ANGLIA RUSKIN UNIVERSITY

FACULTY OF MEDICAL SCIENCE

A LONGITUDINAL MONITORING STUDY OF CARDIOVASCULAR HEALTH IN THE ESSEX REGION

LEON WEBSTER

A thesis in partial fulfilment of the requirements of Anglia Ruskin University for the degree of Doctor of Philosophy (PhD)

Submitted: July 2018

Acknowledgements

The content within this thesis was completed between 2013 and 2018. It was funded by a PhD studentship provided by Anglia Ruskin University (ARU) from funds provided by Basildon and Thurrock University Hospital NHS Foundation Trust (BTUH). There was no duress by BTUH at any time to adjust, redact, or delete any of the date or analyses presented in this thesis.

All of the content within this these, including statistical analyses, generation of results, and manuscript production, was created solely by the author listed on the title page of this thesis, unless stated elsewhere in the document.

I would like to thank my supervisory team (Dr. Ian van der Linde, Prof. James Hampton-Till, and Dr. John R. Davies) for their time, assistance, and helpful suggestions during the production of this thesis. In order to check and verify the statistical analyses and methods featured in this thesis, valuable guidance was provided by Michael Parker, a medical statistician based at Anglia Ruskin University's Postgraduate Medical Institute.

I am especially grateful to the Essex Cardiothoracic Centre (ECTC) and BTUH staff for their assistance in providing access to the data used for all three studies within this thesis. In particular I would like to extend my gratitude to the ECTC Data Manager, Stewart Stent, for his time and effort in providing me with the required data, for which this thesis would not have been possible. The medical expertise of my clinical supervisor (Dr. John R Davies) was extremely valued in the interpretation of results and in the design of the studies.

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ABSTRACT

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DOCTOR OF PHILOSOPHY

A LONGITUDINAL MONITORING STUDY OF CARDIOVASCULAR HEALTH IN THE ESSEX REGION

LEON WEBSTER

August 2017

This thesis investigates the risk factors associated with adverse outcomes following percutaneous coronary intervention (PCI) for patients reporting to the Essex Cardiothoracic Centre (ECTC). The risk prediction model NWQIP (North West Quality Improvement Programme), for in-hospital Major Adverse Cardiac Events (MACE), comprising of at least one of four types of event (Q-wave myocardial infarction, death, emergency coronary artery bypass graft surgery, and cerebrovascular accidents), was externally validated on the ECTC PCI procedure database, using data from 2007 to 2015, to evaluate its effectiveness in a different era of stenting and a different geographical location. It was found the NWQIP model requires recalibration and hence no longer predicts such MACE events accurately. A custom risk prediction model was designed for the outcome of 30-day mortality. This incorporates novel risk factors (pre-operation ventilation and peripheral vascular disease) that were not featured in the NWQIP model. A subsequent analysis was performed on stable (elective) patients to identify those that are likely to either die or require a subsequent coronary revascularisation within three years. These two novel risk models should be tested on PCI cohorts external to the ECTC to identify how effective they are, and if they perform well, then possibly adopted into modern PCI practice for usage by consultants, operators, or patients for informed consent.

Key words: percutaneous coronary intervention; major adverse cardiac events; 30-day mortality; repeat revascularisation; North West Quality Improvement Programme; Essex Cardiothoracic Centre

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List of Abbreviations

Abbreviation	Meaning
ACC	American College of Cardiology
ACE	Angiotensin-Converting Enzyme
ACS	Acute Coronary Syndrome
AHA	American Heart Association
AMI	Acute Myocardial Infarction
AUROC	Area Under the Receiver Operating Characteristic (ROC) curve
AV	Atrioventricular
AVR	Aortic Valve Replacement
BCIS	British Cardiovascular Intervention Society
Bival	Bivalirudin
BMI	Body Mass Index
BMS	Bare Metal Stent
BTUH	Basildon and Thurrock University Hospital NHS Foundation Trust
CABG	Coronary Artery Bypass Graft
CAD	Coronary Artery Disease
CCG	Clinical Comissioning Group
CCS	Canadian Cardiovascular Society
CHD	Coronary Heart Disease
CHF	Congestive Heart Failure
CI	Confidence Interval
CK-MB	Creatine Kinase-MB
COPD	Chronic Obstructive Pulmonary Disease
CTB	Call-To-Balloon
CTO	Chronic Total Occlusion
CVA	Cerebrovascular Accident
CVD	Cardiovascular Disease
CVIS	Cardiovascular Information Management System
DAPT	Dual Antiplatelet Therapy
DES	Drug Eluting Stent
df	Degrees of Freedom

DGH	District General Hospital
DNA	Deoxyribonucleic acid
DTB	Door-To-Balloon
ECTC	Essex Cardiothoracic Centre
ECG	Electrocardiogram
FN	False Negative
FP	False Positive
GFR	Glomerular Filtration Rate
GMC	General Medical Council
GP	Glycoprotein
GPs	General Practitioners
HES-ONS	Hospital Episode Statistics-Office for National Statistics
HR	Hazard Ratio
ICU	Intensive Care Unit
IHD	Ischemic Heart Disease
IMA	Internal Mammary Artery
IRA	Infarct-Related Artery
IV	Intravenous
IVUS	Intravenous Ultrasound
LA	Left Atrium
LAD	Left Anterior Descending (artery)
LADO	Left Anterior Descending (artery) Other
LADP	Left Anterior Descending (artery) Proximal
LCX/LCx	Left Circumflex (artery)
LDL	Low-Density Lipoprotein
LMS	Left Main Stem
LOS	Length Of Stay
LV	Left Ventricle
LVEF	Left Ventricular Ejection Fraction
MACE	Major Adverse Cardiac Events
MCRS	Mayoclinic Risk Score
MI	Myocardial Infarction
MIDCAB	Minimally Invasive Direct Coronary Artery Bypass
MINAP	Myocardial Ischaemia National Audit Project
N/A	Not Applicable

NHS	National Health Service
NICOR	National Institute for Cardiovascular Outcomes Research
NRES	National Research Ethics Service
NSTEMI	Non-ST Elevation Myocardial Infarction
NWQIP	North West Quality Improvement Programme
NYHA	New York Heart Association
ONS	Office for National Statistics
OPCAB	Off-Pump Coronary Artery Bypass
OR	Odds Ratio
PAS	Patient Administration System
PCI	Percutaneous Coronary Intervention
PCT	Primary Care Trust
PPCI	Primary Percutaneous Coronary Intervention
PVD	Peripheral Vascular Disease
QoL	Quality of Life
RA	Right Atrium
RCA	Right Coronary Artery
REC	Research Ethics Committee
ROC	Receiver Operating Characteristic (curve)
RR	Repeat Revascularisation
RRD	Repeat Revascularisation or Death
RV	Right Ventricle
SCTS	Society for Cardiothoracic Surgery
SD	Standard Deviation
SE	Standard Error
SNP	Single Nucleotide Polymorphism
SPECT	Single Photon Emission Computed Tomography
SPSS	Statistical Package for the Social Sciences
STEMI	ST-Elevation Myocardial Infarction
SYNTAX	Synergy between PCI with Taxus and cardiac surgery
TIMI	Thrombolysis In Myocardial Infarction
TLF	Target Lesion Failure
TLR	Target Lesion Revascularisation
TNR	True Negative Rate
TPR	True Positive Rate

TVF	Target Vessel Failure
TVR	Target Vessel Revascularisation
UA	Unstable Angina
UK	United Kingdom
ULMCAD	Unprotected Left Main Coronary Artery Disease
US	United States
VHD	Valvular Heart Disease
VIF	Variance Inflation Factor
VLDL	Very Low Density Lipoprotein

List of Appendices

Published Work

From the second study within this Thesis (Chapter 5, 30-day mortality prediction), an article was written and published to a peer-reviewed cardiovascular intervention journal as referenced below.

Webster, L., van der Linde, I., Davies, J.R., Hampton-Till, J., 2015. Evaluation of the North West Quality Improvement Programme risk prediction model as a 30-day mortality predictor. *Interv. Cardiol.*, 7(5), pp. 431-442

In summary, the research article externally evaluates an established risk prediction model, NWQIP, for in-hospital complications (MACE) and 30-day mortality following percutaneous coronary intervention. This was performed on a modern PCI database for a cohort of patients at the Essex Cardiothoracic Centre (ECTC), part of Basildon and Thurrock NHS University Hospital. Following this, a risk model for predicting 30-day mortality in modern PCI cohorts was developed. The three co-authors of this research article are the three members of the supervisory team for this Thesis.

At the time of writing this thesis, a journal article from the third study within this thesis (Chapter 6, Three-Year Repeat Revascularisation or Death) is in the final production stage and is intended to be submitted to a peer-reviewed interventional cardiology journal.

Two abstracts were submitted in successive years (2014, and 2015) for presentation at the Anglia Ruskin University Student Research conferences. The abstracts received a commended and highly commended award.

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Chapter 1: Introduction

This thesis investigates patient outcomes following coronary revascularisation procedures for patients presenting with cardiovascular disease (CVD) at the Essex Cardiothoracic Centre (ECTC). The ECTC is a tertiary cardiac referral centre that is part of the Basildon and Thurrock University Hospital NHS Foundation Trust (BTUH), located in the county of Essex within the south-east of the United Kingdom (UK).

1.1 Purpose

The purpose of this research project was to identify whether the use of a contemporary cardiovascular patient database can be utilised to assist in the prediction of useful clinical outcomes (in-hospital complications, short and long-term mortality, repeat and revascularisation) for patients within the Essex region following percutaneous coronary intervention (PCI). It was also conducted to ascertain whether any prediction models could be developed that performed to accuracy and thus might be adopted and utilised by not only clinicians and interventional cardiologists at the ECTC, but also those at other hospitals and cardiac referral centres within the UK.

By identifying a set of risk factors (characteristics) which exhibit a strong relationship with adverse outcomes following cardiovascular intervention, certain subgroups of patients most at risk could be determined and subsequently additional care, planning and resources could be allocated to such patients. Conversely, it may be the case that the clinical and procedural characteristics recorded in modern cardiovascular patient databases do not fully explain the important outcomes and hence may have very weak relationships thus rendering the usefulness of any such prediction models as poor.

Whilst there are many published peer-reviewed journal articles (Singh & Lennon et al., 2002; Grayson et al., 2006; Singh & Gersh et al., 2007; Madan et al., 2008; Ranucci et al., 2009; Maluenda et al., 2010; Peterson et al., 2010; Hannan et al., 2013) on the subject of outcome risk prediction following PCI or coronary artery bypass graft (CABG) surgery, there are several important reasons why the studies in this thesis were performed, and why they contribute to knowledge of the field.

There have been numerous changes in different aspects of cardiovascular intervention since many of these risk prediction models were developed, some of which are over a decade old, and consequently their performance may have deteriorated due to several causes briefly explained below, and in more detail in subsequent chapters.

Location

The majority of the peer reviewed research on risk prediction models for outcomes following coronary revascularisation procedures that were identified in this thesis were developed by researchers at hospitals and cardiac centres within the United States (US). The US healthcare system has many differences (McCarthy, 2014; Ham, 2005; Pritchard and Wallace, 2011; Tyrrell, 2016; Jick, 2012) compared to the British National Health Service (NHS). Such differences may include the classification of intervention indications and reasons for performing (or not) PCI or CABG procedures for certain subgroups of patients, and hence the associations between mortality and other important outcomes may be impacted by such differences in healthcare practice. In addition to this, differences in population demographics (Cherlin, 2010) are also present, including but not limited to ethnic background (Chaturvedi, 2003), obesity levels (Poirier et al, 2006), socioeconomic status (Clark et al, 2009), these of which have been identified as having a relationship with developing cardiovascular disease. As well as differences between these factors for comparing countries it is also anticipated that internal differences exist, i.e. states within the US and counties within the UK (Braveman et al, 2010; ONS, 2016). It may also be the case that differences are present within regions, i.e. between towns, primary care trusts (PCTs) or clinical commissioning groups (CCGs).

Increasing Life Expectancy

In England, the average life expectancy in years has increased (ONS, 2016) from 75.9 in 1990 to 81.3 in 2013 (Newton et al., 2015). With increasing age, so too has the incidence of coronary artery disease (CAD) and hence inpatient episodes, caused by CAD (BHF CVD Statistics, 2014). During 2012/13 this figure was 404,000. For many PCI mortality and/or adverse complication risk prediction models, patient age is one of the components whereby an increased risk of adverse events is generated, in general, as age increases. The advanced age tends to act as a surrogate predictor for frailty (Murali-Krishnan et al, 2015). With increasing life expectancy (Leon, 2011) is it anticipated that more elderly patients would be presenting for coronary revascularisation, and hence would affect the overall mortality and complication rates negatively. The increase in the population reporting to PCI centres and hospitals would likely cause a burden on the healthcare system, possibly resulting in lower risk patients with cardiovascular disease having to wait longer for the appropriate procedure. This increased 'load' may alter the decision making process for cardiology consultants, i.e. would a low-risk patient (such as stable angina) now instead be given pharmacological therapy instead of a PCI.

Other Demographic and Comorbidity Trends

In addition to increasing life expectancy there have been trends identified specifically in the UK population rates relating to increasing CVD, diabetes, other comorbidities, and prior PCI. These rates may simply be explained because they are diagnosed at a far earlier stage than previously. For example, individuals with hypertension and renal disease may have a more rapid identification of subsequent cardiovascular disease symptoms and hence a more rapid referral to a consultant cardiologist. Sociodemographic factors may also have an influence on the outcomes following PCI, for example the ECTC is based in the south-east of England, and it has been identified that a north/south divide is present whereby those in the north of England were found to have a lower life expectancy than the southern counterparts (ONS, 2013).

Cardiac Centres and Operators

In the UK there has been a steady increase in the number of cardiac centres and hence locations which perform PCI procedures. This increased from approximately 52 in 1996 to 119 in 2014. This corresponded with an increased number of interventional operators from approximately 300 in 2001 to 731 in 2014 (BCIS Audit, 2015). In 2014, 96,143 PCIs were performed on patients with CAD (BCIS Audit, 2015) at NHS centres.

Clinical Syndrome

The clinical syndrome UK patients are presenting to PCI centres with, when broken down into acute coronary syndromes (ACS) and the counterpart, stable syndromes shows a steady trend over time. ACS has increased from approximately 44% in 2005 to 65% in 2014, and corresponding to this, the stable syndrome decreased from approximately 56% in 2005 to 35% in 2014 (BCIS Audit, 2014).

Stenting Technology and Dual Antiplatelet Therapy (DAPT)

The devices used during modern coronary revascularisation, most notably PCI procedures, have experienced big changes over the last few decades (Simard et al, 2014; Ernst, 2014). One of these biggest changes is the evolution from standard balloon angioplasty to the usage of bare metal stents (BMS), to the usage of drug-eluting stents (DES), subsequent generations of DES (Akin et al, 2011), followed more recently by global clinical trials of bioabsorbable stents, such as the Absorb stent manufactured by Abbott Laboratories. These bioabsorbable stents were developed to address the drawbacks/limitations of current generation metallic stents. They are constructed from a

polylactide material and can be fully absorbed into the coronary artery, usually after a period of 2-3 years. The main aim is to prevent very late stent thrombosis, whereby blood clots form around metallic stents in 1-2% of patients, and thus can cause subsequent adverse events for the patient such as death, myocardial infarctions, or the need for subsequent treatment (target lesion revascularisation, TLR). Once the stent has fully dissolved, it is proposed that the coronary vessel can resume its natural movement, i.e. vasodilation and vasoconstriction. This also should result in the patient not needing to dual anti-platelet therapies (DAPT) for as long as they would if they had a metallic stent. The DAPT combine the usage of aspirin with a stronger aspirin-like drug (e.g. Clopidogrel, Prasugrel, and Ticagrelor), the purpose of its usage is to reduce the risks of future myocardial infarctions (MIs), and blood clotting around the inserted stent (ACC, 2016). These differences in the stent technology such as material, thickness, and drug coating may exhibit differences in restenosis and other adverse events (Smits, 2010; Navarese et al, 2014) for different patient subgroups at the ECTC following PCI, such events may include mortality (all or cardiac-related), myocardial infarction (MI), TLR, or target vessel revascularisation (TVR). As mentioned above, related to the stent type is the post-procedure pharmacological therapy provided to the patient, namely the amount and duration of DAPT (Kereiakes et al, 2015; Tantry et al, 2006).

Recently (September 2017), Abbott Laboratories announced they were ceasing the commercial sales of their first generation Absorb stent (Abbot 2017). They will focus on a next generation bioabsorbable stent by addressing some of the reported limitations including: cost; thickness of the stent (additional polymer is required to make the stent strong compared to metallic stents); long insertion times; inability to use the stent (due to size) on small coronary vessels (< 2.5 mm diameter); recoil issues following expansion; and faster absorption rates. Additionally, there has been a lack of results from trials reporting clear benefits in terms of MACE rates compared to DES (Pandya et al., 2016; Kereiakes et al., 2017).

1.2 Risk Prediction Models

Risk prediction models exist in many different industries and are used to estimate the likelihood of different events occurring. For example, in medicine models exist to predict long-term mortality for patients which have undergone coronary bypass graft surgery (Wu et al, 2012), many others exist that are non-cardiac related also; for example, predicting mortality following kidney transplantation (Jassal et al, 2005), or liver transplantation (Pan et al, 2014). Typically, the models are constructed using a comprehensive database incorporating demographics, procedural, and clinical variables where applicable. The myriad of models in published peer-reviewed journals allow clinicians and researchers to externally validate them on their own cohorts to verify the performance level of the model, and hence if the model performs well enough to be adopted in clinical practice.

The models incorporate risk factors/characteristic variables which are assigned specific weights based on their statistical association with the event/outcome (e.g. three-year mortality), typically, the more risk factors within a prediction model that the patient exhibits, the higher the probability of experiencing the adverse outcome. Variables are first identified in a univariate test with their association for the specific outcome. Those which exhibit a strong statistically significant relationship are then used as candidates for a multivariate logistic regression analysis. In doing so, this eliminates those risk factors with high correlation with each other, i.e. those with high multicollinearity, to ensure the risk model is as parsimonious as possible.

Risk models provide numerous benefits that warrant their research, construction, and subsequent adoption in clinical practice. They can inform consultants and operators or likely outcomes for a patient that exhibits certain characteristics. A model can estimate a probability of an adverse event which could assist in justification of whether to proceed with a certain type of treatment.

Related to the previous benefit, the model could be useful for elective patients such that they can be informed of the likely outcomes should they choose to receive a certain treatment. For example, if a risk model estimated a 95% probability of death within 30 days based on various characteristics exhibited by the patient, they may not want to proceed with such a high risk treatment.

Usage of risk models can allow more efficient planning and management strategies to be implemented for high-risk patients. For example, the highest risk subgroups of patients could be provided more care by the hospital rehabilitation teams or given an increased

hospital length of stay to facilitate their recovery, conversely patients at a very low-risk of adverse events could be discharged more rapidly, this is especially beneficial given shortage of hospital beds (Chang et al., 2002; Kramer and Zimmermant, 2010; Ong and Pua, 2013).

They also have the potential to identify adverse practices. For example, given the release of operator outcomes to the public (BCIS Operator Results, 2015) it allows comparisons between operators and hospitals for complications/mortality to ascertain which are performing above or below national rates (i.e. using a 95% confidence interval). It allows the following points to be addressed: (I) Are certain operators/hospitals unnecessarily putting patients at high risk that should not be. (ii) Whether treatment for certain patients is being avoided to covertly reduce mortality rates. Any significant departures from the estimated mortality rates could be evidence of better/worse than national average patient care.

1.3 Outcomes Analysed and Hypotheses

The important clinical outcomes featured in this thesis were chosen because they are measures considered important with regards to interventional cardiology, and hence why they are selected in a myriad of previous published research studies on outcomes following coronary revascularisation. The outcomes are described briefly below.

In-hospital major adverse cardiac events (MACEs)

This is a composite outcome of the occurrence of at least one of the following events during a patient's index admission at the ECTC: (I) death – this can be any cause even if it is unrelated to an underlying cardiovascular cause; (II) emergency CABG surgery performed; (III) cerebrovascular accident (stroke); (IV) a Q-wave MI in which a heart attack has occurred that produces a new Q-wave on an electrocardiogram (ECG) and whereby certain elevated cardiac biomarkers are detected in the patient (Thygesen et al, 2007). The outcome of in-hospital MACE was particularly important because it is the featured outcome of the widely recognised NWQIP model (North West Quality Improvement Programme, Grayson et al, 2006) developed by a consortium of UK hospitals. The NWQIP model is a multivariate logistic regression model whereby several risk factors are given different weightings based on the strength of their association with the in-hospital MACE outcome and these are combined to generate an odds metric which represents the likelihood that patient with a given set of risk factors, would go on to experience the in-hospital MACE outcome. The risk factors incorporated into the NWQIP model are: age; female gender; stroke; cardiogenic shock; PCI priority; and lesion type treated (i.e. LMS or graft).

30-Day Mortality

This includes a patient's death occurring up to and including 30 days from the date of an index PCI procedure. This measure includes both patients that died pre-discharge and post-discharge so long as the death is within the specified time period of 30 days. This outcome includes all-cause mortality, not just cardiac-related deaths.

Repeat Revascularisation

The type of repeat revascularisation investigated in this thesis is whereby a patient is given a subsequent unplanned coronary revascularisation procedure within three years, whether this is another PCI or a CABG following an initial PCI at the ECTC. The

unplanned classification is where their subsequent revascularisation procedure has not been foreseen, arranged or known about at the time of their initial PCI.

A subset of repeat revascularisation is target vessel revascularisation (TVR) whereby a subsequent unplanned revascularisation procedure is performed on the same coronary vessel as was treated during their index PCI. This does not necessarily have to be a single coronary vessel revascularisation for both procedures, as long as the same vessel was treated during the index PCI and the subsequent PCI/CABG then it is classified as a TVR. The vessels that are treated can be one of the following: right coronary artery (RCA); left circumflex (LCX); left main stem (LMS/Lmain); left anterior descending artery (LAD); or a previously grafted vessel.

1.3.1 Hypotheses

By analysing the specified the outcomes of in-hospital MACE, 30-day mortality, and repeat revascularisation or death it allowed the following hypotheses to be tested. These hypotheses were formulated from the described limitations in section 1.1. In summary, the factors which influenced the development of the hypotheses are:

- Increasing life-expectancy of the UK population (ONS, 2016).
- Increasing overweight and obesity rates amongst the UK population (ONS, 2017)
- Other differences between the characteristics (demographic, clinical, and procedural) between the original NWQIP PCI cohort and the ECTC cohort (as documented in section 3.6).
- high proportions of emergency PCI procedures being performed (e.g. critically ill patients, such as those which have experienced an out-of-hospital myocardial infarction) as reported by the British Cardiovascular Intervention Society (2016)
- Increased numbers of UK cardiac centres/hospitals performing PCI (and CABG)
- Increased numbers of operators/interventional cardiologists (BCIS, 2016)
- Technological evolution in stent design and material (e.g. drug-eluting stents and successive generations such as bioabsorbable materials), which are claimed to reduce various adverse outcomes (Kumar & Mathew, 2010; Forest et al., 2013)

Hypothesis 1: The NWQIP risk model is outdated and will not perform as effectively as it did in its original setting (Grayson et al., 2006), or as it did in the external validation study (Kunadian et al., 2008), when tested on a modern PCI centre patient database.

Hypothesis 2: Relating to hypothesis 1, not all of the NWQIP model risk factors (i.e. age, gender, cerebrovascular disease, cardiogenic shock, PCI priority, left main stem lesions, and graft lesions) will exhibit significant univariate associations with in-hospital MACE. Therefore, it is theorised that due to both increasing numbers and more experienced operators (higher volumes of PCIs performed), performing PCI on patients with such NWQIP risk factors is effectively 'safer' than previously. This therefore suggests that a 'new' risk prediction model will not incorporate all of the NWQIP risk factors.

Hypothesis 3: By performing a multivariate logistic regression analysis on the modern, comprehensive, ECTC PCI database (CVIS), novel risk factors not present in the NWQIP model will be discovered that exhibit a significant association with important clinical outcomes following PCI and hence could lead to the development of risk prediction models that perform well for both discrimination (Hanley & McNeil., 1982; Park et al., 2004) and calibration (Hosmer & Lemeshow, 2013).

1.4 Limitations and Considerations

Risk prediction models are not perfect, especially in medicine. It is extremely unlikely that a mortality prediction model for a certain procedure would produce perfect discrimination. When constructing or using pre-existing risk prediction models there are many potential pitfalls and limitations that should be considered when interpreting results and as such highlighted during the production of this thesis. These are briefly described below.

Variable Definitions and Data Completeness

The variables or 'risk factors' should be easily defined and recognised. For example, the exact definition of various comorbidity classifications such as hypertension or diabetes should be consistent throughout different hospitals and cardiac centres. By misclassification of variables, it will worsen the performance of any association with measured outcome and hence either overestimate or underestimate the strength of the relationship, which subsequently makes any findings less accurate and hence reduces the accuracy of any prediction model. Fortunately, for the studies featured here this is somewhat mitigated by the UK NHS having a similar system of classification regardless of the hospital. This point would be more evident if for example, a risk prediction model were developed in a foreign health service setting (e.g. United States) and then used in a UK hospital or vice versa. An issue also arises if different institutions do not enforce good data completion policies, however with regards to the UK, having a central body that examines each hospital's or cardiac centre's data completeness somewhat addresses this limitation, in the case of the PCI procedures, the British Cardiovascular Intervention Society is responsible for this (BCIS, https://www.bcis.org.uk).

Variable Selection

The risk model should be as parsimonious as possible, whereby only the core set of most important predictors or risk factors are present, and none that do not significantly contribute to the model's performance. The variables utilised in any model should also have a high data completion rate in any database used to develop the model. For example, even though a specific variable yields a very high association with a certain outcome, it may be the case than the given variable is only recorded for a small percentage of patients/procedures and thus for the rest the value of such a variable is unknown. It should also include only those variables that do not incur any significant cost to record or capture thus preventing any barrier for other hospitals to use them.

Medical History

If certain comorbidities such as diabetes, peripheral vascular disease (PVD), or chronic obstructive pulmonary disease (COPD) are identified to be significant predictors of a given outcome (e.g. mortality or in-hospital complications) then it may be the case that many patients which have not been diagnosed with the condition at the time of their PCI are afflicted with it but it is not known, for example it was estimated that 590,000 adults had undiagnosed Type 2 diabetes in 2013-14 within the UK (Diabetes UK, 2015). If this issue was constant over time then any model would be less affected, but if differences in percentages of patients are correctly diagnosed with/without a certain comorbidity then comparing patient populations over different time periods would be inaccurate thus limiting the effectiveness of the model as a decision making tool for clinicians and patients.

Multicollinearity

This occurs when two or more variables/risk factors in a prediction model are highly correlated with each other such that the strength of each predictor cannot be separated. Between these risk factors, one may be linearly predicted from the other, when this is the case the standard error of the variables will be high and thus affect the overall performance of the model.

1.5 Objectives Summary

There are five main objectives which this thesis sets out to complete in order to test the stated hypotheses (section 1.3), these objectives were formulated following review of existing literature, analysis of what was missing, what has changed, and what novel risk factors from the available data might be worthy of analysing for possible associations with adverse outcomes. These intended objectives were selected following synthesis of the information provided in 1.1 to 1.3, and are briefly described below.

(1) To investigate the important clinical outcomes following PCI procedures (as discussed in 1.3) at the ECTC, by using data from the patient PCI database. Such data contained within the database includes demographic, clinical, angiographic, procedural, and mortality data.

(2) To externally validate the NWQIP risk prediction model using the ECTC PCI patient cohort, and to assess its level of performance on a different geographical area within the UK (i.e. South-East England instead of North-West England), and a different era of PCI, namely the NWQIP study was performed in an era of higher BMS usage compared with the modern high usage of DES at the ECTC. Following analysis of the NWQIP performance, identification of any multivariate risk factors that have major changes to the strength of their association with the in-hospital MACE, as an outcome will be investigated.

(3) Extending the analysis above (objective 2), investigate which risk factors within the NWQIP model may no longer be useful in predicting in-hospital MACE, and which risk factors not present in the model are significantly associated with the outcome and should potentially be considered for incorporation into a new risk prediction model that would improve performance on a modern PCI cohort.

(4) As it is already known following many published studies and audit reports of outcomes following PCI that in-hospital MACE events occur at very low rates in elective (stable) patients, identification of other important outcomes would be identified such as extending the in-hospital mortality component of MACE to 30-day mortality. It may be identified that if patients survive the first 30 days following their PCI, then the risk decreases. Identification of such risk factors could then be incorporated into a new risk prediction model and be assessed for its performance, i.e. discrimination and calibration capabilities. Depending on how it performs, it may warrant further testing by other hospitals or cardiac

centres for possible usage in clinical practice (i.e. decision making or better management of high-risk patient subgroups).

(5) At the time of writing this, there is lots of peer-reviewed literature featuring outcomes following PCI such as in-hospital complications and short-term mortality (mostly from the United States), however there is less literature available on the outcome of repeat revascularisation, especially within stable (elective) patients. This study investigates the factors useful in predicting which subgroups of patients are likely to return to the ECTC for a subsequent unplanned (non-staged) revascularisation procedure within three years. Not only could this be useful for PCI operators, but also for patient information and more efficient resource planning.

1.6 Thesis Structure

The Theoretical Background (Chapter 2) provides the fundamental details of cardiovascular disease intervention which will be useful in understanding the context of this Thesis. This section briefly explains the types of treatment available for CVD, namely pharmacological therapy, PCI, and CABG surgery. This also includes a literature review of related published peer-reviewed studies analysed in preparation of this thesis, specifically, those with similar outcomes of interest following coronary revascularisation.

The third chapter, General Methods and Data, lists the general analysis techniques and statistics tests used in this thesis. It lists the details of the cardiovascular patient database used and general data. The approach in designing a risk prediction model and how they have their performance evaluated is also explained.

The first study within this thesis – Evaluation of NWQIP (Chapter 4) externally validates the established PCI risk prediction model for in-hospital complications in the form of MACE. Both the discrimination and calibration performance are validated using a contemporary PCI patient database from the ECTC.

The second study (Chapter 5) modifies the outcome of in-hospital MACE to the more robust outcome of 30-day mortality and validates whether the NWQIP model is a useful predictor of 30-day mortality, or whether significant recalibration/re-identification of risk factors is necessary. A custom multivariate prediction model is then developed to attempt to improve the performance in predicting 30-day mortality using additional characteristics from the cardiovascular PCI patient database.

The third and final study (Chapter 6) investigates three-year repeat revascularisation and death following an initial elective PCI at the ECTC. It aims to identify important outcomes for the low-risk (elective) patients as previous measures (short-term mortality, in-hospital complications) occur a very low rates. Knowing whether an elective patient has a high risk of dying or requiring a subsequent coronary revascularisation procedure (PCI or CABG) is extremely useful for both operators and patients.

