DETERMINANTS OF CLINICAL OUTCOMES FOLLOWING PRIMARY PERCUTANEOUS CORONARY INTERVENTION: THE WEST YORKSHIRE PRIMARY PERCUTANEOUS CORONARY INTERVENTION OUTCOME STUDY.

Dr. Arvindra Krishnamurthy MB ChB, MRCP (UK)

Submitted in accordance with the requirements for the degree of

Doctor of Medicine (MD)

The University of Leeds

Multidisciplinary Cardiovascular Research Centre & The Division of Cardiovascular and Diabetes Research

Leeds Institute of Cardiovascular and Metabolic Medicine

School of Medicine.

December 2017.

Intellectual Property and Publication Statements

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

Abstracts published or presented at National and International Conferences:

1. Krishnamurthy A, Somers K, Burton-Wood N, Anderson M, Harland C, Keeble C, McLenachan J, Blaxill J, Malkin CJ, Blackman DJ, Wheatcroft S, Greenwood JP. 26 Effect of Age and Gender on Outcomes Following Primary Percutaneous Coronary Intervention for ST-elevation Myocardial Infarction in a UK Tertiary Centre. *Heart* 2016;102:A17–A18.

Presented as a poster at the British Cardiovascular Society annual conference in Manchester in June 2016.

2. Krishnamurthy A, Somers K, Burton-Wood N, Anderson M, Harland C, Keeble C, McLenachan JM, Blaxill JM, Malkin CJ, Blackman DJ, Wheatcroft SB, Greenwood JP. 33 Influence of ethnicity on outcomes in primary percutaneous coronary intervention for ST-elevation myocardial infarction. *Heart* 2016; 102:A15.1-A15.

Abstract selected for publication in Heart.

3. Krishnamurthy A, M Keeble C, Burton-Wood N, Somers K, Anderson M, Harland C, M McLenachan J, M Blaxill J, J Blackman D, J Malkin C, B Wheatcroft S, P Greenwood J. 26 Clinical outcomes following primary percutaneous coronary intervention: a comparison of clopidogrel, prasugrel and ticagrelor. *Heart* 2017;103:A22 LP-A22.

Presented as an e-poster at the EuroPCR conference in Paris in May 2017 and as a moderated poster at the British Cardiovascular Society annual conference in Manchester in June 2017.

4. Krishnamurthy A, Keeble C, Somers K, Burton-Wood N, Anderson M, Harland C, McLenachan JM, Blaxill JM, Malkin CJ, Blackman DJ, Wheatcroft SB and Greenwood JP. Radial artery access for primary percutaneous coronary intervention is associated with reduced bleeding and mortality.

Presented as e-poster at the EuroPCR conference in Paris in May 2017 and as a moderated poster at the British Cardiovascular Intervention Society annual conference in London in January 2017.

Manuscripts published or submitted for peer-review

1. Krishnamurthy A, Keeble C, Somers K, Burton-Wood N, Anderson M, Harland C, McLenachan JM, Blaxill JM, Malkin CJ, Blackman DJ, Wheatcroft SB and Greenwood JP. Clinical outcomes following primary percutaneous coronary intervention for ST-elevation myocardial infarction according to sex and race. *Eur Hear J Acute Cardiovasc Care*. October 2017:204887261773580. doi:10.1177/2048872617735803.

Published in European Heart Journal: Acute Cardiovascular Care in October 2017.

2. Krishnamurthy A, Keeble C, Somers K, Burton-Wood N, Anderson M, Harland C, McLenachan JM, Blaxill JM, Malkin CJ, Blackman DJ, Wheatcroft SB and Greenwood JP. The association between operator volume and mortality in primary percutaneous coronary intervention.

Submitted for peer-review.

3. Krishnamurthy A, Keeble C, Somers K, Burton-Wood N, Anderson M, Harland C, McLenachan JM, Blaxill JM, Malkin CJ, Blackman DJ, Wheatcroft SB and Greenwood JP. A real-world comparison of clopidogrel, prasugrel and ticagrelor in patients undergoing primary percutaneous coronary intervention.
Submitted for peer-review.

Thesis chapters:

1. Chapter 3: The association between gender and outcomes following PPCI
2. Chapter 4: The association between ethnicity and outcomes following PPCI.
3. Chapter 5: The association between P2Y12-receptor inhibitor therapy and outcomes following PPCI.
4. Chapter 6: The association between operator volume and outcomes in primary percutaneous coronary intervention.

Candidate contribution:

1. The concept and design of the analyses.
2. Background research.
3. Preparation of data for analyses.
4. Analyses of data.
5. Interpretation of analyses.
6. The drafting, revision and submission of manuscripts for peer-review.

Contribution of others:

1. JPG, SBW: Main supervisors of this research project. Identification of scientific questions that led to the analyses. Supported with manuscript preparation and revision.
2. CMK, PDB: Provided statistical analysis (for chapters 3 and 4), and provided further statistical support and advise for all other chapters, and contributed to the revision of manuscripts.
3. JMM, JMB, DJB, and CJM: Provided external opinion and contributed to revision of manuscripts.

Acknowledgements

Firstly, I would like to thank my Supervisors, Professor John Greenwood and Dr. Stephen Wheatcroft, for setting up this Research Fellowship in the first place. I would also like to thank them for the constant support, feedback and the much-needed periodical shoves towards the completion of my work. Despite their busy schedules, emails were responded to promptly with constructive feedback for queries (however silly) I may have had.

I would like to thank all the Consultants; Dr. Daniel Blackman, Dr. Jonathan Blaxill, Dr. Christopher Malkin and Dr. Jim McLenachan; who had supported the inception of this research post, and had encouraged me with their feedback and enthusiasm towards my work throughout the duration of this fellowship.

A huge thank you to Claire Keeble, Biostatistician with the University of Leeds. Claire had provided me with invaluable statistical support, from statistical analysis to advice. She had also dealt with numerous, often tedious additions or changes to analyses that I may have requested and I am grateful for her help, support and advice.

This research was only possible due to the diligence of the PCI Research Nurses, Kathryn Somers, Natalie Burton-Wood, Michelle Anderson and Charlotte Harland who collected the original source data. My contributions, as clearly indicated in the thesis, were study design, verification of data, identification and correction of errors in the database, data analysis, and preparation of manuscripts. Working very closely with the research team with other

PCI-related research project had also provided me with much-needed variety in my day-to-day work.

A special thank you goes out to Angie, Daniel and Lucy in the Health Research library (X35) at Leeds General Infirmary, who had been very accommodating with my regular requests for the use of their meeting room, especially from early 2017, when my thesis-writing picked up pace.

I would like to thank my parents Mr and Mrs Krishnamurthy, for their support and encouragement towards academic and all-round excellence. Their sacrifices in life had enabled me to pursue my dreams of becoming a doctor. The early influences from my father, an ex-teacher who helped set up and run the main orphanage in my home town, set me on my path towards helping people.

Finally, my deepest gratitude goes to my wife, Kavita, herself a trainee in the NHS. Her invaluable encouragement, positivity, support and the constant sacrifices she has made throughout my career had led me to this point and kept me on this path, and most importantly, she had given me my two beautiful daughters, Aleesha and Annika, to whom this thesis is dedicated. The three of them make all of this worthwhile.

ABSTRACT:

Objectives:

To identify determinants of clinical outcomes following primary percutaneous coronary intervention (PPCI) for ST-segment elevation myocardial infarction (STEMI).

Background:

Although PPCI is currently the gold-standard guideline-indicated care for STEMI in the UK, factors associated with important clinical outcomes are still being explored and discovered. The purpose of this study and the analyses within this study, is to identify factors that were either previously unreported or variably reported.

Methods:

Baseline and procedural data of all consecutive patients undergoing PPCI between 01-01-2009 and 31-12-2011, and between 01-01-2013 and 31-12-2013 in Leeds General Infirmary UK were collected prospectively in the West Yorkshire Primary Percutaneous Coronary Intervention (WY-PPCI) research and audit databases. Patients were followed up to a minimum of 12-months following index-PPCI.

Five analyses were undertaken to assess the association between the following factors and clinical outcomes in PPCI: gender, ethnicity, P2Y12-receptor inhibitor, individual operator PPCI volume, glycoprotein IIb/IIIa inhibitor (GPI) use according to arterial access site. Multivariable analysis was undertaken to adjust for potential confounders. Clinical endpoints (depending on analyses) were: major adverse cardiovascular events (MACE; defined as all-cause mortality, myocardial infarction (MI), and repeat target and non-target vessel revascularisation), and HORIZONS-major bleeding.

Results:

Gender: Although women were older than men at presentation (median age 69 vs 60yr, p <0.01), mortality and MACE were not statistically significantly higher in women after stratification into age groups (<60, 60-79, and ≥80yr) alone, and also after multivariable analysis. Age was most strongly associated with adverse outcomes.

Ethnicity: Univariable and multivariable analysis both revealed no significant differences in MACE and mortality between South Asian and White patients, despite South Asian patients being significantly younger than White patients.

P2Y12-receptor inhibitor therapy: After multivariable analysis, both ticagrelor and prasugrel were associated with lower recurrent MI compared to clopidogrel. However, only prasugrel was associated with reduced mortality, both in comparison with clopidogrel and ticagrelor. There was no difference in bleeding between the three drugs.

Annual operator PPCI volume: Low annual operator-volume (<55 PPCI cases per year) was independently associated with 30-day mortality compared to high operator-volume (≥110 PPCI per year), suggesting a volume-outcome relationship at a significantly higher threshold than the AHA/ACC/SCAI recommendation of ≥11 PPCI cases per year.

GPI-use: In transfemoral PPCI, GPI use was independently associated with higher 30-day bleeding (particularly access-site bleeding) and mortality compared to no GPI-use. In transradial PPCI, GPI use was not associated with increased bleeding or mortality.

Conclusion

This study has identified important factors associated with outcomes following in the real-world, in a large, contemporary “all-comers” registry. Analyses from this study should lead to the interrogation of larger databases and possibly changes in guideline recommendations.

ABBREVIATIONS

ACE – Angiotensin-converting enzyme

ACS - Acute coronary syndrome

ADP - Adenosine Diphosphate

ARB – Angiotensin II receptor blocker

ATP – Adenosine triphosphate

BMS – Bare metal stent

CABG – Coronary artery bypass grafting

CAD – Coronary artery disease

CTB – Call-to-balloon

CVD – Cardiovascular disease

DTB – Door-to-balloon

DES – Drug-eluting stent

ECG – Electrocardiogram

HDL - High-density lipoprotein

LAD – Left anterior descending

LBBB – Left bundle-branch block

LDL - Low-density lipoprotein

MACE – Major adverse cardiovascular event

MI – Myocardial infarction

MINAP – Myocardial Infarction National Audit Project

NSTEMI – Non ST-segment elevation myocardial infarction

PPCI – Primary percutaneous coronary intervention

STEMI – ST-segment elevation myocardial infarction

UA – Unstable angina

Chapter 1:

Introduction

1.1. Acute coronary syndrome

Acute coronary syndrome (ACS) refers to the clinical spectrum describing acute coronary ischaemia – unstable angina (UA), non-ST-segment elevation myocardial infarction (NSTEMI) and the most severe end of this spectrum, ST-segment elevation myocardial infarction (STEMI). Myocardial infarction (MI) can be distinguished from UA by the presence of elevated levels of cardiac biomarkers (Troponin I or T).

When this syndrome exists without ST-segment elevation on a 12-lead electrocardiogram (ECG), it is considered a NSTEMI. Acute cardiac ischaemic chest pains, with or without ST-segment deviation, and with no elevation in plasma concentration of cardiac biomarkers (Troponin I or Troponin T), would constitute UA.

1.1.1. Epidemiology

Cardiovascular disease (CVD) is the leading cause of death worldwide. In 2012, 17.5 million people died from CVD, 7.4 million of whom died from coronary artery disease (CAD)[1]. In the United Kingdom (UK), CAD is the leading single cause of death, accounting for 15% of male deaths and 10% of female deaths in 2014, accounting for 69,000 deaths[2]. CAD was the most common cause of premature death in men (defined as individuals under the age of 75 years), accounting for 16,800 (15%) deaths, while in women, CAD accounted for 5,500 (7%) premature deaths[3].

There has been a significant decline in death from CAD in the UK since 1975. In 1975, the age-standardised death rates for men and women from CAD were 668 and 337 deaths per 100,000 population per annum respectively. This has improved steadily over the years, and

in 2013, the age-standardised death rates in men and women in the UK were 177 and 86 deaths per 100,000 population respectively, accounting for a 73% improvement over this period of time. Similar improvements have been recorded in premature deaths secondary to CAD in the UK, with an 81% improvement over this period[3].

1.1.2 Pathophysiology

Atherosclerotic plaque

Atherosclerosis refers to the presence of intimal plaques. These plaques are lipid-rich lesions covered by fibrous caps. Plaque rupture can then expose the necrotic core of these lipid-rich plaques, promoting platelet aggregation and activation, which in turn releases serotonin, thromboxane A2 and Adenosine Diphosphate (ADP) that can cause coronary vasospasm and further platelet aggregation[4]. Thrombus formation and distal embolization following coronary artery atherosclerotic plaque disruption can cause ACS[5,6]. STEMI typically occurs when a coronary vessel is completely occluded by thrombus.

Ischaemia-driven myocardial cellular injury

There are numerous mechanisms that contribute towards cellular damage in myocardial infarction[4]. Acute ischaemia causes a reduction of mitochondrial oxidative phosphorylation. This in turn leads to a reduction in Adenosine Triphosphate (ATP), which contains the high-energy phosphate required for cellular metabolism. Plasma membrane sodium pumps are ATP-dependent. Therefore, a reduction in ATP causes intracellular sodium accumulation and

potassium efflux. This is accompanied by osmotic migration of water into the injured cell, causing cellular oedema.

Reperfusion of ischaemic tissue can also cause cellular injury. Oxygen-dependent free radicals are generated from infiltrating leucocytes as well as endothelial and parenchymal cells. When reperfusion increases the amount of available oxygen, the concentration of free-radicals may increase. Another postulated mechanism involves the complement activation which can cause cellular injury, mediated by leucocyte influx.

1.2 Diagnosis of STEMI

STEMI can be characterised by the presence of ≥2mm ST-segment elevation in two or more contiguous chest leads, or ≥1mm ST-segment elevation in two or more contiguous limb leads, or presumed new left bundle branch block (LBBB) on a 12-lead electrocardiogram (ECG), in the context of acute cardiac ischaemic chest pain of at least 20 minutes in duration[7].

A variety of presentations have been described for patients presenting with STEMI. Patients typically present with central heavy or "crushing" chest pain, which can radiate to the jaw, arms or to the back. This is commonly accompanied by diaphoresis and nausea. In elderly patients, patients with diabetes mellitus and in patients with cognitive impairment, the symptoms at presentation are not always typical. In addition to atypical symptoms, diabetic patients are known to suffer with "silent MI", which refers to the absence of chest pain, or other angina-equivalent symptoms during myocardial infarction. This is due to possible neuropathy affecting the transmission of cardiac pain signals.

1.3 Treatment of STEMI

1.3.1. Non-invasive treatment of STEMI

Since the 1970s, there has been a progressive evolution in the treatment of ACS. The role of acetyl-salicylic acid (aspirin) in the management of CAD gained prominence in the late 1970s, with growing evidence suggesting improved outcomes in patients with CAD treated with aspirin rather than placebo[8,9]. Beta-adrenergic receptor blockers (beta-blockers) were then shown to be beneficial post-MI in both ISIS-1 and COMMIT[10,11]. The benefits of additional fibrinolytic therapy over standard therapy with aspirin alone were then described in key studies[12,13]. This formed the basis of the "old" treatment of myocardial infarction, with aspirin, beta-blockers, and the subsequent introduction of intravenous fibrinolysis. However, it was estimated that approximately 15%-50% of patients who received intravenous fibrinolysis did not achieve satisfactory reperfusion within 90 minutes of therapy[13–16], which led to the assessment of emergency percutaneous coronary intervention (PCI), either following fibrinolysis (facilitated PCI) or without fibrinolysis (primary PCI (PPCI)) as superior options to fibrinolysis.

1.3.2. Primary percutaneous coronary intervention

PPCI refers to emergency balloon angioplasty (with or without coronary stent deployment) as the primary method of achieving reperfusion, without prior administration of fibrinolytic therapy.

In March of 1993, two major studies were published in the *New England Journal of Medicine*, both showing immediate angioplasty to be advantageous over fibrinolysis. Zijlstra et al demonstrated with only 142 patients presenting with acute MI that immediate

coronary balloon angioplasty was superior to intravenous streptokinase in reducing recurrent ischaemia, residual stenosis and in improving left ventricular systolic function[17]. Grines et al showed that immediate coronary angioplasty reduced recurrent myocardial infarction and death, with mortality benefits particularly significant in the high-risk population (age over 70 years at presentation, anterior MI and heart rate of above 100 beats per minute at presentation)[18].

In 2003, Keeley et al published their landmark meta-analysis comparing primary angioplasty with intravenous fibrinolysis, concluding that primary angioplasty was superior to intravenous fibrinolysis[19]. In 2008, the UK national roll-out for 24/7 PPCI commenced, with Leeds General Infirmary being one of the pilot sites. Since then, there has been a steady temporal rise in the uptake of PPCI in England, Wales and Northern Ireland. In 2011, 81% of patients presenting with STEMI received PPCI. This had increased to 98.4% of patients in 2016[20].

1.3.2.1. Evolution of technologies and techniques in PPCI

There has been significant progress in technique and technology associated with PPCI. The main progress in technique has been the move from transfemoral PPCI to transradial PPCI, informed by several large studies, and subsequent reviews[21–39]. At the time of the national rollout of PPCI, transradial PCI was only undertaken in 34.7% of all PCI cases. By 2014, the proportion of patients undergoing transradial PCI had more than doubled to 75.3%[40].

There have been numerous advances in technology in PPCI. Stent technology has progressed rapidly over the last 9 years. In 2008, only 57% of patients underwent drug-

eluting stent (DES) implantation. This had risen significantly over the following years to 85.7% in 2014, signalling a shift from bare-metal-stent (BMS) implantation to DES implantation, driven by evidence of lower target vessel revascularisation and mortality in newer generation zotaralimus-eluting stents (ZES) and everolimus-eluting stents (EES) in comparison with BMS and older generation sirolimus-eluting stents (SES) and paclitaxel-eluting stents (PES)[41–45].

Sirker et al showed from their analysis of data from the British Cardiovascular Intervention Society (BCIS) database that thrombus aspiration had increased in utilisation from 18% in 2008 to 48% in 2013, following the publication of the TASTE and TAPAS trials[46–48]. However, their analysis revealed no significant advantages in the utilisation of thrombus aspiration over PCI alone. Their study was published soon after the TOTAL trial which also had shown no significant reduction in primary endpoints with routine thrombus aspiration, with a paradoxical rise in the risk of stroke noted in the thrombus aspiration group[49]. The effect of these two studies showing no significant benefit with a possible increased risk of stroke with thrombus aspiration on current practice has yet to be determined, but it is possible that the use of thrombus aspiration may have reduced since the publication of these studies.

1.3.2.2. Factors influencing clinical outcomes following PPCI

Traditional risk factors for CAD that can influence outcomes following PPCI include arterial hypertension, elevated low-density lipoprotein (LDL) and total cholesterol levels, low high-density lipoprotein (HDL) levels, cigarette smoking, advancing age, diabetes mellitus, family history of premature coronary artery disease and central obesity [50–55]. Other well-established predictors of adverse outcomes following PPCI include increasing age at presentation, femoral artery access instead of radial artery access, cardiogenic shock, pre-

procedural cardiac arrest, renal dysfunction, balloon angioplasty (with no stent), bleeding, morbidity (with advanced Charlson Comorbidity Index (CCI)), and unprotected left-main coronary artery intervention[56–58].

1.3.2.3. Other factors associated with outcomes following PPCI

Whilst some of the aforementioned risk factors are also established predictors of poor outcomes following PPCI, other less-established factors have been proposed as predictors of poor clinical outcomes following PPCI, with conflicting evidence presented over the last two decades. The examination and the report of the association of these less frequently-reported factors, which are outlined in the following sections, form the basis of this thesis. Identification and clarification of factors that can influence or are associated with improved or adverse outcomes following PPCI could potentially improve the service provided, if shortfalls are detected, and consequently management is changed.

1.4. Background

1.4.1. Gender

1.4.1.1. Background

Although data pertaining to the influence of gender on clinical outcomes following PPCI have been published in the past, data of patients undergoing PPCI in the contemporary era of PPCI are limited. The progress in technique, pharmacotherapy and in equipment in PPCI, along with progress in secondary prevention therapy could have all further contributed to improved clinical outcomes following PPCI in relation to gender. Studies over the last two decades have reported increased risk of major adverse cardiovascular events (MACE) and mortality in women compared to men in PPCI[59–64]. However, it remains unclear whether there are true sex-related differences in therapeutic efficacy of PPCI, or if differences in baseline characteristics, especially age, and differences in treatment received contribute to poorer outcomes observed in women[60,64–74].

Earlier studies had indicated that gender was an independent predictor of poor clinical outcomes following PPCI[59–64,68,70,75]. However, other studies have shown that adjustment for confounding factors eliminates this excess risk in women. Studies comparing outcomes following PPCI in men and women have found that women present at an older age compared to men[60,61,63,67–71,73–79]. This is likely to be due to the cardio-protective effects of endogenous oestrogen[80]. However these studies also highlighted the fact that along with age at presentation with STEMI, women were more likely to have systemic hypertension, which has been shown to confer a higher hazard ratio for CAD in women compared to men[81]. There were also numerous procedural biases that favoured men. Pre-hospital and/or in-hospital delays to reperfusion, known predictors of adverse clinical outcomes following

STEMI, were more pronounced in women in most of these studies[82–87]. Women were less likely to undergo transradial PPCI, which has been shown to be superior to transfemoral PPCI by reducing major bleeding and all-cause mortality[39,88,89]. Women were also less likely to receive glycoprotein IIb/IIIa inhibitors (GPI) although the reason for this could be their lower pre-procedural TIMI 0 flow in the infarct-related artery (IRA). Other proposed confounders were reduced body surface area, coronary artery diameter and renal function[63].

1.4.1.2. Literature review strategy

Literature search of articles between 1st of January 2000 and 30th of September 2016 was conducted using PubMed in September 2016, and then repeated in July 2017 to include studies published between 30th of September 2016 and 16th of July 2017. The following search of titles and abstracts on PubMed: "(((((((((gender) OR sex) OR female) OR male)) AND ((((outcomes) OR mortality) OR survival) OR death)) AND ((((primary percutaneous coronary intervention) OR primary PCI) OR emergency coronary angioplasty) OR primary transluminal coronary angioplasty))) AND ((((((ST segment elevation myocardial infarction) OR ST elevation myocardial infarction) OR STEMI) OR ST segment elevation acute coronary syndrome) OR ST elevation acute coronary syndrome) OR Acute myocardial infarction)" returned 4176 studies. Review of titles of these studies, followed by abstracts if the titles included the following terms: (gender/sex/female/male) and (myocardial infarction and/or percutaneous coronary intervention and/or angioplasty), were undertaken. This strategy revealed 17 studies that were relevant (published in English, in full-text, which included patients undergoing PPCI for STEMI) as of July 2017.

1.4.1.2.1. Review of relevant studies

In their analysis of 109,708 patients (male: n=74,137; female: n=35,571) whom underwent PCI for all indications between January 1994 and January 1998, Petersen et al found that although unadjusted procedural mortality was higher for women (1.8% vs 1.0%, p<0.001), adjustment for baseline risk factors eliminated the excess risk in women (Odds Ratio (OR) 1.07 (95% Confidence interval (CI) 0.92-1.24))[71]. They concluded that body-surface area (BSA) was a more important predictor of clinical outcomes following PCI compared to gender, showing a direct relationship between increasing BSA and survival following PCI. However, mortality data for this study was limited to in-hospital mortality. Importantly also, the data from this study describe outcomes in all PCI, not specifically PPCI for STEMI. This study also predated the routine use of intracoronary stents, and secondary prevention with DAPT.

Vakili et al then published data of all patients (n=1044; male: n=727; female: n=317) undergoing PPCI for STEMI in New York State in 1995[59]. In their analysis, both unadjusted (7.9% vs 2.3%, p<0.001) and adjusted (for age, hypertension, diabetes mellitus, peripheral or cerebrovascular disease, cardiogenic shock or haemodynamic instability and time to treatment – all of which were significantly different between genders) in-hospital mortality (OR 2.33 (95% CI 1.20-4.60)) was higher in women compared to men. Once again, patients in this study underwent PCI at a time that preceded the routine use of intracoronary stents or secondary prevention with DAPT. Abrupt vessel closure occurred in 4% of women and 2% of men, which is significantly higher than patients undergoing PPCI in the contemporary era, since the routine use of intracoronary stents in PPCI was advocated.

Conversely, in 2002, Mehilli et al published one-year mortality of 1937 patients (male: n=1435; female: n=502) who underwent PCI for STEMI in a single tertiary referral centre between 1995 and 2000 in Germany[90]. Although unadjusted mortality (Hazard Ratio (HR) 1.06 (95% CI 0.80-1.39); p=0.70) was not significantly different in women, after adjustment for potential confounding factors (age, hypertension, diabetes mellitus, smoking, previous MI, previous coronary artery bypass grafting (CABG), previous PCI, anterior MI, and time to admission), women actually had lower mortality compared to men (HR 0.67 (95% CI 0.50-0.91); p=0.01). They concluded that if treatment (both acute and secondary prevention) between genders did not vary, clinical outcomes in women were not adverse compared to men, and when further adjusted for baseline characteristics, the female sex was an independent predictor of lower one-year mortality.

Cheng et al published 30-day mortality from their single-centre analysis of 1032 patients (male: n= 874; female: n=158) who underwent PPCI for STEMI between May 1993 and April 2002[67]. In their study, unadjusted mortality was almost two-fold (14.6% vs 7.4%; p<0.01) in women. However, adjustment for age and other variables (not specified) revealed no statistically significant difference in mortality between women and men (OR 1.06 (95% CI 0.53-2.14)). Reperfusion time was significantly longer in women in their study, and the effect of this was observed in the presence of New York Heart Association (NYHA) III-IV heart failure in 29.1% of women compared to 18.5% of men, and in the presence of myocardial free wall rupture (3.80% in women vs 0.23% in men). However, it was not clear if this was adjusted for in their analysis. Only 50% of patients in their study received stents, and P2Y12 receptor inhibitor therapy was only given up to two weeks post-PPCI. These factors have progressed significantly since and it is possible that outcomes could be different with higher stent usage and better secondary prevention.

In 2007, Milcent et al published their analysis of data of 74389 patients hospitalised for AMI in France in 1999, concluding that both unadjusted (OR 1.37 (95% CI 1.30-1.46)) and adjusted (OR 2.65 (95% CI 2.52-2.79)) in-hospital mortality were higher in women compared to men[91]. However, there was a significant disparity between the treatment received by men and women, with men more likely to undergo interventional procedures (which as a factor, was independently associated with lower mortality in their study), and when the expected probability of death was re-calculated assuming equal treatment strategies, excess mortality was no longer significant in women. However, this is unlikely to be a significant factor at present time, which has seen the rapid growth and acceptance of PPCI as the default treatment for STEMI, with approximately 99% of patients with STEMI receiving PPCI as their main strategy of treatment in England[20].

Analysis of data from 20,290 patients (male: n=14657; female: n=5633) from the AMI Plus registry in Switzerland, that included patients who were admitted with ACS between 1997 and 2006 once again showed higher unadjusted in-hospital mortality in women (10.7% vs 6.3%; $p<0.001$)[61]. However, this study, in keeping with most prior studies, showed that after adjustment for confounders, women were not significantly more likely to have in-hospital mortality compared to men (OR 1.09 (95% CI 0.95-1.25)). They were however, independently less likely to undergo PCI (OR 0.67 (95% CI 0.64-0.76)), suggesting a treatment bias favouring men. This, once again, is unlikely to be a significant factor at present time in the UK with PPCI being the default guideline-recommended therapy for all patients with STEMI.

In 2008, Jneid et al published data from 78,254 patients (male: n=47556; female: n=30698) who were diagnosed with AMI across 420 American hospitals between 2001 and 2006[60]. In

their STEMI subgroup (male: n=25353; female: n=16694), unadjusted analyses revealed significantly higher in-hospital mortality in women (10.5% vs 5.5%). In contrast with previous studies, adjustment for baseline characteristics did not eliminate excess mortality in women (OR 1.12 (95% CI 1.02-1.23)). However, significant differences were observed in the treatment received by women in comparison to men. Women had longer time to reperfusion compared to men, were 23% less likely to receive any reperfusion compared to men, and were also less likely to receive aspirin and beta-blocker therapy compared to men. These factors, however, were not adjusted for, and the differences observed in outcomes were likely to be due to the differences in treatment received between genders, rather than gender itself contributing to poor outcomes following STEMI.

Berger et al published their analysis of 102004 patients (male: n=75972; female: n=26032) with STEMI from 11 ACS trials[78]. Although these were not real-world data, it was important to note that their findings were in keeping with prior real-world registry studies, showing an increase in unadjusted mortality in women (OR 1.15 (95% CI 1.06-1.24)) compared to men. However, as with most observational studies, once baseline characteristics and in addition, angiographic disease severity were adjusted for, mortality was no longer statistically significantly different between genders. As this was a pooled analysis of RCT data, treatment differences between genders were unlikely. This further contributed to the opinion that female gender per se was not an independent predictor of adverse outcomes.

In 2009, data analysed from the American College of Cardiology – National Cardiovascular Data Registry (ACC-NCDR), of 42038 patients (male: n=29703; female: n=12335) who underwent PPCI for STEMI revealed higher unadjusted mortality (2.2% vs 1.4%) in women[64]. However, as with most prior observational studies, risk-adjusted mortality was not

significantly higher in women compared to men (OR 0.97 (95% CI 0.88-1.07)), despite other adverse post-PCI outcomes (cardiogenic shock and bleeding) being significantly higher in women. Once again, there were differences in treatment given to women, as women were noted to have lower rates of stent implantation or and were less likely to have been discharged on aspirin and statin at compared to men. These differences were not adjusted for. Interestingly, despite that, mortality was not statistically significantly different between genders; suggesting, once again, that gender per se was not an independent predictor of mortality.

In 2010, Sjauw et al reported data from their analysis of 3277 consecutive patients (male: n=2367; female n=910) who underwent PPCI for STEMI between 1995 and 2006[92]. Unadjusted 30-day (9.2% vs 8.1%), 12-month (10.5% vs. 12.2%), and three-year (13.8% vs. 15.6%) mortality were not statistically significantly higher in women. They had found that 30-day (HR 1.09 (95% CI 0.77-1-53)), 12-month (HR 1.03 (95% CI 3.76*(presumably 0.76)-1.34) and 3-year (HR 1.10 (95% CI 0.76-1.49)) risk-adjusted mortality were also not statistically significantly different between genders despite longer onset-of-symptom to call-time, further adding to the evidence-base that the female gender in itself is not an independent predictor of mortality.

Duvernoy et al analysed outcomes in 8771 patients (male: n=6229; female: n=2542) undergoing PPCI for STEMI in multiple centres in Michigan, USA between 2003 and 2008[79]. Once again, despite observing higher unadjusted in-hospital mortality in women compared to men (OR 1.79 (95% CI 1.45-2.22)), when propensity-matched, despite higher rates of vascular complications and blood transfusions, women did not have significantly higher mortality compared to men (OR 1.30 (95% CI 0.98-1.72)). Prior to that, they presented their

analysis of 22725 patients (male: n=14848; female: n=7877) who underwent PCI for all indications between 2002 and 2003[63]. Although data specific to PPCI were not presented then, they found that when adjusted for differences in baseline characteristics (excluding BSA and renal function), women had higher post-PCI mortality (OR 1.52 (95% CI 1.16-2.01)) compared to men. However, when BSA and renal function were corrected for in addition to other baseline characteristics, mortality in women was not significantly higher compared to men (OR 1.25 (95% CI 0.90-1.74)). This is despite significant differences in secondary prevention that were not corrected for (women were less likely to receive aspirin, statin, ACE-inhibitors and beta-adrenergic receptor blockers). They therefore concluded that baseline renal function and BSA contributed to differences in outcomes observed between genders.

Benamer et al analysed data from 16760 patients (male: n=13096; female: n=3664) in Paris who were treated with PCI for STEMI within 24-hours of onset[68]. They found that when adjusted for age, diabetes mellitus, cardiogenic shock, left main stem PCI, and number of diseased coronary arteries, female gender was independently associated with adverse outcomes (OR 1.38 (95% CI 1.16-1.63)). However, unlike other studies, other risk factors (prior MI, renal function, prior coronary revascularisation, hypertension, prior stroke or peripheral vascular disease) were not presented or corrected for. Differences in secondary prevention were also not presented. These factors could all have contributed to differences in outcomes observed between genders in their analysis.

A smaller analysis of 240 patients (male: n = 181; female n = 59) who underwent PPCI for STEMI between 2002 and 2004 in Turin, Italy, revealed significantly higher rate of unadjusted death (20.0% vs 8.1%; p=0.029)[76]. They also concluded that when adjusted for

confounders, the female sex was still associated with a significantly higher rate of death compared to the male sex. However, if their rates of death were 12 females (20% of 59 patients) and 15 males (8.1% of 181 patients), it is unlikely that adequate multivariable adjustment would have been conducted. Therefore, it is quite likely that the difference observed in adjusted mortality is likely to be more aligned with the unadjusted difference quoted.

In 2013, Wijnbergen et al presented 2-year outcome data of 870 patients (male: n=668; female: n=202) who underwent PPCI for STEMI between 2006 and 2008 in Eindhoven, The Netherlands[93]. As with previous studies, women had significantly more adverse risk-factor profiles compared to men. Unadjusted death was lower in men (Relative risk (RR) 0.31 (95% CI 0.16-0.62)). However, when adjusted for age, hypertension, smoking status, diameter of stent, and time to reperfusion, men no longer had lower mortality compared to women (HR 0.69 (95% CI 0.30-1.59)), a finding that was in keeping with other studies published prior to theirs.

More recently, in 2013, Otten et al presented their analysis of 6746 patients (male: n=4991; female: n=1755) who underwent PPCI for STEMI between 1998 and 2008 in The Netherlands[70]. Data were analysed according to age (<65 years vs ≥65 years), and gender. Variables included in their Cox Proportional Hazards (Cox PH) models were age, hypertension, Killip class and multivessel disease. However, time to reperfusion was not corrected for despite being significantly longer in women (218 minutes vs 200 minutes in patients under 65; 237 minutes vs 220 minutes in patients aged 65 and over; $p<0.01$ for both), and neither were history of cigarette-smoking and family history of CAD, both of which were significantly higher in women. They had found that unadjusted 30-day death

was higher in women in both age groups compared to men. Unadjusted one-year death was higher in women under 65 years of age, but was not significantly higher in the older age group. However, in contrast with other previous studies, it was found that younger women had higher adjusted one-year mortality compared to men (HR 1.687 (95% CI 1.108-2.569)). It is important to note that renal function was not presented or corrected for, and ACE-inhibitor therapy (which is prognostically important following MI) was lower in women at 1 year (49% vs 53%; p=0.05). It is possible that differences in baseline characteristics that were not presented and in post-MI care (as reflected by lower use of ACE-inhibitors) could account for the difference in adjusted one-year mortality in younger women.

Birkemeyer et al published their analysis of 1104 patients (male: n=823; women: n=281) who underwent PPCI for STEMI in two STEMI networks in Germany between 2001 and 2003 (network 1), and between 2005 and 2007 (network 2)[94]. Unadjusted 12-month mortality was significantly higher in women (14.9% vs 6.9%; p<0.01). However, propensity-matched, multivariable adjustment revealed no significant difference in mortality (OR 1.13 (95% CI 0.61-2.11)) despite lower use of aspirin, clopidogrel, beta-adrenergic receptor blocker and lipid-lowering therapy at discharge in women (p≤0.05 for all medications).

Most recently, Brogan et al presented 5-year mortality data for all patients undergoing PPCI for STEMI in England and Wales between 2005 and 2013 (n=88188; male: n=65178)[56]. Their survival analysis was based on expected survival of comparable UK population, rather than using patients within the PPCI groups as their denominators, and were quoted as excess mortality risk ratio (EMRR). They found that females had a higher ongoing risk of mortality (EMRR 1.33 (95% CI 1.26-1.41)), suggesting mode of presentation, differences in secondary prevention and multimorbidity as potential causes for the differences noted. However,

differences in access sites, medications, stent use, time to reperfusion, age and other baseline characteristics according to gender were not presented for each group, and rather, some of these factors were presented for the entire cohort of patients. These could all account for differences observed in long-term outcomes.

Table 1.1: Summary of studies examining the association between gender and outcomes in PPCI.

Authors	Study design	Country	Data-collection years	Number	Male	Female	Analysis	Endpoints	Findings
Petersen et al[71]	Observational *all PCI[a]*	USA	1994-1998	109708	74137	35571	Logistic regression	In-hospital mortality	Adjusted OR[b] 1.07 (95% CI[f] 0.92-1.24) in women. Body surface area more important predictor of outcomes compared to gender.
Vakili et al[59]	Observational	USA	1995	1044	727	317	Logistic regression	In-hospital mortality	Adjusted OR[b] 2.33 (95% CI 1.20-4.60) in women.
Mehilli et al[90]	Observational	Germany	1995-2000	1937	1435	502	Cox regression	12-month mortality	Adjusted HR[c] 0.67 (95% CI 0.50-0.91) in women.
Cheng et al[67]	Observational	China	1993-2002	1032	874	158	Logistic regression	30-day mortality	Adjusted OR[b] 1.06 (95% CI 0.53-2.14) in women.
Milcent et al[91]	Observational	France	1999	74389	52041	22348	Logistic regression	In-hospital mortality	Adjusted OR[b] 2.65 (95% CI.52-2.79) in women, but women received less invasive procedures compared to men – not matched or adjusted for.
Radovanovic et al[61]	Observational	Switzerland	1997-2006	20290	14657	5633	Logistic regression	In-hospital mortality	Adjusted OR[b] 1.09 (95% CI 0.95-1.25) in women.
Jneid et al[60]	Observational	USA	2001-2006	42347	25353	16994	Logistic regression	In-hospital mortality	Adjusted OR[b] 1.12 (95% CI 1.02-1.23) in women with significant disparity in treatment received (not adjusted for).
Berger et al[78]	Collated RCT[d] data	USA	1993-2006	102004	75972	26032	Logistic regression	30-day mortality	Adjusted OR[b] 1.23 (95% CI 0.96-1.57) in women, once angiographically matched.
Akhter et al[64]	Observational	USA	2004-2006	42038	29703	12335	Logistic regression	Procedural mortality	Adjusted OR[b] 0.97 (95% CI 0.88-1.07) in women.
Sjauw et al[92]	Observational	The Netherlands	1995-2006	3277	2367	910	Cox regression	30-day, 12-month & 3-year mortality.	Adjusted HR[c] in women: 30-day – 1.09 (95% CI 0.77-1-53). 12-month – 1.03 (95% CI 0.76-1.34). 3-year – 1.10 (95% CI 0.76-1.49).
Duvernoy et al[79]	Observational	USA	2003-2008	8771	6229	2542	Logistic regression	In-hospital mortality.	Adjusted OR[b] 1.30 (95% CI 0.98-1.72) in women.

Benamer et al[68]	Observational	France	2003-2007	16760	13096	3664	Logistic regression	In-hospital mortality	Adjusted OR[b] 1.38 (95% CI 1.16-1.63) in women; significant risk factors and differences in treatment not presented or adjusted for.
D'Ascenzo et al[76]	Observational	Italy	2002-2004	240	181	59	Not described	53-58 months	No exact OR[b]/HR[c] given, but stated that there was a difference in adjusted mortality between men and women.
Wijnbergen et al[93]	RCT[d]	The Netherlands	2006-2008	870	668	202	Cox regression	2-years	Adjusted HR[c] 0.69 (95% CI 0.30-1.59) in women.
Otten et al[70]	Observational	The Netherlands	1998-2008	6746	4991	1755	Cox regression	12-month mortality	Adjusted HR[c] 1.687 (95% CI 1.108-2.569) in women <65 years. Adjusted HR[c] 1.022 (95% CI 0.762-1.370) in women ≥65 years. Time to reperfusion not corrected for despite being longer in women.
Birkemeyer et al[94]	Observational	Germany	2001-2003; 2005-2007	1104	823	281	Logistic regression	12-month mortality	Adjusted OR[b] 1.13 (95% CI 0.61-2.11) in women.
Brogan et al[56]	Observational	UK	2005-2013	88188	65178	22725 (285 missing)	Ederer II method of expected survival	5-year mortality	EMRR[e] 1.33 (95% CI 1.26-1.41) in women; secondary prevention and other co-morbidities not adjusted for.

[a]PCI: Percutaneous coronary intervention; [b]OR: Odds ratio; [c]HR: Hazard ratio; [d]RCT: Randomised controlled trial; [e]EMRR: Excess mortality risk ratio; [f]CI: Confidence interval.

