK-wide and in March 2014 it was reported to have approximately 747,000 patients recorded.
- Data quality, i.e. in the course of uploading the data to central servers internal checks for consistency and range checks are done to ensure the data is of high quality. Log files of serious errors are kept to allow for cleaning and correction, and re-uploading.
- Depth of detail of the data

1.6.2.3 Weaknesses

Major weaknesses when using BCIS data include:

- Outcome data, i.e. death data acquired through linkage to ONS data is all-cause death and not cause specific.
- There are no independent data validation checks for BCIS data.
- Missingness in some data fields.

1.6.3 ResearchOne

1.6.3.1 Overview

ResearchOne is a comprehensive pseudo-anonymised clinical research database which was launched in February 2013(37, 38). ResearchOne is potentially one of the largest databases in the world (containing approximately 28 million records held on the TPP SystmOne clinical system), with the data recorded in it being from various settings in England i.e. from both primary and secondary care providers (General Practice, Child Health, Community, Palliative Hospital, Out of Hours, A&E and

Community Hospital)(38). Approximately, 5 million health records (non-identifiable) were approved and became available for researchers in 2013. Over 400 organisations are active members contributing towards data for ResearchOne and data is collected from them weekly. The data collected includes diagnostic codes, procedure codes, pathology test data, prescribing data, deprivation indices and care pathways. ResearchOne was created with the aim to establish a clinical database that enables high quality research that will result to improvement in patient care and health services(38). Projects currently supported by ResearchOne carrying out this type of research include Medical Research, Health Services Research and eHealth Research.

1.6.3.2 Strengths

- ResearchOne offers the opportunity to utilise integrated electronic health records that allow investigation of health care through a whole systems approach i.e. allows for longitudinal assessments.
- Representativeness, i.e. the sample of patients recorded in ResearchOne was derived from a representative sample of the English population (extracted from over 26 million patients (approximately 300 million years of patients records) hosted in SystmOne from 4500 organisations that include 2100 general practices, 170 community services and 80 palliative care organisations).
- Large sample sizes, i.e. five million health records were made available for researchers in 2013.
- Depth of detail of the data, i.e. ResearchOne has consolidated data from various sources that are involved in patients care.
- Data linkage is possible with ResearchOne data i.e. ResearchOne has national ethical and governance approval to request linkage.
- Was created with the aim to improve patient healthcare.
- Timely data i.e. ResearchOne is updated weekly.

1.6.3.3 Weaknesses

- Accessibility of integrated EHRs is still quite difficult thus infrequent use of such data sources.
- ResearchOne requires consent from contributing organisations (based on the “provider opt-in” model). Patients also have the opportunity to opt out from providing non-identifiable data through the “patient opt-out” mechanism. This may compromise ResearchOne data representativeness due to data exclusion of the non-consenting organisations or patients from ResearchOne database.

1.6.4 MINAP

1.6.4.1 Overview

MINAP is a nationwide registry of ACS patients admitted to one of the 247 National Health Service (NHS) hospitals in England and Wales(39). MINAP was started in 2000 and is now mandated by the Department of Health(39). The registry was started for auditing purposes for hospital performances against the National Service Framework for Coronary Heart Disease. Data are collected prospectively at each hospital and transferred online to a central database electronically encrypted(39). The CCAD(40) manages and stores the data for up-to-date analysis and dissemination.

The ACS patients’ information recorded in MINAP is collected across 130 fields, with the information including the method and timing of admission, patient demographics, patient medical history, inpatient investigations, results and treatment, hospital outcome, and (if applicable) date of death from linkage to the ONS(8, 39). Every two years the registry is revised taking into account developments that would have occurred in ACS management as well requirements of the users of the dataset(39). This process includes adding new options to the registry and archiving old fields that would have become redundant. MINAP’s major application, is being an auditing tool for assessing ACS management in participating hospitals and benchmarking against guidelines(39).

1.6.4.2 Strengths

Key strengths of MINAP data include:

- Size and population coverage, i.e. data is collected from every acute hospital in England and Wales (247 hospitals) and participating hospitals are required to enter all patients with suspected MI(8). Annually, approximately 90,000 records are uploaded and to date the registry contains over 1.25 million records, potentially making it the largest database of its kind in the world(8).
- Representativeness, i.e. data in MINAP is collected from 247 acute hospitals in England and Wales.
- Definition of AMI phenotype, i.e. compared with other data sources, MINAP is the only database that distinguishes between STEMI and NSTEMI.
- Data quality, i.e. MINAP data application has error-checking routines as well yearly data validation exercises. Guidance is given to staff entering via a dedicated telephone help desk.
- Completeness, i.e. in 20 key fields completeness is closely monitored and is above 99%, these fields include hospital mortality, hospital discharge diagnosis, NHS number and secondary prevention prescription at hospital discharge. An assessment carried out in 2008 showed that in the other fields completeness was over 80%.
- Depth of detail of the data, i.e. data is collected across 130 fields in MINAP. Data on method and timing of admission, patient demographics, patient medical history, inpatient investigations, results and treatments, hospital outcome and date of death through linkage to ONS.

1.6.4.3 Weaknesses

Major weaknesses when using MINAP data include:

- Case ascertainment, i.e. MINAP reports great majority of patients having STEMI, however there is under-reporting of NSTEMI patients in MINAP. This is mainly due to the difficulty in diagnosing NSTEMI, heterogeneous pathways of care for NSTEMI as well the fact that

some NSTEMI patients are not always admitted to cardiology wards. The 2012 MINAP report, reported that HES data captured approximately 105,000 MI hospital admissions annually with MINAP reporting 30,000 STEMIs admissions vs. only 50,000 NSTEMIs admissions annually. However the actual expected appropriate number of NSTEMI admissions annually is around 80,000.

- Missingness in some data fields, i.e. although completeness of key 20 fields which collect data on discharge diagnosis, NHS number, hospital mortality and secondary prevention medication on discharge has been reported to be > 95%, missingness in the other data fields has been reported to range between 31-80%(39)
- Outcome data, i.e. death data acquired through linkage to ONS data is all-cause death and not cause specific.

1.6.5 HES

1.6.5.1 Overview

Hospital Episodes Statistics (HES) is a data warehouse established in 1987 and it comprises of six datasets namely; inpatient, outpatient, accidents and emergencies (A&E), patient reported outcome measures (PROMs), adult critical care, and mortality data(41). The inpatient dataset contains all admissions to NHS hospitals in England from 1989 onwards (approximately over 16 million episodes annually). The outpatient dataset contains information on all outpatient of hospital appointments of the patients from 2003 onwards (approximately 60 million new records annually), and the A&E dataset contains diagnosis, investigations and treatment codes for all A&E visits from 2007 onwards (approximately 12 million records annually)(41). The mortality dataset was created by linkage to ONS mortality data. The PROMs dataset contains information reporting outcomes and quality of care from the patients' perspective for four procedures, namely: hip replacement, knee replacement, varicose vein, and groin hernia surgery from 2009 onwards(41). The critical care dataset contains all records for adult patients' critical care hospital stays(41). Private patients treated in NHS hospitals are also included in HES.

Patient information recorded in HES include: demographics (age group, gender and ethnicity), diagnoses and operations, administrative information (time waited, dates and methods of admission and discharge) and geographical information (where patients are treated and where they live)(41). HES data was developed for several functions which include:

- studying the epidemiology of hospitalised disease
- monitoring trends and patterns in NHS hospital activity
- assessing effectiveness of delivery of care in hospitals
- revealing health trends over time
- determining fair access to health care
- Hospital payments
- developing, monitoring and evaluating government policy(41).

HES data was derived from the regular exchanges of information between providers and commissioners of healthcare for NHS patients in England(41). Providers submit the data to the Secondary Uses Service (SUS), which makes it available to commissioners as well as being copied to a database(41). Data extraction for HES is done monthly at pre-arranged dates from the SUS data warehouse(41). Providers are allowed to update their monthly submissions in a process called an annual refresh(41).

Three set of codes are used when collecting HES data (World Health Organisation International Classification of Diseases Tenth Revision (ICD-10), Office of Population, Census and Surveys Classification of Interventions and Procedures fourth revision (OPCS-4), and A&E Clinical Codes)(41). The ICD-10 codes are used for collecting data for hospital admission treatment (inpatient data), OPCS-4 codes for data collection for procedures and interventions performed and the A&E clinical codes for data collection for diagnoses, investigations and procedures during A&E attendance.

Data is recorded in HES as finished consultant episodes (FCE), i.e. “time a patient spends under the care of each consultant”. A patient can have one

or more FCEs per hospital admission if the patient is treated by more than one consultant. In the case that a patient has several FECs, they can be grouped together to form spells, i.e. total number of FCEs per single hospital admission for a patient(41).

1.6.5.2 Strengths

Key strengths of HES data include:

- Size and population coverage, i.e. annually, HES data processes over 125 million admitted patient, outpatient and A&E records (unselected sample of hospital episodes).
- Representativeness, i.e. data in HES is collected from all NHS trusts in England, including acute hospitals, primary care trusts and mental health trusts.
- Data quality, i.e. HES data extraction involves thorough procedures and checks. Upon receipt of the data, the data quality team cleans and validates the data in four stages; 1) provider code mapping (which involves ensuring that the hospital codes are correct and usable), 2) duplicate removal, 3) data cleaning (involves removal of errors in the dataset for example extra characters in the codes) and derivations (involves cleaning common and obvious data quality errors as well as deriving additional data items to populate the HES dataset(41).
- Longitudinal linkage, i.e. HES can be linked to other datasets using the HESID and the long period of data collection of approximately 19 years allows for long-term follow-up.
- Use of International Classification of Disease (ICD-10) coding of the data allows for international comparisons since ICD-10 coding is used across UK, Europe, Canada, Australia and New Zealand.

1.6.5.3 Weaknesses

- The major challenge when using HES data is that the data are mainly collected for purposes of administering the health service and not specifically for research purposes as such there maybe limitations to the usefulness of this data for research purposes(42).

- Inaccurate diagnostic coding practices as coding may vary between hospitals(42).
- As with other sources of data arising from EHRs, HES data has missing data and incomplete records(42).
- Data on drugs prescribed through hospital pharmacies to in-patients is not available in HES.

1.6.6 ONS

1.6.6.1 Overview

In the UK the ONS is the source of mortality statistics as well as the database for mortality data and main diseases or injuries causing death. The ONS was created in April 1996 from the merger of the “Central Statistics Office” (CSO) and the “Office of Population Census and Surveys” (OPCS)(43). The ONS provides a wide range of statistical information which includes national accounts, measures of inflation, business statistics, labour market indicators, vital statistics on births, marriages and deaths, and population estimates and projections(43). However for the purpose of this thesis work, the description of ONS will be restricted to the mortality data information. The Births and Deaths Act 1836 made it a legal requirement for all deaths to be registered from July 1837(44). The mortality statistics are derived from information when deaths are certified and registered(45). The medical practitioner using the Medical Certificate of Cause of Death certifies most deaths. An informant, usually a relative of the deceased then takes the certificate to the registrar. Most of deaths are registered this way, with a quarter of the deaths being certified by the coroner(45). The death registration is recorded on an online system (Registration Online (RON)) by the registrars. The death data are coded using the ICD-10 coding system (since January 2001 in England and Wales), which allows for international comparisons(46). The underlying cause of death recording is governed by the recommendation of the World Health Organisation, i.e. defined as;

- the disease or injury that initiated the train of events directly leading to death

- the circumstances of the accident or violence that produced the fatal injury(45).

To ensure that the data are usable for analysis, the data pass through a series of automated validation processes which highlight any inconsistencies(45). The validation checks include; identification of missing data entries, checking for duplicates, misplaced records, checks on registrars who have not sent over their data by the recommended time and for paper records checking for completeness and correct death date vs. registration date ranges(45). The ONS has developed guidelines for measuring statistical quality which are based on five European Statistical System Quality Dimensions to aid quality output from ONS data(45).

1.6.6.2 Strengths

- Representativeness, i.e. the Births and Deaths Registration Act of 1836 made it compulsory for all deaths to be registered from July 1837.
- ONS data not only records date and place of death, but also cause of death. Thich enables a better understanding of specific diseases in the death process.
- Use of International Classification of Disease (ICD-10) coding of the data allows for greater consistency and easier comparison.

1.6.6.3 Weaknesses

- Mortality data made available in registries like MINAP is all-cause mortality data.
- A small proportion of deaths are labelled ‘uncertified’ and these include deaths for which the doctor who completed the medical certificate would have not fulfilled all the legal requirements for completing the medical certificate.
- Recording of multiple causes of death can result to biased recording of underlying cause of death, i.e. some conditions are always selected as the underlying cause of death whenever they appear on the medical certificate for example major cancers and acute cardiovascular events (myocardial infraction and stroke).

Chapter 2 : Literature Review

Quality of care and outcomes of AMI patients

2.1 Introduction

The ESC and ACC/AHA have published consensus guidelines to define ACS care and promote the use of the evidence-based therapies as defined earlier in Chapter one(4, 20-24). Despite the evidence of efficacy of the guideline indicated care interventions, sub-optimal adherence still remains a major public health concern(47-49). In this chapter, I provide a systematic literature review of the existing evidence on the prevalence of adherence to guideline indicated care for AMI patients, predictors of poor adherence and associated outcomes.

Chapter 2 is structured such that the first section comprises of the search strategy implemented (§2.1.1), followed by the results of the search conducted §2.1.2. A detailed discussion on the existing evidence (§2.1.3) follows the results section, followed by a critical appraisal of literature (§2.2), summary of the gaps in knowledge and the PhD aim (§2.3). The chapter is concluded by highlighting the study objectives (§2.3.1).

2.1.1 Methods

The literature review was undertaken on three databases: Medline (1946-2016), Embase + Embase classic (1946-2016) and Google scholar (2005-2016). The literature search was based on the research question “What is the available evidence regarding combined use (optimal medical therapy) of guideline recommended care for AMI patients and associated outcomes?” The question was broken down using the PICO (Population – AMI, Intervention – guideline indicated care, Comparison (not used as there

was no comparator) and Outcomes - mortality) (50) approach to literature reviews. The search was conducted using keywords and medical subheadings of the three categories derived from PubMed given in Table 2.1.

Table 2.1 List of the literature review key words using the PIO strategy.

Patient	Intervention	Outcome
Acute coronary syndrome*	Optimal medical therapy	Mortality
ACS	Optimal medical treatment	Survival
Acute myocardial infarction	Combined therapy	Death
AMI	Combined medical therapy	Dead
Myocardial infarction	Guideline recommended care	Premature mortality
MI	Evidence based care	Premature death
Heart attack*	Process measure*	Outcome*
Infarct, Myocardial	Performance measure*	
Myocardial Infarcts	Guideline indicated care*	
	Early intervention	
	Evidence-based practice	
	Policy compliance	
	Compliance, policy	
	Protocol compliance	
	Compliance	
	Adherence	
	Health care quality	
	Quality of healthcare	

Abbreviations: AMI; acute myocardial infarction**,** ACS; acute coronary syndrome.

2.1.2 Results

Initially, 105 citations were obtained from Medline, 183 from Embase + Embase classic and 35 from Google scholar. From these three databases a total of 273 articles were obtained. 127 articles were excluded after screening for duplication using Endnote, giving a total of 146 non-duplicate papers. Considering the title and abstract 70 articles were excluded from the 146 to give a total of 76 articles. An eligibility criteria which comprised as listed below was set up to further screen the articles:

- Include adult studies only (aged >18 years)
- Include English language and human studies only
- Include studies that assess adherence to guideline indicated care interventions
- Exclude studies investigating single-drug effects for the management of AMI
- Exclude articles that are not full text for example published conference abstracts
- Exclude all case studies.

Thirty articles were excluded as they were focusing on efficacy of individual care interventions and did not assess adherence to optimal/combined guideline indicated care. After full text review of 46 papers, 17 papers were excluded to give a resultant 29 articles for literature reviewing. The details of the papers filtering are shown in Figure 2.1. Table 2.2-Table 2.5 provide the details of the key papers that were considered relevant for this present research study.

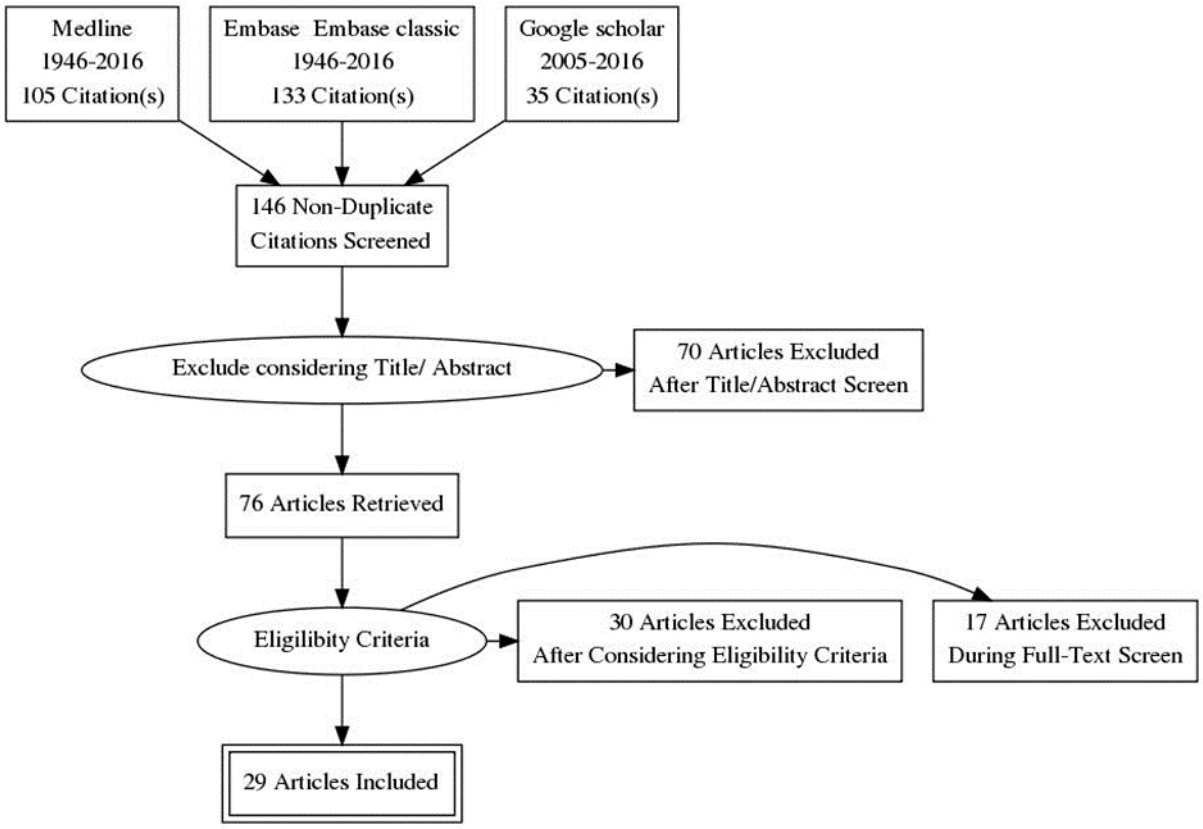


Figure 2.1. Flowchart for literature search and filtering.

2.1.3 Summary of findings from literature

2.1.3.1 Prevalence of adherence to guideline indicated care for AMI

Of the 29 studies retrieved from the literature search, 11 quantified the prevalence of receipt of Optimal Medical Therapy (OMT) (receipt of all guideline indicated care interventions the patients' were eligible for). Receipt of OMT in the studies was low (median 46.2%, IQR 29.1-49.4%) (Table 2.2), with OMT being defined as receipt of all the five main pharmacotherapy drugs (ACEi/ARBs, β-blockers, statins, aspirin and $P2Y_{12}$ inhibitors, unless contraindicated at hospital discharge)(51-61). Only one study defined OMT including reperfusion as well(59). Assessing long term (one year) adherence of the cardio-protective drugs after hospital discharge, OMT adherence rates were noted to be as low as 18.2%, with non-adherence to aspirin, β-blockers, ACEi/ARBs or statins individually being shown to be approximated 50%(60). Comparing 6 months follow-up with 12 months follow up, Bi et al.(54) found that OMT declined from 48% to 41%, with marked reductions for clopidogrel (25%) and combination of antiplatelets (21%)(54). Despite poor receipt of OMT individual prescription of the cardio-protective medication was very high, with one study reporting 84% of the eligible patients receiving statins, 89% aspirin, 70% $P2Y_{12}$ inhibitors, 90% β-blockers and 81% ACEi / ARBs at hospital discharge and other studies showed similar findings(51, 59, 62).

Table 2.2 Literature reviews on studies assessing prevalence of adherence to guideline indicated care for AMI patients.

Author (Year)	Country	Design (Interval data collected)	Setting (N)	Treatment	Outcomes	Statistical analysis	Key findings
Bramlage et al (2010)	Germany	Nationwide registry (February 2003 and October 2004).	Patients with AMI (STEMI or NSTEMI) admitted to 79 hospitals with a cardiology unit or internal medicine department. SAMI (N=5353)	Pharmacotherapy use at hospital discharge (Optimal medical therapy (OMT): aspirin, ACEi/ARB, β-blockers, statin and clopidogrel, unless contraindicated)	Medication adherence.	Data summarised as frequencies and percentages.	At hospital discharge 89% of the patients received aspirin, 90% β-blockers, 84% statins, 81% ACEi / ARB, 70% clopidogrel and 46.2% OMT.
Rasmussen et al (2007)	Canada	Population-based, observational, longitudinal study (April 1, 1999 and May 1, 2003).	Elderly (aged 66 years or older) AMI survivors (surviving at least 1 year 3 months after hospitalization) recorded in the Ontario Myocardial Infraction Database (N=31,455)	Pharmacotherapy medication use following hospital discharge after AMI (β-blockers, statin and calcium channel blockers).	Medication adherence.	Data summarised as frequencies and percentages, and means and standard deviations (SD).	Mean 1-year adherence rates, as determined by the PDC, were 87.5% (SD, 20.5%) for statins, 83.9 (SD, 24%) for β-blockers, and 78.9 (SD, 28.8%) for calcium channel blockers. Within the entire median 2.4 years follow-up time 13.2% (Statins), 19.6% (β-blockers) and 33.5% (calcium channel blockers) of patients permanently discontinued treatment.

Author (Year)	Country	Design (Interval data collected)	Setting (N)	Treatment	Outcomes	Statistical analysis	Key findings
Chew et al (2009)	Australia	Nationwide registry (November 2005 and May 2006). Large-scale randomised clinical trials or meta-analyses.	AMI (STEMI or NSTEMI) admissions from 39 hospitals across Australia recorded in ACACIA. (N=1,630)	Pharmacotherapy use at discharge (aspirin, statin, clopidogrel, ACEi/ARBs and β-blockers). Timely management for STEMI (timely reperfusion and early invasive management with concomitant glycoprotein IIb/IIIa inhibition). Timely management for NSTEMI (timely use of invasive management and glycoprotein IIb/IIIa inhibition).	Medication adherence and revasculari sation.	Data summarised as frequencies and percentages.	26% of the patients received less than four guideline-indicated chronic pharmacotherapies. 13.5% of the STEMI patients received optimal care. 12.4% of the NSTEMI patients received optimal care. 4% of the entire population received optimal care (discharged on four or five drugs) and maintained late adherence.
Bauer et al (2010)	Germany	Multicentre, prospective, observational study. (June 2000 and November 2002)	Hospital survivors of AMI (STEMI or NSTEMI) from 155 hospitals enrolled in the ACOS registry. (N=11,823)	Five discharge medication drugs: acetyl salicylic acid, clopidogrel, β-blockers, ACEi/ sartan and statin. Dichotomised receipt of care	Medication adherence.	Data summarised as frequencies and percentages.	29.1 % (3,439) eligible patients received < four drugs.

Author (Year)	Country	Design (Interval data collected)	Setting (N)	Treatment	Outcomes	Statistical analysis	Key findings
				composite score i.e. patients receiving < 4 drugs (group 1) or receiving 4-5 drugs (group 2).			
Bi et al (2009)	China	Multi-centre prospective study. (September 2004 and May 2006)	Patients diagnosed with suspected AMI or UA admitted to 51 hospitals participating in CPACS. (N=2,973 ; n=345 NSTEMI, n=1,251 UAP and n=1,305 STEMI)	Four drug combination therapy: antiplatelet, β-blockers, ACEi/ ARB and statin.	Medication adherence	Data summarised as frequencies and percentages.	Almost half (48%) of the eligible patients received the 4-drug combination therapy at discharge, with the proportion decreasing to 44% at 6 months and to 41% at 1-year follow-up. Individual prescription of the cardio-protective drugs at discharge was high (> 90% for aspirin, 70% for β-blockers and ACEi, and 80% for statin) with the exception of clopidogrel (44.6%). Decreasing at 6 months follow-up ((88% for aspirin, 72% for β-blockers, 60% ACEi, 35% for clopidogrel and 66% for statin) with a further reduction at 1 year follow-up (87% for aspirin, 70% for β-blockers, 61% ACEi, 19% for clopidogrel and 59% for statin).
Yan et al (2007)	Canada	Prospective, multicentre, observational study	51 hospitals participating in Canadian ACS registry I	Pharmacotherapy (antiplatelet/ anticoagulant, β-blockers, ACEi	Medication adherence. Temporal changes in	Data summarised as frequencies and percentages.	Overall, 35.6% (2,091) received optimal care at discharge.

Author (Year)	Country	Design (Interval data collected)	Setting (N)	Treatment	Outcomes	Statistical analysis	Key findings
		(September 1999-June 2001 and October 2002-December 2003).	(N=5,312; n=4,627 ACS) 36 hospitals participating in Canadian ACS registry II (N=2,359; n=1,956 ACS)	and lipid modifying therapies)	medical management.	Differences in continuous and categorical data were compared using the Mann-Whitney U test and χ^2 test (or χ^2 for trend, where appropriate)	Comparing the receipt of care between ACS I vs ACS II an increase was noted (optimal care 28.9% and 51.8%, antiplatelet/ anticoagulant 94.1% vs 94.3%, β-blockers 76.9% vs 85.3%, ACEi 56.4% vs 67.0% and lipid modifying therapies 55.4% vs 83.5%, respectively; p-value <0.001) The rates of optimal care were similar at discharge and at 1 year (P = 0.46), however use of antiplatelet/anticoagulant (P = .002), β-blocker (P < 0.001), and ACE inhibitor (P = 0.01) therapies declined, whereas the use of lipid modifying agents increased (P < 0.001).
Tuppin et al (2009)	France	Analysis from a large administrative database. (January – June 2006)	All hospitalizations from January to June 2006 with a diagnosis-related group of MI were selected from the PMSI health insurance	Cardio-protective medication (antiplatelet drugs, ACEi\ ARBs, statins and β-blockers).	Post hospital discharge adherence to combined medication 6 months after hospital admission.	Data summarised as frequencies and percentages.	After hospitalisation 82% of the patients were reimbursed for β-blockers, 92% for antiplatelets, 85% for statins, 80% for ACEi/ARBs, 80% clopidogrel, 84% aspirin, 72% both (aspirin and clopidogrel) and 62% for all four classes of drugs.

Author (Year)	Country	Design (Interval data collected)	Setting (N)	Treatment	Outcomes	Statistical analysis	Key findings
			scheme (N=11,671)				
Amar et al (2008)	France	Nationwide cross-sectional PREVENIR-4 study (2006)	Patients recruited by 621 cardiologists in all French regions (N=1700)	Combination therapy consisting of β-blockers, an antiplatelet, statins and ACEi (BASI)	Long term adherence persistence of BASI in 'real world' patients	Data summarised as frequencies and percentages.	Individual drug prescription at discharge had an intermediate to high variation that 82.4% of the patients were prescribed β-blockers, 98.9% antiplatelets, 89.2% statins and 58% ACEi. Persistence to adherence to the drugs was greater than 86% during follow-up to consultation time (14±4 months). Combination medical therapy was initiated in 46.2% of the patients, of whom 80.2% were persistent to adherence during follow-up to consultation time.
Dachin et al (2005)	France	Nationwide French registry (November 1-November 30 2000)	Forty-three university hospitals, 229 public hospitals and 97 private clinics. USIC 2000 study. (N=2,119 AMI)	OMT (combination of antiplatelets agents, β-blockers and statins (triple therapy)).	Medication adherence	Data summarised as frequencies and percentages.	Of the 2,119 patients discharged alive, 52% (1,095) were prescribed a combination of antiplatelet agents, β-blockers, and statins (triple therapy)
Longeneck er et al (2013)	6 middle eastern countries : Bahrain	Prospective cohort study (January-June 2007)	72 hospitals, Gulf GRACE (N=5,813 AMI)	Performance measure:	Adherence to performanc	Data summarised as frequencies and percentages.	Optimal care was provided to 40.4% of the patients.

Author (Year)	Country	Design (Interval data collected)	Setting (N)	Treatment	Outcomes	Statistical analysis	Key findings
	Kuwait Qatar Oman United Arab Emirates and Yemen			•aspirin and β-blockers within 24 h on admission • aspirin, β-blockers and ACEi\ ARB and lipid lowering therapy on discharge •Indicated reperfusion therapy •Measurement of LDL cholesterol levels during hospitalisation. OMT derived as a composite score	e measures for AMI.		Adherence was above 90% for aspirin, reperfusion, and lipid-lowering therapies; between 60% and 82% for β-blockers, ACEi, statins, time-to-balloon within 90 minutes and LDL-cholesterol measurement and 33% for time-to-needle 30 minutes.
Hamood et al (2015)	Israel	Patient based retrospective cohort study (January 2005-December 2010)	Members of the Leumit Health Services (N=4,655, AMI)	Pharmacological treatment: aspirin, β-blockers, ACEi\ ARBs, statins and combined therapy.	Outpatient adherence to evidence-based cardio-protective medications were measured using the PDC metric and defined	Data summarised as frequencies and percentages.	Non-adherence to the cardio-protective drugs individually approximated 50%, with combined use approximating to 18.2%. Adherence to at least one cardio-protective drug was 78.8%.

Author (Year)	Country	Design (Interval data collected)	Setting (N)	Treatment	Outcomes	Statistical analysis	Key findings
					as proportion of days covered ≥80%		
Simms et al (2015)	England and Wales	Prospective cohort data from the nationwide population-based registry; MINAP (January 2003-December 2010	247 hospitals in England and Wales (N=112,286, STEMI)	Nine guideline-recommended care opportunities along the pathway of STEMI care: the recording of a pre-hospital ECG; use of acute aspirin; timely coronary reperfusion (PPCI within 120 minutes or thrombolysis within 60 minutes of the call for help); the individual prescriptions of aspirin, thienopyridine inhibitor, β-blocker, angiotensin converting enzyme inhibitor	Medication adherence	Data summarised as frequencies and percentages. Fixed-effects univariable logistic regression models.	Of patients eligible for all nine components, 50.6% missed ≥1 opportunity. Pre-hospital ECG and timely reperfusion were most frequently missed, predicting further missed care at discharge (pre-hospital ECG incident rate ratio [95% CI]: 1.64 [1.58–1.70]; timely reperfusion 9.94 [9.51–10.40]).

Author (Year)	Country	Design (Interval data collected)	Setting (N)	Treatment	Outcomes	Statistical analysis	Key findings
				(ACEi) or angiotensin receptor blocker (ARB), HMG CoA reductase enzyme inhibitor (statin); and enrolment into a cardiac rehabilitation programme at the time of discharge from hospital.			
Timoteo et al (2008)	Portugal	Retrospective study (2002 and 2005)	368 patients admitted in 2002 and 420 patients admitted in 2005 for ACS (with and without ST-segment elevation).	Pharmacological treatment: aspirin, statins, β-blockers, ACEi, clopidogrel and glycoprotein IIb\ IIIa antagonists. Reperfusion strategy: PCI.	Temporal improvements in medication adherence.	Data summarised as frequencies and percentages.	Treatment with clopidogrel (6% vs 87%), β-blockers (54% vs 79%), ACEi (72% vs 84%) and statins (78% vs 91%) increased (P<0.001). There was slight decrease in the use of aspirin (98% vs 95%, P=0.039). The use of PCI increased (53% vs 67%, P<0.001).
Mehta et al (2006)	United States	CRUSADE (January 2002-September 2004)	434 US hospitals participating in CRUSADE (N=113,595, NSTE-ACS)	Acute measures: aspirin, heparin, β-blocker, glycoprotein IIb\ IIIa antagonists. Discharge measures: aspirin,	Temporal changes in adherence to guideline indicated treatments.	Data summarised as frequencies and percentages.	Comparing the first quarter to the last quarter of the study time : In the acute phase use of antiplatelet agents, β-blockers and heparin increased by 5%, 12% and 6%, respectively. At discharge, antiplatelet agents, β-blockers, clopidogrel, lipid-

Author (Year)	Country	Design (Interval data collected)	Setting (N)	Treatment	Outcomes	Statistical analysis	Key findings
				clopidogrel, β-blocker, ACEi, lipid lowering agent, smoking cessation counselling, dietary modification counselling and cardiac rehabilitation referral.			lowering agents and ACEi use increased by 3%, 8%, 21%, 11% and 5%, respectively. An increase in dietary and lifestyle modification was also noted with an absolute increase varying from 17-28%. Revascularization increased by 8%. Adherence improved over the study period (72% to 81%), however many patients failed to receive 100% indicated treatments (OMT increased from 30 to 48%).

Author (Year)	Country	Design (Interval data collected)	Setting (N)	Treatment	Outcomes	Statistical analysis	Key findings
Mehta et al (2015)	United States	CRUSADE (January 2002-September 2004)	283 US hospitals participating in CRUSADE (N=39,291, NSTE-ACS)	ACC/AHA 2002 Class I guideline recommended therapies which included: aspirin and/or clopidogrel, glycoprotein IIb/IIIa inhibitor, any heparin (unfractionated or low molecular heparin), and β-blockers.	Medication adherence	Data summarised as frequencies and percentages.	Overall composite median adherence rate to the ACC/AHA guidelines recommended therapies was 85% (IQR 82-88%) and the median hospital safe drug-dosing rate was 53% (45-60%). There was a low but statistically significant correlation between composite guideline medications use and the dosing appropriateness (r=0.16, p=0.008). The mostly missed care interventions included aspirin, β-blockers, glycoprotein IIbIIIa inhibitors within 24 hours of admission and ACEi/ARBs, clopidogrel and statins at discharge.

Abbreviations: OMT; optimal medical therapy, ACEi; angiotensin-converting enzyme inhibitors, ARB; angiotensin-receptor blocker, AMI; acute myocardial infarction, ACACIA; Acute Coronary Syndromes Prospective Audit, GWTG-CAD; Get with the Guidelines- Coronary Artery Disease, ACOS; Acute Coronary Syndromes Registry, PCI; percutaneous coronary artery intervention, PPCI; primary PCI, CABG; coronary artery bypass graft, CPACS; Clinical Pathways for Acute Coronary Syndromes in China, GRACE; Global Registry of Acute Coronary Events, BMIR; Berlin Myocardial Infarction Registry, RCTs; Randomised controlled trials, EUROASPIRE; European Action on Secondary and Primary Prevention by Intervention to Reduce Events, CVD; Cardiovascular disease, TASPIC-CRO; Treatment and secondary prevention of ischemic coronary events in Croatia, CHD; Coronary heart disease, PTCA; percutaneous transluminal coronary angioplasty, PCI; percutaneous coronary intervention, CABG; coronary artery bypass graft, PMSI; programme de médicalisation des sytèmes d'information, ENACT; European Network for Acute Coronary Treatment, ACS; acute coronary syndromes, Gulf GRACE; Gulf Registry of Acute Coronary Events, CRUSADE; Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the ACC/AHA Guidelines, RBC; red blood cell, MI; myocardial infarction, OASIS; Organisation to Assess Strategies for Ischaemic Syndromes, AUBMC; American University of Beirut Medical Centre, PDC; proportion of days covered, LHS; Leumit Health Services, BASI; β-blockers, Antiplatelet, statins and ACEi .

2.1.3.2 Regional variation in adherence to guideline indicated care

The results of the studies in literature that have assessed between country geographic variation in receipt of AMI care are summarised in Table 2.3. In Europe the ESC carried out three surveys termed: European Action on Secondary and Primary Prevention by Intervention to Reduce Events (EUROASPIRE) surveys for assessing lifestyle, risk factors, and use of cardio-protective medications in coronary patients(63). The first EUROASPIRE survey was carried out from 1995-96 in 9 European countries, second from 1999-00 in 15 countries and the third from 2006-07 in 22 European countries including eight from EUROASPIRE I and II. A comparison between the three EUROASPIRE surveys found that the incorporation of cardiovascular disease prevention into daily practice was inadequate and there were large between country variation in use of cardio-protective drug treatments across Europe with a continuing gap between the standards set in cardiovascular disease prevention guidelines and clinical practice(63). Results from the surveys gave an insight on the geographic variation in guideline adherence over time.

The main objective of the third survey (EUROASPIRE III) was to investigate whether the Joint European Guidelines on Coronary Vascular Disease (CVD) prevention were being followed in patients with CHD and if the practice of preventive cardiology in patients with established coronary disease had improved by comparison with those centres that had participated in EUROASPIRE I and II(48). Underuse of the evidence-based treatments recommended by the Joint European Societies' guidelines for CVD prevention (aspirin or other platelet modifying drugs unless contraindicated, β-blockers in those after AMI, ACEi/ARBs in those with impaired left ventricular function, lipid lowering drugs (statins) in all patients and anticoagulants in those at risk of systematic embolization) were noted in the survey. β-blockers use ranged from 60% (in Cyprus and Spain) to 90% (in The Czech Republic and Finland), ACEi/ARBs use from 50% (in Belgium and Spain) to 80% (in France, Hungary, Poland and Slovenia), lipid lowering medication use ranged from 42% (in Lithuania) to 90% (in Cyprus,

Finland, Greece, Ireland, The Netherlands and Slovenia). Less than half of the eligible coronary patients were advised to participate in cardiac rehabilitation programmes and three quarters of the advised patients actually attended the sessions(48).

Longenecker et al(59). assessed regional adherence to guideline indicated care for ACS patients from six Middle Eastern Gulf countries (Bahrain, Kuwait, Qatar, Oman, United Arab Emirates and Yemen) and found that full adherence to all indicated treatment only occurred in 40.4% of the patients(59). A comparison study of the patients with ACS in the Arab Middle East with a multinational and predominantly western population found that patients from the Arab Middle East were unlikely to receive guideline indicated treatment compared with the ACS patients from the westernised population for example; ACEi/ARBs receipt 69% vs. 75%, β-blockers 65% vs. 87%, Clopidegrol 54% vs. 73%, Calcium channel blockers 9% vs. 19%, GP IIb/IIa 11% vs. 23% and low molecular weight heparin 47% vs. 61%.(64) However, although receipt of aspirin, nitrates and statins was high in both populations the Arab Middle East had higher proportions (98% vs. 94%, 82% vs. 72% and 91% vs. 81%, respectively)(64). Studies that have been conducted to compare the developed countries with developing countries have found marked underutilisation of all pharmacotherapy drugs in the developing countries(64, 65). Largely most of the inter regional differences have been attributed to differences in health care models and rapidity in adopting evidence-based medicine guidelines with Europe and the United States having been reported to adopt more aggressively than the rest of the world(64, 66).

Table 2.3 Literature reviews on studies assessing geographic variation in adherence to AMI guideline indicated care..

Author (Year)	Country	Design (Interval data collected)	Setting (N)	Treatment	Outcomes	Statistical analysis	Key findings
Maier et al (2008)	Germany	Multi-centre observational study (1999 and 2004)	22 hospitals in Berlin participating in BMIR (N=6,080 ; n=1,766 NSTEMI and n=4,314 STEMI)	Concomitant therapy with aspirin, β-blockers, statins, ACEi, GP IIb/IIIa and acute percutaneous coronary intervention.	Medication adherence.	Data summarised as frequencies and percentages.	An increase in the use of acute PCI was noted for both AMI phenotypes (NSTEMI; 15.3% to 62.3% and for STEMI from 24.7% to 71.8%). Prescription of cardio-protective drugs also increased for the phenotypes of AMI across the considered time period 1999 to 2004 (NSTEMI :aspirin from 89.7% to 97.0%, , β-blockers from 68.1 to 90.8, statins from 32.8% to 71.4%, ACEi from 49.5 to 69.2 and GP IIb/IIIa from 12.3 to 43.7, STEMI: aspirin from 91.8 to 98.0 , β-blockers from 68.5 to 89.5, statins from 30.5 to 72.9, ACEi from 45.8 to 71.6 and GP IIb/IIIa from 16.1 to 53.3) Decrease in hospital mortality was more pronounced for NSTEMI (13.5% vs. 4.6%, p<0.001; OR 0.18, 95 CI 0.08-0.41) than with STEMI patients

Author (Year)	Country	Design (Interval data collected)	Setting (N)	Treatment	Outcomes	Statistical analysis	Key findings
							(13.0% vs. 9.4%, p= 0.005; OR 0.41, 95%CI 0.25-0.71).
Kotseva et al (2009)	22 European countries: The Czech Republic Finland France Germany Hungary Italy The Netherlands Slovenia Spain Belgium Greece Ireland Poland UK Bulgaria Croatia Cyprus Latvia Lithuania Romania	EUROASPIRE III survey 2006-2007	76 centres from selected geographical areas in 22 countries in Europe. (N=13,935 CHD reviewed and 8,966 patients interviewed)	Reported lifestyle and other risk factor management in relation to smoking, diet (including weight reduction), exercise, blood pressure, lipids and glucose. Cardio-protective medication (antiplatelets, β-blockers, ACEi/ARBs, calcium channel blockers and statins). Level of education, school attendance and employment status.	Between country variation in patients' lifestyle, risk factor prevalences and use of cardio-protective medication for a 6 month follow-up time.	Descriptive statistics were used to estimate the prevalence of risk factors and medication by survey, country and diagnostic category.	The use of cardio-protective medication was: antiplatelets 91%, β-blockers 80%, ACEi/ARBs 71%, calcium channel blockers 25% and statins 78%. There was considerable variation between European countries in patients' lifestyle, risk factor prevalences and use of cardio-protective medication. There is still considerable potential throughout Europe to raise standards of preventive care in order to reduce the risk of recurrent disease and deaths in patients with CHD.

Author (Year)	Country	Design (Interval data collected)	Setting (N)	Treatment	Outcomes	Statistical analysis	Key findings
	Russian Federation and Turkey						
Reiner et al (2006)	Croatia	Five surveys (1 June 1998-31 March 2003)	TASPIC-CRO study. Seven university hospitals, 25 general hospitals and three rehabilitation hospitals in 28 Croatian cities covering the geographical area of the whole of Croatia. (N=15,520 CHD)	Cardio-protective medication (aspirin, ACEi, diuretics, calcium antagonists, statin and β-blockers).	Within country variation in patients' risk factor prevalences, use of cardio-protective medication.	Descriptive statistics were used to estimate the prevalence of risk factors and medication	Across the five surveys prevalence of receipt of the care interventions was as follows: At admission; aspirin 46%, 52%, 50%, 47%, and overall 49%, respectively, ACEi 30%, 37%, 39%, 35%, respectively and overall 36%, calcium antagonists 18%, 21%, 18%, 18%, respectively and overall 19%, β-blockers 25%, 32%, 32%, 29%, respectively and overall 30%, diuretics 22%, 23%, 20%, 20%, respectively and overall 21%, statins 15%, 23%, 26%, 28%, respectively and overall 23%. At discharge; aspirin 81%, 85%, 83%, 84%, and overall 83%, respectively, ACEi 51%, 53%, 55%, 52%, respectively and overall 53%, calcium antagonists 18%, 18%, 16%, 19%, respectively and overall

Author (Year)	Country	Design (Interval data collected)	Setting (N)	Treatment	Outcomes	Statistical analysis	Key findings
							18%, β-blockers 41%, 57%, 60%, 49%, respectively and overall 53%, diuretics 35%, 30%, 31%, 30%, respectively and overall 31%, statins 42%, 55%, 57%, 71%, respectively and overall 57%. High use of statins, β-blockers and ACEi, however most coronary heart disease patients are still not achieving the recommended goals. The survey showed high prevalence of modifiable risk factors in Croatian patients with CHD with more men being smokers and having low HDL cholesterol, but more women having elevated total and LDL cholesterol, hypertension and diabetes.
Fox et al (2000)	17 European countries	Survey (April-June 1999)	1638 patients in community hospitals, 1095 in university/teaching hospitals and 343 in	Pharmacological treatment, reperfusion therapy, angiography and percutaneous coronary intervention.	Between country variation in care of ACS patients.	Descriptive statistics were used to estimate the prevalence of risk factors and medication	Most of the participants received aspirin (90%), nitrates (80%) and heparin (90%) and there was little variation between countries. However, there were large inter-country

Author (Year)	Country	Design (Interval data collected)	Setting (N)	Treatment	Outcomes	Statistical analysis	Key findings
			university-affiliated hospitals ENACT study. (N=3,092, n=1,431 UA/NSTEMI, n=1,205 MI and n=445 with suspected ACS)				differences in use cardio-protective medications. There were wide variations in use of care interventions namely; thrombolysis (26-72%), primary PCI (<1-19%), angiography (6-79%), calcium antagonists (3-21%), β-blockers (54-84%), LMW heparin (11-64%) and glycoprotein IIb/IIIa inhibitors (2-34%). Primary PCI was mostly carried out in university teaching (11%) and university-affiliated (17%) hospitals than in community hospitals (4%).
Awad et al (2011)	International comparison: 6 Arab Middle Eastern countries (Kuwait, Oman, United	Non-randomised, prospective, multinational, multicentre study (1999-2007) vs Prospective cohort study	GRACE, (n=4,445 ACS) vs Gulf GRACE, (n=6,706 ACS) (N=11,151).	Pharmacological treatment: aspirin, nitrates, statins, β-blockers, ACEi\ ARB, calcium channel blockers, clopidogrel, glycoprotein IIb\ IIIa antagonists, and intravenous heparin. Reperfusion strategy: thrombolysis or PCI.	Adherence to guideline-indicated care.	Data summarised as frequencies and percentages.	Patients in Gulf RACE had higher odds of receiving aspirin (98% vs 93%), nitrates (74% vs 71%), statins (92% vs 85%) and a lower likelihood of receiving ACEi/ARBs (78% vs 69%), β-blockers (87% vs 67%), and clopidogrel (82% vs 60%) at discharge during their index hospitalization compared with patients in GRACE.

Author (Year)	Country	Design (Interval data collected)	Setting (N)	Treatment	Outcomes	Statistical analysis	Key findings
	Arab Emirates, Yemen, Qatar, and Bahrain) vs 14 countries in North and South America, Europe, Australia, and New Zealand.	(January-June 2007)					Cardiac catheterization was performed nearly 4 times as frequently in GRACE compared to Gulf RACE in patients with STEMI (81.1% vs 18.0%) and those with NSTE-ACS (59.4% vs 13.1%). In-hospital case–fatality rates were not significantly different between patients in Gulf RACE and those in GRACE. Patients in Gulf RACE were at significantly greater risk for developing heart failure (HR 2.23, 95% CI 1.91-2.56), cardiogenic shock (1.39, 1.06-1.83), and stroke (2.45, 1.25-4.82) and at lower risk for developing major bleeding (0.37, 0.25-0.54) during their index hospitalization. Of the two reperfusion strategies, thrombolysis was the strategy of choice for STEMI patients enrolled in Gulf RACE and PPCI for STEMI patients enrolled in GRACE.

Author (Year)	Country	Design (Interval data collected)	Setting (N)	Treatment	Outcomes	Statistical analysis	Key findings
Fox et al (2002)	Argentina, Australia, Austria, Belgium, Brazil, Canada, France, Germany, Italy, New Zealand, Poland, Spain, United Kingdom and United States	Non-randomised, prospective, multinational, multicentre study (April 1999-31 December 2000)	95 hospitals in GRACE were organized into 18 population-based clusters in 14 countries. (N=11,543, n=4,999 UA, n=4,100 MI, n=957 suspected MI, n=745 chest pain, n=381 other cardiac, n=125 non-cardiac)	Use of pharmacological and interventional therapies during hospitalization, discharge and at 6 months follow-up.	Use of pharmacological and interventional therapies during hospitalization and discharge by hospital type. Use of pharmacological and interventional therapies during hospitalization and discharge by geographic region.	Chi-square test was used for categorical variables and t-test for continuous variables.	The use of aspirin was similar across all hospital types and geographical regions (<91%). The use of PCI, glycoprotein IIb/IIIa inhibitors and calcium channel blockers was statistically higher (P<0.01) in teaching hospitals and hospitals with on-site catheterization facilities. The use of LMW heparin was statistically lower (P<0.0001) in teaching hospitals and those with a catheterization laboratory. The use of statins and β-blockers was lower (P<0.0001) in teaching hospitals and hospitals with on-site catheterization facilities. ACEi use was consistent between teaching and non-teaching hospitals but however use was higher (P<0.0001) in hospitals without on-site catheterization facilities.

Author (Year)	Country	Design (Interval data collected)	Setting (N)	Treatment	Outcomes	Statistical analysis	Key findings
							The use of antiplatelet agents and anticoagulants was lower in non-teaching hospitals (P<0.0001) but was similar in hospitals with and without a catheterization laboratory. The use of percutaneous coronary intervention and glycoprotein IIb/IIIa inhibitors was considerably higher in the United States compared with other regions.
The ACCESS investigators (2011)	Africa, Latin America and Middle Eastern countries	Prospective observational, multinational registry. (January 2007-January 2008).	134 sites in 19 countries in North Africa, South Africa, Latin America and the Middle East. (N=11,731 ACS, n=4,936 Latin America, n=4,493 Middle East, n=1,687 North Africa, n=615 South Africa)	All admission and discharge cardio-protective medication. Interventions and procedures (CABG, PCI and coronary angiography)	Adherence to guideline-indicated care.	Data summarised as frequencies and percentages.	In-hospital the use of cardio-protective drugs was high (aspirin 93%, statins or other lipid-lowering drugs 94%, thienopyridines 81%, and β-blockers 78%). Prescription of cardio-protective drugs at discharge was high (aspirin 90%, statins 89%, β-blockers 76%, thienopyridines 76% and dual antiplatelet therapy 89% (of patients who had PCI with a stent)).

Author (Year)	Country	Design (Interval data collected)	Setting (N)	Treatment	Outcomes	Statistical analysis	Key findings
							Fifty eight percent of the patients had an angiogram with 38% having PCI performed. All-cause death at 12 months was 7.3% and was higher in patients with STEMI versus non–ST elevation–ACS. Clinical factors associated with higher risk of death at 12 months included cardiac arrest, antithrombin treatment, cardiogenic shock, and age >70 years.
Mandelzweig et al (2006)	32 European countries and the Mediterranean basin	Prospective survey (March 2004 – October 2004)	190 medical centres in 32 countries. EHS–ACS-I vs EHS–ACS-II (N=6,385 ACS)	Pharmacological treatment: aspirin, statins, β-blockers, ACEi\ ARBs, thienopyridines, and glycoprotein IIb\ IIIa antagonists. In-hospital use of invasive and non-invasive diagnostic and therapeutic techniques.	Adherence to guidelines.	Data summarised as frequencies and percentages.	Proportion of patients with an initial diagnosis of ACS with ST-elevation rose from 42% (EHS-ACS-I) to 47% (EHS-ACS-II). Proportion of patients with an initial diagnosis of ACS with no ST-elevation fell from 51% (EHS-ACS-I) to 48% (EHS-ACS-II) In EHS-ACS-II, more patients were hospitalized in coronary care units (70 vs. 62.4%), whereas fewer were treated in cardiology wards (19.1 vs.

Author (Year)	Country	Design (Interval data collected)	Setting (N)	Treatment	Outcomes	Statistical analysis	Key findings
							22%), and in internal medicine wards (7 vs 13.85%). Coronary angiography, percutaneous coronary interventions (PCIs), and intracoronary stents were used more frequently in ACS-II than in ACS-I (STEMI: 56.3% VS 70.2%, NSTEMI: 52.0% VS 62.9%; STEMI: 40.4% VS 57.8%, NSTEMI: 25.4% VS 37.1%, respectively). A greater proportion of patients received evidence-based medications during their hospitalization and at discharge in ACS-II compared with ACS-I, particularly in the use of thienopyridnes.
Kotseva et al (2009)	Czech Republic, Finland, France, Germany, Hungary, Italy, the Netherlands, and Slovenia	EUROASPIRE I (1995-96), II (1999-00), and III (2006-07) surveys	3,180 patients interviewed in the first survey, 2,975 in the second and 2,392 in the third (AMI and ischaemia patients).	Cardio-protective drug treatments.	Adherence to guidelines.	Data summarised as frequencies and percentages.	The use of cardio-protective drug treatments, apart from anticoagulants and calcium-channel blockers, increased between the first and the third survey, with large variations between countries and diagnostic categories.

Author (Year)	Country	Design (Interval data collected)	Setting (N)	Treatment	Outcomes	Statistical analysis	Key findings
							More men smoked than women in all three surveys. Mean bodyweight was higher in EUROASPIRE III compared to II and I (84.7 kg (SD 15.1), 82.0 kg (SD 14.5) and 79.8 kg (13.4), respectively. Frequencies of overweight and obese patients was also higher in the third survey (5.1% 95% CI 1.1-9.1%, p=0.02).
Yusuf et al (1998)	Australia, Brazil, Canada, USA, Hungary and Poland	Registry-based study; OASIS (1995-96)	95 hospitals in six countries. (N=7,987, unstable angina or suspected myocardial infarction without ST-segment elevation).	Use of invasive cardiac catheterisation and revascularisation procedures.	Between country variation in use of invasive cardiac catheterisation and revascularisation procedures.	Data summarised as frequencies and percentages. Natural randomisation by rates of catheterisation by country.	Rates of angiography during the first 7 days showed wide variations between countries (highest in Brazil and USA (60%; 95% CI 58-63%, 58%; 55-61%, respectively) and lowest in Poland and Hungary (2%; 1-3%, 15%; 13-17%, respectively)). After 7 days the rates of angiography and revascularization showed less variation, however at 6 months the rates showed pronounced variation with a two-fold higher rate in Brazil and the USA.

Author (Year)	Country	Design (Interval data collected)	Setting (N)	Treatment	Outcomes	Statistical analysis	Key findings
							Patients mostly admitted to hospitals with catheterisation facilities were low risk patients.
Karrowni et al (2010)	USA Europe Australia Canada New Zealand Argentina Brazil and Lebanon	Non-randomised, prospective, multinational, multicentre study vs Prospective cohort study	ACS patients admitted at AUBMC (N=1,025) vs ACS patients admissions recorded in GRACE (N=60,000)	Pharmacological treatment: aspirin, clopidogrel, β-blocker, ACEi/ ARBs, statins and glycoprotein IIb\ IIIa antagonists. Interventions and procedures (CABG, PCI, reperfusion and coronary angiography)	Use of cardio-protective drug treatments. Use of invasive cardiac catheterisation and revascularisation procedures.	Data summarised as frequencies and percentages. Chi-square test was used for categorical variables.	The rate of coronary angiography was slightly higher in patients admitted in AUBMC compared with GRACE (74% vs. 69%). PCI was more commonly performed in GRACE (45% vs. 32%, P<0.05) while bypass surgery was more commonly performed in patients admitted in AUBMC (16% vs. 4%, P<0.01). Overall revascularization rate was similar between the two studies (48% vs. 49%). Reperfusion rate for STEMI was higher in GRACE (71% vs. 61%, P<0.05). Utilization rate of the other medications including aspirin (96% vs 84%), clopidogrel (75% vs 57%), β-blockers (91% vs 49%), ACE inhibitors/ARB (79% vs 44%), GP IIb/IIIa inhibitors (27% vs 13%), and statins (84% vs 60%) were consistently higher in GRACE,

Author (Year)	Country	Design (Interval data collected)	Setting (N)	Treatment	Outcomes	Statistical analysis	Key findings
							this was associated with lower in-hospital mortality in GRACE (3.1% vs 3.9%, P<0.05)
Fox et al (2003)	Argentina, Australia, Austria, Belgium, Brazil, Canada, France, Germany, Italy, New Zealand, Poland, Spain, United Kingdom and United States	Non-randomised, prospective, multinational, multicentre study (July 1999-December 2001).	94 hospitals located in 14 countries participating in GRACE (N=12,666, ACS; n=6,041, NSTEMI; n=6,625, STEMI).	Pharmacological treatment: aspirin, statins, β-blockers, ACEi\ ARBs, thienopyridines, and glycoprotein IIb\ IIIa antagonists. In-hospital use of invasive techniques.	Uptake of evidence-based guideline recommendations. Between country variation in uptake of evidence-based guideline recommendations.	Chi-square test for trend. (Sequential 6-month intervals).	Contrasting geographical variations were seen in the use of PCI in NSTEMI: 39.5% USA, 34.6% Europe, 33.5% Argentina/ Brazil, 25.0% Australia/ New Zealand/Canada. Hospital and geographical factors had a marked influence on the uptake of evidence-based therapies in ACS management. The presentation and publication of major international guidelines was not associated with a measurable change in the temporal pattern.

Abbreviations: OMT; optimal medical therapy, ACEi; angiotensin-converting enzyme inhibitors, ARB; angiotensin-receptor blocker, AMI; acute myocardial infarction, ACACIA; Acute Coronary Syndromes Prospective Audit, GWTG-CAD; Get with the Guidelines- Coronary Artery Disease, ACOS; Acute Coronary Syndromes Registry, PCI; percutaneous coronary artery intervention, PPCI; primary PCI, CABG; coronary artery bypass graft, CPACS; Clinical Pathways for Acute Coronary Syndromes in China, GRACE; Global Registry of Acute Coronary Events, BMIR; Berlin Myocardial Infarction Registry, RCTs; Randomised controlled trials, EUROASPIRE; European Action on Secondary and Primary Prevention by Intervention to Reduce Events, CVD; Cardiovascular disease, TASPIC-CRO; Treatment and secondary prevention of ischemic coronary events in Croatia, CHD; Coronary heart disease, PTCA; percutaneous transluminal coronary angioplasty, PCI; percutaneous coronary intervention, CABG; coronary artery bypass graft, PMSI; programme de médicalisation des sytèmes d'information, ENACT; European Network for Acute Coronary Treatment, ACS; acute coronary syndromes, Gulf GRACE; Gulf Registry of Acute Coronary Events, CRUSADE; Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the ACC/AHA Guidelines, RBC; red blood cell, MI; myocardial infarction, OASIS; Organisation to Assess Strategies for Ischaemic Syndromes, AUBMC; American University of Beirut Medical Centre, PDC; proportion of days covered, LHS; Leumit Health Services, BASI; β-blockers, Antiplatelet, statins and ACEi .

2.1.3.3 Predictors of poor adherence to guideline indicated care

Despite the proven beneficial effects of receiving OMT as recommended by the guidelines, the literature review showed that prevalence of sub-optimal care was high(51-61). Potential predictors for this non-adherence to guideline indicated care were identified in the studies considered and explored below. The identified predictors included: patient age, comorbidities, adherence to other guideline indicated care interventions, availability of healthcare facilities, attending physician and AMI phenotype (Table 2.4).

2.1.3.4 Age

Advanced age is an established predictor of receipt of guideline indicated care. Several studies have investigated the association of age and medical therapy adherence using different cut offs to get the specific age range with a positive or negative impact on adherence(53, 55, 56, 67). Age >70 years has been reported as a negative predictor of OMT, for example Bauer et al(53). found that advanced age >70 years was a negative predictor of prescription of statins (OR 1.7, 95% CI: 1.6–1.9) and was associated with high discontinuation rates of aspirin(53, 56, 68). The elderly usually do not receive treatment due to concerns over their vulnerability to comorbidities, adverse drug reactions and problems of consenting. Problems with consenting noted for the elderly patients have been attributed to the high prevalence of psychiatric illnesses and comorbidities such as Parkinson's disease, Alzheimer's disease or dementia in this sub-group of AMI patients(56, 57, 67).

2.1.3.5 Comorbidities

Poor adherence to guideline indicated care was found to be most prevalent in comorbid patients(54, 59). Comorbidities such as prior heart failure, renal dysfunction, chronic obstructive pulmonary disease (COPD), peripheral artery disease, dyslipidemia and hypertension were identified as negative independent predictors of OMT in the literature review(53, 55). In one study high discontinuation rates for aspirin were found to be high in those with heart failure(68). However, after adjusted analysis using multivariable

regression analysis, high rates of use of aspirin were found to be highly associated with care by a cardiologist, β-blockers use with hypertension and AMI phenotype (with STEMIs being more likely to receive β-blockers), ACEi use with prior heart failure, and statin under use with hypertension(68). A study carried out by Bauer et al(53). found that with increasing median number of risk factors the number of secondary prevention drugs prescribed at discharge incrementally decreased. These findings have been attributed to treating physician prescribing preferences and education, that is physicians are more likely to offer care interventions to patients at low risk of adverse events “treatment-risk paradox”, (69). For example COPD (OR 4.1, 95% CI: 3.5–4.8) and peripheral arterial disease (OR 1.7, 95% CI: 1.4–2.1) were negative predictors for prescription of β blockers at hospital discharge (53), this was likely due to the fact that historically β blockers were thought to be contraindicated in patients with these conditions(9). Education and awareness of treating physicians with the current recommendation of the guidelines will help eradicate grey areas when treating AMI patients. Also renal insufficiency was found to be a strong negative predictor of ACEi/ARBs (OR 2.8, 95% CI: 2.2–3.5), a finding which has been attributed to physicians not prescribing the treatment to patients with pre-existing renal impairment in fear of worsening the condition(53). However, no contraindication has been noted in the guidelines for this sub-group of patients(70).

2.1.3.6 AMI phenotype

Although different diagnoses, guideline recommendations for the care management of the two phenotypes of AMI (STEMI and NSTEMI) are relatively similar(71). However several studies have reported that patients presenting with STEMI were more likely to be given more aggressive medical treatment(53, 55, 71). The National Cardiovascular Data Registry report also showed that NSTEMI patients showed lower adherence for statin, ACEi and β-blockers on admission and hospital discharge compared with STEMI patients(72). The low adherence rates to guideline recommended care for the NSTEMI patients have been attributed to “acute referral bias”, whereby emergency medical service systems have been

reported to refer STEMI patients to larger tertiary or teaching hospitals with cardiac-catheterisation facilities and staff(71). These hospitals have been noted to have higher adherence rates compared with smaller non-tertiary or academic hospitals(71). Also the NSTEMI patients have been noted to be a very heterogeneous group of patients, which makes them difficult to treat. The negative predictors of receipt of care have been noted to be highly prevalent among the NSTEMI, i.e. they are usually older and more comorbid(53, 71).

2.1.3.7 Healthcare facilities / attending physician

An association has been reported between healthcare service utilisation and adherence to evidence-based treatment(60, 73). With AMI patients admitted to tertiary or teaching hospitals been noted to have high receipt of guideline indicated care interventions at hospital discharge and those treated in hospitals with cardiac-catheterisation facilities being more likely to be referred for angiography or other invasive procedures(73-75). Care by cardiologists has been reported in the past literature as vital for receipt of guideline-indicated care(56, 68).

2.1.3.8 Adherence to other guideline-indicated care interventions

Patients who received reperfusion were reported to have high receipt rates of the secondary prevention drugs at hospital discharge compared with patients who were treated with fibrinolysis or those who received no treatment at all(53). Not receiving timely PPCI was a negative predictor of being prescribed clopidogrel (Odds ratio (OR) 10.4, 95% CI: 9.4–11.6), ASA (OR 2.6, 95% CI: 2.2–3.1), ACEi/ARBs (OR 1.5, 95% CI: 1.3–1.6) and statins (OR 2.1, 95% CI: 1.9–2.4) (53). Also concomitant treatments have been reported to have a negative impact on receiving care interventions for example chronic oral anticoagulation medications have been found to be a negative predictor of prescription of aspirin (OR 19.6, 95% CI: 15.9–24.0) and clopidogrel (OR 1.5, 95% CI: 1.3–1.6)(53).

2.1.3.9 Other factors

Other factors that were identified in the literature review to influence adherence to guideline-indicated care interventions include treatment side effects, patient refusal and physician education. For example side effects such as muscle pain and liver damage were reported to potentially contribute to underutilisation of statins(53). Incidences of hospital bleeding complications have also been found to be negative predictors of prescription of aspirin (OR 3.0, 95% CI: 2.2–4.2)(53).

Table 2.4 Literature reviews on studies assessing predictors of adherence to guideline indicated care for AMI patients.