Since the 30-day mortality prediction model was developed (in Chapter 5), two 30-day mortality models have been published by other researchers in the UK (McAllister et al, 2016; Wall et al, 2017). The major findings from these studies and how they relate to the model developed using the ECTC cohort, is discussed in Chapter 7 (Conclusions).

Chapter 2: Theoretical Background

Section 2.1 features a very basic description of cardiovascular disease, that would be useful to understand (as a bare minimum) as a foundation for subsequent chapters in this thesis. Section 2.2 includes a basic introduction to interventional cardiology, and describes the percutaneous coronary intervention (PCI) and coronary artery bypass graft (CABG) procedures, both of which are performed at the ECTC. Having a basic knowledge of PCI and CABG would be beneficial in order to set the context of the three studies in chapters 4, 5, and 6.

Section 2.3 begins with an introduction to the first major health related epidemiological study (Framingham Heart Study) conducted, and a second study of a similar nature (Seven Countries Study). The former led the way for longitudinal studies and provided useful information on population cardiovascular health, and the corresponding identification of risk factors and their association with cardiovascular disease. Following this there is a review of published literature relating to risk prediction models developed to estimate the likelihood of clinically important outcomes occurring following PCI. The literature featured here is important because they incorporate outcomes of interest in this thesis (e.g. in-hospital MACE, mortality, and repeat revascularisation) and this provided a framework for constructing prediction models using the ECTC PCI cohort.

2.1 Cardiovascular Disease

The cardiovascular system is primarily responsible for circulating blood around the body for the delivery of oxygen and other nutrients required for powering cells, and subsequent removal of waste by-products such as carbon dioxide. Other functions include transportation of hormones to organs, temperature regulation and defending the host by carrying immune cells and antigens (Horton-Szar & Newby, 2012).

The heart, a double muscular pump, for which the primary function is to collect and pump blood throughout the body achieves this using a combination of four chambers comprising two ventricles, two atria, and several valves which include the tricuspid, pulmonary, mitral, and aortic valves. The other components of the cardiovascular system are the arteries, veins, capillaries, and arterioles.

Figure 2.1.1 shows the basic components of the heart (Adapted from Zoofari, 2010).

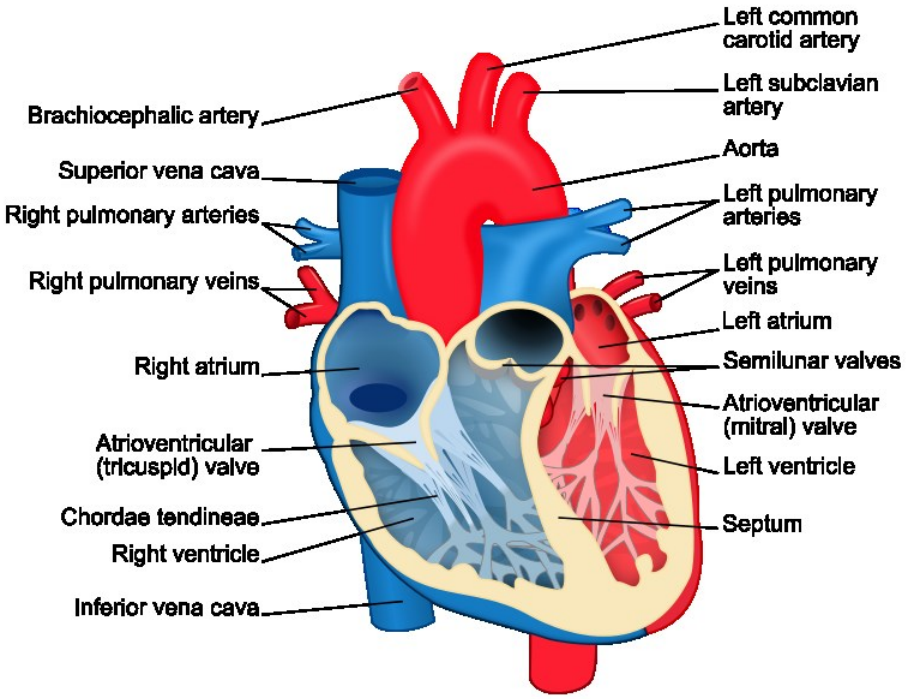


Figure 2.1.1 *– Anatomy of the heart (Zoofari, 2010)*

In brief, the following sequence of events is performed by a functioning heart (Pappano & Wier, 2013, p.2).

(1) Deoxygenated blood enters the right atrium (RA) from the superior/inferior vena cava.
(2) The blood moves from the RA to the right ventricle (RV).
(3) From the RV the blood is pumped to the pulmonary artery and then to the lungs.
(4) The oxygenated blood from the lungs enters the left atrium (LA).
(5) The blood moves into the left ventricle (LV).
(6) The LV pumps the blood to the body via the aorta.

In some people the ability of the cardiovascular system to function effectively and efficiently becomes sabotaged and can subsequently lead to a variety of health problems collectively termed cardiovascular disease (CVD). CVD itself, comprise of numerous afflictions affecting either the heart directly, or the blood vessels/arteries throughout the body, for which the most frequently observed types are briefly described below (Segerson et al., 2011, p.23;p.40;p.45;p.93;p.110;p.114).

Coronary Heart Disease/Coronary Artery Disease (CHD/CAD)

CHD is the biggest single cause of morbidity and mortality in the UK (British Heart Foundation, 2014) and the US. In the UK specifically, approximately 16% of men and 10% of women die from CHD. This occurs when the arteries (coronary) which supply blood to the heart tissue itself become occluded. Such arteries supplying blood to the heart tissue, which can become either partially occluded or fully blocked, include the right coronary artery (RCA), left anterior descending artery (LAD), left main stem (LMS), or the left circumflex artery (LCX). For patients who have undergone a coronary artery bypass graft (CABG) for a previously occluded native coronary artery, it is possible for the graft vessel to become occluded itself and hence require revascularisation treatment. The material causing the occlusion within these arteries are plaque deposits (atherosclerosis) which are formed as a result of fatty acid deposits that collect and accumulate on the arteries inner walls. When the plaques accumulate to a high degree they become part of structures known as atheromas which are responsible for the narrowing and constricting of the arteries. Insufficient blood flow to the heart tissue can result in cell death (necrosis), affecting the heart's electrical system and hence sabotaging the ability of the ventricles to contract and pump blood effectively. When partially blocked a patient may experience chest pain (angina), this can be stable whereby the pain is only experienced upon physical exertion, or unstable whereby the pain seemingly occurs at periods without much exertion, and is not responsive to medication. When a coronary artery becomes fully or

close to fully occluded a patient may experience a myocardial infarction (heart attack) which can be fatal, especially if not treated rapidly.

Angina Pectoris (chest pain)

As briefly described above, angina can occur when there is a reduction of blood flow, and hence oxygen supply to the tissues of the heart itself. The pain experienced by patients with angina can feel like a squeezing pain in the chest, and occurs because too much demand placed upon the heart which is not receiving adequate blood flow. Treatment in the form of pharmacological therapy can often be used for patients suffering with angina, this includes nitroglycerin which causes blood vessels to dilate, or beta-blockers which help control the overactivity of the heart itself. Angina is the most commonly reported symptom of CHD, and if appropriately managed before the patient's condition is too severe, a myocardial infarction can be potentially avoided, or at least have the time until one is experienced extended.

Congestive Heart Failure (CHF)

Heart failure occurs when the heart is unable to pump enough blood to meet the body's requirements, and is commonly caused by damage to the heart's ventricles (muscles) themselves. Due to the lack of circulation, sometimes blood can accumulate in the lungs, ankles, or legs and when this occurs it is known as CHF. Obesity is one the biggest risk factors for CHF, due to a patient having excessive body fat, this causes an increased oxygen demand and hence makes it much harder for the heart to meet such demand.

Stroke (cerebrovascular accident)

A stroke occurs when either a blood vessel within the brain or one supplying the brain becomes blocked via atherosclerosis, the corresponding tissue within the brain which is not getting the required supply of blood from the artery dies, i.e. necrosis. In some cases the stroke can be caused by an embolus, whereby a piece of atherosclerotic matter breaks off from another location within the body, but subsequently travels to the brain and clots an artery and causes tissue death. Depending on the location within the brain where the tissue is dying, it has the ability to cause either temporary or permanent physical or cognitive damage. This is especially fatal if the stroke affects the brain stem as this assists in regulating the heart rate, blood pressure, and respiratory system. Several symptoms of stroke may be present relating to both cognitive and physical functioning such as numbness/weakness of the face/arms/legs (especially on one side of the body), sudden

confusion/difficulty speaking or understanding, visual difficulty in one or both eyes, difficulty walking or a loss of balance, or sudden headaches with an unknown cause.

Atherosclerosis

As already briefly described, atherosclerotic material is a plaque which builds up within the inner walls/lining of the arteries, which is of additional importance when this occurs in the coronary arteries that supply the heart muscle tissue with blood. The build-up can cause the arteries to stiffen and also thicken. The deposits can be comprised of cholesterol, calcium, fibrin, and other cellular waste products.

Arrhythmias

Arrhythmias are caused by abnormalities in the heart's electrical system which subsequently affects the contractions of the left and/or right ventricles which pump blood around the body. The most common forms are tachycardia, bradycardia, and fibrillation. Tachycardia occurs when the heart is beating abnormally fast despite no additional exercise or other stimulus. Bradycardia occurs when the heart is beating abnormally slow, and fibrillation is when the heartbeat features a quivering pattern and is sporadic and uncoordinated.

Risk Factors for Cardiovascular Disease (CVD)

There have been many risk factors identified and verified which contribute to the manifestation of CVD. In general, the more risk factors a patient exhibits, the more likely they will develop a form of CVD. Some risk factors can be controlled such as tobacco consumption, physical activity, diet (e.g. saturated fat and cholesterol), weight (i.e. avoiding obesity), alcohol consumption, blood pressure control through the usage of pharmacological therapy, diabetes management, and stress management. There are however several risk factors that are unavoidable (Horton-Szar & Newby, 2012, p. 85) and hence unchangeable, such as age (increased risk as you age), gender (men have an increased risk even after women experience menopause), ethnicity and other heredity (e.g. African and Asian ethnicities have an increased risk relative to Caucasian/European), and family history (e.g. a parent or close relative which died of CVD can increase the risk for an individual).

Patients with CVD can experience early death or other comorbidities and disabilities, reduction in their quality of life, myocardial infarction (heart attacks), and cerebrovascular accidents (stroke). Some of these symptoms can be alleviated with pharmacological

therapies such as aspirin, statins, beta-blockers, and nitroglycerin. However, for some the CVD may be so severe that a coronary revascularisation procedure in the form of percutaneous coronary intervene (PCI), or a coronary artery bypass graft (CABG), or valve surgery are required to treat the CVD effectively. PCI and CABG are described in brief in section 2.2.

There are many techniques and medical imaging modalities available in modern health care practice for diagnosing CVD, these include an electrocardiogram (ECG) whereby the electrical system of the heart is analysed by placing multiple leads on various locations on the patient's chest and measuring activity at different time periods throughout the hearts contraction. This allows the strength, timing, and other characteristics to be displayed allowing possible diagnosis of certain abnormalities. An angiography utilises a dye that is injected into the body allowing the coronary vessels to become easily visible on an x-ray. The CT scanner performs rotations and allows occlusions and narrowing of arteries to be spotted. Other less frequently used technologies include positron emission tomography (PET), single photon emission tomography (SPECT), magnetic resonance imaging (MRI), and other radionuclide imaging.

2.2 Interventional Cardiology

2.2.1 Percutaneous Coronary Intervention (PCI)

A percutaneous coronary intervention (PCI) procedure, also known as an angioplasty, is a treatment which aims to clear blockages/narrowing of the heart's coronary arteries so that optimal blood flow to the tissues of the heart (myocardium) is restored either partially or fully. The PCI procedure is a non-surgical procedure as opposed to CABG surgery; meaning the chest and heart itself are not exposed. During the procedure an incision is made either into a femoral (groin) or radial (arm) artery to allow a hollow tube known as a catheter to be inserted via the use of a thin guide wire, allowing placement into the correct coronary artery which has the site of the occlusion. The catheter contains a deflated balloon on the tip, often (in modern practice) covered with a metallic stent consisting of a mesh coil. When the balloon is inflated at the site of the blockage the mesh coil remains in place and holds the occluded (stenotic) section of the coronary artery open, after this the balloon is deflated and removed (Kern, 2004, p.14). The inflation of the balloon and hence expansion of the stent presses against the atherosclerotic plaque causing the narrowing, thus allowing an increase in blood flow through that segment of the coronary artery as show in Figure 2.2.1 (created by the author, Webster, L., 2016).

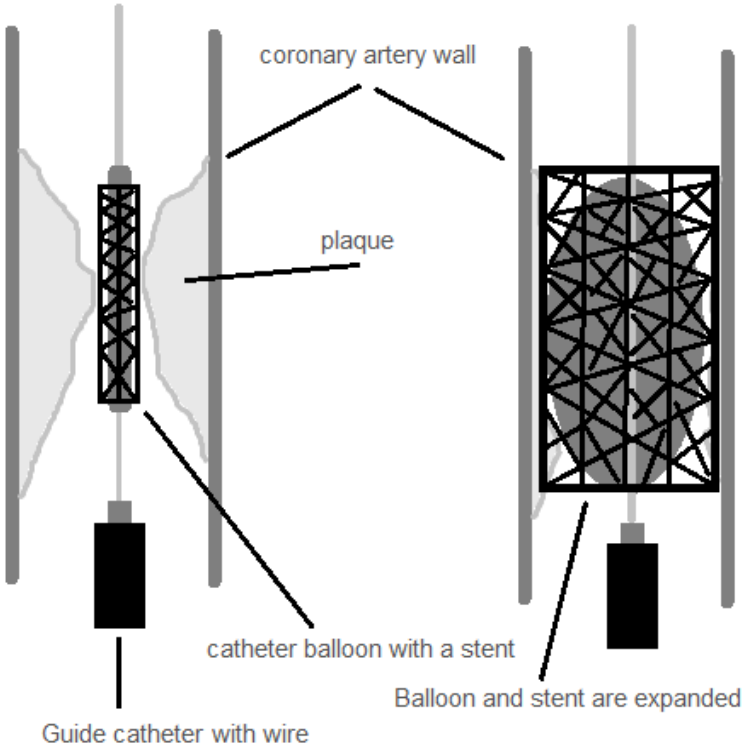


Figure 2.2.1 *–Diagram of a guide catheter, balloon, and stent used during a PCI procedure (Webster, 2016)*

It should be noted that the majority of PCIs performed in the modern era of interventional cardiology will use a stent. Those that do not, occur in rare circumstances and this refers to standard balloon angioplasty, whereby the balloon's expansion alone it used to disrupt the site of the plaque. Fluoroscopy, which is a special type of x-ray, assists operators in visualising the coronary arteries and hence allowing them to see the locations of the blockages or narrowing of the arteries, this technique can elucidate the approximate stenosis (blockage) percentage. This is achieved through the use of a radioactive contrast dye that enhances the arteries, allowing the vessels to be seen more easily on a screen.

Once a stent has been inserted and expanded at the target site, tissue can soon form over it (within several days) following the PCI. After approximately one month the stent can be covered in scar tissue such that antiplatelet medication must be taken by the patient to decrease the 'stickiness' of the platelets within the blood to prevent clots occurring around the site of the stent. For the newer generations of stent, i.e. drug-eluting stents (DES), they are coated with a drug that slowly releases over time that inhibits the growth of tissue within the stent site and thus assisting to stop the artery from becoming narrowed again. Any narrowing of the treated artery will likely however make symptoms such as angina reoccur.

The following sequence of steps briefly describes the process of performing a PCI procedure in the general sense, the exact steps and devices used will differ between hospitals and operators and depending on the type of patient and disease severity being treated (Kern, 2004, p.12-14; Segerson et al, 2011, p.27).

Steps during a PCI procedure

(1) An intravenous (IV) line is inserted into the patient’s hand or arm in order to administer fluids if required.
(2) The patient is connected to an electrocardiogram (ECG) monitor to display vital signs, including blood pressure, heart rate, breathing rate, and oxygen level).
(3) A sedative will be given to relax the patient.
(4) The pulse near the insertion site for the catheter will be verified.
(5) A local anaesthetic will be injected at the insertion site.
(6) A sheath will be inserted into the blood vessel allowing the catheter to be threaded through.
(7) The catheter is threaded through the patient into the heart and is visualised using fluoroscopy.
(8) Once in place, the contrast dye is injected into the coronary arteries.

(9) The X-ray images of the arteries are taken rapidly.
(10) The catheter is advanced to the correct location of the blockage.
(11) The balloon is inflated (and hence stent is used in the PCI)
(12) The balloon is deflated, and angiograms are taken.
(13)The catheter and sheath are removed.
(14) A closure device is used to seal the insertion site artery.

Complications during and following a PCI procedure

Patients which undergo PCI are at risk of developing certain complications either during the procedure itself or afterwards. Some of the complications which may be experienced from PCI can also be experienced by patients that undergo a CABG surgery. Most of the complications that occur following PCI occur almost immediately, some of the most frequently experienced complications are briefly described below.

Artery closure/emergency CABG is one of the most serious complications whereby sudden closure of the target coronary artery occurs, this may be treated by reinserting a balloon/stent, or in more serious cases by performing an emergency CABG. Bleeding/infection at the site at which the catheter is inserted can occur, i.e. the femoral or radial artery. Restenosis occurs when the stent (or balloon if a standard angioplasty) fails to prevent the coronary artery from narrowing again. In some cases a subsequent PCI may be needed, or for more serious cases a CABG may be performed. Major adverse cardiac events (MACE) as described in Chapter 1 can occur, which include in-hospital death, Q-wave myocardial infarctions, emergency CABG, or cerebrovascular accidents (Levine & Kern, 2004, p.162-190). Other complications which are quite rare can include negative contrast medium reactions, stent loss, arterial perforation, or femoral arteriovenous fistula (Mukherjee & Bavry, 2011, p.165-174).

In general, the PCI procedure is considered a success if certain clinical, angiographic, and procedural criteria are met. The PCI should be absent of in-hospital complications (i.e. MACE). The coronary vessel target site stenosis percentage should be substantially reduced relative to the pre-PCI stenosis percentage. Such a reduction in stenosis should relieve any symptoms such as angina either partially of fully following the PCI, after a sufficient recovery period. Most patients that receive PCI recover fully from the procedure within a few days to two weeks and can resume normal activities at a far earlier time than patients which undergo CABG surgery. In general, patients will be informed about lifestyle and diet changes which can reduce the chance of lesions and cardiovascular disease progression from reoccurring. Examples include cessation of smoking, obese patients

losing weight and eating lower-fat food, and getting more regular exercise. Most patients will be on some sort of cardiac rehabilitation programme whereby they will have their recovery monitored and suggested to take pharmacological therapy such as aspirin/anticoagulant medication.

2.2.2 Coronary Artery Bypass Graft (CABG) Surgery

The CABG surgery was the first procedure to be widely adopted by interventional cardiologists for coronary revascularisation. In brief, an artery or vein is removed from another location within the patient's body, and is subsequently surgically grafted from the aorta, past the blocked section of the coronary artery thereby bypassing the blocked segment, and allowing blood to flow again from one end of the artery to the other. During the surgery an incision to the sternum is made to allow the patient's chest to be opened for access to the heart, the heart itself is stopped temporarily to allow the graft vessel to be sewn on. The circulation of blood is performed mechanically using a cardiopulmonary bypass machine. Newer bypass procedures do not require the heart to be stopped for surgery however, i.e. off-pump CABG, and require smaller incisions, i.e. minimally invasive bypass surgery.

Some of the indications that warrant CABG surgery are similar to PCI such as angina (chronic or unstable), acute myocardial infarction (AMI). However CABG in general is performed on patients with complex lesions such as those heavily calcified or in difficult locations within the coronary artery such as branches or bends. CABG also tends to be more popular with patients that exhibit multiple occluded coronary vessels, whereby the stenosis percentage is very high (e.g. 70% occluded). CABG can also be a solution for when a PCI has failed; this failure could be due to lesion complexity despite attempts with using a drill known as a rotablator to try to break up the lesion. In most cases when CABG is to be performed on the right coronary artery (RCA) or circumflex artery (LCX), the vein used for the bypass will be the saphenous vein from the patient's leg. If the target vessel is the left anterior descending artery (LAD) then the internal mammary artery (IMA) is often used.

The three most common coronary arteries requiring a bypass graft are the RCA, LAD, and LCX as detailed in Figure 2.2.2 (Adapted from Tidy, 2017)

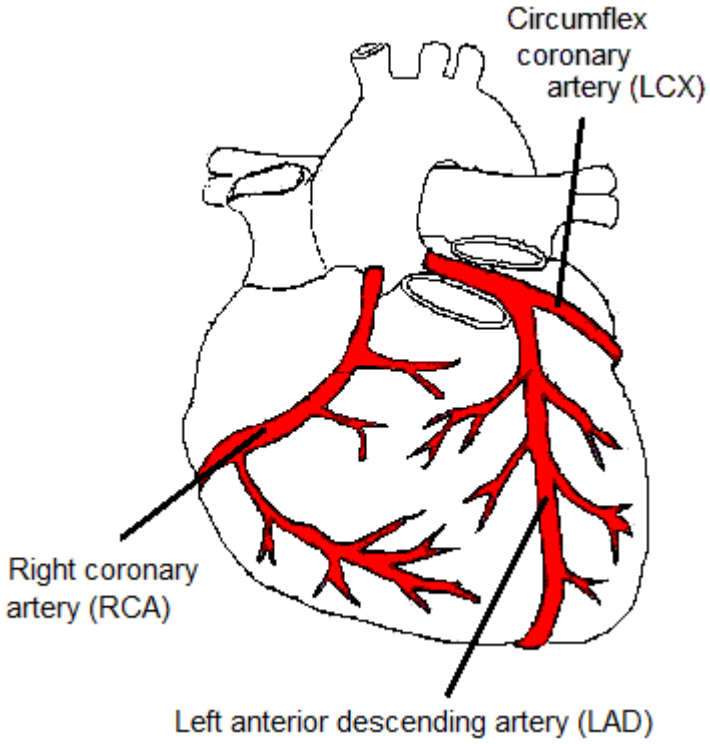


Figure 2.2.2 *– commonly bypassed coronary arteries (Adapted from Tidy, 2017)*

For conventional CABG surgery, angina is relieved in approximately 90% of patients and 80% remain free of such symptoms for at least five years following the procedure. Compared to PCI, CABG has a lower risk of restenosis as the graft itself should provide complete revascularisation compared to partial revascularisation as commonly seen in PCIs. PCI also has the chance of in-stent restenosis which CABG clearly cannot experience. It has been suggested however that after approximately 15 years, 85% of the vein grafts become narrowed or totally occluded and hence may require a subsequent revascularisation, often performed using PCI, and in rare cases another CABG is performed. In addition to the graft vein becoming stenotic, angina itself may recur due to atherosclerosis building up in other coronary vessels not originally bypassed during surgery. Typically about 95% of CABG patients are still alive after one year (Harlan et al, 2008). There are some drawbacks associated with performing a CABG relative to a PCI, for example, the CABG can take 3-6 hours to perform and patients will require much longer length of stays (LOS) in intensive care units (ICUs), and overall hospital bed usage. CABG patients also require a much longer period of recovery usually between three to six

months for a full recovery. For CABG there is a considerably high risk of post-operative complications, affecting approximately 5-10% of patients. The main complications experienced are described briefly below.

Coronary Artery Bypass Graft (CABG) Complications

Compared to PCI, CABG patients have a much higher risk of death during the procedure and in the short recovery period afterwards (i.e. 30 days), especially elderly patients (Safaie et al., 2015). During CABG surgery there are multiple events which have high risks of death such as stopping the heart, surgically grafting the vein/artery onto the heart, and restarting the heart. A high risk of bleeding exists (approximate 30%) either during or after surgery subsequently warranting a blood transfusion, or in rare cases (i.e. < 2%) multiple transfusions and additional surgery to stop the bleeding. There is a high risk of bleeding for patients which have been taking blood thinning medication such as aspirin prior to the surgery; however this should be especially rare in elective CABG because cessation of such medicine before surgery is recommended. Atrial fibrillation whereby a fast and abnormal heart beat rhythm is present can occur in up to 40% of CABG patients, the irregular rhythm has the potential to cause blood clotting within the coronary vessels, or should an existing lesion become dislodged it has the potential to travel to another location, e.g. the brain and subsequently cause a stroke. A large proportion of the patients which experience atrial fibrillation only exhibit it temporarily, it can also be controlled with appropriate medicine. As with any type of surgery there is a risk of infection, in the case of CABG at the graft artery or vein removal site or within the exposed lungs of chest during surgery. Infections can affect approximately 4% of patients undergoing this procedure (CABG Risks, 2013). Approximately 5% of patients may experience a reduction in renal function, which for the majority of cases in only temporary and should resume within several days to weeks. Stroke and other neurological problems such as difficulty concentrating or memory issues can occur in approximately 5% following CABG. In rare circumstances this can be a permanent condition. However the patient should improve within months of recovery after their surgery. Stroke, which is a rare and more serious complication, affects approximately 1 in 50 patients and can temporarily or permanently affect both physical and cognitive functioning in addition to causing death. Because the heart and hence coronary arteries are in a vulnerable state following surgery, especially the sites of the attached graft vessel, there is an increased risk of a myocardial infarction, especially within the short period (i.e. 30 days) following surgery, this is the most common cause of death following CABG procedures. For patients which experience small to moderate myocardial infarctions, these can be detected through the usage of ECG

signatures and elevated levels of cardiac enzymes such as Troponin. In general, patients who undergo surgery to one of the coronary valves are at a higher risk than standard CABG patients.

The risk factors for complications (Hawkes et al., 2006; Diodato & Chedrawy, 2014) are similar to patients who are more likely to exhibit complications following PCI such as old age, female gender (post menopause), multi-vessel disease such that the more vessels requiring a bypass the greater the chance of complications such as bleeding occurring, obese patients requiring deeper incisions hence risk of infection. Emergency CABG exhibits a higher risk, because there is much less time to plan the surgery and the heart itself may be damaged from the myocardial infarction, compared to elective patients, for whom no actual damage may have occurred yet. Other medical conditions such as diabetes, chronic obstructive pulmonary disease (COPD), peripheral vascular disease (PVD), and renal dysfunction also increase the risk of complications occurring following surgery.

2.3 Related Work

This section reviews peer-reviewed published literature relating to this thesis, including cardiovascular longitudinal studies, in-hospital and short-term complications following PCI, risk prediction models for adverse events following PCI, and the factors associated with repeat revascularisation following PCI.

2.3.1 Longitudinal Cardiovascular Epidemiological Studies

The Framingham Heart Study

One of the first and most important cohort studies to prospectively collect longitudinal cardiovascular health data was the Framingham Heart Study (Dawber, 1980) which began in 1948 and is still currently active in its third generation. The study itself is named after the town in Massachusetts, US for which the study cohort were residents of. The study is now being run by the National Heart, Lung, and Blood Institute (NHLBI) and researchers from the Boston University School of Medicine. The study originally recruited 5209 healthy men and women, 5127 of these were confirmed free from cardiovascular disease (CVD). The individuals in the study ranged from 30 to 62 years old and were provided with free comprehensive physical examinations and had detailed medical history recorded. The cohort age ranges were chosen because it was known CVD developed in high rates for this group. Other laboratory tests were performed such as chest x-rays and electrocardiograms (ECGs) every two years. The motivation behind the study was to find out why CVD was responsible for increasing rates of death and why it was becoming the number one cause of mortality in the US. The study design was chosen because it could help explain the behaviour of CVD and identify the set of factors which relate to its manifestation. By identifying such factors it was hypothesised that is would then be possible to inform the public as to avoid such factors and thereby lower the rate of CVD and hence increase life expectancy.

In the US in the 1950s approximately one-third of men were determined to have CVD by the age of 60 years, which was twice the number of people that developed cancer during the same period. The number of deaths relating to CVD specifically per 100,000 individuals saw a linear increase each decade and rose 115% from approximately 260 in 1900 to 575 in 1950. There were four main reasons hypothesised for this increase in CVD death rates: (1) decreased physical activity; (2) dietary changes; (3) introduction of

cigarettes; (4) decreased deaths from infectious diseases – more people who were alive would then go onto develop CVD. Relating to (4), there was a significant reduction in infectious disease deaths due to several reasons such as improvements in hygiene, tuberculosis and pneumococcal disease control, and the introduction of penicillin in 1942. From 1960 to 2005 the number of CVD deaths per 100,000 decreased by approximately 63% from 560 to just over 200. Of these CVD deaths the most common was due to coronary artery disease (CAD), which saw a constant decline since the mid-1960s. There were several hypotheses for this decrease following cardiovascular research which lead to the following: dietary research – identification of the role of cholesterol as a risk factor; more accurate and faster diagnosis of CVD and hence treatment; effective therapy – such as beta-blockers, aspirin, diuretics which treat hypertension; The Surgeon General's report on the negative effects of smoking.

The Framingham study had one major aim and two minor ones (Dawber & Moore, 1952). Firstly to produce epidemiological data on CVD with regards to atherosclerosis and hypertension. Secondly, to produce data on the prevalence of other forms of CVD in a cohort group that is representative of the population. Thirdly, to test the efficiency and accuracy of CVD diagnostic equipment, and tests. The arteriosclerosis CVD was thought to be caused by a loss of elasticity and thickening of the coronary and carotid artery walls. The study itself was a longitudinal monitoring study which observed changes and did not intervene with any actual treatment. The first examination provided on each of the study subjects was to identify whether they were free from known symptoms of CVD, those which were, were then used as part of the official study cohort for which the periodic examinations would be performed, which was planned to continue until a sufficient number of subjects that were re-examined went on to develop CVD, subsequently giving the potential to identify the risk factors which predisposed people to CVD. Over time different tests and measurements were included in the study such as alcohol and smoking status, echocardiograms, lipoproteins, exercise ECGs, fibrinogen, and apolipoprotein levels. These additions were made to test various new hypotheses which were formed following the evolution of medical science.

Before the study officially began several hypotheses were formulated as it was assumed the development of CVD was not as a result of a single cause but multiple ones that collectively led to the disease manifesting. The set of hypotheses were developed by medical specialists and subsequently lead to the types of medical questions and physical examinations being performed to assist in proving/disproving them. The list of hypotheses constructed (Dawber, 1980) were (not in any particular order):

(1) CVD risk increases with age and occurs more frequently and earlier in men.
(2) Elevated cholesterol level increases the risk of CVD.
(3) Regular alcohol consumption and smoking increases the risk of CVD.
(4) Increasing physical activity shows decreased risk of CVD development.
(5) Decreased CVD is experienced following increased thyroid function.
(6) Increasing body weight increases CVD risk.
(7) CVD develops in a higher rate in those with gout.
(8) High levels of haematocrit increases the chances of developing CVD.

