Evaluating care of patients who have undergone percutaneous coronary interventions: the British Cardiovascular Intervention Society database

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Publications

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Other thesis related publications and abstracts

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7. Alabas, O.A., Almudarra, S., Brogan, R.A., Rutherford, M.J., Dondo, T.B., Van Laar, M., Curzen, N., De Belder, M., Ludman, P. and Gale, C.P., 2015, August. Relative survival and excess mortality following unprotected left main stem percutaneous coronary intervention: a national cohort study of 11079 emergent and elective cases. European Heart Journal, 2015. 36: p. 512-512.

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Abstract

Introduction: There is a need to study the level of percutaneous coronary intervention (PCI) care in the UK to promote improvements in care for all patients with cardiovascular disease. The aim of this thesis was to utilise contemporary population-based data to perform a number of investigations and answer several important questions regarding the level of care provided to patients who have undergone PCI in the UK on the basis of outcomes including survival.

Methods: A linked population-based study using the prospectively collected British Cardiovascular Intervention Society (BCIS) registry of patients who have undergone PCI in the UK since January 2005. Three main analyses were performed and for each part; a literature review, analysis (descriptive statistics, comparisons, adjusted associations and survival), multi-level modelling and fit for purpose imputation were conducted.

Results: In the first analysis, 5,065 patients with unprotected left main stem disease (UPLMS) were studied. More than half of patients treated with PCI to the UPLMS presented acutely, their early and late mortality were significantly worse than that for elective patients. Cardiogenic shock was common in ST elevation myocardial infarction (STEMI) and associated with a 1 in 2 risk of early mortality. In acute patients, radial access was associated with improved early outcomes. In the second analysis, 10,827 patients with UPLMS were studied. The number of acute patients with UPLMS PCI increased over the years with stable early and late mortality rates. In the third analysis, 98,637 patients with STEMI were studied. The survival of primary PCI patients was worse than that of facilitated and rescue mainly because majority of the procedures were performed after more than two hours from the onset of symptoms. Old age, cardiogenic shock, more than two hours delay before intervention, inter-hospital transfer and being already in a cardiac centre were independent predictors of worse survival in primary interventions.

Conclusions: The novel prospective data used in this thesis have provided the opportunity to gain more knowledge and understanding of the quality of care provided to patients following PCI which represents a step forward in the assessment and improvement of cardiovascular health services in the UK.

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List of Abbreviations

ACS	Acute Coronary Syndrome
AMI	Acute Myocardial Infarction
ANOVA	Analysis of Variance
BCIS	British Cardiovascular Intervention Society
CABG	Coronary Artery Bypass Graft
CAD	Coronary Artery Disease
CCAD	Central Cardiac Audit Database
CI	Confidence Interval
CSA	Chronic Stable Angina
CVA	Cerebrovascular Accident
CVD	Cardiovascular Diseases
ECG	Electrocardiography
EuroSCORE	European System for Cardiac Operative Risk Evaluation
FREC	Faculty of Medicine and Health Research Ethics Committee
HR	Hazard Ratio
ICD	International Classification of Disease
IMD	Index of Multiple Deprivation
IRA	Infarct-Related Arteries
LMS	Left Main Stem or Left Main Coronary Artery
LVEF	Left Ventricular Ejection Fraction
MACCE	Major Adverse Cardiac and Cerebrovascular Events
MAR	Missing At Random
MCAR	Missing Completely At Random
MCCD	Medical Certificate of Cause of Death

MICE	Multiple imputation by chained equation
MINAP	Myocardial Ischaemia National Audit Project
MNAR	Missing Not At Random
MRIS	Medical Research Information System
NCDs	Non-communicable Diseases
NHS	National Health Service
NICOR	National Institute for Clinical Outcomes Research
NRES	National Research Ethics Service
NSTEACS	Non-ST Elevation Acute Coronary Syndrome
ONS	Office for National Statistics.
OR	Odds Ratio
PCI	Percutaneous Coronary Intervention
P-Complication	Procedural Complication
SD	Standard Deviation
STEMI	ST Elevation Myocardial Infarction
SYNTAX	Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery
TIMI	Thrombolysis in Myocardial Infarction
TLR	Target Lesion Revascularization
TNF	Tumour Necrosis Factor
TVR	Target Vessel Revascularization
UK	United Kingdom
UPLMS	Unprotected Left Main Stem Disease

Chapter 1 Introduction

1.1 Structure of Thesis

The research aim and objectives form the bases on which this thesis is structured. However, they are presented later in Chapter 2 (section 2.6) as they are more effectively reflected and understood by the proceeding backgrounds and literature reviews.

The thesis starts with an expansion of the narrative backgrounds conducted in this chapter. In order to provide more understanding on the topics which the thesis is aiming to research, this chapter describes coronary artery disease (section 1.2), percutaneous coronary intervention (section 1.3) and the data sources used within the thesis, including the British Cardiovascular Intervention Society database, a preliminary description of the data (section 1.4), and the Office for National Statistics (section 1.5) which provides the long-term data on patient mortality.

Chapter 2 explores the available literature which is focused around the research aim and objectives. The review aimed to identify key components of both contextual and compositional influences on patients with coronary artery disease who underwent PCI. This current knowledge base was then used to build the rationale for the proposed research and develop the research questions used to achieve the research aim.

Chapter 3 introduces the practical and conceptual bases of the used methodological approaches, using the knowledge base presented in the same chapter to describe the construction of the BCIS dataset, the data management and the statistical methods used in the thesis.

The main results of the research are presented in three chapters focusing on the clinical determinants of outcomes in patients with UPLMS who received PCI in England and Wales (Chapter 4), the temporal trends of mortality among UK patients with UPLMS who underwent PCI (Chapter 5) and the clinical determinants of primary PCI survival among patients with STEMI in the UK (Chapter 6). Each chapter included: detailed objectives, more specific methods, interpretation of the descriptive, analytical and sensitivity analysis, as well as discussion of the findings.

Chapter 7 discusses the findings of all three analyses as a whole and highlights the key contributions of this work in the context of previous research and policy. The strengths and limitations of the research on which these are based are also discussed. This included the research design, chosen methodologies, their strengths and weaknesses, and the analytical framework used to achieve the research questions. The final part of the chapter discusses recommendations for the enhancement of the BCIS data collection, suggestions for improving the care provided to PCI patients, considerations for future research and the conclusions drawn throughout the thesis.

1.2 Coronary artery disease

1.2.1 Background and pathophysiology

Coronary artery disease (CAD), or what is also known as coronary heart disease or ischemic heart disease, is the commonest type of cardiovascular disease globally [1, 2]. CAD is a series of diseases that arise from the narrowing or obstruction of coronary vessels, which subsequently leads to restriction of the blood flow to the heart [3]. Basically, the term CAD represents a spectrum of diseases that consist of acute coronary syndromes (ACS) and chronic stable angina. ACS include more severe and acute conditions, such as ST elevation myocardial infarction (STEMI), non-ST elevation myocardial infarction (NSTEMI) and unstable angina [4].

1.2.1.1 Chronic stable angina

Chronic stable angina is defined as the presence of chest discomfort or tightness and other concomitant symptoms over a period ranging between at least two months to years. These symptoms, on one hand, are frequently triggered by some precipitants factors, including physical exertion and emotional or psychological stress. On the other hand, these symptoms can be relieved by rest or the use of short acting nitrates [3, 4]. Chronic stable angina is a result of myocardial ischemia, which is the consequence of the mismatching between the oxygen demand and supply in the myocardial muscles. This mismatching is due to steady narrowing of the lining of the affected coronary artery or arteries over a number of years [4].

1.2.1.2 Unstable angina

Unstable angina is differentiated from chronic stable angina by the occurrence of symptoms at rest or on minimal physical effort, and over a shorter period ranging from four to six weeks [4]. The pathophysiology of unstable angina is best explained by an acute myocardial ischemia that occurs in an unpredicted way, caused by vessel spasms

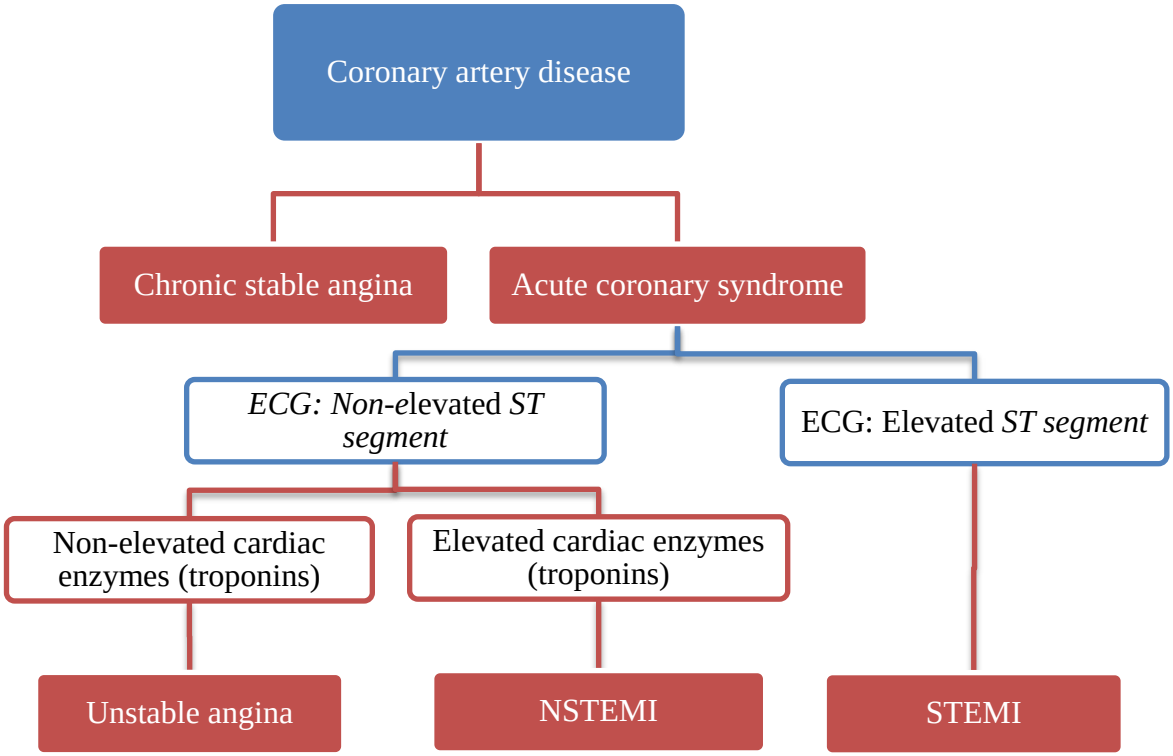
or thrombus formation. Sequentially, this leads to severe restriction or complete abrupt occlusion of the affected coronary artery or arteries [4].

1.2.1.3 Acute myocardial infarction

Arterial occlusion is usually occurs at the site of atherosclerosis in the affected coronary artery or arteries. Atherosclerotic plaque is a derivative of the deposition of lipids on the wall of medium to large arteries, which subsequently decreases the luminal diameter and the blood flow of the affected artery or arteries [5]. Occasionally the plaque may rupture, and that leads to the formation of thrombus, which is the main cause of unexpected complete or incomplete occlusion of the affected artery [5]. Persistent unreserved acute myocardial ischemia of a period more than 15 to 20 minutes often results in necrosis of the myocardium which when, at presentation, associated with electrocardiography (ECG) changes and/or elevated cardiac enzymes, is known as acute myocardial infarction (AMI) [3, 4].

The existence or absence of ST elevation in ECG differentiates between STEMI and NSTEMI, while cardiac enzymes (troponins) have a major role in differentiating NSTEMI from unstable angina (Figure 1.1) [4, 6, 7]. The typical presenting symptom of AMI is persistent or sporadic retro sternal chest pain or discomfort that radiates to the left arm, neck or jaw, lasting over 20 minutes. Such pain usually takes place at rest or on minimal effort with a previous history of similar complaint over the last few days or weeks [3, 4]. Other atypical symptoms of AMI can be either dyspnoea, abdominal pain, nausea or diaphoresis [4].

Figure 1.1: The spectrum of coronary artery disease.



1.2.2 Coronary artery disease and mortality epidemiology

Over the last decade, cardiovascular diseases continue to be the leading cause of morbidity and mortality across the world [2, 8]. In 2008, 36 million deaths (63.0% of all deaths) were due to non-communicable diseases (NCDs), of which 17.3 million (30.0%) were due to cardiovascular diseases (27.0% of male deaths and 32.0% of female deaths) [2, 9]. In 2010, cardiovascular diseases related deaths decreased to 15.6 million (29.6%) [10]. In the same year, more than 147,000 deaths in England (around 33.0% of all deaths) were due to cardiovascular diseases [11]. In 2012, deaths due to cardiovascular diseases declined to 28.0% of all deaths in the UK [12].

Ranging from 4.0% of all premature deaths (deaths at less than 60 years of age) in developed countries to 42.0% in developing countries, cardiovascular diseases related mortality rates have been declining over the years in developed countries. On the contrary, mortality rates due to cardiovascular diseases have been rising tremendously in developing countries, leading to significant economic burdens worldwide [2]. In the same way, deaths due to cardiovascular diseases in the UK have been decreasing from more than 50.0% of all deaths in 1961 to 32.0% in 2009 [13]. Even with the reduction in mortality rates in many European countries, cardiovascular diseases remain responsible for causing more than four million deaths (46.0%) annually (42.0% of male deaths and 51.0% of female deaths) [1]. In the UK, nearly 191,000 deaths are caused by cardiovascular diseases every year [14].

Over time, the prognosis of CAD has changed distinctly along with the changes in certain risk factors at both individual and population levels [13]. These risk factors can be either behavioural (like type of diet, physical activity, smoking or alcohol consumption) or medical (such as obesity, diabetes, hypertension or hypercholesterolemia) [11]. In 2008, 7.3 million cardiovascular deaths worldwide (42.0% of all cardiovascular deaths) were due to CAD; 80.0% of them were in low- to middle-income countries, predominantly in Asian and middle eastern countries [2, 9]. By the year 2013, CAD was still the leading cause of death worldwide, causing more than 8.1 million deaths (16.8%) [15].

In European countries, CAD accounts for about 1.8 million deaths (20.0%) every year [1]. In 2008, 88,236 deaths (46.0% of all cardiovascular deaths) in the UK were caused by CAD [14]. In 2010, more than 65,000 deaths (37,873 males and 27,370 females) occurred because of CAD in England alone [11]. In 2012, CAD accounted for nearly 37,500 deaths (46.0% of all cardiovascular diseases related deaths) in the UK (16.0% of male deaths and 10.0% of female deaths) [12]. Despite the great decline in the number of deaths caused by CAD in the UK, from 166,000 deaths in 1961 to 80,000 deaths in 2009, the number of CAD patients is increasing over the years because of the increase in survival rates and an aging population [13].

In the UK, 28,258 deaths in 2008 caused by CAD were at age less than 75 years, out of which 20,850 deaths (18.0%) were in males and 7,408 deaths (9.0%) were in

females. Among UK countries these premature deaths were mainly in England (22,549 deaths), followed by Scotland (3,333 deaths), then Wales (1,588 deaths) and Northern Ireland (788 deaths) [14]. Furthermore, in 2010, out of the total deaths in CAD patients in the UK, 706,184 deaths (18.0%) were at age less than 75 years and 330,598 deaths (14.0%) were at age less than 65 years [1]. Likewise in the same year, it was estimated that more than 21,000 deaths in England at age less than 75 years were caused by CAD [11]. In 2012, almost 42,000 deaths from cardiovascular diseases in the UK were at age less than 75 years, out of which 15.0% of male deaths and 8.0% of female deaths was a result of CAD [12].

1.2.3 Burden of coronary artery disease in the UK

In the medical literature, it is well known that CAD is a major burden to the UK National Health Service (NHS). In England, the prevalence of CAD in 2006 was estimated to be more than 2.2 million patients (1.3 million males and 860,000 females) [11]. In 2010, about 2.0% (more than 263,000 males and 142,000 females) of all inpatient admissions in England were because of CAD [11]. Between 2012 and 2013, nearly 2.3 million patients in the UK were diagnosed with CAD, with a prevalence of 3.4% in England, 3.9% in Wales, 4.3% in Scotland and 3.9% in Northern Ireland [12]. During the same period in all UK countries, CAD was responsible for 323,776 (3.5%) of all male inpatient admissions and 169,545 (1.5%) of all female inpatient admissions [12].

Furthermore, the costs of disease related outcomes of CAD in 2006 were £3.2 billion and the estimated costs in 2012 were around £7.1 billion [11, 16]. In England alone, between 2012 and 2013, the costs of cardiovascular diseases treatment in the NHS were over £6.8 billion. These expenses were mainly spent on the secondary management of emergency cases (63.4%), followed by primary care (20.9%) [12]. In 2013, the cost of medication prescriptions for cardiovascular diseases were over 300 million in England alone, which is six fold higher than the expenditure on medication prescriptions in 1981 (£1,387.5 million) [12]. In 2012, over 90,000 percutaneous coronary intervention (PCI) procedures were carried out in the UK, which is twice the number of procedures that was performed 10 years ago. Similarly for all UK countries

in 2012, nearly 17,000 coronary artery bypass graft (CABG) surgeries were performed. Although CABG is less prevalent nowadays, the frequency of the surgery remains high [12].

1.2.4 Unprotected left main stem disease

The left main coronary artery or left main stem (LMS) originates from the aorta, and is classically placed above and in front of the left side of the heart exterior wall. The LMS is basically divided into three parts: an ostium, a shaft and a distal part that ends by bifurcating into the left anterior descending and circumflex artery [17]. Significant stenosis of more than 50% of the LMS is a rare, however an important, cause of symptomatic CAD [18, 19]. The LMS stenosis' commonest position is the shaft or at the bifurcation, and usually is associated with significant stenosis of other coronary arteries [17]. In about 5% of all patients with CAD, unprotected LMS disease (UPLMS) takes place, and this can be life threatening when it is occluded [18, 19]. UPLMS is known as a LMS disease that does not have a patent graft to any left-sided coronary artery [20].

CABG remains the standard treatment of choice for all types of LMS disease, nevertheless in contemporary practice, PCI is considered a reasonable line of management since it reduces the in-hospital mortality rate and increases the survival at one year when compared to reported CABG outcomes [21-24]. Furthermore, with the expansions in stent technology (drug eluted stents, equipment and techniques), PCI procedures are yielding higher rates of success with encouraging outcomes in the management of UPLMS [25].

Given the fact that the success of any PCI procedure for UPLMS (in terms of short- and long-term outcomes including survival) is influenced by various risk factors, such as age, cardiogenic shock and diabetes, it is believed that these factors are less common among the elective cases compared to the unstable emergency cases [25-27]. Besides, unless it is not contraindicated, CABG is the recommended line of management for UPLMS, and PCIs would be preserved for more complicated cases, such as the multi-morbid, thus affecting its success further [19, 26, 28].

1.2.5 Why study cohort data about PCI in UPLMS?

There is conflicting evidence regarding what the main independent clinical predictors of PCI outcomes in UPLMS are. However, these predictors can be elucidated through the fact that most UPLMS cases treated by PCI are actually a high-risk group of patients who have previously been rejected from surgical treatment [26]. Besides, regardless of the degree and location of stenosis, the argument continues about these risk factors and their short- and long-term effect on the outcomes and survival of PCI procedures in UPLMS patients [25, 26].

Moreover, there is a gap in the knowledge base regarding the relative merits of PCI to an UPLMS culprit lesion in patients who present with STEMI or NSTEACS [29]. For patients with cardiogenic shock, there are limited data available in the literature, with early outcomes reported in only small 'hypothesis-generating' cohort studies. Ben Dor *et al.* [30] and Schrale *et al.* [31] demonstrated that increased mortality rate was significantly associated with cardiogenic shock. At the present time, the radial approach is considered to be safer and cost-effective than the femoral in patients with STEMI [32-34]. However, although recent international guidelines recommend the radial approach to PCI over that of the femoral approach [35], the wider implications of this have not been studied in patients who receive PCI to disease of the UPLMS.

In addition, details from the existing literature to date regarding the temporal trends in incidence, care and clinical outcomes of UPLMS PCI across the full spectrum of acute and chronic stable patients have been limited. These studies from the literature were small, regional and non-consecutive series of patients or inferred from randomised controlled trials that tend to recruit less high-risk patients [36-42]. Few recent studies, such as Park et al. [43] and Conrotto et al. [44] have reported the temporal trends of UPLMS outcomes. However, the size of the cohort of these studies were small and less representatives since they were performed outside the UK. Notably, in the UK, there are no whole-country studies of the temporal trends in UPLMS PCI and the associated procedural and longer-term outcomes.

The British Cardiovascular Intervention Society (BCIS) registry is a prospective whole-country registry of all adult PCIs that has collected patient-level data for from all centres in the UK since 2005. It provides data that cannot be collected within an RCT,

and few cohort studies have comparable population coverage, long-term follow-up and depth of data detail in relation to clinical risk.

There is, therefore, value in using the BCIS data to address UPLMS knowledge gaps as well as to report contemporary and representative outcomes data for PCI to the UPLMS in order to inform patients, healthcare professionals and regulators of both the benefits and inherent risks of such therapy, and also to highlight areas where novel interventions aimed at improving outcomes may be targeted [31, 42, 45-48].

1.3 Percutaneous coronary intervention

1.3.1 Background

Percutaneous coronary intervention is a non-surgical procedure performed by interventional cardiologists. The procedure is basically the insertion of a catheter, guided by X-ray, into an access vessel (usually femoral or radial arteries). On that catheter a deflated balloon, stent or other devices are carried up through the circulatory system to the occluded vessel in the heart and treat the obstruction [4].

Cardiac catheterisation was introduced in the late 1920s, then later in the 1950s, coronary angiography was technologically established. In the 1960s, balloon angioplasty was first initiated, and was modified to allow the revascularisation of coronary arteries in the late 1970s [49]. In the 1980s, stents were introduced to revascularisation and, over time, the technology and pharmacology around percutaneous revascularisation progressed tremendously (84.2% of all PCIs in 1999) [50].

To treat an occluded coronary artery, CABG and PCI may be used [23]. In spite of the unvarying utilisation of CABG over recent years, the use of PCI for CAD in the UK and globally has increased tremendously, especially after the introduction of the drug eluting stent in 2002 [50]. In 2004, drug eluting stents were used in 53% of UK PCI procedures and the ratio of PCI to CABG had increased to 2.5:1 [51-53].

Furthermore in 2010, more than 87,000 PCI procedures were performed in the UK, which was over seven times more than those performed in 1992 [11]. In 2012, the prevalence of PCI in the UK increased to more than 90,000 procedures, while approximately 17,000 CABGs were performed in the same year [12]. By 2013, the total number of PCIs undertaken in all of the UK was 92,589 procedures: 76,712 (82.9%) in England, 8,515 (9.2%) in Scotland, 3,563 (3.8%) in Northern Ireland and 3,799 (4.1%) in Wales [54].

Lately, PCI has progressed significantly with the combination of experienced practitioners, modern drug therapy and contemporary equipment [55]. At first, PCI was used for the management of patients with stable angina or individual lesions in a single coronary artery. At the present time, though, PCI has numerous indications, including unstable angina, STEMI, multi vessel and complex CAD [55].

1.3.2 Percutaneous coronary intervention and outcomes

In addition to patient stability, the risks at hand, operator experience and the facilities available, the success of any PCI procedure depends on the visualisation of the stenosed or occluded artery and the nearby arterial branches [56, 57]. On the other hand, unfavourable outcomes of PCI procedures can be observed more in the presence of different risk factors such as old age, diabetes, renal failure, cardiogenic shock, unstable angina, previous myocardial infarction, a large area of myocardium at risk and multi vessel disease [52, 53].

Major complications of PCI procedures are rare. However, there was much variation in the reporting of complication rates in the literature. Grech *et al.* [56] reported that 0.2% of PCI procedures developed major complications, including death. However, they concluded that this may be higher in cases with additional risks: myocardial infarction in 1%, stroke in 0.5%, cardiac tamponade in 0.5% and systemic bleeding in 0.5%.

Naik *et al.* [58] concluded that mortality rates at three years and major adverse cardiac and cerebrovascular events (MACCE) were the same in both CABG and PCI, while target vessel revascularisation (TVR) was higher with PCI. A meta-analysis by

Capodanno *et al.* [59] stated that “left main coronary artery (LMCA) disease patients treated with PCI have non-significantly different 1-year rates of MACCE, death, and myocardial infarction, a lower risk of stroke, and a higher risk of TVR compared with CABG”.

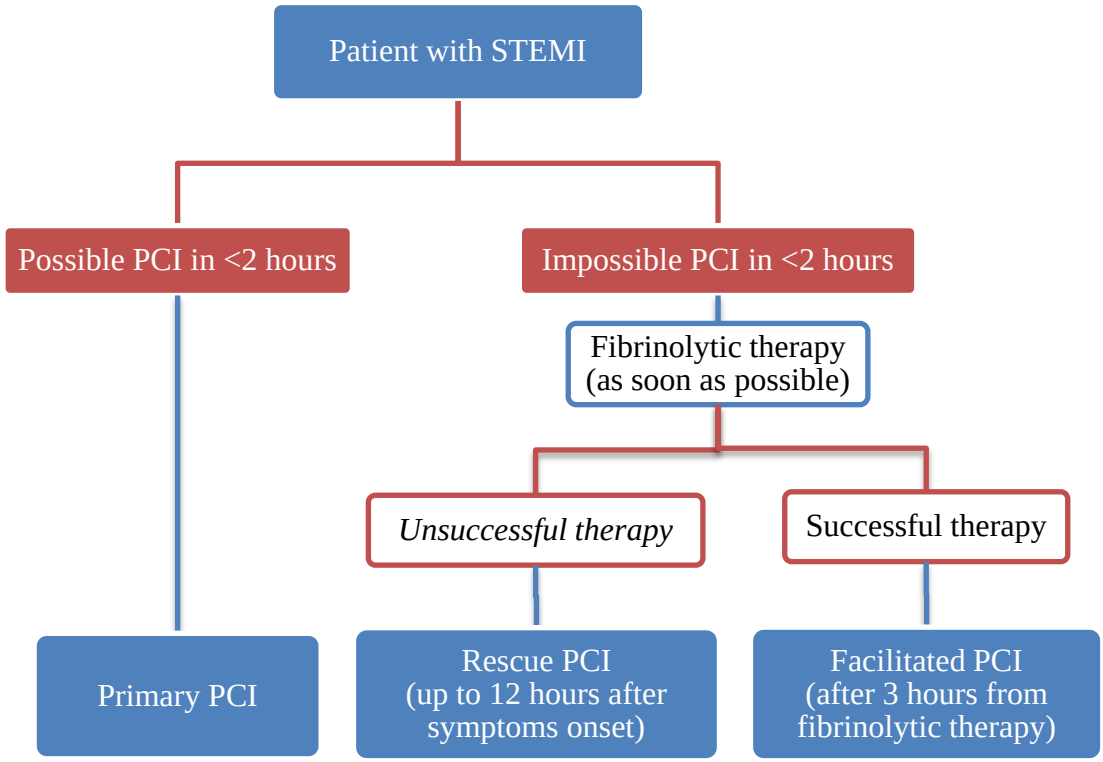
Over the last 30 years, many studies in the medical literature looked into the impact of provider yearly volume, either at hospital or at operator level, on PCI short-term unfavourable outcomes such as mortality. Most of these studies reported a significant inverse impact of volume on the incidence of short-term outcomes after PCIs [60-67]. A meta-analysis by Post *et al.* [68] carried out on ten PCI studies, including 1,322,342 patients in 1,746 hospitals, concluded that high volume hospitals demonstrated significantly lower short-term mortality compared to low volume hospitals.

Enormous increments in the success rate of PCI procedures with obvious decline in post procedure complications were mainly linked to the current advances in implementing guidelines for management, catheter techniques, development of new guide wires, drug eluting stents, atherectomy devices and contemporary medications which have occurred along with the increased understanding of cardiovascular physiology and atherosclerosis pathogenesis [69].

1.3.3 Primary percutaneous coronary intervention

For the treatment of STEMI, the urgency of the intervention procedure and the use of medical treatment such as fibrinolytic therapy is critical. Therefore, PCI can be primary (when it is performed unaided by fibrinolytic therapy in less than two hours after onset), facilitated (when associated with fibrinolytic therapy) or rescue (when it is undertaken after a failed fibrinolytic therapy) (Figure 1.2) [4, 7].

Figure 1.2: The spectrum of STEMI treatment strategy.



Primary PCI is the first line of management for STEMI patients worldwide and in the UK [4, 70]. Between 2004 and 2007 in England and Wales, primary PCI procedures increased from 5.0% to 20.0% [71]. It is well known that the preferred time period for primary PCI is less than two hours after symptoms onset [4]. With delays to the procedure, the outcomes of primary PCI generally worsen [71-73]. For STEMI with cardiogenic shock, primary PCI remains the favoured line of treatment over fibrinolytic therapy [4, 74].

Performing primary PCI for acute myocardial infarction cases has always been an immense challenge for all interventional cardiology centres, and in order to attain such

an approach, interventional cardiology centres within hospitals should always have experienced, well-trained interventional cardiologists and fully equipped operation, high dependency and emergency departments with all needed supporting staff [60]. At present, experienced interventionists in high volume cardiac centres are noted to have better outcomes of primary PCI [4, 71].

Patients with STEMI have a wide range of risk factors, such as old age, cardiogenic shock, hypertension and diabetes, which have impact on the outcomes of primary PCI. Despite this and the increasing burden of STEMI requiring primary PCI, survival rates have improved (up to 97% 3 years survival) [71, 75, 76]. It is believed that primary PCI is cost-effective in treating STEMI, mainly due to the reduced mortality outcomes associated with the procedure [77]. Consequently, a plan by the NHS in England and Wales was initiated to provide a national primary PCI service for all STEMI by 2012; such strategies have significant organisational and financial impact on the NHS [71].

1.3.4 Why investigate survival following primary PCI?

Evidence from the medical literature supports the fact that primary PCI produces better outcomes for STEMI patients [70]. Delays in treatment frequently lead to undesirable complications and outcomes [71-73]. At the same time, the practice of primary PCI is increasing globally and, particularly, in the UK [70]. However, there is a gap of knowledge regarding the clinical determinants of primary PCI survival in particular. In addition, there is a lack of data about the impact of the timing of the procedure in relation to the routes of admission as well as the effect of hospital level factors such as patient volume.

The majority of the literature about primary PCI has arisen from randomised controlled trials, and typically conducted outside the UK; thus it may not be generalisable to the UK. In the UK, there are few population-based studies on survival in patients with STEMI after primary PCI. Likewise, less studies have been conducted about the impact of clinical predictors on survival, including the admission routes and hospital variations [78, 79].

In an observational national-based dataset such as the BCIS database, the availability of contemporary data on primary PCI allow to infer primary patients' survival for the UK population. Consequently, significant results will be important to patients, cardiology professionals and healthcare managers in the UK to quantify the benefits of existing interventional care of patients as well as to highlight to stakeholders all areas where care and/or organisational changes and improvements are required.

1.4 The British Cardiovascular Intervention Society registry

1.4.1 Background

Currently, in the UK, PCI is the most common procedure used in the invasive treatment of CAD. In order to establish organised healthcare services related to PCI procedures within the UK, proposals were made to collect significant reliable data about PCI procedures, operators, survival and outcomes [51, 52, 69]. One of the major organisations which established such data was the British Cardiovascular Intervention Society (BCIS).

In 1988, BCIS was initiated and along with that the collection of data, aiming to describe the national development and practice of PCI in England and Wales [80]. BCIS began as a voluntary group of physicians who gathered to discuss cases and matters relating to PCI and, as the practice expanded and developed, so did the society [80]. The society represents all concerned groups, including physicians, technicians, nurses and regulatory authorities [80]. One of the main aims of BCIS was to create a comprehensive and accurate registry of all PCI procedures performed in England and Wales. This was to review and assess the quality of care, improve and determine the standards of patients care, and provide data for research [80, 81].

Between 1988 and 1991, yearly descriptive surveys of PCI procedures were published in the British Heart Journal. However, since 1992, annual information and

reports have been made available on the society's website [81]. The BCIS data were mainly related to procedure quantities, centre numbers, as well as basic clinical characteristics. Over the years, efforts were made to determine clinical outcomes after PCIs, but it was clear that there were many errors in the data collected. Eventually, the system had a significant improvement with electronic techniques for data collection. This was funded by the Department of Health and developed by the Central Cardiac Audit Database (CCAD) group [80, 81]. In 1996, these techniques were tested as a pilot in some hospitals, and by 2005, full nationwide coverage was attained by using electronic data collection [52, 80, 81].

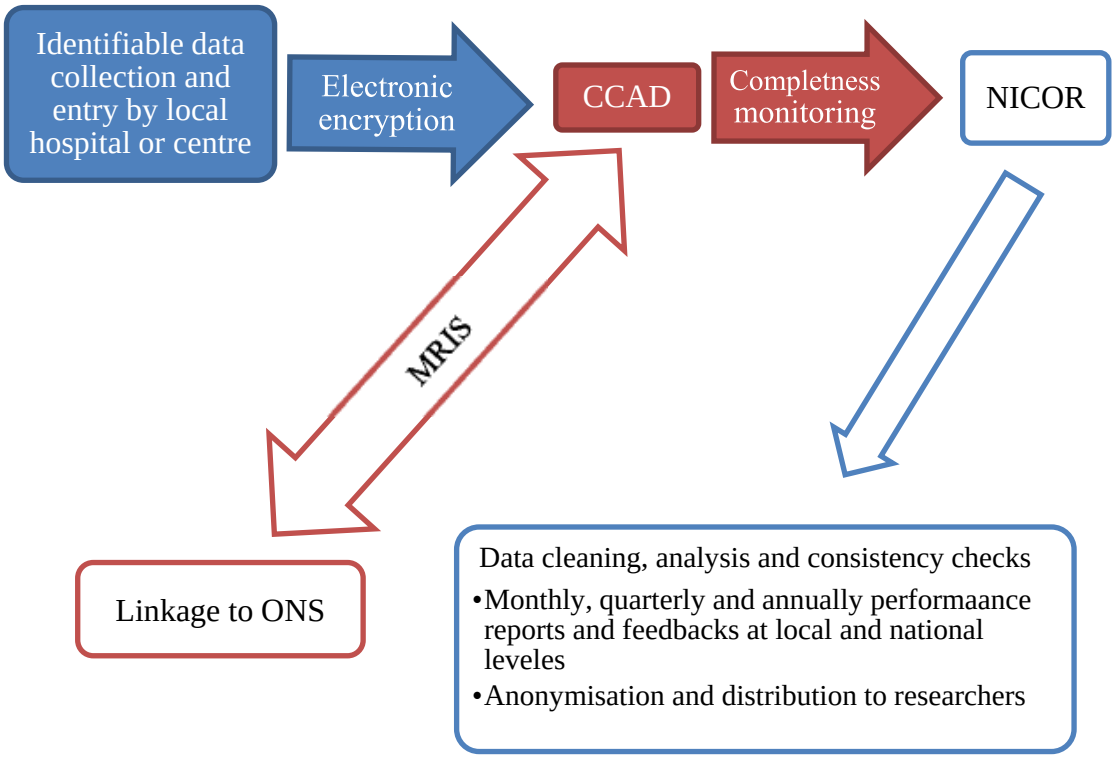
The society has an important role in teaching and education. For example, in 1996 and in 2000, a joint working group between BCIS and the British Cardiac Society set out guidelines for training and continuing competence in PCI. At the same time, BCIS entered into a joint project with other specialised groups in cardiovascular medicine like the Heart Valve Registry, the Society of Cardiothoracic Surgeons, and the Association of Cardiothoracic Anaesthetists. Since April 2011, BCIS and five other UK cardiac audits have been brought together in one organisation called the National Institute for Clinical Outcomes Research (NICOR) [51, 80, 81].

The BCIS database is an electronic registry of all attempts of PCI procedures that have been carried out in all UK hospitals since 1994 [81]. For each PCI attempt, when any coronary device is used to probe or cross one or more coronary lesions with the intention of performing a coronary intervention, a total of 113 variables are regularly collected, which include patient demographics (e.g. age, sex and ethnicity), pre-procedural clinical status (e.g. history of MI, renal disease, diabetes and cardiogenic shock), admission routes, procedures indications, related dates and times, operators' details, procedures technical aspects and outcomes, together with all patient complications up to hospital discharge [81]. Changes to the BCIS database are performed to meet the requirements of care providers and patients' needs; in the last updated version (2005 – 2014) of the BCIS database, the number of variables to be collected increased to 124 [54].

1.4.2 How are the data entered?

As of March 2010, about 460,000 records were in the BCIS registry. Around 80,000 new records are added each year, reaching more than 747,000 by the end of March 2014 [20, 54, 81]. Data entry is usually done by healthcare professionals and data entry clerks. The data are uploaded into local software systems, followed by subsequent electronic encryption to ensure data security, then the data are transferred by internet to CCAD central data servers. As feedback to all PCI centres and others who are concerned (e.g. participating PCI centres and operators), monthly, quarterly and annual reports of PCI activities and outcomes across the UK are regularly distributed [20, 52, 81] (Figure 1.3).

Figure 1.3: British Cardiovascular Intervention Society (BCIS) data flow.



1.4.3 Patient identification, follow-up and mortality

Part of the BCIS-CCAD project is to track subsequent patient's vital status and mortality dates after discharge from hospital. Tracking is carried out by CCAD using the National Health Service (NHS) central register number, which provides a unique identifier for any person registered with the NHS in the UK. The NHS number is pseudo-anonymised within the database; however, other identifiers are available in the database like hospital numbers, dates of birth and postcodes. These kinds of data as well as the hospital identity are protected and researchers do not have access to such data [39, 53] (Figure 1.3).

Analysis of all-cause mortality is executed by the Medical Research Information System (MRIS) by linkage with the Office for National Statistics (ONS) using each patient's unique NHS number. Using each patient's geographical residence, their index of multiple deprivation (IMD) score was linked to their corresponding BCIS record, a linkage that was made by the CCAD as all patients' identifiers such as names, hospital numbers, dates of birth and postcodes, as well as interventionists and hospitals identifiers were secondary anonymised in BCIS data. In this thesis, two versions of BCIS data have been utilised, and the censoring date for the 2010 BCIS database was 10th August 2011 while for the 2014 database it was 1st July 2014 [20, 54].

1.4.4 Data structure

The BCIS data is structured into six themes, each containing specific information. All are described in Table 1.1. Within this thesis, data from two time periods are used:

- The 2010 BCIS dataset: the initially received version, from 1st of January 2005 to 31st of December 2010. The overall description is demonstrated in this chapter (section 1.4.5). This version was used for analysis in Chapter 4.
- The 2014 BCIS dataset: an updated version which was available more recently, from 1st of January 2005 to 31st of March 2014. The overall description is demonstrated in this chapter (section 1.4.6). This version was used for analyses in Chapters 5 and 6.

Table 1.1: BCIS database fields, information and contents.

Theme	Type of information	Examples of contents
Patient	Demographic and identification information of patients.	Patient name, gender, date of birth, ethnicity, post code, NHS number and hospital identifier.
Clinical	Clinical presentation, investigation, medical history, and pre-procedure information.	Clinical syndrome, intervention indications, presence of cardiogenic shock, admission route, presenting ECG, history of previous acute myocardial infarction, previous PCI, Diabetes, pre-procedural LVEF and pre-procedural flow in infarct related artery.
Procedural	Operator, procedural techniques, devices and medications and post-procedural investigation Information.	Operators identifier, number and type of stents used, diagnostic and procedural devices used such as intravascular ultrasound, circulatory support, arterial management and post-procedural flow in infarct related artery.
Outcomes	In-hospital outcomes, post-procedural enzymes and discharge information.	In-hospital outcomes such as acute myocardial infarction, cerebrovascular accident, bleeding or death; troponin biomarker level, status at discharge (dead or alive) and date of discharge.
Miscellanies	Clinical, investigation, procedural and post-procedural information.	Cholesterol level, smoking status, history of renal disease, indication for stenting, arterial access, procedural complications and left main stem protection.
Therapy *	Therapeutic tests and scores; and some specific treatments.	Use of ventilation, hypothermia treatment, arterial blood gas results and Glasgow coma scaling.

* This part was added in the 2014 updated version of BCIS database.

1.4.5 BCIS database (the 2010 version after data cleaning)

The 2010 BCIS database is a linked prospective national registry of all adult percutaneous coronary interventions that holds pseudo-anonymised patient-level data from all centres in the UK registered with the BCIS audit program, in the period between 1st January 2005 and 31st December 2010.

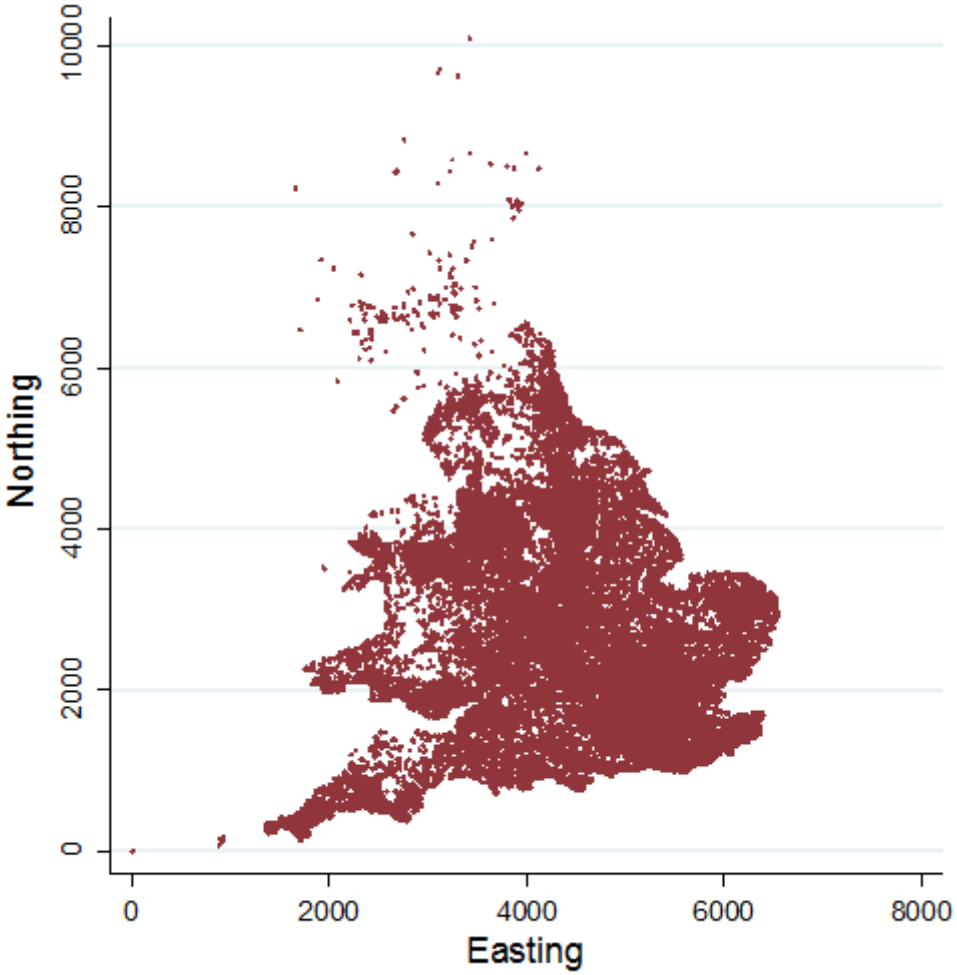
1.4.5.1 Who is in the database?

A total of 114 interventional cardiology centres and hospitals in the UK provide data to the BCIS, including all adult PCIs performed within these centres: 99 (86.8%) in England, eight (7.1%) in Scotland, four (3.5%) in Northern Ireland and three (2.6%) in Wales [20]. Although all four countries in the UK contribute to the BCIS data, robust mortality tracking was only available for patients who live in England and Wales; this represents approximately 89% of the whole adult UK population (based on the Office for National Statistics UK population estimates for 2013) [82] (Figure 1.4).

1.4.5.2 Data description

A comprehensive description of the overall 2010 version of the BCIS data is presented in Appendix I including demographic, clinical, procedural, and outcomes characteristics.

Figure 1.4: Distribution of all PCI patients by country in England and Wales from 2005 to 2010.



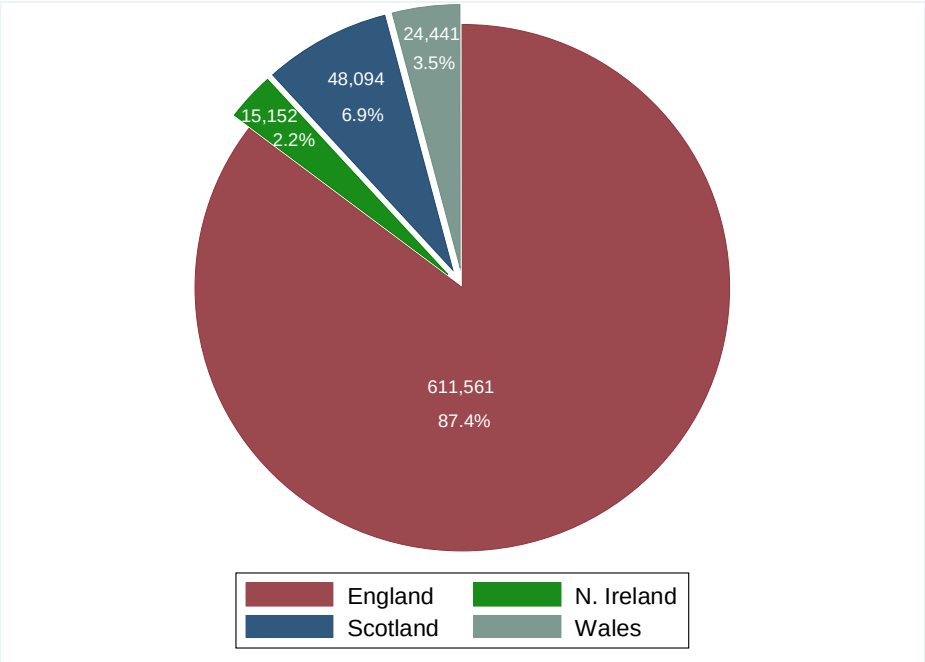
1.4.6 BCIS database (the 2014 version after data cleaning)

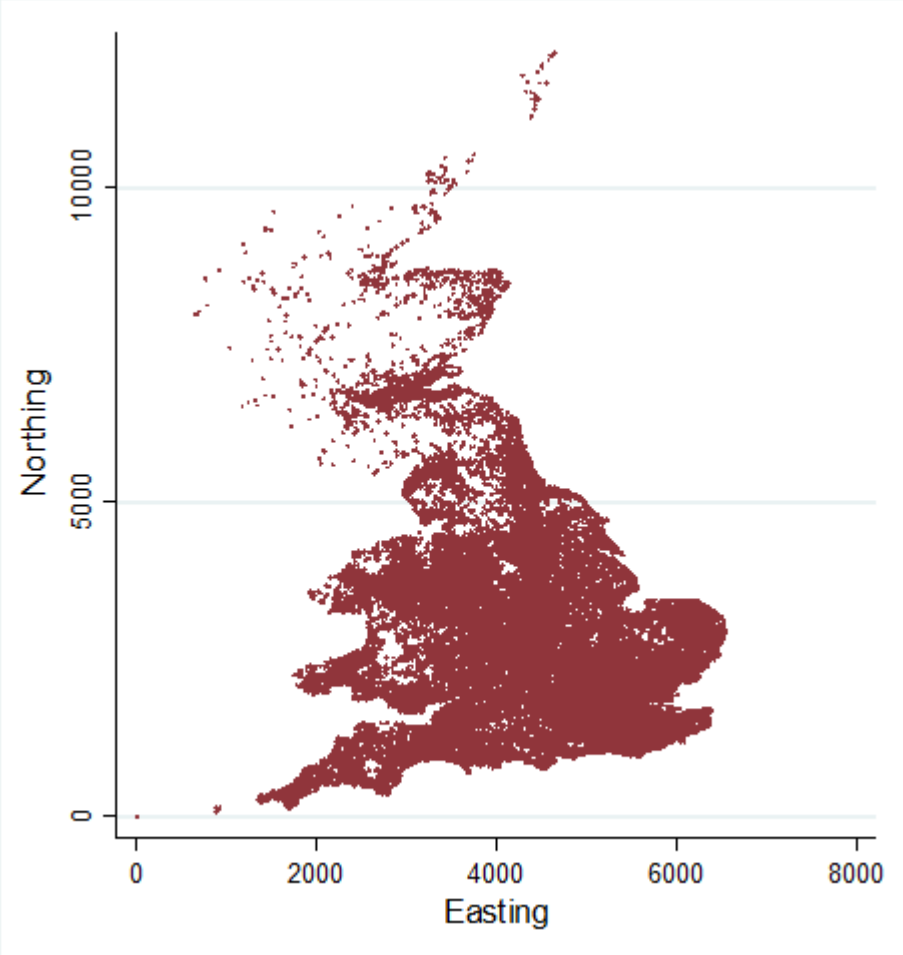
Similar to the 2010 BCIS database, the updated 2014 database is a linked prospective population-based registry of all adult percutaneous coronary interventions, and holds pseudo-anonymised patient-level data from all centres in the UK that were registered with the BCIS audit program in the period between 1st January 2005 and 31st March 2014.

1.4.6.1 Who is in the database?

Other than the data about the extra years from 2011 to 2014, the main difference between the 2014 updated BCIS database and the previous 2010 version was the linkage to mortality tracking which is available for all patients living in the UK. In the 2010 database, mortality tracking was restricted to the patients from England and Wales. All PCI procedures from 117 registered interventional cardiology centres and hospitals in UK provide data to the BCIS, 101 (86.4%) being in England, eight (6.8%) in Scotland, four (3.4%) in Northern Ireland and four (3.4%) in Wales [54]. Figure 1.5 shows the distribution of PCI procedures in all four countries of the UK.

Figure 1.5: Distribution of all PCI patients by country in the UK from 2005 to 2014.





1.4.6.2 Data description

1.4.6.2.1 Demographic characteristics

Table 1.2 illustrates the distribution of baseline demographic characteristics of PCIs in the 2014 BCIS database. A total of 699,248 PCIs were recorded in the 2014 BCIS database. By means of continuance of what had been demonstrated in the previous 2010 version, the number of PCI procedures undertaken per year rose gradually (from 41,031 procedures in 2005 to 96,655 in 2013) (Figure1.6).

The mean age (SD) for all patients increased to 64.6 (11.7) years. Male patients remained dominant (73.5%) out of all patients; the mean age (SD) was 63.4 (11.5) years for male patients and 68.1 (11.5) years for females. Figure 1.7 demonstrates the difference in the frequency and age distribution between males and females. NHS hospitals/centres continued leading in performing the majority of procedures (85.0%), while private hospitals/centres were (3.8%) only. Direct admission to cardiac centre became the main route of admission at 43.9% compared to 33.5% in the 2010 database.

Table 1.2: Baseline demographic characteristics of all PCI patients in the UK from 2005 to 2014.

Variable		Total n= 699,248	Missing values (%)
Mean (SD) age, years		64.6 (11.7)	690 (0.1)
Age	**Less than 65 years (%)**	347,131 (49.6)	
	65 – 80 years (%)	288,670 (41.3)	
	Greater than 80 years (%)	62,757 (9.0)	
Gender	**Female (%)**	181,854 (26.0)	3,407 (0.5)
	Male (%)	513,987 (73.5)	
Ethnic groups	**Caucasian (%)**	442,584 (63.3)	187,946 (26.9)
	Black (%)	3,904 (0.6)	
	Asian (%)	33,283 (4.7)	
	Other (%)	31,531 (4.5)	
Patient type	**NHS (%)**	594,554 (85.0)	78,064 (11.2)
	Private (%)	26,630 (3.8)	
Admission route (ACS only) *	**Direct to cardiac centre (%)**	173,884 (43.9)	55,335 (13.9)
	Inter-hospital transfer (%)	140,351 (35.4)	
	Already in cardiac centre (%)	26,979 (6.8)	
Index of multiple deprivation score, mean (SD)		19.5 (16.5)	65,313 (9.3)

* ACS n= 396,549.

Figure 1.6: Number of PCIs performed per year, from 2005 to 2014.

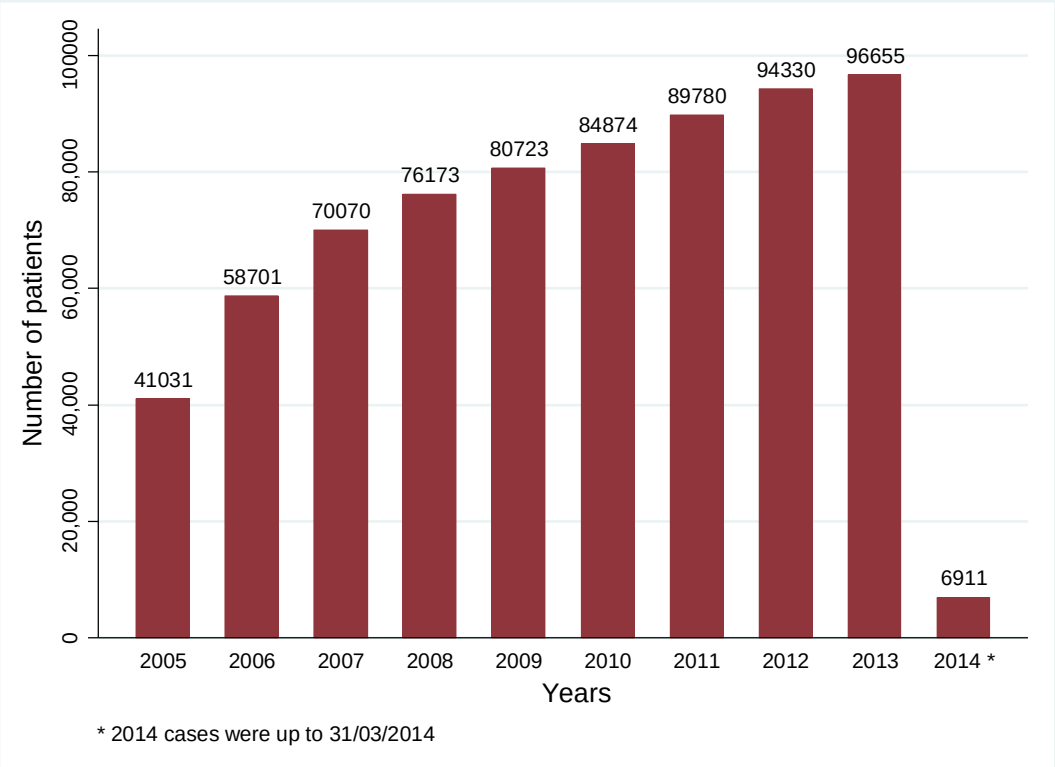
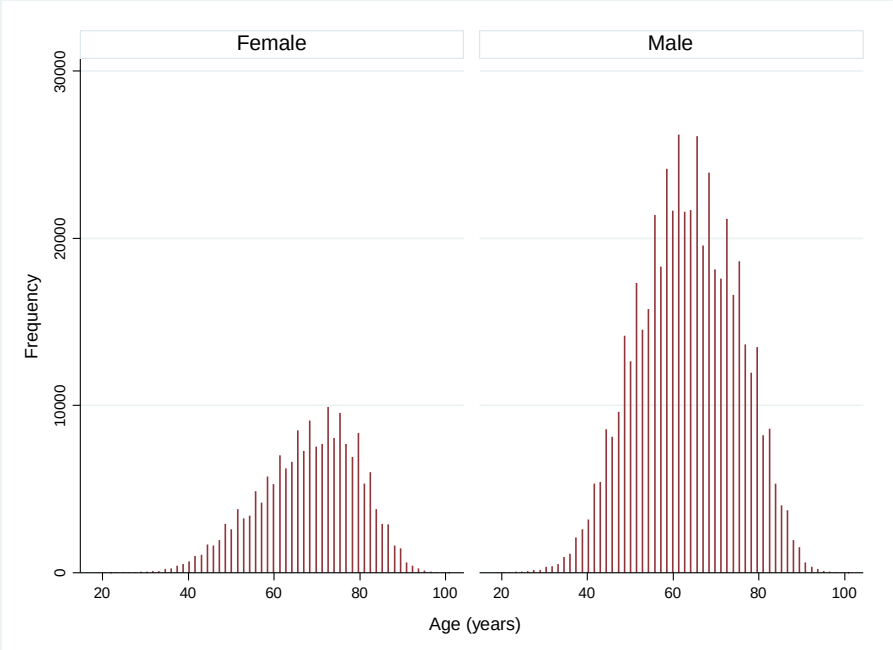


Figure 1.7: Age distribution by gender of all PCI patients in the UK from 2005 to 2014.



1.4.6.2.2 Clinical characteristics

The total number of patients with chronic stable angina decreased remarkably compared to stable patients in the 2010 database (50.3% vs. 39.6%). Though, the number of patients with STEMI and NSTEACS increased (20.0% and 36.8%, respectively). Between 2011 and 2014, the drop in the frequency of chronic stable angina patients continued, however, in slower rates (from 36.5% in 2011 to 35.1% in 2014); similarly, the frequency of STEMI patients increased slowly compared to previous years (25.9% in 2011 to 26.9% in 2014) (Figure 1.8). Compared to data from the 2010 database, the prevalence of primary PCI procedures increased from 67.8% to 87.2% in the 2014 database. Patients with pre-procedural cardiogenic shock were 13,376 (1.9%), and those with severe LVSD (ejection fraction less than 30%) were 34,750 (5.0%) patients. More details on the clinical characteristics of PCI between 2005 and 2014 are listed in Table 1.3.

Figure 1.8: Distribution of all PCI patients in the UK from 2005 to 2014, by clinical syndrome.

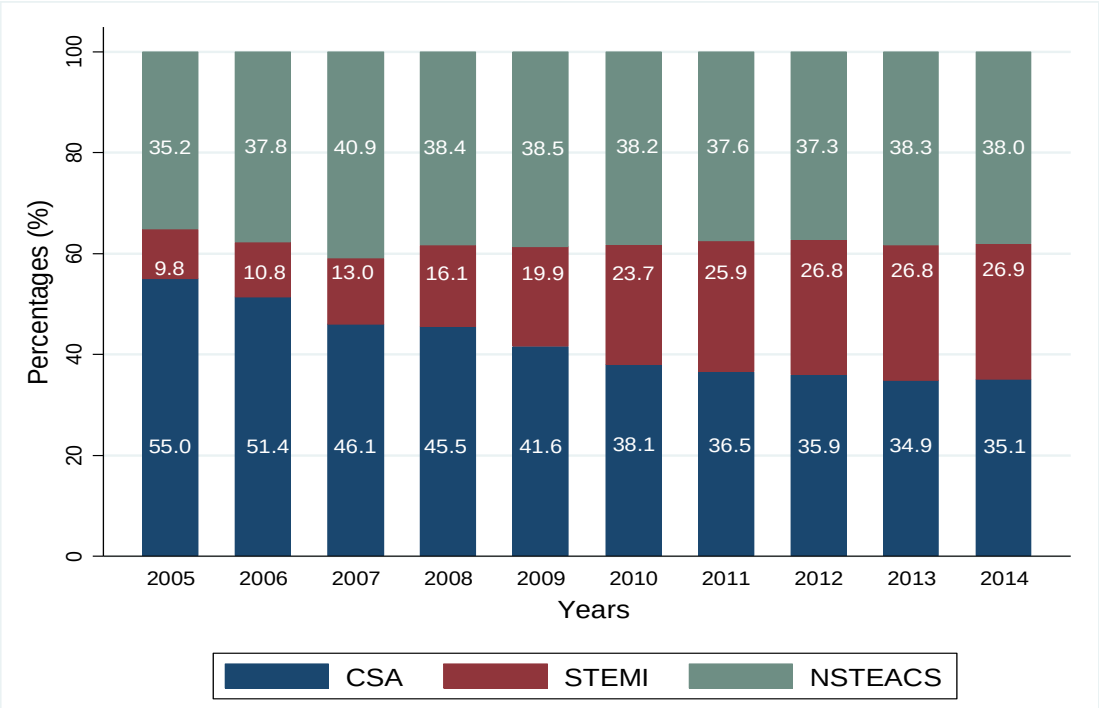


Table 1.3: Baseline clinical characteristics of all PCI patients in the UK from 2005 to 2014.

Variable		Total n= 699,248	Missing values (%)
Clinical syndrome	**CSA (%)**	276,897 (39.6)	25,802 (3.7)
	STEMI (%)	139,607 (20.0)	
	NSTEACS (%)	256,942 (36.8)	
PCI type (STEMI only) *	**Primary (%)**	121,764 (87.2)	4,619 (3.3)
	Facilitated (%)	3,171 (2.3)	
	Rescue (%)	10,053 (7.2)	
Previous acute myocardial infarction (%)		178,696 (25.6)	77,216 (11.0)
Previous PCI (%)		145,192 (20.8)	39,801 (5.7)
Family history of coronary artery disease (%)		269,736 (38.6)	115,669 (16.5)
Diabetes mellitus (%)		123,658 (17.7)	45,610 (6.5)
History of renal disease (%)		16,836 (2.4)	10,127 (1.5)
Smoking status	**Never smoked (%)**	217,961 (31.2)	96,622 (13.8)
	Ex-smoker (%)	235,465 (33.7)	
	Current smoker (%)	149,200 (21.3)	
Recent thrombolysis (%)		28,611 (4.1)	298,006 (42.6)
Cardiogenic shock (%)		13,376 (1.9)	56,488 (8.1)
LVEF (%)	**Good, LVEF ≥ 50%**	250,890 (35.8)	328,460 (47.0)
	Fair, LVEF = 30 – 49%	85,148 (12.2)	
	Poor (sever) LVEF < 30%	34,750 (5.0)	

* STEMI n= 139,607.

1.4.6.2.3 Procedural characteristics

As a whole, the use of femoral artery as an access route was to some extent higher than the use of radial artery (50.5% compared to 45.8%). However, compared to earlier years, femoral artery access became less frequently used (84.7% in 2005 vs. 27.0% in 2014). In contrast, the use of radial artery access became more prevalent (15.3% in 2005 vs. 73.0 in 2014) (Figure 1.9). Pre-procedural TIMI 3 was in 64,267 (16.2%) acute patients and afterward post-procedure increased to be in 207,048 (52.1%) acute patients. Drug eluted stents were used alone in 60.2% of procedures and 4.3% with one or more bare metal stents, while bare metal stents were used alone in 23.2% of procedures. More details on procedural characteristics are presented in Table 1.4.

Figure 1.9: Proportion of femoral and radial access in patients who received PCI in the UK from 2005 to 2014.

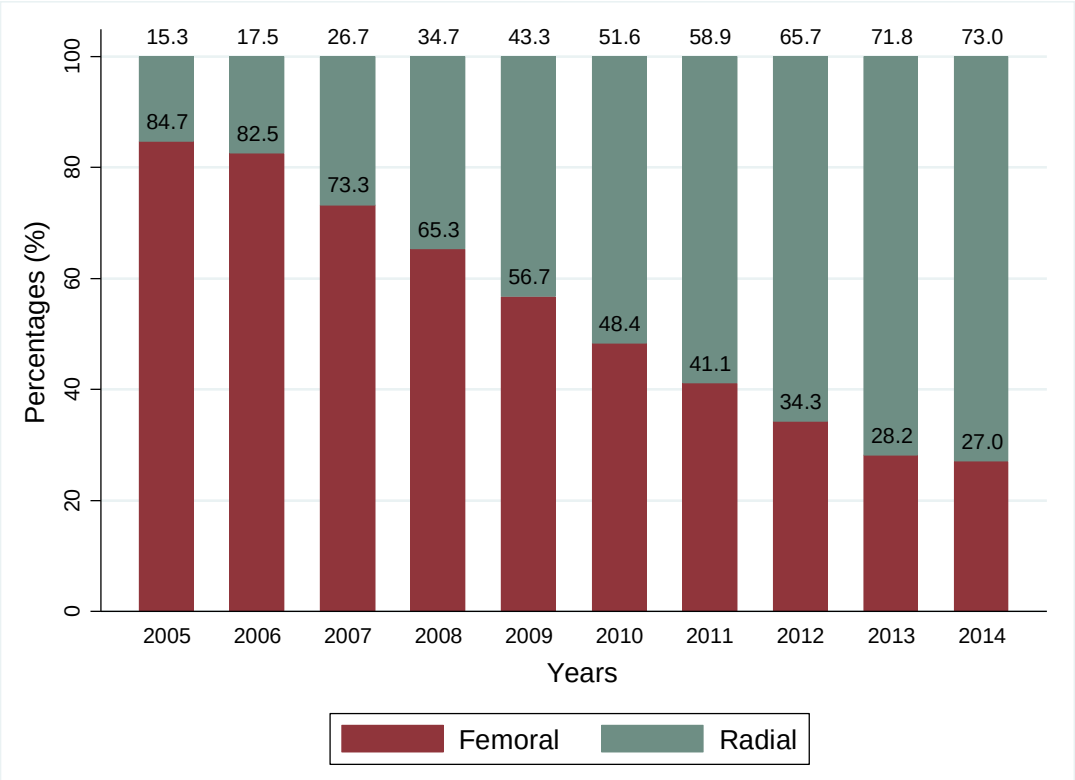


Table 1.4: Baseline procedural characteristics of all PCI patients in the UK from 2005 to 2014.

Variable		Total n= 699,248	Missing values (%)
Pre-procedural flow in infarct related artery (ACS only) *	TIMI 0 (%)	84,375 (21.3)	189,957 (47.9)
	TIMI 1 (%)	15,607 (3.9)	
	TIMI 2 (%)	23,180 (5.9)	
	TIMI 3 (%)	64,267 (16.2)	
	Unknown (%)	19,163 (4.8)	
Arterial access	Femoral artery (%)	353,017 (50.5)	24,371 (3.5)
	Radial artery (%)	320,095 (45.8)	
	Other arteries (%)	1,765 (0.2)	
Total number stents used	1 stent (%)	348,708 (49.9)	88,326 (12.6)
	2 stents (%)	167,381 (23.9)	
	≥ 3 stents (%)	94,833 (13.6)	
Longest stented/treated segment, mean (SD) mm		24.2 (13.6)	155,428 (22.2)
Largest balloon/stent used, mean (SD) mm		3.4 (3.5)	168,268 (24.1)
Type of stent used	Bare metal stent (%)	161,940 (23.2)	86,076 (12.3)
	Drug eluting stent (%)	421,526 (60.2)	
	Both together (%)	29,706 (4.3)	
Type of drug eluting stent used	Taxus liberte (Boston Scientific) (%)	59,373 (8.5)	69,506 (9.9)
	Cypher (Cordis) (%)	36,098 (5.2)	
	Endeavor (Medtronic) (%)	37,613 (5.4)	
	Xience V (Abbott) (%)	57,703 (8.3)	
	Promus (Boston Scientific) (%)	74,561 (10.7)	
	BioMatrix (%)	20,414 (2.9)	
	Promus Element (%)	37,440 (5.4)	
	Xience Prime (%)	27,902 (4.0)	
	Resolute Integrity (%)	25,353 (3.6)	
Drugs used	None (%)	470,191 (67.2)	66,921 (9.6)
	Abciximab (%)	114,110 (16.3)	
	Eptifibitide (%)	17,895 (2.6)	
	Tirofiban (%)	30,131 (4.3)	
Use of intravascular ultra sound (%)		29,825 (4.2)	89,825 (12.9)
Use of intravascular pressure wire (%)		48,428 (6.9)	89,825 (12.9)
Use of Intra-aortic balloon pump (%)		10,692 (1.5)	66,193 (9.5)
Post-procedural flow in infarct related artery (ACS only) *	TIMI 0 (%)	12,094 (3.1)	143,042 (36.1)
	TIMI 1 (%)	2,429 (0.6)	
	TIMI 2 (%)	8,358 (2.1)	
	TIMI 3 (%)	207,048 (52.1)	
	Unknown (%)	23,578 (6.0)	

* ACS n= 396,549.

1.4.6.2.4 Clinical outcomes

Clinical outcomes and mortality rates are listed in Table 1.5. In general, compared to data from the 2010 database, there were no major changes in the prevalence of all procedural complications or in-hospital outcomes, including acute myocardial infarction, MACCE and revascularisation. Likewise, mortality rates increased from 1.4% in-hospital to 1.8% at 30 days post the procedure and to 4.2% at one year post the procedure.

Table 1.5: Outcomes of all PCI patients in the UK from 2005 to 2014.

Variable			Total n= 699,248	Missing values (%)
Procedural complications	Side branch occlusion (%)		4,321 (0.6)	85,451 (12.2)
	Coronary dissection (%)		10,984 (1.6)	
	Coronary perforation (%)		2,000 (0.3)	
	Direct current cardioversion (%)		2,410 (0.3)	
	No flow/slow flow (%)		6,523 (0.9)	
	Ventilated (%)		1,152 (0.2)	
	Cardiogenic shock induced by procedure (%)		1,356 (0.2)	
In-hospital outcomes	Acute myocardial infarction (%)		3,414 (0.5)	29,459 (4.2)
	Stroke (%)		783 (0.1)	
	Renal failure/dialysis (%)		685 (0.1)	
	Blood transfusion (%)		1,427 (0.2)	
	Revascularisation	PCI (%)	2,082 (0.3)	
		Coronary artery bypass graft (%)	1,869 (0.3)	
	Unadjusted MACCE rate (%)		14,128 (2.0)	
Unadjusted in-hospital mortality rate (%)			9,411 (1.4)	22,054 (3.2)
Unadjusted mortality rate at 30 days (%)			12,568 (1.8)	77,96 (11.2)
Unadjusted mortality rate at 1 year * (%)			27,312 (4.2)	71,596 (12.0)

* Censored at 31/7/2014, therefore all PCI procedures performed after 31/7/2013 were not included in describing this rate.