1.4.1.3. Conclusion

All but two of the relevant studies identified were derived from observational data from "all-comers" registries. Only one of these studies, by Brogan et al, included patients who underwent PPCI after 2008, which was when PPCI was rolled out nationally in the UK[56]. Most of these studies were spread over a long period of time, one of which by Berger et al involved patients whom underwent PPCI between 1993 and 2006[78]. Most studies involved patients undergoing PPCI both before and after the landmark publication by Keeley et al showing that PPCI was superior to fibrinolysis in the treatment of STEMI[19].

All of the studies identified employed multivariable analysis to adjust for confounding variables. This was mainly undertaken with logistic regression analysis, although four of the studies employed Cox regression analysis. The reason behind employing logistic regression over Cox regression in these studies were unclear, but it was noted that the largest dataset to employ Cox regression involved analysis of 6746 patients. Larger datasets could have presented significant difficulties in satisfying proportional hazards assumptions, and this could have led to the use of logistic regression analysis. This is especially important considering the fact that in all of these studies, women were older at presentation, were more likely to be hypertensive and were subjected to longer time to reperfusion. Some studies also identified significant differences in treatment strategy and secondary prevention in women. However, these important differences that included differences in prescription of aspirin, P2Y12-receptor inhibitor therapy, statins, beta-adrenergic receptor blockers and ACE-inhibitors, were in most studies, not adjusted for. These may reflect the difference in morbidity between men and women at presentation, but treatment bias cannot be excluded. Time to reperfusion was also significantly longer in women in most of

these studies. Time to reperfusion has been shown to be an important predictor of infarct size and mortality, and it has been shown to be longer in women[95]. Whilst some of these delays were due to longer symptom-onset-to-call-for-help time (patient delay), differences were also noted in call-to-reperfusion time, suggesting gender differences in time to reperfusion within the STEMI pathway. Whilst patient delay may be an important factor in explaining the differences in symptom-onset-to-balloon time (total ischaemic time), including this variable in a regression model may not necessarily be appropriate, as possible differences in characterisation of symptoms and pain thresholds may be inherently different between genders, and as such, may be consequences of differences in genders rather than confounders.

In terms of outcomes, only two studies, by Mehilli et al and Sjauw et al, revealed no difference in unadjusted mortality between men and women following PPCI[90,92]. All other relevant studies showed significant differences in unadjusted outcomes in women compared to men. Most of the studies also showed that once baseline characteristics had been adjusted for by multivariable analysis, mortality was no longer different between genders. This is despite significant disparity in secondary prevention between genders that was not adjusted for. The most recent of the studies identified, by Otten et al and by Brogan et al, suggested that adjusted differences in outcomes exist between men and women. Otten et al concluded that women <65 years of age had more adverse outcomes compared to men <65 years of age, and Brogan et al concluded that although adjusted outcomes may differ between men and women, they could be related to differences in morbidity and secondary prevention, rather than the acute treatment of STEMI.

Considering the heterogeneity in outcomes noted between genders, and the fact that only one of these studies were undertaken following the UK national roll-out of PPCI for the treatment of STEMI, the association between gender and outcomes following PPCI in STEMI warrants further investigation.

1.4.2. Ethnicity

1.4.2.1. Background

South Asian individuals made up 7.5% of the population in England and Wales in the 2011 national census[96]. They are known to have a higher prevalence of insulin resistance and diabetes mellitus compared to other ethnic groups[97]. This is thought to be due to a combination of factors. Higher levels of carbohydrate consumption in South Asian individuals is thought to be a contributing factor to their higher prevalence of diabetes mellitus[97]. However, they are also known to have altered levels of adipokines and pro-diabetic inflammatory mediators compared to White individuals[98–108]. In addition to their higher prevalence of diabetes mellitus, South Asian patients also have a higher prevalence of systemic hypertension, hypercholesterolaemia and pre-existing CAD at presentation with STEMI, despite their younger age at presentation[2,104,105,109–111]. In most of these studies, South Asians were however, less likely to be cigarette smokers. Due to their adverse risk-factor profile, South Asian patients tend to present at an earlier age with CAD[2,98,102,105,106,109,112–116]. When they undergo coronary revascularisation, either percutaneous or surgical, MACE has been reported to be higher in this group, despite their younger age at presentation[105,109]. However, more recent studies suggested that once CAD is manifest, South Asian patients have lower mortality compared to White patients, with age

at presentation playing a key role[2,117]. The wide variability in outcomes reported in studies, of which only one included patients who underwent PPCI following the UK roll-out in 2008, suggests further investigation into this association is required.

1.4.2.2. Literature review strategy

Literature search of studies published between 1st of January 2000 and 30th of September 2016 was undertaken on 30th of September 2016. This search was then repeated in July 2017 to include articles published between 30th September 2016 and 16th July 2017, and between 1st of January 1995 and 31st of December 1999, due to the small number of studies initially identified. The following search term was used to identify relevant articles in PubMed: (((((south asian) OR ethnicity OR race)) AND (((outcome$) OR mortality OR death) OR survival)) AND myocardial infarction) AND (((percutaneous coronary intervention) OR coronary angioplasty) OR emergency angioplasty). Given the paucity of data available in this review, a more inclusive search protocol (compared to the search undertaken for the identification of relevant studies pertaining to the association between gender and outcomes in PPCI) to identify studies pertaining to MI and PCI were utilised. This returned 259 studies. Review of the titles of these studies, followed by abstracts if the titles included the following terms: ((South Asian) and/or (ethnicity or race) and (myocardial infarction and/or percutaneous coronary intervention and/or angioplasty)), were undertaken. This strategy revealed 6 publications that were determined relevant (published in English, in full-text, which included patients undergoing PPCI for STEMI) to this study.

1.4.2.2.1. Review of relevant studies

The earliest published study within the search period was by Wilkinson et al who published six-month mortality data of 462 patients (white: n=313; South Asian: n=149) who were admitted to Newham General Hospital in London between 1988 and 1992 with acute MI (89% STEMI)[102]. In their study, South Asian patients were younger at presentation, were less likely to be current cigarette-smokers (but more likely to have previously smoked cigarettes), had a four-fold greater prevalence of diabetes mellitus, and were more likely to be treated with aspirin and thrombolysis (despite differences in regional ST-elevation being statistically insignificant). Unadjusted outcomes were not statistically significantly different. When adjusted for age, gender, previous MI, treatment received and diabetes mellitus, outcomes remained comparable (HR 1.26 (95% CI 0.68-2.33) in South Asian patients). When diabetes mellitus was not adjusted for, mortality was significantly higher in South Asian patients (HR 2.02 (95% CI 1.14-3.56)). This suggested that diabetes mellitus played a key role in the outcomes of South Asian patients in comparison with white patients. The applicability of this study to current practice however, is debatable as details of invasive management, if at all undertaken, were not presented, and therefore, this study could reflect outcomes observed in the “old” medical treatment of STEMI.

In 2002, Gupta et al analysed in-hospital mortality of 1106 patients (White: n=553, South Asian: n=553), matched by age, gender, hospital of admission and discharge date, who were admitted hospitals in Toronto, Canada with STEMI between 1994 and 1999[118]. South Asian patients were more likely to have diabetes, but were less likely to be cigarette-smokers, hypercholesterolaemic or suffer with peripheral vascular disease. South Asian patients had longer symptom-onset to presentation time (patient delay). This could be due to the

phenomena of “silent ischaemia” and atypical presentation associated with diabetes mellitus, which in this cohort of patients, was almost two-fold in South Asians. Management of MI was not different according to ethnicity. Unadjusted in-hospital mortality was not statistically significantly different in South Asian patients (9.6% vs 7.8%; p=0.27). However, multivariable adjustment to correct for confounders was not undertaken. Nevertheless, this study suggested that South Asian ethnicity was not a predictor of mortality following AMI, albeit in the thrombolysis era (approximately 6.3% of patients underwent coronary revascularisation of any description for index MI).

Khan et al then published their analysis of one-year mortality of 41625 patients (white: n=38479; South Asian: n=2190; Chinese: n=946) who were admitted to hospital in Alberta, Canada between 1994 and 2003 with MI (according *to International Classification of Diseases* Code 410 which could have included NSTEMI)[110]. South Asian patients in their study were more likely to be male, younger, diabetic and hypertensive compared to white patients. In terms of treatment received, rates of PCI within 30 days of admission were not significantly different (OR 1.06 (95% CI 0.9-1.24) in South Asians). Although adjusted 30-day mortality was not statistically significantly different (OR 0.88 (95% CI 0.75–1.03) in South Asian patients), long-term mortality (events/1000 patient-years) was statistically significantly lower in South Asian patients (OR 0.65 (95% CI 0.57–0.72) in South Asian patients). In their study, South Asian patients were more likely to receive diagnostic coronary angiography compared to white patients, but not necessarily revascularisation (as described earlier). They speculated that this could be due to physicians’ perception of cardiovascular risk in this cohort, and therefore the earlier employment of invasive approach. Differences in secondary prevention, and the adherence to it, were not described, and neither were use of stents and additional pharmacotherapy. They had

however, corrected for age, and still found that longer-term mortality was significantly lower in South Asian patients compared to white patients. They had postulated that other non-cardiac causes of death could have been lower in the South Asian patients, a finding that had been described in the past, which is plausible in this comparison as 30-day outcomes were not significantly different between the ethnic groups[119].

Albarak et al then investigated the association between South Asian ethnicity and 30-day and long-term (mean follow-up 4.2 years) mortality in their cohort of 7135 patients (white: n=6648; South Asian: n=487) between 20 and 55 years of age who were admitted to hospital with MI (according to *International Classification of Diseases* Code 410 which included both NSTEMI and STEMI)in British Columbia, Canada, between 1995 and 2002[115]. In this subgroup of younger patients (≤ 55 years), age was not significantly different between white patients and South Asian patients. Despite this, South Asian patients still had two-fold greater prevalence of diabetes mellitus compared to white patients. They were also significantly more likely to be low-income earners compared to white patients. Similar to the study by Khan et al[112], despite higher proportions of South Asian patients undergoing cardiac catheterisation procedures, rates of coronary revascularisation were not significantly different between ethnic groups. Unadjusted short-term (HR 0.83 (95% CI 0.37-1.90)) and long-term (HR 1.14 (95% CI 0.76-1.74)) mortality were not statistically significantly different between white patients and South Asian patients. When adjusted for confounding variables, 30-day (HR 0.90 (95% CI 0.38-2.10)) and long-term (HR 0.81 (95% CI 0.53-1.26)) mortality were still not significantly different between the two groups. Interestingly, amongst diabetic patients, adjusted rate of recurrent MI were significantly higher in South Asian patients (HR 1.48 (95% CI 1.04-2.11)), suggesting additional social or metabolic factors that could contribute to adverse outcomes in South Asian patients.

Analysis of 4729 patients (White: n=4219; South Asian: n=371) who underwent PCI for MI (once again according to *International Classification of Diseases* Code 410) in British Columbia, Canada between 1999 and 2003 once again revealed differences in age at presentation and prevalence of diabetes mellitus between white patients and South Asian patients[109]. Adjusted 30-day (OR 1.63 (95% CI 0.83-3.20) for South Asians) and 12-month mortality (HR 0.77 (95% CI 0.43-1.40) for South Asians) revealed no significant association between ethnicity and outcomes in this particular comparison. However, recurrent MI (HR 1.34 (95% CI 1.08-1.67)) and heart failure (HR 1.81 (95% CI 1.00-3.29)) following index event were both higher in South Asian patients.

The most recent study to examine the association between South Asian ethnicity and long-term mortality (median 2.8 years) was published in 2014[2]. Jones et al analysed data from 279256 (White: n=259318; South Asian: n=19938) patients who had undergone PCI in England and Wales between 2004 and 2011. Of these patients, 36396 White patients and 3047 South Asian patients underwent PPCI for STEMI. In the PPCI subgroup, only mortality was presented, not MACE (as was the case with all PCI). Although unadjusted mortality was lower in South Asian patients (Kaplan-Meier log-rank p=0.0025), adjustment for age and other confounders including diabetes eliminated this difference (HR/OR not quoted). Age was felt to be the strongest factor in differences in outcomes noted in South Asian patients, as adjustment for age alone meant South Asian patients had conversely higher long-term mortality (HR/OR not quoted).

Table 1.2: Summary of studies examining the association between South Asian ethnicity and outcomes in PPCI.

Authors	Study design	Country	Data-collection years	Number	White	South Asian	Identification of ethnicity	Analysis	Endpoints	Findings
Wilkinson et al[102]	Observational	UK	1988-1992	462	313	149	Directly recorded	Cox regression	6-month mortality	Adjusted HR[a] 1.26 (95% CI[e] 0.68-2.33) in South Asians. HR 2.02 (95% CI 1.14-3.56) in South Asians without adjustment for diabetes.
Gupta et al[118]	Observational-retrospective matched	Canada	1994-1999	1106	553	553	Name analysis	Chi-square	In-hospital mortality	Mortality (9.6% in South Asians vs 7.8% in White patients; p=0.27) not significantly different. Further confounders not adjusted for.
Khan et al[110]	Observational	Canada	1994-2003	41625	38479	2190	Name analysis	Logistic regression analysis	30-day and 1 year mortality.	Adjusted 30-day mortality ((OR[b] 0.88 (95% CI 0.75–1.03) in South Asians) not significantly different, but 12-month mortality (OR 0.65 (95% CI 0.57–0.72)) lower in South Asian patients.
Albarak et al[115]	Observational	Canada	1995-2002	7135	6648	487	Name analysis	Cox regression	30-day and long-term mortality	No significant difference in adjusted 30-day (HR 0.90 (95% CI 0.38-2.10)) and long-term (HR 0.81 (95% CI 0.53-1.26)) mortality. Recurrent MI[c] higher in diabetic South Asians compared to diabetic white patients (HR 1.48 (95% CI 1.04-2.11)).
Gasevic et al[109]	Observational	Canada	1999-2003	4729	4219	371	Name analysis	Logistic and Cox regression	30-day, 12-month mortality. Recurrent MI and HF.	Adjusted 30-day (OR 1.63 (95% CI 0.83-3.20)) and 12-month (HR 0.77 (95% CI 0.43-1.40)) mortality not significantly different. Recurrent MI (HR 1.34 (95% CI 1.08-1.67)) and HF[d] (HR 1.81 (95% CI 1.00-3.29)) higher in South Asians.
Jones et al[2]	Observational	UK	2004-2011	39443	36396	3047	Directly recorded	Kaplan-Meier	Long-term mortality	Unadjusted mortality lower in South Asians (Log-rank p=0.0025). Adjusted mortality not significantly different (OR/HR not quoted).

[a]HR: Hazard ratio; [b]OR: Odds ratio; [c]MI: Myocardial infarction; [d]HF: Heart failure; [e]Confidence interval.

1.4.2.3. Conclusion

All of the relevant studies were observational studies from registry data. Only one of the studies by Jones et al was undertaken at the time that PPCI was the guideline-recommended therapy in the relevant country, and that too, for only half the recruitment period.

As with most analyses of the association of gender with clinical outcomes (as described in the previous section), multivariable analysis was undertaken to adjust for confounders to obtain adjusted HR or OR, depending on the regression analysis employed. Logistic regression analysis was the most commonly used multivariable analysis model, followed by Cox regression analysis. Once again, this could be due to violation of proportional hazards assumptions, but reasons for the employment of logistic regression analysis were not specified. Most studies had corrected for major confounders, which in this comparison were age, diabetes mellitus, smoking and socioeconomic status (where appropriate). Acute treatment was not significantly different and hence, this was not corrected for. However, none of the studies assessed details of other secondary prevention, such as aspirin, P2Y12-receptor inhibitors or GPI.

Identification of ethnicity was done by two distinct methods. Four of the 7 studies were from Canadian registries and in these registries, ethnicity was not recorded at the time of procedure/admission. Instead, it was derived from surnames using Nam Pehcan computer software, the use of which has been analysed in the past, showing good sensitivity (90.5%) but poor positive predictive value (63.2%) in identifying South Asian names[120]. This could in theory lead to the ethnicity of significant number of patients being mis-labelled. Surname changes following marriage for instance may not have been picked up. The UK studies

however had directly recorded ethnicity at the time of admission/cardiac catheterisation, which in most cases were recorded following direct questioning of the patient. This is likely to be more reliable. However, although the authors of the Canadian papers have stated that the likelihood of significant discrepancies were low, this important potential source of error cannot be completely discounted, as it forms the very basis of the comparison of one ethnic group with another.

In terms of outcomes, one study had shown that adjusted 12-month mortality was lower in South Asians[112], a finding that no other study observed. Their study was undertaken prior to the acceptance of PPCI as the gold-standard therapy in STEMI. The proportion of patients in their study who had undergone PCI during index admission was less than 20% in both ethnic groups, which is very different compared to the treatment of MI at present time. The applicability of the results of that study to current practice therefore is unclear. All other studies had shown that South Asian ethnicity is not independently associated with mortality. However, South Asian ethnicity was found to be independently associated with recurrent MI, TLR and heart failure (HF)[105,109]. Other metabolic or social factors, in addition to diabetes mellitus and age, could contribute to these differences.

With the advances in PPCI technique and pharmacotherapy, and the advances in the monitoring and treatment of diabetes mellitus (including the acute treatment of patients with diabetes mellitus presenting with MI), which is a significant factor in the association between South Asian ethnicity and adverse outcomes, re-examination of the association between ethnicity and outcomes in the current age of PPCI is warranted.

1.4.3. Oral P2Y12-receptor inhibitor therapy

1.4.3.1. Background

The role of aspirin in the secondary prevention of CAD has been well-established[121–123]. The publication of the CURE, COMMIT and CLARITY-TIMI 28 trials heralded the era of dual-antiplatelet therapy with aspirin and clopidogrel in acute coronary syndromes[124–126]. As stent technology and PCI techniques progressed, a newer-generation of more potent P2Y12-receptor inhibitor therapy emerged. The first of these drugs was prasugrel. The TRITON-TIMI 38 trial showed a reduction in ischaemic endpoints with a rise in bleeding complications when prasugrel was used instead of clopidogrel in ACS with scheduled PCI[127]. The STEMI subgroup analysis by Udell et al demonstrated a reduction in the composite endpoint of cardiovascular death, non-procedural MI or stroke at 30 days with the use of prasugrel over clopidogrel in patients presenting with STEMI who underwent PCI, with no reduction noted in mortality alone[128]. This had led to the National Institute of Clinical Excellence (NICE) UK recommendation that prasugrel should be used within its marketing authorisation in the treatment of patients undergoing PPCI[129]. The PLATO investigators then published their analysis of 18624 patients with ACS randomised to either ticagrelor or clopidogrel, showing that patients treated with ticagrelor had reduced rates of recurrent MI, vascular mortality and importantly, all-cause mortality compared to those treated with clopidogrel[130]. The NICE guidelines were then updated, with ticagrelor replacing prasugrel as the recommended P2Y12-receptor inhibitor therapy, given its survival benefits observed in PLATO[131]. However, there are no available RCTs comparing clinical outcomes of patients treated with ticagrelor and prasugrel. The PRAGUE-18 trial comparing these agents was terminated early due to

futility, and the ISAR-REACT trial is ongoing[132,133]. Therefore, there are little available data to guide clinicians when it comes to choosing between prasugrel and ticagrelor.

1.4.3.2. Literature review strategy

Literature search of studies published between 2000 and 2016 was conducted in September 2016, and then repeated in July 2017 to include studies published in 2017. The following search was undertaken in Pubmed: (((((((((antiplatelet$) OR P2Y12) OR Prasugrel) OR Ticagrelor) OR Clopidogrel)) AND myocardial infarction) AND ((((primary percutaneous coronary intervention) OR primary angioplasty) OR emergency angioplasty) OR percutaneous coronary intervention))) AND ((((((outcome) OR mortality) OR survival) OR death) OR reinfarction$) OR event$), returning 2071 results. Review of titles of these studies, followed by abstracts if the titles included the following terms: ((ticagrelor or prasugrel or clopidogrel or P2Y12) and (myocardial infarction and/or percutaneous coronary intervention and/or angioplasty)), were undertaken, returning 8 studies that were determined to be relevant to this study (published in English, in full-text, which included patients undergoing PPCI for STEMI).

1.4.3.2.1. Review of relevant studies

The TRITON TIMI 38 trial published in 2007 assessed the efficacy of prasugrel in comparison with clopidogrel in 13608 patients (prasugrel: n=6813; clopidogrel: n=6795) who presented between 2004 and 2007 with high-risk ACS[127]. Clopidogrel was at the time, following the publication of the COMMIT trial, the default P2Y12-receptor inhibitor used in acute coronary syndromes in conjunction with aspirin[134]. This study found that treatment with prasugrel in patients with acute coronary syndrome with scheduled PCI was associated with reduced ischaemic endpoints at 15 months, but not mortality. In their STEMI subgroup

analysis[128], amongst patients who underwent PPCI (n=2340) the composite endpoint of cardiovascular death, recurrent MI or stroke was lower at 30 days in patients receiving prasugrel (n=1152) compared to patients receiving clopidogrel (n=1188)(HR 0.53 (95% CI 0.34-0.81)). At 15 months, this was no longer statistically significant (HR 0.76 (95% CI 0.56-1.03)). However, the core group of patients who benefited from treatment with prasugrel were patients under 75 years of age with no prior history of cerebrovascular disease, who weighed ≥60kg[135]. Therefore, this left a two-drug prescription system, with patients aged 75 years and above or weighing <60kg prescribed clopidogrel, and others being prescribed prasugrel.

In 2009, the PLATO investigators published their study comparing ticagrelor with clopidogrel in 18624 patients (ticagrelor: n=9333; clopidogrel: n=9291) recruited between 2006 and 2008, concluding that ticagrelor was associated with reduction in the composite endpoint of vascular death, recurrent MI or stroke (HR 0.84 (95% CI 0.77–0.92)), and importantly, a reduction in all-cause mortality (HR 0.78 (95% CI 0.69–0.89)) compared to clopidogrel, with no significant difference in TIMI-major bleeding (HR 1.03 (95% CI 0.93–1.15))[136]. The incidence of fatal intracranial bleeding in patients treated with ticagrelor was however, ten-fold (0.1% vs 0.01%; p=0.02) compared to clopidogrel. They then published their STEMI subgroup analysis in 2010 (total n=7544; ticagrelor: n=3752; clopidogrel: n=3792), concluding that ticagrelor was associated with lower composite of cardiovascular death, MI and stroke (HR 0.85 (95% CI 0.74-0.97)) and all-cause mortality (HR 0.82 (95% CI 0.67-1.00)). Recurrent MI was also lower in patients receiving ticagrelor (HR 0.80 (95% CI 0.65–0.98)). However, the risk of stroke was higher in patients receiving ticagrelor (HR 1.63 (95% CI 1.07–2.48)).

In 2014, Koshy et al published their observational analysis of 1688 patients (prasugrel: n=822; clopidogrel: n=866) who underwent PPCI for STEMI between 2008 and 2009 in Newcastle, UK[137]. Although the difference in unadjusted 12-month mortality was not statistically significant, adjusted all-cause mortality was lower in patients receiving prasugrel (HR 0.472 (95% CI 0.253–0.881)). In their cohort of patients, potentially due to the temporal trends in the use of prasugrel in comparison with clopidogrel, transradial PPCI was significantly higher in the prasugrel group (78% vs 61.4%; p<0.001). As described in previous sections, transradial PPCI is independently associated with lower short and long-term mortality, as well as bleeding, compared to transfemoral PPCI. Crucially in this study, arterial access site was not included in their Cox regression analysis and thus, could have significantly confounded their findings.

Serebruany et al then published their meta-analysis of 10 RCTs and one retrospective registry, with a total of 26658 patients with STEMI (ticagrelor: n=3719; prasugrel: n=2591; clopidogrel: n=6892) included in their analysis[138]. They found in their analysis of pooled data, prasugrel (OR 0.63 (95% CI 0.46-0.86)) was associated with lower 30-day cardiovascular mortality compared to clopidogrel, ticagrelor was not (OR 0.94 (95% CI 0.76-1.17)). The main limitation in this study is that all-cause mortality was not assessed. Whilst 10 out of the 11 sources of data were RCT data, the remaining source was the observational study by Koshy et al, which as described in the previous paragraph, could have a significant unadjusted confounding factor, transradial PPCI. Importantly, only two of the 10 RCTs they identified involved direct comparisons between two oral P2Y12-receptor inhibitors, the PLATO and TRITON-TIMI 38 trials that have been both critically appraised in this review.

The first study comparing ticagrelor with prasugrel was presented by Larmore et al, who had assessed 30-day clinical outcomes of 5322 propensity-matched patients (prasugrel: n=2661; ticagrelor: n=2661) who were admitted to a single centre in USA between 2011 and 2013 with ACS and managed by PCI, of whom approximately 40% underwent PPCI for STEMI[139]. Thirty-day MACE (composite of all-cause mortality and cardiovascular events) was significantly lower in patients treated with prasugrel (RR 0.80 (95% CI 0.64-0.98)), as was recurrent MI (0.39 (95% CI 0.21–0.75)) and bleeding (0.65 (95% CI 0.45–0.95)). At 90 days, reduction in recurrent MI, but not other endpoints, was still statistically significant in patients treated with prasugrel (RR 0.53 (95% CI 0.34–0.81)). There were significant limitations with this study. The number of patients in each group with cardiogenic shock and/or cardiac arrest were not presented. Temporal trends in the use of ticagrelor and prasugrel were not presented, and neither were arterial access site choice in each group. Propensity matching was undertaken based on baseline characteristics, and other differences, such as GPI use, concomitant use of clopidogrel and bivalirudin, all of which were higher in the ticagrelor group, were not matched or adjusted for. Outcomes specific to patients undergoing PPCI, where the use of prasugrel has been shown to be most beneficial (in comparison with clopidogrel), were not presented.

In 2016, results from the PRAGUE-18 study was published, having terminated early due to interim analysis suggesting futility[132]. This was the first RCT to attempt to compare clinical outcomes (composite of mortality, recurrent MI, urgent target vessel revascularisation, stroke, or major bleeding) in patients treated with prasugrel with those treated with ticagrelor. Initial power calculations suggesting a sample size of 1250 patients in each arm to show a difference of 2.5% with a two-sided alpha of 0.05 and a statistical power of 80%. However, interim analysis after recruitment of 1230 patients suggested no significant

difference in outcomes in patients treated with prasugrel compared to ticagrelor (OR 0.98 (95% CI 0.55-1.73)) at 30 days. This led to the decision of the study group to terminate the study early, suggesting that a much larger study may be required to assess this in a trial.

In 2017, Gosling et al published 12-month mortality and stent thrombosis of 3920 patients (prasugrel: n=1136; clopidogrel: n=1130; ticagrelor: n=1654) who had undergone PPCI for STEMI in Sheffield, UK between 2009 and 2015[140]. They found that adjusted 12-month mortality was lower with both ticagrelor (HR 0.70 (95% CI 0.61-0.99)) and prasugrel (95% CI 0.65 (0.48-0.89)) compared to clopidogrel. No significant difference was observed with prasugrel (HR 0.81 (95% CI 0.61-1.10)) compared to ticagrelor. The variables included in their Cox regression model for STEMI patients were not described. Importantly, choice of arterial access site in each subgroup were not presented or adjusted for, and no attempts were made to adjust for potentially unidentified confounders as a result of a significant temporal trend in the choice of P2Y12-receptor inhibitor therapy.

The most recent relevant study was published by Vercellino et al in 2017, which included 401 patients (ticagrelor: n=142; clopidogrel: n=259) presenting with STEMI between 2011 and 2013 in Sanremo, Italy[141]. Their main positive finding was that ticagrelor was independently associated with lower 12-month mortality after propensity scoring (HR 0.29 (95% CI 0.08–0.99)) compared to clopidogrel. This was the only study amongst the studies identified that had employed propensity scoring analysis, rather than Cox regression or logistic regression analysis. Although they found numerical differences in baseline characteristics, most of these did not reach statistical significance, probably due to the small number of patients studied. Nevertheless, their finding was not particularly controversial, considering its alignment with the PLATO sub-study finding.

Table 1.3: Summary of studies examining the association between P2Y12 receptor inhibitors and outcomes in PPCI.

Authors	Study design	Country	Data-collection years	Number	Clopidogrel	Prasugrel	Ticagrelor	Comparison	Analysis	Endpoints	Findings
TRITON TIMI 38 investigators[127]	RCT[a]	Multi-centre	2004-2007	2340	1188	1152	-	Clopidogrel vs prasugrel	RCT	30-day and 15 month composite endpoints and bleeding	Composite endpoints were lower with prasugrel at 30 days (HR[b] 0.53 (95% CI[f] 0.34-0.81)) but not at 15 months. Bleeding not significantly different.
PLATO investigators[136]	RCT	Multi-centre	2006-2008	7544	3792	-	3752	Clopidogrel vs Ticagrelor	RCT	12-month composite endpoints and bleeding	Composite endpoints lower with ticagrelor (HR 0.85 (95% CI 0.74-0.97)). All-cause mortality lower (HR 0.82 (95% CI 0.67-1.00)). Recurrent MI[c] lower ((HR 0.80 (95% CI 0.65–0.98)).
Koshy et al[137]	Observational	UK	2008-2009	1688	866	822	-	Prasugrel vs Clopidogrel	Cox regression	12-month mortality	Adjusted mortality lower with prasugrel (HR 0.472 (95% CI 0.253–0.881)).
Serebruany et al[138]	Meta analysis	Multi-centre	Multiple studies	26658	6892	2591	3719	Prasugrel vs clopidogrel Ticagrelor vs clopidogrel	Cochran–Mantel–Haenszel	30-day cardiovascular mortality	Prasugrel was associated with lower 30-day cardiovascular mortality compared to clopidogrel (OR[d] 0.63 (95% CI 0.46-0.86)). Ticagrelor was not associated with lower mortality compared to clopidogrel.
Larmore et al[139]	Observational	USA	2011-2013	5322	-	2661	2661	Prasugrel vs ticagrelor	Propensity matching	30-day and 90-day composite events, and bleeding (not according to TIMI/HORIZONS/BARC)	30-day MACE[e] (RR 0.80 (95% CI 0.64-0.98)), recurrent MI (0.39 (95% CI 0.21–0.75)) and bleeding (0.65 (95% CI 0.45–0.95)) were lower with prasugrel. 90-day MI lower with prasugrel (RR 0.53 (95% CI 0.34–0.81)).
PRAGUE-18 investigators[132]	Open-label trial	Multi-centre	2013-2016	1230	-	634	596	Prasugrel vs ticagrelor	Open label randomised trial.	30-day composite endpoints	30-day composite endpoint in prasugrel was not statistically significantly different compared to ticagrelor (OR 0.98 (95% CI 0.55-1.73))
Gosling et al[140]	Observational	UK	2009-2015	3920	1130	1136	1654	Clopidogrel vs prasugrel Clopidogrel vs ticagrelor Prasugrel vs ticagrelor	Cox regression	12-month mortality and stent thrombosis	12-month mortality lower with ticagrelor (HR 0.70 (95% CI 0.61-0.99)) and prasugrel (HR 0.65 (95% CI 0.48-0.89)) compared to clopidogrel. No significant difference between prasugrel and ticagrelor (HR 0.81 (95% CI 0.61-1.10)).
Vercellino et al[141]	Observational	Italy	2011-2013	401	259	-	142	Clopidogrel vs ticagrelor	Propensity scoring	12-month mortality	12-month mortality lower with ticagrelor (HR 0.29 (95% CI 0.08–0.99)) compared to clopidogrel.

[a]RCT: Randomised controlled trial; [b]HR: Hazard ratio; [c]MI: Myocardial infarction; [d]OR: Odds ratio; [e]MACE: Major adverse cardiovascular event;

[f]Confidence interval.

1.4.3.3. Conclusion

The studies identified in the literature review included a mix of established RCTs and observational studies. One study was a meta-analysis of two of the RCTs included in this review, and one of the observational studies. For the observational studies, the analyses used were varied as well, with two using Cox regression, one using propensity matching and one using a relatively less frequently-used propensity scoring analysis.

All studies had shown that the third-generation P2Y12-receptor inhibitors were associated with lower ischaemic events compared to clopidogrel, at both 30 days and at 12 months with no significant increase in the risk of bleeding in the newer agents. Twelve-month mortality was also shown to be lower in ticagrelor and prasugrel compared to clopidogrel by Koshy et al and Gosling et al. The only head-to-head comparison of ticagrelor and prasugrel specifically in STEMI by Gosling et al failed to show a difference in mortality between the two newer drugs. One study that had shown a difference was not specific for STEMI, and therefore its relevance to PPCI remains unclear.

The observational studies all had limitations. Besides the study by Vercellino et al, none of the other studies had presented or adjusted for arterial access site differences, and none of them addressed the potential confounding factor which is time, as choice of P2Y12 receptor inhibitor in all the observational studies were subject to significant temporal trends. Changes over the period of time of recruitment for these observational registries could have included rates of implantation of DES and its generation, aspiration thrombectomy, procedural anticoagulant, and differences in secondary prevention, including primary prevention implantable cardioverter-defibrillator devices (ICD)[142]. However, adjustment for year of admission was not undertaken in any of these studies, and therefore, results quoted

in these studies, where a temporal trend was significant, could have been confounded by other unidentified factors. Another important limitation is the inability to determine switching between P2Y12-receptor inhibitors within the timelines specified for clinical endpoints. Most analyses were conducted based on either procedural or discharge P2Y12-receptor inhibitor and yet in PLATO, premature discontinuation of study drugs occurred over 20% of patients[136]. Therefore, discontinuation or switching between drugs could have occurred over the specified time period, possibly due to adverse events including bleeding that might not have been accounted for.

As at present there are no available real-world studies assessing clinical outcomes according to P2Y12-receptor inhibitor therapy, adjusting for temporal changes in practice and technique, and also importantly, adjusting for choice of arterial access site, the association between P2Y12-receptor inhibitor therapy and clinical outcomes in STEMI warrants re-evaluation.

1.4.4. Individual operator PPCI volume

1.4.4.1. Background

Individual operator volumes in PCI for all indications have previously been shown to be independently and directly associated with survival in numerous studies[143–148]. However, studies examining individual operator volumes of PPCI for STEMI are limited. PPCI for STEMI can be associated with significant challenges, such as recurrent cardiac arrest, active coronary ischaemia, cardiogenic shock, thrombus, acute pulmonary oedema as well as the ability of an operator to perform at a high level in the middle of the night, when PPCI is undertaken on a 24/7 basis. Published studies pre-date the contemporary era of PPCI which is signified by high proportions of transradial PPCI and use of DES. These studies had also assessed only in-hospital outcomes, rather than 30-day or 12-month clinical outcomes. The American Heart Association (AHA) has recommended a minimum operator volume of 11 PPCI per year to maintain procedural standards, based on a single study of the New York PCI registry which analysed outcomes of patients presenting between the years 2000 and 2002[148,149]. Therefore, the relevance of the cut-off of 11 PPCI per year when there has been evidence of a significant temporal trend in the uptake of PPCI, and advances in both procedural technique, technology and pharmacotherapy (all of which were previously described), between 2002 and the current time, is debatable and one which should be re-examined. At present, there are no published data available to assess the association between individual operator annual PPCI volume and 30-day and 12-month mortality in the contemporary era of PPCI.

1.4.4.2. Literature review strategy

Literature search using the PubMed database was undertaken in April 2017, and then repeated in July 2017 to retrieve all relevant studies published between 2000 and 2017. The following search term was used: (((((((operator$) OR physician$) OR interventionist$) OR cardiologist$)) AND (((volume$) OR experience) OR number$)) AND (((primary percutaneous coronary intervention$) OR primary angioplasty) OR emergency angioplasty)) AND ((((((ST segment elevation myocardial infarction$) OR ST elevation myocardial infarction$) OR myocardial infarction$) OR ST segment elevation acute coronary syndrome$) OR ST elevation acute coronary syndrome$)); returning 196 results. Review of titles of these studies, followed by abstracts if the titles included the following terms: (volume OR number OR experience) and (myocardial infarction and/or percutaneous coronary intervention and/or angioplasty), were undertaken. Only two studies analysing outcomes according to annual operator PPCI volume were identified.

1.4.4.2.1. Review of relevant studies

The first of the two relevant studies was undertaken by Vakili et al, who in 2001 published their analysis of 1342 patients who had undergone PPCI in New York, USA in 1995[144]. They divided operator volumes into tertiles (Tertile 1: 1-2 PPCI/year who had performed 65 PPCIs in total; Tertile 2: 2-10 PPCI/year who had performed 300 PPCIs in total; Tertile 3: ≥11 PPCI per year who had performed 977 PPCIs in total). They had combined tertile 1 and 2 to define low-volume operators. The remaining operators (tertile 3) were defined as high-volume operators. They found that PPCI undertaken by high-volume operators in high-volume centres (≥57 PPCI/year) was independently associated with lower in-hospital mortality compared to PPCI performed by low-volume operators in low-volume centres (OR

0.51 (95% CI 0.26-0.99)). The overall comparison of in-hospital mortality of PPCI performed by high-volume operator with low-volume operators (regardless of institutional volume) showed that high operator-volume was independently associated with lower in-hospital mortality (OR 0.43 (95% CI 0.21–0.83)). This was an important study that informed the aforementioned AHA Guideline. However, the relevance of this study in this day and age is unclear. As described in previous sections, the uptake of PPCI, the techniques (transradial PPCI), technology (aspiration thrombectomy, DES, use of intravascular imaging, use of adjunct devices such as Guideliner) and the evolution of secondary prevention (DAPT, ICD) since 1995 has been significant. In essence, although this was an important study at the time in suggesting optimal operator volumes in PPCI, the applicability of the volumes used to define high-volume operators and low-volume operators especially in England and Wales where at present, >90% of patients with a first diagnosis of STEMI are treated with PPCI, is debatable, as those volumes were derived at a time when PPCI was not yet the standard of care for patients with STEMI, and therefore, numbers were likely to be low compared to current time.

The more recent analysis by Srinivas et al, who had analysed in-hospital mortality of 7321 patients undergoing PPCI between 2000 and 2002 in New York had once again suggested a volume-outcome relationship between annual operator PPCI volume and in-hospital mortality[148]. They had found that PPCI performed by operators who undertook >10PPCI per year (as per AHA Guidelines) was independently associated with lower in-hospital mortality than PPCI performed by operators who undertook ≤10 PPCI per year (OR 0.66 (95% CI 0.48-0.92)). When the threshold was increased to >20 PPCI per year, high operator-volume was still independently associated with in-hospital mortality compared to low operator-volume (OR 0.63 (95% CI 0.44–0.91)). No difference was observed at a threshold of 30PPCI per year.

This study reaffirmed the findings of Vakili et al that an operator volume-outcome relationship specific to PPCI exists, and once again, the patients included in this study underwent PPCI in an era when PPCI was not necessarily the standard of care, prior to the landmark analysis by Keeley et al in 2003 confirming the superiority of PPCI over intravenous fibrinolysis. It was also almost a decade prior to the national rollout of PPCI in the UK, before the era of transradial PPCI, DES and newer P2Y12-receptor inhibitors and thus, once again, the applicability of these operator volumes are debatable.

Table 1.4: Summary of studies examining the association between individual operator PPCI volumes and outcomes.

Authors	Study design	Country	Data-collection years	Number	Analysis	Endpoints	Findings
Vakili et al[144]	Observational	USA	1995	1342	Logistic regression	In-hospital mortality	High operator volume (>10PPCI[a]/year) was independently associated with lower in-hospital mortality (OR[b] 0.43 (95% CI 0.21–0.83)).
Srinivas et al[148]	Observational	USA	2000-2002	7321	Logistic regression	In-hospital mortality	Operator volume of >10 PPCI/year was associated with lower in hospital mortality (OR 0.66 (95% CI 0.48-0.92)) compared to operator volume of ≤10 PPCI/year. Operator volume of >20 PPCI/year was associated with lower in-hospital mortality compared to operator volume of ≤20 PPCI/year (OR 0.63 (95% CI 0.44–0.91)).

[a]PPCI: Primary percutaneous coronary intervention; [b]OR: Odds ratio.

1.4.4.3. Conclusion

The current AHA Guideline pertaining to annual operator PPCI volume is informed by only two studies, both from New York, and both prior to the acceptance of PPCI as the standard of care for STEMI. Both studies were observational studies, as is expected for this specific question of operator volumes and outcomes. Both studies utilised logistic regression analysis. Both studies confirmed and operator-volume-outcome relationship specific to PPCI, which had not been reported prior to that, and has not been reported since, in USA or in Europe.

Whilst it is possible to ascertain individual operator PPCI volume and outcomes in larger databases in current time, no study has yet been published. The most recent study by Fanaroff et al examining the operator-volume-outcome relationship (not specific to PPCI) in patients undergoing PCI between 2009 and 2015 (from the NCDR database in USA) had shown that in STEMI (627501 patients), low annual PCI volume (<50 PCI/year) was associated with higher adjusted probability of in-hospital mortality compared to high annual PCI volume (>100 PCI/year) (OR 1.13 (95% CI 1.08–1.19))[150]. This study was relevant to current practice as it was conducted in the contemporary era of PCI, with 73.5% of patients receiving DES, albeit with only 15.2% of patients undergoing transradial PCI.