It had been hypothesised that the onset of CVD could be delayed, i.e. experienced at a much more advanced age than currently seen by using a preventative approach for certain lifestyle choices. The study was seen as significant because it helped identify that those which went on to develop CVD had overall a different set of characteristics to those which did not experience CVD. It was made apparent that poor cardiovascular health was not a simple consequence of ageing but also affected by the choice of lifestyle, inheritance, environmental factors, and other measurable risk factors. The characteristics defined as showing increased probability of developing CVD in the future were identified as: advanced age; male gender; diabetes; elevated serum cholesterol; hypertension; cigarette smoking; and physical inactivity. These risk factors were considered ideal because they meet the following characteristics: associated with the disease; frequently found; easily recognised/distinguished; reversible/treatable – excluding age and gender; the disease can be prevented if treated appropriately. Whilst the study identified the important set of risk factors, it did not explain the pathogenesis of CVD, i.e. the exact detailed biological mechanisms that result in its development.

Of the 5000 subjects used in the study it was predicted that within five years of the first examination, 400 (8%) of these would develop CVD, and within ten years 900 (18%), and within 15 years 1500 (30%), and within the expected end date of 20 years, 2150 (43%) would develop CVD (Gordon & Kannel, 1968). There were drawbacks and criticism of the study design whereby the final cohort of subjects were considered healthier than the general population along with some other biases. The study also focussed on a single town, that being Framingham in Massachusetts (US) which was predominately white middle class people and therefore different ethnic groups may not have been represented sufficiently as well as other socioeconomic and environmental factors. The suggested workaround to this was to set the study up in multiple areas. Another drawback of the study was that it could only be used to analyse incidence rates, i.e. the number of individuals that went on to develop CVD within a certain time interval, however the

prevalence rates would not be accurate for the population because the cohort were healthy to begin with and thus not representative of the population of the town.

The Seven Countries Study

Another important longitudinal monitoring study was the Seven Countries Study which ran from 1958 to 1970 across multiple countries (US, Finland, Netherlands, Italy, Yugoslavia, Greece, and Japan), this was the first epidemiological study to be conducted across multiple nations and it featured 16 cohorts of men aged between 40 and 59 years that were engaged in traditional occupations and this cohort totalled 12,723 subjects. The study had a similar motivation to the Framingham Heart Study whereby it was noticed that an epidemic of middle-aged men were dying from heart attacks. The study found hypothesised this was predominately due to lifestyle choices and other changeable characteristics. A prior study to this conducted in Italy, Spain, Japan, and South Africa from 1952 to 1956 proposed that a diet and the level of serum cholesterol and the rate of heart attacks varied between countries, this was also found in a later study within Finland, Greece and Italy, which subsequently led to the development of the Seven Countries Study.

By spanning the study across multiple countries, it allowed differences in culture and lifestyle to be identified and their apparent link to diet, cholesterol, and subsequent development of coronary heart disease (CHD). This study addressed the main drawback of the Framingham study whereby multiple populations were used rather than a single town in a single country. A large variation in diet, mostly linked to saturated fat was found between the countries, and that as the average percentage of saturated fat increased, so did the serum cholesterol levels, and the rates of death from CHD. The lowest levels of cholesterol and hence incidence of CHD were found in countries with a Mediterranean-style diet which consisted of low animal product usage (i.e. saturated fat). The main source of fat in these countries came from olive oil, which is a monounsaturated fat. This type of diet also consists of high amounts of legumes, fruit, and fish. It was made apparent from this that certain dietary choices can alter an individual's risk of developing CHD. These findings relating to Mediterranean diet and both fatal/non-fatal CHD in middle-age individuals were also identified by other researchers (Martínez-González & García-López, 2010) by observing countries in Northern Europe and the US compared to Southern Europe and controlling for the variables of age, blood pressure, cholesterol levels, physical activity, and smoking status. The study found that from five years onwards CHD and stroke rates were independently linked to serum cholesterol level and this was consistent across different ethnic cultural groups.

Both the Framingham and Seven Countries studies showed that cigarette smoking, i.e. tobacco usage, was a major predictor in developing CHD whereby those which smoked exhibited increased rates of angina, heart attacks, and other CVD related deaths. Hypertension was also again shown to increase the risk of both CHD and stroke. Both studies demonstrated the importance of maintaining healthy lifestyles, such as regular exercise and a healthy diet, in helping to avoid both dementia and CHD. Despite the useful findings there has been disagreement by scientists on whether cholesterol and fat intake can be effectively used as predictors for CHD. Some argued (Taubes, p. 1120) that these adverse conditions were caused by refined carbohydrates instead. Another researcher (Edward H Ahrens Jr) in 1957, also suggested that cholesterol might not be the cause, but instead carbohydrates and triglycerides. Triglycerides were identified as more important than cholesterol level thus saturated fat was not responsible but carbohydrates (Teichoz, P.58-59). It was later suggested that sugar was the main cause of CHD and other adverse conditions instead of fat (Yudkin, 2012). Back in 1956, John Godman, an expert in clinical lipidology proposed an atherogenic index that combined low density lipoprotein (LDL) and very low density lipoprotein (VLDL) which could predict CHD and the development of atherosclerosis (Gofman, 1956) and later suggested that serum cholesterol levels can be misleading in analysing the effect of diet upon lipids.

Conclusions

Both the Framingham Heart Study and the Seven Countries studies were important epidemiological longitudinal studies which although both had some limitations, they showed that this type of study design is important and can assist in identifying important risk factors that have high associations with the adverse outcome of CVD/CHD. These were useful studies which mirrored how simple, easily measurable risk factors can be used to predict adverse outcomes following coronary revascularisation treatment for patients that already have CVD/CHD as evidenced by a myriad of published peer-reviewed literature relating to this thesis which is reviewed in 2.3.2.

2.3.2 PCI Risk Prediction Models

Introduction

The ability to predict the occurrence of major complications following coronary revascularisation procedures such as PCI or CABG is essential for interventional cardiologists. There are several important benefits to having effective prediction models, these include: a decision making tool for clinicians (i.e. is a given patient a suitable candidate for PCI?); decision making tool for elective patients (i.e. if they know the risks, do they want to proceed with a given PCI procedure?); resource planning (i.e. hospital staff can focus more care and resources on high risk patients); and as a comparison tool for operators, hospitals, and patient subgroups (especially useful for audit or performance reports).

For the majority of outcomes used in interventional cardiology prediction models, the dependent variable is dichotomous (binary), i.e. it assumes one of two states such as: alive/dead after 30 days of a procedure; yes/no for experiencing an in-hospital complication. For these outcomes the most widely used technique for constructing prediction models is multivariate logistic regression, wherein the outcome of the regression model is an estimated probability of the outcome occurring given a set of predictors.

Many risk prediction models have been developed (Moscucci, 2001; Singh, 2002; Qureshi, 2003; Grayson, 2006; Madan, 2008; Chowdhary, 2009; Hamburger, 2009; Maluenda, 2010; Peterson, 2010; Sousa, 2010; Curtis, 2012; Mrdovic, 2013) for estimating the risk of various adverse outcomes following PCI procedures. They all feature the usage of multiple risk factors, some of which are present in many different models, and other factors which are present in only a few. Such differences in risk factors among models can be explained by different cohort demographics, socioeconomic factors, stent technology, disease severity etc. These models generate a probability of a patient, given a set of risk factors, experiencing the measured adverse outcome (e.g. in-hospital complications or mortality). One of the most commonly measured outcomes are the occurrence of a major adverse cardiac event (MACE), this is a composite outcome which includes at least one of the following four complications

(1) In-hospital death.
(2) Q-wave myocardial infarction.

(3) Cerebrovascular accident (stroke).
(4) Emergency CABG surgery.

The majority of risk prediction models in usage today use in-hospital outcomes as the end-point whereby mortality or MACE occurs before the patient is discharged from their PCI procedure. The majority of the prediction models identified in this literature review were internally validated, whereby the researchers split their database into a training and validation set, the former of which was used to develop the prediction model, and the latter was used to internally verify the models stability. Whilst different methods exist for splitting the available data into training and validation sets, doing so simply by date (i.e. the oldest data is used for training, and newer data for validation), it is more robust to trends and changes that may exist in the cohort. This is especially applicable for anticipated trends in the ECTC cohort such as increasing proportions of emergency PCIs, patients with comorbidities. Regardless of how well new risk models perform using an internal validation set, they should be externally validated to verify their performance, and hence possible adoption in clinical practice.

The differences in the independent risk factors from the myriad of prediction models as stated above, can be potentially caused by the following:

(1) Changing patient demographics and comorbidities – differences in the general age, priority (e.g. stable angina or acute myocardial infarction), comorbidities such as renal disease/peripheral vascular disease (PVD)/chronic obstructive pulmonary disease (COPD)/diabetes etc. could alter the regression model coefficients especially if more patients are living with comorbidities but have not yet had them diagnosed (e.g. type-2 diabetes mellitus). Trends in proportions of emergency patients and increasing proportions of octogenarians could also affect analysis.

(2) Intervention Technology – If the time difference of two different cohorts used to develop a risk prediction model is large enough, it may be the case that differences in intervention technologies are responsible for differences in adverse outcomes. One anticipated difference relates to stenting technology, for example, differences in cohorts with standard balloon angioplasties, bare metal stents (BMS), and drug eluting stents (DES) may see differences in outcomes such as complications, in-stent restenosis, repeat revascularisation etc.

(3) Operator experience, PCI centres, and cardiovascular disease screening – It would be expected that increasing numbers of operators and PCI centres available to perform PCIs would reduce the percentage of adverse outcomes experienced. For emergency patients, in particular those presenting with ST-elevation myocardial infarction (STEMI), a faster call-to-balloon time (due to more operators and centres) would reduce adverse outcomes. The increase in both operators and centres in the UK has been reported by the British Cardiovascular Intervention Society (BCIS) in its audit reports (BCIS Audit Report, 2014).

In modern practice the risk factors for developing CVD are better known than in previous decades (e.g. obesity, diet, smoking, lack of exercise), the increase in referral speed for patients with CVD would mean a given patient is being treated (either via PCI or by pharmacological therapy) at an earlier stage than they would have previously and are hence much less likely to present with an emergency indication in the future because their condition has been intercepted/identified more rapidly, thus intervention measures can slow the rate at which a patient's cardiovascular system may deteriorate.

Some of the risk factors which have been reported in multiple prediction models are: patient age; diabetes; cerebrovascular disease; cardiogenic shock; left main stem (LMS) lesions. The following literature review features a summary of the published peer-reviewed research in the domain of risk prediction models for adverse outcomes following PCI. This includes many popular models which have been both developed and validated using large PCI databases, most commonly within the US health care system. Such literature in the UK NHS is far scarcer. However, as described in Chapter 1.6, two recent UK models for 30-day mortality prediction have been published. These are both further discussed in Chapter 7 (Conclusions).

2.3.2.1 The North West Quality Improvement Programme (NWQIP) Risk Model

The North West Quality Improvement Programme (NWQIP) was a collaboration between four cardiac centres in the UK, which performed PCI procedures. The centres involved were the Manchester Royal Infirmary, Blackpool Victoria Hospital, Wythenshawe Hospital, and the Cardiothoracic Centre in Liverpool. NWQIP were focussed on the collection of high quality clinical data (both accuracy and completeness) and subsequent validation, with the aim of developing techniques to analyse the data. Grayson et al. (2006) published a study for a prediction model which estimated the occurrence of in-hospital MACE following 9914 consecutive PCI procedures from August 2001 to December 2003, that

were performed at the four centres. This collection allowed meaningful comparisons between the centres and operators following appropriate adjustment of risk.

It was important to identify whether, for a given set of patients of the same estimated risk, there were any differences in adverse outcome rates between the different centres. The study arguably improved upon existing research as it included in-hospital MACE as an outcome. The composite outcome allowed more useful insights than simply using mortality alone as an end-point. The NWQIP model was constructed from several independent risk factors identified using multivariate logistic regression analysis, these variables were:

(1) Advanced age group (70-79 years, or ≥ 80 years).
(2) Priority of PCI (urgent or emergency).
(3) Female sex.
(4) Cerebrovascular disease (stoke).
(5) Cardiogenic shock (pre-procedural).
(6) Location of lesions (i.e. PCI to graft lesions; or PCI to the left main stem lesions).

The overall MACE rate using their cohort of 9914 patients was 1.3% (129 patients), this rate varied between the four centres from 1.1% to 1.4% although the difference was not statistically significant. The majority of the MACE rate was caused by death at 0.7% (66), followed by 0.4% (36) Q-wave myocardial infarctions, 0.15% (15) required an emergency CABG, and 0.2% (20) experienced a cerebrovascular accident.

Grayson et al. (2008) tested the NWQIP model performance using the area under the receiver operating characteristic curve (ROC) for discrimination capability, and the Hosmer-Lemeshow goodness of fit statistic for calibration. They used the bootstrap resampling technique to internally validate the model to ensure overfitting did not occur. The AUROC was 0.74 indicating a good ability to discriminate (0.5 would be randomly guessing) between MACE occurring. The goodness of fit test was not significant (p = 0.43) indicating no large deviations between observed and estimated MACE within groups of ascending predicted risk. The 100 samples used in the bootstrap resampling produced an AUROC of 0.74 (Standard error, SE = 0.032). A validation set was used by Grayson et al. to verify the model stability on 1786 PCIs performed after December 2003, the AUROC was 0.72, which was close to the original. The goodness of fit statistic was not reported for their validation set.

2.3.2.2 External Validation of the NWQIP Risk Model

The NWQIP model was externally validated by Kunadian et al. (2008), they also validated a model developed in the US, the Mayo Clinic Risk Score (MCRS). The performance of both models was assessed using the AUROC value for discrimination, and the Hosmer-Lemeshow goodness of fit test for calibration. By externally validating these models it could be ascertained whether PCI cohorts separate from the original cohort (both geographically and over a different time period) yield stable performance and hence reveal the models are robust or whether the performance is negatively affected, thus rendering them worthless in contemporary practice, and subsequently requiring significant recalibration of the risk factors to become useful. The risk factors within both models and their corresponding odds ratios, regression coefficients, and derived integer scores (based closely on odds ratios) are listed in Table 2.3.1.

Table 2.3.1 – NWQIP and MCRS risk factors (adapted from Kunadian et al., 2008)

	NWQIP model			**MCRS model**		
Risk Factor	**Odds ratio**	**Coefficient**	**Integer score**	**Odds ratio**	**Coefficient**	**Integer score**
Age (decades > 30)				1.37	0.313	
Age 70-79 years	2.02	0.7048	2			4
Age ≥ 80 years	2.75	1.0106	3			5
Female sex	1.58	0.4586	2			
Cardiogenic shock	26.14	3.2636	26	4.95	1.599	5
Cerebrovascular disease	2.37	0.8618	3			
Urgent PCI	1.61	0.4788	2			
Emergency PCI	3.91	1.3625	4			
Urgent or Emergency PCI				2.13	0.758	2
LMS lesion treated	5.21	1.6502	5			
Graft lesion treated	2.48	0.9101	3			
LMS disease				4.34	1.467	5
Serum creatinine > 265 µmol/l				2.41	0.881	3
NYHA class ≥ III				2.11	0.745	2
Thrombus				1.9	0.644	2
Multivessel disease				1.86	0.618	2

The external validation cohort featured 5034 consecutive PCI procedures from September 2002 to August 2006. The baseline demographic, clinical, and procedural characteristics were similar to the NWQIP cohort however an increase in emergency procedures was observed (10.8% to 17.6% respectively), cardiogenic shock also increased from 0.7% to 1.7%, as did the usage of the glycoprotein inhibitor IIb/IIIa from 61.8% to 76.1%. The percentage of patients aged ≥ 80 years increased slightly from 2.1% to 3.8%. Apart from this, the other characteristics were similar.

The in-hospital MACE rate was 2% (104 complications), 1.3% (66) of patients died, and 0.2% (11) had a Q-wave MI, 0.2% (10) experienced a cerebrovascular accident, and 0.1% (7) required an emergency CABG. The AUROC was 0.86 (95% CI 0.82 to 0.89) for the NWQIP model, and for the MCRS model this was 0.87 (0.84 to 0.90). The Hosmer-Lemeshow test for these models were $\chi^2 = 1.7$ ($p = 0.95$) and $\chi^2 = 11.7$ ($p = 0.16$) respectively, the former of which reveals an excellent fit (with 1.0 being perfect). The study showed that the NWQIP model could discriminate in a different geographical cohort and time period better than in it did in the original setting.

With regards to the NWQIP model, Kunadian et al. went a step further and performed a useful additional analysis technique in their study. Integer values were assigned to the independent risk factors within the model based closely on the odds ratios, for example in most cases the integer represented this rounded odds ratio value. Cardiogenic shock as shown in Table 2.3.1 has an odds ratio of 26.14, the integer score used for this was therefore 26. LMS lesions treated has an odds ratio of 5.21 therefore it was assigned an integer score of 5. The total value of all integer scores from the present risk factors in a given patient were stratified into one of five different risk groups (very low, low, moderate, high, and very high). The observed and estimated MACE rates were then plotted for these five groups. This is a similar goodness of fit test to the Hosmer-Lemeshow test. However, it can be more effective because in-hospital MACE occurs at such a low rate and hence frequencies. Some of the risk groups have a small number of events hence their accuracy is questionable as per the requirements of a chi-square test, for which the Hosmer-Lemeshow test is an extension.

The five risk score categories have the PCIs assigned by the range of the total integer score, this being 0-5, 6-8, 9-11, 12-14, and ≥ 14 respectively. Kunadian et al. (2008) produced the following results in Table 2.3.2.

Table 2.3.2 – Integer score system and results developed by Kunadian et al. (2008) for NWQIP

Risk Group	PCI Distribution	Observed MACE (%)	Predicted MACE (%)
Very low (0 to 5)	82.1%	0.8%	0.9%
Low (6 to 8)	12.8%	3.6%	2.9%
Moderate (9 to 11)	3.2%	7.5%	6.3%
High (12 to 14)	0.3%	13.3%	14.4%
Very high (> 14)	1.7%	42%	45%

2.3.2.3 Other Integer Risk Score Models

Risk scores based on integer values were not founded by Kunadian et al. (2008). One of the first PCI risk score models to utilise integer scoring for easy calculation without the need for a programmable calculator, was the Mayo Clinic Risk Score (MCRS), developed in the study by Singh et al. (2002). The study featured 5463 PCIs from January 1996 to December 1999. The outcome was the same as the NWQIP study (MACE). The model used a validation set of PCIs performed in 2000. The MACE rate was 4.0% (220 procedures). The independent risk factors within the model featured several also present in the NWQIP model, which were cardiogenic shock, LMS (disease – not specifically 'lesions'), urgent/emergency PCI, old age, but also some not present in NWQIP, which were: severe renal disease; congestive heart failure (CHF) class III or higher, thrombus present, and multivessel disease. Singh et al. reported an excellent goodness of fit, whereby p = 0.93 (1.0 is perfect), for the Hosmer-Lemeshow test, and an area under the ROC curve of 0.78 (0.018) following bootstrap resampling. Despite the excellent goodness of fit reported, it should be noted that the observed and expected MACE rates for different groups of risk are extremely close in terms of frequency, for example despite showing an almost perfect observed vs. expected rate, several of groups are closely clustered together. This essentially means, for example, that groups 1 and 2 show a very close MACE frequency (3-8) and groups 4, 5, and 6 displays a count (20 to 25). It should be noted also that these values are raw frequencies, and not rates, which is unusual for calibration plots for risk prediction models.

Table 2.3.3 displays the integer assignments based on the independent predictor odds ratios.

Table 2.3.3 – MACE prediction model risk factors from the Mayo Clinic Risk Score (Singh et al., 2002)

Risk Factor	Integer
Age 90-99 years	6
Cardiogenic shock	5
LMS disease	5
Age 80-89 years	5
Age 70-79 years	4
Renal disease	3
Age 60-69 years	3
Urgent/Emergency PCI	2
Multivessel disease	2
NYHA class ≥ III	2
Thrombus	2
Age 50-59 years	2
Age 40-49 years	1

In the article by Singh et al. (2002) a plot of estimated risk for the procedural complications based on the integer score was made. From the above table, the theoretical maximum total integer score is obtained from the following risk factors: Age 90-99 years (6), cardiogenic shock (5), LMS disease (5), renal disease (3), emergency PCI (2), multivessel disease (2), NYHA class ≥ III (2), and a thrombus present (2), which totals to an integer score of 27, this exceeds the risk graph profile (maximum 25), for which the risk is approximately 92.5% chance of in-hospital MACE.

Similar to the Kunadian et al. (2008) method of classifying the integer score into five groups, Singh et al. (2002). did the same, except the five respective groups were classified by estimated percentage: ≤ 2%, 2-5%, 5-10%, 10-25%, and >25%. Only 2.1% were classified as very high-risk in their cohort. The model was appropriately validated using 1781 PCI procedures that were performed in 2000, for which there was a 3.3% (58 procedures) MACE rate. The model performed well for the validation set for which the ROC curve was 0.755, and the Hosmer-Lemeshow test produced a *p* value of 0.64, whilst not as good as the training set (0.93), this still indicates little departure from observed vs. expected MACE. It was found that the model could discriminate best in higher-risk patients such as those presenting with diabetes and LMS lesions, compared to low-risk patients. An interesting point made by Singh et al. (2002) was that good discrimination is very hard to obtain for low-risk patients (i.e. elective PCI) because the MACE complication rate is low.

In a more recent study by Madan et al. (2008), 9494 PCIs were analysed from January 1996 to December 2002, this era was considered BMS dominant. As with Grayson et al.,

Kunadian et al., and Singh et al. studies, MACE was the outcome of interest but the definition was slightly altered to include the following outcomes:

(1) Death (all-cause within 30 days)
(2) Myocardial infarction (Q-wave BCIS definition or chest pain lasting > 20 minutes)
(3) Urgent or emergency CABG (during the index hospitalisation)
(4) cerebrovascular accidents
(5) Repeat PCI (during the same admission)

In should be noted that unlike the other three studies mentioned, patients with pre-procedural cardiogenic shock were excluded, as these were considered at very high risk of adverse outcomes already, hence the omission as a multivariate predictor of MACE. It should also be noted that the operator volume and experience was not analysed and hence a possible limitation of their study.

The multivariate predictors and the corresponding model statistical properties are listed in Table 2.3.4. The model developed was the Texas Heart Institute risk score (Madan et al., 2008).

Table 2.3.4 – The Texas Heart Risk Score for MACE following PCI

Risk Factor	Integer	Coefficient	Odds Ratio	*P* Value
Unstable angina	5	0.465	1.59 (1.22-2.08)	*0.0006*
Renal insufficiency	4	0.364	1.44 (1.01-2.04)	*0.0431*
Hypertension	3	0.349	1.42 (1.04-1.93)	*0.027*
Acute MI	4	0.424	1.53 (1.13-2.06)	*0.0056*
Congestive heart failure	4	0.364	1.44 (1.03-2.02)	*0.0345*
PVD	3	0.330	1.39 (1.01-1.91)	*0.0417*
Urgent PCI	9	0.927	2.53 (1.62-3.93)	*< 0.0001*
Emergency PCI	14	1.397	4.04 (2.71-6.04)	*< 0.0001*
Thrombus	4	0.388	1.48 (1.01-2.15)	*0.0443*
Type C lesion	4	0.389	1.48 (1.13-1.93)	*0.0043*
2 stents placed	4	0.448	1.56 (1.17-2.09)	*0.0023*
≥ 3 stents placed	5	0.526	1.69 (1.16-2.17)	*0.0063*
Intercept	NA	-4.885	NA	NA

The MACE rate was 2.8% (264 procedures), the model displayed good performance with the ROC curve = 0.70 and the Hosmer-Lemeshow test p = 0.67 indicating a good fit of observed vs. expected MACE. The validation cohort featured 5545 PCIs from 2003 to 2006, this displayed an increased MACE rate of 3.43%, and both the discrimination and calibration performances worsened to 0.67 (ROC) and p=0.08 respectively. The increase in MACE could possibly be explained by the validation cohort exhibiting a decrease of patients classified from low risk of 51.6% (training set) to 44.9% (validation) respectively. A major difference between the Singh et al. and Madan et al. studies was that the Texas

Heart Institute risk score model was performed in a DES dominant era that corresponded to a high usage of clopidogrel and glycoprotein inhibitors.

One-Year Mortality Prediction following PCI

Whilst the Grayson et al., Kunadian et al., Singh et al., and Madan studies, described previously, use the outcome of in-hospital MACE, and including 30-day death (Madan et al.), it is beneficial for patients and clinicians to know the likely longer-term outcomes following PCI, such as mortality within one year of a patient's procedure. Whilst extending the 'death' outcome from in-hospital mortality or 30-day mortality to one year is desired, there are considerations which must be noted, such as whether a patient that dies 11 months following PCI died because of a poor procedure (stent insertion) or whether it is completely unrelated to the PCI. When extending the outcome to long intervals such as 1-3 years, other conditions and comorbidities also can become more prominent such as diabetes, PVD, COPD and renal disease, which could all affect mortality rates.

A more recent study conducted by Maluenda et al. (2010) which incorporated a PCI cohort of 6932 procedures from January 2000 to December 2005, identified eight risk factors that were significantly associated with one-year mortality, for which the risk model characteristics are listed in Table 2.3.5 (Maluenda et al. 2010).

Table 2.3.5 – Risk prediction model for one-year mortality (Maluenda et al, 2010)

Risk Factor	Integer	Coefficient	OR	95% OR CI	*P* Value
TIMI grade < 3 flow	7	2.035	7.65	5.3-10.9	< *0.0001*
Heart failure	4	1.155	3.17	2.4-4.1	< *0.0001*
LMS disease	3	0.783	2.19	1.3-3.5	*0.0001*
Chronic renal failure	3	0.730	2.07	1.6-2.7	< *0.0001*
Diabetes mellitus	2	0.527	1.69	1.3-2.2	< *0.0001*
Haematocrit decrease	1	0.382	1.46	1.2-1.7	< *0.0001*
Haematocrit baseline	1	0.374	1.45	1.3-1.7	< *0.0001*
Age (decades > 40 years)	1	0.296	1.34	1.2-1.5	< *0.0001*
Intercept	NA	-5.276	NA	NA	NA

The overall rate of one-year mortality was 5.6% (383 patients). The majority of these had high-risk characteristics such as multivessel disease and other comorbidities. Despite the PCI cohort date range being from 2000 to 2005, the DES usage was fairly high at 60%. Maluenda et al. (2010) reported a good performance for both discrimination and calibration for which the ROC curve was 0.818 (mean bootstrap resampling) and the Hosmer-Lemeshow test produced $p = 0.43$.

The model performed well when applied to a validation PCI cohort which included 973 procedures from January 2006 to December 2007. The one-year mortality rate was much greater than the training cohort at 10.3% (100 patients), for which the model accurately predicted 81.5% of these deaths. An improvement in discrimination was evident whereby the ROC curve was 0.836, although the standard deviations were not reported, it is assumed this difference is not statistically significant. An improvement in the goodness of fit was observed also, with the $p = 0.573$. When the model was tested with AMI patients, the ROC curve increased to 0.903 with $p = 0.625$, indicating excellent performance for both measures. As with the other studies, the operator volume was omitted, in addition to cardiogenic shock patients. This study also only featured a single-centre, which suggests that the model requires external validation to verify its discrimination and calibration performance.

Primary PCI 30-Day MACE Prediction

The risk prediction models reviewed previously in this thesis have included PCI patients of all priorities (i.e. elective, urgent, and emergency) in their analyses and subsequent determination of multivariate predictors. In the majority of models designed with PCI cohorts of all priorities, the priority of the PCI procedure in some form is represented as an independent risk factor, whether this is separate risk factors for urgent and emergency, or combined into a single risk factor (urgent or emergency PCI), relative to the elective PCIs.

Patients presenting with elective conditions such as stable angina are, by definition, less likely to experience adverse outcomes (in-hospital complications or death) than their urgent and emergency counterparts. Indeed, every PCI study (to the author's knowledge) which reports outcome rates by priority shows emergency patient cohorts report higher rates of adverse outcomes. Because of this, research has been conducted using only high-risk (emergency) patients such as those requiring primary PCI (PPCI) for conditions such as ST-elevation myocardial infarction (STEMI).

In a recent study conducted by researchers in Serbia (Mrdovic et al., 2011) which investigated 30-day MACE following PPCI, a risk model was designed (The RISK-PCI score) using a PCI cohort of 2096 consecutive PPCIs from 2006 to 2009, this model also uses a point scoring system (decimal, in this instance). The 2096 PPCIs were split into a training set (80%) and validation set (20%) randomly, for which 1676 and 420 patients were assigned respectively. The reported definition of 30-day MACE was: death, nonfatal reinfarction, or cerebrovascular accident (stroke). This study also excluded patients with cardiogenic shock prior to their PCI procedure. Table 2.3.6 lists the risk factors that were

identified as independent predictors for 30-day MACE following their logistic regression analysis.

Table 2.3.6 – Risk prediction model for 30-day MACE (Mrdovic et al., 2011)

Risk Factor	Coefficient	Points	OR	95% OR CI	*P* Value
Age > 75 years	0.51	1	1.66	1.02-2.65	*0.05*
Prior infarction	0.76	1.5	2.13	1.37-3.39	*0.005*
Anterior infarction	0.57	1	1.77	1.15-2.74	*0.02*
Complete AV block (pre)	0.90	2	2.47	1.34-4.45	*0.004*
Acute bundle branch block	1.68	3.5	5.37	2.63-10.96	*< 0.001*
Leukocyte > 12.0 $^{10\text{-}9/L}$	0.49	1	1.63	1.11-2.39	*0.01*
Creatine clearance 60-89 ml/min	0.62	1	1.84	1.16-2.90	*0.01*
Creatinine clearance < 60 ml/min	0.97	2	2.65	1.50-4.68	*0.001*
LVEF < 40%	0.67	1.5	1.97	1.36-2.83	*0.003*
Reference diameter ≤ 25 mm	0.62	1	1.87	1.14-2.81	*0.03*
TIMI flow 0 (pre)	0.51	1	1.66	1.08-2.55	*0.02*
TIMI flow < 3 (Pre)	1.58	3.5	4.84	2.87-8.16	*< 0.001*
Glucose > 6.6 mmol/L	0.46	1	1.58	1.01-2.83	*0.05*
Intercept	-4.27		0.14		*< 0.001*

From the point scores reported in Table 2.3.6 by Mrdovic et al., the patients were classified into four risk groups based on the total points value of all their risk factors: low (0-2.5), intermediate (3-4.5), high (5-6.5), and very high (> 7), within these groups the observed rates of 30-day MACE were 1.9%, 5.9%, 13.3%, and 39.4% respectively. The RISK-PCI vs. the predicted 30-day MACE % is almost perfectly linear, the following table (2.3.7) displays the approximate predicted rate (based on Fig 1 from Mrdovic et al., 2011).