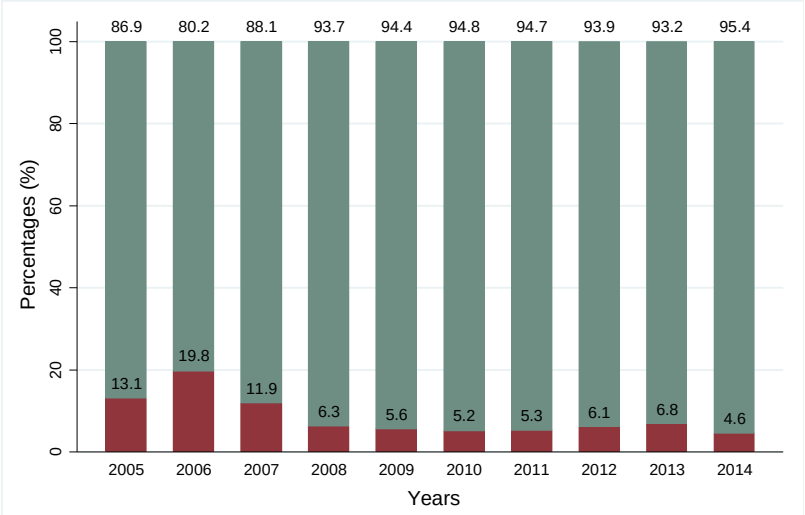
1.4.6.3 Data completeness

A total of 124 variables are in the 2014 BCIS database. Out of them, only two (1.6%) variables were 100% complete, which were the month of operation and the year of operation. The remaining 122 variables had missing information that ranged between 0.1% (clinical syndrome type) and 99.9% (pH level on the arterial blood gas on arrival to catheterisation lab). Tables 1.2 to 1.5 list the missing values of most of the 2014 BCIS database.

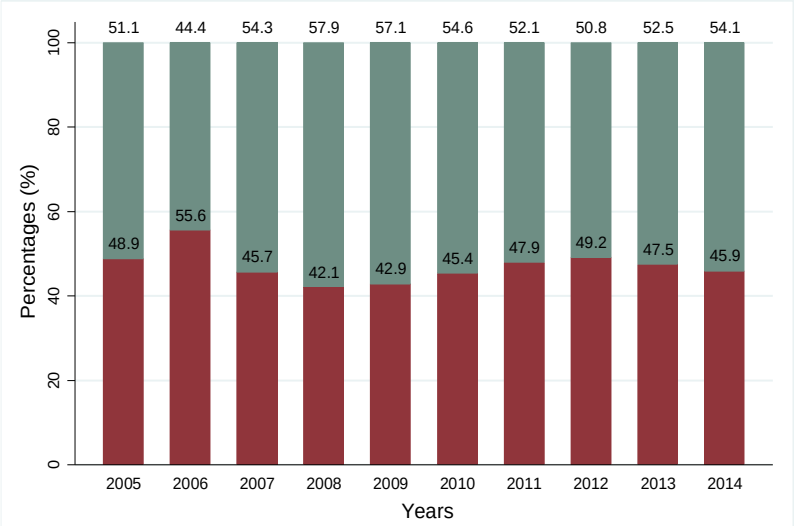
Altogether, between 2011 and 2014, there was a slight decrease in the proportion of missing data; for example, missing values in pre-procedural cardiogenic shock declined from 5.2% in 2011 to 4.6% in 2014, missing values for left ventricular ejection fraction dropped from 47.9% to 45.9%, and missing values for arterial access decreased from 2.1% in 2011 to 1.9% in 2014 (Figure 1.10).

Figure 1.10: Proportions of complete and missing values for pre-procedural cardiogenic shock, left ventricular ejection fraction and arterial access in the UK stratified by years from 2005 to 2014.

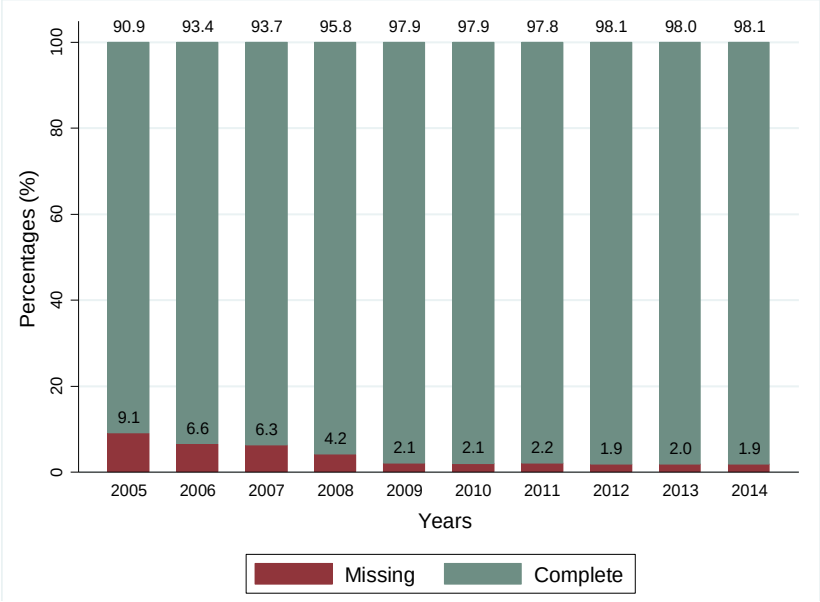
Pre-procedural cardiogenic shock



Left ventricular ejection fraction



Arterial access



1.4.7 BCIS audit and data quality

A national comparative audit is the best description for the BCIS data. Such data offers the opportunity to compare PCI services, techniques and outcomes across the UK [55, 83]. BCIS provides regular recommendations, comprehensive guidelines and technical advices for PCI operators and data entry personnel in order to ensure the continuity of data collection and to maintain data quality to high standards. In order to attain that, a partnership was built between the BCIS audit and the National Institute for Cardiovascular Outcomes Research (NICOR) [55].

Hosted by NICOR, the BCIS data entry spreadsheet is available on the BCIS website, which also includes the definitions of all variables. BCIS-NICOR data entry, cleaning, analysis and consistency checks are designed to minimise common data entry errors and to improve its accuracy [55]. In addition, to keep the BCIS database always relevant and up to date, occasional alterations to data structure are often made whilst aiming to diminish any interference to data entry, management and quality [55].

Although the precision and completeness of any recorded information in the BCIS database is primarily the responsibility of the procedure operator, registered PCI hospitals and centres are mandated to nominate an audit leader who is principally accountable for securing and organising the progression of data collection [55]. Also, it is the responsibility of the local audit to organise the linkage of all post-discharge events of their patients and validate record ascertainment and the completeness of such data [55].

Furthermore, there is no independent validation of the BCIS data and each local audit is accountable for performing consistent data validation and maintains data accuracy and completeness. For example, validation of the data quality for patients who underwent primary PCIs is typically performed for the date/time variables. [55]. Using the patient's NHS number as a unique identifier, the BCIS database has been linked to other databases and national registries within the CCAD group such as the Myocardial Ischaemia National Audit Project (MINAP). The linkage between BCIS and other databases offers a unique opportunity to estimate records ascertainment and to some extent the quality of data especially for acute cases [81].

1.4.8 Publications

In order to expand and promote the interventional research potentials of the BCIS database, anonymised or pseudo-anonymised versions of the data are distributed to researchers through the BCIS research and development group. Currently, 25 research projects are being conducted after approval from the research and development group [84]. Some examples of the publications in peer-reviewed journals include: 'Long-term follow-up of elective chronic total occlusion angioplasty' by Sudhakar *et al*. [85], 'Outcomes after Emergency PCI in patients with Unprotected Left Main stem Occlusion' by Patel *et al*. [86], and 'Arterial access site utilisation in cardiogenic shock in the United Kingdom: is radial access feasible?' by Mamas *et al* [54, 87].

1.4.9 Strengths

As a research source, there are five key strengths of the BCIS database:

1. **Size and population coverage:** BCIS database is a national data source that provides data in a large and unselected consecutive cohort of patients. Currently, there are more than 747,000 records of PCIs in the database [54].
2. **Representativeness:** conducted studies on the BCIS database can be generalised to the UK population as the data collected from all participating hospitals and centres represent all four countries of the UK [54].
3. **The depth of detail of the data:** a wide range of up-to-date PCI related information are recorded in 124 variables in BCIS database that describes patient demographics, pre-procedural clinical features, procedural characteristics, complications, in-hospital outcomes, providers' information and dates and times [54].
4. **Mortality tracking and linkage:** by using the NHS number as an identifier and linking to ONS mortality data.
5. **Less recall bias:** as data collection is executed prospectively.

1.4.10 Weaknesses

Although BCIS database is considered as a unique and valuable source for research, there are three main limitations that need to be pointed out:

1. **Missing data:** out of the 124 variables in the data, 122 variables had missing information that ranged from 0.1% to 99.9%.
2. **Incomplete patient ascertainment:** the variation in reporting all PCIs performed between participating hospitals and centres as some may report acute cases only and the others report stable alone or both stable and acute, which consequently leads to underreporting of one type or more of the clinical presentations.
3. **Funds for data entry:** this is always the responsibility of local hospitals or centres, thus it is subjected to variability in funds as well as the clinical background of the appointed data entry personnel, which will subsequently affect the quality and accuracy of the entered data.

1.5 Office for National Statistics (ONS)

Since the induction of the UK Births and Deaths registration in 1837, death registration became a legal obligation. Four years afterward, in 1841, the cause of death was added to the registry [88]. The database of ONS on mortality statistics is a complete source of mortality data and the underlying causes, which use patient's NHS number as a unique identifier. The coding of ONS mortality data is based on the codes of the 10^{th} revision of the International Classification of Disease (ICD-10), a classification for fatal and non-fatal disease developed by the World Health Organisation (WHO) [88].

All ONS data are entered online by registrars at local registration services. Around 75% of records are referred to the Medical Certificate of Cause of Death (MCCD), which is mostly completed by the treating physician of the deceased patient. The remaining 25% of records, such as unclear cause of death in the MCCD, are managed by a coroner who confirms the cause of death from the MCCD, treating

physician or post-mortem data [89]. To confirm the accuracy and consistency of the entered data, validation checks are initially performed by the online data entry system, and regular diagnostic tests are then implemented by ONS [89].

Chapter 2 Literature reviews and rationale for study

2.1 Summary

The previous chapter outlined an overview to the clinical backgrounds as well as the BCIS data (framework and description). Two motivating questions were explored previously: why study cohort data about PCI in UPLMS? (section 1.2.5) and why investigate survival following primary PCI? (section 1.3.4). This chapter describes and evaluates two literature reviews about these two questions, which are “clinical determinants and temporal trends of outcomes for PCI in UPLMS disease” (section 2.4) and “clinical determinants of survival for primary PCI” (section 2.5). From which the rational, aims and objectives of this thesis are developed (section 2.6).

2.2 Preview

In order to define the best methodological and analytical approaches, different search strategies were built and initial comprehensive literature reviews were performed to answer three research questions: “What are the clinical determinants of outcomes for PCI in UPLMS in the UK and what is the impact of the existence of cardiogenic shock and the type of arterial access on the outcomes?”, “What are the temporal trends of the outcomes for PCI in UPLMS in the UK?”, and “What are the survival and outcomes of primary PCI in the UK and what is the impact of clinical determinants such as the admission route and hospital dissimilarities on survival?”. Answers to the first two questions about UPLMS patients were reviewed together as a whole, while answers to the question on primary PCI were reviewed separately.

2.3 General search strategy

For each of the three research questions, a literature search strategy was built to be restricted to relevant studies on humans only, and to English publications using Ovid Medline and PubMed databases to increase the specificity of the search. Pending unpublished articles, abstract only articles, case reports and case series articles were excluded. A similar strategy was performed in Google and Google Scholar database to identify publications from institutions and governmental departments that would not have been identified on Medline and PubMed. References of the relevant publications were screened and citation trees were followed to identify further articles. In addition, the websites of several institutions, such as BCIS and ONS, were reviewed for relevant information. All identified articles were downloaded into Endnote software and duplicates were removed. Then the articles were screened by titles and abstracts and the relevant ones were fully reviewed.

2.4 Literature review on ‘clinical determinants and temporal trends of outcomes for PCI in UPLMS disease’

2.4.1 Introduction

CABG remains the standard treatment of choice for all types of LMS disease, and with the advances in surgical procedures, CABG has demonstrated that it has better survival benefits compared to other surgical and medical treatments [21-23, 90, 91]. However, in contemporary practice, PCI has been evolving tremendously, particularly in treating LMS disease [2-4]. Percutaneous coronary intervention is now considered a reasonable line of management since it reduces the in-hospital mortality rate and increases the survival at one year when compared to reported CABG outcomes [24]. Furthermore, with the expansions in stent technology (drug eluting stents, equipment and techniques) PCIs are yielding higher rates of success with encouraging outcomes in the management of unprotected LMS (UPLMS), not only for stable elective cases but also for emergency cases when CABG is contraindicated [25, 90, 92].

Given the fact that the success of any PCI procedure for UPLMS (in terms of survival, short- and long-term outcomes) is influenced by different risk factors, for example, increasing age, cardiogenic shock, diabetes, renal failure, and previously derived cardiac risk scores such as EuroSCORE, SYNTAX score and Parsonett score, it is believed that these factors are less common among the elective cases compared to the unstable emergency cases [25-27]. Besides, unless it is not contraindicated, CABG is the recommended line of management for UPLMS, and PCIs would be preserved for contra-indicated cases, thus affecting its success further [19, 26, 28]. It is what this section of the chapter is aiming to review, the clinical determinants of PCI procedural survival and clinical outcomes among patients with UPLMS, as well as to review the temporal trends of such cases.

2.4.2 Search methods

A literature search was conducted using Ovid Medline, PubMed and Google Scholar between January 1996 and September 2015. An initial search of “unprotected left main coronary artery disease” and “unprotected left main stem disease” obtained over 31,000 results, requiring a more tightly focused search strategy. Using Ovid Medline database, two main topics related to UPLMS were therefore targeted: percutaneous coronary interventions and outcomes in UPLMS patients. In terms of percutaneous coronary intervention, keyword searches included “percutaneous coronary intervention”, “PCI” and “stenting”. Keyword searches for outcomes included “outcomes”, “mortality”, and “survival” in conjunction with percutaneous coronary intervention and UPLMS related words.

In addition, articles that did not comprise percutaneous coronary intervention in the management of UPLMS and/or any clinical determinant were also excluded. At the end of the focused literature search, 101 relevant publications were picked up and scanned by titles and abstracts at first, and then only applicable articles were completely reviewed. References of the articles were screened and other related publications and resources from citation trees concerning percutaneous coronary intervention and UPLMS outcomes were correspondingly followed and cited using PubMed and Google Scholar databases. A total of 23 journal papers were included and reviewed.

2.4.3 Statistical analysis

In all reviewed articles, different statistical methods were used in order to describe the relationship between intended clinical predictors and percutaneous coronary intervention survival and outcomes in UPLMS. At the level of multivariate analysis, logistic regression, Kaplan-Meier method and Cox’s proportional hazards regression were the most commonly used statistical methods. Logistic regression was employed in six studies, while Cox’s proportional hazards regression was used in 17 studies. Only three studies employed stepwise Cox’s proportional hazards strategies, and one used a backward stepwise logistic regression model, where the idea behind both methods was that the measured predictors were selected based on a specific significant P value. A detailed list of reviewed studies describing the clinical determinants

associated with PCI survival and outcomes in UPLMS patients are summarised in Table 2.1. Extra papers that did not have sufficient information were mentioned in the review but were not presented in the table.

2.4.4 Age as a determinant of survival and outcomes

Universally, the elderly population is evidently rising especially in developed countries. At the same time, cardiovascular diseases and related risk factors are higher among this age group compared to younger individuals [93]. Previously, due to the increase in post-procedural unfavourable outcomes, PCIs were less commonly performed on elderly patients with LMS disease. However, the number of PCI procedures among this age group has been increasing with time. Currently, more than 20% of all patients treated by PCI are age 75 years or older [93, 94].

Despite the methodological disparities, evidence from medical literature showed that old age is one of the important determinants of poorer prognosis in any PCI procedure [86, 92, 93]. A recent publication by Lee *et al.* [95] showed that age of more than 70 years, among other factors, was a significant predictor of 30-day mortality. Another contemporary publication by Sim *et al.* [96] reported that age 65 years and over was a risk factor of higher 1-year mortality rate (aHR 3.0, 95% CI 1.5 to 6.0, P=0.002).

A review by Marco and Fajadet stated several clinical risk factors that influence the success of PCI procedures and one of the findings was that the higher the age (75 years and over), the higher the risk of developing in-hospital outcomes after PCI for patients with UPLMS [26]. Also, a study by Schrale *et al.* [31] revealed that the age of more than 75 years was among other predictors of mortality (P=0.032).

Maluenda *et al.* [97] concluded that old age (70 years and over) was among eight risk factors that were significantly associated with a high one year mortality rate after PCIs and, as age increased further (80 years and over), the risk became higher. A study by Parma *et al.* [48] showed that one of the predictor risk factors of high early 30-day mortality and midterm three year survival after PCI for UPLMS was the age of 75 years or more. In addition, a study by Min *et al.* [47] on 1102 UPLMS cases treated

with PCI showed that target vessel revascularisation (TVR) was significantly reduced in those with age 75 years and over (aHR 0.5, 95% CI 0.3 to 0.9).

In an observational study by De Luca *et al.* [45], it was concluded that increasing age was a significant independent predictor of major adverse cardiac or cerebrovascular events (MACCE) and overall mortality (aHR 2.1, 95% CI 2.0 to 3.3 and aHR 4.6, 95% CI 2.8 to 12.7) respectively. Similarly, Onuma *et al.* [94] reported that for all UPLMS cases treated by PCIs, age at both univariate and multivariate levels of analysis was a significant predictor of mortality. In the same way, Meliga *et al.* [98] demonstrated that age was a predictor of cardiac mortality (aHR 1.06, 95% CI 1.01 to 1.11).

Moreover, Buszman *et al.* [99] also stated that being over 60 years of age was a risk factor of higher short- and long-term mortality rates (aOR 2.5, 95% CI 1.0 to 5.9). A paper by Kang *et al.* [100] demonstrated that the association between age (65 years and over) and a composite of mortality, myocardial infarction and stroke was significant. Lee *et al.*'s study [101] on 164 UPLMS cases showed that age (per 10 years) was significantly associated with worse 30-day survival.

2.4.5 Clinical determinants of survival and outcomes

There is conflicting evidence regarding what the main independent clinical predictors of PCI outcomes in UPLMS are; however these predictors can be elucidated through the fact that most UPLMS cases treated by PCI are actually a high risk group of patients who have previously been rejected from surgical treatment [26]. What's more, the argument continues on which are the most important risk factors and their short- and long-term effect on the outcomes and survival of PCI procedures for such patients. In the available literature, most studies showed a similar pattern of clinical predictors; however, some of the studies used different modes of scoring mechanisms in order to overcome any interactions between these predictors.

In a meta-analysis study by Vis *et al.* [34] in which 977 patients from 13 observational studies were reviewed, 30-day mortality was 55.0% in cardiogenic shock patients (RR 3.7, 95% CI 2.9 to 4.8, P <0.001). Patel *et al.* [86] demonstrated in their

results that peri-procedural cardiogenic shock as well as age, female gender, acute LVEF, presence of an occlusive lesion, glycoprotein (GP) IIb/IIIa inhibitor use and the presence of post-procedural no-reflow were all significant predictors of 30-day mortality; however, in terms of the predictors at three year mortality, all except acute LVEF were significant predictors.

Likewise, Beak *et al.* [102] stated that the presence of cardiogenic shock at presentation or a heart rate of more than 100 beats per minute were associated with higher cardiac mortality. In the same way, Sim *et al.* [96] concluded that the presence of cardiogenic shock, LVEF of less than 40% and the use of mechanical ventilation were significant determinants of high 1-year mortality rate. Dores *et al.* [36] demonstrated the significant predictors of MACCE at five years for 95 PCI UPLMS cases. These were myocardial infarction (aHR 2.9, 95% CI 1.2 to 6.9, P=0.015), hypertension (aHR 5.7, 95% CI 1.9 to 17.5, P =0.002) and the EuroSCORE I (aHR 1.1, 95% CI 1.0 to 1.1, P =0.001).

In a previously mentioned paper by Parma *et al.* [48], in addition to age, cardiogenic shock at presentation and post PCI TIMI flow grade <3 were also identified as risk factors of higher 30 day and three year mortality. Correspondingly, in Kang *et al.*'s study [100], significant risk factors for a composite of mortality, myocardial infarction, and stroke were cardiogenic shock at presentation and a history of peripheral artery disease as well as old age, and for TVR the risk was significantly higher with emergency procedures.

An observational study by Ben Dor *et al.* [30] found that increased mortality at six months and one year was significantly correlated with cardiogenic shock, emergency procedures, LVEF <35% and renal failure. However, MACCE were correlated with cardiogenic shock, emergency procedures, renal failure and diabetes mellitus. Furthermore, besides age, Schrale *et al.* [31] reported cardiogenic shock (aHR 7.9, 95% CI 1.7 to 3.6) as a predictor of mortality. A paper by Wu *et al.* [103] identified hyperlipidaemia as a significant independent predictor for MACCE after PCI in 55 UPLMS cases.

In an earlier study by Khattab *et al.* [104], where the outcomes of PCI treatment in 82 UPLMS cases were compared to the outcomes in 118 cases with protected LMS disease, significant determinants of increased mortality, higher risk of myocardial infarction and increased TVR were female gender, diabetes mellitus, renal insufficiency, STEMI, cardiogenic shock and LVEF (40% or less). A further earlier study by Lee *et al.* [105] stated that significant univariate predictors of higher MACCE were myocardial infarction, diabetes and Parsonnet score, while the significant independent determinants of the hazard of MACCE were diabetes and Parsonnet score.

Above and beyond the Parsonnet score, the EuroSCORE was extensively studied in medical literature particularly as a determinant for post-PCI outcomes in UPLMS, and the majority of the studies agreed on the fact that the risk of post-PCI unfavourable outcomes increases as EuroSCORE increases. In De Luca *et al.*'s study [45], EuroSCORE was identified as a significant independent determinant of both MACCE and mortality, whereas diabetes was a significant determinant of MACCE and TVR. In addition, a paper by Fernandez *et al.* [46] comparing the risks of PCI treatment in diabetics vs non-diabetics with UPLMS revealed that cardiac mortality and EuroSCORE were significantly higher in diabetic patients.

Likewise, Min *et al.* [47] reported that in UPLMS cases treated by PCI, EuroSCORE ≥6, chronic renal failure and previous congestive heart failure were independent predictors of mortality. An observational study by Brennan *et al.* [42] demonstrated that high logistic EuroSCORE scores (≥33.5%) and high clinical urgency (primary PCI, rescue or facilitated PCI for STEMI, pre-procedural cardiogenic shock, or emergent or salvage status) were significantly associated with higher 30 day MACCE.

Buszman *et al.* [99] also identified LVEF <50% and EuroSCORE on admission >9 as risk factors for higher mortality. Another study on 849 UPLMS cases by Tamburino *et al.* [106] reported that chronic renal disease, LVEF and EuroSCORE were significant predictors of PCI outcomes. In an observational study on 358 UPLMS cases, Meliga *et al.* [98] revealed age, cardiogenic shock, EuroSCORE and LVEF <50% as significant independent predictors of cardiac mortality. At the same time, diabetes and EuroSCORE were significant determinants of MACCE; and diabetes and LVEF <50% were significant determinants for TVR.

Earlier studies on PCI and UPLMS were more focused on individual clinical features and EuroSCORE as the main clinical determinants of procedural outcomes. However, recently, a score quantifying particular patient and operator predictors, the SYNTAX score, has been developed to determine the most appropriate choice of therapy on individual basis [107]. Contemporary studies are more attracted toward the SYNTAX score as the main predictor of interest; for example, Onuma *et al.* [94] reported that at both univariate and multivariate levels of analysis, cardiogenic shock at presentation, 10 points increase in SYNTAX scores and EuroSCORE were significant determinants of 1-year and four year mortality.

Another example is an observational study by Capodanno *et al.* [108] on 255 UPLMS cases treated by PCI demonstrated that SYNTAX scores significantly predicted the rate of both cardiac mortality and MACCE. The authors also found that cardiac mortality was higher among cases with high SYNTAX scores (>34) compared to those with a low score (≤34) (aHR 15.8, 95% CI 3.4 to 73.4). Similarly, a comparison study between 903 cases of LMS treated by PCI and 879 treated by CABG by Serruys *et al.* [109] reported that, in PCI treatment cases, MACCE were significantly higher among those with high SYNTAX scores (23.4%) as compared with those with intermediate scores (16.7%) (P =0.040) and low scores (13.6%) (P =0.002).

A randomised controlled trial by Jolly *et al.* [32] comparing radial and femoral approaches stated that the use of radial access for PCIs have lower vascular complications (such as haematoma) compared to the use of femoral access (aHR 0.4, 95% CI 0.3 to 0.6, P <0.001), although both still considered being equally effective. Another randomised clinical trial by Romagnoli *et al.* [33] supported the results of the former trial, reporting that cardiac mortality and bleeding rates were lower in patients approached through the radial artery compared to those approached through the femoral artery (P =0.020 and P =0.026, respectively). Similarly, a recently published study by Mamas *et al.* [87] demonstrated that the use of radial access in patients with cardiogenic shock was associated with lower 30-day mortality (aHR 0.6, 95% CI 0.5 to 0.7, P <0.001), MACCE (aHR 0.6, 95% CI 0.5 to 0.8, P <0.001) and bleeding aHR 0.4, 95% CI 0.2 to 0.7, P =0.004).

2.4.6 Temporal trends

Up-to-date details regarding the temporal trends in incidence, care and outcomes of UPLMS PCI across the full spectrum of acute and elective patients have been limited by small, regional and non-consecutive series of cases or inferred from randomised controlled trials in highly select groups of patients [36-44].

Several studies have reported the temporal trends of UPLMS PCI, one of the major studies ever performed was by Park *et al.* [43], which included 1,124 UPLMS patients treated by PCI compared to 1,494 UPLMS patients treated by CABG over a period of 12 years (wave one 1995 – 1998, wave two 2003 – 2006 and wave three 2007 – 2010). Their results demonstrated that the use of PCI for the management of UPLMS increased by 17%, MACCE declined significantly (aHR 0.6, 95% CI 0.5 to 0.7, P <0.001), all-cause mortality decreased by 40% (aHR 0.6, 95% CI 0.4 to 0.9, P=0.008), the composite of mortality, myocardial infarction and stroke decreased by 35% (aHR 0.7, 95% CI 0.5 to 0.9, P <0.001) and repeat revascularisation similarly decreased by 46% (aHR: 0.5, 95% CI 0.4 to 0.7, P <0.001).

A multinational study by Conrotto *et al.* [44] compared four year trends of 218 UPLMS patients treated by PCI and 86 UPLMS patients treated by CABG, and concluded that mortality was higher in PCI cases (7.3%) compared to (3.5%) in CABG cases. In the same way, target vessel revascularisation was higher in PCI cases (10.0% vs 4.2%). Another multi-centre study, which was carried out by Naganuma *et al.* [39] on 262 PCI UPLMS patients over four years, showed a trend toward higher target lesion revascularisation (aHR 2.0, 95% CI 0.9 to 4.5, P=0.090); however, there was no significant differences in the trends of MACCE, all-cause mortality, and composite endpoint of all-cause mortality, myocardial infarction and stroke.

2.4.7 Conclusions

In this literature review, several clinical determinants have been identified as predictors of post-PCI outcomes mainly in UPLMS. For instance, older age was found to increase the probability of in-hospital mortality, MACCE and TVR. On the contrary, literature regarding the effect of being elderly on outcomes beyond hospital stay was

inadequate. Cardiogenic shock at presentation, however, was one of the most frequently found significant predictors of PCI short and long-term outcomes (overall mortality, cardiac mortality, myocardial infarction, stroke, MACCE and TVR).

Other significant risk factors revealed from the results of this review were emergency procedures, STEMI, diabetes mellitus and renal failure, which again were associated with mortality, MACCE and TVR. Incongruity was noted in the relationship between LVEF and mortality rate after PCI, where not all the findings were concordant to the evidence from literature [26]. Scoring mechanisms (EuroSCORE and SYNTAX score) were all significant determinants of PCI short- and long-term outcomes. However, the paucity of evidence to support SYNTAX score as a reliable predictor suggests the need for further studies.

Recently, there is an evolution in the use of radial artery as an access point as a replacement for femoral artery [87, 110]. Therefore, further evaluating the associations between the type of arterial access and outcomes in UPLMS PCIs is essential. With the increasingly growing proportion of high-risk UPLMS patients, the need for alternative lines of management, other than CBAG, is rising. Lately, PCI started to be a promising choice of management for such patients. However, risk benefit analysis is always needed to be reviewed and assessed in order to predict favorable and unfavorable procedural outcomes. In addition, there is deficiency in whole-country studies of the temporal trends in UPLMS PCI and the associated procedural and longer-term outcomes [39, 43] therefore, additional investigation in such issue is necessary.

Table 2.1: Summary of clinical predictors associated with percutaneous coronary intervention outcomes in UPLMS from a number of reviewed studies.

Study	Design	Country & data years	Population	Statistical analysis	Regression model	Predictors and Outcomes		
							30-day mortality	3-year mortality
Patel *et al.* 2014 [86]	Observational (population based)	England and Wales 2007 - 2012	2125 UPLMS	Cox hazard regression	Age, sex, cardiovascular risk factors, renal dysfunction, history of previous (MI, PCI, or CABG), symptom to balloon time, recent lysis, Acute LVEF, peri-procedural cardiogenic shock, occlusive LMS disease, multivessel disease, intra-aortic balloon pump support, glycoprotein (GP) IIb/IIIa inhibitor use, thrombus aspiration use and the presence of post-procedural no-reflow	Occlusive UPLMS	HR: 1.6 [1.1, 2.4] P 0.020	HR: 1.5 [1.1, 2.2] P 0.020
						Peri-procedural cardiogenic shock	HR: 5.4 [3.2, 9.1] P < 0.001	HR: 3.0 [2.0, 4.5] P < 0.001
						Age	HR: 1.02 [1.01, 1.03] P 0.040	HR: 1.02 [1.01, 1.03] P 0.030
						Female sex	HR: 0.4 [0.3, 0.7] P 0.001	HR: 0.6 [0.4, 0.9] P 0.020
						Acute LVEF	HR: 2.4 [1.2, 4.8] P 0.010	HR: 1.3 [0.8, 2.2] P 0.260
						GP IIb/IIIa inhibitor	HR: 0.6 [0.4, 0.9] P 0.030	HR: 0.6 [0.4, 0.9] P 0.004
						Post-procedural no-reflow	HR:4.2 [2.2, 7.8] P<0.001	HR: 2.7 [1.6, 4.8] P<0.001
Lee *et al.* 2014 [95]	Observational (hospital based)	Kaohsiung, Taiwan 2010 - 2012	309 UPLMS	logistic regression	30-day mortality with age, female gender, acute kidney injury, body mass index, WBC count, AC sugar and acute ischemic stroke	Age > 70	OR: 4.5 [1.2, 16.3] P 0.024	
						Female sex	OR: 3.7 [1.2, 10.9] P 0.018	
						WBC count	OR: 1.2 [1.0, 1.3] P 0.003	
						acute kidney injury	OR: 16.0 [3.7, 70.2] P < 0.001	
						BMI	OR: 1.2 [1.1, 1.4] P 0.003	
Beak *et al.* 2014 [102]	Observational (population based)	Seoul, Korea 2005 - 2009	61 UPLMS	Cox hazard regression	Cardiac mortality with the presence of shock and the heart rate of more than 100 beat / minute	Presenting in cardiogenic shock	HR, 4.3 [1.0, 18.0] P 0.049	
						Heart rate >100 beat / minute	HR, 5.0 [1.2, 21.0; P 0.029	
Sim *et al.* 2013 [96]	Observational (population based)	Gwangju, Korea 2005 - 2008	587 UPLMS	Stepwise Cox hazards regression	1-year mortality with age ≥ 65, cardiogenic shock, LVEF < 40% and ventilation	Age ≥ 65	HR: 3.0 [1.5, 6.0] P 0.002	
						Cardiogenic shock	HR: 4.8 [2.7, 8.5] P < 0.001	
						LVEF < 40%	HR: 1.9 [1.1, 3.1] P 0.020	
						Ventilation	HR: 7.1 [4.2, 12.1] P < 0.001	
Dores *et al.* (2013) [36]	Observational (hospital based)	Lisbon, Portugal 1999 - 2006	95 UPLMS	Cox hazard regression	MACCE with EuroSCORE I, hypertension and a previous history of myocardial infarction	Myocardial infarction	HR: 2.9 [1.2, 6.9] P 0.015	
						Hypertension	HR: 5.7 [1.9, 17.5] P 0.002	
						EuroSCORE I	HR: 1.1 [1.0, 1.1] P 0.001	
							30 day mortality	3 year survival
Parma *et al.* 2012 [48]	Observational (hospital based)	Rome, Italy 2000 - 2010	58 STEMI due to UPLMS	Backward logistic regression and Cox hazard regression	30 day mortality with cardiogenic shock, age, baseline & post PCI TIMI flow grade in LMS, left ventricular ejection fraction, and logistic EuroSCORE (58patients) 3 year follow up survival with cardiogenic shock, age, post PCI TIMI flow grade in LMC (35 patients)	Age ≥ 75	OR: 5.9 [1.3, 26.5] P 0.019	HR: 3.9 [1.8 , 8.7] P < 0.001
						Cardiogenic shock at presentation	OR: 12.6 [3.0, 53.6] P <0.001	HR: 5.2 [1.8 , 14.3] P 0.002
						Post-PCI TIMI flow grade <3	OR: 3.9 [1.8 , 5.7] P 0.020	HR: 4.9 [1.6 , 14.6] P 0.005

Continued Table 2.1: Summary of clinical predictors associated with percutaneous coronary intervention outcomes in UPLMS from a number of reviewed studies.

Study	Design	Country & data years	Population	Statistical analysis	Regression model	Predictors and Outcomes		
Brennan *et al.* 2012 [42]	Observational (population based)	United States 2004 - 2008	5627 UPLMS	Cox hazard regression	Logistic EuroSCORE values were calculated and classified as high (≥33.5%) or low (<33.5%). High urgency revascularisation procedures included primary, rescue or facilitated PCI for STEMI, those involving pre-procedural cardiogenic shock, or emergent or salvage status	High vs. low logistic EuroSCORE and MACCEs by 30 days		76.6% vs.53.9% P < 0.001
						High vs. low urgency and MACCEs by 30 days		74.2% vs. 52.8% P < 0.001
						Mortality by 30 months (DES vs. BMS)	HR: 0.84, 95% CI: 0.73 to 0.96 P < 0.001	
						MACCE (DES vs. BMS)	HR: 0.95, 95% CI: 0.84 to 1.06 P < 0.001	
Fernandez *et al.* 2011 [46]	Observational (hospital based)	Huelva, Spain 2002 - 2008	334 UPLMS	Logistic regression		EuroSCORE & MACCE	RR: 2.4 [1.2 , 4.9] P 0.016	
De Luca *et al.* 2011 [45]	Observational (hospital based)	Rome, Italy 2006 - 2009	107 UPLMS	Kaplan-Meier and Cox hazard regression	Age, gender, EuroSCORE, hypercholesterolemia, diabetes, cardiogenic shock, LVEF < 50% and stent per patient	Age & MACCE	HR: 2.1 [2.0, 3.3] P 0.030	
						Age & Overall mortality	HR: 4.6 [2.8, 12.7] P 0.004	
						EuroSCORE & MACCE	HR: 1.2 [1.0, 1.3] P < 0.001	
						EuroSCORE & Overall mortality	HR: 3.2 [1.6, 7.8] P 0.008	
						Diabetes & MACCE	HR: 3.5 [1.1, 6.9] P 0.010	
						Diabetes & TVR	HR: 2.9 [1.9, 5.8] P < 0.001	
Onuma *et al.* 2010 [94]	Observational (hospital based)	Rotterdam, Netherlands & Ferrara, Italy 2002 - 2005	227 UPLMS	Kaplan-Meier and Cox hazard regression	Mortality with age, shock at entry, hypertension, hypercholesterolemia, bifurcation angle. the SYNTAX score and EuroSCORE		At 1 year	At 4 years
						Age	HR: 1.1 [1.0, 1.1] P 0.030	HR: 1.0 [1.0, 1.1] P 0.009
						Cardiogenic shock at presentation	HR: 4.2 [1.5, 1.8] P 0.006	HR: 5.5 [2.4, 12.7] P < 0.001
						EuroSCORE	HR: 1.2 [1.1, 1.4] P <0.001	HR: 1.1 [1.0, 1.2] P 0.009
						SYNTAX score	HR: 1.2 [1.1, 1.4] P 0.006	HR: 1.2 [1.0, 1.3] P 0.030
Min *et al.* 2010 [47]	Observational (population based)	Seoul, Korea 2000 - 2006	2240 UPLMS	Cox hazard regression	Mortality with age ≥ 75, chronic renal failure, previous congestive heart failure, atrial fibrillation, right coronary artery disease, EuroSCORE and LMS distal bifurcation disease TVR with age ≥ 75, ACS, previous PCI, and LM distal bifurcation disease		PCI (n=1102)	CABG (n=1138)
						Age ≥ 75 & Mortality	HR: 1.4 [0.8, 2.6] P 0.269	HR: 1.9 [1.2, 3.2] P 0.010
						Age ≥ 75 & TVR	HR: 0.50 [0.3, 0.9] P 0.048	HR: 0.8 [0.2, 3.5] P 0.785
						Chronic renal failure & Mortality	HR: 4.28 [2.1, 8.7] P < 0.001	HR: 1.7 [0.2, 0.7] P 0.216
						Previous congestive heart failure & Mortality	HR: 3.0 [1.4, 6.3] P 0.004	HR: 1.5 [0.7, 3.2] P 0.354
						EuroSCORE ≥ 6 & Mortality	HR: 2.6 [1.4, 4.6] P 0.001	HR: 2.3 [1.5, 3.6] P < 0.001

Continued Table 2.1: Summary of clinical predictors associated with percutaneous coronary intervention outcomes in UPLMS from a number of reviewed studies.

Study	Design	Country & data years	Population	Statistical analysis	Regression model	Predictors and Outcomes		
Wu *et al.* 2010 [103]	Observational (hospital based)	Taipei, Taiwan 2003 - 2007	55 UPLMS	Cox hazard regression		Hyperlipidemia and MACCE	HR: 6.2 [1.3, 30.0] P 0.024	
						Bifurcation involvement and MACCE	HR: 4.4 [1.1, 17.0] P 0.008	
Kang *et al.* 2010 [100]	Observational (hospital based)	Seoul, Korea 2003 - 2006	462 UPLMS	Cox hazard regression	Predictors for composite of mortality, MI, and CVA in CABG group were: older age ≥ 65 years, history of stroke, low ejection fraction < 50%, high EuroSCORE ≥ 6, and use of angiotensin-converting enzyme inhibitors Predictors in PCI group were: older age ≥ 65, shock present at admission, and a history of peripheral artery disease Predictors for TVR in PCI group were: need for an emergency procedure and true bifurcation		PCI (n=205)	CABG (n=257)
						Age ≥ 65 & composite of mortality, MI, and CVA	HR: 2.3 [1.1, 4.6] P 0.022	HR: 2.6 [1.2, 5.5] P 0.010
						Cardiogenic shock at presentation & composite of mortality	HR: 3.7 [1.1, 12.5] P 0.035	---
						Peripheral artery disease & Composite of mortality	HR: 4.8 [2.3, 10.0] P < 0.001	---
						Emergency procedure & TVR	HR: 2.3 [1.0, 5.5] P 0.048	---
Serruys *et al.* 2009 [109]	RCT (multicentre)	United States 2005 - 2007	1782 UPLMS	Kaplan-Meier	SYNTAX scores: low score ≤22, intermediate score as 23 - 32 and high score ≥33	High SYNTAX scores in PCI compared to Intermediate scores		P 0.040
						High SYNTAX scores in PCI compared to Low scores		P 0.002
						Mortality 30 days after PCI procedure		RR: 1.2 [0.8–1.7]
						Mortality 12 months after randomization (PCI)		RR: 1.4 [1.2–1.8]
Buszman *et al.* 2009 [99]	Observational (population based)	Poland 1997 - 2008	252 UPLMS	Logistic regression	Age > 60 years, diabetes, hypertension, hypercholesterolemia, Smoking, Distal LM involvement, Stent diameter (mm), LVEF < 50% and EuroSCORE on admission > 9	Age > 60 & Mortality rate	OR: 2.5 [1.0, 5.9] P 0.030	
						LVEF < 50%& Mortality rate	OR: 3.3 [1.5, 7.3] P 0.010	
						EuroSCORE > 9 & Mortality rate	OR: 2.5 [1.1, 4.6] P 0.040	
Ben-Dor *et al.* 2009 [30]	Observational (hospital based)	Ramat, Israel 2003 - 2007	71 UPLMS	Logistic regression	Cardiogenic shock, emergency procedures, LVEF < 35%, renal failure and diabetes	Emergency procedures with Mortality & MACCE		OR: 2.8 P 0.020
Tamburino *et al.* 2009 [106]	Observational (population based)	Legnano, Italy 2002 - 2006	849 UPLMS	Kaplan-Meier and Cox hazard regression	Age, gender, diabetes, increase of cardiac biomarkers, chronic renal disease, multivessel disease, bifurcation, LVEF, EuroSCORE, and Propensity score	Chronic renal disease & Mortality	HR: 1.86 [1.23, 2.81] P 0.003	
						Chronic renal disease & MI	HR: 3.81 [1.81, 8.03] P < 0.001	
						LVEF& Mortality	HR: 0.97 [0.95, 0.98] P < 0.001	
						LVEF & TLR	HR: 0.98 [0.95, 1.00] P 0.03	
						EuroSCORE & Mortality	HR: 1.16 [1.06, 1.26] P 0.001	
						EuroSCORE & TLR	HR: 0.85 [0.73, 0.99] P 0.04	
						Propensity score & Mortality	HR: 0.96 [0.95, 0.97] P < 0.001	

Continued Table 2.1: Summary of clinical predictors associated with percutaneous coronary intervention outcomes in UPLMS from a number of reviewed studies.

Study	Design	Country & data years	Population	Statistical analysis	Regression model	Predictors and Outcomes	
Capodanno *et al.* 2009 [108]	Observational (hospital based)	Catania, Italy 2003 – 2008	255 UPLMS	Cox hazard regression	Age, gender, smoking, diabetes, acute coronary syndrome, renal dysfunction, LVEF, EuroSCORE, reference vessel diameter, lesion length, bifurcation lesion, emergent setting, complete revascularisation as independent control variables, and the SYNTAX score as the independent study variable of interest. low SYNTAX score ≤34 and high SYNTAX score >34	SYNTAX score & cardiac mortality	HR: 1.2 [1.0, 1.3] P 0.003
						SYNTAX score & MACCE	HR: 1.1 [1.0, 1.1] P 0.005
Lee *et al.* 2008 [101]	Observational (population based)	Los Angeles, United States 1993 - 1998	164 UPLMS	Kaplan-Meier and Cox hazard regression	Age, sex, prior MI, hypertension, diabetes, congestive heart failure, renal failure, smoking, prior CABG, prior PCI, multivessel disease, CABG vs PCI, cardiac index, cardiac power index, systolic BP, and heart rate	Cardiac mortality in high SYNTAX score cases vs. low score cases	HR: 15.8 [3.4, 73.4] P < 0.001
						Age (per 10 years) & 30 days survival rate	HR: 1.0 [1.0, 1.1] P 0.020
						Diabetes mellitus and TVR	HR: 2.9 [1.6, 5.3] P < 0.001
						Cardiogenic shock and cardiac mortality	HR: 11.0 [1.9, 63.9] P 0.008
						EuroSCORE & cardiac mortality	HR: 1.2 [1.0, 1.3] P 0.046
						EuroSCORE & MACCE	HR: 1.1 [1.0, 1.2] P 0.014
						LVEF < 50% & TVR	HR1.0 [1.0, 1.1] P 0.050
Schrale *et al.* 2008 [31]	Observational (hospital based)	Oxford, United Kingdom 2001 - 2005	100 UPLMS	Stepwise Cox hazards regression		BMS & mortality	HR: 4.4 [1.1, 17.0] P 0.034
						Failed thrombolysis & mortality	HR: 8.5 [1.7, 41.7] P 0.008
						Cardiogenic shock & mortality	HR: 7.9 [1.7, 3.6] P 0.008
Khattab *et al.* 2007 [104]	Observational (population based)	Segeberg, Germany 2002 - 2004	118 Protected LMS 82 UPLMS	Kaplan-Meier and logistic regression	Mortality, MI and TVR with gender, diabetes mellitus, renal insufficiency, STEMI, cardiogenic shock and LVEF	Female gender	OR: 2.4 [1.0, 5.9] P 0.044
						Diabetes mellitus	OR: 2.4 [1.0, 5.8] P 0.046
						Renal insufficiency	OR: 3.6 [1.4, 9.5] P 0.006
						STEMI	OR: 6.4 [1.8, 21.9]P 0.001
						Cardiogenic shock	OR: 15.9 [1.4, 182.7] P 0.003
						LVEF ≤ 40%	OR: 3.3 [1.0, 11.1] P 0.038
Lee *et al.* 2006 [105]	Observational	Los Angeles, United States 2003 - 2006	173 UPLMS	Stepwise Cox hazard regression	MACCE free survival with age, gender, diabetes mellitus, Parsonnet score, ejection fraction, chronic renal insufficiency, myocardial infarction, and CABG	Parsonnet score & MACCE free survival	HR: 1.1 [1.0, 1.1] P < 0.010
						Diabetes mellitus & MACCE free survival	HR: 2.2 [1.1, 4.6] P 0.030

2.5 Literature review on 'clinical determinants of survival for primary PCI'

2.5.1 Introduction

The survival of acute myocardial infarction patients, particularly that of STEMI patients, is profoundly affected by the timing (i.e. urgency) of the medical or interventional treatment provided [4, 7]. Globally, the first line of management for STEMI patients with or without cardiogenic shock is primary PCI [4, 74, 76, 111]. In general, any delays to primary PCI procedures of more than two hours after onset of symptoms can lead to unfavourable complications and outcomes [71-73]. Lately, the practice of primary PCI is growing internationally and in the UK in particular; in England and Wales, the frequency of primary PCIs increased by 15.0% from 2004 to 2007 [70, 71].

In contemporary practice, primary PCI survival rates are clearly rising; yet, in STEMI patients there is a wide range of discrepancy related to the presence of certain predictors (such as old age, cardiogenic shock, heart failure, previous myocardial infarction and diabetes mellitus) that subsequently have influence on the outcomes and survival of primary PCIs [71, 75, 76]. Furthermore, the influence of admission route and hospital differences on primary PCI survival rates is not well defined [78, 79]. It is what this section of the chapter is aiming to review: the clinical determinants of primary PCI procedural survival among STEMI patients.

2.5.2 Search strategy

A preliminary literature search of "primary percutaneous coronary intervention" and "primary PCI" acquired 3,589 results. The search was performed using Ovid Medline between January 1996 and October 2015. A more focused search strategy was required; therefore, the term "survival" was added in combination with the search words "primary percutaneous coronary intervention" and "primary PCI" by using Ovid Medline database.

The final result of the search showed 39 relevant articles that have been browsed by titles and abstracts initially. Publications that did not contain information on primary PCI survival were excluded; only applicable articles were completely reviewed. References of the articles were screened and other related publications and resources from citation trees relating to primary PCI survival were correspondingly followed and cited using PubMed and Google Scholar databases. A total of nine journal papers were included and reviewed.

2.5.3 Statistical analysis

Different statistical methods were used in all fully reviewed articles to outline the relationship between the clinical risk factors and primary PCI survival. At the level of multivariate analysis; logistic regression, Cox's proportional hazards regression and Kaplan-Meier method were the most commonly used statistical methods. Cox's proportional hazards regression was used in eight studies, whereas logistic regression was used in two studies. Kaplan-Meier curves were performed in all nine studies. A detailed list of the reviewed studies describing the clinical determinants associated with primary PCI survival and outcomes in STEMI patients are summarised in Table 2.2. More papers that did not have sufficient information were described in the review but were not in the table.

2.5.4 Results

Currently, the available medical literature continued to support the fact that primary PCI produces better outcomes for patients with STEMI [70]. Most of the studies in literature were not on population-based cohorts and/or conducted outside the UK. Therefore, they may not be generalisable to the UK. At the same time, important or key predictors of primary PCI survival rate have been acknowledged in literature. However, there is a gap of knowledge regarding the impact of the routes of admission as well as the effect of hospital level factors such as patient volume [78, 79].

In a recently published paper by McCormick *et al.* [112]; direct stenting, when compared to pre-dilation followed by stenting, was found to be an independent predictive factor of better survival at one year after primary PCI (96.7% vs 91.2%, P <0.001). In addition, McCormick *et al.* demonstrated that the significant clinical predictors of 1-year mortality were age, number of diseased vessels, cardiogenic shock, left main stem intervention, proximal left anterior descending artery intervention and pre-dilation followed by stenting. However, the procedure time from the onset of symptoms was not significantly associated with 1-year mortality (aOR 1.0, 95% CI 0.9 to 1.0, P =0.730).

Taniguchi *e*t *al.* [113] studied the clinical predictors of five-year survival after primary PCI in 3,476 STEMI patients with and without pre-infarction angina pectoris, and found that the significant predictors with better five-year survival with the presence of pre-infarction angina pectoris were total ischemic time of three to six hours, thrombolysis in myocardial infarction flow grade zero, absence of cardiogenic shock, absence of heart failure and anterior myocardial infarction. In a non-randomised trial study by Bergh *et al.* [114] on 139 STEMI patients with cardiogenic shock, the use of intra-aortic balloon pump was not found to be a significant predictor of better survival at 30 days (P =0.720).

Mamas *et al.* [87] concluded that radial approach was significantly associated with lower 30-day mortality (aHR 0.6, 95% CI 0.5 to 0.7, P <0.001). However, they found that age, renal disease, poor left ventricular ejection fraction, the use of intra-aortic balloon pump and the number of diseased vessels were determinants of worse early mortality. They also demonstrated that primary PCI was associated significantly with worse survival at 30 days (aHR 1.5, 95% CI 1.3 to 1.8, P <0.001).

In the same way, De Luca *et al.* [115] demonstrated that age of more than 75 years, diabetes, previous myocardial infarction, anterior myocardial infarction, post-procedural thrombolysis in myocardial infarction flow grade three, myocardial blush grade three, as well as the number of diseased vessels were all significant predictors of survival at 30 days. They also found that the patients' survival at one year was associated significantly with the number of diseased vessels (aHR 1.8, 95% CI 1.3 to 2.3, P =0.002).

The availability of experienced personnel, facilities and suitable timing have an admirable impact on the outcomes of any primary PCI [4, 7, 116]. An ecological study by Laut *et al.* [117], using aggregated data from 12 European countries between 2003 and 2008 to describe the associated country level dissimilarities in primary PCI use, indicated that higher utilisation was associated significantly with the numbers of physicians, nurses and acute care beds available per 100,000 population ($P < 0.001$).

Gale *et al.* [78] used the MINAP database (a population-based database of acute coronary syndrome in England and Wales) and concluded that the differences at hospital level (high volume vs. low volume hospitals and/or centres) have a significant effect on the survival at six months for STEMI patients who undergo primary PCI ($P < 0.001$). One of the findings by Danchin *et al.* [118] demonstrated that fibrinolysis for patients with STEMI had better five-year survival compared to primary PCI after 90 minutes from call (in patients called three hours or less from onset aHR 0.6, 95% CI 0.4 to 0.9, $P = 0.039$).

In 240 STEMI patients, Kritikou *et al.* [119] compared the difference in the survival to discharge between primary PCI capable and non-capable hospitals and stated: “Although there was a statistically significant correlation between the type of the hospital and the delay from the onset of symptoms to PPCI ($P = 0.001$), such correlation was not found between the delay PPCI and the outcome of the patients ($P > 0.05$)”. In another ward, this study concluded that even for STEMI patients who presented to a non-capable hospital, better outcomes from primary PCI were noticed once there was rapid transfer to a capable hospital.

In another set of patients with acute myocardial infarction complicated by cardiogenic shock, Guo *et al.* [120] found a significant association between the time from symptoms onset and in-hospital mortality ($P = 0.036$) as well as mid-term survival ($P = 0.015$). Brodie *et al.* [121] showed that in 2,496 STEMI patients with cardiogenic shock, better late cardiac survival was independently predicted by the age of 70 years or less, cardiogenic shock caused by right ventricular infarction and the time of two hours or less from door to balloon.

In a study by Chan *et al.* [79] which compared between directly transferred (by the ambulance) STEMI patients' survival and inter-hospital emergency transferred STEMI patients' survival, and showed that the existence of a pre-hospital ECG triage in an ambulance has a significant impact on 30-day mortality (aOR 0.3, 95% CI 0.1 to 0.7] P =0.007) and 1-year survival (aHR 0.4, 95% CI 0.2 to 0.8] P=0.006); therefore, direct admission had better outcomes.

Similarly, Ortolani *et al.* [122] demonstrated that more than 80% of STEMI patients who were exposed to pre-hospital ECG triage were re-vascularised within 90 minutes from the first call. Although they found that the overall impact of pre-hospital ECG triage on long-term survival was not statistically significant (P=0.160), the survival of certain high-risk patients (such as patients with diabetes, cardiogenic shock and TIMI risk score >30) was significantly influenced by the direct transfer using pre-hospital ECG triage.

On the other hand, Wöhrle *et al.* [123] illustrated that transfer status (inter-hospital transfer vs. direct admission) was not a significant predictor of 30-day and 1-year survival rate with and without adjusting for treatment times (time from symptoms onset). However, their results showed that Killip class 2-4, creatinine clearance and history of diabetes were significant predictors of 30-day survival with and without adjusting for treatment times. Likewise, their results concluded that 1-year survival with and without adjusting for treatment times was significantly predicted by Bivalirudin, study site in the United States, anterior myocardial infarction, Killip class 2-4, creatinine clearance and history of congestive heart failure. Time from symptom onset to first hospital was a significant predictor of 1-year survival only (aHR 1.1, 95% CI 1.0 to 1.2] P =0.005).

2.5.5 Conclusions

A number of significant predictive factors in this review have been identified as determinants of survival after primary PCI procedures in STEMI patients. Older age, cardiogenic shock, history of diabetes mellitus, previous acute myocardial infarction, heart failure and thrombolysis in myocardial infarction flow were the commonest significant predictors of short-term survival after primary PCI. In addition to the above,

the number of diseased vessels and anterior myocardial infarction were as well associated with worse short- and long-term survival primary PCI.

The procedure time from the symptoms onset was found in one study to be a non-significant determinant of primary PCI survival in STEMI patients; however, many other studies contradicted this finding and concluded that the shorter the time of procedure from onset of symptoms, the better the short- and long-term survival of such patients. The utilisation of pre-hospital ECG triage, leading to more direct admissions of STEMI patients, was also found to have a significant influence on post-procedure survival compared to inter-hospital emergency transfer. Likewise, hospital volume load and capability (in terms of the availability of facilities and trained personnel) were also found as significant predictors of primary PCI survival.

The results of most of the reviewed studies were not representative of the general population as the majority of these studies were implemented at hospital-based level, and only three researches were performed using population-based datasets; thus, further representative studies using national registries are essential. Currently, primary PCI is the first choice of management for STEMI patients and is widely practiced worldwide and on a national scale with encouraging better post-procedure survival rates [4, 70, 71]; though, the predictors of survival have a variety of incongruity that need additional exploration and analysis.

Table 2.2: Summary of clinical predictors associated with survival for primary percutaneous coronary intervention in STEMI patients from a number of reviewed studies.

Study	Design	Country & data years	Population	Statistical analysis	Regression model	Predictors and Outcomes	
Mamas *et al.* 2014 [87]	Observational (multicentre population based)	Manchester, United Kingdom 2006 - 2012	7231 STEMI	Kaplan-Meier and Cox hazards regression	30-day mortality with age, sex, diabetes, hypertension, hypercholesterolemia, peripheral vascular disease, previous stroke (cerebrovascular accident, renal failure, previous AMI, previous PCI, previous coronary artery bypass graft, intra-aortic balloon pump , and ventilation.	Radial vs femoral	HR: 0.6 [0.5, 0.7] P < 0.001
						Age	HR: 1.03 [1.02, 1.04] P < 0.001
						Renal failure	HR: 1.4 [1.1, 1.8] P 0.008
						Primary PCI	HR: 1.5 [1.3, 1.8] P < 0.001
						Poor left ventricular ejection fraction	HR: 2.6 [2.0, 3.3] P < 0.001
						Intra-aortic balloon pump	HR: 1.2 [1.0, 1.4] P 0.031
						Number of diseased vessels	HR: 1.1 [1.0, 1.1] P 0.053
McCormick *et al.* 2014 [112]	Observational (multicentre hospital based)	Cambridge, United Kingdom 2008 - 2010	1562 STEMI	Kaplan-Meier and logistic regression	1-year mortality with age, sex, previous MI, current smoker, left main PCI proximal left anterior descending artery PCI, number of diseased vessels, cardiogenic shock, number of stents, multi-vessel PCI, procedure time (min) and pre-dilatation (followed by stenting)	Age	OR: 1.1 [1.0, 1.1] P < 0.001
						Number of diseased vessels	OR: 1.6 [1.1, 2.4] P 0.009
						Cardiogenic shock	OR: 4.6 [1.7, 12.4] P 0.003
						Left main PCI	OR: 19.8 [4.5, 86.7] P < 0.001
						Proximal left anterior descending PCI	OR: 2.1 [1.2, 3.7] P 0.012
						Procedure time (min)	OR: 1.0 [0.9, 1.0] P 0.730
						Pre-dilatation (followed by stenting)	OR: 2.4 [1.1, 5.5] P 0.032
Taniguchi *et al.* 2014 [113]	Observational (population based)	Japan. 2005 - 2007	3476 STEMI	Kaplan-Meier and Cox hazards regression	5-year survival with age, gender, BMI, medications at discharge, infarct location, hypertension, hemodynamic, presence of multi-vessel disease, current smoker, anemia, TIMI flow grade 0, liver cirrhosis, diabetes, previous MI, total stent length >28 mm, Thrombocytopenia, COPD, minimum stent size <3.0 mm, prior stroke, hours from onset to presentation, hours from onset to balloon and cardiogenic shock	Total ischemic time of 3 - 6 hours	HR: 0.6 [0.4, 0.9] P 0.009
						TIMI flow grad 0	HR: 0.6 [0.4, 0.9] P 0.003
						No cardiogenic shock,	HR: 0.7 [0.5, 0.9] P 0.020
						No heart failure	HR: 0.7 [0.5, 0.9] P 0.030
						Anterior myocardial infarction	HR: 0.6 [0.4, 0.8] P 0.001
Danchin *et al.* 2014 [118]	Observational (population based)	France October 2005	1492 STEMI	Kaplan-Meier and Cox hazards regression	5-year survival with age, sex, type and region of institution; time to first call; history of heart failure, history of diabetes, hypertension, current smoking, prior AMI, stroke, peripheral artery disease, comorbidity; anemia on admission; early use of aspirin, clopidogrel, low molecular weight heparin, or glycoprotein IIB-IIIa inhibitors, and presence of triple-vessel coronary artery disease	Fibrinolysis vs. primary PCI after 90 minutes of call in patients called three hours or less from onset	HR: 0.6 [0.4, 0.9] P 0.039

Continued Table 2.2: Summary of clinical predictors associated with survival for primary percutaneous coronary intervention in STEMI patients from a number of reviewed studies.

Study	Design	Country & data years	Population	Statistical analysis	Regression model	Predictors and Outcomes		
De Luca *et al.* 2013 [115]	Observational (population based)	Italy	1494 STEMI	Kaplan-Meier and Cox hazards regression	30-day mortality with age, diabetes, smoking, previous myocardial infarction, previous revascularisation , anterior myocardial infarction, abciximab administration, post procedural TIMI 3 flow and myocardial blush grade 3	Number of diseased vessel		HR: 1.5 [1.1, 2.2] P 0.022
						Age > 75 years		HR: 7.5 [3.7, 15.1] P < 0.001
						Diabetes		HR: 2.0 [1.1, 3.9] P 0.033
						Previous myocardial infarction		HR: 3.0 [1.1, 8.6] P 0.039
						Anterior myocardial infarction		HR: 2.9 [1.4, 6.0] P 0.003
						Myocardial blush grade3		HR: 0.5 [0.2, 0.9] P 0.043
						Post procedural TIMI 3 flow		HR: 0.5 [0.2, 0.9] P 0.038
Chan et al. 2012 [79]	Observational (multicentre hospital based)	Canada	594 STEMI	Kaplan-Meier, logistic and Cox hazards regression	30-day & 1-year mortality with age, cardiogenic shock, cardiac arrest requiring ventilation, left ventricular ejection fraction <40%, prior history of myocardial infarction and pre-hospital ECG triage strategy	Pre-hospital ECG triage & 30-day mortality		OR: 0.3 [0.1, 0.7] P 0.007
						Pre-hospital ECG triage & 1-year survival		HR: 0.4 [0.2, 0.8] P 0.006
Ortolani et al. 2011 [122]	Observational (hospital based)	Seoul, Korea 2003 - 2007	1619 STEMI	Cox hazard regression	Survival with cardiogenic shock, TIMI risk score >30, diabetes mellitus and pre-hospital ECG triage strategy	Pre-hospital ECG triage & survival		HR: 0.8 [0.6, 1.1] P 0.160
Wöhrle et al. 2010 [123]	RCT (multicentre hospital based)	United States	3602 STEMI	Kaplan-Meier and Cox hazards regression	30-day & 1-year mortality with treatment times, randomization to bivalirudin, age, gender, race, study site in or out US, BMI, Killip class, anterior MI, anemia; platelet counts, creatinine clearance, history of (hypertension, hyperlipidemia, smoking, diabetes, MI, PCI, CABG, CAD, angina, congestive heart failure or peripheral vascular) and medications 5 days before enrolment		30-day mortality	1-year mortality
						Transfer vs. no transfer, not including treatment times	HR: 1.0 [0.6, 1.7] P 0.870	HR: 0.9 [0.6, 1.4] P 0.060
						Transfer vs. no transfer, including treatment times	HR: 1.0 [0.6, 1.7] P 0.980	HR: 0.9 [0.6, 1.5] P 0.890
						Time from symptom onset to first hospital	-----	HR: 1.1 [1.0, 1.2] P 0.005
Brodie et al. 2007 [121]	Observational (hospital based)	United States 1984 - 2004	2496 STEMI	Kaplan-Meier and Cox hazards regression	Late cardiac survival (3.5 years) with age, gender, diabetes, previous infarction, previous bypass surgery, hypertension, multivessel coronary disease, door-to-balloon time, and right ventricle infarction versus left ventricle pump failure	Shock due to right ventricle infarction		HR: 0.3 [0.1, 0.6] P 0.002
						Door to balloon time of 2 hours or less		HR: 0.5 [0.3, 0.9] P 0.020
						Age ≤ 70 years		HR: 0.6 [0.4, 0.9] P 0.020

2.6 Development of research aims and objectives

2.6.1 Rationale

Cardiovascular diseases are the leading cause of morbidity and mortality in the UK and worldwide [2, 8, 10, 11]. In addition, it has always been a major burden to the UK NHS [12]. At the same time, the majority of contemporary studies in literature were conducted outside the UK and were not based on real-world observational data. Therefore, it was not possible to measure the level of care provided to cardiovascular diseases patients in the UK, based on such evidence. However, with the enhancements in NHS treatment strategies and the availability of sufficient clinical data about certain procedures, such as that of BCIS, the care of most cardiovascular diseases in the UK can be monitored and assessed [80, 81]. Nonetheless, there are clinical and statistical concerns about the use of routine clinical data for the purposes of research, which create biases when the datasets have missing and/or implausible values [124]. All that stimulates the need to study percutaneous coronary intervention quality of care, so that a framework for excellence may be defined that will promote improvements in care for all CAD patients admitted to hospital (specifically UPLMS and STEMI patients) regardless of where they live in the UK.

2.6.2 Aims

In this thesis, a variety of statistical techniques are considered to evaluate the effect of missing data on research outcomes and offer the potential to enhance the research strengths of the BCIS database. Full description of the used methods with justification review are in Chapter 3 (sections 3.4.7 and 3.4.8). Subsequently, the main aim of this research is to utilise contemporary population-based data from the BCIS database to perform a number of comparative investigations and answer several important questions regarding the level of care provided to patients who have undergone percutaneous coronary intervention in the UK, on the bases of survival and outcomes. Answering these questions using such type of analyses might be one of the few times they will be tested on a population-based data and on UK data.

2.6.3 Objectives

1. To use BCIS data to evaluate the level of care provided to patients who have undergone PCI in the UK.
2. To evaluate the outcomes and survival of PCI outcomes in UPLMS patients stratified by clinical presentation.
3. To identify the clinical determinants of PCI outcomes in UPLMS and to measure their level of association including the impact of cardiogenic shock and arterial access approach.
4. To quantify the temporal trends in the complications, in-hospital outcomes and mortality of UPLMS patients after PCI.
5. To evaluate the outcomes and survival of primary PCI for STEMI patients compared to facilitated and rescue PCI.
6. To identify the clinical determinants of primary PCI survival in STEMI patients and to measure their level of association including the impact of admission route and procedure time from symptoms onset.
7. To identify potentially modifiable gaps in the care provided to patients who have undergone percutaneous coronary intervention in the UK which may be addressed in subsequent research or specialist societies.

Chapter 3 Data assessment and methodology

3.1 Summary

Further insight about the types of datasets and the statistical methods used in the thesis is described in more detail in this chapter. First, the study design is summarised (section 3.2), then data provision procedures including application, ethics and security is discussed (section 3.3), followed by details on the performed data management activities such as collection, transformation, cleaning and recoding (section 3.4), and lastly, the analyses methodology including a summary of the statistical methods used, model selection methods, imputation methods, how to handle missing values and justification of the multiple imputation method applied (section 3.5).

3.2 Study setting and design

The overall aim of the thesis is to evaluate the level of care provided to patients who have undergone percutaneous coronary intervention in the UK and since the 1st of January 2005. The study design is a linked prospective multi-centre population-based observational study using the BCIS national registry of patients who have undergone percutaneous coronary intervention in the UK. The dataset included all registered interventional cardiology centres and hospitals which have been increasing with time. Presently, 117 registered interventional cardiology centres and hospitals in UK provide data to the BCIS (based on BCIS Audit Returns, Adult Interventional Procedures, January 2013 to December 2013) [54].

This thesis consists of three analyses of data from the BCIS registry on different cohorts of patients who have undergone percutaneous coronary intervention. The time period of the studies varied, from January 2005 to December 2010 in one study and from January 2005 to March 2014 in two studies. After performing a complete analysis using the 2010 versions of the BCIS database in Chapter 4, a new version of the database became available in 2014. The 2014 version was used in the analyses of Chapters 5 and 6 of the thesis. Based on the cohort of intention, more details on each study settings and designs can be found in Table 3.1.

Table 3.1: Summary of settings and designs for the three studies (result chapters) of this thesis.

Results chapters	BCIS database	Time period	Area	Patients' cohort	Participating cardiac centres and hospitals
Chapter 4: Determinants of outcomes after percutaneous coronary intervention for UPLMS disease	2010 version	1st of January 2005 to 31st of December 2010	England and Wales	5,065 patients with UPLMS disease	89
Chapter 5: Mortality trends after percutaneous coronary intervention for UPLMS disease	2014 version	1st of January 2005 to 31st of March 2014	The UK	10,827 patients with UPLMS disease	113
Chapter 6: Determinants of survival after primary percutaneous coronary intervention	2014 version	1st of January 2005 to 31st of March 2014	The UK	98,637 patients with STEMI who received primary, rescue and facilitated PCI	111

3.3 Data provision

3.3.1 Preview

The BCIS national database is a secondary anonymised data relating to patients who have undergone percutaneous coronary intervention in the UK, which has been collected locally and entered by all registered interventional centres and hospitals into the BCIS national audit database via the CCAD [20, 54, 81]. More details on BCIS audit database, data entry, structure and quality are described in Chapter 1 (section 1.4).

3.3.2 Application and eligibility

As mentioned previously in Chapter 1, two versions of the BCIS database are used in this thesis. The first is the 2010 version of the BCIS database that was received in December 2011, which was requested by Dr Gale earlier in the same year. After a successful application, permission for the use of BCIS national audit data to undertake this research has been granted from the BCIS Academic Committee. A full extract of the secondary, anonymised BCIS dataset was received in a zipped, encrypted file on a special CCAD secure web drop box and a username and two passwords were given to me separately (one by e-mail and the other by phone) for additional protection.

In 2014, another application for a more updated BCIS audit data was made in December 2013 and successfully accepted by the BCIS Academic Committee. Likewise, an encrypted file on a CCAD secure web drop box comprising a secondary anonymised BCIS dataset was received in November 2014 with a username. Later on, two passwords were provided separately in the same way as the previous version. The application form is shown in Appendix II.

3.3.3 Ethical considerations

With the intention to undertake statistical and epidemiological research work using secondary anonymised BCIS data, where the identification of patients and providers (either physicians or hospitals) can only be made by BCIS and NICOR, an

enquiry in regard to the need for ethical approval or audit/service evaluation was requested from University of Leeds, the faculty of medicine and health research ethics committee (FREC) on November 2011. In February 2012, a response was received from FREC stating that studies undertaking secondary analysis of anonymised patient data no longer require the National Research Ethics Service (NRES) review or approval. Please see Appendix III for a copy of the form about requirements for review of queries that have been sent to FREC and a copy of the reply e-mail received from FREC.

Furthermore, the National Institute for Cardiovascular Outcomes Research (NICOR), which includes the BCIS database (Ref: NIGB: ECC 1-06 (d)/2011), has support under section 251 of the National Health Service (NHS) Act 2006. Therefore, ethical approval was not required under NHS research governance arrangements for the research.

3.3.4 Data security

For both versions (2010 and 2014), once the dataset was received and downloaded, it was placed on the University of Leeds servers, where it is securely stored and regular back-ups are automatically made frequently. The BCIS data was saved in a special account in the N-drive (the Division of Epidemiology and Biostatistics server). Accessibility to the data was restricted to the research team only.