Hence, the association between individual operator annual volume of PPCI and clinical outcomes in contemporary PPCI is currently unknown, with current guideline-recommendations being based on data from an era of PPCI that may not necessarily reflect current practice and volumes, and therefore outcomes. This therefore warrants further examination with contemporary data.

1.4.5. Glycoprotein IIb/IIIa inhibitor therapy according to arterial access site

1.4.5.1. Background

The evolution from transfemoral PPCI to transradial PPCI has revolutionised PPCI technique and technology. The evidence-base for the use of transradial PCI over transfemoral PCI is extensive, with the benefit of transradial PCI proven in reducing key endpoints of mortality and bleeding. As previously described, there has been a gradual and steady temporal trend in the utilisation of the radial artery as the primary arterial access site for PCI in the UK. Although not objectively proven, it is possible that with the current practice of using the radial artery for access by default, and reverting to transfemoral access if transradial access is not possible, there may be an element of de-skilling in transfemoral PCI over time, especially in more junior operators who may not have necessarily performed as many transfemoral PCIs as their more senior counterparts due to the change in attitudes towards transfemoral PCI. This could in theory widen the gap between outcomes observed in patients undergoing transradial PCI compared to those undergoing transfemoral PCI. The impact of arterial access site is particularly significant in PPCI, as periprocedural pharmacological agents could further increase the possibility of bleeding, particularly access –site bleeding in transfemoral PPCI.

Glycoprotein IIb/IIIa-receptor inhibitor (GPI) therapy, especially abciximab, has been shown in RCTs to reduce re-infarction and target-vessel revascularisation[151]. However, none of these trials were conducted in the era of transradial PPCI, and none of the patients enrolled in these trials received third generation P2Y12-receptor inhibitor therapy.

What is currently not known is the association between GPI use and outcomes according to arterial access sites. It is possible that in the era of transradial PPCI, the use of GPI in

transfemoral PPCI may be associated with increased bleeding complications, particularly arterial access site bleeding. However, this has not been assessed in either trials or real-world data.

1.4.5.2. Literature review strategy

The search term "((((((primary percutaneous coronary intervention$) OR primary angioplasty) OR emergency angioplasty)) AND ((((((ST segment elevation myocardial infarction$) OR ST elevation myocardial infarction$) OR myocardial infarction$) OR ST segment elevation acute coronary syndrome$) OR ST elevation acute coronary syndrome$))) AND ((((glycoprotein) OR abciximab) OR tirofiban) OR eptifibatide)) AND (((mortality) OR death) OR bleeding)" of studies between 2000 and 2017 returned 956 results in July 2017. Review of the titles of these studies, followed by abstracts if the titles included the following terms: (glycoprotein or tirofiban or abciximab) and (myocardial infarction and/or percutaneous coronary intervention and/or angioplasty), returned 5 relevant studies (published in English, in full-text, which included patients undergoing PPCI for STEMI).

1.4.5.2.1. Review of relevant studies

The ADMIRAL study published in 2001 was a RCT that had randomised 300 patients between 1997 and 1998 to either abciximab or placebo in the setting of STEMI prior to coronary intervention (before arterial sheath insertion), and found that abciximab was associated lower incidence of the composite endpoint of mortality, re-infarction or urgent TLR at 30 days (RR 0.41 (95% CI 0.18–0.93)) and at 6 months (RR 0.46 (95% CI 0.22–0.93))[151]. Although TIMI-major bleeding was not statistically significantly higher in the abciximab group, there was an increased incidence of minor bleeding (RR 3.65 (95% CI 1.32–10.08)),

groin haematoma (RR 9.12 (95% CI 1.14–72.89)) and thrombocytopaenia (RR 3.55 (95% CI 0.72–17.35)) with the use of abciximab. This study was undertaken in the early days of PPCI, before it was routinely used as the primary method of reperfusion. All patients who were included in this study were also likely to have undergone transfemoral PPCI (access site not presented, presumably because this study predated the era of transradial PPCI), and therefore, there would not have been the element of de-skilling with transfemoral PPCI. This study was also conducted with patients receiving aspirin and ticlopidine, rather than the newer and more potent P2Y12-receptor inhibitors. There were also numerous exclusion criteria, such that the patients with the highest risk, such as unconscious patients following cardiac arrest or cardiogenic shock, or patients with cognitive difficulties (long-term due to dementia or temporary due to opiates) who were unable to provide written informed consent were excluded. Therefore, whilst this RCT supported the use of abciximab in PPCI, its applicability in the real-world remains under-examined.

The secondary analysis of the CADILLAC trial published in 2003, assessed the performance of abciximab in 2082 patients undergoing PPCI randomised to either abciximab (n=1052) or no abciximab (n=1030)[152]. Patients were randomised to either PTCA alone, PTCA + abciximab, stenting alone, or stenting + abciximab (the primary CADILLAC trial compared primary stenting against primary PTCA[153]). Both 30-day and 12-month endpoints were presented. Abciximab was associated with lower 30-day target vessel revascularisation (TVR) and stent thrombosis, with no significant difference observed at 12-months. There were no observed differences in 30-day and 120-month mortality. Patients in this study were likely to have undergone transfemoral PPCI (access site was not presented, likely because this study predated routine transradial PPCI). Only approximately 56% of patients received intracoronary stents, which were BMS rather than DES. In patients who received stents,

ischaemic TVR was 3.2% with stenting alone, and 1.6% with stenting + abciximab (P=0.004). Ticlopidine was given for 4 weeks in stented patients, and was optional for patients who underwent PTCA alone. Patients receiving abciximab were designated to either "low-risk" group, or "high-risk" group, and had potentially longer in-hospital stay. Patients presenting with cardiogenic shock, vein graft occlusion, vessel <2.5mm in diameter, lesion >64mm in length or those needing urgent CABG were excluded from this trial. The main findings of this study could be difficult to replicate in current practice. Higher proportion of stenting, the use of DES, longer periods of DAPT with more potent P2Y12-receptor inhibitor therapy, and other improvements in secondary prevention could all reduce TVR following PPCI, and thus, in current practice in the real-world, these differences may not be observed.

Most recently, the BRAVE-3 trial compared abciximab with placebo in 800 patients undergoing PPCI between 2003 and 2008. No significant difference in mortality, infarct size or major bleeding was observed between the two groups, suggesting that with adequate P2Y12-loading, the effect of abciximab may not necessarily reflect CADILLAC or ADMIRAL[154]. All patients in this study received clopidogrel, for a minimum of 30 days following index event. Maintenance dose of aspirin was 200mg/day. Only 44% of patients received DES. Arterial access site were not specified. Considering their recruitment period, it is possible that patients could have undergone either transfemoral or transradial PPCI, and if this was not adjusted for, it could have confounded their analysis. The exclusion criteria were extensive: fibrinolytic therapy, bleeding diathesis or bleeding, previous cerebrovascular accident (CVA), major surgery or trauma within one month of index event, oral anticoagulant therapy within 7 days of PPCI, use of GPI within 14 days of PPCI, systolic blood pressure exceeding 180mmHg resistant to therapy, haematological abnormalities, cardiogenic shock, prolonged cardiopulmonary resuscitation (CPR – and thus, possibly a

significant proportion of ventilated patients), age >80 or <18, known or suspected pregnancy and allergy to study drugs; essentially excluding patients at the highest risk of adverse events following PPCI. The important finding of this study was that there was no significant difference in outcomes in patients receiving GPI, in comparison with CADILLAC and ADMIRAL, suggesting an attenuation in the effect of GPI in the presence of more potent P2Y12-receptor inhibitor therapy.

Real-world studies examining this association are limited. In 2006, Heer et al published their analysis of 2184 patients undergoing PPCI between 2000 and 2002 from the Acute Coronary Syndrome (ACOS) registry in Germany[155]. They found that treatment with abciximab (n=946) was associated with improved mid-term (median follow-up 375 days) survival compared to control (n=1238) (HR 0.65 (95% CI 0.49-0.95)). Increased bleeding was noted in patients >75 years of age. Interestingly, in-hospital mortality was not significantly different, and the Kaplan-Meier curves were essentially identical for the first 30-days, diverging thereafter. Therefore, it is unlikely that differences observed in survival were due to abciximab. Patients who received abciximab were more likely to receive aspirin (95% vs 89.3%; p<0.01) and clopidogrel (86.7% vs 75.4%; p<0.01) compared to control, suggesting that patients receiving abciximab were inherently "selected" based on lower bleeding risk, and that these secondary prevention differences could have contributed to differences in outcomes, especially the late divergence in survival.

Most recently, data of 2935 patients undergoing PPCI in Copenhagen, Denmark between 2003 and 2008 were published, showing that the use of GPI (n=1193) was associated with improved mortality in patients with complex lesions (HR 0.62 (95% CI 0.42-0.91))[156]. However, GPI was associated with increased mortality in patients with simple lesions (HR

1.72 (95% CI 1.14-2.58)). Arterial access site were not presented or corrected for in their analysis, and it is possible that some of their patients, especially in the latter years of recruitment, underwent transradial PPCI. However, importantly, in contrast with RCTs, they found that GPI was not beneficial to all patients who underwent PPCI and that certain patients (in this study, those with simple lesions) had worse outcomes with GPI.

Table 1.5: Summary of studies examining the association between GPI-use and outcomes.

Authors	Study design	Country	Data-collection years	Number	GPI used	Access site	P2Y12-receptor inhibitor	Analysis	Endpoints	Findings
ADMIRAL investigators [151]	RCT[a]	France	1997-1998	300	Abciximab	Not described	Ticlopidine for 30 days	RCT	Death, MI[b], TLR[c]	Composite endpoints reduced with abciximab at 30 days and 6 months.
CADILLAC investigators [152]	RCT	Multicentre	1997-1999	2082	Abciximab	Not described	Ticlopidine for 4 weeks if stented	RCT	Death, MI, stroke, TVR[d]	Reduced composite endpoints driven by reduced TVR.
BRAVE investigators [154]	RCT	Germany	2003-2008	800	Abciximab	Not described	Clopidogrel for a minimum of 30 days	RCT	Death, MI, IRA[e] revascularisation	No reduction in efficacy endpoints. Significant thrombocytopaenia with abciximab
Heer et al[155]	Observational	Germany	2000-2002	2184	Abciximab	Not described	Clopidogrel	Cox regression	Mid-term mortality (median 375 days)	Lower mortality with abciximab but survival curves only diverge after 30-days, indicating other mechanisms/factors.
Iversen et al[156]	Observational	Denmark	2003-2008	2935	Abciximab	Not described	Clopidogrel	Cox regression	12-month mortality	Abciximab associated with lower mortality in patients with complex lesions, but higher mortality in patients with simple lesions

[a]RCT: Randomised controlled trial; [b]MI: Myocardial infarction; [c]TLR: Target lesion revascularisation; [d]TVR: Target vessel revascularisation; [e]IRA: Infarct-related artery.

1.4.5.3. Conclusions

The landmark RCTs that showed potential benefit in the use of GPI were conducted with abciximab. The main studies, ADMIRAL and CADILLAC, were both most likely conducted on patients undergoing transfemoral PPCI. In these studies, choice of P2Y12-receptor inhibitor therapy (ticlopidine) and its duration (30 days) and type of stent (BMS) were at the time, contemporary. However, with the evolution of P2Y12-receptor inhibitors, and its duration of use following MI, and the increase in the use of DES, especially newer generation DES, the main endpoints that were reduced in these studies, reduced TLR and reduced TVR, may not be relevant in current practice.

There has been a gradual shift away from transfemoral PPCI, as evidenced by the National Institute of Cardiovascular Outcomes Research (NICOR) report in 2014[157]. In their report, in 2014, only approximately 25% of PPCIs were performed via the femoral artery. It is very likely that this has reduced further over the following years as multiple studies have, as previously described, shown a benefit in transradial PPCI over transfemoral PPCI with reduction in access site or retroperitoneal bleeding and mortality (possibly secondary to the reduction in bleeding).

In this age of transradial PPCI, it is possible that when transfemoral PPCI is undertaken, the risk of access site bleeding could be significant, especially with the use of more potent P2Y12-receptor inhibitors. This could further be compounded by possible de-skilling in transfemoral PPCI, especially amongst more junior operators, who unlike their more senior colleagues, may not have undertaken significant volumes of transfemoral PPCI or even transfemoral PCI. This could potentially lead to increased complications due to lack of familiarity and technique. In this circumstance, using GPI, especially when its use with more

potent P2Y12-receptor inhibitors has been shown to be of no significant benefit, could lead to increased bleeding complications, particularly access site bleeding. The association between the real-world use of GPI and access site bleeding, specifically in transfemoral PPCI, requires further examination.

1.5. Hypothesis

The hypothesis of this study was that retrospective analysis of a bespoke regional registry of consecutive patients undergoing PPCI in a single tertiary referral centre would enable analyses of variables associated with outcomes beyond what is typically available from the interrogation of larger national datasets.

1.6. Aims

The aim of this study was to identify patient, systemic, and treatment variables associated with clinical outcomes in contemporary PPCI.

The first patient characteristic investigated was the association between gender and outcomes following PPCI. This is because the association between gender and outcomes in PPCI continues to be reported with differing results and conclusions. The second patient characteristic investigated was the association between the South Asian ethnicity and outcomes following PPCI. This is because data analysing this association in contemporary PPCI are significantly limited in the number of studies and the era in which the studies were undertaken.

The systemic variable investigated in this study was the association between annual operator PPCI volume and outcomes. This is because the current AHA recommendation that individual operators undertake >10 PPCI per year was based on two non-contemporary

studies in the USA. The association between total PCI volumes and outcomes as well as institutional volumes and outcomes have been reported in contemporary studies.

The first treatment variable investigated was the association between oral P2Y12-receptor inhibitor and outcomes in contemporary PPCI. As described in the literature review, there are little available data to facilitate the comparison of prasugrel with ticagrelor in PPCI. The second treatment variable investigation was the use of GPI according to arterial access site. This is because studies that inform the guideline recommendations were undertaken prior to the routine use of transradial PPCI and third-generation P2Y12-receptor inhibitors. It was therefore possible that in the current era, the use of GPI may not reflect the findings of the early studies that had shown a benefit.

Chapter 2: Methods

2.1. The West Yorkshire PPCI Outcome Study

The West Yorkshire PPCI Outcome Study was set up as a prospective, observational study to ascertain procedural and demographic characteristics, and clinical outcomes in all patients undergoing PPCI for STEMI at Leeds General Infirmary (LGI), United Kingdom. LGI is the largest regional single-centre PPCI centre by volume in the UK, providing a 24/7 PPCI service to a catchment population of 3.2 million people, achieving 100% population coverage, according to NICOR[158]. The period of recruitment was 1st of January 2009 until 31st of December 2011, and 1st of January 2013 until 31st of December 2013 (4 calendar years). Patients who presented for PPCI between 1st of January 2012 and 31st of December 2012 were excluded from this registry, as limited research staff availability did not allow for patient follow-up and data input in 2012. UK National Research Ethics Service approval (0911-11311/60) and NHS institutional approvals from each hospital within the West Yorkshire region were obtained prior to commencement of this registry (Appendix).

2.2 Patient selection

All patients who presented to the cardiac catheter laboratory at LGI for PPCI for STEMI (diagnosed according to standard criteria - with chest pain consistent with myocardial ischaemia for a minimum of 20 minutes with ST-segment elevation of ≥1mm in contiguous limb leads and/or ≥2mm in contiguous chest leads, or with presumed new left bundle-branch block on a 12-lead electrocardiogram) within the specified recruitment period were included in this study. STEMI was usually diagnosed by paramedics in the pre-hospital setting, and when diagnosed patients were transferred directly to the cardiac catheter laboratory at LGI for treatment, with a telephone referral en-route[159]. In the event of cardiovascular instability due to ongoing or refractory cardiac arrest, the patients were taken to the nearest Emergency

Department for emergency treatment, and were transferred to LGI when they were determined to be stable for inter-hospital transfer. Upon arrival at the cardiac catheter laboratory, patients were handed over to either the cardiac catheter laboratory team which includes the interventionist undertaking the procedure, or to the Coronary Care Unit (CCU) team, if out-of-hours and the patient arrived at LGI before the cardiac catheter laboratory team. All ECGs of the patient, with time documented, and a written ambulance transfer sheet that included symptom-onset time, call-for-help time, time of paramedic's arrival at patient's location, vital observations of the patient, arrival time at LGI and emergency treatment received prior to arrival at hospital, were provided to the cardiac catheter laboratory team. Informed consent was then obtained from patients for PPCI, either in written or verbal format. In patients who were unable to provide informed consent for any reason, PPCI was undertaken based on their best interest.

2.3 Treatment

Emergency diagnostic coronary angiography with (if indicated) follow-on PPCI was undertaken if patients presented within 12 hours of symptom-onset. Oral aspirin 300mg was typically given in the pre-hospital setting at the point of first medical contact, and either 600mg clopidogrel, 60mg prasugrel or 180mg oral ticagrelor were administered upon arrival at the cardiac catheter laboratory, depending on guideline recommendations at the time of index PPCI[131,160,161]. Either bivalirudin or unfractionated heparin (± bail-out glycoprotein IIb/IIIa antagonist) were administered during PPCI. Arterial access site, decision to implant stents and the choice of stent (DES or BMS) and aspiration or mechanical thrombectomy, insertion of intra-aortic balloon pump (IABP) or temporary pacing wires were performed according to the operator's experience and discretion based on the clinical condition of the

patient, informed by guideline recommendations. Thrombolysis in Myocardial Infarction (TIMI) classification was used to grade pre-procedure and post-procedure flow in the IRA. Call-for-help time (call time) and time of patient arrival at LGI (door time) were obtained from ambulance reports, if patients were admitted by ambulance. Emergency Department triage notes were used to ascertain call time and door time if patients self-presented. Time of first interventional device (balloon time) was obtained from the electronic cardiac catheter laboratory report (as part of the national audit dataset). From these recorded times, call-to-balloon (CTB) and door-to-balloon (DTB) times were ascertained. Patients were typically observed on CCU post-PPCI for a minimum of 24 hours, and remained in hospital for a minimum of 72 hours post-PPCI. Patients whose local hospitals were not LGI were observed on CCU at LGI for a minimum of 6 hours post-PPCI, after which they were transferred to their local CCU depending on availability of beds. Dual antiplatelet therapy (DAPT) for 12 months followed by indefinite aspirin monotherapy, statin therapy, beta-adrenergic receptor blockers, Angiotensin-converting enzyme inhibitors (or angiotensin II receptor blockers) and (if indicated) mineralo-corticoid receptor antagonists were prescribed according to guideline recommendations at the time. Primary prevention ICDs were implanted according to guideline recommendations at the time of admission.

2.4 Data collection and follow up strategy

Data were initially recorded in a bespoke Microsoft Access-developed interface. This was later replaced with a custom-built web interface built in ASP.net, with a Microsoft SQL backend. All data are held in Leeds Teaching Hospitals NHS Trust, on a central SQL cluster that is managed by the Trust IT services. Individuals with access to the database were: the data manager (employed by Leeds Teaching Hospitals NHS Trust), the Principal Investigators, research nurses involved in data collection, administration support team, and Fellows involved in data analysis and publication. The database was populated via manual data input, with the option of importing relevant data directly from the Trust's BCIS and MINAP modules. Data were then downloaded in .xslx format, for access in Microsoft Excel and statistical packages.

Written and electronic case notes were reviewed at the time of discharge to ascertain patient characteristics, procedural variables, and in-hospital outcomes. Where possible, patient information leaflets were provided to patients either prior to discharge from LGI or prior to repatriation to their local hospital (Appendix 1). Drug therapy and adverse events were identified up to 12 months following index PPCI by a combination of patient telephone contact, accessing clinical information via written or electronic hospital records, or from the responsible Primary Care physician. In patients whose local hospital was LGI, this was done in Leeds. For patients whose local hospitals were other regional hospitals (Calderdale Royal Hospital, Airedale General Hospital, Huddersfield Royal Infirmary, Bradford Royal Infirmary, Mid-Yorkshire Hospitals NHS Trust (comprising of Pinderfields General Hospital and Dewsbury District Hospital), York Hospital and Harrogate and District Hospital), departmental and Research and Development clearance was obtained by research nurses

(KS and NBW) to work on-site at those hospitals to extract relevant data. Mortality data up to a minimum of 12 months post-PPCI were obtained from the Office of National Statistics and central NHS records. The Myocardial Infarction National Audit Project (MINAP) database was used to identify MIs. Review of hospital discharge and clinic letters, and hospital electronic pathology servers for rises in Creatinine Kinase and/or Troponin were undertaken to verify MIs. Identification of repeat coronary revascularisation procedures up to a minimum of 12 months post-PPCI was undertaken by reviewing all regional cardiac catheter laboratory databases and the cardiothoracic surgical database at LGI (which was the tertiary referral centre for CABG in West Yorkshire). Data adjudication was undertaken by blinded clinicians in consensus, to verify logged outcome events at 30 days and at 12 months. Data-checking and validation was undertaken to ensure accuracy and validity of values obtained, and summary statistics were generated.

2.5. Why use local registry data?

Registry data are important sources of information for both performance assessment and for research purposes. Whilst RCT data are useful is assessing the efficacy of a particular treatment in any given population, the stringent inclusion and exclusion criteria usually associated with RCTs mean that a substantial proportion of patients are excluded from analyses. Usually, these are the sickest patients with the most adverse pre-morbid status. As a result, translating the findings of RCTs into clinical practice on a day-to-day basis can be tricky, as in the real-world, when such treatments are reassessed for efficacy and safety, they are not always achievable.

This is where data from “all-comers” registry can be useful. There are usually no selection criteria for inclusion in registry, besides the very purpose of the registry. Important data

have been derived in the past from registries. The Swedish Coronary Angiogram and Angioplasty Register (SCAAR) for instance had facilitated a RCT with a registry-based follow-up for the TASTE study which provided an interesting perspective about thrombus aspiration[46].

Registry interrogation also allows for the examination of a particular factor on a broader population than that of a RCT. This is usually seen when RCT demographics are compared to real-world registries. An example of this is the comparison of baseline characteristics of HORIZONS-AMI, which was a multicentre RCT with multiple exclusion criteria, some of which would have excluded the patients with the highest bleeding risk[162]. In comparison, HEAT-PPCI, which was a RCT, but randomised in an "all-comers" manner, revealed a completely different result, when bivalirudin was compared to heparin[163]. Patients in HORIZONS (median age 60 years) were significantly younger than the patients in the UK presenting with STEMI, which according to MINAP data, were 64 years old at presentation[164]. This has subsequently lead to the re-evaluation of the use of Bivalirudin in PPCI, which according to the most recent publication by Brogan et al, was only 13%[56].

In addition to this, some factors can only be determined from registry data. Factors such as institutional PPCI volumes, operator PPCI volumes, factors associated with centres such as the number of cardiologists and the provision of a 24/7 service, and the association between bleeding or renal failure with outcomes have all been determined with observational data from registries, as these are factors that cannot be assessed using clinical trials. With adequate statistical advice and analyses, important analyses can be undertaken using registry data.

This was the reason that the West-Yorkshire Primary Percutaneous Coronary Intervention Outcome Study was set up; to prospectively collect data that could be used to assess local

clinical outcomes against national and international outcomes, to assess markers of performance, and also to be able to determine novel factors that could be associated with outcomes in contemporary PPCI. In comparison with national databases such as the BCIS or MINAP database, the use of a regional registry (with the involvement of dedicated research nurses prospectively collecting outcome data beyond just mortality and in-hospital complications) facilitates the undertaking of more in-depth analyses that include 30-day bleeding, and 30-day and 12-month re-infarction and repeat coronary revascularisation procedures that would not be picked up with the use of nationally collected data.

2.6. Limitations of the WY-PPCI registry data

This observational study was undertaken in a single centre, and therefore the outcomes observed in this study may not reflect those observed in other regions or countries. Patients were unmatched in this observational study, but multivariable analysis was undertaken to adjust for potential confounders. Regional differences in the management of STEMI have been reported, despite the national framework for STEMI treatment. However, in England and Wales, at present time, >98% of patients with a first diagnosis of STEMI receive PPCI rather than thrombolysis or no treatment. Patients presenting with out-of-hospital cardiac arrest, who due to haemodynamic instability are taken to the nearest Emergency Department for emergency treatment, may not all be referred for PPCI as they may not have been determined as stable or suitable for transfer, and depending on clinical findings and the patient background, referrers may take a view of futility in some of this patients. This could have potentially introduced an element of bias to the population seen in this study, as theoretically, patients who were more unwell or unstable may never have been referred for PPCI. This could not be explored further in this study as the data for this were

unavailable. Killip class and left ventricular systolic function could not be corrected for in this study, as these data were not collected in the registry. However, as this is an "all-comers" registry, differences in Pre-PPCI LV function and Killip class were likely to be attributable to delays to reperfusion, which was adjusted for in specific analyses. This study also only included patients presenting between 2009 and 2013. Since then, heparin, rather than Bivalirudin, is now the procedural anticoagulant of choice and ticagrelor, rather than clopidogrel or prasugrel is now the P2Y12 inhibitor of choice in our centre. Transradial PPCI is now the most common access route for PPCI, and patients are more likely to receive DES (specifically everolimus-eluting stents (EES)) implantation during PPCI at present time. Therefore, temporal changes in outcomes may be present, but unaccounted for. Although significant effort was put into the accurate documentation of events, it is possible that some patients could have undergone repeat coronary revascularisation at hospitals that are outside of our region, and these events could therefore have been missed. This could have led to under-reporting of MACE. Limitations specific to each analysis are described in the relevant chapters.

2.7. Data entry

The data used for research purposes are anonymised at the point of data download. All patients have a unique database ID. Date of birth and gender are recorded in the database to allow for identification of age. Although research ethical approval and local NHS approval from Caldicott guardians (for the collection of data for performance assessment) in each regional hospital were obtained, the remit of this study falls within Section 251 of the NHS Health Service Act 2006, and therefore, informed consent from all patients for data collection for research purposes in this instance was not necessary; as the window for

repatriation to their relevant regional hospitals made this impractical for most patients. The Data Protection Act of 1998 was complied with at all times.

The baseline data that were collected were: date of birth, gender, ethnicity, previous MI, previous PCI, previous CABG, hypertension (pre-existing or new in-hospital diagnosis prior to discharge), hypercholesterolaemia (pre-existing or new in-hospital diagnosis prior to discharge), diabetes mellitus (pre-existing or new in-hospital diagnosis prior to discharge – mode of control: diet, oral hypoglycaemic agents, insulin), atrial fibrillation (pre-existing or new in-hospital diagnosis prior to discharge), peripheral vascular disease (pre-existing or new in-hospital diagnosis prior to discharge), cerebrovascular disease (pre-existing only – previous TIA or strokes), renal insufficiency including dialysis (pre-existing), cigarette-smoking (never, ex- or current-smoker). These were obtained by interrogating admission notes and discharge summaries for the relevant variables. Where the variables above were diagnosed in hospital prior to discharge, it was assumed that they were done according to appropriate criteria at the time of diagnosis.

The clinical data that were recorded were: date and time of symptom-onset, date and time of call for help, date and time of arrival to hospital (either LGI or other regional hospitals), discharging hospital, discharge date from LGI (for patients from other regional centres who were re-patriated to their local CCU, this was their date of transfer from LGI), discharge date from regional hospitals (if applicable), date of death, cardiac or non-cardiac cause of death (part 1 of certificate confirming death), heart rate (in beats per minute), systolic blood pressure (in mmHg as recorded in cardiac catheter laboratory electronic records), weight in kilogram, procedure status (emergency), procedure indication (by default, STEMI),

presentation with cardiogenic shock, ST-segment elevation, type of ST-segment elevation, left-bundle branch block morphology, cardiac rhythm at presentation, pre-procedural aspirin dose, pre-procedural P2Y12-receptor inhibitor and dose of each drug, first operator name, second operator name, time of first interventional device, choice of anticoagulant, GPI use, percentage stenosis in each vessel, arterial access site(s), size of arterial sheath (in French), type of haemostasis, radiation time, radiation dose, post-PPCI complications, baseline and post-PPCI blood tests, discharge aspirin, P2Y12-receptor inhibitor therapy, ACE-inhibitor, beta-blocker, statin, angiotensin receptor blocker.

Procedural data that were recorded into the database were: vessel name, percentage stenosis, TIMI flow pre-PPCI, type of lesion (de novo, in-stent restenosis, stent thrombosis), aspiration and/or mechanical thrombectomy, distal protection device, stent fitted (yes/no; BMS or DES), use of inotropic agents, use of intravascular ultrasound (IVUS), post-PPCI TIMI flow, post-PPCI percentage of stenosis, and procedural complications (as a binary variable – if a complication (aortic dissection, cardiac arrest, contrast medium reaction, cerebrovascular accident, coronary dissection, coronary perforation, cardiac tamponade, vascular complications, or death) was logged in the cardiac catheter laboratory electronic records or in the patient notes).

2.7.1. Identifying missing data

Patients whose outcome data were not collected or unavailable were not included in analyses. Of the remaining patients, the level of baseline, procedural and post-procedural non-outcome data that were unavailable were identified by ascertaining percentages of missing values. Data completeness for the variables in the data download were as follows:

Table 2.1: Variables collected and their completeness in percentages.

Variable	Percentage completeness (%)
Age in years	100.0
Death	100.0
Date of death	100.0
Gender*	100.0
Ethnicity*	94.8
Symptom onset date	99.8
Symptom onset time	100.0
Call for help date	99.6
Call for help time	99.0
Arrival at LGI date[a]	100.0
Arrival at LGI time	100.0
Date of first interventional device	100.0
Time of first interventional device	99.9
Discharge date from LGI	100.0
Discharge date from district hospitals	68.9
Previous MI*[b]	99.6
Previous PCI* [c]	99.6
Previous CABG* [d]	99.6
Hypertension*	99.6
Hypercholesterolaemia*	99.5
Diabetes mellitus*	98.8
Peripheral vascular disease*	99.5
Cerebrovascular disease*	99.5
Renal insufficiency*	99.5
Smoking status*	94.2
Location of ST-segment elevation	99.7
Rhythm	86.2
Aspirin dose	99.9
P2Y12 receptor inhibitor loading dose	99.6
First operator	100.0
Consultant	100.0
Heparin dose	2.4
LMS stenosis [e]	99.0
LAD proximal stenosis [f]	98.4
LAD other stenosis	97.8
RCA stenosis [g]	98.4
Circumflex artery stenosis	97.8
LIMA stenosis [h]	94.7
Vein graft stenosis	96.2
Arterial access 1	100
Arterial access 2	99.5
Largest French size	100.0
Femoral venous access	99.9
Haemostasis	99.5
Fluoroscopy time	94.6
Radiation dose	94.6
Complication – cardiogenic shock	99.9
Complication – ventilation	99.9
Complication – bradycardia requiring pacing	99.7
Complication – intra-aortic balloon pump	99.9
LGI baseline haemoglobin	95.9
LGI baseline platelet count	95.4

LGI baseline creatinine kinase	89.9
LGI baseline troponin	88.7
LGI baseline creatinine	96.8
LGI baseline estimated glomerular filtration rate (eGFR) [i]	45.7
DGH baseline haemoglobin	85.6
DGH baseline platelet	58.5
DGH baseline creatinine	30.6
DGH baseline troponin	40.0
DGH baseline creatinine	59.8
DGH baseline eGFR	25.4
LGI peak creatinine kinase	54.3
LGI lowest haemoglobin	52.4
LGI peak plasma glucose	56.8
LGI lowest platelet count	50.8
LGI total serum cholesterol	53.3
LGI peak creatinine	59.1
DGH peak creatinine kinase	19.5
DGH lowest haemoglobin	48.5
DGH peak plasma glucose	47.0
DGH lowest platelet count	41.8
DGH peak troponin	21.0
DGH total serum cholesterol	50.7
DGH peak creatinine	50.1
Discharge Aspirin	95.6
Discharge ACE-inhibitor [j]	92.3
Discharge statin	92.4
Discharge beta adrenergic receptor blocker	92.5
Discharge angiotensin receptor blocker	91.0
Aspirin at 30 days	82.9
P2Y12-receptor inhibitor at 30 days	81.9
Type of P2Y12 receptor inhibitor at 30 days	74.1
Angina at 30 days	73.7
Blood transfusion at 30 days	91.5
30-day major bleeding	94.6
30-day re-infarction	100.0
30-day unplanned coronary revascularisation	100.0
30-day planned coronary revascularisation	99.4
30-day stent thrombosis	99.8
30-day stroke	92.7
30-day contrast-induced nephropathy	90.7
Aspirin at 12 months	97.1
P2Y12 receptor inhibitor at 12 months	60.2
Type of P2Y12 receptor inhibitor at 12 months	39.1
Angina at 12 months	64.0
12-month re-infarction	100.0
12-month unplanned coronary revascularisation	100.0
12-month planned coronary revascularisation	99.0
12-month stent thrombosis	99.7
12-month stroke	89.6
Infarct-related artery (IRA) [k]	100.0
IRA percent stenosis	99.0
IRA pre-PPCI TIMI flow [l]	99.2
IRA presentation with stent thrombosis	99.8
Failed PCI of IRA	99.8

IRA aspiration thrombectomy	99.9
IRA mechanical thrombectomy	99.9
IRA distal protection device	99.7
IRA inotropes	99.8
IRA intravascular ultrasound (IVUS)[m]	99.8
IRA Post-PPCI TIMI flow	98.1
IRA post-PPCI IRA	97.7
Door-to-balloon (DTB) time [n]	99.2
Call-to-balloon (CTB) time [o]	99.0
Type of stent (BMS/DES) [p,q]	100.0

*Variables ascertained on admission/discharge according patient self-reporting. [a] LGI: Leeds General Infirmary; [b] MI: myocardial infarction; [c] PCI: percutaneous coronary intervention; [d] CABG: coronary artery bypass grafting; [e] LMS: left main stem; [f] LAD: Left anterior descending; [g] RCA: right coronary artery; [h] LIMA: left internal mammary artery; [i] eGFR: estimated glomerular filtration rate; [j] ACE: Angiotensin-converting enzyme; [k] IRA: infarct-related artery; [l] TIMI: thrombolysis in myocardial infarction; [m] IVUS: intravascular ultrasound; [n] DTB: door-to-balloon; [o] CTB: call-to-balloon; [p] BMS: bare-metal stent; [q] DES: drug-eluting stent.

Definitions:

Major-bleeding: HORIZONS-AMI major bleeding.

MI: Defined according to *the Universal Definition of Myocardial Infarction*.

Unplanned coronary revascularisation: Both percutaneous and surgical revascularisation procedures not planned or staged prior to discharge from hospital following index admission.

Planned coronary revascularisation: Planned up to the point of discharge from hospital following index admission.

Stent thrombosis: Definite/probable/possible – according to the Academic Research Consortium criteria[165].

Post-PPCI stroke: Clinically and radiologically confirmed stroke of any aetiology.

Contrast-induced nephropathy: Defined as an increase in serum creatinine of >25%, or a decrease of eGFR of > 25%, within 72 hours of radio-opaque contrast use.

2.7.2. Analysing missing data

Data completeness for the variables (the rationale for the use of selected variables are described in more detail in the description of each survival analysis in their relevant chapters) that were used in each regression was above 80% (specifically 99.07%). Missing data were assumed to have been missing at random. To avoid exclusion of cases (and consequently introducing bias) in the regression models due to missing data, outcome analyses that were undertaken in Chapters 5-7 were undertaken following multiple imputation by chained equations method, generating five imputed datasets in IBM SPSS (version 23.0.0.2)[166–168]. Predictive mean matching was utilised for the imputation of continuous variables (in this thesis, age was analysed as a continuous variable in chapters 6 and 7)[169]. Categorical variables in the regression models were analysed as binary variables, and were imputed using logistic regression. The pooled analyses from imputed datasets using Rubin's rules informed the final results presented in Chapters 5-7. In Chapters 3 and 4, 11 observations were deleted by the R statistical package due to missing data, as complete case analyses were undertaken for these specific chapters.

2.8. Statistical analyses

For all analyses, differences in baseline and procedural characteristics were analysed in IBM SPSS (version 23.0.0.2). Continuous variables were reported as medians with their corresponding interquartile ranges (IQR) and categorical variables were reported as frequencies with their corresponding percentages (n (%)). Categorical variables were compared with Chi-square tests for all analyses. Continuous variables in the analyses of the association between gender and ethnicity and clinical outcomes, the association between P2Y12-receptor inhibitor and outcomes and the association between GPI-use and outcomes according to arterial access site, were compared with Independent samples Student's t-tests and Mann-Whitney u-tests, as appropriate. In the analysis of the association between operator volume and outcome, one-way analysis of variance was used to compare continuous variables of three groups. Continuous variables in the sub-analysis of outcomes according to operator status was undertaken using Independent samples Student's t-tests and Mann-Whitney u-tests. A two-sided p-value of ≤0.05 was considered statistically significant. Analyses of the association between specific variables and outcomes are described in each relevant chapter.

Chapter 3. Gender

3.1. Analysis of the association between gender and ethnicity and outcomes

The first analyses undertaken were the investigation of the association between gender and ethnicity on clinical outcomes following PPCI. As described in section 1.6, given the differences noted in outcomes between genders, even in contemporary studies, it was felt that this was an association that should be re-evaluated, especially in a contemporary UK all-comers cohort. There were little published data examining the association between South Asian ethnicity and outcomes following PPCI. Therefore, the investigation of the association of this baseline characteristic was justified.

3.1.1. Clinical endpoints

For the analyses of the association of both gender and ethnicity and outcomes, the primary endpoints were major adverse cardiovascular events (MACE), within 30 days and 12 months of index PPCI, defined as all-cause mortality, recurrent MI, and repeat target and non-target vessel coronary revascularisation. The secondary endpoints were the individual components of MACE.

3.1.2. Survival analyses

For this analysis, survival analyses were performed in R (version 3.2.1) by the study statistical team (Claire Keeble, PhD, Paul Baxter, PhD)[170]. Only patients presenting between 01-01-2009 and 31-12-2011 (3 calendar years) were included in this analyses as data collection for the period of 01-01-2013 until 31-12-2013 were not completed at the time of analysis. Cox proportional hazards models were fitted to the data (for the variables current or previous history of cigarette smoking, diabetes mellitus, hypertension, hypercholesterolemia, prior revascularization, prior MI, peripheral vascular disease or cerebrovascular disease, age category, gender, ethnicity and cardiogenic shock – known predictors of poor outcomes and therefore clinically justified variables (besides gender and ethnicity that were the variables investigated) and outcomes (all-cause mortality and MACE) of interest (using the 'survival' package). Further variables were not included to avoid "overfitting" of the models. All assumptions, including the proportional hazards assumption, were verified. Age tertiles (<60 years – Group 1, 60 to 79 years – Group 2 and ≥80 years – Group 3) rather than continuous age were used throughout to satisfy the proportional hazards assumptions required where a MACE event (censored for first event) was the outcome of interest. Kaplan-Meier curves were produced to illustrate each unadjusted outcome of interest for age, ethnicity and gender. In the analysis of the association between gender and clinical outcomes, the male gender was used as the reference category. In the analysis of the association between ethnicity and clinical outcomes, white patients were used as the reference category. Hazard ratios were calculated from Cox proportional hazards models and were reported with 95% confidence intervals.

3.2. Results

3049 patients presented between 01-01-2009 and 31-12-2011, and were included in the analyses. Data for MACE at 12 months were available for 3028 (99.3%) patients.

Baseline and procedural characteristics according to gender are listed in Table 3.1. A total of 2223 (72.9%) men and 826 (27.1%) women underwent PPCI during this period. Statistically significant differences in patient and procedural characteristics were observed between men and women. Men were younger at presentation, had a higher prevalence of current or ex-smoking, previous MI and prior coronary revascularisation. Women had a higher prevalence of hypertension, less transradial PPCI, had lower use of Glycoprotein IIb/IIIa antagonists and aspiration thrombectomy, had fewer DES implantations, and importantly, had longer call-to-balloon (CTB) times.

Table 3.1: Baseline and procedural characteristics according to gender.