Table 2.3.7 – RISK-PCI score vs. predicted 30-day MACE (Mrdovic et al, 2011)

RISK-PCI Score	30-Day MACE	RISK-PCI Score	30-Day MACE
0	1.5%	9	40.0%
1	2.0%	9.5	45.0%
1.5	2.5%	10	55.0%
2	3.0%	10.5	57.5%
2.5	4.0%	11	63.0%
3	5.0%	11.5	67.5%
3.5	6.0%	12	72.5%
4	7.5%	12.5	77.0%
4.5	8.5%	13	80.0%
5	10%	14.5	90.0%
5.5	13.5%	15	92%
6	15.0%	15.5	93.5%
6.5	18%	16.5	95.0%
7	22.5%		
7.5	25.0%		
8	30.0%		
8.5	35.0%		

Within the MACE outcome, mortality with 30 days was 0%, 2.3%, 5.7%, and 32.5% respectively. The MACE rate for all PPCI patients was 9.1% (191), comprising 4.9% mortality (102), 3.3% (68) non-fatal reinfarction, and 1.0% (21) cerebrovascular accidents. Out of the 102 patients who died, 86.3% (88) died in hospital, meaning the rest (14) died following discharge but within 30 days.

The RISK-PCI score model performed well on the 1676 PPCI training cohort exhibited very good discrimination (ROC = 0.83) and calibration (Hosmer-Lemeshow, p = 0.72), this level of performance was retained in the validation set (420 PPCIs) with the discrimination and calibration being 0.83 (0.77 to 0.89) and p = 0.72 respectively.

An important point made by Mrdovic et al. (2011) was that even though emergency patients are by nature reasonably high risk, those presenting with STEMI which were classified as low-risk PPCI patients could be discharged early thus reducing costs and freeing up beds and staff resources, and those with an estimated high RISK-PCI score could be given additional length of stay or care prior to discharge. Because patients in the intermediate risk group (RISK-PCI score: 3-4.5) had a peak mortality count at 8 days post PPCI, there could be time to perform additional complete revascularisation within this period via elective PCI to possibly reduce the chance of subsequent MACE. Another interesting point made by Mrdovic et al., which has not been discussed in other published research papers, is that because their study distinguishes PPCI patients into different risk groups (from low to very high), by identifying and excluding low risk patients, future trials can increase their statistical power from a smaller sample size with regards to measuring poor outcomes in the form of MACE, whether this be post-operation drugs, or a comparison between new stent technology.

Long-term Mortality Prediction in a DES Era

An important study conducted in Australia by Wilson et al. (2011) investigated the causes, duration, and predictors of death after a long-term follow-up period for PCI patients. Their cohort of PCI patients was obtained from the Melbourne Interventional Group registry and was linked to the National Death Index database allowing analysis of long-term mortality outcomes following PCI for the first time in Australia. The cohort included 10,682 consecutive PCI procedures performed from February 2004 to November 2009.

Patients that underwent a BMS PCI were recommended to take both aspirin and Clopidogrel (antiplatelet therapy) for at least four weeks, and those which underwent a DES PCI were recommended to take them for at least six months following their PCI. Wilson et al. split their analysis into two groups:

(1) DES group (4662 PCIs) – at least one DES inserted
(2) BMS group (6060 PCIs) – only BMS inserted

The decision to use a DES for the PCI was based on least one of the following criteria: diabetes mellitus (all forms), target vessel diameter ≤ 2.5 mm, target lesion length ≥ 20 mm, bifurcation lesion, ostial lesion, in-stent restenosis, long-term total occlusions.

Table 2.3.8 (adapted from Wilson et al. 2011) displays the mortality rates for all PCIs, DES PCIs, and BMS PCIs by different mortality intervals (ranging from in-hospital to long-term).

Table 2.3.8 – Mortality rates reported by Wilson et al. (2011)

Mortality Interval	Overall (n = 10,262)	DES (n = 4,662)	BMS (n = 6,060)	*P* Value
In-hospital	1.6%	1.0%	2.1%	*< 0.001*
30 days	2.1%	1.3%	2.6%	*< 0.001*
12 months	3.9%	3.1%	4.5%	*< 0.001*
Long-term (median 3.2 years)	8.2%	7.7%	8.7%	0.072

Unlike the other literature discussed so far whereby a risk model was constructed using logistic regression analysis, Wilson et al. (2011) developed a survival analysis form of regression using a Cox proportional hazards regression model, this does not specifically result in a developed model but a set of independent predictors and a corresponding hazard ratio (HR). The predictors and HR variables discovered by Wilson et al. are in Table 2.3.9 (adapted from Wilson et al., 2011, Table 5).

Table 2.3.9 – Independent predictors of long-term mortality (Wilson et al, 2011)

Predictor	HR (95% CI)	*P* Value
Cardiogenic shock	4.58 (3.60-5.83)	*< 0.001*
Renal failure	3.14 (2.58-3.82)	*< 0.001*
Recent heart failure	1.97 (1.60-2.41)	*< 0.001*
STEMI	1.79 (1.47-2.18)	*< 0.001*
PVD	1.72 (1.40-2.11)	*< 0.001*
NSTEMI	1.58 (1.32-1.90)	*< 0.001*
Multivessel disease	1.47 (1.24-.1.74)	*< 0.001*
Current smoker	1.39 (1.12-1.71)	*0.002*
Diabetes	1.36 (1.16-1.59)	*< 0.001*
Previous stroke	1.33 (1.06-1.60)	*0.014*
Previous MI	1.24 (1.06-1.42)	*0.008*
LAD vessel to be treated	1.23 (1.06-1.43)	*0.005*
Hypertension (BP > 140/80 mmHg)	1.21 (1.01-1.45)	*0.034*
Age (per year increase)	1.05 (1.04-1.06)	*< 0.001*
DES usage	0.85 (0.73-0.99)	*0.036*
Dyslipidaemia	0.82 (0.70-0.94)	*0.02*

From the cohort of 10,682 patients, there were reasonably high percentages of characteristics considered to be high risk, such as 24% diabetic patients, 63% reporting with acute coronary syndromes (ACS), 59% presenting with multivessel disease. The procedures percentage of PCIS featuring exclusive DES usage was 43%. The DES group displayed a lower late mortality HR (0.85, 0.73 to 0.99, p = 0.04) compared to the BMS group yet at 30 days the rates were no different. Wilson et al. did however state that the difference in long-term mortality rate between the BMS and DES groups could simply be caused by early BMS mortality (30 day). It is important to consider that the majority of early deaths were cardiac-related, i.e. for in hospital, and 30 days the overall rate was 79% and 79% respectively (BMS: 87% and 82%; DES: 82% and 77% respectively), for the long-term follow-up (median 3.2 years) this was 52% overall (BMS: 54%; DES: 50%). Only half of the long-term deaths were classified as cardiac-related.

As with the other studies which did not exclude cardiogenic shock from their regression analysis and subsequent model development, it has been identified as one of the strongest predictors of mortality (most notably early mortality). Heart failure was identified as a strong predictor of long-term mortality and is associated with a poor left ventricle ejection fraction (LVEF), which has been a predictor in many other models of adverse outcomes.

Table 2.3.10 displays a summary of the multivariate risk factors identified from PCI risk prediction models or Cox regression survival analysis identified from this literature review. Note that not all predictors increase the risk, in some cases such as ‘DES used’, the HR or OR will be below 1.0 and thus a negative regression coefficient.

Table 2.3.10 – summary of multivariate prediction models for outcomes following PCI

Risk Model/Paper	Outcome	Multivariate Predictors
NWQIP	IH-MACE	Age, female sex, LMS lesions, graft lesions, urgent/emergency PCI, cardiogenic shock, stroke
Kunadian (2008)	IH-MACE	Age, renal dysfunction, PVD, cardiogenic shock, AMI, thrombus, urgent/emergency PCI, multivessel disease
Texas HI Risk Score	IH-MACE/30-M	Unstable angina, renal dysfunction, hypertension, AMI, CHF, PVD, urgent/emergency PCI, thrombus, type C lesions, num. of stents placed.
Wilson et al. (2011)	Long-term Mortality	Cardiogenic shock, renal failure, recent HF, STEMI, PVD, NSTEMI, multivessel disease, current smoker, diabetes, prior stroke, prior MI, LAD vessel, hypertension, age, DES used, dyslipidemia
The British Colombia PCI Risk Score	30-Day Mortality	Age, female sex, emergency PCI, LMS disease, 3-vessel disease, LVEF, NYHA ≥ 3/CHF, critical preproc state (shock), STEMI ongoing/recurrent, other ACS, dialysis/creatinine > 200 µmol/L
Mayo Clinic Score	IH-MACE	Age, cardiogenic shock, urgent/emergency PCI, LMS disease, serum creatinine > 265 µmol/l, NYHA class ≥ III, thrombus, multivessel disease
Singh (2002)	IH-MACE	Cardiogenic shock, LMS disease, serum creatinine > 265 µmol/l, urgent/emergency PCI, NYHA ≥ III, thrombus, multivessel disease, age
Maluenda (2010)	1-Year Mortality	TIMI flow < 3, CHF, LMS disease, chronic renal failure, history of diabetes, hematocrit drop (%), baseline hematocrit (%), age
CathPCI Risk Score	30-Day Mortality	Age, Cardiogenic shock, prior CHF, PVD, chronic lung disease, GFR rate, NYHA class, PCI status (STEMI/no-STEMI) priority
Curtis (2012)	30-Day Mortality	[*STEMI/shock group*] age, BMI, chronic lung disease, GRF rate, prior PCI, HF (admission), cardiogenic shock, MI status, LVEF, Priority, vessel, SCAI class,
Curtis (2012)	30-Day Mortality	[*No STEMI/shock group*] age, BMI, history CHF, stroke, PVD, chronic lung disease, diabetes, GFR rate, prior PCI, CHF, NYHA class, MI status, LVEF, priority, vessel, SCAI class

Conclusions

The NWQIP model was the first to be developed in a clinical setting within the UK health care system, and was subsequently validated and found to perform well in an external cohort and different geographical location within the UK. It is however unknown how it will perform in more modern times, i.e. post 2010 with increasing proportions of DES usage, and with the future potential introduction of 2nd generation bioabsorbable stents. The

referral systems have improved and it is anticipated that more patients would be treated at the ECTC as elective patients, whereas previously their disease would have worsened and more likely resulted in them undergoing emergency PCI following an out-of-hospital myocardial infarction. This thesis provides the opportunity to test this hypothesis and identify how well the NWQIP performs on an external cohort in a different era of interventional cardiology.

2.3.2.4 Repeat Revascularisation and Target Vessel Revascularisation (TVR)

Introduction

Reintervention following coronary revascularisation procedures is an important outcome to consider and subsequently warrants analysis of the risk factors that predispose patients to undergoing future treatment (Wang et al., 2012; Taniwaki et al., 2014). If such characteristics (demographic, clinical, or angiographic) are identified which show a high association with the need for further revascularisation in the future, this can be useful for both interventional consultants and patients.

As with mortality prediction, the time period analysed may weaken associations as it is increased, for example a patient or consultant may wish to know the probability that a new elective PCI patient will require another PCI or CABG within three years, however the accuracy and risk factor associations is much more likely to be weaker than that of a model which analyses one-year revascularisation. Two common measures of subsequent coronary revascularisation are: repeat revascularisation (RR) – which involves any type of coronary revascularisation whether this be PCI/CABG, to any coronary artery within a defined time period; target vessel revascularisation (TVR) which involves treatment to the same coronary vessel as the index procedure. As long as one coronary vessel is treated in the subsequent revascularisation procedure that was treated in the initial procedure then it is classified as TVR.

With regards to predicting TVR/RR, it is important to understand that some subsequent procedures are planned/staged, meaning the interventional operator intentionally plans to treat another vessel/lesion at a later date. Commonly a patient that comes to the ECTC following a myocardial infarction (e.g. STEMI) will be treated for the vessel which caused/experienced the infarction, however during the coronary angiogram the operator may identify high stenosis (atheroma) in other coronary arteries, which they plan to treat at a later date, the stenosis is not considered high enough to require immediate

revascularisation so they are placed on a waiting list and are seen within six weeks for subsequent treatment, additionally it may be the case that the radioactive contrast dye would provide too much radiation within a short period of time should the patient be treated for the other non-infarct arteries during the index hospitalisation. It is known that staged/planned procedures are going to occur, and therefore they are omitted from analysis and are not classified within the RR/TVR category.

In many risk models, which were constructed for repeat revascularisation or target vessel revascularisation, death is combined with these outcomes as simply knowing whether a patient has a low percentage chance of requiring a further PCI, would be deceiving if that patient has a high chance of dying within this period. Other models combine the use of myocardial infarction, target lesion failure as predictors although depending on the hospital setting, tracking this data may be difficult for some healthcare systems.

In Japan a study was conducted by Shiomi et al. (2012) across 26 PCI centres, their study cohort featured 1005 consecutive revascularisation procedures from January 2005 to December 2007, 365 of these were PCI and 640 were CABG. The purpose of the study was to compare long-term outcomes of PCI versus CABG for patients that were treated for unprotected left main coronary artery disease (ULMCAD) during their first coronary revascularisation procedure. Patients with AMI were excluded from their analysis. The primary end-point for the analysis was a composite outcome of three year death/MI/cerebrovascular accident (stroke) but repeat coronary revascularisation was a peripheral end-point that was analysed. It was found that the primary end-point had a significantly higher rate in the PCI cohort compared to the CABG counterparts (22.7% vs. 14.8%, $p = 0.0006$) but after having adjusted the risk for possible confounding variables, it was determined that there was no significant difference in risk (adjusted Hazard Ratio = 1.30, 95% CI = 0.79 to 2.15, $p = 0.30$).

There were significant differences in the SYNTAX score between the two methods of revascularisation whereby the PCI cohort had a higher percentage of low (< 23) and intermediate (23-33) scores, of 34.4% vs. 26.8% and 36.6% vs. 30.8% respectively, however the CABG cohort exhibited a higher rate of high SYNTAX scoring (> 33) patients with 42.3% vs. 29.1% (PCI), overall $p < 0.0001$. Several other important 3-year end-points were used in the study, these included:

(1) All-cause death.
(2) Cardiac death.
(3) Myocardial infarction.

(4) Cerebrovascular accidents.
(5) Coronary revascularisation (PCI or CABG).

Both death classifications (all-cause and cardiac) showed higher rates in the PCI cohort (13.6% vs. 9.2%, $p = 0.01$; and 7.4% vs. 3.7%, $p = 0.005$ respectively). However, when risk adjustment was performed, the rates were not significantly different for either outcome for PCI vs. CABG (HR = 0.79, 0.40 to 1.57; and HR = 1.80, 0.64 to 5.09, $p = 0.27$ respectively).

For the myocardial infarction end-point, a higher rate was identified in the PCI cohort compared to the CABG group (5.5% vs. 2.3%, $p = 0.003$). However, following adjustment, this was not significant either (HR = 2.47, 0.81 to 7.54, $p = 0.11$). The reported rate of definite stent thrombosis was very low (1.5%), the rate of stent and DES usage were high at 98% and 78% respectively. Unlike the other outcomes (described above), the pre-adjusted rate for stroke was not significantly different between the PCI and CABG cohorts (6.6% vs. 5.5%, $p = 0.43$; and HR = 0.79, 0.30 to 2.08, $p = 0.63$). The end-point of subsequent coronary revascularisation was the only outcome that was significantly different between the PCI and CABG cohorts, following risk adjustment. The PCI cohort exhibited almost four times the rate of further revascularisation than the CABG cohort (43.4% vs. 11.2%, $p = 0.0001$; and HR = 5.83, 3.74 to 9.09, $p < 0.0001$). Despite the overall 3-year primary end-point (death/MI/stroke) not showing a significant between PCI and CABG following adjustment, when the analysis was limited to patients classified into the high scoring SYNTAX group (> 33), a significant difference was identified even after adjustment (27.4% vs. 16.8%, $p = 0.006$; and HR = 2.61, 1.32 to 5.16, $p = 0.006$). No statistically significant differences were identified in either the low or intermediate SYNTAX score groups.

As with other studies, there may have been selection bias for patients being administered PCI or CABG. Secondly, longer follow up periods (i.e. more than three years) may have been difficult to perform, but the rates may have been different and identified whether PCI or CABG performs better when considered over longer intervals. For example, it could be that the CABG cohort starts to manifest higher adverse outcome rates after three years, but these are not known due to the follow-up period being limited to three years.

In a recent study by Hess et al. (2014), the end-point of target vessel revascularisation (TVR) within 1-year of PCI was used. The cohort included elderly patients aged ≥ 65 years that were having *de novo* (not previously treated) lesions treated. The study included a very large sample size of 343,173 PCIs from 2005 to 2009 from more than

1400 hospitals in the US. One of the motivations for this study was the increase life expectancy and hence the proportion of elderly patients being treated with PCI. The paper reported that approximately 40% of the PCIs performed in the US were on those aged ≥ 65 years. Due to increasing life expectancy, it was important to consider which of the patients needed subsequent treatment for the same vessel, this would allow more efficient planning based on estimated risk of TVR, it would be known approximately, what numbers of patients would be expected to be seen again within one year. Other studies have analysed TVR rates with regards to BMS versus DES over different time intervals and have typically found that patients with DES inserted during their procedure have a significantly reduced rate of TVR compared to BMS counterparts of a similar condition. Despite DES showing lower rates of TVR (e.g. from restenosis) compared to BMS, it does not necessarily mean DES should be favoured for all PCIs: (i) DES are more expensive than BMS; (ii) DES have a higher risk of very late stent thrombosis; (iii) prolonged use of dual antiplatelet therapy is required (or at least recommended). The rate of DES usage in their cohort of PCI patients was high at 76.5% (262,496). Hess et al. (2014) analysed the 1-year TVR rates by splitting their PCI cohort into two groups: (i) BMS exclusive PCIs; (ii) DES exclusive PCIs. The overall TVR rate was 3.3% (11,217 patients). When grouped by the endpoint, i.e. 1-year TVR group vs. non-TVR group, the former exhibited (as expected) a higher percentage of comorbidities, most commonly hypertension, diabetes, prior MI, and prior revascularisation. The prior revascularisation PCIs were only those for which the vessel treated was different, i.e. prior TVRs were excluded from analysis. Hess et al. created four different TVR models using multivariate logistic regression:

(1) BMS: pre-procedural variables only.
(2) BMS: both pre-procedural and procedural variables.
(3) DES: pre-procedural variables only.
(4) DES: both pre-procedural and procedural variables.

By producing a model featuring only pre-procedure (proc.) variables, it allows prospective use of a risk prediction model to be taken advantage of, which is especially useful for elective patients. The strongest predictors identified for each of the four models were:

(1) BMS (pre-proc.): insulin and non-insulin-treated diabetes, and prior PCI.
(2) BMS (pre-proc. and proc.): smallest stent diameter, longer stent length, and multivessel PCI.
(3) DES (pre-proc.): prior PCI, age, insulin-treated diabetes.
(4) DES (pre-proc. and proc.): multivessel PCI, smallest stent length, and prior PCI.

Once the regression models had been constructed, the estimated probabilities of TVR were assigned to each PCI record and then split into three groups based on the ascending order of estimated risk (low, medium, and high). The following table (2.3.12) identifies the estimated mean 1-year TVR rate and range for each group, the corresponding odds ratios are for the medium and high groups (the low risk group is the reference).

Table 2.3.11 – estimated TVR risk for BMS and DES cohort groups (Hess et al, 2014)

Group	Mean Risk (%)	Range (%)	Odds Ratio
BMS			
Low	2.5%	0.4% to 3.2%	Reference
Medium	3.8%	3.2% to 4.5%	1.5
High	6.2%	4.5% to 29.8%	2.6
DES			
Low	1.6%	0.3% to 2.0%	Reference
Medium	2.4%	2.0% to 2.9%	1.5
High	4.0%	2.9% to 18.2%	2.4

Table 2.3.11 shows that in the highest risk group for 1-year TVR there is an apparent reduction from 6.2% to 4.0% for BMS vs. DES, this is an overall reduction of 35.5%.

The BMS and DES models (pre-procedure and procedural factors) produced an AUROC of 0.54, 0.60, 0.57, and 0.60 respectively, in terms of discrimination performance this is poor compared to other important endpoints such as in-hospital MACE/mortality, and 30-day mortality. The models used a 2:1 ratio for development and validation respectively. It is important to note that the study excluded the following PCIs from analysis: procedures without stents (e.g. standard balloon angioplasty); procedures featuring a mixture of BMS and DES inserted into the patient; procedures with PCIs to graft lesions; patients with STEMI; target vessel lesion previously treated; in-hospital deaths/CABG; and CABG within one year of the patient's index PCI. Calibration goodness of fit statistics have not been reported (e.g. Hosmer-Lemeshow). The calibration plots present do reveal closely matched observed and estimated 1-year TVR however there is little differentiation between risk groups, with several of the models within a 2% range of each other. It would be beneficial if additional variables could be identified to better distinguish between risk groups, and hence allow better judgement of whether a patient might experience 1-year TVR. Other factors may have an important impact, such as the duration over which a patient continues their antiplatelet therapy.

In Sydney, Australia another study relating to TVR was conducted by Shugman et al. (2012). This was an investigation into a PCI cohort which had BMS inserted from 2003 to 2010, and included 1059 PCIs in the final analysis. The study limited the indication for intervention to patients presenting with STEMI, as to identify whether BMS insertion into large infarct related arteries (IRAs) produces lower rates of TVR compared to a cohort of patients which experience STEMI in smaller IRAs. The study excluded patients presenting with stable CHD and NSTEMI, and PCIs repeated on the same patient. One of the reasons for conducting this study was because it was known that DES overall show reduced reintervention rates compared to BMS, but it was unknown whether patients who receive DES keep up with dual antiplatelet therapy after 12 months (from their index PCI), therefore would using BMS in large arteries be beneficial and produce low TVR rates.

The BMS PCI cohort was split into three categories based on the size in millimetres of the IRAs:

(1) Large artery group: ≥ 3.5 mm.
(2) Moderate group: 3.0 mm to 3.49 mm.
(3) Small group: ≤ 3.00 mm.

The distributions of the PCIs performed for the three groups were 512 (48%), 333 (31%), and 214 (20%), respectively. The 1-year TVR overall rate was 5.8% and for the three groups this was 2.2%, 9.2%, and 9.0% respectively. The 1-year death/MI rate for these groups was 6.6%, 11.7%, and 9.0%, respectively. The predictors of 1-year TVR are listed in Table 2.3.12

Table 2.3.12 – Predictors for 1-year TVR in BMS patients (Shugman et al., 2012)

Predictor	**Odds Ratio**	**95% CI OR**	**P Value**
Vessel diameter	4.39	2.24 to 8.60	*< 0.001*
Proximal LAD lesions	1.89	1.08 to 3.31	*0.027*
Hypertension	2.01	1.17 to 3.48	*0.011*
Prior PCI	3.46	1.21 to 9.85	*0.020*

The predictors for 1-year death/MI are listed below in Table 2.3.13.

Table 2.3.13 – predictors for 1-year death/MI in BMS patients (Shugman et al, 2012)

Predictor	**Odds Ratio**	**95% CI OR**	**P Value**
Cardiogenic shock (pre-PCI)	8.16	4.16 to 16.01	*< 0.001*
Age ≥ 65 years	2.63	1.58 to 4.39	*< 0.001*
LAD lesions	1.95	1.19 to 3.21	*0.019*
Female gender	1.93	1.12 to 3.32	*0.008*
ACC/AHA Type B2 and C lesions	2.17	1.10 to 4.27	*0.026*

In summary, it was found that STEMI in IRAs ≥ 3.55mm were associated with a low 1-year TVR rate (2.2%) when treated with BMS, and should therefore be considered for future interest as this could alleviate the problems of using DES whereby patients prematurely discontinue their antiplatelet therapy, which can subsequently lead to late stent thrombosis.

2.3.3 Conclusions

Following review of the published journal articles featuring risk prediction models design for outcomes following PCI, it is apparent that the vast majority of the models were constructed by researchers outside of the UK. The original NWQIP study (Grayson et al., 2006) and external validation study (Kunadian et al., 2008) were initially the only literature available that utilised a UK PCI database, however, since the completion of the studies in Chapters 4 and 5, two new publications (McAllister et al, 2016; Wall et al, 2017) have been made featuring the development of a 30-day mortality prediction model, the findings within this thesis and how they relate to both models is discussed in Chapter 7. This lack of research gives rise to the need to verify whether NWQIP performs as well as it originally did on PCI cohorts of a different era. In order to test the first and second hypothesis (section 1.3), a study utilising the ECTC's PCI cohort is performed in Chapter 4. To restate these hypotheses in brief, it is predicted that due to the myriad of changes in terms of patient demographics, clinical, and procedural characteristics, that the NWQIP risk model will not perform as well it once did for predicting in-hospital MACE. Subsequent logistic regression analysis, as heavily featured in published literature relating to PCI risk prediction models, should allow a risk model to be constructed that can more accurately predict important clinical outcomes such as in-hospital MACE, or short and long-term mortality following PCI. Chapter 5 extends the validation study of NWQIP, to investigate 30-day mortality, and to ascertain whether the incorporated NWQIP risk factors are effective predictors for all-cause death within 30 days of a patient undergoing PCI.

At the time of writing, there is no peer-reviewed research available that has been conducted in the UK to examine the impact of repeat revascularisation. Similarly, there is little available information prediction models for longer-term outcomes for stable PCI patients. Hess et al. (2014) showed that DES cohorts typically have lower estimated TVR rates compared to BMS cohorts for the same relative risk groups (i.e. low, medium, and high). Both the Shugman and Hess studies yielded useful information to investigate in the ECTC cohort, specifically that the types lesions and vessel diameter are useful predictors for TVR. As with many models that report MACE/mortality, comorbidities are also prominent in repeat revascularisation and TVR models. Many of the different risk factors in these published models are available in the ECTC CVIS database and can be investigated in an univariate association analysis. This analysis may provide useful insights into which risk factors predispose patients to requiring a subsequent coronary revascularisation. This is especially beneficial for elective patients, whereby the other clinical outcomes such as in-hospital MACE, or short-term mortality (i.e. 30 days) occurs a

very low rates. Chapter 6 investigates the outcomes of repeat revascularisation and longer-term death (i.e. 3 years) for stable (elective) patients.

Chapter 3: General Methods and Data

3.1 Setting

The data used in this thesis was obtained from the Essex Cardiothoracic Centre (ECTC), part of Basildon and Thurrock University Hospital's NHS Foundation Trust (BTUH). The site is located in Basildon, Essex, United Kingdom. The data was provided following NRES Ethical Approval (detailed in section 3.3). All patient-identifiable information was removed, i.e. names, addresses, contact details, dates of birth etc. The ECTC is a tertiary cardiac referral centre which serves the county of Essex, which includes a population of approximately 1.7 million people (ONS, 2014).The ECTC opened in July 2007, and performs coronary procedures for elective, urgent, and emergency patients, comprising approximately 3000 per annum. Many patients are referred to the ECTC by several district general hospitals (DGHs) in the county of Essex, these being Southend University Hospital NHS Foundation Trust (Westcliff-on-sea, Essex), Colchester Hospital University NHS Foundation Trust (Colchester, Essex), Princess Alexandra Hospital NHS Trust (Harlow, Essex), Mid Essex Hospital Services NHS Trust (Chelmsford, Essex), and Basildon and Thurrock NHS Foundation Trust (Basildon, Essex).The ECTC initially began performing elective PCI procedures when it first opened in 2007 which is why approximately 83% of all PCIs during that year were elective. In the third quarter of 2009 the ECTC started its primary care activation programme whereby patients which experienced out-of-hospital ST-elevation myocardial infarctions (STEMI) were sent straight to ECTC for coronary revascularisation instead of being treated at another non-PCI hospital with thrombolytic therapy and then transferred to the ECTC at a later stage. This is why from quarter three of 2009 onwards there is a rise in the proportion of emergency PCI procedures performed.

The ECTC offers four principle clinical services (BTUH, 2014). These are:

1. Cardiovascular surgery – conventional CABG, off-pump coronary bypass (OPCAB), minimally invasive direct coronary bypass (MIDCAB), aortic valve replacement (AVR), mitral valve replacement/repair, and others.
2. Interventional Cardiology – PCI, including standard balloon angioplasty, bare metal stent (BMS) insertion, and drug-eluting stent (DES) insertion.
3. Thoracic Surgery
4. Cardiac Electrophysiology

The ECTC facilitates for over 100 patients and includes 22 critical care beds, a rehabilitation gym, and a dedicated cardiac rehabilitation team (SCTS, 2014).

3.2 Patient Database

The ECTC uses a cardiovascular information management system (CVIS) from Philips (Philips CVIS, 2014). In 2014, this was used by approximately 26% of the PCI centres in the UK (BCIS Audit Report, 2015). This is a comprehensive relational database system that performs numerous functions relating to the management of patients and coronary procedures in a cardiovascular treatment setting. The relational database structure schema itself is confidential and cannot be described in detail here. However, it contains common tables and fields as expected such as patient, procedure, history, devices used etc. The CVIS system itself is also known as Tomcat, although it is usually used to describe the system front-end. According to the national audit project for PCI centres, the British Cardiovascular Intervention Society (BCIS), CVIS/Tomcat is the most commonly used front-end database for PCI centres in the UK (BCIS Audit Project, p. 68, 2014). The total number of PCIs was 15,865 and procedure dates ranges from 2nd July 2007 to 12th March 2015. The CVIS application front-end supports, and hence has tailored interfaces for numerous specialities within cardiology such as catherisation, electrophysiology, echocardiography, nuclear cardiology, cardiac surgery labs, and several others. The system supports the scheduling of patients for treatment, the management of staff and resources, capturing of costs, and also allows for the rapid generation of reports. The CVIS application allows detailed patient information to be stored and easily retrieved for review, whether this be by cardiac operators, consultants, or nurses. Detailed discharge and treatment letters can also be created, stored, and accessed from the system. In addition to PCI and CABG procedures, support for other cardiovascular databases and imaging software is supported, thus overall allowing a single comprehensive system to be used for the majority of the work performed at the ECTC. There are several benefits to utilising a single cardiovascular information management system over using multiple software systems from different vendors, these include (but are not limited to) the following:

Less training – it may confuse staff (operators, consultants, and nurses) if multiple systems were used, and utilising a single system less training may be required for effective usage.

Easier backup and security – backing up a single database and implementing security may be more easily performed on a single database. Data managers would also only need to know the inner workings of a single database schema rather than multiple, which is beneficial should any problems or issues arise.

Data Redundancy – by using a single database not only will the data be up-to-date, it will also not be duplicated as the functionality is contained within one system and no overlapping of data can occur between different systems, thus reducing the resources required. It also reduces the risk of inconsistency.

Centres such as the ECTC which perform procedures for patients with cardiovascular disease are required to submit certain data audits to various cardiovascular national audit projects (in England, Wales, and Northern Ireland). These audits allow various hospitals and cardiac centres to be compared. They also allow identification of how they performing compared to the national average with respect to important clinical outcomes, such as in-hospital complications and mortality. The audits themselves specify a minimum dataset (list of variables required for submission) although a schema for extra data are often provided and appreciated. These audits allow patients to be educated on a given hospital or cardiac centre's performance, which may subsequently influence their decision to undergo a certain choice of treatment there. In addition to this it can allow the under-performing centres to reassess their processes and attempt to improve upon their services. The audits have the potential to detect operators or surgeons that are underperforming and allow questions to be answered such as “which operators show unusually high associations with adverse outcomes?”. Public outcomes may also tempt certain operators or institutions to avoid higher-risk patients as to avoid potentially adverse outcomes, despite the operation being most preferred. Many of these cardiovascular audits are managed by the National Institute for Cardiovascular Outcomes Research (NICOR) which is based at University College London (NICOR, 2015). By having these national bodies that process and make hospital/cardiac centre and operator outcomes publicly available it allows patients to have a better informed consent before they undergo a procedure at a certain centre or with a certain operator.