For additional security, the team agreed that the data should not be accessed from networks other than the university network and/or server. At the same time, and since the size of data file was too big to be handled by the available Stata software in the university student account, a single user Stata version 12 perpetual licence (updated later on to Stata version 13 and then to version 14) was purchased and installed on the university desktop C-drive.

3.4 Data management

3.4.1 Preview

Data management is an important part of any research. It ensures a robust statistical analysis by removing duplicates as well as improving the accuracy, completeness and reliability of the data, consequently, enhances the producibility and impact of findings [125]. The data management part was a vital step in establishing good quality modified data for this thesis and for other related research. In fact, both modified versions (2010 and 2014) of the BCIS dataset have been used by other researchers [81, 87, 126-129]. As part of this thesis and with the support of the research team, all the steps of data management for both versions of the BCIS database were performed. The data management included data transformation, cleaning and recoding, followed by the intended analyses.

3.4.2 Using a Delphi group to develop optimal clinical definitions

The Delphi group or method was best defined by Linstone *et al.* [130] as "a method for structuring a group communication process so that the process is effective in allowing a group of individuals, as a whole, to deal with a complex problem". In order to achieve the best outcomes from the data management and the afterward analyses in this thesis; a Delphi group was formed. In addition to the primary investigator, the group included, Dr Chris Gale, Dr Paul Baxter, Dr Sarah Fleming, Dr Peter Ludman, Dr Mark de Belder and Dr Nick Curzen.

This Delphi group was simply a combination of the individual knowledge as well as the group decisions and revisions. Using the available BCIS data, the Delphi group was structured to communicate and agree on the best means to define clinical and statistical diagnostic groupings. For example, the group agreed on the methods used in defining the study cohort (the UPLMS cohort, the clinical presentation type and the primary PCI cohort). Another example was during data cleaning and recoding such as cleaning the route of admission variable and incorrect entries particularly in numeric variables.

3.4.3 Data collection and entry

The data are collected and entered locally by data clerks and/or interventional cardiologist into local software systems. Subsequently, electronic encryption takes place by NICOR to ensure data security, and then transfer the data to CCAD central servers. More details on BCIS data collection, entry and quality are mentioned in Chapter 1 (section 1.4).

Following data linkage, encryption, cleaning and consistency checks performed by NICOR to improve data accuracy, more than 411,000 records of raw data in the 2010 version and more than 747,000 records in the 2014 version of the BCIS dataset were available for research in 2014 [20, 54, 81]. However, the raw data in both versions were not in an appropriate form and required extensive management and processing to be converted into a suitable research-ready format for further analysis.

3.4.4 Data transformation and statistical software

At first, for both versions (2010 and 2014), the initially received files were in the form of Microsoft Office Excel comma separated values files that have been transformed later into Stata dataset files. In order to be handled easily by the available software, the huge sizes of both datasets files (411,324 and 699,248 records, respectively) required splitting initially, transforming to Stata files then merging later on. Afterward, all the variables in the raw data were extracted and coded into a Stata suitable format to be ready for cleaning and recoding if required. Stata 12 and Stata 13 software were utilised to transform, clean and recode the 2010 and 2014 BCIS datasets respectively.

3.4.5 Data cleaning and recoding

In spite of the importance of data collection and analysis, data quality remains a persistent problem in most databases, particularly in clinical datasets such as this, which have been collected over a long period [125]. The main disadvantages of routine

clinical data, such as the BCIS include: large datasets with a lot of errors, mismatches and incomplete information [125, 131].

From January to May 2012, the 2010 version required five months of data cleaning and recoding, while the 2014 version required only one month (December 2014) of data management as most of the cleaning codes were available from the previous version of data management. The majority of data cleaning and recoding codes were according to clinical opinion of the Delphi group.

As mentioned previously, recoding of most of the variables in the BCIS data was essential in order to transform the whole dataset. This was achieved by recoding all string format variables to numeric format, then all categorical variables were re-labelled (categorised). All continuous variables in the raw data file were in string format and required cleaning and recoding to numeric format so they can be recognised and analysed by the Stata software. For analytical reasons, some continuous variables required recoding to categorical format.

During the recoding process, each variable was assessed for data mismatches and/or errors, and all entries that were considered as such were cleaned by recoding them as missing in most situations, or by recoding them to another entry when applicable. Entries like “Unknown” and “Unlisted” were also recoded as missing in most of the variables however, this value was kept in some entries as they were meaningful. For continuous variables (such as the number of stents used, attempted vessels and creatinine level), numbers that were clinically implausible were excluded and recoded as missing.

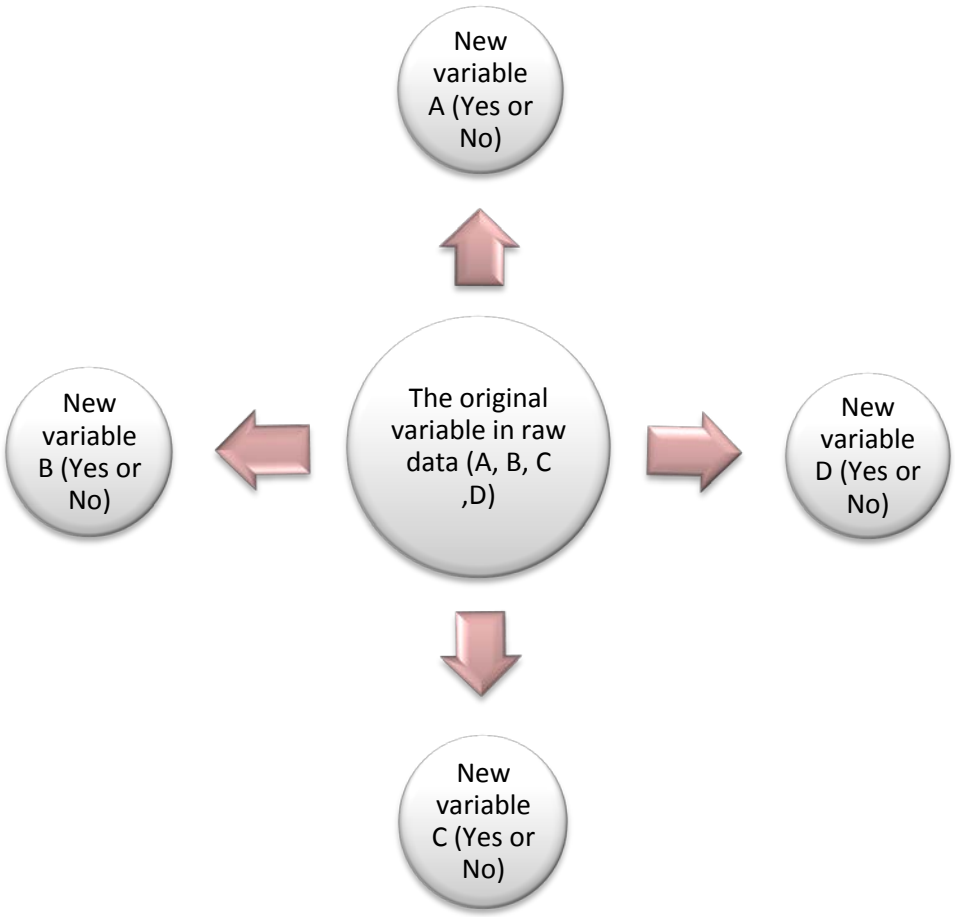
3.4.5.1 2010 BCIS data

Out of 127 variables a total of 98 variables were transformed and/or recoded. Most required recoding and cleaning like gender, indication for intervention and procedure urgency variables. Others required transformation from string format to numeric using “destring” command in Stata like height, weight and creatinine level variables. Moreover, variables that contain dates and times were recorded as Stata data string format using “date (variable, "DMY")” and “format variable %td” commands. To

be exact, nine new dummy variables were also created from one or more existing variables, for example clinical presentation variable which was drawn from three different variables.

At the same time, some variables (for example PCI hospital outcome, procedural complications and history of renal disease) contained multiple entries for each case record, and most of these entries were integrated with each other. Therefore, in order to overcome this problem and for easier future analysis, new binary variables were created in a way that each new generated variable is an entry from the original variable (Figure 3.1). In addition, a few other variables were generated from the variables containing dates for the necessity in future analysis (such as number of hospital stay days, help days and number of days between procedure and death or census dates).

Figure 3.1: Graphic illustration of recoding a variable with multiple entries.



A, B, C and D are categories in the original variable.

3.4.5.2 2014 BCIS data

The overall number of variables in the received 2014 version was 151, out of which 143 variables were transformed and/or recoded. As in the previous version, most of the variables required recoding from string to numeric format, with or without cleaning, such as ethnic groups, history of previous myocardial infarction and life status at discharge variables.

Variables containing dates were not entirely provided in this version; however, durations or time intervals based on dates were provided separately and were recoded and cleaned accordingly. Most of the numeric variables (continuous and discrete) required cleaning, yet few needed recoding to categorical format as required in the analysis. An example for such variables is age at procedure as it was cleaned from all ages less than 18 years and more than 100, then recoded into categories.

Similarly, to the previous BCIS version, seven new variables were created from the existing variables. These variables were clinical presentation, procedure date, biennial years, type of stents used, censoring date, survival time, and life status at censoring. In the same way, multiple entry variables were recoded as in the 2010 version. A few examples of how some variables have been recoded and cleaned are shown in table 3.1.

Table 3.2: Examples of some recoded variables in 2014 version of the BCIS database.

Variable name	Row data format	Recoded data format	
Examples for recoded variables from string to numeric with data cleaning			
Gender	1. Male	1 = Male	
	2. Female	0 = Female	
	"."	. = Missing	
	0. Not known		
	1.07.Gender		
	9. Not specified		
	X1.07.Gender		
Admission route	1. Direct to cardiac centre (from the community)	1 = Direct to Cardiac Centre	
	2. Inter-hospital transfer	2 = Inter-hospital transfer	
	3. Already in cardiac centre	3 = Already in cardiac centre	
	"."	. = Missing	
	Unlisted		
An example for recoded date variables			
Date of procedure	Month of procedure (1 – 12)	01jan2005 01feb2005 01mar2005 … … …. 01mar2014	
	Year of procedure (2005 – 2014)		
An example for recoded multiple entry variables			
Diagnostic devices used during procedure	0. None 63,398	None	0 = No
	0. None; 2. Pressure wire		1 = Yes
	0. None; 3. Flow wire		. = Missing
	0. None; 99. Unlisted	IVUS	0 = No
	1. IVUS		1 = Yes
	1. IVUS; 2. Pressure wire		. = Missing
	1. IVUS; 2. Pressure wire; 3. Flow wire	Pressure wire	0 = No
	1. IVUS; 2. Pressure wire; 99. Unlisted		1 = Yes
	2. Pressure wire; 3. Flow wire		. = Missing
	… … …. … … ….	… … …. … … ….	

An example for numeric variables date cleaning and recoding to categorical format

	Row (numeric)	Cleaned (18 - 100)	Recoded (categorical)
Age (years)	Minimum (8)	Minimum (19.6)	1 = <65 years
	Maximum (1062.8)	Maximum (99.5)	2 = 65 – 80 years
	Median (65)	Median (72)	3 = >80 years
	Mean (64.9)	Mean (70.5)	. = Missing

3.5 Data analysis

3.5.1 Statistical analyses

3.5.1.1 Summary of descriptive methods

All analyses were conducted using Stata IC version 12 for the 2010 BCIS database and Stata IC version 13 for the 2014 BCIS database (Stata Corp LP, Texas, USA). Data in both versions were described throughout this thesis using crude unadjusted numerical data. Results for categorical variables were expressed as frequencies and percentages (%). Continuous variables were described by mean and standard deviation (SD) or if the values weren't normally distributed median and interquartile range [132, 133]. Missing data were excluded from all measured proportions. The linear-by-linear Chi square test was used to compare distributions of observed and expected proportions for categorical variables. However, for continuous variables, groups were compared using Student's t-test and ANOVA whenever normal distribution is plausible. If not normally distributed, Mann-Whitney U test was used [132, 133].

3.5.1.2 Summary of analytical methods

Cumulative event rates were estimated using the Kaplan-Meier survival curves, and differences were compared using the log-rank method. Using multivariate logistic regression and/or Cox regression models, the associations between an outcome and predictors were measured by adjusted odds ratios (aOR) and adjusted hazard ratios (aHR) with 95% confidence interval (CI) respectively. For all tests, a P value < 0.05 was considered a cut-off point for statistical significance [132, 133].

3.5.1.3 Logistic regression

Binary categorical outcome variables for instance mortality rate are the kind of outcomes (dependent variables) used in logistic regression. The application of logistic regression is relatively common. Le [133] described it as the method that is used to measure the association between an outcome variable and one or more predictor

(independent) variables. In a way, logistic regression is comparable to linear regression; however, the hypothesis of normality does not stand for binary outcomes [133].

The probability in the regression model undergoes repeated estimated logistic transformations (the maximum likelihood) ensuing variables coefficients of the model. A coefficient exponential gives the estimated odds ratio (OR) which is simply for a binary outcome, the ratio between the probability of one category against the probability of the other category [133]. When the model has more than one predictor to adjust for the confounding effect of the predictors, then the ratio is termed adjusted odds ratio (aOR) and the model is termed multivariate logistic model.

Multivariate logistic regression modelling was employed in the analysis of Chapter 4 “predictors of outcomes in UPLMS patients who underwent percutaneous coronary intervention” and in Chapter 5 “mortality trends after UPLMS percutaneous coronary intervention”. This method fulfils the aims and objectives of both analysis, and the choice was supported by the conclusions from the literature review provided in Chapter 2 (section 2.4).

3.5.1.4 Survival analysis

Modelling the duration or time period for an event to occur is known as survival analysis. It was termed “survival” as death is the typically measured event. Estimation of the direct risk of an event at a period of time is termed as the hazard function. Quantifying the association between an event survival (dependent variable) and a predictor or more (independent variables) is known as survival modelling. The most common method of survival modelling is Cox proportional hazards regression modelling [134].

Cox proportional hazards model is similar to a linear regression model; however, it requires the hazard function or the log hazard measurement in the model [134]. In the same way like logistic regression, the exponential of a coefficient is termed the estimated hazard ratio (HR), and when there is more than one predictor in the model, then the ratio is called adjusted hazard ratio (aHR).

Multivariate Cox regression modelling was implemented in the analysis of Chapter 6 “predictors of survival for primary percutaneous coronary intervention in STEMI patients”. Cox regression modelling accomplishes the aims and objectives of the analysis, and the choice was supported by the conclusions from the literature review provided in Chapter 2 (section 2.5). The same method was used in the majority of the reviewed studies.

3.5.1.5 Multi-level regression

In a fixed effects model, either a logistic regression or a Cox regression model, the observations at the patients’ level are assumed to be independent. However, this may not always be true as patients sometimes come from different groups or clusters (e.g. from different hospitals). Multi-level regression or mixed effects modelling help to overcome this dilemma. The effect of each cluster is measured using shared collective information, not only from the cluster but also from the other clusters. Simply, a mixed effects model accounts for the variance in the predictor (independent) variables as well as the variance in the higher level (e.g. hospitals) [133].

Multi-level regression modelling measures the association between a dependent variable and a predictor or more (independent variables) at level of each cluster. This method was used as a sensitivity analysis in Chapters 4, 5 and 6 to adjust for hospital clustering of patient’s observations and outcomes.

3.5.1.6 Model selection summary

Logistic and Cox regression models in this thesis were selected by identifying a set of independent variables as potential predictors of the intended dependent variable. The predictors’ identification was based on the clinical and statistical input from the Delphi group as well as the literature review provided in Chapter 2 (sections 2.4 and 2.5).

Afterward, each predictor was fitted individually in a univariable model with the dependent variable. Odds ratios (OR) or hazard ratios (HR), 95% confidence intervals

and P values were computed to assess the statistical association of each predictor with the dependent variable. All variables with significant predictive value of a P value < 0.05 were then added to the multivariate model. In addition, variables of specific clinical importance and interest to the analysis were also added to the model.

The likelihood ratio test was used to assess any interactions between the predictors and the dependent variable. After estimation, the same test was used to evaluate the goodness of fit of the logistic and Cox regression models. The test compares the fit of one model with the fit of the second model by simply likening the two models log likelihoods. A statistically significant Chi square statistic indicates that the second model prediction fits the data significantly better than the first and vice versa.

3.5.2 Handling missing values and multiple imputation method justification

3.5.2.1 Introduction

In most of medical research, missing values can occur in any variable collected, whether it is an explanatory or an outcome variable. Any missing value can arise from not being collected at all, being lost after collection or deleted intentionally after collection due to inaccuracy [124, 135]. Missing data in any database can lead to biased results as well as decrease in the power, inference and validity of the analysis undertaken. Together and due to the paucity of understanding such statistical phenomena, medical researchers frequently fail to appreciate the importance of the influence of missing data on the analysis of their research [124, 136].

Relevant literature concerning missing data and multiple imputation was identified using Ovid Medline, PubMed and Google Scholar between January 1996 and October 2015. The search terms used include “missing data”, “missing values”, “missingness” as well as “multiple imputation”. Also, the focused literature search entailed only reviewing relevant publications. Bibliographies of the publications were screened and other related publications and resources from citation trees concerning

missing data and multiple imputation were correspondingly followed, reviewed and cited using PubMed, Google and Google Scholar databases.

3.5.2.2 Types and implications of missing data

As it is well known to all statisticians and most researchers, missing data can be one of three different types based on the reasons these data where missing for; this was clearly described in several occasions in the statistics literature [135, 137-140]. Rubin (1976) [135] was the first to describe these three types. The first type is when the data have no systematic differences between the missing and non-missing values; in another words, missingness does not depend on the non-missing observed values or the unobserved values. This type is called Missing Completely At Random (MCAR) and the best example for it is when a laboratory blood sample is accidently dropped and spoiled. A complete case analysis of a dataset containing such type of missing data usually leads to loss in precision but does not cause bias [135, 137-141].

Second is when there are systematic differences between the missing and non-missing values which can be fully explained by the observed non-missing values in the dataset, this type is called Missing At Random (MAR). The presence of other covariates that can help in predicting the missing values in one variable increases the likelihood that the missingness in this variable is MAR. A good example for MAR values is when there are missing readings in blood pressure data for elderly patients who tend to have their blood pressure recorded; therefore, the missing values are conditioned to the observed patients' age and these values can be predicted by other variables in their database such as age and/or previous readings [135, 137-140, 142].

The third type is when there are again systematic differences between the missing and non-missing values but at the same time the missingness is dependent on unobserved values or events. This one is called Missing Not At Random (MNAR) or non-ignorable missingness. For example, when there are missing readings in blood pressure data for patients who were commonly assumed to have normal blood pressure by health professionals and, therefore, do not get their blood pressure measured and/or recorded at most occasions and the missing values here cannot be explained by any other variables in the database [135, 137-140].

For any research analysis, it is crucial to know the type of missing values in the dataset in order to treat it properly [140, 143]. Dealing with missing data, as illustrated by Graham and Donaldson (1993) [144], can be either accessible or inaccessible. Referring to that treating missing data can be accessible when accounting for the cause of missingness is possible; these include MCAR and most MAR values. Conversely, it is inaccessible when the missingness mechanism itself cannot be measured and these include any MNAR values as well as MAR values with known but unmeasured cause of missing data.

As mentioned previously, ignoring missing data in any analysis can lead to lack of power, loss of precision, as well as the likelihood to generate inaccurate or biased estimates. Moreover, a confounder variable with missing data cannot be excluded from any analysis as such action can cause bias and as a consequence lead to misleading results. Likewise, excluding an outcome variable with missing values from the analysis is not a practical option [124]. The inefficiency of most estimates generated after the analysis of such variables stimulates the need for dealing with missing data.

3.5.2.3 Handling missing data

Over the last ten years, determining the best statistical and analytical approach a statistician or a researcher could utilise to deal with missing value problems was a perplexing question. Including only complete records in the analysis while ignoring those with missing values (complete case analysis) is what most researchers usually do with this problem [138, 140, 143]. This method of exclusion is the simplest technique of handling missing data as no further data manipulation is necessary before any analysis. For that reason, it is the default method of analysis in most statistical packages. Complete case analysis mostly will cause a biased sample that will then have an effect on the precision and power of such research (see Figure 3.2) [137, 138, 140, 143].

Figure 3.2: Graphic illustration of complete case analysis.

ID	Age	Gender	Ethnicity	Heart rate
1	44	Female	Caucasian	75
2	37	Male	.	80
3	60	.	Black	.
4	52	Female	Caucasian	80
5	59	Female	.	85
6	38	Male	Asian	77

Complete case analysis

ID	Age	Gender	Ethnicity	Heart rate
1	44	Female	Caucasian	75
~~2~~	~~37~~	~~Male~~	~~.~~	~~80~~
~~3~~	~~60~~	~~.~~	~~Black~~	~~.~~
4	52	Female	Caucasian	80
~~5~~	~~59~~	~~Female~~	~~.~~	~~85~~
6	38	Male	Asian	77

Other examples of statistical methods that can be used to treat missing values are available case analysis, ad hoc replacement and mean substitution [137, 138, 140]. Generally, these methods can cause biased inefficient estimates and none of them is statistically valid. Single imputation is another way of treating missing data by imputing single alternative value for each missing value and, at that point, analyse the completed data as if it is true data. Unfortunately, this technique usually fails to account for missing data uncertainty and thus leads to small standard errors. Consequently, to overcome this uncertainty dilemma, most data analysts and statisticians use multiple imputation to deal with missing values [137, 138, 140].

3.5.2.4 Multiple imputation

In multiple imputation, existing non-missing values from an observed variable or variables are used to predict the missing values for another variable. When these predicted values (imputes) are used to replace the missing values, a new full dataset (imputed dataset) is created. Furthermore, multiple imputed datasets can be created by carrying out this method several times and that is why it is called multiple imputation. Ultimately, each imputed dataset can be statistically analysed using standard statistical

techniques (such as regression modelling) creating multiple results which are then combined and pooled together to generate one overall result or estimate (Figure 3.3) [144-146].

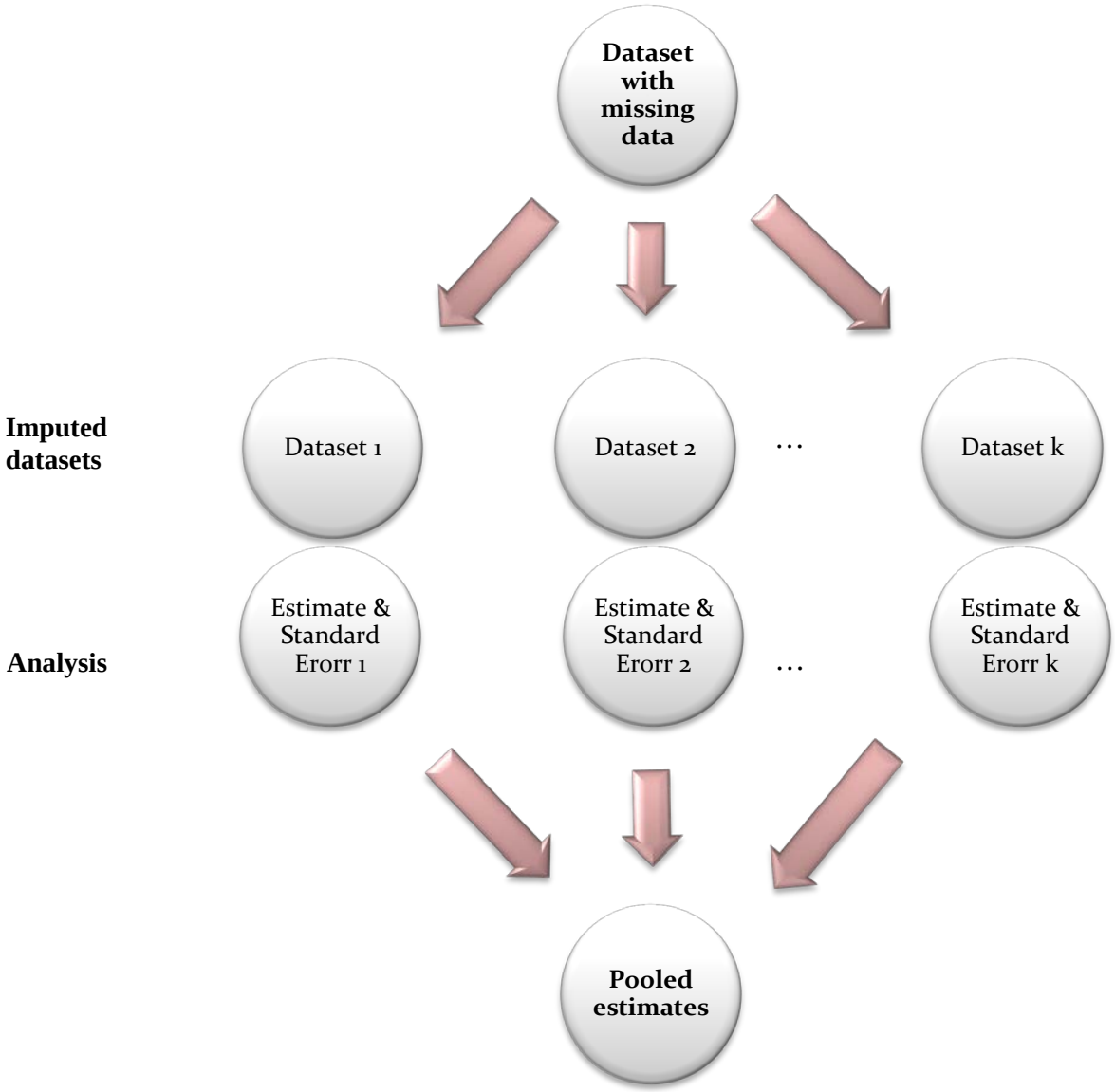
Imputing missing data using the other variables in the dataset means that these variables and the causes of missing data are correlated, and through this the natural variability of missing data is maintained. Moreover, pooling of the analysis of imputed datasets using Rubin's rules (represented by the equation below) will always take account of the variability between the imputed datasets by creating unbiased parameter estimates which reflect the missing data uncertainty. In addition to that, multiple imputation offers efficient estimates when treating datasets with small sample size and/or high rates of missingness giving major advantages over complete case analysis [138, 143, 146].

Equation A : Rubin's rule [146].

$$T = \frac{1}{k}\sum_{i=1}^{k} \coprod_{i}^{\wedge} + \frac{k+1}{k}\ [\frac{1}{k-1}\sum_{i=1}^{k}\ (Q_i - Q)^{-2}]$$

$\bar{Q} = Variance$
$T = Total\ estimated\ variance\ associated\ with\ \bar{Q}$
$k = Number\ of\ imputed\ datasets$
$i = The\ analysed\ group\ (1,2,3, \ldots\ldots\ldots, k)$
$Q_i = Estimation\ of\ the\ i^{th}\ group$
$\coprod_{i}^{\wedge} = \boldsymbol{Variance\ for\ the\ i^{th}\ group}$

Figure 3.3: Graphic illustration of multiple imputation application and the analysis afterward.



k = number of imputed datasets

3.5.2.5 Multiple imputation for multivariate missing data

Multiple imputation was first introduced in 1977 by Rubin, and then was described in more detail in 1987 and 1996 again by Rubin, and also in 1997 by Schafer. In 1996, Rubin described multiple imputation in three distinctive steps: firstly the creation of multiply imputed datasets in which unsystematic draws from correlated complete variables replace the missing values in a variable, secondly complete statistical analysis of each imputed dataset, and finally pooling or combining the results of each dataset analysis into one valid estimate [145, 147-149].

However, Rubin's original rule in 1987 failed to elucidate the application of multiple imputation when there are missing values in more than one variable in the dataset, i.e. multivariate missing data. Since then, various methods have been proposed to deal with the complexity of imputing multivariate missing data which can be summarised into two broad methods: joint modelling and fully conditional specification [150-154].

Joint modelling is simply one model for all multivariate missing data that include a set of correlated complete variables (predictors) as well as the incomplete variables (to be imputed); the same model is for both imputation and analysis afterward [150, 151]. This method has some pitfalls in the created imputation, particularly in the presence of differences between the variables in terms of type (binary, categorical or continuous), which consequently lead to bias by generating unrealistic assumptions and/or incorrect combinations in the imputed variables (e.g. pregnant male) [153, 155].

Fully conditional specification imputation method, first introduced by Buuren *et al.* in 1999, is a more flexible alternative of joint modelling method in which separate individual conditional models for each incomplete variable are specified for the imputation alone. Afterward, separate analysis models are applied to the imputed datasets and then pooled together in one estimate. Multiple imputation by chained equation (MICE) is another name for conditional specification method which have been applied in various statistical software such as R, S-Plus and SPSS [154, 155]. A similar software package in Stata called (ice) was introduced be Royston in 2004 [156].

The flexibility of the fully conditional specification method is more recognisable in the way that different conditional models are specific for each variable type (binary, categorical or continuous); more details can be seen in table 3.2. Another advantage of this method is the option to comprise constraints to make certain that the imputed values do not have incorrect combinations [155]

Table 3.3: Imputation methods based on the type of the variable with missing data.

Type of variable	Imputation method
Binary	Logistic regression [145]
Categorical	Polytomous logistic regression [157, 158]
Continuous	Linear regression [145, 159]
	Predictive mean matching [159, 160]
Semi-continuous (mixed discrete and continues)	Two step (logistic + linear regression) [145]

3.5.2.6 The number of imputations

Rubin in 1987 demonstrated statistically that the number of imputations depends on the fraction of missing data [145]. Imputations between five and ten were the number suggested by early publications [154, 161]; however, more recent researches suggested that increasing the number of imputation datasets would be more beneficial, since they concluded that the lower the number of imputations the lower the loss of statistical power for detecting small effect sizes, and the more the variability between important statistics are, such as standard errors, P value and 95% confidence interval. The final number of imputation datasets suggested more recently was 20 [162-164].

3.5.2.7 Multiple imputation model specification

Faultily specified imputation models will always lead to inaccurate imputation and consequently wrong estimates, and in order to avoid this some approaches have been proposed in literature:

- Including all the variables in the dataset into the imputation model minimises bias [154]. However, in several medical datasets where the number of variables are too high, this kind of model is not achievable as it tends to produce multicollinearity between the variables. Thus, it was recommended in the literature that in such datasets, the number of variables to be included in the imputation model should be between 15 and 25 variables [154].
- MAR assumption is more plausible if as many predictors as possible are included in the model [142, 150, 165].
- The congenial imputation model is a model that comprises all the variables to be applied in the analysis (including the outcome variable). The absence of congeniality in an imputation model will lead to inaccurate underestimation of the predictive associations [166]. At the same time, additional auxiliary variables that are not important to the analysis but contribute to the prediction of missing values should be included [167]. The inclusion of auxiliary variables to an imputation model reduces the bias produced from the pooled analyses estimates later on [138, 142].
- Non-linear transformations as well as interactions should always be included in the imputation model as they also lead to underestimation of the predictive associations [164].
- The assumption of normality for the included continuous variables should be confirmed before running any imputation model; non-normality creates a lack of face validity (i.e. the imputation sets produced will be closer to normal distribution rather than the original distribution) [164]. To avoid such an issue, any non-normally distributed variable should be transformed to an approximate normal distribution before the imputation. Then, the imputed data should be transformed back to the original scale before any analysis [164].

3.5.2.8 Multiple imputation application in the medical literature

Lately, deliberations were raised either toward or against the use of multiple imputation, in particular, and the other statistical methods in general in order to deal with missingness in datasets. Twenty years ago, Greenland and Finkle [139] pointed out that the use of missing data treatment methods in epidemiological researches was not so common, and this was due to their complexity as well as the lack of accessibility, mainly owing to the paucity of statistical software packages that implement multiple imputation at that time. Similarly, Rubin [168] concluded that statistical software packages are important for implement multiple imputation to be the standard method to deal with missing data.

Further, Klebanoff and Cole [136] demonstrated that less than 2% of epidemiological published papers has used missing data treatment methods, and multiple imputation was one of these methods. However, several researchers used multiple imputation in analysing their datasets, which showed promising performance. Good examples of such researchers are Graham et al., Wayman as well as Schafer and Graham [136, 169].

However, after the introduction of some statistical software packages that implement multiple imputation such as MICE packages by Buuren *et al.* in 1999 [154] and the ice software package by Royston in 2004 [156], there was an increase in the use of multiple imputation in the recent years, particularly in the medical researches. As a matter of fact, the use of multiple imputation in the medical literature has been rising slowly but gradually over the last ten years.

Barzi and Woodward [170] used multiple imputation of serum cholesterol level to compare the results of 28 studies in the Asia pacific cohort studies collaboration. In this study, eight different imputation methods were used for each study. Cholesterol level values of <10% were missing in 22 studies, and the pooled analysis showed comparable results between the methods. Four studies, however, with 10 to 60% missing values showed differences between the methods and proposed that multiple imputation is the method of choice. Cholesterol level values of > 60% missing values were present in two studies, and none of the imputation methods were effective.

Schiattino *et al.* [146] used multiple imputation to evaluate differences in serum tumour necrosis factor (TNF) concentrations increment in rheumatoid arthritis patients receiving anti-TNF therapy. The results of this study showed that multiple imputation is > 98% efficient, and this association was statistically significant (P <0.001). Another published study by Eisemann *et al.* [171] used different models for multiple imputation to analyse stage specific numbers of cases of malignant melanoma and female breast cancer in a population-based cancer registry. They concluded that with reasonable levels (< 20%) of cases of missingness in tumour stages, multiple imputation is a suitable approach to handle missing values in such population-based registries.

Heron *et al*. [172] used full information maximum likelihood and multiple imputation to compare their estimators in a UK-based birth cohort to analyse smoking frequency in young adolescents. The complete case analysis showed that smoking prevalence was lower than that estimated by the pooled 100 imputed datasets and the full information maximum likelihood method. It also showed that the relationship between smoking patterns and covariates was also varying between the methods used.

In another study, undertaken by Cattle *et al.* [141], they utilised multiple imputation to complete the missingness in the database of a national register of heart attacks (Myocardial Ischemia National Audit Project or MINAP). In this study, the authors concluded that multiple imputation improved the quality and value of the MINAP database by giving it better precision of estimates of odds ratios, which was achieved by using the measured variables from the incomplete records.

Montealgre *et al.* [173] used multiple imputation of the birth place variable to describe and compare the survival between the United States born vs. foreign born patients with cervical, prostate or colorectal cancer. The results of this study indicated that multiple imputation of the birth place status disclosed different associations between birth place and cancer survival when compared to complete case analyses of the same cohort.

3.5.2.9 Conclusions and justifications

Although the influence of missing data on any kind of analysis is well established and well understood in the statistical society, most of the applied medical studies failed to appreciate the importance of using statistical methods to deal with missing data. Ignoring the missing values in any analysis can create biased estimates, loss of the statistical power and loss of precision, which mean results may not be valid to clinical practice. Even though multiple imputation is not a perfect method to treat missing values, it is clear that other alternative statistical methods produce less precision and power in any analysis results compared to multiple imputation.

In published medical research since the introduction of statistical software packages that implement multiple imputation, there was a slow, steady increase in the use of multiple imputation. Accordingly, and since the BCIS databases (both 2010 and 2014 versions) have a large number of missing values in most of the variables (as described earlier in Chapter 1 (sections 1.3.4.3 and 1.3.53)), multiple imputation was selected to be the statistical method of choice, together with the complete case analysis, to treat the missing data in the analysis of all the studies included in this thesis.

Furthermore, multiple imputation in the recent literature has been the most common method used to deal with missing data. However, it was clear that multiple imputation was not widely used in the cardiovascular literature, and employing the method in the analysis of this thesis will make it better known. Details of the specific methodology used in the thesis as well as a full description of the imputation models specifications are provided in the next section. However, thorough descriptions of the missing data patterns as well as the imputed data specification and analysis are provided separately in Chapters 4, 5 and 6.

3.5.3 Multiple imputation method

To enhance the research potential of the BCIS database, multiple imputation was performed ‘fit for purpose’. Imputation models were specified twice for UPLMS patients who underwent percutaneous coronary intervention as well as STEMI patients

treated by primary percutaneous coronary intervention. The models included all the variables of interest in the main regression or survival analyses. At the same time, auxiliary variables were included to the imputation models in order to improve the prediction of missing data in the regression/survival selected variables.

The outcome variables (30-day and 1-year mortality), survival estimates and censoring indicators were retained in the imputation models. The inclusion of the outcome variables to imputation models decreases the bias from the pooled estimates [166]. Imputation variables (predictors and auxiliaries) were selected based on comprehensive literature reviews and the Delphi group clinical agreements on the clinical plausibility of some variables.

Based on the cohort of intention, the datasets were inspected for the percentages of missing values. Assuming that they were missing at random, the missing values in all selected variables (predictors and auxiliaries) in the imputation models were imputed except for those with more than 40% missingness, as it is not recommended [174]. This assumption simply vindicates the certainty that the missingness can be predicted by the available observed information. MAR assumption is more plausible if as many predictors as possible are included in the model [142, 150, 165].

In order to test for collinearity, disease specific statistical predictor matrices were designed based on clinical judgement as well as using thresholded P values of less than 5% as related and ≥ 0.05 as unrelated. For continuous-continuous and continuous-categorical associations (continuous variables were modelled as the response) linear regression was used. While for categorical-categorical (including binary and ordinal variables), Chi-squared test was used.

All imputations were conducted using Stata IC versions 12.0 and 13.0 (Stata Corp LP, Texas, USA). The recommended number of imputations datasets was 20 [162-164]. Therefore, for each of the selected variables with missing values, 20 datasets were imputed using the chained equation method. Fully conditional specification imputation method was used in all imputations; a detailed explanation of the method was mentioned earlier (section 3.4.3.5). Continuous variables were imputed using predictive mean matching and the categorical data imputed using either logistic regression or polytomous regression (Table 3.2).

In predictive mean matching, the predicted model is estimated from the observed data, which ensures that the extra uncertainty about the unknown true model is reflected [175]. The normality assumption of all continuous variable used in imputation were verified graphically using histograms. However, in both 2010 and 2014 versions of the BCIS database, one variable (IMD score) was not normally distributed. The variable needed logarithmic transformation before multiple imputation and then reversed back later for the intended analysis.

Interaction terms were considered during the imputation process as well as in the analyses later on. Imputation diagnostics were evaluated and did not give any cause for concern. To be more precise, the likelihood ratio was the test used to assess any interactions between the predictors and to evaluate the goodness of fit of the imputation models. Furthermore, and in order to test for any implausible values in the imputations, descriptive statistics of the imputed datasets were inspected and compared to those of the complete case datasets. In all the imputations performed in this thesis, the distributions of the imputed and complete case datasets were comparable. This comparability added more reliability to the MAR assumption as well as signifying that the imputation models were acceptable. Finally, imputed datasets for each predictor were pooled together using Rubin's rule and followed by the intended regression or survival analyses.

Chapter 4 Determinants of outcomes after PCI for UPLMS

4.1 Summary

In the previous three chapters, clinical background, literature reviews, data discerption and overall methodologies were illustrated (Chapters 1, 2 and 3). This chapter concerns an analysis using the 2010 BCIS data to answer one of the questions regarding the care provided to the patients who received PCI in the UK; the clinical determinants of outcomes in patients with UPLMS. Brief definitions of the types of clinical presentation of patients with coronary artery disease as well as a full introduction to UPLMS PCI were described in Chapter 1 (sections 1.2.1, 1.2.4 and 1.2.5). A literature review regarding 'the clinical determinants and temporal trends of outcomes for PCI in UPLMS disease' was provided in Chapter 2 (section 2.4). This chapter is split into five sections covering: the background, rationale and aims (section 4.2), methodology including study design, population, stratification, definitions, follow-up as well as statistical and sensitivity analyses (section 4.3), results including completeness, descriptive statistics, survival time, multivariate modelling results and sensitivity results (section 4.4) and discussion and conclusion (section 4.5).

4.2 Introduction

4.2.1 Background and rationale

In contemporary practice, PCI has become an alternative strategy to CABG in patients who have UPLMS, particularly in those deemed at high risk for surgery [176], even though, repeat revascularisation procedures are increased with LMS disease PCI compared to CABG [23]. Notably, higher rates of success are not confined to chronic stable angina patients, and favourable outcomes have been reported in emergency cases when CABG is often contraindicated [24, 25, 28]. Yet, for patients who receive PCI for disease of the UPLMS, there is a paucity of data that measures outcomes in unselected patients on a large scale, and in a consecutive series.

For UPLMS, a variety of clinical risk factors or determinants (such as old age, cardiogenic shock, diabetes and renal failure) have an impact on the outcomes of most PCI procedures. These determinants are believed to be less common among elective patients compared to those with acute onset [25-27]. Furthermore, unless it is not contraindicated; CABG is the recommended line of management and PCI procedures for UPLMS are usually the choice of treatment in patients with contra-indications; therefore, affecting its success further [19, 26, 28]. Additionally, there is a gap in the knowledge base regarding the relative merits of PCI to an UPLMS culprit lesion in patients who present with ST-elevation myocardial infarction (STEMI) or non ST-elevation acute coronary syndrome (NSTEACS) [29].

In the literature, data relating to UPLMS patients with cardiogenic shock are very limited and early outcomes reported in only small cohort studies. Likewise, current international guidelines recommend the radial access to PCI over that of the femoral [35, 87, 110]. However, additional evaluation of the wider implications of radial access on the outcomes in UPLMS after PCIs is necessary.

There is, therefore, value in reporting contemporary and representative outcome data for PCI to the UPLMS in order to inform patients, healthcare professionals and regulators of both the benefits and inherent risks of such therapy, and also to highlight areas where novel interventions aimed at improving outcomes may be targeted [25, 31, 42, 45-48].

4.2.2 Aims

The overall rationale and aims of the thesis were outlined in Chapter 2 (section 2.6). The primary aim of this chapter was to perform a population-based comparative investigation into the clinical outcomes of patients who received PCI to UPLMS according to clinical syndrome at presentation over a period of six years (from January 1, 2005 to December 31, 2010):

1. To report the overall completeness of the 2010 BCIS data for all patients with UPLMS.
2. To describe demographic and clinical characteristics of patients by clinical presentation.
3. To describe the procedural characteristics of patients by clinical presentation.
4. To describe the outcomes and survival for patients with UPLMS after PCI by clinical presentation.
5. To identify the clinical determinants of PCI outcomes in patients with UPLMS and to measure their level of association by clinical presentation.
6. To quantify the impact of cardiogenic shock on the clinical outcomes of patients by clinical presentation.
7. To report the impact of the radial versus femoral access approach on the clinical outcomes of patients by clinical presentation.

4.3 Methodology

4.3.1 Study setting and design

The study design was a prospective population based linked cohort study using data of patients having PCI to an UPLMS from 89 interventional cardiology centres and hospitals in England and Wales registered with the BCIS audit program between 2005 and 2010 (based on BCIS Audit Returns, Adult Interventional Procedures, January 2010 to December 2010) [20].

4.3.2 Patients, procedures and treatments (study population)

Although BCIS collects data from all countries in the UK, robust mortality tracking was only available for patients who live in England and Wales; this represents approximately 89% of the whole adult UK population (based on the Office for National Statistics UK population estimates for 2013) [82]. Thus, the sampling frame comprised all patients in England and Wales.

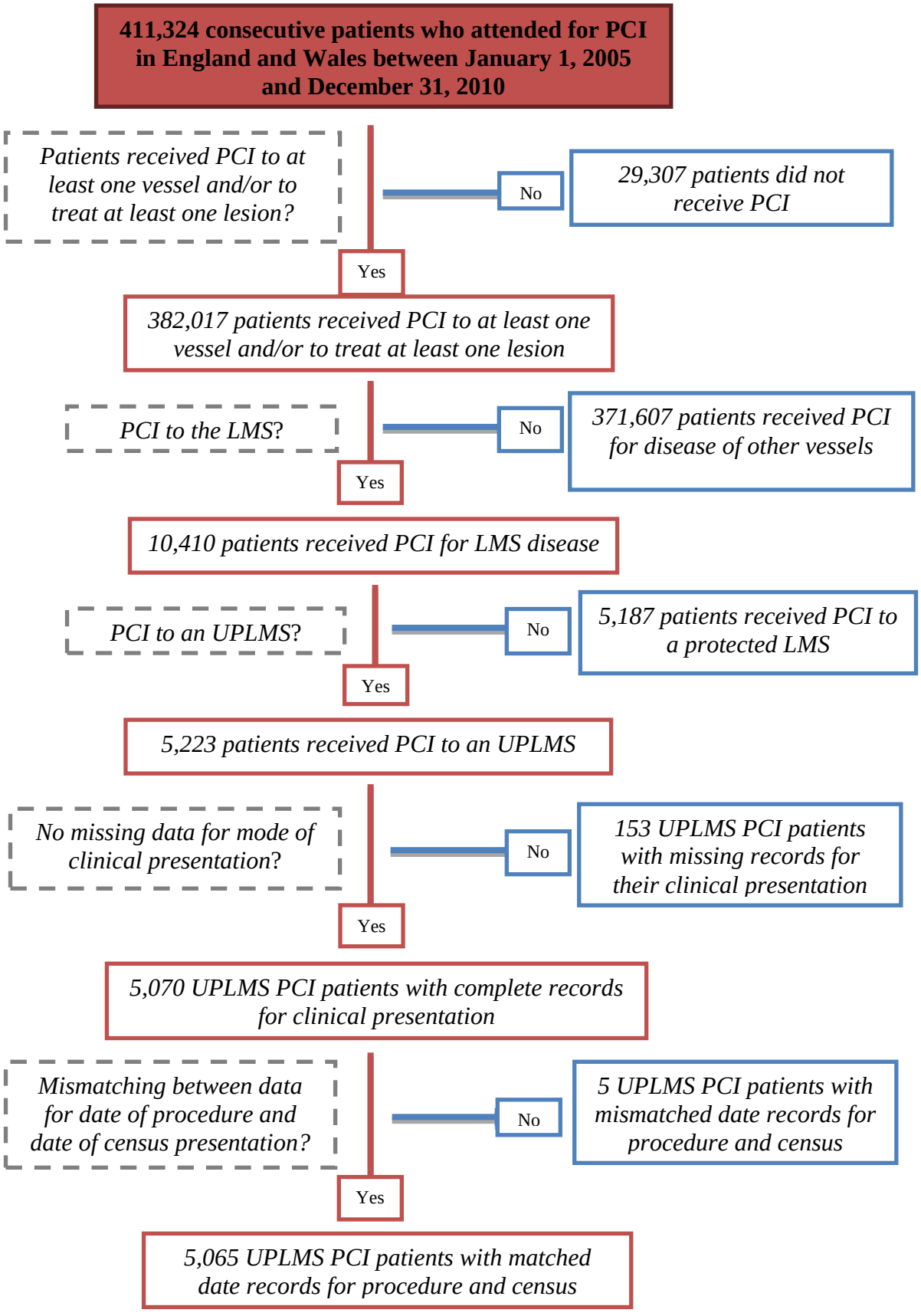
In the 2010 BCIS dataset, the total number of consecutive patients who attended for PCI in England and Wales between the 1st of January, 2005 and the 31st of December, 2010 was 411,324 patients. Out of these, eligible patients for the UPLMS analyses were; patients aged 18 years or more who had received PCI to a diseased UPLMS over the six year period (from 2005 to 2010). For those with multiple admissions, the earliest intervention record was used.

Furthermore, in order to specifically select the appropriate analytical cohort population, an inclusion and exclusion criteria was identified (based on the Delphi group clinical agreement):

- Firstly, patients who had no vessels attempted or missing information about that were excluded. In the same way, those who had no lesions attempted or missing information about that were also excluded. The remaining number of PCI patients was 382,017.
- Secondly, 10,410 patients were included as they were drawn from those who had the left main stem as the treated vessel. Simultaneously, 371,607 patients who received PCI for disease of other vessels were excluded.
- Thirdly, patients with a history of previous CABG, missing information on that or who had any number of grafts present pre-procedure were excluded. At the same time, patients with an UPLMS were defined as those who did not have a patent graft to any left sided coronary artery [20]. Therefore, 5,223 patients were included as they received PCI for UPLMS.
- Finally, 153 patients with missing records for their clinical presentation and another 5 patients with mismatched date records for procedure and census were

excluded. Thus, the final population included was 5,065 patients. A detailed flow chart of the selected cohort population is shown in Figure 4.1.

Figure 4.1: Flow chart of the selected cohort population.



4.3.3 Stratification of cohort population

According to the mode of clinical presentation of UPLMS patients who were treated by PCI, the whole analysis of this chapter was divided into three main strata:

- ST-elevation myocardial infarction (STEMI).
- Non ST-elevation acute coronary syndrome (NSTEACS).
- Chronic stable angina (CSA).

This stratification was selected and agreed by the Delphi group based on the results from the literature review in order to compare and understand the difference between these three groups of patients. The clinical definition of each stratum was described previously in Chapter 1 (section 1.2). The definitions from the BCIS database spreadsheet version 5.6.x are shown in Table 4.1.

Table 4.1: Clinical presentation strata definitions from on the BCIS database spread sheet version 5.6.x.

CSA	**Stable - angina** Stable patients off waiting list with symptomatic or silent ischaemia.
	Stable - coronary/LV anatomy Stable patients off waiting list without angina because PCI believed to offer prognostic benefit or would improve ventricular function to include PCI for arrhythmia.
NSTEACS	**ACS - PCI for NSTEMI** Acute coronary syndrome with or without enzyme release and a history typical of acute myocardial infarction.
STEMI	**ACS - Primary PCI for STEMI (no lysis)** Emergency PCI for acute STEMI, no thrombolysis given. Includes patients presenting with a clear history of AMI and LBBB.
	ACS - Facilitated PCI for STEMI (lysis + PCI) Emergency PCI performed in the acute setting as soon as possible after thrombolysis for acute STEMI (or new LBBB) with a clear history of AMI, provided as a routine treatment in addition to thrombolysis.
	ACS - Rescue PCI for STEMI (failed lysis) Emergency PCI for acute STEMI for failed thrombolysis - defined as failure of the ST segment to fall by 50% or more in the ECG lead showing the greatest ST elevation prior to thrombolysis, 1-3 hours after starting thrombolysis.
	ACS - PCI for reinfarction (no lysis) Emergency PCI for acute STEMI for reinfarction in the same territory as the admission infarct, but no thrombolysis given for the new event.
	ACS - Rescue PCI for reinfarction (failed lysis) Emergency PCI for acute STEMI for reinfarction in the same territory as admission infarct, when thrombolysis for the new event has failed.

4.3.4 Definitions

The consensus document of the Joint European Society of Cardiology / American College of Cardiology was used as the diagnostic standard for acute myocardial infarction (AMI) and provided the basis for categorisation by the local supervising cardiologist into STEMI and NSTEACS, according to the clinical presentation, electrocardiogram and troponin level where appropriate [177, 178].

The STEMI group included patients receiving primary PCI, rescue PCI, PCI for re-infarction and facilitated PCI for STEMI. Percutaneous coronary intervention was defined as a procedure that has been performed using any coronary device approaches, probes or crosses one or more coronary lesions, with the intention of carrying out a coronary intervention [81].

Cardiogenic shock was defined as a systolic blood pressure less than 100 mmHg and pulse greater than 100 bpm in a patient who was peripherally shut down and/or who required inotropes, an intra-aortic balloon pump or cardiopulmonary support for circulation [81]. Major Adverse Cardiac and Cerebrovascular Events (MACCE) were defined as a group of complications or events that occurred in-hospital after an intervention. MACCE included stroke, heart attack, need for emergency coronary bypass surgery or death.

4.3.5 Follow-up and mortality

Detailed information regarding patients' follow up and morality can be found in Chapter 1 (section 1.4.3 and Figure 1.3). However in short, the analysis of all-cause mortality was performed by the MRIS by linkage with the ONS using each patient's unique NHS number. Subsequently, using each patient's geographical residence and IMD score; a linkage that was made by the CCAD to their corresponding BCIS record.

Patients, interventionists or hospitals identifiers were secondary anonymised in the 2010 versions of the BCIS database that we received. Due to the date of linkage for censored data (10th August 2011), mortality data at 1-year were not available for 519 (10.2%) patients. Therefore, patients with a follow-up period of less than 12 months

were excluded from the analysis of 1-year mortality rate; however those patients were included in all other parts of the analysis.

4.3.6 Statistical analysis

4.3.6.1 Descriptive data analysis

Initially, a descriptive analysis for the overall cohort was performed to gain a better understanding of patients' characteristics followed by a detailed description of the extent of missing data in the cohort. The exploration of data that was missing included all the variables in the 2010 BCIS database. Later, missing data patterns were measured and assessed based on the percentage of missing data.

As mentioned previously, the whole analysis was stratified by the mode of clinical presentation of UPLMS patients (CSA, STEMI and NSTEACS). The aim of this stratification was to compare the differences between stable and acute patients. It is believed that acute patients are liable to more clinical risk factors, such as cardiogenic shock, that have an obvious impact on PCI outcomes [48, 51, 52]. Types of tests and methods used for data description have been outline previously in detail in Chapter 3 (section 3.5).

The described characteristics included baseline demographics, clinical features, pre-procedural, procedural and post-procedural characteristics as well as clinical outcomes. The clinical outcomes of intention included:

- Procedural complications such as side branch occlusion, coronary dissection, the need for ventilation and cardiogenic shock.
- In-hospital outcomes such as acute myocardial infarction, renal failure, blood transfusion, revascularisation and MACCE.
- Mortality rate at 30 days and at one year.

4.3.6.2 Survival curves

Cumulative unadjusted survival estimates of patients with UPLMS disease who received PCI were depicted using the Kaplan-Meier method from the time of the procedure to 6.6 years. The differences across strata were compared using the Mantel-

Cox log-rank test. The same analysis was repeated to compare the differences between patients with and without cardiogenic shock in STEMI and NSTEACS groups.

4.3.6.3 Adjusted in-hospital MACCE

Adjustment for in-hospital MACCE (predicted MACCE) was undertaken using the factors age, female sex, procedure urgency, procedure emergency cardiogenic shock, left main stem PCI, graft PCI, history of a stroke and the corresponding published coefficients from the North West Quality Improvement Project (NWQIP) risk model [179]. The adjustment was simply performed by generating a new variable using the following Stata commands:

- `gen Predicted_MACCE = (-5.4959 + [age 71 to 79 years * 0.7048] + [age 80 years and more * 1.0106] + [female sex * 0.4586] + [procedure urgency * 0.4788] + [procedure emergency * 1.3625] + [cardiogenic shock * 3.2636001]+ [left main stem PCI * 1.6502] + [graft PCI * 0.9101] + [history of a stroke * 0.8618])`
- `replace  Predicted_MACCE = Predicted_MACCE^2`

4.3.6.4 Multivariate regression modelling

All clinical outcomes were analysed without adjustment apart from the predicted in-hospital MACCE, 30-day mortality and 1-year mortality which was analysed with adjustment (multivariate logistic regression). The associations between the clinical determinants and the predicted MACCE, 30-day and 1-year mortality were quantified using fixed effects multivariate logistic models and estimates were expressed as adjusted odds ratios (aOR) with 95% confidence intervals (CI).

The first regression model aimed to measure the association between the clinical outcomes (predicted in-hospital MACCE, 30-day mortality and 1-year mortality) and the mode of clinical presentation. The adjusted estimate of each of the three models were standardised for age groups, sex, history of diabetes mellitus, history of renal disease, post-procedural complications (side branch occlusion, coronary dissection and shock induced by procedure) and the mode of clinical presentation.

For 30-day and 1-year mortality rates, each model estimate was adjusted using covariates selected after a literature review on ‘the clinical determinants and temporal

trends of outcomes for PCI in UPLMS disease', see Chapter 2 (section 2.4). Furthermore, based on the clinical significance recommended by the Delphi group for each clinical determinant (predictor), the estimates of the multivariate logistic regression model were adjusted by different covariates. The selected predictors are listed by clinical presentation and mortality outcomes in Table 4.2. Multivariate model selection process, interaction assessment and the evaluation of goodness of fit were outlined in detail in Chapter 3 (section 3.4.6.5).

Table 4.2: Summary of the multivariate logistic models used including the selected predictor variables and covariates, by clinical presentation and mortality outcomes.

Clinical presentation, outcome and method	Predictors	Covariates
30-day mortality and 1-year mortality using fixed effects multivariate logistic regression model in patients with UPLMS who underwent PCI (CSA patients)	Age groups	Age groups, sex, history of diabetes mellitus, history of renal disease and post-procedural complications (side branch occlusion, coronary dissection and shock induced by procedure)
	Sex	
	History of diabetes mellitus	
	History of renal disease	
	Procedural complications	
	History of acute myocardial infarction	
	History of percutaneous coronary intervention	
	Left ventricular ejection fraction	
	Vessels attempted	
	Number of stents used	
	Drugs used during procedure	
	Intravascular ultrasound use during procedure	
	Use of intra-aortic balloon pump	
	Arterial access	
	Longest stented/treated segment	
	In-hospital acute myocardial infarction & stroke	
30-day mortality and 1-year mortality using fixed effects multivariate logistic regression model in patients with UPLMS who underwent PCI (STEMI and NSTEACS patients)	Age groups	Age groups, sex, pre-procedural cardiogenic shock, history of diabetes mellitus, history of renal disease and post-procedural complications (side branch occlusion, coronary dissection and shock induced by procedure)
	Sex	
	Pre-procedural cardiogenic shock	
	History of diabetes mellitus	
	History of renal disease	
	Procedural complications	
	History of acute myocardial infarction	
	History of percutaneous coronary intervention	
	Left ventricular ejection fraction	
	Vessels attempted	
	Number of stents used	
	Drugs used during procedure	
	Intravascular ultrasound use during procedure	
	Use of intra-aortic balloon pump	
	Arterial access	
	Longest stented/treated segment	
	In-hospital acute myocardial infarction & stroke	

4.3.7 Sensitivity analyses

A series of sensitivity analyses were performed in order to assess potential bias from the fixed effect regression methods used. First, the impact of mixed effects models (multi-level logistic regression models) was evaluated. Second, multivariate logistic regression analyses were considered after multiple imputation.

4.3.7.1 Multi-level regression modelling

Models were fitted with a hierarchy of patients clustered in each hospital using random intercepts for hospitals thus allowing for correlations between patient outcomes. Therefore, the mixed effects models accounted for the variance in the predictor variables as well as the variance in the hospitals level [133]. More explanation on the methods of multi-level regression modelling can be found in Chapter 3 (section 3.5.1.5).

Similar to the fixed effect multivariate logistic regression models, the same outcomes (predicted in-hospital MACCE, 30-day mortality and 1-year mortality), predictor variables and adjustment covariates (Table 4.2) were fitted in the mixed effect models. Subsequently, estimates were compared with those from equivalent fixed effects models.

4.3.7.2 Multiple imputation method

In total 24 imputation predictors were selected based on clinical consensus and a literature review, Chapter 2 (section 2.4) [26, 30, 31, 45, 48, 94, 97, 104]. More details on general methods of multiple imputation were presented in Chapter 3 (sections 3.5.2 and 3.5.3). Table 4.3 displays the list of imputation predictor variables of the outcomes of patients with UPLMS who had PCI with a summary of missing data and the methods used for imputation.

The frequency of missing values ranged from 0.06% to 35.50% and all missing values were assumed to be missing at random. No data were missing for five of these variables ‘clinical presentation’, ‘cardiogenic shock’, ‘year of operation’, ’30-day mortality’ and ‘1-year mortality’. Yet, these variables were still used as auxiliary variables in the imputation for the remaining 19 variables. Two other variables, ‘largest balloon/stent’ and ‘longest stented segment’, were not imputed or even included in the predictor matrix due to collinearity.

A predictor matrix was designed based on clinical judgement as well as using thresholded P values of less than 0.05 as related and greater than or equal to 0.05 as unrelated. The predictor matrix is shown in Table 4.4. For continuous-continuous and continuous-categorical associations, linear regression was used. While for categorical-categorical, Chi-squared test was used. For each of the 19 predictors with missing values, 20 datasets were imputed using the chained equation method and the fully conditional specification imputation method [141, 153, 180].

All 19 variables were categorical and were all imputed using either logistic regression (if binary) or polytomous regression (if ordinal). For each of STEMI, NSTEACS and CSA, 20 separate imputation datasets were created for 30-day mortality and then 20 others for 1-year mortality. Finally, imputed datasets for each predictor were pooled together using Rubin's rule and followed by the intended regressions. The adjusted estimates from both complete case and multiple imputation data were compared in order to test for the sensitivity of this analyses.

Table 4.3: Imputation predictor variables of the outcomes of patients with UPLMS who PCI with a summary of missing data and the methods used for imputation.

	Variables	Variable type	Missing %	Imputation method
1	**Age groups**	Ordinal	0.06	Polytomous regression
2	**Sex**	Binary	1.09	logistic regression
3	**Clinical presentation**	Ordinal	0.00	Auxiliary (not imputed)
4	**Pre-procedural cardiogenic shock**	Binary	0.00	Auxiliary (not imputed)
5	**History of acute myocardial infarction**	Binary	13.58	logistic regression
6	**History of percutaneous coronary intervention**	Binary	1.40	logistic regression
7	**History of diabetes mellitus**	Binary	5.19	logistic regression
8	**Left ventricular ejection fraction**	Ordinal	35.50	Polytomous regression
9	**Year of operation**	Continuous	0.00	Auxiliary (not imputed)
10	**Major adverse cardiac and cerebrovascular event**	Binary	5.77	logistic regression
11	**History of renal disease**	Binary	7.82	logistic regression
12	**Vessels attempted**	Binary	0.59	logistic regression
13	**Procedural complication: Side branch occlusion**	Binary	10.11	logistic regression
14	**Procedural complication: Coronary dissection**	Binary	10.11	logistic regression
15	**Procedural complication: No flow / slow flow**	Binary	10.11	logistic regression
16	**Procedural complication: Shock induced by procedure**	Binary	10.11	logistic regression
17	**Number stents used**	Ordinal	0.43	Polytomous regression
18	**Stent type**	Ordinal	3.51	Polytomous regression
19	**Drugs used during procedure**	Ordinal	5.88	Polytomous regression
20	**Intravascular ultrasound use during procedure**	Binary	13.35	logistic regression
21	**Use of intra-aortic balloon pump**	Binary	6.36	logistic regression
22	**Arterial access**	Ordinal	1.68	Polytomous regression
23	**30-day mortality**	Binary	0.00	Auxiliary (not imputed)
24	**1-year mortality**	Binary	0.00	Auxiliary (not imputed)

Table 4.4: Predictor matrix of the outcomes of patients with UPLMS who received PCI using the 2010 BCIS database.

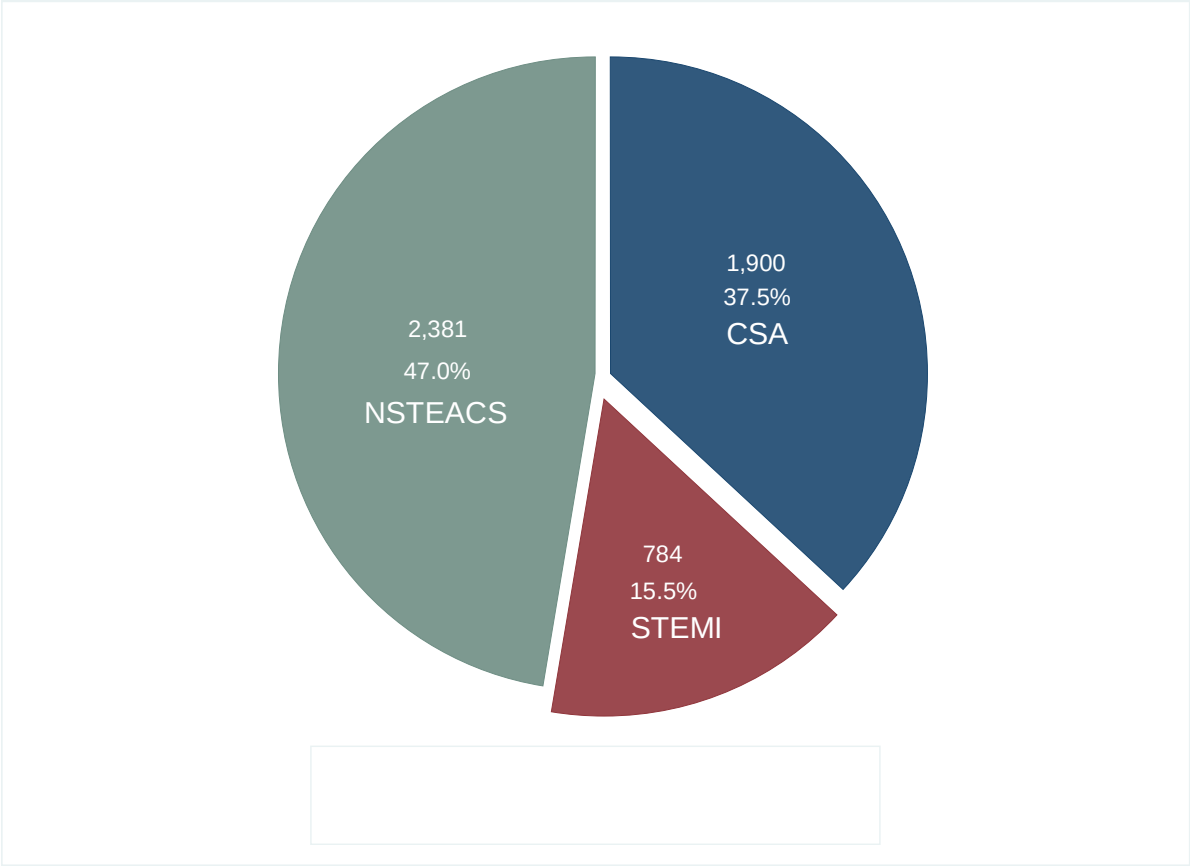
	Variables	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
1	Age																								
2	Sex	1																							
3	Clinical presentation	1	1																						
4	Pre-procedural cardiogenic shock	1	0	1																					
5	History of Acute myocardial infarction	1	0	1	1																				
6	History of Percutaneous coronary intervention	1	0	1	1	1																			
7	History of Diabetes mellitus	1	0	1	1	1	1																		
8	Left ventricular ejection fraction	1	0	1	1	1	1	1																	
9	Year of operation	1	0	0	1	0	1	0	0																
10	Major adverse cardiac and cerebrovascular event	1	1	1	1	0	1	0	1	0															
11	History of Renal disease	1	1	1	1	1	0	1	1	1	1														
12	Vessels attempted	1	1	1	0	1	0	1	1	0	1	1													
13	P-complication: side branch occlusion	1	0	0	0	0	0	0	0	0	1	0	0												
14	P-complication: coronary dissection	0	1	0	0	1	0	0	0	0	1	0	1	1											
15	P-complication: no / slow flow phenomenon	0	1	1	1	1	0	0	1	0	1	0	0	1	1										
16	P-complication: shock induced by procedure	0	0	1	1	0	0	0	1	0	1	0	1	1	1	1									
17	Number of stents used	1	0	1	1	1	1	0	1	1	1	1	1	1	1	0	0								
18	Stent Type	1	0	1	1	1	1	1	1	1	1	1	1	0	1	1	0	1							
19	Drugs used during procedure	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1						
20	Intravascular ultrasound use during procedure	1	0	1	1	0	1	0	1	1	1	0	0	0	1	1	1	1	1	1					
21	Use of intra-aortic balloon pump	1	0	1	1	0	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1				
22	Arterial access	1	1	1	1	1	1	1	1	1	1	1	0	0	0	0	0	1	1	1	1	1			
23	30-day mortality	1	0	1	1	0	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	1		
24	1-year mortality	1	1	1	1	1	0	1	1	1	1	1	1	0	0	1	1	1	1	0	1	1	0	1	

0: not related, 1: related, P-complication: procedural complication.

4.4 Results

Across 89 (78.1%) hospitals in England and Wales, a total of 10,410 patients received PCI to a left main stem from 2005 to 2010. Of these 5,065 (48.7%) had PCI to UPLMS met all eligibility criteria (Figure 4.1). There were 784 (15.5%) patients with STEMI, 2,381 (47.0%) with NSTEACS and 1,900 (37.5%) with CSA (Figure 4.2).

Figure 4.2: Frequency of patients with UPLMS who received PCI by clinical presentation.



4.4.1 Data completeness

A total of 103 variables were used in this analysis, 13 (12.6%) variables were 100% complete. These variables were ‘clinical presentation type’, ‘indication for intervention’, ‘pre-procedure cardiogenic shock’, ‘previous CABG’, ‘number of grafts present pre-PCI’, ‘number of grafts patent pre-PCI’, ‘date of operation’, ‘number of vessels attempted not Epicardial’, ‘7-day mortality’ ‘30-day mortality’, ‘180-day mortality’, ‘1-year mortality’ and ‘predicted MACCE NQWIP risks’.

Conversely, the remaining 90 variables had missing information that ranged between 0.02% and 96.84%. The one with the least missing values was ‘number of lesions attempted’ (0.02%) followed by ‘age at procedure’ (0.04%). The highest missingness was in ‘date of electrocardiography triggering (primary PCI)’ (96.84%). In total, 31 (30.1%) variables had less than 10% missing values, 50 (48.5%) had missing values from 10 to 50%, five (4.9%) had missing values from more than 50 to 90% and four (3.9%) had missing values of more than 90%. The variable with the greatest missingness was ‘date of electrocardiography triggering’, (96.84%), ‘patient location at time of STEMI onset (94.39%), ‘creatinine level’ (95.76%) and ‘third operator status’ (94.47%).

The mean (SD) level of values missing was 19.05% (23.98%) and the median percentage of missing values was 11.96%.The frequency and percentages of values missing in the variables of UPLMS cohort from the 2010 BCIS data are shown in Table 4.5.

Table 4.5: Recoded variables and summary of missing data in the variables of UPLMS cohort from the 2010 BCIS data.