Author (Year)	Country	Design (Interval data collected)	Setting (N)	Treatment	Outcomes	Statistical analysis and potential predictors investigated	Key findings
Rasmussen et al (2007)	Canada	Population-based, observational, longitudinal study (April 1, 1999 and May 1, 2003).	Elderly (aged 66 years or older) AMI survivors (surviving at least 1 year 3 months after hospitalization) recorded in the Ontario Myocardial Infraction Database (N=31,455)	Pharmacotherapy medication use following hospital discharge after AMI (β-blockers, statin and calcium channel blockers).	Predictors of receipt of guideline-indicated care.	Multivariable logistic regression models. Age, sex, socioeconomic status, year of admission, speciality of attending physician, comorbidity at index AMI, inter-current hospitalisations and use of respective drug within six months prior to admission, concomitant use of ACEi, statins, β-blockers and calcium channel antagonists.	Increasing age, psychiatric illnesses and increasing number of admissions within the year following AMI were independent determinants of poorer adherence.
Bauer et al (2010)	Germany	Multicentre, prospective, observational study. (June 2000 and November 2002)	Hospital survivors of AMI (STEMI or NSTEMI) from 155 hospitals enrolled in the ACOS registry. (N=11,823)	Five discharge medication drugs: acetyl salicylic acid, clopidogrel, β-blockers, ACEi/ sartan and statin. Dichotomised receipt of care composite score i.e. patients receiving < 4	Predictors of receipt of guideline-indicated care.	Multiple logistic regression models. Age >70, sex, prior MI, prior stroke, diabetes mellitus, peripheral artery disease, smoking, hypercholesterolemia, hypertension, chronic obstructive lung disease, renal insufficiency,	Patients in group one were more likely to be older (median age 71.1 IQR 61.8-79.0), more co-morbid (prior MI 24% vs 17.7%; P-value<0.0001, prior stroke 8.6 vs 5.7; P-value<0.0001, peripheral artery disease 10.2 vs 6.2; P-value<0.0001, chronic obstructive lung disease 11.8 vs 5.0; P-

Author (Year)	Country	Design (Interval data collected)	Setting (N)	Treatment	Outcomes	Statistical analysis and potential predictors investigated	Key findings
				drugs (group 1) or receiving 4-5		malignancy, atrial fibrillation, left bundle branch block, reduced left ventricular function, acute NSTEMI and percutaneous coronary intervention within 48 hours.	value<0.0001, chronic obstructive lung disease 11.8 vs 5.0; P-value<0.0001, diabetes mellitus 31.3 vs 26.1; P-value<0.0001, renal insufficiency 5.3 vs 2.1; P-value<0.0001, cardiogenic shock 7.1 vs 3.5; P-value<0.0001, atrial fibrillation 12.9 vs 4.6; P-value<0.0001, ejection fraction ≤ 40% 28.0 vs 19.1; P-value<0.0001), more likely to be NSTEMIs (58.6 vs 47.7; P-value<0.0001) and less often received reperfusion therapy (68.9 vs 32.7; P-value<0.0001). Patients in group two were hypertensive (65.1 vs 61.3; P-value<0.001), smokers (35.1 vs 24.4; P-value<0.0001) and had hypercholesterolemia (70.0 vs 52.1; P-value<0.0001). Patients with STEMI (4.1) were discharged with more

Author (Year)	Country	Design (Interval data collected)	Setting (N)	Treatment	Outcomes	Statistical analysis and potential predictors investigated	Key findings
							drugs than those with NSTEMI (3.8, P < 0.0001). Comorbidities and no interventional treatment were strong negative predictors for guideline-adherent discharge medication.
Bi et al (2009)	China	Multi-centre prospective study. (September 2004 and May 2006)	Patients diagnosed with suspected AMI or UA admitted to 51 hospitals participating in CPACS. (N=2,973 ; n=345 NSTEMI, n=1,251 UAP and n=1,305 STEMI)	4 drug combination therapy: antiplatelet, β-blockers, ACEi/ ARB and statin.	Reasons for non-adherence at 6 and 12 months follow-up.	Logistic regression Age ≥65, education level (completion high school), manual labour, high income (≥12,000), medical insurance, interaction between medical insurance and high income, interaction between high school and manual labour, whether the patient had invasive therapy, whether the patient had MI, diabetes, hypertension, and dyslipidemia, and smoking status.	4 drug combination prescription was low for high risk patients (GRACE score 200-300) at discharge (35%). Medical insurance, dyslipidemia, hypertension, and administration of invasive therapy (PCI / CABG) were important in determining use of treatment at discharge and during follow-up. Reasons for non-adherence for antiplatelet therapy or β-blockers was mainly patient refusal and for ACEi or stains were adverse effects and financial costs, respectively.
Yan et al (2007)	Canada	Prospective, multicentre, observational	51 hospitals participating in Canadian ACS	Pharmacotherapy (antiplatelet/ anticoagulant, β-	Predictors of receipt of guideline-	Hierarchical multivariate logistic regression.	Advanced age, female sex, prior heart failure, renal dysfunction and coronary by-

Author (Year)	Country	Design (Interval data collected)	Setting (N)	Treatment	Outcomes	Statistical analysis and potential predictors investigated	Key findings
		study (September 1999-June 2001 and October 2002-December 2003).	registry I (N=5,312; n=4,627 ACS) 36 hospitals participating in Canadian ACS registry II (N=2,359; n=1,956 ACS)	blockers, ACEi and lipid modifying therapies)	indicated care.	Enrolment into ACS II registry, age > 65, sex, previous heart failure, dyslipidemia, previous PCI, previous CABG, ST-segment elevation, abnormal cardiac biomarker in hospital, serum creatinine >120 µmol/L and CABG during index admission.	pass surgery during surgery were negative independent predictors of optimal medical therapy.
Tuppin et al (2009)	France	Analysis from a large administrative database. (January – June 2006)	All hospitalizations from January to June 2006 with a diagnosis-related group of MI were selected from the PMSI health insurance scheme (N=11,671)	Cardio-protective medication (antiplatelet drugs, ACEi\ ARBs, statins and β-blockers).	Predictors of receipt of guideline-indicated care.	Multivariable logistic regression analysis. Sex, age, full healthcare coverage for low earners, one or more outpatient cardiologist appointments, admission unit, hospital type, hospital volume, stent implantation, length of stay, comorbidities and concomitant medication.	Age had a significant effect on use statins, ACEi/ARBs, β-blockers, antiplatelet agents and combined therapy with low β-blockers use being observed in those aged ≤ 75 years, low antiplatelet agents use in those aged ≤ 85 years and combined therapy being less frequently observed in those aged ≤ 75 years. High use rates of statins, ACEi/ARBs, β-blockers, antiplatelet agents and combined therapy were observed in patients admitted to university hospitals, those who had at least one visit to a

Author (Year)	Country	Design (Interval data collected)	Setting (N)	Treatment	Outcomes	Statistical analysis and potential predictors investigated	Key findings
							private cardiologist and those with a stent implantation. Comorbidities such as cancer, kidney failure, Parkinson's disease and Alzheimer's were found to have a negative impact on the use of the individual drugs as well combined use, however diabetes was associated with higher rates of use.
Amar et al (2008)	France	Nationwide cross-sectional PREVENIR-4 study (2006)	Patients recruited by 621 cardiologists in all French regions (N=1700)	Combination therapy consisting of β-blockers, an antiplatelet, statins and ACEi (BASI)	Predictors of receipt of guideline-indicated care	Multivariate logistic regression model. History of atrial fibrillation, at least one severe non-cardiovascular disease and significant coronary stenosis.	Negative predictors of BASI included atrial fibrillation (OR 2.98, 95%CI 1.65-5.41) and at least one severe non-cardiovascular disease (OR 1.72, 95%CI 1.09-2.73), i.e. depression, Alzheimer's disease or dementia, severe renal failure, respiratory failure, cancer and cirrhosis.
Longeneck er et al (2013)	6 middle eastern countries : Bahrain Kuwait Qatar Oman	Prospective cohort study (January-June 2007)	72 hospitals, Gulf GRACE (N=5,813 AMI)	Performance measure: •Aspirin and β-blockers within 24 h on admission •Aspirin, β-blockers and ACEi\ ARB and lipid lowering	Predictors of adherence to performanc e measures	Multivariate logistic regression model. Age, sex, nationality, cardiovascular disease, hypertension, any diabetes, smoking, Killip class, and GRACE score.	Patient characteristics that were significantly associated with high performance composite score (>85%) included Asian ethnicity compared to Gulf Arabs (adjusted OR, AOR=1.3; p=0.01) and history of hyperlipidemia (AOR=1.4;

Author (Year)	Country	Design (Interval data collected)	Setting (N)	Treatment	Outcomes	Statistical analysis and potential predictors investigated	Key findings
	United Arab Emirates and Yemen			therapy on discharge •Indicated reperfusion therapy •Measurement of LDL cholesterol levels during hospitalisation. OMT derived as a composite score.			p=0.001). those associate with a low performance score included age>65 (AOR=0.8; p-trend =0.03), atypical chest pain versus typical chest pain (AOR=0.6; p=0.003), symptoms other than chest pain (AOR=0.5; pb0.0001) and high GRACE score (AOR=0.6; p<0.001).
Hamood et al (2015)	Israel	Patient based retrospective cohort study (January 2005-December 2010)	Members of the Leumit Health Services (N=4,655, AMI)	Pharmacological treatment: aspirin, β-blockers, ACEi\ ARBs, statins and combined therapy.	Predictors of medication adherence.	Multiple logistic regression models. Age, gender, ethnicity, district, comorbid conditions, revascularisation, prior use of drug, severity of disease, and health services utilisation.	Factors significantly associated with reduced adherence were presence of comorbid conditions, particularly chronic ischemic heart disease (AOR 0.69; 95% CI, 0.57–0.83) and readmissions (AOR, 0.65; 95% CI, 0.55–0.78).
Eagle et al (2004)	14 countries : Argentina Australia Austria Belgium Brazil Canada	Non-randomised, prospective, multinational, multicentre study (April 1999 and March 2003)	MI or UA patients admitted to 104 tertiary and community hospitals participating in GRACE (N=21,408 ; n=4,137	Pharmacotherapy (aspirin, β-blockers, statins and ACEi)	Medication adherence rates at 6 months after hospital discharge	Logistic regression models with a random effect included. Region of care (United States vs. other country), age, sex, prior medical diseases including heart failure, diabetes, renal insufficiency,	Patients who discontinued aspirin were older (OR=0.65, 95% CI: 0.53 to 0.80), more likely to have heart failure (OR=0.80, 95% CI: 0.65 to 0.99) and more likely to be treated by non-cardiologists. Care by cardiologist was a positive predictor for adherence to aspirin

Author (Year)	Country	Design (Interval data collected)	Setting (N)	Treatment	Outcomes	Statistical analysis and potential predictors investigated	Key findings
	France Germany Italy New Zealand Poland Spain United Kingdom United States		NSTEMI, n=5,031 UAP and n=4,662 STEMI)			hypertension, in-hospital development of pulmonary edema or shock, type of acute coronary syndrome (STEMI, NSTEMI, or unstable angina), type of caregiver (cardiologist vs. non-cardiologist), and type of hospital providing care (teaching vs. nonteaching).	(OR=1.45, 95% CI: 1.19 to 1.75). Higher rates of adherence to β-blockers were noted in patients treated in the United States, hypertensive (OR=1.33, 95% CI: 1.15 to 1.54) and are STEMI (OR=1.33, 95% CI: 1.11 to 1.61). Male sex (1.32, 1.09-1.61) and prior heart failure (1.67, 1.23-2.22) were independent predictors of ACEi adherence. Hypertension was a negative predictor for statin therapy adherence (OR=0.85, 95% CI: 0.74 to 0.99).
Soma et al (2012)	USA	National registry (May 1, 2006 and March 21, 2010)	AMI (STEMI or NSTEMI) admissions from 237 hospitals participating in the GWTG-CAD registry. (N=72,352 ; n=48,966	Performance measures: •Aspirin therapy before hospital admission or within 24 hours. •Discharge medications (aspirin, β-	Predictors of adherence to guideline indicated medical therapy.	Multivariable logistic regression. Generalized estimating equations. Age, sex, race (white versus non-white), medical history of chronic obstructive pulmonary disease or	STEMI patients were more likely to be treated at larger hospitals (35.7% vs 28.45, P-value<0.0001), more likely to be treated at academic medical centres (58.0 vs 54.4, P-value<0.0001) and mostly likely to smoke (41.2 vs 27.3, P-value<0.0001).

Author (Year)	Country	Design (Interval data collected)	Setting (N)	Treatment	Outcomes	Statistical analysis and potential predictors investigated	Key findings
			NSTEMI and n=23,386 STEMI)	blockers, ACEi/ARBs, lipid lowering therapy, smoking cessation counselling) •Composite compliance with all performance measures •β-blockers before hospital admission or within 24 hours. •Discharge medications (ACEi/ARBs, clopidogrel, lipid lowering therapy) •Rehabilitation, diabetes mellitus treatment, physical activity and weight		asthma, diabetes mellitus (combined insulin dependent and noninsulin dependent), hyperlipidemia, hypertension, peripheral vascular disease, stroke or transient ischemic attack, heart failure, renal insufficiency, smoking, geographic region of the United States, teaching hospital and hospital size represented by number of beds	The composite of compliance with all applicable performance measures was higher in STEMI patients (94.3% versus 91.1%; P<0.0001). After confounder adjustment, STEMI patients were more likely to receive: •Aspirin within 24 hours 98.5% vs 97.1% (AOR, 1.63; 95%CI 1.32-2.02) •Aspirin at discharge 98.5 vs 97.3 (1.33; 1.19-1.49) •β-blockers 98.2 vs 96.9 (1.48; 1.35-1.63) •β-blockers within 24hours 93.9 vs 90.8 (1.57; 1.37-1.79) •Lipid lowering medication 96.8 vs 91.0 (1.85; 1.61-2.13) •ACEi/ARBs at discharge 85.3 vs 77.4 (1.62; 1.51-1.75) •Clopidogrel at discharge 85.6 vs 67.0 (2.42; 2.23-2.61) •Lipid lowering drugs at discharge 94.8 vs 88.0 (1.71; 1.56-1.86).

Author (Year)	Country	Design (Interval data collected)	Setting (N)	Treatment	Outcomes	Statistical analysis and potential predictors investigated	Key findings
Mehta et al (2015)	United States	CRUSADE (January 2002-September 2004)	283 US hospitals participating in CRUSADE (N=39,291, NSTE-ACS)	ACC/AHA 2002 Class I guideline recommended therapies which included: aspirin and/or clopidogrel, glycoprotein IIb/IIIa inhibitor, any heparin (unfractionated or low molecular heparin), and β-blockers. Composite use of ACC/AHA guideline-indicated therapies (adherence) score.	Predictors of adherence to guideline indicated medical therapy.	Logistic generalized estimating equations method. Age, male sex, body mass index, white race, insurance status, hypertension, diabetes mellitus, current/recent smoking, previous myocardial infarction, renal insufficiency, positive cardiac markers, clinical signs of heart failure on presentation, presenting heart rate, and systolic blood pressure. Hospital characteristics in the model included total number of hospital beds, geographic region (West, Northeast, Midwest, or South), revascularization capabilities (no services, diagnostic catheterization only, percutaneous coronary intervention without on-	Patients who were treated in low composite adherence to guideline-based therapies and medication dosing safety profiles were older, female, have higher heart rate, have lower systolic blood pressure, have low creatinine clearance on admission and more likely to be comorbid (e.g. having diabetes mellitus or prior congestive heart failure). The hospitals were smaller, less likely to have revascularization capabilities and the patients less likely to be treated by a cardiologist.

Author (Year)	Country	Design (Interval data collected)	Setting (N)	Treatment	Outcomes	Statistical analysis and potential predictors investigated	Key findings
						site cardiac surgery, percutaneous coronary intervention with on-site cardiac surgery), and hospital affiliation (academic versus non-academic)	

Abbreviations: OMT; optimal medical therapy, ACEi; angiotensin-converting enzyme inhibitors, ARB; angiotensin-receptor blocker, AMI; acute myocardial infarction, ACACIA; Acute Coronary Syndromes Prospective Audit, GWTG-CAD; Get with the Guidelines- Coronary Artery Disease, ACOS; Acute Coronary Syndromes Registry, PCI; percutaneous coronary artery intervention, PPCI; primary PCI, CABG; coronary artery bypass graft, CPACS; Clinical Pathways for Acute Coronary Syndromes in China, GRACE; Global Registry of Acute Coronary Events, BMIR; Berlin Myocardial Infarction Registry, RCTs; Randomised controlled trials, EUROASPIRE; European Action on Secondary and Primary Prevention by Intervention to Reduce Events, CVD; Cardiovascular disease, TASPIC-CRO; Treatment and secondary prevention of ischemic coronary events in Croatia, CHD; Coronary heart disease, PTCA; percutaneous transluminal coronary angioplasty, PCI; percutaneous coronary intervention, CABG; coronary artery bypass graft, PMSI; programme de médicalisation des sytèmes d'information, ENACT; European Network for Acute Coronary Treatment, ACS; acute coronary syndromes, Gulf GRACE; Gulf Registry of Acute Coronary Events, CRUSADE; Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the ACC/AHA Guidelines, RBC; red blood cell, MI; myocardial infarction, OASIS; Organisation to Assess Strategies for Ischaemic Syndromes, AUBMC; American University of Beirut Medical Centre, PDC; proportion of days covered, LHS; Leumit Health Services, BASI; β-blockers, Antiplatelet, statins and ACEi .

2.1.3.10 Non-adherence and associated outcomes

The results of the studies in literature that have assessed poor adherence to guideline indicated AMI care and associated outcomes are summarised in Table 2.5. Receiving OMT is essential for improved outcomes for AMI patients(51-53, 55, 58). Bramlage et al.(51) found that AMI patients who received OMT, 1-year mortality was reduced by 74% (adjusted odds ratio (OR), 0.26; 95% CI 0.18 to 0.38) compared with those not receiving OMT. The OMT risk reduction disappeared after withdrawal of β-blockers and or a combination of aspirin and clopidogrel(51). The risk reduction finding was consistent with findings by a study by Yan et al.(55) who reported a 46% reduction in 1-year mortality for optimally treated patients (adjusted OR 0.54, 95% CI 0.36-0.81) compared with sub-optimally treated patients. Bauer et al (2010)(53) found that patients in group 1 (those who were prescribed <4 of the five main cardio-protective drugs) had an elevated risk for death at 1-year follow-up (OR 1.6, 95% CI: 1.4–1.9).

A study by Chew et al.(52) assessing the AMI mortality benefits of OMT in terms of avoidable deaths found that across the AMI analytical cohort 4 lives/10,000 (for STEMI 23 lives/10,000 and for NSTEMI 43 lives/10,000) could have been potentially saved if all the AMI patients received OMT. The study reported that for STEMI patients 213/10,000 non-fatal events could have been prevented if all the patients received OMT, likewise 55/10,000 patients for NSTEMIs(52). Furthermore taking into account long term adherence, Chew et al.(52) found that a further 104 lives/10,000 and 191 recurrent ischaemic events/10,000 could have been prevented if all patients received guideline-recommended treatments at hospital discharge and fully adhered to them long term. Lower incidence of non-fatal strokes have been noted when AMI patients received OMT(53).

Although many of the studies have reported mortality benefits for AMI patients receiving OMT as stated above, Danchin et al.(58) found that in patients with an ejection fraction of ≤ 35% combined therapy had no survival

benefit. Also Bi et al.(54) found that at 12 months follow-up 20 patients from the initial analytical cohort had been readmitted for AMI (reinfarction), of whom 80% had been adherent to the four drug combination therapy. However, Danchin et al.(58) found no survival benefits were observed after receipt of OMT for AMI patients with an ejection fraction ≤35%, only β blockers and ACEi use had a prognostic value.

Table 2.5 Literature reviews on studies assessing health outcomes associated with poor adherence to guideline indicated care for AMI patients.

Author (Year)	Country	Design (Interval data collected)	Setting (N)	Treatment	Outcomes	Statistical analysis and confounders adjusted for	Key findings
Bramlage et al (2010)	Germany	Nationwide registry (February 2003 and October 2004).	Patients with AMI (STEMI or NSTEMI) admitted to 79 hospitals with a cardiology unit or internal medicine department. SAMI (N=5353)	Pharmacotherapy use at hospital discharge (Optimal medical therapy (OMT): aspirin, ACEi/ARB, β-blockers, statin and clopidogrel, unless contraindicated)	1-year mortality	Logistic regression. Age, cardiac arrest on presentation, heart rate, systolic blood pressure, Killip class, ST-segment deviation, abnormal cardiac biomarker, serum creatinine, previous MI and heart failure, and in-hospital revascularisation.	Total mortality was reduced by 74% in patients receiving OMT (adj OR 0.26; 95% CI 0.18 to 0.38). Withdrawal of β-blockers (adj OR 0.63; 95% CI 0.34 to 1.16) and/or a combination of aspirin/clopidogrel (adj OR 0.59; 95% CI 0.20 to 1.17) abolished the risk reduction conferred by OMT.
Rasmussen et al (2007)	Canada	Population-based, observational, longitudinal study (April 1, 1999 and May 1, 2003).	Elderly (aged 66 years or older) AMI survivors (surviving at least 1 year 3 months after hospitalization) recorded in the Ontario Myocardial Infraction Database	Pharmacotherapy medication use following hospital discharge after AMI (β-blockers, statin and calcium channel blockers).	Long term mortality (Maximum follow-up time: 6 years 4 months, median : 2.4 years)	Kaplan-Meier plots and the log-rank test. Cox proportional hazards models. Age, sex, socioeconomic status, year of admission, speciality of attending physician, severity of	Mortality was not associated with adherence to calcium channel blockers. Risk of mortality was highest for low statin adherers (deaths in 261/1071 (24%) vs 2310/14 345 (16%); adjusted hazard ratio, 1.25; 95% confidence interval, 1.09-1.42; P=.001 and intermediary for intermediate adherers (deaths in 472/2407 (20%); adj HR,

Author (Year)	Country	Design (Interval data collected)	Setting (N)	Treatment	Outcomes	Statistical analysis and confounders adjusted for	Key findings
			(N=31,455)			illness, inter-current hospitalisations and use of respective drug within six months prior to admission, concomitant use of ACEi, statins, β-blockers and calcium channel antagonists.	1.12; 95% CI, 1.01-1.25; P=.03). A similar but less pronounced dose-response–type adherence-mortality association was observed for β-blockers. (low adherers, HR 1.13, 95% CI: 1.03-1.25)
Chew et al (2009)	Australia	Nationwide registry (November 2005 and May 2006). Large-scale randomised clinical trials or meta-analyses.	AMI (STEMI or NSTEMI) admissions from 39 hospitals across Australia recorded in ACACIA. (N=1,630)	Pharmacotherapy use at discharge (aspirin, statin, clopidogrel, ACEi/ARBs and β-blockers). Timely management for STEMI (timely reperfusion and early invasive management with concomitant glycoprotein IIb/IIIa inhibition). Timely management for	MI or stroke by 30 days and 30 days to 12 months.	Mant–Hicks cumulative relative-benefit approach for quality of care assessment. Analysis-of-extremes methodology.	Optimal secondary treatment saved 23/10,000 (STEMI, 213 non-fatal events/10,000) and 43/10,000 (NSTEMI, 55 recurrent events/10,000) lives by 30 days, 104/10,000 by 12months (both phenotypes combined) and prevented 191 recurrent ischaemic events/10,000. The novel treatment would save a further 4/10,000 lives by 12 months.

Author (Year)	Country	Design (Interval data collected)	Setting (N)	Treatment	Outcomes	Statistical analysis and confounders adjusted for	Key findings
				NSTEMI (timely use of invasive management and glycoprotein IIb/IIIa inhibition).			
Bauer et al (2010)	Germany	Multicentre, prospective, observational study. (June 2000 and November 2002)	Hospital survivors of AMI (STEMI or NSTEMI) from 155 hospitals enrolled in the ACOS registry. (N=11,823)	Five discharge medication drugs: acetyl salicylic acid, clopidogrel, β-blockers, ACEi/ sartan and statin. Dichotomised receipt of care composite score i.e. patients receiving < 4 drugs (group 1) or receiving 4-5	1-year survival.	Multiple logistic regression models. Age >70, sex, prior MI, prior stroke, diabetes mellitus, peripheral artery disease, smoking, hypercholesterolemia, hypertension, chronic obstructive lung disease, renal insufficiency, malignancy, atrial fibrillation, left bundle branch block, reduced left ventricular function, acute NSTEMI and percutaneous coronary intervention within 48 hours.	Sub-optimal treatment was associated with an increased risk of death at 1-year follow-up (OR 1.6, 95% CI: 1.4–1.9).
Bi et al (2009)	China	Multi-centre prospective study.	Patients diagnosed with suspected AMI	4 drug combination therapy:	Non-fatal outcomes	N/A	At 12 months of follow-up, 20 patients had been readmitted for MI or

Author (Year)	Country	Design (Interval data collected)	Setting (N)	Treatment	Outcomes	Statistical analysis and confounders adjusted for	Key findings
		(September 2004 and May 2006)	or UA admitted to 51 hospitals participating in CPACS. (N=2,973 ; n=345 NSTEMI, n=1,251 UAP and n=1,305 STEMI)	antiplatelet, β-blockers, ACEi/ ARB and statin.			reinfarction, of whom most (80%) were adherent to 4-drug combination therapy.
Yan et al (2007)	Canada	Prospective, multicentre, observational study (September 1999-June 2001 and October 2002-December 2003).	51 hospitals participating in Canadian ACS registry I (N=5,312; n=4,627 ACS) 36 hospitals participating in Canadian ACS registry II (N=2,359; n=1,956 ACS)	Pharmacotherapy (antiplatelet/ anticoagulant, β-blockers, ACEi and lipid modifying therapies)	1-year mortality.	Hierarchical multivariate logistic regression. Propensity score analysis. GRACE risk score variables (age, cardiac arrest on presentation, heart rate, systolic blood pressure, Killip class, ST-segment deviation, abnormal cardiac biomarker and serum creatinine) and in hospital revascularisation.	Patients receiving optimal care had a significantly lower 1-year mortality (adjusted OR 0.54, 95% CI 0.36-0.81, p=0.003). Optimal care was a strong independent predictor of one year mortality.(adjOR 0.58, 95%CI 0.37-0.91, p-value=0.017; propensity adjusted OR 0.51, 95%CI 0.31-0.84, p-value=0.008).

Author (Year)	Country	Design (Interval data collected)	Setting (N)	Treatment	Outcomes	Statistical analysis and confounders adjusted for	Key findings
Dachin et al (2005)	France	Nationwide French registry (November 1-November 30 2000)	Forty-three university hospitals, 229 public hospitals and 97 private clinics. USIC 2000 study. (N=2,119 AMI)	OMT (combination of antiplatelets agents, β-blockers and statins (triple therapy)).	1-year survival	Multivariate Cox regression analysis including a propensity score analysis for prescription of combined therapy. Age, sex, history of hypertension, diabetes mellitus, current smoking, history of myocardial infarction, history of congestive heart failure, history of peripheral arterial disease, history of stroke, history of chronic renal failure, anterior location of infarction, admission systolic blood pressure, admission heart rate, use and type of reperfusion therapy, LVEF, worst Killip class during hospital stay, development of atrial fibrillation, high-degree	Compared with the prescription of any single class of secondary prevention medications, combination therapy offers additional protection in patients with AMI (HR 0.52, 95% CI 0.33-0.81). In patients with ejection fraction ≤35%, β-blockers and angiotensin-converting enzyme inhibitors were independent predictors of survival, and combination therapy had no additional prognostic value.

Author (Year)	Country	Design (Interval data collected)	Setting (N)	Treatment	Outcomes	Statistical analysis and confounders adjusted for	Key findings
						atrioventricular block, use of percutaneous coronary intervention during hospital stay, prescription of diuretics, digitalis, nitrates, triple combination therapy at discharge, and propensity score for the use of triple combination therapy.	
Longeneck er et al (2013)	6 middle eastern countries : Bahrain Kuwait Qatar Oman United Arab Emirates and Yemen	Prospective cohort study (January-June 2007)	72 hospitals, Gulf GRACE (N=5,813 AMI)	Performance measure: •Aspirin and β-blockers within 24 h on admission • Aspirin, β-blockers and ACEi\ ARB and lipid lowering therapy on discharge •Indicated reperfusion therapy •Measurement of LDL cholesterol	In-hospital mortality.	Multivariate logistic regression. Age, sex, nationality, cardiovascular disease, hypertension, any diabetes, smoking, Killip class, and GRACE score.	Low in-hospital mortality was associated with provision of reperfusion therapy (OR 0.54, p=0.047) and β-blockers within 24 hours (OR 0.33, P=0.005).

Author (Year)	Country	Design (Interval data collected)	Setting (N)	Treatment	Outcomes	Statistical analysis and confounders adjusted for	Key findings
				levels during hospitalisation. OMT derived as a composite score			
Hamood et al (2015)	Israel	Patient based retrospective cohort study (January 2005-December 2010)	Members of the Leumit Health Services (N=4,655, AMI)	Pharmacological treatment: aspirin, β-blockers, ACEi\ ARBs, statins and combined therapy.	All-cause mortality	Multiple logistic regression models. Age, gender, ethnicity, district, comorbid conditions, revascularisation, prior use of drug, severity of disease, and health utilisation.	Compared with patients adherent to all four drugs, the risk of mortality was 38% higher for patients non-adherent to all medications (adj HR, 1.38; 95% CI, 1.06-1.80; P=0.017).
Simms et al (2015)	England and Wales	Prospective cohort data from the nationwide population-based registry; MINAP (January 2003-December 2010	247 hospitals in England and Wales (N=112,286, STEMI)	Nine guideline-recommended care opportunities along the pathway of STEMI care: the recording of a pre-hospital ECG; use of acute aspirin; timely coronary reperfusion (PPCI within 120 minutes or thrombolysis	Risk-adjusted 30-day mortality 1-year mortality	Fixed-effects univariable logistic regression models. Kaplan–Meier curves. Multi-level fixed effects models. GRACE risk score variables, previous history of AMI, angina, diabetes mellitus, hypertension, peripheral	Patients ineligible for care had higher RAMR than those eligible for care (30-days: 1.7% vs. 1.1%; 1-year: 8.6% vs. 5.2%), whilst those with no missed care had lower mortality than patients with ≥4 CMOC (30-days: 0.5% vs. 5.4%, adjusted OR (aOR) per CMOC group 1.22, 95% CI: 1.05–1.42; 1-year: 3.2% vs. 22.8%, aOR 1.23, 1.13–1.34).

Author (Year)	Country	Design (Interval data collected)	Setting (N)	Treatment	Outcomes	Statistical analysis and confounders adjusted for	Key findings
				within 60 minutes of the call for help); the individual prescriptions of aspirin, thienopyridine inhibitor, β-blocker, angiotensin converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB), HMG CoA reductase enzyme inhibitor (statin); and enrolment into a cardiac rehabilitation programme at the time of discharge from hospital.		vascular disease, previous revascularisation, coronary angiography, stroke, chronic obstructive pulmonary disease, chronic renal failure and chronic heart failure.	
Timoteo et al (2008)	Portugal	Retrospective study (2002 and 2005)	368 patients admitted in 2002 and 420 patients admitted in 2005 for ACS (with	Pharmacological treatment: aspirin, statins, β-blockers, ACEi, clopidogrel and	In-hospital mortality. 30-day mortality.	Data summarised as frequencies and percentages.	There was no difference in in-hospital mortality (8.2% vs 6.4%) or 30-day mortality (9.0% vs 8.6%), but mortality was lower at one-year follow-

Author (Year)	Country	Design (Interval data collected)	Setting (N)	Treatment	Outcomes	Statistical analysis and confounders adjusted for	Key findings
			and without ST-segment elevation).	glycoprotein IIb\ IIIa antagonists. Reperfusion strategy: PCI.	1-year mortality.	Multivariable logistic regression. Age and sex.	up (17.1% vs 11.7%, P=0.039). Statins and β-blockers were independent predictors of mortality during follow-up, with a protective effect.
Yusuf et al (1998)	Australia, Brazil, Canada, USA, Hungary and Poland	Registry-based study; OASIS (1995-96)	95 hospitals in six countries. (N=7,987, unstable angina or suspected myocardial infarction without ST-segment elevation).	Use of invasive cardiac catheterisation and revascularisation procedures.	Mortality, stroke, bleeding, refractory angina and readmission for unstable angina.	Multilevel logistic regression modelling. Natural randomisation by rates of catheterisation by country. Age, heart rate, systolic blood pressure, abnormal ECG, diabetes, and history of heart failure.	No association was noted between rates of cardiac catheterisation and major cardiac outcomes (death, myocardial infarction and stroke) at 7 days. Rates of refractory angina at 6 months were lower in the two countries with highest rates of catheterisation, however rates of stroke and major bleeding were higher in the two countries with highest rates of invasive strategies.
Mehta et al (2015)	United States	CRUSADE (January 2002-September 2004)	283 US hospitals participating in CRUSADE (N=39,291, NSTE-ACS)	ACC/AHA 2002 Class I guideline recommended therapies which included: aspirin and/or clopidogrel, glycoprotein	All cause in-hospital mortality and major bleeding.	Logistic generalized estimating equations method. age, male sex, body mass index, white race, insurance status, hypertension, diabetes mellitus, current/recent	For every 10% increase in composite adherence at a centre, the patients' in-hospital mortality fell by 20% (OR 0.80, 95% CI 0.67-0.94) and for every 10% increase in appropriate dosing (safety) at a centre, patients' in-hospital

Author (Year)	Country	Design (Interval data collected)	Setting (N)	Treatment	Outcomes	Statistical analysis and confounders adjusted for	Key findings
				IIb/IIIa inhibitor, any heparin (unfractionated or low molecular heparin), and β-blockers. Composite use of ACC/AHA guideline-indicated therapies (adherence) score.		smoking, previous myocardial infarction, renal insufficiency, positive cardiac markers, clinical signs of heart failure on presentation, presenting heart rate, and systolic blood pressure. Hospital characteristics in the model included total number of hospital beds, geographic region (West, Northeast, Midwest, or South), revascularization capabilities (no services, diagnostic catheterization only, percutaneous coronary intervention without on-site cardiac surgery, percutaneous coronary intervention with on-site cardiac surgery), and hospital affiliation (academic versus non-academic)	mortality fell by 10% (OR 0.90, 95% CI 0.83-0.98). Non-CABG in-hospital major bleeding was directly related to guideline-based adherence, with a 10% increase being associated with an increased risk of bleeding (OR 1.25, 95% CI 1.08-1.44). Safety was inversely related to major bleeding (10% increment OR 0.93, 95% CI 0.87-0.98).

Author (Year)	Country	Design (Interval data collected)	Setting (N)	Treatment	Outcomes	Statistical analysis and confounders adjusted for	Key findings
Wald et al (2003)	N/A	Systematic review (RCTs)	Published meta-analyses of randomised trials and cohort studies and a meta-analysis of 15 trials of low dose (50-125 mg/day) aspirin	Formulation of statin, three blood pressure lowering drugs (thiazide, β-blockers and ACEi), folic acid and aspirin. The formulation defined as the pollypill	Proportional reduction in ischaemic heart disease (IHD) events and strokes; life years gained; and prevalence of adverse effects	N/A	The polypill strategy was estimated to reduce ischaemic heart disease events by 88% (95% CI 84%-91%) and stroke by 80% (71%-87%) The polypill strategy could largely prevent heart attacks and stroke if taken by everyone aged 55 and older, and everyone with existing cardiovascular disease.

Abbreviations: OMT; optimal medical therapy, ACEi; angiotensin-converting enzyme inhibitors, ARB; angiotensin-receptor blocker, AMI; acute myocardial infarction, ACACIA; Acute Coronary Syndromes Prospective Audit, GWTG-CAD; Get with the Guidelines- Coronary Artery Disease, ACOS; Acute Coronary Syndromes Registry, PCI; percutaneous coronary artery intervention, PPCI; primary PCI, CABG; coronary artery bypass graft, CPACS; Clinical Pathways for Acute Coronary Syndromes in China, GRACE; Global Registry of Acute Coronary Events, BMIR; Berlin Myocardial Infarction Registry, RCTs; Randomised controlled trials, EUROASPIRE; European Action on Secondary and Primary Prevention by Intervention to Reduce Events, CVD; Cardiovascular disease, TASPIC-CRO; Treatment and secondary prevention of ischemic coronary events in Croatia, CHD; Coronary heart disease, PTCA; percutaneous transluminal coronary angioplasty, PCI; percutaneous coronary intervention, CABG; coronary artery bypass graft, PMSI; programme de médicalisation des sytèmes d'information, ENACT; European Network for Acute Coronary Treatment, ACS; acute coronary syndromes, Gulf GRACE; Gulf Registry of Acute Coronary Events, CRUSADE; Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the ACC/AHA Guidelines, RBC; red blood cell, MI; myocardial infarction, OASIS; Organisation to Assess Strategies for Ischaemic Syndromes, AUBMC; American University of Beirut Medical Centre, PDC; proportion of days covered, LHS; Leumit Health Services, BASI; β-blockers, Antiplatelet, statins and ACEi .

2.2 Critical appraisal of literature

Critical appraisal of the considered papers was conducted guided by the Critical Appraisal Skills Programme (CASP) checklist for cohort studies(76). The critical appraisal tool for cohort studies was used because the review papers were cohort studies. Of the 29 studies considered for the literature review, eleven studies assessed the impact of optimal medical therapy on survival of AMI patients(51-61). Assessment of these studies showed that although there have been major improvements in the care and outcomes of patients with AMI, which is mostly attributed to upstroke in the prescription of evidence-based pharmacological therapy, invasive strategies and cardiac rehabilitation, a large proportion of eligible patients (median 46.2%, IQR 29.1-49.4%), fail to receive appropriate care(51-56, 58-61).

Definition of optimal medical therapy (OMT) was mainly based on the “all or none approach”, which compares AMI patients who have received all the considered care interventions they were eligible for versus those who miss one or more, for most of the studies(51, 54-58). Chew et al.(52) defined receipt of optimal care as being discharged on four or five of the main cardio-protective drugs whilst Longenecker et al.(59) created a composite score of receipt of care by dividing the total number of care interventions received by the patients divided by the total number of care interventions they were eligible for amongst the considered care interventions for the study. The score was then dichotomised at >85%, using the median to guide the cut-off choice. Of the methods applied by the studies the “all or none approach has been considered the most robust way of assessing quality of care, with this method being considered as the gold standard when assessing optimal management of AMI patients. However, the “all or nothing” approach has been criticized on being too strict of a criteria to use when trying to capture ‘real world’ clinical practice. There is a gap in knowledge on the best way to assess quality of care for AMI patients capturing ‘real world’ clinical practice.

Randomised clinical trials (RCTs) have been conducted and have determined the efficacy of the care interventions indicated by the guidelines, that is antiplatelet agents, β-blockers, statins, ACEi/ARBs, revascularization and reperfusion procedures, and anticoagulants(4, 21-23). However, all the studies mainly focused on assessing combined use (OMT) focusing on certain care interventions on the AMI care management pathway i.e. the main five cardio-protective drugs (aspirin, β-blockers, statins, ACEi/ARBs and $P2Y_{12}$ inhibitors). Only one study included (beyond the five cardio-protective drugs) reperfusion in the definition of receipt of optimal care(59). A major benefit should be expected in receiving all the care interventions for which the patient is eligible i.e. coronary angioplasty, enrolment into cardiac rehabilitation as well as the cardio-protective drugs. Limiting the assessment of optimal medical therapy to select care interventions can potentially bias the survival benefits of OMT. Further research is thus required investigating the survival benefits offered by the combined use of all guideline-indicated care interventions for which the AMI patients are eligible, that is across the entire AMI care pathway.

Most of the studies (n=21) considered in the literature review focusing on association of mortality or morbidity and quality of care for AMI were based on select cohorts (median sample size 6,080, IQR 3,180-11,671), which can compromise generalisability as well as statistical power of the studies. Data are lacking on evaluation of guideline adherence as well as associated outcomes for the larger populations of AMI patients mirroring “real-life practice”. In this “Big Data” era, increased availability of vast quantities of clinical and administrative data provides an opportunity to evaluate AMI adherence to guideline-indicated care and associated outcomes on a nationwide basis(77). These electronic health records also provide an important opportunity to continuously monitor clinical practice(77).

Receipt of guideline-indicated care as mentioned earlier has been confirmed to improve survival for AMI patients in RCTs and similarly in this

literature review survival benefits have been reported in past studies for patients who receive OMT. However, most of the studies investigated in-hospital, 30 day and one year survival(51-53, 55, 58, 59, 64, 78). Only one study by Rasmussen et al.(67) investigated the association of adherence to guideline-indicated care and survival post one year(67). It should be expected that optimal care offers survival benefits beyond one year, thus further research is needed to assess what impact OMT has on long term survival beyond 1 year and to quantify the burden (preventable harm) of not receiving optimal care. Excess mortality associated with non-adherence to guideline-indicated care for AMI patients should be evaluated. Although most of the studies found that combined use of AMI care interventions/optimal medical therapy conferred survival benefits, Danchin et al.(58) found that for AMI patients with an ejection fraction ≤35% optimal medical therapy (defined as combined use of antiplatelet agents, β blockers and statins) had no survival benefits. However only β blockers and ACEi use had a prognostic value(58).

Of the two phenotypes of AMI, NSTEMI patients care was reported in the literature review to be sub-optimal as they were less likely to receive guideline-indicated care interventions compared with their STEMI counterparts(53, 71, 79). A lot of extensive work focusing on STEMI quality of care only has been undertaken (61, 80, 81), yet the NSTEMI patients are possibly the most vulnerable of the AMI phenotypes as they are usually significantly older and more comorbid(71) and have poorer survival outcomes(53, 78). Extensive research of NSTEMI management is essential.

2.2.1 Limitations of statistical methods used in previous research

Logistic regression analysis was employed by most of the studies to assess impact of receipt sub-optimal care for AMI patients on mortality i.e. using a binary outcome (died: yes/no). With some of the studies implementing

multilevel logistic regression models to take into account the clustered nature of the data i.e. patients nested within hospitals, which is the correct strategy of modelling data as not taking into account data clustering can result in underestimation of standard errors hence biased estimates. However, implementing logistic regression for time to event data (in this instance time to death as they were assessing mortality) can bias the impact on mortality of any exposure(82). Analysing time to event data using survival models takes into account not only the fact that the event occurred but also when the event occurred(83). Methods like logistic regression are not suited to take into account both the event and time aspects during modelling. Logistic regression analysis is not designed to handle censoring, which is a special type of missing data that occurs in time to event data analysis when participants do not suffer the event during the study time (follow-up time) or are lost to follow-up (due to change of address/migration or they withdraw from the study)(83). Survival models utilize the partial information on each subject with censored data to provide unbiased survival estimates. The studies found in the literature review should have implemented time to event methods such as survival models that cope with censored data. However, the logistic regression has been reported to suffice for time to event data were the condition is rare and the follow-up time short. So the studies that had really short follow-up time for example in-hospital mortality, the bias from using this approach could have been minimal(82). A few studies did use time to event models in their survival modelling; the methods undertaken include Kaplan Meier curves and the cox proportional hazards modelling. However, none of the studies gave details of checking if the proportional hazards assumption was assessed after fitting the cox model.

The main challenge when using observational data is the bias inherent due to systematic differences between the observations. The literature review conducted mainly focused on observational studies, however only two studies used advanced causal inference techniques (i.e. propensity scoring and instrumental variable analysis) beyond simple confounder adjustment

using multivariable regression models (which is heavily flawed if confounder selection is not done correctly). Yan et al.(55) in their study to evaluate optimal medical therapy at hospital discharge in patients with ACS used propensity scoring to even out systematic differences between cases and controls in their modelling. Yusuf et al.(73) in their study to investigate variations between countries in invasive cardiac procedures and outcomes in patients with unstable angina or MI without initial ST elevation used a natural randomisation approach modelling rates of catheterisation by country than the actual catheterisation treatment which is affected by selection bias. The rest of the studies did adjust for confounders, however no extra detail was given on what governed the choice made to adjust for the particular variables adjusted for as confounding variables. Usually clinical as well statistical input should be considered when deciding on the choice of confounders. Casual diagrams approaches such Directed Acyclic Graphs (DAGs)(84) can be used to aid applied researchers when choosing a minimal set of variables to adjust for as confounders in statistical modelling when using observational data(84, 85). Adjusting for variables on the causal pathway for example mediators can further bias the estimates and this is known as the Simpson's paradox in Epidemiological research(84). None of the studies considered in the literature review used DAGs to inform their confounder variable choices.

2.3 Key Gaps in the Knowledge and PhD aim

The literature review conducted in this study showed that the majority of previous studies focused on survival benefits of receipt of optimal care of up to one year after AMI. There is a paucity of studies of survival benefits beyond one year. Furthermore the definitions of optimal care used by previous studies were limited in that they did not include all the care interventions for which the patients were eligible for on the AMI care pathway. Traditional statistical methods such as multivariable logistic regression used by some of the previous studies may produce biased results because they do not take into account the time to event aspect of

survival data. There is need for more research to assess survival benefits beyond one year of receipt of optimal care considering all the care interventions on the AMI care pathway beyond the five main pharmacotherapy drugs.

However, extensive work needs to be focused on the more vulnerable of the two AMI phenotypes which is NSTEMI. Advanced time to event statistical methods need to be applied when assessing the efficacy of optimal care. Also, appropriate techniques to minimise measured and unmeasured confounding inherent when using observational data need to be applied. The increased availability and accessibility to electronic health records data allow for higher resolution investigation of sequential care deficits significantly associated with premature cardiovascular death. Therefore, the aim of this PhD project was to investigate the quality of care and associated outcomes of patients hospitalised with AMI using electronic health records focusing mainly on NSTEMI patients. The utility of using robust statistical methods of adjusting for potential confounders was also explored.

2.3.1 Research objectives

1. Quantifying excess mortality (avoidable deaths) associated with sub-optimal treatment of NSTEMI patients and determining predictors of sub-optimal treatment (results reported in Chapter 4).
2. Assess geographic variation in receipt of care for NSTEMI patients and determine the factors that explain the variation (results reported in Chapter 5).
3. Investigating the association of clinical factors and therapeutic strategies with improvements in survival following STEMI. (results reported in Chapter 6).
4. Determining the efficacy of β-blockers during and after AMI in patients without heart failure or LVSD. (results reported in Chapter 7).

Chapter 3 : Materials and Methods

3.1 Introduction

This chapter gives an account of the methods used in the thesis. Firstly, an overview of the study population and design is given in §3.2. This is followed by a description of the data source (§3.3) that was used for the thesis as well as a detailed description of the corresponding ethical considerations (§3.3.1). The details of the guideline-indicated care pathway for NSTEMI patients as recommended by the ESC guidelines and ESC Expert Consensus Documents (published from 2002-2011) will then follow (§3.4), including a detailed description of how the NSTEMI care interventions were mapped to MINAP data fields (Table 3.1). Quality of care definition is given in §3.4.1. §3.5 focuses on statistical analyses methodology used throughout the thesis, this includes details of the descriptive data analyses, methods for handling missing data, and statistical modelling for each of the PhD objectives in turn as listed below;

- Quantifying excess mortality (avoidable deaths) associated with sub-optimal implementation of care for NSTEMI patients and determining predictors of sub-optimal care (**objective 1**, results reported in Chapter 4). §3.6
- Assess geographic variation in receipt of care for NSTEMI patients and determine the factors that explain the variation (**objective 2**, results reported in Chapter 5).§3.7
- Investigating the association of clinical factors and therapeutic strategies with improvements in survival following STEMI. (**objective 3**, results reported in Chapter 6).§3.8
- Determining the efficacy of β-blockers during and after AMI in patients without heart failure or LVSD. (**objective 4**, results reported in Chapter 7).§3.9

3.2 Study population and design

The study aimed to provide a comprehensive investigation of quality of care and outcomes of patients hospitalised with AMI using electronic health records (EHRs), therefore a retrospective analysis of all patients recorded in MINAP was carried out. The study population consisted of all patients aged over 18 years recorded within MINAP between 1st January 2003 and 30th June 2013 (787,202 AMI observations to date), who had been hospitalised with AMI. For patients with multiple admission of AMI recorded in MINAP, only the first record was used. Focusing on the first record of each patient was conducted so as to reduce potential bias from previous treatment in relation to subsequent admissions.

3.3 Data sources

Of the data sources discussed in Chapter 1, §1.6, MINAP was considered most appropriate to carry out the work for the thesis. MINAP was deemed appropriate as it is a comprehensive large national registry of ACS across one health system (the National Health Service (NHS) in England and Wales). MINAP strengths also lies in that it was specifically designed to assess quality of ACS care and its diagnostic records (highly likely to fulfil international diagnostic criteria) are not available in other data sources(86).

3.3.1 Ethical approval and data security

Ethical approval was not required for this study as the National Institute for Cardiovascular Outcomes Research (NICOR), where the MINAP database (Ref: NIGB: ECC 1-06 (d)/2011) was obtained has support under section 251 of the NHS Act 2006 to use patient information for medical research without consent. The MINAP data obtained from NICOR was pseudonymised patient data, and according to the Health Research Association (HRA), secondary use of anonymised patient data for research purposes were not subject to further ethical approval. I also used the HRA decision tool to further confirm I did not need approval from the NHS

Research Ethics Committee (REC) for my study. Approval was not needed by the NHS REC. (See Appendix A for HRA-decision tool output)

The MINAP patient data used for this thesis were fully anonymised and stored on the University of Leeds N Drive, which has restricted access only to the authorised members within the Cardiovascular Epidemiology research group. Access to University of Leeds computing resources requires a credential check on log in, and compulsory data security training.

3.4 Guideline indicated care interventions

Treatment of AMI patients is defined by several national and international guidelines(4, 16, 22-24, 87). Cardiologists in the UK use guidelines from the NICE and from the ESC to guide clinical decision making(88). Recommendations from both guidelines are based on the same evidence base(88). For this thesis, the ESC international guidelines were used to assess adherence to guidelines during the management of NSTEMI patients because the ESC guidelines are updated more frequently/timely in response to temporal developments in management of AMI compared to NICE guidelines and ESC guidelines are more generalisable to an international audience as they are derived intended for implementation across 56 countries. The full NSTEMI care pathway as described within the ESC guidelines and ESC consensus documents (published from 2002-2011) is summarised in Figure 3.1. (21, 89-92)

The identified NSTEMI care interventions from the treatment pathway as recommended by the guidelines, were mapped to MINAP data fields in order to determine which care interventions could be reliably assessed, based on data availability and adequate data quality or recording, using MINAP (Table 3.1). Figure 3.1 also gives information on which interventions from the full care pathway were and were not used and Table 3.1 gives a detailed description of the reasons why the excluded care interventions were not considered for the analyses.

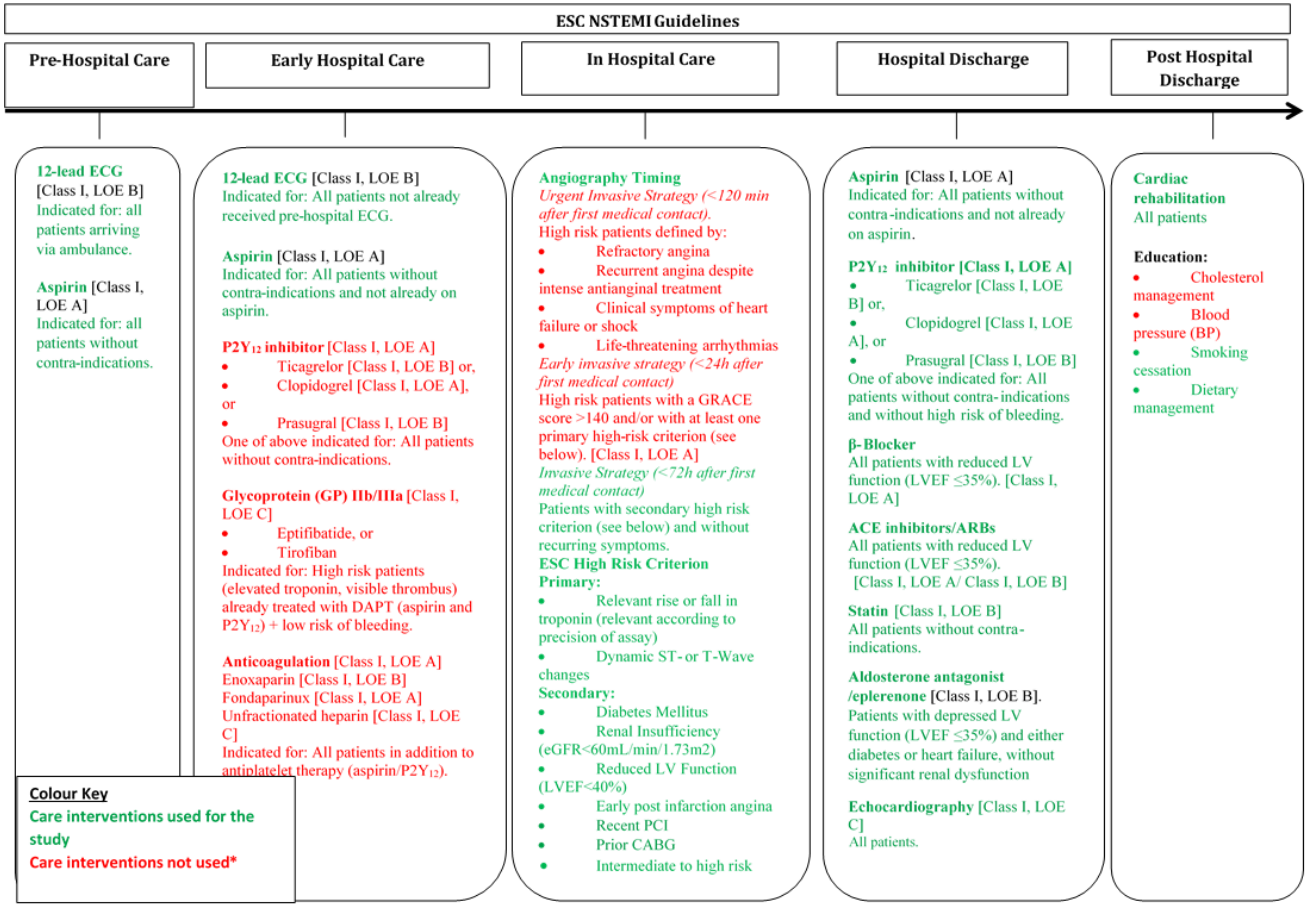


Figure 3.1 European Society of Cardiology guidelines for the management of NSTEMI, care interventions and corresponding MINAP data availability.

Table 3.1. Mapping of corresponding ESC guidelines for the management of NSTEMI to MINAP data fields.

Care Pathway Components – Detail			
Care Pathway Components	**Eligibility Criteria**	**Opportunity Received**	**Include in OMT definition (Yes/No)**
12 lead ECG			
Pre-Hospital	All patients arriving via ambulance if admission method=1 (2.39)	ecg_place (1.23) = 1	Yes
In-Hospital	All patients not already received ECG pre-hospital if pre hospital ecg = no.	(Ecg_app!=. or ecg_place!=.) and no pre-hospital ECG.	Yes
Aspirin			
Pre-Hospital	All patients arriving via ambulance and not already on aspirin or contraindicated if admission method=1 (2.39) AND where was aspirin given (2.04)!=1,4 or 8	Where was aspirin given (2.04)=2	Yes
In-Hospital	All patients not already on aspirin or contraindicated if pre-hospital aspirin = no AND where was aspirin given (2.04)!=1,4 or 8	Where was aspirin given (2.04)=3	Yes
At Discharge	All patients not already on aspirin or contraindicated if pre-hospital aspirin= no AND in-hospital aspirin=no AND where was aspirin given (2.04)!=1,4 or 8 AND discharged on aspirin (4.08)!=2,3,4 or 8.	Discharged on aspirin (4.08)=1	Yes
$P2Y_{12}$ inhibitor			
In-Hospital	All patients not contraindicated and without high risk of bleeding	If thienopyridine (3.22)=1	No- not well recorded in MINAP.

Care Pathway Components – Detail			
Care Pathway Components	**Eligibility Criteria**	**Opportunity Received**	**Include in OMT definition (Yes/No)**
At Discharge	All patients not contraindicated and without high risk of bleeding If discharged on thienopyridine (4.27)!=2,3,4 or 8 Or if discharged on ticagrelor!=2,3,4,8	If discharged on thienopyridine=1 or if discharged on ticagrelor=1	Yes
Glycoprotein (GP) IIb/IIIa	High risk patients already treated with aspirin and $P2Y_{12}$ inhibitor and low risk of bleeding. If aspirin=yes at any time point (including taken at home) AND if $P2Y_{12}$ is yes at any time point AND patient is "high risk" Where "high risk" in this case is any of the following: High risk nSTEMI=1 (4.32) OR Troponin elevated OR Grace>140 UK Guidelines only: People who received angiography/PCI within 24hours were also eligible.	If IV_2b/3a (3.24) = 1	No, can't identify all eligibility criteria (low risk of bleeding and visible thrombus data not available).
Anticoagulation	All patients	If unfractioned heparin (3.20) =1 OR if low molecular weight heparin (3.21) = 1 OR if fondaparinux (3.38) =1	No- not well recorded in MINAP.
Angiography Timing			
Urgent Invasive (<120 min)	High risk patients defined by refractory angina, recurrent angina despite intense antianginal treatment,clinical symptoms of heart failure or shock, life-threating arrhythmias.	If time from first medical contact to angiography is <120 minutes	No – cannot accurately define all "high risk" factors for this (i.e. refractory angine, recurrent angina).

Care Pathway Components – Detail			
Care Pathway Components	**Eligibility Criteria**	**Opportunity Received**	**Include in OMT definition (Yes/No)**
	Shock=yes: If Systolic blood pressure>90 OR killip class=2, 3 or 4 Heart Failure=yes: if heart failure (2.13)=1 Cardiac arrest=yes if delay before treatment (3.10)=5 OR cardiac arrest location=2,3,4,5,6,7 or 8 OR arrest presenting rhythm (3.15)=1,2, or 3 OR outcome of arrest=1,2,3,4,5 or 6.		
Early Invasive (<24 hours)	High risk patients as defined below. If high risk nSTEMI=1 (4.32) OR Troponin elevated OR GRACE>140	If time from first medical contact to angiography is <24 hours	No – cannot accurately define all “high risk” factors for this (i.e. dynamic ST or T wave changes).
Invasive (<72 hours) [adjust as necessary for different guidelines].	Patients with one or more secondary high risk criterion as defined below. If Diabetes (2.17)=1,2,3,4,5 OR chronic renal failure=1 OR creatine (2.14)>200 OR LV function (2.31)=3 OR history of CHD (2.32)=1 OR previous PCI (2.18)=1 OR previous CABG (2.19)=1 OR Intermediate GRACE >109 & <=140.	If time from first medical contact to angiography is <72 hours	Yes.
β-Blocker	All patients with reduced LV function and no contraindications. If LV Function (2.31)=3 OR history of CHD (2.32)=1 AND discharged on beta blocker (4.05)!=2,3,4 or 8. *NOTE: For UK guidelines everyone is eligible for β-Blockers.*	If discharged on beta blocker(4.05)=1 If oral beta blocker (3.43)=1 and if discharged on beta blocker(4.05)=1	Yes

Care Pathway Components – Detail			
Care Pathway Components	**Eligibility Criteria**	**Opportunity Received**	**Include in OMT definition (Yes/No)**
ACE inhibitors/ARBs	All patients with reduced LV function and no contraindications. If LV Function (2.31)=3 OR history of CHD (2.32)=1 AND if discharged on ACEi/ARB (4.06)!= 2,3,4,8.	If ACEi/ARB (3.32)=1 OR if discharged ACEi/ARB (4.06)=1	Yes
Statin	All patients unless contraindicated If statin (4.06) is yes or no (i.e. exclude contraindications, not applicable, unknown etc).	If statin (4.06)=1	Yes
Aldosterone antagonist/eplerenone	Patients with depressed LV function (LVEF ≤35%) and either diabetes or heart failure, without significant renal dysfunction and already treated with ACE inhibitors and β blockers	If aldosterone (4.33)=yes.	Yes
Echocardiography	All patients unless not indicated. If stress echo!=8 OR if echocardiography (4.11)!=8	If stress echo=1 or 2 OR if echocardiography=1 OR 2.	Yes.
Referral for Cardiac Rehabilitation	All patients eligible unless not indicated If cardiac rehabilitation (4.09)!=8	If cardiac rehabilitation (4.09)=1 or 3	Yes
Smoking Cessation Advice	All patients eligible unless not applicable If smoking cessation (5.01)!=3	If smoking cessation (5.1)=1 OR 2	Yes

Care Pathway Components – Detail			
Care Pathway Components	**Eligibility Criteria**	**Opportunity Received**	**Include in OMT definition (Yes/No)**
Dietary Advice	All patients eligible if applicable. If dietary advice (5.2)!=4	If dietary advice (5.2)=1 OR 3	Yes

Abbreviations: CHD, coronary heart disease; PCI, percutaneous coronary intervention; OMT, optimal medical therapy, ESC; European Society Of Cardiology; MINAP, Myocardial Ischaemia National Audit Project, LVEF, left ventricular ejection fraction; ACEi, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blockers.

3.4.1 Quality of care definition

The 13 guidelines indicated care interventions that were considered for the present study after mapping and data assessment were as follows:

- recording of an electrocardiogram (pre-hospital and on admission combined)
- prescription of aspirin acutely (pre-hospital and on admission prescription of aspirin)
- $P2Y_{12}$ inhibitors at discharge
- aspirin at discharge
- β blockers at discharge
- ACEi or ARBs at discharge
- a HMG CoA reductase enzyme inhibitors (statins) at discharge
- aldosterone antagonists in patients with left ventricular systolic dysfunction and either diabetes or heart failure without significant renal dysfunction
- echocardiogram
- coronary angiography
- smoking cessation advice
- dietary advice
- enrolment into a cardiac rehabilitation programme.

Patients were deemed eligible for each treatment as recommended by ESC guidelines and patients were considered ineligible if a care intervention was contra-indicated, not indicated, not applicable or if the patient declined treatment as documented in MINAP. If a patient was hospitalised before treatment was introduced into the guidelines, they were also considered ineligible for the treatment (for example, $P2Y_{12}$ inhibitors were not introduced to the guidelines until 2004 and aldosterone antagonists until 2007). The considered guideline-indicated care interventions were chosen as they are representative of the guideline-indicated care interventions that

span the full NSTEMI care pathway and give an opportunity to assess the impact of cumulative missed opportunities for care on avoidable deaths after suffering an NSTEMI. In order to assess quality of care, a suitable aggregation method of the multiple, individual care interventions had to be employed to define receipt of optimal care for NSTEMI patients.

Composite performance measures that are commonly used for healthcare performance assessment include; opportunity scoring, linear combinations approach, regression-based composite measures, latent trait composite measures, all-or-none scoring/defect-free scoring, and any-or-none scoring of outcome measures(93). Of these various approaches the all-or-none scoring/defect-free scoring, opportunity scoring, and latent trait composite measures were used for objective one and two of the thesis.

The all-or-none scoring/defect-free scoring was chosen as it promotes a high standard of health care assessment, it gives greater variation in scores of receipt of care and is structured at patient level(94, 95). Using this approach, for each patient a score was calculated by dividing the total number of care interventions for which the patient received by the total number they were eligible for (opportunity scoring) and then grouping the patients by their score into an optimal care group (received all care interventions) vs. sub-optimal care group (missed one or more care interventions for which they were eligible)(95). This method has been deemed the gold standard measure of assessing quality of care for patients.

However, because the all-or-none scoring/defect-free scoring is a strict method of defining optimal care (although it offers a gold standard definition), it weights less important commonly prescribed care interventions equally to infrequently prescribed more important care interventions and does not capture ‘real world’ clinical practice, an alternative method had to be employed as a sensitivity analysis. The latent trait composite measures approach: Latent Class Analysis (LCA) was conducted. LCA identifies

complex patterns of association among observations based on observed characteristics(96). This method is commonly implemented when variables are related due to unobserved influences. For this thesis, LCA was used to identify the underlying subgroups of receipt of care based on the 13 guideline-indicated care interventions considered, with the underlying unobserved influence in this case being quality of receipt of care. LCA is used when the underlying unobserved variables are classes, categories or discrete(96). The method estimates the latent class prevalences (class probabilities) as well as the probabilities of specific response given class membership (conditional item probabilities)(96). The conditional item probabilities are specific to a given class and provide information about the probability that an individual in that class will endorse that item (97, 98). The class probabilities specify the proportion of the population that is in a particular class(97, 98).

The advantage of using the LCA approach compared with the all-or-none scoring/defect-free scoring is that it allows modelling the real life scenario of receipt of care, which goes beyond a dichotomised composite measure by considering the actual combinations of care interventions which the patients receive and classifying them into groups which are both statistically valid and clinically interpretable. The demographic and socioeconomic factors associated with the latent classes can be determined to help characterise the subgroups. The classes are latent in that the underlying sub-groups are not directly observed(99). Latent classes of receipt of care using the 13 observed guideline-indicated care interventions were derived using Mplus software(99, 100).