The audits which the ECTC is known to submit to national sources include:

1. Myocardial Ischaemia National Audit Project (MINAP) – this includes data that relates to the management of patients which have a myocardial infarction/heart attack (MINAP, 2015).
2. Society for Cardiothoracic Surgery (SCTS) – this includes data relating to all patients which undergo any form of cardiac surgery, such as CABG, aortic/mitral valve surgery etc. (SCTS, 2014).
3. British Cardiovascular Intervention Society (BCIS) – this includes data for patients which undergo PCI and includes all procedure priorities from elective to emergency (BCIS, 2014).

The primary set of data used in this thesis was acquired from the ECTC CVIS database through the usage of structured query language (SQL). This allowed relevant data relating to each patient procedure to be extracted, and stored in a spreadsheet for subsequent analysis. The SQL queries and construction of the corresponding spreadsheets were designed and executed by the ECTC Data Manager following provision of NRES ethical approval and data anonymisation. The majority of queries executed were already designed for extraction of the CVIS data for audit reports in order to submit them to the three national bodies above (MINAP, SCTS, and BCIS), these were modified and additional variables added for analysis in the studies within this thesis. The mortality data was extracted in the background; the CVIS database links up the BTUH PAS database that contains the date of death and any relevant deaths for patients that have had a PCI procedure at the ECTC are retrieved. The characteristics of fields relating to each of the three audits are listed in Appendix B. In summary, each cardiac procedure performed at the ECTC has a detailed set of information stored about it in the CVIS database that relates to: (I) patient demographics; (ii) comorbidities/medical history; (III) procedural aspects; (IV) and angiographic characteristics.

This study, whilst including analysis on CABG, primarily focusses on PCI (BCIS) outcomes. As listed previously, BCIS are responsible for the national PCI audit. The audits themselves are submitted digitally following the appropriate extraction through SQL into a standard flat text file. The required information is specified in the BCIS dataset documentation version 5.6.2 (BCIS Dataset, 2014). In brief, the data required by BCIS includes: patient demographics; intervention indication; procedure priority; cardiogenic shock (pre-procedural); angina status (Canadian Cardiovascular Society Classification, CCS); date and times of operation/symptom onset/ambulance transport/balloon inflation; prior myocardial infarction/CABG/PCI; diabetes; left ventricle ejection fraction (LVEF); stenosis percentages of coronary vessels (left main stem, circumflex, right coronary artery, left anterior descending artery); number and type of stents inserted; drugs given pre and post-procedure; medical history; complications during and after the procedure; and status at discharge.

Data Completion and Recommended Minimum Dataset for PCI Procedures

The data is recorded by a combination of interventional operators, trained nurses, and junior doctors. Although not every piece of information may be recorded due to time constraints or a lack of training, in recent times the majority of the minimum data fields specified by BCIS are complete and should be encouraged for anyone recording procedure details.

Table 3.2.1 lists the minimum dataset standard for audit submission as specified by NICOR. Some of the data is only required depending on the PCI type and this has remained a requirement since November 2010. It is also a requirement that at least 90% of the following data fields are complete upon submission. The 'All PCIs' type represents every single PCI procedure performed, 'Primary PCI' type represents PCIs performed on STEMI patients, and the 'ACS PCI Types' represents any procedure performed on acute coronary syndrome patients (i.e. non-stable patients).

Table 3.2.1 – Recommended minimum PCI procedure audit submission dataset

Field Code	Field Name	PCI Type
1.03	NHS Number	All PCIs
1.06	Birth Date	All PCIs
1.07	Sex	All PCIs
2.03	Procedure Urgency	All PCIs
2.04	Cardiogenic shock (Pre-PCI)	All PCIs
2.07	Date/Time of symptom onset	ACS PCI Types
2.08	Date/Time arrival at first hospital	ACS PCI Types
2.16	Diabetes	All PCIs
2.18	Weight	All PCIs
3.02	Consultant Responsible Name	All PCIs
3.09	Vessels Attempted	All PCIs
3.26	Date/Time of first balloon inflation	Primary PCIs
4.01	PCI Hospital Outcome	All PCIs
4.03	Status at discharge	All PCIs
4.04	Discharge date	All PCIs
5.05	Medical History	All PCIs
5.06	History of renal disease	All PCIs
5.26	Date/Time of arrival at PCI hospital	ACS PCI Types
5.27	Date/Time call for help	ACS PCI Types
5.30	Location of Patient at STEMI onset	Primary PCIs
5.31	Consultant Responsible GMC Number	All PCIs
5.35	Creatinine	All PCIs

In this study, the NHS Number, Consultant Responsible GMC Number, and Birth Date were not available or needed in this dataset due to confidentiality and ethical approval reasons. The age in years was however available and represented the patient's age at the time of their procedure.

Table 3.2.2 lists the minimum required variable as specified in Table 3.2.1 and the percentage completeness from July 2007 to March 2015, which were provided from the CVIS database for analysis.

Table 3.2.2 – ECTC CVIS Data completeness (BCIS minimum dataset)

Variable	2007	2008	2009	2010	2011	2012	2013	2014	2015
Age	100	100	100	100	100	100	100	100	100
Sex	100	100	99.9	100	100	100	100	100	100
Status at Discharge	62.3	99.5	94.6	97.6	98.8	98.1	97.7	94.2	91.7
Shock	28.4	97.4	86.1	93.2	94.2	92.1	96.4	97.4	97.8
Urgency	94.4	99.9	99.7	99.8	100	99.9	100	99.8	100
Medical History	88.8	98.6	92.1	92.05	98.8	92.6	97.2	91.7	92.4
Discharge Date	59.8	99.7	90.1	98.0	98.9	97.9	98.7	85.0	77.3
Diabetes	91.3	91.5	95.5	96.6	98.5	95.2	96.8	95.1	94.6
Weight	65.4	31.5	48.7	42.7	42.3	22.7	22.2	37.7	68.6
Vessels Attempted	29.3	99.8	97.8	98.09	99.3	99.1	99.6	98.5	99.1
Consultant Responsible	97.5	86.6	95.4	100	100	100	99.9	97.1	96.9
History Renal Disease	84.5	90.2	82.9	65.0	73.0	97.2	68.2	79.8	82.0
D/T 1st Balloon inflation	N/A	100	97.5	98.3	97.7	97.8	97.2	97.7	98.0
D/T symptom onset	22.2	82.4	66.7	85.4	86.7	91.5	93.1	84.8	89.3
D/T arrival 1st hospital	22.2	81.9	54.2	43.2	39.3	47.8	39.3	40.6	55.5
D/T arrival PCI hospital	5.5	63.7	49.2	67.9	76.9	81.2	85.7	83.6	78.3
PCI Hospital Outcome	32.7	94.9	86.0	92.4	90.2	90.3	97.9	89.6	87.4

As expected the age and sex data are fully complete. Several of the variables show very high completion rates overall, these being pre-procedural cardiogenic shock, procedure priority, coronary vessel(s) attempted, date/time of first balloon inflation, and the consultant responsible. Those which show relatively low data completion rates were discharge date, patient weight, date/time of arrival at first hospital, date/time arrival at PCI hospital. It should be noted that in 2015 for some variables there is a reduction in completion rate that could be explained by staff not completing fields by the time the data was provided for this Thesis. For example, the latest month in the 2015 data is March and therefore there may have been some patients not discharged, or at least there discharge date was not completed and recorded in the data immediately thus why a drop from 85% in 2014 to 77% in 2015 exists. In some cases an apparent low data completion rate such as the date/time arrival at first hospital can be explained by the fact that it is required for 'ACS PCI Types' however, this is explained by the fact than patients with an ACS type since the third quarter of 2009 are sent directly to the ECTC, therefore this is somewhat overridden by the date/time arrival at first PCI hospital variable, which exhibits a much higher data completion rate compared to the former, at 55.5% and 78.3% respectively. Other variables completion rates can also be related to the type of priority, for example, the patient weight variable although it exhibits a sudden rise from 37.7% in 2014 to 68.7% in 2015, this would mostly be completed in elective patients. For emergency procedures the planning and information about a patient (i.e. from their general practitioner) is scarcer relative to the elective counterparts, which is why weight would be missing.

ECTC Data Completion Profile Compared to Other PCI Centres

The BCIS audit reports, provide statistics from the UK PCI centres allowed comparisons to be made between the ECTC PCI profile (patients and procedure characteristics), other national centres, and the national averages for certain variables and data completion rates. By having data available allowing certain comparisons between centres it can reveal information about how closely patients and procedures match, and possibly explain differences in outcomes, for example if a centre had an overall very high rate of emergency/STEMI patients versus another centre which exhibited a very high rate of elective/stable patients then the anticipated difference in overall adverse outcomes would be easily deduced simply by procedure priorities. In summary, these comparisons using audit data allow more accurate comparisons and conclusions to be made with regards to certain outcomes.

In the PCI audit report (BCIS Audit Report 2014) the ECTC is listed on various figures as 'BAS' and its data completion is classified as 'Almost Excellent' with only the following fields exhibiting a completeness below 90%.

- Medical history – 88.14%
- Renal disease – 85.49%
- Weight – 40.3%

Approximately 62% (2000) of the ECTC PCIs were performed on ACS patients. This is slightly below the national average of 65.1% (BCIS, 2014). Of the 119 UK PCI centres, only seven of these perform a greater number of PCIs on ACS patients than the ECTC. The entire ECTC cohort of PCI patients are on average older at approximately 65.6 years compared to the national average of 65.1 years.

Data Accuracy/Validity

When analysing the ECTC CVIS dataset it was important to consider accuracy, validity, and completeness of data. If such considerations were ignored it may result in false conclusions being drawn from the data. During the undertaking of this project certain issues were discovered with some data fields, either from discussions with interventional cardiologists, or by observations of the database. It is unknown whether these issues exist at other UK centres, but if the same level of staff inputting data into the system exists, then it is likely it is not limited to the ECTC. By highlighting such issues it might prove useful in the future for educating hospital staff on what should be input in certain data fields and the use of having accurate and complete data for risk prediction models. Several methods exist for handling missing data such as multiple imputation, whereby an unknown/missing variable is predicted by using multiple others that show a high association as detailed for its usage by Sterne et al. (2009) for epidemiological and clinical research usage. This technique was considered for usage where appropriate in the analysis of the ECTC CVIS data for this thesis.

Many of the input fields relating to procedures are drop down boxes and therefore feature a limited number of possible values for selection (e.g. 'yes', 'no', blank) thus avoiding free text problems such as 'y','yes','Y','YES', all representing the same value 'yes' in the data.

Within the database, there is a field that represents medical notes/history for each patient's procedure. This field is free text and therefore among difference operators, consultants and staff this has many different formats, and short-hand words thus making automatic extraction very difficult.

Examples of such a notes issue are the pre-procedural patient symptoms, pharmacological therapies administered, cardiovascular disease present in relatives, etc. For this reason, and the fact that the medical notes could contain confidential information (i.e. patient names etc.) this was not available in the dataset for analysis.

Detailed information relating to the procedure is also displayed on a discharge letter, and other documents, one of which features a graphic diagram of the coronary arteries and the location of the lesions detected, and subsequently where the stents (if applicable) have been inserted. Some of the information in the discharge letter and other documents are also free text and therefore is not specifically listed in any separate data field.

It has been made known from some of the interventional cardiologists at the ECTC that certain data fields within CVIS may not be correct in the sense that the field might only be set to 'Yes' if the patient experiences/has a certain characteristic. Therefore in some cases instead of entering 'No' the field is left blank. Two common examples of this are cardiogenic shock (pre-procedural), and ventilation (pre-procedural) both of which are associated with the emergency/STEMI patients. In these cases because both these conditions are very important, for analysis the blank fields are interpreted as 'No' as recommended by the ECTC staff that were consulted with.

For the coronary 'vessels attempted' field it was determined that there were differences in how graft vessels treated were stored. For example, if the PCI was being performed on a graft vessel during the procedure then the 'vessels attempted' field should include the value 'Graft(s)' to indicate this. The actual graft vessel to which the PCI was administered to had to be identified from another field (not originally available in the provided dataset), this was the 'Events' field, which would list details such as 'PCI to RCA Graft', in a small percentage of cases with Graft(s) listed it was found that the value also listed the graft vessel beside the 'Graft(s)' value, e.g. 'Graft(s), RCA', however this in most cases would represent multi-vessel PCI, whereby the 'RCA' native vessel is different from the graft vessel being treated. These were manually corrected by reading the 'Event' and 'Event failures' fields for the correct graft vessel (if it existed).

An issue with the 'Devices' field was identified whereby it listed every device used/planned to be used during the procedure (i.e. stent, balloon catheter, sheath, and guide wire) regardless of whether it was inserted into the patient, i.e. if a stent did not get inserted due to not being able to bypass/penetrate the lesion, it would still be listed in this field. To remedy this issue, the field was cross referenced with the following fields: 'stents used'; 'stents successful'; and 'event failures'.

Where available the body mass index (BMI) was calculated (NHS BMI Calculator, 2016) using the patient's weight and height by dividing the weight in kilograms (Kg) by the height in metres, squared. In the CVIS dataset the patient's height and weight at the time of their procedure is stored in centimetres (cm) and kilograms respectively. It was determined that a small proportion of records (< 1%) displayed unusually high or low values for either one of both of the weight and height fields. The cause of this was due to staff inputting the values in the incorrect measurement type (e.g. pounds or stone instead of kilograms), or inputting the decimal place incorrectly (e.g. 18.2 cm instead of 182 cm), these are clearly erroneous and were manually amended to the value assumed to be correct. Similar issues were found with the weight field. Without amending these erroneous values, this affected the calculated BMI metric.

During the initial basic analysis of the dataset, suspiciously long length of stay (LOS) durations where discovered, i.e. this is supposed to represent the interval in days between the operation date and the discharge date. Usually for elective patients presenting with low-risk conditions such as stable angina, they are discharged the same day or the following day. Critically ill patients such as those treated with primary PCI (PPCI) for STEMI, they may be expected to have longer LOS, of a few days. The only factor in the dataset which helped explain certain long LOS intervals was the presence of certain PCI complications. It was determined that several records had a discharge date that had more than likely been incorrectly input. For example, a PCI procedure may have been performed on 16/06/2009 and the discharge date was set to 17/06/2010, thus resulting in a LOS of 366 days, the discharge date should have however been set to 17/06/2009, thus being a single day LOS. Where an error in the input date was likely, thus was manually changed in the dataset after first having been confirmed using the CVIS front-end to view the discharge letter details.

Another important point to consider in the interpretation of the data was that comorbidities were not backdated (and correctly so), for example, if a patient underwent a PCI in 2009 and their diabetes status was unknown, then they came back in 2012 for another PCI but their diabetes status had in this interim been tested (positive), then only the 2012 PCI data would have diabetes listed in medical history, and not the 2009 data, even though technically the patient may have been diabetic during the 2009 procedure.

In a very small number of records (< 0.1%) the priority was unknown because despite being transferred from another hospital (before September 2009 when the ECTC started the primary care activation pathway) it was unknown whether these patients were classified as urgent or emergency due to the use thrombolytic agents provided elsewhere

and the duration since their myocardial infarction. They may have been classified as emergency patients when they arrived at another hospital, but when they were transferred to the ECTC the condition may be been downgraded to urgent.

3.3 Ethical Approval

The data used for this Thesis was provided following the ethical approval granted by the Solihull Research Ethics Committee (REC) after the submission of an application through the Integrated Research Application System (IRAS) website. The application allowed the use and access to the CVIS database, along with subsequent publication of research findings in peer-reviewed journals. Following REC approval, the appropriate authorisation was granted by the Basildon and Thurrock NHS University Foundation Trust. The procedure records were anonymised prior to access so that no patient-identifiable information was available or used, i.e. no names, addresses, contact details, date of births, or any other identifiers were ever provided. The REC reference number for the granted ethical approval is 13/WM/0289.

3.4 Statistical Analysis

Integer variables such as the patient age (in years) are expressed using the mean and standard deviation (SD), and discrete variables such as the patient age group are represented as a percentage. Univariate analysis was performed to identify which variables in the dataset, comprising demographic, procedural, clinical were significantly associated (i.e. $p < 0.05$ unless stated elsewhere) with the outcomes featured in this thesis (in-hospital MACE, 30-day mortality, and three-year repeat revascularisation or death). Nominal variables were analysed using chi-square tests of Fisher's exact test where appropriate, and continuous data was tested using the Student's t-test. The odds ratios, corresponding 95% confidence limits, and significance values were calculated for each variable and displayed in a column for each corresponding univariate association table displayed in the results sections.

The variables from the univariate association analysis that exhibited a *p* value that was considered statistically significant, in addition to those considered clinically important predictors, were used as candidates for entry into subsequent multivariate logistic regression analysis (Sperandei, 2014), using the forward stepwise selection technique. This uses the Wald test to assess whether the presence of the candidate variable significantly contributes to the model whilst also controlling for covariates already accepted into the model. This is done by dividing the coefficient of the candidate by its standard error, then retaining the variable as a risk factor if the significance is $p < 0.05$. By using the Wald test, it reduces the likelihood of candidate predictors incorrectly being regarded as significant by statistical chance (i.e. type I errors), and hence avoids potential incorrect conclusions about which characteristics are truly associated with the measured outcome. At the end of this regression analysis, only the variables that contain a significant relationship with the outcome should be retained. The Wald test is one of the available correction tools incorporated into the statistical analysis software package (SPSS) that used for the analyses in this thesis. The assumptions for the logistic regression analysis (Burns & Burns, 2009) in brief are: no linear association between the dependent and independent variables; dependent variable is dichotomous/binary (i.e. one of 2 categories); no assumptions of normal distribution, equal variance, or linear relationships in the independent variables; the independent variable groups must be mutually exclusive (i.e. a patient can only be in a single age group, not multiple); large sample databases are requirement for analysis in order to produce stable estimates.

Multicollinearity

When creating multivariate regression models it is important to detect variables which exhibit high collinearity and multicollinearity with others in the same model and to handle this appropriately. Multicollinearity will always be present however the degree to which must be investigated to determine whether this causes any issues, in some cases even small levels has the potential to cause problems. It occurs when two or more of the predictor variables in the model are correlated with each other such that it is difficult to determine each individual predictor's effects on the dependent variable alone, hence making the model less accurate along with the statistical power of the estimates whilst making the standard error large. In an ideal risk model the predictors should possess a strong variance with the dependent (outcome) variable but a low variance with each of the other predictors.

A simple potential indicator of high multicollinearity is to iterate through each predictor and remove/drop it from the model whilst retaining all others and observe any large changes in the estimated regression coefficients. Ideally for a model with low multicollinearity, these changes should be minute. Whilst there is no gold standard, there are two collinearity diagnostic measures (Baguley, 2012) which can be used to identify how severe the issue of multicollinearity is. These are tolerance and variance inflation factor (VIF). The tolerance statistic in brief represents the amount of unique information which a given predictor is responsible for in the regression model. The tolerance value itself in essence reports the amount of information the multicollinearity is responsible for in the analysis. It is calculated using the proportion of a predictor's variance which overlaps with the other predictors; this is then subtracted from 1.0. If other predictors in the model explain 65% of a predictor's variance then the tolerance value of that predictor is 1.0 – 0.65 = 0.35. If the calculated tolerance value is 0.35 this means that the predictor estimates and their corresponding confidence intervals are using only 35% of the available information to explain the dependent variable. The perfect tolerance value would be 1.0 although this unlikely in the real world, as this would indicate no multicollinearity for the predictor at all, conversely the worst value would be 0.0 or any values close to this, indicating a strong level of multicollinearity. The VIF in brief, is the factor which the sample size needs to increase to be considered free from multicollinearity, for example, if the VIF were 2.7 then this means a sample size 2.7 times greater than the actual one used in the multiple regression analysis would be needed to overcome the level of multicollinearity. The VIF is calculated by 1/tolerance, for example if the tolerance were 0.35 then the VIF would be 1/0.35 = 2.86.

In this thesis, unless otherwise stated a VIF ≥ 4.0 and/or a tolerance < 0.2 were considered indicator threshold values for concern regarding multicollinearity (Van Steen et al., 2002) and thus warranted attention in how to handle the issue.

There is no gold standard for how to handle predictors which exhibit a low tolerance value or a high VIF. Several approaches exist and are widely used however no method is perfect, each has its own limitation. One method is to simply remove/drop the predictor (or one of) however this can be argued that it is hiding the issue rather than actually solving the problems caused by the multicollinearity, and it could be misleading when testing any hypotheses about predictors. Secondly the predictors can be combined or transformed as done by factor analysis, by either adding or average the predictors, this obviously cannot be done if the majority of the dataset contains nominal variables. Using weightings or the difference between predictors can also be utilised. The other method is to simply leave the predictors which exhibit high multicollinearity in the model and report this in the accompanying literature whilst stating more data is desired to distinguish the individual effects apart effectively, as small samples sizes cause poor estimates of the individual effects.

Software

Data were analysed using the statistical analysis software SPSS for Windows, release 20.0.0 (IBM Corp., 2010).

3.5 Risk Prediction Model Testing

Multivariate logistic regression risk prediction models have three widely reported measures that can be used to assess and compare their performance levels, these are discrimination, calibration, and pseudo R^2.

Discrimination

Two important measures for binary/dichotomous classification tests are sensitivity and specificity. In the context of this thesis the sensitivity, also known as the true positive rate (TPR), is the percentage of patients which are correctly classified as experiencing a given outcome (e.g. in-hospital MACE, or 30-day mortality, or repeat revascularisation within three years). The specificity, also known as the true negative rate (TNR), is the percentage of patients which do not experience the outcome and have been correctly predicted as not. The false positive (FP) measurement refers to the patients that did not experience the outcome which were incorrectly predicted to, and conversely the false negative (FN) measurement is the patients which experienced the outcome but were incorrectly predicted not to. The equations for both measures are as follows:

Equation 1. (Sensitivity)

$$\text{Sensitivity} = TP / (TP + FN)$$

Equation 2. (Specificity)

$$\text{Specificity} = TN / (TN + FP)$$

Clearly the ideal risk prediction model would have both 100% sensitivity and specificity (i.e. only true positives and true negatives) although this is highly unlikely in the real world of clinical medicine, especially when related to mortality prediction following a given procedure. The effect of having a poor sensitivity and specificity could be the failure to provide the correct type of treatment to a patient.

With these measures there is a trade-off, one commonly used technique to visualise this and identify an optimal cut-off is the receiver operator characteristic curve (ROC), specifically the measurement of the area under the curve is reported (AUROC). The ROC curve itself is a plot of the sensitivity (TP rate) against 1-specificity (FP rate) (Hanley & McNeil, 1982; Park et al, 2004). Any test which produces an equal rate of TP and FP

would display a 45° diagonal from the origin. The optimal cut-off point on a ROC curve is the point closest to the upper left corner, i.e. the highest sensitivity and lowest FP rate, this will yield the largest AUROC. The usage of the AUROC statistic can be used to compare different risk prediction models; generally the one which yields the higher AUROC would be preferred (Hajian-Tilaki, 2013).

The AUROC will be in the range from 0.5 to 1.0 whereby the latter is desired, and the former shows a poor performance that is no better than randomly guessing/classifying a patient's predicted outcome. Whilst the AUROC ranges depend on the type of prediction model and the outcome used, other peer-reviewed literature have suggested the following ratings for the AUROC ranges (Metz, 1978; Obuchowski, 2003; Ludemann et al., 2006).

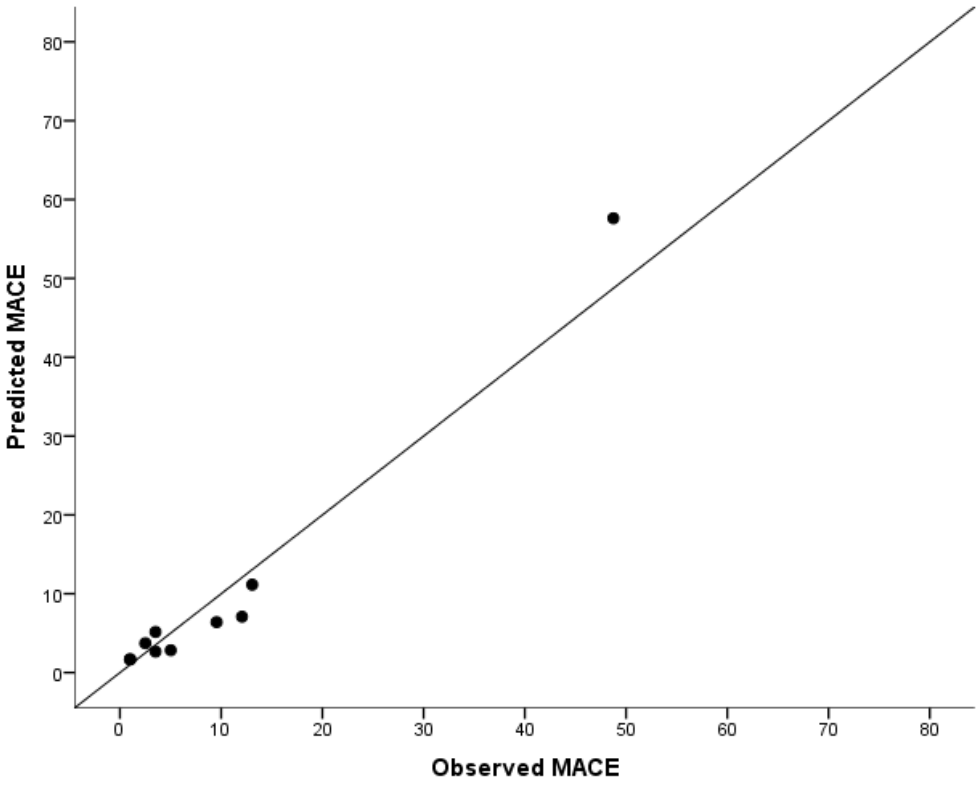
- 0.5 to 0.6 – Failed
- 0.6 to 0.7 – Poor
- 0.7 to 0.8 – Fair
- 0.8 to 0.9 – Good
- 0.9 to 1 – Excellent

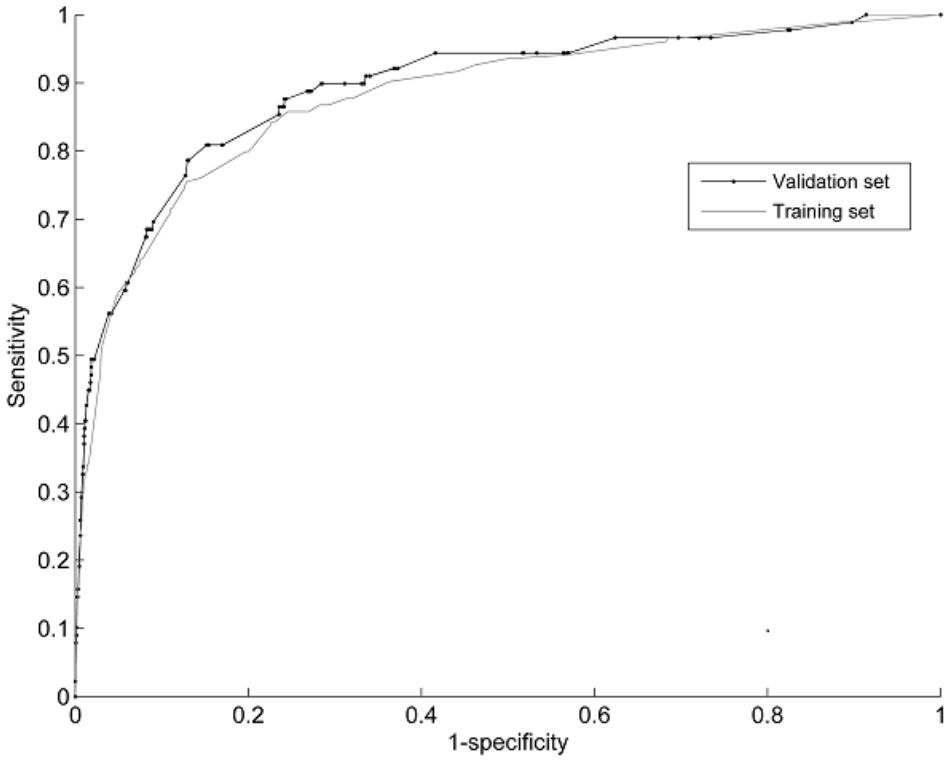
Calibration

The calibration refers to how well the observed and estimated outcomes rates match across different risk groups. Typically, from the estimated outcome probabilities, patients are ordered by ascending risk and placed in one of several risk equally sized (if possible) groups (e.g. eight). A goodness of fit test (Hosmer & Lemeshow, 2013), commonly the Hosmer-Lemeshow test, which is an extension of the chi-square test it used for logistic regression model goodness of fit testing. The test produces an overall significance value, i.e. a p value for which values lower than 0.05 indicating a large deviation between observed and estimated rates. The closer the p value is to 1.0, the better the calibration. A risk model that has a $p = 1$ means across every risk group, the observed and estimated outcome rates are identically matched, this is obviously unrealistic to achieve using real world data.

An example of a calibration plot and ROC curve example are displayed in Figure 3.5.1.

Figure 3.5.1 – calibration plot (top); and ROC curve (bottom)





The perfectly calibrated risk model would see all data points fall across the line (y = x), and for the ROC curve, the closer the line to the upper left corner, the better the discrimination performance.

3.6 General Data

Listed below are the details of the basic descriptive statistics of the entire PCI dataset (n = 15,865) by year of PCI. By visualising differences in demographic, clinical, and procedural characteristics over time, certain trends may be identified about the PCI patient cohorts in modern times. All figures and tables in section 3.6 display percentages relative to the non-missing data unless otherwise stated.

3.6.1 PCIs by year

Table 3.6.1 and Figure 3.6.1 display the total number of PCIs performed each year at the ECTC from 2007 to 2015 (2007 and 2015 are partial years).