Variable Name	Missing Frequency	Missing %
Age At Procedure	3	0.06
Sex	55	1.09
Ethnic Group	1,760	34.75
Patient Status	345	6.81
Clinical presentation type	0	0.00
Indication for Intervention	0	0.00
Procedure Urgency	4	0.08
Cardiogenic Shock Pre-PCI	0	0.00
Angina Status Pre-Surgery	1,815	35.83
Dyspnoea Status Pre-PCI (Stable Only)	301	15.84
Date Symptom Onset PCI (ACS Only)	874	27.61
Date Arrival At Hospital (ACS Only)	945	29.86
Admission Route (ACS Only)	355	11.22
Presenting electrocardiography (ACS Only)	632	19.97
Recent Lysis (ACS Only)	408	12.89
Cardiac Enzymes/Markers Raised (ACS Only)	945	29.86
Previous acute myocardial infarction	688	13.58
Previous coronary artery bypass graft (CABG)	0	0.00
Previous percutaneous coronary intervention (PCI)	71	1.40
Diabetes	263	5.19
Height	2,327	45.94
Weight	2,058	40.63
Left Ventricular Ejection Fraction Category	1,798	35.50
Left Ventricular Ejection Fraction	3,859	76.19
Number of Grafts Present Pre-PCI, CABG Only	0	0.00
Number of Grafts Patent Pre- PCI, CABG Only	0	0.00
Left Main Stem Stenosis Pre-PCI	548	10.82
Left anterior descending Proximal Stenosis Pre-PCI	823	16.25
Left anterior descending Other Stenosis Pre-PCI	949	18.74
Right coronary artery Stenosis Pre-PCI	954	18.84
Circumflex coronary artery Stenosis Pre-PCI	882	17.41
Flow In infarct related artery Pre-PCI (ACS Only)	3,257	64.30
Pseudonymised First Operator Status	165	3.26
Primary Operator	202	3.99
Second Operator Status	1,722	34.00
Third Operator Status	4,785	94.47

Red (no missing data), Green (less than 10% missing data), Blue (More than 90% missing data)

(Continued) Table 4.5: Recoded variables and summary of missing data in the variables of UPLMS cohort from the 2010 BCIS data.

Variable Name	Missing Frequency	Missing %
Date of Operation	0	0.00
Vessels Attempted	30	0.59
Number of vessels attempted not Epicardial	0	0.00
Number Of Lesions Attempted	1	0.02
Number Of Chronic Occlusions Attempted	306	6.04
Number Restenosis Attempted	290	5.73
Number Instant Stenosis Attempted	793	15.66
Number Stents Used	22	0.43
Number Drug-Eluting Stents Used	173	3.42
Type of stent used	178	3.51
Drugs Eluted By Stents	558	11.02
Drugs Used During Procedure	298	5.88
Intravascular ultrasound use during procedure	676	13.35
pressure wire use during procedure	676	13.35
Use of intra-aortic balloon pump	322	6.36
Left Main Stem Stenosis Post-PCI	606	11.96
Left anterior descending Proximal Stenosis Post-PCI	915	18.07
Left anterior descending Other Stenosis Post-PCI	1,046	20.65
Right coronary artery Stenosis PCI	1,076	21.24
Circumflex coronary artery Stenosis PCI	970	19.15
Number Lesions Successful	119	2.35
Number Coronary Grafts Patent PostOp	1,993	39.35
Flow In infarct related artery PostOp (ACS only)	1,378	43.54
Device Failure	687	13.56
PCI Hospital Outcome: No Complications	777	15.34
PCI Hospital Outcome: AMI or CVA	711	14.04
PCI Hospital Outcome: Renal disease	742	14.65
PCI Hospital Outcome: MACCEs	292	5.77
PCI Hospital Outcome: Revascularisation	292	5.77
Enzymes Post-PCI	3,863	76.27
Status At Discharge	156	3.08
Discharge Date	435	8.59
Cholesterol	3,833	75.68
Smoking Status	769	15.18

Red (no missing data), Green (less than 10% missing data), Blue (More than 90% missing data)

(Continued) Table 4.5: Recoded variables and summary of missing data in the variables of UPLMS cohort from the 2010 BCIS data.

Variable Name	Missing Frequency	Missing %
Family History Of coronary artery disease	996	19.66
Date of 1st Balloon Inflation PCI (ACS) Only)	1,448	45.75
History Of Renal Disease	396	7.82
Ventilated Pre-PCI	731	14.43
Q Wave On electrocardiography	983	19.41
Electrocardiography Ischaemia	817	16.13
Drug Therapy Pre-PCI	250	4.94
Follow On AdHoc Procedure	286	5.65
Why No IIb/IIIA During Procedure	1,412	27.88
Indication For Stent	579	11.43
Surgical Cover	751	14.83
Left Main Stem Protected	0	0.00
Date of electrocardiography Triggering (primary PCI)	613	96.84
Patient Location at Time of STEMI Onset (STEMI)	740	94.39
Creatinine	4,850	95.76
Training Procedure	474	9.36
Research Procedure	513	10.13
Arterial Access	85	1.68
Largest Balloon/Stent Used	819	16.17
Longest Stented/Treated Segment	811	16.01
Procedural Complication	512	10.11
Patient Status During Transfer To Theatre	1,310	25.86
Call For Help Date	4,194	82.80
Pseudonymised Hospital Code	5	0.10
Life Status	300	5.92
Date Of Death Or Census Date	300	5.92
Days between operation & census	300	5.92
7-day mortality	0	0.00
30-day mortality	0	0.00
180-day mortality	0	0.00
1-year mortality	0	0.00
Index of Multiple Deprivation Score	2,029	40.06
Predicted MACCE NQWIP Risks	0	0.00

Red (no missing data), Green (less than 10% missing data), Blue (More than 90% missing data)

4.4.2 Baseline demographic characteristics

The mean (SD) age of the UPLMS who received PCI in England and Wales was 70.2 (12.3) years; which was 67.3 (13.7) years for STEMI patients, 72.2 (12.1) years for NSTEACS and 68.9 (11.3) years for those with CSA (P <0.001). There were 3,483 (69.5%) males and 1,527 (30.5%) females. In all three groups, there was a preponderance of male gender (STEMI: 568 (72.8%), NSTEACS: 1,368 (87.9%) and CSA: 1,036 (86.2%) (P <0.001)), and Caucasian ethnicity (STEMI: 484 (88.5%), NSTEACS: 1,565 (66.3%) and 1,350 (72.2%) (P =0.770)).

Private patients were more frequent in CSA patients, whereas NHS patients were the majority in all three groups; NHS (STEMI: 712 (99.0%), NSTEACS: 2,191 (98.5%) and CSA: 1,611 (90.8%)) and private (STEMI: 7 (1.0%), NSTEACS: 32 (1.5%) and CSA: 163 (9.2%)) (P <0.001). Most of the STEMI patients were admitted directly to the cardiac centre or hospital, 448 (60.0%). Then again, 1,067 (51.7%) NSTEACS patients were treated after being transferred from another hospital (P <0.001). The overall mean (SD) of index of multiple deprivation score was 21.4 (13.9). Table 4.6 shows the distribution of baseline demographic characteristics of patients with UPLMS disease who received PCI, by clinical presentation.

Table 4.6: Baseline demographic characteristics of patients with UPLMS disease who received PCI, by clinical presentation.

Variable		CSA n=1900	STEMI n=784	NSTEACS n=2381	P value *
Mean (SD) age, years		68.9 (11.3)	67.3 (13.7)	72.2 (12.1)	<0.001
Age	**Less than 65 years (%)**	676/1,900 (35.6)	331/782 (42.3)	626/2,380 (26.3)	<0.001
	65 - 80 years (%)	890/1,900 (46.8)	294/782 (37.6)	1,014/2,380 (42.6)	
	More than 80 years (%)	334/1,900 (17.6)	157/782 (20.1)	740/2,380 (31.1)	
Gender	**Female (%)**	519/1,869 (27.8)	212/780 (27.2)	796/2,361 (33.7)	<0.001
	Male (%)	1,350/1,869 (72.2)	568/780 (72.8)	1,565/2,361 (66.3)	
Ethnic groups	**Caucasian (%)**	1,036/1,202 (86.2)	484/547 (88.5)	1,368/1,556 (87.9)	0.770
	Black (%)	11/1,202 (0.9)	4/547 (0.7)	9/1,556 (0.6)	
	Asian (%)	66/1,202 (5.5)	28/547 (5.1)	82/1,556 (5.3)	
	Other (%)	89/1,202 (7.4)	31/547 (5.7)	97/1,556 (6.2)	
Patient type	**NHS hospital or centre (%)**	1,611/1774 (90.8)	713/720 (99.0)	2,191/2,223 (98.5)	<0.001
	Private hospital or centre (%)	163/1774 (9.2)	7/720 (1.0)	32/2,223 (1.5)	
Admission route (ACS only) (%)	**Direct to cardiac centre**	---	448/747 (60.0)	629/2,063 (30.5)	<0.001
	Inter-hospital transfer	---	231/747 (30.9)	1,067/2,063 (51.7)	
	Already in cardiac centre	---	68/747 (9.1)	367/2,063 (17.8)	
Index of multiple deprivation score, mean (SD)		20.1 (13.2)	23.9 (14.8)	21.8 (14.0)	<0.001

Proportions exclude missing data.
* P-value was calculated using Chi-square test for categorical variables and analysis of variance (ANOVA) for continues variables.

4.4.3 Clinical characteristics

Diabetes mellitus, a family history of coronary artery disease, previous PCI and previous acute myocardial infarction were less frequent in STEMI (all P <0.001). A history of chronic renal failure was more frequent in patients with NSTEACS (STEMI: 30 (4.4%), NSTEACS: 216 (9.8%) and CSA: 80 (4.5%) (P <0.001)). Current smokers were more common in STEMI patients (STEMI: 221 (34.0%), NSTEACS: 358 (17.8%) and CSA: 162 (9.9%) (P <0.001)).

In total, 323 (41.2%) STEMI and 222 (9.3%) NSTEACS presented with cardiogenic shock (P <0.001). The proportion of missing data for severe left ventricular systolic dysfunction was 35.5%, reflecting the lack of a left ventricular angiogram or urgent echocardiogram in the acute setting at the time when the procedural part of the database was completed.

Recent thrombolysis was more frequent in patients with STEMI (STEMI: 105 (14.3%) and NSTEACS: 123 (6.1%) (P <0.001)). Overall, the frequency of severe left ventricular systolic dysfunction, defined as a left ventricular ejection fraction less than 30%, was 584 (17.9%), and was present in 148 (44.3%) cases of STEMI. The distribution of the clinical characteristics of patients with UPLMS who received PCI stratified by clinical presentation can be seen in more detail in Table 4.7.

Table 4.7: Baseline clinical characteristics of patients with UPLMS disease who received PCI, by clinical presentation.

Variable		CSA n=1900	STEMI n=784	NSTEACS n=2381	P value *
Previous acute myocardial infarction (%)		482/1,637 (29.4)	130/694 (18.7)	823/2,046 (40.2)	<0.001
Previous percutaneous coronary intervention (%)		539/1,892 (28.5)	73/764 (9.6)	429/2,338 (18.4)	<0.001
Family history of coronary artery disease (%)		803/1,560 (51.5)	220/594 (37.1)	845/1,915 (44.1)	<0.001
Diabetes mellitus (%)		359/1,805 (19.9)	111/736 (15.1)	519/2,261 (23.0)	<0.001
History of renal disease (%)		80/1,774 (4.5)	30/690 (4.4)	216/2,205 (9.8)	<0.001
Smoking status	**Never smoked (%)**	622/1,637 (38.0)	231/650 (35.5)	670/2,009 (33.6)	<0.001
	Ex-smoker (%)	853/1,637 (52.1)	198/650 (30.5)	981/2,009 (48.8)	
	Current smoker (%)	162/1,637 (9.9)	221/650 (34.0)	358/2,009 (17.8)	
Recent thrombolysis (ACS only) (%)		---	105/733 (14.3)	123/2,024 (6.1)	<0.001
Cardiogenic shock (%)		---	323/784 (41.2)	222/2,381 (9.3)	<0.001
Severe left ventricular systolic dysfunction (%)		118/1,298 (9.1)	148/334 (44.3)	318/1,635 (19.5)	<0.001
Raised cardiac enzymes (%)		---	297/378 (78.6)	1,434/1,842 (77.9)	<0.001

Proportions exclude missing data.
* P-value was calculated using Chi-square test for categorical variables and analysis of variance (ANOVA) for continues variables.

4.4.4 Procedural characteristics

Tables 4.8 shows the distribution of baseline pre-procedural, procedural and post-procedural characteristics by strata of clinical presentation. Pre-procedural TIMI 3 was more common in NSTEACS patients (STEMI: 117 (17.6%) and NSTEACS: 451 (70.9%) (P <0.001)). Left main stem stenosis of more than or equal to 50% and the use of ventilation prior to PCI procedures were more frequent in STEMI (all P <0.001).

The femoral approach was more frequent than the radial (STEMI: 526 (68.5%) vs. 231 (30.1%), NSTEACS: 1,497 (63.7%) vs. 791 (33.7%) (P =0.057)), the former occurring more frequently in STEMI and NSTEACS complicated by cardiogenic shock (255 (80.7%) and 167 (75.6%), respectively). Multi-vessel PCI was frequent in each stratum (STEMI: 595 (76.2%), NSTEACS: 1,722 (72.6%) and CSA: 1,314 (69.8%) (P =0.003)).

Drug eluting stents were deployed in 450 (59.4%) STEMI, 1,644 (71.1%) NSTEACS and 1,414 (77.8%) CSA. When bare metal stents were used, they were deployed more frequently in STEMI (STEMI: 271 (35.8%), NSTEACS: 576 (24.9%), CSA: 249 (13.7%) (P <0.001). Of all stents, Taxus liberte were used most often, in 925 (18.3%) patients (STEMI: 82 (11.3%), NSTEACS: 447 (21.4%) and CSA: 396 (21.8%) (P <0.001). The second most common type of stent was Xience V in 464 (9.2%) patients.

An intravascular ultrasound (IVUS) was used more frequently in elective than emergency cases (STEMI: 97 (14.6%), NSTEACS: 617 (30.1%) and CSA: 602 (35.9%) (P <0.001)). Pressure wire assessment was performed in 4 (0.6%) of STEMI, 100 (4.9%) of NSTEACS and 202 (12.0%) of CSA (P <0.001). An intra-aortic balloon pump was inserted in 284 (39.1%) of STEMI and 371 (16.7%) of NSTEACS (P <0.001). Rotational atherectomy was undertaken in 3 (0.4%) STEMI, 160 (6.7%) NSTEACS and 115 (6.1%) CSA and the glycoprotein IIb IIIa inhibitor, Abciximab used in 456 (59.9%) STEMI, 660 (29.4%) NSTEACS and 415 (23.6%) CSA (both P <0.001).

Table 4.8: Baseline pre-procedural, procedural and post-procedural characteristics of patients with UPLMS disease who received PCI, by clinical presentation.

Variable		CSA n=1900	STEMI n=784	NSTEACS n=2381	P value *
Left main stem stenosis (%)	**0%**	209/1,674 (12.5)	71/729 (9.7)	211/2,114 (10.0)	<0.001
	1-49%	296/1,674 (17.7)	75/729 (10.3)	258/2,114 (12.2)	
	≥ 50%	1,169/1,674 (69.8)	583/729 (80.0)	1,645/2,114 (77.8)	
Flow in infarct related artery	**TIMI 0 (%)**	---	343/666 (51.5)	58/636 (9.1)	<0.001
	TIMI 1 (%)	---	89/666 (13.3)	40/636 (6.3)	
	TIMI 2 (%)	---	117/666 (17.6)	87/636 (13.7)	
	TIMI 3 (%)	---	117/666 (17.6)	451/636 (70.9)	
Drug therapy	**Aspirin (%)**	1,542/1,805 (85.4)	606/743 (81.6)	1,949 /2,267 (86.0)	0.012
	Thienopyridines (%)	1,484/1,805 (82.2)	561/743 (75.5)	1,946 /2,267 (85.8)	<0.001
Use of ventilation (%)		6/1,545 (0.4)	117/706 (16.6)	84/2,083 (4.0)	<0.001
Consultant as the primary operator (%)		1,460/1,827 (79.9)	661/751 (88.0)	1,831/2,285 (80.1)	<0.001
Vessels attempted (%)	**Left main stem only (%)**	569/1.883 (30.2)	186/781 (23.8)	649/2,371 (27.4)	0.003
	Multi-vessels (%)	1,314/1,883 (69.8)	595/781 (76.2)	1,722/2,371 (72.6)	
Number of lesions attempted (%)	**1 (%)**	696/1,899 (36.7)	267/784 (34.1)	791/2,381 (33.2)	0.070
	2 (%)	622/1,899 (32.7)	287/784 (36.6)	814/2,381 (34.2)	
	3 or more (%)	581/1,899 (30.6)	230/784 (29.3)	776/2,381 (32.6)	
Total number stents used	**0 (%)**	196/1,893 (10.4)	45/781 (5.8)	118/2,369 (5.0)	<0.001
	1 (%)	548/1,893 (28.9)	249/781 (31.9)	738/2,369 (31.1)	
	2 (%)	522/1,893 (27.6)	252/781 (32.2)	681/2,369 (28.8)	
	3 or more (%)	627/1,893 (33.1)	235/781 (30.1)	832/2,369 (35.1)	
Type of stents used (%)	**Bare metal stents**	249/1,663 (13.7)	271/721 (35.8)	576/2,220 (24.9)	<0.001
	Drug eluted stents	1,414/1,663 (77.8)	450/721 (59.4)	1,644/2,220 (71.1)	
Arterial access	**Femoral (%)**	1,243/1,864 (66.7)	526/768 (68.5)	1,497/2,348 (63.7)	0.057
	Radial (%)	580/1,864 (31.1)	231/768 (30.1)	791/2,348 (33.7)	
	Others (%)	41/1,864 (2.2)	11/768 (1.4)	60/2,348 (2.6)	

Proportions exclude missing data.

* P-value was calculated using Chi-square test for categorical variables and analysis of variance (ANOVA) for continues variables.

(Continued) Table 4.8: Baseline pre-procedural, procedural and post-procedural characteristics of patients with UPLMS disease who received PCI, by clinical presentation.

Variable		CSA n=1900	STEMI n=784	NSTEACS n=2381	P value *
Type of DES used	Taxus liberte (Boston Scientific) (%)	396/1,692 (21.8)	82/726 (11.3)	447 /2,089 (21.4)	<0.001
	Cypher (Cordis) (%)	159/1,692 (9.4)	45/726 (6.2)	169/2,089 (8.1)	0.048
	Endeavor (Medtronic) (%)	111/1,692 (6.6)	58/726 (8.0)	146/2,089 (7.0)	0.307
	Xience V (Abbott) (%)	171/1,692 (10.1)	79/726 (10.9)	214/2,089 (10.2)	0.627
	Promus (Boston Scientific) (%)	91/1,692 (5.4)	44/726 (6.1)	144/2,089 (6.9)	0.198
Largest balloon/stent used in millimetres, mean (SD)		3.9 (0.6)	3.7 (0.6)	3.9 (0.6)	<0.001
Longest stented/treated segment in millimetres, mean (SD)		25.7 (15.3)	25.9 (14.0)	26.1 (15.6)	0.734
Drugs used	None (%)	1273/1758 (72.4)	236/761 (31.0)	1361/2,248 (60.5)	<0.001
	Abciximab (%)	415/1758 (23.6)	456/761 (59.9)	660/2,248 (29.4)	
	Eptifibitide (%)	40/1758 (2.3)	31/761 (4.1)	63/2,248 (2.8)	
	Tirofiban (%)	30/1758 (1.7)	38/761 (5.0)	164/2,248 (7.3)	
Use of intravascular ultra sound (%)		602/1,679 (35.9)	97/663 (14.6)	617/2,047 (30.1)	<0.001
Use of intravascular pressure wire (%)		202/1,679 (12.0)	4/663 (0.6)	100/2,047 (4.9)	<0.001
Use of Intra-aortic balloon pump (%)		74/1,792 (4.1)	284/727 (39.1)	371/2,224 (16.7)	<0.001
Number of lesions successful	1 (%)	687/1,793 (38.3)	259/722 (35.9)	809/2,285 (35.4)	0.072
	2 (%)	579/1,793 (32.3)	270/722 (37.4)	792/2,285 (34.7)	
	3 or more (%)	527/1,793 (29.4)	193/722 (26.7)	684/2,285 (29.9)	
Left main stem stenosis (%)	0%	1,281/1,665 (76.9)	510/720 (70.9)	1,613/2,074 (77.8)	<0.001
	1-49%	298/1,665 (17.9)	158/720 (21.9)	385/2,074 (18.6)	
	≥ 50%	86/1,665 (5.2)	52/720 (7.2)	76/2,074 (3.6)	
Flow in infarct related artery	TIMI 0 (%)	8/567 (1.4)	46/680 (6.8)	23/1,107 (2.0)	<0.001
	TIMI 1 (%)	2/567 (0.4)	26/680 (3.8)	3/1,107 (0.3)	
	TIMI 2 (%)	7/567 (1.2)	72/680 (10.6)	22/1,107 (2.0)	
	TIMI 3 (%)	550/567 (97.0)	536/680 (78.8)	1,059/1,107 (95.7)	

Proportions exclude missing data.
* P-value was calculated using Chi-square test for categorical variables and analysis of variance (ANOVA) for continues variables.

4.4.5 Procedural complications and in-hospital outcomes

Direct current cardioversion, no flow/slow flow, ventilated patients and cardiogenic shock induced by procedure were more frequent in STEMI (all P <0.001). Table 4.9 illustrates the clinical outcomes of patients with UPLMS disease who received PCI stratified by clinical presentation. In-hospital outcomes were infrequent and comparable in all three strata. Table 4.10 demonstrates the in-hospital outcomes and mortality rates of patients with UPLMS disease who received PCI stratified by clinical presentation.

4.4.6 In-hospital MACCE

Crude in-hospital MACCE rates were highest in STEMI (STEMI: 193 (27.0%), NSTEACS: 147 (6.5%), CSA: 60 (3.4%) (P <0.001)). For acute cases with cardiogenic shock, in-hospital MACCE rates were significantly higher, occurring in 50.2% cases of STEMI and 21.7% NSTEACS compared with 10.8% and 5.0%, respectively, for patients without shock (P <0.001). Likewise, in ventilated patients, in-hospital MACCE occurred in 53.6% of STEMI and 24.7% of NSTEACS (P <0.001).

Using the corresponding published coefficients from the NWQIP risk model, see (section 4.3.6.3), the highest mean (SD) of the predicted in-hospital MACCE rate was in STEMI (STEMI: 39.2 (32.1), NSTEACS: 14.0 (19.2) and CSA: 4.1 (3.2) (P <0.001)). After adjustment using multivariate regression, the risk of in-hospital MACCE was eleven-fold higher for STEMI and two-fold higher for NSTEACS than for CSA (STEMI: aOR 10.91, 95% CI 7.81 to 15.24, NSTEACS: aOR 1.85, 95% CI 1.33 to 2.59).

4.4.7 Crude mortality and survival time

The median follow-up period of the cohort was 910 days (range: 1 day to 2,406 days). Overall there were 1,280 (25.3%) deaths over a total follow-up period of 4,052,783 patient years. The length of follow-up was not imbalanced (STEMI: 311 (39.7%) deaths over 388,339 patient years, NSTEACS: 696 (29.2%) deaths over 1,871,624 patient years and CSA: 273 (14.4%) deaths over 1,792,820 patient years).

Across the strata of clinical presentation, crude 30-day and 1-year mortality rates were: STEMI 28.3% and 37.6%, NSTEACS 8.9% and 19.5%, CSA 1.4% and 7.0%, respectively. Figure 4.3 shows the Kaplan–Meier curves for unadjusted survival time (from time of procedure to 6 years) to all-cause mortality in UPLMS patients who received PCI. After adjustment, acute cases remained at a significantly elevated risk of death (30-day mortality; STEMI: aOR 29.45, 95% CI 19.37 to 44.80, NSTEACS: aOR 6.45, 95% CI 4.27 to 9.76, 1-year mortality; STEMI: aOR 4.95, 95% CI 4.07 to 6.02, NSTEACS: aOR 2.07, 95% CI 1.76 to 2.43).

Mortality rates in patients with STEMI who had cardiogenic shock were higher than in STEMI patients without shock (30-days: 52.0% vs. 11.7%, 1-year: 61.1% vs. 20.9%). The Kaplan–Meier curves for unadjusted survival time (from time of procedure to 6 years) to all-cause mortality in UPLMS patients with and without cardiogenic shock who received PCI is shown in Figure 4.4. For STEMI and NSTEACS, the presence of cardiogenic shock was associated with significantly worse outcomes. In acute cases without cardiogenic shock, compared with the femoral approach, the radial approach was associated with lower crude rates of mortality – but only at 30-days (STEMI: 30-days: 14.8% vs. 6.2%, 1-year: 20.8% vs. 19.4%; NSTEACS: 30-days: 7.4% vs. 5.7%, 1-year 17.0% vs. 15.8%). Figure 4.5 shows the unadjusted 30-day and 1-year mortality of patients with UPLMS who received percutaneous coronary intervention stratified by arterial access and clinical presentation.

Table 4.9: Procedural complications of patients with UPLMS disease who received PCI, by clinical presentation.

Variable		CSA n=1900	STEMI n=784	NSTEACS n=2381	P value *
Haemorrhage	**Radial access (%)**	0/580 (0.0)	3/231 (1.3)	2/791 (0.3)	0.010
	Femoral access (%)	3/1,243 (0.2)	3/526 (0.6)	4/1,497 (0.3)	0.485
Side branch occlusion (%)		17/1,710 (1.0)	8/714 (1.1)	24/2,129 (1.1)	0.917
Coronary dissection (%)		106/1,710 (6.2)	50/714 (7.0)	125/2,129 (5.9)	0.553
Coronary perforation (%)		13/1,710 (0.8)	4/714 (0.6)	20/2,129 (0.9)	0.592
Direct current cardioversion (%)		6/1,710 (0.4)	24/714 (3.4)	15/2,129 (0.7)	<0.001
No flow/slow flow (%)		11/1,710 (0.6)	38/714 (5.3)	27/2,129 (1.3)	<0.001
Ventilated (%)		4/1,710 (0.2)	29/714 (4.1)	15/2,129 (0.7)	<0.001
Cardiogenic shock induced by procedure (%)		11/1,710 (0.6)	44/714 (6.2)	45/2,129 (2.1)	<0.001

Proportions exclude missing data.

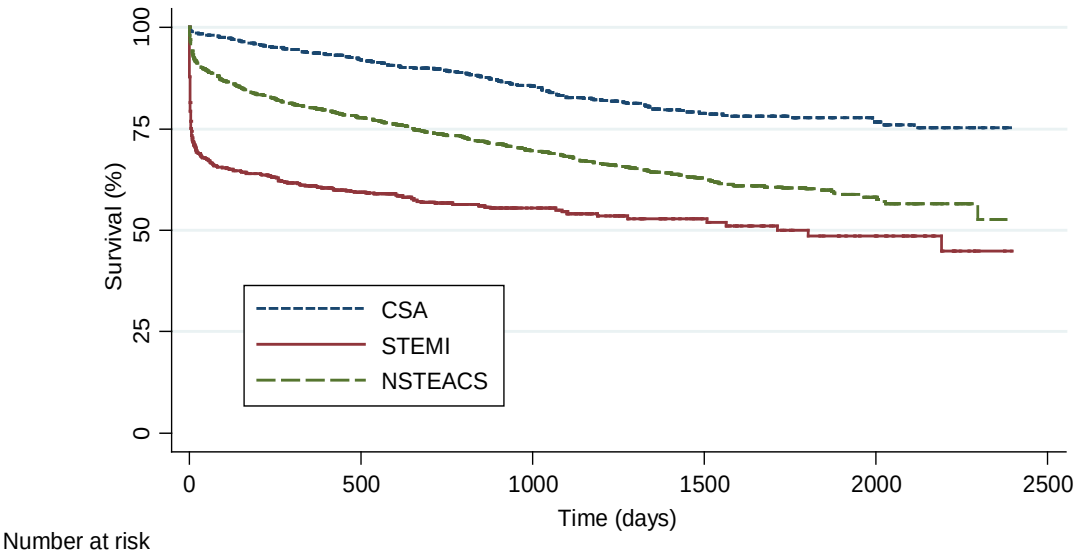
* P-value was calculated using Chi-square test for categorical variables and analysis of variance (ANOVA) for continues variables.

Table 4.10: In-hospital outcomes and mortality rates of patients with UPLMS disease who received PCI, by clinical presentation.

Variable		CSA n=1900	STEMI n=784	NSTEACS n=2381	P value *
Acute myocardial infraction (%)		35/1,767 (2.0)	7/525 (1.3)	22/2,062 (1.1)	0.067
Stroke (%)		0/1,767 (0.0)	1/525 (0.2)	1/2,062 (0.1)	
Renal failure/dialysis (%)		4/1,736 (0.2)	7/524 (1.3)	24/2,063 (1.2)	0.002
Blood transfusion	**Radial access (%)**	0/580 (0.0)	5/231 (2.2)	5/791 (0.6)	0.002
	Femoral access (%)	4/1,243 (0.3)	7/526 (1.3)	19/1,497 (1.3)	0.020
Gastro-intestinal bleeding	**Radial access (%)**	0/580 (0.0)	1/231 (0.4)	2/791 (0.3)	0.365
	Femoral access (%)	1/1,243 (0.1)	4/526 (0.8)	2/1,497 (0.1)	0.012
Revascularisation	**Percutaneous coronary intervention (%)**	5/1,807 (0.3)	4/789 (0.6)	10/2,240 (0.5)	0.555
	Coronary artery bypass graft (%)	5/1,807 (0.3)	4/789 (0.6)	12/2,240 (0.5)	
Mean (SD) predicted in-hospital MACCE rates **		4.1 (3.2)	39.2 (32.1)	14.0 (19.2)	<0.001
Unadjusted in-hospital mortality rate (%)		14/1,830 (0.8)	228/755 (30.2)	139/2,324 (6.0)	<0.001
Unadjusted 7-day mortality rate (%)		19/1,900 (1.0)	193/784 (24.6)	130/2,381 (5.5)	<0.001
Unadjusted 30-day mortality rate (%)		27/1,900 (1.4)	222/784 (28.3)	212/2,381 (8.9)	<0.001
Unadjusted 6-month mortality rate (%)		75/1,900 (4.0)	263/784 (33.6)	373/2,381 (15.7)	<0.001
Unadjusted 1-year mortality rate (%) **		122/1,736 (7.0)	257/683 (37.6)	414/2,127 (19.5)	<0.001

Proportions exclude missing data.
* P-value was calculated using Chi-square test for categorical variables and analysis of variance (ANOVA) for continues variables.
** Censored at 10/8/2011, therefore all PCI procedures performed after 10/8/2010 were not included in describing this rate.

Figure 4.3: Kaplan-Meier curves for unadjusted survival time to all-cause mortality in patients who received PCI to an UPLMS, stratified by STEMI, NSTEACS and CSA from time of procedure to 6.6 years.

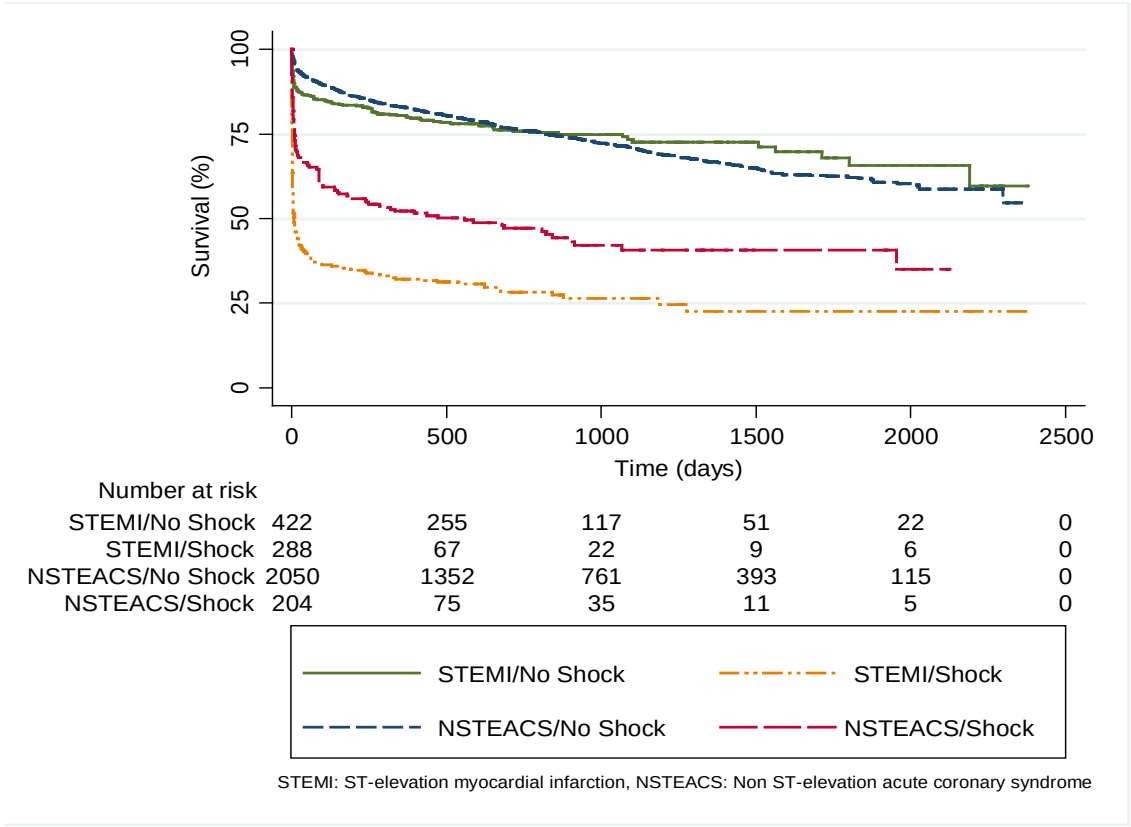


Number at risk						
CSA	1801	1367	799	395	138	0
STEMI	710	322	139	60	28	0
NSTEACS	2254	1427	796	404	120	0

CSA: Chronic stable angina, STEMI: ST-elevation myocardial infarction, NSTEACS: Non ST-elevation acute coronary syndrome

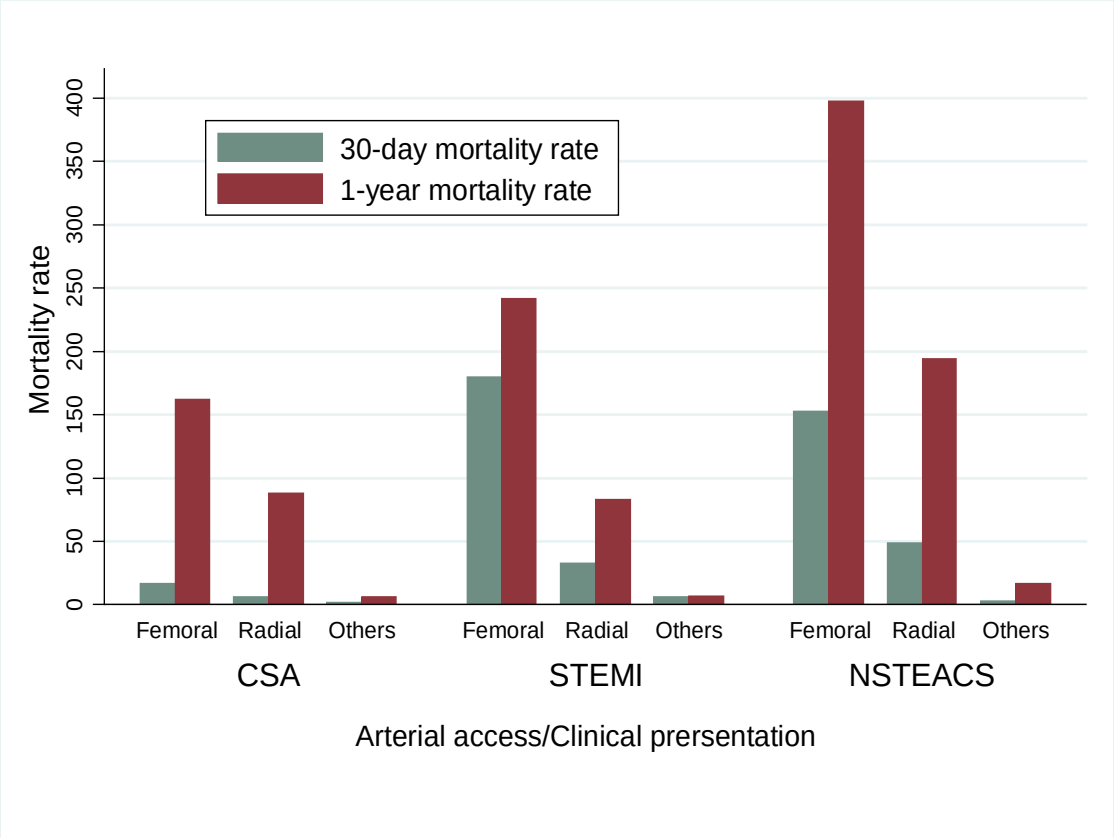
The survival distributions of both strata were significantly different (Mantle-Cox log rank test, P<0.001).

Figure 4.4: Kaplan-Meier curves for unadjusted survival time to all-cause mortality in patients with and without cardiogenic shock who received PCI to an UPLMS, stratified by STEMI and NSTEACS from time of procedure to 6.6 years.



The survival distributions of both strata were significantly different (Mantle-Cox log rank test, P<0.001).

Figure 4.5: unadjusted 30-day and 1-year mortality of patients with UPLMS disease who received percutaneous coronary intervention, stratified by arterial access and clinical presentation.



Proportions exclude missing data.

4.4.8 Clinical determinants of outcomes

Multivariate logistic regression modelling was used for this section of the analysis. Different covariates were used in the adjustment of the estimates in all the types of clinical presentation. More detail was given earlier in this chapter (section 4.3.6.4 and Table 4.2).

4.4.8.1 Clinical presentations as a determinant of outcomes

Compared with CSA, STEMI and NSTEACS were at higher risk of early MACCE (STEMI: aOR 9.2, 95% CI 7.0-12.1 and NSTEACS: aOR 3.4, 95% CI 2.6-4.4; P <0.001). Likewise, both STEMI and NSTEACS were again at higher risk of early mortality (STEMI: aOR 19.1, 95% CI 13.7-26.4 and NSTEACS: aOR 8.3, 95% CI 6.0-11.4; P <0.001). In the same way, risk of 1-year mortality in acute patients was higher compared with CSA, more than three folds higher for STEMI (OR 3.6, 95% CI 3.1 to 4.3) and more than two folds higher for NSTEACS (OR 2.5, 95% CI 2.2 to 2.8; P<0.001).

4.4.8.2 Clinical determinants of 30-day mortality

Figure 4.6 shows the significant clinical determinants (predictors) of 30-day mortality by strata of clinical presentation. In all three strata, each one year increase in a patient's age was significantly associated with an increased risk of death at 30 days (STEMI: aOR 1.03, 95% CI 1.01 to 1.04; NSTEACS: aOR 1.04, 95% CI 1.02 to 1.06 and CSA: aOR 1.07, 95% CI 1.01 to 1.13).

For STEMI and NSTEACS, predictors of 30-day mortality were age greater than 80 years (STEMI: aOR 2.24, 95% CI 1.25 to 4.01 and NSTEACS: aOR 3.26, 95% CI 1.95 to 5.46), pre-procedural cardiogenic shock (STEMI: aOR 10.11, 95% CI 6.44 to 15.88 and NSTEACS: aOR 6.13, 95% CI 4.10 to 9.16), poor Left ventricular ejection fraction (STEMI: aOR 6.02, 95% CI 1.52 to 23.79 and NSTEACS: aOR 3.21, 95% CI 1.72 to 6.00), pre-procedural ventilation (STEMI: aOR 3.00, 95% CI 1.72 to 5.24 and NSTEACS: aOR 4.62, 95% CI 2.45 to 7.08), peri-procedural shock (STEMI: aOR 3.18, 95% CI 1.43 to 5.59 and NSTEACS: aOR 7.11, 95% CI 3.28 to 15.43), the use of IVUS

(STEMI: aOR 0.27, 95% CI 0.11 to 0.67 and NSTEACS: aOR 0.56, 95% CI 0.34 to 0.92), and the radial approach over femoral (STEMI: aOR 0.27, 95% CI 0.22 to 0.62 and NSTEACS: aOR 0.66, 95% CI 0.45 to 0.97).

After adjustment, the mortality benefit of the radial approach was stronger in STEMI patients without cardiogenic shock, and not evident in NSTEACS without shock (STEMI: aOR 0.38, 95% CI 0.17 to 0.86 and NSTEACS: aOR 0.75, 95% CI 0.49 to 1.15). Other significant predictors of poorer 30-day mortality in NSTEACS patients were chronic renal failure and peri-procedural AMI. In contrast, significant predictors for CSA were age greater than 80 years and peri-procedural coronary dissection. There was no difference in risk of 30-day mortality by radial or femoral approach in patients with CSA.

4.4.8.3 Clinical determinants of 1-year mortality

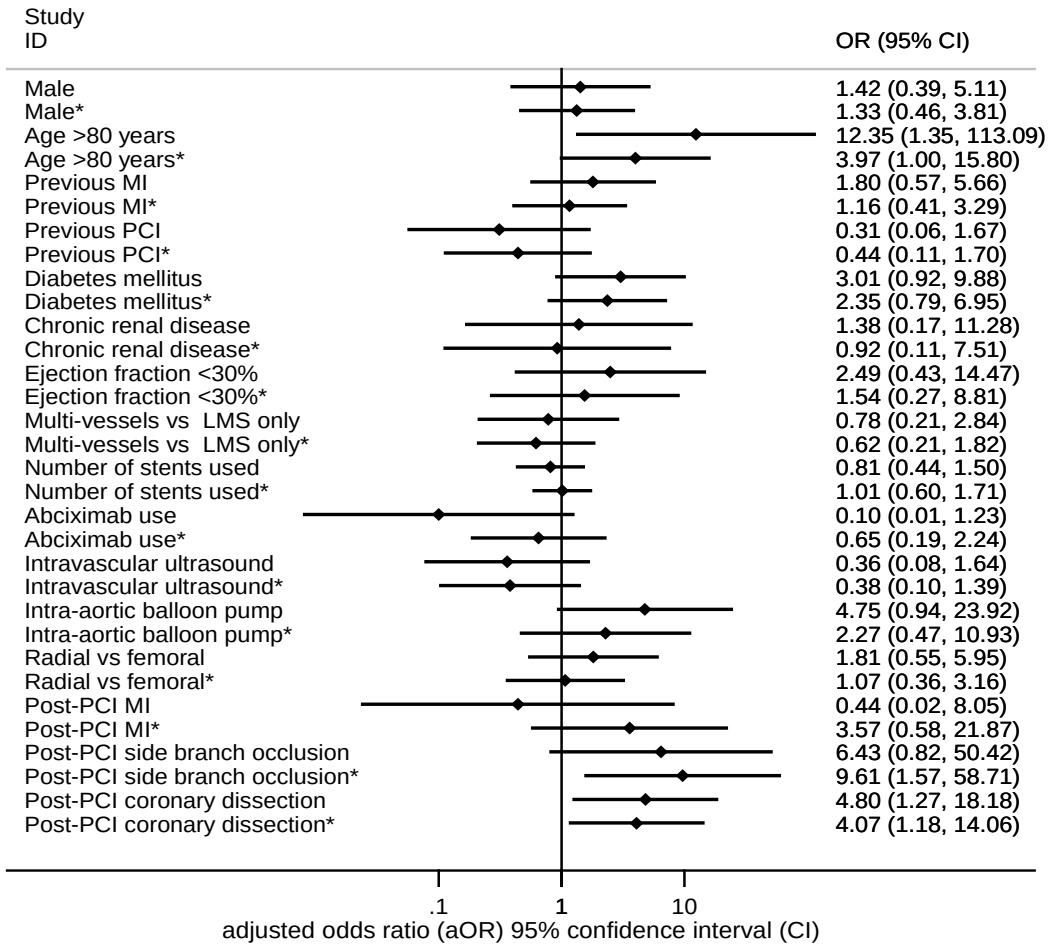
Figure 4.7 shows the significant clinical determinants of 1-year mortality by clinical presentation. After adjustment, for each one year increase in a patient's age there was a significant increase in the risk of death at one year (STEMI: aOR 1.02, 95% CI 1.01 to 1.04; NSTEACS: aOR 1.03, 95% CI 1.02 to 1.04 and CSA: aOR 1.02, 95% CI 1.01 to 1.03).

For STEMI, predictors of 1-year mortality were age greater than 80 years (aOR 2.09, 95% CI 1.27 to 3.43), pre-procedural cardiogenic shock (aOR 5.32, 95% CI 3.67 to 7.71), poor left ventricular ejection fraction (aOR 3.72, 95% CI 1.41 to 9.79), pre-procedural ventilation (aOR 1.97, 95% CI 1.14 to 3.40), peri-procedural coronary dissection (aOR 2.05, 95% CI 1.05 to 4.01), and peri-procedural shock (aOR 2.62, 95% CI 1.19 to 5.79).

For NSTEACS, the predictors were age greater than 80 years (aOR 2.26, 95% CI 1.67 to 3.05), pre-procedural cardiogenic shock (aOR 2.86, 95% CI 2.07 to 3.96), previous MI (aOR 1.37, 95% CI 1.10 to 1.70), chronic renal failure (aOR 1.94, 95% CI 1.40 to 2.68), poor left ventricular ejection fraction (aOR 1.59, 95% CI 1.11 to 2.27), pre-procedural ventilation (aOR 2.70, 95% CI 1.56 to 4.68), peri-procedural AMI (aOR 4.67, 95% CI 1.55 to 14.10), peri-procedural shock (aOR 3.32, 95% CI 1.62 to 6.80), and the use of Abiximab (aOR 0.55, 95% CI 0.43 to 0.71).

For CSA, the significant predictors were age greater than 80 years and the use of Abciximab. For STEMI, NSTEACS and CSA, the radial approach was not a statistically significant predictor of 1-year mortality. In emergency patients without cardiogenic shock, the radial over the femoral approach was not significantly associated with lower risk of mortality at 1-year (STEMI: aOR 0.98, 95% CI 0.60 to 1.61 and NSTEACS: aOR 1.11, 95% CI 0.88 to 1.41).

Figure 4.6: Adjusted risks for 30-day mortality for CSA (complete case & imputed).

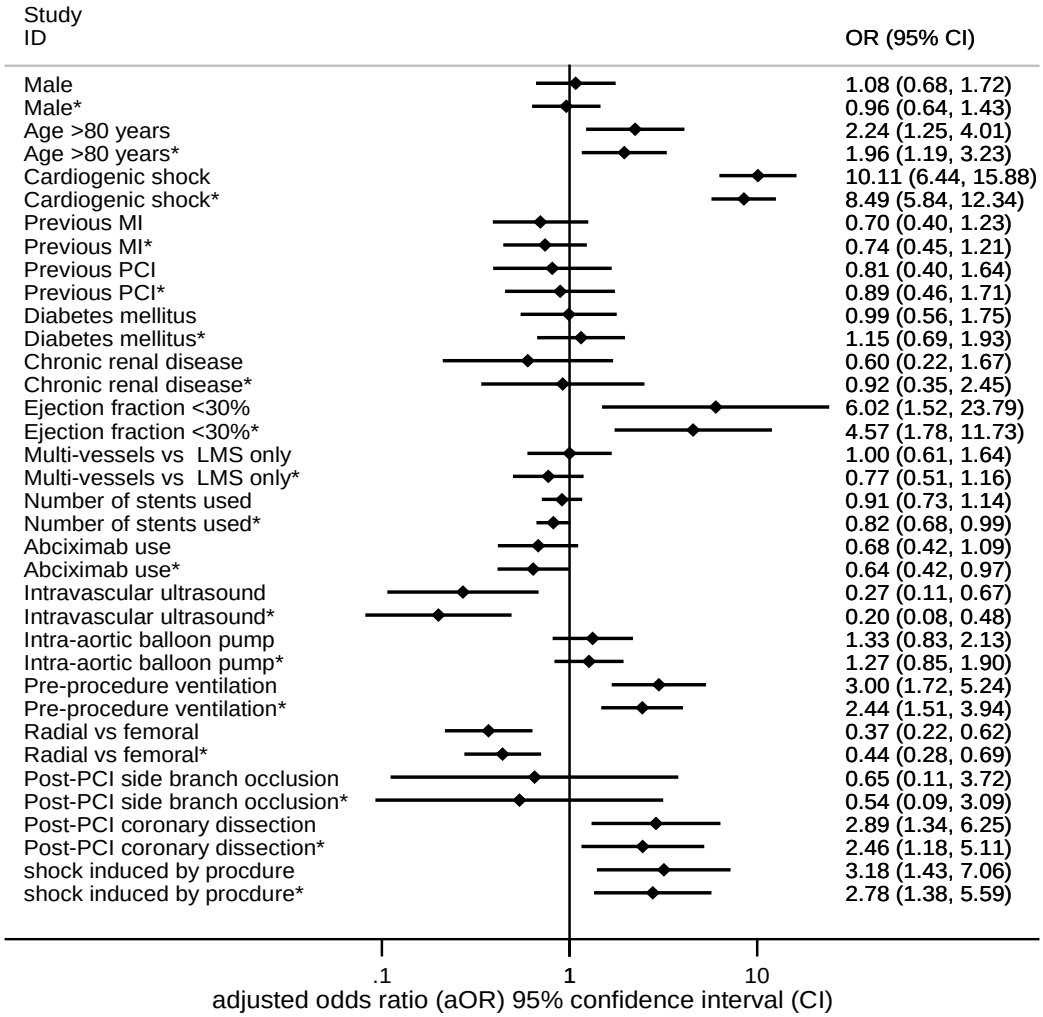


* Imputed data

MI: myocardial infarction, PCI: percutaneous coronary intervention, LMS: left main stem

OR and 95%CI were calculated using multivariate logistic regression for both complete case and pooled imputed data.

(Continued) Figure 4.6: Adjusted risks for 30-day mortality for STEMI (complete case & imputed).

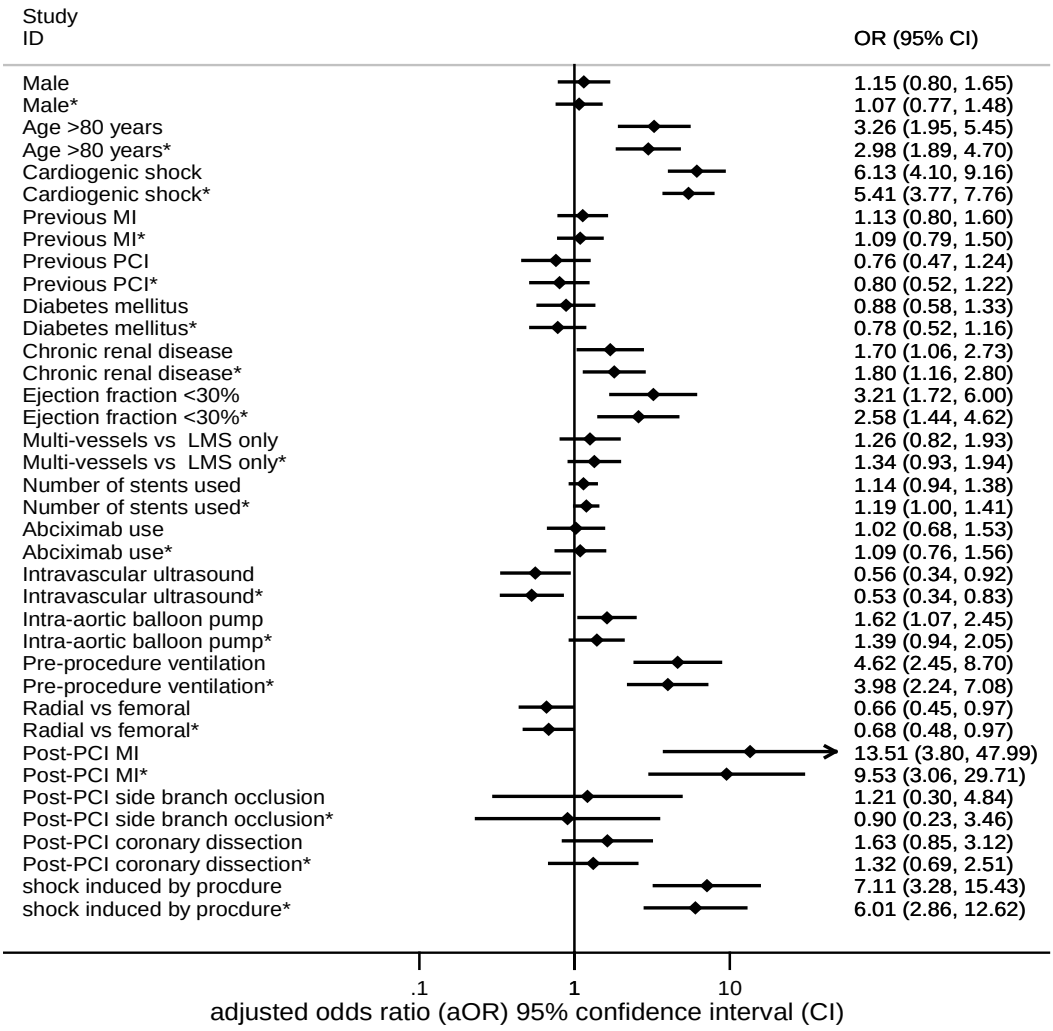


* Imputed data

MI: myocardial infarction, PCI: percutaneous coronary intervention, LMS: left main stem

OR and 95%CI were calculated using multivariate logistic regression for both complete case and pooled imputed data.

(Continued) Figure 4.6: Adjusted risks for 30-day mortality for NSTEACS (complete case & imputed).

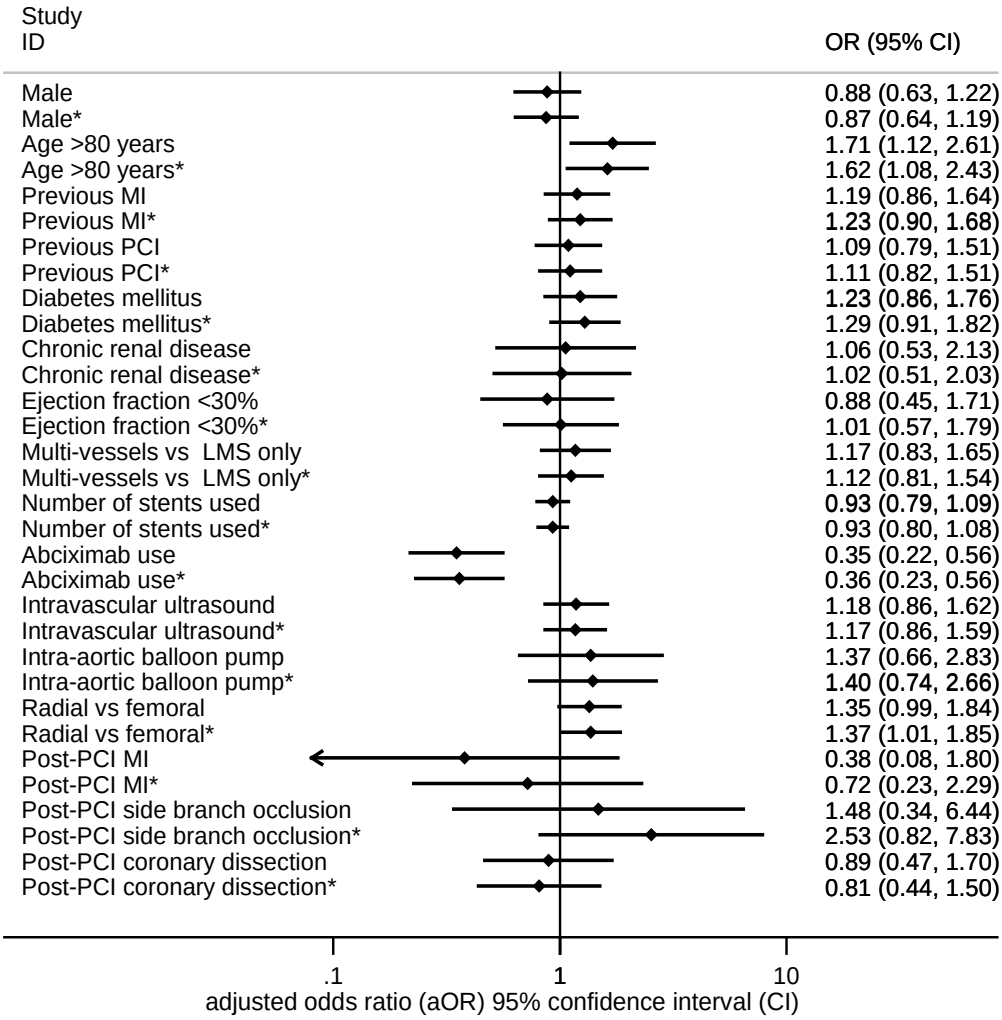


* Imputed data

MI: myocardial infarction, PCI: percutaneous coronary intervention, LMS: left main stem

OR and 95%CI were calculated using multivariate logistic regression for both complete case and pooled imputed data.

Figure 4.7: Adjusted risks for 1-year mortality rate for CSA (complete case & imputed).

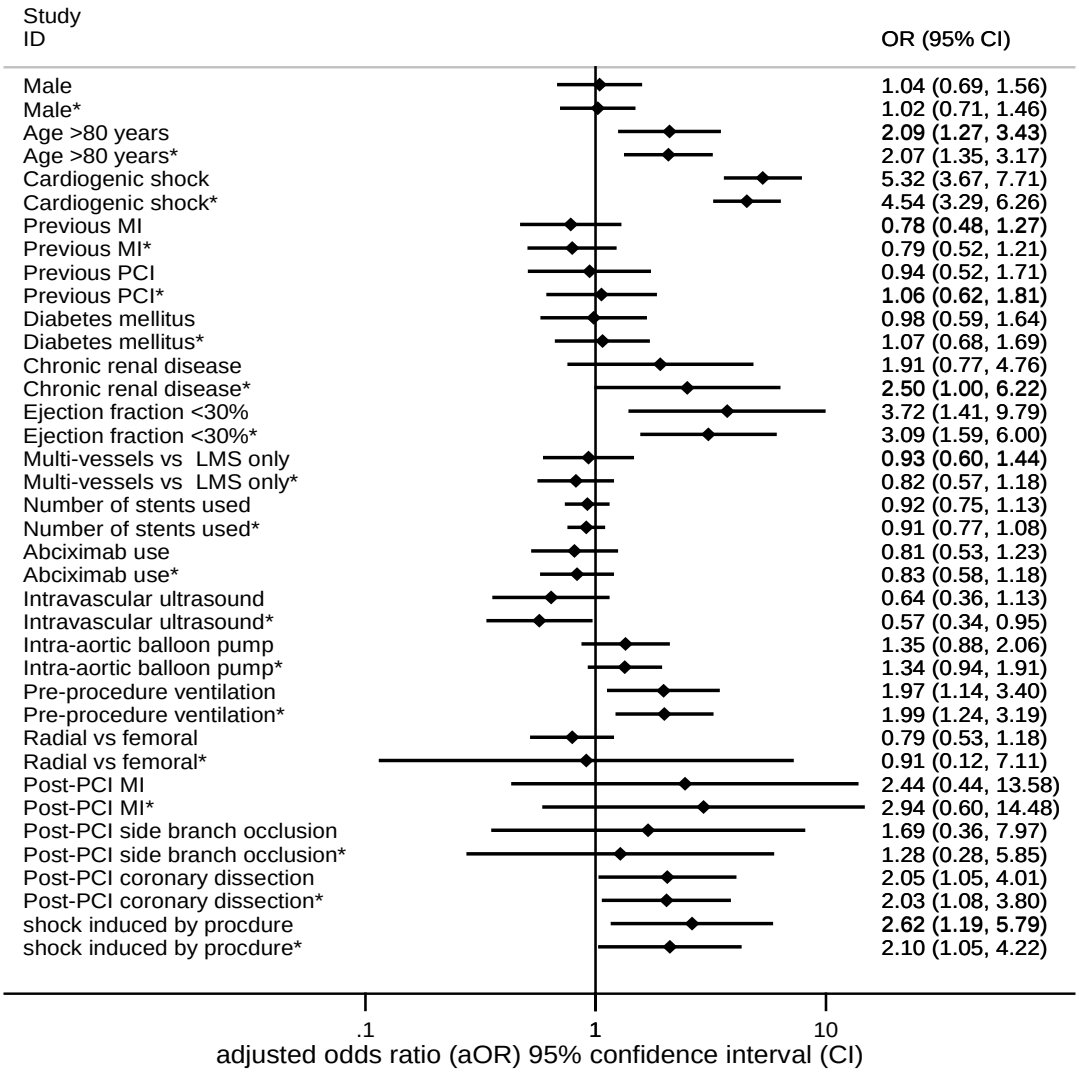


* Imputed data

MI: myocardial infarction, PCI: percutaneous coronary intervention, LMS: left main stem

OR and 95%CI were calculated using multivariate logistic regression for both complete case and pooled imputed data.

(Continued) Figure 4.7: Adjusted risks for 1-year mortality rate for STEMI (complete case & imputed).

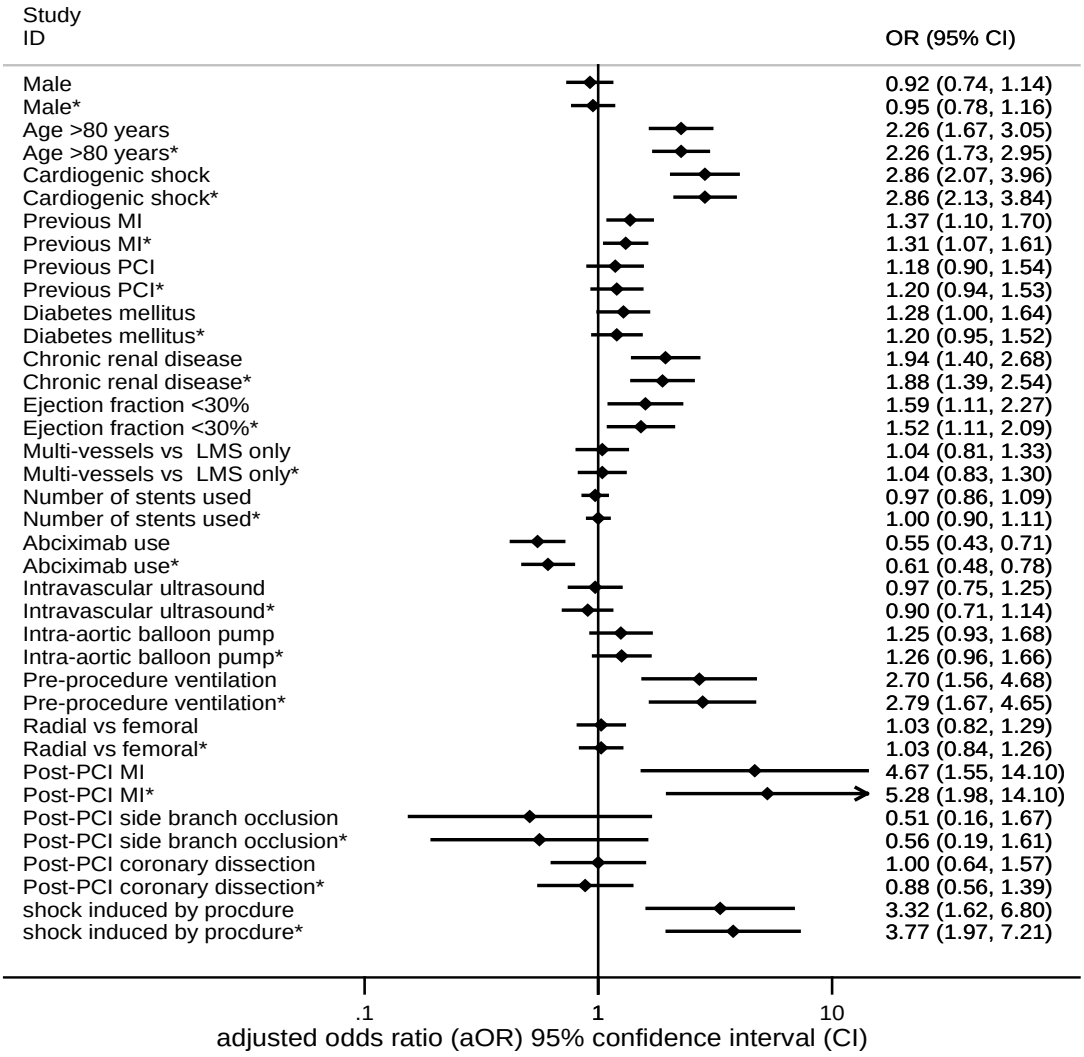


* Imputed data

MI: myocardial infarction, PCI: percutaneous coronary intervention, LMS: left main stem

OR and 95%CI were calculated using multivariate logistic regression for both complete case and pooled imputed data.

(Continued) Figure 4.7: Adjusted risks for 1-year mortality rate for NSTEACS (complete case & imputed).



* Imputed data

MI: myocardial infarction, PCI: percutaneous coronary intervention, LMS: left main stem

OR and 95%CI were calculated using multivariate logistic regression for both complete case and pooled imputed data.

4.4.9 Sensitivity analyses

4.4.9.1 Mixed effects modelling at hospital level

Table 4.11 demonstrates a summary of mixed effects models adjusted odds ratios of 1-year mortality for UPLMS patients who underwent PCI. The results of 30-day mortality were similar to those of 1-year mortality. Taking into account the hierarchical level of cardiac hospitals or centres ‘mixed effects modelling’, the same logistic regression models used in the adjusted analysis ‘fixed effects modelling’ were repeated. These models were described in detail in this chapter (section 4.3.6.4). In almost all mixed effect models for all types of clinical presentation, the likelihood ratio statistics were statistically significant (P <0.001) indicating that there was similarities between the patients within each hospital and significant difference between hospitals. With the evidence for hospital (level 2) effects, the use of mixed effects models did not substantially affect the patient (level 1) estimates.

The adjusted estimates of age of more than 80 years, for example, in the fixed and mixed effects models of 1-year mortality were; (STEMI: fixed estimates aOR 2.1, 95% CI 1.3 to 3.4, mixed estimates aOR 2.1, 95% CI 1.2 to 3.6, NSTEACS: fixed estimates aOR 2.3, 95% CI 1.7 to 3.1, mixed estimates aOR 2.3, 95% CI 1.7 to 3.1 and CSA: fixed estimates aOR 1.7, 95% CI 1.1 to 2.6, mixed estimates aOR 1.7, 95% CI 1.1 to 2.6). Another example was the impact of pre-procedural cardiogenic shock in acute UPLS patients on 1-year mortality (STEMI: fixed estimates aOR 5.3, 95% CI 3.7 to 7.7, mixed estimates aOR 6.2, 95% CI 4.1 to 9.5 and NSTEACS: fixed estimates aOR 2.9, 95% CI 2.1 to 4.0, mixed estimates aOR 2.9, 95% CI 2.1 to 4.1) (Figure 4.7 and Table 4.11).

Table 4.11: multi-level (mixed effects) modelling at hospital level adjusted odds ratios of 1-year mortality for UPLMS patients underwent PCI.

Variable		At hospital level								
		CSA			STEMI			NSTEACS		
		aOR	95% confidence interval	likelihood ratio P value	aOR	95% confidence interval	likelihood ratio P value	aOR	95% confidence interval	likelihood ratio P value
Male		0.9	0.6 - 1.3	0.015	1.0	0.9 – 1.5	<0.001	0.9	0.7 – 1.2	<0.001
Age more than 80 years		1.7	1.1 - 2.6	0.015	2.1	1.2 – 3.6	<0.001	2.3	1.7 – 3.1	<0.001
Cardiogenic shock		---	---	---	6.2	4.1 – 9.5	<0.001	2.9	2.1 – 4.1	<0.001
Diabetes mellitus		1.3	0.9 – 1.8	0.015	0.9	0.6 – 1.6	<0.001	1.3	1.0 – 1.7	<0.001
Chronic renal disease		1.8	0.5 – 2.2	0.015	2.5	0.9 – 6.8	<0.001	2.0	1.4 – 2.8	<0.001
Previous acute myocardial infarction		1.2	0.8 – 1.7	0.002	0.9	0.5 – 1.4	<0.001	1.4	1.1 – 1.7	<0.001
Previous PCI		1.1	0.8 – 1.5	0.015	0.9	0.5 - 1.6	<0.001	1.1	0.9 – 1.5	<0.001
Ejection fraction <30%		0.9	0.4 – 1.7	0.142	9.5	3.5 – 25.7	0.002	1.8	1.3 – 2.6	<0.001
Number of stents used		0.9	0.8 – 1.1	0.012	0.9	0.8 – 1.1	<0.001	1.0	0.9 – 1.1	<0.001
Abciximab use		0.3	0.2 – 0.6	0.005	0.9	0.6 – 1.4	<0.001	0.5	0.4 – 0.7	<0.001
Intravascular ultrasound		1.2	0.9 – 1.8	0.008	0.4	0.2 – 0.7	0.015	1.0	0.7 – 1.3	<0.001
Intra-aortic balloon pump		1.3	0.6 – 2.8	0.014	2.9	1.9 – 4.3	<0.001	1.6	1.2 – 2.1	<0.001
Pre-procedure ventilation		3.1	0.5 – 20.1	0.001	3.9	2.2 – 6.7	<0.001	5.1	3.0 – 8.9	<0.001
Radial vs femoral access		1.5	0.9 – 2.1	0.006	0.5	0.3 – 0.8	0.002	1.0	0.8 – 1.3	<0.001
Longest stented/treated segment		1.0	0.0 – 1.0	0.008	1.0	0.9 – 1.0	0.002	1.0	0.9 – 1.0	<0.001
Multi-vessel vs. single vessel		1.2	0.8 – 1.6	0.015	0.7	0.5 – 1.1	<0.001	1.0	0.8 – 1.3	<0.001
Post-procedure acute myocardial infarction		0.4	0.1 – 1.8	0.018	3.4	0.5 – 22.5	<0.001	5.0	1.6 – 15.9	<0.001
Procedural complication	**Side branch occlusion**	1.5	0.3 – 1.6	0.015	1.7	0.3 – 8.9	<0.001	0.5	0.2 – 1.8	<0.001
	Coronary dissection	0.8	0.4 – 1.6	0.015	1.9	0.9 – 3.8	<0.001	0.9	0.6 – 1.5	<0.001
	Shock	0.7	0.3 – 2.0	0.015	2.7	1.1 – 6.3	<0.001	3.5	1.6 – 7.4	<0.001

4.4.9.2 Multiple imputation

The distribution for most variables of the imputed datasets matched those of the complete case dataset very closely. Multivariate adjustment of the pooled imputed data for the missing data made only small changes to point estimates generated from the logistic regression models. Although, due to the increase in the available number of patients in the imputed dataset, multiple imputation improved the estimates precision.