Baseline and procedural characteristics	Women (n=826)	Men (n=2223)	p value
Age in years, median(IQR)	69 (20)	60 (19)	<0.01
Diabetes mellitus n (%)	119 (14.4)	278 (12.5)	0.51
Current/Ex-smoker n (%)	492 (59.6)	1565 (70.4)	<0.01
Hypertension n (%)	389 (47.1)	781 (35.1)	<0.01
Hypercholesterolaemia n (%)	253 (30.6)	679 (30.5)	0.95
Renal insufficiency n (%)	21 (2.5)	56 (2.5)	0.81
Previous MI n (%)*	83 (10.0)	300 (13.5)	0.02
Previous revascularisation n (%)	59 (7.1)	256 (11.5)	<0.01
Peripheral vascular disease n (%)	17 (2.1)	63 (2.8)	0.43
Cerebrovascular disease n (%)	54 (6.5)	117 (5.3)	0.23
Anterior MI n (%)	328 (39.7)	946 (42.6)	0.15
Pre-procedure cardiogenic shock n (%)	37 (4.5)	86 (3.9)	0.45
Pre-procedure cardiac arrest n (%)	63 (7.6)	206 (9.3)	0.25
Call-to-balloon time in minutes median (IQR)	138 (72)	130 (64)	<0.01
Door-to-balloon time in minutes median (IQR)	52 (33)	51 (31)	0.10
Radial access n (%)	463 (56.1)	1450 (65.2)	<0.01
Infarct-related artery			
Left main stem n (%)	7 (0.8)	26 (1.2)	0.44
Left anterior descending n (%)	337 (40.8)	951 (42.8)	0.31
Circumflex n (%)	95 (11.5)	321 (14.4)	0.03
Right coronary n (%)	377 (45.6)	875 (39.4)	<0.01
Bypass graft n (%)	8 (1.0)	43 (1.9)	0.06
Multivessel PCI n (%)†	59 (7.1)	216 (9.7)	0.03
Drug-eluting stents n (%)	411 (49.8)	1221 (54.9)	0.03
Pre-procedural Aspirin n (%)	819 (99.2)	2199 (98.9)	0.57
Pre-procedural Clopidogrel n (%)	495 (59.9)	1205 (54.2)	<0.01
Pre-procedural Prasugrel n (%)	322 (39.0)	994 (44.7)	<0.01
Glycoprotein IIb/IIIa antagonist n (%)	115 (13.9)	412 (18.5)	<0.01
Heparin n (%)	33 (4.0)	112 (5.0)	0.23
Bivalirudin n (%)	787 (95.3)	2095 (94.2)	0.26
Aspiration thrombectomy n (%)	532 (64.4)	1536 (69.1)	0.05
Mechanical thrombectomy n (%)	8 (1.0)	43 (1.9)	0.17
Pre-procedural TIMI 0 flow n (%)‡	543 (65.7)	1556 (70.0)	0.05
Post-procedural TIMI 3 flow n (%)‡	718 (86.9)	1929 (86.8)	0.91

Data are expressed as median (IQR), or number (%);*MI: Myocardial Infarction; †PCI:

Percutaneous coronary intervention; ‡TIMI: Thrombolysis in Myocardial Infarction.

Advancing age was adversely associated with clinical outcomes. Higher rates of mortality (HR 4.17 (95% CI 2.86-6.09)) and MACE (HR 2.03 (95% CI 1.60-2.57)) at 12 months were observed in age group 2 (60-79 years) compared to age group 1 (<60 years). Age group 3 (≥80 years) was associated with the highest rates of mortality (HR 10.53 (95% CI 7.07-15.67) and MACE (HR 3.93 (95% CI 2.99-5.17)) when compared to age group 1 (Figure 3.1).

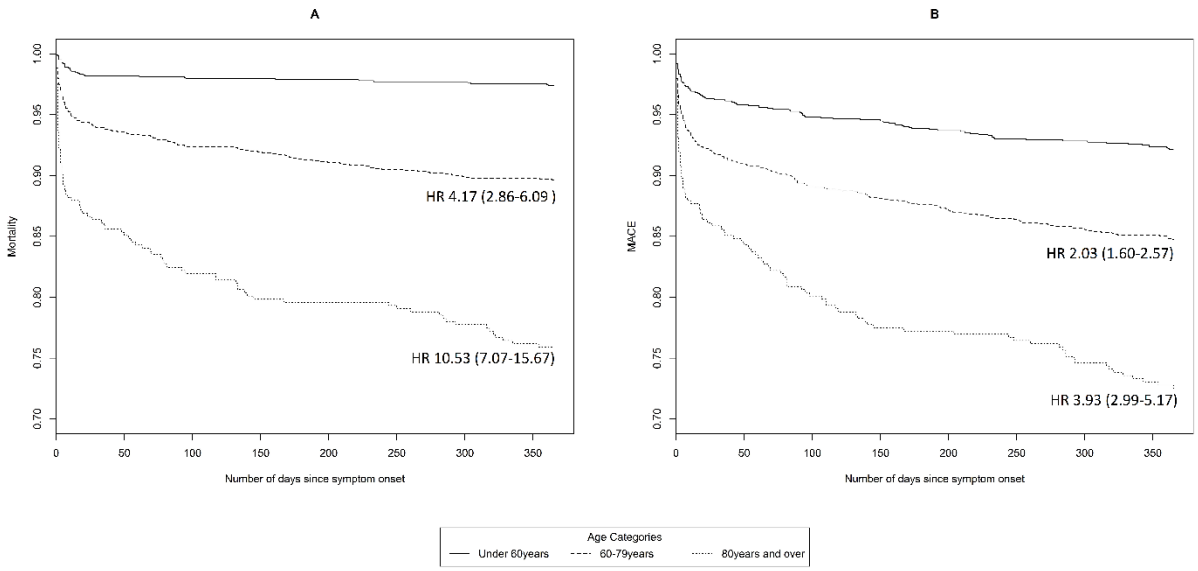


Figure 3.1: Kaplan-Meier survival curves illustrating unadjusted mortality (A) and MACE (B) in the three age tertiles.

In univariable analyses, women had significantly higher mortality (HR 1.48 (95% CI 1.15-1.90)) and MACE (HR 1.40 (95% CI 1.14-1.72)) at 12 months compared to men (Table 3.2; Figures 2A&B) for both first adjudicated MACE and all MACE. However, age-stratification alone by categorising into age groups 1-3 eliminated the excess risk of mortality and MACE in women (Figures 3.2C&D). When adjustment for potential confounders (including age) was carried out by multivariable analysis, once again, no statistically significant differences in MACE (HR 1.10 (95% CI 0.89-1.37)) or mortality (HR 0.99 (95% CI 0.76-1.30)) in women compared to men.

Table 3.2: Clinical outcomes at 12 months according to gender.

Event		Men (n=2223)	Women (n=826)	P-value
First adjudicated MACE	MACE* (n=427)	284 (13)	143 (17)	<0.01
	Mortality (n=247)	159 (7)	88 (11)	<0.01
	MI† (n=118)	77 (3)	41 (5)	0.06
	Revascularisation (n=62)	48 (2)	14 (2)	0.42
All MACE	MACE* (615)	18.4	24.9	<0.01
	Mortality (n=269)	7.9	11.4	<0.01
	MI† (n=203)	6.0	8.4	0.02
	Revascularisation (n=143)	4.5	5.2	0.41

Data for first adjudicated MACE are expressed as n (%). Data for all MACE are expressed per 100 patient years; *MACE: Major adverse cardiovascular event; †MI: Myocardial Infarction.

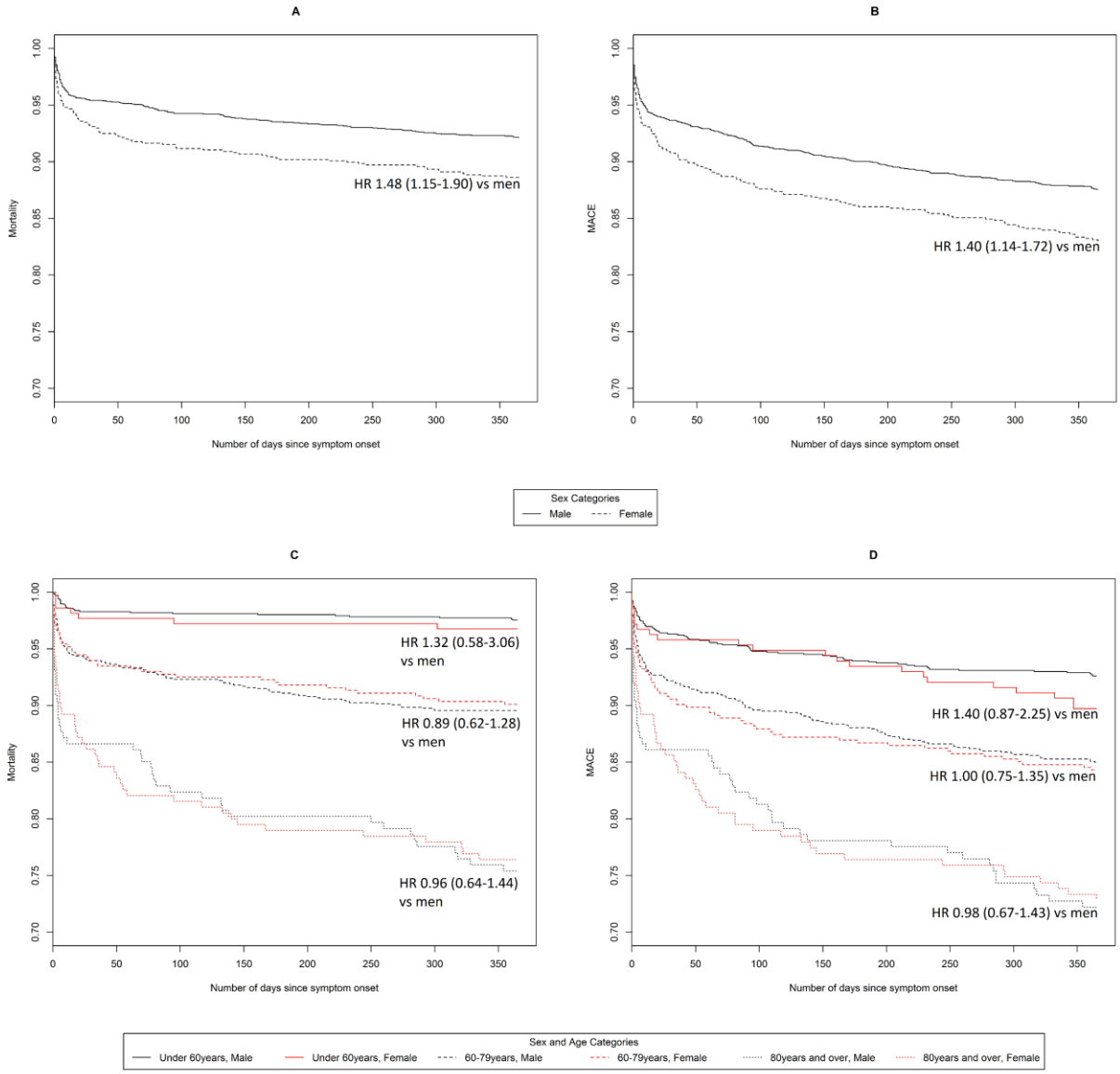


Figure 3.2: Kaplan-Meier survival curves comparing crude mortality and MACE in men and women (A, B), and age-stratified mortality and MACE in men and women (C, D).

3.3. Discussion

Our analysis of real-world data from truly consecutive patients undergoing PPCI at a very large heart attack centre provides important insights into the association between gender and clinical outcomes following PPCI. Women had significantly higher rates of mortality and MACE compared to men in univariable analysis. However, age-stratification alone eliminated this excess risk. Multivariable analysis for adjustment for risk factors (including age) showed that female gender *per se* is not associated with adverse clinical outcomes. The difference in outcomes between genders is driven by age.

Important differences between men and women in terms of baseline characteristics and procedural variables in a population of patients in the "contemporary" PPCI era were observed in this study. Previous studies had also observed these differences in chracteristics[60,67–70,76]. Previous studies have shown that women have higher rates of MACE despite correction for age and risk factors[60,61,68,70,75]. However, as described in Section 1.4.1.2, there has been increasing evidence in recent studies that female gender *per se* is does not independently predict poor clinical outcomes following PPCI and rather, adverse risk factor profile and patient delays contributed to poorer outcomes in women[74]. Our analysis has shown that the difference in age and baseline characteristics at the time of PPCI contributed to the differences in clinical outcomes between men and women, as suggested in previous studies[63,67,71,73,74,78,79]. However, importantly, we have shown that adjustment for age alone eliminates this excess risk, suggesting that age is the strongest determinant of clinical outcomes in this comparison.

Delays to reperfusion have been identified in previous studies as potential explanations for poorer outcomes following PPCI in women[66,70,79]. In this study, statistically significantly longer CTB times were observed in women compared to men. However, In contrast to these studies statistically significant differences in door-to-balloon (DTB) times between men and women were not observed, and the DTB times in both genders in this study were comparable to these studies. Clinical outcomes in women could potentially be improved further by minimising pre-hospital delays.

In this study, radial access for PPCI which is independently associated with improved clinical outcomes compared to femoral access, was significantly lower in women compared to men. Transradial PPCI was not included in the Cox-regression model, as reduced rates of radial access could be due to size-mismatch between 6-French arterial sheaths and the diameter of the radial artery, or increased incidence of radial artery spasm in women[171]. Therefore differences in transradial PPCI, rather than being a confounder, is likely to be due to anatomical and physiological differences between genders. However, with the development of sheath-less guide catheter and hydrophilic sheaths, along with newer techniques such as balloon-tracking, the differences noted between genders in transradial PPCI could be improved further with time.

3.4. Limitations

In addition to the limitations described in Chapter 2, in the female < 60 years group, the lack of statistical significance in outcomes compared to men could be to the relatively smaller number of patients (compared to women aged 61-79 years) in this group, as it has been suggested in the literature that younger women may have more adverse outcomes

compared to younger men. However, it is important to recognise that a larger population may not have necessarily revealed differences in outcomes. Complete case analyses rather than multiple imputation analyses were undertaken, as the number of cases with missing data were only 11 (0.36%). Despite the very small number of cases excluded with complete case analyses, the possibility that this may have introduced bias could not be excluded.

Chapter 4. Ethnicity

4.1. Results

A total of 2570 (84.3%) White patients and 297 (9.7%) South Asian patients underwent PPCI between 01-01-2009 and 31-12-2011 (Table 4.1). Multiple statistically significant differences in baseline and procedural characteristics between South Asian and White patients were observed. Although South Asian patients presented with STEMI at a younger age, their prevalence of other established risk factors (diabetes mellitus, systemic hypertension, hypercholesterolaemia and pre-existing coronary disease) were higher compared to White patients.

There was no statistically significant difference in mortality (HR 0.97 (95% CI 0.64-1.47)) or MACE (HR 1.21 (95% CI 0.89-1.64)) between South Asian and White patients in univariable analysis of first adjudicated MACE (Figure 4.1). However, when individual components of MACE (mortality, MI, and coronary revascularisation) were considered separately, a higher incidence of MI was observed in South Asian patients (Table 4.2). Multivariable analysis confirmed that South Asian patients do not have statistically significant difference in MACE (HR 1.30 (95% CI 0.94-1.80)) compared to White patients.

Table 4.1: Baseline and procedural characteristics according to ethnicity.

Baseline and procedural characteristics	White (n=2570)	South Asian (n=297)	p value
Age in years, median (IQR)	64 (20)	56 (21)	<0.01
Diabetes mellitus n (%)	277 (10.8)	94 (31.6)	<0.01
Current/Ex-smoker n (%)	1783 (69.4)	151 (50.8)	<0.01
Hypertension n (%)	971 (37.8)	134 (45.1)	0.02
Hypercholesterolaemia n (%)	753 (29.3)	121 (40.7)	<0.01
Renal insufficiency n (%)	66 (2.6)	10 (3.4)	0.51
Previous MI n (%)*	318 (12.4)	49 (16.5)	0.07
Previous revascularisation n (%)	250 (9.7)	45 (15.2)	<0.01
Peripheral vascular disease n (%)	70 (2.7)	3 (1.0)	0.21
Cerebrovascular disease n (%)	153 (6.0)	14 (4.7)	0.54
Anterior MI n (%)	1044 (40.6)	147 (49.5)	<0.01
Pre-procedure cardiogenic shock n (%)	103 (4.0)	11 (3.7)	0.82
Pre-procedure cardiac arrest n (%)	220 (8.6)	20 (6.7)	0.49
Call-to-balloon time in minutes median (IQR)	139 (64)	131 (68)	0.06
Door-to-balloon time in minutes median (IQR)	51 (32)	52 (35)	0.53
Radial access n (%)	1610 (62.6)	185 (62.3)	0.72
Infarct-related artery			
Left main stem n (%)	26 (1.0)	1 (0.3)	0.25
Left anterior descending n (%)	1062 (41.3)	149 (50.2)	<0.01
Circumflex n (%)	357 (13.9)	36 (12.1)	0.40
Right coronary n (%)	1081 (42.1)	105 (35.4)	0.03
Bypass graft n (%)	42 (1.6)	5 (1.7)	0.95
Multivessel PCI n (%) †	230 (8.9)	24 (8.1)	0.62
Drug-eluting stents n (%)	1336 (52.0)	195 (65.7)	<0.01
Pre-procedural Aspirin n (%)	2546 (99.1)	293 (98.7)	0.49
Pre-procedural Clopidogrel n (%)	1425 (55.4)	184 (62.0)	0.03
Pre-procedural Prasugrel n (%)	1121 (43.6)	109 (36.7)	0.02
Glycoprotein IIb/IIIa antagonist n (%)	440 (17.1)	51 (17.2)	0.94
Heparin n (%)	119 (4.6)	20 (6.7)	0.11
Bivalirudin n (%)	2438 (94.9)	276 (92.9)	0.34
Aspiration thrombectomy n (%)	1752 (68.2)	198 (66.7)	0.88
Mechanical thrombectomy n (%)	45 (1.8)	4 (1.3)	0.28
Pre-procedural TIMI 0 flow n (%) ‡	1769 (68.8)	201 (67.7)	0.90
Post-procedural TIMI 3 flow n (%)‡	2235 (87.0)	258 (86.9)	0.96

Data are expressed as median (IQR), or number (%); *MI: Myocardial Infarction; †PCI: Percutaneous coronary intervention; ‡TIMI: Thrombolysis in Myocardial Infarction.

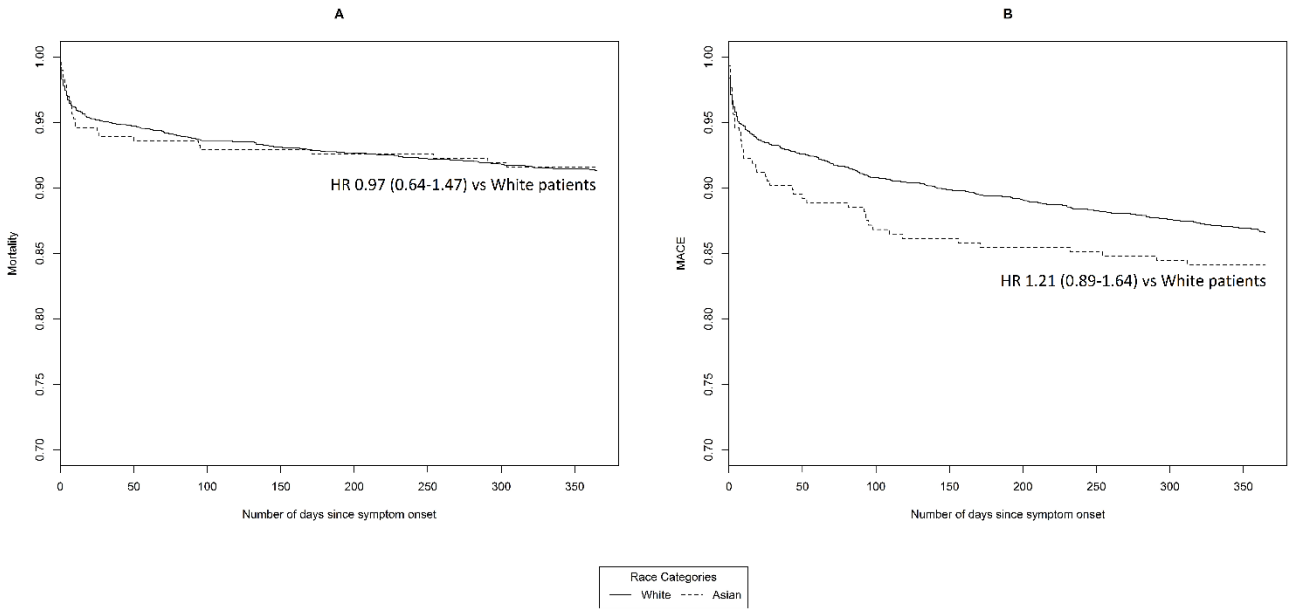


Figure 4.1: Kaplan-Meier survival curve illustrating 12-month unadjusted mortality (A) and MACE (B) in South Asian and White patients.

Table 4.2: Clinical outcomes at 12 months according to ethnicity.

Event		White (n=2570)	South Asian (n=297)	P-value
First adjudicated MACE	MACE* (n=427)	354 (14)	48 (16)	0.26
	Mortality (n=247)	207 (8)	19 (6)	0.32
	MI† (n=118)	93 (4)	22 (7)	<0.01
	Revascularisation (n=62)	54 (2)	7 (2)	0.77
All MACE	MACE* (615)	19.3	27.9	<0.01
	Mortality (n=269)	8.7	8.4	0.88
	MI† (n=203)	6.3	12.1	<0.01
	Revascularisation (n=143)	4.4	7.4	0.02

Data for first adjudicated MACE are expressed as n (%). Data for all MACE are expressed per 100 patient years; *MACE: Major adverse cardiovascular event; †MI: Myocardial Infarction.

4.2. Discussion

This is the first study to assess the association between South Asian ethnicity and outcomes in the contemporary era of PPCI. No statistically significant difference in mortality or MACE was observed in univariable and multivariable analysis comparing clinical outcomes of South Asian patients with those of White patients. However, South Asian patients had higher incidence of recurrent MI within 12 months of index PPCI.

There are limited published data assessing clinical outcomes in South Asian individuals undergoing PPCI in the contemporary era. Multiple statistically significant differences in baseline characteristics were found between South Asian and White patients: higher prevalence of diabetes mellitus, hypertension, hypercholesterolaemia and pre-existing coronary artery disease in South Asian patients despite their younger age at presentation. These were consistent with previous studies[2,104,105,109–111]. Metabolic syndromes (including insulin resistance and diabetes mellitus) and altered levels of adipokines and inflammatory mediators have been shown to contribute to the younger age of onset of CAD and poorer clinical outcomes following coronary events in South Asian individuals compared to White individuals[98–108]. Multiple statistically significant differences in procedural variables between South Asian and White patients were observed in this study. Importantly, South Asian patients were statistically significantly more likely to present with anterior MIs, with the left anterior descending (LAD) artery being the infarct-related artery. This is associated with adverse clinical outcomes and a greater risk of in-stent restenosis[172,173].

The statistically significant difference in the prevalence of risk factors, particularly the prevalence of diabetes mellitus in South Asian patients, which in our cohort was three times

higher than in White patients, is likely to contribute to the higher incidence of recurrent MIs in South Asian patients. Despite their higher rates of recurrent MIs, when only first adjudicated events were analysed, South Asian patients did not have higher mortality or MACE. Younger age at presentation and some patients experiencing multiple events, with subsequent events not being included when censored for first adjudicated event, could explain this difference.

4.3. Limitations

Although a large number of South Asian patients were included in this study, distinguishing those born in the UK from those born outside the UK and immigrated to the UK in later life was not possible. This is potentially an important factor to recognise, as standardized mortality ratios from CAD are higher in South Asian countries compared to the UK. It is therefore possible that South Asian patients who had emigrated to the UK may have higher risk of adverse events from CAD compared to those who were born in the UK[174]. Finally, determination of continuation of secondary prevention medication at 12 months, which may have been different between genders and ethnicities, was not possible. However, this is unlikely to be different between the ethnicities, and if there were differences, compliance was likely to be higher in the South Asian population[175,176].

Chapter 5: Oral P2Y12-receptor inhibitor therapy

5.1. Analysis of the association between oral P2Y12-receptor inhibitors and outcomes

There are limited available data reporting the association between the choice of oral P2Y12 receptor inhibitors and outcomes following PPCI. Data comparing prasugrel with ticagrelor are limited to two studies (one trial that was terminated early and one observational study that may have been confounded by differences in arterial access site that were not presented) as described in Chapter 1. This association therefore warranted investigation from this registry.

5.1.1. Clinical endpoints

The primary efficacy endpoints were 30-day and 12-month MACE. The secondary efficacy endpoints were 30-day and 12-month all-cause mortality. The primary safety endpoint was 30-day major bleeding according to HORIZONS criteria (bleeding from an intracranial or intraocular source; arterial access site bleeding measuring ≥5cm, or intervention for bleeding; a haemoglobin-reduction of ≥4g/dL with no overt source of bleeding, or a haemoglobin-reduction of ≥3g/dL with an identifiable source of bleeding; red cell transfusion; bleeding requiring re-operation) [177].

5.1.2. Survival analyses

Logistic regression analyses were undertaken in IBM SPSS (version 23.0.0.2) by AK, to evaluate outcomes adjusted for confounding variables. Patients presenting between 01-01-2009 and 31-12-2011, and between 01-01-2013 and 31-12-2013 were included in this analysis, and all subsequent survival analyses. The pre-procedural P2Y12-receptor inhibitor therapy was used to define choice of P2Y12-receptor inhibitor. Confounders were identified in exploratory analyses of variables that were known in scientific literature to contribute positively or

negatively to outcomes, and were included on the logistic regression models if there were differences within groups with $P \leq 0.10$. Exploratory analyses revealed the following variables with $P \leq 0.10$: Age over 65 years, radial artery access, P2Y12-receptor inhibitor therapy, hypertension, hypercholesterolaemia, diabetes mellitus, renal dysfunction, anterior STEMI, prior MI, pre-existing peripheral vascular disease or cerebrovascular disease, CTB > 120 minutes, GPI-use, cardiogenic shock at presentation, year PPCI was performed (adjusting for temporal advances in PPCI that were otherwise not identified or recorded, such as advancement in secondary prevention, rise in primary prevention ICD devices[142]), and DES implantation. Year of PPCI was assessed in exploratory analyses due to the strong temporal trend in the choice of P2Y12-receptor inhibitor (Figure 5.1). As with the analysis of the association between gender and ethnicity and outcomes, although there are more known predictors of poor outcomes following PPCI, the variables that were assessed were only those that were recorded in the database. Further variables, even if recorded in the database, were not included in the regression models to avoid "overfitting" of the models. In the comparison of prasugrel and ticagrelor against clopidogrel, the reference category was clopidogrel. In the comparison of prasugrel with ticagrelor, the reference category was ticagrelor. All odds ratios from the logistic regression models were reported with 95% confidence intervals.

5.2. Results

Between 01-01-2009 and 31-12-2011, and between 01-01-2013 and 31-12-2013 (four calendar-year period), 4056 patients underwent PPCI, of whom 3703 (91.3%) were followed up to a minimum of 12 months, all of whom had data for 30-day and 12-month mortality and MI collected at follow-up. These patients were therefore included in the analysis. Follow-up data for 30-day HORIZONS-major bleeding were available for 3449 (93.1%) of the 3703 patients who were included in this analysis.

The breakdown of the choice of P2Y12-receptor inhibitor were as follows: 1648 (44.5%) patients received clopidogrel, 1244 (33.6%) patients received prasugrel and 811 (21.9%) patients received ticagrelor. Comparison of baseline and procedural variables revealed multiple statistically significant differences amongst the patients receiving each P2Y12-receptor inhibitor (Table 5.1). This is likely to be due to the temporal trend of use of each P2Y12-receptor inhibitor over the recruitment period, which is illustrated in Figure 5.1. Unadjusted and adjusted 30-day and 12-month mortality and recurrent MI, and 30-day bleeding are listed in Table 5.2.

Table 5.1: Baseline and procedural details according to procedural P2Y12-receptor inhibitor.

Baseline and procedural characteristics	Prasugrel (n=1244)	Ticagrelor (n=811)	p-value	Clopidogrel (n=1648)	Prasugrel (n=1244)	p value	Ticagrelor (n=811)	Clopidogrel (n=1648)	p-value
Age in years, median (IQR)	61 (17)	63 (19)	<0.01	65 (21)	61 (17)	<0.01	63 (19)	65 (21)	<0.01
Male n (%)	941 (75.6)	587 (72.4)	0.10	1178 (71.5)	941 (75.6)	0.01	587 (72.4)	1178 (71.5)	0.64
White n (%)	1061 (85.3)	707 (87.2)	0.23	1388 (84.2)	1061 (85.3)	0.43	707 (87.2)	1388 (84.2)	0.05
Diabetes mellitus n (%)	152 (12.2)	133 (16.4)	<0.01	235 (14.3)	152 (12.2)	0.05	133 (16.4)	235 (14.3)	0.37
Current/Ex-smoker n (%)	885 (71.1)	510 (62.9)	<0.01	1070 (64.9)	885 (71.1)	<0.01	510 (62.9)	1070 (64.9)	0.54
Hypertension n (%)	424 (34.1)	317 (39.1)	<0.01	688 (41.7)	424 (34.1)	<0.01	317 (39.1)	688 (41.7)	<0.01
Hypercholesterolaemia n (%)	365 (29.3)	269 (33.2)	<0.01	524 (31.8)	365 (29.3)	0.15	269 (33.2)	524 (31.8)	<0.01
Renal insufficiency n (%)	15 (1.2)	16 (2.0)	<0.01	66 (4.0)	15 (1.2)	<0.01	16 (2.0)	66 (4.0)	<0.01
Previous MI n (%)[1]	122 (9.8)	101 (12.5)	<0.01	237 (14.4)	122 (9.8)	<0.01	101 (12.5)	237 (14.4)	0.02
Peripheral/Cerebrovascular disease n (%)	53 (4.3)	54 (6.7)	<0.01	180 (10.9)	53 (4.3)	<0.01	54 (6.7)	180 (10.9)	<0.01
Cardiogenic shock n (%)	36 (2.9)	59 (7.3)	<0.01	75 (4.6)	36 (2.9)	0.02	59 (7.3)	75 (4.6)	<0.01
Anterior ST-Elevation MI n (%)	542 (43.6)	320 (39.5)	0.07	673 (40.8)	542 (43.6)	0.14	320 (39.5)	673 (40.8)	0.51
Call-to-balloon time in minutes median (IQR)	122 (43)	125 (52)	0.02	142 (79)	122 (43)	<0.01	125 (52)	142 (79)	<0.01
Door-to-balloon time in minutes median (IQR)	51 (30)	48 (28)	<0.01	51 (33)	51 (30)	0.83	48 (28)	51 (33)	<0.01
Radial access n (%)	876 (70.4)	663 (81.8)	<0.01	843 (51.2)	876 (70.4)	<0.01	663 (81.8)	843 (51.2)	<0.01
Multivessel PCI n (%)[2]	100 (8.0)	63 (7.8)	0.83	160 (9.7)	100 (8.0)	0.12	63 (7.8)	160 (9.7)	0.12
Drug-eluting stents n (%)	785 (63.1)	669 (82.5)	<0.01	773 (46.9)	785 (63.1)	<0.01	669 (82.5)	773 (46.9)	<0.01
Glycoprotein IIb/IIIa antagonist n (%)	197 (15.8)	88 (10.9)	<0.01	302 (18.3)	197 (15.8)	0.08	88 (10.9)	302 (18.3)	<0.01
Bivalirudin n (%)	1202 (96.6)	771 (95.1)	0.08	1532 (93.0)	1202 (96.6)	<0.01	771 (95.1)	1532 (93.0)	0.04
Aspiration thrombectomy n (%)	917 (73.7)	621 (76.8)	0.23	1053 (63.9)	917 (73.7)	<0.01	621 (76.8)	1053 (63.9)	<0.01
Post-procedural TIMI 3 flow n (%)[3]	1121 (90.1)	737 (90.9)	0.24	1410 (85.6)	1121 (90.1)	<0.01	737 (90.9)	1410 (85.6)	<0.01

Data are expressed as median (IQR), or number (%); [1] MI: Myocardial Infarction; [2] PCI: Percutaneous coronary intervention; [3] TIMI: Thrombolysis in Myocardial Infarction. These are hypothesis-generating analyses and therefore, p-values should be interpreted with caution.

Table 5.2: Clinical outcomes according to P2Y12-receptor inhibitor therapy.

		Clopidogrel vs ticagrelor		Clopidogrel vs prasugrel		Ticagrelor vs prasugrel	
		Clopidogrel (n=1648)	Ticagrelor (n=811)	Clopidogrel (n=1648)	Prasugrel (n=1244)	Ticagrelor (n=811)	Prasugrel (n=1244)
30-day outcomes	Mortality n (%) Adjusted OR (95%CI)[1,2]	117 (7.0) 1.00	56 (6.9) 1.05 (95% CI 0.61-1.80)	117 (7.0) 1.00	40 (3.2)* 0.53 (95% CI 0.34-0.85)*	56 (6.9) 1.00	40 (3.2)* 0.51 (95% CI 0.29-0.91)*
	MI n (%)[3] Adjusted OR (95%CI) [1,2]	48 (2.9) 1.00	9 (1.1)* 0.40 (95% CI 0.17-0.94)*	48 (2.9) 1.00	21 (1.7)* 0.58 (95% CI 0.32-1.05)	9 (1.1) 1.00	21 (1.7) 1.44 (95% CI 0.61-3.42)
	Major bleeding n (%) Adjusted OR (95%CI) [1,2]	95 (6.1) 1.00	37 (4.6) 0.98 (95% CI 0.64-1.52)	95 (6.1) 1.00	52 (4.6) 1.05 (95% CI 0.73-1.52)	37 (4.6) 1.00	52 (4.6) 1.07 (95% CI 0.67-1.70)
12-month outcomes	Mortality n (%) Adjusted OR (95%CI) [1,2]	193 (11.7) 1.00	77 (9.5) 0.84 (95% CI 0.55-1.29)	193 (11.7) 1.00	68 (5.5)* 0.55 (95% CI 0.38-0.78)*	77 (9.5) 1.00	68 (5.5)* 0.65 (95% CI 0.41-1.02)
	MI n (%)[3] Adjusted OR (95%CI) [1,2]	108 (6.6) 1.00	26 (3.2)* 0.54 (95% CI 0.32-0.93)*	108 (6.6) 1.00	47 (3.8)* 0.63 (95% CI 0.42-0.94)*	26 (3.2) 1.00	47 (3.8) 1.16 (95% CI 0.67-2.01)

Data are expressed as n (%); [1] OR: Odds ratio; [2] CI: Confidence interval; [3] MI: Myocardial infarction; *p-value ≤ 0.05.

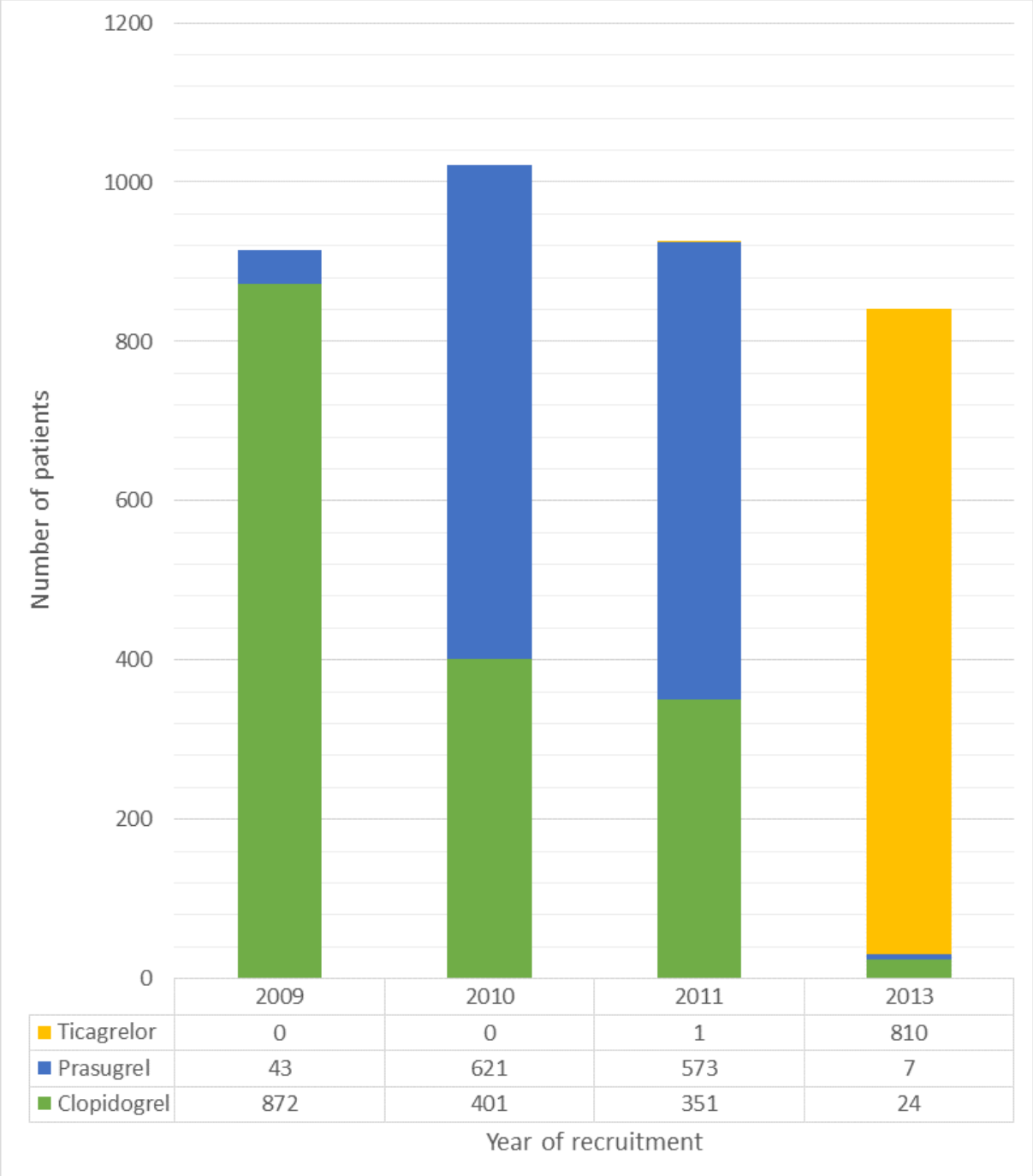


Figure 5.1: P2Y12-receptor inhibitor administration over the study period.

Prasugrel vs ticagrelor

Statistically significant differences in both unadjusted and adjusted 30-day mortality were observed in the comparison of prasugrel with ticagrelor, with patients receiving prasugrel observed to have lower mortality. Multivariable analysis revealed no statistically significant difference in adjusted 12-month mortality between patients receiving prasugrel and patients receiving ticagrelor, although unadjusted 12-month mortality was significantly higher in patients receiving ticagrelor. Neither univariate nor multivariable analysis revealed a significant difference in 30-day bleeding between the two groups (Table 5.2).

Prasugrel vs clopidogrel

Thirty-day and 12-month mortality were significantly less likely in patients receiving prasugrel compared to patients receiving clopidogrel, in both unadjusted and adjusted analyses. In addition, unadjusted and adjusted 30-day MI, and adjusted 12-month MI were also statistically significantly lower in patients receiving prasugrel compared to clopidogrel. There were no statistically significant difference in 30-day major bleeding between the two groups (Table 5.2).

Ticagrelor vs clopidogrel

There were no significant differences in unadjusted and adjusted 30-day and 12-month mortality, or 30-day major bleeding between patients receiving ticagrelor and patients receiving clopidogrel. However, patients receiving ticagrelor had lower unadjusted and adjusted 30-day and 12-month MI compared to patients receiving clopidogrel (Table 5.2).

5.3. Discussion

This analysis of contemporary real-world data from a large consecutive patient series has provided an important direct comparison of clinical outcomes between patients treated with prasugrel and ticagrelor in the setting of PPCI for STEMI, with the first direct comparison of bleeding between ticagrelor and prasugrel. Prasugrel and ticagrelor were also individually compared with clopidogrel. Patients treated with prasugrel were observed to have statistically significantly lower adjusted mortality at both 30 days and 12 months, compared to patients treated with clopidogrel. This finding was not observed in patients receiving ticagrelor in comparison with patients receiving clopidogrel. Crucially, for the first time, patients receiving prasugrel have been shown to have lower risk-adjusted 30-day mortality compared to those receiving ticagrelor. This finding approached, but did not reach statistical significance at 12 months (*P*=0.06). Repeat MI were lower in both third-generation P2Y12-reecptor inhibitor therapies, compared to clopidogrel, with the difference observed with ticagrelor being statistically significantly different at both 30-days and 12-months. No differences in major bleeding were observed amongst the three drugs.

In comparison to the analysis by Gosling et al[140], reduction in mortality were not observed in patients treated with ticagrelor compared to clopidogrel. Prasugrel, however, was associated with reduced mortality at 30 days and 12 months compared to clopidogrel, and at importantly, 30 days compared to ticagrelor, which was partly in keeping with their findings. Key differences in statistical analyses might account for the differences in findings. Gosling et al did not present or adjust for arterial access site, which could have been different between the groups if there was a temporal trend in the use of relevant P2Y12-receptor antagonist, which was also not presented and if necessary, adjusted for. Radial artery access was included

in the regression models in this study, and was found to be independently associated with lower adjusted 30-day (OR 0.28 (95% CI 0.19-0.40)) and 12-month (OR 0.50 (95% CI 0.38-0.66)) mortality, and 30-day bleeding (OR 0.40 (95% CI 0.28-0.56)) compared to femoral artery access. Year of presentation was also corrected for in this study, to minimise the effect of potentially unrecorded confounders such as progress with DES platforms and non-pharmacological secondary prevention. The key finding of this study that in the real-world, the third-generation P2Y12-receptor inhibitors were associated with better outcomes compared to clopidogrel was in keeping with their study.