Table 3.6.1 – PCIs by year

Year	Count	Percentage
2007	162	1.02%
2008	1708	10.77%
2009	1980	12.48%
2010	2303	14.52%
2011	2440	15.38%
2012	2351	14.82%
2013	2198	13.85%
2014	2260	14.25%
2015	463	2.92%

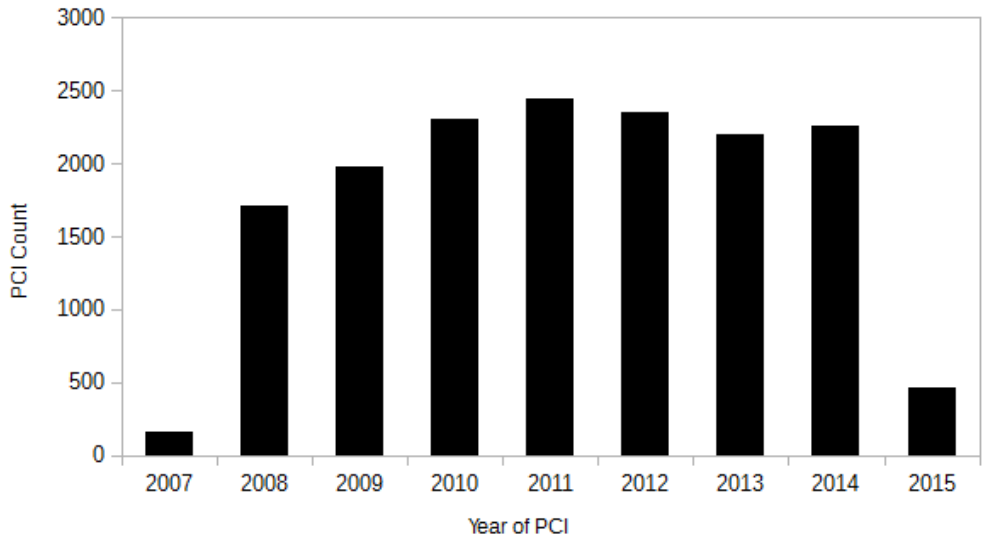


Figure 3.6.1 – PCIs (frequency) by year

The number of PCI procedures performed at the ECTC peaked in 2011 wherein 2440 were carried out. This has seen a slight decrease in successive years. This could be for a variety of reasons such as faster diagnosis of CVD by general practitioners and hence some patients could be treated with pharmacological therapy at an earlier stage in their disease progression and hence avoid the necessity of having a PCI, although this is just one possible explanation.

3.6.2 PCIs by yearly quarter

Table 3.6.2 and Figure 3.6.2 show the quarterly breakdown of PCIs (January-March, April-June, July-September, and October-December). This allows identification of whether certain periods within the year show increased rates of PCIs performed. Years 2007 and 2015 have been excluded from the figure because they are partial years.

Table 3.6.2 – PCIs by yearly quarter

Year	Q1	Q2	Q3	Q4
2007	-	-	134	62
2008	367	429	437	475
2009	457	456	518	549
2010	575	563	552	613
2011	600	622	609	609
2012	597	595	577	582
2013	581	519	535	563
2014	538	536	618	568
2015	463	-	-	-

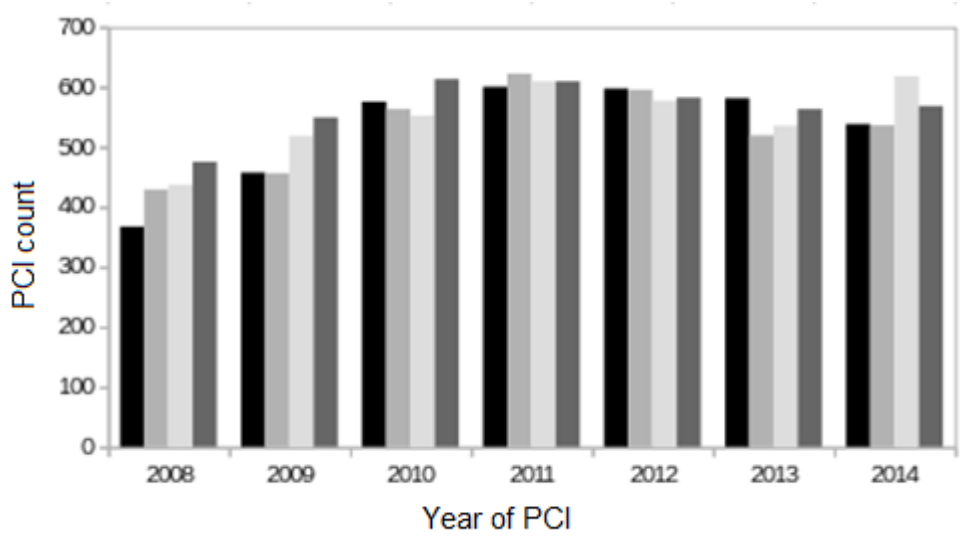


Figure 3.6.2 – PCIs by yearly quarter (bars from left to right: Q1, Q2, Q3, Q4)

There is little variation in breakdown by quarter however 2008, 2009, and 2014 show a slight increase in the number of PCIs performed in the last two quarters of the year.

3.6.3 PCIs by Priority

Table 3.6.3 and Figure 3.6.3 details the breakdown by PCI year and procedure priority (elective, urgent, or emergency).

Table 3.6.3 – PCIs by priority

Year	All PCIs	Elective (%)	Urgent (%)	Emergency (%)
2007	162	127 (83%)	23 (15.0%)	3 (2.0%)
2008	1708	1103 (64.6%)	400 (23.4%)	204 (12.0%)
2009	1980	844 (42.8%)	724 (36.7%)	406 (20.6%)
2010	2303	935 (40.7%)	619 (26.9%)	745 (32.4%)
2011	2440	977 (40.0%)	680 (27.9%)	783 (32.1%)
2012	2351	919 (39.1%)	680 (28.9%)	752 (32.0%)
2013	2198	879 (40.0%)	613 (27.9%)	706 (32.1%)
2014	2260	883 (39.1%)	629 (27.9%)	745 (33.0%)
2015	463	175 (37.8%)	131 (28.3%)	157 (33.9%)

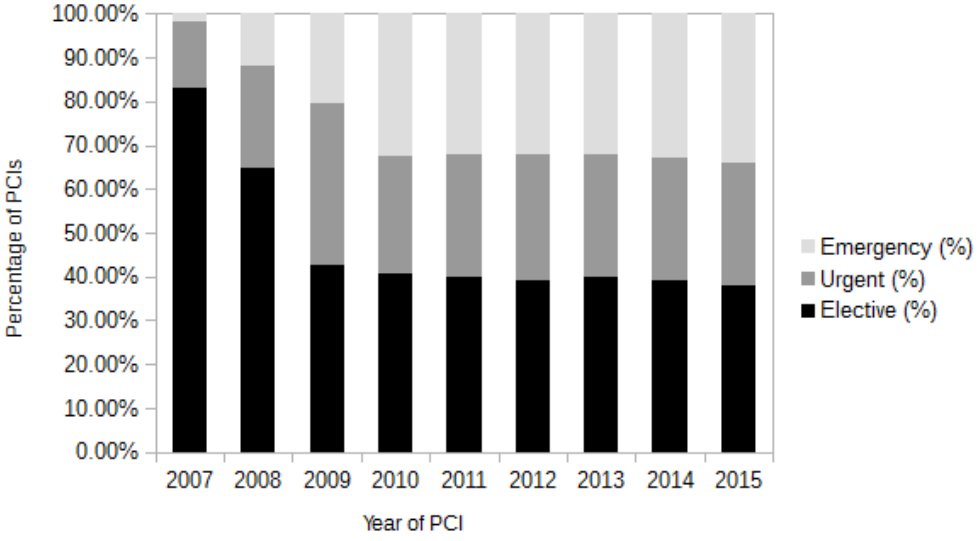


Figure 3.6.3 – PCIs by priority

The proportion of elective PCIs by year, shows an almost (excluding year 2013) year-on-year decrease from 83% in 2007 to 37.8% in 2015. A sudden jump from 64.6% in 2008 to 42.8% in 2009 can be explained by the fact that the ECTC started the primary care activation programme towards the latter part of 2009 and hence a rapid increase of emergency patients were treated. The proportion of urgent PCIs performed remains fairly stable from 2010 (26.9%) to 2015 (28.3%).

3.6.4 Indication for PCI

Table 3.6.4 and Figure 3.6.4 represent the breakdown of PCIs by the indication (or reason), these are classified into one of four categories: (1) STEMI; (2) Unstable angina/NSTEMI; (3) Stable angina; (4) Other.

Table 3.6.4 – Indication for PCI

Year	STEMI	NSTEMI/UA	Stable	Other	STEMI (%)	NSTEMI/UA (%)	Stable (%)	Other (%)
2007	0	3	26	2	0.00%	9.68%	83.87%	6.45%
2008	13	436	1101	156	0.76%	25.56%	64.54%	9.14%
2009	260	773	810	95	13.42%	39.89%	41.80%	4.90%
2010	661	646	897	59	29.21%	28.55%	39.64%	2.61%
2011	652	770	962	26	27.05%	31.95%	39.92%	1.08%
2012	646	730	897	16	28.22%	31.89%	39.19%	0.70%
2013	601	699	873	17	27.44%	31.92%	39.86%	0.78%
2014	654	697	834	13	29.75%	31.71%	37.94%	0.59%
2015	127	141	155	4	29.74%	33.02%	36.30%	0.94%

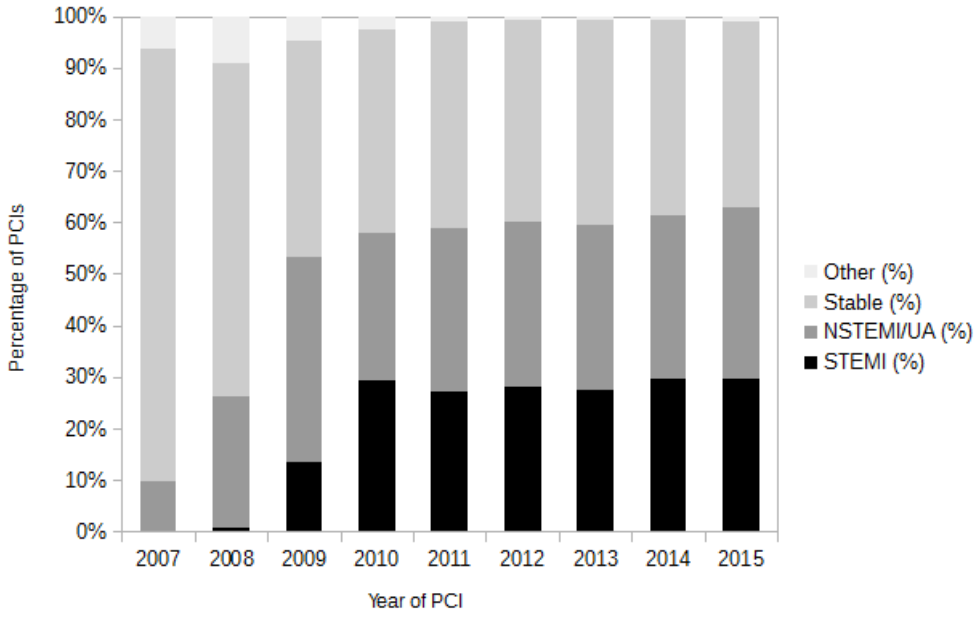


Figure 3.6.4 – Indication for PCI

As expected, in 2009 there is a sudden rise in the proportion of PCIs for the STEMI indication from 0.76% in 2008 to 13.4% in 2009, and again to 29.21% in 2010, this as previously mentioned is when the ECTC started treating STEMI patients directly on its primary care activation programme. The proportion of urgent patients or those with non-ST elevation myocardial infarctions/unstable angina has remained fairly consistent from 2010 (28.6%) to 2015 (33.0%). Again, the number of stable PCIs has decreased almost year-on-year from 83.9% in 2007 to 36.3% in 2015, which as previously explained could

be simply explained by a sudden increase in emergency patient numbers and hence rates thus amending the relative proportions.

3.6.5 Average patient age

Table 3.6.5 and Figure 3.6.5 display the mean PCI patient age and standard deviation for each year.

Table 3.6.5 – Mean (SD) PCI patient age

Year	Age (Mean)	SD
2007	64.52	10.85
2008	64.64	11.07
2009	64.78	11.70
2010	65.65	12.03
2011	66.00	11.98
2012	65.80	12.11
2013	65.29	11.99
2014	65.70	12.19
2015	65.32	12.08

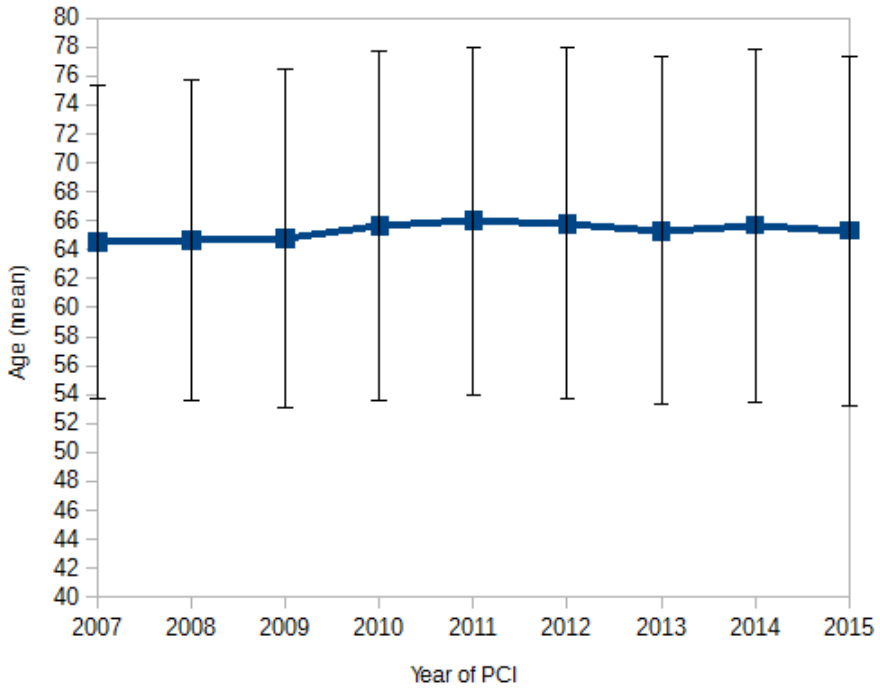


Figure 3.6.5 – Mean (SD) PCI patient age

The average (mean) age of the PCI patients remains fairly static from 2007 to 2015. The standard deviations are large therefore indicating a wide range (variation) in patient ages. There are no statistically significant differences in the mean age between any of the years.

3.6.6 Average patient age by Priority

The following table (3.6.6) and figure (3.6.6) display the mean patient age (SD) split by the priority of PCI (i.e. elective, urgent, or emergency).

Table 3.6.6 – mean (SD) PCI patient age by priority

Year	Elective	SD	Urgent	SD	Emergency	SD
2007	65.35	10.33	61.26	12.34	55.67	10.02
2008	65.33	10.55	63.87	11.83	62.30	11.86
2009	65.57	10.82	64.42	11.85	63.72	13.04
2010	66.64	10.49	65.21	12.14	64.79	13.60
2011	66.17	10.36	67.06	12.15	64.87	13.54
2012	67.02	10.90	65.67	12.31	64.39	13.15
2013	65.92	10.98	65.53	12.31	64.30	12.85
2014	66.94	11.05	66.20	12.43	63.74	12.99
2015	65.83	11.47	66.48	12.17	63.88	12.57

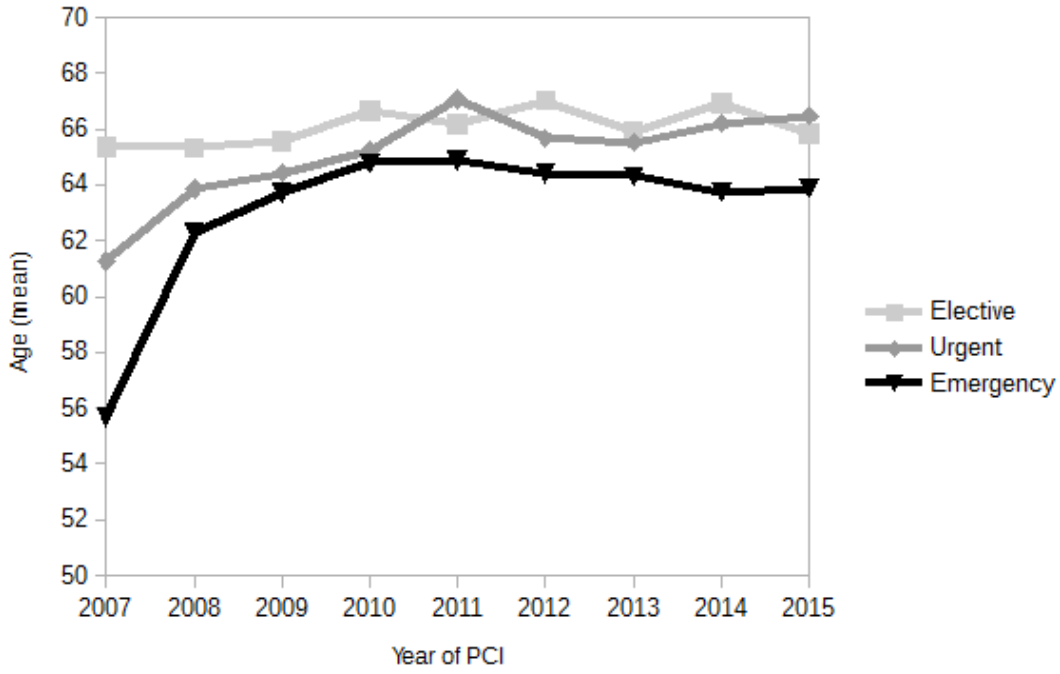


Figure 3.6.6 - mean (SD) PCI patient age by priority

When breaking the PCIs down by priority and mean patient age there no significant differences between the mean ages either within the same year versus the other priorities, or for the same priority over time. The error bars have been omitted from Figure 3.6.6. However, they are present in Table 3.6.6. Whilst not statistically significant the mean age of emergency patients is slightly lower each year than the elective and urgent counterparts. The exact reason behind this is unknown, it could be that younger individuals are more likely to survive an out-of-hospital myocardial infarction and make it

to the ECTC for emergency treatment relative to elderly individuals who might die from the myocardial infarction before an ambulance arrives, or whilst on route to the ECTC, and hence do not undergo an actual PCI.

3.6.7 Gender by Priority

The overall (all priorities of PCI) percentage of male and female PCI patients remains fairly consistent with approximately 3:1 ratio (i.e. 75% male and 25% female). Table 3.6.7 and Figure 3.6.7 break this down by the priority of PCI to identify whether there are any hidden differences at this level.

Table 3.6.7 – Gender by priority

	Elective		Urgent		Emergency	
Year	**Male (%)**	**Female**	**Male (%)**	**Female**	**Male (%)**	**Female**
2007	91 (71.65%)	36	15 (65.22%)	8	0 (0%)	3
2008	825 (74.80%)	278	293 (73.25%)	107	161 (78.92%)	43
2009	648 (76.87%)	195	545 (75.28%)	179	302 (74.38%)	104
2010	709 (75.83%)	226	456 (73.67%)	163	542 (72.75%)	203
2011	761 (77.89%)	216	496 (72.94%)	184	573 (73.18%)	210
2012	725 (78.89%)	194	491 (72.21%)	189	566 (75.37%)	185
2013	671 (76.34%)	208	463 (75.53%)	150	512 (72.52%)	194
2014	690 (78.14%)	193	461 (73.29%)	168	525 (70.56%)	219
2015	134 (76.57%)	41	95 (72.52%)	36	123 (78.85%)	33

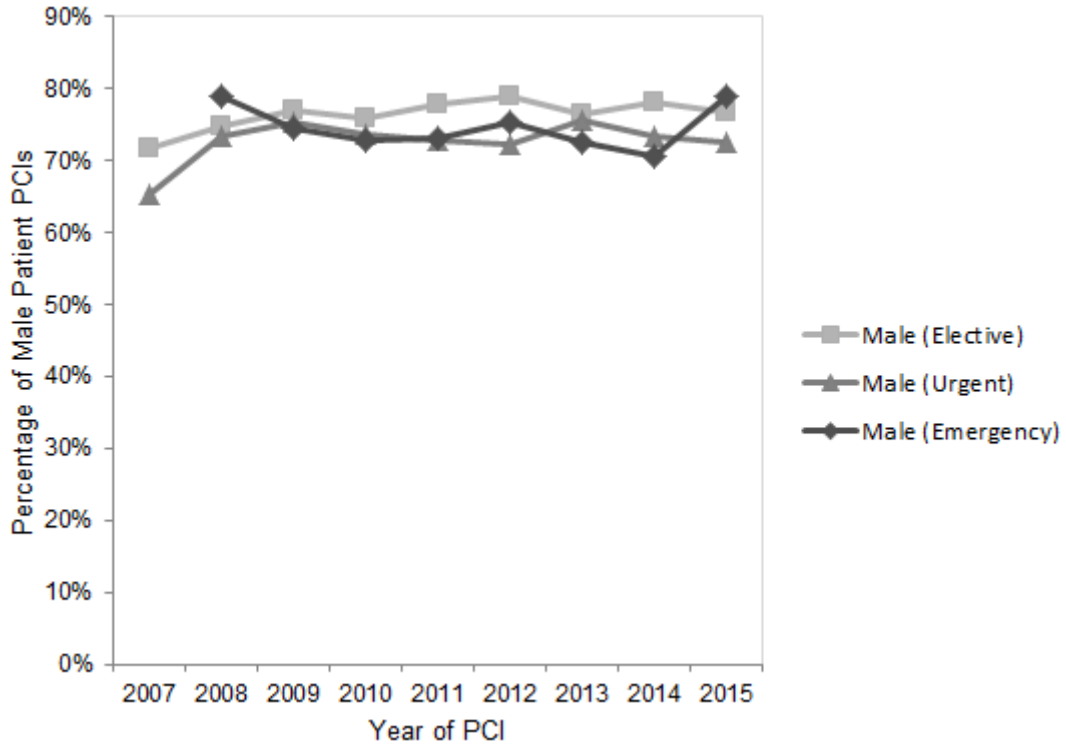


Figure 3.6.7 – Gender by priority

As previously mentioned, the emergency PCIs are low in 2007 because the ECTC only just opened and hence almost all priorities were either elective or urgent. There are no statistically significant differences in the gender proportions across time.

3.6.8 Emergency priority by PPCI vs. Non-PPCI

Table 3.6.8 and Figure 3.6.8 display the indications within the emergency PCIs, i.e. a breakdown of Primary PCI (for STEMI) versus non-PPCI (e.g. unstable angina, NSTEMI etc.).

Table 3.6.8 – Emergency priority by PPCI vs. Non-PPCI

Year	PPCI	Non-PPCI	Emergency	PPCI (%)
2007	0	3	3	0.00%
2008	13	191	204	6.37%
2009	260	146	406	64.04%
2010	661	84	745	88.72%
2011	651	132	783	83.14%
2012	646	105	751	86.02%
2013	601	105	706	85.13%
2014	653	91	744	87.77%
2015	127	29	156	81.41%

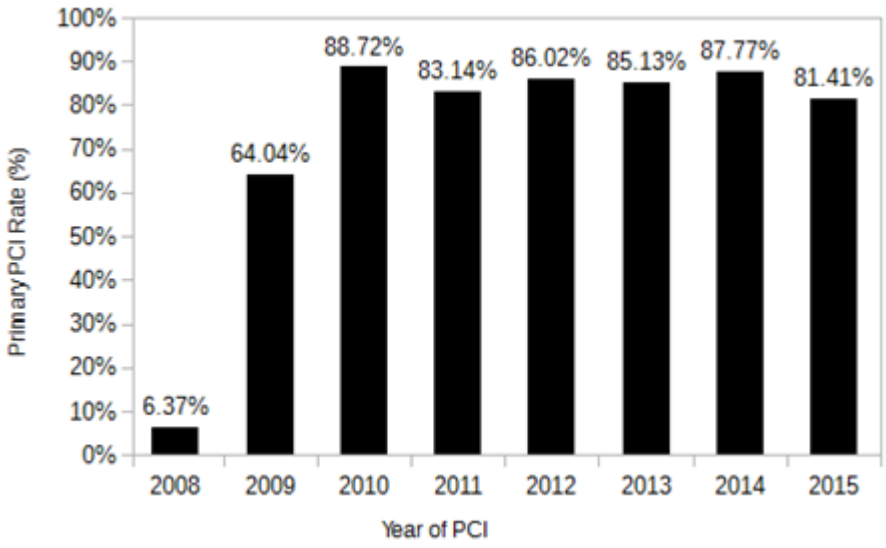


Figure 3.6.8 – Emergency priority by PPCI rates

In the third quarter of 2009 the ECTC began their primary care activation programme for treating patients with STEMI hence the sudden rise from 6.4% in 2008 to 64.0% in 2009, and the subsequent rise to 88.7% in 2010. The proportion of PPCI from 2010 onwards remains fairly constant with over four out of every five emergency PCIs being a PPCI indication.

3.6.9 Average Total Stent Length

Table 3.6.9 and Figure 3.6.9 detail the total average length of the stents which were used in the PCI procedures at the ECTC, the data represents those procedures for which at least one stent was used (i.e. PCIs with no stent usage such as standard balloon angioplasty are excluded).

Table 3.6.9 – Average total stent length (mm)

Year	Total PCIs	PCIs ≥ 1 stent	Stent used (%)	Mean	SD
2007	162	136	83.95	30.51	17.39
2008	1708	1627	95.26	31.21	20.38
2009	1980	1853	93.59	31.93	20.57
2010	2303	2126	92.31	30.9	19.45
2011	2440	2238	91.72	30.61	18.97
2012	2351	2169	92.26	30.09	19.2
2013	2198	1964	89.35	29.42	19.58
2014	2260	1994	88.23	31.48	21.24
2015	463	421	90.93	33.79	24.48

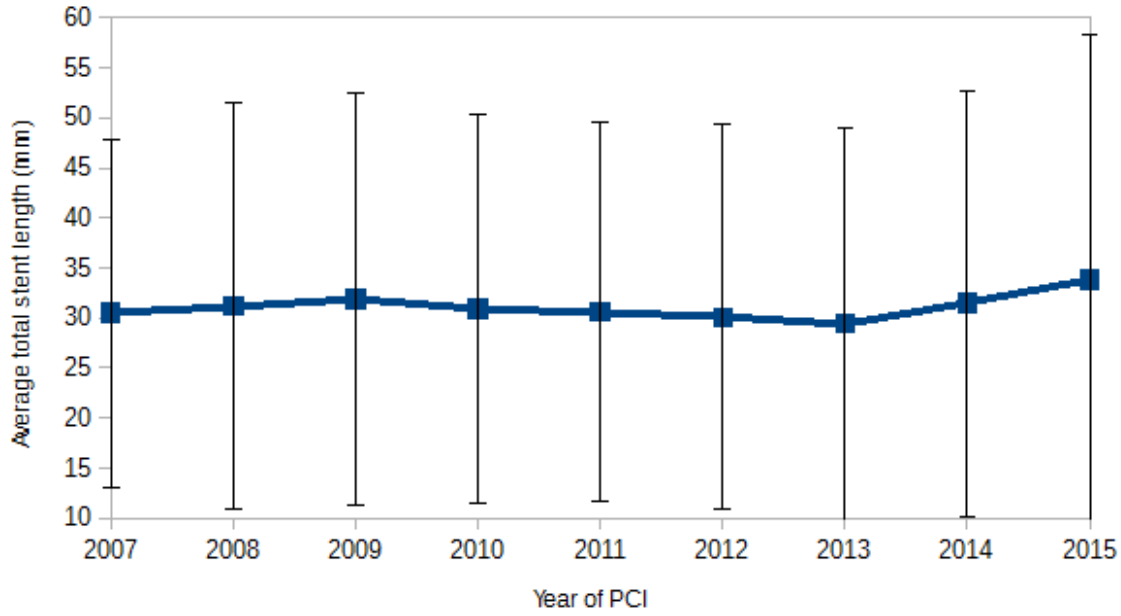


Figure 3.6.9 *– Average total stent length (mm)*

The standard deviations for all average total stent lengths are large and hence represent a wide variety of stent lengths used in the PCI procedure. There are no statistically significant differences across the years. This could mean that single-vessel PCIs are still as common as multi-vessel PCIs, if not it would be anticipated that the average total stent length increase, i.e. more vessels treated results in increased total stent length.

3.6.10 Average Total Stent Length by Priority

Table 3.6.10 and figure 3.6.10 detail the average total stent length across the three different PCI priorities to identify whether there are any differences present.

Table 3.6.10 – Average total PCI stent length (mm) by priority

	Elective			Urgent			Emergency		
Year	**n**	**Mean (mm)**	**SD**	**n**	**Mean (mm)**	**SD**	**n**	**Mean (mm)**	**SD**
2007	107	30.56	17.61	17	30.94	18.54	3	21.00	9.54
2008	1048	30.86	20.39	386	32.59	20.91	192	30.43	19.28
2009	771	33.19	21.56	705	30.93	19.81	372	31.03	19.75
2010	866	31.83	21.04	590	30.32	18.99	669	30.20	17.66
2011	909	31.21	20.69	631	30.92	18.78	698	29.53	16.64
2012	853	31.81	21.33	632	29.20	18.53	683	28.81	16.73
2013	780	31.81	23.26	566	28.30	18.24	618	27.43	14.85
2014	761	34.86	24.24	572	29.83	19.71	659	29.04	18.14
2015	161	35.66	27.88	120	36.34	26.95	139	29.59	16.37

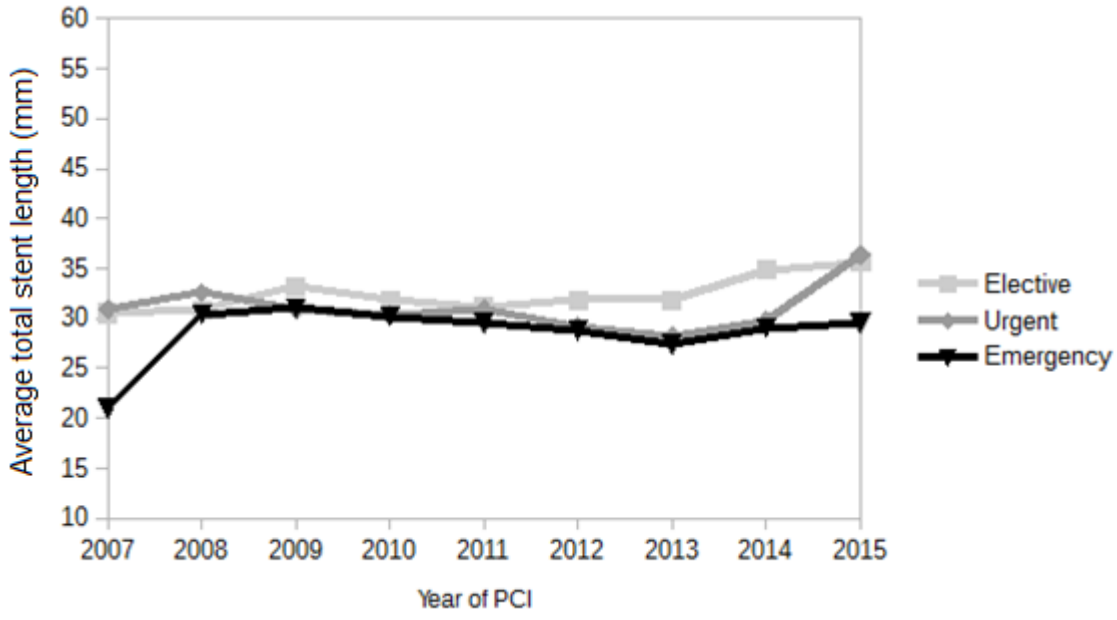


Figure 3.6.10 – Average total stent length (mm) by Priority of PCI

The mean (SD) total stent length in millimetres (mm) for elective, urgent and emergency priorities were 32.19 (21.9), 30.39 (19.52), and 29.28 (17.26) respectively. A one-way ANOVA was conducted on the total mean stent length for each priority to identify whether a significant difference in total stent length was present, $F(2,14507)$ = 27.47 and p < 0.001, this indicated a significant difference between at least one of the priorities. To further identify which groups, a t-Test was performed (assuming unequal variances) between each group: elective-urgent, $t(9693) = 4.4$, $p < 0.001$; elective-emergency, $t(9878) = 7.49$, $p < 0.001$; and urgent-emergency, $t(8202) = 2.72$, $p = 0.006$. Each group showed a significant difference in total stent length, this however is likely to be explained by the fact that emergency/STEMI patients may have a myocardial infarction in a single coronary vessel and hence only one vessel gets treated during the procedure, whereas elective patients are more likely to have multivessel PCI, because the procedure is planned in advance, and hence this may be why the mean total stent length increases between elective, urgent, and emergency priorities. Following an emergency PCI in a single vessel, lesions may be found in other coronary arteries that are not immediately considered severe enough treat, but will be scheduled for the future as an elective PCI.