After adjustment, the generated point estimates of regression from the pooled imputed data were statistically insignificant. There was no changes observed on the significance of the overall association result of the same models from the complete case data across the types of clinical presentation. The comparison between the complete case data and pooled multiply imputed data are shown in Figures 4.6 and 4.7 which shows the adjusted odds ratios for the clinical determinants of the 30-day and 1-year mortality for UPLMS patients PCI stratified by the type of clinical presentation.

For example at 30-day mortality, the adjusted odds ratios for the radial approach over femoral were (STEMI: aOR 0.3, 95% CI 0.2 to 0.6 in complete case data compared to aOR 0.4, 95% CI 0.3 to 0.7 in imputed data, NSTEACS: aOR 0.7, 95% CI 0.5 to 0.9 in complete case data compared to aOR 0.7, 95% CI 0.5 to 0.9 in imputed data and CSA: aOR 1.8, 95% CI 0.6 to 6.0 in complete case data compared to aOR 1.1, 95% CI 0.4 to 3.4 in imputed data). The adjusted ratios at 1-year mortality for chronic renal failure were (STEMI: aOR 1.9, 95% CI 0.8 to 4.8 in complete case data compared to aOR 2.5, 95% CI 1.0 to 6.2 in imputed data, NSTEACS: aOR 1.9, 95% CI 1.4 to 2.7 in complete case data compared to aOR 1.9, 95% CI 1.4 to 2.5 in imputed data and CSA: aOR 1.1, 95% CI 0.5 to 2.1 in complete case data compared to aOR 1.0, 95% CI 0.5 to 2.0 in imputed data) (Figures 4.6 and 4.7).

4.5 Discussion

4.5.1 Summary of key findings

- These national observational data from the BCIS registry showed that over half of patients treated with PCI to UPLMS presented acutely.
- Most of the procedural complications and in hospital outcomes were infrequent across the types of clinical presentation.
- Acute patients were having substantially higher risks of in-hospital MACCE as well as 30-day and 1-year mortality when compared with elective patients.
- Mortality rates at one year for CSA patients approached one in 10.
- For STEMI and NSTEACS patients, the significant predictors of worse early and late mortality were age greater than 80 years, pre-procedural cardiogenic shock, poor Left ventricular ejection fraction, pre-procedural ventilation and peri-procedural shock.
- The use of Abiximab was associated with lower mortality rate at one year for CSA and NSTEACS but not STEMI patients.
- For CSA patients, age greater than 80 years was a significant predictor of worse early and late mortality, while peri-procedural coronary dissection was only a predictor of worse early mortality.
- Cardiogenic shock was common in STEMI and was associated with a nine-fold increase in risk of mortality at 30 days and a five-fold increase in risk of mortality at one year.
- The radial approach to access was associated with improved early mortality in acute patients, but was not supported by lower mortality in the longer-term.
- Multiple imputation made slight improvement on the precision of the generated adjusted hazard ratios which were statistically insignificant as they did not change the overall association result of the same models from the complete case data.
- Even though there was evidence for hospital effects, the use of mixed effects models did not largely affect the adjusted estimates at patient’s level.

4.5.2 Findings in the context of literature

This analysis is the first whole country comparative outcomes study of patients with UPLMS who received PCI stratified by the types of clinical presentation. This study is more representative of UK patients with UPLMS since most of the reviewed population based studies were performed outside the UK [42, 47, 86, 96, 99, 101, 104, 106]. Non-representative studies are prone to selection bias very easily, caused by the expected variations between cardiac centres facilities and the experience of the interventionist [76, 117].

After consideration of case mix, patients who present with STEMI and NSTEACS in the context of UPLMS PCI have substantially higher risks of in-hospital MACCE as well as 30-day and 1-year mortality when compared with elective cases. Vakili et al. reported that mortality after primary PCI for acute patients was around five-fold higher than that after elective PCI [76]. Furthermore, over 40% of patients who presented with STEMI had evidence of cardiogenic shock and this was associated with a nine-fold increase in risk of 30-day mortality rate and a five-fold increase in risk of 1-year mortality rate. Despite this, rates of 30-day all-cause mortality in patients with STEMI and NSTEACS were lower than the suggested benchmark of 55% [34]. These findings are of particular clinical relevance at a time when international guidelines recommend primary angioplasty in patients with STEMI and as complete revascularisation as possible in those with established cardiogenic shock [76, 111]. The outcome data that we report in this observational study will be of value when considering the early and longer-term risk of outcomes after PCI for patients with UPLMS stenosis in an elective setting.

In terms of adjuvant technologies, this analysis found that the use of an IABP was high in both STEMI and NSTEMI. In the light of recent trial data suggesting limited or no outcome benefit of IABP in the context of cardiogenic shock [181], it will be interesting to see if the use of this device decreases in these subgroups over time. By contrast, the use of IVUS was lower than reported in other studies, but when used was associated with improved outcomes which is consistent with data previously published in the context of left main stem treated by PCI [182-184].

This study demonstrated that overall the radial approach to access was associated with better outcomes, but only at 30-day mortality rate and only in patients with STEMI and NSTEACS. The differences in bleeding rates in radial versus femoral were small. This finding may be an important observation, since it adds weight to the recently reported finding that the radial access route is safer than the femoral route in STEMI patients and suggests that this benefit extends to NSTEACS patients in the real world [32-34]. Radial access may, however, reflect a less sick population and/or more skilled operators. Benefit of radial access is no longer evident at 1-year, possibly due to factors other than the index intervention that are associated with longer-term outcomes. For example, mortality at 1-year is more likely to be influenced by non-cardiac factors than at 30-days.[185] Notably, the early mortality effect interacted significantly with the presence of cardiogenic shock (a much lower risk of 30-day mortality was evident in patients without cardiogenic shock). In this study, limited descriptive analysis on post procedure bleeding was presented. This was because detailed modelling analysis is beyond the remit of this analysis and is the subject of a separate study of the BCIS data which specifically addressed these interesting and complex issues [87].

Furthermore, this analysis identified a number of additional factors associated with outcomes in patients treated by PCI to UPLMS. In keeping with results from other cohort studies, STEMI and NSTEACS were significantly associated with higher in-hospital MACCEs and 30-day and 1-year mortality compared with stable presentations [48, 104]. For STEMI and NSTEACS, the significant predictors of 30-day mortality were cardiogenic shock, poor left ventricular ejection fraction, pre-procedural ventilation, age greater than 80 years and peri-procedural shock: all factors which have previously been reported [30, 42, 45, 48, 99]. For CSA, the significant predictors of early mortality (age greater than 80 years and peri-procedural coronary dissection) were superseded by age greater than 80 years which independently predicted 1-year mortality.

Similarly, chronic renal impairment and poor left ventricular ejection fraction were not significant predictors of 1-year mortality in elective cases; in this group increasing age remained a strong predictor. Notably, the absolute level of 1-year mortality in the CSA cohort was higher than expected from previously reported data on UPLMS PCI. There is no formal explanation available for this finding, but it is of

potential clinical relevance, and indeed requires closer scrutiny, when some cardiac interventionists seek to extend the envelope for UPLMS PCI to include some patients who are suitable for CABG surgery.

In keeping with results from other published studies [86, 96, 101], older age (more than 80 years) was associated with worse 30-day and 1-year mortality rates across the stable and acute patients with UPLMS. This finding, which was well-matched with other publications such as that by Parma *et al.* [48], showed that age of more than or equal to 75 years was associated with increased 30-day mortality (aOR 5.9, 95% CI 1.3 to 26.5). Other studies by De Luca *et al.* [45] and Onuma *et al.* [94], both demonstrated that age was significantly related to overall mortality and one year mortality, respectively. Similarly, Buszman *et al.* [99] presented significant association between age of more than 60 and mortality (aOR 2.5, 95% CI 1.0 to 5.9) and Lee *et al.* 2014 [95] showed similar association with 30-day mortality (aOR 4.5, 95% CI 1.2 to 16.3). Most of these studies were executed in a single cardiac centre and/or on a small number of UPLMS patients, demonstrating further advantage of this analysis.

In acute UPLMS patients who were treated with PCI, poor Left ventricular ejection fraction was found to be a significant determinant of increased mortality at 30 days and at one year. Many other studies shared similar findings to this study [86, 96, 98, 106]. Khattab *et al.* [104] and Buszman *et al.* [99] found significant relationship between severe poor left ventricular ejection fraction and worse mortality (aOR 3.3, 95% CI 1.0 to 11.1 and aOR 3.3, 95% CI 1.5 to 7.3, respectively). Being an acute patient, of its own accord, was a significant predictor of early and late mortality rates, a finding that correlated with the literature. Khattab *et al.* [104] concluded that being a patient with STEMI was significantly associated with increased mortality (aOR 6.4, 95% CI 1.8 to 21.9). Khattab's study related to a small number of patients; yet, was to some extent representative based on the study design.

Mortality rates summarised over the 6 years of our national study were lower than those reported by others. Parma *et al* described crude 30-day mortality rates for UPLMS PCI patients of 39.7% [48] and Brennan *et al* reported crude in-hospital mortality rates of 2.9% for CSA and 45.1% for emergent cases [42]. A recent meta-analysis of UPLMS primary PCI outcomes in patients with AMI estimated an average 30-day all-cause mortality rate of 55% for patients with cardiogenic shock, which supports our observed rate of 52% for patients with STEMI [34]. In addition, mortality rates at one year for CSA patients approached one in 10, which may have a bearing on

the selection of elective patients for UPLMS PCI who were also suitable for CABG surgery.

More discussion on the temporal trends over ten years for UPLMS patients after PCI in the UK is given in Chapter 5 (section 5.5). Broader discussions on the methodologies used, such as those relating to the importance of multi-level analysis as well as multiple imputation, are outlined in the discussion chapter (see Chapter 7) along with more detailed discussion on the overall strengths, limitations and implications of this thesis.

4.5.3 Conclusion

The study presented comprehensive findings in regard to the clinical determinants of the outcomes of patients with UPLMS in the UK who underwent PCI. The analysis of this study was divided into three main strata (STEMI, NSTEACS and CSA). In this national data from the BCIS registry, more than half of patients treated with PCI to the UPLMS presented acutely. For these patients, early and late outcomes were significantly worse than that of elective patients. Cardiogenic shock was common in STEMI and associated with a 1 in 2 risk of early mortality. The radial approach to access was associated with improved early outcomes in acute cases, but was not supported by lower mortality in the longer-term. Finally, 1-year mortality rates for CSA cases approached 1 in 10, which may have a bearing on the selection of elective cases for UPLMS PCI who are also suitable for CABG surgery.

Chapter 5 Mortality trends after PCI for UPLMS

5.1 Summary

The previous chapter (Chapter 4) described the clinical outcomes and the clinical determinants of early and late mortality according to clinical syndrome at presentation over a period of six years as well as the impact of cardiogenic shock and arterial access approach on the clinical outcomes. Subsequently, this chapter, using the updated 2014 BCIS registry, describes the changes over time in the clinical presentation and types of treatment offered by biennial years as well as the temporal trends of mortality among UK patients with UPLMS who underwent PCI over a period of 9.6 years between 2005 and 2014. A literature review about 'the clinical determinants and temporal trends of outcomes for PCI in UPLMS disease' was provided in Chapter 2 (section 2.4). This chapter is split into five sections covering: the background, rationale and aims (section 5.2), methodology including study design, population, stratification, follow-up as well as statistical and sensitivity analyses (section 5.3), results including completeness, descriptive statistics, multivariate modelling results and sensitivity results (section 5.4) followed by a discussion and conclusion (section 5.5).

5.2 Introduction

5.2.1 Background and rationale

With the improvements in stents technology and pharmacology as well as evolving practice and experience, PCI has become an alternative strategy of treatment for patients with UPLMS; mainly in those at high risk for surgery [44, 117, 176, 186]. In addition, the international diffusion of primary percutaneous coronary intervention for acute STEMI is likely to have contributed to the case load of '*de novo*' UPLMS PCI [117, 187].

Nevertheless, up-to-date details regarding the temporal trends in incidence, care and outcomes of UPLMS PCI across the full spectrum of acute and elective patients has been limited by small, regional and non-consecutive series of patients or inferred from randomised controlled trials (RCT) in highly select groups of patients [36-44].

A 12 year temporal study by Park *et al.* [43] concluded that the use of PCI for the management of UPLMS increased by 17%; while, repeat revascularisation, MACCE, all-cause mortality, the composite endpoint of mortality, myocardial infarction and stroke decreased significantly (all P <0.001). Another study by Naganuma *et al.* [39] investigated the temporal trend on 262 PCI UPLMS patients over four years. Naganuma and his colleagues demonstrated a trend toward higher target lesion revascularisation with no significant differences in the trends of MACCE, all-cause mortality, and the composite endpoint of all-cause mortality, myocardial infarction and stroke.

Notably, there is a shortage of whole country studies of the temporal trends in UPLMS PCI and the associated procedural and longer-term outcomes [39, 43]. Therefore, further investigation into such an issue using contemporary multi-centre population based data such as BCIS data is essential. Knowing what the trends of mortality are after PCI in patients with UPLMS in the UK helps contribute to the improvement of care provided to those patients.

5.2.2 Aims

The overall rationale and aims of this thesis were mentioned in Chapter 2 (section 2.6). The primary aim of this chapter was to perform a population-based comparative investigation of all UPLMS patients who received PCI in the UK over a period of 9.6 years (from January 1, 2005 to March 31, 201:

1. To describe the overall completeness of 2014 updated BCIS data for all patients with UPLMS and the changes in missing data by biennial years.
2. To describe demographic and clinical characteristics of patients by biennial years, including:
    a. Trends in baseline risk profile (age over 80 years, severe left ventricular systolic dysfunction and cardiogenic shock).
    b. To describe the changes in clinical presentation characteristics.
3. To describe the changes in procedural characteristics and types of treatment offered to patients by biennial years, including:
    a. Trends in techniques, medications, types of equipment and types of stents.
    b. Trends in the use of radial approach versus femoral approach across all clinical presentation types.
4. To quantify temporal trends in procedural complications and in-hospital outcomes including MACCE, by biennial years.
5. To quantify temporal trends in 30-day and 1-year mortality rates in the cohort as a whole, and across all clinical presentation types, by biennial years.

5.3 Methodology

5.3.1 Study setting and design

The study design was a prospective population based linked cohort study using data of patients with UPLMS who received PCI. The data were collected from 113 interventional cardiology centres and hospitals in England, Scotland, Northern Ireland

and Wales. All were part of 117 cardiology centres and hospitals registered with the BCIS audit program between 2005 and 2014 (based on BCIS Audit Returns, Adult Interventional Procedures, January 2013 to December 2013) [54]**.**

5.3.2 Patients, procedures and treatments (study population)

The sampling frame was based on the updated 2014 BCIS dataset and included all patients from all countries in the UK (England, Scotland, Northern Ireland and Wales). The total number of patients who attended for PCI in all countries in the UK between the 1st of January, 2005 and the 31st of March, 2014 was 699,248 (2014 BCIS data). The inclusion and exclusion criteria (based on the Delphi group clinical agreement) for the derivation of the analytical cohort were:

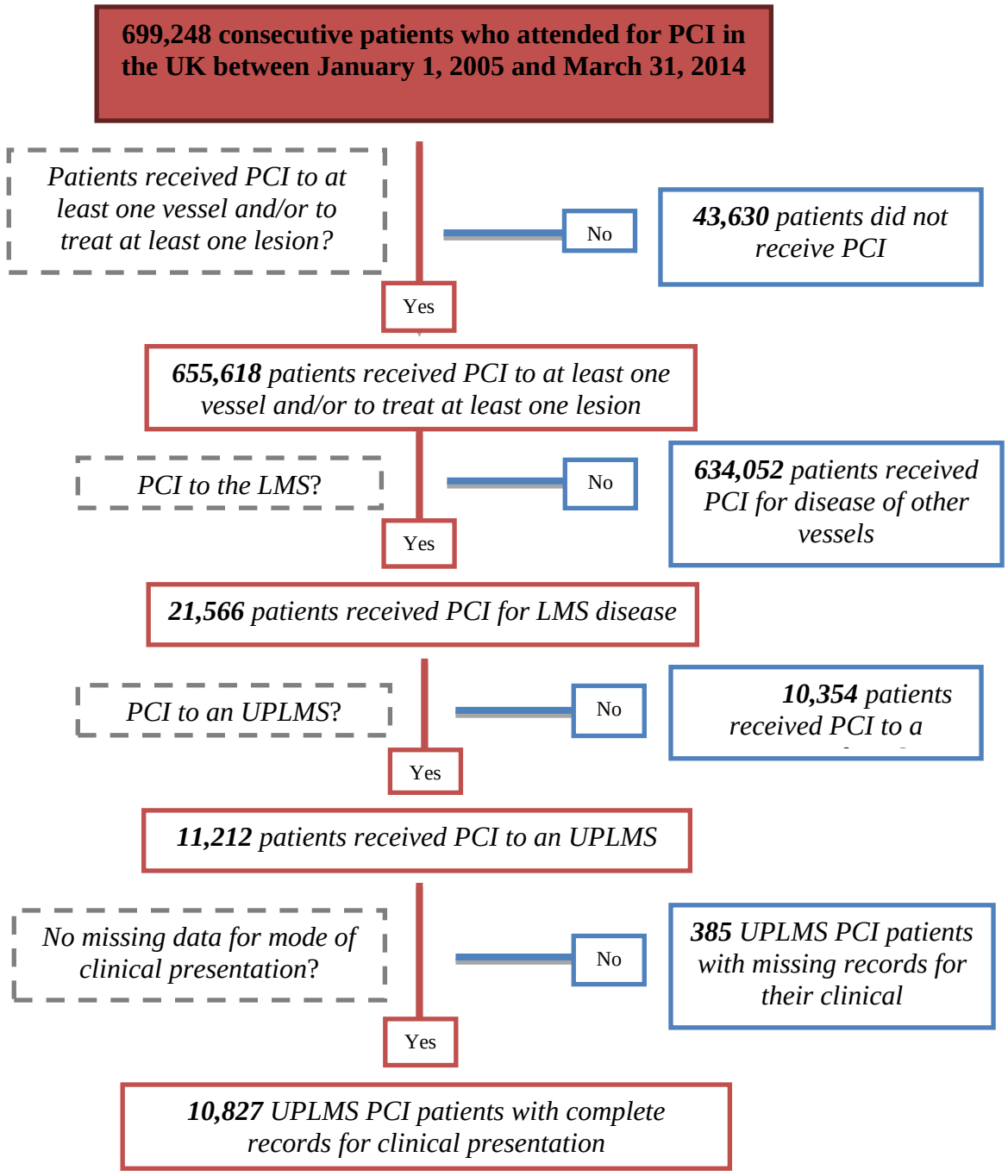
- Patients aged less than 18 years were excluded.
- Patients with multiple admissions, the earliest intervention record was used.
- Patients who had received PCI to a diseased UPLMS over the 9.6 year period (from 2005 to 2014).
- Patients who had no vessels attempted or missing information about that were excluded. In the same way, those who had no lesions attempted or missing information about that were also excluded. The remaining number of PCI patients was 655,618.
- Then, 21,566 patients were included as they were drawn from those who had the left main stem as the treated vessel. At the same time, 634,052 patients who received PCI for disease of other vessels were excluded.
- Patients with history of previous CABG, missing information on that or had any number of grafts present pre-procedure were excluded. The remaining number of patients was 11,212.
- Finally, the same definition of patients with UPLMS from Chapter 4 (section 4.3.2) was used [20]. Therefore, 10,827 patients with UPLMS who received PCI were included. A detailed flow chart of the selected cohort population is shown in Figure 5.1.

5.3.3 Stratification of cohort population

According to the year of PCI procedure for patients with UPLMS, the analysis of this chapter was stratified into five biennial calendar periods (2005-06, 2007-08, 2009-10, 2011-12 and 2013-14). This stratification was selected and agreed by the Delphi group in order to compare and understand the difference between these five biennial years.

Merging every two years into one biennial period increases patient numbers as a group and give more power to the comparison. In addition, the five biennial year groups were easier to present and compare. However; data about all procedures performed in the year 2014 was not complete (up to 31st of March). Similar to Chapter 4 (section 4.3.3 and Table 4.1), three strata according to the mode of clinical presentation were defined (STEMI, NSTEACS and CSA).

Figure 5.1: Flow chart of the selected cohort population.



5.3.4 Definitions

All the key clinical definitions were mentioned in Chapter 4 (section 4.3.4). In this analysis, two variables were defined for better exploration of the data, these variables were:

- Cardiac centres participating: simply the frequency of the registered cardiac centres or hospitals in the BCIS registry, stratified by biennial years.
- Standardised number of PCI per centre: in which the standardisation was performed by dividing the total number of patients with UPLMS who underwent PCI in each biennial year by the number of cardiac centres in that biennial year.

5.3.5 Follow up and mortality

More details concerning patients follow up and mortality can be found in Chapter 1 (section 1.4.3 and Figure 1.3). In the 2014 versions of the BCIS database received, because of the date of linkage for censored data (31st July 2014), data rgarding mortality at 1-year were not available for 119 (1.1%) patients. As a consequence, patients with a follow-up period of less than 12 months were excluded from the analysis regarding the trends of 1-year mortality rate, still those patients were included in all other parts of the analysis.

5.3.6 Statistical analysis

5.3.6.1 Descriptive data analysis

Types of tests and methods used for data description were mentioned previously in detail in Chapter 3 (section 3.5). As already stated (section 5.3.3), the whole analysis was stratified into five biennial calendar periods (2005-06, 2007-08, 2009-10, 2011-12 and 2013-14). The aim of this stratification was to compare the temporal changes over the study period looking first at a detailed description of the extent of missing data in the cohort. Exploration of missingness included all the variables in the updated 2014 BCIS database. Later, missing data patterns were measured and assessed based on the percentage of missing data.

Subsequently, a descriptive analysis for the cohort was performed in order to gain more understanding of patients' characteristics. The described characteristics included: baseline demographics, clinical features, pre-procedural, procedural and post-procedural characteristics as well as clinical outcomes. The clinical outcomes of intention included: procedural complications, in-hospital outcomes, 30-day mortality rate and 1-year mortality rate.

5.3.6.2 Multivariate regression modelling

Multivariate model selection process, interaction assessment and the evaluation of goodness of fit were outlined in detail in Chapter 3 (section 3.4.6.5). Clinical outcomes (30-day and 1-year mortality rates) were analysed with and without adjustment for relevant covariates, while the analyses was focused on the three strata of clinical presentation across the five biennial years. Associations with 30-day and 1-year mortality were quantified using fixed effects multivariate logistic models and estimates were expressed as adjusted odds ratios (aOR) with 95% confidence intervals (CI).

Each model estimate was adjusted using seven covariates selected following a literature review on 'the clinical determinants and temporal trends of outcomes for PCI in UPLMS disease', see Chapter 2 (section 2.4). Furthermore, based on the clinical significance recommended by the Delphi group the estimates of the multivariate logistic regression model were adjusted by different covariates. A list of the selected predictors and covariates is shown in Table 5.1.

Table 5.1: Summary of the multivariate logistic models used including the selected covariates, by biennial years and mortality outcomes.

Outcome and method	Biennial years	Covariates
30-day mortality and 1-year mortality using fixed effects multivariate logistic regression model in patients with UPLMS who underwent PCI	2005-06 (as a reference)	Age groups, sex, cardiogenic shock, history of diabetes mellitus, history of renal disease, clinical presentation and post-procedural complications (side branch occlusion, coronary dissection and shock induced by procedure)
	2007-08	
	2009-10	
	2011-12	
	2013-14	

5.3.7 Sensitivity analyses

To test for sensitivity, two sensitivity analyses were performed in order to assess potential bias from the fixed effect regression methods used. Similar to the previous chapter (Chapter 4), the effect of multi-level logistic regression models was evaluated. Subsequently, multivariate logistic regression analyses were considered after multiple imputation.

5.3.7.1 Multi-level regression modelling

Multi-level regression or mixed-effects modelling was defined earlier in Chapter 3 (section 3.5.1.5). Models were fitted with a hierarchy of patients clustered in each hospital using random intercepts for hospitals thus permitting for correlations between patient outcomes. The mixed-effects models took into account the variance in the predictor variables as well as the variance in the hospitals level [133].

Resembling the fixed effect multivariate logistic regression models, the same outcomes (mortality rates at 30 days and one year) and adjustment covariates were fitted

in the mixed effect models (Table 5.1). Afterward, estimates were compared with those from equivalent fixed effects models.

5.3.7.2 Multiple imputation method

A total of 21 imputation predictors were selected, that were based on clinical consensus and a literature review, Chapter 2 (section 2.4) [36-44]. Table 5.2 displays the list of imputation predictor variables of the outcomes of patients with UPLMS who had PCI with a summary of missing data and the methods used for imputation. More details on multiple imputation general methods were presented in Chapter 3 (sections 3.5.2 and 3.5.3).

The frequency of missing values ranged from 0.05% to 35.40% and all missing values were assumed to be missing at random. No data were missing for three variables ‘clinical presentation’, ‘year of operation’ and ‘vessels attempted’. However, these variables were still used as auxiliary variables in the imputation for the remaining 18 variables.

A predictor matrix was designed based on clinical judgement as well as using thresholded P values of less than 0.05 as related and greater than or equal to 0.05 as unrelated. The predictor matrix is shown in Table 5.3. For continuous-continuous and continuous-categorical associations, linear regression was used. While for categorical-categorical, Chi-squared test was used. For each of the 18 predictors with missing values, 20 datasets were imputed using the chained equation method and the fully conditional specification imputation method [141, 153, 180].

All 18 variables were categorical and all were imputed using either logistic regression (if binary) or polytomous regression (if ordinal). For each outcome, 30-day mortality and 1-year mortality, 20 separate imputation datasets were created. Lastly, imputed datasets for each predictor were pooled together using Rubin's rule and followed by the intended regressions. The adjusted estimates from both complete case and multiple imputation data were compared to test for the sensitivity of this analyses.

Table 5.2: Imputation predictor variables of the outcomes of patients with UPLMS who PCI with a summary of missing data and the methods used for imputation.

	Variables	Variable type	Missing %	Imputation method
1	**Age groups**	Ordinal	0.05	Polytomous regression
2	**Gender**	Binary	0.59	logistic regression
3	**Clinical presentation**	Ordinal	0.00	Auxiliary (not imputed)
4	**Pre-procedural cardiogenic shock**	Binary	3.47	logistic regression
5	**History of Acute myocardial infarction**	Binary	9.24	logistic regression
6	**History of Percutaneous coronary intervention**	Binary	1.15	logistic regression
7	**History of diabetes mellitus**	Binary	4.44	logistic regression
8	**Left ventricular ejection fraction**	Ordinal	35.40	Polytomous regression
9	**Year of operation**	Ordinal	0.00	Auxiliary (not imputed)
10	**Major adverse cardiac and cerebrovascular event**	Binary	2.33	logistic regression
11	**History of renal disease**	Binary	0.88	logistic regression
12	**Vessels attempted**	Continuous	0.00	Auxiliary (not imputed)
13	**Procedural complication: Shock induced by procedure**	Binary	4.79	logistic regression
14	**Number stents used**	Ordinal	0.43	Polytomous regression
15	**Stent Type**	Ordinal	2.61	Polytomous regression
16	**Drugs used during procedure**	Ordinal	5.26	Polytomous regression
17	**Intravascular ultrasound use during procedure**	Binary	4.96	logistic regression
18	**Use of intra-aortic balloon pump**	Binary	4.03	logistic regression
19	**Arterial access**	Ordinal	1.83	Polytomous regression
20	**30-day mortality**	Binary	11.19	logistic regression
21	**1-year mortality**	Binary	18.26	logistic regression

Table 5.3: Predictor matrix of the outcomes of patients with UPLMS who received PCI using the 2014 BCIS database.

	Variables	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
1	**Age**																					
2	**Gender**	1																				
3	**Clinical presentation**	1	1																			
4	**Pre-procedural cardiogenic shock**	1	0	1																		
5	**History of acute myocardial infarction**	1	0	1	1																	
6	**History of percutaneous coronary intervention**	1	0	1	1	1																
7	**History of diabetes mellitus**	1	0	1	1	1	1															
8	**Left ventricular ejection fraction**	1	0	1	1	1	1	1														
9	**Year of operation**	1	0	0	1	0	1	0	0													
10	**Major adverse cardiac and cerebrovascular event**	1	1	1	1	0	1	0	1	0												
11	**History of renal disease**	1	1	1	1	1	0	1	1	1	1											
12	**Vessels attempted**	1	1	1	0	1	0	1	1	0	1	1										
13	**P-complication: shock induced by procedure**	0	0	1	1	0	0	0	1	0	1	0	1									
14	**Number of stents used**	1	0	1	1	1	1	0	1	1	1	1	1	0								
15	**Stent type**	1	0	1	1	1	1	1	1	1	1	1	1	0	1							
16	**Drugs used during procedure**	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1						
17	**Intravascular ultrasound use during procedure**	1	0	1	1	0	1	0	1	1	1	0	0	1	1	1	1					
18	**Use of intra-aortic balloon pump**	1	0	1	1	0	1	1	1	0	1	1	1	1	1	1	1	1				
19	**Arterial access**	1	1	1	1	1	1	1	1	1	1	1	0	0	1	1	1	1	1			
20	**30-day mortality**	1	0	1	1	0	1	1	1	0	1	1	1	1	1	1	1	1	1	1		
21	**1-year mortality**	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	0	1	1	0	1	

0: not related, 1: related, P-complication: procedural complication.

5.4 Results

Across 113 hospitals in the UK, and of 21,566 patients who received PCI to a diseased left main stem; 10,827 (50.2%) patients had PCI to an UPLMS (Figure 5.1). Compared with 2005-06, in 2013-14 the annual numbers of patients increased from 864 to 2,279. There were 1,914 (17.7%) ST-elevation myocardial infarction (STEMI), 5,114 (47.2%) non ST-elevation acute coronary syndrome (NSTEACS) and 3,799 (35.1%) chronic stable angina (CSA) patients.

5.4.1 Data completeness

The frequency and percentages of missing values in the variables of the BCIS dataset (2014 updated version) are shown in Table 5.4. The mean (SD) level of missingness was 22.37 (27.53) and the median percentage of missing values was 11.18%. In total, 109 variables were used for the analysis of this chapter, out of them only 12 (11.0%) variables were 100% complete. These included ‘clinical presentation type’, ‘indication for intervention’, ‘procedure urgency’, ‘presenting electrocardiography’, ‘date of operation’, ‘previous CABG’, ‘biennial years’, ‘electrocardiography ischaemia’, ; vessels attempted’, ‘life status at censored date’, ‘pseudonymised hospital code’ and ‘country hospital in’. In contrast, the remaining 97 variables had missing information that ranged from 0.04% to 99.56%.

There were 40 (36.7%) variables that had less than 10% missing information. The one with the least missing values was procedure urgency (0.04%) followed by age at procedure (0.05%) and censored date and survival time (0.35%). On the other hand, only five (4.6%) variables had missing values of more than 90%. The variable with the greatest missingness was ‘use of ventilation’ (99.56%) then ‘bleeding up to discharge’ (99.18%), ‘PCI for stent thrombosis’ (98.04%), ‘third operator status’ (94.50%) and ‘time to bypass’ (95.21%). In total, 40 (36.7%), of the variables had missing values between 10 to 50% and only 12 (11.0%) variables had missing values of more than 50% to 90%.

Overall, from 2005-06 to 2013-14, there was a decrease in the proportion of missing data. For example, absence of values for left ventricular ejection fraction decreased from 40.9% to 35.5%. Similarly for pre-procedural cardiogenic shock, missing values decreased from 12.8% to 2.3%. On the other hand, the proportion of missing values for a few other variables did not show too many changes over the study period, for example, the missing values for arterial access which was 1.3% in 2005-06 and 1.6% in 2013-14 (Figure 5.2).

Table 5.4: Recoded variables and summary of missing data in the variables of UPLMS cohort from the 2014 BCIS data.

Variable Name	Missing Frequency	Missing %
Age At Procedure	5	0.05
Sex	64	0.59
Ethnic Group	3,705	34.22
Patient Status	676	6.24
Clinical presentation type	0	0.00
Indication for Intervention	0	0.00
Procedure Urgency	4	0.04
Cardiogenic Shock Pre-PCI	376	3.47
Angina Status Pre-Surgery	3,723	34.39
Dyspnoea Status Pre-PCI (Stable Only)	406	10.69
Admission Route (ACS Only)	491	6.99
Presenting electrocardiography (ACS Only)	1,082	15.40
Recent Lysis (ACS Only)	768	10.93
Cardiac Enzymes/Markers Raised	1,797	25.57
Previous acute myocardial infarction	1,000	9.24
Previous coronary artery bypass graft (CABG)	0	0.00
Previous percutaneous coronary intervention (PCI)	124	1.15
Diabetes	481	4.44
Height	4,577	42.27
Weight	4,034	37.26
Left Ventricular Ejection Fraction Category	3,833	35.40
Left Ventricular Ejection Fraction	8,371	77.32
Number of Grafts Present Pre-PCI, CABG Only	3,181	29.38
Number of Grafts Patent Pre- PCI, CABG Only	3,497	32.30
Left Main Stem Stenosis Pre-PCI	821	7.58
Left anterior descending Proximal Stenosis Pre-PCI	1,412	13.04
Left anterior descending Other Stenosis Pre-PCI	1,778	16.42
Right coronary artery Stenosis Pre-PCI	1,796	16.59
Circumflex coronary artery Stenosis Pre-PCI	1,558	14.39
Flow In infarct related artery Pre-PCI (ACS Only)	5,912	54.60
Date Of Operation	0	0.00
Date Of Operation (biennial years)	0	0.00
Pseudonymised Consultant Responsible	270	2.49
Pseudonymised First Operator Status	209	1.93
Primary Operator	515	4.76
Second Operator Status	3,810	35.19
Third Operator Status	10,232	94.50

Red (no missing data), Green (less than 10% missing data), Blue (More than 90% missing data)

(Continued) Table 5.4: Recoded variables and summary of missing data in the variables of UPLMS cohort from the 2014 BCIS data.

Variable Name	Missing Frequency	Missing %
Vessels Attempted	0	0.00
Number of vessels attempted not Epicardial	0	0.00
Number Of Lesions Attempted	0	0.00
Number Of Chronic Occlusions Attempted	540	4.99
Number Restenosis Attempted	396	3.66
Number Instant Stenosis Attempted	1,625	15.01
Number Stents Used	47	0.43
Number Drug-Eluting Stents Used	254	2.35
Type of stent used	283	2.61
Drugs Eluted By Stents	767	7.08
Drugs Used During Procedure	570	5.26
Intravascular ultrasound use during procedure	537	4.96
pressure wire use during procedure	537	4.96
Use of intra-aortic balloon pump	436	4.03
Left Main Stem Stenosis Post-PCI	968	8.94
Left anterior descending Proximal Stenosis Post-PCI	1,631	15.06
Left anterior descending Other Stenosis Post-PCI	1,981	18.30
Right coronary artery Stenosis PCI	2,070	19.12
Circumflex coronary artery Stenosis PCI	1,771	16.36
Number Lesions Successful	149	1.38
Number Coronary Grafts Patent PostOp	3,688	34.06
Flow In infarct related artery PostOp (ACS only)	2,301	32.74
Device Failure	865	7.99
PCI Hospital Outcome	252	2.33
Enzymes Post-PCI	8,328	76.92
Status At Discharge	254	2.35
Discharge Date	601	5.55
Cholesterol	6,977	71.09
Smoking Status	1,270	11.73
Family History Of coronary artery disease	1,849	17.08
Medical History	354	3.27
History Of Renal Disease	95	0.88
Ventilated Pre-PCI	1,160	10.71
Q Wave On electrocardiography	1,449	13.38
Electrocardiography Ischaemia	1,340	12.38
Drug Therapy Pre-PCI	457	4.22
Follow On AdHoc Procedure	492	4.54

Red (no missing data), Green (less than 10% missing data), Blue (More than 90% missing data)

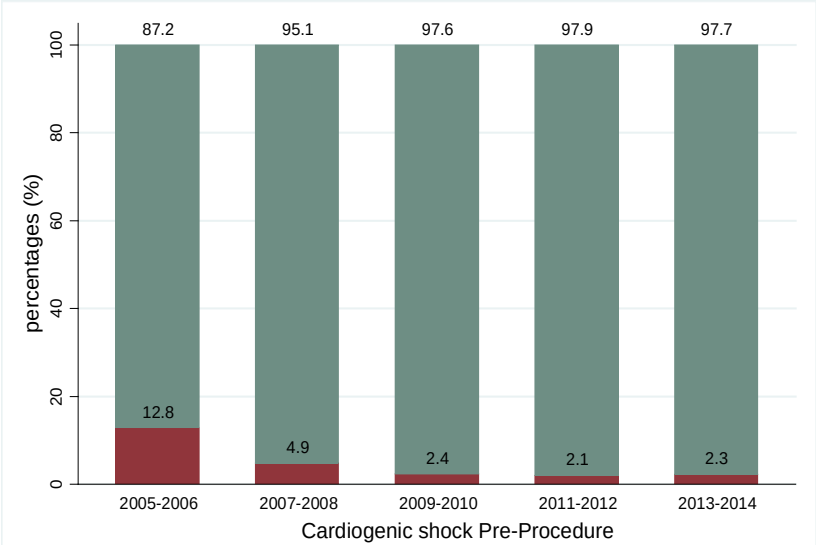
(Continued) Table 5.4: Recoded variables and summary of missing data in the variables of UPLMS cohort from the 2014 BCIS data.

Variable Name	Missing Frequency	Missing %
Why No IIb/IIIA During Procedure	2,636	24.35
Indication For Stent	746	6.89
Surgical Cover	1,222	11.29
Left Main Stem Protected	0	0.00
Referral Hospital	7,603	70.22
Date of electrocardiography Triggering primary PCI	1,404	82.25
Patient Location at Time of STEMI Onset	9,699	89.58
Creatinine	7,584	70.05
PCI for stent thrombosis	10,615	98.04
Training Procedure	735	6.79
Research Procedure	1,210	11.18
Arterial Access	198	1.83
Largest Balloon/Stent Used	1,277	11.79
Longest Stented/Treated Segment	1,192	11.01
Procedural Complication	857	7.92
Arterial Complication	519	4.79
Time to Bypass	10,308	95.21
Patient Status During Transfer To Theatre	1,968	18.18
Bleeding up to discharge	10,738	99.18
Ventilation	10,779	99.56
Pseudonymised Hospital Code	0	0.00
Country Hospital In	0	0.00
Length of Stay in Hospital (days)	5,927	54.73
Index of Multiple Deprivation Score	2,570	23.74
Life Status at 7days	1,210	11.18
Life Status at 30days	1,211	11.19
Life Status at 1year	1,977	18.26
Life Status at 2years	3,368	31.11
Life Status at 3years	4,472	41.30
Life Status at 4years	5,426	50.12
Life Status at 5years	6,150	56.80
Death after Procedure (days)	7,880	72.78
Censored date	38	0.35
Survival time	38	0.35
Life Status at censored date	0	0.00

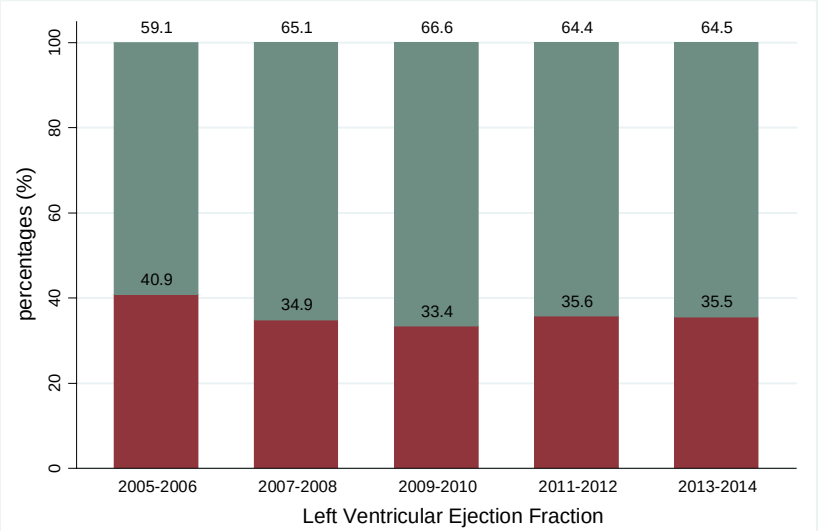
Red (no missing data), Green (less than 10% missing data), Blue (More than 90% missing data)

Figure 5.2: Proportions of complete and missing values for pre-procedural cardiogenic shock, left ventricular ejection fraction and arterial access in biennial years from 2005 to 2014.

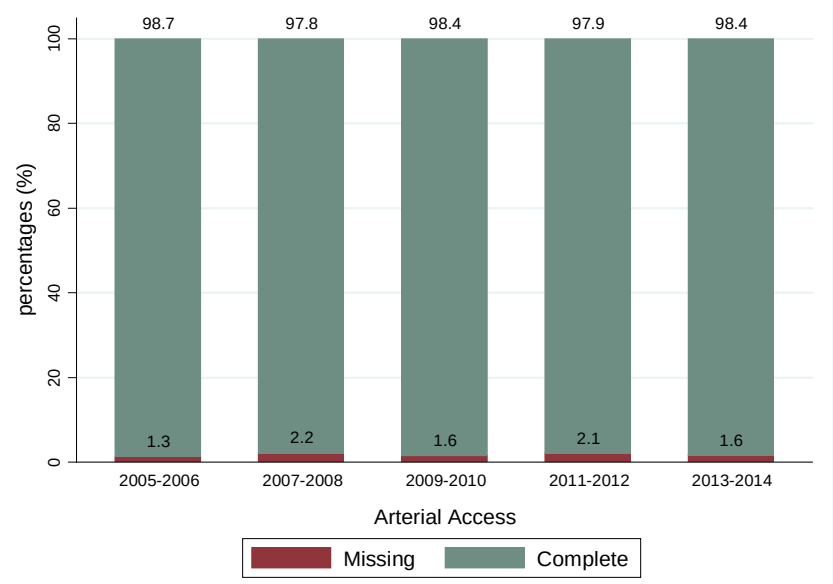
Pre-procedural cardiogenic shock



Left ventricular ejection fraction



Arterial access



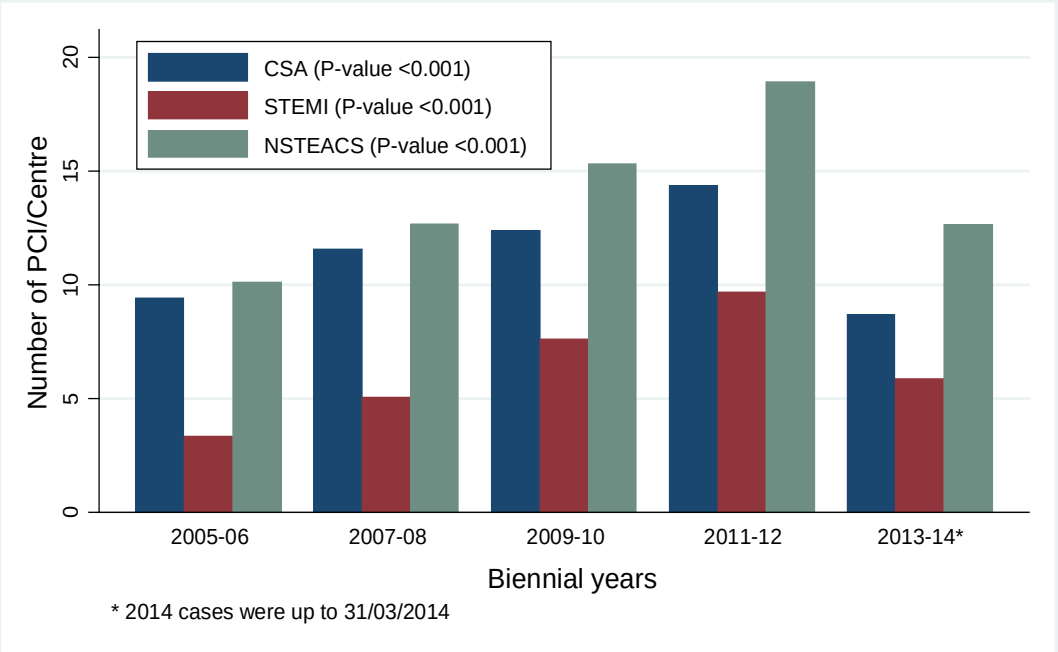
5.4.2 Trends of demographic characteristics

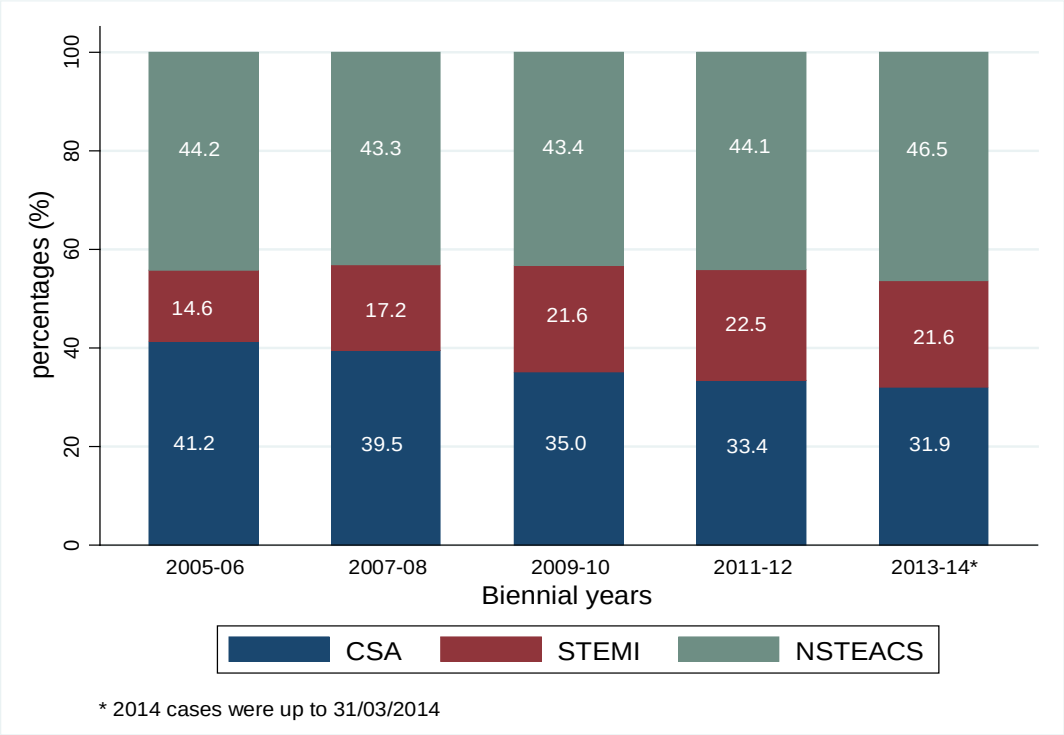
From 2005-06 to 2013-14, the proportion of STEMI patients increased from 90 (10.4%) to 441 (19.4%), the proportion of NSTEACS remained similar from 425 (49.2%) to 1,100 (48.3%) and the proportion of CSA fell slightly from 349 (40.4%) to 738 (32.4), P <0.001. After standardizing for the expansion in PCI capable centres the increase in patients was upheld (Figure 5.3). The method of standardisation was outlined earlier (section 5.3.4).

In all five biennial year groups, there was a preponderance of males (overall: 7,490 (69.6%) males). The mean (SD) age of the whole cohort was 70.5 (12.1) years, which to some extent increased over the years (2005-06: 69.6 (11.8) and 2013-14: 70.6 (12.2), P =0.004). Patients older than 80 years of age were more frequent over the years (2005-06: 179 (20.7%) and 2013-14: 552 (24.2%) patients, P =0.022). The majority of patients were of a Caucasian ethnicity in all five biennial years; however, they decreased over the years from 90.0% of patients in 2005-06 to 86.7% in 2013-14 (P <0.001).

From 2005-06 through to 2013-14, there were more NHS patients (2005-06: (94.4%) and 2013-14: (97.0%) of patients) compared to private patients (2005-06: (5.6%) and 2013-14: (3.0%) of patients), P =0.025. For acute patients, in 2005-06 direct admission to a cardiac centre was the second route of admission after inter-hospital transfer (38.8% and 45.9%, respectively). However, over the years, admission directly to hospital became more predominant (36.9% vs 53.0%), P <0.001. Table 5.5 shows the distribution of baseline demographic characteristics by biennial year of date of procedure.

Figure 5.3: Standardized number of patients who received PCI to an UPLMS per centre in biennial years from 2005 to 2014, stratified by STEMI, NSTEACS and CSA (frequency and percentage).





Proportions exclude missing data.
P-values are for differences between years
Standardization was done by dividing the total number of UPLMS patients underwent PCI in each biennial year over the number of PCI centres in that biennial year.

Table 5.5: Baseline demographic characteristics of patients with UPLMS disease who received PCI, by biennial year of date of procedure.

Variable		2005-06 n=864	2007-08 n=1,560	2009-10 n=2,494	2011-12 n=3.630	2013-14 n=2.279	P value *
Cardiac centres participating		47	67	83	95	98	0.018
Standardized number of PCI per centre		18.4	23.3	30.0	38.2	23.3	<0.001
CSA (%)		349 (40.4)	613 (39.3)	879 (35.2)	1,220 (33.6)	738 (32.4)	<0.001
STEMI (%)		90 (10.4)	212 (13.6)	465 (18.7)	706 (19.5)	441 (16.3)	
NSTEACS (%)		425 (49.2)	735 (47.1)	1,150 (46.1)	1,704 (49.9)	1,100 (48.3)	
Mean (SD) age, years		69.6 (11.8)	69.8 (12.1)	70.5 (12.5)	71.0 (12.0)	70.6 (12.2)	0.004
Greater than 80 years (%)		179 (20.7)	366 (23.5)	633 (25.4)	906 (25.0)	552 (24.2)	0.022
Male (%)		577 (70.8)	1,095 (70.3)	1,689 (67.8)	2,513 (69.4)	1,616 (71.0)	0.141
Ethnic groups	**Caucasian (%)**	515 (90.0)	808 (84.1)	1,468 (88.4)	2,226 (88.9)	1,234 (86.7)	<0.001
	Black (%)	5 (0.9)	6 (0.6)	12 (0.7)	16 (0.6)	10 (0.7)	
	Asian (%)	29 (5.1)	46 (4.8)	86 (5.2)	125 (5.0)	78 (5.5)	
	Other (%)	23 (4.0)	101 (10.5)	95 (5.7)	137 (5.5)	102 (7.1)	
Patient type	**NHS (%)**	756 (94.4)	1,382 (95.4)	2,240 (96.5)	3,273 (96.4)	2,115 (97.0)	0.025
	Private (%)	45 (5.6)	67 (4.6)	80 (3.5)	124 (3.6)	65 (3.0)	
Admission route (ACS only)	**Direct to cardiac centre (%)**	190 (38.8)	383 (43.6)	785 (46.6)	1,264 (50.9)	827 (53.0)	<0.001
	Inter-hospital transfer (%)	225 (45.9)	363 (41.3)	671 (39.8)	944 (38.0)	577 (36.9)	
	Already in cardiac centre (%)	75 (15.3)	133 (15.1)	229 (13.6)	274 (11.1)	157 (10.1)	
Index of multiple deprivation score, mean (SD)		21.9 (14.2)	21.2 (13.7)	20.9 (13.6)	21.1 (13.5)	20.7 (13.2)	0.380

Proportions exclude missing data.

* P-value was calculated using Chi-square test for categorical variables and analysis of variance (ANOVA) for continues variables.

5.4.3 Trends of clinical characteristics

Table 5.6 shows the distribution of baseline clinical characteristics by biennial year of procedure date. For the entire cohort, from 2005-06 through to 2013-14, there were fewer patients with a family history of coronary artery disease (46.8% to 40.3%, P <0.001). Similarly, from 2005-06 to 2013-14, there were fewer cases of failed thrombolysis for STEMI patients (36.7% to 3.1%, P <0.001) and for NSTEACS patients (8.4% to 0.9%, P <0.001). In contrast, from 2005-06 to 2013-14, there were more patients with a history of previous PCI (18.1% to 25.1%, P <0.001) and diabetes mellitus (18.9% to 22.6%, P =0.012).

In total, 818 (43.1%) STEMI and 466 (9.2%) NSTEACS presented with cardiogenic shock, and for the cohort, the proportion of cases with cardiogenic shock increased from 9.0% in 2005-06 to 13.3% in 2013-14 (P =0.027). The proportion of cardiogenic shock in patients with STEMI decreased (from 49.4% in 2005-06 to 44.6% in 2013-14 (P =0.027)) and increased in NSTEACS (from 7.1% in 2005-06 to 9.1% in 2013-14 (P =0. 450)). Likewise for severe left ventricular systolic dysfunction, the percentage of cases in the whole cohort increased from 15.3% to 19.3% (P =0. 327).

Table 5.6: Baseline clinical characteristics of patients with UPLMS disease who received PCI, by biennial year of date of procedure.

Variable		2005-06 n=864	2007-08 n=1,560	2009-10 n=2,494	2011-12 n=3.630	2013-14 n=2.279	P value *
Previous acute myocardial infarction (%)		248 (33.7)	434 (34.3)	733 (32.9)	1,148 (33.9)	724 (32.8)	0.824
Previous PCI (%)		152 (18.1)	318 (20.7)	547 (22.1)	761 (21.2)	567 (25.1)	<0.001
Family history of coronary artery disease (%)		301 (46.8)	548 (47.1)	983 (45.9)	1,268 (41.0)	781 (40.3)	<0.001
Diabetes mellitus (%)		142 (18.9)	293 (19.8)	512 (21.1)	811 (23.3)	497 (22.6)	0.012
History of renal disease (%)		44 (5.4)	99 (6.9)	172 (6.9)	222 (6.2)	137 (6.1)	0.525
Smoking status	**Never smoked (%)**	245 (36.5)	413 (32.0)	843 (37.5)	1,247 (38.0)	862 (41.6)	<0.001
	Ex-smoker (%)	312 (46.5)	646 (50.1)	1,019 (45.4)	1,440 (44.0)	879 (42.4)	
	Current smoker (%)	114 (17.0)	230 (17.9)	385 (17.1)	589 (18.0)	333 (16.1)	
Recent thrombolysis	**Overall (%)**	59 (11.6)	82 (9.0)	81 (5.3)	57 (2.5)	22 (1.5)	<0.001
	STEMI (%)	29 (36.7)	38 (18.8)	34 (7.8)	22 (3.3)	13 (3.1)	<0.001
	NSTEACS (%)	30 (8.4)	44 (7.2)	47 (4.6)	35 (2.3)	9 (0.9)	<0.001
Cardiogenic shock	**Overall (%)**	68 (9.0)	172 (11.69)	303 (12.5)	453 (12.8)	297 (13.3)	0.027
	STEMI (%)	40 (49.4)	95 (44.8)	186 (40.1)	302 (43.0)	195 (44.6)	0.450
	NSTEACS (%)	28 (7.1)	77 (10.6)	113 (9.9)	150 (8.9)	98 (9.1)	0.327
Severe left ventricular systolic dysfunction	**Overall (%)**	78 (15.3)	211 (20.8)	288 (17.3)	441 (18.9)	283 (19.3)	0.052
	STEMI (%)	15 (41.7)	46 (50.0)	85 (42.7)	107 (35.8)	79 (45.4)	0.088
	NSTEACS (%)	49 (18.9)	107 (21.1)	159 (19.3)	248 (21.3)	165 (21.4)	0.635

Proportions exclude missing data.

* P-value was calculated using Chi-square test for categorical variables and analysis of variance (ANOVA) for continues variables.

5.4.4 Trends of procedural characteristics

The distribution of procedural characteristics by biennial year of procedure date is shown in Table 5.7. From 2005-06 to 2013-14, the proportion of pre-procedural TIMI 3 increased over the study period (95 (33.0%) patients in 2005-06 versus 577 (52.7%) patients in 2013-14, P <0.001). Through all five strata of biennial years of procedure date, there was an increase in the proportion of cases that had more than one vessel stented (from 614 (71.1%) patients in 2005-06 to 1,681 (73.8) patients in 2013-14, P =0.027).

As would be expected following the development of interventional technologies [44, 117, 176, 186], drug eluting stents were used more frequently than bare metal stents from 2005-06 to 2013-14 (drug eluting stents in 58.7% of patients in 2005-06 to 82.8% in 2013-14 while bare metal stents in 22.6% of patients in 2005-06 to 6.5% in 2013-14). Compared to 2005-06, the stent types that were used more often in 2013-14 were Promus (Boston Scientific) in 504 (22.9%) patients, followed by Promus Element in 316 (14.4%) patients, Xience Prime in 254 (11.6%) patients and Resolute Integrity in 240 (10.9%) patients (all P <0.001). Conversely, the use of Taxus liberte, Cypher and Endeavor stents decreased over the biennial years (from 43.7%, 15.4% and 6.3% in 2005-06 vs. 0.4%, 0.0% and 1.5% in 2013-14, respectively (both P <0.001)).

Later in the study period, intravascular ultrasound was performed more frequently (17.4% in 2005-06 vs. 40.3% in 2013-14, P <0.001) and pressure wire assessment increased (2.8% in 2005-06 vs. 7.1% in 2013-14, P <0.001). An intra-aortic balloon pump was inserted less frequently (16.7% in 2005-06 vs. 10.4% in 2013-14, P <0.001), especially in STEMI (46.3% vs. 25.8%) and NSTEACS (18.6% vs. 10.2%) (P <0.001). For CSA, rotational atherectomy was undertaken more frequently (3.9% in 2005-06 vs. 7.2% in 2013-14, P <0.001). The glycoprotein IIb IIIa inhibitor, Abciximab, was used less frequently for STEMI patients (74.4% in 2005-06 vs. 30.3% in 2013-14), NSTEACS patients (54.1% in 2005 vs. 5.5% in 2013-14) and CSA patients (45.1% in 2005-06 vs. 4.2% in 2013-14) (P <0.001).

For the cohort, while the practice of femoral PCIs decreased over the years from 685 (80.3%) in 2005-06 to 863 (38.5%) in 2013-14, radial PCIs increased from 157 (18.4%) in 2005-06 to 1,375 (61.3%) in 2013-14. Figure 5.4 shows the temporal change in access for PCIs for the cohort as a whole and stratified by clinical presentation (all P

<0.001). For patients presenting with STEMI associated with cardiogenic shock, femoral access was always more frequently used than radial access (in 2005-06 86.8% femoral vs. 10.6% radial and in 2013-14 60.6% femoral vs. 39.4% radial, P <0.001), similarly for NSTEACS patients with cardiogenic shock (in 2005-06 82.1% femoral vs. 14.3% radial and in 2013-14 64.2% femoral vs. 33.7% radial, P value =0.004).

Table 5.7: Procedural characteristics of patients with UPLMS disease who received PCI, by biennial year of date of procedure.

Variable		2005-06 n=864	2007-08 n=1,560	2009-10 n=2,494	2011-12 n=3.630	2013-14 n=2.279	P value *
Pre-procedural flow in infarct related artery	TIMI 0 (%)	48 (16.7)	128 (19.8)	245 (20.8)	388 (22.7)	236 (21.5)	<0.001
	TIMI 1 (%)	14 (4.9)	39 (6.0)	82 (7.0)	119 (7.0)	76 (6.9)	
	TIMI 2 (%)	29 (10.0)	83 (12.9)	119 (10.1)	217 (12.7)	123 (11.2)	
	TIMI 3 (%)	95 (33.0)	250 (38.7)	583 (49.5)	847 (49.6)	577 (52.7)	
	Unknown (%)	102 (35.4)	146 (22.6)	148 (12.6)	137 (8.0)	84 (7.7)	
Vessels attempted	Left main stem only (%)	250 (28.9)	470 (30.1)	738 (29.6)	995 (27.4)	598 (26.2)	0.027
	Multi-vessels (%)	614 (71.1)	1,090 (69.9)	1,756 (70.4)	2,635 (72.6)	1,681 (73.8)	
Total number stents used	1 stent (%)	241 (29.0)	457 (32.2)	784 (34.3)	1,181 (34.7)	686 (32.2)	0.002
	2 stents (%)	240 (28.9)	438 (30.9)	731 (32.0)	1,021 (30.0)	682 (32.3)	
	≥ 3 stents (%)	350 (42.1)	524 (36.9)	771 (33.7)	1,204 (35.3)	754 (35.2)	
Type of stent used	Bare metal stent (%)	186 (23.1)	385 (27.5)	480 (21.3)	502 (15.0)	147 (6.5)	<0.001
	Drug eluting stent (%)	484 (60.3)	818 (58.3)	1,581 (70.1)	2,678 (79.7)	1,862 (87.8)	
	Both together (%)	133 (16.6)	199 (14.2)	193 (8.6)	179 (5.3)	112 (5.3)	
Type of DES used	Taxus liberte (Boston Scientific)(%)	333 (43.7)	301 (23.1)	225 (9.9)	12 (0.3)	8 (0.4)	<0.001
	Cypher (Cordis) (%)	117 (15.4)	131 (10.0)	106 (4.7)	11 (0.3)	0 (0.0)	
	Endeavor (Medtronic) (%)	48 (6.3)	132 (10.1)	196 (8.6)	110 (3.1)	32 (1.5)	
	Xience V (Abbott) (%)	1 (0.1)	87 (6.7)	388 (17.1)	393 (11.2)	97 (4.4)	
	Promus (Boston Scientific) (%)	0 (0.0)	16 (1.2)	335 (14.8)	638 (18.1)	504 (22.9)	
	BioMatrix (%)	0 (0.0)	0 (0.0)	82 (3.6)	324 (9.2)	205 (9.3)	
	Promus Element (%)	0 (0.0)	0 (0.0)	61 (2.7)	481 (13.7)	316 (14.4)	
	Xience Prime (%)	0 (0.0)	0 (0.0)	28 (1.2)	448 (12.7)	254 (11.6)	
	Resolute Integrity (%)	0 (0.0)	0 (0.0)	9 (0.4)	347 (9.9)	240 (10.9)	
Longest stented/treated segment, mean (SD) mm		24.2 (14.6)	26.7 (16.5)	26.4 (15.9)	27.1 (16.1)	28.9 (19.1)	<0.001

Proportions exclude missing data**.**

* P-value was calculated using Chi-square test for categorical variables and analysis of variance (ANOVA) for continues variables.

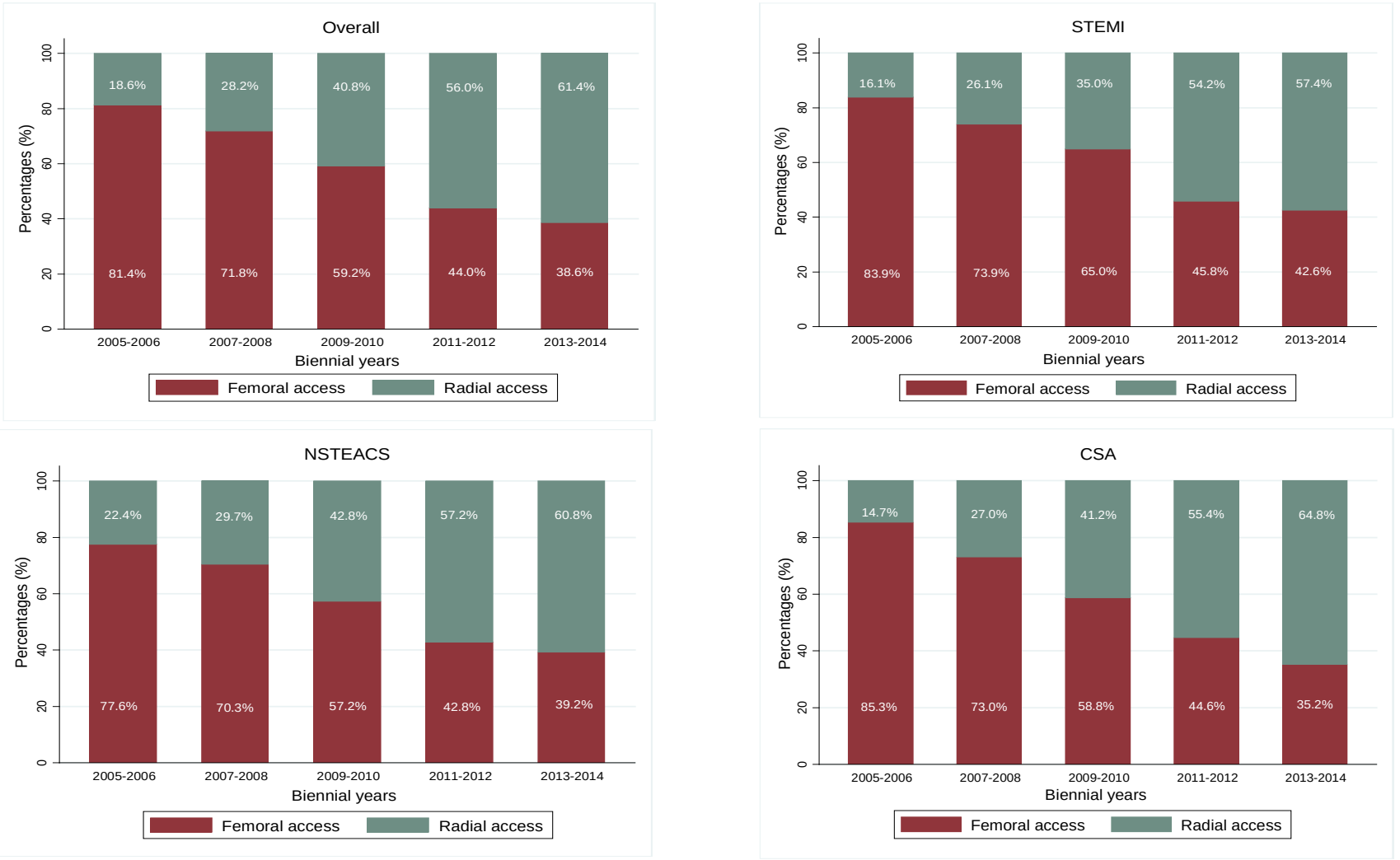
(Continued) Table 5.7 Procedural characteristics of patients with UPLMS disease who received PCI, by biennial year of date of procedure.

Variable			2005-06 n=864	2007-08 n=1,560	2009-10 n=2,494	2011-12 n=3.630	2013-14 n=2.279	P value *
Use of ventilation (%)			21 (3.0)	50 (4.0)	131 (5.8)	217 (6.5)	137 (6.4)	<0.001
Drugs used		**None (%)**	319 (40.4)	882 (59.0)	1,583 (67.6)	2,577 (74.6)	1,712 (78.4)	<0.001
		Abciximab (%)	415 (52.6)	490 (32.8)	574 (24.6)	493 (14.3)	215 (9.9)	
		Eptifibitide (%)	18 (2.3)	42 (2.8)	65 (2.8)	174 (5.0)	116 (5.3)	
		Tirofiban (%)	37 (4.7)	80 (5.4)	116 (5.0)	209 (6.1)	140 (6.4)	
Use of intravascular ultra sound (%)			119 (17.4)	435 (30.2)	870 (36.3)	1,377 (38.9)	898 (40.3)	<0.001
Use of intravascular pressure wire (%)			19 (2.8)	93 (6.4)	195 (8.2)	253 (7.2)	157 (7.1)	<0.001
Use of Intra-aortic balloon pump (%)			130 (16.7)	235 (16.4)	373 (15.6)	458 (12.8)	230 (10.4)	<0.001
Arterial access	**Overall**	**Femoral artery (%)**	685 (80.3)	1,092 (71.6)	1,446 (58.9)	1,555 (43.8)	863 (38.5)	<0.001
		Radial artery (%)	157 (18.4)	428 (28.0)	996 (40.6)	1,981 (55.7)	1,375 (61.3)	
		Other arteries (%)	11 (1.3)	6 (0.4)	12 (0.5)	18 (0.5)	4 (0.2)	
	STEMI patients with cardiogenic shock	**Femoral artery (%)**	33 (86.8)	77 (82.8)	149 (81.4)	188 (65.3)	117 (60.6)	<0.001
		Radial artery (%)	4 (10.6)	16 17.2)	34 (18.6)	99 (34.4	76 (39.4)	
		Other arteries (%)	1 (2.6)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	
	NSTEACS patients with cardiogenic shock	**Femoral artery (%)**	23 (82.1)	62 (81.6)	77 (70.6)	85 (58.6)	61 (64.2)	0.004
		Radial artery (%)	4 (14.3)	14 (18.4)	31 (28.4)	60 (41.4)	32 (33.7)	
		Other arteries (%)	1 (3.6)	0 (0.0)	1 (0.9)	0 (0.0)	2 (2.1)	
Post-procedure left main stem stenosis		**0% stenosis (%)**	637 (84.0)	981 (74.4)	1,661 (73.9)	2,600 (76.8)	1,618 (75.4)	<0.001
		1-49% stenosis (%)	100 (13.2)	268 (20.3)	466 (20.7)	620 (18.3)	405 (18.9)	
		≥ 50% stenosis (%)	21 (2.8)	70 (5.3)	121 (5.4)	167 (4.9)	124 (5.7)	
Post-procedure flow in infarct related artery		**TIMI 0 (%)**	9 (2.4)	24 (2.8)	44 (2.9)	75 (3.2)	47 (3.1)	<0.001
		TIMI 1 (%)	1 (0.3)	9 (1.1)	21 (1.4)	22 (1.0)	14 (0.9)	
		TIMI 2 (%)	9.(2.4)	28 (3.3)	62 (4.0)	87 (3.8)	40 (2.7)	
		TIMI 3 (%)	247 (66.4)	592 (70.8)	1,228 (80.1)	1,982 (85.5)	1,297 (86.3)	
		Unknown (%)	106 (28.5)	183 (22.0)	179 (11.6)	152 (6.5)	105 (7.0)	

Proportions exclude missing data**.**

* P-value was calculated using the Chi-square test for categorical variables and analysis of variance (ANOVA) for continues variables.