There were several differences between the findings of this study and that of TRITON-TIMI 38. In this study, lower 30-day and 12-month mortality, and lower MI within 30 days of index PPCI were observed in patients treated with prasugrel compared to clopidogrel. We also observed lower rates of recurrent MI within 30-days in patients receiving prasugrel compared to clopidogrel, which was in keeping with TRITON TIMI 38. Differences in outcomes between this study and the PPCI subgroup of TRITON TIMI 38 could be explained by differences in baseline and procedural characteristics. The patients in this study appeared older (median age 62 vs 59), had higher prevalence of tobacco use (67.5 % vs 45.0 %), lower prevalence of diabetes mellitus (14.3% vs 16.8%), hypertension (38.0% vs 48.7%) and hypercholesterolaemia (32.1% vs 37.6%), compared to those undergoing PPCI in TRITON TIMI 38. The patients included in this study were also more likely to receive DES (60.1% vs 28.5%), were mostly anticoagulated with bivalirudin (95.5% vs 1.0%) and were less likely to receive GPI (85.3% vs 66.2%) compared to patients in the PPCI subgroup of TRITON TIMI 38. Patients in this study also mostly underwent transradial PPCI (59.4% in the prasugrel and clopidogrel group), whereas in TRITON TIMI 38, arterial access site was not presented and was likely to

be femoral artery. Analysis of 30-day bleeding in this cohort of patients was in keeping with TRITON TIMI 38, which also found no statistically significant difference in bleeding at 30 days.

Koshy et al[137] compared prasugrel with clopidogrel for 12-month mortality, and reported that patients receiving prasugrel had lower adjusted 12-month mortality compared to patients receiving clopidogrel, which was similar to the results observed in this study. However, in contrast with this study, choice of arterial access site was not included in their multivariable analysis, despite a higher proportion of patients in their prasugrel subgroup undergoing transradial PPCI, compared to their clopidogrel subgroup. Post-procedural TIMI 3 flow was also included in their Cox model. This was not included in the regression model of this study as it was plausible post-PPCI microvascular function could be influenced by the choice of P2Y12 receptor inhibitor, and therefore, differences in TIMI flow should not be considered a confounding factor[178]. Age of patient at presentation and DTB times also appeared different between this study and that of Koshy et al, and higher rates of use of GPI were observed in their study compared to this study. In this study, as described earlier, given the significant temporal trends in the use of each P2Y12 receptor inhibitor, year of PPCI was included in the regression models. Importantly, despite the difference in statistical analysis, along with differences in baseline and procedural characteristics, a similar association between treatment with prasugrel and survival, in comparison with clopidogrel, was observed in both studies. Additionally, an inverse association between prasugrel and recurrent MI within 12 months of index PPCI was observed in our analysis.

The PPCI subgroup analysis from the PLATO investigators [179] revealed a reduction in all-cause mortality in patients treated with ticagrelor compared to patients treated with clopidogrel

that approached statistical significance (p=0.05) at 12 months. This finding was not observed in this study. In this study, patients treated with ticagrelor had lower rates of recurrent MI at 30 days and at 12 months compared to patients treated with clopidogrel. Patients treated with ticagrelor did not have a higher risk of bleeding compared to patients treated with clopidogrel, which was in keeping with the PLATO sub-study analysis. There were, however, important differences in clinical characteristics between the PLATO sub-study and the study population for this study that could account for the differences observed. In the PLATO sub-study, patients who received open-label clopidogrel pre-randomization were then given an additional 600mg loading dose of clopidogrel upon randomization (if randomized to clopidogrel). The majority of their patients received BMS instead of DES, which if reversed, may have reduced recurrent ischaemic events. Procedural anticoagulation in PLATO was achieved with unfractionated heparin rather than bivalirudin in most patients, with higher use of GPI in comparison with this study.

Significant differences in baseline and procedural characteristics between the three groups of patients were observed in this study. As illustrated in Figure 1, in 2009, most patients undergoing PPCI in LGI received clopidogrel, with the rest receiving prasugrel. In 2010 and 2011 however, the majority of patients received prasugrel rather than clopidogrel, and in the final year of recruitment (2013), the majority of patients received ticagrelor. Over the course of recruitment, there were significant changes in the rates of transradial PPCI (39.6% in 2009 vs 81.8% in 2013) and the use of DES (41.3% in 2009 vs 82.2% in 2013). A higher proportion of patients in the ticagrelor cohort underwent PPCI for cardiogenic shock, which is traditionally regarded as a marker of poor prognosis[180]. This is likely to be due to a gradual reduction in the threshold for accepting patients for PPCI. There were also advances in

secondary prevention over the study period, including an increased rate of implantation of primary-prevention ICDs following MI[142]. These and other confounders such as changes in clinical practice, improvements in operator proficiency, particularly in transradial PPCI, and improvements in the PPCI pathway could have all contributed to the differences in unadjusted outcomes. However, multivariable analysis, including adjustment for year of PPCI to adjust for unquantifiable time-dependent confounders, was undertaken to correct for major confounding factors.

5.4. Limitations

As described previously, temporal advances in PPCI could have introduced unidentified or unquantified confounders to the results of this study. However, this was addressed and corrected for by adjusting for year of admission. Continuation and/or switching of P2Y12-receptor inhibitors following discharge could not be adequately determined. However, this limitation was also present in the only other comparable real-world studies[137,140]. Switching from ticagrelor was noted in PLATO due to dyspnoea, but also perhaps due to compliance with its twice-daily administration. However, in this study, differences in outcomes were observed in all three comparisons of P2Y12-receptor inhibitors, which should not have been observed if switching of P2Y12-receptor inhibitor therapy contributed to differences in outcomes. Event rates in this study were low compared to PLATO or TRITON-TIMI 38 that involved larger numbers of patients, as under-reporting of adverse events is more likely in observational studies compared to RCTs. Therefore play of chance could not be excluded. Details of other changes to secondary prevention that could also be of prognostic value (aspirin, beta-adrenergic receptor blockers, ACE-inhibitors, statins) at 30-days and 12-months

could not be determined. However, differences across the groups were unlikely as all patients in this study received guideline-indicated care. Multiple comparisons of baseline and procedural characteristics were undertaken (Table 5.1). However, as with other comparisons of baseline and procedural characteristics in this study (Tables 3.1, 4.1, 5.1, 6.1, and 7.1), p-values presented in in Table 5.1 were not adjusted for multiple testing. This is because the p-values presented were descriptive rather than inferential, and were therefore, uncorrected. Finally, the findings of this study should be considered hypothesis-generating. Interrogation of larger national databases would facilitate larger-scale propensity-matched comparisons between P2Y12-receptor inhibitors that may inform future guideline-recommendations pertaining to DAPT strategy following PPCI for STEMI.

Chapter 6. Individual operator annual PPCI volume

6.1. Analysis of the association between individual operator annual PPCI volumes and outcomes

The current international guideline recommendation of >11PPCI per year as adequate operator volume was informed by two non-contemporary studies undertaken in the USA, where the practice of PPCI, particularly operator volume, does not necessarily reflect that in the UK. As described by Fanaroff et al, there is a significant geographical variability in operator volumes in the USA[143]. Therefore, the association between annual operator PPCI volume and outcomes in contemporary PPCI was an important study to undertake.

6.1.1. Calculation of annual operator PPCI volumes

PPCI in LGI is undertaken by internal operators who are primarily employed by Leeds Teaching Hospitals NHS Trust undertaking in-hours PPCI (Monday to Friday from 0800 hours to 1800 hours) and out-of-hours PPCI (Monday to Friday 1800 hours to 0800 hours, all day Saturday and all day Sunday) PPCI only at LGI, or external or visiting operators who are primarily employed by other regional hospitals, performing predominantly out-of-hours PPCI only at LGI.

Annual operator PPCI volumes were then calculated by deriving the mean number of PPCI undertaken by each operator over the time they were on the PPCI rota in LGI, which varied between 6 months and 4 years. The 33rd (55.5 PPCI per year) and 67th (110.3 PPCI per year) centiles of annual operator PPCI volumes were then calculated based on all PPCI performed over the four-year recruitment period. These centiles were then used to define operator volume tertiles, which were 1-54 PPCI per year (low-volume tertile), 55-109 PPCI per year (intermediate-volume tertile), and ≥110 PPCI per year (high-volume tertile).

6.1.2. Clinical endpoints

For this analysis, the primary endpoints were 30-day and 12-month mortality.

6.1.3. Survival analyses

Multivariable analyses were undertaken by AK using Cox proportional hazards regression analyses in IBM SPSS (version 23.0.0.2), to adjust for confounding variables. The proportional hazards assumptions were verified both graphically with log-minus-log curves, and with time-dependent covariate analyses. The variables included in the Cox models were: individual operator volume tertile, patient age (as a continuous variable), prior MI, hypercholesterolaemia, hypertension, pre-existing peripheral vascular disease or cerebrovascular disease, diabetes mellitus, current or previous history of cigarette-smoking, left main coronary artery IRA, out-of-hours PPCI (as defined above), DTB of ≥ 90 minutes (a combination of known predictors of poor outcomes following PPCI and variables that differed between groups with $P<0.10$. The high-volume tertile was used as the reference category for survival analyses when comparing clinical outcomes of low-volume and intermediate-volume operators against those of high-volume operators. In the comparison of low-volume operators and intermediate-volume operators, the reference category was intermediate-volume operator. The Cox regression analyses were then repeated to compare 30-day and 12-month mortality between PPCI performed by internal operators and PPCI performed by visiting operators, by substituting operator volumes with the categorical variable "internal operator", using internal operator as the reference category for survival analyses. All hazard ratios in this study were obtained from the Cox regression models, and were quoted with their corresponding 95% confidence intervals.

6.2. Results

During the study period (01-01-2009 and 31-12-2011, and between 01-01-2013 and 31-12-2013 (four calendar-years)), a total of 4056 patients underwent PPCI in LGI, of whom 3703 (91.3%) patients were followed up to a minimum of 12 months. All patients who were followed up were included in this analysis. Thirty-day and 12-month mortality data were available for all patients included in this analysis. Of the 3703 procedures, 1122 PPCI were performed by 23 low-volume operators, 1284 PPCI were performed by five intermediate-volume operators, and 1297 PPCI were performed by three high-volume operators. Baseline and procedural characteristics are detailed in Table 6.1.

Table 6.1: Baseline and procedural details according to annual operator PPCI volume.

Clinical characteristics	Operator volume			
	Low (n=1122)	Intermediate (n=1284)	High (n=1297)	*P*
Number of PPCI per year, median (IQR)†	27 (9)	100 (24)	113 (9)	<0.01
Out-of-hours PPCI n (%)†	767 (68.4)	733 (57.1)	657 (50.7)	<0.01
Age in years, median (IQR)	63 (19)	63 (20)	63 (20)	0.88
Male n (%)	828 (73.8)	950 (74.0)	928 (71.5)	0.31
Diabetes mellitus n (%)	165 (14.7)	160 (12.5)	195 (15.0)	0.38
Current/Ex-smoker n (%)	744 (66.3)	857 (66.7)	864 (66.6)	0.99
Hypertension n (%)	451 (40.2)	488 (38.0)	490 (37.8)	0.44
Hypercholesterolemia n (%)	351 (31.3)	398 (31.0)	409 (31.5)	0.90
Renal insufficiency n (%)	26 (2.3)	33 (2.6)	38 (2.9)	0.76
Previous MI n (%)*	137 (12.2)	162 (12.6)	161 (12.4)	0.78
Peripheral/Cerebrovascular disease n (%)	82 (7.3)	95 (7.4)	110 (8.5)	0.62
Cardiac arrest n (%)	92 (8.2)	134 (10.4)	128 (9.9)	0.16
Door-to-balloon time in minutes median (IQR)	51 (29)	47 (30)	53 (31)	<0.01
Radial access n (%)	694 (61.9)	822 (64.0)	866 (66.8)	0.04
Multivessel PCI n (%)†	110 (9.8)	104 (8.1)	109 (8.4)	0.30
Stent implantation n (%)	1029 (91.7)	1206 (93.9)	1232 (95.0)	<0.01
Third generation P2Y12-receptor inhibitor n (%)	628 (56.0)	747 (58.2)	680 (52.4)	0.01
Glycoprotein IIb/IIIa antagonist n (%)	215 (19.2)	156 (12.1)	216 (16.7)	<0.01
Bivalirudin n (%)	1065 (94.9)	1221 (95.1)	1219 (94.0)	0.41
Aspiration thrombectomy n (%)	759 (67.7)	982 (76.5)	850 (65.6)	<0.01
Post-procedural TIMI 3 flow in IRA n (%)§	956 (88.3)	1155 (92.7)	1157 (92.0)	<0.01

Data are expressed as median (interquartile range), or number (%) as described; *MI: Myocardial Infarction; †PCI: Percutaneous coronary intervention; ‡TIMI: Thrombolysis in Myocardial Infarction; § IRA: Infarct-related artery.

Patient baseline characteristics did not significantly differ between the three tertiles. However, there were statistically significant differences in procedural characteristics; proportion of out-of-hours PPCI, choice of pre-procedural P2Y12-receptor inhibitor therapy, radial artery access for PPCI, glycoprotein IIb/IIIa antagonist use, the use of thrombus aspiration catheters, rates of stent implantation, CTB and DTB times, and post-procedural TIMI 3 flow in the IRA were significantly different across the tertiles (Table 6.1).

In the low-volume tertile, 30-day mortality was observed in 76 (6.8%) patients, in comparison with 71 (5.5%) patients in the intermediate-volume tertile, and 66 (5.1%) patients in the high-volume tertile (Chi-square p-value = 0.19). Twelve-month mortality was recorded in 112 (10.0%) patients in the low-volume tertile, 116 (9.0%) patients in the intermediate-volume tertile, and 110 (8.5%) of patients in the high-volume tertile (Chi-square p-value = 0.44). After adjusting for potential confounding factors, a statistically significant difference in 30-day mortality (HR 1.48 (95% CI 1.05-2.08); p=0.02) was observed in PPCI performed by low-volume operators compared to high-volume operators. However, the difference in 12-month mortality approached, but did not reach statistical significance (HR 1.26 (95% CI 0.96-1.65); p=0.09). When PPCI performed by intermediate operators were compared to those performed by high-volume operators, no statistically significant difference in adjusted rates of 30-day (HR 1.29 (95% CI 0.91-1.81); p=0.15) and 12-month mortality (HR 1.21 (95% CI 0.93-1.58); p=0.15) (Table 6.2, Figures 6.1 & 6.2) were observed. Thirty-day (HR 1.15 (95% CI 0.83-1.60); p=0.40) and 12-month (HR 1.04 (95% CI 0.80-1.35); p=0.78) adjusted mortality between PPCI performed by low and intermediate-volume operators were also not statistically significantly different.

When analyses were repeated with operator status rather than operator volumes, PPCI performed by visiting operators (n=22) was not associated with higher 30-day (HR 1.18 (95% CI

0.88-1.56)) and 12-month (HR 1.12 (95% CI 0.89-1.40)) mortality compared to internal operators (n=9).

Other factors that were independently associated with mortality in the Cox regression models were advancing age, prior MI, pre-existing peripheral vascular disease or cerebrovascular disease, diabetes mellitus, left-main coronary artery as the IRA, and DTB time of ≥90 minutes (Table 6.2). Left-main coronary artery as the IRA was most strongly associated with 30-day and 12-month mortality in this analysis.

Table 6.2: Adjusted 30-day and 12-month mortality for all variables included in Cox proportional hazards models analysing operator volumes and potential confounders.

Factors	30-day mortality Adjusted HR (95% CI) †	12-month mortality Adjusted HR (95% CI) †
Low-volume operators	1.48 (95% CI 1.05-2.08)*	1.26 (95% CI 0.96-1.65)
Intermediate-volume operators	1.29 (95% CI 0.91-1.81)	1.21 (95% CI 0.93-1.58)
Out-of-hours presentation	1.02 (95% CI 0.77-1.35)	1.12 (95% CI 0.89-1.39)
Previous myocardial infarction	1.48 (95% CI 1.02-2.14)*	1.51 (95% CI 1.13-2.00)*
Hypertension	1.09 (95% CI 0.80-1.49)	1.14 (95% CI 0.90-1.46)
Hypercholesterolemia	0.79 (95% CI 0.56-1.11)	0.79 (95% CI 0.61-1.03)
Diabetes mellitus	1.54 (95% CI 1.07-2.22)*	1.64 (95% CI 1.24-2.17)*
Peripheral / cerebral vascular disease	1.44 (95% CI 0.96-2.17)	1.92 (95% CI 1.43-2.57)*
Current / Ex-smoker	0.79 (95% CI 0.57-1.10)	0.91 (95% CI 0.70-1.17)
Left main coronary artery culprit vessel	7.27 (95% CI 4.11-12.85)*	5.00 (95% CI 2.93-8.52)*
Advancing age (per year)	1.05 (95% CI 1.04-1.07)*	1.06 (95% CI 1.05-1.08)*
Door-to-balloon time ≥ 90 minutes	1.46 (95% CI 1.05-2.03)*	1.52 (95% CI 1.17-1.97)*

The reference category for operator volume is high-volume operators; †HR: Hazard ratio; CI: Confidence intervals; * p-value ≤ 0.05. All hazard ratios were obtained from Cox models used to analyse operator volumes.

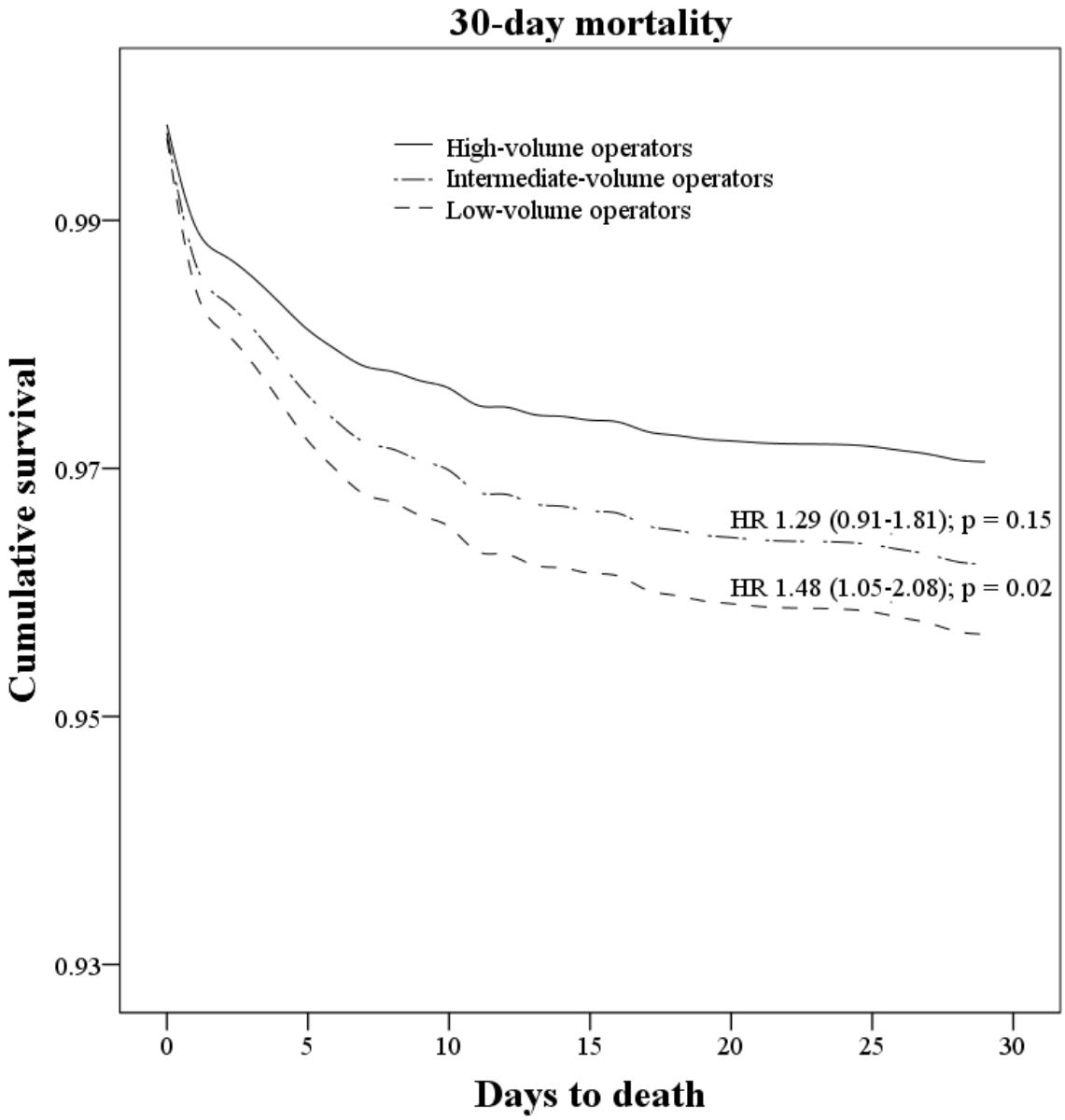


Figure 6.1: Kaplan-Meier curves illustrating adjusted 30-day mortality according to operator tertiles. High-volume operator tertile was used as the reference tertile.

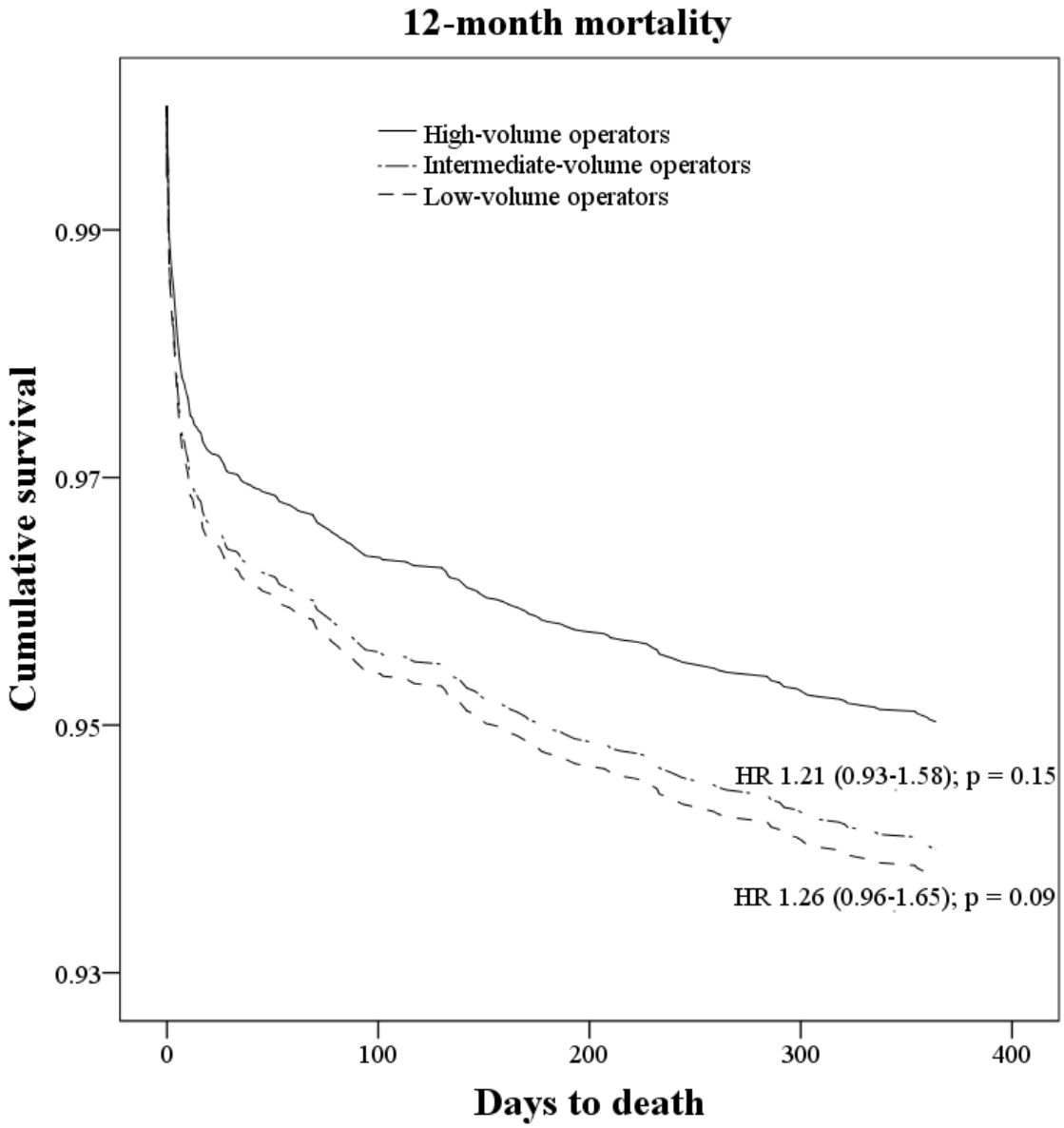


Figure 6.2: Kaplan-Meier curves illustrating adjusted 12-month mortality according to operator tertiles. High-volume operator tertile was used as the reference tertile.

6.3. Discussion

In this study, annual operator volume of PPCI for STEMI has been shown to be independently and inversely associated with 30-day mortality following the index-PPCI. PPCI performed by low volume operators (<55 PPCI per year) were associated with statistically significantly higher adjusted 30-day mortality than those performed by high-volume operators (≥110 PPCI per year). This suggests that an operator volume-outcome relationship specific to PPCI exists at a threshold far higher than those quoted current AHA guideline recommendation of ≥11 PPCI per year per individual operator[181].

Vakili et al demonstrated that in a cohort of patients who underwent PPCI in 1995, PPCI performed by high-volume operators (defined as ≥11 PPCI per operator per year) in high-volume centres (≥57 PPCI per centre per year) was associated with significantly lower in-hospital mortality compared to low-volume operators in low-volume centres[144]. However, contradictory to the findings of this study, this difference was not observed when comparing low-volume operators with high-volume operators in high-volume centres. The difference between their study and this study might be explained by the advances in PPCI between 1995 and 2009 in procedural techniques (radial artery access, smaller arterial sheaths), stent implantation (only 18% of patients received stents in their study, compared to 93.6% of patients in our study), pharmacotherapy (their study population predated the DAPT-era), and general trends in the acceptance of PPCI as the gold-standard reperfusion strategy in STEMI, following the landmark meta-analysis by Keeley et al in 2003[19]. Importantly, this study has shown a difference in mortality at 30 days (compared to just in-hospital outcomes in their study). Although their study was important in informing the AHA Guideline recommendation pertaining to operator volumes of PPCI, its relevance in contemporary

PPCI is not clear, as the uptake of PPCI, evolution of techniques, technology and the evolution of secondary prevention since 1995 has been significant.

In comparison with the analysis by Srinivas et al[148], this study has shown that operator-volume-outcome relationship exists at a threshold higher than previously found. This could be due to a few factors. Their period of recruitment was between 2000 and 2002, which predated the routine utilisation of DAPT and transradial PPCI, both of which have been shown to be associated with outcomes, and the latter of which has a significant learning curve, which may be a marker of operator skill and experience. The principal finding of this study is that within a single high-volume institution, annual PPCI operator volume was independently and inversely associated with mortality at a higher operator-volume threshold, and after a longer follow-up period than previously reported. This is the first study to show that a difference in 30-day mortality according to operator PPCI volume in a high-volume centre, in a "contemporary era" of PPCI. This is also the first study outside USA to assess this association.

In this study, differences in outcomes according to operator characteristics has been shown to be driven by annual operator PPCI volume, rather than operator status (internal vs external). Differences in procedural characteristics were identified that could potentially contribute to the differences observed in adjusted mortality. In the low-volume tertile, lower rates of radial access for PPCI, which is independently associated with improved outcomes in PPCI, was observed when compared with the intermediate-volume and high-volume tertiles[24,36,39,182]. Higher proportion of patients with post-procedural TIMI 3 flow in the IRA were also noted in the high-volume operator tertile compared to the low-volume operator tertile, which, in addition to radial artery access, may be a reflection of operator

skill and experience. PPCI is also believed to involve clinical and procedural skills not usually seen in elective or urgent PCI, such as the use of thrombus aspiration, adjunct pharmacotherapy to manage slow/no-reflow, and the ability to safely perform PCI in the setting of active cardiac ischemia, cardiogenic shock or refractory cardiac arrest. Therefore, development and maintenance of these skills, along with familiarity with institutional staff and equipment could also explain the volume-outcome relationship, although these factors are difficult to objectively quantify. There were also differences in the proportion of PPCI undertaken out-of-hours. As described in previous sections, the low-volume operators undertake more out-of-hours PPCI compared to the intermediate and high-volume operators. However, there may not necessarily be an association between time of admission and outcomes in a 24/7 tertiary referral centre[183,184].

Although institutional PCI volumes have been shown to not be associated with clinical outcomes[185], the finding of this study that PPCI performed by operators undertaking <55 PPCI per year is associated with significantly higher risk-adjusted 30-day mortality compared to PPCI performed by high-volume operators, suggests the need to re-examine the AHA recommendation that ≥11 PPCI per year per operator (which was derived from old-non-contemporary studies) is recommended for the safe provision of PPCI.

6.4. Limitations

As with other observational studies, despite data being prospectively collected, it is possible that some confounders remain unadjusted for. However, this was observed in prior analyses of operator volumes, and is likely to be the case with future analyses of operator volumes and outcomes, as data for this particular scientific question is likely to be derived only from

registry data. In this study, the difference between median annual PPCI volumes between intermediate-volume operators and high-volume operators was not numerically large. However, the difference in mean operator volumes in these two groups was strongly statistically significant (P<0.01). Clinically, dividing these groups may not be relevant or even appropriate. However, in this study, and any other study examining annual operator volumes of procedures, this was an expected finding due to the right-skewed distribution of operator-volume. Therefore, the use of operator volume tertiles based on institutional operator-volumes was statistically justified. Some visiting operators may have undertaken in-hours PPCI in their own regional hospitals. However, according data form to the British Cardiovascular Intervention Society database, between 2012 and 2014 (3 calendar years), only 25 PPCI procedures (less than 1% of total PPCI volumes undertaken in West Yorkshire during this period) were undertaken in four regional hospitals by 13 of the 21 visiting operators. This only adds approximately 0.6 PPCI per year per operator. Therefore, the PPCI undertaken by visiting cardiologists in Leeds General Infirmary is likely to be representative of their actual annual PPCI volume. Although play of chance could not be excluded with observational data, the findings of this study are scientifically plausible as transradial PPCI and post-procedural TIMI 3 flow in IRA, both of which are associated with improved outcomes following PPCI, were noted to be more likely in PPCI undertaken by high-volume operators compared to low-volume operators. Another potential source of bias is the 8% loss to follow up at 12 months. However, as these patients were distributed randomly across the volume tertiles, the population included in the analyses should be representative of the total PPCI population. The high-volume tertile was populated by three high-volume operators. This is significantly fewer than the other tertiles, as expected following a division by the number of cases done. The difference in outcomes observed in the high-volume

group could potentially be due to individual practice and technique, rather than case volume. Although outcomes in this study were analysed according to volume tertiles, as were the two prior studies examining this association, future studies could analyse the association between operator volumes and outcomes as a continuous variable, rather than volume tertiles. As with prior chapters, although multiple comparisons were shown in the comparison of baseline and clinical characteristics (Table 6.1), these comparisons were not corrected for multiple testing as the p-values shown were only descriptive. Although PPCI undertaken by low-volume operators was associated with higher risk-adjusted mortality, the benefit of this life-saving procedure, regardless of operator volume, has to be weighed against that of thrombolysis, which has been shown to be significantly less efficacious and more risky compared to PPCI. The results of this study therefore should be considered hypothesis-generating, and examination of larger national/international datasets should be considered to confirm the findings.

Chapter 7. Glycoprotein IIb/IIIa inhibitor use according to arterial access site

7.1. Analysis of the association between the use of GPI and outcomes, according to arterial access site

The evidence surrounding the use of GPI in PPCI is based on studies that were undertaken prior to the routine utilisation of radial artery access for PPCI, the use of third-generation P2Y12-receptor inhibitors, and the acceptance of PPCI as the default treatment strategy for STEMI in the UK. The progress with all of these factors could have led to a change in outcomes observed in patients undergoing PPCI, particularly in those undergoing transfemoral PPCI (the less-favoured and consequently less-utilised access site).

7.1.1. Study population

As described in section 2.3, GPI was typically used as a bail-out drug, most commonly in patients with significant thrombus burden, or slow or no-reflow phenomenon following PTCA or deployment of stent. Therefore, these patients, by default, had more adverse angiographic findings compared to patients in whom GPI was not used. Therefore, prior to any further adjustment, only patients with pre-PPCI TIMI flow (TIMI 0 in IRA) and post-PPCI TIMI flow (TIMI 3 in IRA) were considered for further analyses.

7.1.2. Clinical endpoints

The co-primary endpoints in this study were 30-day and 12-month mortality, and 30-day major bleeding according to HORIZONS criteria. The secondary endpoints were arterial access site and non-access site bleeding within 30 days of index PPCI.

7.1.3. Survival analyses

Cox proportional hazards regression models, performed by AK in IBM SPSS (Version 23.0.0.2) were used for survival analyses. All proportional hazards assumptions were verified visually with log-minus-log curves, and with time-dependent covariate analyses. Multivariable analyses were undertaken to adjust for potential confounding factors. Separate analyses were undertaken for based on arterial access site (Figure 7.1). In the analysis of mortality and bleeding, the variables included in the regression models were: GPI use, patient age at the time of index PPCI, gender, prior MI, prior coronary revascularisation (either PCI or CABG), diabetes mellitus, systolic blood pressure of less than 90mmHg (defined as a binary categorical variable), use of third-generation P2Y12-receptor inhibitors (prasugrel or ticagrelor), use of bivalirudin, and CTB time of > 120 minutes. In the analysis of access-site bleeding, variables included in the Cox models were: use of GPI, procedural bivalirudin and use of third generation P2Y12-receptor blockers. Further variables were not included to avoid overfitting of the models, based on the number of events observed. All hazard ratios quoted in this analysis were obtained from the Cox proportional hazards models, and were presented with their relevant 95% confidence intervals.

7.2. Results

During the period 01-01-2009 and 31-12-2011, and between 01-01-2013 and 31-12-2013 (four calendar-years), a total of 4056 patients underwent PPCI, of whom 12-month follow-up was completed for 3703 (91.3%) patients. A total of 2369 (64.0%) of the 3703 patient satisfied the inclusion criteria (pre-procedural TIMI 0 flow and post-procedural TIMI 3 flow in IRA), and were therefore included in the final analyses (Figure 7.1).

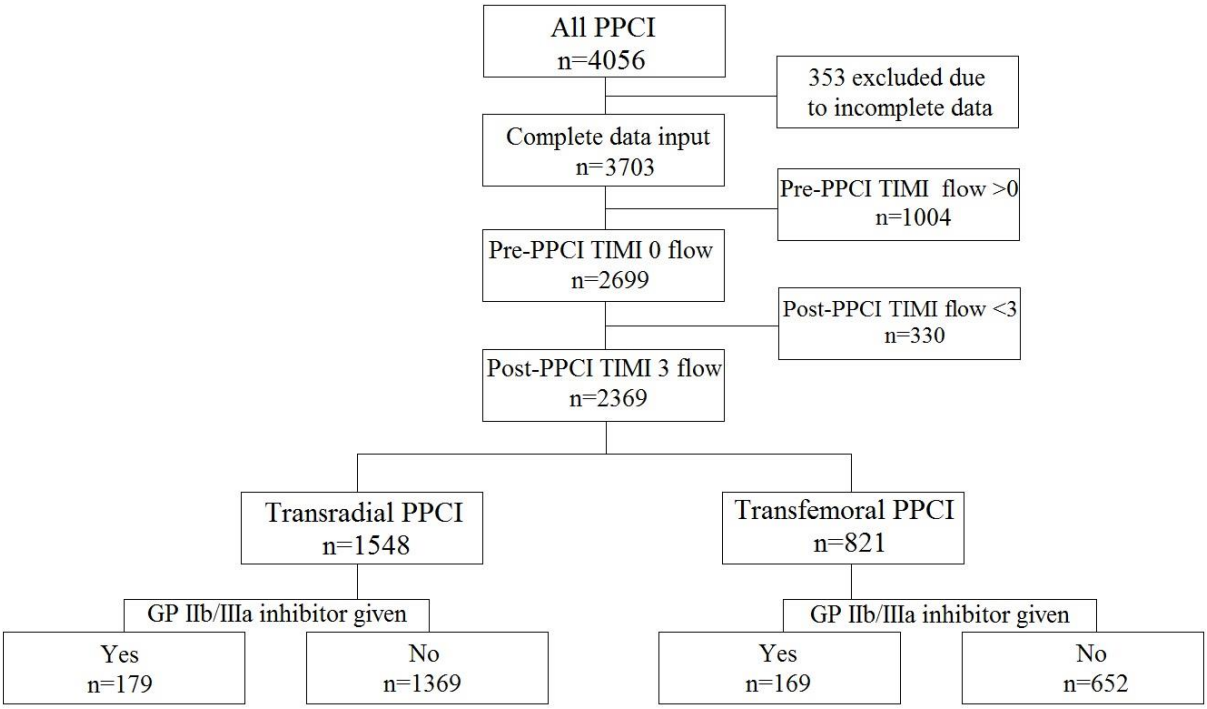


Figure 7.1: Inclusion algorithm for this analysis.

Of these patients, 1548 (65.3%) underwent transradial PPCI, 179 (11.6%) of whom received GPI (abciximab: n=176 (98.3%); tirofiban: n=3 (1.7%)). The remaining 821 (34.7%) patients who underwent transfemoral PPCI, 169 (20.6%) of whom received GPI (abciximab: n=166 (98.2%); tirofiban: n=2(1.2%); eptifipatide: n=1 (0.6%)). Comparison of baseline and procedural characteristics are detailed in Table 7.1. Comparison of clinical outcomes are shown in Table 7.2. In both groups of patients (transfemoral PPCI and transradial PPCI), statistically significant differences in baseline and procedural characteristics were observed in patients receiving GPI, in comparison to patients who did not receive GPI.

Table 7.1: Baseline and procedural characteristics according to arterial access site and use of glycoprotein IIb/IIIa inhibitors.

Characteristics	Transradial PPCI			Transfemoral PPCI		
	No GP IIb/IIIa inhibitor n=1369	GP IIb/IIIa inhibitor n=179	*P*	No GP IIb/IIIa inhibitor n=652	GP IIb/IIIa inhibitor n=169	*P*
Age in years median (IQR)	61 (18)	59 (18)	0.01	63 (21)	62 (21)	0.10
Male n (%)	1053 (76.9)	147 (82.1)	0.12	444 (68.1)	125 (74.0)	0.14
Diabetes mellitus n (%)	171 (12.5)	23 (12.8)	0.98	90 (13.8)	25 (14.8)	0.62
Cigarette smoking (current/ex-) n (%)	961 (70.2)	123 (68.7)	0.85	431 (66.1)	106 (62.7)	0.44
Hypertension n (%)	484 (35.4)	64 (35.8)	0.82	248 (38.0)	70 (41.4)	0.34
Previous MI n (%)*	127 (9.3)	21 (11.7)	0.45	72 (11.0)	40 (23.7)	<0.01
Previous CABG	5 (0.4)	0 (0.0)	0.59	25 (3.8)	13 (7.7)	<0.01
Previous revascularisation (percutaneous and surgical) n (%)	104 (7.6)	19 (10.6)	0.16	66 (10.1)	39 (23.1)	<0.01
Renal insufficiency n (%)	20 (1.4)	3 (1.6)	0.82	22 (3.3)	7 (4.2)	0.58
Systolic blood pressure < 90mmHg n (%)	55 (4.0)	8 (4.5)	0.77	51 (7.8)	18 (10.7)	0.24
Anterior MI n (%)*	512 (37.4)	70 (39.1)	0.66	271 (41.6)	74 (43.8)	0.60
Aspiration thrombectomy n (%)	1163 (85.0)	146 (81.6)	0.24	484 (74.3)	124 (73.4)	0.80
Third-generation P2Y12 inhibitors n (%)	910 (66.5)	121 (67.6)	0.76	294 (45.1)	54 (32.0)	<0.01
Drug-eluting stents n (%)	903 (66.0)	111 (62.0)	0.30	393 (60.3)	98 (58.0)	0.59
Call-to-balloon time median (IQR)	123 (55)	129 (46)	0.17	131 (66)	135 (67)	0.58
Bivalirudin n (%)	1348 (98.5)	149 (83.2)	<0.01	648 (99.4)	105 (62.1)	<0.01

Data are expressed as median (IQR), or number (%) as described; *MI: Myocardial Infarction.

Table 7.2: Clinical outcomes in patients treated with glycoprotein IIb/IIIa-inhibitors according to arterial access site.