In order to determine the optimal class solution that could adequately describe the patterns of receipt of care for the NSTEMI patients, several class solutions starting from two up to seven classes were explored. The preferred latent class solution was selected based on minimisation of the Bayesian Information Criteria (BIC) and Akaike’s Information Criterion (AIC)

(101), clinical interpretability of the emergent latent classes and the class solution where the log likelihood plot started to level off. The log likelihood plot is a plot of the log likelihood of the different class solutions models against the number of latent classes. The best class solution is determined by the point where the plot levels off. When using AIC and BIC criteria to compare nested models, the model with minimal AIC and BIC are indicative of best fit. When there is a discrepancy between the AIC vs. BIC when determining the optimal class solution, the BIC would be considered as BIC has been shown to outperform AIC especially when small classes are present(102). A seven class solution was considered as the maximum as class solutions beyond seven were not clinically interpretable. The entropy statistic was also calculated to evaluate classification quality of the optimal class solution. Entropy values range from 0 to 1 and closer to 1 indicates a latent class solution that is more distinct(103).

3.5 Statistical analysis

Statistical analyses were performed in Stata MP64, version 14 (StataCorp,www.stata.com). R version 3.1.2 (https://cran.r-project.org/bin/windows/base/) was used to perform multiple imputation by chained equations (MICE) using the 'mice' package and Mplus version 7 was used to conduct latent class analyses. All the tests were two-sided and *P-values* of <0.05 were considered statistically significant.

3.5.1 Descriptive data analysis

For each of the four objectives, four different analytical cohorts were derived from the MINAP database based on the exclusion criteria for the specific objective (§3.6.1, §3.7.1, §3.8.1, §3.9.1). Baseline characteristics for the analytical cohorts for the four objectives of the thesis were summarised as frequencies and percentages for categorical data and continuous data as means and standard deviations (normally distributed) or medians and interquartile ranges (IQR) (non-normally distributed). Unadjusted and

adjusted Kaplan-Meier curves were used to assess survival differences for objective one and four. The log rank test was used to compare survival differences for the unadjusted Kaplan-Meier curves for objective one. For objectives three and four differences in characteristics were assessed using two sample *t*-tests and, for categorical data, the Chi-square tests, and test of proportions.

3.5.2 Handling missing data

Electronic health records offer a vast amount of routine data, however the major weakness of using these resources is missing data, which if left unaddressed could result in biased estimates (e.g. regression parameters), biased standard errors (e.g. incorrect p-values and confidence intervals) and inefficiency due to exclusion of observations with missing data hence limiting the generalisability of study findings(104). There are several reasons why data ends up missing which include; data never being collected , being lost accidentally, incorrectly recorded such that it has to be deleted or even wrongly deleted(104). Thus missing data have different mechanisms of missingness which must be taken into account when making inference using the data. The missing data mechanisms that are recognised in literature are as follows; missing completely at random (MCAR), missing at random (MAR), and the missing not at random (MNAR)(105, 106). There is no definitive way of determining which mechanism the missing data follows therefore the decision is centred on assumptions that should be reasonable and sensible given the situation. The missing data mechanisms mentioned are assumptions made on why the data is missing and they inform on the type of strategy that is utilised to handle the missing data. MCAR mechanism is assumed when the missingness of the data is not dependent on observed or unobserved values of the data, such that there are no systematic differences between the observed and missing data(105). For the MCAR mechanism the existing data cannot be used to predict the missing data(105). An example of when data can be said to be missing by the MCAR mechanism is when a laboratory sample is dropped accidentally(105). MAR mechanism is

assumed when the missingness of the data depends on observed data but not on the unobserved, such that the systematic differences between the observed and missing data can be explained by the observed data(105). An example of when data can be said to be missing by the MAR mechanism is when data on PCI for elderly comorbid AMI patients is missing. PCI data would be MAR conditional on the patients' age and comorbidity profile. Under the MAR mechanism assumption the observed data can be used to predict the missing data(105). MNAR mechanism is assumed when the missingness of the data depends on unobserved data (non-ignorable or informative missingness), such that the observed data cannot explain the systematic differences between the missing and observed data(105). An example of when data can be said to be missing by the MNAR mechanism is when a patient misses an appointment because they are feeling unwell and their illness is related to the data intended to be collected(105). As I mentioned before identifying the missing data mechanism is important when deciding the strategy to handle missing data to minimise the negative implications of drawing inference from incomplete datasets. Several methods have been used in literature to handle missing data and these include listwise deletion, single imputation, single regression imputation, multiple imputation, maximum likelihood estimation and inverse probability weighting(107). Of these methods, the most commonly used in epidemiological research are listwise deletion, single imputation, single regression imputation, and multiple imputation. The techniques have been proven to be robust when handling ignorable missing data, i.e. data missing at MCAR and MAR. Details on the methods for handling missing data are given below:

3.5.2.1 Listwise deletion

The listwise deletion methods which involve excluding subjects with missing data (complete case analysis) usually suffice for data that is missing under the MCAR mechanism(107). The methods are very simple and easy to implement however exclusion of subjects with missing data compromises precision. Complete case analysis has also been reported to suffice in incidences when there is minimal missingness (~5%)(108, 109). For this

thesis this mechanism was not implemented as some of the variables considered for the various analyses had missing data >5%.

3.5.2.2 Single imputation

Single imputation involves filling in missing data with an alternative value and then analysing it as if it were the true complete data(107). Examples of this technique are single mean imputation and the “last observation carried forward”(107). The single mean imputation approach is specifically for continuous data whereby the missing data is replaced with the mean. The “last observation carried forward” approach is most commonly used for imputing longitudinal data with main assumption being that after loss to follow-up the value that was last recorded will suffice to replace the missing data(107). The single imputation methods have the same advantage as the listwise deletion methods in that they are simple and easy to implement however this results in reduced standard errors as they produce data that is highly concentrated around the mean. Single imputation does not take into account uncertainty in the missing data. It only works well when there is minimal missing data. In this thesis single imputation was not used because of the limitations described in this section.

3.5.2.3 Regression imputation

Regression imputation involves using a regression model adjusted for variables that are predictive of the missing data to predict the missing data(107). Similar to the techniques discussed before, this technique is simple and easy to implement however the method does not take it account the uncertainty in the missing values and usually exaggerates correlations. The predictor variables used in the regression model should not have missing data in them or else this will bias the predicted data.

3.5.2.4 Multiple imputation

Multiple imputation is regression imputation repeated many times to account for uncertainty about the missing data(110). This is achieved by creating several ‘complete’ datasets whereby in each dataset the missing values are filled in by regression imputation(110). Analysis is then undertaken on each of the imputed datasets and the parameter estimates

are pooled using Rubin's rules(111) to get the final parameter estimate. The multiple imputation approach is highly applicable when data are MAR and the more predictive variables included in the multivariate model the more accurate the predictions(110). Multiple imputation has advantages over the other missing data techniques in that it accounts for the uncertainty about the missing data by the use of multiple 'complete' datasets which yields more precise standard errors. The technique is very flexible in that it can handle different types of variables i.e. continuous or categorical data(110). Also multiple imputation is useful when there is high levels of missing data. An example of a multiple imputation approach is MICE.

As with other sources of data arising from EHRs, MINAP also has missing data that needs to be addressed before making inference using it. So before proceeding on to analyses for each of the four objectives of the thesis missing data were imputed using the multiple imputation approach; MICE (using `mice` package in R software)(105, 112). The decision to use this approach was informed by past literature that has imputed missing data for MINAP(105) and from prior statistical knowledge (discussed in §3.5.2.4) on the utility of the multiple imputation approach compared with other techniques discussed in the earlier section (§3.5.2). Also, the same default imputation strategy used for medical history and drug therapies by Cattle et al.(105) was used for medical history and drug therapies for the work of this thesis. The default imputation strategy involves replacing the missing data for the binary medical history and drug therapies variables with a "no". As upon consultation with the medical and clerical staff involved in derivation of MINAP, Cattle et al.(105) reported that it was more likely that a condition or treatment would go unrecorded if the patient had no history of the condition or did not receive treatment. Other studies considered in the literature review have also implemented the default imputation strategy approach(71). The imputation strategies detailing the variables that were imputed, the variable types, level of missing data per variable, and imputation method employed for the four objectives are given in Table 3.2-Table 3.4 below.

Table 3.2. Imputation Strategy for **objective 1**(§2.3.1) and **objective 2** (§2.3.1).

Variable	Variable Type	Missing (%)	Imputation method
ECG appearances on which treatment was based	Categorical	9.2	Polytomous regression
Cardiac arrest	Binary	5.9	Logistic regression
Uncensored peak troponin measurement in ng/ml	Continuous	4.9	Predictive mean matching
Age	Continuous	0.2	Predictive mean matching
Systolic blood pressure	Continuous	17.1	Predictive mean matching
Heart rate	Continuous	16.9	Predictive mean matching
Loop diuretic used	Binary	17.4	Logistic regression
Creatinine level	Continuous	42.6	Predictive mean matching
Ethnicity	Categorical	9.8	Polytomous regression
Sex	Binary	0.2	Logistic regression
Index of multiple deprivation score	Continuous	7.8	Predictive mean matching
Latent classes	Categorical	0	Predictor/ Auxiliary /Partially Observed
Cumulative receipt of care	Continuous	0	Predictor/ Auxiliary /Partially Observed
Optimal care*	Binary	0	Predictor/ Auxiliary /Partially Observed
Year of admission	Continuous	0	Predictor/ Auxiliary /Partially Observed
Nelson-Aalen survival estimate	Continuous	0	Predictor/ Auxiliary /Partially Observed
Censoring indicator	Binary	0	Predictor/ Auxiliary /Partially Observed
Previous myocardial infarction	Binary	8.0	Predictor/ Auxiliary and Default imputed
Previous angina	Binary	8.9	Predictor/ Auxiliary and Default imputed
Hypercholesterolaemia	Binary	11.0	Predictor/ Auxiliary and Default imputed
Previous hypertension	Binary	8.3	Predictor/ Auxiliary and Default imputed
Peripheral vascular disease	Binary	11.5	Predictor/ Auxiliary and Default imputed
Cerebrovascular disease	Binary	10.6	Predictor/ Auxiliary and Default imputed
Chronic obstructive pulmonary disease or asthma	Binary	11.4	Predictor/ Auxiliary and Default imputed
Congestive cardiac failure	Binary	10.4	Predictor/ Auxiliary and Default imputed
Previous percutaneous coronary intervention	Binary	10.1	Predictor/ Auxiliary and Default imputed
Previous coronary artery bypass graft	Binary	9.8	Predictor/ Auxiliary and Default imputed
Smoker (current or previous smoker vs. non-smoker)	Binary	7.5	Predictor/ Auxiliary and Default imputed

Variable	Variable Type	Missing (%)	Imputation method
Diabetes mellitus	Binary	7.1	Predictor/ Auxiliary and Default imputed
Family history of chronic heart disease	Binary	37.3	Predictor/ Auxiliary and Default imputed
Care by cardiologist	Binary	39.1	Predictor/ Auxiliary and Default imputed

*Defined as receipt of all care interventions for which the patients were eligible for.
Abbreviations: ECG, Electrocardiogram.

Table 3.3. Imputation Strategy for **objective 3** (§2.3.1).

Variable	Variable Type	Missing (%)	Imputation method
Cardiac arrest	Binary	7.9	Logistic regression
Uncensored peak troponin measurement in ng/ml	Continuous	22.0	Predictive mean matching
Age	Continuous	0.1	Predictive mean matching
Systolic blood pressure	Continuous	22.3	Predictive mean matching
Heart rate	Continuous	21.9	Predictive mean matching
Loop diuretic used	Binary	24.0	Logistic regression
Creatinine level	Continuous	45.6	Predictive mean matching
Ethnicity	Categorical	12.3	Polytomous regression
Sex	Binary	0.4	Logistic regression
Index of multiple deprivation score	Continuous	8.3	Predictive mean matching
Year of admission	Continuous	0	Predictor/ Auxiliary /Partially Observed
Nelson-Aalen survival estimate	Continuous	0	Predictor/ Auxiliary /Partially Observed
Censoring indicator	Binary	0	Predictor/ Auxiliary /Partially Observed
Hypercholesterolaemia	Binary	16.5	Predictor/ Auxiliary and Default imputed
Previous hypertension	Binary	13.2	Predictor/ Auxiliary and Default imputed
Previous myocardial infarction	Binary	12.8	Predictor/ Auxiliary and Default imputed
Previous angina	Binary	14.1	Predictor/ Auxiliary and Default imputed
Previous PCI	Binary	15.0	Predictor/ Auxiliary and Default imputed
Previous CABG	Binary	14.8	Predictor/ Auxiliary and Default imputed
Peripheral vascular disease	Binary	16.2	Predictor/ Auxiliary and Default imputed
Cerebrovascular disease	Binary	15.6	Predictor/ Auxiliary and Default imputed
Chronic obstructive pulmonary disease or asthma	Binary	16.2	Predictor/ Auxiliary and Default imputed
Smoker (current or previous smoker vs non-smoker)	Binary	9.7	Logistic regression
Diabetes mellitus	Binary	11.2	Predictor/ Auxiliary and Default imputed

Variable	Variable Type	Missing (%)	Imputation method
Family history of chronic heart disease	Binary	36.3	Predictor/ Auxiliary and Default imputed
Care by cardiologist	Binary	38.3	Predictor/ Auxiliary and Default imputed
Chronic renal failure	Binary	15.5	Predictor/ Auxiliary and Default imputed
Congestive cardiac failure	Binary	15.3	Predictor/ Auxiliary and Default imputed
Electrocardiogram appearance	Categorical	3.5	Polytomous regression
Preadmission medication			
Aspirin	Categorical	0	Predictor/ Auxiliary and Default imputed
β-blockers	Categorical	33.7	Predictor/ Auxiliary and Default imputed
Statins	Categorical	31.1	Predictor/ Auxiliary and Default imputed
ACEi or ARBs	Categorical	33.8	Predictor/ Auxiliary and Default imputed
$P2Y_{12}$ inhibitors	Categorical	63.2	Predictor/ Auxiliary and Default imputed
Warfarin	Categorical	23.9	Predictor/ Auxiliary and Default imputed
Discharge medication			
Aspirin	Categorical	9.3	Polytomous regression
$P2Y_{12}$ inhibitors	Categorical	60.4	Polytomous regression
ACEi/ARBs	Categorical	10.5	Polytomous regression
Statins	Categorical	31.1	Polytomous regression
β blockers	Categorical	18.2	Polytomous regression
Aldosterone antagonist	Categorical	72.3	Polytomous regression
Use of an invasive strategy	Categorical	7.2	Polytomous regression
Enzyme elevation	Binary	10.8	Predictor/ Auxiliary variable
Admission diagnosis	Categorical	0	Predictor/ Auxiliary variable
Admitting consultant	Binary	5.4	Predictor/ Auxiliary variable
Serum cholesterol	Continuous	25.6	Predictor/ Auxiliary variable
Coronary angiography	Categorical	12.7	Polytomous regression
Coronary intervention	Categorical	18.6	Polytomous regression
Cardiac rehabilitation	Categorical	11.5	Polytomous regression

Abbreviations: ECG, Electrocardiogram; CABG, coronary artery bypass graft; PCI, percutaneous coronary intervention; ARB, angiotensin receptor blocker; ACE, angiotensin converting enzyme.

Table 3.4. Imputation Strategy for **objective 4** (§2.3.1).

Variable	Variable Type	Missing (%)	Imputation method
Cardiac arrest	Binary	3.6	Logistic regression
Uncensored peak troponin measurement in ng/ml	Continuous	11.9	Predictive mean matching
Age	Continuous	0.07	Predictive mean matching
Systolic blood pressure	Continuous	19.5	Predictive mean matching
Heart rate	Continuous	19.6	Predictive mean matching
Loop diuretic used	Binary	17.4	Logistic regression
Creatinine level	Continuous	17.8	Predictive mean matching
Ethnicity	Categorical		Polytomous regression
Sex	Binary	0.3	Logistic regression

Variable	Variable Type	Missing (%)	Imputation method
Index of multiple deprivation score	Continuous	5.8	Predictive mean matching
Derived identification	Continuous	0	Predictor/ Auxiliary /Partially Observed
Arrival year	Continuous	0	Predictor/ Auxiliary /Partially Observed
Nelson-Aalen survival estimate	Continuous	0	Predictor/ Auxiliary /Partially Observed
Censoring indicator	Binary	0	Predictor/ Auxiliary /Partially Observed
Hypercholesterolaemia	Binary	12.2	Predictor/ Auxiliary and Default imputed
Previous hypertension	Binary	9.6	Predictor/ Auxiliary and Default imputed
Peripheral vascular disease	Binary	12.9	Predictor/ Auxiliary and Default imputed
Cerebrovascular disease	Binary	11.5	Predictor/ Auxiliary and Default imputed
Chronic obstructive pulmonary disease or asthma	Binary	12.1	Predictor/ Auxiliary and Default imputed
Smoker (current or previous smoker vs. non-smoker)	Binary	5.9	Logistic regression
Diabetes mellitus	Binary	4.0	Predictor/ Auxiliary and Default imputed
Family history of chronic heart disease	Binary	20.1	Predictor/ Auxiliary and Default imputed
Care by cardiologist	Binary	39.1	Predictor/ Auxiliary and Default imputed
Chronic renal failure	Binary	11.6	Predictor/ Auxiliary and Default imputed
Electrocardiogram appearance	Categorical	5.8	Polytomous regression
Aspirin at discharge	Categorical	7.9	Polytomous regression
$P2Y_{12}$ inhibitors at discharge	Categorical	34.7	Polytomous regression
ACEi/ARBs at discharge	Categorical	9.2	Polytomous regression
Statins at discharge	Categorical	8.2	Polytomous regression
Coronary angiography	Categorical	6.1	Polytomous regression
Enzyme elevation	Binary	6.0	Predictor/ Auxiliary variable
Admission diagnosis	Categorical	0.02	Predictor/ Auxiliary variable
Care by cardiologist	Binary	8.4	Logistic regression
Admitting consultant	Binary	5.4	Predictor/ Auxiliary variable
Discharge diagnosis	Binary	0	Predictor/ Auxiliary variable
Serum cholesterol	Continuous	31.3	Predictor/ Auxiliary variable
Admission method	Categorical	66.9	Predictor/ Auxiliary variable
Coronary intervention	Categorical	19.7	Polytomous regression
β blockers at discharge	Binary	17.5	Logistic regression
Cardiac rehabilitation	Categorical	9.6	Polytomous regression

Abbreviations: ARB, angiotensin receptor blocker; ACE, angiotensin converting enzyme.

Prior to each imputation process a predictor matrix was constructed using the automated `predmatrix` command in R(113). The predictor matrix defines the variables that would be used as predictors in the imputation models(113). The i'th row of the matrix consist of zeros and ones, with a one in the j'th column indicating the j'th variable be used as a covariate when imputing the i'th variable(113). The variables included in the imputation models were confirmed to be predictive of the missingness which confirmed that the MAR missing mechanism assumption was plausible in this instance so as the application of MICE as a method to handle the missing data.

The choice of number of imputations is usually governed by the proportion of missing data (114). There is inconclusive evidence in literature on the level of missingness in the data that is appropriate for the application of MICE. Some studies have suggested that if the level of missingness is >70% more imputations than the five imputed datasets that have been suggested in literature should be carried out(115). However, with the use of a greater number of imputed datasets, factors such as, reproducibility of the results and computational time to run the imputation model (especially when the dataset is large) have to be considered. Most of the variables considered to be imputed for the work of the thesis had <45% missing data with only two variables having >60%.

Monte Carlo error estimates were used to assess the reliability and consistency of the imputation results. These error estimates reflect the variability of the imputation results which is useful for determining whether an adequate number of imputation datasets were used to create stable results(112). In this thesis Monte Carlo errors less than 10% of the estimated standard errors gave evidence that the imputed datasets used gave stable estimates of the results(107). Ten imputation datasets were found to suffice for the analyses after considering reliability of the findings as well as computational time and power required to run the imputation

models. The parameter estimates from the analyses were pooled using Rubin's rules (111) over the imputed datasets using the `mi estimate` in Stata command. Using Rubin's rules the pooled estimate is derived as an average of the estimates from each of the multiple imputations datasets(111). The within-imputation variance and between-imputation variance are estimated and the total variance associated with the pooled estimate is the total(111).

3.6 Objective 1: Quantifying excess mortality associated with sub-optimal implementation of care of NSTEMI patients and determining predictors of sub-optimal care.

This section details the analyses methods that were carried out for objective one of the thesis i.e. to quantify the excess mortality (avoidable deaths) associated with receiving sub-optimal care after suffering an NSTEMI. Initially the derivation of the analytical cohort (§3.6.1) will be described, followed by model selection (§3.6.2), model assessment (§3.6.3), and finally, avoidable deaths estimation (§3.6.4).

3.6.1 Analytical cohort derivation

Of the 787,202 AMI patients recorded in MINAP, 441,945 had a discharge diagnosis of NSTEMI. The final analytical cohort of n=389,057 was arrived at after excluding 31,321 (7.1%) patients because they died in hospital and 21,567 (4.9%) patients due to missing death data Figure 3.2. Patients who died in hospital were excluded as it was not possible to determine their receipt of pharmacological therapies upon discharge from hospital. Patients with missing mortality data were excluded as it was difficult to ascertain their mortality data and a correctly imputed outcome adds nothing except Monte Carlo error, whereas an incorrectly imputed outcome adds more error(105).

As previously reported in §3.5.2 missing data were imputed using MICE in R software and details of the strategy are mentioned in §3.5.2.

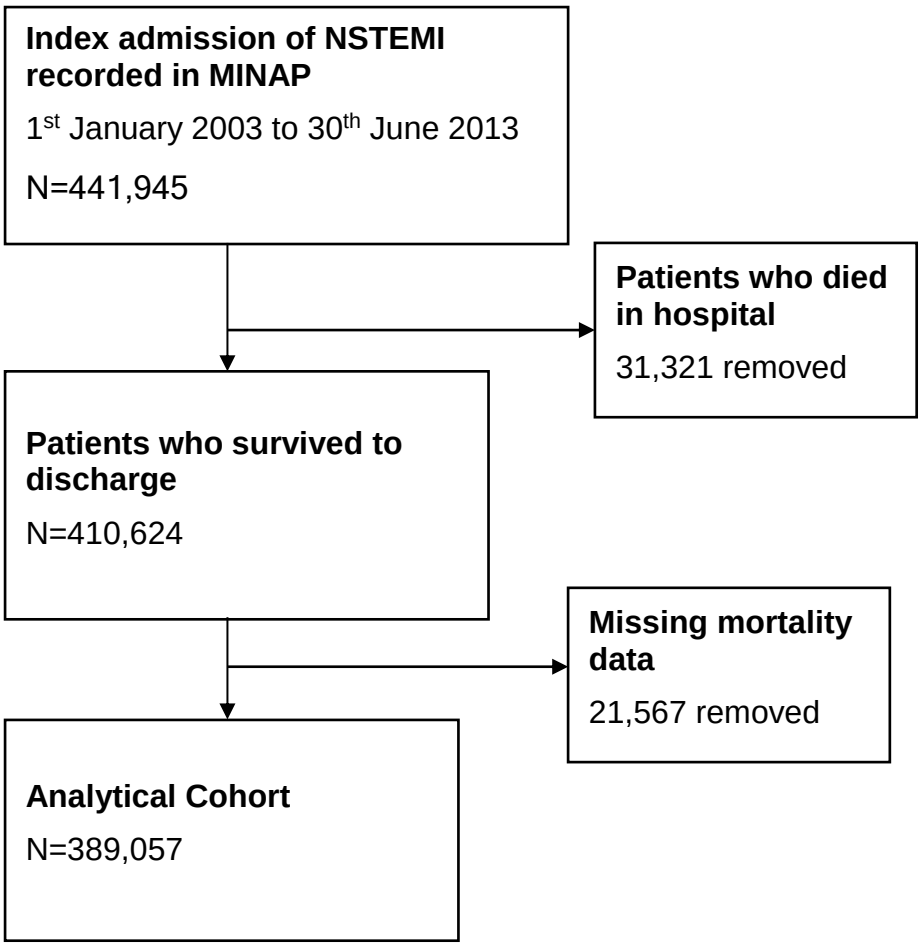


Figure 3.2 Analytical cohort derivation flowchart. STROBE diagram showing the derivation of the analytical cohort from the Myocardial Ischaemia National Audit Project (MINAP) dataset.

3.6.2 Model selection process for objective 1

3.6.2.1 Survival analysis

Time to event data analysis was conducted initially using the Cox Proportional Hazard (PH) model to investigate the association between receiving sub-optimal care (defined by all-or-none scoring/defect-free scoring and latent classes) and time to all-cause mortality. The advantage of using the Cox PH model is that it is a semi-parametric approach, the distribution of the baseline hazard function does not have to be specified in the model and is estimated non-parametrically(116). However the Cox PH assumption must not be violated for inference to be accurate. The Cox PH model assumes that the effects of the covariates in the model are the same throughout the study or follow-up time(116). The proportional hazards assumption was assessed using the log cumulative hazard plots for each variable adjusted for in the model. For categorical covariates the log cumulative hazard plots enable a visual test of the proportional hazards assumption by plotting –log[-log S(t)] against time for each strata of each covariate(117).

The PH assumption was found to be violated and the log-log plots for the variables for which the assumption was violated (shown by the non-parallel or crossing curves) are presented in Figure 3.3, Figure 3.4, and Figure 3.5. After the PH assumption for the Cox PH model was violated, the Cox model with time-dependent covariates was implemented using the `tvc` option in Stata software. However, model convergence problems were encountered as the survival models became more complex by the introduction of each time varying covariate. Since the semi-parametric model could not be used a parametric approach had to be implemented. Unlike semi parametric approaches, parametric approaches assume a distribution for the baseline hazard function. However assuming a distribution for the baseline hazard is a limitation because if there is misspecification of the baseline hazard in the modelling this may potentially bias the estimates.

Accelerated Failure Time models (AFT)(118) were employed instead. The AFT model was used because it has been proposed as an alternative to the Cox PH model in literature(118-120). The AFT model quantifies the impact on survival time using Time Ratios (TR), by measuring the effect of the exposure of interest on the mean survival time(118). The TR gives an intuitive summary measure of survival that is more interpretable in a clinical setting as it is based on survival time instead of hazard(118, 121). The TR is the estimated ratio of the expected survival times of two groups. A TR greater than one for a covariate indicates that this covariate prolongs expected survival time and a TR less than one indicates decreased expected survival time. For example, if missing one or more care interventions decreases survival by 70%, the estimated TR would be 0.30.

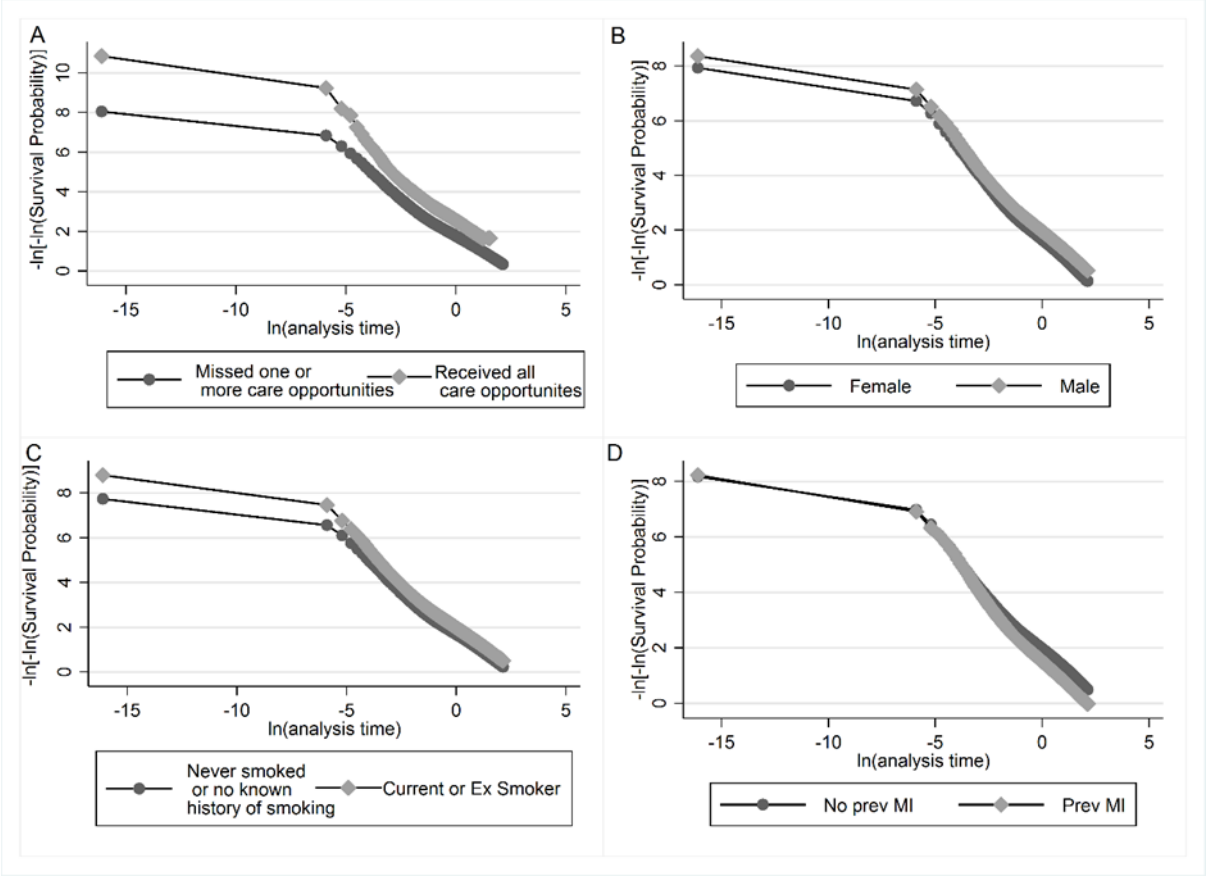


Figure 3.3 Log-log plots for variables: A) optimal care, B) sex, C) smoking status, and D) previous myocardial infarction.

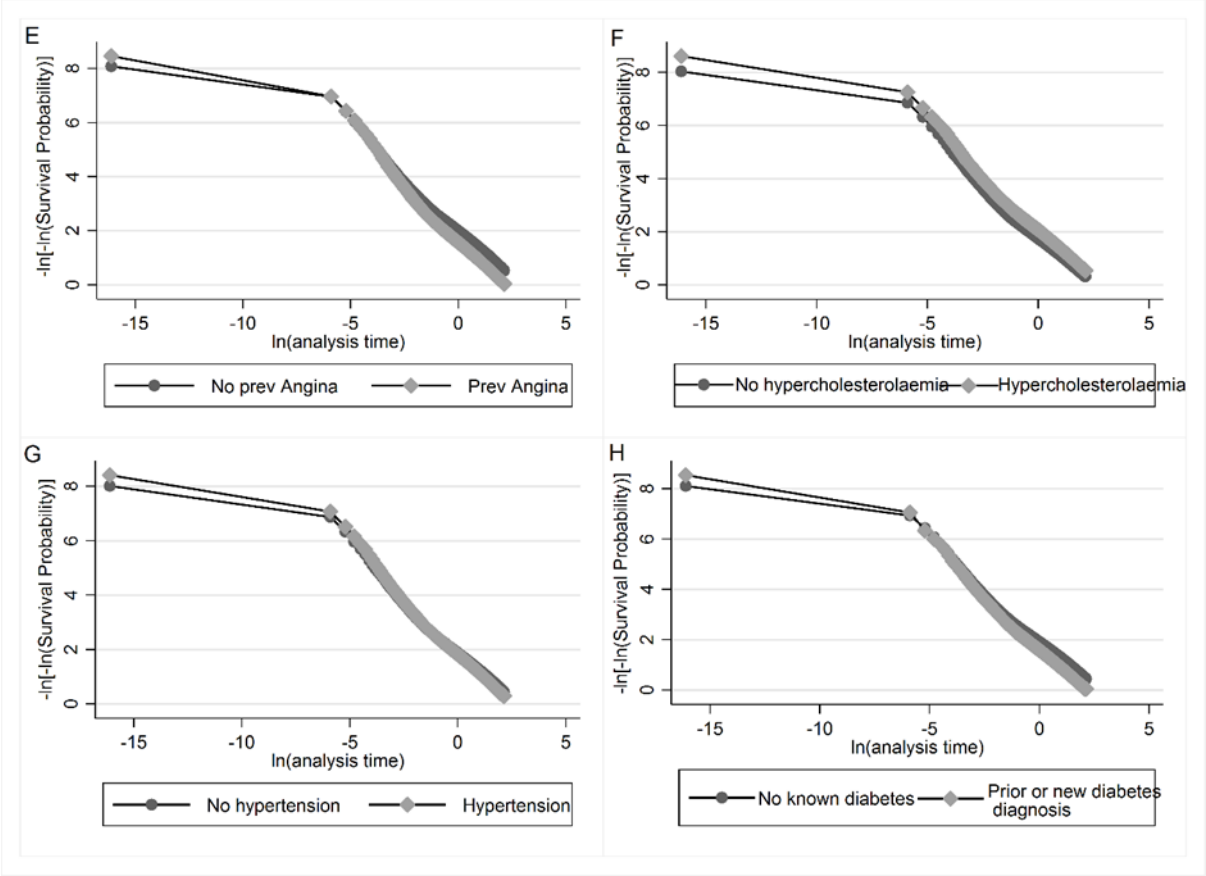


Figure 3.4 Log-log plots for variables: E) previous angina, F) hypercholesterolemia, G) hypertension, and H) prior or new diabetes.

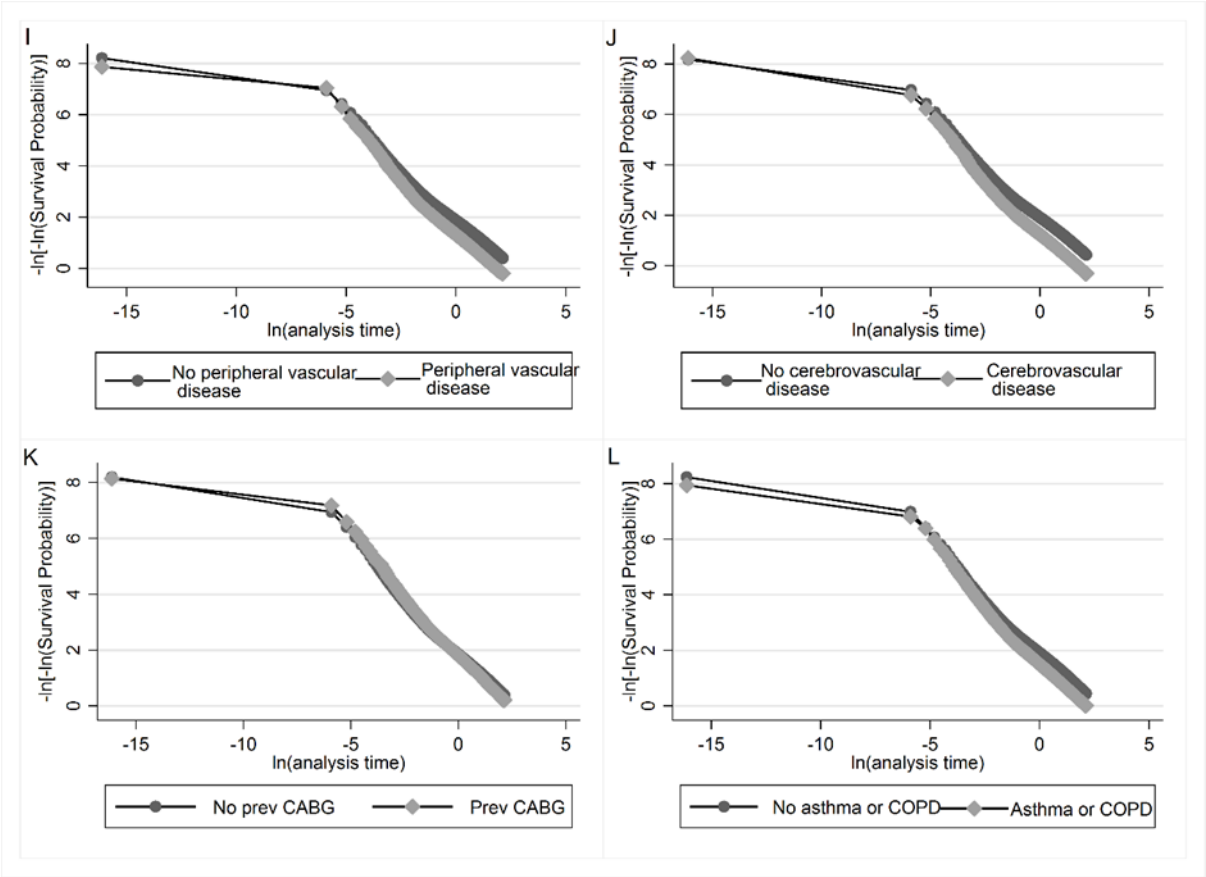


Figure 3.5 Log-log plots for variables: I) peripheral vascular disease, J) cerebrovascular disease, K) asthma/ COPD, and L) prior or previous CABG.

MINAP data consists of patients nested within hospitals, thus to account for the multilevel structure of the data, the shared frailty AFT models were used. Failure to account for the clustering in the data will bias the statistical inference by underestimating the standard errors. Thus all the models comprised of a shared frailty term to account for the hierarchical structure of the data.

The shared frailty AFT models were adjusted for case mix using the adjusted six-month mini–GRACE risk score (categorised in line with NICE guidelines (16) as lowest (≤70), low (71 to 87), and intermediate to high risk (>88)) (31), the 2010 Index of Multiple Deprivation (IMD) score (categorised according to the 2010 cut-offs), previous history of AMI, cerebrovascular disease, angina, previous CABG, diabetes, hypertension, peripheral vascular disease, a family history of CHD, COPD/asthma, hypercholesterolaemia, and previous coronary revascularisation. Details of the adjusted six-month mini-GRACE risk score are given in §1.5.3, in Chapter one. Methods commonly used for variable selection such as forward, backward and stepwise selection approaches were not used as they are data driven approaches that could result in omission of key variables for case mix adjustment as choice of inclusion is based on a pre-specified significance level which does not take into account clinical expert opinion(116). DAGs could have been used to determine the minimal adjustment set of confounder variables to adjust for in multivariable analyses. However for this objective DAGs would have not been suitable to inform variable selection for the modelling as they are more suited for use in instances where there is one main exposure not a composite exposure derived from multiple indicators. The main exposure for this objective was a composite score of receipt of care derived from 13 variables and latent classes of receipt of care.

Establishing causal relationships between covariates and a composite exposure of treatment can be difficult as there is limited evidence for such

causal links in literature, unlike if one is considering causal relationships between covariates and individual guideline-indicated care interventions. The utility of DAGs in identifying confounders is reliant on prior knowledge and assumed causal effects(122). Deriving a DAG with limited knowledge on the causal mechanisms can result in inaccurate determination of minimal adjustment set of confounders thus introducing more bias to the parameter estimates of the findings. Thus, for the work for this thesis DAGs were not implemented. The choice of potential confounders adjusted for in the models that were fitted for objective one was based on clinical input from Professor CP Gale and past literature reviewed in Chapter two.

Fifteen shared frailty AFT models were fitted, 13 models for each of the considered guideline-indicated care interventions to assess the impact of each of the care interventions on survival as well as one for the dichotomised receipt of optimal care (**primary outcome model**), and one for the latent class receipt of care. All the shared frailty AFT models were adjusted for the case mix variables mentioned above. The separate individual assessment models for each care intervention were fitted to assess the impact of each of the care interventions on survival as using aggregate composite measures only suffers the weakness that it weights less important commonly prescribed care interventions equally to infrequently prescribed more important care interventions, as a result making it difficult for clinicians and policy makers to determine specific targets for quality improvements in receipt of care. Individual assessments of the care interventions were conducted to determine the robustness of the composite measure, as the measure maybe degraded if the included individual care interventions used to derive it have weak associations with the outcome of interest.

3.6.2.2 Patient-level predictors of optimal care for NSTEMI

To determine patient level predictors of optimal care for NSTEMI, a descriptive table of patient baseline characteristics by the dichotomised “all-or-none” receipt of optimal care variable, and by the determined latent

classes of receipt of care was produced as an exploratory approach. Data exploration using descriptive statistics was followed by fitting logistic regression models to determine the predictors of receipt of optimal NSTEMI care. Logistic regression models were fit for the “all-or-none” receipt of optimal care binary variable and for the individual care interventions separately. Detail on the variables that were investigated as potential predictors for this objective are given in Table 3.5. The omitted variables for each care intervention were excluded because the variable was part of the eligibility criteria for the care intervention.

Table 3.5 Potential predictor variables for receipt of optimal care and each guideline indicated care interventions.

	Care interventions													
	Optimal care	ECG	Acute aspirin	ACEi/ ARBs	β blockers	Statins	$P2Y_{12}$ inhibitors	Aldosterone antagonist	Echo	Coronary angio	Aspirin	Smoking cessation advice	Dietary advice	Cardiac rehab
Predictors														
Age	×	✓	✓	✓	✓	✓	✓	✓	✓	×	✓	✓	✓	✓
Sex (male vs female)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Deprivation (IMD)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Cardiovascular History														
Myocardial infarction	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Congestive cardiac failure	×	✓	✓	×	×	✓	✓	×	✓	×	✓	✓	✓	✓
PCI	×	✓	✓	✓	✓	✓	✓	✓	✓	×	✓	✓	✓	✓
CABG	×	✓	✓	✓	✓	✓	✓	✓	✓	×	✓	✓	✓	✓
Angina	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Cerebrovascular disease	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Peripheral vascular disease	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Cardiovascular Risk Factors														
Diabetes	×	✓	✓	✓	✓	✓	✓	×	✓	×	✓	✓	✓	✓
Chronic renal failure	×	✓	✓	✓	✓	✓	✓	×	✓	×	✓	✓	✓	✓
Hypercholesterolaemia	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

	Care interventions													
	Optimal care	ECG	Acute aspirin	ACEi/ ARBs	β blockers	Statins	$P2Y_{12}$ inhibitors	Aldosterone antagonist	Echo	Coronary angio	Aspirin	Smoking cessation advice	Dietary advice	Cardiac rehab
Predictors														
Hypertension	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Current/ ex-smoker	×	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	×	✓	✓
Asthma or COPD	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Family history of CHD	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Care by cardiologist	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Presenting Characteristics														
Systolic blood pressure (<90 mmHg)	×	✓	✓	✓	✓	✓	✓	✓	✓	×	✓	✓	✓	✓
Heart rate (>110 bpm)	×	✓	✓	✓	✓	✓	✓	✓	✓	×	✓	✓	✓	✓
Peak troponin (≥ 0.06)	×	✓	✓	✓	✓	✓	✓	✓	✓	×	✓	✓	✓	✓
Creatinine (>200 (μmol/l))	×	✓	✓	✓	✓	✓	✓	×	✓	×	✓	✓	✓	✓
Use of a loop diuretic	×	✓	✓	✓	✓	✓	✓	×	✓	×	✓	✓	✓	✓
Cardiac arrest	×	✓	✓	✓	✓	✓	✓	✓	✓	×	✓	✓	✓	✓

✓ predictor variable included in model as potential predictor; × predictor variable not included as it is part of the eligibility criteria for the care intervention.

Abbreviations: IMD, Index of multiple deprivation; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; coronary heart disease; COPD, chronic obstructive pulmonary disease; Echo, echocardiography.

3.6.3 Model assessment for objective 1

3.6.3.1 Parametric survival analysis

Parametric survival analysis assume several distributions for the baseline hazard function and these include the exponential, Weibull, Gompertz, log-logistic and generalised gamma distributions(116). Preliminary models were fit in order to determine the distribution of the survival times that best fit the data. The distributions explored and combination frailty distributions are summarised in Table 3.6. The default gamma distribution for frailty was adopted as the alternative inverse Gaussian distribution option models all failed to converge.

Table 3.6 Model fit diagnostics for the Shared frailty AFT models

Model		**Model fit criteria**
Distribution	**Frailty**	**BIC**
Weibull	Gamma	142263.6
Exponential	Gamma	146808.2
Log logistic	Gamma	141736.2
Log normal	Gamma	141338.4

Abbreviations: BIC, Bayesian Information Criteria.

The selected model was selected based on the minimisation of the BIC. According to the BIC criterion, the log normal distribution was the appropriate distribution to assume as it had the minimum BIC.

3.6.3.2 Patient-level predictors of optimal care for NSTEMI

As previously described in §3.6.2.2, a logistic regression model was fitted to investigate the patient level predictors of receipt of optimal care for NSTEMI patients. Model fit for the logistic regression models was assessed using the Hosmer-Lemeshow test (123), discriminatory power (the sensitivity versus one minus specificity) of the model was assessed using Area Under the Receiver Operator Curve (AUROC) (also known as the C statistic), and Pseudo R squared(124). Good models have a discriminatory C statistic of >0.80, Pseudo R squared (usually ranges from 0 to 1) higher values indicate better model fit and a non-significant Hosmer-Lemeshow *P*

value >0.05. The Hosmer-Lemeshow test goodness of fit test, tests the null hypothesis that the observed probability of the event (receipt of care) and the expected probability of the event obtained from the model are the same, such that a non-significant result provides no evidence against model fit(123). These thresholds were used in this thesis to judge the goodness of fit of the logistic regression models that were used. The results are summarised in Table 3.7. The discriminatory power of the fitted models were low, with only models for $P2Y_{12}$ inhibitors prescription at discharge, smoking cessation advice, dietary advice, and recording of an electrocardiogram being having an ROC >0.80. The low pseudo-R^2 values observed for the models strongly indicated that some important predictors beyond the ones evaluated were missing. However, because the covariates included in the models were statistically significant therefore important conclusions could still be drawn from them in terms of the covariates associated with receipt of care for NSTEMI patients.

Table 3.7 Model fit statistics for the logistic regression models

Predictor model for:	Hosmer-Lemeshow test P value	C-statistic	Pseudo-R^2
Optimal care	<0.001	0.77	0.190
ECG	<0.001	0.82	0.183
Acute aspirin	0.234	0.63	0.029
ACEi/ARBs	<0.001	0.59	0.022
β blockers	<0.001	0.63	0.045
Statins	<0.001	0.66	0.050
$P2Y_{12}$ inhibitors	<0.001	0.82	0.315
Aldosterone antagonist	0.141	0.70	0.087
Echocardiography	<0.001	0.62	0.033
Coronary angiography	<0.001	0.76	0.154
Aspirin	<0.001	0.65	0.039
Smoking cessation advice	<0.001	0.88	0.329
Dietary advice	<0.001	0.81	0.287
Cardiac rehabilitation	<0.001	0.66	0.052

Abbreviations: ARB, angiotensin receptor blocker; ACE, angiotensin converting enzyme; ECG, electrocardiogram.

3.6.4 Avoidable deaths estimation

In order to calculate the avoidable deaths associated with NSTEMI patients not receiving optimal care (receiving all guideline-indicated care interventions for which they were eligible), a method developed by Ford et

al(125). was used as it has been used by previous studies to estimate avoidable deaths associated with sub-optimal care(52). The risk associated with receiving sub-optimal care (adjusted time ratios derived from the shared frailty AFT survival models, (a)), was multiplied by the total number of NSTEMI admissions from 2003-2013 (b). The product was then multiplied by the proportion at risk (c) that is the proportion of NSTEMI patients who had received sub-optimal care. The resultant figure was then multiplied by the 12-month case fatality rate (d) for the NSTEMI patients who had received sub-optimal care. The formula to summarise the method is given below:

$$Avoidable\ deaths = a \times b \times c \times d \qquad 3.1$$

For example in chapter 4, the results show that not receiving OMT reduces time to death by 56% (a=0.44), 86.9% of the NSTEMI patients did not receive OMT (b=0.87), total number of NSTEMI admissions for the study duration was 389,057 (d=389,057), and the sub-optimally managed patients' 12 month case fatality rate was 22.1% (c=0.22). Calculating the total number of avoidable/premature deaths using formula 3.1 would give:

$\big((0.44 \times 0.87)\big) \times 0.22 \times 389{,}057$ =32,765 avoidable/preventable deaths. The same approach was adopted for calculating potential avoidable deaths that were associated to being in a latent class of sub-optimal care compared to being in a latent class of high receipt of care, by substituting the appropriate time ratio into the formula.

3.7 Objective 2: Assess geographic variation in receipt of care for NSTEMI patients and, predominantly, to develop an online, interactive platform.

This section details the analyses that were carried out for objective two of this thesis, to investigate the geographical variation in receipt of care for NSTEMI patients. The analyses were conducted using the same analytical

cohort that was used for objective one of the thesis (§3.6.1). Objective two of the thesis was an extension of objective one in order to assess the geographic variation in receipt of care for the NSTEMI patients. The analytical cohort data was geocoded and linked to boundary data of the areas under investigation in order to allow the for the geographic variation assessment in receipt of NSTEMI care. The UK boundary data used were of the 211 Clinical Commissioning Groups (CCGs) and 12 Strategic Clinical Networks (SCNs).(126) These data boundaries were selected because for the NHS of England the CCGs working in partnership with hospitals via SCNs are responsible for commissioning the management of AMI.(126) This section of the methodology chapter will detail the geocoding information of the data(§3.7.1), temporal trends assessments methodologies used(§3.7.2), model selection process(§3.7.3) and model assessment for the statistical analyses(3.7.4).

3.7.1 Data geocoding and quality of care

The analytical cohort data was geocoded and linked to the April 2015 Geographic Information System CCGs and SCNs layer data which were accessed from NHS England.(127) As MINAP data was anonymised, full patient postcodes were not available. Instead, the data were mapped by the aid of eastings and northings recorded in MINAP. The eastings and northings of the centroid of the output area of residence shared between one and 80 addresses are made available in MINAP data to enable geographic mapping(39). Of the 389,057 NSTEMI patients, 357,228 were mapped successfully to boundary data. The failure to map of the other observations was due to missing eastings and northings information to geocode on. To assess the geographic variation in receipt of guideline-indicated care interventions for NSTEMI choropleth maps were created using ArcGIS version 10.2.2.

Two composite measure approaches were used to define quality of care for objective 2 of this thesis, and these are opportunity scoring and the all-or-

none scoring/defect-free scoring (described in §3.4.1, earlier). Briefly, opportunity scoring composite measure was derived by dividing the total number of patients who received a care intervention by CCGs and SCNs (numerator) by the total number of patients eligible for the care intervention in the CCGs and SCNs (denominator)(95). The opportunity score by CCGS and SCNs was derived for receipt of optimal care variable (receiving all (up to 13) guideline-indicated treatments for which patients were eligible) (derived using the all-or-none scoring/defect-free scoring)), as well as for each of the 13 considered guideline-indicated care interventions. To aid categorisation and presentation on the choropleth maps the opportunity scores data were divided into quintiles. Also for descriptive purposes cut-offs that are frequently used by other studies in past literature were used to categorise the score (high receipt (>79%), intermediate (40 to ≤79%), and low (≤40%))(67, 128).

3.7.2 Temporal changes assessments methodologies

In order to determine whether there were any improvements in guideline recommended care over time, temporal trends in receipt of care were assessed. The Spearman's correlation coefficient was used to assess the correlation of receipt of care in the earlier years (2003-2004) compared to the later years (2012-2013) by CCGs as the receipt of care distribution was skewed thus the Pearson's correlation test could not be used as the test requires the data to be normally distributed. A correlation coefficient close to 1 indicated strong correlation.

3.7.2.1 Web platform development

Evaluation of receipt of care for AMI patients' needs to be an on-going process to guarantee continuous assessment in AMI management. In order to allow for this on-going assessment a platform termed "Cardiovascular Landscapes: Using Data to Improve Cardiovascular Care and Outcomes" was created. This work was done in collaboration with the Leeds Institute for Data Analytics (LIDA) IT team. The platform was created to aid better data visualisation and aid wider dissemination of the results from the

assessment of geographic variation in receipt of care. The platform will be used by patients as well as clinicians and commissioners to allow them the opportunity to identify variation and take action to reduce unwarranted variation in AMI care within or between their localities and other areas of the country such that new policy initiatives can be implemented to improve quality of care for AMI patients. Receipt of care data of the 13 guideline-indicated care interventions was uploaded on to the interactive web platform and presented on choropleth maps, heat maps over time and summary statistics by CCGs.

Optimal care was derived based on the opportunity scoring composite measure that is dividing the total number of patients receiving optimal care (derived using the all-or-none scoring/defect-free scoring) in a CCG by the total number of NSTEMI patients in the CCG over a time period from 2010-2013. The opportunity scoring approach was also used to derive receipt of the 13 guideline-indicated care interventions by CCGs over a time period from 2010-2013. Besides the care interventions more variables were added for presentation on the platform to give the patient profile per area and these included comorbidities: diabetes, COPD/asthma, chronic heart failure, chronic renal failure, peripheral vascular disease and hypertension. A high resolution investigation into Yorkshire and Humber was undertaken as was commissioned by NHS England. Receipt of care data was assessed for a period from 2003-2013, for 49,499 NSTEMI patients. For each of the care interventions that were assessed, a proportion was derived for receipt of care at CCG level. Similar to the Cardiovascular Landscapes web development, the 13 guideline-indicated care interventions and optimal care were assessed. The care interventions were described by numbers and percentages, means and standard deviations or medians and IQRs for normally and non-normally distributed continuous data, respectively. These data were presented in funnel plots and temporal trend line graphs. Choropleth maps were used to show the distribution of receipt of guideline-indicated treatments using ArcGIS and class intervals with equal cut-offs for categorisation were used. In order to assess hospital performances funnel

plots(129) were employed. The standardised receipt of care ratios (SRR) were derived by dividing the observed receipt of care rates by the expected receipt of care rates (derived from a multilevel Poisson model adjusted for age, sex and year of admission), The SRRs were plotted against the total number of patients eligible for each care intervention by Clinical Commissioning Groups (CCG) (volume by CCG) and superimposing 95% (2 standard deviation) and 99.9% (3 standard deviations) control limits around the overall receipt of care rates. CCGs performing well were plotted within and over the upper control limits with underperforming CCGs plotted outside and under the lower control limits. The results were summarised in a report titled “Acute Myocardial Infarction: A Report of Care in Yorkshire and Humber, 2003-2013” and the first user feedback session was held on the 3rd of May 2017 at the University of Leeds. Both the “Cardiovascular Landscapes: Using Data to Improve Cardiovascular Care and Outcomes” platform and Yorkshire and Humber report are still under development and are yet to be released for wider dissemination to the public.

3.7.3 Model selection process for objective 2

As mentioned earlier in §2.3.1, objective two of the thesis was to assess geographic variation in receipt of care for NSTEMI patients and determine whether the source of variation in receipt of guideline indicated care for NSTEMI patients was as a result of differing management at hospital level or differing planning and commissioning of health care services at CCGs or SCNs level. To assess the source of variation in rates of receipt of care Poisson regression modelling was undertaken. The outcome variable was (receipt of care: derived by using the opportunity scoring approach) was modelled as a count variable with a conditional Poisson distribution and all NSTEMI patients in the cohort as the exposure. The Poisson model was chosen because it is used for modelling count data(130). Furthermore Poisson regression has several extensions that can prove useful when analysing count data and these include: negative binomial regression which can be employed for over dispersed count data, zero-inflated regression models which can be employed to account for excess zeros in count data,

and ordinary least squares (OLS) regression which can only be employed if the count data follow a normal distribution(130). Hierarchical modelling also known as multilevel modelling was taken as the data were hierarchical constituting patients nested within hospitals, hospitals nested within CCGs and CCGs nested within SCNs. Ignoring the hierarchical nature of the data was considered inappropriate as this may result in underestimation of regression coefficients standard errors thereby inflating type 1 errors.

A multilevel Poisson model with fixed effects and random effects was fitted. The random effects partition variance into within unit and between unit variation hence known as variance components. The patient baseline characteristics described in §3.6.2.1 were adjusted for in the model. Model convergence issues were encountered such that the model had to be run using the `meqrpoisson` Stata command to aid model convergence. The Interclass Correlation Coefficient (ICC) derived from the regression modelling was used to quantify the proportion of variation in receipt of guideline indicated care interventions attributable to hospitals, CCGs and SCNs, respectively. The ICC is the proportion of variance that is explained by the grouping structure of the multilevel model and it is calculated as a ratio of group level error variance over the total error variance(131). The ICC reports the amount of variation unexplained by any predictors already adjusted for in the model that can be attributed to the grouping variable, as compared to the overall unexplained variance(131). Avoidable deaths at hospital level were also determined using the shared frailty AFT models.

3.7.4 Model assessment for objective 2

The goodness of fit for the Poisson model was tested using the `estat gof` command in Stata, which reports the Hosmer-Lemeshow goodness of fit test. The Hosmer-Lemeshow test goodness of fit test was described earlier on in §3.6.3.(123). The Poisson model fit the data well (P-value not significant). Violation of the non-over dispersion assumption of the Poisson model often means implementation of the negative binomial model instead.

In this thesis there was evidence of overdispersion hence the multilevel negative binomial model was fitted as a sensitivity analysis (using the `menbreg` Stata command). Due to the complex nature of the model serious convergence problems were encountered such the model took over three weeks to run without converging ultimately. Due to the convergence limitation of the multilevel negative binomial model, the multilevel Poisson model was by default used as the regression model of choice. The results obtained made sense clinically and the modelling approach was adopted. OLS regression could not be considered as the data were skewed.

3.8 Objective 3: Investigating the association of clinical factors and therapeutic strategies with improvements in survival following STEMI.

Previous studies have assessed quality of care and associated outcomes for STEMI patients as well as predictors of receipt of STEMI care.(61) Still following the quality of care and impact on mortality framework, objective three of the thesis focused on determining the factors (i.e. changes in patient demographics, comorbidities, pharmacological and reperfusion treatments) associated with the temporal improvements in six months and one year mortality that have been observed over the last decade (between 2004 and 2013) for STEMI patients. This section details the analyses that were carried out for this objective. Initially the analytical cohort derivation will be described (§3.8.1), followed by the model selection process (§3.8.2) and model assessment detail (§3.8.3).

3.8.1 Analytical cohort derivation

The analytical cohort for the objective 3 of the thesis was derived from 272,263 STEMI admissions recorded in MINAP from January 2004-June 2013. For patients with multiple admissions the index event was considered in order to reduce potential bias from previous treatment. The derivation of

the analytical cohort to get to n=232,353 is shown in Figure 3.6. The reasons why patients with missing mortality data and those who had died in hospital were excluded for this thesis were mentioned earlier in §3.6.1. Missing data were imputed using MICE in R software and details of the imputation strategy are mentioned in §3.5.2.

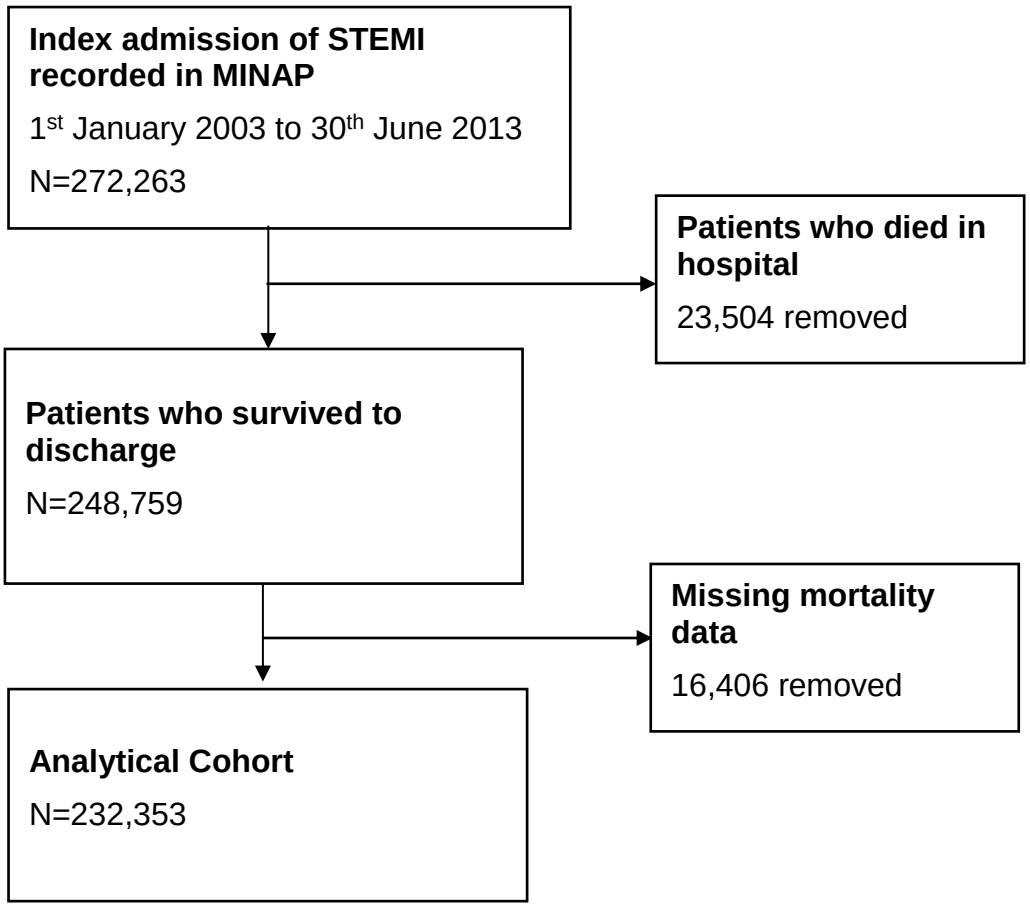


Figure 3.6 Analytical cohort derivation flowchart. STROBE diagram showing the derivation of the analytical cohort from the Myocardial Ischaemia National Audit Project (MINAP) dataset.

3.8.2 Model selection process for objective 3

3.8.2.1 Flexible parametric survival models

To investigate the association of clinical factors and therapeutic strategies with improvements in survival following STEMI, Royston-Parmar flexible parametric survival models (132) were adopted for the survival analysis. These models fall under the parametric time to event modelling approach but instead of assuming the baseline hazard function follows a pre-defined distribution, flexible parametric models model the shape of the baseline hazard using restricted splines(132). This allows for flexibility in the shape but restricts the function to be linear on the ends were the data is sparse(132). The conventional survival modelling approach Cox PH modelling was not employed due to the violation of the proportional hazards assumption. The primary outcome of interest was one year survival and the exposure of interest was year of admission to hospital.

The covariates that were included in the survival models comprised: patient demographics (age, sex, deprivation (2010 IMD score), cardiovascular risk factors (diabetes, hypercholesterolaemia, hypertension, smoking status, COPD, family history of coronary heart disease, chronic renal failure, chronic cardiac failure), cardiovascular history (cerebrovascular disease, peripheral vascular disease, previous angina, previous AMI, previous PCI, previous CABG), hospital discharge medications (statins, aspirin, $P2Y_{12}$ inhibitors, ACEi)/ARBs), year of admission to hospital, reperfusion (dichotomised to received PPCI or not) and cardiac rehabilitation. The discharge medication variables had to be included in the models as binary (receipt: yes/no), as including them as three level categorical variables (receipt: yes/no/contraindicated) was biasing the analysis in such a way that change in contraindication over time as well as prescription of the drugs was being captured. As a result masking the change in the prescription of the secondary drugs over time, of which this was one of the exposures of interest.

Twenty iterations of the survival models were run, the first model was a univariable unadjusted model including year of admission only (to determine the overall temporal trend by year), then a series of models (nine) including the following categories of variables individually (as well as year of admission) : reperfusion, comorbidities and risk factors, cardiac rehabilitation, aspirin at discharge, statin at discharge, $P2Y_{12}$ inhibitors at discharge, ACEi/ARBs at discharge, β-blockers at discharge and all the hospital discharge drugs (together rather than individually). Change in temporal trend by year was noted after addition of these categories of variables. To these nine models age, sex and IMD scores (demographics) were added and change in temporal trend was also noted after addition of these three variables. The final model then included all the considered variables. This pattern of adding variables to the model was followed in order to map out how the category of variables being added to the model affected temporal changes in one year survival. The flexible parametric models were fitted using the `stpm2` command for each imputation, and model estimates combined using Rubin's rules via the `mi estimate` command. The analysis was repeated but focusing on the secondary outcome, six month survival.