3.6.11 Stent Type Used

Table 3.6.11 and Figure 3.6.11 detail the PCI procedures when classified into categories based on the type of stent used. These categories are: (1) exclusive BMS usage; (2) exclusive DES usage; (3) a combination of BMS and DES usage. The percentages displayed are relative to all PCI procedures (n = 15,865), not just the three categories (hence why they do not add up to 100%).

Table 3.6.11 – Stent Type Used

Year	Total PCIs	BMS (%)	DES (%)	Mixed (%)
2007	162	64 (39.51%)	56 (34.57%)	16 (9.88%)
2008	1708	745 (43.62%)	752 (44.03%)	130 (7.61%)
2009	1980	624 (31.52%)	1137 (57.42%)	92 (4.65%)
2010	2303	583 (25.31%)	1446 (62.79%)	97 (4.21%)
2011	2440	458 (18.77%)	1655 (67.83%)	125 (5.12%)
2012	2351	335 (14.25%)	1812 (77.07%)	22 (0.94%)
2013	2198	214 (9.74%)	1718 (78.16%)	32 (1.46%)
2014	2260	143 (6.33%)	1837 (81.28%)	14 (0.62%)
2015	463	22 (4.75%)	394 (85.10%)	5 (1.08%)

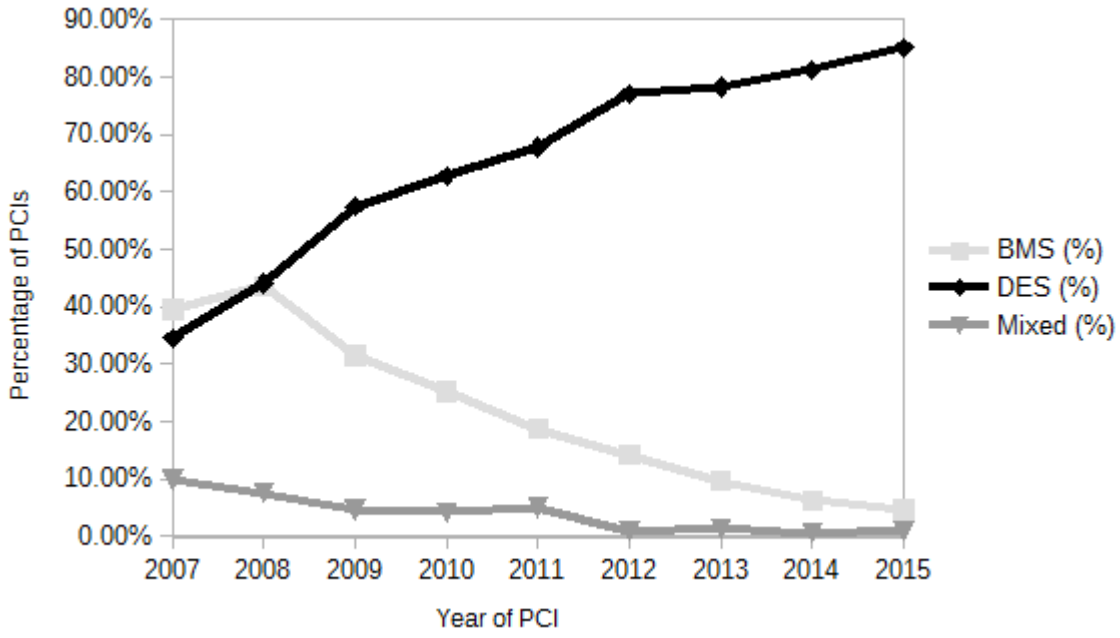


Figure 3.6.11 – Stent type used

The proportion of PCIs which feature DES exclusively increases in a linear fashion from 34.6% in 2007 to 85.1% in 2015. The opposite trend exists with BMS, whereby a high usage of 39.5% in 2007 drops almost year-on-year to 4.8% in 2015. The proportion of mixed stent procedures drops to circa 1% in 2015 from 9.9% in 2007. If the usage of BMS stents themselves are reducing then so would 'mixed' procedures. Whilst not listed here,

when the above three stent categories are broken down by PCI priority, similar trends are exhibited between the elective, urgent, and emergency groups respectively.

3.6.12 Average Minimum Stent Diameter

Table 3.6.12 and Figure 3.6.12 display the average smallest stent diameter (smallest if multiple used) used in the PCI procedure in millimetres (mm) by stent type group (i.e. BMS, DES, or mixed).

Table 3.6.12 – average minimum stent diameter (mm)

Year	Total PCIs	≥ 1 stent	DES/BMS	SD	BMS only	SD	DES only	SD
2007	162	136	2.983	0.423	3.133	0.456	2.893	0.343
2008	1708	1627	2.977	0.459	3.224	0.463	2.775	0.338
2009	1980	1853	2.926	0.449	3.191	0.470	2.803	0.375
2010	2303	2126	2.907	0.471	3.231	0.504	2.789	0.395
2011	2440	2238	2.887	0.476	3.257	0.550	2.796	0.403
2012	2351	2169	2.882	0.467	3.205	0.498	2.825	0.435
2013	2198	1964	2.891	0.479	3.304	0.556	2.842	0.442
2014	2260	1994	2.926	0.489	3.357	0.634	2.892	0.458
2015	463	421	2.911	0.499	3.545	0.751	2.876	0.458

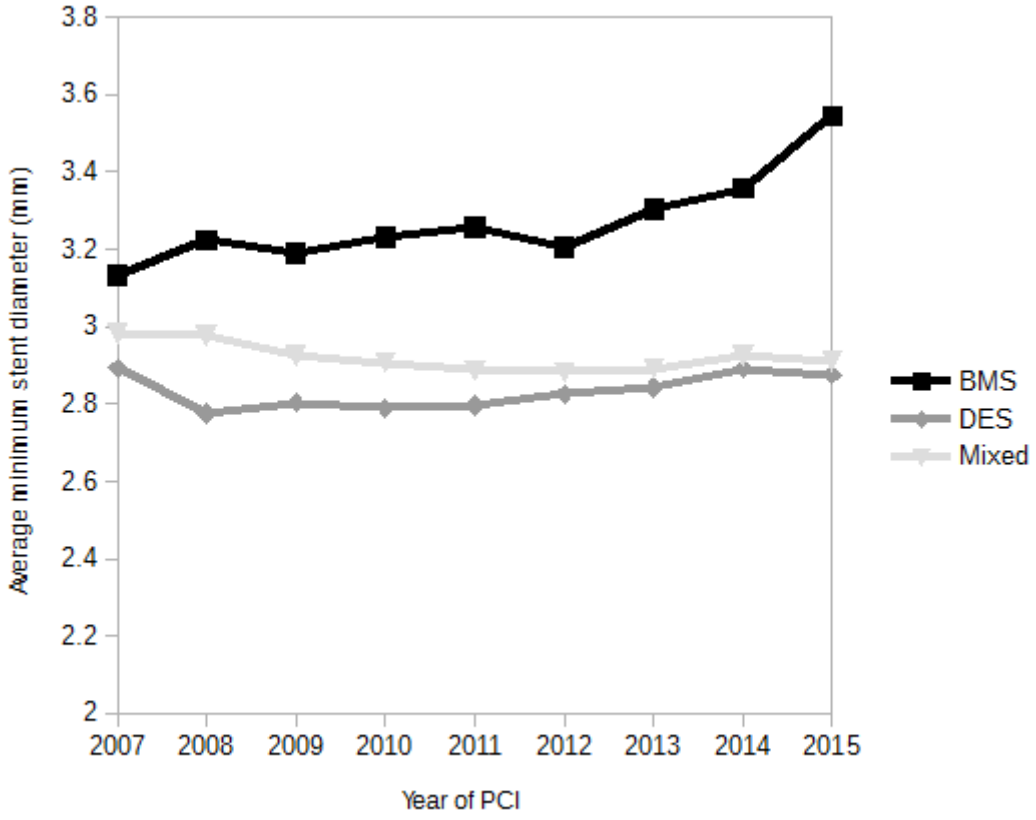


Figure 3.6.12 – Average minimum stent diameter (mm)

Whilst the SD error bars are not listed, there were no significant differences in minimum stent diameter however in general the BMS PCIs did have larger minimum stent diameters than the DES counterparts.

3.6.13 Average Minimum Stent Diameter by Priority

Table 3.6.13 and Figure 3.6.13 display the average minimum stent diameter (mm) by priority of PCI.

Table 3.6.13 – average minimum stent diameter (mm) by priority

	Elective			Urgent			Emergency		
Year	n	Diameter	SD	n	Diameter	SD	n	Diameter	SD
2007	107	2.97	0.40	17	2.96	0.35	3	3.00	0.00
2008	1048	2.95	0.44	386	2.98	0.47	192	3.13	0.48
2009	771	2.88	0.43	705	2.92	0.45	372	3.04	0.46
2010	866	2.84	0.46	590	2.88	0.46	669	3.02	0.48
2011	909	2.83	0.46	631	2.84	0.48	698	3.01	0.48
2012	853	2.82	0.46	632	2.87	0.47	683	2.97	0.45
2013	780	2.81	0.47	566	2.91	0.49	618	2.98	0.46
2014	761	2.82	0.45	572	2.92	0.51	659	3.05	0.48
2015	161	2.85	0.56	120	2.84	0.40	139	3.04	0.49

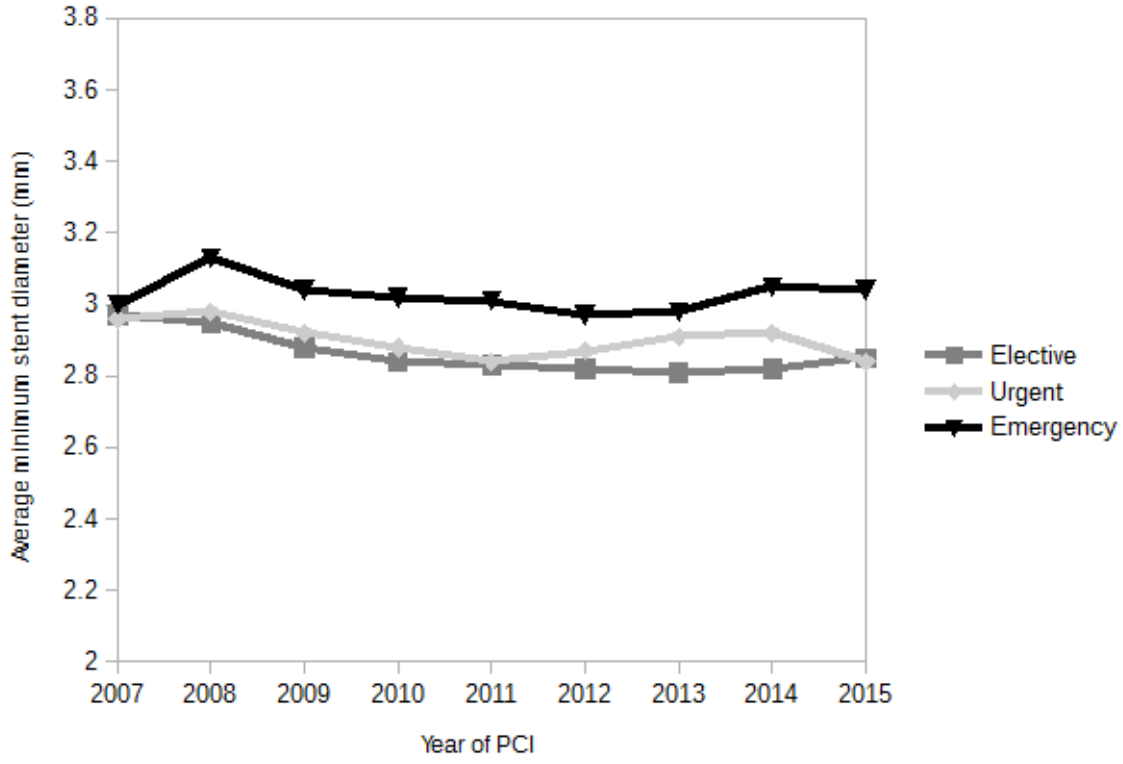


Figure 3.6.13 – average minimum stent diameter (mm) by priority

The SD error bars have been omitted for clarity, however, there are no statistically significant differences each year between any of the PCI priorities in terms of average minimum stent diameter. Emergency PCIs do in general exhibit larger average minimum

stent diameters compared to both urgent and emergency PCIs. Whilst not displayed here, when these procedures are broken down into stent type group (BMS, DES, or mixed) the BMS category in all priorities show increased minimum diameters although this too is not statistically significant. The reason for emergency showing larger diameters could be because there is not sufficient time to determine the optimal size.

3.6.14 Number of Stents Used

Table 3.6.14 and Figure 3.6.14 show the numbers of stent used for each PCI procedure within the year when classified into one of three categories: 1, 2, 3 or more stents.

Table 3.6.14 – Number of stents used

Year	Total PCIs	1 stent	2 stents	≥ 3 stents	1 stent (%)	2 stents (%)	≥ 3 stents (%)	Total
2007	162	79	31	26	48.77%	19.14%	16.05%	83.95%
2008	1708	887	427	313	51.93%	25.00%	18.33%	95.26%
2009	1980	1020	521	312	51.52%	26.31%	15.76%	93.59%
2010	2303	1209	600	317	52.50%	26.05%	13.76%	92.31%
2011	2440	1248	665	325	51.15%	27.25%	13.32%	91.72%
2012	2351	1273	598	298	54.15%	25.44%	12.68%	92.26%
2013	2198	1206	534	224	54.87%	24.29%	10.19%	89.35%
2014	2260	1233	507	254	54.56%	22.43%	11.24%	88.23%
2015	463	246	110	65	53.13%	23.76%	14.04%	90.93%

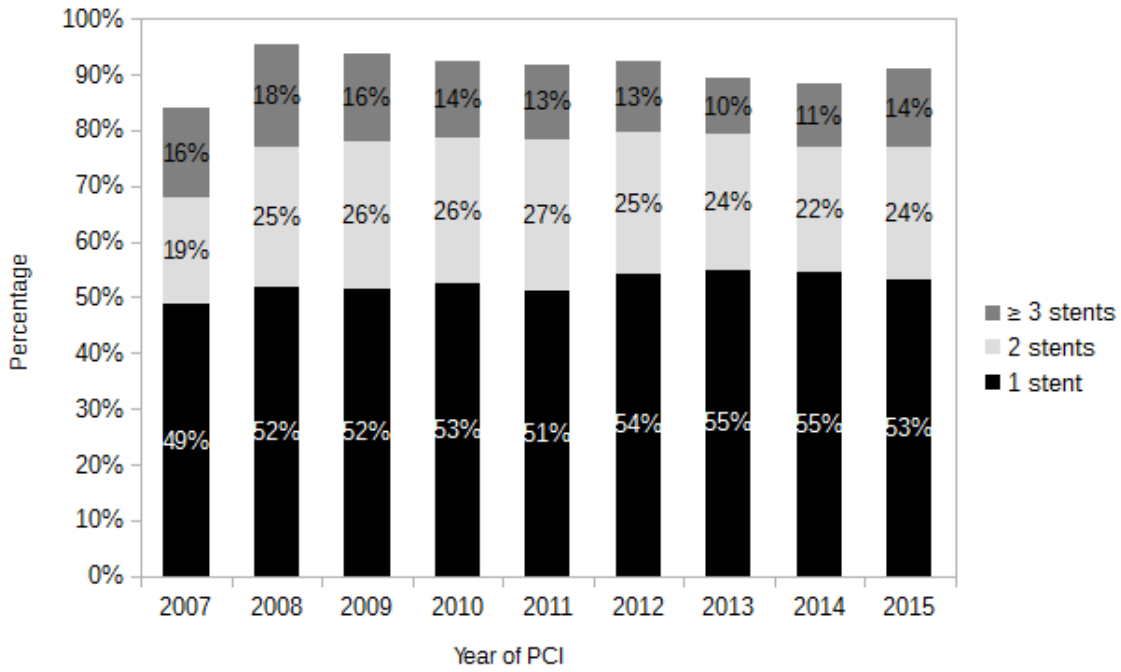


Figure 3.6.14 – Number of stents used

Throughout the years from 2007 to 2015 there has not been much of a fluctuation in the number of stents used for each PCI procedure overall. The majority of PCIs have a single stent (approx. 53%) followed by approx. one quarter of PCIs using two stents, and approx. 15% using three or more stents. A lot of the single stent PCIs for as explained previously are likely to be emergency PCIs.

3.6.15 Vessels Treated

Table 3.6.15A, 3.6.15B and Figure 3.6.15 display the coronary vessels treated. It should be noted that each represents at least one of the vessels treated this does not mean the vessel has been exclusively treated. For example, a multivessel PCI (such as RCA and LAD) would count twice, once for RCA and once for LAD.

Table 3.6.15A –Vessels treated (frequencies)

Year	PCIs	RCA	LCX	LAD	Lmain	Graft
2007	162	17	13	24	2	0
2008	1708	615	418	881	24	1
2009	1980	724	444	962	40	26
2010	2303	824	589	1076	43	28
2011	2440	893	585	1190	58	47
2012	2351	853	553	1151	61	40
2013	2198	839	486	1028	44	48
2014	2260	834	514	1078	63	35
2015	463	172	104	222	10	8

Table 3.6.15B –Vessels treated (%)

Year	PCIs	RCA	LCX	LAD	Lmain	Graft
2007	162	10.49%	8.02%	14.81%	1.23%	0.00%
2008	1708	36.01%	24.47%	51.58%	1.41%	0.06%
2009	1980	36.57%	22.42%	48.59%	2.02%	1.31%
2010	2303	35.78%	25.58%	46.72%	1.87%	1.22%
2011	2440	36.60%	23.98%	48.77%	2.38%	1.93%
2012	2351	36.28%	23.52%	48.96%	2.59%	1.70%
2013	2198	38.17%	22.11%	46.77%	2.00%	2.18%
2014	2260	36.90%	22.74%	47.70%	2.79%	1.55%
2015	463	37.15%	22.46%	47.95%	2.16%	1.73%

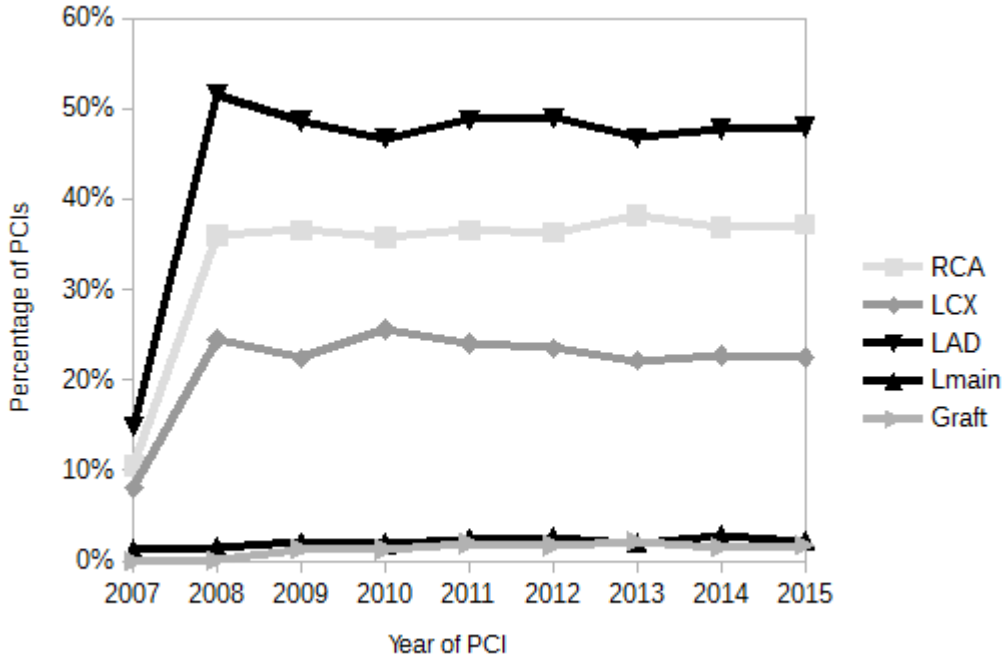


Figure 3.6.15 – vessels treated (not mutually exclusive)

The LAD was the most commonly treated coronary vessel in each year by at least 10% since 2008 with approximately 50% of all PCIs involving this vessel. The RCA is the second most frequently treated vessel with approximately 36% of PCIs treating this vessel, and thirdly, the LCX with approximately 22% of PCIs.

3.6.16 LAD Vessel by Priority

Table 3.6.16 and Figure 3.6.16 display the PCIs involving the LAD vessel being treated when broken down by PCI priority.

Table 3.6.16 – LAD vessel by priority

Year	Elective	Urgent	Emergency	Elective	Urgent	Emergency
2007	20	2	2	15.75%	8.70%	66.67%
2008	580	207	94	52.58%	51.75%	46.08%
2009	432	331	199	51.18%	45.72%	49.01%
2010	446	294	336	47.70%	47.50%	45.10%
2011	500	319	371	51.18%	46.91%	47.38%
2012	489	330	332	53.21%	48.53%	44.15%
2013	431	304	293	49.03%	49.59%	41.50%
2014	434	306	335	49.15%	48.65%	44.97%
2015	91	59	71	52.00%	45.04%	45.22%

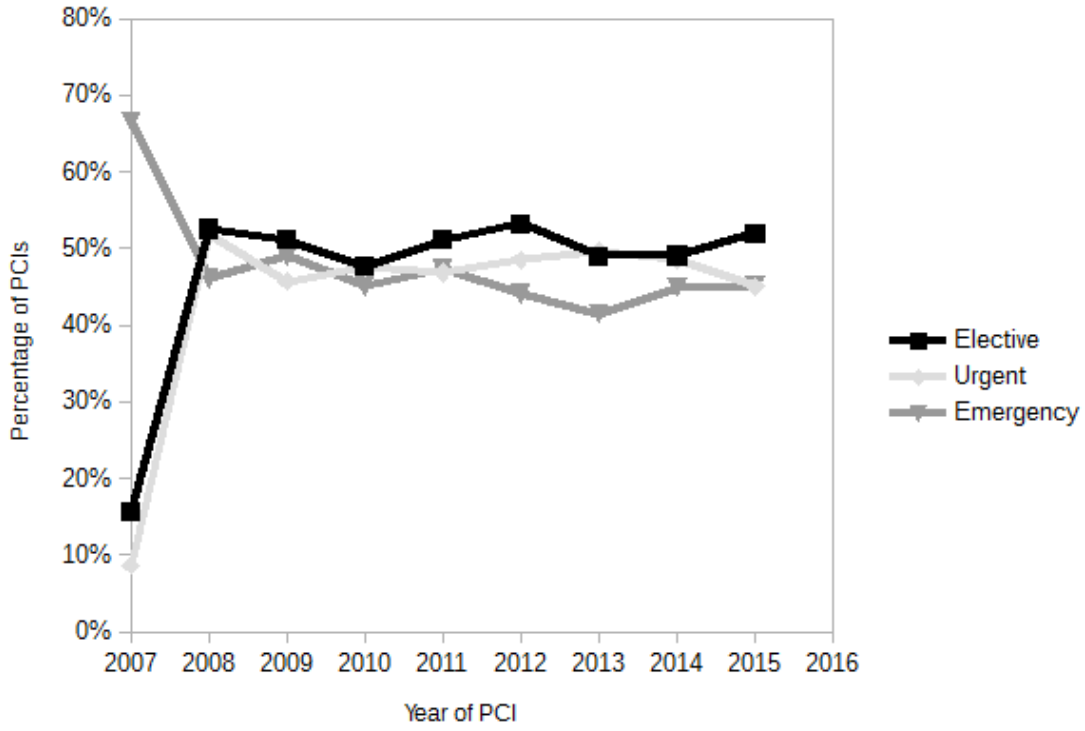


Figure 3.6.16 – LAD vessel treated by priority

From 2008 the percentage of all PCIs each year that feature the LAD vessel being treated remain fairly stable, elective PCIs in general have a slightly higher percentage treated that the other priorities. However, they all range from approximately 42% to 53%.

3.6.17 RCA Vessel by Priority

Table 3.6.17 and Figure 3.6.17 display the PCIs featuring treatment to the RCA vessel when broken down by priority of PCI.

Table 3.6.17 – RCA vessel by priority

Year	Elective (%)	Urgent	Emergency
2007	13 (10.24%)	0 (0.00%)	1 (33.33%)
2008	379 (34.36%)	147 (36.75%)	88 (43.14%)
2009	279 (33.06%)	285 (39.36%)	160 (39.41%)
2010	303 (32.41%)	211 (34.09%)	310 (41.61%)
2011	340 (34.80%)	237 (34.85%)	316 (40.36%)
2012	309 (33.62%)	223 (32.79%)	321 (42.69%)
2013	317 (36.06%)	192 (31.32%)	330 (46.74%)
2014	311 (35.22%)	206 (32.75%)	316 (42.42%)
2015	52 (29.71%)	53 (40.46%)	66 (42.04%)

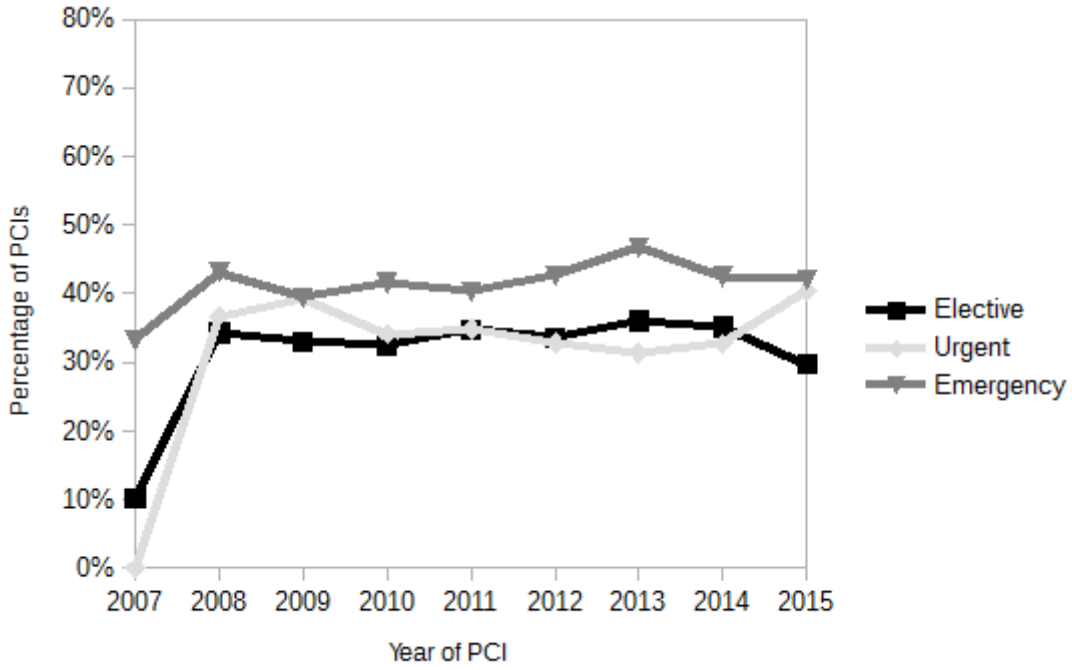


Figure 3.6.17 – RCA vessel by priority

As with the LAD, the RCA PCIs remain fairly stable over the years, however in this instance the RCA vessel has a higher percentage of PCIs under the emergency priority classification in contrast to elective as with the LAD.

3.6.18 LCX Vessel by Priority

Table 3.6.18 and Figure 3.6.18 display the third most commonly treated coronary vessel, the LCX by PCI priority.

Table 3.6.18 – LCX vessel by priority

Year	Elective (%)	Urgent (%)	Emergency (%)
2007	11 (8.66%)	2 (8.70%)	0 (0.00%)
2008	275 (24.93%)	110 (27.50%)	33 (16.18%)
2009	197 (23.34%)	190 (26.24%)	57 (14.04%)
2010	267 (28.56%)	199 (32.15%)	123 (16.51%)
2011	265 (27.12%)	207 (30.44%)	113 (14.43%)
2012	239 (26.01%)	205 (30.15%)	109 (14.49%)
2013	222 (25.26%)	162 (26.43%)	102 (14.45%)
2014	220 (24.92%)	184 (29.25%)	110 (14.77%)
2015	39 (22.29%)	43 (32.82%)	22 (14.01%)

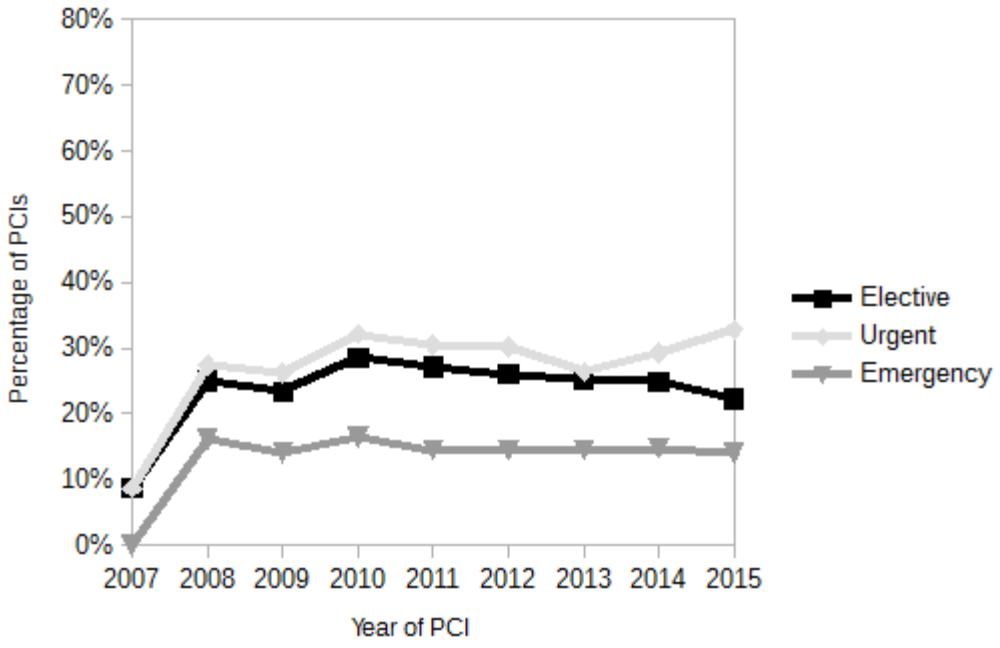


Figure 3.6.18 – LCX vessel by priority

As with the LAD and the RCA coronary vessels, the LCX PCIs remain fairly stable over the years when broken down by PCI priority. In this instance the urgent PCIs show the highest percentage treated relative to the elective and emergency PCIs

3.6.19 LMS Vessel by Priority

Table 3.6.19 and Figure 3.6.19 display the LMS PCIs by priority of PCI.