	Transfemoral PPCI		Transradial PPCI	
	No GP IIb/IIIa inhibitor n=652	GP IIb/IIIa inhibitor n=169	No GP IIb/IIIa inhibitor n=1369	GP IIb/IIIa inhibitor n=179
30-day mortality n (%)	53 (8.0)	21 (12.4)	25 (1.8)	4 (2.2)
Adjusted HR (95%CI)[†‡]	1.00	2.04 (95% CI 1.05-3.94)*	1.00	1.27 (95% CI 0.39-4.16)
12-month mortality n (%)	77 (11.6)	24 (14.1)	69 (4.9)	10 (5.5)
Adjusted HR (95%CI)[†‡]	1.00	1.48 (95% CI 0.82-2.67)	1.00	1.21 (95% CI 0.58-2.51)
30-day total bleeding n (%)	47 (7.1)	27 (15.9)*	29 (2.1)	8 (4.4)
Adjusted HR (95%CI)[†‡]	1.00	2.05 (95% CI 1.07-3.93)*	1.00	1.93 (95% CI 0.73-4.76)
30-day arterial access site bleeding n (%)	13 (2.0)	12 (7.1)*	1 (0.1)	0 (0.0)
Adjusted HR (95%CI)[†‡]	1.00	2.71 (95% CI 1.00-7.37)*	N/A	N/A

Data are expressed as n (%); [†] HR: Hazard ratio; [‡] CI: Confidence interval; *p-value ≤ 0.05.

Transfemoral PPCI

In patients undergoing transfemoral PPCI, patients receiving GPI were statistically significantly more likely to have had prior MI, prior coronary revascularisation, received clopidogrel rather than prasugrel or ticagrelor, and received heparin rather than bivalirudin compared to patients who did not receive GPI (Table 7.1). Other variables were not statistically significantly different between patients who received GPI and patients who did not receive GPI.

Unadjusted analyses revealed no statistically significant differences in 30-day and 12-month mortality in patients receiving GPI compared to patients who did not receive GPI (Table 7.2; Figure 7.2). However, after adjustment for confounding factors, GPI use in transfemoral PPCI was independently associated with increased 30-day mortality, but not 12-month mortality in patients receiving GPI (Table 7.2; Figure 7.3 (A) & (B)).

Thirty-day major bleeding was significantly higher in patients receiving GPI in both unadjusted and adjusted analyses (Table 7.2; Figures 7.2 & 7.3(C)). Importantly, higher adjusted (for P2Y12-receptor inhibitor therapy and procedural anticoagulant therapy) arterial access-site related bleeding (HR 2.71 (95% CI 1.00-7.37); p=0.05)), but not non-access-site bleeding (HR 1.65 (95% CI 0.78-3.48); p=0.19), was observed in patients treated with GPI compared to patients not treated with GPI (Table 7.2; Figure 7.2).

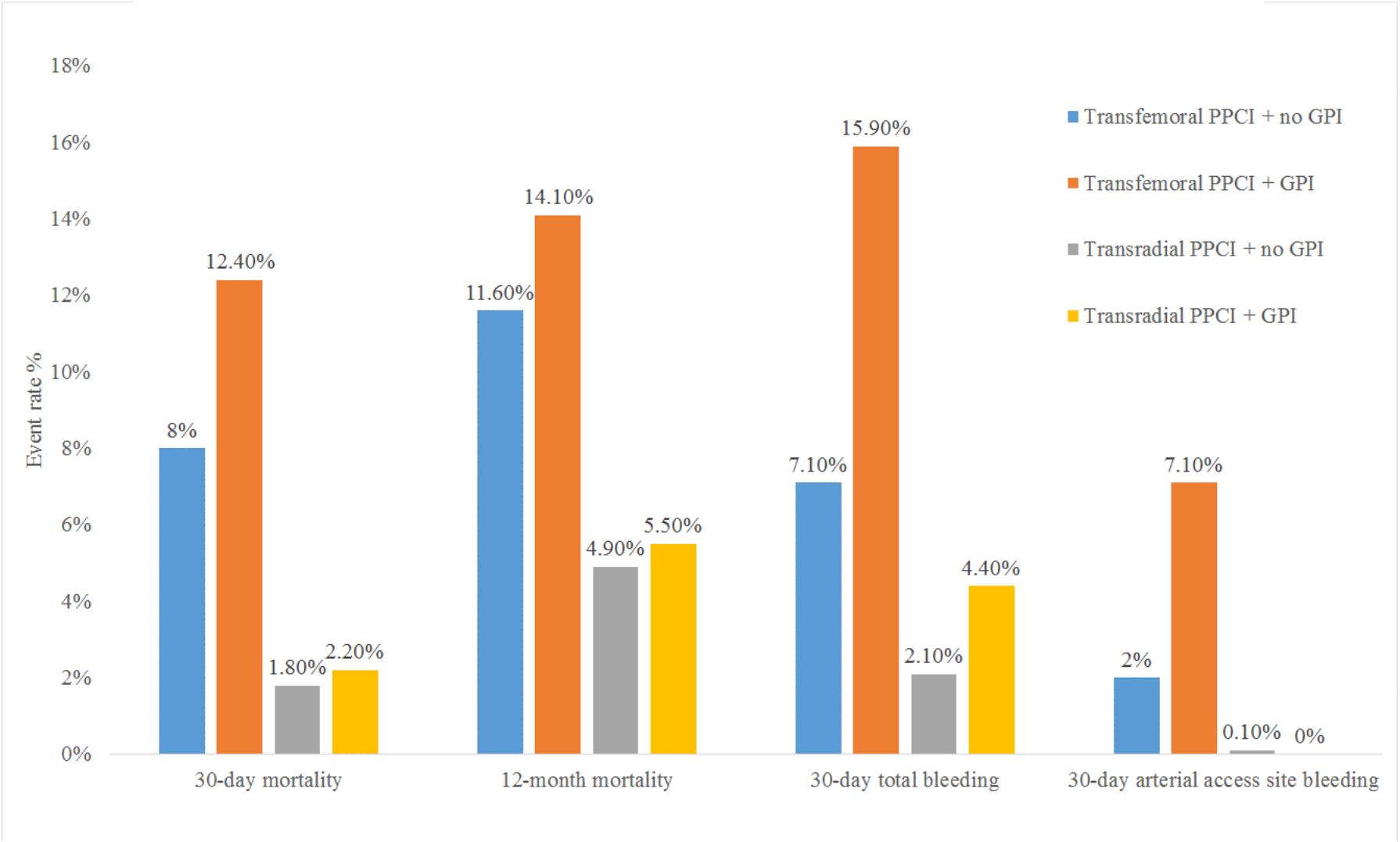
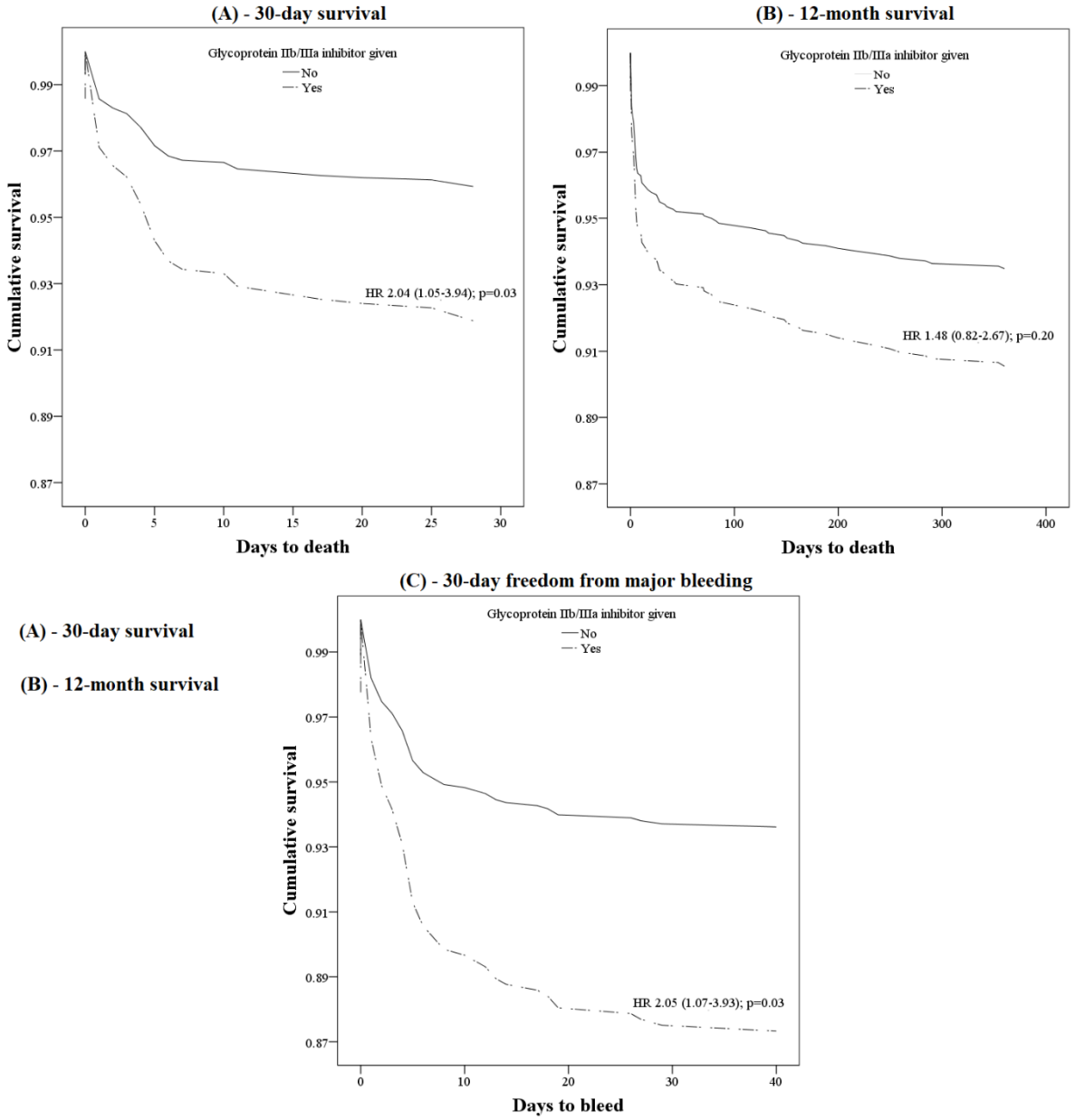


Figure 7.2: Unadjusted outcomes according to arterial access site and use of glycoprotein IIb/IIIa inhibitor therapy.



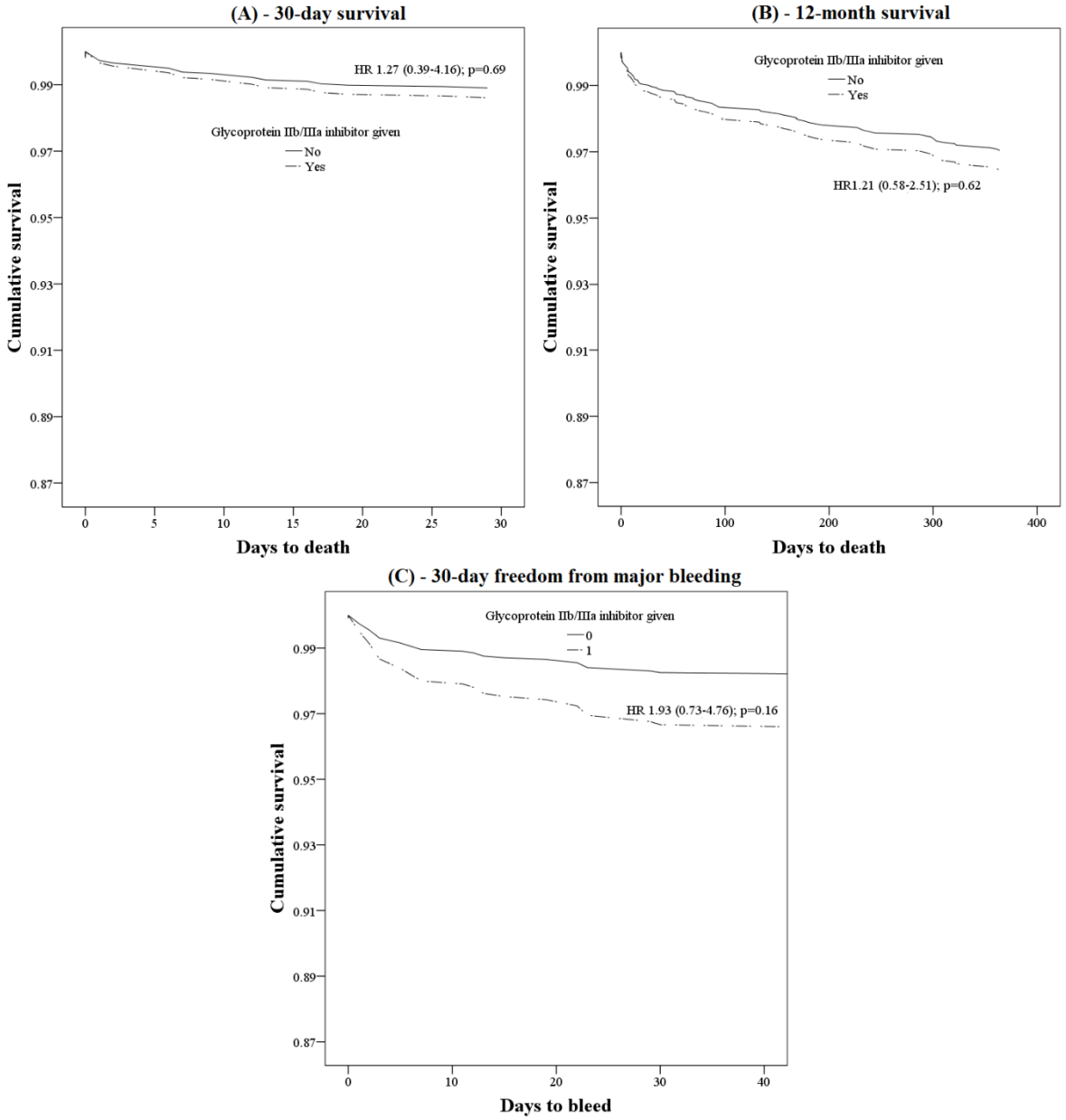
Figures 7.3 (A)-(C): Kaplan-Meier curves illustrating GPI use and adjusted 30-day survival, 12-month survival and 30-day freedom from major bleeding in patients undergoing transfemoral PPCI.

Transradial PPCI

In the transradial PPCI cohort, patients receiving GPI were likely to be younger and were more likely to receive intra-procedural heparin rather than bivalirudin compared to patients who did not receive GPI (Table 7.1). No other statistically significant differences in baseline or procedural characteristics were noted.

Unadjusted 30-day and 12-month mortality were not statistically significantly higher in patients receiving GPI (Table 7.2; Figure 7.1). Multivariable analysis confirmed no significant difference in adjusted 30-day and 12-month mortality in patients receiving GPI compared to patients not receiving GPI (Table 7.2; Figures 7.4 (A) & (B)).

Analysis of unadjusted 30-day bleeding showed that total bleeding, arterial access-site bleeding, and non-access-site bleeding were not significantly higher in patients who received GPI (Table 2; Figure 2). Multivariable analysis confirmed no statistically significant difference in adjusted total bleeding in patients receiving GPI (HR 1.93 (95% CI 0.73-4.76); p=0.16) (Figure 7.4 (C)). When procedural anticoagulation and P2Y12-receptor inhibitor were adjusted for, non-access-site bleeding was not statistically significantly higher in patients treated with GPI (HR 1.60 (95% CI 0.67-3.83); p=0.29). Multivariable analysis of arterial access site bleeding in patients undergoing transradial PPCI was not undertaken due to low incidence (only one patient undergoing transradial PPCI was recorded to have access-site bleeding).



Figures 7.4 (A)-(C): Kaplan-Meier curves illustrating GPI use and adjusted 30-day survival, 12-month survival and 30-day freedom from major bleeding in patients undergoing transradial PPCI.

7.3. Discussion

This analysis of patients undergoing PPCI in the "contemporary" era has revealed GPI use in patients undergoing transfemoral PPCI in the real-world was independently associated with increased 30-day mortality and 30-day bleeding, in particular arterial access-site bleeding. However, in patients undergoing transradial PPCI, GPI use was not associated with increased unadjusted or risk-adjusted mortality or bleeding.

Heer et al published real-world data collected between 2000 and 2002 from the German Acute Coronary Syndrome (ACOS) database, showing that treatment with abciximab was associated with improved mid-term mortality (HR 0.65 (95% CI 0.49-0.95)), with increased bleeding events noted in patients over 75 years of age[155]. However, in-hospital mortality was not significantly different. In contrast to their study, this study has shown an early divergence in risk-adjusted survival, which makes attributing adverse events with GPI-treatment more plausible. Patients treated with abciximab in their analysis were also more likely to have received aspirin (95% vs 89.3%; $p<0.01$) and were also 10% more likely to receive P2Y12-receptor inhibitor therapy. Patients receiving abciximab in their study were also younger, with fewer co-morbidities at presentation. In comparison, only one patient in this study did not receive aspirin due to allergy, and all patients received P2Y12-receptor inhibitors (a significant proportion of whom received the more potent third-generation P2Y12-receptor inhibitors), with a loading dose prior to PPCI. It is possible that patients who received abciximab in their study may have had lower bleeding risk, reflected in the difference in use of aspirin and clopidogrel, and may have been less frail compared to those who did not receive abciximab. In contrast, patients who received GPI in this study were mainly prescribed it as a "bailout", and therefore had a more adverse angiographic and clinical profile compared to patients who did not receive GPI, which may account for the

differences in outcomes between the two studies. Perhaps most importantly, the adjusted survival analysis in their study revealed a divergence in survival from approximately day 20, which should not be attributable to GPI therapy, whereas in this study, divergence is noted earlier. This suggests the more plausible possibility that other factors, such as frailty and differences in secondary prevention, particularly aspirin and clopidogrel, may have contributed to differences in survival in their study.

In comparison with the study by Iversen et al, this study was a comparison of GPI use according to arterial access site, and their study was a comparison of GPI use according to lesion complexity. In comparison with our study, arterial access site was not presented in this study, which could potentially have included both patients whom underwent transfemoral PPCI and transradial PPCI, particularly towards to latter years of recruitment. The principal finding of both this study and that of Iversen et al's was that in a real-world setting, treatment with abciximab was associated with improved clinical outcomes in a specific cohort of patients, and conversely, was associated with adverse clinical outcomes in the opposite cohort, which was in contrast with RCT data. Although our findings are not comparable to their study, due to differences in analyses, it is important to acknowledge that in keeping with our study, their real-world data pertaining to GPI use were not reflective of RCT data.

In terms of RCTs, the ADMIRAL and CADILLAC trials both demonstrated a benefit in the use of abciximab, driven by reduced target vessel revascularisation[151,152]. This was offset by higher rates of TIMI-minor bleeding in ADMIRAL, and higher rates of thrombocytopenia and blood transfusion in CADILLAC. Abciximab use was not associated with improvement in mortality in both trials. Arterial access site was not presented in either study, but they were both likely to have included patients who mainly underwent transfemoral PPCI, based on

the recruitment timeline. There were important differences in the patients recruited to ADMIRAL and CADILLAC in comparison to this study. Patients receiving GPI in this study appeared older (mean age 62 years-old vs 60 years-old). Only patients with pre-PPCI anterograde flow in IRA of TIMI 0 and post-PPCI anterograde flow in IRA of TIMI 3 were included in this study, to adjust for potential differences in thrombus-burden, and to adjust for final angiographic findings. Patients in ADMIRAL and CADILLAC received ticlopidine as their P2Y12-receptor inhibitor, compared to the newer and more potent clopidogrel, prasugrel and ticagrelor used in this study. They also received intraprocedural heparin rather than bivalirudin, which was the intraprocedural anticoagulant of choice in this. In ADMIRAL, abciximab was administered prior to arrival at the cardiac catheter laboratory, and possibly as a consequence, patients receiving abciximab had were less likely to have pre-procedural TIMI 0 flow (67.0% vs 81.5%; p=0.02), and were more likely to have post-procedural TIMI 3 flow (95.1% vs 86.7%; p=0.04) in their IRA, which could have in turn affected post-MI left-ventricular ejection fraction. In contrast, in this study and in current practice for STEMI, GPI is not routinely administered prior to arrival at the cardiac catheter laboratory. In the CADILLAC trial, patients who received GPI were less likely to have had prior MI (14.5% vs 23.7%), prior coronary revascularisation (14.2% vs 23.1%) or presented with ST-segment elevation or presumed new-onset left-bundle-branch-block (88.0% vs 100%) compared to this study. Patients receiving GPI in CADILLAC were less likely to have had their LAD as the IRA (34.6%vs 38.9%; p=0.04). In contrast to our study and to ADMIRAL, patients with cardiogenic shock were excluded from this trial. Both trials were undertaken at a time when transfemoral PPCI was the standard of treatment, in comparison to the era of transradial PPCI, with the femoral artery typically used as the second-choice arterial access site for most operators. Differences in patient characteristics, advances in

pharmacological therapy and PPCI technique and access site utilisation might account for the differences observed between this study and the RCTs.

More recently, the BRAVE-3 investigators compared abciximab with placebo in 800 patients undergoing PPCI between June 2003 and January 2008, showing no statistically significant difference in infarct size, mortality or major bleeding between the two groups[154]. However, there were several important differences between their study and ours. In BRAVE-3, all patients received clopidogrel as their P2Y12-receptor inhibitor. In contrast, only 990 (41.8%) of patients included in our study received clopidogrel, the remainder of whom received the more potent prasugrel (n=831 (35.1%)) and ticagrelor (n=548 (23.1%)). Maintenance dose of aspirin was also lower in our study (75mg/day vs 200mg/day). There were also several important exclusion criteria in BRAVE-3: thrombolytic therapy, previous stroke, bleeding diathesis or bleeding, major surgery or trauma within one month of PPCI, treatment with oral anticoagulant therapy within 7 days of PPCI, use of GPI within 14 days of PPCI, systolic blood pressure > 180mmHg, resistant to therapy, haematological abnormalities, cardiogenic shock, prolonged cardiopulmonary resuscitation (CPR), age >80 or <18, known or suspected pregnancy and allergy to study drugs. In contrast, the only patients excluded in our analysis, in addition to those whose follow-up data were unavailable, were patients who had pre-procedural TIMI flow > 0 and post-procedural TIMI flow < 3. Arterial access site was not presented in BRAVE-3, and it is possible that their study population included patients who underwent transradial PPCI as well as patients who underwent transfemoral PPCI. Therefore, assessing the association between GPI use and outcomes according to arterial access site was not possible. In our study, 1505 (63.5%) patients received DES, compared to 44% in BRAVE-3. These differences, in addition to potential patient-selection bias that can

be present in RCTs as a result of stringent inclusion criteria, could account for the differences in outcomes between BRAVE-3 and our study.

There is a widely reported association between transfemoral PPCI and adverse outcomes, in comparison to transradial PPCI[39,186,187]. As a result, the radial artery is the preferred access site for PPCI, with the femoral artery utilized as a "backup" arterial access site, and there has been a steady temporal trend in the uptake of transradial PCI in the UK[157]. In our study, 65.3% of patients underwent transradial PPCI. However, only 11.6% of patients who underwent transradial PPCI received GPI, compared to 20.6% of patients receiving GPI in the transfemoral PPCI cohort. This could be due to clinician approach towards GPI, which has evolved from routine use to bail-out use over the course of this study, which has also seen a parallel temporal rise in transradial PPCI. In the transfemoral cohort, patients receiving GPI were more likely to have had previous coronary revascularisation (both PCI and CABG), and were less likely to have received third-generation P2Y12 receptor inhibitors compared to patients who did not receive GPI. Although these differences could have contributed to higher unadjusted mortality in patients receiving GPI in the transfemoral PPCI cohort, correcting for them using multivariable analysis did not eliminate excess mortality observed at 30 days following index PPCI. The significant difference in adjusted mortality is likely to be due to increased arterial access site bleeding observed in patients receiving GPI during transfemoral PPCI, a finding which has been previously reported[177,188–191]. In patients undergoing transradial PPCI, there was no difference in adjusted mortality or bleeding in patients receiving GPI, as access site bleeding is rare in transradial PPCI compared to transfemoral PPCI, and in this study, was only observed in one patient who was not treated with GPI[192].

Although current guidelines provide a Class II indication for the use of GPI in PPCI, the findings of this study should prompt interrogation of larger databases to clarify the association between GPI use and outcomes in transfemoral PPCI in a "real-world" setting, which could in turn inform future guideline recommendations pertaining to GPI use[161,193].

7.4. Limitations

As with single-centre observational studies, outcomes observed in this study may not represent outcomes in other regions or centres. However, as our STEMI-management model is the default model in the UK, we are confident that our findings are representative of PPCI in the UK. As with most observational studies, it was not possible to correct for all potential confounding factors. This is especially important as the use of GPI has evolved from routine use to "bail-out" use, and therefore patients receiving GPI were possibly "selected" based on adverse angiographic findings, particularly thrombus burden. However, we attempted to attenuate the possible selection bias by matching patients according to pre-PPCI and post-PPCI TIMI flow, and then conducting multivariable analysis to adjust for remaining confounders. Nevertheless, it remains possible that some confounders may not have been corrected for. However, it is important to acknowledge that any further studies published pertaining to GPI use in transfemoral PPCI are likely to be derived from observational registry data, as there may be ethical issues with conducting RCTs assessing the impact of GPI in transfemoral PPCI, as it would involve routine use of GPI rather than the currently-accepted bail-out usage, and it may involve assignment to transfemoral PPCI, which is associated with adverse outcomes compared to transradial PPCI. We were also unable to determine details of changes to secondary prevention therapy following discharge from hospital. Therefore, changes to antiplatelet therapy, which in turn could have led to ischaemic or bleeding events, although unlikely to be different between the cohorts, could

not be excluded. Although mortality data were available for all patients in this analysis, under-reporting of bleeding events following discharge from hospital could not be excluded. However, this was unlikely to have been different across the groups of patients, and importantly, post-discharge (>72 hours) bleeding may not necessarily be due to intra-procedural GPI therapy.

Chapter 8: Conclusions

The five studies undertaken from this large “all-comers” registry have provided important outcome information in regard to contemporary PPCI. Three of these studies (Chapters 3, 4 and 6) examined patient and operator variables associated with clinical outcomes following PPCI, whilst the other two (Chapters 5 and 7) examined the association between treatment received and clinical outcomes following PPCI. Although the populations in each study were unmatched, multivariable analyses were undertaken to correct for confounding factors. Some of the findings in these studies were not in keeping with RCT data. This discrepancy is common in observational “real-world” datasets, as there is less control over patients included in these registries. The findings of these studies may need to be further validated with interrogation of larger datasets, such as the UK British Cardiovascular Intervention Society database, the Swedish Coronary Angiography and Angioplasty Register database, or the New York PCI database, as the results of single-centre studies may not necessarily reflect the results obtained in other centres or regions. However, whilst the number of patients from these larger databases may be significantly higher compared to the WY-PPCI registry, with this being a single-centre prospectively recruited study, obtaining data pertaining to events that did not occur in the same hospital that PPCI was undertaken, such as bleeding and recurrent MI, was possible in this study. This advantage was particularly notable as a balanced comparison of therapies, namely P2Y12-receptor inhibitors and GPI was possible with data obtained from other regional hospitals.

The key conclusions from each study are summarised as follows:

8.1. The association between gender and ethnicity and outcomes following PPCI

The female gender is not an independent predictor of poor clinical outcomes. Instead, the difference in age at presentation is the strongest predictor of clinical outcomes in the comparison between men and women. Improvements in service provision, particularly minimising delays in women, and in transradial PPCI, could further improve outcomes in women following PPCI.

Despite experiencing higher rates of recurrent MI, univariable and multivariable analysis showed that South Asian patients did not have statistically significantly higher rates of mortality or MACE compared to White patients. The significantly higher rate of recurrent MI in South Asian patients is likely to be due to their higher prevalence of diabetes mellitus compared to white patients.

8.2. Clinical outcomes in PPCI according to P2Y12-receptor inhibitor

This study has shown that in patients undergoing PPCI, treatment with prasugrel was independently associated with lower adjusted 30-day and 12-month mortality, and 12-month MI when compared with clopidogrel. Importantly, for the first time, treatment with prasugrel has been shown to be independently associated with lower adjusted 30-day mortality compared to ticagrelor in PPCI. Recurrent MI within 30 days and 12 months following index PPCI were lower in patients treated with ticagrelor compared to clopidogrel. However, there were no significant differences in 30-day and 12-month mortality between patients treated with ticagrelor and clopidogrel. Overall, both prasugrel and ticagrelor were

associated with lower adverse events compared to clopidogrel, with no associated excess bleeding within 30 days.

8.3. The association between individual operator annual PPCI volume and outcomes

Low operator-volume in PPCI for STEMI was independently associated with higher 30-day mortality compared to high operator-volume, suggesting an operator volume-outcome relationship exists at a threshold significantly higher than current guideline recommendations. If confirmed, annual recommended operator volumes for PPCI in national and international guidelines may need to be re-defined to ensure optimal patient outcomes following PPCI.

8.4. The association between GPI use and outcomes in PPCI according to arterial access site

In patients undergoing transfemoral PPCI, GPI use was independently and directly associated with increased 30-day mortality and 30-day bleeding, which was driven by increased arterial access-site bleeding, findings that were not observed in patients undergoing transradial PPCI. If confirmed in larger studies, clarification of guideline-recommendations for GPI use in transfemoral PPCI may be necessary.

Funding

1. Daiichi Sankyo – provided a 1 year unrestricted educational grant to support a Research Nurse salary and statistical support for data analysis.

2. LGI consultant interventional cardiologists – funded the salary for 2 years for Dr Arvindra Krishnamurthy to undertake his MD.

References:

1. Mendis S, Puska P, Norrving B. Global atlas on cardiovascular disease prevention and control. *World Heal Organ*. 2011:2-14. doi:NLM classification: WG 120.

2. Jones DA, Gallagher S, Rathod KS, et al. Mortality in South Asians and Caucasians after percutaneous coronary intervention in the United Kingdom: an observational cohort study of 279,256 patients from the BCIS (British Cardiovascular Intervention Society) National Database. *JACC Cardiovasc Interv*. 2014;7(4):362-371. doi:10.1016/j.jcin.2013.11.013.

3. Townsend N, Bhatnagar P, Wilkins E, Wickramasinghe K, Rayner M. *Cardiovascular Disease Statistics 2015*.; 2015. doi:CVDSTATS15.

4. Kumar V, Abbas AK, Aster JC. *Robbins & Cotran Pathologic Basis of Disease*.; 2013.

5. Camm AJ, Lüscher TF, Serruys PW. The ESC Textbook of Cardiovascular Medicine. //oxfordmedicine.com/10.1093/med/9780199566990.001.0001/med-9780199566990.

6. Davies MJ, Woolf N, Robertson WB. Pathology of acute myocardial infarction with particular reference to occlusive coronary thrombi. *Br Heart J*. 1976;38(7):659-664. http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=483064&tool=pmcentrez&rendertype=abstract. Accessed August 18, 2016.

7. Thygesen K, Alpert JS, Jaffe AS, et al. Third universal definition of myocardial infarction. *Circulation*. 2012;126(16):2020-2035. doi:10.1161/CIR.0b013e31826e1058.

8. Lewis HD, Davis JW, Archibald DG, et al. Protective effects of aspirin against acute

myocardial infarction and death in men with unstable angina. Results of a Veterans Administration Cooperative Study. *N Engl J Med*. 1983;309(7):396-403. doi:10.1056/NEJM198308183090703.

9. Fuster V, Chesebro JH. Antithrombotic therapy: role of platelet-inhibitor drugs. I. Current concepts of thrombogenesis: role of platelets. (first of three parts). *Mayo Clin Proc*. 1981;56(2):102-112. http://europepmc.org/abstract/med/7007748. Accessed August 18, 2016.

10. Randomised trial of intravenous atenolol among 16 027 cases of suspected acute myocardial infarction: ISIS-1. First International Study of Infarct Survival Collaborative Group. *Lancet (London, England)*. 1986;2(8498):57-66. http://www.ncbi.nlm.nih.gov/pubmed/2873379. Accessed August 18, 2016.

11. Chen ZM, Pan HC, Chen YP, et al. Early intravenous then oral metoprolol in 45,852 patients with acute myocardial infarction: randomised placebo-controlled trial. *Lancet (London, England)*. 2005;366(9497):1622-1632. doi:10.1016/S0140-6736(05)67661-1.

12. Randomised trial of intravenous streptokinase, oral aspirin, both, or neither among 17,187 cases of suspected acute myocardial infarction: ISIS-2. ISIS-2 (Second International Study of Infarct Survival) Collaborative Group. *Lancet (London, England)*. 1988;2(8607):349-360. http://www.ncbi.nlm.nih.gov/pubmed/2899772. Accessed August 18, 2016.

13. TIMI Study Group. *The Thrombolysis in Myocardial Infarction (TIMI) Trial. Phase I Findings. TIMI Study Group.* Vol 312.; 1985. doi:10.1056/NEJM198504043121435.

14. Anderson JL, Karagounis LA, Becker LC, Sorensen SG, Menlove RL. TIMI perfusion grade 3 but not grade 2 results in improved outcome after thrombolysis for myocardial infarction. Ventriculographic, enzymatic, and electrocardiographic evidence from the TEAM-3 Study. *Circulation*. 1993;87(6):1829-1839. http://www.ncbi.nlm.nih.gov/pubmed/8504495. Accessed September 2, 2016.

15. Investigators TGA. The effects of tissue plasminogen activator, streptokinase, or both on coronary-artery patency, ventricular function, and survival after acute myocardial infarction. The GUSTO Angiographic Investigators. *N Engl J Med*. 1993;329(22):1615-1622. doi:10.1056/NEJM199311253292204.

16. Neuhaus KL, von Essen R, Tebbe U, et al. Improved thrombolysis in acute myocardial infarction with front-loaded administration of alteplase: results of the rt-PA-APSAC patency study (TAPS). *J Am Coll Cardiol*. 1992;19(5):885-891. http://www.ncbi.nlm.nih.gov/pubmed/1552106. Accessed September 26, 2016.

17. Zijlstra F, de Boer MJ, Hoorntje JC, Reiffers S, Reiber JH, Suryapranata H. A comparison of immediate coronary angioplasty with intravenous streptokinase in acute myocardial infarction. *N Engl J Med*. 1993;328(10):680-684. doi:10.1056/NEJM199303113281002.

18. Grines CL, Browne KF, Marco J, et al. A Comparison of Immediate Angioplasty with Thrombolytic Therapy for Acute Myocardial Infarction. *N Engl J Med*. 1993;328(10):673-679. doi:10.1056/NEJM199303113281001.

19. Keeley EC, Boura JA, Grines CL. Primary angioplasty versus intravenous thrombolytic therapy for acute myocardial infarction: a quantitative review of 23 randomised trials. *Lancet (London, England)*. 2003;361(9351):13-20. doi:10.1016/S0140-6736(03)12113-

7.

20. Weston CFM, Reinoga kathleen LJ, Dubos richard FR, Demian V. The Myocardial Ischaemia National Audit Project (MINAP) annual report 2015-2016. 2017. doi:10.1136/hrt.2009.192328.

21. Komócsi A, Aradi D, Kehl D, et al. Meta-analysis of randomized trials on access site selection for percutaneous coronary intervention in ST-segment elevation myocardial infarction. *Arch Med Sci*. 2014;10(2):203-212. doi:10.5114/aoms.2014.42570.

22. Park K-H, Jeong MH, Ahn Y, et al. The impact of vascular access for in-hospital major bleeding in patients with acute coronary syndrome at moderate- to very high-bleeding risk. *J Korean Med Sci*. 2013;28(9):1307-1315. doi:10.3346/jkms.2013.28.9.1307.

23. Rathod KS, Jones DA, Bromage DI, et al. Radial primary percutaneous coronary intervention is independently associated with decreased long-term mortality in high-risk ST-elevation myocardial infarction patients. *J Cardiovasc Med (Hagerstown)*. July 2014. doi:10.2459/JCM.0000000000000122.

24. Jolly SS, Yusuf S, Cairns J, et al. Radial versus femoral access for coronary angiography and intervention in patients with acute coronary syndromes (RIVAL): a randomised, parallel group, multicentre trial. *Lancet*. 2011;377(9775):1409-1420. doi:10.1016/S0140-6736(11)60404-2.

25. Michael TT, Alomar M, Papayannis A, et al. A randomized comparison of the transradial and transfemoral approaches for coronary artery bypass graft angiography and intervention: the RADIAL-CABG Trial (RADIAL Versus Femoral Access for Coronary

Artery Bypass Graft Angiography and Intervention). *JACC Cardiovasc Interv*. 2013;6(11):1138-1144. doi:10.1016/j.jcin.2013.08.004.

26. Eichhöfer J, Horlick E, Ivanov J, et al. Decreased complication rates using the transradial compared to the transfemoral approach in percutaneous coronary intervention in the era of routine stenting and glycoprotein platelet IIb/IIIa inhibitor use: A large single-center experience. *Am Heart J*. 2008;156(5):864-870. doi:10.1016/j.ahj.2008.06.044.

27. Romagnoli E, Biondi-Zoccai G, Sciahbasi A, et al. Radial Versus Femoral Randomized Investigation in ST-Segment Elevation Acute Coronary Syndrome. *J Am Coll Cardiol*. 2012;60(24):2481-2489. doi:10.1016/j.jacc.2012.06.017.

28. Hromádka M, Bernat I, Seidlerová J, et al. Access-site bleeding and radial artery occlusion in transradial primary percutaneous coronary intervention: influence of adjunctive antiplatelet therapy. *Coron Artery Dis*. 2016;27(4):267-272. doi:10.1097/MCA.0000000000000352.

29. Kedev S, Sukmawan R, Kalpak O, et al. Transradial versus transfemoral access for female patients who underwent primary PCI in STEMI: Two years follow-up data from acute STEMI interventional registry. *Int J Cardiol*. 2016;217 Suppl:S16-20. doi:10.1016/j.ijcard.2016.06.222.

30. Arzamendi D, Ly HQ, Tanguay J-F, et al. Effect on bleeding, time to revascularization, and one-year clinical outcomes of the radial approach during primary percutaneous coronary intervention in patients with ST-segment elevation myocardial infarction. *Am J Cardiol*. 2010;106(2):148-154. doi:10.1016/j.amjcard.2010.02.028.

31. Cafri C, Zahger D, Merkin M, Weinstein JM, Kobal S, Ilia R. Efficacy of the radial approach for the performance of primary PCI for STEMI. *J Invasive Cardiol*. 2013;25(3):150-153. http://www.ncbi.nlm.nih.gov/pubmed/23468447. Accessed November 16, 2016.

32. Marti V, Brugaletta S, García-Picart J, et al. Radial versus femoral access for angioplasty of ST-segment elevation acute myocardial infarction with second-generation drug-eluting stents. *Rev Esp Cardiol (Engl Ed)*. 2015;68(1):47-53. doi:10.1016/j.rec.2014.02.024.

33. Fujii T, Masuda N, Ijichi T, et al. Transradial intervention for patients with ST elevation myocardial infarction with or without cardiogenic shock. *Catheter Cardiovasc Interv*. 2014;83(1):E1-7. doi:10.1002/ccd.24896.

34. Bernat I, Abdelaal E, Plourde G, et al. Early and late outcomes after primary percutaneous coronary intervention by radial or femoral approach in patients presenting in acute ST-elevation myocardial infarction and cardiogenic shock. *Am Heart J*. 2013;165(3):338-343. doi:10.1016/j.ahj.2013.01.012.

35. Bauer T, Hochadel M, Brachmann J, et al. Use and outcome of radial versus femoral approach for primary PCI in patients with acute ST elevation myocardial infarction without cardiogenic shock: results from the ALKK PCI registry. *Catheter Cardiovasc Interv*. 2015;86 Suppl 1:S8-14. doi:10.1002/ccd.25987.

36. Mamas MA, Ratib K, Routledge H, et al. Influence of arterial access site selection on outcomes in primary percutaneous coronary intervention: are the results of randomized trials achievable in clinical practice? *JACC Cardiovasc Interv*. 2013;6(7):698-706. doi:10.1016/j.jcin.2013.03.011.

37. Lee MS, Wolfe M, Stone GW. Transradial versus transfemoral percutaneous coronary intervention in acute coronary syndromes: re-evaluation of the current body of evidence. *JACC Cardiovasc Interv*. 2013;6(11):1149-1152. doi:10.1016/j.jcin.2013.08.003.

38. Mehta SR, Jolly SS, Cairns J, et al. Effects of radial versus femoral artery access in patients with acute coronary syndromes with or without ST-segment elevation. *J Am Coll Cardiol*. 2012;60(24):2490-2499. doi:10.1016/j.jacc.2012.07.050.

39. Romagnoli E, Biondi-Zoccai G, Sciahbasi A, et al. Radial versus femoral randomized investigation in ST-segment elevation acute coronary syndrome: the RIFLE-STEACS (Radial Versus Femoral Randomized Investigation in ST-Elevation Acute Coronary Syndrome) study. *J Am Coll Cardiol*. 2012;60(24):2481-2489. doi:10.1016/j.jacc.2012.06.017.