3.8.2.2 Mediation analysis

As a sensitivity analysis, mediation analysis was carried out to investigate the causal mechanisms by examining the role of the potential mediators (determined through flexible parametric modelling) thought to lie on the causal pathway between year of admission of the STEMI patients and survival (one year (primary outcome) and six months mortality). A mediating variable is a variable that appears on the causal pathway of an exposure outcome relationship (post-treatment variable that occurs before the outcome happens(133)) for example the variable M shown in Figure 3.7 is a mediator as it lies on the causal pathway between exposure T and outcome Y(134). Mediation analysis falls under the Structural Equation Modelling (SEM) framework and the illustration of mediation analysis given in this section follow that as in Linden et al.(134).

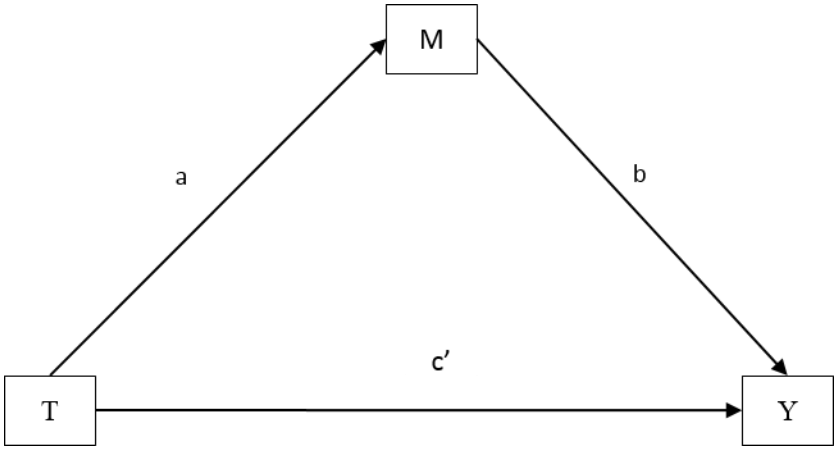


Figure 3.7 The conceptual mediation model with a single mediator.
where T: is treatment assignment.

M: is the mediating variable

Y: is the outcome

a,b,c': represent the SEM coefficients.

The mediating variable (M) explains the relationship between the dependent (T) and the independent variable (Y) . However it's not always the case that the mediator explains 100% of the relationship as there maybe other unmeasured mediators, such that the total treatment effects are the sum of both the direct (c) and indirect effects (a+b). The direct and indirect effects are quantified as illustrated by the equations below:

$$\mathrm{Y}_i = \alpha_1 + c\mathrm{T}_i + \beta_1\mathrm{X}_i + \varepsilon_i \qquad 3.2$$

$$\mathrm{M}_i = \alpha_2 + a\mathrm{T}_i + \beta_2\mathrm{X}_i + \varepsilon_i \qquad 3.3$$

$$\mathrm{Y}_i = \alpha_3 + b\mathrm{M}_i + c'T_i + \beta_3\mathrm{X}_i + \varepsilon_i \qquad 3.4$$

Equation 3.2 represents the outcome model estimating the average total effects of the intervention by regressing Y (outcome variable) on T (treatment variable) adjusted for X (pre-treatment covariates)(134).

Equation 3.3 represents the *a* pathway in Figure 3.7 in which M (mediating variable) is regressed on T (treatment variable) and X (pre-treatment covariates)(134). All the equations were adopted from Linden et al.(134)

Equation 3.4 represents both the *b* and *c'* pathways shown in Figure 3.7 which regress Y (outcome variable) on T (treatment variable), M (mediating variable) and X (pre-treatment covariates).

After modelling as shown in the equations, the mediated effects can be estimated using the "product of coefficients" approach or "difference in coefficients" approach. The "product of coefficients" approach uses the product of *a* and *b* paths to quantify the indirect effects (mediated effects) and the "difference in coefficients" subtracts the direct effects *c'* from the total effects *c*(135, 136). The total effect can also be quantified by adding the indirect and direct effects *(c=ab+c').*The advantage of using mediation analysis is that it not only gives point estimates of the mediation, but also the extent to which a variable mediates a relationship(134). The mediated effects are derived as a ratio of the indirect to the total direct effect and quantified as a percentage(134). The estimation described so far is for a single mediator model and in the event of multiple mediators, each mediator is regressed individually on the treatment (including pre-intervention characteristics) and then the outcome model regresses the outcome (Y) on all the mediators as well as on T and X(134).

The SEM approach described above utilizes the ordinary least squares regression with the assumption that the mediator and outcome variables are continuous, however for the thesis the outcome and potential mediators were binary hence an approach that is suitable for binary outcomes and mediators was needed. For the purpose of this thesis the mediation analysis was carried out using the R package; `mediation`(137). This R `mediation` package accommodates a larger class of statistical models but still based

on model-based causal mediation analysis under the assumption of sequential ignorability similar to the SEM approach(137). This is achieved through the `mediate` function(137). The mediation analysis was undertaken following a two-step approach represented by equations 3.2 and 3.3. A logistic regression model for the mediating models (equation 3.3) was fitted, as the potential mediators were binary. For the outcome models (equation 3.2), a Poisson regression modelling framework with log survival time as the offset was used. The Poisson modelling approach was undertaken as to the best of my knowledge there were no software packages available to fit flexible parametric survival models for mediation analysis).

The potential pre-treatment covariates that were used for the analyses include; age, IMD score, sex, previous history of AMI, angina, previous CABG, diabetes, hypertension, peripheral vascular disease, a family history of coronary heart disease, COPD/asthma, hypercholesterolaemia, and previous coronary revascularisation, chronic renal failure, elevated cholesterol, current or ex-smoker status, and cardiac rehabilitation. In addition to these covariates in the outcome model the discharge medications (aspirin, β blockers, ACEi/ARBs and statins) not determined as potential mediators.

The analyses were undertaken for the primary outcome one year mortality and secondary outcome six month mortality. Average Direct Effects (ADE) (represented by *c'* in Figure 3.7) and Average Causal Mediation Effects (ACME) (represented by paths *a* and *b*) were derived to quantify the percentage mediated by the potential mediator. The ACME and ADE are estimated under the potential outcomes framework whereby the impact of the mediator on the outcome is quantified comparing impact on outcomes if everyone in the population received treatment/mediating variable vs. if no one in the population received treatment/mediating variable(133). The potential outcomes come into play in the sense that not everyone has an

observed outcome if shifted to the different treatment groups other than their observed treatment group, thus the employment of counterfactual outcomes (potential outcomes)(133). Causal inference can only be concluded if the sequential ignorability assumption is not violated(134). The mediation analysis was only conducted on the complete STEMI cases only (n=82,637).

3.8.3 Model assessment for objective 3

The flexible parametric modelling used in this thesis employs cubic splines(132) to estimate the baseline hazard function. Cubic splines are defined as piecewise cubic polynomials with a separate cubic polynomial fit in a predefined number of intervals and the splits points for the intervals are known as knots(132). The cubic polynomial function being defined as shown in equation 3.5 below:

$$y = \beta_0 + \beta_1 x + \beta_2 x^2 + \beta_3 x^3 \qquad 3.5$$

The number of knots to be used is usually defined by the user thus optimal scale and complexity of the splines had to be estimated. The degrees of freedom of the spline part of the model were selected based on the minimisation of the AIC and BIC. These parameters were also used to select the scale part (the distribution of the baseline function) of the model. Scales that were considered included; normal, theta, odds and hazard scale. The degrees of freedom ranged from one to seven. Default knot positions corresponding to the best model according to the AIC and BIC were used.

In order to infer causal inference the mediation analysis main assumption is the sequential ignorability assumption. The sequential ignorability assumption assumes that the mediator is effectively randomly assigned given baseline covariates and the randomised treatment(134). There is no

formal test for this assumption however there is a sensitivity analysis for possible existence of unobserved covariates using the `medsens` function in R. However the sensitivity analysis could not be carried out for the mediation analysis carried out for this thesis work as it has only been developed so far to fit linear structural equation models framework(137).

3.9 Objective 4: Determining the efficacy of β-blockers during and after AMI in patients without heart failure or LVSD.

This section details the analyses that were carried out in order to determine the effectiveness of β-blockers in reducing mortality for AMI patients without heart failure or left ventricular systolic dysfunction (LVSD). Initially the analytical cohort derivation (§3.9.1) will be described, followed model selection (§3.9.2), and model assessment (§3.9.3) detail.

3.9.1 Analytical cohort derivation

The analytical cohort for this objective of the thesis was derived from 531,282 AMI admissions from MINAP. This cohort was derived from admissions recorded in MINAP from 2007-2013. This time period was considered as it is the era all major cardio-protective medications and care interventions were recommended in the guidelines and MINAP had minimal missing data. For patients with multiple admissions the index event was considered in order to reduce potential bias from previous treatment. The derivation of the analytical cohort to get to n=179,810 is shown in Figure 3.8.

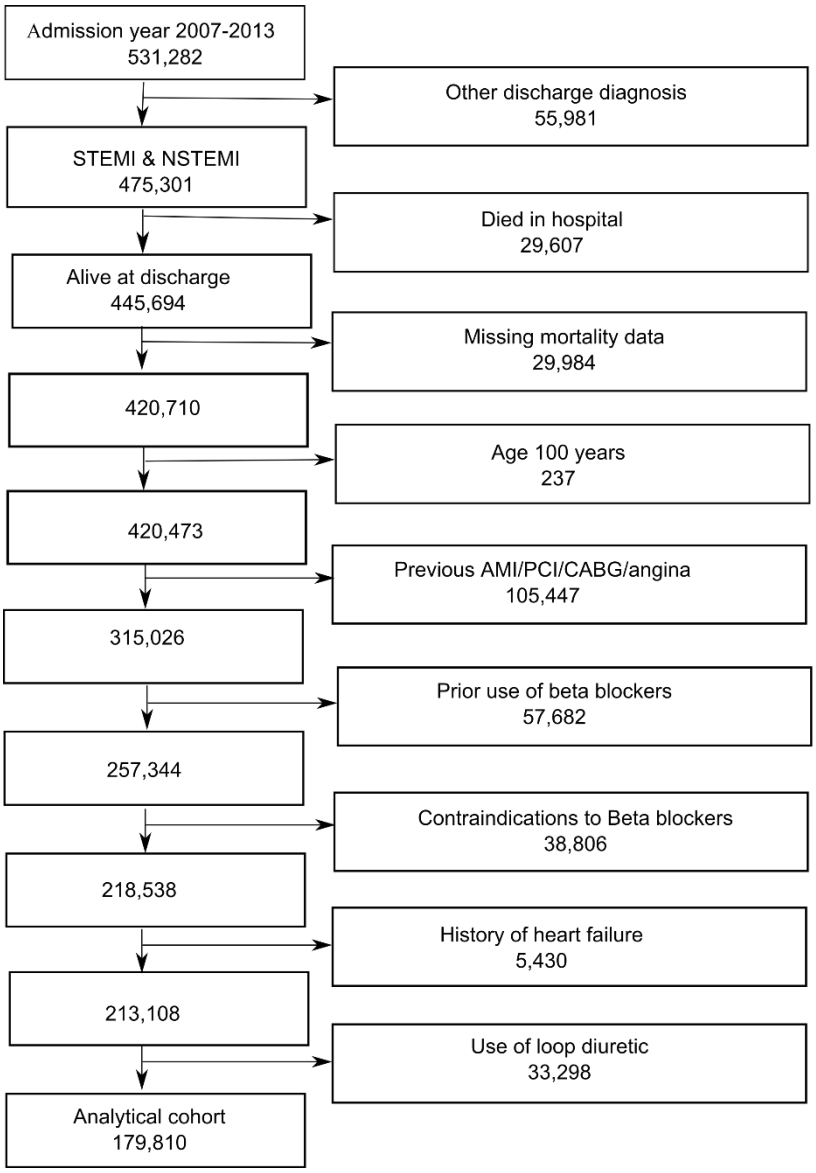


Figure 3.8 Analytical cohort derivation flowchart. STROBE diagram showing the derivation of the analytical cohort from the Myocardial Ischaemia National Audit Project (MINAP) dataset.

Patients with missing mortality data were excluded as it was difficult to ascertain their mortality data and a correctly imputed outcome adds nothing except Monte Carlo error, whereas an incorrectly imputed outcome adds more error(105). Those who had died in hospital were excluded also as it was difficult to ascertain their receipt of guideline-indicated care interventions. In order to minimise potential bias from prior β-blockers use, patients who had a prior use were excluded as well those with a previous history of AMI, angina and those who had received previous PCI and CABG. AMI patients eligible for the study were those without heart failure or LVSD, so patients with a history of heart failure and use of a loop diuretic were excluded.

Heart failure was defined as a previous history of heart failure as recorded in MINAP and also those used a loop diuretic (on admission and during admission) and/or left ventricular ejection fraction(LVEF) <30% as recorded in MINAP. The choice to use a cut off <30% LVEF than the <40% frequently used in literature was made due to data recording restrictions in MINAP. LVEF is recorded in MINAP as a categorical variable defined as 'good' for an LVEF ≥ 50%, 'moderate' for an LVEF 30-49% and 'poor' for an LVEF <30%. So it was difficult to assess LVEF at different cut-offs other than the ones given in MINAP. Ultimately, for the analysis for this objective LVEF <30% category was used to define heart failure. Although a cut off of <40% due to data restrictions could not be used, a sensitivity analysis using both the moderate (30-49%) and poor (<30%) LVEF categories to define heart failure was also performed. Missing data were imputed using mice in R and details of the strategy used are mentioned in §3.5.2. β blockers receipt was assessed as receipt of β blockers on hospital discharge unless contraindicated.

3.9.2 Model selection process for objective 4

Due to the causal inference nature of objective 4 of the thesis, the methods that account for treatment selection bias in observational studies had to be

considered. Literature has suggested propensity scoring and instrumental variable analysis as the best methods to employ for treatment effects studies(138, 139). Propensity scoring and instrumental variable analysis (as a sensitivity analysis) were adopted over the multivariable model risk adjustment (the conventional modelling approach) for the thesis.

Propensity scoring (with the propensity score been defined as the probability of receiving treatment conditioning on observed baseline patient characteristics (139)) only removes overt bias conditional on observed covariates, however because the propensity score model can be adjusted for as many observed patient characteristics as available if a large comprehensive dataset is used (in this instance MINAP registry) bias may be removed adequately. The score from propensity scoring is used to create comparable treatment groups in terms of baseline covariates by either matching, stratification, inverse probability of treatment weighting on the propensity score or covariate adjustment using the propensity score(139). For the thesis weighting using the inverse of probability of treatment was used. This is because inverse probability weighting is the most robust way of balancing covariates without losing patient information as matching and stratification involve excluding patients that fail to match on the propensity score, thereby potentially losing important information as well as reducing study power. The primary outcome for this objective of the thesis was one year all-cause mortality. Secondary outcomes included six months and 30 day mortality. Due to the survival nature of the study, a survival model had to be employed and this case a survival model under propensity scoring modelling. The survival-time inverse-probability weighting propensity score analysis was adopted for propensity scoring survival modelling. This method was adopted as it incorporates propensity scoring for survival data for causal inference. The method works by estimating the treatment effects as Average Treatment Effects (ATE) and Average Treatment Effect on the Treated (ATET) through two models: 1) the treatment assignment model which estimates the propensity for treatment assignment and 2) the survival model which is the outcome model

were the treatment effects estimated(140, 141). The ATE coefficients derived are the absolute difference in survival times when all patients receive treatment compared to when all the patients do not receive treatment. The ATET is then the absolute difference in survival time only for those who were treated compared to when they did not receive treatment. The ATE and ATET are derived as follows:

Each patient, the treatment effect is a difference of two potential outcomes which can be denoted by the equation below:

$$Yi\ (1) - Yi\ (0) \qquad 3.6$$

Where $Yi\ (0)$: outcome (survival time) when the patient does not receive treatment.

$Yi\ (1)$: outcome (survival time) when the patient receives treatment.

The ATE is the average of moving the entire population from treated to untreated as shown by the equation below:

$$E\ [Yi\ (1) - Yi\ (0)] \qquad 3.7$$

The ATET is then the average treatment on the treated patients only, i.e. the conditional expectation as shown below:

$$E\ [Yi\ (1) - Yi\ (0)|\ Z = 1] \qquad 3.8$$

where $Z = 1$: is for the treated patients only(142).

The treatment assignment model (propensity scoring model) is used to derive inverse-probability weights that are used to weight the data before the survival model is fitted in order to balance the systematic differences between the treatment and control observations so that the treatment effects can only be attributed to the treatment administered.

For this thesis a non-parsimonious multivariable logistic regression model was adopted as the treatment assignment model and a Weibull model for

the survival model. The treatment assignment model was adjusted for 24 variables: patient demographics (sex, deprivation (index of multiple deprivation score), year of admission to hospital), cardiovascular risk factors (diabetes, hypercholesterolaemia, hypertension, smoking status, COPD, family history of coronary heart disease), cardiovascular history (cerebrovascular disease, peripheral vascular disease), hospital discharge medications (statins, aspirin, $P2Y_{12}$ inhibitors, ACEi/ARBs), adjusted mini-GRACE risk score variables (age, cardiac arrest, elevated enzyme, systolic blood pressure and heart rate at hospitalisation and creatinine) and care by cardiologist. The treatment assignment model should be adjusted for as many pre-treatment covariates (that can potentially predict treatment assignment) as possible in order to ensure the propensity scores derived can be adequately used to even out the systematic differences between the treated vs. the non-treated, such that the treatment effects observed can be accurately attributed to the care intervention under investigation(138). The 24 variables adjusted for in the model were the pre-treatment variables available in the data source (MINAP) used for the analysis. Choice of variables to add to the treatment assignment model was also guided by literature and clinical input from Professor CP Gale.

Using the inverse probability weights derived from the treatment assignment model to balance the covariate distribution between the treated vs. the non-treated, the survival model was fitted also adjusted for the earlier mentioned covariates as well as cardiac rehabilitation. This further adjustment of the covariates was done to reduce residual confounding in the survival model and cardiac rehabilitation was only included in the survival model as it was a post treatment variable and could therefore not predict treatment assignment. Adjusted Kaplan-Meier curves to assess survival differences between patients who received β blockers and those who did not were derived using the `survci` command. The models were adjusted for the propensity scores derived from the non-parsimonious multivariable logistic regression model, i.e. the treatment assignment model.

As mentioned earlier in this section, propensity scoring adjusts for measured confounding adequately especially in the incidence of use of large comprehensive datasets. However, because unmeasured confounding is also a major problem when analysing observational data instrumental variable analysis had to be employed as a sensitivity analysis. The method allows for the determination of treatments effects that are similar to those obtained from randomised clinical trials by the use of an instrumental variable that behaves like a natural randomisation of patients to “treatment groups” that differ in their likelihood of receiving care(138). The instrumental variable acts as an unconfounded proxy of treatment and allows for comparison of groups of patients that differ in their likelihood of receiving treatment instead of comparing the actual treatment groups(143). This allows for the estimation of causal effects after accounting for measured and unmeasured confounding(143). However, for the analysis to be robust the instrument should be a strong predictor of treatment and should not be associated with the outcome of interest(138).

In literature several examples of instrumental variables have been employed which include: physician prescribing preferences, differential distances, density of cardiologists, distance to healthcare facilities, personal beliefs, calendar time, exogenous shocks (sudden shift in patient or physician behaviour) and state laws/policies(143, 144). Physician Prescribing Preferences (PPP) has been found to be a good instrument in clinical epidemiology for investigating drug effectiveness when using instrumental variable analysis(143). So for the current thesis PPP was chosen as the instrumental variable. However, because in MINAP there is not actual data capture of PPP a proxy was derived using hospital prescribing rates of guideline-indicated hospital discharge medications (aspirin, $P2Y_{12}$ inhibitors, β blockers, statins and ACEi/ARBs).

To the best of my knowledge, at the time of analysis there were no packages that allowed survival analysis for instrumental variables. Most studies have adopted a logistic regression approach, however this has potential for survivorship bias as it does not consider follow-up time. In order to avoid this survivorship bias a Poisson regression modelling approach with an offset of the log of survival time was used for the thesis as has been adopted in other studies(145). To further mitigate potential bias from residual confounding the 24 case mix variables were also adjusted for in the Poisson model.

For both the instrumental variable analysis and survival-time inverse-probability weighting propensity score analysis, the analyses were conducted by overall AMI cohort and stratified by AMI phenotype (STEMI and NSTEMI) for three survival time points (one month, six months and one year).

3.9.3 Model assessment for objective 4

Propensity score modelling is based on strongly ignorable treatment assignment assumption(146). The assumption consists of two components, which are:

- treatment assignment is independent of the outcomes, conditional on observed covariates(141, 146)
- probability of treatment assignment is bounded away from 0 and 1, “the overlap assumption” (implying that for propensity score to assume confoundedness, the estimated propensity scores for all patients should be greater than zero and less than one)(146).

To assess the first assumption, balance in covariate distributions between the treated (those that received β blockers at hospital discharge) and control (those that did not receive) patients was assessed using standardised differences and variance ratios (a perfectly balanced covariate had a standardised difference of zero and variance ratio of one). A comparison

was done between the raw data versus the weighted data (weights derived from the treatment assignment model). Using standardised differences and variance ratios as mode of assessment is an exploratory diagnostic approach, a formal over-identification test was also used to test for covariate balance(140). If the treatment assignment model is well specified the weights derived from the model will balance the covariates. Balance checks were only performed for the main effects. The over-identification test further assessed whether the main effects as well as the interactions terms were balanced. Violation of the overlap assumption was assessed using overlap plots and summarising the estimated probabilities of treatment assignment. A method to determine the cut-offs of how farther away from 0 and 1 the propensity scores of the patients have to be avoid the violation of the overlap assumption has been proposed by Crump et al. (2009)(147). They derived that limited overlap could be achieved by discarding patients that had a propensity scores outside the range: $[\alpha, 1-\alpha]$(146).

Based on this line of thought Crump et al.(147) managed to suggest a rule of thumb for trimming, which is to discard all observations with an estimated propensity score outside the range 0.1-0.9(146). For this thesis, the rule of thumb proposed by Crumb et al.(147) was used for trimming the analytical cohort. The models were fitted using trimmed data according to the Crumb et al.(147) rule of thumb, i.e. after excluding all patients that had their propensity scores outside the range 0.1-0.9. A sensitivity analysis to check the robustness of the balanced analysis was done were the models were fitted including all the patient despite their propensity scores. For the AMI and NSTEMI groups, aspirin and ACEi/ARBs at hospital discharge were found to be poorly balanced, thus interaction terms of these variables with all of the other 24 model variables were added to the treatment assignment model to improve balance. Predictive ability of the treatment assignment model was assessed using the area under the receiver operator characteristic (AUROC) curve. The `tebalance` post estimation diagnostics commands in Stata software were used and the assessments were done across each of the ten imputed datasets separately as methods to pool the

diagnostics estimates have not been defined, only those for pooling the estimates for the treatment effects had been established.

For the instrumental variable analysis, the validity of the instrument was assessed by checking that the instrument was a strong predictor of prescription of β blockers at discharge using a multilevel logistic regression model to predict prescription of β blockers as a function of hospital prescription rates. To investigate if the instrumental variable was not associated with the outcome of interest, mortality was regressed on the instrumental variable after adjusting for β blockers use and other patient characteristics. Also independence of the instrumental variable on other patient characteristics was assessed by comparing patient characteristics across quintiles of the instrument.

3.9.4 Chapter conclusion

This chapter described the methods that were used in this thesis for the four objectives of the thesis. The chapter also provides a critique of analytical methods that were used in previous studies and justification of the methods that were used. The methodology that was used in this current thesis was supported by literature and the utility of the methods has been demonstrated in previous studies. The next chapters (4 to 7) present the results of each of the four specific objectives of the thesis.

Chapter 4 : Results

Excess mortality and guideline-indicated care following non ST-elevation myocardial infarction

The following publications have arisen from the analysis and results in this chapter:

1. **Dondo TB**, Hall M, Timmis A, Gilthorpe M, Alabas O, Batin P, Deanfield J, Hemingway H, Gale CP. (2016). Excess mortality and guideline-indicated care following non ST-elevation myocardial infarction. *Eur Heart J Acute Cardiovasc Care*.
2. **Dondo TB**, Hall M, Timmis A, Gilthorpe M, Alabas O, Batin P, Deanfield J, Hemingway H, Gale CP. (2015) Guideline recommended care and excess mortality for NSTEMI: A national cohort study. *Eur Heart J* (Vol. 36, pp. 174-174). Conference abstract (Presented as a moderated poster at the European Society Congress 2015, London).

4.1 Introduction

This chapter presents the results for objective one of the thesis: quantifying the excess mortality associated with sub-optimal implementation of care for NSTEMI patients. Initially, general descriptive statistics are presented in the following categories:

- Study population (§4.2.1)
- Guideline indicated interventions (§4.2.2)
- Patterns of care (§4.2.3).

This will be followed by the results sections on the predictors of receipt of NSTEMI care (§4.3.1), the association between receipt of care and long-term survival (§4.4), and finally estimation of potentially avoidable deaths

associated with sub-optimal care for NSTEMI patients (§4.4.1.1). The final section will be a summary of the key findings (§4.5) as well as a chapter conclusion §4.6. A detailed description of the methods employed for the analyses is given in Chapter 3, §3.6.

4.2 Descriptive statistics

4.2.1 Study population

The total number of NSTEMI patients used as the analytical cohort for thesis objective one was n=389,057. Details on the analytical cohort derivation are given in Chapter 3, §3.6.1. The mean age for the NSTEMI patients in the analytical cohort was 70.9 years (SD 13.3) and 63.1% (n=244,837) were male (Table 4.1). A third of the patients (31.5%, n=122,566) had previous angina, a quarter (24.9%, n=97,002) had previous AMI, with well over half of them (71.8%, n=279,178) being current or ex-smokers. Almost half (48.5%, n=188,503) of the NSTEMI patients were hypertensive, 20.9% (n=81,469) were diabetic and 14.6% (n=56,708) had COPD or asthma. According to the mini-GRACE risk score, 79.8% (n=146,456) patients were at intermediate or high risk. In terms of electrocardiographic changes 56.8% (n=200,905) of the patients had ST-segment deviation and 15.7% (n=55,498) had no acute changes. Over 90% (n=327,625) of the analytical cohort were white. Patient's ethnic group is recorded in MINAP as perceived by the patient. The classification criteria used for recording the ethnicity data is consistent with the NHS classification criteria and is listed below:

1. White – Includes British, Irish, any other White background
2. Black – Incudes Caribbean, African, Black British, any other Black background
3. Asian – Includes Indian, Pakistani, Bangladeshi, Asian British, any other Asian background
4. Mixed – Includes White and Black Caribbean, White and Black African, White and Asian, any other mixed background.

5. Not stated – Where the patient cannot or does not wish to state his/her ethic background
6. Other – Includes Chinese, any other ethnic group
7. Unknown

Table 4.1 Baseline demographic and clinical characteristics of the 2003-2013 NSTEMI cohort.

Characteristics N=389,057	**Cases**	**Missing**
Age, years*	70.9 (13.3)	638 (0.2)
Male	244,837 (63.1)	832 (0.2)
Deprivation (IMD score, (categorised according to the 2010 cut-offs))		
Least deprived (1)(<8.49)	61,697 (17.2)	
2 (8.49 to <13.79)	70,526 (19.7)	
3 (13.79 to <21.35)	75,459 (21.0)	30,417 (7.8)
4 (21.35 to 34.17)	72,539 (20.2)	
Most deprived (5) (≥34.17)	78,419 (21.8)	
Year of admission		
2003-2005	102,207 (26.3)	
2006-2008	102,324 (26.3)	0
2009-2011	127,877 (32.9)	
2012-2013	56,649 (14.6)	
Ethnicity		
White	327,625 (93.3)	
Black	2,560 (0.7)	
Asian	15,422 (4.4)	37,922 (9.8)
Mixed	424 (0.1)	
Other	5,104 (1.5)	
Cardiovascular history		
Myocardial infarction	97,002 (24.9)	0¥
Congestive cardiac failure	24,529 (6.3)	0¥
PCI	32,663 (8.4)	0¥
CABG	27,637 (7.1)	0¥
Angina	122,566 (31.5)	0¥
Cerebrovascular disease	34,146 (8.9)	0¥
Peripheral vascular disease	18,324 (4.7)	0¥
Cardiovascular risk factors		
Diabetes	81,469 (20.9)	0¥
Chronic renal failure	21,938 (5.6)	0¥
Hypercholesterolaemia	121,243 (31.2)	0¥
Hypertension	188,503 (48.5)	0¥
Smoker ever / current	279,178 (71.8)	0¥
Asthma or COPD	56,708 (14.6)	0¥
Family history of CHD	77,288 (19.9)	0¥
Presenting characteristics		
Systolic blood pressure, mmHg*	142.5 (28.4)	66,688 (17.1)
Systolic blood pressure, <90 mmHg	6,483 (2.0)	66,688 (17.1)
Heart rate*	80 (67-95)	65,863 (16.9)
Heart rate >110 bpm	177,810 (55.0)	65,863 (16.9)
Creatinine*	92 (76-114)	165,622 (42.6)
Creatinine >200 (μmol/l)	9,546 (4.3)	165,622 (42.6)
Peak troponin§*	1.2 (0.3-8.2)	19,114 (4.9)
Peak troponin ≥ 0.06§	350,368 (94.7)	19,114 (4.9)
Cardiac arrest	6,740 (1.8)	22,901 (5.9)

Characteristics N=389,057	Cases	Missing
Electrocardiographic characteristics		
No acute changes	55,498 (15.7)	
ST-segment elevation	15,962 (4.5)	
Left bundle branch block	23,066 (6.5)	35,699 (9.2)
ST segment depression	92,227 (26.1)	
T wave changes only	92,716 (26.2)	
Other acute abnormality	73,889 (20.9)	
Use of a loop diuretic	97,972 (30.5)	67,556 (17.4)
Grace risk score classification		
Lowest (≤70)	16,657 (9.1)	
Low (71-87)	20,483 (11.2)	205.461 (52.8)
Intermediate to high (>88)	146,456 (79.8)	

*All are numbers (%), unless normally distributed continuous data (mean (SD)), or non-normally distributed continuous data (median (IQR)).

Abbreviations. IMD, Index of multiple deprivation; CABG, coronary artery bypass graft; CHD, coronary heart disease; COPD, chronic obstructive pulmonary disease; PCI, percutaneous coronary intervention; SD, standard deviation; IQR, interquartile range; ¥ missing data default imputed to "No", § peak troponin values truncated at 50.

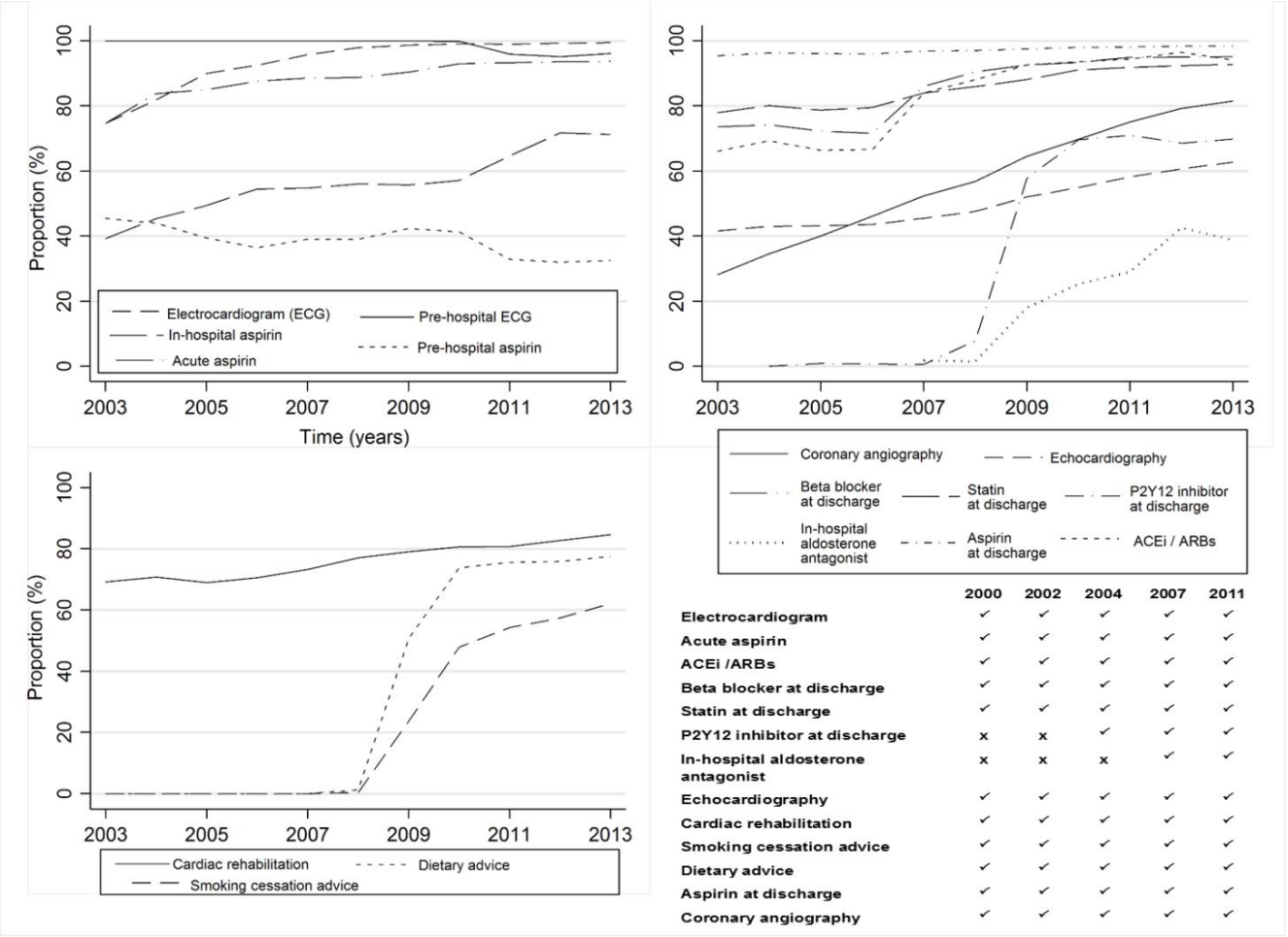
4.2.2 Guideline-indicated care interventions

A small proportion of the patients received optimal care (13.2%, n=51,176), with the most frequently missed care interventions being dietary advice (68.1%, n=254,869), smoking cessation advice (87.9%, n=245,357), echocardiography (49.7%, n=193,483), $P2Y_{12}$ inhibitors at discharge from hospital (n=192,906, 66.3%), coronary angiography (43.4%, n=161,853) and in-hospital aspirin (45.0%, n=106,407) (Table 4.2). Pre-hospital care interventions which were assessed but not included in the derivation of the OMT score included pre-hospital electrocardiogram (96.2%, n=115,702) and pre-hospital aspirin (55.0%, n=49,682). Increases in receipt of the ESC guideline-indicated care interventions from 2003-2013 were noted (Figure 4.1), with exceptions for pre-hospital aspirin and pre-hospital electrocardiogram where decreases over time were observed. Figure 4.1 also shows over the years, the time the care interventions were already recommended by the guidelines shown by a tick and when they were not yet recommended shown by an **x**. Most of the care interventions were already recommended in the ESC guidelines during the time of the study except for $P2Y_{12}$ inhibitors which came in 2004 and in-hospital aldosterone antagonists in 2007.

Table 4.2 Eligibility and receipt of guideline-indicated care for NSTEMI between 2003 and 2013.

Treatment	Patients receiving treatment n (%)	Patients eligible
Pre-hospital electrocardiogram	115,702 (96.2)	120,270
Pre-hospital aspirin	49,682 (55.0)	90,304
Electrocardiogram	364,760 (93.8)	389,057
Acute aspirin	230,822 (88.7)	260,384
In-hospital aspirin	130,185 (55.0)	236,592
Echocardiography	195,537 (50.3)	389,020
Coronary angiography	211,267 (56.6)	373,120
Coronary angiography in high risk patients	29,274 (53.9)	54,325
Aspirin at discharge	301,639 (88.5)	340,982
$P2Y_{12}$ inhibitors at discharge	126,995 (39.7)	319,901
ACE inhibition or ARB	91,159 (67.5)	135,131
β Blockers at discharge	90,185 (74.5)	121,094
Statin at discharge	297,045 (85.4)	347,701
In-hospital aldosterone antagonists	144 (24.3)	592
Dietary advice	119,321 (31.9)	374,190
Smoking cessation advice	33,821 (12.1)	279,178
Cardiac rehabilitation	279,027 (76.0)	366,938
Care by cardiologist	220,208 (56.6)	389,057
Optimal care	51,176 (13.2)	389,057

Abbreviations: ARB, angiotensin receptor blocker; ACE, angiotensin converting enzyme.



	2000	2002	2004	2007	2011
Electrocardiogram	✓	✓	✓	✓	✓
Acute aspirin	✓	✓	✓	✓	✓
ACEi /ARBs	✓	✓	✓	✓	✓
Beta blocker at discharge	✓	✓	✓	✓	✓
Statin at discharge	✓	✓	✓	✓	✓
P2Y12 inhibitor at discharge	x	x	✓	✓	✓
In-hospital aldosterone antagonist	x	x	x	✓	✓
Echocardiography	✓	✓	✓	✓	✓
Cardiac rehabilitation	✓	✓	✓	✓	✓
Smoking cessation advice	✓	✓	✓	✓	✓
Dietary advice	✓	✓	✓	✓	✓
Aspirin at discharge	✓	✓	✓	✓	✓
Coronary angiography	✓	✓	✓	✓	✓

Figure 4.1 Temporal trends of guideline-indicated interventions by year of publication in ESC guidelines.

4.2.3 Patterns of care

Considering the latent trait composite measure approach derived using latent class analysis, the three class solution was selected as the optimal class solution to define receipt of care for NSTEMI patients (Table 4.3,Figure 4.2). The methods used to derive this three class solution have already been described in Chapter 3 (§3.4.1). Statistical model fit improved with increasing class sizes beyond the three class solution. However, the change in log likelihood and difference in BIC, and increase in entropy became minimal beyond the class three solution. The conditional probabilities of receipt of care for the class solutions are provided in Table 4.4-Table 4.8. The higher class solutions did not offer improved separation between the classes beyond the separation shown in the three class solution, for example for the four class solution (Table 4.5), class 2, 3 and class 4 probabilities of receipt of care were similar to those observed for class 2, 1 and 3 of the three class solution, respectively. However, the fourth class defined was difficult to characterise as it was quite similar to the class 3 of the three class solution but with a lower receipt of statin and aspirin at discharge, but higher receipt of diet advice and coronary angiography. The three class solution was deemed the best class solution to model the real life scenario of management of care of NSTEMI patients for this thesis.

Table 4.3 Model fit statistics for class solutions

	Latent classes						
	1	**2**	**3**	**4**	**5**	**6**	**7**
No of free parameters	25	51	77	103	129	155	181
Log likelihood	-3532640.519	-3054522.657	-2937808.427	-2851964.135	-2773145.008	-2740668.520	-2713668.637
Bayesian information criteria	7065602.826	6109701.760	5876607.957	5705254.032	5547950.438	5483332.121	5429667.012
Lo-Mendell-Rubin LRT (P)		953386.889 (0.0000)	232733.027 (0.0000)	171177.086 (0.0000)	157168.614 (0.0000)	64751.750 (0.0000)	53838.890 (0.6908)
Entropy		0.928	0.946	0.952	0.958	0.960	0.938
AIC	7065331.039	6109147.315	5875770.853	5704134.269	5546548.017	5481647.041	5427699.273
SSABIC	7065523.375	6109539.680	5876363.247	5704926.693	5547540.469	5482839.523	5429091.785
Best H0 replicated	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Difference in BIC		955901.066	233093.803	171353.925	157303.594	64618.317	53665.109

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; SSABIC, Sample size adjusted BIC.

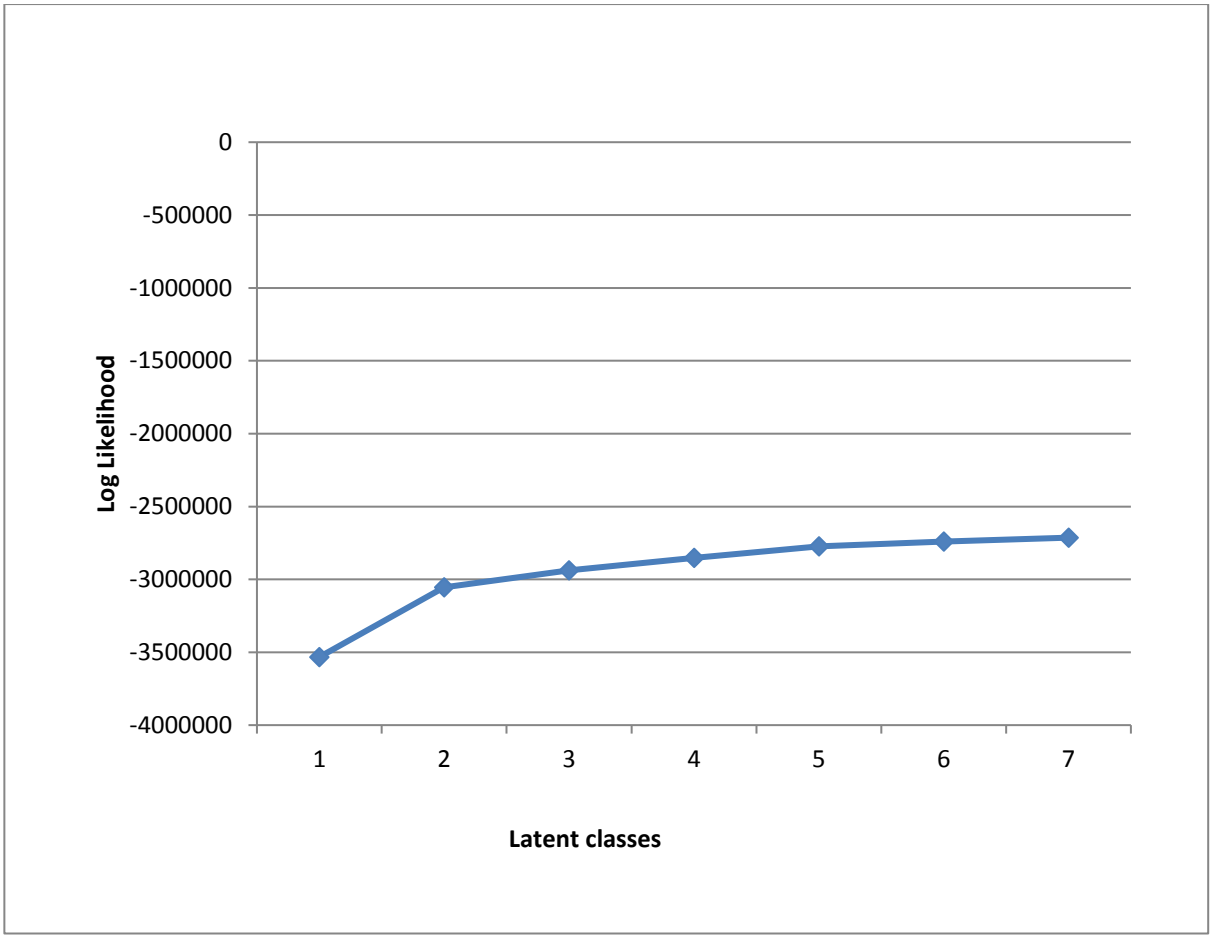


Figure 4.2 Plot of the log likelihood for the different classes.

Table 4.4 Latent class structure identifying three classes of received care patterns for patients with NSTEMI showing the probability of receipt per care opportunity within each class.

Care Opportunity	Latent Class Structure (probabilities)		
	Class1 High receipt of care	**Class 2 Intermediate receipt of care**	**Class 3 Low receipt of care**
Electrocardiogram	0.99	0.85	0.97
Acute aspirin	0.65	0.55	0.58
ACE inhibitor or ARB	0.01	0.67	0.01
β blockers	0.04	0.61	0.03
Statin at discharge	0.78	0.77	0.73
$P2Y_{12}$ inhibitors	0.72	0.004	0.18
Aldosterone antagonist	0.001	0.000	0.000
Echocardiography	0.60	0.43	0.46
Cardiac rehabilitation	0.80	0.69	0.65
Smoking cessation advice	0.22	0.000	0.004
Dietary advice	0.78	0.000	0.01
Coronary angiography	0.69	0.38	0.54
Aspirin at discharge	0.78	0.80	0.74

Abbreviations. ARB, angiotensin receptor blocker; ACE, angiotensin converting enzyme.

Table 4.5 Latent class structure identifying four classes of received care patterns for patients with NSTEMI showing the probability of receipt per care opportunity within each class.

	Latent class structure			
Care opportunity	**Class 1**	**Class 2**	**Class 3**	**Class 4**
Electrocardiogram	0.99	0.85	0.99	0.97
Acute aspirin	0.63	0.54	0.65	0.58
ACE inhibition or ARB	0.001	0.67	0.01	0.01
β Blocker	0.005	0.61	0.05	0.03
Statin at discharge	0.07	0.77	0.95	0.80
$P2Y_{12}$ inhibitors	0.012	0.004	0.88	0.19
Aldosterone antagonist	0.000	0.000	0.001	0.000
Echocardiography / Stress echocardiography	0.48	0.43	0.62	0.46
Cardiac rehabilitation	0.69	0.68	0.81	0.65
Smoking cessation advice	0.17	0.000	0.22	0.002
Diet advice	0.56	0.000	0.79	0.01
Coronary angiography	0.75	0.38	0.67	0.53
Aspirin at discharge	0.04	0.80	0.96	0.80

Abbreviations. ARB, angiotensin receptor blocker; ACE, angiotensin converting enzyme.

Table 4.6 Latent class structure identifying five classes of received care patterns for patients with NSTEMI showing the probability of receipt per care opportunity within each class.

	Latent class structure				
Care opportunity	**Class 1**	**Class 2**	**Class 3**	**Class 4**	**Class 5**
Electrocardiogram	0.995	0.90	0.99	0.97	0.85
Acute aspirin	0.63	0.54	0.65	0.58	0.55
ACE inhibition or ARB	0.000	0.06	0.01	0.01	0.77
β Blocker	0.007	0.01	0.05	0.03	0.71
Statin at discharge	0.09	0.01	0.94	0.85	0.90
$P2Y_{12}$ inhibitors	0.012	0.01	0.88	0.19	0.01
Aldosterone antagonist	0.000	0.000	0.001	0.000	0.00
Echocardiography / Stress echocardiography	0.49	0.33	0.62	0.48	0.45
Cardiac rehabilitation	0.69	0.52	0.81	0.68	0.72
Smoking cessation advice	0.18	0.03	0.22	0.001	0.00
Diet advice	0.62	0.11	0.79	0.004	0.00
Coronary angiography	0.75	0.59	0.67	0.53	0.35
Aspirin at discharge	0.04	0.05	0.96	0.85	0.92

Abbreviations. ARB, angiotensin receptor blocker; ACE, angiotensin converting enzyme.

Table 4.7 Latent class structure identifying six classes of received care patterns for patients with NSTEMI showing the probability of receipt per care opportunity within each class.

	Latent class structure					
Care opportunity	**Class 1**	**Class 2**	**Class 3**	**Class 4**	**Class 5**	**Class 6**
Electrocardiogram	0.97	0.99	0.995	0.96	0.85	0.85
Acute aspirin	0.58	0.65	0.63	0.58	0.55	0.49
ACE inhibition or ARB	0.01	0.01	0.00	0.002	0.77	0.12
β Blocker	0.03	0.05	0.01	0.01	0.72	0.02
Statin at discharge	0.85	0.95	0.09	0.07	0.90	0.03
$P2Y_{12}$ inhibitors	0.19	0.88	0.01	0.05	0.01	0.00
Aldosterone antagonist	0.00	0.001	0.00	0.00	0.00	0.00
Echocardiography / Stress echocardiography	0.48	0.62	0.49	0.36	0.45	0.31
Cardiac rehabilitation	0.68	0.81	0.69	0.56	0.72	0.49
Smoking cessation advice	0.001	0.22	0.18	0.08	0.00	0.00
Diet advice	0.003	0.79	0.62	0.26	0.00	0.00
Coronary angiography	0.53	0.67	0.75	0.63	0.35	0.52
Aspirin at discharge	0.85	0.96	0.04	0.07	0.92	0.10

Abbreviations. ARB, angiotensin receptor blocker; ACE, angiotensin converting enzyme.

Table 4.8 Latent class structure identifying seven classes of received care patterns for patients with NSTEMI showing the probability of receipt per care opportunity within each class.

Care opportunity	Latent class structure						
	Class 1	**Class 2**	**Class 3**	**Class 4**	**Class 5**	**Class 6**	**Class 7**
Electrocardiogram	0.995	0.97	0.993	0.994	0.85	0.96	0.85
Acute aspirin	0.64	0.59	0.68	0.52	0.55	0.59	0.49
ACE inhibition or ARB	0.00	0.01	0.01	0.003	0.77	0.002	0.12
β Blocker	0.001	0.03	0.04	0.08	0.72	0.003	0.02
Statin at discharge	0.05	0.85	0.97	0.82	0.90	0.05	0.03
$P2Y_{12}$ inhibitors	0.002	0.18	0.91	0.70	0.01	0.04	0.00
Aldosterone antagonist	0.00	0.00	0.001	0.00	0.00	0.00	0.00
Echocardiography / Stress echocardiography	0.50	0.48	0.66	0.45	0.45	0.36	0.31
Cardiac rehabilitation	0.73	0.70	0.94	0.26	0.72	0.58	0.49
Smoking cessation advice	0.20	0.002	0.26	0.06	0.00	0.08	0.00
Diet advice	0.64	0.003	0.91	0.29	0.00	0.27	0.00
Coronary angiography	0.82	0.55	0.77	0.26	0.35	0.66	0.52
Aspirin at discharge	0.01	0.85	0.97	0.85	0.92	0.03	0.10

Abbreviations. ARB, angiotensin receptor blocker; ACE, angiotensin converting enzyme.

The three classes derived were labelled as follows: class 1 “high”, class 2 “intermediate” and class 3 “low” receipt of care according to the conditional item probabilities of receipt of each of the 13 ESC recommended care interventions considered for the thesis work, to aid with understanding and interpretation. Class 1 was labelled as “high” because of the observed high conditional item probabilities for receipt of care for most of the care interventions (use of an electrocardiogram (0.99), acute aspirin (0.65), statin at hospital discharge (0.78), $P2Y_{12}$ inhibitors at hospital discharge (0.72), echocardiography (0.60), cardiac rehabilitation (0.80), dietary advice (0.78), coronary angiography (0.69) and aspirin at hospital discharge (0.78). The conditional item probabilities were highest in the high receipt class compared to the other 2 classes. The low conditional item probabilities of receipt of ACEi/ARBs and β-blockers observed in the class labelled as high receipt of care class were because this group of patients consisted mainly of patients who were not eligible to receive the care interventions (see Table

B 1-Table B 26, Appendix B). ACEi/ARBs and β-blockers are indicated for patients who have an ejection fraction ≤ 35% (21), this shows that the patients in the high receipt group were the healthier patients of the NSTEMI patients considered for the study. Use of an electrocardiogram, aspirin at discharge and statins at discharge were high in all three classes (>0.70), thus these interventions were not distinguishing factors from the other latent classes. Patients in the intermediate class had a low probability of echocardiography and coronary angiography (0.43 and 0.38, respectively) and very low (<0.01) probabilities of receiving $P2Y_{12}$ inhibitors, aldosterone antagonist, smoking cessation advice, and dietary advice. Patients in the low class had, in addition to the care probabilities of those in the intermediate class, very low probabilities of receiving ACEi/ARBs and β-blockers (0.01 and 0.03, respectively). The findings are summarised in Table 4.4.

4.3 Predictors of receipt of care

Overall, there were minor differences in baseline patient characteristics of the patients in the different latent classes. Marked class differences were only observed in: period of hospitalisation, 99.5% of those in the high receipt of care class were hospitalised between 2009 and 2013 compared with 0.5% being hospitalised between 2003 and 2008 (Table 4.9).

However comparing the patients stratified according to the all or none approach (comparing patients who received optimal care with those who did not), the sub-optimal care receivers had a higher proportion of advanced age (>85 years) patients (15.3 vs. 6.7%), previous angina (40.0 vs. 28.3%), congestive cardiac failure (6.6. vs. 4.1%), cerebrovascular disease (8.9 vs. 7.8%) and use of a loop diuretic (30.9 vs. 23.7%) (Table 4.9). The optimal care receivers had a higher proportion of males (68.3 vs 62.3%), a higher proportion of patients with hypercholesterolaemia (38.9 vs. 30.0%), diabetes (22.6 vs. 20.7%), hypertension (53.5 vs. 47.7%), family history of

CHD (30.5 vs. 18.3%) and were current or ex-smokers (63.5 vs. 54.6%) (Table 4.9). Similar to what was observed for the latent classes, a marked difference between those who received optimal care and those who did not was most apparent by period of hospitalisation: 99.8% of those in the optimal care group were hospitalised between 2009 and 2013 compared with 0.2% being hospitalised between 2003 and 2008 (Table 4.9). Beyond the descriptive statistics, further analyses were conducted to determine the predictors of receipt of care using logistic regression analysis.

Table 4.9 Patient characteristics by receipt of care for NSTEMI patients between 2003 and 2013.

	Receipt of care groups			**Latent classes**			
Characteristics N=389,057	**Optimal care** n=51,176 (13.2%)	**Sub-optimal care** n=337,881 (86.9%)	**P value**	**High receipt** n= 151,010 (38.8%)	**Intermediate receipt** n=133,546 (34.3%)	**Low receipt** n=104,501 (26.9%)	**P value**
Age							
Below 55	9,916.6 (19.4)	45,059.1 (13.3)	<0.001	23,467.2 (15.5)	17,416.2 (13.0)	14,092.3 (13.5)	<0.001
Between 55-65	11,493 (22.5)	58,879.6 (17.4)	<0.001	28,394.4 (18.8)	23,810 (17.8)	18,168.2 (17.4)	<0.001
Between 66-75	13,839 (27.0)	82,390.2 (24.4)	<0.001	36,767.7 (24.4)	34,570.2 (25.9)	24,891.3 (23.8)	<0.001
Between 76-85	12,484 (24.4)	99,762.2 (29.5)	<0.001	41,289.1 (27.3)	40,504.7 (30.3)	30,452.4 (29.1)	<0.001
Above 85	3,443.4 (6.7)	51,789.9 (15.3)	<0.001	21,091.6 (14.0)	17,2449 (12.9)	16,896.8 (16.2)	<0.001
Male	34,925.1 (68.3)	210,426.5 (62.3)	<0.001	96,481.1 (63.9)	83,470.5 (62.5)	65,400 (62.6)	<0.001
Deprivation (IMD)							
Least deprived (1)	8,922.8 (17.4)	58,054.3 (17.2)	0.128	26,177.3 (17.3)	22,198.4 (16.6)	18,601.4 (17.8)	<0.001
2	9,640.8 (18.8)	66,910.7 (19.8)	<0.001	29,360.2 (19.4)	26,054.4 (19.5)	21,136.9 (20.2)	<0.001
3	10,407.6 (20.3)	71,599.7 (21.2)	<0.001	31,478.3 (20.9)	28,173.3 (21.1)	22,355.7 (21.4)	<0.001
4	10,327.7 (20.2)	68,383.3 (20.2)	0.695	30,408 (20.1)	27,170.6 (20.4)	21,132.4 (20.2)	<0.001
Most deprived (5)	11,877.1 (23.2)	72,933 (21.6)	<0.001	33,586.2 (22.2)	29,949.3 (22.4)	21,274.6 (20.4)	<0.001
Year of Admission							
2003-2005	*(<0.1)	102,205 (30.3)	<0.001	12 (0.01)	100,986 (75.6)	1,209 (1.2)	<0.001

	Receipt of care groups			Latent classes			
Characteristics N=389,057	**Optimal care** n=51,176 (13.2%)	**Sub-optimal care** n=337,881 (86.9%)	**P value**	**High receipt** n= 151,010 (38.8%)	**Intermediate receipt** n=133,546 (34.3%)	**Low receipt** n=104,501 (26.9%)	**P value**
2006-2008	115 (0.2)	102,209 (30.3)	<0.001	671 (0.4)	32,429 (24.3)	69,224 (66.2)	<0.001
2009-2011	31,152 (60.9)	96,725 (28.6)	<0.001	100,127 (66.3)	111 (0.1)	27,639 (26.5)	<0.001
2012-2013	19,907 (38.9)	36,742 (10.9)	<0.001	50,200 (33.2)	20 (0.01)	6,429 (6.2)	<0.001
Ethnicity							
White	47,277.4 (92.4)	315,784.7 (93.5)	<0.001	140,581.1 (93.1)	124,633.5 (93.3)	97,847.5 (93.6)	<0.001
Black	451.1 (0.9)	2,357.2 (0.7)	<0.001	1,209.4 (0.8)	853.6 (0.6)	745.3 (0.7)	<0.001
Asian	2,892.6 (5.7)	14,058.6 (4.2)	<0.001	7,712.9 (5.1)	4,654.2 (3.5)	4,584.1 (4.4)	<0.001
Mixed	101.8 (0.2)	352.1 (0.1)	<0.001	238.2 (0.2)	13.6 (0.01)	202.1 (0.2)	<0.001
Other	453.1 (0.9)	5,328.4 (1.6)	<0.001	1,268.4 (0.80)	3,391.1 (2.5)	1,122 (1.1)	<0.001
Cardiovascular History							
Myocardial infarction	11,771 (23.0)	85,231 (25.2)	<0.001	39,423 (26.1)	31,535 (23.6)	26,044 (24.9)	<0.001
Congestive cardiac failure	2,089 (4.1)	22,440 (6.6)	<0.001	9,492 (6.3)	7,326 (5.5)	7,711 (7.4)	<0.001
PCI	5,364 (10.5)	27,299 (8.1)	<0.001	16,601 (11.0)	7,000 (5.2)	9,062 (8.7)	<0.001
CABG	3,847 (7.5)	23,790 (7.0)	<0.001	12,768 (8.5)	7,204 (5.4)	7,665 (7.3)	<0.001
Angina	14,498 (28.3)	108,068 (40.0)	<0.001	46,872 (31.0)	42,255 (31.6)	33,439 (32.0)	<0.001
Cerebrovascular disease	3,988 (7.8)	30,158 (8.9)	<0.001	14,496 (9.6)	10,180 (7.6)	9,470 (9.1)	<0.001
Peripheral vascular disease	2,393 (4.7)	15,931 (4.7)	0.698	7,254 (4.8)	6,124 (4.6)	4,946 (4.7)	0.022
Cardiovascular Risk Factors							
Diabetes	11,555 (22.6)	69,914 (20.7)	<0.001	35,614 (23.6)	22,914 (17.2)	22,941 (22.0)	<0.001
Chronic renal failure	2,773 (5.4)	19,165 (5.7)	0.020	10,767 (7.1)	4,463 (3.3)	6,708 (6.4)	<0.001
Hypercholesterolaemia	19,896 (38.9)	101,347 (30.0)	<0.001	52,935 (35.1)	33,972 (25.4)	34,336 (32.9)	<0.001
Hypertension	27,355 (53.5)	161,148 (47.7)	<0.001	79,539 (52.7)	55,931 (41.9)	53,033 (50.8)	<0.001
Current/ ex-smoker	32,483 (63.5)	184,633 (54.6)	<0.001	89,221 (59.1)	70,613 (52.9)	57,282 (54.8)	<0.001
Asthma or COPD	7,603 (14.9)	49,105 (14.5)	0.053	23,844 (15.8)	17,108 (12.8)	15,756 (15.1)	<0.001
Family history of CHD	15,584 (30.5)	61,704(18.3)	<0.001	38,015 (25.2)	14,659 (11.0)	24,614 (23.6)	<0.001
Presenting Characteristics							
Systolic blood pressure, (Mean (SD))	143.1 (27.1)	142.3 (28.7)	<0.001	142.2 (27.6)	142.8 (29.4)	142.0 (28.5)	

	Receipt of care groups			Latent classes			
Characteristics N=389,057	**Optimal care** n=51,176 (13.2%)	**Sub-optimal care** n=337,881 (86.9%)	**P value**	**High receipt** n= 151,010 (38.8%)	**Intermediate receipt** n=133,546 (34.3%)	**Low receipt** n=104,501 (26.9%)	**P value**
<90 mmHg	843.2 (1.7)	8,928.1 (2.6)	<0.001	3,007.8 (2.0)	3,835.6 (2.9)	2,927.9 (2.8)	<0.001
Heart rate (Median (IQR))	78 (66-91)	80 (67-95)	<0.001	78 (66-92)	80 (68-96)	80 (68-95)	
>110 bpm	4,388.1 (8.6)	38,834 (11.5)	<0.001	14,009.6 (9.3)	16,932 (12.7)	12,280.5 (11.8)	<0.001
Cardiac arrest	1,029.6 (2.0)	6,207.6 (1.8)	0.011	2,427.8 (1.6)	3,071.8 (2.3)	1,737.6 (1.7)	<0.001
Peak troponin (Median (IQR))	3.3 (0.4-50)	1.1 (0.2-6.5)	<0.001	2.3 (0.3-44)	1 (0.3-4.3)	0.8 (0.2-4.3)	
≥ 0.06	48,753 (95.3)	319,716.7 (94.6)	<0.001	142,886.6 (94.6)	128,090 (95.9)	97,493.1 (93.3)	<0.001
Creatinine (Median (IQR))	88 (74-106)	96 (79-120)	<0.001	90 (74-112)	99 (82-125)	96 (80-119)	
>200 (µmol/l)	1,340 (2.7)	8,206 (4.7)	<0.001	5,779 (4.1)	127 (4.6)	3,640 (4.5)	<0.001
Use of a loop diuretic	12,141.8 (23.7)	104,404.4 (30.9)	<0.001	41,649.9 (27.6)	43,657.3 (32.7)	31,239 (29.9)	<0.001
Electrocardiographic characteristics							
No acute changes	10,274.7 (20.1)	49,764.6 (14.7)	<0.001	29,564.8 (19.6)	15,150.3 (11.3)	15,324.2 (14.7)	<0.001
ST-segment elevation	1,359.1 (2.7)	16,824.1 (5.0)	<0.001	3,894.9 (2.6)	11,489.5 (8.6)	2,798.8 (2.7)	<0.001
Left bundle branch block	2,599.4 (5.1)	23,020.2 (6.8)	<0.001	9,119.6 (6.0)	9,340.5 (7.0)	7,159.5 (6.9)	<0.001
ST segment depression	12,707.9 (24.8)	89,212.9 (26.4)	<0.001	36,637.3 (24.3)	37,212.4 (27.9)	28,071.1 (26.9)	<0.001
T wave changes only	15,083.9 (29.5)	86,323.1 (25.6)	<0.001	41,854.6 (27.7)	32,200.8 (24.1)	27,351.6 (26.2)	<0.001
Other acute abnormality	9,151 (17.9)	72,736.1 (21.5)	<0.001	29,938.8 (19.8)	28,152.5 (21.1)	23,795.8 (22.8)	<0.001
Grace risk score classification							
Lowest (≤70)	1,174.3 (2.3)	5,157.5 (1.5)	<0.001	2,698 (1.8)	1,886.1 (1.4)	1,747.7 (1.7)	<0.001
Low (71-87)	3,817.4 (7.5)	17,166.5 (5.1)	<0.001	9,040.9 (6.0)	6,297.5 (4.7)	5,645.5 (5.4)	<0.001

	Receipt of care groups			Latent classes			
Characteristics N=389,057	**Optimal care** n=51,176 (13.2%)	**Sub-optimal care** n=337,881 (86.9%)	**P value**	**High receipt** n= 151,010 (38.8%)	**Intermediate receipt** n=133,546 (34.3%)	**Low receipt** n=104,501 (26.9%)	**P value**
Intermediate to high (>88)	46,184.3 (90.3)	315,557 (93.4)	<0.001	139,271.1 (92.2)	125,362.4 (93.9)	97,107.8 (92.9)	<0.001

*All are numbers (%), unless normally distributed continuous data (mean (SD)), or non-normally distributed continuous data (median (IQR)).

Abbreviations. IMD, Index of multiple deprivation; CABG, coronary artery bypass graft; CHD, coronary heart disease; COPD, chronic obstructive pulmonary disease; PCI, percutaneous coronary intervention; SD, standard deviation; IQR, interquartile range.