Figure 5.4: Proportion of femoral and radial access in patients who received PCI to an UPLMS in biennial years from 2005 to 2014, stratified by STEMI, NSTEACS and CSA.



Proportions exclude missing data.

5.4.5 Trends of procedural complications and in-hospital outcomes

The rates of side branch occlusion, coronary dissection, coronary perforation, direct current cardioversion, no flow/slow flow, ventilation and cardiogenic shock occurring during the procedure did not change significantly over the study period. During the hospital stay, there were no significant changes in the proportion of patients with acute myocardial infarction, stroke, renal failure/dialysis and requiring blood transfusion or revascularisation. The distribution of procedural complications and in-hospital outcomes by biennial year of procedure date is shown respectively in Tables 5.8 and 5.9.

5.4.6 Trends of Crude mortality

From 2005-06 to 2013-14, unadjusted in-hospital MACCE rate decreased to some extent (10.4% vs. 8.8%, P =0.209) while unadjusted in-hospital mortality rate slightly increased (7.8% vs. 8.7%, P =0.404). Overall, there were 2,843 (26.3%) deaths over a total follow-up period of 9,329,661 patient years. There were significant interactions between biennial year, clinical strata and early and late mortality (all P <0.001). Unadjusted 30-day and 1-year mortality rates in UPLMS patients who received PCI in biennial years from 2005 to 2014, stratified by clinical presentation are shown respectively in Figure 5.5.

For STEMI patients, 30-day and 1-year crude mortality rates decreased from 35.3% and 42.4% in 2005-06 to 31.6% and 40.1% in 2013-14, respectively. Similarly for NSTEACS patients, 30-day and 1-year mortality rates decreased from 10.6% and 21.3% in 2005-06 to 8.7% and 17.8% in 2013-14, respectively.

5.4.7 Trends of adjusted mortality

5.4.7.1 Clinical presentation and mortality

Compared with 2005-06 and once adjusted for confounders, 30-day mortality in 2013-14 did not change (STEMI: adjusted odds ratio (aOR) 0.9, 95% confidence interval (CI), 0.5 to 1.6; NSTEACS aOR 0.9, 95% CI 0.6 to 1.4; CSA aOR 1.2, 95% CI 0.2 to 6.4). Figure 5.6 shows the adjusted risk of 30-day mortality for patients who

received PCI to UPLMS in biennial years from 2005 to 2014, stratified by clinical presentation (complete case data and pooled imputed data). Likewise, 1-year mortality remained stable in 2013-14 (STEMI aOR 0.9, 95% CI 0.5 to 1.6; NSTEACS aOR 0.9, 95% CI 0.6 to 2.3; CSA aOR 1.1, 95% CI 0.5 to 2.4). Adjusted risk of 1-year mortality for patients who received PCI to UPLMS in biennial years from 2005 to 2014, stratified by clinical presentation (complete case data and pooled imputed data) can be seen in Figure 5.7.

5.4.7.2 Cardiogenic shock and mortality

In STEMI patients with cardiogenic shock, 30-day and 1-year mortality rates decreased by 13.3% (95% CI, 10.8% to 15.9%) and 7.0% (95% CI 5.1% to 9.2%), but remained high in 2013-14 at 52.5% and 64.0%, respectively. After multivariable adjustment, in 2013-14 these temporal improvements were upheld significantly in both early and late mortality (30-day mortality: aOR 0.3, 95% CI, 0.1 to 0.7; 1-year mortality: aOR 0.3, 95% CI 0.1 to 0.9). Figure 5.8 shows the adjusted risk of 30-day and 1-year mortality for patients with cardiogenic shock who received PCI to UPLMS in biennial years from 2005 to 2014, stratified by STEMI and NSTEACS.

5.4.7.3 Radial approach and mortality

At 30-days and 1-year, a decline in mortality for radial PCI cases was only evident in those who presented acutely; for STEMI: 9.7% (95% CI 3.9% to 19.6%) at 30-day and 11.3% (95% CI 4.4% to 22.5%) at 1-year, and for NSTEACS: 3.8%, (95% CI 1.7% to 7.7%) at 30-day and 7.5% (95% CI 3.9% to 12.4%) at 1-year. After adjustment, the improvements at 30-days and 1-year were not significant except for NSTEACS patients at 1-year; for STEMI patients (at 30-days: aOR 0.50, 95% CI 0.14 to 1.78 and at 1 year: aOR 0.50, 95% CI 0.14 to 1.75) and for NSTEACS patients (at 30-days: aOR 0.57, 95% CI 0.26 to 1.25 and at 1 year: aOR 0.42, 95% CI 0.22 to 0.83).

Table 5.8: Procedural complications for patients with UPLMS disease who received PCI, by biennial year of date of procedure.

Variable	2005-06 n=864	2007-08 n=1,560	2009-10 n=2,494	2011-12 n=3.630	2013-14 n=2.279	P value *
Side branch occlusion (%)	7 (0.9)	18 (1.3)	23 (1.0)	40 (1.2)	24 (1.1)	0.909
Coronary dissection (%)	35 (4.5)	110 (7.9)	123 (5.5)	185 (5.4)	95 (4.4)	<0.001
Coronary perforation (%)	5 (0.7)	11 (0.8)	19 (0.8)	25 (0.7)	14 (0.7)	0.949
Direct current cardioversion (%)	6 (0.8)	17 (1.2)	30 (1.3)	39 (1.2)	20 (0.9)	0.622
No flow/slow flow (%)	17 (2.2)	30 (2.2)	32 (1.4)	45 (1.3)	24 (1.1)	0.045
Ventilated (%)	11 (1.4)	26 (1.9)	46 (2.0)	64 (1.9)	39 (1.8)	0.866
Cardiogenic shock induced by procedure (%)	14 (1.8)	24 (1.7)	42 (1.9)	45 (1.3)	34 (1.6)	0.548

Proportions exclude missing data**.**

* P-value was calculated using Chi-square test for categorical variables and analysis of variance (ANOVA) for continues variables

Table 5.9: In-hospital outcomes for patients with UPLMS disease who received PCI, by biennial year of date of procedure.

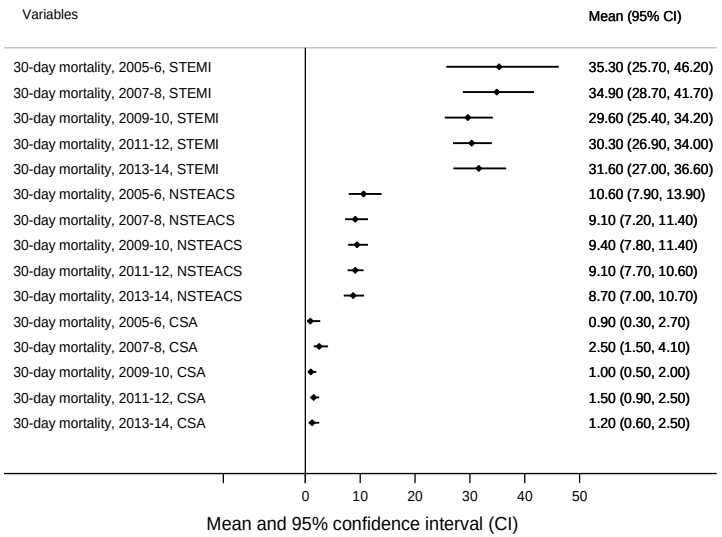
Variable		2005-06 n=864	2007-08 n=1,560	2009-10 n=2,494	2011-12 n=3.630	2013-14 n=2.279	P value *
Acute myocardial infarction (%)		17 (2.1)	18 (1.2)	26 (1.1)	26 (0.7)	19 (0.9)	0.036
Stroke (%)		2 (0.3)	2 (0.1)	8 (0.3)	7 (0.2)	3 (0.1)	
Renal failure/dialysis (%)		5 (0.6)	10 (0.7)	18 (0.7)	15 (0.4)	8 (0.4)	0.330
Blood transfusion (%)		10 (1.2)	13 (0.9)	22 (0.9)	25 (0.7)	15 (0.7)	0.521
Revascularisation	**Percutaneous coronary intervention (%)**	5 (0.6)	5 (0.3)	9 (0.4)	16 (0.5)	7 (0.3)	0.170
	Coronary artery bypass graft (%)	4 (0.5)	19 (1.3)	12 (0.5)	21 (0.6)	14 (0.6)	
Unadjusted in-hospital MACCE rate (%)		84 (10.4)	120 (7.9)	207 (8.5)	286 (8.1)	198 (8.8)	0.209
Unadjusted in-hospital mortality rate (%)		61 (7.8)	108 (7.1)	208 (8.5)	305 (8.5)	194 (8.7)	0.404

Proportions exclude missing data**.**

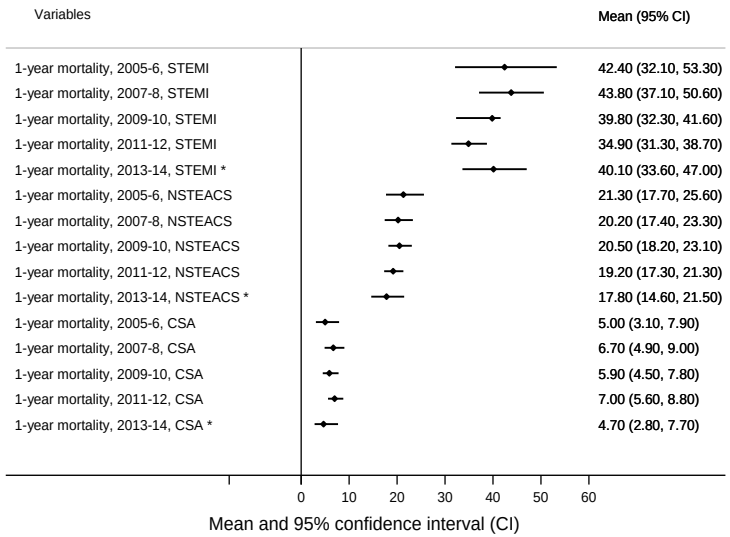
* P-value was calculated using Chi-square test for categorical variables and analysis of variance (ANOVA) for continues variables.

Figure 5.5: Unadjusted 30-day and 1-year mortality rates in patients who received PCI to an UPLMS in biennial years from 2005 to 2014, stratified by STEMI, NSTEACS and CSA.

30-day mortality rates

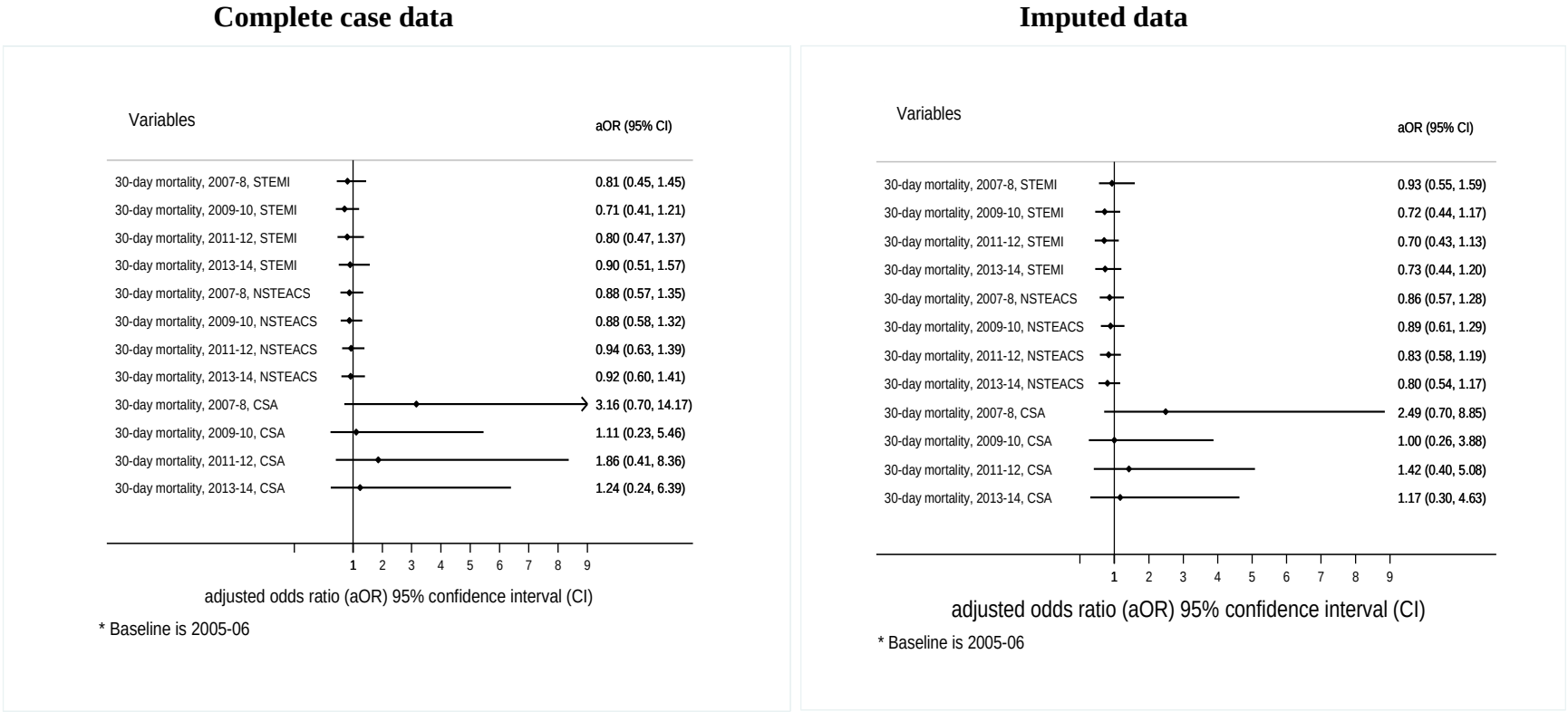


1-year mortality rates



Proportions exclude missing data.
** For 1-year mortality: Censored at 31/7/2014, therefore all PCI procedures performed after 31/7/2013 were not included in describing this rate.

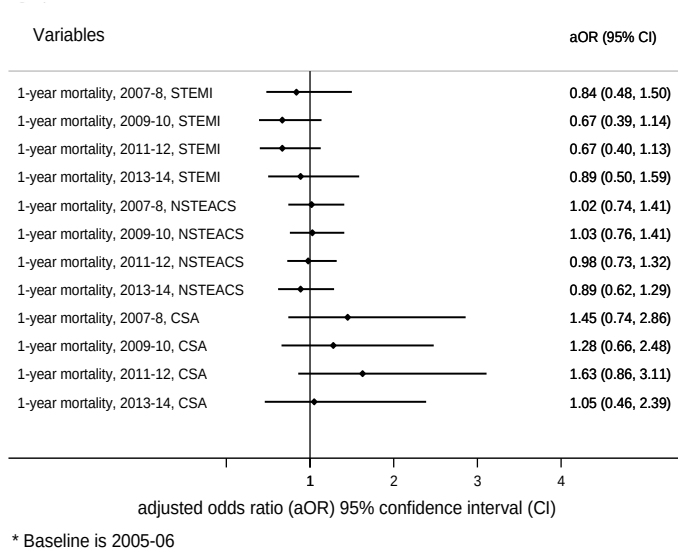
Figure 5.6: Multivariable adjusted risk of 30-day mortality for patients who received PCI to an UPLMS in biennial years from 2005 to 2014, stratified by STEMI, NSTEACS and CSA (complete case data and imputed data).



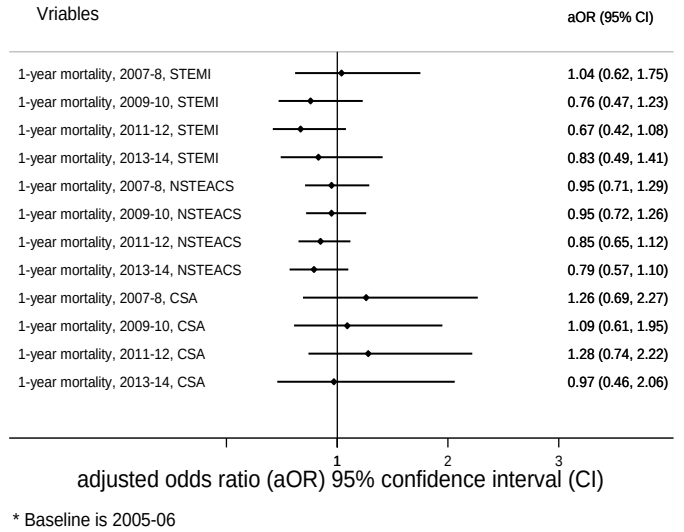
aOR and 95%CI were calculated using multivariate logistic regression for both complete case and pooled imputed data.

Figure 5.7: Multivariable adjusted risk of 1-year mortality for patients who received PCI to an UPLMS in biennial years from 2005 to 2014, stratified by STEMI, NSTEACS and CSA (complete case data and imputed data).

Complete case data

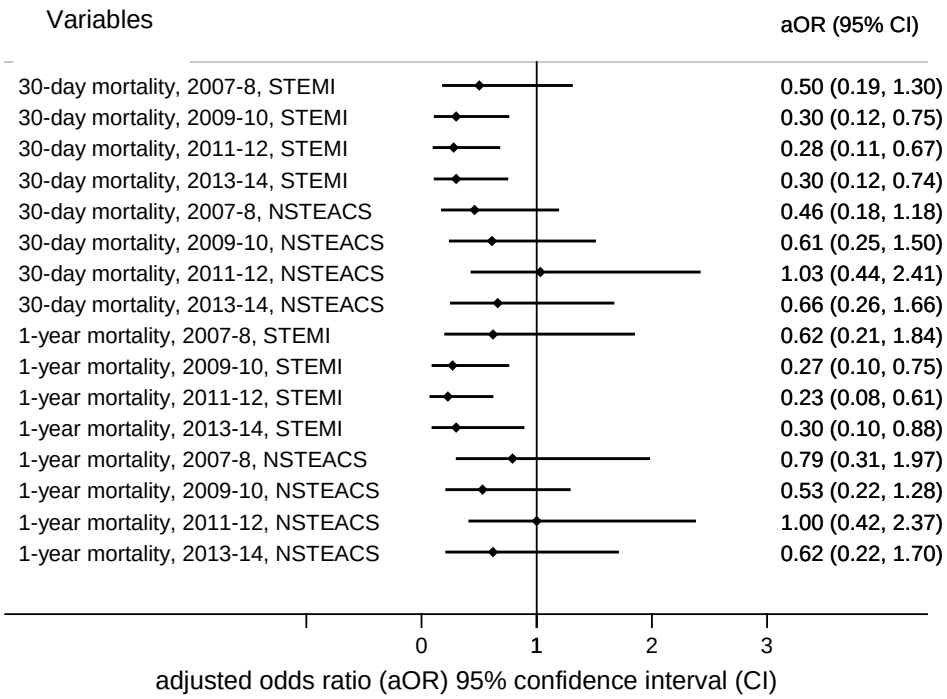


Imputed data



aOR and 95%CI were calculated using multivariate logistic regression for both complete case and pooled imputed data.
** Censored at 31/7/2014, therefore all PCI procedures performed after 31/7/2013 were not included in describing this rate.

Figure 5.8: Multivariable adjusted risk of 30-day and 1-year mortality for patients with cardiogenic shock who received PCI to an UPLMS in biennial years from 2005 to 2014, stratified by STEMI and NSTEACS.



* Baseline is 2005-06

aOR and 95%CI were calculated using multivariate logistic regression for both complete case and pooled imputed data.

** For 1-year mortality only: Censored at 31/7/2014, therefore all PCI procedures performed after 31/7/2013 were not included in describing this rate.

5.4.8 Sensitivity analyses

5.4.8.1 Mixed effects modelling

Table 5.10 shows a summary of mixed effects models adjusted odds ratios of 1-year mortality for UPLMS patients who underwent PCI. Logistic regression models that were used in the adjusted 'fixed effects' analysis, described in detail earlier in this chapter (section 5.3.6.2), were repeated taking into account the hierarchical level of hospitals 'mixed effects'.

There was evidence for hospital (level 2) effects indicating that the use of mixed effects models did not substantially affect the patient (level 1) estimates. In the mixed effect models for the types of clinical presentation (STEMI and NSTEACS), the likelihood ratio statistics were statistically significant indicating that there were similarities between the patients within each hospital and there was significant difference between hospitals

For example, the adjusted odds ratios at 30-day mortality in 2013-14 for STEMI patients were (fixed effects estimates: aOR 0.9, 95% CI 0.5 to 1.6 and mixed effects estimates: aOR, 0.9, 95% CI 0.5 to 1.6, the likelihood ratio statistic was significant, P = 0.004). In the same way, the adjusted odds ratios at 1-year mortality in 2013-14 for STEMI patients were (fixed effects estimates: aOR 0.9, 95% CI 0.5 to 1.6 and mixed effects estimates: aOR, 0.9, 95% CI 0.5 to 1.6, the likelihood ratio statistic was significant, P <0.001) (Figure 5.6, Figure 5.7 and Table 5.10).

Table 5.10: multi-level (mixed effects) modelling at hospital level adjusted odds ratios of 30-day and 1-year mortality for UPLMS patients who underwent PCI.

Outcome	Variable	At hospital level								
		2007-08 n=1,560		2009-10 n=2,494		2011-12 n=3.630		2013-14 n=2.279		likelihood ratio P value
		aOR	95% CI	aOR	95% CI	aOR	95% CI	aOR	95% CI	
30-day mortality	CSA	3.2	0.7 – 14.2	1.1	0.2 – 5.4	1.9	0.4 – 8.4	1.2	0.2 – 6.4	1.000
	STEMI	0.8	0.4 – 1.5	0.7	0.4 – 1.2	0.8	0.4 – 1.4	0.9	0.5 – 1.6	0.004
	NSTEACS	0.8	0.6 – 1.4	0.9	0.6 – 1.3	0.9	0.6 – 1.4	0.9	0.6 – 1.4	0.002
	STEMI with cardiogenic shock	0.4	0.1 – 1.1	0.3	0.1 – 0.7	0.3	0.1 – 0.7	0.3	0.1 – 0.8	0.093
	Radial vs femoral access in STEMI	0.8	0.4 – 1.6	0.9	0.5 – 1.6	0.8	0.4 – 1.4	1.0	0.5 – 1.9	0.203
1-year mortality	CSA	1.5	0.7 – 2.9	1.3	0.7 – 2.6	1.7	0.9 – 3.2	1.1	0.5 – 2.4	0.200
	STEMI	0.8	0.5 – 1.5	0.7	0.4 – 1.2	0.7	0.4 – 1.2	0.9	0.5 – 1.6	<0.001
	NSTEACS	1.0	0.7 – 1.4	0.9	0.7 – 1.4	0.9	0.7 – 1.3	0.9	0.6 – 1.3	<0.001
	STEMI with cardiogenic shock	0.4	0.1 – 1.0	0.3	0.1 – 0.7	0.2	0.1 – 0.6	0.3	0.1 – 0.7	0.078
	Radial vs femoral access in STEMI	0.8	0.4 – 1.5	0.8	0.4 – 1.5	0.7	0.4 – 1.3	1.0	0.5 – 2.1	0.068

5.4.8.2 Multiple imputation

Figures 5.6 and 5.7 show the adjusted odds ratios for 30-day and 1-year mortality in patients with UPLMS who received PCI in biennial years from 2005 to 2014, stratified by clinical presentation using complete case data and imputed data. In general, the multivariate adjustment of the pooled multiple imputation of the missing data made only small changes to point estimates generated from the models. However, the imputation improved the precision of the estimates (smaller confidence intervals) due to the increment in patients' number in the imputed dataset.

Compared with 2005-06, 30-day mortality rates in 2013-14 for STEMI patients were (adjusted odds ratio (aOR), 95% confidence interval (CI) 0.9, 0.5 to 1.6 in complete case data compared to 0.7, 0.4 to 1.2 in imputed data), for NSTEACS patients (aOR, 95% CI 0.9, 0.6 to 1.4 in complete case data compared to0.8, 0.5 to 1.2 in imputed data) and CSA patients (aOR, 95% CI 1.2, 0.2 to 6.4 in complete case data compared to 1.2, 0.3 to 4.6 in imputed data). Similarly, 1-year mortality rates in 2013-14 for STEMI patients were (aOR, 95% CI 0.9, 0.5 to 1.6 in complete case data compared to 0.8, 0.5 to 1.4 in imputed data), for NSTEACS patients (aOR, 95% CI 0.9, 0.6 to 1.3 in complete case data compared to0.8, 0.6 to 1.1 in imputed data) and CSA patients (aOR, 95% CI 1.1, 0.5 to 2.4 in complete case data compared to 1.0, 0.5 to 2.1 in imputed data).

After multivariable adjustment of the pooled imputed data, by 2013-14 the temporal changes to the generated point estimates were statistically irrelevant as they did not change the overall association result of the models and at the same time no changes were observed in the significance of these associations at 30-day mortality and 1-year mortality. A compression between the complete case data and pooled multiply imputed data can be seen in Figures 5.6 and 5.7 which shows the adjusted risk of 30-day and 1-year mortality rates for patients who received PCI to an UPLMS in biennial years from 2005 to 2014, stratified by clinical presentation.

5.5 Discussion

5.5.1 Summary of key findings

- The number of patients with UPLMS who underwent PCI increased by over six-fold in cases, particularly patients who presented acutely.
- Baseline risk profile (reflected in a range of parameters including severe left ventricular systolic dysfunction, age over 80 years and cardiogenic shock) increased.
- Over the study period, several procedural characteristics in UPLMS PCI changed, including an increase in drug eluting stents and intravascular ultrasound use and considerably less glycoprotein IIbIIIa inhibitor (Abciximab) use.
- The use of the radial approach across all clinical strata increased by biennial years. However, it remained less frequent than the femoral approach in STEMI and NSTEACS patients with cardiogenic shock.
- Mortality rates across the spectrum of clinical presentations following UPLMS PCI remained remarkably static despite the significant increase in the number and severity of cases.
- For very high risk cases such as UPLMS PCI for patients with STEMI, complicated by cardiogenic shock, 30-day and 1-year mortality rates have declined over the study period by about 13% and 7%, respectively.
- Multiple imputation made a slight improvement on the precision of the generated adjusted hazard ratios which were statistically insignificant as they did not change the overall association result of the same models from the complete case data.
- Even though there was evidence for hospital effects, the use of mixed effects models did not largely affect the adjusted estimates at patient’s level.

5.5.2 Findings in the context of literature

This whole country observational cohort study of consecutive cases clearly demonstrates substantial changes in both the clinical presentation and the treatment of patients who received UPLMS PCI between 2005 and 2014. Overall, the number of UPLMS cases treated by PCI increased by over six-fold. By contrast to UPLMS PCI, the overall number of cases of PCI in the UK has increased, but at a much slower rate [20, 54].

The increase in patients with UPLMS who underwent PCI in the UK is likely to be the result of a combination of factors including:

1. The improvements in both technology and technique of PCI procedures with the augmentation of experience among interventional cardiologists [25, 60].
2. The relatively recent publication of clinical registry and trial data from a small number of PCI centres (in several countries) showing favourable short and long term clinical efficacy and mortality rates [126, 188].
3. The move from thrombolysis to primary PCI for the treatment of patients with STEMI [76, 189].

In addition, this study identified that the absolute numbers of UPLMS PCI for STEMI with and without cardiogenic shock increased more than for the other clinical syndromes. This was probably a consequence of the increase in the provision of primary PCI services in the UK during this period [76, 117]. Furthermore, the logistics of arranging emergency CABG in the setting of STEMI remains prohibitive, and poor outcomes from CABG in this group have led to a reluctance to operate in this clinical setting [25, 90, 92].

When feasible, PCI is therefore the most practical mode of revascularisation for UPLMS disease presenting as STEMI in this situation. Whilst observational data suggests that there is an outcome benefit for the use of intravascular ultrasound in left main stem PCI [190] in this study, even in 2013-2014, it was used in only slightly more than one third of cases (40.3%). The lack of high quality randomised trial data demonstrating outcome benefit from routine use of intravascular ultrasound represents an important unanswered question that will guide clinical practice.

A decline was noted in the proportion of patients who received more than three stents and more patients received multi-vessel PCI (from 42.1% in 2005-06 to 35.2% in 2013-14). There was a change in the deployment of stents with more frequent deployment of drug eluting stents and, in particular second generation drug eluting stents in the later years of the study. This study showed that there was an increase in the proportion of patients with post-procedure left main stem stenosis greater than 50%. On the other hand, there was no substantial improvement in the proportion of patients with post-procedure TIMI 3 flow in the infarct related artery.

An increase in the use of the radial approach across all clinical strata was noted. However, it remained less frequent than the femoral approach in STEMI and NSTEACS patients with cardiogenic shock, in whom the use of intra-aortic balloon pump was highest. Across the study population as a whole, the radial approach was associated with a lower 30-day, but not 1-year mortality, a finding aligned with other recent publications [191, 192]. Nonetheless, for patients with CSA, the radial approach was not associated with a significant decline in mortality. However, it is likely that despite adjustment for case mix, our results are confounded by indication because higher risk patients were more likely to be selected for a femoral approach.

The results of the temporal investigation suggested that early and late mortality rates across the spectrum of clinical presentations did not change, except for STEMI patients with cardiogenic shock which demonstrated a significant decline in the risk of death (30-day mortality: aOR 0.3, 95% CI, 0.1 to 0.7; 1-year mortality: aOR 0.3, 95% CI 0.1 to 0.9). However, the mortality rate in this group of patients was very high (52.5% and 64.0%, respectively), calling for research into interventions which may address these potentially avoidable deaths. Park *et al.* [43] reported a decline by 40% in all-cause mortality over 12 years (aHR 0.6 95% CI 0.4 to 0.9). Although, Park's findings were similar to the findings in this analysis; the size of the cohort of Park's study was small and less representative since it was performed outside the UK.

Of note was the lack of decline in mortality rates when on the whole cardiovascular outcomes have improved substantially over the last few years [76, 78, 193]. There was an increase in the baseline risk of patients with UPLMS who received PCI and it is possible that this may have attenuated any decline in mortality associated with advances in interventional technologies, adjunctive pharmacology as well as the

quality of care provided. Data from the Swedish Coronary Angiography and Angioplasty Registry (SCAAR) registry [194] over the same period of study included 144,039 PCI procedures from 1990 to 2010. An investigation that also revealed stable 1-year adjusted mortality rates after PCI to any vessel. It is possible that PCI has reached a plateau phase where patient characteristics (co-morbidities) as well as mode of presentation rather than procedural factors now dominate outcomes. Whilst this is possible, we found no change in the crude or adjusted rates, suggesting that other factors come into play, or that our adjustment regression model was not sufficient to comprehensively incorporate cardiovascular risk.

Broader discussions on the methodologies used, such as those relating to the importance of multi-level analysis as well as multiple imputation, are outlined in the discussion chapter. Moreover, more detailed discussion on the overall strengths, limitations and implications of this thesis will be debated in the discussion chapter (see Chapter 7). The next chapter investigates the determinants of survival in patients with STEMI after primary PCI.

5.5.3 Conclusion

Over the study period, these contemporary multicentre observational data show considerable changes in the presentation and treatment but not mortality of patients with UPLMS who underwent PCI. Substantial increase in the number of UPLMS PCI patients was noted, predominantly in acute patients. Early and late mortality rates were stable across all clinical presentation groups. Early and late mortality rates for STEMI with cardiogenic shock declined; however, both mortality rates persisted to be high. The use of the radial approach increased by biennial years. Nevertheless, the radial approach in STEMI and NSTEACS patients with cardiogenic shock was used less frequently than the femoralapproach.

Chapter 6 Determinants of survival after primary PCI

6.1 Summary

In the previous two chapters (Chapters 4 and 5), the determinants and temporal trends of outcomes after PCI in UPLMS patients were evaluated. For more understanding to the quality of care for the patients who received PCI in the UK, this chapter concerns an investigation using the BCIS data into the clinical determinants of primary PCI survival in patients with STEMI. Brief definitions of the types of PCIs (facilitated, rescue and primary) in the management of patients with STEMI as well as a full introduction to primary PCI were described in Chapter 1 (sections 1.3.3 and 1.3.4). A literature review about 'the clinical determinants of the survival for patients with STEMI who underwent primary PCI' was provided in Chapter 2 (section 2.5). This chapter is split into four sections covering: the background, rationale and aims (section 6.2); methodology including study design, population, stratification, definitions, follow-up as well as statistical and sensitivity analyses (section 6.3); results including completeness, descriptive statistics, survival time, multivariate modelling results and sensitivity results (section 6.4); and discussion and conclusion (section 6.5).

6.2 Introduction

6.2.1 Background and rationale

Worldwide, the recommended first line treatment in the management of acute STEMI with or without cardiogenic shock is primary PCI [4, 74]. Survival following acute myocardial infarction patients, particularly among those with STEMI, is profoundly affected by the timing (i.e. urgency) of the medical or interventional treatment provided [4, 7]. Delays to the treatment of patients with STEMI can lead to undesirable complications and potentially avoidable adverse outcomes [71-73]. The practice of primary PCI is increasing globally and particularly in the UK [70-73, 195]. In England and Wales, the frequency of primary PCIs increased by 15.0% from 2004 to 2007 [70, 71, 195].

Evidence from the medical literature supports the fact that primary PCI is associated with better outcomes and survival for patients with STEMI than rescue or facilitated PCI [70]. However, some studies in the literature contradicted these findings and concluded that the impact of primary PCI on survival was worse than the facilitated and rescue PCI [118, 196]. Furthermore, there is a gap of knowledge regarding the predictors of survival after primary PCI. These predictors subsequently have influence on the outcomes and survival of primary PCI [71, 75, 76]. The influence of admission route and hospital differences on primary PCI survival rates is not well defined [78, 79]. Therefore, clinical determinants of survival have a variety of incongruity that need additional exploration and analysis.

In addition, the majority of the existing literature about primary PCI has arisen from randomised controlled trials and is typically conducted outside the UK. Thus they may not be generalisable to the UK. Likewise, there are few prospective studies of the survival in the UK STEMI patients who underwent primary PCI [78, 79, 87]. The results of most of the reviewed studies were not representative of the general population as the majority of these studies were implemented at a local, hospital level and only three studies were performed using population-based datasets; thus, further representative studies using national registries are essential.

Using contemporary primary PCI data available in an observational national-based dataset such as BCIS database allows us to infer all primary PCI survival to the

UK population. Consequently, significant results are worth reporting to patients, cardiology professionals and healthcare managers in the UK on the benefits of existing interventional care of such patients as well as to highlight to stakeholders all areas where care and/or organisational changes and improvements are required.

6.2.2 Aims

The overall rationale and aims of the thesis were mentioned in Chapter 2 (section 2.6). The primary aim of this chapter was to perform a population-based comparative investigation of all patients with STEMI who received facilitated, rescue and primary PCI in the UK over a period of ten years (from January 1 2005 to March 31 2014) in order to:

1. Describe the overall completeness of the 2014 updated BCIS data for all patients with STEMI.
2. Describe demographic and clinical characteristics of patients stratified by the type of PCI (‘facilitated or rescue’ versus primary).
3. Describe the procedural characteristics of patients stratified by the type of PCI, including:
    a. Techniques, medications, types of equipment and types of stents used.
    b. The use of radial approach versus the femoral approach.
4. Evaluate the outcomes including survival of primary PCI for patients with STEMI compared to facilitated and rescue PCI.
5. Identify the clinical determinants of primary PCI survival in patients with STEMI and to measure their level of association compared to facilitated and rescue PCI.
6. Measure the impact of admission route (using multi-level analysis) on the effect of the clinical determinants of survival in patients with STEMI after primary PCI procedures.
7. Measure the influence of hospitals’ dissimilarities (using multi-level analysis) on the survival in patients with STEMI stratified by the type of PCI
8. Generate imputed BCIS datasets ‘fit for purpose’ using multiple imputation in order to test for the analysis sensitivity.

6.3 Methodology

6.3.1 Study setting and design

The study design was a prospective population-based linked cohort study using data of patients with STEMI who receive any one of facilitated, rescue and primary PCI. The data were collected from 111 interventional cardiology centres and hospitals in England, Scotland, Northern Ireland and Wales. All were part of 117 cardiology centres and hospitals registered with the BCIS audit program between 2005 and 2014 (based on BCIS Audit Returns, Adult Interventional Procedures, January 2013 to December 2013) [54].

6.3.2 Patients, procedures and treatments (Study population)

The sampling frame was based on the updated BCIS dataset and included all patients from all countries in the UK (England, Scotland, Northern Ireland and Wales). The total number of patients who attended for PCI in all countries in the UK between the 1st of January, 2005 and the 31st of March, 2014 was 699,248 patients (2014 BCIS data). The inclusion and exclusion criteria (based on the Delphi group clinical agreement) for the derivation of the analytical cohort were:

- Patients who were age less than 18 years were excluded.
- The earliest intervention record was used for patients with multiple admissions.
- Chronic stable angina patients (279,894) and NSTEACS patients (256,815) were excluded. In the same way, patients who had received PCI for ‘other reasons’, ‘unlisted reasons’ or ‘with missing information’ were also excluded (31,140 patients).
- The remaining number of PCI records (134,710) were all patients with STEMI who had received PCI in the UK over a period of ten years (from January 1 2005 to March 31 2014).
- Out of these, 36,073 patients who did not meet electrocardiography criteria for STEMI were excluded.

- Therefore, the final population used for the analysis in this chapter was 98,637 patients with STEMI undergoing PCI. A detailed flow chart of the selected cohort population is shown in Figure 6.1.

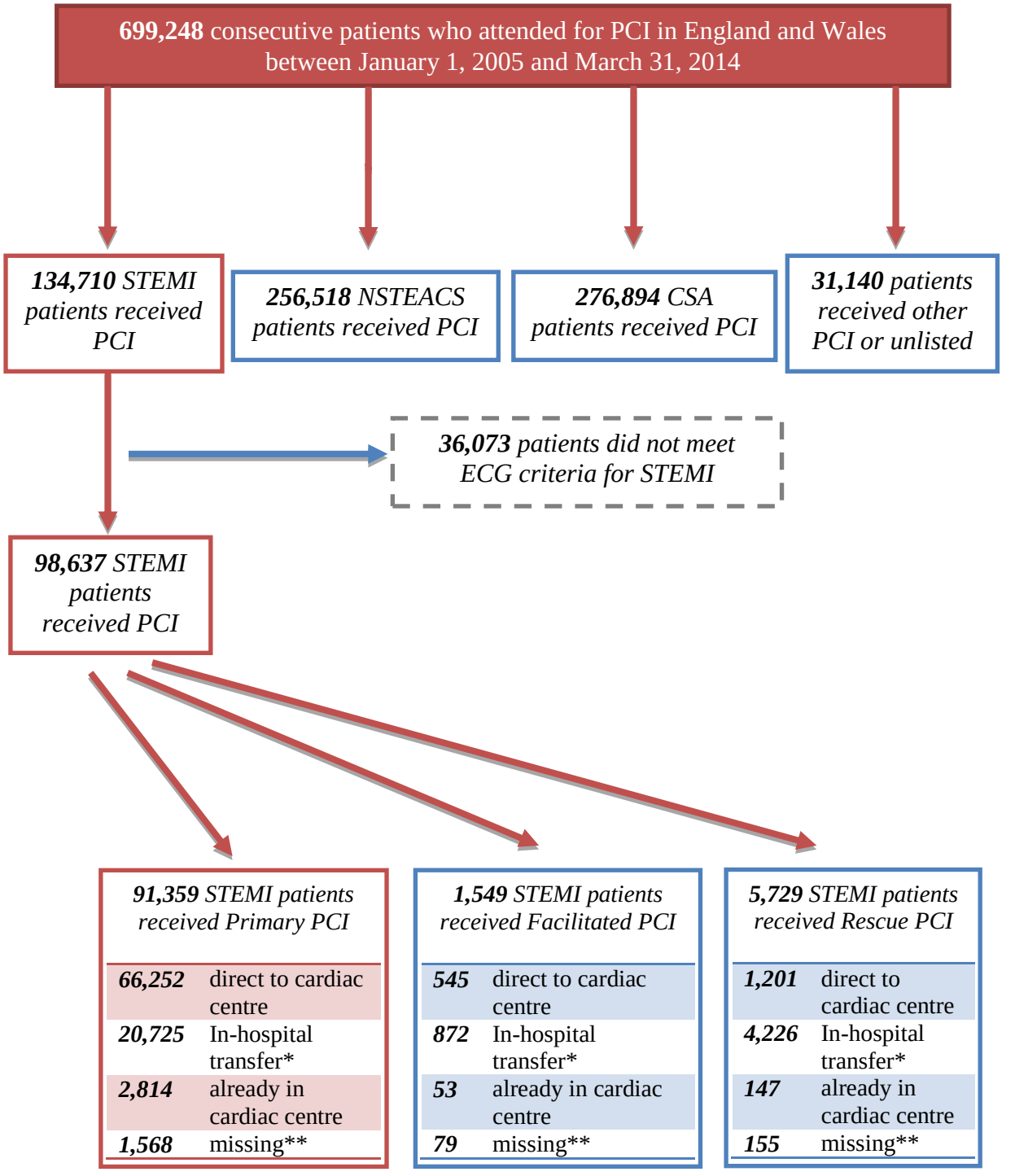
6.3.3 Stratification of cohort population

The designated strata of the cohort population are shown in the flow chart, Figure 6.1. Based on the type of PCI provided to treat patients with STEMI, the whole analysis of this chapter was conducted across two main strata:

1. Patients with STEMI who had received primary PCI (91,359 patients).
2. Patients with STEMI who had received 'facilitated or rescue' PCI (7,278 patients):
    - Facilitated PCI (1,549 patients)
    - Rescue PCI (5,729 patients)

Assuming both types have similar patterns of risk factors, the patients of both facilitated and rescue PCI were joined together in one group for statistical and analytical reasons. Due to the low number of patients in both types compared to primary PCI, combining facilitated and rescue PCI increases the patients number as a group and gives more power to the comparison. The clinical definition of each stratum was described previously in Chapter 1 (section 1.3.3 and Figure 1.2) and in Chapter 4 (Table 4.1).

Figure 6.1: Flow chart of the selected cohort population.



* Only STEMI patients who had their symptoms before or after admission to the referring hospital were added to this group by comparing symptom onset date to Door 1date.

** Missing records + STEMI patients who had mismatch in their symptom onset date (by comparing symptom onset date to Door 1 date).

6.3.4 Other definitions

Please refer to Chapter 4 (section 4.3.4) for the definitions of acute myocardial infarction, patients with STEMI, PCI, cardiogenic shock and MACCE. The categories of the routes of admission were defined in the BCIS database spreadsheet version 5.6.x as follows:

- Direct admission to a cardiac centre: is simply when any patient admitted from the community where he/she developed his/her symptoms.
- Inter-hospital transfer: a patient whose admission was because of ACS and was then transferred to another hospital for PCI.
- Already in a cardiac centre: a patient who developed new symptoms of chest pain after being admitted to a hospital for a different reason. For example, the patient was admitted with a chest infection and then developed chest pain and ECG changes while still in hospital.

However, some patients in the 'already in a cardiac centre' category had mismatched symptom onset and admission dates. Therefore, further data cleaning was performed and any patient with such an issue was considered to have missing information about his/her admission, a process that led to the drop out of more records in the complete case analysis of that variable. More details can be seen in Figure 6.1.

6.3.5 Follow-up and mortality

More details concerning patients' follow-up and mortality can be found in Chapter 1 (section 1.4.3 and Figure 1.3). In summary, the analysis of all-cause mortality was produced by the MRIS by linkage with the ONS using each patient's unique NHS number. Afterwards, using each patient's geographical residence and IMD score, a linkage was made by the CCAD to their corresponding BCIS record.

In the received 2014 versions of the BCIS database, patients, interventionists and hospital identifiers were secondary anonymised. Due to the date of linkage for censored data (31st July 2014), mortality at 1-year and survival data were not available for 519 (10.2%) patients. Thus, patients with a follow-up period of less than 12 months

were excluded from the analysis of patients' survival and 1-year mortality rate; however, those patients were included in all other parts of the analysis.

6.3.6 Statistical analysis

6.3.6.1 Descriptive data analysis

With the intention of obtaining more understanding of patients' characteristics, an initial overall description of the cohort was executed, followed by an exploration of missing data for all the variables in the selected cohort (from the 2014 BCIS database). Missing data patterns were measured and assessed based on the percentage of missingness. Later, a few examples were described on the extent of missing data in both strata, 'facilitated or rescue' and primary PCI.

As mentioned earlier, the whole analysis was stratified by the type of PCI performed for patients with STEMI ('facilitated or rescue' and primary). The purpose of this stratification was to compare the differences between the patients in both intervention groups. It is well understood that primary PCI in patients with STEMI produces better outcomes compared to rescue or facilitated PCI [70]. Later in the analysis, this stratification gave the opportunity to identify and compare the clinical determinants of survival in both intervention groups. Types of tests and methods used for data description are mentioned before in detail in Chapter 3 (section 3.5).

The described includes: baseline demographics, clinical features and procedural characteristics (including pre-procedural and post-procedural). Clinical outcomes were also described (including procedural complications, in-hospital outcomes, 30-day mortality rate and 1-year mortality rate). The frequency of 30-day and 1-year mortality rates were measured further, stratified by the type of arterial approach used.

6.3.6.2 Survival curves

Cumulative unadjusted survival estimates of patients with STEMI who received facilitated, rescue and primary PCI were illustrated using the Kaplan-Meier method from the time of the procedure to 9.6 years. The differences across strata were compared

using the Mantel-Cox log-rank test. The same analysis was repeated to compare the differences between the unadjusted survival times in both ‘facilitated or rescue’ and primary PCI groups stratified by three routes of admission (direct admission to a cardiac centre, inter-hospital transfer and already in a cardiac centre).

6.3.6.3 Survival modelling

The general principle of survival modelling was described earlier in Chapter 3 (section 3.4.6.3). A survival modelling strategy with adjustment was executed to identify the clinical determinants of the survival of patients with STEMI in both intervention groups. The associations with survival at 9.6 years were quantified using fixed effects multivariate Cox proportional hazards models, and estimates were expressed as adjusted hazard ratios (aHR) with 95% confidence intervals (CI). For all tests, a P value less than 5% was considered a cut-off point for statistical significance. All analyses were conducted using Stata IC version 13.0 (StataCorp LP, Texas, USA).

The chosen clinical determinants (predictors) are listed in Table 6.1. The predictors and model covariates were selected based on a literature review on ‘the clinical determinants of survival for primary percutaneous coronary intervention’; see Chapter 2 (section 2.5). In addition, they were selected in light of the clinical importance recommended by the Delphi group. Multivariate model selection process, interaction assessment and the evaluation of goodness of fit were mentioned in detail in Chapter 3 (section 3.4.6.5). In brief, variables with significant predictive value of a P value < 0.05 after univariable modelling were added to the multivariate model. The likelihood ratio test was used to assess for interactions and to evaluate the model goodness of fit.

For each predictor, the estimates of the multivariate Cox hazards regression model in both intervention groups were adjusted by eight different covariates. These selected covariates included ‘age groups’, ‘sex’, ‘pre-procedural cardiogenic shock’, ‘history of diabetes mellitus’, ‘history of renal disease’ and ‘post-procedural complications (side branch occlusion, coronary dissection and shock induced by procedure)’ (Table 6.1).

Table 6.1: Summary of the multivariate Cox hazards models used including the selected predictor variables and covariates.

Outcome and method	Predictors	Covariates
Survival at 9.6 years using fixed effects multivariate Cox proportional hazards model in patients with STEMI who underwent 'facilitated or rescue' and primary PCI	Age groups	Age groups, sex, cardiogenic shock, history of diabetes mellitus, history of renal disease and post-procedural complications (side branch occlusion, coronary dissection and shock induced by procedure)
	Sex	
	Routes of admission	
	Pre-procedural cardiogenic shock	
	History of Acute myocardial infarction	
	History of PCI	
	History of hypertension	
	History of Diabetes mellitus	
	History of Renal disease	
	Left ventricular ejection fraction	
	Vessels attempted	
	Longest Stented/Treated Segment	
	Number stents used	
	Drugs used during procedure	
	Intravascular ultrasound use during procedure	
	Use of intra-aortic balloon pump	
	Arterial Access	
	Time from start of the first symptom to the intervention	
	In-hospital acute myocardial infarction & stroke	
	Procedural complication: Side branch occlusion	
	Procedural complication: Coronary dissection	
	Procedural complication: Shock induced by procedure	

6.3.7 Sensitivity analyses

Three sensitivity analyses were performed to evaluate potential bias from using fixed effect regression methods. Like the previous chapters, the influence of mixed effects Cox hazards models at hospital level was evaluated. Then, the multivariate Cox hazards regression analyses were considered after multiple imputation of missing data.

6.3.7.1 Multi-level regression modelling

The general concept of multi-level regression or mixed effects modelling was defined previously in Chapter 3 (section 3.5.1.5). Models were fitted with a hierarchy of patients clustered in each hospital using random intercepts for hospitals, therefore, allowing for correlations between patient outcomes. Consequently, the mixed effects models accounted for the variance in the predictor variables as well as the variance at the hospital level [133].

This method was performed separately for the ‘facilitated or rescue’ PCI group and for the primary PCI group. Like fixed effect multivariate Cox hazards regression models, the same predictor variables and covariates (Table 6.1) were fitted in the mixed-effect models. Afterward, the adjusted hazard ratio estimates were compared with those from the equivalent fixed effects model.

6.3.7.2 Multiple imputation method

A detailed explanation of multiple imputation method was mentioned earlier in Chapter 3 (sections 3.4.7 and 3.4.8). Table 6.2 show the list of imputation predictor variables of the survival of patients with STEMI who received ‘facilitated or rescue’ and primary PCI with a summary of missing data and the methods used for imputation. In total, 22 imputation predictors were selected, which were based on clinical consensus and a literature review; see Chapter 2 (section 2.5). The frequency of missing values ranged from 0.10% to 65.43%, and all missing values were assumed to be missing at random.

No data were missing for four of these variables: ‘routes of admission’, ‘type of PCI’, ‘year of operation’ and ‘life status at censoring time’. Though, these factors were still used in the imputation as auxiliary variables. As mentioned before in Chapter 3 (section 3.4.8), imputation is not recommended for variables with more than 40% missingness [174]. Therefore, the variable ‘left ventricular ejection fraction’ was not imputed as the missing values were (65.43%). Yet again, the variable was used in the imputation model as an auxiliary variable.

A predictor matrix of 22 variables was designed based on clinical agreement as well as using thresholded P values of less than 0.05 as related and greater than or equal to 0.05 as unrelated (Table 6.3). Chi-squared tests were used for categorical-categorical associations while linear regression was used for continuous-continuous and continuous-categorical associations. From the beginning, the variable ‘time from start of the first symptom to the intervention’ was not included in the predictors list due to collinearity with the ‘routes of admission’ variable.

For each of the remaining 16 predictors with missing values, 20 datasets were imputed using the chained equation method [141, 180]. The fully conditional specification imputation method was used. Separate, individual conditional models for each incomplete predictor were specified and imputed in another ward [153]. The categorical variables were 15 in total. All were imputed using either logistic regression or polytomous regression methods. Only one variable, ‘survival time’, was a normally distributed continuous variable. The method used to impute this variable was the predictive mean matching. The outcome variables ‘survival time’ and ‘life status at censoring time’ were included in the imputation model in order to decrease the pooled estimates bias [166].

For each type/group of PCI (‘facilitated or rescue’ and primary), 20 separate imputation datasets were created. Using the likelihood ratio test to evaluate the goodness of fit, the imputation models diagnostics did not give any cause for concern. Lastly, the 20 imputed datasets for each predictor were pooled together using Rubin's rule and followed by the intended regression model. A comparison between the adjusted hazard ratios from both complete case and imputed data was used to test for the sensitivity of this analysis.

Table 6.2: Imputation predictor variables of the survival of patients with STEMI who received 'facilitated or rescue' and primary PCI with a summary of missing data and the methods used for imputation.

	Variables	Variable type	Missing %	Imputation method
1	**Age groups**	Ordinal	0.10	Polytomous regression
2	**Sex**	Binary	0.36	logistic regression
3	**Routes of admission**	Ordinal	0.00	Auxiliary (not imputed)
4	**Type of PCI**	Ordinal	0.00	Auxiliary (not imputed)
5	**Pre-procedural cardiogenic shock**	Binary	0.81	logistic regression
6	**History of acute myocardial infarction**	Binary	4.20	logistic regression
7	**History of PCI**	Binary	2.08	logistic regression
8	**History of diabetes mellitus**	Binary	4.31	logistic regression
9	**Left ventricular ejection fraction**	Ordinal	65.43	Auxiliary (not imputed)
10	**Year of operation**	Continuous	0.00	Auxiliary (not imputed)
11	**History of renal disease**	Binary	0.41	logistic regression
12	**Longest stented/treated segment**	Continuous	9.46	Collinearity (not imputed)
13	**Number stents used**	Ordinal	0.83	Polytomous regression
14	**Drugs used during procedure**	Ordinal	6.38	Polytomous regression
15	**Intravascular ultrasound during procedure**	Binary	3.64	logistic regression
16	**Use of intra-aortic balloon pump**	Binary	2.95	logistic regression
17	**Arterial access**	Ordinal	1.68	Polytomous regression
18	**Procedural complication: side branch occlusion**	Binary	3.06	logistic regression
19	**Procedural complication: coronary dissection**	Binary	3.06	logistic regression
20	**Procedural complication: shock induced by procedure**	Binary	3.06	logistic regression
21	**Survival time**	Continuous	0.28	Predictive mean matching
22	**Life status at censoring time**	Binary	0.00	Auxiliary (not imputed)

Table 6.3: Predictor matrix of the survival of patients with STEMI who received 'facilitated or rescue' and primary PCI using the 2014 BCIS database.

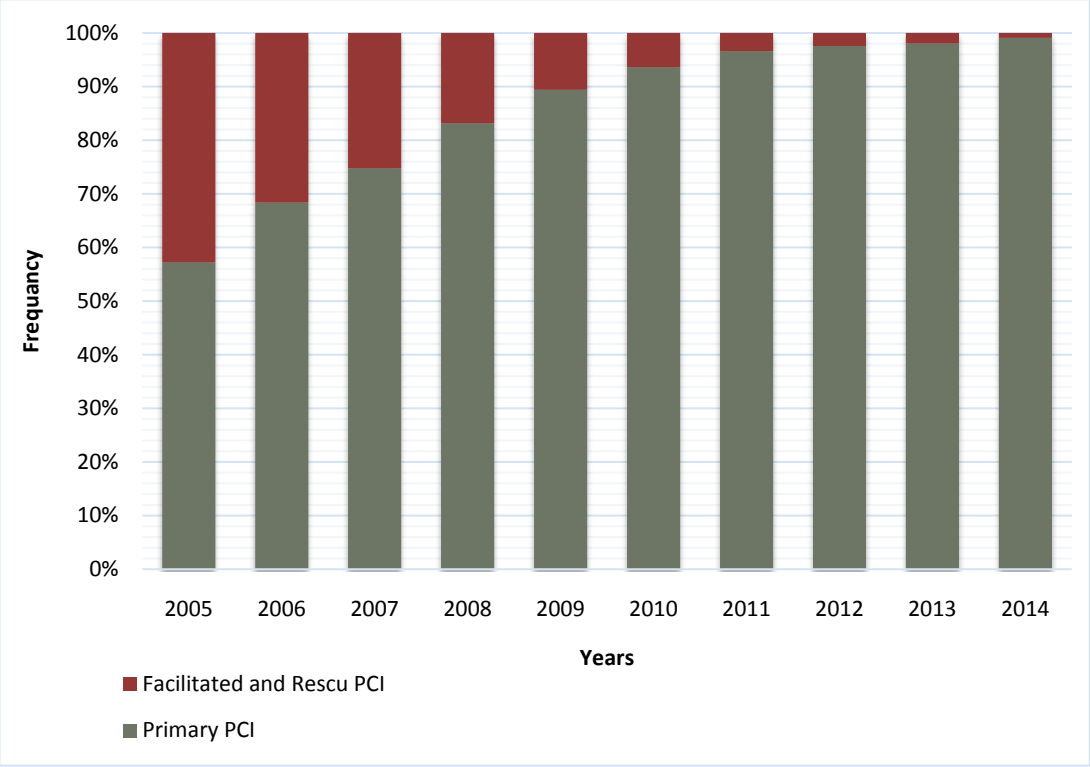
	Variables	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22
1	**Age**																						
2	**Sex**	1																					
3	**Routes of admission**	1	1																				
4	**Type of PCI**	1	1	1	1																		
5	**Pre-procedural cardiogenic shock**	1	1	1	1																		
6	**History of Acute myocardial infarction**	1	1	1	1	1																	
7	**History of PCI**	1	1	1	1	1	1																
8	**History of diabetes mellitus**	1	1	1	1	1	1	1															
9	**Left ventricular ejection fraction**	1	0	1	1	1	1	1	1														
10	**Year of operation**	1	1	1	1	1	1	1	1	1													
11	**History of renal disease**	1	1	1	0	1	1	0	1	1	1												
12	**P-complication: side branch occlusion**	1	0	0	0	0	0	0	0	1	1	0											
13	**P-complication: coronary dissection**	1	1	0	1	1	0	0	0	1	1	0	1										
14	**P-complication: shock induced by procedure**	1	1	0	0	1	0	0	1	1	1	1	1	1	1								
15	**Longest stented/treated segment**	1	1	0	0	1	0	0	1	1	1	1	1	1	1								
16	**Number of stents used**	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1							
17	**Drugs used during procedure**	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1						
18	**Intravascular ultrasound use during procedure**	1	0	0	1	1	0	1	0	1	1	0	0	1	0	0	1	1					
19	**Use of intra-aortic balloon pump**	1	1	0	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1				
20	**Arterial access**	1	1	1	1	1	1	1	1	1	1	1	0	1	0	1	1	1	1	1			
21	**Survival time**	1	1	1	1	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1		
22	**Life status at censoring time**	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	

0: not related, 1: related, P-complication: procedural complication.

6.4 Results

Between 2005 and 2014, the overall cohort of patients with STEMI who received PCI was 98,637. Out of which 91,359 (92.6%) patients were treated by primary PCI, 1,549 (1.6%) patients were treated by facilitated intervention and 5,729 (5.8%) patients were treated by rescue PCI. Over the study period, the frequency of primary interventions increased (from 887 (57.2%) in 2005 to 19,744 (98.1%) in 2013). While, the facilitated or rescue interventions declined (from 663 (42.8%) in 2005 to 400 (2.0%) in 2013). In 2014, the data were collected up to the 21st of March (1,456 (99.0%) primary interventions and 14 (1.0%) facilitated or rescue interventions (Figure 6.2).

Figure 6.2: Frequency of patients with STEMI who received 'facilitated or rescue' and primary PCI by years of procedure.



6.4.1 Data completeness

The mean (SD) level of missingness was 19.92% (27.74%) and the median percentage of missing values was 7.36%. Out of the total 109 variables used for the analysis of this chapter, only 10 (9.2%) variables were 100% complete. These variables were ‘clinical presentation type’, ‘indication for intervention’, ‘procedure urgency’, ‘presenting electrocardiography’, ‘date of operation’, ‘biennial years’, ‘electrocardiography ischaemia’, ‘life status at censored date’, ‘pseudonymised hospital code’ and ‘country hospital in’. However, the remaining 100 variables had missing information that ranged from 0.10% to 99.63%.

Overall, 82 (75.2%) of the variables had missing values of 50% or less, while only 17 (15.6%) variables had missing values of more than 50%. There were 55 (50.5%) variables that had less than 10% missing values. The one with the least missing values was ‘age at procedure’ (0.10%) followed by ‘number of lesions attempted’ (0.17%) and ‘censored date and survival time’ (0.28%). Conversely, only five (3.7%) variables had more than 90% missing information. These included ‘use of ventilation’ (99.63%), ‘bleeding up to discharge’ (99.08%), ‘PCI for stent thrombosis’ (98.52%), ‘third operator status’ (97.49%) and ‘time to bypass’ (92.57%). The frequency and percentages of missing values in the variables of this cohort from the BCIS dataset (2014 version) are shown in Table 6.4.

Furthermore, few examples of the missing values proportions stratified by ‘facilitated or rescue’ and primary PCI are shown in Figure 6.3. One of the variables with high missing values was ‘left ventricular ejection fraction’, which was 63.79% in the facilitated or rescue group and 65.61% in the primary intervention group. The missing values in ‘pre-procedural cardiogenic shock’ were far less in both groups (facilitated or rescue: (1.12%) and primary (0.82%)). The proportion of missing values in few other variables were slightly higher in the facilitated or rescue intervention group, such as ‘life status at discharge’ (facilitated or rescue: (3.48%) and primary (1.91%)). Another example was ‘major adverse cardiac and cerebrovascular event (MACCE)’ (facilitated or rescue: (4.23%) and primary (2.81%)).

Figure 6.3: Examples of the missing values proportions for some variables stratified by 'facilitated or rescue' and primary PCI.

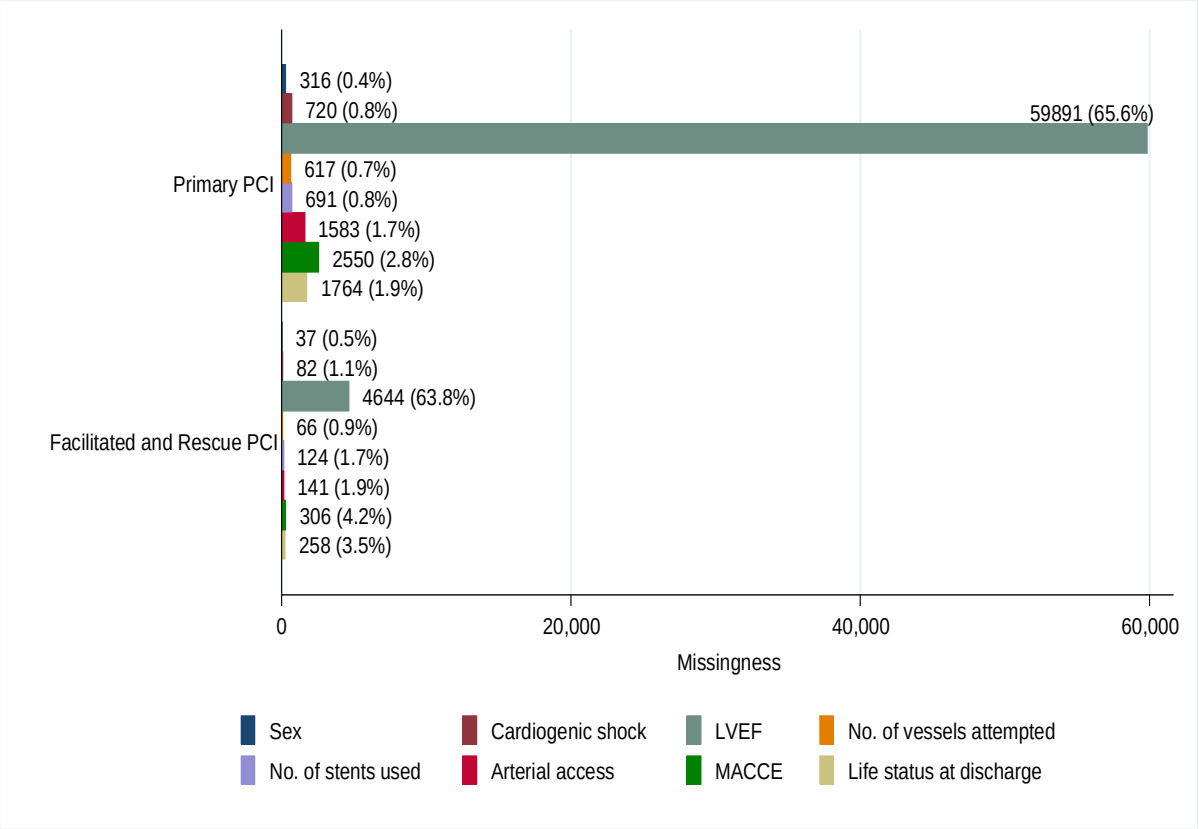


Table 6.4: Recoded variables and summary of missing data in the variables of STEMI cohort from the 2014 BCIS data.

Variable Name	Missing Frequency	Missing %
Age At Procedure	96	0.10
Sex	353	0.36
Ethnic Group	22,041	22.35
Patient Status	8,851	8.97
Clinical presentation type	0	0.00
Indication for Intervention	0	0.00
Procedure Urgency	0	0.00
Cardiogenic Shock Pre-PCI	802	0.81
Angina Status Pre-Surgery	55,546	56.31
Dyspnoea Status Pre-PCI (Stable Only)	57,332	58.12
Admission Route (ACS Only)	1,097	1.11
Presenting electrocardiography (ACS Only)	0	0.00
Recent Lysis (ACS Only)	1,845	1.87
Cardiac Enzymes/Markers Raised	45,586	46.22
Previous acute myocardial infarction	4,146	4.20
Previous coronary artery bypass graft (CABG)	2,398	2.43
Previous percutaneous coronary intervention (PCI)	2,054	2.08
Diabetes	4,249	4.31
Height	48,162	48.83
Weight	36,997	37.51
Left Ventricular Ejection Fraction Category	66,068	66.98
Left Ventricular Ejection Fraction	64,535	65.43
Number of Grafts Present Pre-PCI, CABG Only	24,032	24.36
Number of Grafts Patent Pre- PCI, CABG Only	27,917	28.30
Left Main Stem Stenosis Pre-PCI	14,432	14.63
Left anterior descending Proximal Stenosis Pre-PCI	9,244	9.37
Left anterior descending Other Stenosis Pre-PCI	11,296	11.45
Right coronary artery Stenosis Pre-PCI	7,853	7.96
Circumflex coronary artery Stenosis Pre-PCI	10,772	10.92
Flow In infarct related artery Pre-PCI (ACS Only)	7,255	7.36
Date Of Operation	0	0.00
Date Of Operation (biennial years)	0	0.00
Pseudonymised Consultant Responsible	3,159	3.20
Pseudonymised First Operator Status	1,894	1.92
Primary Operator	4,129	4.19
Second Operator Status	34,551	35.03
Third Operator Status	96,165	97.49

Red (no missing data), Green (less than 10% missing data), Blue (More than 90% missing data)

(Continued) Table 6.4: Recoded variables and summary of missing data in the variables of STEMI cohort from the 2014 BCIS data

Variable Name	Missing Frequency	Missing %
Vessels Attempted	718	0.73
Number of vessels attempted not Epicardial	683	0.69
Number Of Lesions Attempted	164	0.17
Number Of Chronic Occlusions Attempted	3,967	4.02
Number Restenosis Attempted	1,921	1.95
Number Instant Stenosis Attempted	8,448	8.56
Number Stents Used	815	0.83
Number Drug-Eluting Stents Used	1,228	1.24
Type of stent used	989	1.00
Drugs Eluted By Stents	3,557	3.61
Drugs Used During Procedure	6,296	6.38
Intravascular ultrasound use during procedure	3,591	3.64
pressure wire use during procedure	3,591	3.64
Use of intra-aortic balloon pump	2,914	2.95
Left Main Stem Stenosis Post-PCI	13,978	14.17
Left anterior descending Proximal Stenosis Post-PCI	10,869	11.02
Left anterior descending Other Stenosis Post-PCI	12,948	13.13
Right coronary artery Stenosis PCI	9,705	9.84
Circumflex coronary artery Stenosis PCI	13,530	13.72
Number Lesions Successful	723	0.73
Number Coronary Grafts Patent PostOp	28,742	29.14
Flow In infarct related artery PostOp (ACS only)	7,844	7.95
Device Failure	3,280	3.33
PCI Hospital Outcome	2,856	2.90
Enzymes Post-PCI	75,836	76.88
Status At Discharge	2,022	2.05
Discharge Date	2,801	2.84
Cholesterol	66,579	67.50
Smoking Status	9,524	9.66
Family History Of coronary artery disease	14,023	14.22
Medical History	2,684	2.72
History Of Renal Disease	400	0.41
Ventilated Pre-PCI	3,587	3.64
Q Wave On electrocardiography	5,273	5.35
Electrocardiography Ischaemia	0	0.00
Drug Therapy Pre-PCI	4,697	4.76
Follow On AdHoc Procedure	6,057	6.14

Red (no missing data), Green (less than 10% missing data), Blue (More than 90% missing data)

(Continued) Table 6.4: Recoded variables and summary of missing data in the variables of STEMI cohort from the 2014 BCIS data

Variable Name	Missing Frequency	Missing %
Why No IIb/IIIA During Procedure	26,794	27.16
Indication For Stent	5,531	5.61
Surgical Cover	3,762	3.81
Left Main Stem Protected	24,592	24.93
Referral Hospital	67,591	68.52
Date of electrocardiography Triggering primary PCI	81,360	82.48
Patient Location at Time of STEMI Onset	47,629	48.29
Creatinine	66,521	67.44
PCI for stent thrombosis	97,174	98.52
Training Procedure	5,112	5.18
Research Procedure	7,268	7.37
Arterial Access	1,573	1.59
Largest Balloon/Stent Used	10,664	10.81
Longest Stented/Treated Segment	9,335	9.46
Procedural Complication	3,017	3.06
Arterial Complication	3,837	3.89
Time to Bypass	91,306	92.57
Patient Status During Transfer To Theatre	14,376	14.57
Bleeding up to discharge	97,734	99.08
Ventilation	98,270	99.63
Pseudonymised Hospital Code	0	0.00
Country Hospital In	0	0.00
Length of Stay in Hospital (days)	20,026	20.30
Index of Multiple Deprivation Score	19,725	20.00
Life Status at 7days	8,569	8.69
Life Status at 30days	8,574	8.69
Life Status at 1year	16,480	16.71
Life Status at 2years	32,076	32.52
Life Status at 3years	46,675	47.32
Life Status at 4years	59,460	60.28
Life Status at 5years	69,197	70.15
Death after Procedure (days)	84,962	86.14
Censored date	275	0.28
Survival time	275	0.28
Life Status at censored date	0	0.00

Red (no missing data), Green (less than 10% missing data), Blue (More than 90% missing data)

6.4.2 Baseline demographic characteristics

In the UK, patients with STEMI who received PCI were treated in 111 different hospitals or centres. As mentioned earlier, the analysis in this chapter was split into two groups of patients: 91,359 (92.6%) who received primary PCI and 7,278 (7.4%) patients who were treated by either facilitated or rescue intervention. The mean (SD) age of the overall cohort was 63.2 (13.0) years, which was 61.0 (11.8) years for those who received facilitated or rescue intervention and 63.4 (13.1) years for those who received primary intervention (P<0.001). Patients older than 80 years of age were more frequent in the primary intervention group at 10,458 (11.5%) patients compared to 384 (5.3%) patients in facilitated or rescue intervention group (P <0.001).