40. Herrett E, Smeeth L, Walker L, Weston C. The Myocardial Ischaemia National Audit Project (MINAP). *Heart*. 2010;96(16):1264-1267. doi:10.1136/hrt.2009.192328.

41. Jensen LO, Thayssen P, Christiansen EH, et al. Safety and Efficacy of Everolimus- Versus Sirolimus-Eluting Stents. *J Am Coll Cardiol*. 2016;67(7):751-762. doi:10.1016/j.jacc.2015.11.051.

42. Sarno G, Lagerqvist B, Fröbert O, et al. Lower risk of stent thrombosis and restenosis with unrestricted use of “new-generation” drug-eluting stents: a report from the nationwide Swedish Coronary Angiography and Angioplasty Registry (SCAAR). *Eur Heart J*. 2012;33(5):606-613. doi:10.1093/eurheartj/ehr479.

43. Palmerini T, Biondi-Zoccai G, Riva D Della, et al. Stent thrombosis with drug-eluting

and bare-metal stents: evidence from a comprehensive network meta-analysis. *Lancet*. 2012;379(9824):1393-1402. doi:10.1016/S0140-6736(12)60324-9.

44. Sabaté M, Brugaletta S, Cequier A, et al. Clinical outcomes in patients with ST-segment elevation myocardial infarction treated with everolimus-eluting stents versus bare-metal stents (EXAMINATION): 5-year results of a randomised trial. *Lancet*. 2016;387(10016):357-366. doi:10.1016/S0140-6736(15)00548-6.

45. Smits PC, Kedhi E, Royaards K-J, et al. 2-Year Follow-Up of a Randomized Controlled Trial of Everolimus- and Paclitaxel-Eluting Stents for Coronary Revascularization in Daily Practice. *J Am Coll Cardiol*. 2011;58(1):11-18. doi:10.1016/j.jacc.2011.02.023.

46. Fröbert O, Lagerqvist B, Olivecrona GK, et al. Thrombus Aspiration during ST-Segment Elevation Myocardial Infarction. *N Engl J Med*. 2013;369(17):1587-1597. doi:10.1056/NEJMoa1308789.

47. Svilaas T, Vlaar PJ, van der Horst IC, et al. Thrombus Aspiration during Primary Percutaneous Coronary Intervention. *N Engl J Med*. 2008;358(6):557-567. doi:10.1056/NEJMoa0706416.

48. Sirker A, Mamas M, Kwok CS, Kontopantelis E, Ludman P, Hildick-Smith D. Outcomes From Selective Use of Thrombectomy in Patients Undergoing Primary Percutaneous Coronary Intervention for ST-Segment Elevation Myocardial Infarction. *JACC Cardiovasc Interv*. 2016;9(2):126-134. doi:10.1016/j.jcin.2015.10.047.

49. Jolly SS, Cairns JA, Yusuf S, et al. Randomized Trial of Primary PCI with or without Routine Manual Thrombectomy. *N Engl J Med*. 2015;372(15):1389-1398. doi:10.1056/NEJMoa1415098.

50. Alexander RW. Hypertension and the Pathogenesis of Atherosclerosis : Oxidative Stress and the Mediation of Arterial Inflammatory Response: A New Perspective. *Hypertension*. 1995;25(2):155-161. doi:10.1161/01.HYP.25.2.155.

51. Stamler J, Neaton JD, Wentworth DN. Blood pressure (systolic and diastolic) and risk of fatal coronary heart disease. *Hypertens (Dallas, Tex 1979)*. 1989;13(5 Suppl):I2-12. http://www.ncbi.nlm.nih.gov/pubmed/2490825. Accessed August 17, 2016.

52. Lee KL, Woodlief LH, Topol EJ, et al. Predictors of 30-Day Mortality in the Era of Reperfusion for Acute Myocardial Infarction : Results From an International Trial of 41 021 Patients. *Circulation*. 1995;91(6):1659-1668. doi:10.1161/01.CIR.91.6.1659.

53. Beckman JA, Creager MA, Libby P. Diabetes and Atherosclerosis. *JAMA*. 2002;287(19):2570. doi:10.1001/jama.287.19.2570.

54. Wilson PWF, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, Kannel WB. Prediction of Coronary Heart Disease Using Risk Factor Categories. *Circulation*. 1998;97(18):1837 LP-1847. http://circ.ahajournals.org/content/97/18/1837.abstract.

55. Kahn MB, Cubbon RM, Mercer B, et al. Association of diabetes with increased all-cause mortality following primary percutaneous coronary intervention for ST-segment elevation myocardial infarction in the contemporary era. *Diabetes Vasc Dis Res*. 2012;9(1):3-9. doi:10.1177/1479164111427752.

56. Brogan RA, Alabas O, Almudarra S, et al. Relative survival and excess mortality following primary percutaneous coronary intervention for ST-elevation myocardial infarction. 2017. doi:10.1177/2048872617710790.

57. Mamas MA, Fath-Ordoubadi F, Danzi GB, et al. Prevalence and Impact of Co-

morbidity Burden as Defined by the Charlson Co-morbidity Index on 30-Day and 1- and 5-Year Outcomes After Coronary Stent Implantation (from the Nobori-2 Study). *Am J Cardiol*. 2015;116(3):364-371. doi:10.1016/j.amjcard.2015.04.047.

58. Radovanovic D, Seifert B, Urban P, et al. Validity of Charlson Comorbidity Index in patients hospitalised with acute coronary syndrome. Insights from the nationwide AMIS Plus registry 2002-2012. *Heart*. 2014;100(4):288-294. doi:10.1136/heartjnl-2013-304588.

59. Vakili BA, Kaplan RC, Brown DL. Sex-Based Differences in Early Mortality of Patients Undergoing Primary Angioplasty for First Acute Myocardial Infarction. *Circulation*. 2001;104(25):3034-3038. doi:10.1161/hc5001.101060.

60. Jneid H, Fonarow GC, Cannon CP, et al. Sex differences in medical care and early death after acute myocardial infarction. *Circulation*. 2008;118(25):2803-2810. doi:10.1161/CIRCULATIONAHA.108.789800.

61. Radovanovic D, Erne P, Urban P, Bertel O, Rickli H, Gaspoz J-M. Gender differences in management and outcomes in patients with acute coronary syndromes: results on 20,290 patients from the AMIS Plus Registry. *Heart*. 2007;93(11):1369-1375. doi:10.1136/hrt.2006.106781.

62. Singh M, Rihal CS, Gersh BJ, et al. Mortality differences between men and women after percutaneous coronary interventions. A 25-year, single-center experience. *J Am Coll Cardiol*. 2008;51(24):2313-2320. doi:10.1016/j.jacc.2008.01.066.

63. Duvernoy CS, Smith DE, Manohar P, et al. Gender differences in adverse outcomes after contemporary percutaneous coronary intervention: an analysis from the Blue

Cross Blue Shield of Michigan Cardiovascular Consortium (BMC2) percutaneous coronary intervention registry. *Am Heart J*. 2010;159(4):677-683.e1. doi:10.1016/j.ahj.2009.12.040.

64. Akhter N, Milford-Beland S, Roe MT, Piana RN, Kao J, Shroff A. Gender differences among patients with acute coronary syndromes undergoing percutaneous coronary intervention in the American College of Cardiology-National Cardiovascular Data Registry (ACC-NCDR). *Am Heart J*. 2009;157(1):141-148. doi:10.1016/j.ahj.2008.08.012.

65. Diercks DB, Owen KP, Kontos MC, et al. Gender differences in time to presentation for myocardial infarction before and after a national women's cardiovascular awareness campaign: a temporal analysis from the Can Rapid Risk Stratification of Unstable Angina Patients Suppress ADverse Outcomes wi. *Am Heart J*. 2010;160(1):80-87.e3. doi:10.1016/j.ahj.2010.04.017.

66. Kaul P, Armstrong PW, Sookram S, Leung BK, Brass N, Welsh RC. Temporal trends in patient and treatment delay among men and women presenting with ST-elevation myocardial infarction. *Am Heart J*. 2011;161(1):91-97. doi:10.1016/j.ahj.2010.09.016.

67. Cheng C-I, Yeh K-H, Chang H-W, et al. Comparison of baseline characteristics, clinical features, angiographic results, and early outcomes in men vs women with acute myocardial infarction undergoing primary coronary intervention. *Chest*. 2004;126(1):47-53. doi:10.1378/chest.126.1.47.

68. Benamer H, Tafflet M, Bataille S, et al. Female gender is an independent predictor of in-hospital mortality after STEMI in the era of primary PCI: insights from the greater Paris area PCI Registry. *EuroIntervention*. 2011;6(9):1073-1079.

doi:10.4244/EIJV6I9A187.

69. Milcent C, Dormont B, Durand-Zaleski I, Steg PG. Gender Differences in Hospital Mortality and Use of Percutaneous Coronary Intervention in Acute Myocardial Infarction: Microsimulation Analysis of the 1999 Nationwide French Hospitals Database. *Circulation*. 2007;115(7):833-839. doi:10.1161/CIRCULATIONAHA.106.664979.

70. Otten AM, Maas AH, Ottervanger JP, et al. Is the difference in outcome between men and women treated by primary percutaneous coronary intervention age dependent? Gender difference in STEMI stratified on age. *Eur Hear J Acute Cardiovasc Care*. 2013;2(4):334-341. doi:10.1177/2048872612475270.

71. Peterson ED, Lansky AJ, Kramer J, Anstrom K, Lanzilotta MJ. Effect of gender on the outcomes of contemporary percutaneous coronary intervention. *Am J Cardiol*. 2001;88(4):359-364. doi:10.1016/S0002-9149(01)01679-4.

72. Sadowski M, Gasior M, Gierlotka M, Janion M, Poloński L. Gender-related differences in mortality after ST-segment elevation myocardial infarction: a large multicentre national registry. *EuroIntervention*. 2011;6(9):1068-1072. doi:10.4244/EIJV6I9A186.

73. Barthélémy O, Degrell P, Berman E, et al. Sex-related differences after contemporary primary percutaneous coronary intervention for ST-segment elevation myocardial infarction. *Arch Cardiovasc Dis*. 2015;108(8-9):428-436. doi:10.1016/j.acvd.2015.03.002.

74. van der Meer MG, Nathoe HM, van der Graaf Y, Doevendans PA, Appelman Y. Worse outcome in women with STEMI: A systematic review of prognostic studies. *Eur J Clin*

Invest. 2015;45(2):226-235. doi:10.1111/eci.12399.

75. Jacobs AK. Women, ischemic heart disease, revascularization, and the gender gap: what are we missing? *J Am Coll Cardiol*. 2006;47(3 Suppl):S63-5. doi:10.1016/j.jacc.2004.12.085.

76. D'Ascenzo F, Gonella A, Quadri G, et al. Comparison of Mortality Rates in Women Versus Men Presenting With ST-Segment Elevation Myocardial Infarction. *Am J Cardiol*. 2011;107(5):651-654. doi:10.1016/j.amjcard.2010.10.038.

77. Jakobsen L, Niemann T, Thorsgaard N, et al. Sex- and age-related differences in clinical outcome after primary percutaneous coronary intervention. *EuroIntervention*. 2012;8(8):904-911. doi:10.4244/EIJV8I8A139.

78. Berger JS, Elliott L, Gallup D, et al. Sex differences in mortality following acute coronary syndromes. *JAMA*. 2009;302(8):874-882. doi:10.1001/jama.2009.1227.

79. Jackson EA, Moscucci M, Smith DE, et al. The association of sex with outcomes among patients undergoing primary percutaneous coronary intervention for ST elevation myocardial infarction in the contemporary era: Insights from the Blue Cross Blue Shield of Michigan Cardiovascular Consortium (BMC2). *Am Heart J*. 2011;161(1):106-112.e1. doi:10.1016/j.ahj.2010.09.030.

80. Rosano GMC, Vitale C, Marazzi G, Volterrani M. Menopause and cardiovascular disease: the evidence. *Climacteric*. 2007;10 Suppl 1:19-24. doi:10.1080/13697130601114917.

81. Wilson PWF, Agostino RBD, Levy D, Belanger AM, Kannel WB. Prediction of Coronary Heart Disease Using Risk Factor Categories. *Circulation*. 1998;97:1837-1847.

82. Terkelsen CJ, Sørensen JT, Maeng M, et al. System delay and mortality among patients with STEMI treated with primary percutaneous coronary intervention. *JAMA*. 2010;304(7):763-771. doi:10.1001/jama.2010.1139.

83. Hudson MP, Armstrong PW, O'Neil WW, et al. Mortality implications of primary percutaneous coronary intervention treatment delays: insights from the Assessment of Pexelizumab in Acute Myocardial Infarction trial. *Circ Cardiovasc Qual Outcomes*. 2011;4(2):183-192. doi:10.1161/CIRCOUTCOMES.110.945311.

84. McNamara RL, Wang Y, Herrin J, et al. Effect of door-to-balloon time on mortality in patients with ST-segment elevation myocardial infarction. *J Am Coll Cardiol*. 2006;47(11):2180-2186. doi:10.1016/j.jacc.2005.12.072.

85. Nallamothu B, Fox KAA, Kennelly BM, et al. Relationship of treatment delays and mortality in patients undergoing fibrinolysis and primary percutaneous coronary intervention. The Global Registry of Acute Coronary Events. *Heart*. 2007;93(12):1552-1555. doi:10.1136/hrt.2006.112847.

86. Cannon CP, Gibson CM, Lambrew CT, et al. Relationship of symptom-onset-to-balloon time and door-to-balloon time with mortality in patients undergoing angioplasty for acute myocardial infarction. *JAMA*. 2000;283(22):2941-2947. http://www.ncbi.nlm.nih.gov/pubmed/10865271. Accessed September 7, 2016.

87. Varcoe RW, Clayton TC, Gray HH, de Belder MA, Ludman PF, Henderson RA. Impact of call-to-balloon time on 30-day mortality in contemporary practice. *Heart*. July 2016. doi:10.1136/heartjnl-2016-309658.

88. Jolly SS, Yusuf S, Cairns J, et al. Radial versus femoral access for coronary angiography

and intervention in patients with acute coronary syndromes (RIVAL): a randomised, parallel group, multicentre trial. *Lancet (London, England)*. 2011;377(9775):1409-1420. doi:10.1016/S0140-6736(11)60404-2.

89. Jolly SS, Amlani S, Hamon M, Yusuf S, Mehta SR. Radial versus femoral access for coronary angiography or intervention and the impact on major bleeding and ischemic events: A systematic review and meta-analysis of randomized trials. *Am Heart J*. 2009;157(1):132-140. doi:10.1016/j.ahj.2008.08.023.

90. Mehilli J. Sex-Based Analysis of Outcome in Patients With Acute Myocardial Infarction Treated Predominantly With Percutaneous Coronary Intervention. *JAMA*. 2002;287(2):210. doi:10.1001/jama.287.2.210.

91. Milcent C, Dormont B, Durand-Zaleski I, Steg PG. Gender differences in hospital mortality and use of percutaneous coronary intervention in acute myocardial infarction: microsimulation analysis of the 1999 nationwide French hospitals database. *Circulation*. 2007;115(7):833-839. doi:10.1161/CIRCULATIONAHA.106.664979.

92. Sjauw KD, Stegenga NK, Engström AE, et al. The influence of gender on short- and long-term outcome after primary PCI and delivered medical care for ST-segment elevation myocardial infarction. *EuroIntervention*. 2010;5(7):780-787. http://www.ncbi.nlm.nih.gov/pubmed/20142191. Accessed October 8, 2015.

93. Wijnbergen I, Tijssen J, van 't Veer M, Michels R, Pijls NHJ. Gender differences in long-term outcome after primary percutaneous intervention for ST-segment elevation myocardial infarction. *Catheter Cardiovasc Interv*. 2013;82(3):379-384. doi:10.1002/ccd.24800.

94. Birkemeyer R, Schneider H, Rillig A, et al. Do gender differences in primary PCI mortality represent a different adherence to guideline recommended therapy? a multicenter observation. *BMC Cardiovasc Disord*. 2014;14:71. doi:10.1186/1471-2261-14-71.

95. Guerchicoff A, Brener SJ, Maehara A, et al. Impact of Delay to Reperfusion on Reperfusion Success, Infarct Size, and Clinical Outcomes in Patients With ST-Segment Elevation Myocardial Infarction. *JACC Cardiovasc Interv*. 2014;7(7):733-740. doi:10.1016/j.jcin.2014.01.166.

96. Office for National Statistics. Ethnicity and National Identity in England and Wales. *Http://www.ons.gov.uk*. 2012;(December):1-12. https://www.ons.gov.uk/peoplepopulationandcommunity/culturalidentity/ethnicity/articles/ethnicityandnationalidentityinenglandandwales/2012-12-11/pdf.

97. Hanif W, Khunti K, Bellary S, Bharaj H. Type 2 diabetes in the UK South Asian population An update from the South Asian Health Foundation Vinod Patel , on behalf of the Diabetes Working Group of the South Asian Health Foundation Type 2 diabetes in the UK South Asian population An update from th. 2014. http://www.sahf.org.uk/sites/default/files/publications/Type 2 Diabetes in the UK South Asian population.pdf.

98. Bhopal R, Unwin N, White M, et al. Heterogeneity of coronary heart disease risk factors in Indian, Pakistani, Bangladeshi, and European origin populations: cross sectional study. *BMJ*. 1999;319(7204):215-220. doi:10.1136/bmj.319.7204.215.

99. Snehalatha C, Mukesh B, Simon M, Viswanathan V, Haffner SM, Ramachandran A. Plasma Adiponectin Is an Independent Predictor of Type 2 Diabetes in Asian Indians.

Diabetes Care. 2003;26(12):3226-3229. doi:10.2337/diacare.26.12.3226.

100. Anand SS, Razak F, Yi Q, et al. C-reactive protein as a screening test for cardiovascular risk in a multiethnic population. *Arterioscler Thromb Vasc Biol*. 2004;24(8):1509-1515. doi:10.1161/01.ATV.0000135845.95890.4e.

101. McKeigue PM. Metabolic consequences of obesity and body fat pattern: lessons from migrant studies. *Ciba Found Symp*. 1996;201:54-64-7, 188-193. http://www.ncbi.nlm.nih.gov/pubmed/9017274. Accessed April 19, 2016.

102. Wilkinson P, Sayer J, Laji K, et al. Comparison of case fatality in south Asian and white patients after acute myocardial infarction: observational study. *BMJ*. 1996;312(7042):1330-1333. doi:10.1136/bmj.312.7042.1330.

103. Raji A, Gerhard-Herman MD, Warren M, et al. Insulin resistance and vascular dysfunction in nondiabetic Asian Indians. *J Clin Endocrinol Metab*. 2004;89(8):3965-3972. doi:10.1210/jc.2004-0087.

104. Albarak J, Nijjar APK, Aymong E, Wang H, Quan H, Khan NA. Outcomes in young South Asian Canadians after acute myocardial infarction. *Can J Cardiol*. 28(2):178-183. doi:10.1016/j.cjca.2011.10.014.

105. Toor IS, Jaumdally R, Lip GYH, et al. Differences between South Asians and White Europeans in five year outcome following percutaneous coronary intervention. *Int J Clin Pract*. 2011;65(12):1259-1266. doi:10.1111/j.1742-1241.2011.02776.x.

106. Ramaraj R, Chellappa P. Cardiovascular risk in South Asians. *Postgrad Med J*. 2008;84(996):518-523. doi:10.1136/pgmj.2007.066381.

107. Meadows TA, Bhatt DL, Cannon CP, et al. Ethnic differences in cardiovascular risks

and mortality in atherothrombotic disease: insights from the Reduction of Atherothrombosis for Continued Health (REACH) registry. *Mayo Clin Proc*. 2011;86(10):960-967. doi:10.4065/mcp.2011.0010.

108. Ridker PM. C-Reactive Protein, the Metabolic Syndrome, and Risk of Incident Cardiovascular Events: An 8-Year Follow-Up of 14 719 Initially Healthy American Women. *Circulation*. 2003;107(3):391-397. doi:10.1161/01.CIR.0000055014.62083.05.

109. Gasevic D, Khan NA, Qian H, et al. Outcomes following percutaneous coronary intervention and coronary artery bypass grafting surgery in Chinese, South Asian and White patients with acute myocardial infarction: administrative data analysis. *BMC Cardiovasc Disord*. 2013;13(1):121. doi:10.1186/1471-2261-13-121.

110. Khan NA, Grubisic M, Hemmelgarn B, Humphries K, King KM, Quan H. Outcomes after acute myocardial infarction in South Asian, Chinese, and white patients. *Circulation*. 2010;122(16):1570-1577. doi:10.1161/CIRCULATIONAHA.109.850297.

111. Kumar RS, Douglas PS, Peterson ED, et al. Effect of race and ethnicity on outcomes with drug-eluting and bare metal stents: results in 423 965 patients in the linked National Cardiovascular Data Registry and centers for Medicare & Medicaid services payer databases. *Circulation*. 2013;127(13):1395-1403. doi:10.1161/CIRCULATIONAHA.113.001437.

112. Khan NA, Grubisic M, Hemmelgarn B, Humphries K, King KM, Quan H. Outcomes After Acute Myocardial Infarction in South Asian, Chinese, and White Patients . http://circ.ahajournals.org/content/122/16/1570/T1.expansion.html. Accessed April 18, 2016.

113. McKeigue PM, Ferrie JE, Pierpoint T, Marmot MG. Association of early-onset coronary heart disease in South Asian men with glucose intolerance and hyperinsulinemia. *Circulation*. 1993;87(1):152-161. doi:10.1161/01.CIR.87.1.152.

114. Mather HM, Chaturvedi N, Fuller JH. Mortality and morbidity from diabetes in South Asians and Europeans: 11-year follow-up of the Southall Diabetes Survey, London, UK. *Diabet Med*. 1998;15(1):53-59. doi:10.1002/(SICI)1096-9136(199801)15:1<53::AID-DIA521>3.0.CO;2-V.

115. Albarak J, Nijjar APK, Aymong E, Wang H, Quan H, Khan NA. Outcomes in young South Asian Canadians after acute myocardial infarction. *Can J Cardiol*. 2012;28(2):178-183. doi:10.1016/j.cjca.2011.10.014.

116. Chaturvedi N, Fuller JH. Ethnic differences in mortality from cardiovascular disease in the UK: do they persist in people with diabetes? *J Epidemiol Community Heal*. 1996;50(2):137-139. doi:10.1136/jech.50.2.137.

117. Zaman MJS, Philipson P, Chen R, et al. South Asians and coronary disease: is there discordance between effects on incidence and prognosis? *Heart*. 2013;99(10):729-736. doi:10.1136/heartjnl-2012-302925.

118. Gupta M, Doobay A V, Singh N, et al. Risk factors, hospital management and outcomes after acute myocardial infarction in South Asian Canadians and matched control subjects. *CMAJ*. 2002;166(6):717-722. http://www.ncbi.nlm.nih.gov/pubmed/11944758. Accessed July 23, 2017.

119. Sheth T, Nair C, Nargundkar M, Anand S, Yusuf S. Cardiovascular and cancer mortality among Canadians of European, south Asian and Chinese origin from 1979 to 1993: an

analysis of 1.2 million deaths. *CMAJ*. 1999;161(2):132-138. http://www.ncbi.nlm.nih.gov/pubmed/10439820. Accessed July 21, 2017.

120. Cummins C, Winter H, Cheng KK, Maric R, Silcocks P, Varghese C. An assessment of the Nam Pehchan computer program for the identification of names of south Asian ethnic origin. *J Public Health Med*. 1999;21(4):401-406. http://www.ncbi.nlm.nih.gov/pubmed/11469361. Accessed July 23, 2017.

121. Fuster V, Badimon L, Badimon JJ, Chesebro JH. The pathogenesis of coronary artery disease and the acute coronary syndromes (1). *N Engl J Med*. 1992;326(4):242-250. doi:10.1056/NEJM199201233260406.

122. Roux S, Christeller S, Lüdin E. Effects of aspirin on coronary reocclusion and recurrent ischemia after thrombolysis: A meta-analysis. *J Am Coll Cardiol*. 1992;19(3):671-677. doi:10.1016/S0735-1097(10)80290-6.

123. STUDY I-2 (SECOND I, GROUP ISC. RANDOMISED TRIAL OF INTRAVENOUS STREPTOKINASE, ORAL ASPIRIN, BOTH, OR NEITHER AMONG 17 187 CASES OF SUSPECTED ACUTE MYOCARDIAL INFARCTION: ISIS-2. *Lancet*. 1988;332(8607):349-360. doi:10.1016/S0140-6736(88)92833-4.

124. Sabatine MS, Cannon CP, Gibson CM, et al. Addition of Clopidogrel to Aspirin and Fibrinolytic Therapy for Myocardial Infarction with ST-Segment Elevation. *N Engl J Med*. 2005;352(12):1179-1189. doi:10.1056/NEJMoa050522.

125. Yusuf S, Zhao F, Mehta SR, et al. Effects of Clopidogrel in Addition to Aspirin in Patients with Acute Coronary Syndromes without ST-Segment Elevation. *N Engl J Med*. 2001;345(7):494-502. doi:10.1056/NEJMoa010746.

126. Chen ZM, Jiang LX, Chen YP, et al. Addition of clopidogrel to aspirin in 45 852 patients with acute myocardial infarction: randomised placebo-controlled trial. *Lancet*. 2005;366(9497):1607-1621. doi:10.1016/S0140-6736(05)67660-X.

127. Wiviott SD, Braunwald E, McCabe CH, et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med*. 2007;357(20):2001-2015. doi:10.1056/NEJMoa0706482.

128. Udell JA, Braunwald E, Antman EM, et al. Prasugrel versus clopidogrel in patients with ST-segment elevation myocardial infarction according to timing of percutaneous coronary intervention: a TRITON-TIMI 38 subgroup analysis (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Plate. *JACC Cardiovasc Interv*. 2014;7(6):604-612. doi:10.1016/j.jcin.2014.01.160.

129. National Institute of Clinical Excellence U. Prasugrel with percutaneous coronary intervention for treating acute coronary syndromes | Guidance and guidelines. 2014. https://www.nice.org.uk/guidance/ta317. Accessed July 14, 2017.

130. Wallentin L, Becker RC, Budaj A, et al. Ticagrelor versus Clopidogrel in Patients with Acute Coronary Syndromes. February 2010. http://www.nejm.org/doi/full/10.1056/NEJMoa0904327#t=article. Accessed July 15, 2016.

131. Myocardial infarction with ST-segment elevation: acute management | 1-Recommendations | Guidance and guidelines | NICE. https://www.nice.org.uk/guidance/CG167/chapter/1-Recommendations. Accessed July 15, 2016.

132. Motovska Z, Hlinomaz O, Miklik R, et al. Prasugrel Versus Ticagrelor in Patients With Acute Myocardial Infarction Treated With Primary Percutaneous Coronary InterventionClinical Perspective. *Circulation*. 2016;134(21):1603-1612. doi:10.1161/CIRCULATIONAHA.116.024823.

133. Schulz S, Angiolillo DJ, Antoniucci D, et al. Randomized comparison of ticagrelor versus prasugrel in patients with acute coronary syndrome and planned invasive strategy--design and rationale of the iNtracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment (ISAR-REA. *J Cardiovasc Transl Res*. 2014;7(1):91-100. doi:10.1007/s12265-013-9527-3.

134. Chen ZM, Jiang LX, Chen YP, et al. Addition of clopidogrel to aspirin in 45,852 patients with acute myocardial infarction: randomised placebo-controlled trial. *Lancet (London, England)*. 2005;366(9497):1607-1621. doi:10.1016/S0140-6736(05)67660-X.

135. Wiviott SD, Desai N, Murphy SA, et al. Efficacy and safety of intensive antiplatelet therapy with prasugrel from TRITON-TIMI 38 in a core clinical cohort defined by worldwide regulatory agencies. *Am J Cardiol*. 2011;108(7):905-911. doi:10.1016/j.amjcard.2011.05.020.

136. Wallentin L, Becker RC, Budaj A, et al. Ticagrelor versus Clopidogrel in Patients with Acute Coronary Syndromes. *N Engl J Med*. 2009;361(11):1045-1057. doi:10.1056/NEJMoa0904327.

137. Koshy A, Balasubramaniam K, Noman A, Zaman AG. Antiplatelet therapy in patients undergoing primary percutaneous coronary intervention for ST-elevation myocardial infarction: a retrospective observational study of prasugrel and clopidogrel. *Cardiovasc Ther*. 2014;32(1):1-6. doi:10.1111/1755-5922.12051.

138. Serebruany VL, Cherepanov V, Tomek A, Kim MH. Among antithrombotic agents, prasugrel, but not ticagrelor, is associated with reduced 30 day mortality in patients with ST-elevated myocardial infarction. *Int J Cardiol*. 2015;195:104-110. doi:10.1016/j.ijcard.2015.05.062.

139. Larmore C, Effron MB, Molife C, et al. "Real-World" Comparison of Prasugrel With Ticagrelor in Patients With Acute Coronary Syndrome Treated With Percutaneous Coronary Intervention in the United States. *Catheter Cardiovasc Interv*. 2016;88(4):535-544. doi:10.1002/ccd.26279.

140. Gosling R, Yazdani M, Parviz Y, et al. Comparison of P2Y $_{12}$ inhibitors for mortality and stent thrombosis in patients with acute coronary syndromes: Single center study of 10 793 consecutive "real-world" patients. *Platelets*. 2017;0(0):1-7. doi:10.1080/09537104.2017.1280601.

141. Vercellino M, Sànchez FA, Boasi V, et al. Ticagrelor versus clopidogrel in real-world patients with ST elevation myocardial infarction: 1-year results by propensity score analysis. *BMC Cardiovasc Disord*. 2017;17(1):97. doi:10.1186/s12872-017-0524-3.

142. Murgatroyd F. National Audit of Cardiac Rhythm Management Devices. 2014;(MARCH):239.

143. Fanaroff AC, Zakroysky P, Dai D, et al. Outcomes of PCI in Relation to Procedural Characteristics and Operator Volumes in the United States. *J Am Coll Cardiol*. 2017;69(24):2913 LP-2924. http://www.onlinejacc.org/content/69/24/2913.abstract.

144. Vakili BA, Kaplan R, Brown DL. Volume-outcome relation for physicians and hospitals performing angioplasty for acute myocardial infarction in New York state. *Circulation*.

2001;104(18):2171-2176. http://www.ncbi.nlm.nih.gov/pubmed/11684626. Accessed March 9, 2017.

145. Moscucci M, Share D, Smith D, et al. Relationship between operator volume and adverse outcome in contemporary percutaneous coronary intervention practice: an analysis of a quality-controlled multicenter percutaneous coronary intervention clinical database. *J Am Coll Cardiol*. 2005;46(4):625-632. doi:10.1016/j.jacc.2005.05.048.

146. Hulme W, Sperrin M, Rushton H, et al. Is There a Relationship of Operator and Center Volume With Access Site-Related Outcomes? An Analysis From the British Cardiovascular Intervention Society. *Circ Cardiovasc Interv*. 2016;9(5):e003333. doi:10.1161/CIRCINTERVENTIONS.115.003333.

147. Badheka AO, Patel NJ, Grover P, et al. Impact of annual operator and institutional volume on percutaneous coronary intervention outcomes: a 5-year United States experience (2005-2009). *Circulation*. 2014;130(16):1392-1406. doi:10.1161/CIRCULATIONAHA.114.009281.

148. Srinivas VS, Hailpern SM, Koss E, Monrad ES, Alderman MH. Effect of physician volume on the relationship between hospital volume and mortality during primary angioplasty. *J Am Coll Cardiol*. 2009;53(7):574-579. doi:10.1016/j.jacc.2008.09.056.

149. Levine GN, Bates ER, Blankenship JC, et al. 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention. A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. *J Am Coll Cardiol*. 2011;58(24):e44-122. doi:10.1016/j.jacc.2011.08.007.

150. Fanaroff AC, Zakroysky P, Dai D, et al. Outcomes of PCI in Relation to Procedural Characteristics and Operator Volumes in the United States. *J Am Coll Cardiol*. 2017;69(24). http://www.onlinejacc.org/content/69/24/2913?sso=1&sso_redirect_count=1&access_token=. Accessed June 15, 2017.

151. Montalescot G, Barragan P, Wittenberg O, et al. Platelet Glycoprotein IIb/IIIa Inhibition with Coronary Stenting for Acute Myocardial Infarction. *N Engl J Med*. 2001;344(25):1895-1903. doi:10.1056/NEJM200106213442503.

152. Tcheng JE, Kandzari DE, Grines CL, et al. Benefits and Risks of Abciximab Use in Primary Angioplasty for Acute Myocardial Infarction The Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications (CADILLAC) Trial. doi:10.1161/01.CIR.0000087601.45803.86.

153. Stone GW, Grines CL, Cox DA, et al. Comparison of Angioplasty with Stenting, with or without Abciximab, in Acute Myocardial Infarction. *N Engl J Med*. 2002;346(13):957-966. doi:10.1056/NEJMoa013404.

154. Mehilli J, Kastrati A, Schulz S, et al. Abciximab in Patients With Acute ST-Segment–Elevation Myocardial Infarction Undergoing Primary Percutaneous Coronary Intervention After Clopidogrel Loading A Randomized Double-Blind Trial. doi:10.1161/CIRCULATIONAHA.108.818617.

155. Heer T, Zeymer U, Juenger C, et al. Beneficial effects of abciximab in patients with primary percutaneous intervention for acute ST segment elevation myocardial infarction in clinical practice. *Heart*. 2006;92(10):1484-1489. doi:10.1136/hrt.2005.085456.

156. Iversen AZ, Galatius S, Pedersen S, Abildgaard U, Jensen JS. Mortality Reduction with Administration of Abciximab during Primary PCI is Confined to STEMI Patients with Complex Lesions. *Cardiovasc Pharmacol Open Access*. 2013;2(1). doi:10.4172/2329-6607.1000103.

157. Peter D, Ludman F, Md M, Fesc F, Gavalova L. National Audit of Percutaneous Coronary Interventions Annual Report 2015. 2014. http://www.ucl.ac.uk/nicor/audits/adultpercutaneous/documents/2014-annual-report.pdf. Accessed June 1, 2017.

158. National Institute for Clinincal Outcomes Research, Herrett E, Smeeth L, Walker L, Weston C. Myocardial Ischaemia National Audit Project. *Heart*. 2010;96(16):1264-1267. doi:10.1136/hrt.2009.192328.

159. Dorsch MF, Greenwood JP, Priestley C, et al. Direct ambulance admission to the cardiac catheterization laboratory significantly reduces door-to-balloon times in primary percutaneous coronary intervention. *Am Heart J*. 2008;155(6):1054-1058. doi:10.1016/j.ahj.2008.01.014.

160. Steg PG, James SK, Atar D, et al. ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. *Eur Heart J*. 2012;33(20):2569-2619. doi:10.1093/eurheartj/ehs215.

161. O'Gara PT, Kushner FG, Ascheim DD, et al. 2013 ACCF/AHA Guideline for the Management of ST-Elevation Myocardial InfarctionA Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2013;61(4):e78-e140. http://dx.doi.org/10.1016/j.jacc.2012.11.019.

162. Stone GW, Witzenbichler B, Guagliumi G, et al. Bivalirudin during Primary PCI in Acute Myocardial Infarction. *N Engl J Med*. 2008;358(21):2218-2230. doi:10.1056/NEJMoa0708191.

163. Shahzad A, Kemp I, Mars C, et al. Unfractionated heparin versus bivalirudin in primary percutaneous coronary intervention (HEAT-PPCI): An open-label, single centre, randomised controlled trial. *Lancet*. 2014;384(9957):1849-1858. doi:10.1016/S0140-6736(14)60924-7.

164. Hall M, Laut K, Dondo TB, et al. Patient and hospital determinants of primary percutaneous coronary intervention in England, 2003-2013. *Heart*. January 2016:heartjnl-2015-308616-. doi:10.1136/heartjnl-2015-308616.

165. Cutlip DE, Windecker S, Mehran R, et al. Clinical end points in coronary stent trials: a case for standardized definitions. *Circulation*. 2007;115(17):2344-2351. doi:10.1161/CIRCULATIONAHA.106.685313.

166. Rubin DB. Multiple Imputation for Nonresponse in Surveys. In: John Wiley & Sons, Inc., Hoboken, NJ, USA.; 1987:1-26. doi:10.1002/9780470316696.ch1.

167. Sterne JAC, White IR, Carlin JB, et al. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. *BMJ*. 2009;338:b2393. doi:10.1136/BMJ.B2393.

168. Little RJA. Missing-Data Adjustments in Large Surveys. *J Bus Econ Stat*. 1988;6(3):287-296. doi:10.1080/07350015.1988.10509663.

169. Schenker N, Taylor JMG. Partially parametric techniques for multiple imputation. *Comput Stat Data Anal*. 1996;22(4):425-446. doi:10.1016/0167-9473(95)00057-7.

170. Team R. R Development Core Team. *R A Lang Environ Stat Comput*. 2015;55:275-286. http://www.mendeley.com/research/r-language-environment-statistical-computing-96/%5Cnpapers2://publication/uuid/A1207DAB-22D3-4A04-82FB-D4DD5AD57C28.

171. Jia D-A, Zhou Y-J, Shi D-M, et al. Incidence and predictors of radial artery spasm during transradial coronary angiography and intervention. *Chin Med J (Engl)*. 2010;123(7):843-847. http://www.ncbi.nlm.nih.gov/pubmed/20497675. Accessed July 31, 2017.

172. Dangas GD, Claessen BE, Caixeta A, Sanidas EA, Mintz GS, Mehran R. In-stent restenosis in the drug-eluting stent era. *J Am Coll Cardiol*. 2010;56(23):1897-1907. doi:10.1016/j.jacc.2010.07.028.

173. Haim M, Hod H, Reisin L, et al. Comparison of Short- and Long-Term Prognosis in Patients With Anterior Wall Versus Inferior or Lateral Wall Non-Q-Wave Acute Myocardial Infarction. *Am J Cardiol*. 1997;79(6):717-721. doi:10.1016/S0002-9149(96)00856-9.

174. Finegold JA, Asaria P, Francis DP. Mortality from ischaemic heart disease by country, region, and age: statistics from World Health Organisation and United Nations. *Int J Cardiol*. 2013;168(2):934-945. doi:10.1016/j.ijcard.2012.10.046.

175. Ben-Shlomo Y, Naqvi H, Baker I. Ethnic differences in healthcare-seeking behaviour and management for acute chest pain: secondary analysis of the MINAP dataset 2002–2003. *Heart*. 2008;94(3):354 LP-359. http://heart.bmj.com/content/94/3/354.abstract.

176. Zaman MJS, Philipson P, Chen R, et al. South Asians and coronary disease: is there

discordance between effects on incidence and prognosis? *Heart*. 2013;99(10):729 LP-736. http://heart.bmj.com/content/99/10/729.abstract.

177. Stone GW, Mehran R, Goldstein P, et al. Bivalirudin versus heparin with or without glycoprotein IIb/IIIa inhibitors in patients with STEMI undergoing primary percutaneous coronary intervention: pooled patient-level analysis from the HORIZONS-AMI and EUROMAX trials. *J Am Coll Cardiol*. 2015;65(1):27-38. doi:10.1016/j.jacc.2014.10.029.

178. Khan JN, Greenwood JP, Nazir SA, et al. Infarct Size Following Treatment With Second- Versus Third-Generation P2Y12 Antagonists in Patients With Multivessel Coronary Disease at ST-Segment Elevation Myocardial Infarction in the CvLPRIT Study. *J Am Heart Assoc*. 2016;5(6). doi:10.1161/JAHA.116.003403.

179. Steg PG, James S, Harrington RA, et al. Ticagrelor versus clopidogrel in patients with ST-elevation acute coronary syndromes intended for reperfusion with primary percutaneous coronary intervention: A Platelet Inhibition and Patient Outcomes (PLATO) trial subgroup analysis. *Circulation*. 2010;122(21):2131-2141. doi:10.1161/CIRCULATIONAHA.109.927582.

180. Bengtson JR, Kaplan AJ, Pieper KS, et al. Prognosis in cardiogenic shock after acute myocardial infarction in the intervencional era. *J Am Coll Cardiol*. 1992;20(7). http://www.onlinejacc.org/content/20/7/1482. Accessed May 22, 2017.

181. Levine GN, Bates ER, Blankenship JC, et al. 2011 ACCF/AHA/SCAI guideline for percutaneous coronary intervention. *J Am Coll Cardiol*. 2011;58(24):e44-e122. doi:10.1016/j.jacc.2011.08.007.

182. Généreux P, Mehran R, Palmerini T, et al. Radial access in patients with ST-segment elevation myocardial infarction undergoing primary angioplasty in acute myocardial infarction: the HORIZONS-AMI trial. *EuroIntervention*. 2011;7(8):905-916. doi:10.4244/EIJV7I8A144.