4.3.1 Predictors of receipt of care

The results from the logistic regression analysis to investigate the predictors of receipt of care are summarised in Table 4.10. Being cared for by a cardiologist was a positive predictor for receipt of optimal care (OR: 55.04, 95% CI: 51.41-58.91),recording of an electrocardiogram (OR: 4.35, 95% CI: 4.04-4.69), prescription at discharge of ACEi/ARBs (OR: 1.48, 95% CI: 1.32-1.67), β blockers (OR: 2.94, 95% CI: 2.65-3.26), statins (OR: 2.63, 95% CI: 2.55-2.72), $P2Y_{12}$ inhibitors (OR: 8.50, 95% CI: 8.25-8.77), aldosterone antagonists (OR: 4.80, 95% CI: 1.43-16.12), aspirin (OR: 2.70, 95% CI: 2.60-2.81), getting an echocardiogram (OR: 1.97, 95% CI: 1.92-2.01), coronary angiography (OR: 4.01, 95% CI: 3.95-4.07), receipt of dietary advice (OR: 12.28, 95% CI: 11.85-12.72) and smoking cessation advice (OR: 16.61, 95% CI: 15.43-17.88). Being a current or ex-smoker was a positive predictor for receipt of acute aspirin (OR: 1.37, 95% CI: 1.32-1.42) and having a peak troponin ≥0.06 a positive predictor (OR: 2.26, 95% CI: 2.18-2.34) for enrolment into cardiac rehabilitation. Having a creatinine concentration >200 μmol/l was a negative predictor for recording of an electrocardiogram (OR: 0.16, 95% CI: 0.15-0.18), receipt of acute aspirin (OR: 0.60, 95% CI: 0.56-0.64), prescription of $P2Y_{12}$ inhibitors (OR: 0.22, 95% CI: 0.21-0.23) and receipt of dietary advice (OR: 0.30, 95% CI: 0.29-0.31). Having previous angina was found to be a negative predictor of receipt of optimal care (OR: 0.84, 95% CI: 0.82-0.86), for prescription of β blockers having COPD/asthma (OR: 0.38, 95% CI: 0.37-0.40), ACEi/ARBs having chronic renal failure (OR: 0.46, 95% CI: 0.43-0.49), and for statins and aspirin prescription, having a cardiac arrest (OR: 0.57, 95% CI: 0.53-0.61, OR: 0.53, 95% CI: 0.49-0.57, respectively) and for getting an angiogram having cerebrovascular disease (OR: 0.48, 95% CI: 0.46-0.49). Advanced age was found to be a negative predictor of enrolment into cardiac rehabilitation (OR: 0.55, 95% CI: 0.53-0.57) and receiving smoking cessation advice (OR: 0.11, 95% CI: 0.10-0.12).

Table 4.10. Predictors of receipt of optimal care and individual guideline indicated care interventions, according to multivariable multilevel logistic regression analyses.

Care intervention	Positive predictors	Negative predictor
Optimal care	Care by cardiologist (OR: 55.04, 95% CI: 51.41-58.91) Family history of CHD (OR: 1.32, 95% CI: 1.29-1.34) Hypercholesterolaemia (OR: 1.24, 95% CI: 1.21-1.27) Sex (OR: 1.23, 95% CI: 1.20-1.25)	Previous angina (OR: 0.84, 95% CI: 0.82-0.86) Previous MI (OR: 0.85, 95% CI: 0.83-0.87) Cerebrovascular disease (OR: 0.86, 95% CI: 0.83-0.89)
Electrocardiogram	Care by cardiologist (OR: 4.35, 95% CI: 4.04-4.69) Family history of CHD (OR: 1.89, 95% CI: 1.78-2.02)	Creatinine (>200 (μmol/l)) (OR: 0.16, 95% CI: 0.15-0.18)
Acute aspirin	Current or ex-smoker (OR: 1.37, 95% CI: 1.32-1.42)	Creatinine (>200 (μmol/l)) (OR: 0.60, 95% CI: 0.56-0.64)
ACEi/ARBs	Care by cardiologist (OR: 1.48, 95% CI: 1.32-1.67) Hypertension (OR: 1.38, 95% CI: 1.34-1.43) Diabetes (OR: 1.26, 95% CI: 1.21-1.31) Use of a loop diuretic (OR: 1.26, 95% CI: 1.22-1.31) Previous MI (OR: 1.28, 95% CI: 1.24-1.33)	Chronic renal failure (OR: 0.46, 95% CI: 0.43-0.49) Creatinine (>200 (μmol/l)) (OR: 0.58, 95% CI: 0.50-0.68) Systolic blood pressure (<90 mmHg) (OR: 0.72, 95% CI: 0.66-0.79) Advanced age (>85) (OR: 0.75, 95% CI: 0.71-0.80) Cardiac arrest (OR: 0.78, 95% CI: 0.71-0.86)
β blockers	Care by cardiologist (OR: 2.94, 95% CI: 2.65-3.26)	Asthma or COPD (OR: 0.38, 95% CI: 0.37-0.40) Creatinine (>200 (μmol/l)) (OR: 0.48, 95% CI: 0.42-0.54) Cardiac arrest (OR: 0.60, 95% CI: 0.54-0.66) Systolic blood pressure (<90 mmHg) (OR: 0.71, 95% CI: 0.64-0.79) Advanced age (OR: 0.74, 95% CI: 0.69-0.79)
Statins	Care by cardiologist (OR: 2.63, 95% CI: 2.55-2.72) Hypercholesterolaemia (OR: 1.47, 95% CI: 1.43-1.51)	Cardiac arrest (OR: 0.57, 95% CI: 0.53-0.61) Systolic blood pressure (<90 mmHg) (OR: 0.73, 95% CI: 0.68-0.79) Advanced age (OR: 0.80, 95% CI: 0.76-0.83)
$P2Y_{12}$ inhibitors	Care by cardiologist (OR: 8.50, 95% CI: 8.25-8.77) Chronic renal failure (OR: 2.32, 95% CI: 2.23-2.42) Advanced age (OR: 1.30, 95% CI: 1.25-1.36)	Creatinine (>200 (μmol/l)) (OR: 0.22, 95% CI: 0.21-0.23) Cardiac arrest (OR: 0.69, 95% CI: 0.64-0.74) Heart rate (>110 bpm) (OR: 0.69, 95% CI: 0.67-0.70)

Care intervention	Positive predictors	Negative predictor
		Systolic blood pressure (<90 mmHg) (OR: 0.73, 95% CI: 0.68-0.79)
Aldosterone antagonists	Care by cardiologist (OR: 4.80, 95% CI: 1.43-16.12) Peripheral vascular disease (OR: 2.80, 95% CI: 1.54-5.08)	
Echocardiogram	Care by cardiologist (OR: 1.97, 95% CI: 1.92-2.01) Cardiac arrest (OR: 1.86, 95% CI: 1.75-1.97) Use of a loop diuretic (OR: 1.72, 95% CI: 1.69-1.75)	Previous PCI (OR: 0.77, 95% CI: 0.75-0.80) Advanced age (OR: 0.81, 95% CI: 0.78-0.83)
Cardiac rehabilitation	Peak troponin (≥ 0.06) (OR: 2.26, 95% CI: 2.18-2.34) Care by cardiologist (OR: 2.17, 95% CI: 2.11-2.23) Current or ex-smoker (OR: 1.24, 95% CI: 1.21-1.26) Family history of CHD (OR: 1.22, 95% CI: 1.19-1.26)	Advanced age (OR: 0.55, 95% CI: 0.53-0.57) Most deprived (OR: 0.72, 95% CI: 0.70-0.74) Systolic blood pressure (<90 mmHg) (OR: 0.72, 95% CI: 0.68-0.76)
Smoking cessation advice	Care by cardiologist (OR: 16.61, 95% CI: 15.43-17.88) Most deprived (OR: 1.95, 95% CI: 1.86-2.04) Asthma or COPD (OR: 1.45, 95% CI: 1.39-1.51) Peripheral vascular disease (OR: 1.40, 95% CI: 1.31-1.50) Chronic renal failure (OR: 1.39, 95% CI: 1.29-1.50)	Advanced age (OR: 0.11, 95% CI: 0.10-0.12) Creatinine (>200 (µmol/l)) (OR: 0.38, 95% CI: 0.36-0.41) Heart rate (>110 bpm) (OR: 0.64, 95% CI: 0.61-0.66)
Dietary advice	Care by cardiologist (OR: 12.28, 95% CI: 11.85-12.72) Chronic renal failure (OR: 1.81, 95% CI: 1.74-1.88) Peak troponin (≥ 0.06) (OR: 1.34, 95% CI: 1.29-1.39)	Creatinine (>200 (µmol/l)) (OR: 0.30, 95% CI: 0.29-0.31) Heart rate (>110 bpm) (OR: 0.73, 95% CI: 0.71-0.75) Systolic blood pressure (<90 mmHg) (OR: 0.76, 95% CI: 0.71-0.82)
Coronary angiography	Care by cardiologist (OR: 4.01, 95% CI: 3.95-4.07) Family history of CHD (OR: 2.41, 95% CI: 2.37-2.46) Sex (OR: 1.82, 95% CI: 1.80-1.85) Hypercholesterolaemia (OR: 1.62, 95% CI: 1.60-1.65) Current or ex-smoker (OR: 1.44, 95% CI: 1.42-1.46)	Cerebrovascular disease (OR: 0.48, 95% CI: 0.46-0.49) Previous MI (OR: 0.68, 95% CI: 0.67-0.69) Asthma or COPD (OR: 0.75, 95% CI: 0.73-0.76)
Aspirin at discharge	Care by cardiologist (OR: 2.70, 95% CI: 2.60-2.81) Advanced age (OR: 1.64, 95% CI: 1.55-1.73)	Cardiac arrest (OR: 0.53, 95% CI: 0.49-0.57) Systolic blood pressure (<90 mmHg) (OR: 0.70, 95% CI: 0.65-0.76)

Abbreviations: ARB, angiotensin receptor blocker; ACE, angiotensin converting enzyme; MI, myocardial infarction; CHD, coronary heart disease; COPD, chronic obstructive pulmonary disease; PCI, percutaneous coronary intervention; OR, odds ratio.

4.4 Impact of quality of care on survival for patients with NSTEMI

4.4.1 Survival

The median time to death for the analytical cohort was 1.1 (IQR 0.3 to 2.4) years, with 29.2% (113,586) deaths, corresponding to 10.5 deaths per 100 person years (1,079,044 person years). The crude mortality rates were lower for the optimally cared for patients ((10.4% (5,342) vs. 32.0% (108,244), P<0.001)) and there was a significant difference in unadjusted survival rates between those who received optimal care compared with those who did not (Figure 4.3). Similarly, there were significant differences in unadjusted survival rates for the latent classes between the high receipt class compared with the intermediate and low receipt classes, with the poorest survival being observed in the low receipt class (Figure 4.3). However, overlapping confidence intervals were observed in later follow-up times due to the low numbers at risk in the high receipt class at the time point (Figure 4.3).

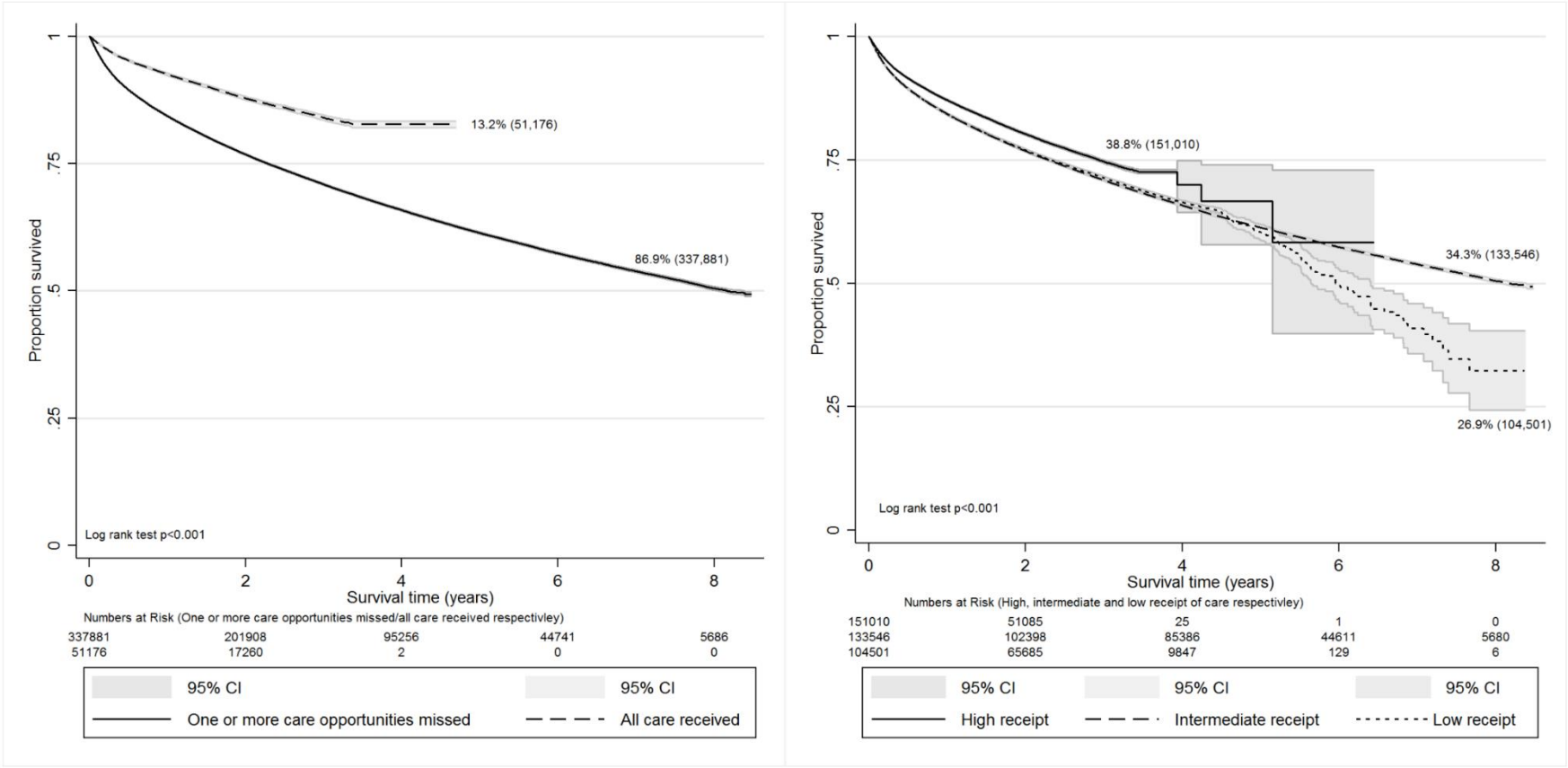


Figure 4.3. Unadjusted Kaplan-Meier curves for time to death by receipt of guideline-indicated care for NSTEMI patients.

After adjustment, patients who received sub optimal care's survival time was reduced by 56% (Time ratio (TR) 0.44, 95% CI 0.41–0.45) compared with those who received all the guideline indicated care interventions for which they were eligible (Figure 4.4). For the latent classes, patients in the intermediate receipt of care class's survival was shortened by 16% (TR 0.84, 95% CI 0.79–0.88) and those in the low receipt of care class by 23% (TR 0.77, 95% CI 0.74–0.80), compared with the patients in the high receipt of care class (Figure 4.4). Individual assessments of the impact of missing each of the 13 care interventions considered were done and not getting a coronary angiogram was found to have the biggest impact on survival i.e. survival time was shortened by 82% (TR 0.18, 95% CI 0.17–0.18) when NSTEMI patients missed this care intervention. Other care interventions that were found to have a strong impact on survival included cardiac rehabilitation (TR 0.49, 95% CI 0.48–0.50), smoking cessation advice (TR 0.53, 95% CI 0.51–0.57), and statins (TR 0.56, 95% CI 0.55–0.58), with the ones with the lowest impact being recording of an Electrocardiogram (TR 0.92, 95% CI 0.89-0.96) and echocardiography (TR 0.94, 95% CI 0.92-0.96) (Figure 4.4).

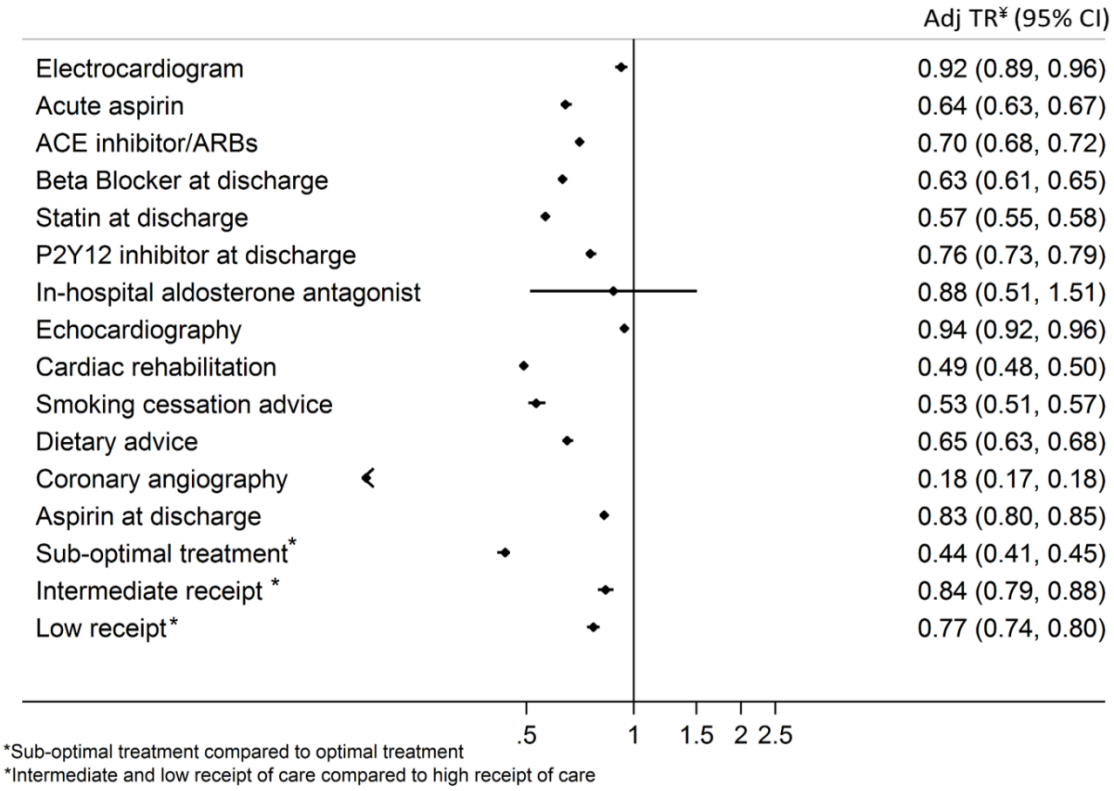


Figure 4.4 Impact of missing specific guideline-indicated interventions, sub-optimal care, and intermediate and low receipt of care on survival.

4.4.1.1 Avoidable deaths

If all the NSTEMI patients in the analytical cohort had received all the guideline recommended care for which they were eligible, 32,765 (28.9%) (95% CI 30,531-33,509) deaths could have been potentially avoided or postponed (Table 4.11). By latent classes, 17,778 (15.7%) (95% CI 16,720–18,625) deaths could have been potentially prevented or postponed if patients in the intermediate class of receipt of care had been treated equivalent to those in the high receipt of care class and 16,177 (14.3%) (95% CI 15,547–16,807) deaths could have been prevented or postponed in the low receipt class if the patients had been treated similar to those in the high receipt class (Table 4.11). For the individual assessments of the

13 guideline indicated care interventions, avoidable deaths ranged from 123-40,228 (median 7,104, IQR 4,653-23,383) deaths (Table 4.11).

Table 4.11 Estimated number of preventable deaths and median survival times by quality of care and by care interventions.

Treatment	Preventable deaths (based on imputed data estimates)	Median (IQR) survival time (years)
Sub-optimal care	32,765 (30,531 - 33,509)	2.5 (1.2 – 4.4)
Intermediate receipt class*	17,778 (16,720 - 18,625)	5.0 (2.3 -6.5)
Low receipt class*	16,177 (15,547 – 16,807)	2.5 (1.4 – 3.3)
Electrocardiogram	3,866 (3,740 – 4,034)	4.5 (1.7 – 6.7)
Acute aspirin	4,653 (4,438 – 4,796)	2.6 (1.2 – 5.1)
ACE inhibition or ARBs	5,991 (5,820 – 6,163)	4.9 (1.6 – 6.4)
β blockers	4,118 (3,987 – 4,249)	4.7 (1.5 -6.2)
Statin at discharge	7,081 (6,954 – 7,334)	2.6 (1.0 – 4.9)
$P2Y_{12}$ inhibitors at discharge	25,133 (24,141 – 26,125)	3.2 (1.7 – 5.07)
Aldosterone antagonist	123 (71 – 211)	1.7 (0.8 - 2.5)
Echocardiography	40,228 (39,373 – 41,084)	2.5 (1.2 – 4.4)
Cardiac rehabilitation	11,400 (11,167 – 11,633)	2.4 (1.0 – 4.4)
Smoking cessation advice	23,383 (22,501 – 25,148)	3.2 (1.6 – 5.3)
Dietary advice	31,712 (30,736 – 33,176)	3.1 (1.5 – 5.2)
Coronary angiography	8,236 (7,778 – 8,236)	2.4 (0.8 – 4.6)
Aspirin at discharge	7,104 (6,847 – 7,275)	3.0 (1.3 – 5.1)

*compared to the high receipt class.

Abbreviations: ARB, angiotensin receptor blocker; ACE, angiotensin converting enzyme.

4.4.1.1.1 Monte Carlo Errors (MCE)

A sensitivity analysis was conducted by making comparisons of the results from univariable unadjusted analysis, complete case analysis and imputed data analysis and a difference was noted (see Appendix C) in the estimates thus warranting the imputed data analysis to be carried out. After assessment of the MCEs, they were found to be sufficiently less than 10% of the estimated standard errors (Table 4.12), which gave evidence that the results from the 10 imputed datasets used were stable estimates of the results.

Table 4.12 Multivariable hierarchical accelerated failure time survival model for the effect of latent classes of receipt of care on survival.

Variable	Coefficient	Coefficient ± MCE	P-value	P-value ± MCE
Latent class				
High receipt	1	-	-	-
Intermediate receipt	-0.18	-0.1802, -0.1798	<0.001	<0.001, <0.001
Low receipt	-0.26	-0.2602, -0.2598	<0.001	<0.001, <0.001
Receipt of care group				
Optimal care	1	-	-	-
Sub-optimal care	-0.84	-0.8401, -0.8399	<0.001	<0.001, <0.001
Care intervention				
Electrocardiogram	-0.08	-0.0805, -0.0795	<0.001	<0.001, <0.001
Acute aspirin	-0.44	-0.4405, -0.4395	<0.001	<0.001, <0.001
Echocardiography	-0.06	-0.0602, -0.0598	<0.001	<0.001, <0.001
Coronary angiography	-1.73	-1.7301, -1.7299	<0.001	<0.001, <0.001
Aspirin at discharge	-0.19	-0.1903, -0.1897	<0.001	<0.001, <0.001
P2Y12 inhibitors at discharge	-0.28	-0.2802, -0.2798	<0.001	<0.001, <0.001
ACE inhibition or ARBs	-0.35	-0.3504, -0.3496	<0.001	<0.001, <0.001
β blockers	-0.46	-0.4602, -0.4596	<0.001	<0.001, <0.001
Statin at discharge	-0.57	-0.5702, -0.5698	<0.001	<0.001, <0.001
Aldosterone antagonist	-0.13	-0.1324, -0.1276	0.639	0.633, 0.645
Dietary advice	-0.43	-0.4298, -0.4302	<0.001	<0.001, <0.001
Smoking cessation advice	-0.63	-0.6296, -0.6304	<0.001	<0.001, <0.001
Cardiac rehabilitation	-0.71	-0.7103, -0.7097	<0.001	<0.001, <0.001

Abbreviations: MCE, Monte Carlo errors.

4.5 Summary of key findings

- Over half of the NSTEMI patients in the analytical cohort were either previous or current smokers, a third had previous angina, a quarter had previous AMI, a fifth were diabetic and over half were hypertensive.
- A large proportion (86.8%) of the NSTEMI patients in the analytical cohort received sub-optimal care (missed one or more guideline indicated care interventions), with most frequently missed care interventions being dietary advice, smoking cessation advice, echocardiography, $P2Y_{12}$ prescription at discharge, prescription of in-hospital aspirin and coronary angiography.
- A three class solution was found optimal in defining 'real life' clinical practice patterns of receipt of care for NSTEMI patients recorded in the nationwide registry MINAP and the classes were nominally labelled 'high', 'intermediate', and 'low' depending on the conditional item probabilities of receipt of each of the 13 guideline indicated care interventions in each class. Use of an electrocardiogram, aspirin at discharge and statins at discharge were high in all three classes with receipt of $P2Y_{12}$ inhibitors at discharge, echocardiography, cardiac rehabilitation, dietary advice, coronary angiography and acute aspirin being highest in the high receipt class. Patients in the high receipt class had low conditional item probabilities for ACEi/ARBs and β blockers, however the intermediate receipt class had highest conditional item probabilities of receipt for ACEi/ARBs and β blockers compared to the two other classes.
- Of the potential predictors of receipt of care (optimal or individual care interventions) care by cardiologist was a positive predictor of receipt of guideline indicated care, with the exception for acute aspirin and cardiac rehabilitation were being a current or ex-smoker and peak troponin ≥0.06 were positive predictors, respectively.
- Not receiving all the guideline recommended care interventions for NSTEMI patients resulted to a shortened survival time by over 50%

compared to the NSTEMI patients who received optimal medical care.

- Individual assessments of the 13 considered care interventions showed that coronary angiography, cardiac rehabilitation, smoking cessation advice and statins had the strongest impact on reduced survival, with coronary angiography having the strongest impact of all the care interventions.
- Receipt of sub-optimal NSTEMI care was found to be associated with 32,765 avoidable/preventable deaths.

4.6 Conclusion

The results presented in this chapter focused on the potentially avoidable harm associated with sub-optimal care management of NSTEMI patients across a single national health care system. The findings show that if all the patients during the study period (2003-2013) had received all the guideline indicated care interventions for which they were eligible for then approximately 33,000 deaths may have been prevented. This equates to about one avoidable death per month per hospital over the last decade in the National Health Service.

This present chapter has given evidence of excess mortality associated with sub-optimal NSTEMI care, highlighted the care interventions that are being frequently missed, and also identified the most important predictor of receipt of guideline indicated care. The next chapter (Chapter 5) presents results on how NSTEMI care varied between hospitals, Strategic Clinical Networks and Clinical Commissioning Group.

Chapter 5 : Results

Geographic variation in the treatment of non ST-segment myocardial infarction in the English National Health Service: a cohort study.

The following publications have arisen from the analysis and results in this chapter:

1. **Dondo, TB**, Hall, M, Timmis, AD, Yan, AT, Batin, PD, Oliver, G, Alabas, OA, Norman, PD, Deanfield, JE, Bloor, K, Hemingway, H, Gale, CP. (2016). Geographic variation in the treatment of non ST-segment myocardial infarction in the English National Health Service: a cohort study. *BMJ Open*. doi: 10.1136/bmjopen-2016-011600.
2. **Dondo, TB**, Hall, M, Timmis, AD, Yan, AT, Batin, PD, Oliver, G, Alabas, OA, Norman, PD, Deanfield, JE, Bloor, K, Hemingway, H, Gale, CP. (2016). Geographic variation in the treatment of non ST-segment elevation myocardial infarction: a national cohort study. Eur Heart J (Vol. 37, No. S1, pp. 1177-1178). Oxford University Press. (Presented as a poster at the European Society Congress 2016, London).

5.1 Introduction

Following on from quantifying avoidable deaths associated with sub-optimal care of NSTEMI patients and highlighting the care interventions that were mostly missed in Chapter 4, geographic variation in receipt of the guideline indicated care was assessed. This chapter summarises the analyses' results of objective two of the thesis that aimed to study the geographic variation in receipt of care for NSTEMI patients. The chapter includes five sections of results as listed below:

- Descriptive statistics: Study population and guideline indicated care interventions (§5.2)
- Geographic variation in receipt of care for NSTEMI patients (§5.3)
- Variance components from multi-level models (§5.4)
- Temporal changes in receipt of care for NSTEMI patients (§5.5)
- Avoidable deaths associated with sub-optimal care for NSTEMI patients (§5.6)
- Summary of key findings (§5.7)
- Conclusion (§5.8).

A detailed description of the methods employed for the analyses has already been given in Chapter 3, §3.7.

5.2 Descriptive statistics

5.2.1 Study population and guideline indicated care interventions

Of the 389,057 NSTEMI patients used as the analytical cohort, 357,228 patients were geocoded to boundary data and the remaining 31,829 (8.2%) cases excluded from analyses in this chapter due to missing location data. The distribution of the patient characteristics for the geocoded patients was similar to the full analytical cohort, i.e. mean age 70.9 (SD 13.3) years, 63.1% (n=225,009) male, majority white (93.1%, n=301,312), a third with previous history of angina (31.7% (n=113,059)), a quarter with previous myocardial infarction (21.5% (n=89,571)), over half previous or current smokers (71.2% (n=254,215)), almost half hypertensive (48.9% (n=174,596)), a fifth diabetic (21.1% (n=75,433)), 14.6% (n=52,030) having asthma or COPD and over half of the patients were not treated by a cardiologist (n=207,355, 58.1%) (Table 5.1). With similar distributions being noted for the rest of the characteristics summarised in Table 5.1, these results showed that exclusion of the non-geocoded patients (8.1%) did not affect the generalisability of the geocoded patients to the full cohort. Receipt of guideline-indicated care ranged from 12.5% to 94.1% (median 67.9%, IQR 41.0% to 86.2%) (Table 5.2). According to the cut-offs ≤40%, >40% to ≤79% and >79% (commonly used in past studies(67, 128)), 11.8% (n=42,229) patients received ≤40% of the guideline indicated care interventions for which they were eligible, 58.5% (n=208,930) received >40% to ≤79% and 29.7% (n=106,069) received >79%.

Table 5.1 Baseline characteristics of geo coded patients, NSTEMI, 2003-2013.

Characteristics	Cases n=357,228	Missing
Age, years; mean (sd)	70.9 (13.3)	504 (0.1)
Male	225,009 (63.1)	593 (0.2)
Deprivation according to IMD score		
1 (least deprived)	61,235 (17.2)	
2	70,084 (19.6)	419 (0.1)
3	74,842 (21.0)	
4	72,121 (20.2)	
5(most deprived)	78,527 (22.0)	
Past medical history		
Myocardial infarction	89,571 (25.1)	0¥
Heart failure	22,581 (6.3)	0¥
PCI	30,835 (8.6)	0¥
CABG	26,021 (7.3)	0¥
Angina	113,059 (31.7)	0¥
Cerebrovascular disease	31,366 (8.8)	0¥
Peripheral vascular disease	16,868 (4.7)	0¥
Diabetes	75,433 (21.1)	0¥
Chronic renal failure	20,349 (5.7)	0¥
Hypercholesterolaemia	112,713 (31.5)	0¥
Hypertension	174,596 (48.9)	0¥
Previous or current smoker	254,215 (71.2)	0¥
Asthma or COPD	52,030 (14.6)	0¥
Family history of CHD	72,444 (20.3)	0¥
Presenting characteristics		
Systolic blood pressure, mmHg, mean (sd)	142.5 (28.4)	59,962 (16.8)
Systolic blood pressure, <90 mmHg	7,280 (2.5)	59,962 (16.8)
Heart rate, bpm, mean (sd)	80 (67-95)	59,177 (16.6)
Heart rate >110 bpm	32,964 (11.1)	59,177 (16.9)
Creatinine; mean (sd)	92 (76-114)	147,959 (41.4)
Troponin elevation	321,212 (94.6)	17,559 (4.9)
Cardiac arrest	6,178 (1.8)	21,038 (5.9)
Electrocardiogram changes		
No acute changes	51,214 (15.7)	
ST-segment elevation	14,336 (4.4)	
Left bundle branch block	21,149 (6.5)	31,825 (8.9)
ST-segment depression	84,821 (26.1)	
T wave changes only	85,474 (26.3)	
Other acute abnormality	68,409 (21.0)	
Use of a loop diuretic	89,438 (30.2)	61,294 (17.1)
GRACE risk score category		
Low (≤88)	25,787 (18.2)	
Intermediate (88-110)	38,897 (27.5)	215,599 (60.4)
High (>110)	76,945 (54.3)	

Abbreviations: NSTEMI, non-ST-segment elevation myocardial infarction; sd, standard deviation; IMD, Index of multiple deprivation; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; COPD, chronic obstructive pulmonary disease; CHD, coronary heart disease; bpm, beats per minute; GRACE risk score category as defined by NICE. ¥ missing data default imputed to “No”.

Table 5.2. Eligibility and receipt of guideline-indicated interventions in geo coded patients, NSTEMI, 2003-2013.

Guideline-indicated intervention	Number (%) of NSTEMI who received a guideline-indicated intervention	Number of NSTEMI eligible for a guideline-indicated intervention
Electrocardiogram	336,094 (94.1)	357,228
Acute aspirin	212,837 (88.7)	239,876
Echocardiography	178,851 (50.1)	357,195
Coronary angiography	196,781 (57.4)	342,856
Aspirin at discharge	279,584 (89.1)	313,901
P2Y12 inhibitors	121,427 (41.0)	296,450
ACEis/ARBs	81,176 (67.9)	119,625
β Blockers	80,600 (74.8)	107,698
Statins at discharge	275,626 (86.2)	319,747
Aldosterone antagonists	134 (23.7)	566
Dietary advice	111,759 (32.6)	342,960
Smoking cessation advice	31,683 (12.5)	254,215
Cardiac rehabilitation	257,875 (76.7)	336,146

Abbreviations: ACEis, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blockers.

5.3 Geographic variation in receipt of care for NSTEMI patients

5.3.1 Variation by Clinical Commissioning Groups (CCGs)

At CCG level a low proportion of patients received optimal care (median 12.8%, interquartile range (IQR) 0.7 to 18.1%) (Figure 5.1). High prescription rates of aspirin acutely (median 92.8%, interquartile range 88.6 to 97.1%), aspirin at discharge from hospital (90.1%, 85.1 to 93.3%) and statins (86.4%, 82.3 to 91.2%) were noted consistently across the CCGs (Figure 5.1). The greatest variation was noted for in hospital aldosterone antagonists (median 16.7%, IQR 0.0 to 40.0%) and least for use of an electrocardiogram (96.7%, 92.5 to 98.7%) (Figure 5.1). The provision of echocardiography (50.3%, 38.3 to 61.9%), cardiac rehabilitation (79.7%, 68.2 to 87.1%), coronary angiography (57.4%, 48.8 to 66.7%), the prescription of ACEi/ARBs (69.0%, 63.6 to 74.0%) and β blockers (76.3%, 70.4 to 82.0%) was intermediate and varied, whilst the provision of smoking cessation advice (11.6%, 8.7 to 16.6%), dietary advice (32.4%, 23.9 to 41.7%) and $P2Y_{12}$ inhibitors (39.7%, 32.4 to 46.9%) was poor (Figure 5.1).

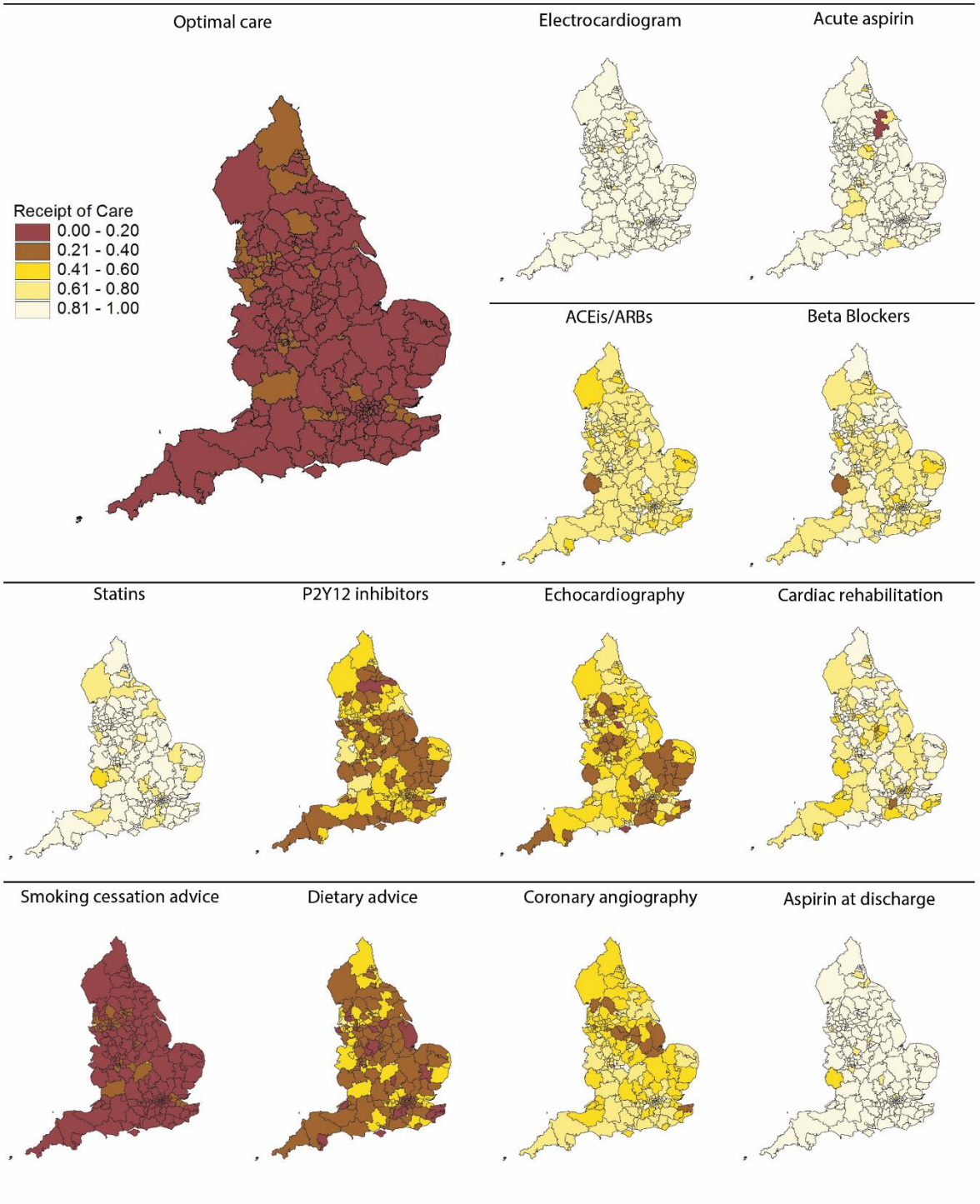


Figure 5.1 Geographic variation proportions of eligible patients who received guideline-indicated interventions, for each intervention and for optimal care, by CCG.

5.3.2 Variation by Strategic Clinical Networks (SCNs)

Similar to the CCGs, proportion of patients who received optimal care was low across the SCNs (median 12.2%, IQR 11.5 to 15.9%) (Table 5.3). North East and North Cumbria, and East Midlands had the highest proportion of patients receiving optimal care (20.0% (n=7,045) and 10.3% (n=3,409), respectively) (Table 5.3). Low receipt rates were noted consistently for $P2Y_{12}$ inhibitors (median 40.0%, IQR 39.0 to 42.0%), aldosterone antagonists (27.0%, 20.0 to 28.0%), smoking cessation advice (13.0%, 12.0 to 17.0%) and dietary advice (32.0%, 28.0 to 37.0%) across the SCNs (Table 5.3). Intermediate to high receipt rates with minimal variation were noted for electrocardiogram (median 95.0%, IQR 92.0 to 96.0%), acute aspirin (91.0%, 88.0 to 92.0%), statins (86.0%, 84.0 to 87.0%), aspirin on discharge (89.0%, 87.0 to 90.0%), cardiac rehabilitation (79.0, 72.0 to 82.0%), β blockers (76.0%, 73.0 to 76.0%), the prescription of ACEi/ARBs (68.0%, 67.0 to 70.0%) across the SCNs, with echocardiography and coronary angiography being received at an intermediate rate (median 50.0%, IQR 45.0 to 55.0% and 58.0%, 52.0 to 61.0%, respectively) (Table 5.3).

Table 5.3. Proportions of patients (of the eligible) receiving each care intervention by SCNs.

	GEOGRAPHIC REGION (SCNs)											
Treatments n (%)	**Cheshire and Merseyside**	**East Midlands**	**East of England**	**G Manchester Lancashire and S Cumbria**	**London**	**North East and N Cumbria**	**South East coast**	**South West**	**Thames Valley**	**Wessex**	**West Midlands**	**Yorkshire and Northern**
ECG	18,412 (94.3)	32,080 (96.7)	45,553 (95.9)	26,346 (88.8)	32,524 (94.6)	34.149 (96.9)	24,522 (95.8)	27,612 (94.6)	9,236 (94.9)	14,903 (93.1)	28,563 (90.7)	42,194 (92.3)
Acute aspirin	11,921 (91.6)	18,412 (92.3)	30,302 (91.5)	19,993 (90.5)	20,143 (90.3)	18,733 (88.4)	16,291 (92.6)	17,045 (90.0)	6,034 (94.2)	10,385 (95.1)	20,103 (85.3)	23,475 (76.3)
ACEi/ARB	3,577 (64.5)	7,522 (68.1)	10,670 (66.8)	6,746 (70.6)	7,654 (70.1)	8,440 (64.4)	5,667 (67.3)	6,824 (66.3)	2,402 (72.3)	4,333 (73.7)	6,892 (70.0)	10,449 (67.7)
β blockers	3,252 (68.9)	7,849 (74.7)	10,046 (72.7)	6,834 (76.2)	7,543 (75.5)	8,720 (73.1)	5,798 (75.9)	6,612 (71.5)	2,367 (76.3)	4,089 (78.9)	7,032 (76.4)	10,458 (78.3)
Statins	13,292 (84.9)	25,153 (84.9)	35,808 (84.4)	24,896 (90.6)	27,022 (86.7)	25,154 (84.4)	20,574 (86.2)	22,005 (83.2)	8,060 (88.5)	12,260 (88.1)	24,513 (87.4)	36,889 (87.4)
$P2Y_{12}$ inhibitors	5,564 (39.3)	11,180 (39.9)	15,646 (39.1)	11,836 (42.3)	12,388 (42.3)	11,570 (43.2)	9,388 (41.5)	9,863 (41.4)	3,944 (46.7)	4,599 (40.0)	10,468 (40.4)	14,981 (38.4)
Aldosterone antagonists	8 (33.3)	9 (18.4)	15 (27.3)	10 (33.3)	20 (27.4)	19 (18.1)	12 (28.6)	7 (20.0)	5 (31.3)	6 (14.6)	12 (21.1)	11 (28.2)
Echocardiography	11,918 (61.0)	17,252 (52.0)	21,268 (44.8)	15,938 (53.7)	19,453 (56.6)	20,788 (59.0)	10,666 (41.7)	14,001 (50.0)	4,524 (46.5)	8,850 (55.3)	14,570 (46.3)	19,623 (42.9)
Cardiac rehabilitation	14,120 (74.2)	22,050 (71.8)	35,708 (81.4)	21,464 (77.7)	21,295 (65.1)	26,916 (78.8)	17,418 (71.8)	17,147 (64.9)	7,029 (79.1)	13,443 (87.0)	24,180 (81.9)	37,105 (85.4)
Smoking cessation advice	2,215 (17.0)	2,888 (11.8)	3,310 (9.3)	3,396 (17.2)	2,983 (11.5)	3,709 (14.6)	2,052 (11.7)	2,033 (9.9)	848 (13.1)	1,227 (10.5)	2,515 (11.5)	4,507 (14.1)

	GEOGRAPHIC REGION (SCNs)											
Treatments n (%)	**Cheshire and Merseyside**	**East Midlands**	**East of England**	**G Manchester Lancashire and S Cumbria**	**London**	**North East and N Cumbria**	**South East coast**	**South West**	**Thames Valley**	**Wessex**	**West Midlands**	**Yorkshire and Northern**
Dietary advice	7,488 (39.6)	8,214 (26.3)	16,187 (34.9)	10,946 (38.7)	8,592 (26.1)	12,627 (36.9)	7,632 (31.3)	7,721 (27.9)	3,510 (38.7)	4,980 (31.8)	9,712 (33.0)	14,150 (31.6)
Coronary angiography	8,569 (47.6)	15,379 (47.8)	26,371 (57.7)	14,618 (51.3)	23,269 (69.6)	17,773 (52.6)	14,718 (59.6)	16,869 (61.3)	5,741 (59.9)	10,493 (66.1)	20,370 (67.0)	22,611 (52.3)
Aspirin on discharge	12,887 (86.9)	25,395 (87.3)	36,255 (87.4)	24,797 (93.2)	27,371 (88.8)	26,056 (88.0)	21,060 (90.1)	23,441 (89.8)	8,179 (89.9)	12,940 (91.5)	24,450 (88.6)	36,753 (89.3)
Optimal care	3,099 (15.9)	3,409 (10.3)	5,498 (11.6)	5,128 (17.3)	4,194 (12.2)	7,045 (20.0)	3,133 (12.2)	3,342 (11.5)	1,757 (18.0)	2,386 (14.9)	4,356 (13.8)	4,910 (10.7)

Abbreviations: ARB, angiotensin receptor blocker; ACE, angiotensin converting enzyme.

5.4 Variance components from multi-level models

As described in the methodology section in Chapter 3 (§3.7), multilevel models were fitted to quantify the proportion of variance in receipt of optimal care for NSTEMI patients that is explained by the clustering structure (patients nested within hospitals, nested within CCGs, nested within SCNs) of the hierarchical model. After adjustment for case mix (fixed effects), the between unit variance was low for SCNs (0.004, 95% CI 0.0004 to 0.03), for CCGs (0.004, 0.001 to 0.03) and higher for hospitals (1.92, 95% CI 1.51 to 2.44) (Table 5.4). The findings showed that 99.6% of the remaining variability in provision of optimal guideline indicated care after case mix adjustment was between hospitals (ICC 0.996, 95% CI 0.976 to 0.999) with 0.2% between SCNs (ICC 0.002, 95% CI 0.0002 to 0.01) and 0.2% between CCGs (ICC 0.002, 95% CI 0.0007 to 0.01).

Table 5.4. Results from the multi-level Poisson model fitted to investigate variation in optimal receipt of care (Parameter estimates, p-values, standard errors and 95% CIs).

Fixed Effects	Incidence ratios	P-value	95% CI
Sex (male vs. female)	1.12	>0.001	1.11, 1.15
Deprivation according to IMD score			
1 (least deprived)	1	-	1
2	0.98	0.34	0.95, 1.02
3	0.99	0.41	0.95, 1.02
4	0.97	0.06	0.93, 1.00
5 (most deprived)	0.96	0.02	0.92, 0.99
Ethnicity			
White	1	-	1
Black	0.99	0.78	0.90, 1.08
Asian	1.02	0.32	0.98, 1.07
Mixed	1.21	0.07	0.98, 1.48
Other	0.92	0.10	0.84, 1.02
GRACE risk score category			
Low (≤88)	1	-	1
Intermediate (88-110)	0.97	0.16	0.94, 1.01
High (>110)	0.78	>0.001	0.76, 0.81
Current or ex-smokers (Yes vs. No)	1.16	>0.001	1.14, 1.19
Prior diabetes (Yes vs. No)	0.99	0.88	0.98, 1.02
Prior MI (Yes vs. No)	0.90	>0.001	0.88, 0.92
Prior angina (Yes vs. No)	0.91	>0.001	0.89, 0.93
rior PCI (Yes vs. No)	0.98	0.33	0.95, 1.02
Prior CABG (Yes vs. No)	0.95	0.01	0.92, 0.99

Prior peripheral vascular disease (Yes vs. No)	0.95	0.03	0.91, 0.99
Hypercholesterolemia	1.11	>0.001	1.08, 1.13
Prior hypertension (Yes vs. No)	1.02	0.08	1.00, 1.04
Prior cerebrovascular disease (Yes vs. No)	0.88	>0.001	0.84, 0.90
Prior chronic obstructive pulmonary disease/asthma (Yes vs. No)	0.94	>0.001	0.92, 0.97
Family history of CHD (Yes vs. No)	1.15	>0.001	1.13, 1.17
Year	1.60	>0.001	1.60, 1.62
Random Effects	**Variance**	**Standard error**	**95% CI**
Hospital variance	1.92	0.24	1.51, 2.44
CCG variance	0.004	0.004	0.001, 0.03
SCN variance	0.004	0.004	0.0004, 0.03

Abbreviations: IMD, Index of multiple deprivation; CABG, coronary artery bypass graft; CHD, coronary heart disease; COPD, chronic obstructive pulmonary disease; PCI, percutaneous coronary intervention; Clinical Commissioning Groups (CCGs); Strategic Clinical Networks (SCNs).

5.5 Temporal changes in receipt of care for NSTEMI patients

An improvement in the provision of care for NSTEMI patients was observed after comparing rates of receipt of care for the years 2003/04 with 2012/13 across CCGs (Table 5.5). Improvement in provision of care was most pronounced for smoking cessation advice (median CCG rates: 0.00 vs. 69%), dietary advice (0.00 vs.84%), coronary angiography (33 vs. 83%), ACEis/ARBs (71 vs. 100%) and β blockers (77 vs. 100%). An improvement was also observed for receipt of optimal care (0.00 vs. 43%) and although the correlation between care in CCGs over the study period was significant, it was weak (*rho* = 0.36, *P*<0.001).

Table 5.5. Temporal changes in the proportion of NSTEMI receiving guideline-indicated treatments, 2003/04 vs. 2012/13 in CCGs.

Guideline-indicated intervention	Biennial year	
	2003/04 Median (IQR)	2012/13 Median (IQR)
Optimal care	0.00	0.34 (0.23-0.46)
Electrocardiogram	0.86 (0.69-0.96)	1.00 (0.99-1.00)
Acute aspirin	0.88 (0.81-0.94)	0.97 (0.93-0.99)
ACEis/ARBs	0.71 (0.65-0.76)	1.00 (1.00-1.00)
β blockers	0.77 (0.71-0.83)	1.00 (0.93-1.00)
Statins	0.83 (0.77-0.88)	0.95 (0.91-0.98)
$P2Y_{12}$ inhibitors	0.00	0.94 (0.88-0.98)
Aldosterone antagonist	-	0.00 (0.00-1.00)
Echocardiography	0.41 (0.27-0.57)	0.63 (0.51-0.76)
Cardiac rehabilitation	0.73 (0.60-0.83)	0.87 (0.74-0.94)
Smoking cessation advice	0.00	0.69 (0.47-0.87)
Dietary advice	0.00	0.84 (0.62-0.93)
Coronary angiography	0.33 (0.21-0.47)	0.83 (0.75-0.89)
Aspirin on discharge	0.89 (0.83-0.93)	0.97 (0.94-0.99)

Median represents the median of the proportion of eligible NSTEMI who received the.

Abbreviations. IQR, interquartile range; ACEis, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blockers.

5.6 Avoidable deaths associated with sub-optimal care for NSTEMI patients

In order to determine the potentially preventable deaths associated with sub-optimal treatment for hospitals, the adjusted mortality risk (Table 5.6) obtained from the multilevel accelerated failure time modelling were multiplied by the corresponding mortality rates and proportions of patients in the sub-optimal treatment groups per hospital. The product was then multiplied by the total number of NSTEMI between 2003 and 2013 for each hospital. The quantified avoidable deaths associated with sub-optimal care at hospital level over the study period (2003-2013) varied between hospitals (median number of deaths 39, interquartile range 15 to 62).

Table 5.6. Impact of receiving sub-optimal care on NSTEMI patients' survival

Treatment	Complete case analysis Adjusted TRs (95% CI)	Multiple imputation analyses Adjusted TRs (95% CI)	P-value
Optimal care	1	1	-
Sub-optimal care	0.40 (0.38, 0.43)	0.44 (0.41, 0.45)	< 0.001

5.7 Summary of key findings

- Over a 10 year study period, evidence for wide spread sub-optimal use of guideline indicated care for the management of NSTEMI was found.
- The greatest variation in provision of care across CCGs was for aldosterone antagonists and least for use of an electrocardiogram, with high prescription rates and minimal variation for prescription of aspirin acutely, aspirin at discharge from hospital and statins. Intermediate provision rates and wide variation across CCGs were observed for provision of echocardiography, cardiac rehabilitation, coronary angiography, prescription of ACEi/ARBs and β blockers, with low provision rates for and little variation across CCGs for provision of smoking cessation advice, dietary advice and $P2Y_{12}$ inhibitors.
- Across SCNs the areas that had the highest proportion of patients receiving optimal care were North East and North Cumbria, and East Midlands.
- Similar to the CCGs, low provision of care rates with minimal variation between SCNs were noted for provision of smoking cessation advice, dietary advice, aldosterone antagonists and $P2Y_{12}$ inhibitors, and high provision rates with minimal variation were noted for use of an electrocardiogram, acute aspirin, statins, aspirin on discharge, cardiac rehabilitation, β blockers and prescription of ACEi/ARBs, with an intermediate provision of coronary angiography and echocardiography.

- The between unit variance, standardised for case mix, was low for SCNs and CCGs but much higher for hospitals.
- Improvements in provision of guideline indicated care for NSTEMI management were observed over the 10 year study period (2003-2013), with notable improvements being noted for smoking cessation advice, dietary advice, coronary angiography, ACEi/ARBs and β blockers. However a modest improvement in receipt of optimal care was found.
- Geographical variation in receipt of optimal care was identified and was found to be associated with geographical variation in excess deaths.

5.8 Conclusion

The findings presented in this chapter provide evidence that there is variation in provision of care for NSTEMI patients in the UK, and that most of the variation was explained by differences in the provision of care by hospitals. The next chapter presents results for objective three of this thesis.

Chapter 6 : Results

Association of clinical factors and therapeutic strategies with improvements in survival following STEMI.

6.1 Introduction

Quality of care and associated outcomes for NSTEMI patients have been assessed and the results presented in chapters four and five. These aspects for the STEMI phenotype have been undertaken in previous literature.(61) Over the years marked improvements in outcomes for STEMI patients have been noted, for example the MINAP 2014 report reported unadjusted 30-day mortality rates for STEMI patients had fallen by a third over the last 10 years, equating to an estimated 110 fewer deaths each month. Similarly, reductions in length of stay in hospital for STEMI patients have been reported. For STEMI patients the most obvious care intervention that has been reported to drive this improvement is the change to PPCI. However, there is a paucity of contemporary studies of sufficient duration and representation from a population perspective that enable a detailed evaluation of the association of baseline risk and guideline-indicated therapies with temporal trends in mortality among patients with STEMI.

This chapter comprises of sections presenting results for objective three of the thesis which aimed to investigate using MINAP data whether temporal improvements in one year mortality between 2004 and 2013 were associated with changes in patients' baseline clinical risk or use of guideline-indicated treatments for management of STEMI and estimate the relative contribution of

the determined factors going beyond the estimation of simple point association effects. The chapter sections are outlined as listed below:

- Study population descriptive statistics (§6.2)
- Temporal trends in clinical characteristics (§6.3)
- Temporal trends in guideline-indicated treatments (§6.4)
- Temporal trends in mortality (§6.5)
- Association between changing risk profile and improved outcomes (§6.6)
- Mediation analysis (§6.6.2)
- Summary of key findings (§6.7)
- Conclusion (§6.8).

A detailed description of the methods employed for the analyses has already been given in Chapter 3, §3.8.

6.2 Study population descriptive statistics

Of the total analytical cohort (N= 232,353), 72.0% (n=166,690) were male and had a median age of 64.6 (IQR 55.0 to 75.0). Their median survival time was 2.5 years (IQR 1.4 to 4.1 years) (maximum, 7.5 years; 666,576.4 person years). A high proportion of the STEMI patients were hypertensive (37.9 % (n=87,990)), had a family history of coronary heart disease (25.7% (n=59,709)) and were current or ex-smokers (68.1% (n=143,508) (Table 6.1). There were 33,311 (14.3%) deaths during the full follow up time and at one year after hospital discharge 16,239 (7.0%) deaths (5,517 (2.4%) and 12,143 (5.2%) at 30 day and six months after hospital discharge, respectively).

6.3 Temporal trends in clinical characteristics

Over the study period, the proportion of the STEMI patients who had previous AMI (12.9 vs. 10.8%) and previous angina (16.5 vs. 10.9%), and were current or ex-smokers (69.9 vs. 66.0%) decreased (all P<0.001 for trend) whilst the proportion of patients who had diabetes (12.3 vs. 13.9%), chronic renal failure (1.4 vs. 2.1%) and previous PCI (3.5 vs. 6.3%) increased (all P<0.001 for trend). The temporal trends in the baseline characteristics are shown in Table 6.1 and Figure 6.1. A reduced ejection fraction (EF<50%) was present in 53.2% in 2004-05 and decreased to 49.5% in 2012-13 (Table 6.1).

6.4 Temporal trends in guideline-indicated treatments

Overall of the eligible STEMI patients the use of the secondary prevention drugs was high (<90% for all five drugs) and temporal improvements in the prescription of the drugs were noted over the study *p*eriod (Figure 6.2) i.e. prescription of aspirin (98.1 vs. 99.2%, difference, 1.1%, 95% CI 1.0-1.3), β-blockers (94.1 vs. 97.5%, difference, 3.4%, 95% CI 3.1-3.7), statins (97.3 vs.

98.8%, difference, 1.5%, 95% CI 1.3-1.7) and ACEi/ARBs (93.1 vs. 97.3%, difference, 4.2%, 95% CI 3.8-4.5) (Table 6.1). Overall reperfusion rates, 39.6% (n=83,627) of the STEMI patients received PPCI and 39.6% (n=83,800) received thrombolysis. Of those admitted in the years 2004/05 81.1% (n=30,220) received thrombolysis and of those admitted in the years 2012/13 80.2% (n=26,799) received PPCI.

Table 6.1 Patients' characteristics according to date of hospitalisation.

Variable		**2004-2013 N=232,353 (Total cohort)**	**2004-2005 N=42,799 (18.4% of the cohort)**	**2012-2013 N=37,081 (16.0% of cohort)**	**Difference between 2004-2005 and 2012-2013 (95% CI)**	***P*-value for linear trend, 2004-2013[a]**	**Missing (%)**
Age (years)	Median (IQR)	64.6 (55.0-75.0)	65.3 (55.8-74.9)	64.0 (54.5-74.9)	1.30 (1.04-1.56)	<0.001	118 (0.1)
Sex (male)	N (%)	166,690 (72.0)	30,332 (71.2)	26,590 (72.2)	0.93 (0.30-1.56)	0.004	796 (0.3)
Deprivation (IMD Score)	Median (IQR)	18.4 (10.5-32.2)	18.7 (10.6-32.6)	18.4 (10.5-32.1)	0.37 (0.08-0.66)	0.012	17,613 (7.6)
Systolic blood pressure (mm Hg)	Mean (sd)	136.5 (28.2)	139.9 (29.2)	132.8 (26.9)	-7.18 (-7.61 to -6.74)	<0.001	42,949 (18.5)
Heart rate (beat per min)	Mean (sd)	77.9 (20.8)	77.1 (21.4)	77.9 (19.4)	0.83 (0.51-1.14)	<0.001	41,967 (18.1)
Total cholesterol (mg/dL)	Median (IQR)	5.1 (4.2-6.0)	5.4 (4.5-6.3)	4.9 (4.0-5.8)	0.50 (0.47-0.53)	<0.001	60,629 (26.1)
Creatinine (mg/dL)	Median (IQR)	87.0 (74.0-104.0)	101.0 (90.0-116.0)	82.0 (70.0-99.0)	19.0 (17.3-20.7)	<0.001	95,721(41.2)
Ejection fraction < 50%	N (%)	38,634 (49.3)	1,753 (53.2)	9,598 (49.5)	-3.72 (-5.56 to -1.88)	<0.001	153,942 (66.3)
Medical history							

Variable		2004-2013 N=232,353 (Total cohort)	2004-2005 N=42,799 (18.4% of the cohort)	2012-2013 N=37,081 (16.0% of cohort)	Difference between 2004-2005 and 2012-2013 (95% CI)	*P*-value for linear trend, 2004-2013[a]	Missing (%)
Previous diabetes	N (%)	29,083 (12.5)	5,265 (12.3)	5,158 (13.9)	1.61 (1.14-2.08)	<0.001	0[d]
Current or ex-smoker	N (%)	143,508 (68.1)	27,098 (69.9)	22,338 (66.0)	3.93 (-4.61 to 3.25)	<0.001	21,662 (9.3)
Family history of CHD	N (%)	59,709 (25.7)	4,633 (10.8)	10,249 (27.6)	16.8 1 (16.27-17.34)	<0.001	0[d]
Hypertension	N (%)	87,990 (37.9)	15,938 (37.2)	13,960 (37.7)	0.41 (-0.26 to 1.08)	0.235	0[d]
Previous myocardial infarction	N (%)	26,892 (11.6)	5,525 (12.9)	4,012 (10.8)	-2.09 (-2.54 to -1.64)	<0.001	0[d]
Previous angina	N (%)	31,060 (13.4)	7,050 (16.5)	4,036 (10.9)	-5.59 (-6.06 to -5.11)	<0.001	0[d]
Peripheral vascular disease	N (%)	5,868 (2.5)	1,168 (2.7)	950 (2.7)	-0.17 (-0.39 to 0.06)	0.143	0[d]
Cerebrovascular disease	N (%)	10,415 (4.5)	1,896 (4.4)	1,612 (4.4)	-0.08 (-0.37 to 0.20)	0.569	0[d]
COPD or asthma	N (%)	23,404 (10.1)	4,444 (10.4)	3,745 (10.1)	-0.28 (-0.71 to 0.14)	0.187	0[d]

Variable		2004-2013 N=232,353 (Total cohort)	2004-2005 N=42,799 (18.4% of the cohort)	2012-2013 N=37,081 (16.0% of cohort)	Difference between 2004-2005 and 2012-2013 (95% CI)	*P*-value for linear trend, 2004-2013[a]	Missing (%)
Chronic renal failure	N (%)	4,410 (1.9)	576 (1.4)	793 (2.1)	0.79 (0.61-0.98)	<0.001	0[d]
Congestive cardiac failure	N (%)	3,593 (1.6)	762 (1.8)	529 (1.4)	-0.35 (-0.53 to -0.18)	<0.001	0[d]
Previous PCI	N (%)	12,006 (5.2)	1,488 (3.5)	2,318 (6.3)	2.77 (2.47-3.08)	<0.001	0[d]
Previous CABG	N (%)	5,217 (2.3)	921 (2.2)	840 (2.3)	0.11 (-0.09 to 0.32)	0.276	0[d]
Admission diagnosis							
ACS or probable myocardial infarction	N (%)	217,563 (93.6)	40,231 (94.0)	35,270 (95.1)	1.12 (0.80-1.43)	<0.001	4 (<0.1)
Chest pain unknown cause	N (%)	6,810 (2.9)	1,313 (3.1)	797 (2.2)	-0.92 (-1.14 to 0.70)	<0.001	
Other	N (%)	7,976 (3.4)	1,255 (2.9)	1,014 (2.7)	-0.20 (-0.43 to 0.03)	0.093	
Preadmission medication[b]							
Aspirin	N (%)	146,742 (64.4)	26,121 (62.9)	25,229 (68.8)	5.88 (5.22-6.55)	<0.001	0
β-blocker	N (%)	37,199 (22.3)	4,294 (32.2)	6,097 (20.3)	-11.94 (-12.85 to -11.0)	<0.001	65,383 (28.1)

Variable		2004-2013 N=232,353 (Total cohort)	2004-2005 N=42,799 (18.4% of the cohort)	2012-2013 N=37,081 (16.0% of cohort)	Difference between 2004-2005 and 2012-2013 (95% CI)	*P*-value for linear trend, 2004-2013[a]	Missing (%)
Statin	N (%)	54,151 (31.2)	5,008 (37.7)	9,654 (30.2)	-7.47 (-8.44 to -6.50)	<0.001	58,835 (25.3)
ACEi or ARBs	N (%)	45,897 (27.5)	4,264 (32.2)	8,424 (28.0)	-4.20 (-5.14 to -3.25)	<0.001	65,633 (28.3)
$P2Y_{12}$ inhibitor	N (%)	13,136 (14.2)	-	4,566 (14.8)	-		139,488 (60.03)
Warfarin	N (%)	6,891 (3.7)	1,558 (4.6)	1,060 (3.6)	-1.00 (-1.31 to -0.69)	<0.001	46,897 (20.2)
Discharge medication[b]							
Aspirin	N (%)	186,098 (98.8)	35,753 (98.1)	30,197 (99.2)	1.13 (0.96-1.30)	<0.001	19,497 (8.4)
β-blocker	N (%)	165,472 (95.7)	30,375 (94.1)	28,207 (97.5)	3.40 (3.09-3.72)	<0.001	37,691 (16.2)
Statin	N (%)	185,710 (98.1)	35,708 (97.3)	30,029 (98.8)	1.46 (1.26-1.67)	<0.001	20,063 (8.6)
ACEi or ARB	N (%)	173,303 (95.3)	32,616 (93.1)	28,567 (97.3)	4.16 (3.83-4.48)	<0.001	21,322 (9.2)
$P2Y_{12}$ inhibitor	N (%)	89,676 (96.7)	190 (94.5)	28,694 (97.6)	3.05 (-0.10 to 6.20)	0.005	121,483 (52.3)
Aldosterone antagonist	N (%)	7,296 (12.6)	0(0)	3,031 (15.8)	-	-	131,778 (56.7)

Variable		2004-2013 N=232,353 (Total cohort)	2004-2005 N=42,799 (18.4% of the cohort)	2012-2013 N=37,081 (16.0% of cohort)	Difference between 2004-2005 and 2012-2013 (95% CI)	*P*-value for linear trend, 2004-2013[a]	Missing (%)
Reperfusion strategy							
PPCI	N (%)	83,627 (39.6)	148 (2.1)	26,799 (80.2)	78.15 (77.61-78.69)	<0.001	
Thrombolysis	N (%)	83,800 (39.6)	30,220 (81.1)	1,218 (15.6)	-65.54 (-66.44 to -64.65)	<0.001	20,934 (9.0)
None	N (%)	43,992 (20.8)	7,045 (18.8)	6,613 (19.1)	0.30 (-0.27 to 0.87)	0.307	
Cardiac rehabilitation	N (%)	182,575 (92.4)	33,933 (89.8)	30,387 (94.3)	4.44 (4.05-4.84)	<0.001	26,591 (11.4)
GRACE risk score category							
Lowest (<70)	N (%)	5,034 (5.0)	30 (5.6)	1,099 (4.7)	-0.84 (-2.79 to 1.11)	0.362	
Low (70-87)	N (%)	11,541 (11.4)	61 (11.3)	2,654 (11.4)	0.08 (-2.61 to 2.78)	0.952	131,188 (56.5)
Intermediate to high (≥88)	N (%)	84,509 (83.6)	450 (83.2)	19,612 (83.9)	0.76 (-2.43 to 3.95)	0.635	
Crude mortality							

Variable		2004-2013 N=232,353 (Total cohort)	2004-2005 N=42,799 (18.4% of the cohort)	2012-2013 N=37,081 (16.0% of cohort)	Difference between 2004-2005 and 2012-2013 (95% CI)	*P*-value for linear trend, 2004-2013[a]	Missing (%)
30 day	N (%)	5,517 (2.4)	1,046 (2.4)	836 (2.3)	-0.18 (-0.40 to 0.02)	0.078	
Six months	N (%)	12,143 (5.2)	2,347 (5.5)	1,703 (4.6)	-0.89 (-1.19 to -0.59)	<0.001	0
One year	N (%)	16,239 (7.0)	3,221 (7.5)	2,090 (5.6)	-1.89 (-2.23 to -1.55)	<0.001	

[a]P-value for linear trend across all study years (2004 to 2013) derived using linear regression for continuous variables and the non-parametric test for trend across ordered groups for categorical variables. [b]Only patients eligible to receive treatments were included in the denominator. [c]PPCI or thrombolysis. [d]Missing data default imputed to "No".