In total, there were more males than females who were recorded as having STEMI and PCI 73,332 (74.4%) males versus 24,952 (25.3%) females (males in facilitated or rescue: 5,806 (80.2%) and primary: 67,526 (74.2%) patients, P <0.001). Caucasian patients were the most common ethnic group in the cohort (facilitated or rescue: 4,080 (87.9%) and primary: 62,853 (87.4%) patients, P<0.001). The majority of the patients were treated in NHS hospitals or centres, (98.8%) in facilitated or rescue intervention group and (98.1%) in the primary intervention group (P<0.001). Predominantly, most of the patients with STEMI were treated in English hospitals or centres (facilitated or rescue: 5,897 (81.0%) and primary: 83,509 (91.4%) patients, P <0.001).

Direct to cardiac centre was the commonest route of admission in patients with STEMI who were treated by primary PCI at 66,252 (73.8%) which was much higher than the proportion of inpatients admitted and treated by facilitated or rescue intervention compared to 1,746 (24.8%). On the other hand, inter-hospital transfer was the most frequent route of admission in patients who were treated by facilitated or rescue intervention (facilitated or rescue: 5,098 (72.4%) and primary: 20,725 (23.1%) patients, P <0.001). Table 6.5 shows the distribution of baseline demographic characteristics stratified by ‘facilitated or rescue’ and primary PCI.

Table 6.5: Baseline demographic characteristics of patients with STEMI who received 'facilitated or rescue' and primary PCI.

Variable		Facilitated or Rescue PCI n=7,278	Primary PCI n=91,359	P value *
Mean (SD) age, years		61.0 (11.8)	63.4 (13.1)	< 0.001
Age	**Less than 65 years (%)**	4,548/7,273 (62.5)	49,525/91,268 (54.2)	< 0.001
	65 - 80 years (%)	2,341/7,273 (32.2)	31,285/91,268 (34.3)	
	More than 80 years (%)	384/7,273 (5.3)	10,458/91,268 (11.5)	
Gender	**Female (%)**	1,435/7,241 (19.8)	23,517/91.043 (25.8)	< 0.001
	Male (%)	5,806/7,241 (80.2)	67,526/91.043 (74.2)	
Ethnic groups	**Caucasian (%)**	4,080/4,640 (87.9)	62,853/71,956 (87.4)	< 0.001
	Black (%)	11/4,640 (0.2)	635/71,956 (0.9)	
	Asian (%)	141/4,640 (3.0)	5,100/71,956 (7.1)	
	Other (%)	408/4,640 (8.9)	3,368/71,956 (4.6)	
Patient type	**NHS hospital or centre (%)**	6,561/6,689 (98.1)	82,073/83,097 (98.8)	< 0.001
	Private hospital or centre (%)	128/6,689 (1.9)	1,024/83,097 (1.2)	
Country	**England (%)**	5,897/7,278 (81.0)	83,509/91,359 (91.4)	< 0.001
	North Ireland (%)	491/7,278 (6.8)	1,333/91,359 (1.5)	
	Scotland (%)	334/7,278 (4.6)	3,623/91,359 (4.0)	
	Wales (%)	556/7,278 (7.6)	2,894/91,359 (3.1)	
Admission route	**Direct to cardiac centre (%)**	1,746/7,044 (24.8)	66,252/89,791 (73.8)	< 0.001
	Inter-hospital transfer (%)	5,098/7,044 (72.4)	20,725/89,791 (23.1)	
	Already in cardiac centre (%)	200/7,044 (2.8)	2,814/89,791 (3.1)	
Index of multiple deprivation score, mean (SD)		19.7 (12.8)	22.6 (14.2)	< 0.001

Proportions exclude missing data.
* P-value was calculated using Chi-square test for categorical variables and analysis of variance (ANOVA) for continues variables.

6.4.3 Clinical characteristics

History of previous acute myocardial infarction was slightly higher in facilitated or rescue intervention patients (17.4%) compared to the primary intervention patients (13.1%) (P <0.001). History of previous PCI was, to some extent, more frequent in the primary intervention patients, 8,028 (9.0%) compared to 448 (6.3%) in facilitated or rescue intervention patients (P <0.001). The frequency of family history of coronary artery disease was more in facilitated or rescue intervention patients (facilitated or rescue: 2,769 (45.5%) and primary: 29,423 (37.5%) patients, P <0.001).

The proportions of patients with a history of diabetes mellitus, renal disease or hypertension were higher in the primary PCI group (all P <0.001), whereas the presence of hypercholesterolemia, current smoking, pre-procedural cardiogenic shock and severe left ventricular systolic dysfunction showed the opposite distribution, as the proportions were slightly higher in the facilitated or rescue intervention group of patients (all P <0.001). The distribution of the clinical characteristics stratified by ‘facilitated or rescue’ and primary PCI can be seen in more detail in Table 6.6.

Table 6.6: Baseline clinical characteristics of patients with STEMI who received 'facilitated or rescue' and primary PCI.

Variable		Facilitated or Rescue PCI n=7,278	Primary PCI n=91,359	P value *
Previous acute myocardial infarction (%)		1,218/7,007 (17.4)	11,425/87,484 (13.1)	<0.001
Previous percutaneous coronary intervention (%)		448/7,086 (6.3)	8,028/89,497 (9.0)	<0.001
History of previous coronary artery bypass graft (%)		149/7,125 (2.1)	2,483/89,114 (2.8)	0.001
Family history of coronary artery disease (%)		2,769/6,086 (45.5)	29,423/78,528 (37.5)	<0.001
History of diabetes mellitus (%)		875/6,953 (12.6)	12,290/87,435 (14.1)	0.001
History of renal disease (%)		104/7,253 (1.4)	1,448/90,984 (1.6)	0.300
Hypercholesterolemia (%)		2,817/7,033 (40.1)	34,939/88,920 (39.3)	0.208
Hypertension (%)		2,673/7,033 (38.0)	35,838/88,920 (40.3)	<0.001
Smoking status	**Never smoked (%)**	1,762/6,493 (27.1)	26,967/82,620 (32.6)	<0.001
	Ex-smoker (%)	1,922/6,493 (29.6)	21,707/82,620 (26.3)	
	Current smoker (%)	2,809/6,493 (43.3)	33,946/82,620 (41.1)	
Recent thrombolysis (%)		6,525/7,166 (91.1)	0/89,626 (0.0)	<0.001
Cardiogenic shock (%)		529/7,196 (8.2)	6,772/90,639 (7.5)	0.019
Severe left ventricular systolic dysfunction - <30% (%)		392/2,634 (14.9)	4,309/31,468 (13.7)	<0.001

Proportions exclude missing data.
* P-value was calculated using Chi-square test for categorical variables and analysis of variance (ANOVA) for continues variables.

6.4.4 Procedural characteristics

With regard to the use of pre-procedural medications, aspirin was the most prevalent medication in both groups (facilitated or rescue: 6,127 (88.5%) and primary: 74,475 (85.6%) patients, P <0.001). The second frequently used medication was clopidogrel (facilitated or rescue: 5,923 (85.6%) and primary: 50,465 (58.0%) patients, P <0.001). The proportion of pre-procedural TIMI 3 was higher in the facilitated or rescue intervention group while TIMI 0 was higher in the primary intervention patients (P <0.001). More details on the distribution of pre-procedural characteristics stratified by 'facilitated or rescue' and primary PCI can be seen in Table 6.7.

The majority of patients in both groups had their procedures more than two hours from the onset of symptoms (facilitated or rescue: 7,146 (99.1%) and primary: 75,618 (83.4%) patients, P <0.001). In both groups, patients who had only one vessel stented were more common than those who had stents in more than one vessel (one vessel stented in facilitated or rescue: 6,218 (86.2%) patients and primary: 80,979 (89.2%), P <0.001). One stent was the most frequent number of stents used in both groups (facilitated or rescue: 4,193 (58.6%) and primary: 53,463 (59.0%) patients, P <0.001). The most prevalent type of the utilised drug eluted stents in the primary intervention group were Promus (13.0%), Xience V (8.2%) and Resolute Integrity (7.0%). For the facilitated or rescue intervention group, Taxus liberte were used in (9.2%) of patients and Promus in (7.5%) of patients.

The mean (SD) of the longest stented segment was 24.4 (11.9) mm for the patients who received facilitated or rescue intervention and 24.8 (12.6) mm for those who received primary intervention, (P =0.017). Femoral access was used more frequently than radial access in the facilitated or rescue intervention group (femoral: 3,831 (53.7%) and radial: 3,291 (46.1%), P <0.001). In contrast, the radial artery was accessed more frequently in the primary intervention patients (femoral: 38,095 (42.4%) and radial: 51,554 (47.4%), P <0.001). Predominantly, femoral access was used more frequently in female patients (facilitated or rescue: 811 (57.5%) and primary: 10,670 (46.2%) patients, both P <0.001).

The use of intravascular ultrasound was not that prevalent; however, to some extent, it was performed more in the primary intervention patients (facilitated or rescue:

127 (1.8%) patients and primary: 2,033 (2.3%), P =0.007). At the same time, intra-aortic balloon pump was inserted less frequently in the primary intervention group (facilitated or rescue: 417 (6.0%) patients and primary: 4,601 (5.2%), P =0.006).

The glycoprotein IIb IIIa inhibitor, Abciximab, was the commonest medication used during procedures. However, Abciximab was used less frequently for the facilitated or rescue intervention patients (facilitated or rescue: 2,399 (34.4%) and primary: 35,438 (41.5%) patients, P <0.001). In both intervention groups, post-procedural TIMI 3 flow was the commonest type of flow (P <0.001). The distribution of procedural characteristics stratified by 'facilitated or rescue' and primary PCI can be seen in more detail in Table 6.8.

Table 6.7: Pre-procedural characteristics of patients with STEMI who received 'facilitated or rescue' and primary PCI.

Variable		Facilitated or Rescue PCI n=7,278	Primary PCI n=91,359	P value *
Pre-procedural medications	**Aspirin (%)**	6,127/6,923 (88.5)	74,475/87,017 (85.6)	<0.001
	Clopidogrel (%)	5,923/6,923 (85.6)	50,465/87,017 (58.0)	
	Heparin (%)	2,653 /6,923 (38.3)	20,656 /87,017 (23.7)	
	Bivalirudin (%)	144/6,923 (2.1)	11,698 /87,017 (13.4)	
	Nitrates (%)	858/6,923 (12.4)	5,205/87,017 (6.0)	
	Prasugrel (%)	108/6,923 (1.6)	13,882/87,017 (16.0)	
	Ticagrelor (%)	68/6,923 (1.0)	5,808/87,017 (6.7)	
Pre-procedure flow in IRA	**TIMI 0 (%)**	2,484/6,823 (36.4)	58,650/84,559 (69.4)	<0.001
	TIMI 1 (%)	740/6,823 (10.8)	6,730/84,559 (8.0)	
	TIMI 2 (%)	1,117/6,823 (16.4)	7,888/84,559 (9.3)	
	TIMI 3 (%)	1,881/6,823 (27.6)	9,160/84,559 (10.8)	
	Unknown (%)	601/6,823 (8.8)	2,131/84,559 (2.5)	

Proportions exclude missing data.
* P-value was calculated using Chi-square test for categorical variables and analysis of variance (ANOVA) for continues variables.

Table 6.8: Procedural characteristics of patients with STEMI who received 'facilitated or rescue' and primary PCI.

Variable		Facilitated or Rescue PCI n=7,278	Primary PCI n=91,359	P value *
Time from the onset of symptoms to PCI	**2 hours or less (%)**	61/7,207 (0.9)	15,100/90,718 (16.6)	<0.001
	More than 2 hours (%)	7,146/7,207 (99.1)	75,618/90,718 (83.4)	
Vessels attempted	**None (%)**	59/7,212 (0.8)	426/90,742 (0.5)	<0.001
	Single vessel (%)	6,218/7,212 (86.2)	80,979/90,742 (89.2)	
	Multi-vessels (%)	935/7,212 (13.0)	9,337/90,742 (10.3)	
Total number stents used	**0 (%)**	369/7,154 (5.2)	6,963/90,668 (7.7)	<0.001
	1 (%)	4,193/7,154 (58.6)	53,463/90,668 (59.0)	
	2 (%)	1,815/7,154 (25.4)	21,761/90,668 (24.0)	
	≥ 3 (%)	777/7,154 (10.8)	8,481/90,668 (9.3)	
Type of drug eluted stents used	**Taxus liberte (Boston Scientific) (%)**	652/7,089 (9.2)	2,081/87,991 (2.4)	<0.001
	Cypher (Cordis) (%)	362/7,089 (5.1)	1,963/87,991 (2.2)	
	Endeavor (Medtronic) (%)	430/7,089 (6.1)	3,451/87,991 (3.9)	
	Xience V (Abbott) (%)	424/7,089 (6.0)	7,216/87,991 (8.2)	
	Promus (Boston Scientific) (%)	529/7,089 (7.5)	11,445/87,991 (13.0)	
	BioMatrix (%)	115/7,089 (1.6)	3,393/87,991 (3.9)	
	Promus Element (%)	284/7,089 (4.0)	5,844/87,991 (6.6)	
	Xience Prime (%)	125/7,089 (1.8)	5,808/87,991 (6.6)	
	Resolute Integrity (%)	108/7,089 (1.5)	6,133/87,991 (7.0)	
Longest stented/treated segment/mm, mean (SD)		24.4 (11.9)	24.8 (12.6)	0.017
Arterial access	**Femoral (%)**	3,831/7,137 (53.7)	38,095/89,776 (42.4)	<0.001
	Radial (%)	3,291/7,137 (46.1)	51,554/89,776 (57.4)	
	Others (%)	15/7,137 (0.2)	127/89,776 (0.2)	
Intravascular ultrasound (%)		127/7,007 (1.8)	2,033/88,039 (2.3)	0.007
Pressure wire (%)		22/7,007 (0.3)	356/88,039 (0.4)	0.247
Intra-aortic balloon pump (%)		417/7,008 (6.0)	4,601/88,715 (5.2)	0.006
Use of ventilation (%)		292/7,071 (4.1)	3,479/87,979 (4.0)	0.468
Medications used during procedure	**None (%)**	3,793/6,970 (54.4)	39,027/85,371 (45.7)	<0.001
	Abciximab (%)	2,399/6,970 (34.4)	35,438/85,371 (41.5)	
	Eptifibitide (%)	211/6,970 (3.0)	5,558/85,371 (6.5)	
	Tirofiban (%)	567/6,970 (8.2)	5,348/85,371 (6.3)	
Post-procedure flow in IRA	**TIMI 0 (%)**	273/6,683(4.1)	4,687/84,110 (5.6)	<0.001
	TIMI 1 (%)	121/6,683(1.8)	1,097/84,110 (1.3)	
	TIMI 2 (%)	506/6,683(7.6)	4,195/84,110 (5.0)	
	TIMI 3 (%)	5,221/6,683(78.1)	72,232/84,110 (85.9)	
	Unknown (%)	562/6,683(8.4)	1,899/84,110 (2.3)	

Proportions exclude missing data.

* P-value was calculated using Chi-square test for categorical variables and analysis of variance (ANOVA) for continues variables.

6.4.5 Clinical outcomes

The distribution of the procedural complications of patients with STEMI stratified by 'facilitated or rescue' and primary PCI can be seen in Table 6.9. The proportions of side branch occlusion, coronary dissection, coronary perforation, heart block requiring pacing, need for direct current cardioversion, ventilation and cardiogenic shock occurring during the procedure were very rare and comparable in both groups. However, no flow/slow flow occurred slightly more during the procedures of facilitated or rescue intervention patients (facilitated or rescue 240 (3.4%) and primary 2,195 (2.5%) patients, P <0.001).

Most of the in-hospital outcomes were infrequent in both groups of intervention. They were comparable, although they were more to some extent in facilitated or rescue intervention patients. Gastro-intestinal bleeding and the need for blood transfusion were less frequent in both groups of intervention when approached through the radial artery. The prevalence of the unadjusted MACCE complications was slightly higher in the facilitated or rescue intervention group (facilitated or rescue 367 (5.3%) and primary 4,260 (4.8%) patients, P =0.080). More details on in-hospital outcomes of patients stratified by 'facilitated or rescue' and primary PCI are shown in Table 6.10.

Table 6.9: Procedural complications of patients with STEMI who received 'facilitated or rescue' and primary PCI.

Variable	Facilitated or Rescue PCI n=7,278	Primary PCI n=91,359	P value *
Side branch occlusion (%)	40/7,121 (0.6)	472/88,499 (0.5)	0.752
Coronary dissection (%)	70/7,121 (1.0)	1,208/88,499 (1.4)	0.007
Coronary perforation (%)	15/7,121 (0.2)	207/88,499 (0.2)	0.695
Heart block requiring pacing (%)	54/7,121 (0.8)	662/88,499 (0.8)	0.923
Direct current cardioversion (%)	76/7,121 (1.1)	1,327/88,499 (1.5)	0.004
No flow/slow flow (%)	240/7,121 (3.4)	2,195/88,499 (2.5)	<0.001
Ventilated (%)	43/7,121 (0.6)	532/88,499 (0.6)	0.977
Cardiogenic shock induced by procedure (%)	39/7,121 (0.6)	486/88,499 (0.5)	0.987

Proportions exclude missing data.
* P-value was calculated using Chi-square test for categorical variables and analysis of variance (ANOVA) for continues variables.

Table 6.10: In-hospital outcomes and mortality rates of patients with STEMI who received 'facilitated or rescue' and primary PCI.

Variable			Facilitated or Rescue PCI n=7,278	Primary PCI n=91,359	P value *
Acute myocardial infarction (%)			59/6,972 (0.9)	355/88,809 (0.4)	<0.001
Stroke (%)			35/6,972 (0.5)	257/88,809 (0.3)	
Renal failure/dialysis (%)			27/6,972 (0.4)	237/88,809 (0.3)	0.065
Blood transfusion		**Radial access (%)**	13/3,165 (0.4)	133/50,125 (0.3)	0.129
		Femoral access (%)	33/3,659 (0.9)	286/37,001 (0.8)	0.399
Gastro-intestinal bleeding		**Radial access (%)**	14/3,165 (0.4)	114/50,125 (0.2)	0.017
		Femoral access (%)	18/3,659 (0.5)	142/37,001 (0.4)	0.319
Revascularisation		**Percutaneous coronary intervention (%)**	40/6,972 (0.6)	592/88,809 (0.7)	0.267
		Coronary artery bypass graft (%)	24/6,972 (0.3)	404/88,809 (0.5)	
Unadjusted in-hospital MACCE rate (%)			367/6,972 (5.3)	4,260/88,809 (4.8)	0.080
Unadjusted in-hospital mortality rate (%)			336/7,020 (4.8)	4,330/89,595 (4.8)	0.861
Unadjusted 30-day mortality rate	**Overall mortality (%)**		409/6,282 (6.5)	5,058/83,781(6.0)	0.130
	Arterial access	**Radial access (%)**	123/2,546 (4.8)	1,832/46,130 (4.0)	<0.001
		Femoral access (%)	283/3,626 (7.8)	3,135/36,397 (8.6)	
	Routes of admission	**Direct admission (%)**	108/1,587 (6.8)	3,441/61,380 (5.6)	<0.001
		Interhospital transfere (%)	274/4,357 (6.3)	1,295/19,014 (6.8)	
		Already in hospital (%)	17/185 (9.2)	264/2,507 (10.5)	
Unadjusted 1-year mortality rate **	**Overall mortality (%)**		531/6,198 (8.6)	7,168/75,220 (9.5)	0.013
	Arterial access	**Radial access (%)**	187/2,507 (7.5)	3,188/40,246 (7.9)	<0.001
		Femoral access (%)	354/3,608 (9.8)	4,561/34,583 (13.2)	
	Routes of admission	**Direct admission (%)**	144/1,555 (9.3)	5,412/55,372 (9.8)	<0.001
		Interhospital transfere (%)	367/4,329 (8.5)	1,992/17,469 (11.4)	
		Already in hospital (%)	22/182 (12.1)	405/2,308 (17.6)	

MACCE: major adverse cardiac and cerebrovascular event
Proportions exclude missing data.

* P-value was calculated using Chi-square test for categorical variables and analysis of variance (ANOVA) for continues variables.

** Censored at 31/7/2014, therefore all PCI procedures performed after 31/7/2013were not included in describing this rate.

6.4.6 Crude mortality

The median follow-up period of the cohort was 910 days (range: 1 day to 3,435 days). In total, there were 13,476 (13.6%) deaths over a total follow-up period of 90,709,415 patient years. For the facilitated or rescue intervention patients, there were 975 (13.4%) deaths over a total follow-up period of 10,062,299 patient years. For the primary PCI patients, 12,501 (13.7%) deaths over a total follow-up period of 80,647,116 patient years. The unadjusted crude mortality rate at 30 days was similar in both intervention groups (facilitated or rescue: 409 (6.5%) and primary: 5,058 (6.0%) patients, P =0.130). On the other hand, the unadjusted crude mortality rate at one year was more in the primary intervention patients (facilitated or rescue: 531 (8.6%) and primary: 7,168 (9.5%) patients, P =0.013) (Table 6.10).

6.4.7 Clinical variables and crude mortality

Compared with the femoral artery access, the radial artery access was associated with lower crude 30-day and 1-year mortality rates in both intervention groups (all P <0.001). In the facilitated or rescue intervention patients, the rate of 30-day mortality was 123 (4.8%) in radial access versus 283 (7.8%) in femoral, while the rate of 1-year mortality was 187 (7.5%) in radial versus 354 (9.8%) in femoral. Likewise, for the primary intervention patients, the rate of 30-day mortality was 1,832 (4.0%) in radial access versus 3,135 (8.6%) in femoral, while the rate of 1-year mortality was 3,188 (7.9%) in radial versus 4,561 (13.2%) in femoral access (Table 6.10).

Compared to the other routes of admission, direct admission to a cardiac hospital or centre was associated with lower crude 30-day and 1-year mortality rates in the primary intervention patients (all P <0.001). In the facilitated or rescue intervention patients, inter-hospital transfer as a route of admission was associated with the lowest crude 30-day and 1-year mortality rates (Table 6.10).

6.4.8 Survival time

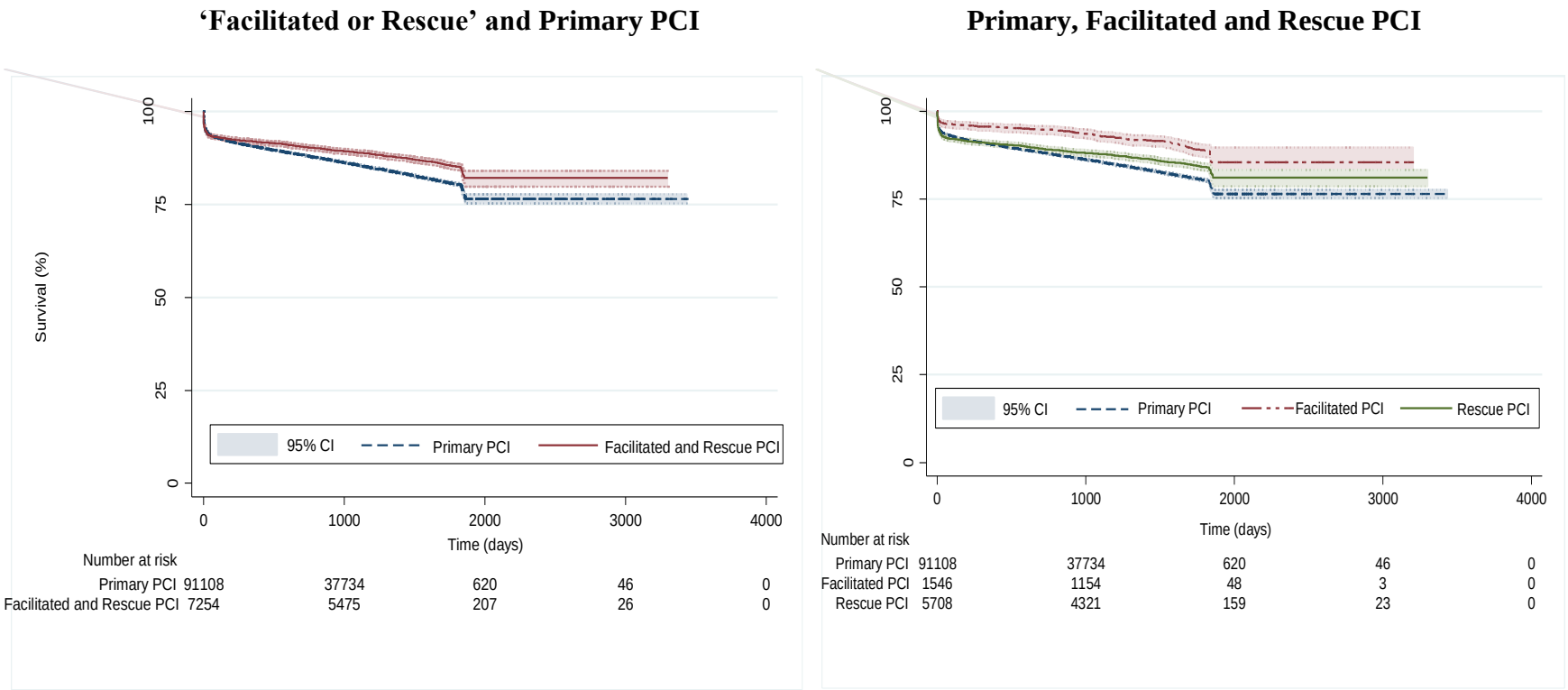
Figure 6.4 illustrates the Kaplan–Meier curves for unadjusted survival estimates to all-cause mortality in patients with STEMI who received facilitated, rescue and primary PCI from time of procedure to 9.6 years. The survival distributions of all strata were significantly different, showing that the survival of patients with STEMI who were treated by primary intervention was significantly less than the facilitated and/or rescue intervention patients (P <0.001).

The Kaplan–Meier curves in Figure 6.5 demonstrates the unadjusted survival time (from time of procedure to 9.6 years) to all-cause mortality in patients who received ‘facilitated or rescue’ and primary PCI, stratified by time from symptoms onset to the procedure. Patients who received primary PCI before or at two hours from the onset of symptoms had better survival over the first five years of the study period. For procedures performed after two hours, primary PCI patients had worse survival compared to the ‘facilitated or rescue’ group P <0.001).

Further stratified by age groups, Figure 6.6 shows the Kaplan–Meier curves for unadjusted survival time (from time of procedure to 9.6 years) to all-cause mortality in patients who received ‘facilitated or rescue’ and primary PCI. The survival of elderly (more than 80 years) patients with STEMI in both PCI groups was significantly worse than younger patients (‘60 to 80 years’ then ‘less than 60 years’) (P <0.001).

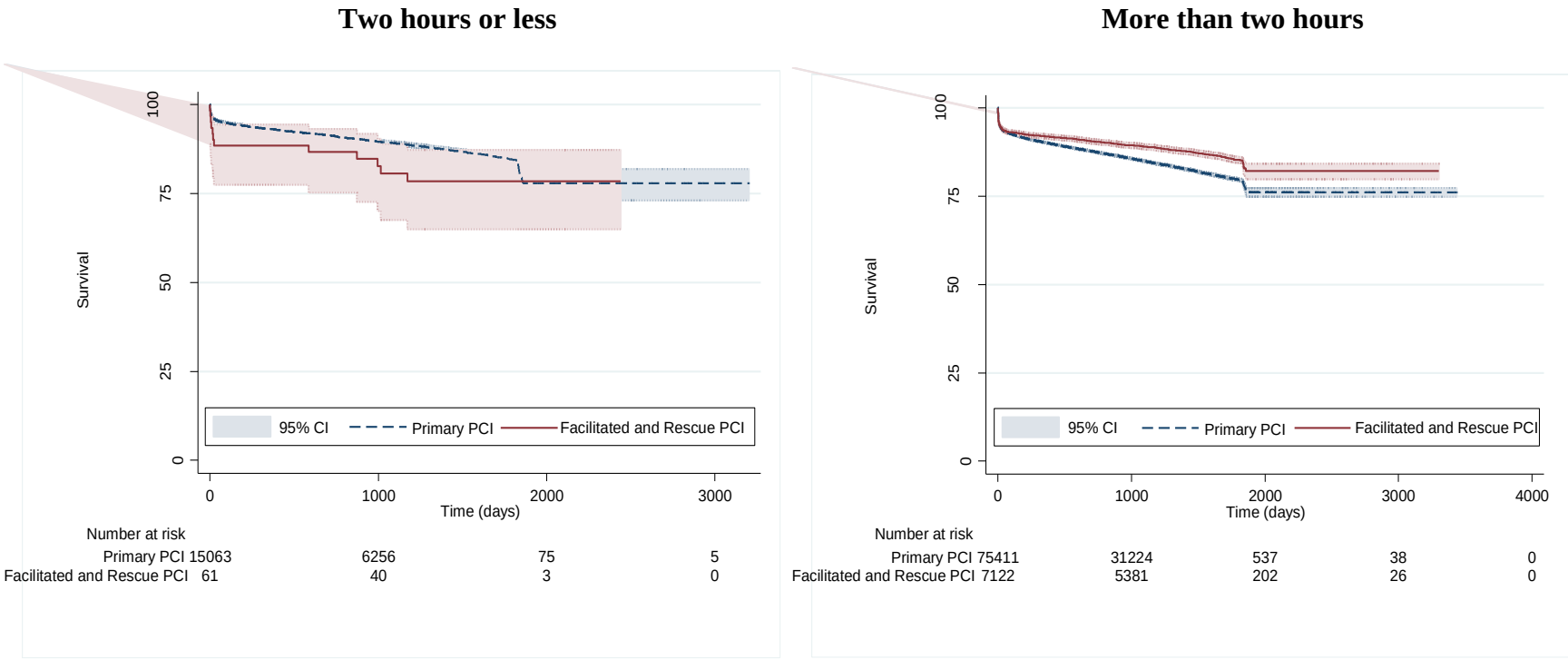
Figure 6.7 shows the Kaplan–Meier curves for unadjusted survival time (from time of procedure to 9.6 years) to all-cause mortality in patients who received ‘facilitated or rescue’ and primary PCI, further stratified by three routes of admission. Once more, the survival distributions of all routes of admission in both groups of intervention were significantly different (P <0.001). In both intervention groups, the survival of patients who received their PCI while they were already in a cardiac centre was significantly less than those who were treated after a direct admission or an inter-hospital transfer.

Figure 6.4: Kaplan-Meier curves for unadjusted survival time to all-cause mortality in patients who received facilitated, rescue and primary PCI from time of procedure to 9.6 years.



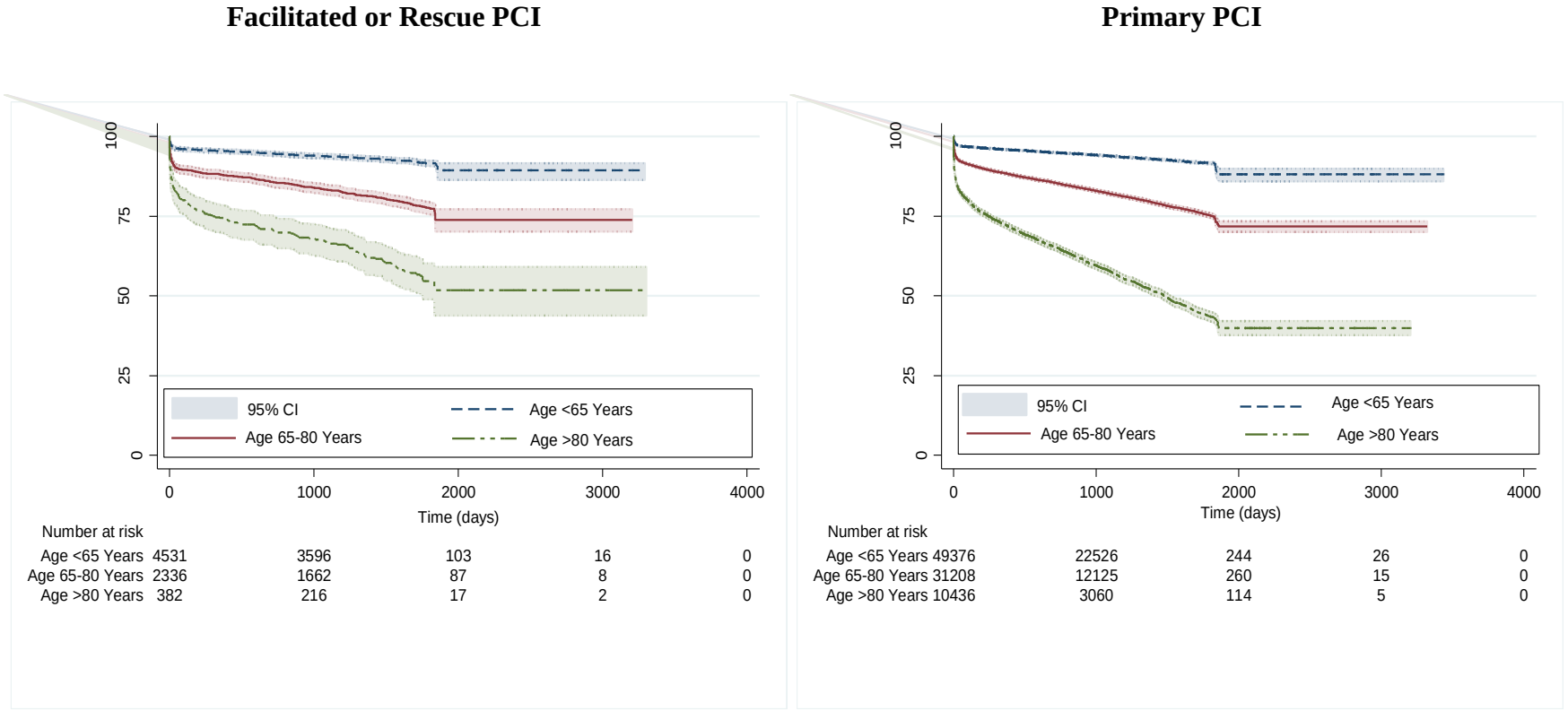
The survival distributions of all strata were significantly different (Mantle-Cox log rank test, P<0.001).
PCI: percutaneous coronary intervention

Figure 6.5: Kaplan-Meier curves for unadjusted survival time to all-cause mortality in patients who received 'facilitated or rescue' and primary PCI, stratified by time from symptoms onset to procedure, from time of procedure to 9.6 years.



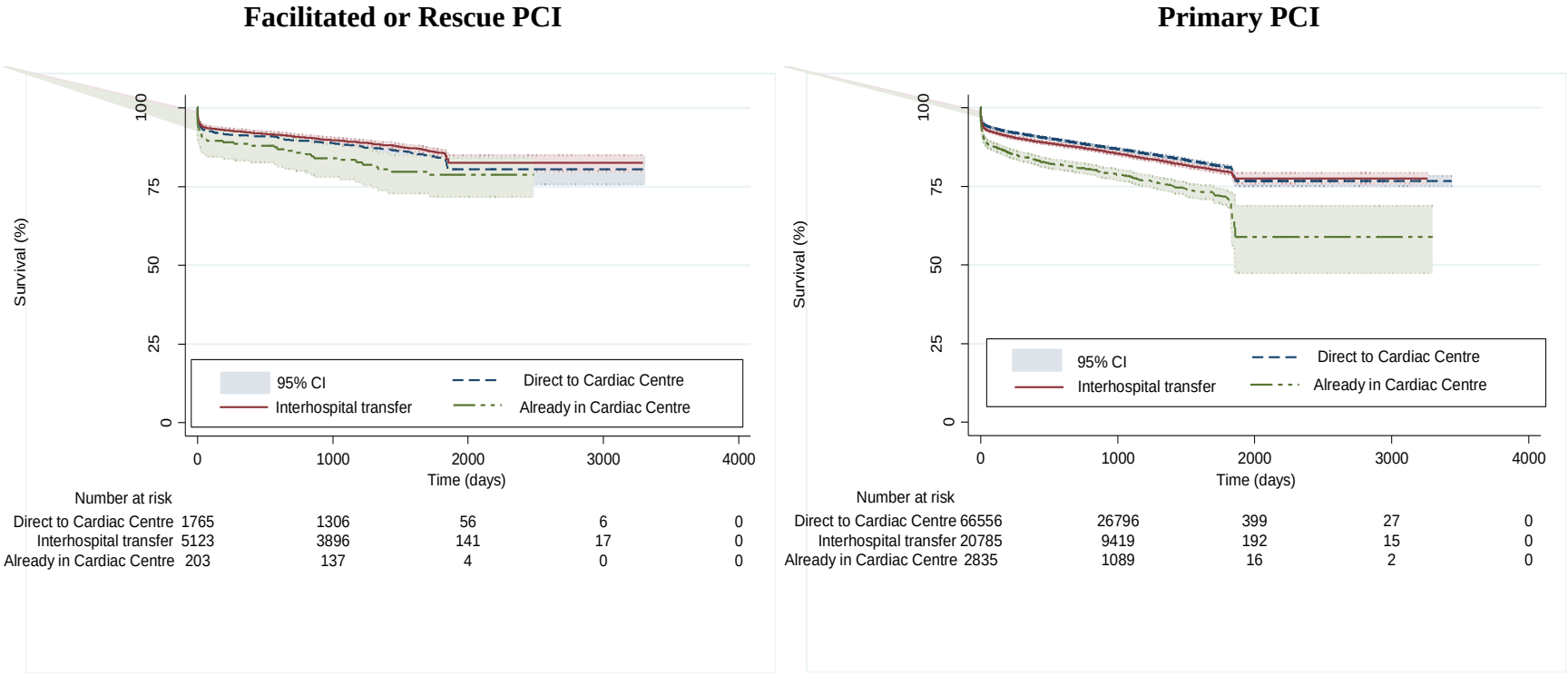
The survival distributions of all strata were significantly different (Mantle-Cox log rank test, P<0.001).
PCI: percutaneous coronary intervention

Figure 6.6: Kaplan-Meier curves for unadjusted survival time to all-cause mortality in patients who received 'facilitated or rescue' and primary PCI, further stratified by age groups, from time of procedure to 9.6 years.



The survival distributions of all strata were significantly different (Mantle-Cox log rank test, P<0.001).
PCI: percutaneous coronary intervention

Figure 6.7: Kaplan-Meier curves for unadjusted survival time to all-cause mortality in patients who received 'facilitated or rescue' and primary PCI, further stratified by admission route, from time of procedure to 9.6 years .



The survival distributions of all strata were significantly different (Mantle-Cox log rank test, P<0.001).
PCI: percutaneous coronary intervention

6.4.9 Clinical determinants of survival

Multivariate Cox regression modelling was used for this section of the analysis. Eight different covariates were used in the adjustment of the estimates in both intervention groups. More details were described earlier in this Chapter (section 6.3.6.3 and Table 6.1). After adjustment, patients with STEMI who were treated by primary PCI remained at a significantly elevated risk of death compared to the 'facilitated or rescue' intervention group, adjusted hazard ratio (aHR) 1.1, 95% confidence interval (CI) 1.0 to 1.2. This association was significantly upheld for primary PCI that were performed after two hours from the onset of symptoms (two hours or less: aHR 0.8, 95% CI 0.4 to 1.5 and more than two hours: aHR 1.2, 95% CI 1.1 to 1.3).

6.4.9.1 Age and sex

In both intervention groups, each one year increase in a patient's age was significantly associated with an increased risk of death (facilitated or rescue: aHR 1.1, 95% CI 1.0 to 1.2 and primary: aHR 1.1, 95% CI 1.0 to 1.2). Similarly, 80 years of age and over was a significant determinant of worse survival in both intervention groups (facilitated or rescue: aHR 5.9, 95% CI 1.7 to 20.0 and primary: aHR 7.8, 95% CI 5.2 to 11.8). After adjustment, male patients with STEMI had better survival than females. An association that was statistically significant in the primary intervention patients only (facilitated or rescue: aHR 0.90, 95% CI 0.78 to 1.03 and primary: aHR 0.91, 95% CI 0.88 to 0.95) (Figures 6.8 and 6.9).

6.4.9.2 Clinical determinants of survival ('facilitated or rescue' intervention)

Figure 6.8 demonstrates the adjusted hazard ratios for the independent predictors of survival in the facilitated or rescue PCI group. The only significant independent predictor of better survival in the facilitated or rescue intervention patients was the use of radial artery approach (aHR 0.8, 95% CI 0.7 to 0.9). However, the significant independent predictors of worse survival were age greater than 80 years, pre-procedural cardiogenic shock, diabetes mellitus, chronic renal disease, history of a previous acute myocardial infarction, poor ventricular ejection fraction, pre-procedural ventilation and the use of intra-aortic balloon pump (all $P < 0.001$).

6.4.9.3 Clinical determinants of survival (primary intervention)

Figure 6.9 displays the adjusted hazard ratios for the independent predictors of survival in the primary PCI group. The significant independent predictors of better survival in the primary intervention patients were male sex, the used number of stents (aHR 0.93, 95% CI 0.92 to 0.95), the use of Abciximab (aHR 0.80, 95% CI, 0.77 to 0.82), and the use of radial artery approach (aHR 0.80, 95% CI 0.77 to 0.82). In contrast, the significant independent predictors of worse survival in this group of patients were age greater than 80 years, pre-procedural cardiogenic shock, diabetes mellitus, chronic renal disease, history of a previous acute myocardial infarction, history of a previous PCI, poor ventricular ejection fraction, pre-procedural ventilation, the use of intra-aortic balloon pump, post-procedural acute myocardial infarction and post-procedural acute stroke (all P <0.001).

6.4.9.4 Hypertension and thrombolysis in myocardial infarction flow

A medical history of hypertension was a significant determinant of worse survival in the primary PCI patients (facilitated or rescue: aHR 1.1, 95% CI 0.9 to 1.3 and primary: aHR 1.1, 95% CI 1.0 to 1.2). In both intervention groups, pre-procedural thrombolysis in myocardial infarction flow 0 (TIMI0) was significantly associated with worse survival in patients with STEMI (facilitated or rescue: aHR 1.3, 95% CI 1.0 to 1.5 and primary: aHR 1.1, 95% CI 1.0 to 1.1) (Figure 6.10).

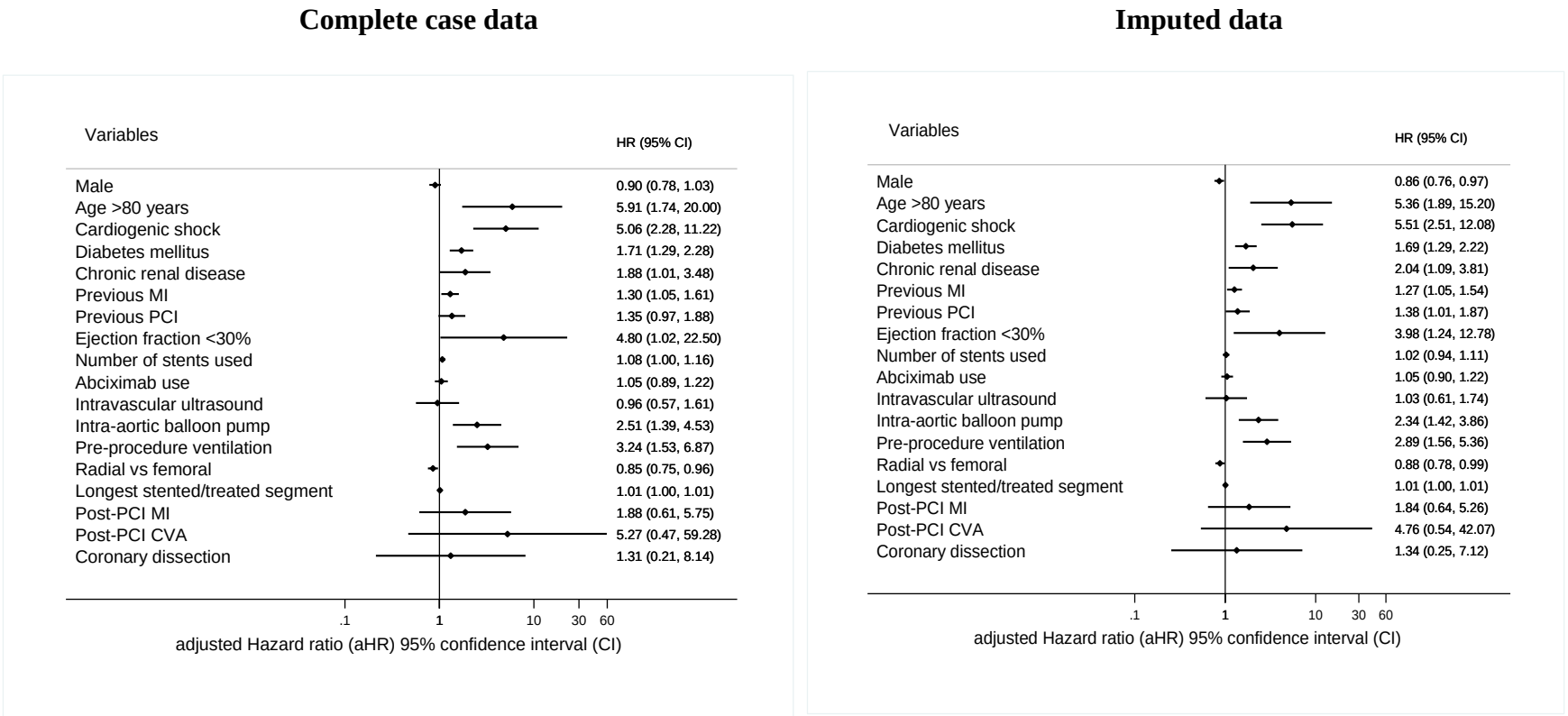
6.4.9.5 Time from symptoms to intervention

Compared to ‘two hours or less’, the length of time ‘more than two hours’, from the start of the first symptom to the intervention, was a significant determinant of worse survival in patients with STEMI who underwent primary PCI (facilitated or rescue: aHR 1.2, 95% CI 0.7 to 1.9 and primary: aHR 1.2, 95% CI 1.1 to 1.2).

6.4.9.6 Routes of admission

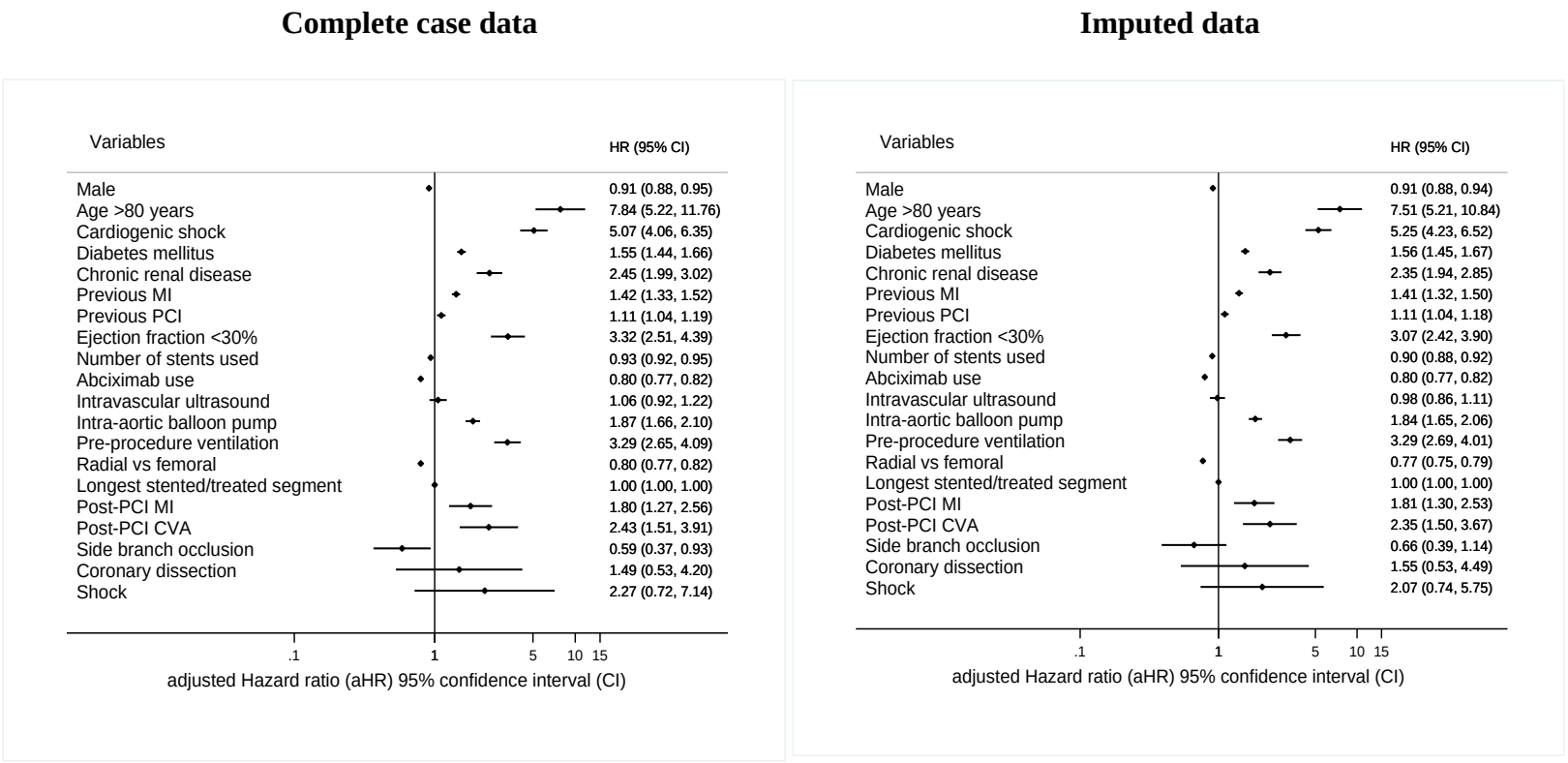
The relationship between the routes of admission and survival was adjusted and measured by using the direct admission route as a baseline for comparison. In the facilitated or rescue intervention group, inter-hospital transfer route, and already in a cardiac hospital or centre route, were not significantly associated with the patients' survival. However, for the primary intervention patients, the survival was worse in both routes of admission (inter-hospital transfer: aHR 1.1, 95% CI 1.0 to 1.2 and already in cardiac centre aHR 1.4, 95% CI 1.2 to 1.5) (Figure 6.11).

Figure 6.8: Adjusted hazard ratios for the clinical determinants of the survival of STEMI patients underwent 'facilitated or rescue' PCI (Complete case vs Imputed).



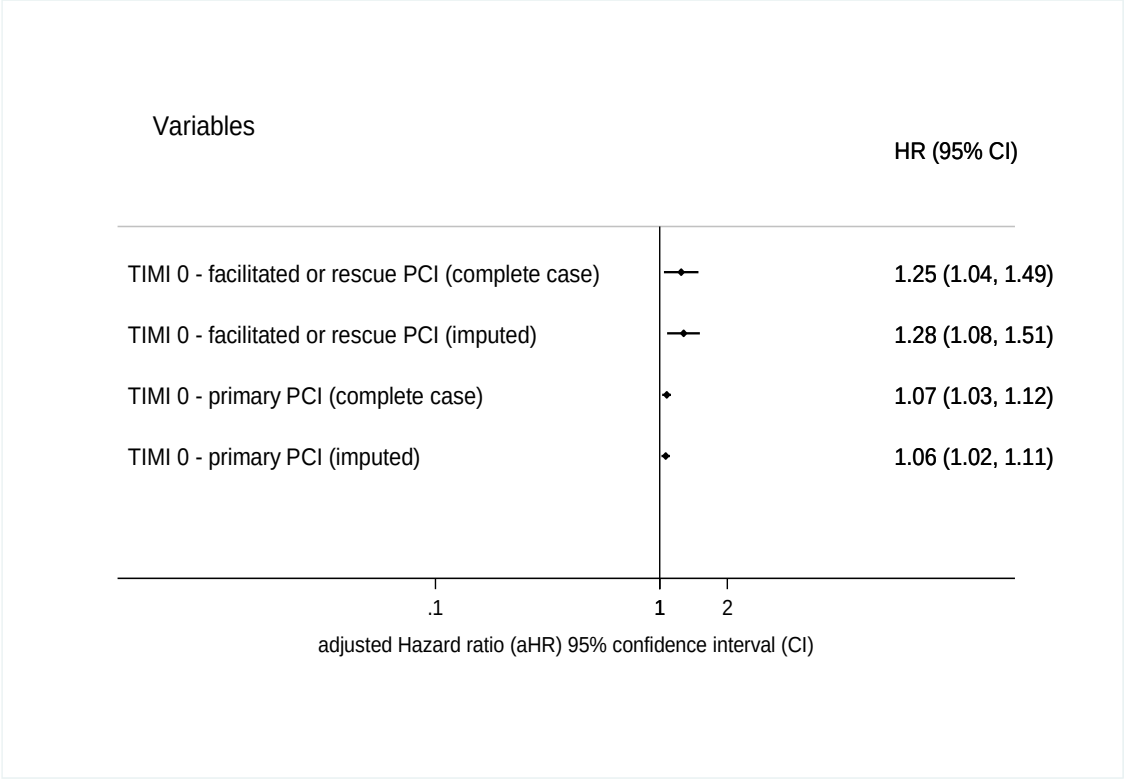
HR and 95%CI were calculated using multivariate Cox hazards regression for both complete case and pooled imputed data.

Figure 6.9: Adjusted hazard ratios for the clinical determinants of the survival of STEMI patients underwent primary PCI (Complete case vs Imputed).



HR and 95%CI were calculated using multivariate Cox hazards regression for both complete case and pooled imputed data.

Figure 6.10: Adjusted hazard ratios for pre-procedural TIMI 0 as determinants of the survival of STEMI patients underwent 'facilitated or rescue' and primary PCI (Complete case vs Imputed).

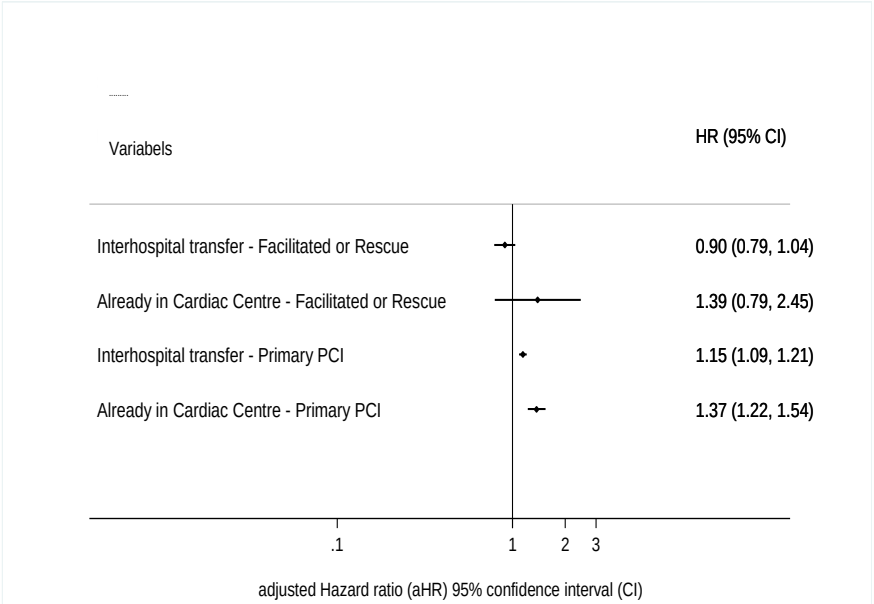


HR and 95%CI were calculated using multivariate Cox hazards regression for both complete case and pooled imputed data.

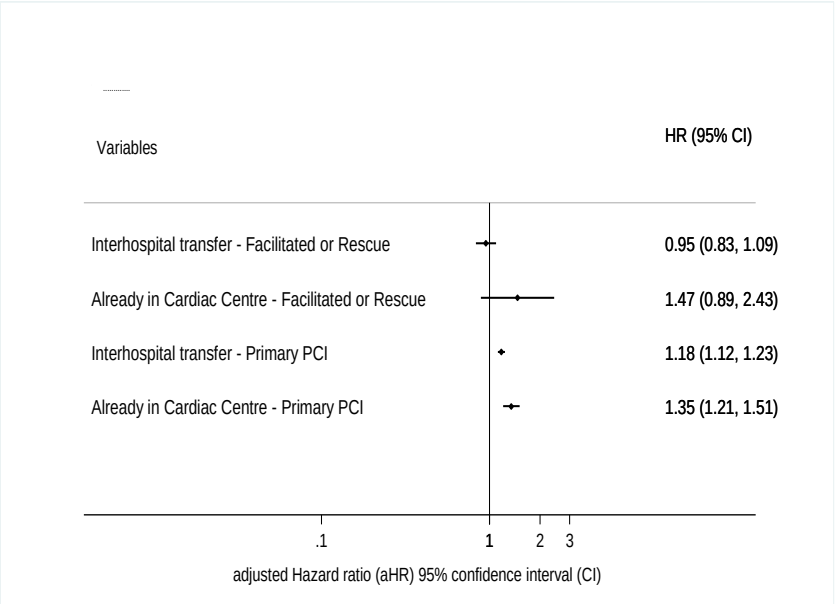
* Baseline is 'TIMI 3'

Figure 6.11: Adjusted hazard ratios for the routes of admission as determinants of the survival of STEMI patients underwent 'facilitated or rescue' and primary PCI (Complete case vs Imputed).

Complete case data



Imputed data



HR and 95%CI were calculated using multivariate Cox hazards regression for both complete case and pooled imputed data.

* Baseline is 'direct admission to cardiac centre'

6.4.10 Sensitivity analyses

6.4.10.1 Mixed effects modelling at hospitals level

The same Cox proportional hazards models that were used in the adjusted analysis 'fixed effects modelling' of this chapter (described in section 6.3.6.3) were repeated, taking into account the hierarchical level of cardiac hospitals or centres 'mixed effects modelling'. In almost all mixed effect models for both intervention groups, the likelihood ratio statistics were statistically significant (P <0.001). Indicating that there were similarities between the patients within each hospital and there was significant difference between hospitals. See Table 6.11 for full summary of mixed effects models adjusted hazard ratios at hospital level for patients underwent 'facilitated or rescue' and primary PCI.

Whilst there was evidence for hospital (level 2) effects, the use of mixed effects models did not substantially affect the patient (level 1) estimates. For example, in the fixed effects model, the adjusted hazard ratio (aHR), 95% confidence interval (CI) of pre-procedural cardiogenic shock for the facilitated or rescue intervention patients was 5.1, 2.2 to 11.2, while in the mixed effects model, aHR, 95% CI of pre-procedural cardiogenic shock for the same patients was 5.1, 2.2 to 11.5. Another example for the facilitated or rescue intervention patients was the presence of a history of diabetes mellitus (fixed effects estimates: aHR, 95% CI 1.7, 1.3 to 2.3 and mixed effects estimates: aHR, 95% CI 1.7, 1.3 to 2.3) (Figure 6.8 and Table 6.11).

Examples for the primary intervention patients were age more than 80 years (fixed effects estimates: aHR, 95% CI 7.8, 5.2 to 11.8 and mixed effects estimates: aHR, 95% CI 7.8, 5.2 to 11.7), left ventricular ejection fraction of less than 30% (fixed effects estimates: aHR, 95% CI 3.3, 2.5 to 4.4 and mixed effects estimates: aHR, 95% CI 3.6, 2.6 to 5.0) and the use of pre-procedural ventilation (fixed effects estimates: aHR, 95% CI 3.3, 2.7 to 4.1 and mixed effects estimates: aHR, 95% CI 3.3, 2.7 to 4.2) (Figure 6.9 and Table 6.11).

Table 6.11: Shared-frailty (mixed effects modelling) at hospital level adjusted hazard ratios for patients underwent 'facilitated or rescue' and primary PCI.

Variable		At hospital level					
		Facilitated and Rescue PCI			Primary PCI		
		aHR	95% confidence interval	likelihood ratio P value	aHR	95% confidence interval	likelihood ratio P value
Male		0.9	0.8 - 1.0	<0.001	0.91	0.87 – 0.94	<0.001
Age more than 80 years		6.1	1.7 - 22.0	<0.001	7.8	5.2 – 11.7	<0.001
Cardiogenic shock		5.1	2.2 - 11.5	<0.001	5.2	4.1 – 6.6	<0.001
Diabetes mellitus		1.7	1.3 – 2.3	<0.001	1.5	1.4 – 1.6	<0.001
Chronic renal disease		1.8	1.0 – 3.2	<0.001	2.5	2.0 – 3.1	<0.001
Previous acute myocardial infarction		1.4	1.1 – 1.7	<0.001	1.4	1.3 – 1.5	<0.001
Previous PCI		1.4	1.0 – 2.0	<0.001	1.1	1.0 – 1.2	<0.001
Ejection fraction <30%		4.9	0.9 – 25.9	0.211	3.6	2.6 – 5.0	<0.001
Number of stents used		1.1	1.0 – 1.2	<0.001	0.93	0.91 – 0.95	<0.001
Abciximab use		0.9	0.8 – 1.1	<0.001	0.77	0.75 – 0.80	<0.001
Intravascular ultrasound		0.9	0.6 – 1.6	<0.001	1.0	0.9 – 1.2	<0.001
Intra-aortic balloon pump		2.5	1.4 – 4.5	<0.001	1.9	1.7 – 2.2	<0.001
Pre-procedure ventilation		3.3	1.5 – 7.2	<0.001	3.3	2.7 – 4.2	<0.001
Radial vs femoral access		0.9	0.7 – 1.0	<0.001	0.78	0.75 – 0.80	<0.001
Longest stented/treated segment		1.01	1.00 – 1.02	<0.001	0.97	0.96 – 0.99	<0.001
Post-procedure acute myocardial infarction		2.2	0.6 – 8.5	<0.001	1.9	1.3 – 2.7	<0.001
Post- procedure stroke		4.7	0.5 – 42.1	<0.001	2.3	1.5 – 3.7	<0.001
Procedural complication	**Side branch occlusion**	---	---	---	0.6	0.4 – 0.9	<0.001
	Coronary dissection	1.0	0.2 – 4.5	<0.001	1.4	0.5 – 3.8	<0.001
	Shock	---	---	---	2.2	0.7 – 6.8	<0.001

6.4.10.2 Multiple imputation

The overall distribution for most variables of the imputed datasets matched those of the complete case dataset very closely. Multivariate adjustment of the pooled imputed data for the missing data made only small changes to point estimates generated from the Cox proportional hazards models. Although, due to the increase in patients' number available in the imputed dataset, multiple imputation improved the estimates precision (smaller confidence intervals).

After adjustment, the generated point estimates of survival from the pooled imputed data were statistically insignificant as they did not change the overall association result of the same models from the complete case data. More accurately, no changes were noticed on the significance of these associations for both 'facilitated and rescue' and primary PCI. A comparison between the complete case data and pooled multiply imputed data can be seen in Figures 6.8 to 6.11, which shows the adjusted hazard ratios for the clinical determinants of the survival of STEMI patients who underwent PCI stratified by the type of intervention.

For example, the adjusted hazard ratios for left ventricular ejection fraction of less than 30% were (facilitated and rescue: aHR, 95% CI 4.8, 1.0 to 22.5 in complete case data compared to aHR, 95% CI 4.0, 1.2 to 12.8 in imputed data and primary: aHR, 95% CI 3.3, 2.7 to 4.1 in complete case data compared to aHR, 95% CI 3.1, 2.4 to 3.9 in imputed data). The adjusted ratios for post-procedural acute myocardial infarction were (facilitated and rescue: aHR, 95% CI 1.9, 0.6 to 5.8 in complete case data compared to aHR, 95% CI 1.8, 0.6 to 5.3 in imputed data and primary: aHR, 95% CI 1.8, 1.3 to 2.6 in complete case data compared to aHR, 95% CI 1.8, 1.3 to 2.5 in imputed data) (Figures 6.8 and 6.9).

Compared with direct admission to cardiac hospital or centre, the adjusted hazard ratios for inter-hospital transfer were (facilitated and rescue: aHR, 95% CI 0.9, 0.8 to 1.0 in complete case data compared to aHR, 95% CI 0.9, 0.8 to 1.1 in imputed data and primary: aHR, 95% CI 1.1, 1.1 to 1.2 in complete case data compared to aHR, 95% CI 1.2, 1.1 to 1.2 in imputed data). The adjusted estimates for already in a cardiac centre route were (facilitated and rescue: aHR, 95% CI 1.4, 0.8 to 2.5 in complete case data compared to aHR, 95% CI 1.5, 0.9 to 2.4 in imputed data and primary: aHR, 95% CI

1.4, 1.2 to 1.5 in complete case data compared to aHR, 95% CI 1.4, 1.2 to 1.5 in imputed data) (Figure 6.11).

6.5 Discussion

6.5.1 Summary of key findings

- The majority of the STEMI cohort were treated by primary PCI. From 2005 to 2014, the frequency of primary interventions increased and ‘facilitated or rescue’ interventions decreased.
- Majority of the procedural complications and in-hospital outcomes (including MACCE) were infrequent in both intervention groups.
- Crude late mortality rate was higher in the primary intervention patients compared with patients who received facilitated and/or rescue PCI. After adjustment, the association between primary PCIs ‘two hours from symptom onset’ and long-term survival was significantly upheld.
- Overall, the survival rate of primary intervention patients was significantly less than that of facilitated and/or rescue intervention patients.
- In both intervention groups, elderly patients had worse survival rates.
- More than two hours’ delay from the time of symptoms onset to the intervention was a significant predictor of worse survival in primary intervention patients.
- In primary intervention patients, worse survival was associated significantly with both routes of admission ‘inter-hospital transfer’ and ‘already in a cardiac centre’.
- Radial access was used more frequently than femoral in primary interventions. In both intervention groups, radial access was associated with lower crude early and late mortality rates. After adjustment, the association with long-term survival was significantly maintained.
- Other clinical determinants of better survival in primary PCIs were male gender, the number of used stents and the use of Abciximab.

- Clinical determinants of worse survival in primary intervention group were old age, pre-procedural cardiogenic shock, hypertension, diabetes mellitus, renal disease, previous myocardial infarction, previous PCI, poor ventricular ejection fraction, pre-procedural ventilation, pre-procedural TIMI 0 and the use of intra-aortic balloon pump.
- One-tenth of the variables had no missingness, three quarters had 50% or less missing values and only five variables had missing values of more than 90%.
- Multiple imputation made slight improvement on the precision of the generated adjusted hazard ratios, which were statistically insignificant as they did not change the overall association result of the same models from the complete case data.
- Even though there was evidence for hospital effects, the use of mixed effects models did not largely affect the adjusted estimates at patient's level.

6.5.2 Findings in the context of literature

Compared to the other studies from literature, this study is more representative of the UK patients with STEMI, simply because most of those other studies were international and executed outside the UK. In addition, only few other multi-centre studies have prospectively evaluated the clinical determinants of survival of patients with STEMI after primary PCI using a population-based national cohort [113, 115, 118]. Majority of the reviewed studies were not representative of the general population as they were implemented at hospital-based level [79, 112, 114, 119-123]. Such studies produce selection bias very easily due to the expected variations between cardiac centres facilities and the experience of interventionists [76, 117].

This prospective analysis of consecutive patients with STEMI in the UK between 2005 and 2014 shows important differences between both types of PCIs. More importantly, it demonstrates many significant clinical determinants of survival over a fairly long period (9.6 years). Over that period, the number of patients with STEMI who were treated by primary PCI increased. This increment over the years was comparable to the overall number of patients who underwent primary PCI in the UK [54, 71].

The increase in primary PCI in the UK is likely to be the result of a combination of factors including:

1. The shifting from treating patients with STEMI by thrombolysis medications to primary PCI [76, 117, 189].
2. The enhancements in technology by means of highly equipped intervention laboratories and emergency rooms, along with the improvements in techniques as well as the availability of more well trained and experienced interventional cardiologists and departments [60].
3. The progress in pre- and post-procedural care provided by well-equipped high dependency intensive care units [60].
4. The initiation of a plan by the NHS in England and Wales which aimed to provide a national primary PCI service for all patients with STEMI by 2012 [189, 195].

Overall, crude late mortality rates and survival time were worse after primary PCI when compared to 'facilitated or rescue' interventions. These findings were aligned with other recent publications [118, 196]. As a matter of fact, this study matched the findings of two previous studies by Danchin *et al.* [118] and Westerhout *et al.* [196] that primary interventions is a significant predictor of worse survival. In this study, the association of primary interventions with patients' survival was aHR, 95% CI 1.1, 1.0 to 1.2 compared to 'facilitated and rescue' interventions. Compared to primary PCI, the association of fibrinolysis with patients' five-year survival in Danchin's study was aHR, 95% CI 0.6, 0.4 to 0.9. Likewise, the combined CAPTIM and WEST trials by Westerhout reported that within the first two hours after symptoms, the association of pre-hospital fibrinolysis with patients' survival at one year was aHR, 95% CI 0.4 0.2 to 0.9.

Similar to this study, Danchin's study was on a large number of STEMI patients and was representative of the general population since the study was a multi-centre observational in design. The findings in Danchin's study were comparable to this study findings as 84% of the fibrinolysis patients received PCI afterward. However, the plausibility of reporting bias was a limitation in this study as well as in Danchin's study, since the cause of mortality was not available. The main weakness of the CAPTIM and WEST trials was the lack of generalizability as well as comparability to this study, based on the fact that rescue PCI was performed in around 25% of the pre-hospital

fibrinolysis patients. Data about the timing of PCIs from fibrinolysis was measured and presented in CAPTIM and WEST trials; yet, this kind of data was not available in the BCIS database. Primary PCI as a determinant of worse survival in this study can be explained by the fact that more than 83% of the primary PCI were after two hours from the onset of symptoms. Delayed primary PCIs lead to unwanted complications and outcomes [71-73]. Besides, in early interventions (two hours or less) there was no difference between 'facilitated and rescue' and primary PCI. However, the lack of power due to the small number in 'facilitated and rescue' (61 PCIs) may be the reason behind this non-significant association [118]. Another explanation might be that these findings were biased by the effect of confounding by indication, since the type of procedure is the treatment variable which might be an intermediate phase in the causation pathway [197].