183. Noad R, Stevenson M, Herity NA. Analysis of weekend effect on 30-day mortality among patients with acute myocardial infarction. *Open Hear*. 2017;4(1):e000504. doi:10.1136/openhrt-2016-000504.

184. Gonzalez MA, Ben-Dor I, Wakabayashi K, et al. Does on- versus off-hours presentation impact in-hospital outcomes of ST-segment elevation myocardial infarction patients transferred to a tertiary care center? *Catheter Cardiovasc Interv*. 2010;76(4):484-490. doi:10.1002/ccd.22515.

185. O'Neill D, Nicholas O, Gale CP, et al. Total Center Percutaneous Coronary Intervention Volume and 30-Day Mortality. *Circ Cardiovasc Qual Outcomes*. 2017;10(3):e003186. doi:10.1161/CIRCOUTCOMES.116.003186.

186. Cantor WJ, Puley G, Natarajan MK, et al. Radial versus femoral access for emergent percutaneous coronary intervention with adjunct glycoprotein IIb/IIIa inhibition in acute myocardial infarction--the RADIAL-AMI pilot randomized trial. *Am Heart J*. 2005;150(3):543-549. doi:10.1016/j.ahj.2004.10.043.

187. Mamas MA, Ratib K, Routledge H, et al. Influence of access site selection on PCI-related adverse events in patients with STEMI: meta-analysis of randomised controlled trials. *Heart*. 2012;98(4):303-311. doi:10.1136/heartjnl-2011-300558.

188. Lincoff AM, Bittl JA, Harrington RA, et al. Bivalirudin and Provisional Glycoprotein

IIb/IIIa Blockade Compared With Heparin and Planned Glycoprotein IIb/IIIa Blockade During Percutaneous Coronary Intervention<SUBTITLE>REPLACE-2 Randomized Trial</SUBTITLE> *JAMA*. 2003;289(7):853. doi:10.1001/jama.289.7.853.

189. Généreux P, Mehran R, Palmerini T, et al. Radial access in patients with ST-segment elevation myocardial infarction undergoing primary angioplasty in acute myocardial infarction: the HORIZONS-AMI trial. *EuroIntervention*. 2011;7(8):905-916. doi:10.4244/EIJV7I8A144.

190. Mehran R, Pocock SJ, Stone GW, et al. Associations of major bleeding and myocardial infarction with the incidence and timing of mortality in patients presenting with non-ST-elevation acute coronary syndromes: a risk model from the ACUITY trial. *Eur Heart J*. 2009;30(12):1457-1466. doi:10.1093/eurheartj/ehp110.

191. Jolly SS, Yusuf S, Cairns J, et al. Radial versus femoral access for coronary angiography and intervention in patients with acute coronary syndromes (RIVAL): a randomised, parallel group, multicentre trial. *Lancet (London, England)*. 2011;377(9775):1409-1420. doi:10.1016/S0140-6736(11)60404-2.

192. Philippe F, Larrazet F, Meziane T, Dibie A. Comparison of transradial vs. transfemoral approach in the treatment of acute myocardial infarction with primary angioplasty and abciximab. *Catheter Cardiovasc Interv*. 2004;61(1):67-73. doi:10.1002/ccd.10675.

193. Windecker S, Kolh P, Alfonso F, et al. 2014 ESC/EACTS Guidelines on myocardial revascularizationThe Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS)Developed with the special contribution of . *Eur Heart J*. 2014;35(37):2541. doi:10.1093/eurheartj/ehu278.

Appendix 1: Patient information leaflet for prospective recruitment into WY-PPCI

The Leeds Teaching Hospitals NHS
NHS Trust

Cardiology & Respiratory Directorate

G Floor
Jubilee Wing

Leeds General Infirmary

Great George Street

Leeds LS1 3EX

Study information Sheet

West Yorkshire Primary Percutaneous Coronary Intervention Outcome Study

(WY-PPCI Outcome Study)

Patient Information Sheet A

Version 1.5 May 2012

Dear Patient,

You are being invited to take part in this study. Before you decide it is important for you to understand why the study is being done and what it will involve. Please take time to read the following information carefully and discuss it with friends and relatives if you wish. Please do ask if there is anything that is not clear or if you would like more information.

WHY HAVE I BEEN CHOSEN?
We are inviting all patients who have suffered a heart attack and had a stent put into their heart artery (PCI) to take part. This study is looking at people like you who were admitted to the Leeds General Infirmary for this treatment.

WHAT IS THE PURPOSE OF THE STUDY?

The purpose of this study is to look at what the main factors are which influence the health of patients who have been treated with Primary Percutaneous Coronary Intervention (PPCI) as the first treatment for a heart attack. We are therefore aiming to undertake the follow up of all patients who have been treated with PPCI in West Yorkshire. This requires us to contact you by telephone after 30 days and again after one year. The aim of contacting you is to ask you for up-to-date information about your on-going health. All the information you give us will be confidential.

DO I HAVE TO TAKE PART?

It is up to you to decide whether or not to take part. If you decide not to take part, your clinical details will still be held on the NHS database, as this is normal clinical practice. We will however not be telephoning you for further follow-up or be obtaining any blood or saliva samples from you.

If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form. If you decide to take part you are still free to withdraw at any time and without giving a reason. This will not affect the standard of care you would receive.

WHAT WILL HAPPEN TO ME IF I TAKE PART?

As you are currently under our care and have been treated with a primary PCI for your heart attack, we already have your details on the NHS clinical databases. We are asking you if you would consent to being contacted by a research nurse by telephone. We would in addition like to ask your consent for a blood sample (9 mls or approximately 2 teaspoonfuls) or a saliva sample (approximately 5 mls) to be used for genetic testing for genes that relate to heart disease. The type of sample to be collected can be chosen by you. If you agree then we will collect the sample whilst you are still in hospital. Any results obtained will not be made available to individual participants, as these tests are designed to give us information that might be relevant to groups of future heart patients rather than individuals.

Any sample you give us will be securely stored within the University of Leeds Integrated Molecular Cardiology laboratories. Your sample may be used in future research projects that have been approved by an NHS Research Ethics Committee.

To enable us to study how well patients do after a heart attack in the longer term, we would like your consent to have access to central NHS records or use information from the NHS Information Centre.

WHAT ARE THE RISKS AND DISCOMFORTS?

There are no foreseeable risks to you in this study. If you have consented to giving your blood, you may experience minor discomfort or bruising at the needle site when that is performed but we will minimise any inconvenience to you.

BENEFITS TO YOU

There is no direct personal benefit to you. However, the information gained from this study may help us in evaluating the most appropriate treatment for patients in the future

WILL MY TAKING PART BE KEPT CONFIDENTIAL?

All information collected about you during the course of the study will be kept strictly confidential. This information will be securely stored, electronically on the Leeds General Infirmary secure server, and on paper, under the provisions of the 1998 Data Protection Act. You will not be identified in any publication that may result from this research.

We may contact the NHS Information Service at a later stage for information which they hold on your health status. This means some of your personal data will be shared with the NHS Information Service. Any information exchanged between us and the NHS Information Service will be subject to strict data protection regulations.

With your permission, your data may also provide a resource for future studies. If any information from this study is used to develop new research, data protection regulations will be observed and strict confidentiality maintained. Ethical approval will be obtained for any future studies involving your data. You will not be identified in the results of any future studies.

If you withdraw consent from further study follow-up, your data will remain on file and will be included in the final study analysis. You may withdraw your samples if you so wish.

WHAT WILL HAPPEN TO THE RESULTS OF THE ON-GOING STUDY?

At different stages of the study, results will be presented at local and regional audit and clinical governance meetings. In addition, results may be published in medical journals, but no individual patients will be identified.

INDEMNITY/COMPENSATION

If you are harmed as a direct result of taking part in this study, there are no special compensation arrangements. If you are harmed due to someone's negligence, then you may have grounds to a legal action. Regardless of this, if you have any cause to complain about any aspect of the way you have been approached or treated during the course of this study, the normal National Health Service complaints mechanisms are available to you.

WHO IS ORGANISING AND FUNDING THE STUDY?

This study is part of a whole range of studies into heart disease conducted by Cardiovascular Research Unit at Leeds General Infirmary, which is part-funded by the British Heart Foundation.

WHO HAS REVIEWED THE STUDY?
The study has been reviewed and approved by York NHS Research Ethics Committee

For further information please contact:

Dr John P Greenwood

Consultant Cardiologist

Academic Unit of Cardiovascular Medicine

'G' Floor, Jubilee Wing

Leeds General Infirmary

LS1 3EX

Or,

Kathryn Somers

Research Nurse

Academic Unit of Cardiovascular Medicine

'G' Floor, Jubilee Wing

Leeds General Infirmary

LS1 3EX

Tel. no. 0113 39 28483

The Leeds Teaching Hospitals NHS
NHS Trust

Cardiology & Respiratory Directorate

G Floor
Jubilee Wing

Leeds General Infirmary

Great George Street

Leeds LS1 3EX

Consent for follow-up only.

WY-PPCI Outcome Study

West Yorkshire Primary Percutaneous Coronary Intervention

Outcome Study

Patient Study Number: …….. Date of Birth:……

Hospital Number: ……. Initials: …….. ***Please initial boxes***

1. I have read the Patient Information Sheet dated May 2012 (Version 1.5) for the above study and I have had the opportunity to ask questions and discuss the research study and I am satisfied with the answers to my questions. ☐

2. I have received enough information about this study. ☐

3. I understand that my participation is voluntary and that I am free to withdraw from the study at any time without giving a reason and without this affecting my future care. ☐

4. I understand that information held by the NHS and records maintained by the NHS Information Centre, the NHS Central Register and by my General Practitioner may be used to contact me and provide information about my health ☐

status. I give permission for this information to be obtained from the NHS Information Centre, the NHS Central Register and/or my GP if necessary.

5. I agree that my medical data maybe used to help develop future research studies and I understand that my identity will remain anonymous. ☐

6. I understand that if I were to lose capacity, the information collected will be kept and used for the purposes of the study. ☐

7. I understand that sections of any of my medical notes may be looked at by responsible individuals from the study team or from regulatory authorities where it is relevant to my taking part in research. I give permission for these individuals to have access to my records. ☐

8. I agree to take part in this study. ☐

Signature.....

Name (block capitals)..... Date.....

Signature of witness.....

Name (block capitals).....Date……

Appendix 2: Patient information leaflet for retrospective recruitment into WY-PPCI

The Leeds Teaching Hospitals NHS
NHS Trust

Cardiology & Respiratory Directorate

G Floor
Jubilee Wing

Leeds General Infirmary

Great George Street

Leeds LS1 3EX

Study information Sheet

West Yorkshire Primary Percutaneous Coronary Intervention Outcome Study

(WY-PPCI Outcome Study)

Patient Information Sheet B

Version 1.5 May 2012

Dear Patient,

You are being invited to take part in this study. Before you decide it is important for you to understand why the study is being done and what it will involve. Please take time to read the following information carefully and discuss it with friends and relatives if you wish. Please do ask if there is anything that is not clear or if you would like more information.

WHY HAVE I BEEN CHOSEN?
We are inviting all patients who have suffered a heart attack and had a stent put into their heart artery (PCI) to take part. This study is looking at people like you who were admitted to the Leeds General Infirmary for this treatment.

WHAT IS THE PURPOSE OF THE STUDY?

The purpose of this study is to look at what the main factors are which influence the health of patients who have been treated with Primary Percutaneous Coronary Intervention (PPCI) as the first treatment for a heart attack. We are therefore aiming to undertake the follow up of all patients who have been treated with PPCI in West Yorkshire. This requires us to contact you. It may be that you have been discharged and are no longer under our routine clinical follow-up. The aim of contacting you is to ask you for up-to-date information about your on-going health. All the information you give us will be confidential.

DO I HAVE TO TAKE PART?

It is up to you to decide whether or not to take part. If you decide not to take part, your clinical details will still be held on the NHS database, as this is normal clinical practice. We will however not be contacting you for further follow-up or be obtaining any blood or saliva samples from you.

If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form. If you decide to take part you are still free to withdraw at any time and without giving a reason. This will not affect the standard of care you would receive should you require further treatment.

WHAT WILL HAPPEN TO ME IF I TAKE PART?

As you have previously been under our care and were treated with a primary PCI for your heart attack, we already have your details on the NHS clinical databases. We are writing to you to ask if you would consent to being contacted by a research nurse by telephone.

We would in addition like to ask your consent for a blood sample (9 mls or approximately 2 teaspoonfuls) or a saliva sample (approximately 5 mls) to be used for genetic testing for genes that relate to heart disease. The type of sample to be collected can be chosen by you. We will make all the necessary arrangements (including postage paid envelopes for saliva samples), and any costs you might incur will be reimbursed by us. Any results obtained will not be made available to individual participants, as these tests are designed to give us information that might be relevant to groups of future heart patients rather than individuals.

Any sample you give us will be securely stored within the University of Leeds Integrated Molecular Cardiology laboratories. Your sample may be used in future research projects that have been approved by an NHS Research Ethics Committee.

To enable us to study how well patients do after a heart attack in the longer term, we would like your consent to have access to central NHS records or use information from the NHS Information Centre.

WHAT ARE THE RISKS AND DISCOMFORTS?

There are no foreseeable risks to you in this study. If you have consented to giving your blood, you may experience minor discomfort or bruising at the needle site when that is performed but we will minimise any inconvenience to you.

BENEFITS TO YOU

There is no direct personal benefit to you. However, the information gained from this study may help us in evaluating the most appropriate treatment for patients in the future

WILL MY TAKING PART BE KEPT CONFIDENTIAL?

All information collected about you during the course of the study will be kept strictly confidential. This information will be securely stored at the Leeds General Infirmary secure server electronically and on paper, under the provisions of the 1998 Data Protection Act. You will not be identified in any publication that may result from this research.

We may contact the NHS Information Service at a later stage for information which they hold on your health status. This means some of your personal data will be shared with the NHS Information Service. Any information exchanged between us and the NHS Information Service will be subject to strict data protection regulations.

With your permission, your data may also provide a resource for future studies. If any information from this study is used to develop new research, data protection regulations will be observed and strict confidentiality maintained. Ethical approval will be obtained for any future studies involving your data. You will not be identified in the results of any future studies.

If you withdraw consent from further study follow-up, your data will remain on file and will be included in the final study analysis. You may withdraw your samples if you so wish.

WHAT WILL HAPPEN TO THE RESULTS OF THE ON-GOING STUDY?

At different stages of the study, results will be presented at local and regional audit and clinical governance meetings. In addition, results may be published in medical journals, but no individual patients will be identified.

INDEMNITY/COMPENSATION

If you are harmed as a direct result of taking part in this study, there are no special compensation arrangements. If you are harmed due to someone's negligence, then you may have grounds to a legal action. Regardless of this, if you have any cause to complain about any aspect of the way you have been approached or treated during the course of this study, the normal National Health Service complaints mechanisms are available to you.

WHO IS ORGANISING AND FUNDING THE STUDY?

This study is part of a whole range of studies into heart disease conducted by Cardiovascular Research Unit at Leeds General Infirmary, which is part-funded by the British Heart Foundation.

WHO HAS REVIEWED THE STUDY?
The study has been reviewed and approved by York NHS Research Ethics Committee

For further information please contact:

Dr John P Greenwood

Consultant Cardiologist

Academic Unit of Cardiovascular Medicine

'G' Floor, Jubilee Wing

Leeds General Infirmary

LS1 3EX

Or,

Kathryn Somers

Research Nurse

Academic Unit of Cardiovascular Medicine

'G' Floor, Jubilee Wing

Leeds General Infirmary

LS1 3EX

Tel. no. 0113 39 28483

The Leeds Teaching Hospitals NHS
NHS Trust

Cardiology & Respiratory Directorate

G Floor
Jubilee Wing

Leeds General Infirmary

Great George Street

Leeds LS1 3EX

Consent for follow-up only.

WY-PPCI Outcome Study

West Yorkshire Primary Percutaneous Coronary Intervention

Outcome Study

Patient Study Number: …….. Date of Birth: ……

Hospital Number: ……. Initials: ……..

Please initial boxes

1. I have read the Patient Information Sheet dated May 2012 (Version 1.5) for the above study and I have had the opportunity to ask questions and discuss the research study and I am satisfied with the answers to my questions. ☐

2. I have received enough information about this study.

3. I understand that my participation is voluntary and that I am free to withdraw from the study at any time without giving a reason and without this affecting my future care. ☐

4. I understand that information held by the NHS and records maintained by the NHS Information Centre, the NHS Central Register and by my General Practitioner may be used to contact me and provide information about my health status. I give permission for this information to be obtained from the ☐

NHS Information Centre, the NHS Central Register and/or my GP if necessary.

5. I agree that my medical data maybe used to help develop future research studies and I understand that my identity will remain anonymous. ☐

6. I understand that if I were to lose capacity, the information collected will be kept and used for the purposes of the study. ☐

7. I understand that sections of any of my medical notes may be looked at by responsible individuals from the study team or from regulatory authorities where it is relevant to my taking part in research. I give permission for these individuals to have access to my records. ☐

8. I agree to take part in this study. ☐

Signature.....

Name (block capitals)..... Date.....

Signature of witness.....

Name (block capitals).....Date……

Appendix 3: Proposal to obtain data for clinical audit

The Leeds Teaching Hospitals NHS
NHS Trust

CLINICAL AUDIT PROPOSAL/TOOLKIT

WY-PPCI Outcome project

Name of Auditor:	Prof John Greenwood / Dr Daniel Blackman
Audit supervisor:	Prof John Greenwood / Dr Daniel Blackman
Specialty:	Cardiology
Proposed audit start date:	01/01/2009
Proposed audit end date:	31/12/2014

1. BACKGROUND

There is now an overwhelming evidence base in support of primary percutaneous coronary intervention (PPCI) for the treatment of ST segment elevation myocardial infarction (STEMI). Currently in excess of 1000 patients per year in West Yorkshire suffer a STEMI (heart attack). These patients are transferred immediately (24/7) to the Leeds General Infirmary (LGI) for PPCI as the first line treatment.

Leeds is currently the largest provider of PPCI in the UK. Routinely the clinical details of all patients undergoing PPCI in West Yorkshire are entered and stored into NHS clinical databases. Information obtained from these databases is used (in a non-identifiable format) for audit, service evaluation (clinical governance) and for improving/developing clinical care via monitoring of trends and outcomes. This information may be used locally, regionally as well as nationally for these purposes. Some of this information is in the public domain, e.g. 'Treatment of heart attack national guidance: final report of the National Infarct Angioplasty Project (NIAP)' published on October 20th 2008 by the Department of Health.

This audit will attempt to quantify the characteristics of patients undergoing PPCI at LTHT, identifying trends and comparing outcomes against the changes in practice that have occurred since 01/01/2009. These service adjustments have occurred due to changes in the evidence base and best practice guidelines. The PPCI service at LTHT is growing, and therefore there is a need to audit past and current outcomes.

2. AIM/OBJECTIVES

What will the audit tell us? Specify the main objective(s)

E.g. To ensure patients with X condition are being managed in accordance with Trust guidelines

The aim of the West Yorkshire Primary Percutaneous Intervention Outcome project (WY-PPCI Outcome project) is to characterize a population of unselected, consecutive patients undergoing percutaneous coronary intervention in an acute setting in terms of outcomes of clinical care. Because angioplasty technology is constantly changing and developing, as are the drugs available to treat heart disease, it is important to evaluate these changes in clinical practice in a large unselected patient population, to understand how change impacts on clinical outcomes and patient survival. If we are to assess the long-term effectiveness of this intervention we require long-term surveillance in the format of an unselected consecutive registry. The establishment of the WY-PPCI Outcome project will enable us to examine the changing trends both locally and regionally.

In addition to studying survival following a heart attack, we want to examine other important cardiovascular outcomes such as the need for further revascularisation i.e. Angioplasty or Bypass surgery, and re-admissions to hospital for any other cardiovascular cause including stroke and bleeding.

3. STANDARDS/EVIDENCE BASE

Practice will be compared against NICE guidelines

Patient outcomes will be compared to national averages

4. METHODOLOGY

To include:

- *Sample size*

We aim to collect data on all patients in Yorkshire that have received PPCI in Leeds. Currently, this is approximately 1,000 patients per year. Therefore our total sample size will be approximately 4000 patients.

How will cases be identified, including inclusion/exclusion criteria

Inclusion Criteria

All patients undergoing Primary Percutaneous Coronary Intervention at the Leeds General Infirmary are potentially eligible for inclusion.

Exclusion Criteria

Patients less than 18 years of age

There are no further exclusion criteria

- *How will the data be obtained*

Data on all patients treated by PPCI at the LGI will be collected from local and regional sources, including:

- Electronic clinical information systems
    - Cardiobase
    - Results service
    - ePRO
    - eDAN
    - WinDip
- Patient notes
- Records kept by local departments
    - E.g. transfusion records

(Please note that the above systems refer to those at LTHT - the district hospitals are expected to have equivalent systems)

The audit will require the collation of existing information only. No primary data collection will be conducted. Data will be entered into a secure bespoke database held within LTHT.

Patients will be identified by experienced nurses working within the Cardiovascular Research department, using the Cardiobase system.

For those patient who are referred for PPCI treatment from a district general hospital (or bypass their local hospital and are brought directly to LTHT), it may be necessary to obtain data from their local hospital - up to 12 months post procedure. This will allow us to capture outcomes data on all patients undergoing intervention. Although it is anticipated that this will be a demanding task, a high proportion of patients fall into this category - and therefore must be included to make this audit robust. We will therefore require access to clinical systems and/or patient notes at the following locations:

- Calderdale & Hudderfield NHS Foundation Trust
- Airedale NHS foundation Trust
- Bradford Teaching Hospitals NHS Foundation Trust
- York Teaching Hospitals NHS Foundation Trust
- Harrogate and District NHS Foundation Trust
- Mid Yorkshire Hospitals NHS Trust

Please see Appendix A for a list of data items that will be required for all patients. Patient identifiers will be kept - to allow us to link the various pieces of information obtained from different sources. Data will be anonymised before it is released to the analysis team.

Description of methodology should be sufficient to allow the clinical audit to be replicated by someone who had no previous involvement or knowledge of it.

The WY-PPCI Outcome project will compare the clinical outcomes of patients undergoing PPCI up to 12 months post procedure. Data to be collected include death, hospital admissions including any further cardiac events and/or revascularization, and current medication. All data will be sourced from routine medical records. The patient will not be contacted. We intend to interrogate Cardiobase, PAS, the Results Service, and transfusion records.

As LTHT is a regional provider of the PPCI service, patients from the districts are treated at LTHT and repatriated to their local hospital circa 6 hours post procedure. In order for us to capture a full picture of the outcomes of our patients – we will require access to patient records at these surrounding centres. Approximately 60% of the patients treated at Leeds are repatriated to a District General Hospital – and therefore it is very important for us to capture this data. Honorary contracts / letters of access will be sought, to enable us to collect key information from these sources. It is also hoped that we may be able to obtain some assistance from research colleagues in post at each of the hospitals.

Appendix 4: Data items to be collected

WY-PPCI field list

Demographics

NHS Number

Forename

Surname

Postcode

Date of birth

Gender

Ethnicity

Death

Date of death

Cardiac related

Other

Free text

Admission

Symptom onset date

Symptom onset time

Call for help date

Call for help time

Arrival hospital 1

Arrival hospital 1 date

Arrival hospital 1 time

Arrive LGI date

Arrive LGI time

Discharge hospital

Discharge date LGI

Discharge date DGH

Cardiac history prior to admission

Previous MI

Previous PCI

Previous CABG

Hypertension

Hypercholestorolemia

Diabetes

Atrial fibrillation

Non Cardiac History

Peripheral vascular disease

Cerebrovascular disease

Renal insufficiency

Dialysis

Smoking status

Pre procedure

Physical examination on admission

Cardiac arrest

Heart rate

BP Systolic

Weight (kg)

Procedure status

Indication

Cardiogenic shock

ST elevation

ST elevation type

LBBB

Rhythm

Rhythm other

Medications given immediately before PCI

Aspirin Dose

Antiplatelet

Dose

Procedure

Procedure

Operator 1

Operator 2

First balloon / device date

First balloon / device time

PCI medication

Bivalirudin given

II/III Inhibitor given

Heparin dose

Angiographic variables

LMS stenosis

LAD proximal

LAD other

RCA

LCX

LIMA

Vein graft 1

Vein graft 2

Vein graft 3

Other

Arterial access

Arterial access 2

French size

Femoral venous access

Haemostasis

Fluoroscopy time

Total x-ray

Vessel 1/2/3

Vessel name

Lesion type

% stenosis

TIMI flow pre

Stent thrombosis

Stent thrombosis level

Failed PCI

Aspiration thrombectomy

Mechanical thrombectomy

Distal protection device

Stent fitted

Inotropes

IVUS

TIMI flow post

% stenosis post

Stents fitted (may be multiple)

Stent name

Overlap

Length

Diameter

Complications

Procedural complications

Cardiogenic shock

Ventilated

Bradycardia / Temporary pacing

IABP

Other

Post procedure

LGI - Baseline bloods - first available result

Hb

Platelets

CK

Troponin

Creatinine

eGFR

DGH - Baseline bloods - first available result

Hb

Platelets

CK

Troponin

Creatinine

eGFR

LGI - Post precedure bloods - peak / lowest value

Peak CK

Lowest Hb

Drop in Hb

Peak glucose

Peak CKMB

Lowest platelets

Peak troponin

Total cholesterol

Peak creatinine

Rise creatinine

% rise creatinine

DGH - Post precedure bloods - peak / lowest value

Peak CK

Lowest Hb

Drop in Hb

Peak glucose

Peak CKMB

Lowest platelets

Peak troponin

Total cholesterol

Peak creatinine

Rise creatinine

% rise creatinine

Discharge medications

AntiPlatelet

Aspirin

ACE inhibitor

Statin

Beta blocker

Angiotensin blocker

Discharge drugs notes

<u>Outcomes (up to 12 months post procedure)</u>

Medication

Aspirin

Aspirin reasons why not

Antiplatelet

Antiplatelet type

Antiplatelet reasons why not

Events

Angina

CCS Class

Blood transfusion

Red blood cells

Platelets

FFP units

MajorBleeding

Major bleeding date

Intracranial haemorrage

Hb drop >=4g no source

Intraocular

>=5cm haematoma

Access site requiring intervention

Retroperationeal bleed

Hb drop >=3g with source

Re-operation for bleed

Diagnosis procedure for bleeding

Surgical intervention for bleeding

Reinfarction

Number of re-infarctions

Reinfarction STEMI (1)

Re-infarction date (1)

Reinfarction STEMI (2)

Re-infarction date (2)

Unscheduled revascularisation

Number of CABG

CABG target vessel date

CABG non target vessel date

Repeat PCI - target vessel date

Repeat PCI - non target vessel date

Planned revascularisation

CABG target vessel Date

CABG non target vessel Date

PCI - target vessel date

PCI - other vessel date

Revasc comments

Stent thrombosis

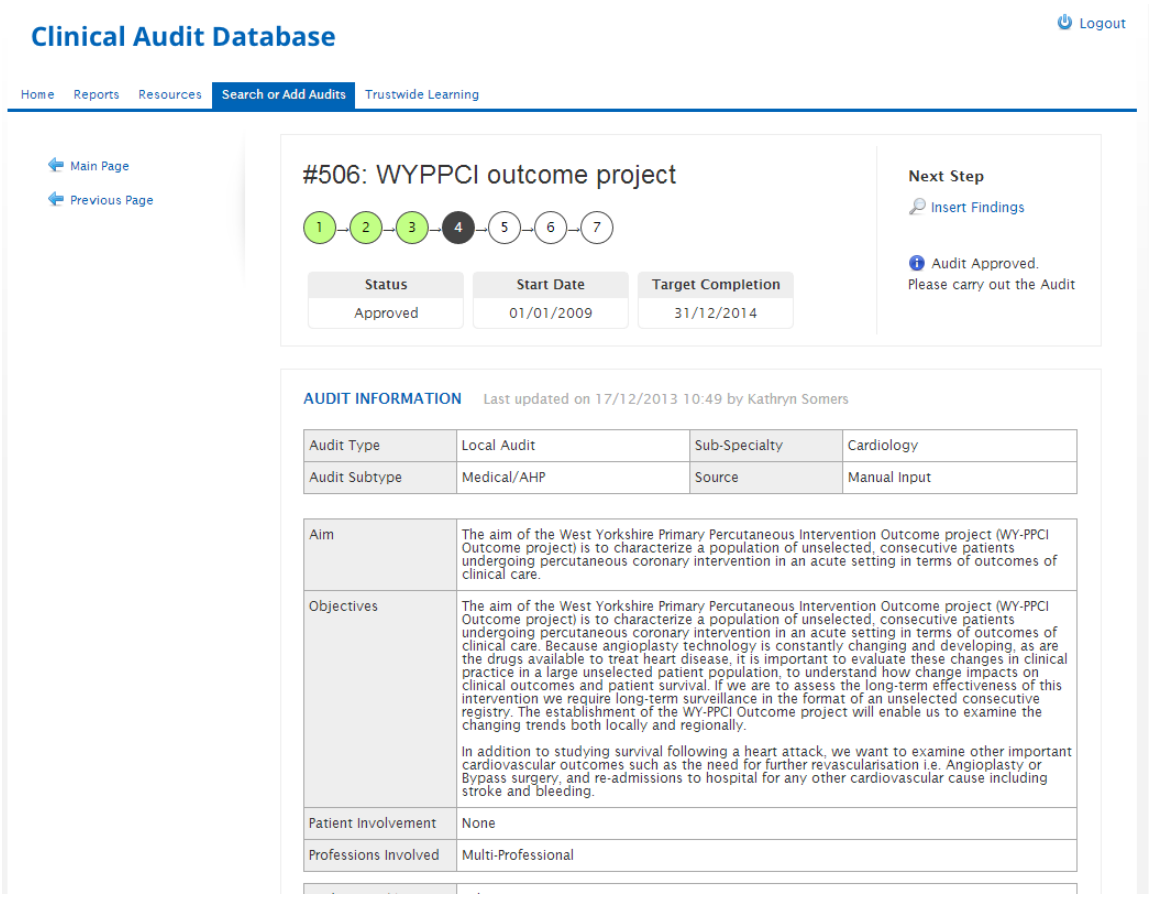
Stent thrombosis date

Stent thrombosis time

Stroke

Contrast nephropathy

Appendix 5: Confirmation of approval to obtain data for clinical audit



Clinical Audit Database

Logout

Home | Reports | Resources | Search or Add Audits | Trustwide Learning

Main Page

Previous Page

#506: WYPPCI outcome project

1 – 2 – 3 – 4 – 5 – 6 – 7

Status	Start Date	Target Completion
Approved	01/01/2009	31/12/2014

Next Step

Insert Findings

Audit Approved.
Please carry out the Audit

AUDIT INFORMATION Last updated on 17/12/2013 10:49 by Kathryn Somers

Audit Type	Local Audit	Sub-Specialty	Cardiology
Audit Subtype	Medical/AHP	Source	Manual Input

Aim	The aim of the West Yorkshire Primary Percutaneous Intervention Outcome project (WY-PPCI Outcome project) is to characterize a population of unselected, consecutive patients undergoing percutaneous coronary intervention in an acute setting in terms of outcomes of clinical care.
Objectives	The aim of the West Yorkshire Primary Percutaneous Intervention Outcome project (WY-PPCI Outcome project) is to characterize a population of unselected, consecutive patients undergoing percutaneous coronary intervention in an acute setting in terms of outcomes of clinical care. Because angioplasty technology is constantly changing and developing, as are the drugs available to treat heart disease, it is important to evaluate these changes in clinical practice in a large unselected patient population, to understand how change impacts on clinical outcomes and patient survival. If we are to assess the long-term effectiveness of this intervention we require long-term surveillance in the format of an unselected consecutive registry. The establishment of the WY-PPCI Outcome project will enable us to examine the changing trends both locally and regionally. In addition to studying survival following a heart attack, we want to examine other important cardiovascular outcomes such as the need for further revascularisation i.e. Angioplasty or Bypass surgery, and re-admissions to hospital for any other cardiovascular cause including stroke and bleeding.
Patient Involvement	None
Professions Involved	Multi-Professional

AUDIT STAFF Last updated on 17/12/2013 10:49 by Kathryn Somers

ROLE	NAME	PHONE
Auditor	Kathryn Somers	x28483
Audit Supervisor	Prof John Greenwood	x22650
Audit Lead	Klaus Witte	

Appendix 6: Documents confirming NHS National Research Ethics Committee approval.

NHS

National Research Ethics Service

York Research Ethics Committee

Learning and Research Centre
York Hospital
Wigginton Road
York
YO31 8HE

Telephone: 01904 725125
Facsimile: 01904 731297

05 June 2009

Dr John P Greenwood
Consultant Cardiologist, Senior Lecturer
Academic Unit of Cardiovascular Medicine
G floor, Jubilee Wing
Leeds General Infirmary
LS1 3EX

Dear Dr Greenwood

Study Title:	**West Yorkshire Primary Percutaneous Coronary Intervention (WY-PPCI) Outcome Study**
REC reference number:	**09/H1311/60**
Protocol number:	**1.2 March 2009**

The Research Ethics Committee reviewed the above application at the meeting held on 01 June 2009. Our thanks go to Ms Petra Bijsterveld for her attendance to discuss the study.

Documents reviewed

The documents reviewed at the meeting were:

Document	*Version*	*Date*
Rejection letter from Oxfordshire REC C		30 April 2009
Telephone follow up questionnaire	1.0 March 2009	
Participant Consent Form: DNA Analysis of blood and sputum sample only		
Participant Consent Form: Clinical Follow-up		
Participant Information Sheet	1.2	14 May 2009
Letter of invitation to participant	1.1	31 March 2009
Compensation Arrangements		02 October 2008
Letter from Sponsor		13 May 2009
Covering Letter		14 May 2009
Protocol	1.2 March 2009	
Investigator CV		14 May 2009
Application	16214/38368/1/859	15 May 2009

1,

National Research Ethics Service
York Research Ethics Committee
Learning and Research Centre
York Hospital
Wigginton Road
York
YO31 8HE

Telephone 01904 725125
Facsimile 01904 721297

18 June 2009

Dr John P Greenwood
Consultant Cardiologist, Senior Lecturer
University of Leeds
Academic Unit of Cardiovascular Medicine
6 floor, Jubilee Wing
Leeds General Infirmary
LS1 3EX

Dear Dr Greenwood

Study Title:	**West Yorkshire Primary Percutaneous Coronary Intervention (WY-PPCI) Outcome Study**
REC reference number:	**09/11-11311/60**
Protocol number:	**1.2 March 2009**

Thank you for your letter of 12 June 2009, responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the condition specified below.

Ethical review of research sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion' below).

Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of the study.

Mana ement permission or a royal must be obtained from each host o anisation nor to the start of the study at the site concerned.

For NHS research sites only, management permission for research ("R&D approval") should be obtained from the relevant care organisation(s) in accordance with NHS research governance arrangements. Guidance on applying for NHS permission for research is available in the Integrated Research Application System or at http://www.rdforum.nhs.uk.

NHS
National Research Ethics Service

Leeds West Research Ethics Committee
Room 22
CD Floor, Block 40, Old Nurses Home
Leeds General Infirmary
Leeds
LS1 3EX

Tel: 0113 392 6788

15 April 2010

Dr John P Greenwood
Consultant Cardiologist, Senior Lecturer
Academic Unit of Cardiovascular Medicine
G floor, Jubilee Wing
Leeds General Infirmary
LS1 3EX

Dear Dr Greenwood

Study title:	**West Yorkshire Primary Percutaneous Coronary Intervention (WY-PPCI) Outcome Study**
REC reference:	**09/H1311/60**
Amendment number:	**1**
Amendment date:	**16 March 2010**

The above amendment was reviewed at the meeting of the Sub-Committee held on 15 April 2010.

Ethical opinion

The members of the Committee taking part in the review gave a favourable ethical opinion of the amendment on the basis described in the notice of amendment form and supporting documentation

Approved documents

The documents reviewed and approved at the meeting were:

Document	Version	Date
Participant Consent Form: B: Consent for DNA analysis	1.4	01 March 2010
Participant Consent Form: B: Consent for follow up	1.4	01 March 2010
Participant Consent Form: A: Consent for DNA analysis	1.4	01 March 2010
Participant Consent Form: A: Consent for follow up	1.4	01 March 2010
Participant Information Sheet: Sheet B	1.4	01 March 2010
Participant Information Sheet: Sheet A	1.4	01 March 2010
Protocol	1.3	01 January 2010
Notice of Substantial Amendment (non-CTIMPs)		16 March 2010
Covering Letter		16 March 2010

NHS
Health Research Authority

NRES Committee Yorkshire & The Humber - Leeds West
First Floor
Millside
Mill Pond Lane
Leeds
LS6 4RA

Tel: 0113 3050122
Fax: 0113 0550191

27 February 2012

Dr John P Greenwood
Consultant Cardiologist, Senior Lecturer
University of Leeds
Academic Unit of Cardiovascular Medicine
G floor, Jubilee Wing
Leeds General Infirmary
LS1 3EX

Dear Dr Greenwood

Study title:	**West Yorkshire Primary Percutaneous Coronary Intervention (WY-PPCI) Outcome Study**
REC reference:	**09/H1311/60**
Amendment number:	**2**
Amendment date:	**19 December 2011**

The above amendment was reviewed by the Sub-Committee in correspondence.

Ethical opinion

The members of the Committee taking part in the review gave a favourable ethical opinion of the amendment on the basis described in the notice of amendment form and supporting documentation.

Approved documents

The documents reviewed and approved at the meeting were:

Document	Version	Date
Notice of Substantial Amendment (non-CTIMPs)	2	19 December 2011
Covering Letter		03 February 2012

Membership of the Committee

The members of the Committee who took part in the review are listed on the attached sheet.

R&D approval

All investigators and research collaborators in the NHS should notify the R&D office for the relevant NHS care organisation of this amendment and check whether it affects R&D approval of the research.

NHS
Health Research Authority

NRES Committee Yorkshire & The Humber - Leeds West
First Floor
Millside
Mill Pond Lane
Leeds
LS6 4RA

Tel: 0113 3050122
Fax: 0113 8556191

27 July 2012

Dr John P Greenwood
Consultant Cardiologist, Senior Lecturer
University of Leeds
Academic Unit of Cardiovascular Medicine
G floor, Jubilee Wing
Leeds General Infirmary
LS1 3EX

Dear Dr Greenwood

Study title:	**West Yorkshire Primary Percutaneous Coronary Intervention (WY-PPCI) Outcome Study**
REC reference:	**09/H1311/60**
Amendment number:	**3**
Amendment date:	**01 June 2012**

The above amendment was reviewed by the Sub-Committee in correspondence.

Ethical opinion

The members of the Committee taking part in the review gave a favourable ethical opinion of the amendment on the basis described in the notice of amendment form and supporting documentation.

Approved documents

The documents reviewed and approved at the meeting were:

Document	Version	Date
Protocol tracked changes	1.4	15 June 2012
Participant Consent Form: Prospective-Leeds-follow up	1.5	15 June 2012
Participant Consent Form: Prospective-Leeds-DNA anaysis	1.5	15 June 2012
Participant Consent Form: Retrospective-Leeds-follow up	1.5	15 June 2012
Participant Consent Form: Retrospective-Leeds-DNA analysis	1.5	15 June 2012
Participant Information Sheet: Retrospective generic	1.5	15 June 2012
Participant Information Sheet: Prospective generic	1.5	15 June 2012

NHS
Health Research Authority

NRES Committee Yorkshire & The Humber - Leeds West
First Floor
Millside
Mill Pond Lane
Leeds
LS6 1RA

Tel: 0113 3050122
Fax: 0113 8556181

27 June 2012

Dr John P Greenwood
Consultant Cardiologist, Senior Lecturer
University of Leeds
Academic Unit of Cardiovascular Medicine
G floor, Jubilee Wing
Leeds General Infirmary
LS1 3EX

Dear Dr Greenwood

Study title:	**West Yorkshire Primary Percutaneous Coronary Intervention (WY-PPCI) Outcome Study**
REC reference:	**09/H1311/60**
Amendment number:	3
Amendment date:	**01 June 2012**

Thank you for submitting the above amendment, which was received on 26 June 2012. I can confirm that this is a valid notice of a substantial amendment and will be reviewed by the Sub-Committee of the REC at its next meeting.

Documents received

The documents to be reviewed are as follows:

Document	Version	Date
Protocol tracked changes	1.4	15 June 2012
Participant Consent Form: Prospective-Leeds-follow up	1.5	15 June 2012
Participant Consent Form: Prospective-Leeds-DNA analysis	1.5	15 June 2012
Participant Consent Form: Retrospective-Leeds-follow up	1.5	15 June 2012
Participant Consent Form: Retrospective-Leeds-DNA analysis	1.5	15 June 2012
Participant Information Sheet: Retrospective generic	1.5	15 June 2012
Participant Information Sheet: Prospective generic	1.5	15 June 2012
Participant Information Sheet: Prospective-Leeds	1.5	15 June 2012
Participant Information Sheet: Retrospective-Leeds	1.5	15 June 2012
Protocol	1.4	15 June 2012