Abbreviations: ACS – Acute coronary syndrome; ARB – Angiotensin receptor blocker; ACEi – angiotensin-converting enzyme inhibitor; CABG – coronary artery bypass grafting; COPD – chronic obstructive pulmonary disease; CHD- coronary heart disease; GRACE – Global Registry of Acute Coronary Events; IMD – index of multiple deprivation; PCI – percutaneous coronary intervention; SBP – systolic blood pressure.

6.5 Temporal trends in mortality

From 2004 to 2013, a temporal decline in mortality was observed for six months and one year mortality, with no pronounced decline being observed for 30 days mortality (Figure 6.3). Comparing 2004-2005 vs. 2012-2013, unadjusted crude mortality rates at six months following hospital discharge decreased from 5.5% (95% CI, 5.5%-5.6%) to 4.6% (95% CI, 4.5%-4.6%), at one year from 7.5% (95% CI, 7.4%-7.6%) to 5.6% (95% CI, 5.5%-5.7%) and no statistical significant differences were noted for 30 days mortality.

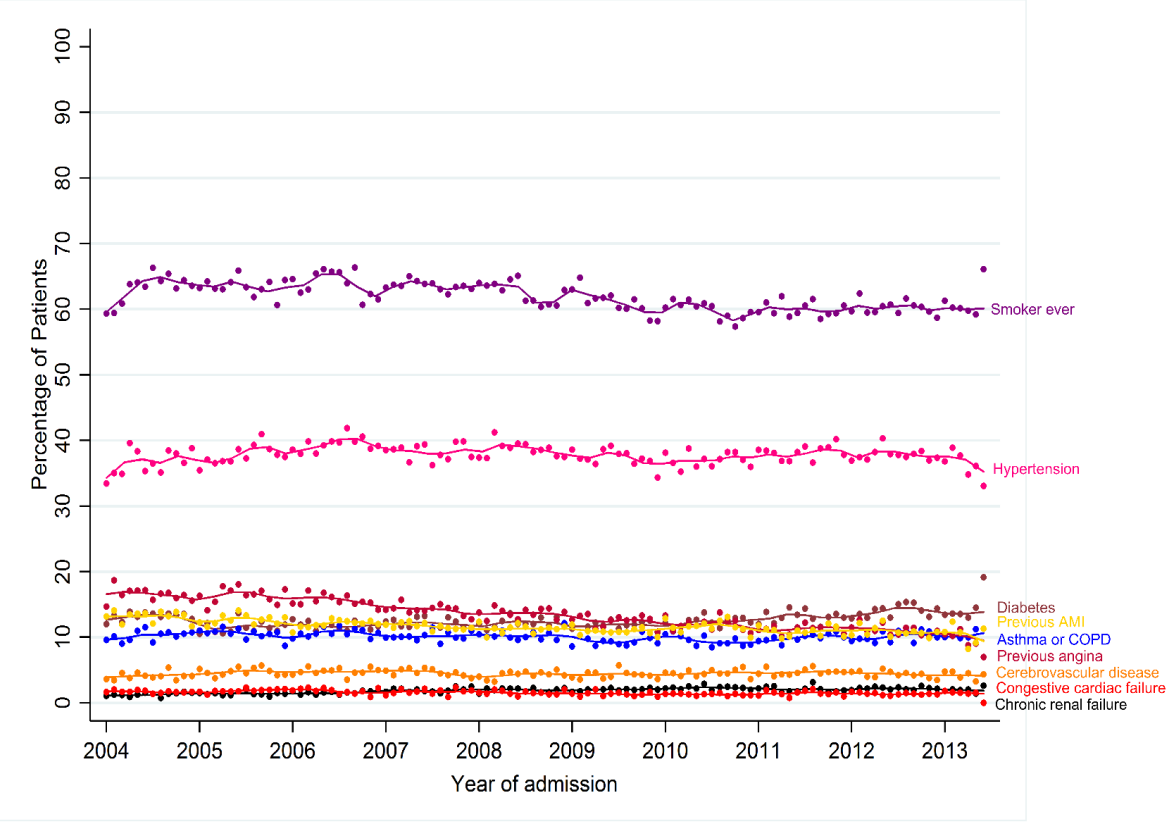


Figure 6.1. Local polynomial smoothed curves showing temporal trends in comorbidities and risk factors per month, 2004-2013.

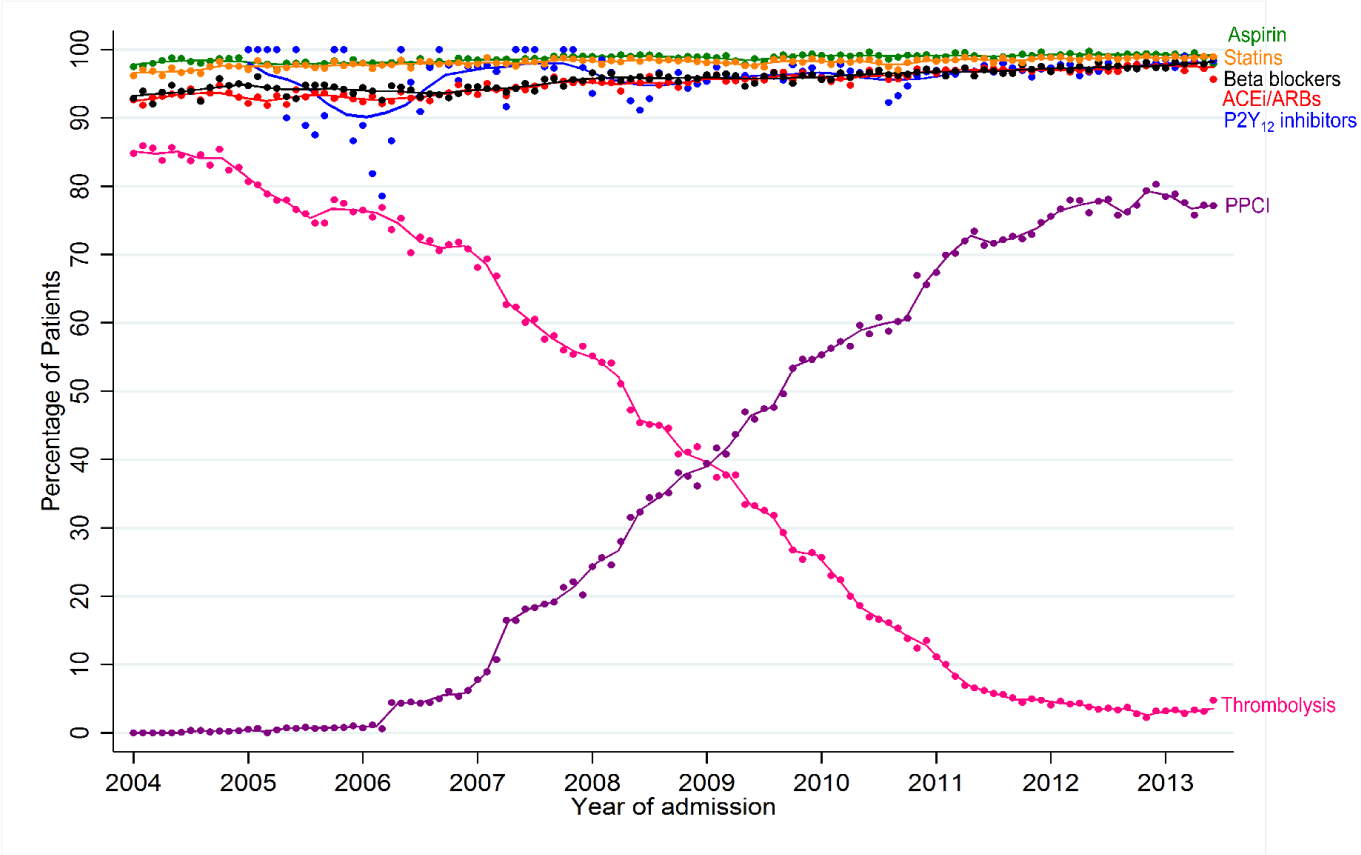


Figure 6.2. Local polynomial smoothed curves showing temporal trends in use of care interventions for the management of STEMI per month, 2004-2013.

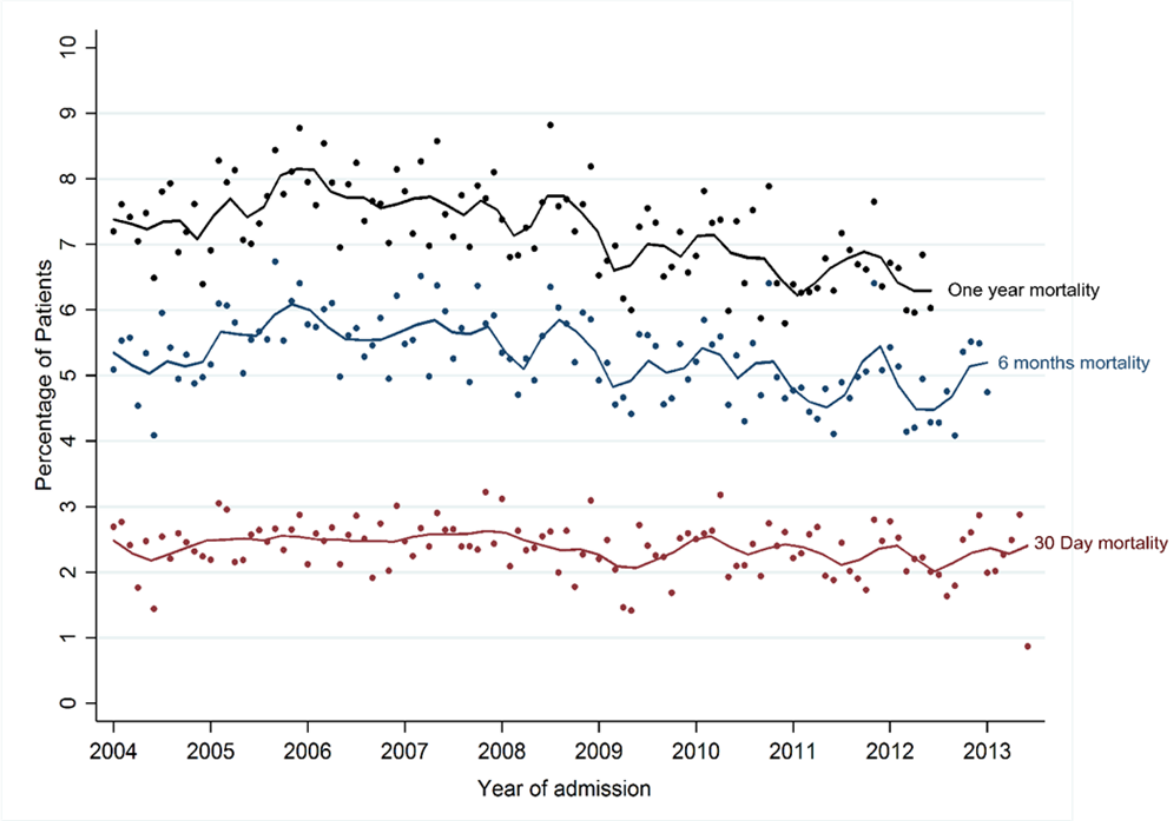


Figure 6.3. Local polynomial smoothed curves showing monthly crude all-cause mortality at 30 days, six months and one year, 2004-2013.

6.6 Association between changing risk profile and improved outcomes

6.6.1 Flexible parametric modelling results

6.6.1.1 Six months survival

The results are summarised in Table 6.2. Unadjusted all-cause six months survival improved by 0.9% per year on average over the study period (hazard ratio [HR] 0.991, 95% CI 0.988-0.994). This temporal improvement remained after adjusting for age, sex and deprivation (HR 0.991 [95% CI, 0.988-0.994]), cardiac rehabilitation (HR 0.990 [95% CI, 0.987-0.993]) and Comorbidities and risk factors (HR 0.994 [95% CI, 0.991-0.997]). However, the direction of association was reversed after adjustment for PPCI (HR 1.025 [95% CI, 1.021-1.029]) and there was no temporal trend after adjusting for pharmacotherapies (HR 0.998 [95% CI, 0.993-1.002]). Individual assessments of the pharmacotherapy drugs showed that the temporal improvement remained after adjusting for aspirin (HR, 0.988 [95% CI, 0.985-0.992]), statins (HR, 0.987 [95% CI, 0.984-0.990]), β blockers (HR, 0.994 [95% CI, 0.991-0.998]), ACEi/ARBs (HR, 0.991 [95% CI, 0.987-0.993]) and only after adjustment of $P2Y_{12}$ inhibitors (HR 1.055 [95% CI, 1.050-1.060]) was the direction of association reversed. In the fully adjusted model including all the variables under investigation the direction of association was reversed (HR, 1.006 [95% CI, 0.1.001-1.011]).

6.6.1.2 One year survival

The results are summarised in Table 6.2. Unadjusted all-cause one year survival improved by 1.0% per year on average over the study period (hazard ratio [HR] 0.990, 95% CI 0.987-0.993). This temporal improvement remained after adjusting for age, sex and deprivation (HR 0.990 [95% CI, 0.987-0.993]), cardiac rehabilitation (HR 0.989 [95% CI, 0.986-0.992]) and Comorbidities and risk factors (HR 0.993 [95% CI, 0.990-0.996]). However, the direction of association was reversed after adjustment for PPCI (HR 1.025 [95% CI, 1.021-1.028]) and there was no temporal trend after adjusting for pharmacotherapies (HR 0.998 [95% CI, 0.994-1.002]).

Individual assessments of the pharmacotherapy drugs showed that the temporal improvement remained after adjusting for aspirin (HR, 0.988 [95% CI, 0.985-0.991]), statins (HR, 0.987 [95% CI, 0.984-0.989]), β blockers (HR, 0.993 [95% CI, 0.990-0.996]), ACEi/ARBs (HR, 0.989 [95% CI, 0.986-0.992]) and only after adjustment of $P2Y_{12}$ inhibitors (HR 1.035 [95% CI, 1.031-1.039]) was the direction of association reversed. In the fully adjusted model including all the variables under investigation the direction of association was reversed (HR, 1.006 [95% CI, 0.1.001-1.011]).

Table 6.2 Temporal Trends by Year in Overall Survival between 2003 and 2013 for Unadjusted and Adjusted Flexible Parametric Survival Models.

Model number	Variables included	Six months Hazard ratio (95% CI)	P-value	One year Hazard ratio (95% CI)	P-value
Model 1	Year	0.991 (0.988-0.994)	<0.001	0.990 (0.987-0.993)	<0.001
Model 2	Year + Age, sex, IMD	0.991 (0.988-0.994)	<0.001	0.990 (0.987-0.993)	<0.001
Model 3	PPCI	1.025 (1.021-1.029)	<0.001	1.025 (1.021-1.028)	<0.001
Model 4	Comorbidities and risk factors	0.994 (0.991-0.997)	<0.001	0.993 (0.990-0.996)	<0.001
Model 5	Five discharge drugs	0.998 (0.993-1.002)	0.404	0.998 (0.994-1.002)	0.379
Model 6	Aspirin	0.988 (0.985-0.992)	<0.001	0.988 (0.985-0.991)	<0.001
Model 7	Statins	0.987 (0.984-0.990)	<0.001	0.987 (0.984-0.989)	<0.001
Model 8	$P2Y_{12}$ inhibitors	1.040 (1.037-1.045)	<0.001	1.035 (1.031-1.039)	<0.001
Model 9	ACEi/ARBs	0.991 (0.987-0.993)	<0.001	0.989 (0.986-0.992)	<0.001
Model 10	β-blockers	0.994 (0.991-0.998)	<0.001	0.993 (0.990-0.996)	<0.001
Model 11	Cardiac rehabilitation	0.990 (0.987-0.993)	<0.001	0.989 (0.986-0.992)	<0.001
Model 12	Year + age + sex + IMD + PPCI	1.014 (1.010-1.018)	<0.001	1.013 (1.009-1.016)	<0.001
Model 13	Comorbidities and risk factors	0.992 (0.989-0.996)	<0.001	0.991 (0.988-0.994)	<0.001
Model 14	Five discharge drugs	0.993 (0.988-0.988)	0.003	0.993 (0.989-0.997)	0.001
Model 15	Aspirin	0.987 (0.984-0.991)	<0.001	0.987 (0.984-0.990)	<0.001
Model 16	Statins	0.968 (0.983-0.990)	<0.001	0.986 (0.982-0.989)	<0.001
Model 17	$P2Y_{12}$ inhibitors	1.040 (1.035-1.044)	<0.001	1.034 (1.030-1.038)	<0.001
Model 18	ACEi/ARBs	0.990 (0.986-0.993)	<0.001	0.988 (0.985-0.992)	<0.001
Model 19	β-blockers	0.994 (0.991-0.998)	0.001	0.993 (0.990-0.996)	<0.001
Model 20	Cardiac rehabilitation	0.991 (0.987-0.994)	<0.001	0.989 (0.986-0.992)	<0.001
Model 21	Year + age + sex + IMD + PPCI + Comorbidities and risk factors + Aspirin + Statins + $P2Y_{12}$ inhibitors + ACEi/ARBs + β-blockers + Cardiac rehabilitation	1.006 (1.001-1.011)	0.014	1.006 (1.001-1.011)	0.013

Abbreviations: IMD – index of multiple deprivation; PPCI – primary percutaneous coronary intervention; ARB – Angiotensin receptor blocker and ACEi – angiotensin-converting enzyme inhibitor.

6.6.2 Mediation analysis results

A mediation analysis was conducted to determine the proportion of temporal improvements in survival that were mediated by use of PPCI and prescription of $P2Y_{12}$ inhibitors (Figure 6.4). The mediation analysis was carried out as a sensitivity analysis and was undertaken on complete cases (n=82,637).

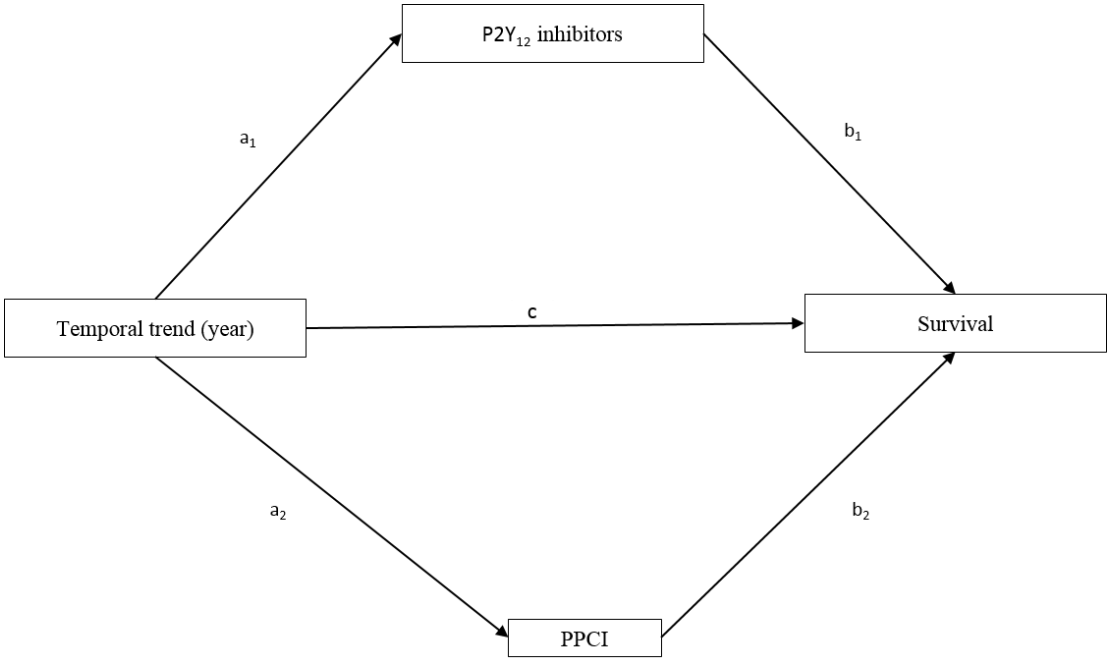


Figure 6.4. A path diagram indicating PPCI and $P2Y_{12}$ inhibitors as potential mediators for the temporal trend in survival.

6.6.2.1 One year survival

The results are reported following a four step procedure to represent the mediation analysis technique(148).

Step 1-Show that the causal variable is associated with the outcome.

The main analysis (Table 6.2) showed that there was a temporal trend in survival at one year (HR=0.990, 95% CI 0.987-0.993). Therefore, there was potential for this effect to be mediated.

Step 2-Show that the causal variable is associated with the mediator (s)

In order to test this assumption, an adjusted model with each mediator (PPCI or $P2Y_{12}$ inhibitors) treated as the outcome variable consecutively was fitted to determine whether there was an effect for paths a_1 and a_2 (Figure 6.4). The paths were tested using logistic regression with binary outcome for the mediators with year as the exposure variable and all other variables as confounders. All the paths were non-zero (standardised coefficients -0.16, 95% CI -0.19 to -0.14 (a_1 path) and 0.33, 95% CI 0.32 to 0.34 (a_2 path), therefore meeting the requirements for the mediation analysis.

Step 3 – Show that the mediator variable(s) are associated with the outcome.

In order to test this assumption, an adjusted Poisson regression model with one year mortality as the outcome and log survival time as the offset was fitted adjusting for each mediator consecutively to test the significance of paths b_1 and b_2. All paths were non-zero (standardised coefficients -0.08, 95% CI -0.19 to 0.03 (path b_1) and -0.37, 95% CI -0.43 to -0.31 (path b_2). Path b_1 was found not statistically significant thereby violating the mediator outcome association assumption for $P2Y_{12}$ inhibitors. The assumption was not violated for PPCI.

Step 4 – To establish the degree of mediation.

The degree of mediation was established by estimating the direct (path c) and indirect effects (a_2 multiplied by path b_2) as well as the proportion of the effects that were mediated by the potential mediator. Indirect effects and 95%

confidence intervals were calculated using bootstrap methods over 1000 simulations. Degree of mediation was only undertaken for PPCI as the $P2Y_{12}$ inhibitors were found not to be associated with the outcome in step 3 thus no mediation analysis could be undertaken.

Proportion mediated by PPCI.

The introduction of PPCI explained 27.9% (95% CI, 15.5-83.8%) of the observed temporal improvements in one year survival for the STEMI patients.

6.6.2.2 Six months survival

The results are reported following a four step procedure to represent the mediation analysis technique(148).

Step 1-Show that the causal variable is associated with the outcome.

The main analysis (Table 6.2) showed that there was a temporal trend in survival at six months (HR=0.991, 95% CI 0.988-0.994). Therefore, there was potential for this effect to be mediated.

Step 2-Show that the causal variable is associated with the mediator (s)

In order to test this assumption, an adjusted model with each mediator (PPCI or $P2Y_{12}$ inhibitors) treated as the outcome variable consecutively was fitted to determine whether there was an effect for paths a_1 and a_2 (Figure 6.4). The paths were tested using logistic regression with binary outcome for the mediators with year as the exposure variable and all other variables as confounders. All the paths were non-zero (standardised coefficients -0.16, 95% CI -0.19 to -0.14 (a_1 path) and 0.33, 95% CI 0.32 to 0.34 (a_2 path), therefore meeting the requirements for the mediation analysis.

Step 3 – Show that the mediator variable(s) are associated with the outcome.

In order to test this assumption, an adjusted Poisson regression model with one year mortality as the outcome and log survival time as the offset was fitted adjusting for each mediator consecutively to test the significance of paths b_1 and b_2. All paths were non-zero (standardised coefficients -0.02, 95% CI -0.15

to 0.13 (path b_1) and -0.40, 95% CI -0.47 to -0.32 (path b_2). Path b_1 was found not statistically significant thereby violating the mediator outcome association assumption for $P2Y_{12}$ inhibitors. The assumption was not violated for PPCI.

Step 4 – To establish the degree of mediation.

The degree of mediation was established by estimating the direct (path c) and indirect effects (a_2 multiplied by path b_2) as well as the proportion of the effects that were mediated by the potential mediator. Indirect effects and 95% confidence intervals were calculated using bootstrap methods over 1000 simulations. Degree of mediation was only undertaken for PPCI as the $P2Y_{12}$ inhibitors were found not to be associated with the outcome in step 3 thus no mediation analysis could be undertaken.

Proportion mediated by PPCI.

The proportion mediated by the introduction of PPCI for six months survival was not statistically significant.

6.7 Summary of key findings

- Overall, a high proportion of the STEMI patients were hypertensive, had a family history of coronary heart disease, and were current or ex-smokers.
- Over the study period the proportion of STEMI patients who had previous AMI, previous angina and were current or ex-smokers decreased whilst the proportion of patients who had diabetes, hypertension, chronic renal failure and received previous PCI increased.
- Overall of the eligible STEMI patients the use of the secondary prevention drugs was high and temporal improvements in the prescription of the drugs were noted over the study period.

- The determined mediators for the temporal improvements in one year survival noted for patients hospitalized with STEMI between 2004 and 2013 were reperfusion (PPCI) and $P2Y_{12}$ inhibitors.

6.8 Conclusion

Among patients hospitalized with STEMI in England and Wales, improvements in all-cause mortality were observed between 2004 and 2013. This was significantly associated with the introduction of PPCI and $P2Y_{12}$ inhibitors. The next chapter presents results of objective 4 of this thesis.

Chapter 7 : Results

Role of β-blockers during and after AMI in patients without heart failure or LVSD.

The following publications have arisen from the analysis and results in this chapter:

1. **Dondo, TB**, Hall, M, West, RM, Jernberg, T, Lindahl, B, Bueno, H, Danchin, N, Deanfield, JE, Hemingway, H, Fox, KAA, Timmis, AD, Gale, CP. (2017). β-Blockers and Mortality After Acute Myocardial Infarction in Patients Without Heart Failure or Ventricular Dysfunction. *JACC*, *69*(22), 2710-2720.
2. **Dondo, TB**, Hall, M, West, R, Jernberg, T, Lindahl, B, Bueno, H, Danchin, N, Deanfield, JE, Hemingway, H, Fox, KAA, Timmis, AD, Gale, CP. (2016, August). Beta blocker use and mortality in hospital survivors of acute myocardial infarction without heart failure. Congress of the European-Society-of-Cardiology (ESC).

7.1 Introduction

Assessment of quality of care for AMI patients also involves assessments of efficacy of individual care interventions on the AMI care pathway. This chapter presents results on the investigation of efficacy of β blockers as there has been uncertainty on their effectiveness in reducing mortality among AMI patients who do not have heart failure or LVSD, especially in the reperfusion era.(4) There are no contemporary randomised data for survivors of AMI without heart failure or LVSD in relation to the use of β blockers, as such international guidelines differ in their recommendation about the use of β blockers in this

group of patients.(4, 22-24) The results presented in this chapter to date, are the first (to the best of my knowledge) large scale dataset analyses results after investigating the impact of β blockers on survival after AMI among patients without heart failure or LVSD in the reperfusion era.

The chapter will be outlined as shown below:

- Study population descriptive statistics (§7.2)
- Impact of β blockers use on survival: Propensity score analyses (§7.3)
- Impact of β blockers use on survival: Instrumental variable analyses (§7.4)
- Summary of key findings (§7.5)
- Conclusion (§7.6).

A detailed description of the methods employed for the analyses has already been given in Chapter 3, §3.9.

7.2 Study population descriptive statistics

Details on the analytical cohort derivation are given in Chapter 3, §3.9. Over half of the analytical cohort (N=179,810) were STEMI patients (51.1% (n=91,895)) with 48.9 % (n=87,915) being NSTEMI patients. Significant differences in baseline characteristics were found between the patients who received β blockers vs. those who did not receive β blockers at discharge (Table 7.1). Comparing the β blockers receivers to the non-receivers, those who received were younger (mean 63.3 (SD 13.4)) years vs. mean 68.6 (SD 15.1) years), male (71.1 vs. 61.7%) and less co-morbid (diabetes-11.6 vs.15.4%, chronic renal failure-1.6 vs. 3.2%, cerebrovascular disease-3.8 vs. 7.0%, peripheral vascular disease-1.9 vs. 3.3%, hypertension-36.4 vs. 42.0% and asthma or COPD-7.8 vs. 20.6%. Higher rates of receipt of secondary prevention drugs were observed for the β blocker receipt patients compared to

the non-receipt patients (aspirin-99.4 vs. 84.3%, $P2Y_{12}$ inhibitors-97.3 vs. 72.9%, ACEi/ARBs-95.6 vs. 60.2% and statins-98.9 vs. 76.8%) (Table 7.1). Enrolment into cardiac rehabilitation was higher for patients in the receipt of β blockers group compared to the non-receipt patients (94.7 vs. 76.9%) (Table 7.1). The patients who did not receive β blockers were also of higher ischaemic risk (intermediate or high GRACE risk score (76.5 vs. 69.8%)) upon admission with AMI.

Table 7.1 Baseline characteristics of hospital survivors of AMI without heart failure or LVSD according to prescription of β blockers at hospital discharge

	β blockers at time of discharge from hospital			
Variable	**Yes (n=141,097)**	**No (n=7,217)**	***P*-value**	**Missing n (%)**
Age, mean (SD), years	63.3 (13.4)	68.6 (15.1)	<0.001	130 (0.07)
Male	100,774 (71.6)	4,441 (61.7)	<0.001	537 (0.3)
Deprivation (IMD)				
Least deprived (1)	24,615 (18.3)	1,379 (20.1)	<0.001	
2	26,677 (19.9)	1,381 (20.1)	0.639	
3	27,604 (20.6)	1,408 (20.5)	0.894	10,429 (5.8)
4	26,616 (19.8)	1,392 (20.3)	0.376	
Most deprived (5)	28,818 (21.5)	1,314 (19.2)	<0.001	
Year of admission				
2007	17,709 (12.6)	1,298 (18.0)	<0.001	
2008	19,369 (13.7)	1,230 (17.0)	<0.001	
2009	21,899 (15.5)	1,255 (17.4)	<0.001	
2010	23,720 (16.8)	1,107 (15.3)	0.001	
2011	24,925 (17.7)	1,115 (15.5)	<0.001	
2012	25,387 (18.0)	930 (12.9)	<0.001	0
2013	8,088 (5.8)	282 (3.9)	<0.001	
Cardiovascular history				
Cerebrovascular disease	4,835 (3.8)	457 (7.0)	<0.001	20,754 (11.5)
Peripheral vascular disease	2,365 (1.9)	210 (3.3)	<0.001	23,107 (12.9)
Cardiovascular risk factors				
Diabetes	15,785 (11.6)	1,076 (15.4)	<0.001	7,195 (4.0)
Chronic renal failure	1,953 (1.6)	208 (3.2)	<0.001	20,924 (11.6)
Hypercholesterolaemia	33,788 (26.9)	1,710 (26.3)	0.305	21,838 (12.2)
Hypertension	47,040 (36.4)	2,814 (42.0)	<0.001	17,306 (9.6)
Current or ex-smoker	88,468 (65.7)	3,898 (58.5)	<0.001	10,654 (5.9)
Asthma or COPD	9,813 (7.8)	1,348 (20.6)	<0.001	21,752 (12.1)
Family history of CHD	44,056 (38.2)	1,699 (30.1)	<0.001	36,139 (20.1)
Presenting characteristics				
Systolic blood pressure, mmHg , mean (SD)	140.4 (27.1)	138.7 (27.8)	<0.001	35,001 (19.5)

	β blockers at time of discharge from hospital			
Variable	**Yes (n=141,097)**	**No (n=7,217)**	***P*-value**	**Missing n (%)**
Systolic blood pressure, <90 mmHg	2,824 (2.5)	200 (3.3)	<0.001	
Heart rate, median (IQR)	76.0 (66.0 to 89.0)	77.0 (64.0 to 90.0)	0.134	35,176 (19.6)
Heart rate >110 bpm	6,070 (5.3)	416 (7.0)	0.196	
Creatinine, median (IQR)	85.0 (72.0 to 99.0)	87.0 (74.0 to 106.0)	<0.001	32,003 (17.8)
Creatinine >200 (µmol/l)	1,159 (1.0)	166 (2.8)	<0.001	
Peak troponin§, median (IQR)	4.8 (0.7 to 50.0)	1.7 (0.2 to 19.0)	<0.001	21,359 (11.9)
Peak troponin ≥ 0.06§	119,302 (95.5)	6,146 (93.0)	<0.001	
Cardiac arrest	5,449 (4.0)	178 (2.5)	<0.001	6,428 (3.6)
Electrocardiographic characteristics				
No acute changes	13,816 (10.4)	942 (14.5)	<0.001	
ST-segment elevation	69,888 (52.3)	2,364 (36.3)	<0.001	
Left bundle branch block	2,523 (1.9)	219 (3.4)	<0.001	10,360 (5.8)
ST segment depression	15,063 (11.3)	867 (13.3)	<0.001	
T wave changes only	20,150 (15.1)	1,171 (18.0)	<0.001	
Other acute abnormality	12,094 (9.1)	954 (14.7)	<0.001	
Grace risk score				
Lowest (≤70)	11,358 (12.7)	496 (11.4)	0.011	
Low (71-87)	15,709 (17.5)	531 (12.2)	<0.001	68,471 (38.1)
Intermediate to high (>88)	62,676 (69.8)	3,342 (76.5)	<0.001	
Index event				
STEMI	75,697 (53.7)	2,539 (35.2)	<0.001	0
NSTEMI	65,400 (46.4)	4,678 (64.8)	<0.001	0
Medication at discharge[a]				**Missing[b] n (%)**
Aspirin (n=176,040[c])	137,509 (99.4)	5,929 (84.3)	<0.001	13,942 (7.9)
$P2Y_{12}$ inhibitors (n=173,967[c])	95,292 (97.3)	3,313 (72.9)	<0.001	60,385 (34.7)
ACEi/ARBs (n=165,575[c])	126,812 (95.6)	4,222 (60.2)	<0.001	15,584 (9.2)
Statin (n=176,979[c])	137,402 (98.9)	5,479 (76.8)	<0.001	14,483 (8.2)
In-hospital procedures[a]				
Coronary angiography (n=173,473[c])	91,738 (71.3)	4,024 (61.3)	<0.001	10,543 (6.1)
Coronary intervention (PCI/CABG) (n=171,906[c])	65,937 (58.7)	2,158 (41.9)	<0.001	33,905 (19.7)
Rehabilitation[a]				
Enrolment into cardiac rehabilitation (n=173,473[c])	120,371 (94.7)	4,544 (76.9)	<0.001	16,505 (9.6)

All values are expressed as numbers (%) unless otherwise indicated.

Abbreviations: ACE, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; CABG, coronary artery bypass graft; CHD, coronary heart disease; COPD, chronic obstructive pulmonary disease; IMD, Index of multiple deprivation; IQR, interquartile range; M, missing; N, number; NSTEMI, non ST-segment elevation myocardial infarction; [a] Of the eligible patients for the care intervention; PCI, percutaneous coronary intervention; , [b] Proportion missing of the eligible patients for the care intervention; SD, standard deviation; [c] Total eligible for care intervention; § peak troponin was truncated at 50. Patients with missing information for β blocker use at hospital discharge totalled 31,496.

7.3 Impact of β blocker use on survival: Propensity score analysis

There were 5.2% (n=9,373) deaths and 163,772 person years of observation (follow-up capped to one year) for the total analytical cohort. Unadjusted one year mortality was significantly lower for patients who received β blockers compared with those who did not (4.9 vs. 11.2%, P<0.001).

7.3.1 Propensity score analysis approach results

7.3.1.1 Treatment Assignment model

Observations with estimated propensity scores outside the pre-specified range 0.1 to 0.9 were discarded to avoid violation of the overlap assumption (see Methods §7.3). After trimming the analytical cohort at the tails of the estimated propensity score distribution, 16,683 patients (29.6% (n=4,932) STEMI and 70.4% (n=11,751) NSTEMI) were left for inclusion in further analysis. The results of the assessment of the overlap assumption are shown in Figure 7.1-Figure 7.5; the minimum propensity score for each treatment level was sufficiently greater than zero and the maximum propensity score for each treatment level sufficiently less than 1 thus providing evidence that the assumption was not violated. Balance checks comparing the standardised differences and variance ratios between the raw and the weighted data were performed for the main effects and most of the standardised differences and variance ratios for variables in the weighted data were close to zero and one, respectively (Table 7.2-Table 7.11). The over-identification which tested whether the main effects as well as the interactions terms were balanced, showed that there was no evidence against the null hypothesis that the covariates were balanced thus the treatment assignment models were well specified (Table 7.12). Assessment was done across each of the ten imputed datasets individually as methods to pool the balance checks results, to the best of my knowledge have not been defined, however the treatment effects were estimated

based on pooled estimates from the imputed data. The diagnostic assessments suggested that weighting by the inverse probability of treatment created a sample in which the prevalence of baseline characteristics were similar between the treated and control subjects. The area under the curve for the propensity score model was 0.80 (Figure 7.6), which indicated a good discrimination for the model.

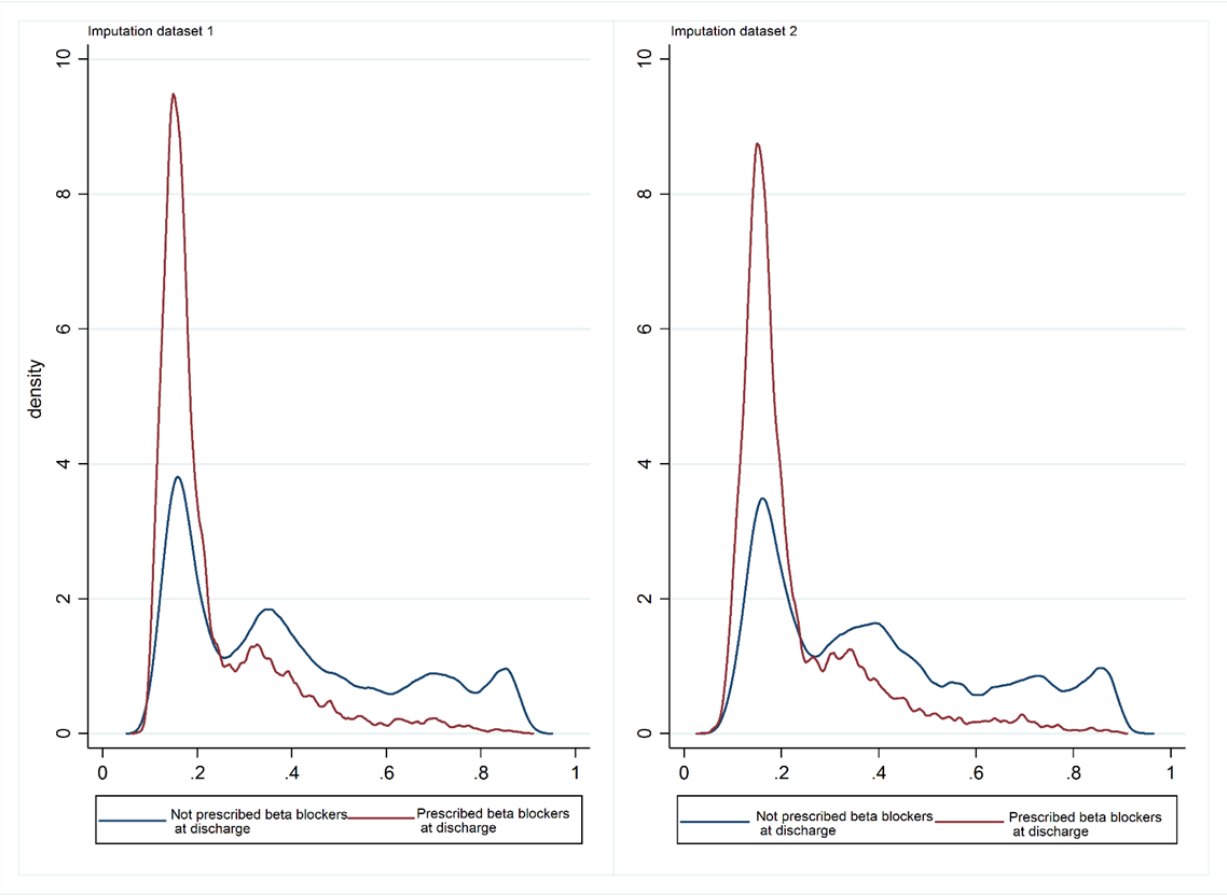


Figure 7.1. Overlap assumption assessment plots showing the estimated densities of probability of getting each treatment level for the patients in the analytical cohort for imputation 1 and 2 (treated vs non-treated).

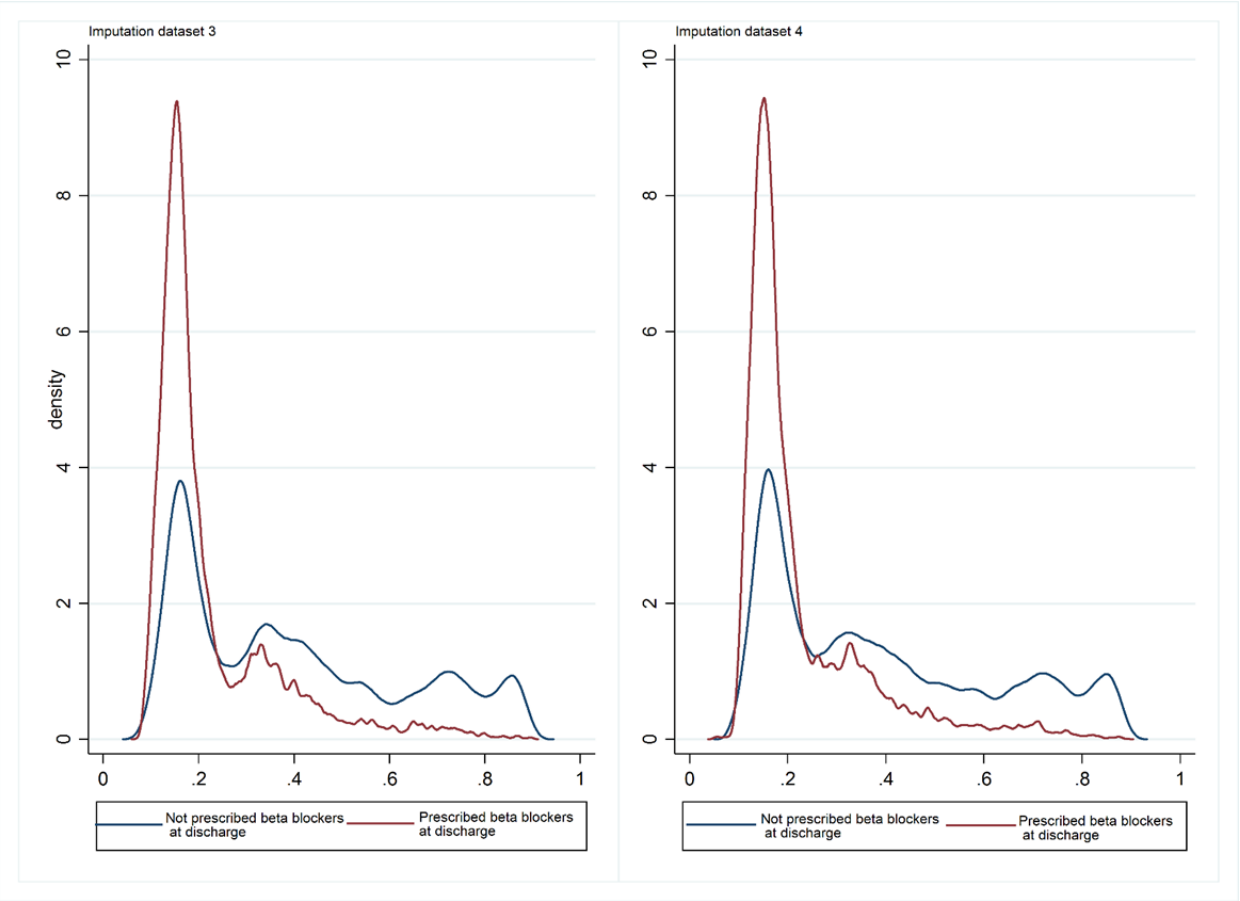


Figure 7.2. Overlap assumption assessment plots showing the estimated densities of probability of getting each treatment level for the patients in the analytical cohort for imputation 3 and 4.

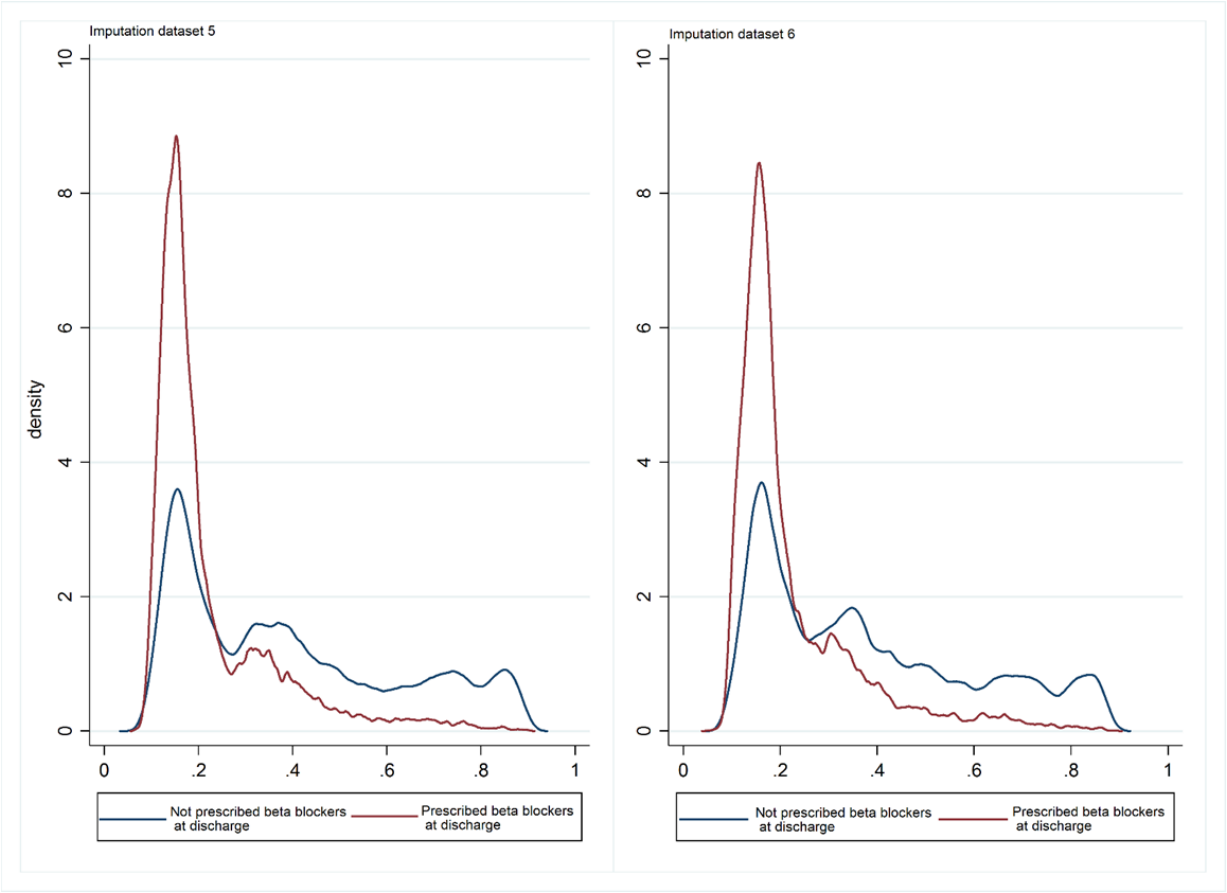


Figure 7.3. Overlap assumption assessment plots showing the estimated densities of probability of getting each treatment level for the patients in the analytical cohort for imputation 5 and 6.

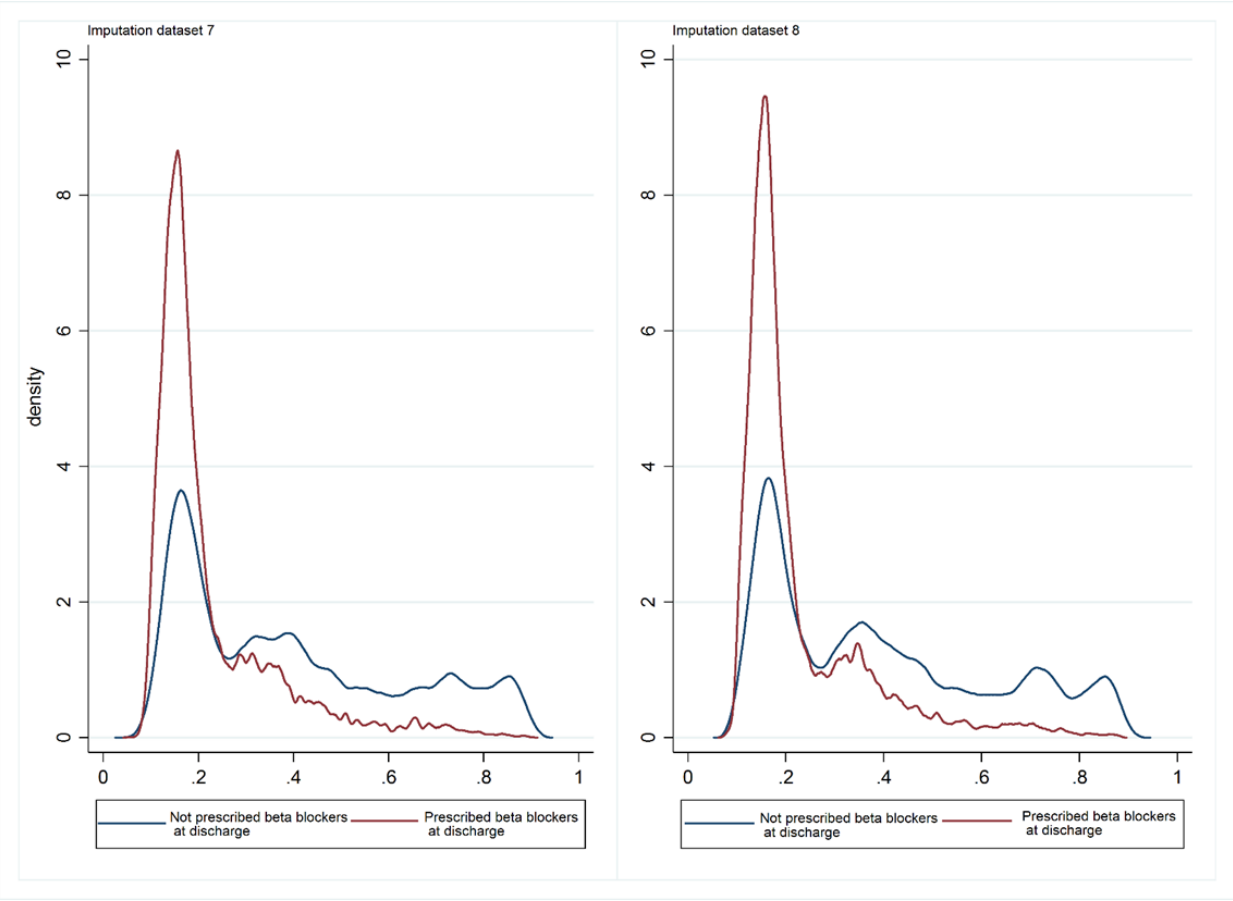


Figure 7.4. Overlap assumption assessment plots showing the estimated densities of probability of getting each treatment level for the patients in the analytical cohort for imputation 7 and 8.

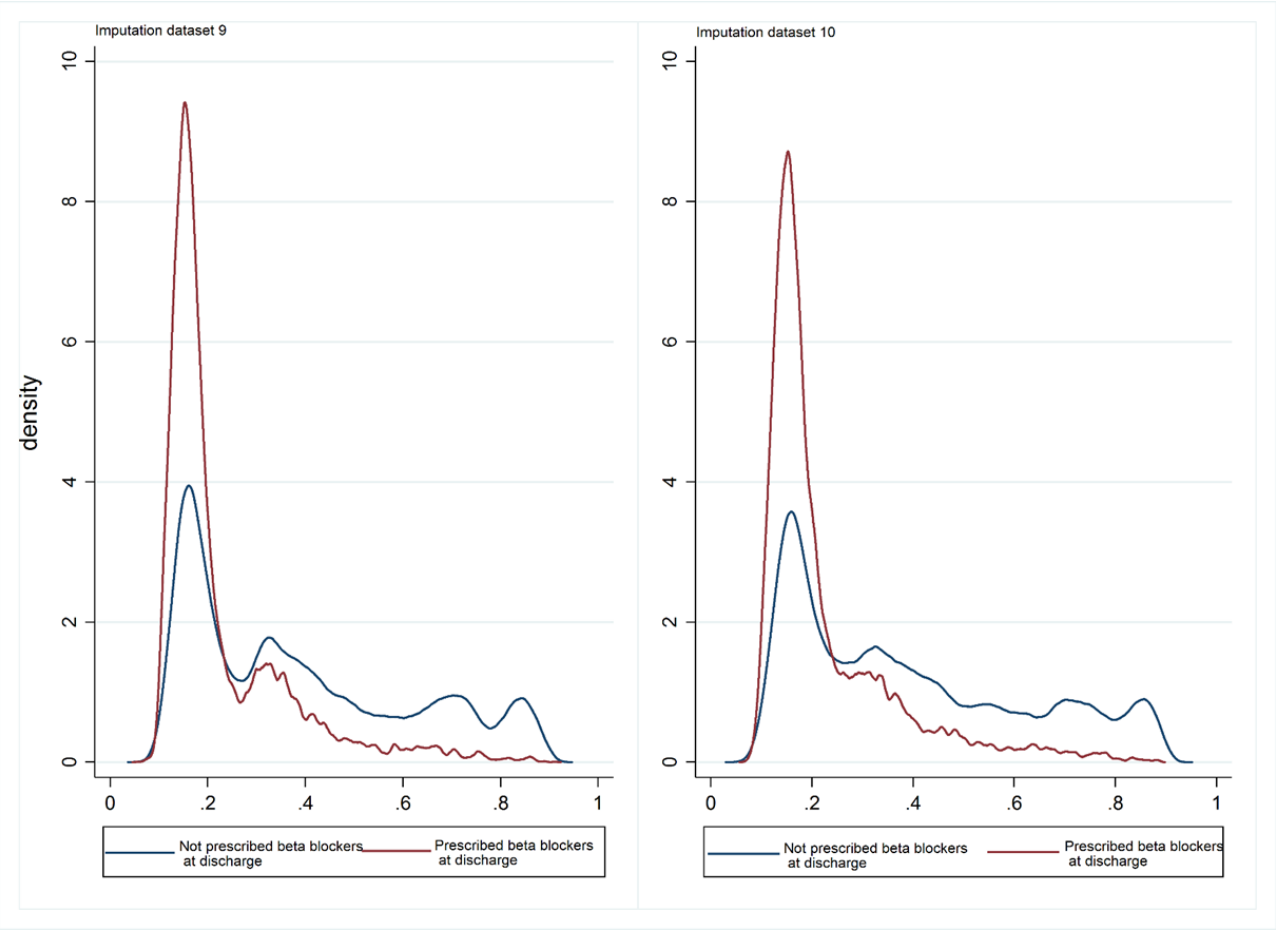


Figure 7.5. Overlap assumption assessment plots showing the estimated densities of probability of getting each treatment level for the patients in the analytical cohort for imputation 9 and 10.

Table 7.2. Balance check parameters using standardized differences and variance ratios (imputation dataset 1).

	Standardized differences		**Variance ratios**	
Data	**Raw**	**Weighted**	**Raw**	**Weighted**
Age				
Below 55	ref	ref	ref	ref
55-65	0.03	0.02	1.05	1.04
66-75	0.06	0.01	1.08	1.01
76-85	0.03	-0.02	1.04	0.98
Above 85	-0.08	-0.01	0.87	0.99
Male	0.02	0.001	0.99	1.00
Deprivation (IMD)				
Least deprived (1)	re	ref	re	ref
2	0.02	0.02	1.03	1.03
3	0.03	-0.002	1.05	1.00
4	-0.02	-0.01	0.97	0.99
Most deprived (5)	-0.003	-0.00001	0.99	1.00
Year of admission				
2007	ref	ref	ref	ref
2008	0.05	0.01	1.08	1.01
2009	-0.02	0.02	0.96	1.03
2010	-0.02	0.01	0.96	1.02
2011	-0.04	-0.02	0.90	0.95
2012	-0.05	-0.001	0.87	1.00
2013	-0.06	-0.01	0.71	0.93
Cardiovascular history				
Cerebrovascular disease	0.003	0.003	1.01	1.01
Peripheral vascular disease	0.05	0.01	1.31	1.05
Cardiovascular risk factors				
Diabetes	0.05	0.02	1.10	1.03
Hypercholesterolaemia	0.05	-0.01	1.07	0.99
Hypertension	0.07	0.003	1.03	1.00
Current or ex-smoker	0.07	1.56×10^{-6}	0.98	1.00
Asthma or COPD	0.07	0.002	1.05	1.00
Family history of CHD	0.05	-0.002	1.08	1.00
Presenting characteristics				
Heart rate >110 bpm	-0.03	-0.03	0.90	0.93
Creatinine >200 (µmol/l)	-0.03	-0.02	0.86	0.91
Peak troponin	0.02	0.01	0.94	0.98
Cardiac arrest	0.01	-0.02	1.11	0.86
Electrocardiographic characteristics				
ST-segment deviation	0.03	-0.01	1.01	1.00
Care by cardiologist	-0.01	-0.01	1.00	1.00
Medication at discharge				
Aspirin				
Received	0.46	0.03	0.44	0.94
Contraindicated/ not applicable	0.01	0.01	1.07	1.07
$P2Y_{12}$ inhibitors				
Received	0.58	0.02	0.63	0.98

	Standardized differences		Variance ratios	
Data	**Raw**	**Weighted**	**Raw**	**Weighted**
Contraindicated/ not applicable	0.05	0.02	1.28	1.09
ACEi/ARBs				
Received	0.45	0.01	1.25	1.00
Contraindicated/ not applicable	0.12	0.01	2.27	1.05
Statins				
Received	0.61	0.03	0.50	0.96
Contraindicated/ not applicable	0.04	-0.001	1.43	0.99
In-hospital procedures				
Coronary angiography				
Received	0.13	-0.001	0.97	1.00
Contraindicated/ not applicable	-0.03	0.003	0.88	1.01
Coronary intervention (PCI/CABG)				
Received	0.06	0.002	1.03	1.00
Contraindicated/ not applicable	0.0002	0.01	1.00	1.02

Abbreviations. ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; CABG, coronary artery bypass graft; CHD, coronary heart disease; COPD, chronic obstructive pulmonary disease; IMD, Index of multiple deprivation; PCI, percutaneous coronary intervention; ref, reference category.

Table 7.3. Balance check parameters using standardized differences and variance ratios (imputation dataset 2).

	Standardized differences		Variance ratios	
Data	**Raw**	**Weighted**	**Raw**	**Weighted**
Age				
Below 55	ref	ref	ref	ref
55-65	0.02	0.01	1.04	1.02
66-75	0.07	0.003	1.10	1.00
76-85	0.03	-0.004	1.03	1.00
Above 85	-0.08	-0.02	0.87	0.97
Male	0.02	-0.01	0.99	1.00
Deprivation (IMD)				
Least deprived (1)	ref	ref	ref	ref
2	0.02	0.01	1.02	1.01
3	0.04	-0.004	1.06	1.00
4	0.004	-0.003	1.01	1.00
Most deprived (5)	-0.02	0.01	0.98	1.01
Year of admission				
2007	ref	ref	ref	ref
2008	0.05	0.004	1.07	1.01
2009	-0.02	0.0003	0.97	1.00
2010	-0.03	0.0001	0.93	1.00
2011	-0.05	-0.01	0.89	0.97
2012	-0.06	-0.01	0.85	0.98
2013	-0.05	-0.03	0.74	0.83
Cardiovascular history				
Cerebrovascular disease	0.01	-0.003	1.03	0.99

	Standardized differences		Variance ratios	
Data	**Raw**	**Weighted**	**Raw**	**Weighted**
Peripheral vascular disease	0.04	0.01	1.21	1.05
Cardiovascular risk factors				
Diabetes	0.03	0.02	1.05	1.03
Hypercholesterolaemia	0.06	-0.002	1.08	1.00
Hypertension	0.07	0.001	1.03	1.00
Current or ex-smoker	0.09	0.02	0.97	0.99
Asthma or COPD	0.06	-0.002	1.04	1.00
Family history of CHD	0.06	-0.002	1.09	1.00
Presenting characteristics				
Heart rate >110 bpm	-0.06	-0.003	0.84	0.99
Creatinine >200 (µmol/l)	-0.04	-0.002	0.77	0.99
Peak troponin	0.02	0.02	0.94	0.94
Cardiac arrest	0.03	-0.01	1.19	0.95
Electrocardiographic characteristics				
ST-segment deviation	0.03	-0.006	1.01	1.00
Care by cardiologist	-0.02	-0.04	1.01	1.02
Medication at discharge				
Aspirin				
Received	0.46	0.03	0.43	0.94
Contraindicated/ not applicable	0.01	-0.01	1.09	0.97
$P2Y_{12}$ inhibitors				
Received	0.56	0.02	0.63	0.98
Contraindicated/ not applicable	0.04	0.004	1.24	1.02
ACEi/ARBs	0.11	-0.02	1.11	0.98
Received	0.44	-0.01	1.24	1.00
Contraindicated/ not applicable	0.10	0.03	1.99	1.20
Statins				
Received	0.61	0.02	0.50	0.97
Contraindicated/ not applicable	0.03	0.004	1.26	1.03
In-hospital procedures				
Coronary angiography				
Received	0.16	-0.01	0.96	1.00
Contraindicated/ not applicable	-0.04	0.002	0.84	1.01
Coronary intervention (PCI/CABG)				
Received	0.09	-0.01	1.06	1.00
Contraindicated/ not applicable	0.003	0.002	1.01	1.01
Contraindicated/ not applicable	0.003	0.002	1.01	1.01

Abbreviations: ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; CABG, coronary artery bypass graft; CHD, coronary heart disease; COPD, chronic obstructive pulmonary disease; IMD, Index of multiple deprivation; PCI, percutaneous coronary intervention; ref, reference category

Table 7.4. Balance check parameters using standardized differences and variance ratios (imputation dataset 3).