Across the study population and primary intervention patients, in particular, older age was associated with worse survival (aHR 7.8, 95% CI 5.2 to 11.8). A finding that was well matched with other recent publications: McCormick *et al.* [112] (adjusted odds ratio (aOR) 1.1, 95% CI 1.0 to 1.1), De Luca *et al.* [115] (aHR 7.5, 95% CI 3.7 to 15.1) and Brodie *et al.* [121] (younger age: aHR 0.6, 95% CI 0.4 to 0.9). De Luca's results were the closest to this study's results. The best possible explanation might be because both share a similar and more reprehensive study design (population-based) with large number of STEMI patients. Older age and survival association can elucidate the possible causes behind the worse survival in the primary intervention patients as they tended to be older than those who underwent 'facilitated and rescue' interventions which may also reflect the type of patients referred or accepted for PCI following fibrinolysis.

Compared with females, males in the primary intervention group had a better survival (aHR 0.9, 95% CI 0.8 to 0.9), Patel et al. [86] demonstrated similar finding (aHR 0.4, 95% CI 0.3 to 0.7). The results of this study showed that femoral access was used more frequently in female patients with STEMI; therefore, this may explain to some extent why females had worse survival. It has been shown in this study that femoral access was associated with worse survival in patients with STEMI who underwent primary intervention (radial vs. femoral approach: aHR, 95% CI 0.8, 0.7 to 0.8). This result is similar to other published findings in the literature on radial access as a safer access route than femoral in patients with STEMI [32, 33, 87, 191, 192]. In this

study, radial access was used for more than half the primary intervention patients and small differences in bleeding rates were noticed compared to femoral. Furthermore, crude early and late mortality rates were far less compared with femoral access. These observations were in parallel with the conversion of UK interventionists to the radial access rather than the femoral (from 32% in 2005 to 71.5% in 2013) [54].

International guidelines recommended that primary PCI is the best treatment in STEMI patients with cardiogenic shock; primary PCI is associated with a 37% relative risk reduction compared with fibrinolysis [4, 74, 76, 111]. However, and as expected, pre-procedural cardiogenic shock was another significant determinant of worse survival in the primary intervention group, a result that matched those of other reviewed studies [71, 75, 76, 112, 113]. The results of Chapter 4 of this thesis, specifically (Figures 4.3 and 4.4), showed a worse survival time and a significant impact of cardiogenic shock on mortality in patients with STEMI after PCI. This study confirms these findings further and over a longer period of time. Such findings were of specific clinical relevance, calling for the need for advanced longer-term risk management for patients with STEMI with established cardiogenic shock [198].

Histories of previous acute myocardial infarction or previous PCI were associated with worse survival in patients with STEMI after primary PCI (aHR 1.4, 95% CI 1.3 to 1.5 and aHR 1.1, 95% CI 1.0 to 1.2, respectively). De Luca *et al.* [115] reported a similar finding in regard to previous myocardial infarction (aHR 3.0, 95% CI 1.1 to 8.6). Probably such history may reflect the existence of a more complicated coronary artery disease or a pre-existent multi-vessel involvement, which have negative influence on patients' survival [199, 200].

In keeping with results from other published studies [45, 48, 115, 181], additional numbers of clinical determinants were identified to be associated with worse survival in patients with STEMI treated by primary PCI. These included hypertension, pre-existing diabetes mellitus, chronic renal disease, poor ventricular ejection fraction, pre-procedural ventilation, the use of intra-aortic balloon pump, post-procedural acute myocardial infarction and post-procedural acute stroke. Pre-procedural TIMI 0 was another predictor of worse survival after primary interventions (aHR 1.1, 95% CI 1.0 to 1.1). De Luca *et al.* [115] demonstrated a similar result (TIMI 3 with 30-day mortality: aHR 0.5, 95% CI 0.2 to 0.9). However, contradicting findings were presented by Taniguchi *et al.* [113] (TIMI 0 with 5-year survival: aHR 0.6, 95% CI 0.4 to 0.9). The

explanation for such contradiction was not entirely clear and possibly in need for further confirming studies.

In this study, the time from the symptoms onset to the intervention ‘more than two hours’ was found to be a significant determinant of worse survival after primary PCI (aHR 1.2, 95% CI 1.1 to 1.2). A study by McCormick *et al.* [112] presented opposing findings (aOR 1.0, 95% CI 0.9 to 1.0). Nevertheless, many other studies shared similar findings to this study [113, 120-123]. These studies illustrated that the shorter the time of primary intervention from onset of symptoms, the better the short- and long-term survival of STEMI patients. In general, it is well established that more than two-hour delays after symptoms onset to primary PCI procedures can lead to unfavourable complications and outcomes compared to earlier primary PCI [71-73].

In alignment with results from other reviewed studies [79, 119, 123, 201], the admission routes ‘inter-hospital transfer’ and ‘already in a cardiac centre’ predicted worse survival in the primary intervention patients (aHR, 95% CI 1.1, 1.0 to 1.2 and aHR, 95% CI 1.4, 1.2 to 1.5, respectively). This might be best explained by the fact that some routes of admission are directly correlated with the time from symptoms to intervention. Patients who were admitted directly to a cardiac centre were treated earlier than those who required inter-hospital transfer or needed to be observed further in the cardiac hospital or centre. Lastly, despite near ‘saturation’ of primary PCI for STEMI throughout the cardiac centres and hospitals in the UK, there was evidence of between hospital variations in rates of primary PCI utilisation, which were only in part determined by patient-level factors [195].

Broader discussions on the used methodologies, such as those about the importance of multi-level analysis as well as multiple imputation, will be in the discussion chapter. Moreover, more detailed discussion on the overall strengths, limitations and implications of this thesis will be in the discussion chapter (see Chapter 7).

6.5.3 Conclusion

The study presented comprehensive findings in regard to the determinants of long-term survival (9.6 years) of patients with STEMI in the UK who underwent facilitated, rescue and primary PCIs. The analysis of this study was stratified into two main strata (‘facilitated or rescue’ and primary). In this UK whole-country study, survival of primary intervention patients was significantly less than that of facilitated and rescue intervention patients, particularly when performed after two hours from the onset of symptoms. Therefore, earlier primary PCI (two hours or less) is advocated for better survival. In primary intervention patients, worse survival was associated with old age, pre-procedural cardiogenic shock, hypertension, diabetes mellitus, renal disease, previous myocardial infarction, previous PCI, poor ventricular ejection fraction, pre-procedural ventilation, pre-procedural TIMI 0 and the use of intra-aortic balloon pump. More than two-hour delays of intervention, inter-hospital transfer and being already in a cardiac centre were independent predictors of worse survival in primary interventions. Significant predictors of better survival in the primary intervention patients were male sex, the used number of stents, the use of Abciximab and the use of radial artery approach.

Chapter 7 Discussion

7.1 Summary

The two literature reviews outlined in Chapter 2 (sections 2.4 and 2.5) demonstrated the lack of current publications relating to the objectives of this thesis. The reviews revealed many gaps in knowledge about the care of patients undergoing PCI. Furthermore, there was paucity in population based studies on the long-term outcomes of PCI, particularly in the UK. The UK population has a large burden of cardiovascular disease and its outcomes, in terms of morbidity and mortality [11]. Together, most of contemporary research were conducted outside the UK. Therefore, understanding the clinical determinants of treatment outcomes is crucial as health services in the UK differ to that in other countries, such as the United States. Consequently, important risk factors or determinants may be different across countries and need quantifying. Furthermore, several major risk factors already known or postulated needed to be explored in more detail in the BCIS data. The aim of this thesis was to fill some of these gaps in knowledge by presenting the first population based study in the UK evaluating the care provided to coronary artery disease patients who underwent PCI.

This chapter brings together the main findings and key discussion points of the previous three results Chapters 4, 5, and 6 presented in this thesis. First “a summary of the research is presented (section 7.2)”, followed by “a statement of the key findings of each study (section 7.3)”, “a critical evaluation of the main findings in the context of other research (section 7.40)”, “the overall strengths and limitations of the thesis (section 7.5)” then “study implications and future considerations (sections 7.6 and 7.7)” and lastly “thesis conclusions (section 7.8)”.

7.2 Summary of research undertaken

In this thesis, different literature reviews were performed to build up the research questions, the reviews were:

- What are the clinical determinants and temporal trends of outcomes for PCI in patients with UPLMS in the UK?
- What are the clinical determinants of long-term survival after primary PCI in patients with STEMI in the UK?

Subsequently, in order to answer the research questions, several retrospective analyses of prospectively collected data were undertaken:

- To describe the overall population included in the 2010 and 2014 versions of the BCIS data.
- To identify the clinical determinants of outcomes for UPLMS patients who underwent PCI in England and Wales as well as to compare these determinants between STEMI, NSTEACS and stable patients.
- To quantify the temporal trends in the complications, in-hospital outcomes and mortality of UPLMS patients after PCI in the UK.
- To identify the clinical determinants of primary PCI survival in patients with STEMI in the UK.

7.3 Key findings

7.3.1 The clinical determinants of PCI outcomes in UPLMS patients in the UK, from 2005 to 2010 (Chapter 4)

- Compared to elective patients, the risks of in-hospital MACCE, 30-day mortality and 1-year mortality were higher in STEMI and NSTEACS patients.
- The clinical determinants of worse 30-day and 1-year mortality in acute patients were ‘old age’, ‘pre-procedural cardiogenic shock’, ‘poor ventricular ejection fraction’, ‘pre-procedural ventilation’ and ‘peri-procedural shock’. In elective patients, ‘old age’ was a significant determinant of worse 30-day and 1-year

mortality and ‘peri-procedural coronary dissection’ was a predictor only of worse 30-day mortality.

- The use of radial approach was associated with lower 30-day mortality in STEMI and NSTEACS patients, but was not supported by lower mortality in the longer-term. The use of Abciximab was associated with improved 1-year mortality rate for elective and NSTEACS patients but not STEMI patients.
- Over 40% of patients with STEMI presented with cardiogenic shock which was associated with a nine-fold increase in risk of 30-day mortality and a five-fold increase in risk of 1-year mortality.

7.3.2 Mortality trends after unprotected left main stem PCI in the UK, from 2005 to 2014 (Chapter 5)

- Over the study period, there was a substantial rise in the number of PCIs recorded in UPLMS, particularly acute patients. At the same time, the baseline risk profile increased which was reflected in a series of parameters including increasing numbers of patients with ‘poor left ventricular systolic function’, ‘old age’ and ‘cardiogenic shock’.
- The use of the radial approach increased across biennial years. Yet, the femoral approach continued to be the most common approach in STEMI and NSTEACS patients with cardiogenic shock. Over the study period, the use of drug eluting stents and intravascular ultrasound increased while Abciximab was used less frequently.
- For patients with STEMI with the complication of cardiogenic shock, 30-day and 1-year mortality rates have declined over the study period by about 13% and 7%, respectively. After adjustment for patient-related covariates, these temporal improvements remained significant.
- Despite the significant increase in the number and severity of UPLMS patients who underwent PCI, 30-day and 1-year mortality rates remained remarkably stable.

7.3.3 The clinical determinants of primary PCI survival in STEMI patients in the UK, from 2005 to 2014 (Chapter 6)

- In comparison with ‘facilitated or rescue’ interventions, the survival of primary intervention patients was significantly worse and overall elderly patients had the worst survival.
- Radial access was used more frequently than femoral in primary interventions. In both intervention groups, radial access was associated with lower crude early and late mortality rates. After adjustment, the significant association with long-term survival was maintained.
- Clinical determinants of better survival in primary PCIs were ‘male gender’, ’the use of radial approach’, ‘the number of stents used’ and ‘the use of Abciximab’.
- Clinical determinants of worse survival in primary intervention patients were ‘old age’, ‘pre-procedural cardiogenic shock’, ‘hypertension’, ‘diabetes mellitus’, ‘renal disease’, ‘previous myocardial infarction’, ‘previous PCI’, ‘poor ventricular ejection fraction’, ‘pre-procedural ventilation’, ‘the use of intra-aortic balloon pump’, ‘pre-procedural TIMI 0’, ‘more than two hours delay to intervention’, ‘inter-hospital transfer’ and ‘already being in a cardiac centre’.

7.4 The main findings in context with other research

Most of the presented results in this thesis were consistent with those from the studies identified in the literature. However, the findings of this thesis added more consistency and generalisability to the literature because it used large population based data from the UK. In addition, efforts were made to minimise any plausible bias including data management, as well as choosing the best possible type of methodologies during the analyses. The findings of each study in this thesis were discussed in detail in Chapters 4, 5 and 6 (sections 4.5, 5.5 and 6.5). However, this section summarises the main findings and places them in the wider clinical context.

7.4.1 Survival time and mortality rates

For patients with UPLMS disease, the survival among those who presented to hospital with STEMI was the worst compared to NSTEACS and stable patients. Similarly, survival time was worse after primary PCI when compared to 'facilitated or rescue' interventions. After adjustment, long-term survival was significantly worse after a primary PCI. These findings were consistent with other recent publications [118, 196]. Previous authors have suggested that this could be due to the delay in performing primary PCI for more than 90 to 120 minutes from the onset of symptoms [118]. Furthermore, this thesis demonstrated that early mortality rates were lower than those reported by others in the literature [34, 42, 48] possibly due to the different sets of covariates used for adjusting the analyses in each study. Parma *et al.* [48] presented higher mortality rates; however, this was a hospital based study on a small group of acute patients (58 patients with STEMI). Therefore, Parma's findings cannot be compared with the findings of this thesis.

Other than the decline in mortality for STEMI patients with cardiogenic shock, no temporal changes were observed on mortality rates across the types of clinical presentations even though patient volume and patients from populations known to have a higher risk of poorer outcomes were increasing. The crude early and late mortality rates in STEMI patients with cardiogenic shock were very high (52.5% at 30 days and 64.0% at one year, in 2013-14,), particularly in those who underwent primary percutaneous coronary intervention. Thus, further research is worthy in order to understand whether these are potentially preventable deaths. For example the long-term use of clopidogrel (an antiplatelet agent) after PCI. Mehta *et al.* [202] demonstrated an association between clopidogrel and less cardiovascular mortality (RR 0·7, 95% CI 0·5 to 0·9, P =0·030).

7.4.2 Old age

Old age, greater than 80 years, was a significant determinant of worse short and long-term outcomes in stable and acute patients who underwent PCI; a finding that matched those of other reviewed studies [86, 92, 93, 95, 96]. Aging by itself and alongside other associated medical conditions may be the underlying cause of these relationships. That is to say, late mortality after PCI is more liable to be influenced by

other non-cardiac risk factors [185]. However, since the data were secondary, further information on such possible confounders were out of reach. For that reason, linkage with other databases that have more information on all-cause real world mortality is essential for any future research on the same relationship. For example, the linkage to hospitalisation and procedure data from Hospital Episode Statistics database on previous admissions, prescription data or GP data [203].

With an aging population there will be a greater number of those treated who will be older, possibly over 90 years old. In elderly patients, more complications and unfavourable outcomes are expected after myocardial infarction and PCI procedures. There is also the argument of whether these patient groups are not always offered all treatment options because of their old age [204]. Therefore, the need for more research on this population is necessary to identify whether alternative treatment options are needed, particularly after PCI treatment, for example, antiplatelet medications or cardiac rehabilitation (like physical activity) [202, 204].

7.4.3 Cardiogenic shock

In alignment with findings from literature [30, 42, 45, 48, 71, 75, 76, 99, 112, 113], pre-procedural cardiogenic shock was an alarming determinant of worse outcomes in PCI patients. Cardiogenic shock in UPLMS patients who presented acutely (STEMI and NSTEACS) was associated with an increased risk of early and late mortality. Similarly, long-term survival was worse in STEMI patients with cardiogenic shock. Therefore, more room for improvement is required for advanced longer term risk management and care in PCI patients with such a condition [198]. Cardiac rehabilitation is an alternative post-procedural treatment that minimise the impact of cardiogenic shock on the outcomes [205].

7.4.4 Radial approach

In acute STEMI patients, several studies in the literature have reported an association between the use of radial approach and lower rates of bleeding and short-term mortality as well as better long-term survival [32-34, 191, 192]; a result that was repeated in the findings of this thesis. Radial access was demonstrated to be safer than

femoral in STEMI and NSTEACS patients with UPLMS. Better bleeding rates with less hospital stay as well as lower early mortality rates make the use of radial access a cost-effective approach [206]. Nevertheless, there was lack of association between radial access and mortality at one year. Again, this might be due to the greater effect of non-cardiac risk factors on late mortality, or the fact that radial access may reflect more skilled operators and/or a less sick population (different case-mix).

Whether the associations described in the literature were artefacts of poorly conducted analysis with unmeasured confounders, or whether the sample of patients in this thesis was biased, is unclear. This is unlikely because it is a whole population study and therefore all patients should be included. Overall, the trends of radial access used in this thesis were increasing gradually. A finding that was similar to the trends of current practice which is calling for further research with the inclusion of more confounding risk factors.

7.4.5 Delayed interventions

After primary PCIs, ‘more than two hours delay after symptoms onset to the intervention’, ‘being transferred between hospitals’ and ‘already being in a cardiac centre’ were associated with worse long-term survival. Results that matched those of other reviewed studies [71-73, 79, 113, 119-123], and re-emphasise the need for prompt treatment as seen in the increased risk of unfavourable outcomes with more than two hours delay to primary PCI.

7.4.6 Other determinants

The use of Abciximab (a platelet aggregation inhibitor) was associated with improved late mortality rate for stable and NSTEACS but not STEMI in patients with UPLMS. Still, better survival in all patients with STEMI after primary, facilitated or rescue PCIs was significantly associated with Abciximab use. Poor left ventricular ejection fraction and pre-procedural ventilation were associated with worse early and late mortality rates in UPLMS patients, as well as worse long-term survival in STEMI patients after primary, facilitated or rescue PCIs. These were consistent with other

findings from the literature and reflects patients who are more likely to be unstable [45, 48, 115, 181].

7.5 Strengths and limitations

Throughout the analyses of this thesis, every effort has been made to enhance strengths and decrease limitations. The main strengths and weaknesses of the BCIS database were described in Chapter 1 (sections 1.4.9 and 1.4.10). The following section summarises the overall strengths and limitations of the thesis.

7.5.1 Strengths

- The patients included in all three studies are likely to be representative of all patients who underwent PCI in the UK during the data collection period. The BCIS database is one of the largest population based whole country (multi-centre) registries in the world. It is designed for the detailed evaluation of quality of care and outcomes of unselected patients who receive PCI. The participating cardiac centres represent all four countries of the UK and reflect real practices and outcomes. Representing the general population of such patients in the UK make the scope of this thesis a unique and significant strength. The BCIS database is up-to-date and covers the collection of PCIs over a reasonably long time period which adds more strengths to the data.
- The BCIS data undergoes regular checks of validity and consistency to ensure data quality [55]. The depth of detail of data as well as the robust tracking of mortality by linkage through NHS number were major strengths of the BCIS database. The quality of the linked ONS mortality data was another strength of this study that allowed accurate tracking of all-cause mortality. The compulsion of mortality registration in the UK makes the ONS data almost complete.
- Comparative stratification was performed in all three analyses (by clinical presentation in Chapter 4, by biennial years in Chapter 5 and by type of intervention in Chapter 6). This allowed for better understanding of the compared group’s characteristics, outcomes and clinical determinants. Stratification strategies before

complex analyses (e.g. multivariate regression modelling) were used as a method to deal with the possible confounding effect of the stratification variables (i.e. clinical presentation, biennial years and type of intervention) [207].

- Other strengths of this study were the tests implemented for the sensitivity of the analysis (multiple imputation of missing data and mixed effect analysis at the level of hospitals and routes of admission).

7.5.2 Limitations

- During the stages of data cleaning and recording, some variables required cross-matching between two or more variables in order to categorise them. This process was performed to minimise any possible entry errors and missingness from such variables. For example, the type of clinical presentation variable was categorised into CSA, STEMI and NSTEACS using three different variables from the row BCIS data (‘clinical syndrome’, ‘indication for intervention’ and ‘presenting ECG’). Although unlikely, this could however lead to some misclassification in the variables that have attenuated the described associations.
- Like many prospective observational data, the utilised 2010 and 2014 BCIS databases were dependent and reliant on the accuracy of the ascertainment of all eligible cases and the quality of the data recorded from each operator and hospital; case ascertainment was high at 92.6% by the end of 2010 and 97.6% by September 2014 [20, 54].
- No sufficient data fields were available to calculate the EuroSCORE [39] or other clinical, established risk scores. For instance, extra cardiac arteriopathy, chronic lung disease and mobility status were not available in the BCIS database, indicating that case-mix adjustment using a calculated score was not plausible. This could mean that some of the findings are not fully adjusted for the underlying case-mix.
- Information bias due to selective reporting was a possibility in some of the main variables (such as procedural complications and in-hospital outcomes like MACCE). The validation of such information was not possible which may have had an impact on the presented results. In addition, as mentioned earlier, the lack of complete information regarding the all-cause mortality may have caused information bias.

- Lastly, the analyses of this thesis have disclosed many important associations; but as an observational study, cannot provide evidence for causation but may be suggested [208].

7.5.3 Evaluation of the methodologies used

All three analyses in this thesis have potential pitfalls. The strengths and limitations of the cohort study methodologies in relation to other methodologies and in relation to the minimisation of bias are discussed in this section.

7.5.3.1 Population and design

Careful identification and definition of each study population was an essential part of these analyses. Several steps were taken in order to minimise bias during the selection procedure, this included using a clear inclusion and exclusion criteria based upon advice and agreements from the Delphi group (Section 3.4.2) and using several variables in the BCIS database to define clinical group rather than relying on only one to gain full information. This ensured the findings in this thesis were generalisable to patients across the UK.

All the three analyses in this thesis were based on prospectively collected, secondary observational data. The majority of the reviewed studies from literature were also observational studies. Thus, all may be subject to some level of residual confounding from poorly measured or unmeasured confounding variables, but they are the most comprehensive datasets currently available and where several studies agree on the effect of a particular variable and background evidence indicates plausibility it can suggest a likely effect [209]. Therefore, the evidence for causation in these studies cannot be confirmed but may be suggested. One of the emerging methods that could help to allow for the suggesting causation in any future analysis is the use of directed acyclic graphs [208].

One of the important limitations in all secondary data, such as the BCIS database, is the inability to have input on the type of data collected and any information biases in measurement that may be produced [210]. The BCIS data was collected by

many different cardiac interventionists and clerks in multiple cardiac hospitals and centres all over the UK. This will influence both the accuracy and completeness of the data, creating selection bias. A bias of this kind in a large sample of secondary data may lead to underestimation or overestimation of associations [211]. To limit such errors, all data entry staff should receive proper training [212]. In order to further compensate for some of the collection and selection bias in the analyses of this thesis, data cleaning and multiple imputation were utilised.

7.5.3.2 Descriptive analyses

In the descriptive analyses of this thesis, many differences were highly statistically significant. A possible reason behind this was the large cohorts of patients analysed, particularly that of patients with STEMI in Chapter 6. Future analytical work might be needed by using more strict cut-offs for significant P values or other statistical methods. For instance, by comparing effects sizes (the magnitude of the difference between the size of the groups) to see what variables are clinically significant [213].

7.5.3.3 Multivariate regression modelling

Both logistic and Cox hazards regression modelling were used in the analyses of this thesis. Directed acyclic graphs, a method for describing causal relationships between variables [214], was considered as a way to understand the relationships between confounders, but due to the size and the number of the variables of the BCIS database, it was not feasible to generate them in this data-set. However, comprehensive sets of confounders were adjusted for in the multivariable regression analyses based on literature reviews in addition to clinical input from the Delphi group. The regression analyses were based on the complete case data as the generated model estimates did not considerably change after multiple imputation.

All attempts for model adjustment were made in order to avoid problems such as collinearity [133]. In such a large and complex database, collinearity was still plausible and could have arisen during the analyses in this thesis. These limitations were minimised by removal or categorisation of offending predictor variables.

Other methods that have been used and increased the appropriateness of regression modelling, were stratification (such as the types of clinical presentation and the types of PCI) or recoding continuous covariates to categorical covariates. The variables ‘age’ and ‘time from onset to intervention’ were recorded into categories. The limitation of categorisation of the continuous variables is when the categorised variables are then used in Cox hazards regression and modelled on survival. This approach might have an impact on the significance of the association between the predictors and survival [133].

7.5.3.4 Multi-level regression modelling

Multi-level regression models account for the variance in the independent variables and in the clusters level e.g. cardiac hospitals. The effect of each cluster is measured using shared collective data not only from the cluster in question but also from the other clusters [133]. This method was used as a sensitivity test in all the studies of this thesis.

The multivariate regression models were repeated taking into account the ‘random effects’ of cardiac hospitals or centres. The random effects terms were statistically significant and indicated that there was similarities between the patients within each hospital and there was significant difference between hospitals (i.e. clustering). Similar results were demonstrated at the level of the routes of admission for primary percutaneous coronary interventions. However, the use of multi-level regression models did not markedly change the adjusted estimates at patient level. Therefore, the adjusted estimates from the fixed effects models were used in the analyses of this thesis.

7.5.3.5 Multiple imputation

A full justification and description of the methodology of multiple imputation was reviewed earlier in Chapter 3 (sections 3.4.7 and 3.4.8, respectively). In the analyses of this thesis, missing data was noted and it was assumed to be missing at random which permitted for multiple imputation. In all three studies, no considerable changes were observed on the generated adjusted estimates. Therefore, multiple

imputation was employed as a sensitivity test for the complete case analyses. In some cases, complete case analysis can create biased estimates, loss of statistical power and loss of precision [164]. But in this thesis estimates did not change significantly after multiple imputation inferring that the overall association result of the same models from both complete case and imputed data were comparable.

One of the limitations was the existence of high rates of missingness (more than 40%) in some important predictor variables (for example ‘left ventricular ejection fraction’ variable in the STEMI cohort, the missing values were 65.43%). The imputation of such variables introduces selection bias to the estimates and limits the statistical power of regression modelling [174]. To avoid that, predictors with more than 40% missing values were excluded from the imputation models.

Variables of different types were present in the data-set (binary e.g. ‘sex’, categorical e.g. ‘clinical presentation type’ or continuous e.g. ‘survival time’). Such differences create bias by generating unrealistic assumptions and/or incorrect combinations in the imputed variables [153, 155]. Therefore, the fully conditional specification imputation method was the imputation method of choice in all three studies. A method in which separate individual conditional models for each incomplete predictor variable are specified for the imputation [153].

The accuracy of the employed multiple imputation was increased by the number of variables (predictors and auxiliary) in the imputation model. The recommended number of variables to be included from the literature was between 15 and 25 [154]. The number of variables used in each imputation model in all three studies were within this range. In the same way, the number of all imputations datasets produced in the analyses of this thesis was 20 datasets for each predictor variable with missingness. Increasing the number of imputation datasets decreases the variability between important statistics such as standard errors and P values [162-164]. Overall, there was slight improvement in the level of completeness over the 9.6 years study period for all PCI patients in the BCIS data. Yet, the absence of important information in most of the variables is still a concern and a key gap in the BCIS database.

7.5.4 Using the BCIS for audit and research – practicalities and data quality arrangements

Monthly, quarterly and annual feedback reports are provided by NICOR to all PCI centres and consultants across the UK. Therefore, operators are able to monitor, appraise and revalidate their activities and outcomes [20, 52, 81]. In order to expand and promote the interventional research potentials of the BCIS database, the data are distributed to researchers. More than 50 papers have been published using the BCIS data. Currently, 25 research projects are being conducted following approval from the research and development group [84].

As previously stated, as in other secondary databases, missing data in most of the variables in the BCIS database is a main concern to BCIS, NICOR, cardiologists and researchers. Unrecorded data and entry errors are the best possible explanations behind missing information in the BCIS database [55]. Consequently, both the accuracy and completeness of the entered data may be compromised, creating selection bias [212]. The studies in this thesis exposed plenty of high rate missing data in some variables (such as ‘use of ventilation’ variable (99.63%)) and data entry errors (such as that in ‘the routes of admission’ variable). To minimise the bias produced by entry errors, data cleaning and recoding as well as multiple imputation were employed.

Details on data cleaning and recoding were mentioned in Chapter 3 (section 3.4.4). Consuming a significant amount of efforts and time, data cleaning and recoding were performed twice, for the 2010 and 2014 versions of the BCIS database. However, both were critical steps in the course of this thesis. They improved the data quality and enhanced the research potential of the BCIS database in this thesis and for future researchers.

With multiple imputation being limited to the variables with less than 40% missingness, improvement of the completeness and quality of the BCIS data is crucial. Most researchers use the complete case method to overcome the dilemma of missing data. Others prefer to default impute (i.e. use ‘9’ as the number meaning missing data) to allow more patients to be included in regression models [215]. However, additional imputation techniques that deal with missing data, such as multiple imputation are becoming more of a practical consideration as computing power increases. The use of multiple imputation can be as the main method of analysis or a sensitivity analysis as in

this thesis. Using such methods gives reassurance if the results of the same models using complete case and imputed data are comparable.

The underlying problems of missing data can only be properly corrected at sources (i.e. better data entry). Several recommendations for the improvement of data entry are suggested based on findings made throughout the data management process and the analyses of this thesis. The suggested changes (improvements) are mainly to the BCIS local entry system to increase the accuracy and completeness of the data entered:

- The entry of date variables should be connected and sequenced to prevent missing and/or mismatched information. In this thesis, for example, situations were observed during the analyses in which 'the discharge date' of the patient was earlier than 'the date for the intervention'. Simply, a system rejection of mismatched or empty dates would prevent such errors.
- Limits should be added to the open-ended continuous variables such as 'the number of stents used', 'the number of attempted vessels' and 'the longest stented/treated segment'. Clinically implausible numbers (outliers) were noticed and cleaned for most of the continuous variables.
- Mandatory entry is another suggestion particularly for all important variables. Again to avoid too much absent information, entry personnel must complete all the information required for a variable to move on to the next one.
- Adding jumps to the entry system will help in saving time during data entry as well as avoiding unnecessary or wrong entries. For example, if the choice in 'the intervention type' was primary percutaneous coronary intervention, answering the variable 'recent thrombolysis' is not required and should be skipped. Such errors were noticed during data cleaning and recoding.

Of course, the feasibility and accessibility of all the above recommendations needs to be assessed. At the same time, continued training and awareness of the importance of data accuracy and completeness is required to ensure the enhancement of clinical practice and future research.

7.5.5 Data ethical measures

Throughout this thesis, careful attention has been paid to ethical aspects at all stages of the analyses:

- Data was kept securely in accordance with the University of Leeds regulations.
- Patients' privacy, anonymity and confidentiality were upheld at all times. The data were pseudo-anonymised. Therefore, the identification of patients, operators and cardiac hospitals is not possible.

7.6 Vision for percutaneous coronary intervention

In this thesis, comparison tables and figures for each study were presented and discussed. At the same time, future considerations for improved practice were suggested. Such comparative analyses relating to PCI for coronary artery disease in the UK have rarely been described in such detail. The output of this thesis is expected to have an impact on the improvement of knowledge on how PCI procedures are delivered nationally. This thesis had provided an evidence base on which stakeholders and interventional cardiologists can change future practice to improve hospital care for those who receive PCI.

This thesis comes at an important time as there is a need to continue to improve quality of care in the NHS, aiming to build on the improvement of short and long-term survival and quality of life [216]. There is a need for more comprehensive determinants of the quality of care related to the outcomes after PCI [25, 26, 71, 75, 76]. The studies in this thesis demonstrated some important characteristics in relation to the clinical determinants of UPLMS patients' outcomes after PCI and STEMI patients' survival after primary PCI. Accordingly, the findings of these studies may have important implications for policy makers in order to improve patient care and to establish more evidence based management choices and policies.

For reasonably equal PCI delivery across the NHS trusts, the national implementation of PCI, particularly primary PCI, should continue to be 24 hour/all week service with adequate numbers of interventionist and other supporting staff to deliver this. Strict compliance with policies and clinical guidelines is mandatory for the

improvement of PCI patients care. For example, delayed primary PCIs should be avoided as much as possible. In such situations, early fibrinolysis followed by PCI may have better outcomes.

Using a representative data, reporting the benefits and inherent risks of PCI to inform patients and other healthcare professionals have many implications and help to quantify the relative effect of different risk factors and clinical characteristics on long and short-term outcomes. Communicating such results will highlight areas where novel interventions aimed at improving outcomes may be targeted. For example, the need for increased implementation of the radial approach as this research has confirmed previous studies and demonstrated it to be safer (less bleeding complications and better survival) than femoral access [35]. Establishing ways in which pre and post-procedural care for acute patients with established cardiogenic shock can be improved is another important example.

7.7 Future considerations

The investigative nature of this thesis has uncovered further questions of interest in relation to the care of patients after percutaneous coronary intervention. The results have illustrated complex associations and have led to recognition of the value of further validation and exploration of large multi-centre datasets, such as the BCIS data. Further validation of the reliability and reproducibility of the findings is needed for both the descriptive statistics and the regression models.

The possibility of confounding by indication in patients receiving facilitated, rescue and primary percutaneous coronary interventions cannot be unravelled using observational data [197]. Therefore, randomised clinical trials should be considered, although the utilisation of multiple imputation to deal with missing data in this thesis showed clear advantage as a sensitivity test. Yet, its use in medical research remains uncommon and the use of multiple imputation techniques should be more frequent. More fundamentally, the accuracy and completeness of the BCIS data needs to improve from the early stages of data entry. One of the possible future considerations might be the utilisation of data mining as potential alternatives to the data management methods used.

Calculating and measuring the scoring mechanisms such as EuroSCORE and SYNTAX score in such data will be a challenge for any research. The main advantage of using these clinical scores is that they allow for underlying differences in case-mix. The addition of more variables related to these scores is one feasible way to distinguish them. Further linkages to other electronic databases (such as the MINAP database) is another way. In addition, linkage to other database with more information on cardiac surgical procedures (e.g. CABG) or medical treatments (e.g. thrombolysis) will allow for additional comparative research opportunity with percutaneous coronary intervention. Such linkages will permit more investigation into the differences in characteristics, determinants and outcomes between these lines of management. Linkage to primary care databases should be sought to evaluate the early (preventive) and late (clinical or rehabilitative) determinants of outcomes for the patients who received percutaneous coronary intervention.

What are the geographical differences in the temporal trends of early and late mortality across the clinical presentation groups or the type of intervention? What is the impact of geographical differences on the survival of the same groups? Both are other important research questions that may need further exploration. Further exploration into how patients' socio-economic status or IMD may affects the relationship between some clinical determinants (such as old age or diabetes mellitus) and PCI outcomes or survival. This could be achieved by using a hierarchical multi-level modelling with socio-economic status as an upper level.

Assessment of the relative survival of both cohorts (UPLMS patients and primary PCI patients) and international comparisons with the UK data are other motivating scope. Future research on patient outcomes across other after-effects of interest such as quality of life, other health outcomes and costs as an outcome will help the evaluation of the quality of care for PCI patients.

7.7.1 Future planned publications

In addition the published papers and abstracts arising from this thesis, two more papers based on the results from Chapters 5 and 6 will be submitted to peer-reviewed journals. The first entitled:' Mortality trends after unprotected left main stem PCI in the UK, 2005-2014: Analysis of 10,825 cases from the British Cardiovascular Intervention

Society (BCIS) national registry', the manuscript is written and ready for submission to Euro Intervention journal. The second entitled: 'Clinical determinants of long-term survival for STEMI after primary PCI in the UK, 2005-2014: the British Cardiovascular Intervention Society (BCIS) national registry', aiming for submission to Euro Intervention.

7.8 Thesis conclusions

Currently in the UK, there is an increasing need for more detailed clinical determinants of outcome in patients who receive percutaneous coronary intervention as the patient population increases in volume and complexity due to an aging population and increasing co-morbidities. This comes with the existence of a prospect to define the quality of care plan for such patients. The work in this thesis has utilised population based data in the UK which provided a unique opportunity to study the quality of care provided to patients who underwent percutaneous coronary intervention.

In examining the determinant and temporal trends of the outcomes in UPLMS patients, the studies of consecutive patients clearly demonstrates significantly associated clinical determinants of early and late mortalities. Furthermore, they illustrated substantial changes in the clinical presentation, the treatment and the outcomes of patients who received UPLMS PCI over a period of ten years. In the final analysis, the study presented comprehensive and original results with regard to the clinical determinants of survival in primary percutaneous coronary intervention patients over a reasonably long period (9.6 years). These findings were compared to facilitated and rescue interventions as a group, most of these findings were consistent with those in the literature.

Together, these findings provided a unique insight into gaining more knowledge and understanding of these intervention procedures. These results represent a step forward in assessing the quality of care for patients after percutaneous coronary intervention.

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Appendices

9.1 Appendix I: The 2010 BCIS data description

9.1.1 Demographic characteristics

In total, 411,324 PCI patients were recorded in the 2010 BCIS database in England and Wales between 2005 and 2010. Over the study period, the number of PCIs performed per year was steadily increasing (from 41,023 procedures in 2005 to 84,608 in 2010) (Figure 9.1). The mean age (SD) for all patients was 64.4 (11.4) years and the age range was from 18.6 years to 100.0 years. Patients older than 80 years of age were the least frequent (8.1%) patient to undergo the PCI procedure.

Males were dominant out of all patients at 301,765 (73.4%). The mean age (SD) was 63.2 (11.3) years for male patients and 67.8 (11.2) years for females. Figure 9.2 shows the difference in the frequency and age distribution between males and females. The majority of patients (82.8%) were treated in NHS hospitals/centres and most (62.5%) were of Caucasian ethnicity. Table 9.1 demonstrates the distribution of baseline demographic characteristics of all patients' records in the 2010 BCIS database.

Figure 9.1: Number of PCIs performed per year, from 2005 to 2010.

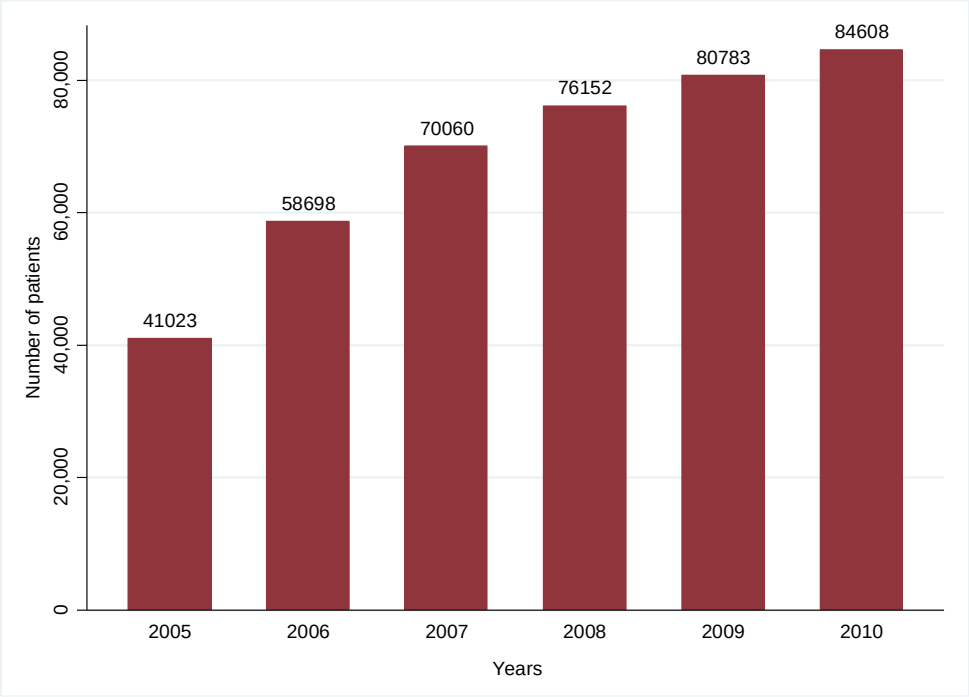


Figure 9.2: Age distribution by gender of all PCI patients in England and Wales from 2005 to 2010

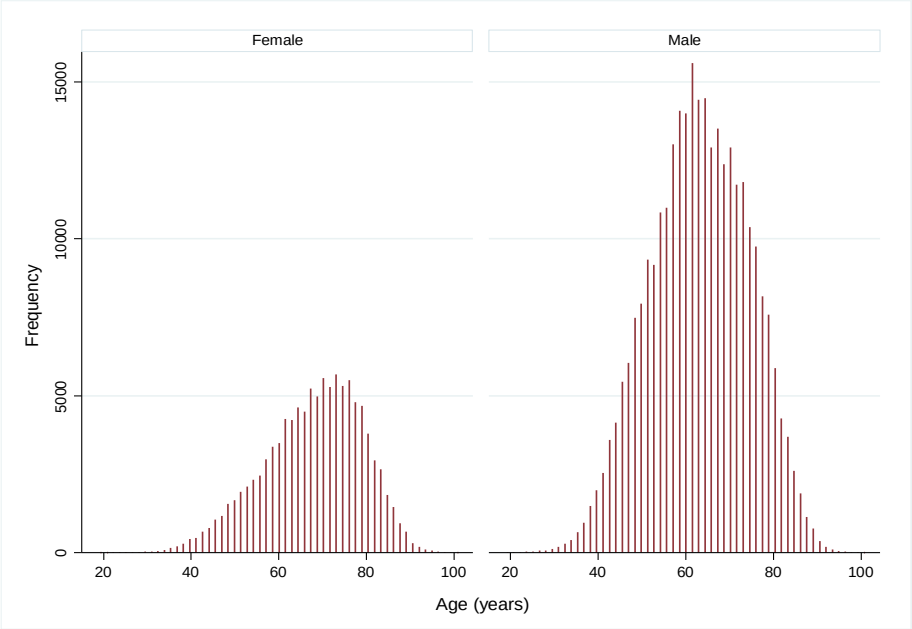


Table 9.1: Baseline demographic characteristics of all PCI patients in England and Wales from 2005 to 2010

Variable		Total n= 411,324	Missing values (%)
Mean (SD) age, years		63.1 (12.6)	471 (0.1)
Age	**Less than 65 years (%)**	208,717 (50.7)	
	65 – 80 years (%)	168,930 (41.1)	
	Greater than 80 years (%)	33,206 (8.1)	
Gender	**Female (%)**	106,988 (26.0)	2,571 (0.6)
	Male (%)	301,765 (73.4)	
Ethnic groups	**Caucasian (%)**	257,160 (62.5)	115,378 (28.1)
	Black (%)	2,157 (0.5)	
	Asian (%)	18,994 (4.6)	
	Other (%)	17,635 (4.3)	
Patient type	**NHS (%)**	340,592 (82.8)	53,884 (13.1)
	Private (%)	16,848 (4.1)	
Admission route (ACS only) *	**Direct to cardiac centre (%)**	68,445 (33.5)	47,258 (23.2)
	Inter-hospital transfer (%)	73,309 (35.9)	
	Already in cardiac centre (%)	15,048 (7.4)	
Index of multiple deprivation score, mean (SD)		21.6 (13.9)	167,934 (40.8)

* ACS n= 204,070.

9.1.2 Clinical characteristics

Clinical characteristics of PCI between 2005 and 2010 are listed in Table 9.2. Around half (50.3%) of the patients recorded were chronic stable angina patients, while STEMI patients were 18.2% and NSTEACS were 31.5%. Over the study period, patients with chronic stable angina gradually decreased (from 56.7% in 2005 to 45.4% in 2010) and the number of STEMI patients steadily increased (13.1% in 2005 to 24.6% in 2010) (Figure 9.3). Primary PCI was performed for 50,445 (67.8%) acute patients (12.3% of all patients); in addition, only 6,155 (1.5%) of all patients had pre-procedural cardiogenic shock. Severe left ventricular systolic dysfunction (less than 30%) was in 23,752 (5.8%) patients.

Figure 9.3: Distribution of all PCI patients in England and Wales from 2005 to 2010, by clinical syndrome

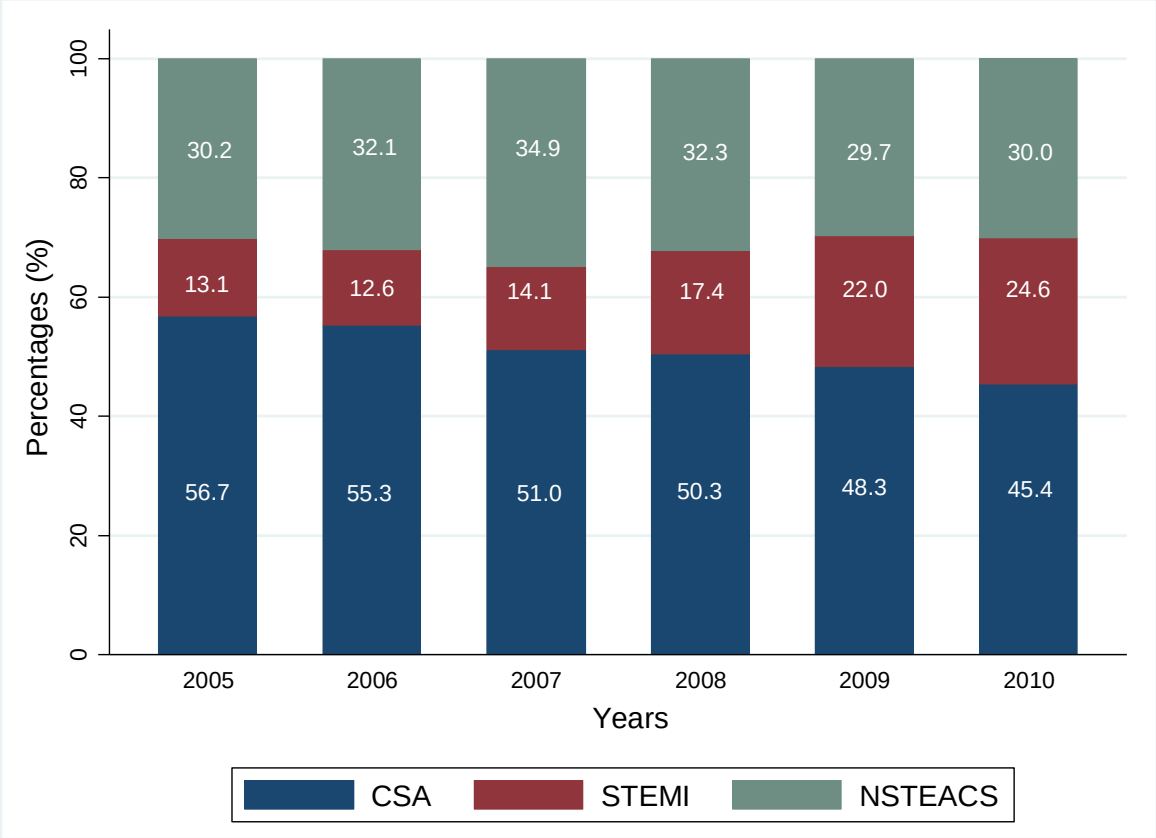


Table 9.2: Baseline clinical characteristics of all PCI patients in England and Wales from 2005 to 2010

Variable		Total n= 411,334	Missing values (%)
Clinical syndrome	CSA (%)	207,254 (50.3)	0 (0.0)
	STEMI (%)	74,369 (18.2)	
	NSTEACS (%)	129,701 (31.5)	
PCI type (STEMI only) *	Primary (%)	50,445 (67.8)	12,633 (17.0)
	Facilitated (%)	2,591 (3.5)	
	Rescue (%)	8,690 (11.7)	
Previous acute myocardial infarction (%)		105,221 (25.6)	56,985 (13.9)
Previous PCI (%)		77,600 (18.9)	32,640 (7.5)
Family history of coronary artery disease (%)		161,337 (39.2)	77,363 (18.8)
Diabetes mellitus (%)		68,718 (16.7)	31,244 (7.6)
History of renal disease (%)		9,420 (2.3)	45,764 (11.1)
Smoking status	Never smoked (%)	120,628 (29.3)	68,172 (16.6)
	Ex-smoker (%)	138,465 (33.7)	
	Current smoker (%)	84,059 (20.4)	
Recent thrombolysis (%)		24,174 (5.9)	190,095 (46.2)
Cardiogenic shock (%)		6,155 (1.5)	38,985 (9.5)
LVEF (%)	Good, LVEF ≥ 50%	147,761 (35.9)	189,742 (46.1)
	Fair, LVEF = 30 – 49%	50,074 (12.2)	
	Poor (sever), LVEF < 30%	23,752 (5.8)	

* STEMI n= 74,369.

9.1.3 Procedural characteristics

Pre-procedural thrombolysis in myocardial infarction type 3 (TIMI 3) was in 30,350 (14.9%) ACS patients (7.4% of all patients), and subsequently post-procedure increased to be in 89,950 (44.1%) ACS patients (21.9% of all patients). One stent was used in 200,680 (48.8%) of the patients; at the same time, drug eluted stents were deployed more frequently than bare metal stents. Overall, the use of the femoral artery as an access route was one fold higher than the use of radial artery (62.4% compared to 32.8%). More details about the procedural characteristics are shown in Table 9.3.

Table 9.3: Baseline procedural characteristics of all PCI patients in England and Wales from 2005 to 2010

Variable		Total n= 411,334	Missing values (%)
Pre-procedural flow in infarct related artery (ACS only) *	TIMI 0 (%)	36,981 (18.1)	103,077 (50.5)
	TIMI 1 (%)	7,893 (3.9)	
	TIMI 2 (%)	11,339 (5.6)	
	TIMI 3 (%)	30,350 (14.8)	
	Unknown (%)	14,420 (7.1)	
Arterial access	Femoral artery (%)	256,671 (62.4)	18,619 (4.5)
	Radial artery (%)	134,986 (32.8)	
	Other arteries (%)	1.048 (0.3)	
Total number stents used	1 stent (%)	200,680 (48.8)	51,704 (12.6)
	2 stents (%)	99,632 (24.2)	
	≥ 3 stents (%)	59,308 (14.4)	
Longest stented/treated segment, mean (SD) mm		23.5 (11.8)	110,958 (27.0)
Largest balloon/stent used, mean (SD) mm		3.2 (0.6)	117,448 (28.6)
Type of stent used	Bare metal stent (%)	119,244 (29.0)	50,488 (12.3)
	Drug eluting stent (%)	218,986 (53.2)	
	Both together (%)	22,606 (5.5)	
Type of drug eluting stent used	Taxus liberte (Boston Scientific) (%)	21,415 (5.2)	53,522 (13.0)
	Cypher (Cordis) (%)	35,147 (8.5)	
	Endeavor (Medtronic) (%)	30,886 (7.5)	
	Xience V (Abbott) (%)	33,450 (8.1)	
	Promus (Boston Scientific) (%)	23,148 (5.6)	
	BioMatrix (%)	3,029 (0.7)	
	Promus Element (%)	3,716 (0.9)	
	Xience Prime (%)	1,481 (0.4)	
Drugs used	None (%)	256,095 (62.3)	44,028 (10.7)
	Abciximab (%)	87,600 (21.3)	
	Eptifibitide (%)	6,577 (1.6)	
	Tirofiban (%)	17,024 (4.1)	
Use of intravascular ultra sound (%)		11,809 (2.9)	88,176 (21.4)
Use of intravascular pressure wire (%)		21,291 (5.2)	88,176 (21.4)
Use of Intra-aortic balloon pump (%)		5,893 (1.4)	51,693(12.6)
Post-procedural flow in infarct related artery (ACS only) *	TIMI 0 (%)	6,983 (3.4)	101,807 (49.9)
	TIMI 1 (%)	1,156 (0.6)	
	TIMI 2 (%)	4,164 (2.0)	
	TIMI 3 (%)	89,950 (44.1)	

* ACS n= 204,070.

9.1.4 Clinical outcomes

Coronary dissection was the most frequent procedural complication (1.7%) and the need for ventilation was the least 0.1%. During the hospital stay, MACCE occurred in 7,403 (1.8%) patients, while acute myocardial infarction occurred in 2,412 (0.6%) patients. PCI revascularisation was performed for 1,173 (0.3%) of patients. In-hospital mortality was in 1.1% of patients, which increased to 1.6% after 30 days post the procedure, and increased further to 4.7% after one year post the procedure. Procedural complications, in-hospital outcomes and mortality rates are shown in Table 9.4.

Table 9.4: Clinical outcomes of all PCI patients in England and Wales from 2005 to 2010

Variable			Total n= 411,334	Missing values (%)
Procedural complications	Side branch occlusion (%)		2,696 (0.7)	65,482 (15.9)
	Coronary dissection (%)		7,153 (1.7)	
	Coronary perforation (%)		1,078 (0.3)	
	Direct current cardioversion (%)		1,188 (0.3)	
	No flow/slow flow (%)		3,608 (0.9)	
	Ventilated (%)		367 (0.1)	
	Cardiogenic shock induced by procedure (%)		866 (0.2)	
In-hospital outcomes	Acute myocardial infarction (%)		2,412 (0.6)	24,193 (5.9)
	Stroke (%)		56 (0.1)	
	Renal failure/dialysis (%)		399 (0.1)	
	Blood transfusion (%)		836 (0.2)	
	Revascularisation	PCI (%)	1,173 (0.3)	
		CABG (%)	451 (0.1)	
	Unadjusted MACCE rate (%)		7,403 (1.8)	
Unadjusted in-hospital mortality rate (%)			4,373 (1.1)	14,155 (3.4)
Unadjusted mortality rate at 30 days (%)			6,505 (1.6)	259 (0.1)
Unadjusted mortality rate at 1 year * (%)			17,895 (4.7)	259 (0.1)

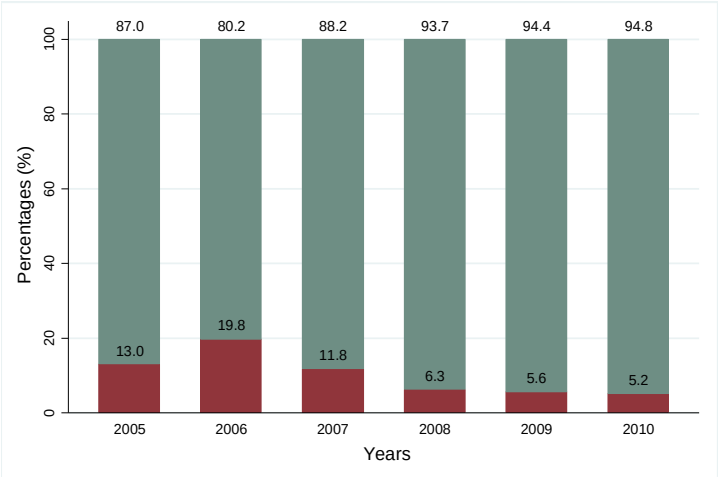
MACCE: major adverse cardiovascular and cerebrovascular event.
* Censored at 10/8/2011, therefore all PCI procedures performed after 10/8/2010 were not included in describing this rate.

9.1.5 Data completeness

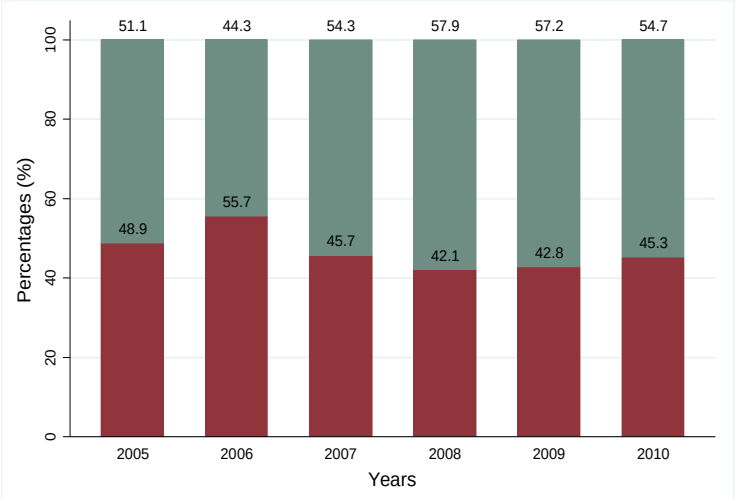
A total of 113 variables are in the 2010 BCIS database (after cleaning). Of them, only two (1.8%) variables were 100% complete, which were clinical presentation type and date/time of operation. Furthermore, the remaining 111 variables had missing information that ranged between 0.1% (such as age at procedure) and 96.0% (creatinine level). Tables 9.1 to 9.4 list the missing values of most of the 2010 BCIS database. Overall, between 2005 and 2010, there was a decrease in the proportion of missing data. Some examples of changes over the period were pre-procedural cardiogenic shock (missing values decreased from 13.0% to 5.2%), left ventricular ejection fraction (missing values decreased from 48.9% to 45.3%) and arterial access (missing values decreased from 9.2% to 2.2%) (Figure 9.4).

Figure 9.4: Proportions of complete and missing values for pre-procedural cardiogenic shock, left ventricular ejection fraction and arterial access in England and Wales stratified by years from 2005 to 2010

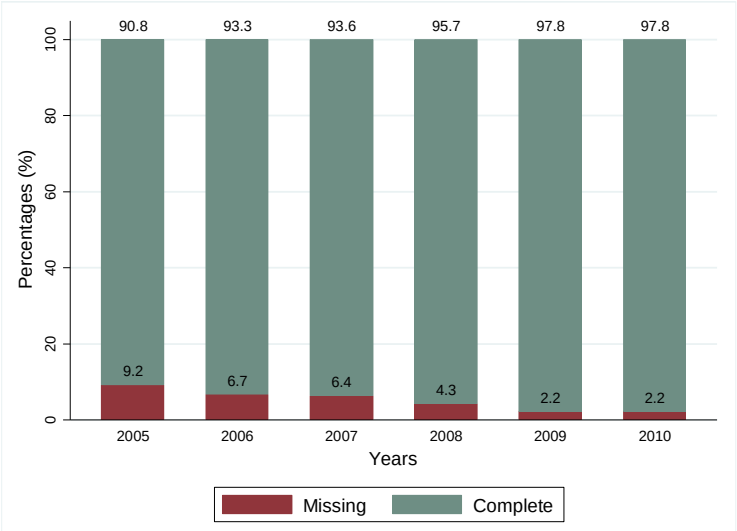
Pre-procedural cardiogenic shock



Left ventricular ejection fraction



Arterial access



9.2 Appendix II: NICOR Data Application Form

Ref number:

(Office use)

1.PROJECT TITLE

An investigation into primary PCI diffusion and provider effects on survival.

2.PRINCIPAL INVESTIGATOR

Title, forename, surname:	Dr Chris Gale
Employing organisation:	Division of Epidemiology and Biostatistics, University of Leeds.
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Please attach the Principal Investigator's Curriculum Vitae.

3.RESEARCH PROJECT

3.1 SUMMARY

Evidence continues to support the fact that primary PCI is associated with better outcomes for STEMI patients. However, the majority of studies have been randomised controlled trials and conducted outside England and Wales, thus cannot be fully generalisable to England and Wales. On the other hand, there is local variation at both levels of operators and hospitals, in the implementation of, outcomes and survival from this service which require further investigation. Using primary PCI data available in an observational national dataset such as the BCIS database will allow us to characterise all primary PCI survival estimates and the impact of provider (at hospital level and operator level) on these estimates in England and Wales population. This research proposal, therefore aims to quantify, on a national scale, the survival estimates as well as hospital level and operator level effects on survival after primary PCI and measure the impact of changes over time. Our application will not cover what is to be undertaken at NICOR. We will undertake a shared frailty survival analysis to report variance components, a spatial diffusion analysis, and a relative survival analysis. We also wish to improve the data using statistical techniques such as multiple imputation for missing data to try to overcome some of the expected biases. This will permit the evaluation of the effect of missing data on research outcomes and offer the potential to enhance the research strengths of the BCIS database.

3.2 CONTEXT

This will form part of a larger 5 year programme of research funded by the National Institute for

Health Research (Dr CP Gale, PI), studying variation in cardiovascular care and outcomes in England and Wales.

3.3 PROJECT DESCRIPTION

Background

For patients presenting with acute STEMI, primary PCI is now considered the favoured line of management especially when performed within the first 90 to 120 minutes of medical attention.[60, 217, 218] This is because, when compared with thrombolysis, primary PCI is associated with better outcomes.[219, 220] and is cost effective.[77] Consequently, a national primary PCI strategy has been adopted in England and Wales. However, the evidence uptake and its implementation has been prolonged and varied,[4] and may have prevented avoidable deaths if undertaken earlier and more uniformly across the country.

t is well established that patient level (case-mix) and hospital level (volume) are associated with early outcomes after primary PCI.[1,5-8] For example, many observational cohorts have reported significant centre volume outcome effects, suggesting a need for dedicated heart attack centres, whereby high throughput high volume centres are able to provide optimal care and outcomes.[9] Operator level factors may also impact on outcomes, for which there are only limited data in the literature. The invstigation of transparent reporting of operator level adjusted outcomes provides an ideal opportunity to quantify nationally if this impacts on survival after primary PCI after accounting for patient level and hospital level influences.

Providing a local primary PCI service for acute STEMI has been an immense challenge for many centres and resultantly there are a range of services provided. Indeed, there has been geographical inequity in primary PCI diffusion (and format of its uptake, for example, 24 hours service versus non 24 hour service) such that variation in potentially avoidable outcomes may have resulted over time and be present to this day. Yet, there are no independently published analyses to support or refute this notion.

Scientific hypothesis

We hypothesise that there have been significant temporal improvements in survival after primary PCI, but that are significant residual hospital level and operator level effects.

Objectives

1.To report crude and adjusted survival estimates after primary PCI.

2. To quantify the hospital level and operator level effects on survival after primary PCI.

3.To describe the national diffusion of primary PCI, and quantify associated avoidable death.

4.To investigate the temporal trends in survival after primary PCI.

Methodology and planned statistical analyses

Data:

BCIS database

Sampling frame:

Patients over 18 years of age who revived primary PCI for acute STEMI

Methods

1)Missing data: Multiple imputation of missing data specific for survival analyses
2)Survival analysis: a) Shared frailty using accelerated failure, b) relative survival, c) crude and adjusted estimates with 95% confidence intervals, d) hospital and operator variance components will be quantified and compared with fixed effects coefficients
3)Diffusion: a) rates of primary PCI per population estimates, b) linear models to quantify associations with regional level ecological data where available
4)Avoidable deaths: derived from SMRs and numbers of centre procedures

Please refer to our published manuscripts which detail the above methods for use in the NICOR national cardiovascular registries.

We are aware that a centre volume outcome analysis is to be undertaken through NICOR UCL. We do not plan to duplicate this project.

We, therefore, request a further download of the psuedoanonymised BCIS dataset to include contemporary cases from 2005 to 2013, linked to status and date of death / time to death.

Competing interests

None.

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3.4 PLANNED SCIENTIFIC OUTPUTS

Publication in peer-review journals and presentation at national and international scientific meetings.

4. RESEARCH TEAM / CO-APPLICANTS

Details of each Research team member involved in the proposed project.

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5. PUBLICATIONS OF THE RESEARCH TEAM MEMBERS

List of the main publications of each Research team member involved in the project.

Gale CP

An assessment of composite measures of hospital performance and associated mortality for patients with acute myocardial infarction. Analysis of individual hospital performance and outcome for the National Institute for Cardiovascular Outcomes Research (NICOR).
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6. PREVIOUS APPLICATIONS

Have you or any of the Research team members/co-applicants applied for NICOR data in the past?

Yes.

If Yes, please give details:

Main Applicant	Application Date	Project Title	Scientific Outputs
Dr Chris Gale	December 2010	Primary PCI in England and Wales: defining a framework for excellence	Project application accepted
Dr Chris Gale	June 2011	Multiple imputation for completion of the British Cardiovascular Intervention Society (BCIS) database	Project application accepted

7. FUNDING

Do you already have funding to carry out this project?

N/A.

If you are planning to seek funding to carry out this project and the grant application is to be partially or totally based in the use of NICOR data, please give details about the funding application.

Name of funding body
Dr Chris Gale is funded by the NIHR. The project will be undertaken by members of staff from the University of Leeds.

8. DATA REQUESTED

8.1 Patient identifiable data	NO
8.2 Proposed linkage:	NO
List datasets	BCIS dataset
TTP (if used)	
8.3 Please refer to the audit dataset:	
Dataset items required	A cleaned BCIS dataset with: 1.Mortality tracking (date of censor, date of response, and status) 2.Unique BCIS patient code, which will then allow data tracking to the

	original BCIS dataset for the purposes of third party linkage and / data updating (if necessary) for identification of index procedure 3.Hospital-level identifiers 4.Hospital-specific information – eg number of PCIs, no of Drs etc 5.Anonymised operator id.
Time period	From 1st of January 2005 to 2013 (or the latest possible)
Geographical location	Data for England and Wales Data for Northings and Eastings for each patient
Annual updates required	Yes

9. PROPOSED PROJECT COMPLETION DATE

2014

MEETING DATE (Office use):

9.3 Appendix III: Ethical requirements

9.3.1 Research/audit/service evaluation queries

Information about the person undertaking the project

Who:

Dr Sami Almudarra, a PhD research postgraduate, Centre for Epidemiology and Biostatistics, School of Medicine, Faculty of Medicine & Health, University of Leeds.

Why the study is being conducted:

To use anonymised (secondary) data from the British Cardiovascular Intervention Society (BCIS) to evaluate the care of patients who have undergone percutaneous coronary interventions (PCI).

Why I am seeking an opinion:

As part of my Ph.D in Cardiovascular Epidemiology, I would like to undertake statistical work using anonymised BCIS data which aims to evaluate the care of patients who have undergone PCI and I would like to know whether this requires ethical approval or audit / service evaluation. Dr Chris Gale, my supervisor, works with this and a similar anonymised database – the Myocardial Ischaemic National Audit Project (MINAP), and after similar enquiry to you, it has been suggested that this type of work does not require formal application for ethical review.

Purpose/aims of the study

Project (thesis) title:

Evaluating the care of patients who have undergone PCI using the BCIS database.

Summary of proposed work:

The proposed work aims to utilise contemporary data from BCIS. BCIS data arise from a retrospective multi-centre observational study. The data that we will access from the BCIS is anonymised – we cannot trace it back to and therefore cannot identify individual patients, physicians or hospitals. We wish to improve the data using statistical techniques such as multiple imputation for missing data, and also evaluate quality of care by analysing the data.

Context:

This work is under the auspice of the National Institute for Health Research Clinician Scientist Award (held by Dr Chris Gale).

Project description:

Background

There are clinical and statistical concerns about the use of routine clinical data for the purposes of research which create biases when the datasets have missing and/or implausible values. So, as part of my PhD, I will consider a variety of statistical techniques such as multiple imputation to try to overcome some of the biases. This will permit the evaluation of the effect of missing data on research outcomes and offer the potential to enhance the research strengths of the BCIS database. Afterwards, we aim to utilise BCIS data to study PCI quality of care so that a framework for excellence may be defined that will promote improvements in care for all patients admitted to hospital with acute coronary syndrome regardless of where they live in England and Wales. We will, for example, consider studying the impact of primary PCI, outcomes from PCI to the left main stem coronary artery.

Scientific uncertainty

1) This is a retrospective observational study and not a randomised controlled trial; substantial biases will challenge the analyses – many of which difficult to overcome.

2) Modelling will never adjust for all potential confounders.

3) New statistical techniques will be applied and evaluated.

4) An imputed BCIS dataset 'fit for purpose' will be an outcome of this research.

Expected value of results

We feel that this project will help answer several important questions regarding the level of care provided to patients who have undergone PCI in England and Wales.

Scientific hypothesis

What is the level of care provided to patients who have undergone PCI in England and Wales based on the national BCIS database?

Objectives

1)To use BCIS data to evaluate the care of patients who have undergone PCI in England and Wales.
2)To enhance the research potential of BCIS database through multiple imputation.

Competing interests

None

Eligibility criteria

Permission for the use of the data to undertake this work has been granted from the BCIS Academic Committee.

Sample size There are over 650,000 acute coronary syndrome events recorded in the BCIS database 2005-2010, of which 411,324 underwent PCI.

Recruitment We will not be recruiting patients – rather we will use secondary anonymised data from a national audit database.

Population Anonymised data relating to patients who have undergone PCI, entered into the BCIS database between 2005 and 2010. We will not be recruiting patients. We cannot identify patients, hospital or physicians.

If patients or their records/material are to be part of the study the following information should be provided:

- Whether there will be any direct patient contact. No
- Details on whether the person undertaking the project will be part of the clinical team. No
- If they are not part of the clinical team, who will access the medical records and will all data passed on to them be fully anonymised.

Only secondary (anonymised) data will be used that has been collected locally and sent to BCIS via the Central Cardiac Audit Database (CCAD).

Information should be provided on whether any vulnerable groups, such as children, the elderly or those with a mental illness, will be included in the study

All submission to BCIS who present to hospital with acute coronary syndrome and have undergone PCI.

Procedure If the study involves clinical interventions, details should be provided on whether these are part of routine clinical practice or new interventions.

It does not involves clinical interventions

Data collection If data collection is via questionnaires, information should be given on how many will be used and whether they are validated. If subject are to be interviewed, brief details of the interview themes should be given.

Data is collected by CCAD and sent to BCIS, whereby upon successful application anonymised data is released to academics.

Methodology and planned statistical analyses

Multi-centre retrospective observational study. Contemporary BCIS data (+/- imputed data). Statistical modelling.

9.3.2 Copy of the reply e-mail received from FREC

----- Message from FMHUniEthics@leeds.ac.uk ---------
Date: Wed, 8 Feb 2012 14:33:37 +0000
From: Medicine and Health Univ Ethics Review
<FMHUniEthics@leeds.ac.uk>
Reply-To: Medicine and Health Univ Ethics Review
<FMHUniEthics@leeds.ac.uk>
Subject: RE: Requirements for review of queries
To: 'Sami Almudarra' <umssal@leeds.ac.uk>

Dear Sami,

Apologies for the delay in getting back to you about this. I have re-contacted the FREC Chair would has agreed that we do not need to require ethics review for research utilising anonymised datasets such as this.

Best wishes,

Georgina