	Standardized differences		Variance ratios	
Data	**Raw**	**Weighted**	**Raw**	**Weighted**
Age				
Below 55	ref	ref	ref	ref
55-65	0.03	0.01	1.05	1.02
66-75	0.06	0.002	1.09	1.00
76-85	0.03	-0.01	1.03	0.99
Above 85	-0.08	-0.02	0.88	0.96
Male	0.02	0.004	0.99	1.00
Deprivation (IMD)				
Least deprived (1)	ref	ref	ref	ref
2	-0.01	0.01	0.99	1.01
3	0.05	0.002	1.07	1.00
4	-0.01	-0.01	0.98	0.99
Most deprived (5)	-0.01	0.01	0.98	1.01
Year of admission				
2007	ref	ref	ref	ref
2008	0.05	0.001	1.08	1.00
2009	-0.02	0.01	0.97	1.01
2010	-0.01	-0.02	0.97	0.95
2011	-0.05	-0.01	0.89	0.98
2012	-0.07	0.001	0.83	1.00
2013	-0.05	-0.01	0.75	0.93
Cardiovascular history				
Cerebrovascular disease	-0.0001	-0.003	0.99	0.99
Peripheral vascular disease	0.05	0.01	1.27	1.06
Cardiovascular risk factors				
Diabetes	0.04	0.02	1.07	1.04
Hypercholesterolaemia	0.06	-0.01	1.08	0.98
Hypertension	0.06	-0.01	1.03	0.99
Current or ex-smoker	0.09	0.01	0.97	1.00
Asthma or COPD	0.08	0.002	1.06	1.00
Family history of CHD	0.06	0.001	1.09	1.00
Presenting characteristics				
Heart rate >110 bpm	-0.05	-0.01	0.88	0.97
Creatinine >200 (µmol/l)	-0.04	-0.01	0.80	0.94
Peak troponin	-0.003	-0.001	1.01	1.00
Cardiac arrest	0.03	0.02	1.23	1.14
Electrocardiographic characteristics				
ST-segment deviation	0.03	-0.003	1.01	1.00
Care by cardiologist	-0.01	-0.02	1.01	1.02
Medication at discharge				

	Standardized differences		Variance ratios	
Data	**Raw**	**Weighted**	**Raw**	**Weighted**
Aspirin				
Received	0.45	0.03	0.45	0.95
Contraindicated/ not applicable	0.03	0.003	1.17	1.01
$P2Y_{12}$ inhibitors				
Received	0.56	0.02	0.64	0.98
Contraindicated/ not applicable	0.06	0.001	1.37	1.01
ACEi/ARBs				
Received	0.44	0.01	1.25	1.00
Contraindicated/ not applicable	0.12	0.01	2.31	1.04
Statins				
Received	0.62	0.03	0.50	0.96
Contraindicated/ not applicable	0.05	0.002	1.63	1.02
In-hospital procedures				
Coronary angiography				
Received	0.13	0.003	0.97	1.00
Contraindicated/ not applicable	-0.04	-0.003	0.85	0.99
Coronary intervention (PCI/CABG)				
Received	0.06	-0.003	1.04	1.00
Contraindicated/ not applicable	-0.01	0.01	0.96	1.02

Abbreviations: ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; CABG, coronary artery bypass graft; CHD, coronary heart disease; COPD, chronic obstructive pulmonary disease; IMD, Index of multiple deprivation; PCI, percutaneous coronary intervention; ref, reference category.

Table 7.5. Balance check parameters using standardized differences and variance ratios (imputation dataset 4).

	Standardized differences		Variance ratios	
Data	**Raw**	**Weighted**	**Raw**	**Weighted**
Age				
Below 55	ref	ref	ref	ref
55-65	0.01	0.02	1.02	1.04
66-75	0.06	-0.02	1.09	0.97
76-85	0.03	-0.01	1.03	0.99
Above 85	-0.08	-0.01	0.87	0.99
Male	0.01	-0.01	1.00	1.00
Deprivation (IMD)				
Least deprived (1)	ref	ref	ref	ref
2	0.02	-0.01	1.03	0.99
3	0.03	0.02	1.04	1.03
4	-0.01	0.004	0.99	1.01
Most deprived (5)	-0.01	0.01	0.98	1.02
Year of admission				

	Standardized differences		Variance ratios	
Data	**Raw**	**Weighted**	**Raw**	**Weighted**
2007	ref	ref	ref	ref
2008	0.05	0.01	1.08	1.01
2009	-0.01	-0.02	0.98	0.97
2010	-0.02	0.01	0.95	1.02
2011	-0.07	0.01	0.86	1.01
2012	-0.06	-0.01	0.84	0.99
2013	-0.06	-0.01	0.72	0.95
Cardiovascular history				
Cerebrovascular disease	-0.003	-0.002	0.99	0.99
Peripheral vascular disease	0.05	0.003	1.28	1.02
Cardiovascular risk factors				
Diabetes	0.03	0.01	1.06	1.01
Hypercholesterolaemia	0.06	-0.01	1.08	0.98
Hypertension	0.06	0.004	1.03	1.00
Current or ex-smoker	0.09	0.01	0.97	1.00
Asthma or COPD	0.06	0.01	1.04	1.00
Family history of CHD	0.07	0.01	1.11	1.02
Presenting characteristics				
Heart rate >110 bpm	-0.07	-0.01	1.01	1.00
Creatinine >200 (µmol/l)	-0.05	0.004	0.94	1.02
Peak troponin	0.02	-0.02	0.94	1.04
Cardiac arrest	0.02	-0.02	1.16	0.87
Electrocardiographic characteristics				
ST-segment deviation	0.02	-0.003	1.01	1.00
Care by cardiologist	-0.01	-0.01	1.00	1.01
Medication at discharge				
Aspirin				
Received	0.47	0.03	0.43	0.94
Contraindicated/ not applicable	0.01	-0.004	1.04	0.98
$P2Y_{12}$ inhibitors				
Received	0.54	0.03	0.64	0.96
Contraindicated/ not applicable	0.07	-0.02	1.42	0.98
ACEi/ARBs				
Received	0.45	0.02	1.27	1.01
Contraindicated/ not applicable	0.12	-0.02	2.24	0.88
Statins				
Received	0.63	0.04	0.50	0.95

	Standardized differences		Variance ratios	
Data	**Raw**	**Weighted**	**Raw**	**Weighted**
Contraindicated/ not applicable	0.03	-0.03	1.42	0.77
In-hospital procedures				
Coronary angiography				
Received	0.14	-0.002	0.97	1.00
Contraindicated/ not applicable	-0.04	-0.001	0.86	1.00
Coronary intervention (PCI/CABG)				
Received	0.07	0.002	1.04	1.00
Contraindicated/ not applicable	-0.01	0.01	0.97	1.03

Abbreviations: ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; CABG, coronary artery bypass graft; CHD, coronary heart disease; COPD, chronic obstructive pulmonary disease; IMD, Index of multiple deprivation; PCI, percutaneous coronary intervention; ref, reference category.

Table 7.6. Balance check parameters using standardized differences and variance ratios (imputation dataset 5).

	Standardized differences		Variance ratios	
Data	**Raw**	**Weighted**	**Raw**	**Weighted**
Age				
Below 55	ref	ref	ref	ref
55-65	0.03	0.01	1.05	1.02
66-75	0.07	-0.001	1.10	1.00
76-85	0.02	-0.02	1.02	0.98
Above 85	-0.09	0.001	0.87	1.00
Male	0.01	0.0001	1.00	1.00
Deprivation (IMD)				
Least deprived (1)	ref	ref	ref	ref
2	0.03	-0.002	1.04	1.00
3	0.04	-0.01	1.05	1.00
4	-0.03	0.01	0.96	1.01
Most deprived (5)	-0.01	0.01	0.98	1.01
Year of admission				
2007	ref	ref	ref	ref
2008	0.06	0.004	1.09	1.01
2009	-0.02	0.01	0.97	1.01
2010	-0.04	0.004	0.92	1.01
2011	-0.05	-0.01	0.89	0.97
2012	-0.06	-0.01	0.83	0.96
2013	-0.05	-0.02	0.77	0.91
Cardiovascular history				
Cerebrovascular disease	0.01	-0.02	1.01	0.95
Peripheral vascular disease	0.05	0.01	1.28	1.06
Cardiovascular risk factors				

	Standardized differences		Variance ratios	
Data	**Raw**	**Weighted**	**Raw**	**Weighted**
Diabetes	0.03	0.03	1.06	1.05
Hypercholesterolaemia	0.05	-0.01	1.06	0.99
Hypertension	0.05	0.002	1.02	1.00
Current or ex-smoker	0.08	0.0002	0.98	1.00
Asthma or COPD	0.08	0.0003	1.06	1.00
Family history of CHD	0.05	0.002	1.07	1.00
Presenting characteristics				
Heart rate >110 bpm	-0.05	-0.01	0.88	0.98
Creatinine >200 (µmol/l)	-0.04	-0.003	0.79	0.99
Peak troponin	0.01	-0.002	0.97	1.00
Cardiac arrest	0.03	-0.03	1.23	0.84
Electrocardiographic characteristics				
ST-segment deviation	0.04	-0.001	1.01	1.00
Care by cardiologist	-0.01	-0.03	1.00	1.02
Medication at discharge				
Aspirin				
Received	0.46	0.02	0.44	0.97
Contraindicated/ not applicable	0.02	0.01	1.13	1.06
$P2Y_{12}$ inhibitors				
Received	0.58	0.02	0.63	0.98
Contraindicated/ not applicable	0.07	0.01	1.41	1.04
ACEi/ARBs				
Received	0.44	0.01	1.26	1.00
Contraindicated/ not applicable	0.10	0.01	2.03	1.09
Statins				
Received	0.63	0.02	0.50	0.97
Contraindicated/ not applicable	0.02	-0.01	1.20	0.95
In-hospital procedures				
Coronary angiography				
Received	0.16	-0.01	0.96	1.00
Contraindicated/ not applicable	-0.04	-0.01	0.83	0.98
Coronary intervention (PCI/CABG)				
Received	0.07	0.01	1.04	1.00
Contraindicated/ not applicable	-0.01	-0.01	0.97	0.98

Abbreviations: ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; CABG, coronary artery bypass graft; CHD, coronary heart disease; COPD, chronic obstructive pulmonary disease; IMD, Index of multiple deprivation; PCI, percutaneous coronary intervention; ref, reference category.

Table 7.7. Balance check parameters using standardized differences and variance ratios (imputation dataset 6).

	Standardized differences		Variance ratios	
Data	**Raw**	**Weighted**	**Raw**	**Weighted**
Age				
Below 55	ref	ref	ref	ref
55-65	0.04	0.02	1.08	1.04
66-75	0.06	-0.01	1.08	0.99
76-85	0.03	-0.02	1.03	0.98
Above 85	-0.09	0.001	0.86	1.00
Male	0.05	-0.01	0.99	1.00
Deprivation (IMD)				
Least deprived (1)	ref	ref	ref	ref
2	0.03	-0.001	1.04	1.00
3	0.04	0.01	1.06	1.01
4	-0.03	0.01	0.95	1.01
Most deprived (5)	-0.01	-0.02	0.98	0.97
Year of admission				
2007	ref	ref	ref	ref
2008	0.06	0.004	1.10	1.01
2009	-0.02	0.02	0.97	1.04
2010	-0.03	-0.03	0.94	0.94
2011	-0.05	-0.01	0.88	0.98
2012	-0.06	-0.002	0.84	0.99
2013	-0.06	-0.01	0.69	0.92
Cardiovascular history				
Cerebrovascular disease	-0.01	-0.01	0.98	0.97
Peripheral vascular disease	0.05	0.002	1.33	1.01
Cardiovascular risk factors				
Diabetes	0.03	0.02	1.06	1.03
Hypercholesterolaemia	0.05	-0.01	1.07	0.99
Hypertension	0.07	0.01	1.03	1.00
Current or ex-smoker	0.08	0.01	0.97	1.00
Asthma or COPD	0.06	-0.004	1.04	1.00
Family history of CHD	0.06	0.01	1.09	1.01
Presenting characteristics				
Heart rate >110 bpm	-0.05	-0.04	0.85	0.88
Creatinine >200 (µmol/l)	-0.05	-0.001	0.75	0.99
Peak troponin	0.01	0.003	0.97	0.99
Cardiac arrest	0.02	-0.02	1.19	0.89
Electrocardiographic characteristics				
ST-segment deviation	0.05	-0.01	1.02	1.00
Care by cardiologist	-0.02	-0.01	1.02	1.01

	Standardized differences		Variance ratios	
Data	**Raw**	**Weighted**	**Raw**	**Weighted**
Medication at discharge				
Aspirin				
Received	0.46	0.04	0.44	0.93
Contraindicated/ not applicable	0.03	0.001	1.17	1.00
$P2Y_{12}$ inhibitors				
Received	0.53	0.03	0.66	0.97
Contraindicated/ not applicable	0.08	0.01	1.52	1.05
ACEi/ARBs				
Received	0.43	0.02	1.24	1.01
Contraindicated/ not applicable	0.10	-0.03	1.98	0.85
Statins				
Received	0.61	0.05	0.51	0.94
Contraindicated/ not applicable	0.06	-0.06	1.62	0.65
In-hospital procedures				
Coronary angiography				
Received	0.15	-0.01	0.96	1.00
Contraindicated/ not applicable	-0.03	-0.004	0.88	0.98
Coronary intervention (PCI/CABG)				
Received	0.09	-0.01	1.06	0.99
Contraindicated/ not applicable	-0.02	0.0003	0.94	1.00

Abbreviations: ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; CABG, coronary artery bypass graft; CHD, coronary heart disease; COPD, chronic obstructive pulmonary disease; IMD, Index of multiple deprivation; PCI, percutaneous coronary intervention; ref, reference category.

Table 7.8. Balance check parameters using standardized differences and variance ratios (imputation dataset 7).

	Standardized differences		Variance ratios	
Data	**Raw**	**Weighted**	**Raw**	**Weighted**
Age				
Below 55	ref	ref	ref	ref
55-65	0.02	0.02	1.04	1.03
66-75	0.06	0.02	1.09	1.03
76-85	0.02	-0.03	1.03	0.97
Above 85	-0.08	0.01	0.88	1.01
Male	0.03	-0.001	0.99	1.00
Deprivation (IMD)				
Least deprived (1)	ref	ref	ref	ref
2	0.01	0.01	1.02	1.02
3	0.03	-0.002	1.04	1.00
4	-0.01	0.01	0.99	1.02

	Standardized differences		Variance ratios	
Data	**Raw**	**Weighted**	**Raw**	**Weighted**
Most deprived (5)	-0.01	0.003	0.99	1.00
Year of admission				
2007	ref	ref	ref	ref
2008	0.04	0.02	1.06	1.03
2009	-0.02	0.02	0.97	1.03
2010	-0.01	-0.03	0.98	0.93
2011	-0.05	-0.01	0.89	0.98
2012	-0.05	-0.01	0.86	0.98
2013	-0.04	-0.02	0.77	0.89
Cardiovascular history				
Cerebrovascular disease	-0.004	-0.02	0.99	0.95
Peripheral vascular disease	0.06	0.01	1.34	1.06
Cardiovascular risk factors				
Diabetes	0.04	0.02	1.08	1.03
Hypercholesterolaemia	0.06	0.004	1.08	1.01
Hypertension	0.06	0.001	1.03	1.00
Current or ex-smoker	0.07	0.02	0.97	0.99
Asthma or COPD	0.07	-0.01	1.05	1.00
Family history of CHD	0.05	-0.02	1.08	0.97
Presenting characteristics				
Heart rate >110 bpm	-0.05	-0.02	0.88	0.96
Creatinine >200 (µmol/l)	-0.04	0.002	0.82	1.01
Peak troponin	-0.01	-0.01	1.01	1.04
Cardiac arrest	0.03	-0.01	1.20	0.91
Electrocardiographic characteristics				
ST-segment deviation	0.04	-0.003	1.01	1.00
Care by cardiologist	0.01	-0.02	1.00	1.01
Medication at discharge				
Aspirin				
Received	0.47	0.02	0.43	0.96
Contraindicated/ not applicable	0.004	0.01	1.02	1.06
$P2Y_{12}$ inhibitors				
Received	0.55	0.02	0.65	0.98
Contraindicated/ not applicable	0.07	-0.001	1.43	1.00
ACEi/ARBs				
Received	0.45	0.01	1.27	1.00
Contraindicated/ not applicable	0.12	-0.03	2.31	0.85
Statins				
Received	0.61	0.03	0.51	0.96
Contraindicated/ not applicable	0.06	-0.04	1.71	0.72
In-hospital procedures				
Coronary angiography				

	Standardized differences		Variance ratios	
Data	**Raw**	**Weighted**	**Raw**	**Weighted**
Received	0.13	-0.01	0.97	1.00
Contraindicated/ not applicable	-0.03	-0.01	0.86	0.98
Coronary intervention (PCI/CABG)				
Received	0.07	-0.003	1.04	1.00
Contraindicated/ not applicable	0.01	0.0002	1.02	1.00

Abbreviations: ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; CABG, coronary artery bypass graft; CHD, coronary heart disease; COPD, chronic obstructive pulmonary disease; IMD, Index of multiple deprivation; PCI, percutaneous coronary intervention; ref, reference category.

Table 7.9. Balance check parameters using standardized differences and variance ratios (imputation dataset 8).

	Standardized differences		Variance ratios	
Data	**Raw**	**Weighted**	**Raw**	**Weighted**
Age				
Below 55	ref	ref	ref	ref
55-65	0.02	0.02	1.04	1.03
66-75	0.06	-0.01	1.08	0.99
76-85	0.02	-0.01	1.03	0.99
Above 85	-0.07	-0.01	0.89	0.98
Male	0.03	0.01	0.99	1.00
Deprivation (IMD)				
Least deprived (1)	ref	ref	ref	ref
2	0.01	0.004	1.02	1.01
3	0.04	-0.01	1.06	0.99
4	-0.002	0.01	1.00	1.02
Most deprived (5)	-0.02	0.001	0.97	1.00
Year of admission				
2007	ref	ref	ref	ref
2008	0.05	0.01	1.08	1.02
2009	-0.02	0.01	0.97	1.02
2010	-0.03	-0.003	0.94	0.99
2011	-0.04	-0.02	0.91	0.95
2012	-0.06	-0.008	0.84	0.98
2013	-0.06	-0.02	0.73	0.89
Cardiovascular history				
Cerebrovascular disease	0.01	0.001	1.04	1.00
Peripheral vascular disease	0.05	0.003	1.27	1.02
Cardiovascular risk factors				
Diabetes	0.03	0.01	1.05	1.03
Hypercholesterolaemia	0.04	-0.003	1.06	1.00
Hypertension	0.07	0.004	1.03	1.00
Current or ex-smoker	0.06	0.01	0.98	0.99
Asthma or COPD	0.07	0.01	1.05	1.00
Family history of CHD	0.05	-0.02	1.08	0.97

	Standardized differences		Variance ratios	
Data	**Raw**	**Weighted**	**Raw**	**Weighted**
Presenting characteristics				
Heart rate >110 bpm	-0.06	-0.01	0.83	0.97
Creatinine >200 (µmol/l)	-0.04	-0.0003	0.80	1.00
Peak troponin	0.0001	-0.01	1.00	1.01
Cardiac arrest	0.02	-0.01	1.17	0.90
Electrocardiographic characteristics				
ST-segment deviation	0.03	0.01	1.01	1.00
Care by cardiologist	-0.003	-0.02	1.00	1.01
Medication at discharge				
Aspirin				
Received	0.45	0.03	0.44	0.94
Contraindicated/ not applicable	0.03	0.01	1.17	1.06
$P2Y_{12}$ inhibitors				
Received	0.56	0.02	0.65	0.98
Contraindicated/ not applicable	0.07	0.01	1.37	1.06
ACEi/ARBs				
Received	045	0.01	1.26	1.00
Contraindicated/ not applicable	0.12	-0.01	2.30	0.95
Statins				
Received	0.62	0.03	0.50	0.96
Contraindicated/ not applicable	0.04	-0.01	1.39	0.95
In-hospital procedures				
Coronary angiography				
Received	0.14	-0.01	0.97	1.00
Contraindicated/ not applicable	-0.03	-0.01	0.88	0.97
Coronary intervention (PCI/CABG)				
Received	0.06	-0.01	1.03	0.99
Contraindicated/ not applicable	-0.0003	0.0003	1.00	1.00

Abbreviations: ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; CABG, coronary artery bypass graft; CHD, coronary heart disease; COPD, chronic obstructive pulmonary disease; IMD, Index of multiple deprivation; PCI, percutaneous coronary intervention; ref, reference category.

Table 7.10. Balance check parameters using standardized differences and variance ratios (imputation dataset 9).

	Standardized differences		**Variance ratios**	
Data	**Raw**	**Weighted**	**Raw**	**Weighted**
Age				
Below 55	ref	ref	ref	ref
55-65	0.028	0.026	1.05	1.05
66-75	0.08	0.01	1.11	1.01
76-85	0.02	-0.02	1.02	0.98
Above 85	-0.09	-0.02	0.86	0.97
Male	0.02	0.001	0.99	1.00
Deprivation (IMD)				
Least deprived (1)	ref	ref	ref	ref
2	0.01	0.004	1.01	1.01
3	0.04	-0.02	1.06	0.97
4	-0.02	0.01	0.97	1.01
Most deprived (5)	-0.02	-0.001	0.96	1.00
Year of admission				
2007	ref	ref	ref	ref
2008	0.07	-0.01	1.12	0.99
2009	-0.02	0.01	0.97	1.01
2010	-0.02	0.001	0.95	1.00
2011	-0.05	-0.01	0.89	0.97
2012	-0.06	-0.01	0.84	0.97
2013	-0.06	-0.02	0.72	0.92
Cardiovascular history				
Cerebrovascular disease	0.01	-0.003	1.02	0.99
Peripheral vascular disease	0.04	0.004	1.22	1.02
Cardiovascular risk factors				
Diabetes	0.02	0.02	1.05	1.03
Hypercholesterolaemia	0.05	-0.002	1.06	1.00
Hypertension	0.05	0.001	1.02	1.00
Current or ex-smoker	0.09	0.02	0.97	0.99
Asthma or COPD	0.06	-0.01	1.04	0.99
Family history of CHD	0.06	0.001	1.09	1.00
Presenting characteristics				
Heart rate >110 bpm	-0.07	-0.02	0.82	0.95
Creatinine >200 (µmol/l)	-0.05	-0.01	0.76	0.94
Peak troponin	0.01	0.01	0.97	0.98
Cardiac arrest	0.03	-0.03	1.21	0.81
Electrocardiographic characteristics				
ST-segment deviation	0.03	0.001	1.01	1.00
Care by cardiologist	-0.02	-0.02	1.02	1.01
Medication at discharge				
Aspirin				

	Standardized differences		Variance ratios	
Data	**Raw**	**Weighted**	**Raw**	**Weighted**
Received	0.45	0.03	0.44	0.93
Contraindicated/ not applicable	0.03	-0.001	1.18	0.99
$P2Y_{12}$ inhibitors				
Received	0.55	0.03	0.65	0.97
Contraindicated/ not applicable	0.08	0.01	1.47	1.04
ACEi/ARBs				
Received	0.43	0.02	1.25	1.01
Contraindicated/ not applicable	0.11	-0.03	2.15	0.86
Statins				
Received	0.60	0.03	0.51	0.96
Contraindicated/ not applicable	0.04	-0.01	1.37	0.94
In-hospital procedures				
Coronary angiography				
Received	0.14	0.002	0.97	1.00
Contraindicated/ not applicable	-0.04	-0.01	0.84	0.98
Coronary intervention (PCI/CABG)				
Received	0.07	-0.01	1.04	0.99
Contraindicated/ not applicable	-0.02	-0.001	0.93	1.00

Abbreviations: ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; CABG, coronary artery bypass graft; CHD, coronary heart disease; COPD, chronic obstructive pulmonary disease; IMD, Index of multiple deprivation; PCI, percutaneous coronary intervention; ref, reference category.

Table 7.11. Balance check parameters using standardized differences and variance ratios (imputation dataset 10).

	Standardized differences		Variance ratios	
Data	**Raw**	**Weighted**	**Raw**	**Weighted**
Age				
Below 55	ref	ref	ref	ref
55-65	0.03	0.02	1.06	1.04
66-75	0.07	-0.01	1.09	0.99
76-85	0.02	-0.01	1.02	0.99
Above 85	-0.09	-0.01	0.86	0.99
Male	0.02	0.02	1.00	1.00
Deprivation (IMD)				
Least deprived (1)	ref	ref	ref	ref
2	0.01	-0.003	1.02	1.00
3	0.03	-0.01	1.04	0.98
4	-0.02	-0.01	0.97	0.99
Most deprived (5)	0.004	0.01	1.01	1.02
Year of admission				
2007	ref	ref	ref	ref
2008	0.07	0.02	1.11	1.02
2009	-0.01	0.01	0.98	1.01

	Standardized differences		Variance ratios	
Data	**Raw**	**Weighted**	**Raw**	**Weighted**
2010	-0.03	-0.01	0.94	0.99
2011	-0.05	-0.01	0.90	0.97
2012	-0.06	-0.01	0.83	0.97
2013	-0.06	-0.01	0.72	0.92
Cardiovascular history				
Cerebrovascular disease	-0.003	-0.01	0.99	0.96
Peripheral vascular disease	0.06	0.01	1.37	1.07
Cardiovascular risk factors				
Diabetes	0.03	0.02	1.07	1.04
Hypercholesterolaemia	0.05	-0.01	1.07	0.99
Hypertension	0.05	-0.01	1.02	1.00
Current or ex-smoker	0.10	0.01	0.97	1.00
Asthma or COPD	0.08	-0.002	1.06	1.00
Family history of CHD	0.08	-0.02	1.12	0.98
Presenting characteristics				
Heart rate >110 bpm	-0.06	-0.02	0.85	0.95
Creatinine >200 (µmol/l)	-0.05	-0.01	0.76	0.95
Peak troponin	0.02	0.02	0.94	0.95
Cardiac arrest	0.03	-0.01	1.27	0.93
Electrocardiographic characteristics				
ST-segment deviation	0.04	-0.01	1.01	1.00
Care by cardiologist	0.004	-0.02	1.00	1.01
Medication at discharge				
Aspirin				
Received	0.46	0.03	0.44	0.93
Contraindicated/ not applicable	0.02	0.003	1.10	1.01
$P2Y_{12}$ inhibitors				
Received	0.55	0.03	0.64	0.97
Contraindicated/ not applicable	0.06	-0.01	1.37	0.95
ACEi/ARBs				
Received	0.44	0.01	1.25	1.00
Contraindicated/ not applicable	0.12	0.02	2.34	1.13
Statins				
Received	0.63	0.03	0.50	0.96
Contraindicated/ not applicable	0.04	0.01	1.38	1.10
In-hospital procedures				
Coronary angiography				
Received	0.15	-0.001	0.96	1.00
Contraindicated/ not applicable	-0.03	-0.01	0.89	0.95
Coronary intervention (PCI/CABG)				

	Standardized differences		Variance ratios	
Data	**Raw**	**Weighted**	**Raw**	**Weighted**
Received	0.07	-0.01	1.04	1.00
Contraindicated/ not applicable	-0.002	0.01	0.99	1.02

Abbreviations: ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; CABG, coronary artery bypass graft; CHD, coronary heart disease; COPD, chronic obstructive pulmonary disease; IMD, Index of multiple deprivation; PCI, percutaneous coronary intervention; ref, reference category.

Table 7.12. Over-identification test results for each of the imputed datasets used for the analysis.

Imputation	P-value for AMI analysis	P-value for STEMI analysis	P-value for NSTEMI analysis
1	0.20	0.27	0.47
2	0.07	0.87	0.10
3	0.89	0.48	0.35
4	0.39	0.87	0.17
5	0.55	0.36	0.70
6	0.07	0.64	0.10
7	0.25	0.87	0.05
8	0.29	0.89	0.60
9	0.36	0.88	0.22
10	0.28	0.53	0.71

Abbreviations: AMI, acute myocardial infarction; NSTEMI, non ST-segment elevation myocardial infarction; STEMI, ST-segment elevation myocardial infarction.

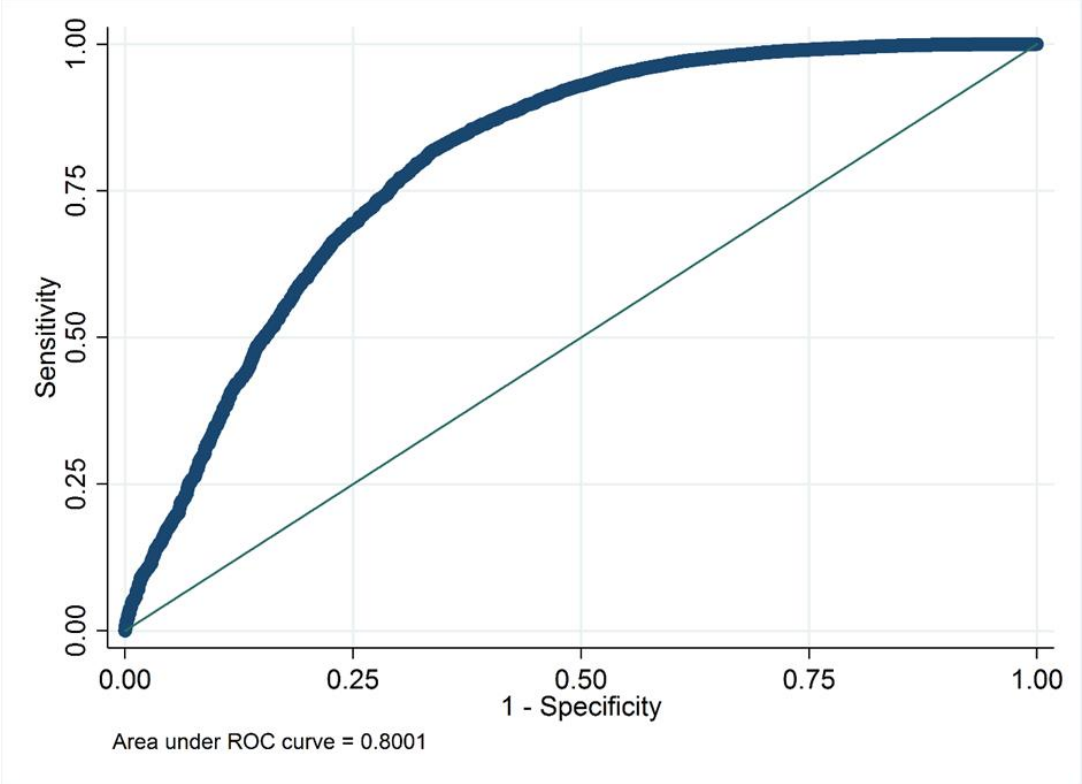


Figure 7.6. Area under ROC curve for the propensity scoring model.

7.3.2 Outcome model

After weighting and adjustment, there were no survival differences between AMI patients without heart failure or LVSD who received β blockers and those who did not at any time point to one year (Figure 7.7 and Figure 7.8). No significant treatment effects were found if all patients in the analytical cohort had received β blockers compared with if no patients in the analytical cohort had not received β blockers for the three survival times investigated (ATE coefficient 0.47, 95% CI -2.99 to 3.94, P=0.785; 0.06, -0.35 to 0.46, P=0.768; 0.07, -0.60-0.75, P=0.827, respectively) (Table 7.13). The stratified analysis by AMI phenotype (STEMI and NSTEMI) found no significant treatment effects for the use of β blockers at 1 month, 6 months and 1 year for both phenotypes (Table 7.13). Sensitivity analysis results of the untrimmed analytical cohort (n=179,810), after weighting and adjustment showed consistent results with the balanced analysis (trimmed analytical cohort analysis, n=16,683). There was no significant association of β blockers use with survival at 1 month, 6 months and 1 year, for AMI analysis combined as well as separately for STEMI and NSTEMI (Table 7.13). A complete case analysis was carried out too and consistent results with the imputed data were found (see Appendix D), however with convergence problems for some of the models due to the small sample sizes in the groups thus the imputation employed was warranted.

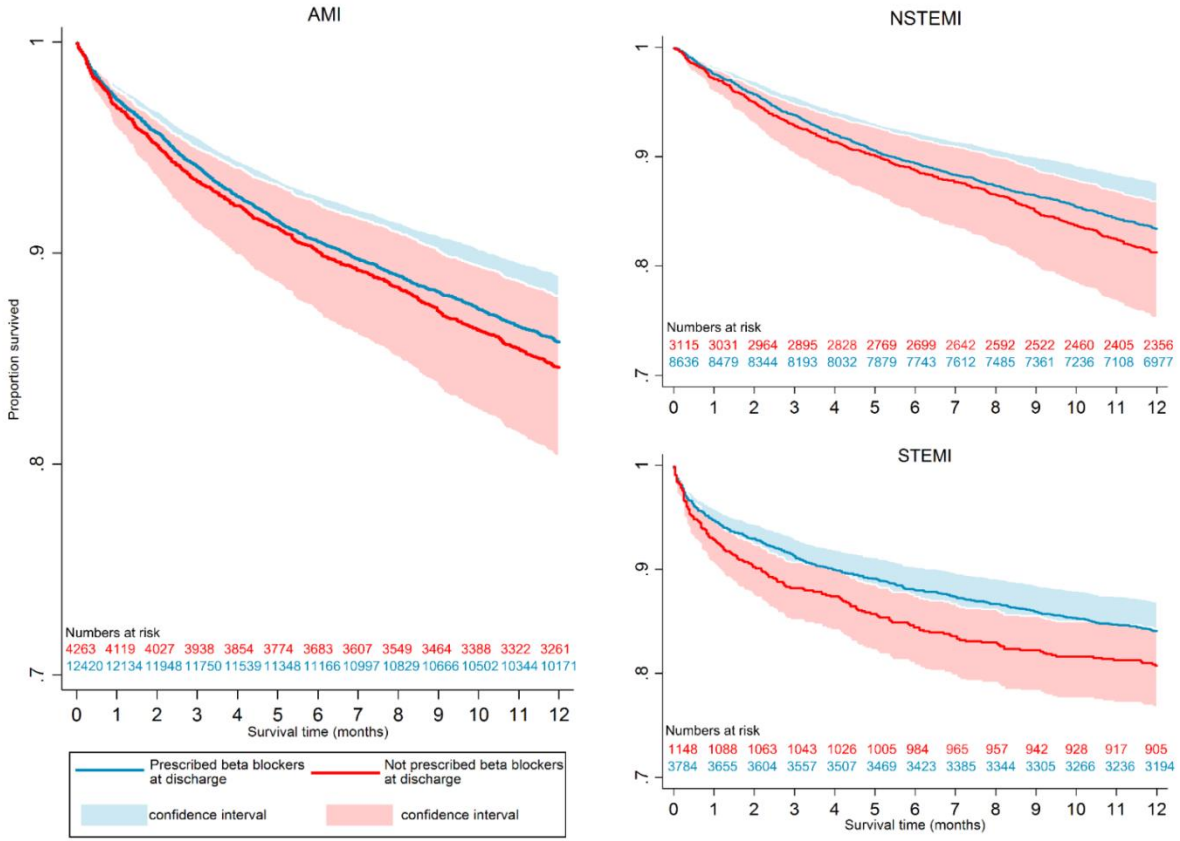


Figure 7.7. Adjusted survival (Kaplan-Meier estimates) among patients prescribed β blockers at discharge and those not prescribed (For trimmed analytical cohort (n=16,683)).

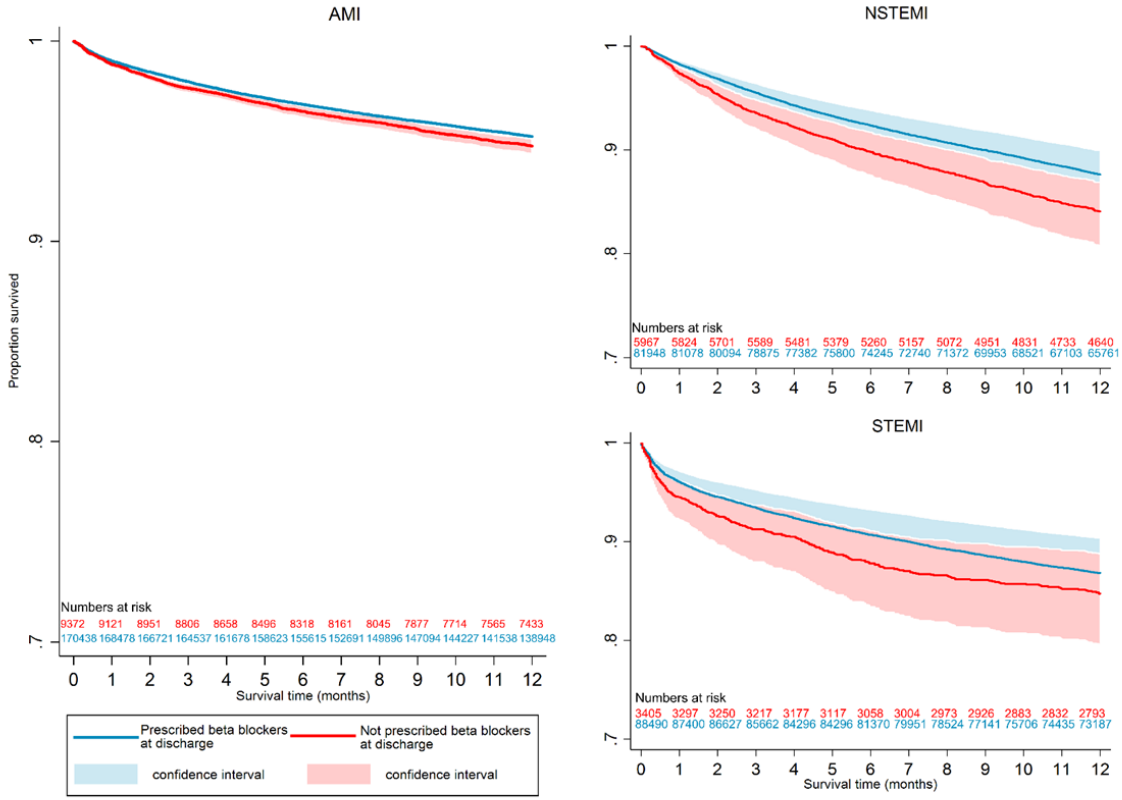


Figure 7.8. Adjusted survival (Kaplan-Meier estimates) among patients prescribed β blockers at discharge and those not prescribed (For full analytical cohort (N= 179,810)).

Table 7.13. Effect of β blockers at time of discharge from hospital on all-cause mortality for hospital survivors of AMI without heart failure or LVSD estimated using survival-time inverse-probability weighting propensity score analysis.

Trimmed cohort analysis					**Full analytical cohort analysis**				
	Average treatment effects		**Average treatment effects on the treated only**			**Average treatment effects**		**Average treatment effects on the treated only**	
Follow-up	**Coefficients¥ (95%CI)**	**P-value**	**Coefficients¥ (95%CI)**	**P-value**	**Follow-up**	**Coefficients¥ (95%CI)**	**P-value**	**Coefficients¥ (95%CI)**	**P-value**
AMI (N=16,683)					**AMI (N=179,810)**				
One month	0.47 (-2.99-3.94)	0.785	0.08 (-4.13-4.29)	0.971	One month	0.04 (-1.54-1.61)	0.964	-0.11 (-1.78-1.56)	0.897
Six months	0.06 (-0.35-0.46)	0.768	-0.05 (-0.52-0.43)	0.849	Six months	0.0001 (-0.29-0.29)	0.999	-0.04 (-0.35-0.28)	0.820
One year	0.07 (-0.60-0.75)	0.827	0.02 (-0.80-0.85)	0.954	One year	0.47 (-0.13-1.08)	0.121	0.47 (-0.19-1.12)	0.159
STEMI (n=4,932)					**STEMI (n=91,895)**				
One month	-0.14 (-5.89-5.61)	0.960	-0.50 (-7.06-6.06)	0.879	One month	0.57 (-2.31-3.45)	0.693	0.54 (-2.20-3.28)	0.697
Six months	-0.15 (-0.97-0.67)	0.712	-0.28 (-1.27-0.72)	0.575	Six months	-0.33 (-0.87-0.20)	0.223	-0.40 (-0.95-0.15)	0.158
One year	0.30 (-0.98-1.58)	0.637	0.26 (-1.37-1.88)	0.748	One year	0.49 (-0.34-1.32)	0.246	0.49 (-0.36-1.36)	0.260
NSTEMI (n=11,751)					**NSTEMI (n=87,915)**				

Trimmed cohort analysis					Full analytical cohort analysis				
	Average treatment effects		Average treatment effects on the treated only			Average treatment effects		Average treatment effects on the treated only	
Follow-up	**Coefficients[¥] (95%CI)**	**P-value**	**Coefficients[¥] (95%CI)**	**P-value**	**Follow-up**	**Coefficients[¥] (95%CI)**	**P-value**	**Coefficients[¥] (95%CI)**	**P-value**
One month	0.12 (-3.34-3.58)	0.947	-0.72 (-4.95-3.52)	0.735	One month	-0.16 (-3.62-3.31)	0.926	-0.45 (-4.22-3.33)	0.812
Six months	0.10 (-0.26-0.46)	0.565	0.02 (-0.38-0.42)	0.932	Six months	0.19 (-0.16-0.55)	0.286	0.18 (-0.20-0.56)	0.357
One year	-0.07 (-0.68-0.54)	0.819	-0.11 (-0.84-0.64)	0.777	One year	0.40 (-0.39-1.18)	0.314	0.39 (-0.48-1.26)	0.368

Abbreviations. AMI, Acute myocardial infarction; [¥] The average treatment effects (ATE) represents the absolute difference in survival time (months, respective to the follow-up time category) between β blocker treatment vs. no treatment across the whole cohort (comparing survival times in a scenario in which all patients were treated with survival times in a scenario in which no patients were treated). The average treatment effects on the treated (ATET) represents the absolute difference in survival time between β blocker treatment vs. no β blocker treatment estimated only amongst those who were treated (comparing survival times for all β blocker patients with the potential survival time in the scenario that the treated patients did not receive β blockers). The ATE and ATET are presented as coefficients with 95% confidence interval for the respective follow-up time categories. ; NSTEMI, non ST-elevation myocardial infarction; STEMI, ST-elevation myocardial infarction.

7.4 Instrumental variable analysis

The instrumental variable used for the analysis was "hospital rates of prescription of guideline-indicated treatments (aspirin, $P2Y_{12}$ inhibitors, β blockers, statins and ACEi/ARB))". Detail on the choice of the instrumental variable is given in Chapter 3, §3.9.2. The instrumental variable was found to be valid i.e. the instrument was a good predictor of use of β blockers, was well balanced across patient characteristics (Table 7.14) and was independent of patient outcomes (OR for 30 day mortality 1.11, 95% CI 0.38 to 3.23, P=0.847, 6 months mortality; 1.45, 0.68 to 3.07, P=0.337 and 1 year mortality; 1.25, 0.63 to 2.46, P=0.522).

Table 7.14. Patient characteristics and mortality according to quintiles of hospital prescribing rates of five drugs at discharge*.

	Quintile of hospital prescribing rates of five drugs at discharge				
Variable[a]	**1 N=28,870**	**2 N=35,981**	**3 N=33,775**	**4 N=39,021**	**5 N=42,163**
Age, mean (SD), years	65.0 (13.7)	64.4 (13.7)	64.0 (13.8)	64.1 (13.5)	63.7 (13.6)
Male	19,767 (68.5)	25,166 (69.9)	23,258 (68.9)	27,641 (70.8)	30,029 (71.2)
Deprivation (IMD score), median (IQR)	17.7 (10.6 -30.1)	16.5 (9.5-28.4)	20.1 (11.6-35.1)	17.0 (9.9-30.2)	17.5 (9.7-32.4)
Year of admission					
2007	5,090 (17.6)	5,398 (15.0)	4,607 (13.6)	5,228 (13.4)	4,703 (11.2)
2008	4,905 (17.0)	5,026 (14.0)	4,675 (13.8)	5,956 (15.3)	5,556 (13.2)
2009	5,195 (18.0)	5,242 (14.6)	5,086 (15.1)	6,264 (16.1)	6,911 (16.4)
2010	4,522 (15.7)	6,148 (17.1)	5,534 (16.4)	6,277 (16.1)	7,425 (17.6)
2011	4,166 (14.4)	6,064 (16.9)	5,935 (17.6)	6,551 (16.8)	7,487 (17.8)
2012	3,973 (13.8)	6,114 (17.0)	5,970 (17.7)	6,577 (16.9)	7,609 (18.1)
2013	1,019 (3.5)	1,989 (5.5)	1,968 (5.8)	2,168 (5.6)	2,472 (5.9)
Cardiovascular history					
Cerebrovascular disease	1,272 (4.4)	1,271 (3.5)	1,542 (4.6)	1,374 (3.5)	1,456 (3.5)
Peripheral vascular disease	476 (1.7)	644 (1.8)	818 (2.4)	668 (1.7)	805 (1.9)
Cardiovascular risk factors					
Diabetes	3,266 (11.3)	4,253 (11.8)	3,985 (11.8)	4,614 (11.8)	4,637 (11.0)
Chronic renal failure	505 (1.8)	537 (1.5)	631 (1.9)	578 (1.5)	652 (1.6)

Variable[a]	Quintile of hospital prescribing rates of five drugs at discharge				
	1 N=28,870	**2 N=35,981**	**3 N=33,775**	**4 N=39,021**	**5 N=42,163**
Hypercholesterolaemia	6,371 (22.1)	7,955 (22.1)	8,122 (24.1)	8,577 (22.0)	10,925 (25.9)
Hypertension	10,012 (34.7)	11,955 (33.2)	11,754 (34.8)	12,392 (31.8)	14,231 (33.8)
Current or Ex-smoker	18,555 (64.3)	23,175 (64.4)	22,306 (66.0)	25,401 (65.1)	27,899 (66.2)
Asthma or COPD	3,348 (11.6)	3,698 (10.3)	3,922 (11.6)	3,930 (10.1)	4,442 (10.5)
Family history of CHD	9,052 (31.4)	9,850 (27.4)	10,211 (30.2)	10,946 (28.1)	13,140 (31.2)
Presenting characteristics					
Systolic blood pressure, mmHg , mean (SD)	141.3 (27.2)	140.4 (27.5)	140.6 (27.7)	139.1 (27.4)	138.1 (27.0)
Heart rate, (beat/min), median (IQR)	77.0 (66.0-90.0)	78.0 (67.0-90.0)	77.0 (66.0-90.0)	76.0 (66.0-89.0)	76.0 (65.0-89.0)
Creatinine, (mg/dL), median (IQR)	86.0 (73.0-101.0)	86.0 (73.0-101.0)	84.0 (71.0-99.0)	85.0 (72.0-99.0)	85.0 (73.0-100.0)
Peak troponin[§], median (IQR)	3.3 (0.4-45.3)	3.6 (0.4-50.0)	4.3 (0.5-44.7)	5.8 (0.7-50.0)	3.7 (0.5-45.7)
Cardiac arrest	860 (3.0)	1,222 (3.4)	1,106 (3.3)	1,535 (3.9)	1,900 (4.5)
Electrocardiographic characteristics					
No acute changes	3,862 (13.4)	3,981 (11.1)	4,177 (12.4)	3,807 (9.8)	3,401 (8.1)
ST-segment elevation	11,879 (41.2)	17,137 (47.6)	16,105 (47.7)	20,617 (52.8)	23,281 (55.2)
Left bundle branch block	612 (2.1)	860 (2.4)	704 (2.1)	852 (2.2)	828 (2.0)
ST segment depression	4,185 (14.5)	4,429 (12.3)	3,797 (11.2)	4,373 (11.2)	4,534 (10.8)
T wave changes only	5,146 (17.8)	5,761 (16.0)	4,951 (14.7)	6,105 (15.7)	6,516 (15.5)
Other acute abnormality	3,186 (11.0)	3,813 (10.6)	4,041 (12.0)	3,267 (8.4)	3,603 (8.6)
Grace risk score					
Lowest (≤70)	3,195 (11.1)	3,749 (10.4)	3,402 (10.1)	3,321 (8.5)	3,659 (8.7)
Low (71-87)	4,235 (14.7)	5,207 (14.5)	4,693 (13.9)	5,040 (12.9)	5,684 (13.5)
Intermediate to high (>88)	21,440 (74.3)	27,025 (75.1)	25,680 (76.0)	30,660 (78.6)	32,820 (77.8)
Index event					
NSTEMI	16,435 (56.9)	18,285 (50.8)	17,038 (50.5)	17,661 (45.3)	18,496 (43.9)
Medication at discharge[b]					
Aspirin	27,309 (97.0)	34,402 (98.0)	32,715 (99.1)	37,869 (99.2)	40,965 (99.4)
$P2Y_{12}$ inhibitors	25,535 (91.7)	32,368 (94.1)	30,911 (96.5)	36,063 (96.8)	39,094 (97.3)
ACEi/ARBs	23,618 (86.2)	31,322 (92.3)	30,035 (94.7)	34,463 (95.5)	38,255 (97.4)
Statin	27,060 (94.9)	34,206 (96.7)	32,634 (98.1)	37,704 (98.6)	40,807 (99.0)

Variable[a]	Quintile of hospital prescribing rates of five drugs at discharge				
	1 N=28,870	2 N=35,981	3 N=33,775	4 N=39,021	5 N=42,163
β blockers	25,835 (89.5)	33,650 (93.5)	32,262 (95.5)	37,680 (96.6)	41,063 (97.4)
In-hospital procedures[b]					
Coronary angiography	19,751 (71.1)	24,455 (69.8)	24,055 (74.3)	23,628 (63.3)	28,978 (71.6)
Coronary intervention	14,846 (54.6)	18,610 (54.3)	18,895 (59.3)	18,071 (49.9)	23,606 (59.7)
Rehabilitation[b]					
Enrolment into cardiac rehabilitation	24,665 (89.2)	32,398 (94.1)	29,885 (92.7)	34,571 (92.2)	38,444 (96.3)

Abbreviations: ACE, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; CABG, coronary artery bypass graft; CHD, coronary heart disease; COPD, chronic obstructive pulmonary disease; PCI, percutaneous coronary intervention; IMD, Index of multiple deprivation; IQR, interquartile range; SD, standard deviation; § peak troponin was truncated at 50; *****Five discharge drugs (aspirin, $P2Y_{12}$ inhibitors, β blockers, statins and angiotensin converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARB)).

7.4.1 Treatments effects

Similar to the propensity score analysis results, the instrumental variable analysis found no significant difference in mortality at 1 month, 6 months and 1 year for patients who did not receive β blockers (coefficient -0.003, 95% CI -1.56 to 1.55, P=0.997; 0.18, -0.76 to 1.12, P=0.712; 0.02, -0.64 to 0.68, P=0.953, respectively), a result which was consistent across cases of STEMI and NSTEMI (Table 7.15).

Table 7.15. Effect of β blockers at time of discharge from hospital on all-cause mortality for hospital survivors of AMI without heart failure or LVSD estimated using instrumental variable analysis.

Follow-up	Treatment effects Coefficient[¥] (95% CI)	*P*-value
AMI (n=179,810)		
One month	-0.003 (-1.56-1.55)	0.997
Six months	0.18 (-0.76-1.12)	0.712
One year	0.02 (-0.64-0.68)	0.953
STEMI (n=91,895)		
One month	-0.42 (-2.81-1.96)	0.725
Six months	0.32 (-2.54-3.18)	0.826
One year	0.03 (-1.82-1.87)	0.976
NSTEMI (n=87,915)		
One month	-0.57 (-1.64-0.49)	0.291
Six months	-0.34 (-0.91-0.22)	0.235
One year	-0.50 (-1.57-0.58)	0.365

Abbreviations: AMI, acute myocardial infarction; [¥]Estimate represents the effect of β blockers on survival for the respective follow-up time categories; NSTEMI, non ST- elevation myocardial infarction; STEMI, ST- elevation myocardial infarction.

7.5 Summary of key findings

- β blocker users tended to be younger, male, less co morbid and lower risk compared with the non β blocker users.
- After propensity weighting and confounder adjustment, if all the patients in the population had received β blockers, there was no significant difference in the average time to death compared with if no patients had received β blockers.

7.6 Conclusion

In this nationwide observational study of survivors of hospitalisation with AMI without heart failure or LVSD, the use of β blockers was not associated with a lower risk of death at up to year. The next Chapter is the discussion of the findings of this thesis.

Chapter 8 : Discussion

8.1 Introduction

Cardiovascular disease is the main cause of death in Europe, with CHD being the most common cause of premature death in the UK(1, 14). Despite substantial improvements in its treatment, the global burden persists and a large proportion of patients fail to receive appropriate care. This thesis set out to evaluate quality of care and associated outcomes for the most common manifestation of CHD, ACS using readily available electronic health records and applying advanced statistical techniques.

The study makes a contribution to knowledge by being the first ever study to provide a comprehensive assessment of receipt of optimal care (considering care interventions beyond the five main cardio-protective drugs on the AMI care pathway) for the more vulnerable of the two AMI phenotypes, NSTEMI as well as quantify the associated harm of missing care interventions. The study also sought out to determine whether temporal changes in STEMI treatments or patient characteristics were associated with improvements in survival, and finally determine the efficacy of β blockers for AMI patients without heart failure or LVSD since there is no contemporary randomised data for survivors of AMI without heart failure or LVSD in relation to the use of β blockers. As such, international guidelines differ in their recommendation on the use of β blockers following AMI.

The findings from the four objectives of the thesis were presented in the earlier chapters:

- Chapter 4 reports findings for objective one of the thesis whereby avoidable deaths associated with sub-optimal care for NSTEMI patients were quantified and predictors of receipt of NSTEMI care determined.
- Chapter 5 reports findings for objective two of the thesis whereby within country variation in receipt of care for NSTEMI patients was evaluated.

- Chapter 6 reports findings for objective three of the thesis whereby factors (temporal changes in treatments or patient baseline characteristics) attributed to the temporal improvements in six months and one year survival for STEMI patients were determined.
- Chapter 7 reports findings for objective four of the thesis whereby the efficacy of β blockers use at hospital discharge was determined for AMI patients without heart failure or LVSD.

Summary of key findings of the objectives of the thesis are given in §8.2 as well as detailed discussion and synthesis of the results in §8.3. This will be followed by a detailed discussion of strengths and limitations of the thesis in §8.4, implications of the study in §8.5, recommendations for future research in §8.6, and future publications in §8.7. Finally an overall conclusion is given in §8.8.

8.2 Summary of key findings from thesis

Excess mortality (avoidable deaths) and guideline-indicated care following non ST-elevation myocardial infarction. (Objective one)

The study quantified the excess mortality associated with poor receipt of international guideline indicated care for patients hospitalised with NSTEMI across a single healthcare system (the National Health Service of England and Wales). Only 13.2% of the NSTEMI patients received all the care interventions they were eligible for (optimal care). In total approximately 33,000 deaths were estimated to have been potentially avoidable if all patients during the study period had received the investigations and treatments for which they were eligible. The care interventions that were frequently missed included: dietary and smoking cessation advice, echocardiography to evaluative left ventricular systolic function, coronary angiography, the prescription of $P2Y_{12}$ inhibitors at hospital discharge, and pre-hospital aspirin. All of the 13 care interventions if missed, except aldosterone antagonists, had significant and strong associations with reduced survival, in particular coronary angiography, cardiac rehabilitation, smoking cessation advice and the use of statins. This current study found that the care intervention that had

the strongest impact on survival if missed was coronary angiography. Care by a cardiologist was found to be a positive predictor of receipt of optimal care.

Geographic variation in the treatment of non ST-segment myocardial infarction in the English National Health Service: a cohort study. (Objective two)

Receipt of optimal care varied geographically, however wider variations were observed when individual assessments of the care interventions were undertaken. The greatest variation in provision of care across CCGs was for aldosterone antagonists and least for use of electrocardiogram, with high prescription rates and minimal variation for prescription of aspirin acutely, aspirin at discharge from hospital and statins. Intermediate provision rates and wide variation across CCGs were observed for provision of echocardiography, cardiac rehabilitation, coronary angiography, prescription of ACEi/ARBs and β blockers, with low provision rates for and little variation across CCGs for provision of smoking cessation advice, dietary advice and $P2Y_{12}$ inhibitors. Similar findings were noted for SCNs, with high receipt of optimal care being observed in North East and North Cumbria, and East Midlands. Most of the variation (after accounting for differences in patients) was explained by differences in the provision of care by hospitals.

Association of clinical factors and therapeutic strategies with improvements in survival following STEMI. (Objective three)

Among patients hospitalized with STEMI in England and Wales, improvements in all cause six months, and one year mortality were observed between 2004 and 2013. This was significantly associated with the introduction of PPCI and $P2Y_{12}$ inhibitors use at hospital discharge, with introduction of PPCI having the greatest impact on one year mortality.

Role of β-blockers during and after AMI in patients without heart failure or LVSD. (Objective four)

In the first large cohort study to investigate the impact of β blockers on survival following AMI among patients without heart failure or LVSD, the use of β blockers at hospital discharge among nearly 17,000 (propensity score

balanced) and 180,000 (instrumental variable analysis) patients between 2007 and 2013 was not associated with a lower risk of death at up to one year.

8.3 Findings in the context of literature

8.3.1 Excess mortality (avoidable deaths) and guideline-indicated care following non ST-elevation myocardial infarction.

Prevalence of patients who received optimal care

The ESC and the ACC/AHA have defined care for NSTEMI patients, with the recommendations from the guidelines being supported by evidence from clinical trials and observational data(4, 21, 23). Several cohort studies have reported the survival benefits from adherence to these evidence based interventions after suffering an AMI(67, 149, 150). Even so, a large proportion of patients fail to get optimal care. This current study of 389,057 NSTEMI patients found that 86.8% of the patients received sub-optimal care. Comparing these findings to past literature, similar findings were observed. Prevalence of sub optimal care has been reported to be high for AMI patients (median 53.8%, IQR 50.6-70.9%)(51-61). For example a study by Bramlage et al.(51) of 5,353 AMI patients found that optimal care was provided to just about half of the patients, with optimal care being defined as prescription of the five main pharmacotherapy at hospital discharge (aspirin, ACEi/ARBs, β-blockers, statin and clopidogrel) unless contraindicated. Similarly to the Bramlage et al.(51) study, the majority of past studies that have assessed receipt of optimal care for AMI patients have focused mainly on prescription of the five main cardio-protective drugs (of the entire AMI care pathway), with the exception of one study by Longenecker et al.(59) that also considered reperfusion in their definition. The major concern with defining optimal care defined restricted to prescription of the five cardio-protective drugs is that it restricts the analyses to focus more on patients who are managed the conservative approach of care and it biases the survival benefits inherent if the AMI patients receive all care interventions for which they were eligible across the entire guideline indicated AMI care pathway. It should be expected

that greater survival benefits would be observed when a patient receives all the guideline-indicated care interventions for which they are eligible including the cardio-protective drugs.

Only one study by Simms et al.(61) assessed receipt of optimal care including care interventions beyond receipt of the five cardio-protective drugs. However the work was only restricted to STEMI patients, as a result the work for this thesis focused mainly on NSTEMI patients as no comprehensive analysis equivalent to the work carried out by Simms et al.(61) has been undertaken for NSTEMI patients. For STEMI patients, Simms et al.(61) found of the nine STEMI care interventions (i.e. pre-hospital ECG, acute use of aspirin, timely reperfusion, five pharmacotherapies and referral for cardiac rehabilitation) they considered only half (50.6%) of the STEMI patients (N=112,286) received optimal care.

Unlike other previous studies, this current study assessed optimal care focusing on care interventions that span the entire NSTEMI care pathway (13 guideline-indicated care interventions). Focusing on receipt of 13 care interventions makes this study's findings more novel and comprehensive compared to other studies found in literature that carried out similar research work. The definition of optimal care based on the 13 care interventions used in this current study may potentially explain the higher proportion of receipt of sub-optimal NSTEMI care observed for this current work compared to the other studies as it considered more care interventions on the NSTEMI pathway i.e. beyond the five drugs prescription at hospital discharge. Assessing quality of care focusing on the five cardio-protective drugs only can also be miss-leading (potentially over estimates receipt of optimal care) as prescription rates of the drugs at discharge has been reported in literature to be high compared to the other care interventions(51, 52, 54, 59, 62). The care interventions that were found to be frequently missed in the this current study included: dietary and smoking cessation advice, echocardiography to evaluative left ventricular systolic function, the prescription of $P2Y_{12}$ inhibitors, coronary angiography and the acute prescription of aspirin (pre-hospital).

Comparing these findings to other studies in literature (just restricted to the five cardio-protective drugs to aid comparability), prescription of $P2Y_{12}$ inhibitors (i.e. termed clopidogrel in some of the other studies) was found to be consistently frequently missed compared to the other cardio-protective drugs(51-53).

Impact of individual care interventions on survival

In addition to assessing prevalence of optimal care amongst NSTEMI patients, the impact of the individual care interventions on survival were undertaken. Non-adherence to the frequently missed care interventions that were identified in this study was associated with reduced survival. Coronary angiography had the greatest impact on survival i.e. not getting an angiogram was associated with a reduction in time to death by 82%, cardiac rehabilitation 51%, smoking cessation advice 47%, dietary advice 35%, and $P2Y_{12}$ inhibitors 24%. Of the studies considered in the literature review only Bramlage et al.(51), Danchin et al.(58) and Hamood et al.(60) assessed the relative importance of individual components of their composite definitions of receipt of optimal care. Bramlage et al.(51) assessed the impact of withdrawing each of the cardio-protective drugs from their receipt of all five drugs scores. The optimal care survival benefits observed in the study by Bramlage et al.(51) disappeared after withdrawal of β blockers and antiplatelet therapy (aspirin/clopidogrel) from the composite score definition of optimal care used for the study. Hamood et al.(60) found that individual pharmacotherapy non-adherence was associated with increased risk of all-cause mortality, aspirin non-adherence by 28%, statins by 36%, ACEi/ARBs by 57% with no survival benefits being observed for β blockers non-adherence. However it is quite difficult to compare their findings to the work of the thesis due their restricted definition of optimal care and select cohorts used for their studies.

However, consistently with the findings of this study a study by Hall et al.(145) investigating the association of changes in NSTEMI patients' characteristics or treatment with temporal improvements in survival noted between 2003 to 2013 found that the temporal survival improvements noted in the study were

significantly associated with the temporal increase of receipt of an angiogram. The mediation analysis carried by this study found 88.3% of the temporal change in survival was explained by the increased use of angiography(145).

Reasons for not receiving optimal care and predictors of receiving optimal care

Reasons behind the noted care deficits for NSTEMI patients have been attributed to constraints around the availability of specialists and associated equipment. Also the management of NSTEMI patients is heterogeneous and the decision to prescribe evidence based medications or to proceed to coronary angiography is determined by the treating physician. NSTEMI care is heavily influenced by treating physician preferences. STEMI management is not as heterogeneous as the NSTEMI, in the UK it is institutionally operationalised through a national primary PCI programme(151, 152). Other studies in literature have attributed the physician treating preferences to be the major contribution to AMI patients not receiving appropriate care(68, 153-155). It has been reported that physicians are more likely to treat lower risk patients more aggressively compared to high risk patients, a recognised practice in literature termed the “treatment paradox”.

Care by cardiologist was determined as the most important positive predictor of receipt of optimal care in this study. This has been attributed to the fact that cardiologists are continuously exposed to clinical trials findings, local/international conferences such as the annual ESC congress and recommendations by international guidelines compared with other health experts such that they are highly knowledgeable on the management of AMI patients and are always updated on the developments in AMI care(68). Only 56.6% of the NSTEMI patients in the study received care from a cardiologist which can potentially explain the care deficits observed. NSTEMI patients are rarely treated by cardiologists as there is a perception that NSTEMI patients are at lower risk of mortality compared with the other AMI phenotype STEMI(156).

Most of the patients who received optimal care in the study were found to be hospitalised between 2009-13. This potentially is a reflection of utility of the guidelines. In the earlier years treatment was mainly informed by consensus documents, with more specific (for each phenotype) detailed guidelines to inform NSTEMI treatment being developed in the recent years. Also marked improvements in NSTEMI care have been noted over the years(145).

Optimal care definition

In Chapter 4, LCA was used to define receipt of care for NSTEMI patients based on 13 guide-indicated care interventions. This study is the first to define receipt of care using the LCA approach which is very useful when trying to define receipt of care using multiple indicators mimicking 'real world clinical practice'. Compared to the other approaches that have been used in past literature such as the dose response technique or all or none approach, LCA captures 'real world clinical practice' by identifying unmeasured class membership (latent prescribing patterns) among subjects based on observed variables of the subjects. A three class solution was determined optimal and labelled high, intermediate, and low receipt of care classes to aid interpretation. However, the classes were representative of more complex patient patterns of care rather than all patients receiving either high, intermediate or low levels of care. Patients in the high class had low probabilities for receipt of ACEis/ARBs and β blockers. The reason for low receipt of ACEi/ARBs and β blockers within this class is because most of the patients in this class were not eligible for these two care interventions (see Table B 1-Table B 4 in Appendix B). ACEi/ARBs and β blockers are indicated for patients with left ventricular dysfunction, and, therefore, form a distinct group of patients. In effect, the high latent class patients were healthier and more likely to receive evidence-based care and confirm findings from others who have shown that the patients who are most likely to receive guideline-indicated treatments tend to be the lower risk patients(157-159). These findings implicate treatment of NSTEMI patients in that it confirms that patients who are multi-morbid have a lower chance of receiving optimal care.

As a sensitivity analysis a cross tabulation of the rest of the care interventions with the latent class sub-groups was undertaken and confirmed that the low probability of use captured in the intermediate and low receipt classes was indeed because of poor receipt and not contraindication (as noted for ACEi/ARBs and β blockers in the high receipt class) (see Table B 1-Table B 26 in Appendix B) as a lot of the eligible patients were not receiving treatment.

Analytical cohort size

Compared to the other studies in past literature that have evaluated adherence to guideline-indicated care interventions and associated outcomes for AMI patients the current study is the largest to date with an analytical cohort of 389,057 NSTEMI patients from a comprehensive registry of ACS (MINAP) across a single health system (the National Health Service, England and Wales). The other studies used select cohorts (median sample size 6,080, IQR 3,180-11,671) that may not be representative of the general population and thus compromise generalisability. Data are lacking on assessment of receipt of optimal care and associated outcomes for the larger populations of AMI patients mirroring “real-life clinical practice”(77) and the current work fills this gap in knowledge. The use of national registries such as MINAP allows higher resolution investigation of sequential care deficits significantly associated with premature cardiovascular death. Addressing these care deficits has potential to save lives.

However, although there has been much enthusiasm for the use of ‘big data’ from EHRs for health research, basing on the assumption that large sample sizes yield less biased findings than small sample sizes. There can be systematic biases in the sample of people in the EHR system or biases in the way information is captured or recorded, such that even with a large sample size the analytical cohort of a study may not be representative of the population to which the results will be generalised. Caution has to be taken

when drawing inference from data from EHRs (even with large sample sizes) and necessary steps have to be taken to reduce the potential inherent bias.

Impact of not receiving optimal care

This thesis found that 32,765 deaths could have been postponed if all the NSTEMI patients received optimal care. Chew et al.(52) using an analytical cohort of n=1,630 investigated the impact of combined use AMI care and reported that if all the AMI patients in their analytical cohort had received optimal care (defined as prescription of four or more pharmacotherapies) 104 lives could have been saved and 191 recurrent events prevented per 10,000 presentations. Our findings are similar to Chew et al.(52) in that both studies showed that negative impact of sub-optimal care on survival and both studies quantified the burden (preventable deaths) associated with sub-optimal care. However, unlike the Chew et al.(52) study that quantified preventable recurrent ischaemic events, the current work was restricted to only focusing on mortality as MINAP does not record non-fatal outcomes. An ideal approach would have been to focus on both fatal and non-fatal outcomes as receipt of optimal guideline-indicated care should result to better outcomes besides reduced mortality only.

The current work found that patients who received sub-optimal care had a 56% shortened mean time to death compared with patients who received optimal care. Besides the current study and the study by Chew et al.(52) that quantified the preventable deaths associated with sub-optimal AMI care, a vast amount of literature have quantified the impact on survival using risk ratios such as hazard of dying or odds of dying without estimating avoidable deaths(51-53, 55, 58, 59, 64, 78). Bramlage et al.(51) found that total mortality was reduced by 74%, Yan et al.(55) by 42%, Danchin et al.(58) by 48%, Hamood et al.(60) and Bauer et al.(53) found that those who received sub-optimal care had an increased risk of death by 38% and 60%, respectively compared with those who received optimal care. The differing percentages on impact on survival noted for the studies compared with the current study can be attributed to the heterogeneity in definitions of optimal care definitions across the studies thus differing impact on survival.

The research work conducted in this current thesis on quantifying the excess mortality due to non-adherence to guideline recommended care following NSTEMI might yield important actionable insights to guide healthcare policy and clinical practice to improve the quality of health systems and prevent avoidable deaths from acute myocardial infarction.

8.3.2 Geographic variation in the treatment of non ST-segment myocardial infarction in the English National Health Service: a cohort study.

The body of evidence prior to this thesis has focused mainly on between country evaluation of variations in receipt of care for ACS patients (48, 59, 63, 66, 68, 73, 160, 161), including international comparisons by Awad et al.(64) and Karrowni et al.(65). The current study is the first to assess within country geographic variation in receipt of NSTEMI care (the most common and vulnerable type of AMI) in the UK using a nationwide clinical registry designed specifically to evaluate quality of NSTEMI care.

For the NHS of England it is the responsibility of the 211 CCGs who work in partnership with hospitals, via SCNs to commission NSTEMI care(126). Over the 10 year evaluation receipt of optimal care for the NSTEMI patients varied between CCGs, with wider variations being observed for the individual care interventions. The greatest variation in provision of care across CCGs was for aldosterone antagonists and least for use of an electrocardiogram, with high prescription rates and minimal variation for prescription of aspirin acutely, aspirin and statins at discharge from hospital. Intermediate provision rates and wide variation across CCGs were observed for provision of echocardiography, cardiac rehabilitation, coronary angiography, prescription of ACEi/ARBs and β blockers, with low provision rates for and little variation across CCGs for provision of smoking cessation advice, dietary advice and $P2Y_{12}$ inhibitors. Similar findings were noted for SCNs, with high receipt of optimal care being observed in North East and North Cumbria, and East Midlands. One can only

speculate that since Northern England and East Midlands compared to other SCNs in England have a greater proportion of high volume hospitals (hospitals that perform <400 PCIs per annum)(162), AMI patients treated in these high volume hospitals are more likely to receive optimal care. It has been reported in past literature that higher volume hospitals have better care pathways because they follow more structured protocols and practice more evidence based treatment (163-165).

After adjusting for case mix, most of the remaining variation (99.6%) was explained by differences in provision of care by hospitals and to a much lesser extent by CCGs or SCNs. This finding is consistent with evidence from previous studies that also found that type and size of hospital influenced receipt of AMI care(55, 56, 160, 166, 167). For example, Mehta et al.(166) reported that hospitals that had both low adherence to guideline-indicated care and low safety metrics for dosage were the smaller non-teaching hospitals which were less likely to have percutaneous or surgical coronary revascularisation. Fox et al.(160) also found that PPCI was mostly carried out in university or university affiliated hospitals than community hospitals. Similarly, Tuppin et al.(56) reported that high rates of statins, ACEi/ARBs, β blockers, antiplatelet agents and optimal care were observed in patients treated in university hospitals or high volume centres.

The causes of the healthcare variations observed are complex and have been attributed to differences in patient characteristics, clinicians' behaviour or the effects of incentives in the financing of healthcare(168, 169). The work of this thesis found that variation in the provision of NSTEMI treatment remained after adjusting for patient sociodemographic and clinical characteristics, suggesting that modifiable factors such as procurement, infrastructure, availability of specialist services and physician treating preferences/education are critical(168). Treating physicians have been reported to select lower risk and less comorbid patients for more aggressive treatment under the perception that the risk that may be associated with aggressive treatment for higher risk, multimorbid and elderly patients may outweigh the benefits from treatment(156).

The research work conducted in this thesis on variation in NSTEMI care was conducted to specifically target evaluation of variation at CCG level to allow commissioners to identify where and what service may require closer attention. The findings from this study suggested variation in care was mostly attributed to providers (hospitals). Initiatives such as the introduction of a performance-based tariff for NSTEMI (or an additional best practice payment(170)) may reduce hospital variation and potentially improve patient outcomes. An example were performance-based commissioning has been applied and found to be associated with favourable outcomes is the introduction of the Advancing Quality Program (171) across all NHS hospitals in the north-west of England. The program was found to be associated with a significant reduction in combined short-term mortality for pneumonia, heart failure and acute myocardial infarction(171).

8.3.3 Association of clinical factors and therapeutic strategies with improvements in survival following STEMI.

The work for objective three of the thesis was conducted in the framework of assessing quality of care and associated outcomes for AMI patients focusing on the STEMI phenotype, i.e. to determine whether temporal changes in STEMI treatments and patient characteristics were associated with improvements in survival. The study found that among patients hospitalized with STEMI in England and Wales, temporal improvements in all cause six months, and one year mortality were observed between 2004 and 2013. This was significantly associated with PPCI and $P2Y_{12}$ inhibitors use at hospital discharge, with introduction of PPCI having the greatest impact on one year mortality. Other studies in literature that have carried out similar work have found consistent findings as this thesis. Puymirat et al.(172) and Szummer et al.(173) found that greater use of reperfusion therapy and recommended medications amongst STEMI patients was associated with improved temporal survival improvements.

International studies have reported a decline in mortality following AMI(174-178). Comprehensive work has previously been undertaken quantifying the avoidable harm associated with sub-optimal care for STEMI patients(61) and also determining the factors associated with temporal improvements in survival for NSTEMI patients(145). However there is a paucity of contemporary studies of sufficient duration and representation from a population perspective that enable a detailed evaluation of the association of baseline risk and guideline-indicated therapies with mortality among patients with STEMI(145, 172, 173, 179-181), with only two studies in past literature focusing mainly on STEMI patients(172, 173).

The most recent study by Szummer et al.(173) evaluating the association of baseline risk factors, guideline-indicated therapies and fatal or non-fatal outcomes among patients with STEMI found that increased use of new and established evidence-based treatments during the 20 years follow-up was associated with prolonged survival and lower risk of ischaemic events. Changes in treatment and outcomes were most distinct between 1994 and 2008. Reperfusion increased from 66 to 94% (PPCI) between 1995/96 and 2013/14 over the 20 years, similarly for medical treatments: aspirin increased from 82-94%, dual antiplatelet therapy 0-90%, β blockers 78-91%, ACEi/ARBs 41-85% and statins 14-94%. Of all the factors considered, change in reperfusion and PPCI were found to be associated with improved in-hospital outcomes and change in discharge medications as well as change in reperfusion and PPCI were found to be associated with improved within one year outcomes. It is not surprising that the discharge medications had no impact on in-hospital outcomes as the patients would have not received the care interventions as they died in hospital before hospital discharge prescription. The modelling approach undertaken by Szummer et al.(173) of including all the cardio-protective drugs into the mediation model is concerning as it makes it difficult to identify which of the drugs has the greatest impact on survival. It may also give a misleading impression that all the drugs are associated with improved temporal improvements in survival yet it might be a specific drug. For example as observed in the current study's findings when the five drugs were adjusted for in the mediation model the temporal trend

became non-significant which implied that the increased prescription of all cardio-protective drugs explained temporal improvements in survival. However, it was upon further investigation by adjusting for each drug individually that it was revealed that it was the increased prescription of $P2Y_{12}$ inhibitors at hospital discharge that actually explained the temporal survival improvements.

Marked changes in the prescription of the cardio-protective drugs were observed in the Swedish study, yet for the current UK study prescription of the drugs the entire study (although improved) was very high (>90%) with the introduction of PPCI in 2007 onwards which came with a $P2Y_{12}$ inhibitors indication (Class I, Level A) for all STEMI patients before or at latest at time of PPCI.(182) Which explains the finding that the introduction of PPCI and $P2Y_{12}$ inhibitors were found to be associated with improved survival in the current work.

The care intervention for which the improvements in survival for STEMI patients have been mostly attributed is PPCI (172), and past literature has reported that for STEMI patients the introduction of PPCI has been reported to be associated with a decline in mortality (151, 183-185), as has the use of antithrombotic therapies and secondary prevention medications(172, 173, 186, 187). Consistently with the findings of the current study, PPCI and $P2Y_{12}$ inhibitors at hospital discharge were associated with six month and one year temporal survival improvements. No pronounced decline was observed for 30 day mortality for the STEMI patients recorded in MINAP between 2004-2013 used as the analytical cohort for objective three of the thesis. No association was found between introduction of PPCI and improved 30 day mortality, this could be attributed to lack of statistical power to draw inference on the impact of introduction of PPCI on 30 day mortality.

However upon conducting the mediation analysis improvements in one year survival between 2004 and 2013 were significantly explained by the uptake of

PPCI for in-hospital survivors of STEMI. Short term survival (six months), the mediated effects by PPCI were not significant. However the mediated effects identified for $P2Y_{12}$ inhibitors were found to be non-significant in the mediation analysis. Potentially this could be explained by a potential moderation relationship between PPCI and $P2Y_{12}$ inhibitors. Individually the care interventions confer survival benefits, however when used in combination they have a greater impact.

Compared with past literature, the current study is the first study to date to quantify temporal trends survival improvements for STEMI patients using mediation analysis to explore various causal pathways, going beyond the estimation of simple treatment effects. The mediated effects by PPCI for six months survival were not significant; this finding is consistent with what past literature has found i.e. survival benefits of an invasive strategy were most pronounced long term after suffering an ACS(188).

The mediation analysis showed that the determined mediators did not account for all the one year survival improvements for STEMI patients observed (only accounted for 27%). This shows that there are other unmeasured factors beyond those measured in MINAP that have also accounted for the survival improvements observed for the STEMI patients in the considered analytical cohort. Other studies in literature have suggested that factors beyond change in treatment effects and patients baseline characteristics are also important in explaining MI mortality trends, for example changes in health seeking behaviours when confronted with symptoms of MI have significant associations with temporal improvements in survival trends(172). Further work considering variables that measure such aspects needs to be undertaken and unfortunately for this thesis MINAP did not have such information.

8.3.4 Role of β-blockers during and after AMI in patients without heart failure or LVSD.

Beta blockers have been a cornerstone in the treatment of patients with AMI. However, uncertainty exists on their efficacy among AMI patients without heart failure or LVSD in contemporary practice. The 2015 ESC NSTEMI guidelines highlighted that there is a gap in knowledge on the efficacy of β blockers for patients with normal or mildly depressed LV function(4). Many of the RCT data to support β blockers use in AMI in this sub group of patients predate contemporary medical therapy and the available recent studies findings to date are conflicting such that international guidelines differ in their recommendation on the use of β blockers in this group of patients(4, 22-24). There is sufficient evidence to support the efficacy of β blockers use in patients with AMI and heart failure(189-193). The current study is the first large scale population based analysis investigating the impact of β blockers on survival after AMI among patients without heart failure or LVSD in the reperfusion era.

This current study found that among survivors of hospitalisation with AMI (hospitalised between 2007 and 2013) who did not have heart failure or LVSD as recorded in hospital, the use of β blockers was not associated with a lower risk of death at one month, six months and at one year. The results remained consistent when the analyses were carried out stratified by AMI phenotype i.e. NSTEMI and STEMI. The findings from this study are similar with findings from other studies in literature which have focused on similar work(194-197). An individual patient data meta-analysis of 11 trials by Cleland et al.(194) found that β blockers reduced all cause and cardiovascular mortality compared to the placebo, an effect that was consistent across the considered LVEF strata except in those in the sub-group with LVEF≥ 50% were no survival benefits in use of β blockers were observed.

A study by Puymirat et al.(195) conducted using the nationwide French registry; FAST-MI found that early use of β blockers (within 48 hours of admission) was associated with a substantial decrease in 30 day mortality (56% reduction), however no significant survival effects were observed for one

year and five year survival(195). In contrast to the results of no beneficial effect of β blockers, other studies have reported survival benefits(198). Misumida et al.(198) found that for STEMI patients who received PPCI survival benefits were observed for patients with oral β blockers compared with those without. Conflicting evidence in literature as such warrants the need for a clinical trial testing the efficacy of β blockers among patients with AMI who do not have heart failure or LVSD which will lead to a better understanding on the impact of β blockers on fatal and non-fatal outcomes in this sub group of AMI patients.

The lack in survival benefits observed for β blocker use in the reperfusion era has been attributed to both reperfusion and aggressive contemporary medical therapy (i.e. increased use of ACEI/ARBs, dual antiplatelet therapy and statins)(197). The pre-invention of reperfusion and lack of aggressive contemporary medical therapy in the pre-reperfusion era meant that after suffering an AMI the patients were most likely to get extensive myocardial scarring. This would result to the AMI patients suffering fatal ventricular arrhythmias. Use of β blockers for such patients was found to prevent the sudden death, hence the observed efficacy of β blockers in the pre-reperfusion era(197). Prompt reperfusion which is readily available in the contemporary era means reduced scarring for AMI patients thus reduced risk of arrhythmic deaths, thereby further reducing the impact of β blockers(197). Use of reperfusion therapy, aspirin and statins reduces infarct size(197). Bangalore et al.(197), reported that the use of β blockers in the contemporary era had no mortality benefit; however use reduced recurrent myocardial infarction and angina at the expense of increased risk of heart failure, cardiogenic shock and drug discontinuation. The current study's findings were limited to an all-cause mortality outcome since MINAP only records all-cause mortality data (through linkage to ONS data) and no other forms of non-fatal outcomes. Further work needs to be undertaken using advanced methodologies and comprehensive datasets (similar to the current study) exploring non-fatal outcomes, for example heart failure, cardiogenic shock, angina and recurrent MI.

Based on findings from this study and complimentary findings from other studies that have been identified, secondary prevention medications at discharge from hospital for AMI patients without heart failure or LVSD may not need to include β blockers in the contemporary era. Continued use might put the patients at increased risk of developing heart failure or cardiogenic shock as highlighted by the Bangalore et al.(197) study and poor adherence to other cardio-protective drugs that actually confer survival benefits after use(199).

The findings from this study add to the increasing body of evidence that the routine prescription of β blockers may not be indicated in patients with a normal ejection fraction or without heart failure post AMI patients. However, because the current study was only limited to all-cause mortality further work is required focusing on non-fatal outcomes. A randomised controlled trial is a necessary next step for the contemporary evaluation of β blockers in AMI without heart failure or LVSD.

8.4 Strengths and Limitations of the Study

The major strength of the work in this thesis is that it is based on a detailed population-based national clinical registry designed specifically to evaluate quality of heart attack care, MINAP and is mandated by the department of health in England and Wales(39). A detailed evaluation of MINAP is given in Chapter one, §1.6.4. Besides the Swedish Web-System for Enhancement and Development of Evidence-Based Care in Heart Disease Evaluated According to Recommended Therapies (SWEDEHEART) registry(200), there are no other databases of comparable size, coverage and quality which include all hospitals within a country across a single national health care system. In this big data era and increased use of electronic health records, MINAP offered data on a 10 year evaluation of quality of care and outcomes (over one million person years of follow-up) for AMI patients. The findings from this study provided comprehensive and original findings on the care deficits and associated avoidable harm for NSTEMI patients (the most vulnerable of the AMI phenotypes) in an otherwise modern and efficient national health care

system. NSTEMI patients have been under represented in research, yet they are highest risk of death and have the most heterogeneous pathways of care.

Other strengths of the thesis work include use of advanced statistical techniques such as latent class analysis to capture real life clinical practice in management of NSTEMI patients. Latent class analysis has not been used to define quality of care before for NSTEMI patients or even for ACS patients in past literature. The technique allowed for high resolution analysis of combinations of pathways of care according to their eligibility and receipt. The work also employed advanced statistical time to event modelling techniques, which include; shared frailty accelerated failure time models, flexible parametric models and survival-time inverse-probability weighting propensity score analysis for objectives one, three and four of the thesis. The literature review revealed that most studies use simple traditional approaches like logistic regression. Traditional regression methods are not suited to accommodate both the event and time aspect nature of time to event data in the modelling. This aspect challenges the utility of logistic regression models when analysing survival data. Ignoring the time-dependent information in the data may bias the analysis i.e. parameter estimates maybe overestimated especially in scenarios with high event rates which maybe misleading to clinicians when quantifying treatment effects of medications(82). Also unlike survival analysis techniques, traditional methods like logistic regression do not cater for a special type of missing data inherent when using time to event data which is called censoring. Censoring occurs when subjects do not experience the event under investigation during the follow-up time. Other advanced statistical techniques that are outside the time to event techniques framework used in the thesis include mediation analysis. The technique was undertaken to quantify the impact of the determined mediators on the STEMI six months and one year survival temporal improvements noted. The mediation analysis was carried out to substantiate the flexible parametric modelling findings of association going beyond simple point estimates by exploring various causal pathways as well as the extent (percentage) to which the mediating variable explained the exposure outcome relationship. This makes the findings more useful and interpretable clinically. Mediation analysis has rarely been used in

past literature in AMI research and the thesis is one of the few studies to demonstrate its utility in this field.

Most of the studies that assessed variation in receipt of NSTEMI care considered in the literature review used simple descriptive statistics (i.e. frequencies, percentages, means and medians) and univariate statistics such as Chi-square test for comparing categorical variables and t-test for comparing continuous variables. This thesis employed a four level hierarchical Poisson model which allowed for a robust extensive evaluation of the source of variation in receipt of care for NSTEMI patients in the English NHS. The multilevel Poison model accounted for the clustering in the data. Analysing the data, ignoring the clustering in the data creates bias by underestimating the standard errors of regression coefficients hence inflating type I errors in hypothesis testing. Furthermore the hierarchical modelling provides estimates of ICC statistics that are relevant for providing information on the proportion of variance in the outcome explained by the grouping variables in the hierarchical structure. The multilevel structure comprised of patients nested within hospitals, hospitals nested within CCGs and CCGs nested within SCNs. This allowed for the identification of the source, i.e. is the variation due to poor commissioning thus at CCGs and SCNs level or due to differences in treatment by providers thus at hospital level or due to differences in patients characteristics thus at patient level. Tackling inequalities in care at the level of the healthcare professional, services provider and commissioner will allow identification of where and what service require close attention. Which will lead to improved receipt of guideline-indicated care for NSTEMI patients and result to a reduction in avoidable deaths.

The efficacy of β blocker use after suffering an AMI for patients without heart failure or LVSD work carried out in this thesis is to date the largest analysis focusing on this work (comprising of 179,810 cases). The analytical cohort was derived from a population-based national clinical registry, MINAP. Novel advanced causal inference methods that have been recommended in literature when using observational data to quantify treatment effects,

including instrumental variable analysis and propensity scoring (survival-time inverse-probability weighting propensity score analysis) were used. Both methods minimise measured and unmeasured bias due to systematic differences between patients when using observational data from electronic health records such as MINAP. The utility of the techniques is in that employing them allows for quantification of marginal treatment effects that are similar to those that would have been obtained had a clinical trial been carried out instead. However the strength offered by using these techniques beyond the use of clinical trials is that treatment effects are estimated using 'real world clinical population' whilst trials tend to focus on very select non-complex patient groups that rarely represent the general population. Inference from such studies is very useful for informing policy making.

The thesis work, however, has limitations. All the work that was undertaken is reliant upon the accurate recording of data in MINAP. One of the major weaknesses of using electronic health records is missing data, and MINAP is no exception. Missing data could have potentially biased the results of the work, as missing data can result to exclusion of observations. Excluding observations from the analytical cohorts reduces the power and precision of the study as well as compromise generalisability of the study findings. However robust missing data approaches that have been used in past literature for MINAP data were employed i.e. MICE and default imputation strategies. Recording bias could have been inherent for receipt of smoking cessation and dietary advice as a sudden upstroke was noted for these care interventions around 2008. Imputation strategies informed by past literature that have used MINAP data were implemented to account for the missing data for the care interventions(105). This would have potentially minimised the impact of the missing data. Also the poor receipt of smoking cessation and dietary advice observed for objective one of the thesis may be inflated because advice about smoking and diet are embedded in cardiac rehabilitation programmes and there may have been preferencing by coders towards recording cardiac rehabilitation rather than counselling. However the occurrence of this should be minimal as high rates of smoking cessation and dietary advice as well as cardiac rehabilitation were noted in later years if

preferred recording of cardiac rehabilitation instead of the advice was consistent then the poor recording of smoking cessation and dietary advice should have been consistent throughout the study follow-up time.

Data on prescription of anticoagulants was not well recorded in MINAP such that investigation of ESC guideline-indicated care for NSTEMI was not able to be extended to all Class 1 Level A recommendations for the management of NSTEMI. It is therefore possible that the deficits and their consequences are greater than reported. The eligibility criteria used for in-hospital aldosterone as defined by the ESC guidelines reduced the sample size of the patients eligible for this care intervention such that the resultant estimates could be imprecise. For example the lack of association with improved survival noted in the results for objective one of the thesis.

Poor case ascertainment for NSTEMI patients in MINAP could have potentially biased the findings of the thesis . The Myocardial Ischaemia National Audit Project has almost half a million NSTEMI admissions recorded, however it is estimated that MINAP captures less than half of all NSTEMI patients in England and Wales which can compromise generalisability of the study's findings. Such that although MINAP offers a large NSTEMI analytical cohort compared to other data sources, the NSTEMI data recorded in MINAP may not be representative of the population to which the results will be generalised. The avoidable deaths quantified and underuse of care interventions for NSTEMI patients determined in this thesis could also be underestimated. However for the STEMI patients' generalisability of the study's findings is not compromised as MINAP captures the great majority of patients suffering a STEMI in England and Wales.

MINAP only records in-hospital management of AMI patients and patient baseline characteristics so there was no information beyond hospital stay such as long term drug adherence and primary care visits to account for in the various analyses carried out. Objective one of the thesis focused on assessing

the impact of receipt of optimal care for NSTEMI patients on long term survival, in-hospital management information would only suffice if impact on short term survival (i.e. 30 days) was under investigation. Considering that usually patients are discharged from hospital with a month's supply of pharmacotherapies. Assessment of the quality of care and associated outcomes long term could have been more precise if follow-up information on number of cardiac rehabilitation sessions attended as well as adherence of pharmacotherapies was taken into account. However, past literature has highlighted that usually care interventions not initiated in-hospital are less likely to be picked up after discharge thus in-hospital management of the NSTEMI patients can to a certain extent capture use of care interventions by NSTEMI patients with less information on discontinuation rates of the initiated care interventions. This limitation also applies for work for objectives three and four. Information on long term adherence of β blocker could have made the findings on efficacy of β blocker use for AMI patents without heart failure or LVSD more precise. However the causal inference technique used to estimate the treatment effects, instrumental variable analysis removed measured and unmeasured confounding meaning the hidden confounding from the unrecorded long term adherence rates of β blockers was removed thus reducing the bias from not accounting for this information in the modelling. The mediation analysis conducted for objective three of the thesis showed that introduction PPCI accounted for 27% of temporal improvements in one year survival meaning more information beyond that recorded in MINAP could have influenced survival for example outpatient care of the STEMI patients.

Survival was evaluated using all-cause mortality, however this may bias the results as non-cardiovascular deaths may not be attributable to underuse of AMI guideline-indicated care. CCGs were used to evaluate variation in receipt of NSTEMI care, however they were created in 2012 and replaced Primary Care Trusts April 2013 which is toward the end of the study. However, since the CCGs are in charge of commissioning of care it would be useful to identify care deficits at CCGs so that going forward they can address them. Also another limitation of using CCGs to assess variation in receipt of NSTEMI care is that it is always not clear if the patients living in a CCG were treated in the

same CCG as the northings and eastings supplied in MINAP used to merge the data to CCG boundary data were based on the patients' postcode not hospital postcode. However, the bias inherent with this approach implemented for objective two of the thesis was minimised by the use of the multilevel approach were by treating hospital was included into the hierarchical structure thus taking into account the treating hospital into the evaluation of variation of receipt of care. Hospital level evaluation could not be done directly as hospital identification is not permitted or given in MINAP data made available for research.

Of the methodologies used the predictors of receipt of NSTEMI care models' predictive power was very low, as noted by the observed low pseudo-R^2 and AUROC estimates for all the 13 care interventions considered as well for optimal care. This was a strong indication that some important predictors beyond the ones available in MINAP were missing. These important predictors could include information on treating physicians prescribing/treatment preferences for different risk profiles patients or treating physicians' education and awareness on management of AMI patients as well as provider level characteristics such as hospital facilities, size and type. However the predictors determined in this thesis were statistically significant in the prediction of receipt of care models thereby showing that they had predictive power for receipt or non-receipt of care interventions for AMI patients. The findings are still insightful.

For objective one of the thesis, of the 13 care interventions considered, receipt of an angiogram was found to be associated with the greatest impact on survival for NSTEMI patients (associated with an 82% reduction in survival time if missed). However, this finding could be potentially confounded by the fact that angiograms could have been performed in the healthier NSTEMI patients, for example elderly multi-morbid NSTEMI patients are less likely to receive an angiogram (201). Such that the improved outcomes associated with angiography may not relate to the effects of angiography but, to the underlying condition of the patients(21). However, for the purpose of the work

of this thesis, patients were classified as ineligible if treatment was: contra-indicated, not indicated, not applicable or patient declined treatment as recorded in MINAP. Thus, the bias inherent due to the 'healthy adherer effect' could have been minimised.

8.5 Implications of the study

The findings from this study have shown that NSTEMI patients, despite being the more vulnerable of the AMI phenotypes did not receive optimal care. The study showed that the preventable deaths associated with this receipt of sub optimal care were approximately 33,000 deaths. Care deficits across the NSTEMI guideline-indicated care pathway identified included; dietary and smoking cessation advice, echocardiography to evaluate left ventricular systolic function, the prescription of $P2Y_{12}$ inhibitors and coronary angiography. The evaluation of geographic variation in receipt of care for NSTEMI patients showed that most of the variation was as a result of differing treatment approaches by care providers (hospitals). The study clearly shows that, across a modern healthcare system such as in the UK, there are substantial opportunities to improve receipt of guideline-indicated care for NSTEMI patients thereby resulting to improved outcomes. Primary PCI and $P2Y_{12}$ inhibitors were identified as mediators for the long term temporal survival improvements noted for STEMI patients.

The findings from this thesis yield important actionable insights to guide policy and clinical practice to improve the quality health systems and prevent avoidable harm from AMI which is line with the World Health Organisation Global Action Plan for non-communicable disease to protect people from premature deaths from heart and lung diseases, cancers and diabetes(202). Also these findings can also be inferred to other developed and developing countries which lag behind Northern Europe and North America in their provision of care and where greater gains in healthcare maybe realised. Work from objective one and two of the thesis was foundation to the development of a web platform "Cardiovascular Landscapes: Using Data to Improve

Cardiovascular Care and Outcomes". The work is being undertaken in collaboration with LIDA and once completed will aid better data visualisation and wider dissemination of the results from the assessment of geographic variation in receipt of AMI care as well as on-going assessment of variation in receipt of AMI care by employing new downloads of receipt of care data going forward. The development of CV landscapes will provide a platform for engaging clinicians, commissioners or providers and patients.

The study findings of lack of association of β blockers and one, six and twelve months survival adds to the increasing body of evidence that the routine prescription of β blockers may not be indicated in patients with a normal ejection fraction or without heart failure post AMI patients and could be useful in informing policy on β blockers use in this subgroup of patients.

The advanced statistical techniques employed in this thesis have implications for future research in cardiovascular epidemiology. Utility of causal inference techniques such as instrumental variable, survival-time inverse-probability weighting propensity score and mediation analysis was demonstrated as they are rarely used when quantifying treatment effects in cardiovascular research in the absence of clinical trial evidence using observational data for research. Also utility of using latent class analysis to capture real life clinical practice receipt of NSTEMI care was demonstrated in this thesis. Future cardiovascular epidemiologists can employ the technique in their research as LCA is also rarely used in this field. The utility of using electronic health records was also demonstrated in this thesis. The MINAP registry allowed for the completion of the four research strands of the thesis at a population level, nationwide. The absence of clinical trial evidence should not be limiting to health research, in this big data era observational data can suffice if appropriate methods to draw inference are applied. This supports NHS Digital's ambition for a paperless NHS capturing routinely collected data and create EHR that will provide a repository for data for audit and research(203). The USA is focusing on the same initiative through the 'EHR Meaningful Use Programme'(204, 205).

This work can also be translational to other areas of cardiovascular epidemiology were electronic health records are available for use for research for example heart failure (using the National Heart Failure National Audit (NHFA)) or stroke (using the Sentinel Stroke National Audit Programme (SSNAP).

8.6 Future Research Recommendations

Whilst significant findings of the thesis can contribute to improving quality of care for AMI patients, further research needs to be undertaken. The work carried out for objective four of the thesis evaluating the impact of β blockers use at hospital discharge on survival for AMI patients without heart failure or LVSD adds to the increasing body of evidence that the routine prescription of β blockers may not be indicated in patients with a normal ejection fraction or without heart failure post AMI patients as it the largest study to focus on this work to date. However, a randomised controlled trial is a necessary next step for the contemporary evaluation of β blockers. Evidence is strongly needed to decide on a potentially unnecessary over-utilization of β blockers that could potentially translate to AMI patients developing heart failure and cardiogenic shock(197).

All-cause mortality was considered as the main outcome for the thesis, however as mentioned in the strengths and limitations section non-cardiovascular deaths may not be attributable to underuse of AMI guideline-indicated care. Further work is required focusing not only on specifically cardiovascular deaths but also on non-fatal outcomes for example major cardiovascular and cerebrovascular events. Potentially this can be made possible by linking MINAP to other National Institute for Cardiovascular Outcomes Research (NICOR) cardiovascular registries as well as HES data to get the non-fatal outcomes data.

More insight is required on physician's treating preferences for the different risk profiles of AMI patients as well as their awareness of the ever evolving AMI guidelines. Most of the readily available data sources do not capture such information. A mixed methods approach could be employed which involves the use of qualitative methods as well as quantitative methods. The qualitative methods will aid in capturing the treatment/prescribing preferences of the treating physicians. This data can also be linked to cardiac EHRs such as MINAP to aid a comprehensive evaluation of quality of care and associated outcomes for AMI patients.

Most of the work that has assessed quality of care and outcomes for NSTEMI (or even AMI) patients in past literature as well as the current study has focused entirely on measurement of receipt of guideline-indicated care interventions without taking into considering safety metrics of receipt of care i.e. appropriate dosing of the medication(166). Further work should be undertaken assessing quality of care including receipt of appropriate dosage as well as long term adherence beyond hospital discharge. The feasibility of an EHR for routinely collected cardiac outpatient data for the NHS has been demonstrated by Bodagh et al.(206), linkage of MINAP to such kinds of datasets could allow for future evaluation of quality of care and associated outcomes without the restriction of focusing on in-hospital treatment only.

Most of the variation in receipt of care shown in this study was found to be at the provider level. However this study was limited in determining the hospital level factors that were associated with this variation as MINAP does record hospital level data. MINAP needs to be linked to hospital level data and further work needs to be done to investigate the hospital level predictors of this variation in receipt of NSTEMI care. Also temporal changes in geographical variation in receipt of NSTEMI care need to be assessed for future work as this would identify if an improvement has occurred in management of AMI over time. If not, highlight the guideline recommended care interventions that are persistently being missed.

8.7 Future planned publications

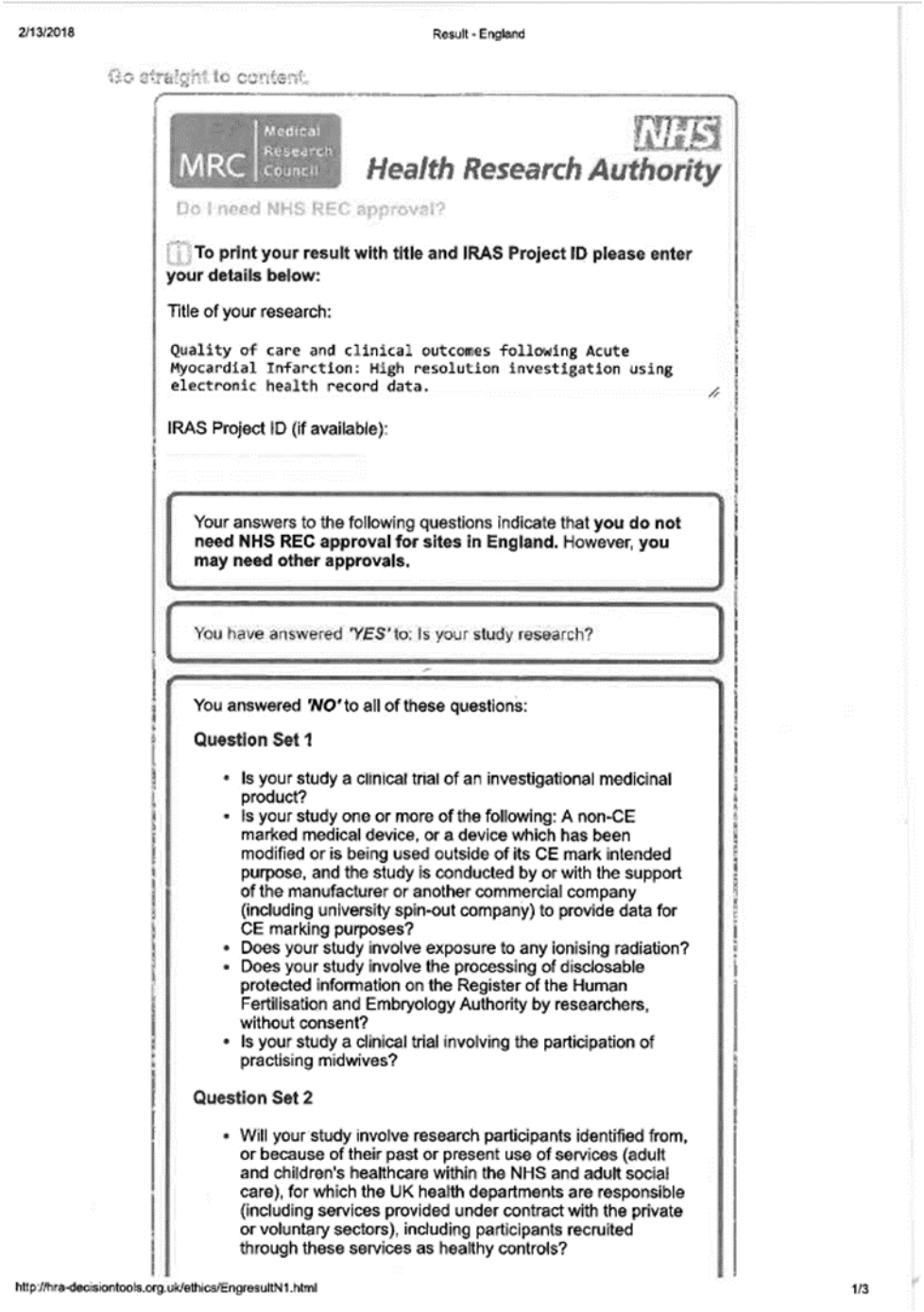
In addition to the already published papers arising from this thesis (207-209), the results from chapter 6 will be submitted for a publication to the Journal of the American Medical Association.

8.8 Conclusion

In this first study of the pathway of care for NSTEMI patients in England and Wales, the optimal use of guideline-indicated treatments was low. The thesis identified substantial gaps in the provision of guideline-indicated interventions as recommended by the ESC. The deficits in receipt care identified were found to be associated with avoidable deaths. Most of the variation in receipt of NSTEMI care was explained by hospital differences in provision of care. Six month and one year temporal survival improvements that have been noted for STEMI patients over the last decade were found to be partly attributed to prescription of $P2Y_{12}$ inhibitors at hospital discharge and introduction of PPCI. For AMI patients without heart failure or LVSD, prescription of β blockers at hospital discharge was not associated with lower all-cause mortality at any time point up to one year. Whilst cardiovascular care has substantially improved in modern healthcare systems with the resultant reductions in mortality, only through higher resolution investigations using whole healthcare system clinical registries can modifiable deficits of care be identified and, therefore, addressed.

Appendices

Appendix A



2/13/2018 Result - England

Go straight to content.

MRC Medical Research Council

NHS Health Research Authority

Do I need NHS REC approval?

To print your result with title and IRAS Project ID please enter your details below:

Title of your research:

Quality of care and clinical outcomes following Acute Myocardial Infarction: High resolution investigation using electronic health record data.

IRAS Project ID (if available):

Your answers to the following questions indicate that **you do not need NHS REC approval for sites in England.** However, **you may need other approvals.**

You have answered *'YES'* to: Is your study research?

You answered ***'NO'*** to all of these questions:

Question Set 1

- Is your study a clinical trial of an investigational medicinal product?
- Is your study one or more of the following: A non-CE marked medical device, or a device which has been modified or is being used outside of its CE mark intended purpose, and the study is conducted by or with the support of the manufacturer or another commercial company (including university spin-out company) to provide data for CE marking purposes?
- Does your study involve exposure to any ionising radiation?
- Does your study involve the processing of disclosable protected information on the Register of the Human Fertilisation and Embryology Authority by researchers, without consent?
- Is your study a clinical trial involving the participation of practising midwives?

Question Set 2

- Will your study involve research participants identified from, or because of their past or present use of services (adult and children's healthcare within the NHS and adult social care), for which the UK health departments are responsible (including services provided under contract with the private or voluntary sectors), including participants recruited through these services as healthy controls?

http://hra-decisiontools.org.uk/ethics/EngresultN1.html 1/3

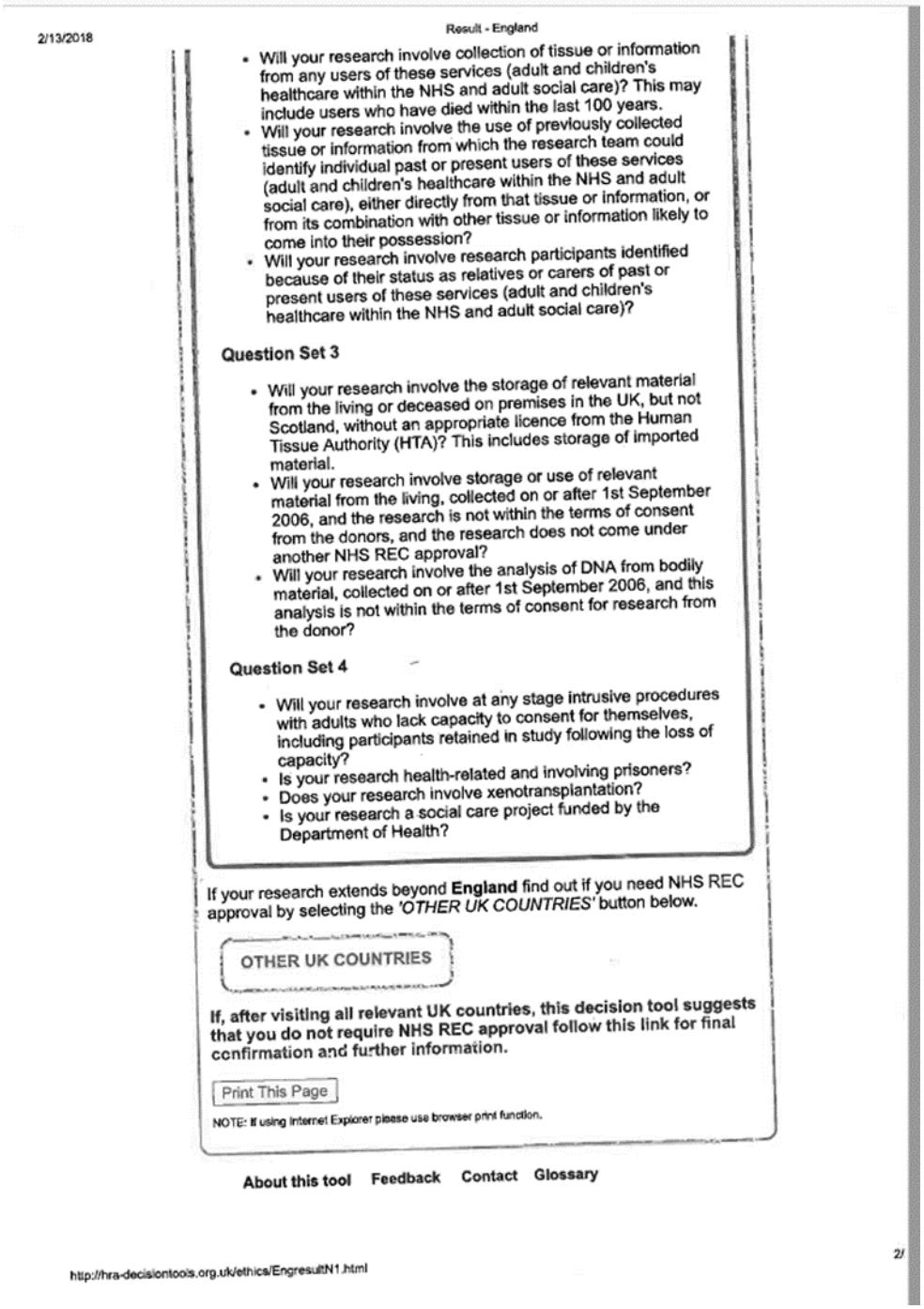


Figure A 1 HRA-decision tool output for sites in England.

Go straight to content.

MRC Medical Research Council | NHS Health Research Authority

Do I need NHS REC approval?

To print your result with title and IRAS Project ID please enter your details below:

Title of your research:

Quality of care and clinical outcomes following Acute Myocardial Infarction: High resolution investigation using electronic health record data.

IRAS Project ID (if available):

Your answers to the following questions indicate that **you do not need NHS REC approval for sites in Wales.** However, **you may need other approvals.**

You have answered ***'YES'*** to: Is your study research?

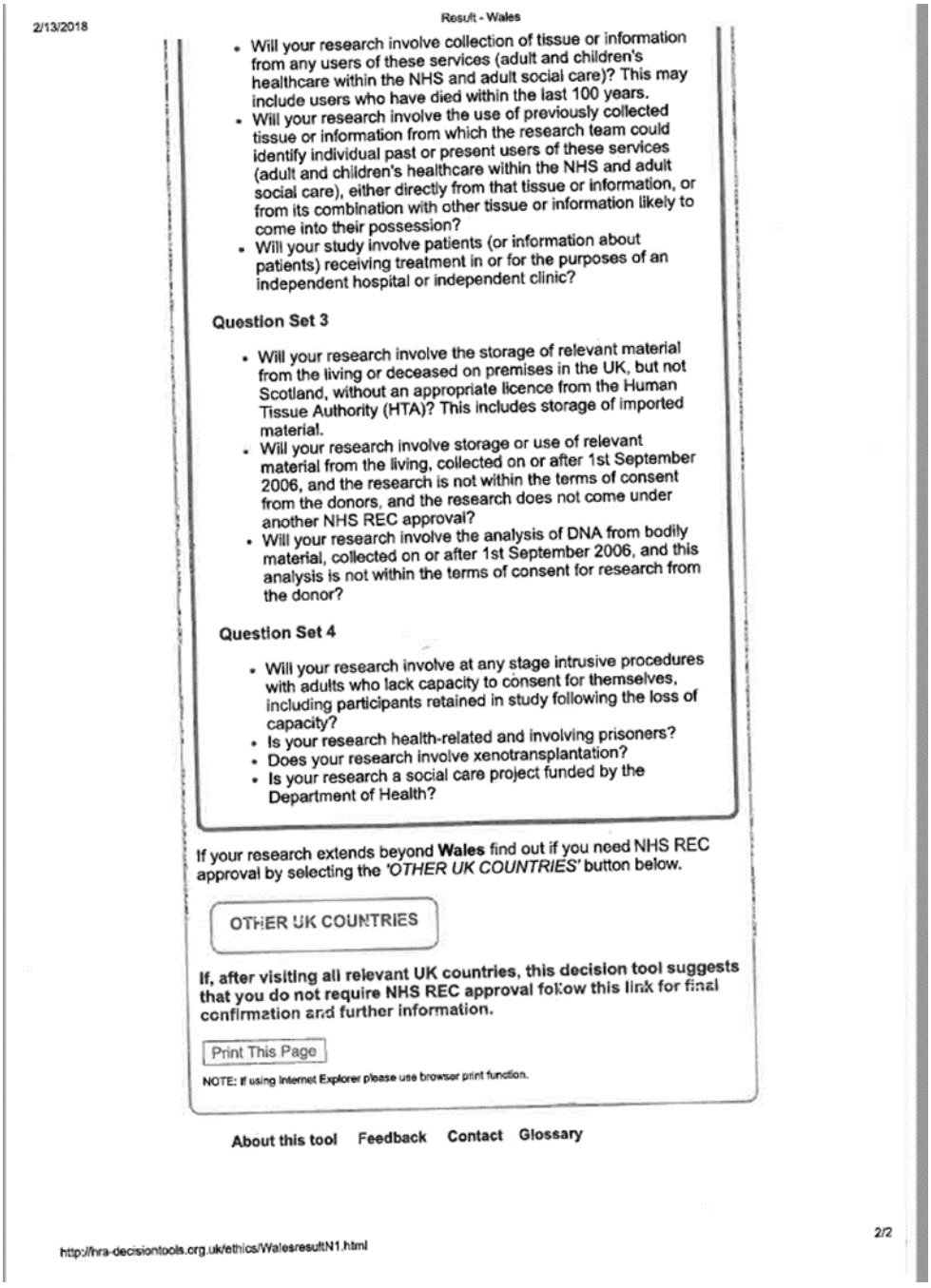
You answered ***'NO'*** to all of these questions:

Question Set 1

- Is your study a clinical trial of an investigational medicinal product?
- Is your study one or more of the following: A non-CE marked medical device, or a device which has been modified or is being used outside of its CE mark intended purpose, and the study is conducted by or with the support of the manufacturer or another commercial company (including university spin-out company) to provide data for CE marking purposes?
- Does your study involve exposure to any ionising radiation?
- Does your study involve the processing of disclosable protected information on the Register of the Human Fertilisation and Embryology Authority by researchers, without consent?
- Is your study a clinical trial involving the participation of practising midwives?

Question Set 2

- Will your study involve research participants identified from, or because of their past or present use of services (adult and children's healthcare within the NHS and adult social care), for which the UK health departments are responsible (including services provided under contract with the private or voluntary sectors), including participants recruited through these services as healthy controls?



2/13/2018 Result - Wales

- Will your research involve collection of tissue or information from any users of these services (adult and children's healthcare within the NHS and adult social care)? This may include users who have died within the last 100 years.
- Will your research involve the use of previously collected tissue or information from which the research team could identify individual past or present users of these services (adult and children's healthcare within the NHS and adult social care), either directly from that tissue or information, or from its combination with other tissue or information likely to come into their possession?
- Will your study involve patients (or information about patients) receiving treatment in or for the purposes of an independent hospital or independent clinic?

Question Set 3

- Will your research involve the storage of relevant material from the living or deceased on premises in the UK, but not Scotland, without an appropriate licence from the Human Tissue Authority (HTA)? This includes storage of imported material.
- Will your research involve storage or use of relevant material from the living, collected on or after 1st September 2006, and the research is not within the terms of consent from the donors, and the research does not come under another NHS REC approval?
- Will your research involve the analysis of DNA from bodily material, collected on or after 1st September 2006, and this analysis is not within the terms of consent for research from the donor?

Question Set 4

- Will your research involve at any stage intrusive procedures with adults who lack capacity to consent for themselves, including participants retained in study following the loss of capacity?
- Is your research health-related and involving prisoners?
- Does your research involve xenotransplantation?
- Is your research a social care project funded by the Department of Health?

If your research extends beyond **Wales** find out if you need NHS REC approval by selecting the *'OTHER UK COUNTRIES'* button below.

OTHER UK COUNTRIES

If, after visiting all relevant UK countries, this decision tool suggests that you do not require NHS REC approval follow this link for final confirmation and further information.

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http://hra-decisiontools.org.uk/ethics/WalesresultN1.html 2/2

Figure A 2 HRA-decision tool output for sites in Wales.

Appendix B

Table B 1 Patients eligible to receive β blockers by latent class.

	β blockers eligible	
	Yes	No
Latent class		
High receipt	6,081	112,595
Intermediate	111,314	22,232
Low	3,699	78,858

Table B 2 Receipt of β blockers by latent class.

	β blockers		
	Received	Did not receive	Contraindicated/not applicable
Latent class			
High receipt	5,830	251	144,929
Intermediate	81,076	30,238	22,232
Low	3,279	420	100,802

Table B 3 Patients eligible ACEi/ARBs by latent class.

	ACEi/ARBs eligible	
	Yes	No
Latent class		
High receipt	967	150,043
Intermediate	133,436	110
Low	728	103,773

Table B 4 Receipt of ACEi/ARBs by latent class.

	ACEi/ARBs		
	Received	Did not receive	Contraindicated/not applicable
Latent class			
High receipt	933	34	150,043
Intermediate	89,957	47,479	110
Low	269	459	103,773

Table B 5 Patients eligible to receive Electrocardiogram by latent class.

	Electrocardiogram	
	Yes	No
Latent class		
High receipt	151,010	0
Intermediate	133,546	0
Low	104,501	0

Table B 6 Receipt of Electrocardiogram by latent class.

	Electrocardiogram		
	Received	Did not receive	Contraindicated / not applicable
Latent class			
High receipt	150,023	987	0
Intermediate	113,290	20,256	0
Low	101,447	3,054	0

Table B 7 Patients eligible to receive acute aspirin by latent class.

	Acute aspirin eligible	
	Yes	No
Latent class		
High receipt	103,168	47,842
Intermediate	87,953	45,593
Low	69,263	35,238

Table B 8 Receipt of acute aspirin by latent class.

	Acute aspirin		
	Received	Did not receive	Contraindicated / not applicable
Latent class			
High receipt	97,358	5,810	47,842
Intermediate	72,843	15,110	45,593
Low	60,621	8,642	35,238

Table B 9 Patients eligible to receive statins by latent class.

	Statins eligible	
	Yes	No
Latent class		
High receipt	125,336	25,674
Intermediate	130,218	3,328
Low	92,147	12,354

Table B 10 Receipt of statins by latent class.

	Statin		
	Received	Did not receive	Contraindicated / not applicable
Latent class			
High receipt	117,639	7,697	25,674
Intermediate	102,912	27,306	3,328
Low	76,494	15,653	12,354

Table B 11 Patients eligible to receive P2Y12 inhibitor/ticagrelor by latent class.

	$P2Y_{12}$ inhibitor/ticagrelor eligible	
	Yes	No
Latent class		
High receipt	117,187	33,823
Intermediate	103,358	73
Low	99,356	5,007

Table B 12 Receipt of P2Y12 inhibitor/ ticagrelor by latent class.

	$P2Y_{12}$ inhibitor/ticagrelor		
	Received	Did not receive	Contraindicated / not applicable
Latent class			
High receipt	108,150	9,037	33,823
Intermediate	548	102,810	30,188
Low	18,297	81,059	5,145

Table B 13 Patients eligible to receive aldosterone antagonists by latent class.

	Aldosterone antagonists eligible	
	Yes	No
Latent class		
High receipt	397	2,027
Intermediate	195	133,029
Low	0	3,125

Table B 14 Receipt of aldosterone antagonists by latent class.

	Aldosterone antagonists		
	Received	Did not receive	Contraindicated / not applicable
Latent class			
High receipt	129	268	150,613
Intermediate	15	180	133,351
Low	0	0	104,501

Table B 15 Patients eligible to receive echocardiography by latent class.

	Echocardiography eligible	
	Yes	No
Latent class		
High receipt	150,973	37
Intermediate	133,546	0
Low	104,501	0

Table B 16 Receipt of echocardiography by latent class.

	Echocardiography		
	Received	Did not receive	Contraindicated / not applicable
Latent class			
High receipt	90,296	60,677	37
Intermediate	57,483	76,063	0
Low	47,758	56,743	0

Table B 17 Patients eligible to receive cardiac rehabilitation by latent class.

	Cardiac rehabilitation eligible	
	Yes	No
Latent class		
High receipt	138,941	12,069
Intermediate	130,713	2,833
Low	97,284	7,217

Table B 18 Receipt of cardiac rehabilitation by latent class.

	Cardiac rehabilitation		
	Received	Did not receive	Contraindicated / not applicable
Latent class			
High receipt	119,457	19,484	12,069
Intermediate	91,589	39,124	2,833
Low	67,981	29,303	7,217

Table B 19 Patients eligible to receive smoking cessation advice by latent class.

	Smoking cessation advice eligible	
	Yes	No
Latent class		
High receipt	43,654	107,356
Intermediate	133,538	8
Low	101,986	2,515

Table B 20 Receipt of smoking cessation advice by latent class.

	Smoking cessation advice		
	Received	Did not receive	Contraindicated/not applicable
Latent class			
High receipt	33,545	10,109	107,356
Intermediate	0	133,538	8
Low	276	101,710	2,515

Table B 21 Patients eligible to receive dietary advice by latent class.

	Dietary advice eligible	
	Yes	No
Latent class		
High receipt	136,275	14,735
Intermediate	133,546	0
Low	104,369	132

Table B 22 Receipt of dietary advice by latent class.

	Dietary advice		
	Received	Did not receive	Contraindicated/not applicable
Latent class			
High receipt	118,411	17,864	14,735
Intermediate	7	133,539	0
Low	903	103,466	132

Table B 23 Patients eligible to receive coronary angiography by latent class.

	Coronary angiography eligible	
	Yes	No
Latent class		
High receipt	136,835	14,175
Intermediate	133,544	2
Low	102,741	1,760

Table B 24 Receipt of coronary angiography by latent class.

	Coronary angiography		
	Received	Did not receive	Contraindicated / not applicable
Latent class			
High receipt	103,400	33,435	14,175
Intermediate	50,366	83,178	2
Low	57,501	45,240	1,760

Table B 25 Patients eligible to receive aspirin at discharge by latent class.

	Aspirin at discharge eligible	
	Yes	No
Latent class		
High receipt	123,294	27,716
Intermediate	127,569	5,977
Low	90,119	14,382

Table B 26 Receipt of coronary angiography by latent class.

	Aspirin at discharge		
	Received	Did not receive	Contraindicated / not applicable
Latent class			
High receipt	117,988	5,306	27,716
Intermediate	106,661	20,908	5,977
Low	76,990	13,129	14,382

Appendix C

Table C 1 Modelling results (univariate unadjusted vs complete case vs imputed) by care interventions.

Treatment	Unadjusted TRs (95% CI)	Complete case analysis Adjusted TRs (95% CI)	Multiple imputation analyses Adjusted TRs (95% CI)	P-value
Sub-optimal care¥	0.34 (0.32, 0.35)	0.40 (0.38, 0.43)	0.44 (0.41, 0.45)	< 0.001
Intermediate receipt class	0.73 (0.72, 0.75)	0.59 (0.47, 0.72)	0.84 (0.79, 0.88)	< 0.001
Low receipt class	0.77 (0.75, 0.79)	0.79 (0.74, 0.83)	0.77 (0.74, 0.80)	< 0.001
Electrocardiogram	0.76 (0.73, 0.79)	0.84 (0.72 ,0.98)	0.92 (0.89, 0.96)	< 0.001
Acute aspirin	0.54 (0.52, 0.56)	0.66 (0.58, 0.74)	0.65 (0.62, 0.67)	< 0.001
ACE inhibition or ARBs	0.70 (0.68, 0.72)	0.65 (0.47, 0.90)	0.70 (0.68, 0.72)	< 0.001
Beta Blockers	0.55 (0.53, 0.57)	0.82 (0.65, 1.04)	0.63 (0.61, 0.65)	< 0.001
Statin at discharge	0.50 (0.49, 0.52)	0.53 (0.50, 0.57)	0.56 (0.55, 0.58)	< 0.001
P2Y12 inhibitors at discharge	0.69 (0.67, 0.71)	0.72 (0.68, 0.77)	0.76 (0.73, 0.79)	< 0.001
Aldosterone antagonist	1.11 (0.63, 1.98)	0.91 (0.45, 1.83)	0.88 (0.51, 1.51)	0.639
Echocardiography	0.91 (0.89, 0.92)	0.74 (0.71, 0.76)	0.94 (0.92, 0.96)	< 0.001
Cardiac rehabilitation	0.38 (0.38, 0.39)	0.39 (0.37, 0.41)	0.49 (0.48, 0.50)	< 0.001
Smoking cessation advice	0.31 (0.30, 0.33)	0.57 (0.53, 0.62)	0.53 (0.51, 0.57)	< 0.001
Dietary advice	0.58 (0.57, 0.60)	0.63 (0.60, 0.67)	0.65 (0.63, 0.68)	< 0.001
Coronary angiography	0.12 (0.11, 0.12)	0.16 (0.15, 0.17)	0.18 (0.17, 0.18)	< 0.001
Aspirin at discharge	0.80 (0.78, 0.83)	0.79 (0.73, 0.85)	0.83 (0.80, 0.85)	< 0.001

¥Patients who missed ≥1 care interventions for which they were eligible to receive.

Abbreviations: ARB, angiotensin receptor blocker; ACE, angiotensin converting enzyme.

Appendix D

Table D 1 Effect of β blockers at discharge on all-cause mortality following AMI (survival-time inverse-probability weighting propensity score analysis) (trimmed analysis)

Average treatment effects			**Average treatment effects on the treated only**		
Follow-up	**Coefficient[¥] (95% CI)**	***P*-value**	**Follow-up**	**Coefficient[¥] (95% CI)**	***P*-value**
AMI			**AMI**		
One month	-	-	One month	-	-
Six months	-0.15 (-0.63 to 0.34)	0.554	Six months	-0.23 (-0.76 to 0.29)	0.386
One year	-0.32 (-1.23 to 0.60)	0.495	One year	-0.35 (-1.35 to 0.64)	0.488
STEMI			**STEMI**		
One month	-	-	One month	-	-
Six months	0.32 (-0.64 to 1.29)	0.511	Six months	0.02 (-1.04 to 1.08)	0.972
One year	0.15 (-1.96 to 2.26)	0.887	One year	-0.52 (-2.81 to 1.77)	0.656
NSTEMI			**NSTEMI**		
One month	-	-	One month	-	-
Six months	-0.19 (-0.71 to 0.32)	0.460	Six months	-0.19 (-0.73 to 0.35)	0.494
One year	-0.53 (-1.58 to 0.53)	0.327	One year	-0.50 (-1.64 to 0.64)	0.389

Abbreviations: AMI, acute myocardial infarction; [¥]Estimate represents the effect of β blockers on survival for the respective follow-up time categories; NSTEMI, non ST-segment elevation myocardial infarction; STEMI, ST-segment elevation myocardial infarction,- model converge problems.

Table D 2 Effect of β blockers at discharge on all-cause mortality following AMI (survival-time inverse-probability weighting propensity score analysis)

Average treatment effects			**Average treatment effects on the treated only**		
Follow-up	**Coefficient[¥] (95% CI)**	***P*-value**	**Follow-up**	**Coefficient[¥] (95% CI)**	***P*-value**
AMI			**AMI**		
One month	0.48 (-2.82 to 3.79)	0.776	One month	0.24 (-3.26 to 3.73)	0.895
Six months	-0.08 (-0.63 to 0.47)	0.782	Six months	-0.13 (-0.71 to 0.45)	0.666
One year	0.64 (-0.26 to 1.56)	0.164	One year	0.70 (-0.27 to 1.66)	0.156
STEMI			**STEMI**		
One month	-0.002 (-1.99 to 1.98)	0.999	One month	-0.10 (-2.13 to 1.93)	0.924
Six months	-0.68 (-1.67 to 0.29)	0.168	Six months	-0.73 (-1.74 to 0.28)	0.155
One year	0.69 (-0.89 to 2.27)	0.393	One year	0.68 (-0.94 to 2.31)	0.411
NSTEMI			**NSTEMI**		
One month	-	-	One month	-	-
Six months	0.42 (-0.17 to 1.01)	0.166	Six months	0.44 (-0.19 to 1.08)	0.169
One year	0.74 (-0.24 to 1.71)	0.138	One year	0.86 (-0.18 to 1.90)	0.104

Abbreviations: AMI, acute myocardial infarction; [¥]Estimate represents the effect of β blockers on survival for the respective follow-up time categories; NSTEMI, non ST-segment elevation myocardial infarction; STEMI, ST-segment elevation myocardial infarction,- model converge problems.

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