***Table 3.6.19** – LMS vessel by priority*

Year	Elective (%)	Urgent (%)	Emergency (%)
2007	2 (1.57%)	0 (0.00%)	0 (0.00%)
2008	17 (1.54%)	5 (1.25%)	2 (0.98%)
2009	21 (2.49%)	10 (1.38%)	9 (2.22%)
2010	17 (1.82%)	16 (2.58%)	10 (1.34%)
2011	24 (2.46%)	14 (2.06%)	20 (2.55%)
2012	22 (2.39%)	23 (3.38%)	15 (1.99%)
2013	15 (1.71%)	15 (2.45%)	14 (1.98%)
2014	29 (3.28%)	23 (3.66%)	11 (1.48%)
2015	4 (2.29%)	3 (2.29%)	3 (1.91%)

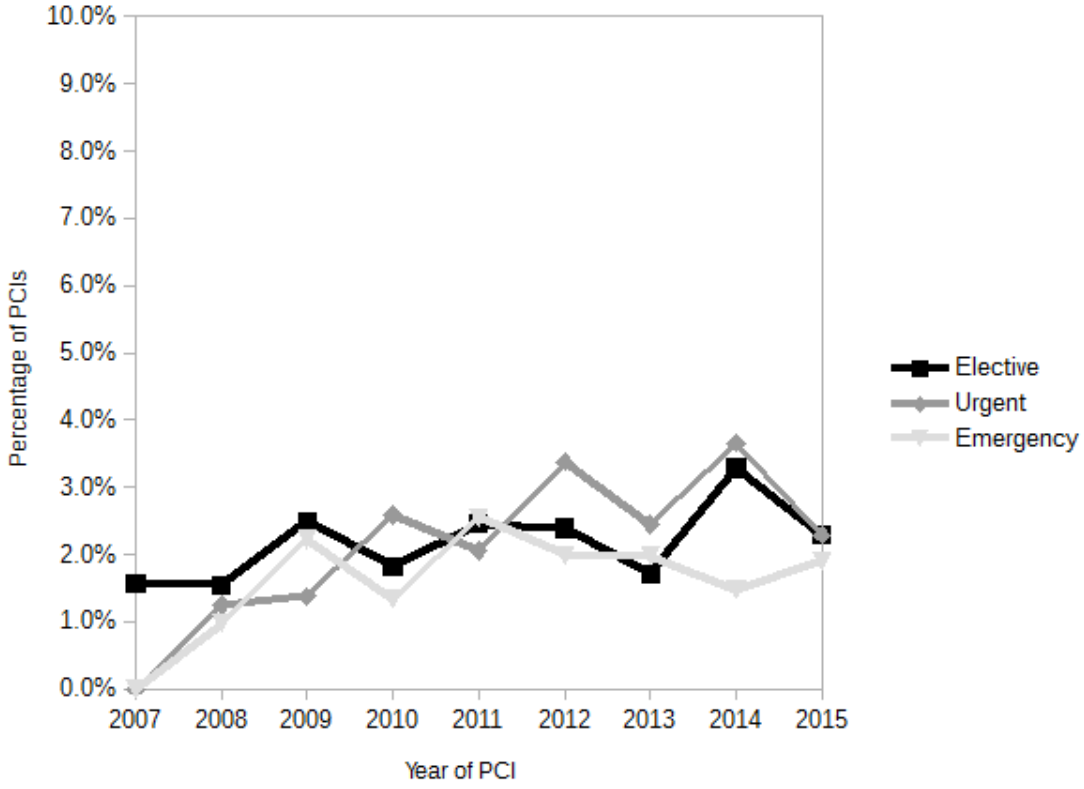


Figure 3.6.19 *– LMS vessel by priority*

There is a slight increase in the overall percentage of PCIs which feature treatment to the LMS, from approximately 1% in 2008 to 3% in 2015. There are no major differences between any of the PCI priorities with regards to treatment of the LMS. The slight increase can be explained by more complex PCIs (i.e. multivessel) being utilised, whereas previously lesions in the left main stem may have been treated with CABG, now it may be the case that PCI is more preferred in some of these LMS cases.

3.6.20 Graft Vessels by Priority

Table 3.6.20 and Figure 3.6.20 display the PCIs to coronary vessels that have previously been grafted, i.e. the patient has had a prior CABG. In the available dataset the exact native vessel that was grafted was not available, neither was the type/location the graft vein/vessel was obtained from.

Table 3.6.20 – Graft vessels by priority

Year	Elective (%)	Urgent (%)	Emergency (%)
2007	0 (0%)	0 (0%)	0 (0%)
2008	1 (0.09%)	0 (0%)	0 (0%)
2009	9 (1.07%)	13 (1.80%)	4 (0.99%)
2010	11 (1.18%)	10 (1.62%)	7 (0.94%)
2011	17 (1.74%)	19 (2.79%)	11 (1.40%)
2012	14 (1.52%)	19 (2.79%)	7 (0.93%)
2013	19 (2.16%)	22 (3.59%)	7 (0.99%)
2014	12 (1.36%)	13 (2.07%)	10 (1.34%)
2015	3 (1.71%)	3 (2.29%)	2 (1.27%)

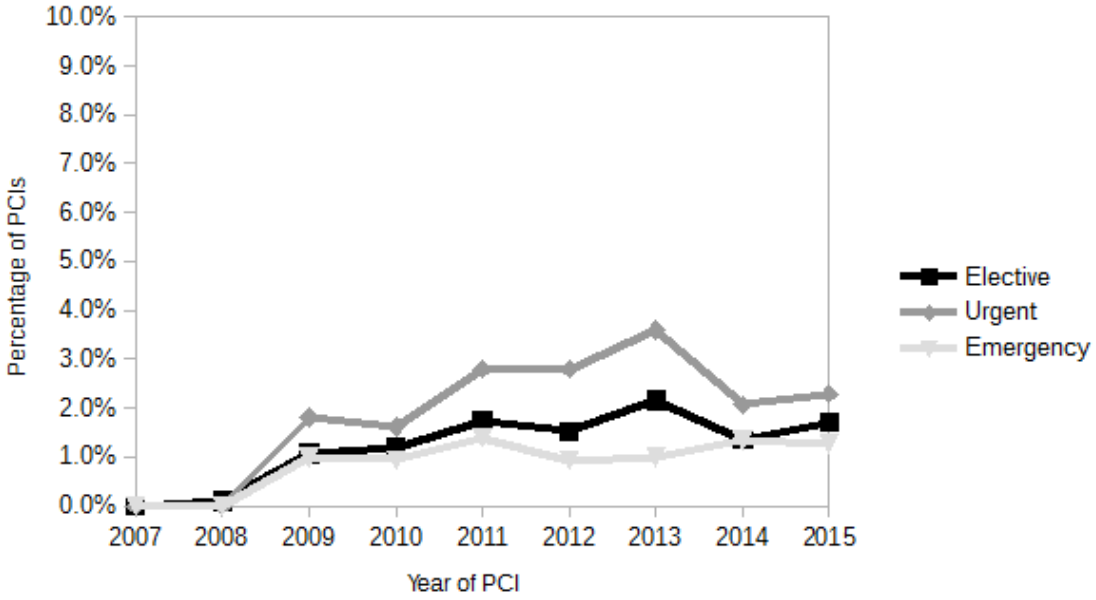


Figure 3.6.20– Graft vessels by priority

Treatment to graft vessels represents a small proportion of the total PCIs (i.e. less than 2.8% over all priorities). There is not much fluctuation between the priorities however those classified as urgent have a slight increase in rate relative to elective and emergency.

3.6.21 Number of Lesions Attempted

Table 3.6.21 and Figure 3.6.21 represent the number of lesions that were attempted, they may not have all actually been treated, but it is the number the operator(s) anticipated treating before the actual PCI started. These are broken down into three categories: 1 lesion; 2 lesions; three or more lesions.

Table 3.6.21 – Number of lesions attempted

Year	1	2	3	4	5	6	1 lesion (%)	2 lesions (%)	≥ 3 lesions (%)
2007	33	10	2	1	1	0	70.21%	21.28%	8.51%
2008	1100	404	123	30	6	0	66.15%	24.29%	9.56%
2009	1215	431	129	22	5	2	67.35%	23.89%	8.76%
2010	1572	501	121	20	0	0	71.00%	22.63%	6.37%
2011	1577	599	163	24	4	0	66.62%	25.31%	8.07%
2012	1530	541	115	21	4	1	69.17%	24.46%	6.37%
2013	1561	449	99	12	2	1	73.49%	21.14%	5.37%
2014	1510	430	100	22	4	3	72.98%	20.78%	6.23%
2015	311	98	21	5	1	0	71.33%	22.48%	6.19%

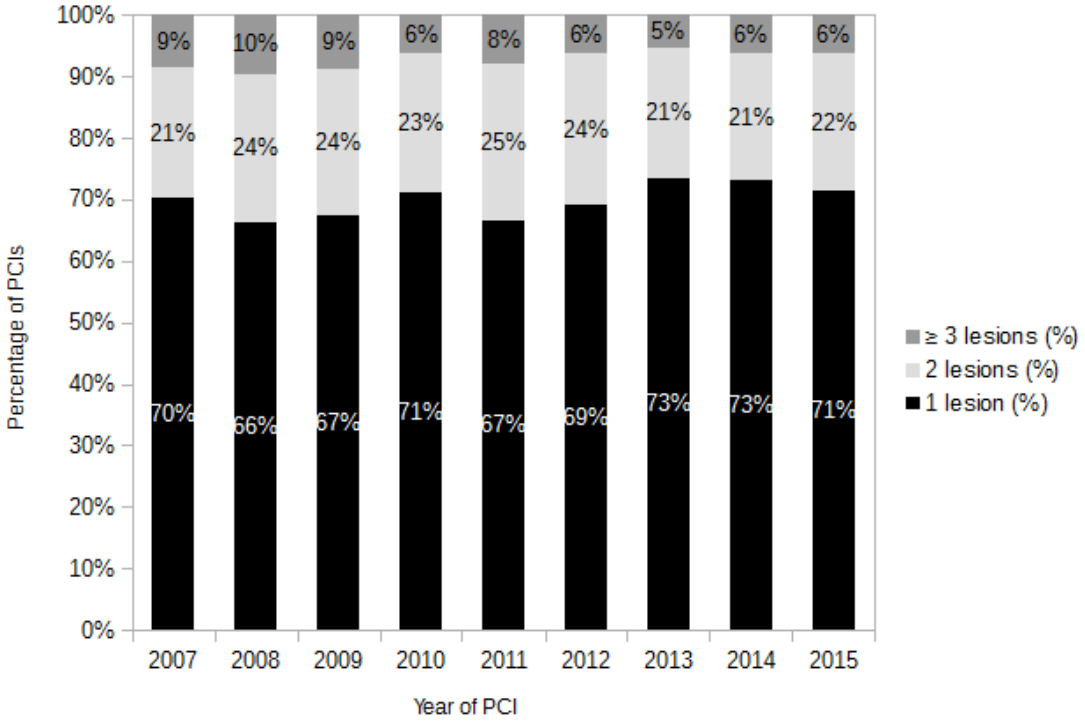


Figure 3.6.21 – Number of lesions attempted

The majority of PCI procedures feature treatment to a single lesion only. Although the information is similar to the number of stents used, there is a slight difference. A coronary vessel may have multiple lesions within it separated by a short distance and hence only a single stent may be used. Most emergency procedures would fall under the single lesion category.

3.6.22 Prior PCI

Table 3.6.22 and Figure 3.6.22 show whether the patients given PCI have had at least one previous PCI performed at the ECTC.

Table 3.6.22 – Prior PCI status

Year	Unknown	No	Yes	Unknown (%)	No (%)	Yes (%)
2007	11	117	34	6.79%	72.22%	20.99%
2008	84	1358	266	4.92%	79.51%	15.57%
2009	52	1571	357	2.63%	79.34%	18.03%
2010	49	1773	481	2.13%	76.99%	20.89%
2011	34	1850	556	1.39%	75.82%	22.79%
2012	41	1735	575	1.74%	73.80%	24.46%
2013	21	1654	523	0.96%	75.25%	23.79%
2014	52	1691	517	2.30%	74.82%	22.88%
2015	9	348	106	1.94%	75.16%	22.89%

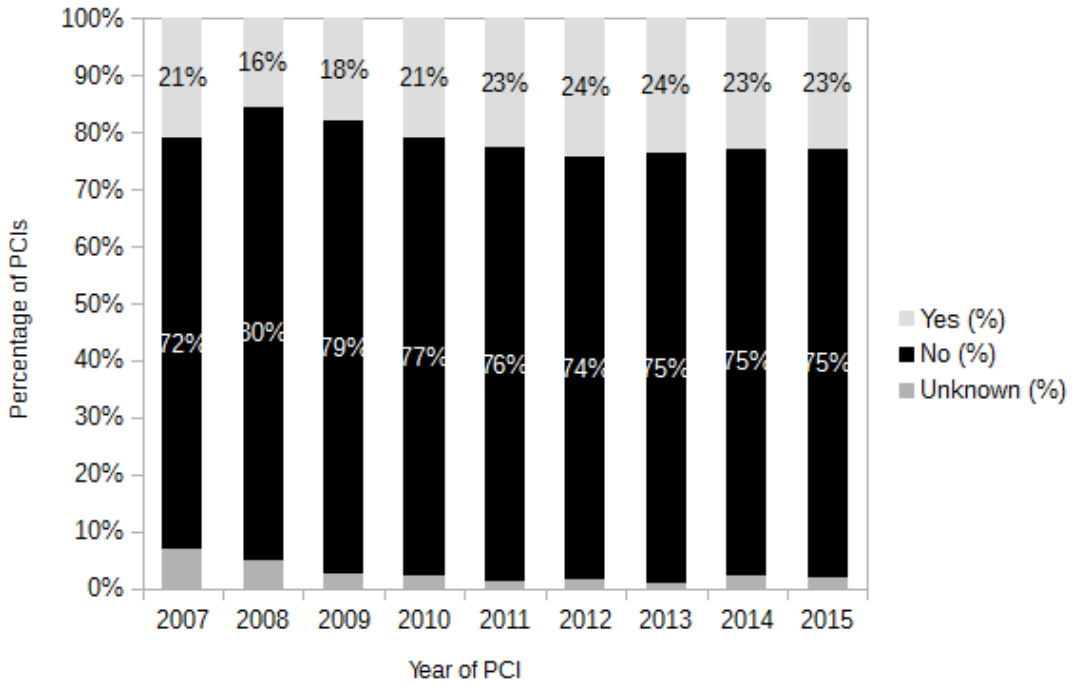


***Figure 3.6.22** – Prior PCI status*

The proportion of patients receiving PCI, which have previously had a PCI (at the ECTC) remains fairly stable over years at approximately 75%. Almost one quarter have previously had a PCI there and a likely explanation for most of these is that they previously had an emergency PCI possibly due to a STEMI and had the causative lesion

treated but it was also discovered that other coronary vessels have high stenosis and thus they were scheduled for a subsequent elective PCI in the future.

3.6.23 Prior CABG

Table 3.6.23 and Figure 3.6.23 show the prior CABG status. Note this does not necessarily mean that the PCI will be treating a graft vessel, it simply means that at least one coronary vessel in the patient's heart has been previously grafted.

Table 3.6.23 – Prior CABG status

Year	Unknown	No	Yes	Unknown (%)	No (%)	Yes (%)
2007	23	131	8	14.20%	80.86%	4.94%
2008	60	1528	120	3.51%	89.46%	7.03%
2009	50	1809	121	2.53%	91.36%	6.11%
2010	46	2090	167	2.00%	90.75%	7.25%
2011	21	2245	174	0.86%	92.01%	7.13%
2012	36	2163	152	1.53%	92.00%	6.47%
2013	12	2031	155	0.55%	92.40%	7.05%
2014	46	2069	145	2.04%	91.55%	6.42%
2015	9	427	27	1.94%	92.22%	5.83%

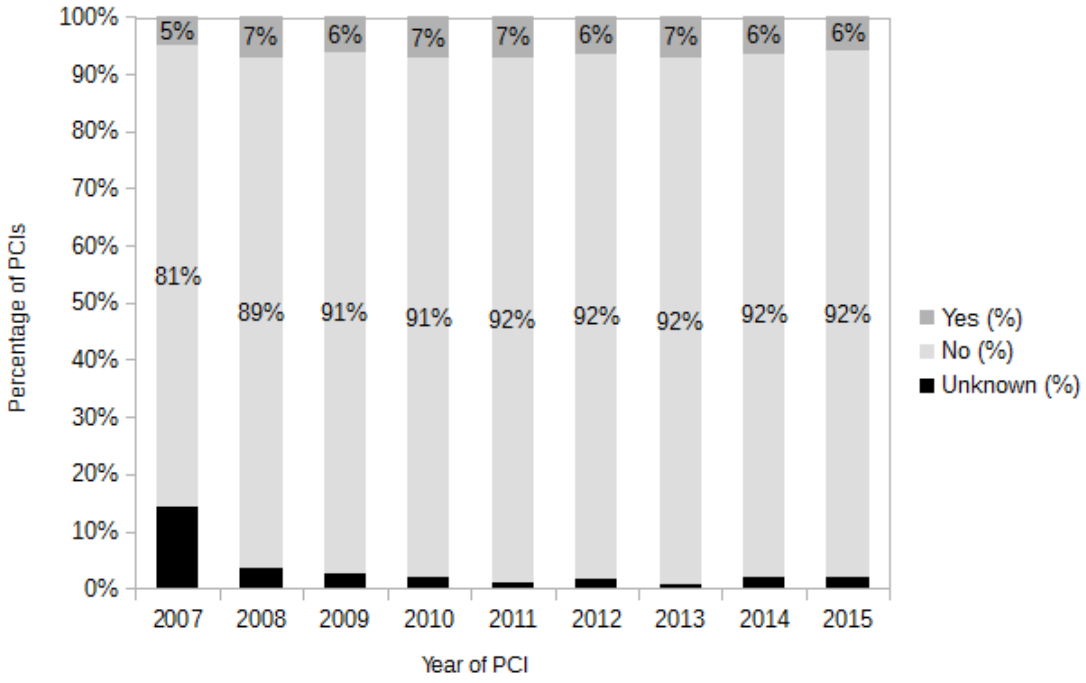


Figure 3.6.23 – Prior CABG status

As anticipated, the vast majority (approx. 92%) of PCI patients did not have any prior CABG surgery. Only a small proportion did (approx. 7%) and this figure remains fairly stable over the years.

3.6.24 Prior MI

Table 3.6.24 and Figure 3.6.24 represent the PCIs which feature patients that have had a prior myocardial infarction (heart attack), this prior MI does not necessarily mean this is the reason they are requiring a PCI, it could be the case that many years ago they had a MI and the current PCI is to a completely different coronary vessel than previously treated.

Table 3.6.24 – Prior MI status

Year	Unknown	No	Yes	Unknown (%)	No (%)	Yes (%)
2007	26	84	52	16.05%	51.85%	32.10%
2008	199	995	514	11.65%	58.26%	30.09%
2009	64	1389	527	3.23%	70.15%	26.62%
2010	85	1629	589	3.69%	70.73%	25.58%
2011	50	1715	675	2.05%	70.29%	27.66%
2012	76	1696	579	3.23%	72.14%	24.63%
2013	41	1606	551	1.87%	73.07%	25.07%
2014	66	1591	603	2.92%	70.40%	26.68%
2015	15	323	125	3.24%	69.76%	27.00%

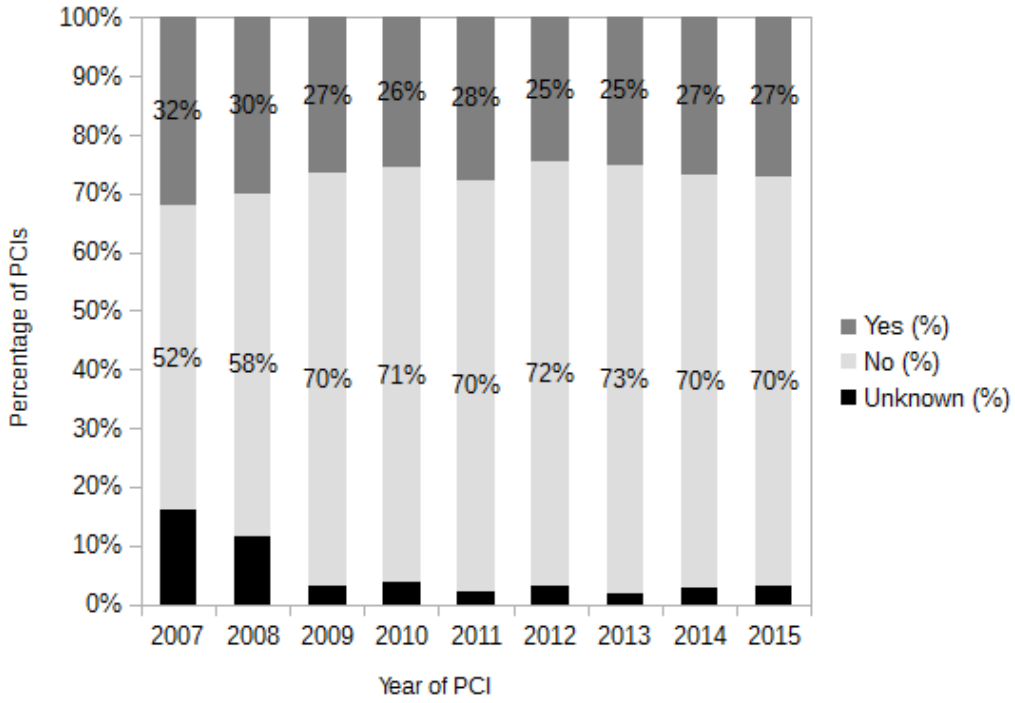


Figure 3.6.24 – Prior MI status

The majority of patients approximately (70%) have not have a prior MI, there is a jump from 58% in 2008 to 70% in 2009 which is explained by the ECTC starting their primary care activation programme in 2009 and hence beginning to directly treat STEMI patients as opposed them being treated elsewhere and transferred to the ECTC as urgent patients. Approximately 27% have had prior myocardial infarctions, again the resolution at this level does not explain whether it is directly responsible for the current PCI or not.

3.6.25 Diabetes Mellitus

Table 3.6.25 and Figure 3.6.25 list the patients diagnosed with any form of diabetes mellitus. The table also breaks this down further by display the type (e.g. Type 1 or Type 2).

Table 3.6.25 –PCIs to diabetic patients

Year	PCIs	Not Diabetic (%)	Diabetic (%)	Type 1	Type 2	Missing (%)
2007	162	74.07%	17.28%	4.32%	12.96%	8.64%
2008	1708	77.34%	14.23%	1.81%	12.41%	8.43%
2009	1980	79.90%	15.66%	0.81%	14.34%	4.44%
2010	2303	81.59%	15.07%	1.13%	13.89%	3.34%
2011	2440	80.82%	17.75%	1.15%	16.23%	1.43%
2012	2351	77.03%	18.21%	0.77%	17.35%	4.76%
2013	2198	80.03%	16.83%	1.18%	15.51%	3.14%
2014	2260	77.30%	17.83%	1.06%	16.59%	4.87%
2015	463	77.75%	16.85%	1.51%	15.33%	5.40%

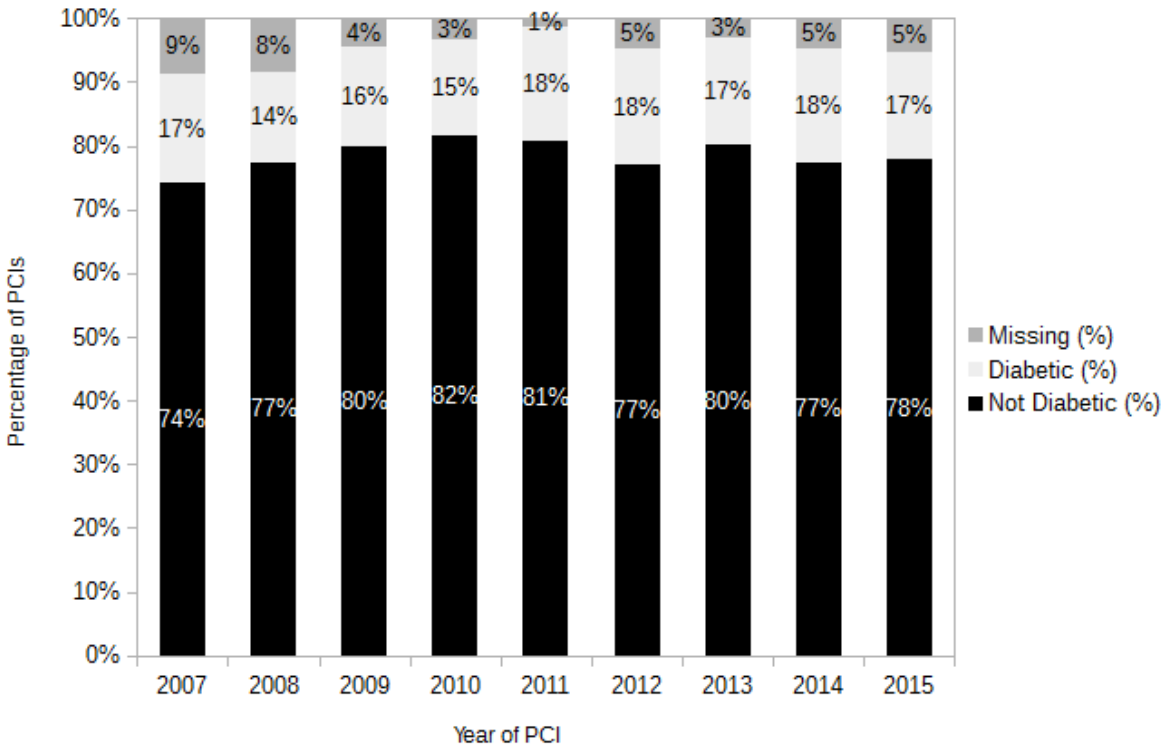


Figure 3.6.25 – PCIs to diabetic patients

The majority of patients (approx. 78%) presenting for PCI treatment were not diagnosed as diabetic. Less than 19% of patients each year were diagnosed as having a type of diabetes. These figures remain fairly stable over the years.

3.6.26 Cerebrovascular Disease

Table 3.6.26 and Figure 3.6.26 display information relating to the patients that have had a prior cerebrovascular accident (stroke). It should be noted that the timing of the stroke is irrelevant, i.e. it may have happened many years prior to the PCI procedure.

Figure 3.6.26 –PCIs to cerebrovascular disease patients

Year	PCIs	Missing	No Stroke	Stroke	Missing (%)	No (%)	Stroke (%)
2007	162	18	144	0	11.11%	88.90%	0.00%
2008	1708	23	1649	36	1.35%	96.56%	2.11%
2009	1980	156	1730	94	7.88%	87.37%	4.757%
2010	2303	183	2025	95	7.95%	87.93%	4.13%
2011	2440	29	2299	112	1.19%	94.22%	4.59%
2012	2351	173	2114	64	7.36%	89.92%	2.72%
2013	2198	61	2068	69	2.78%	94.09%	3.14%
2014	2260	187	2013	60	8.27%	89.07%	2.66%
2015	463	35	408	20	7.56%	88.12%	4.32%

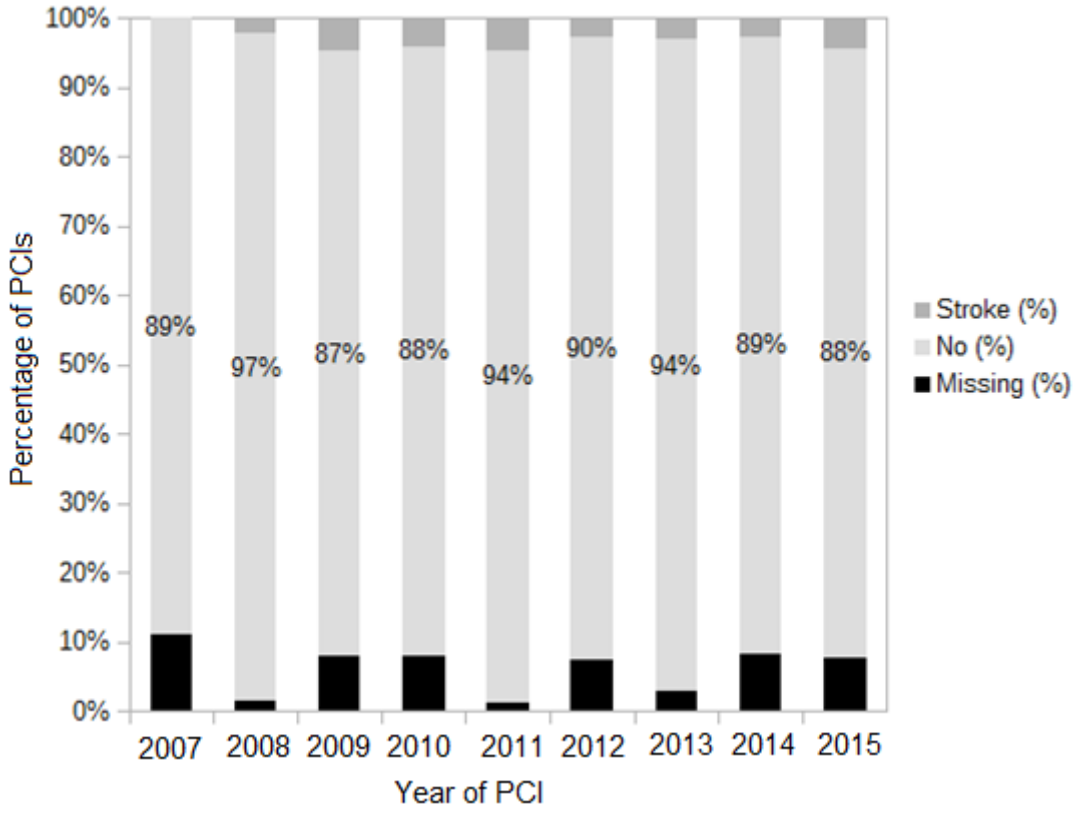


Figure 3.6.26 – PCIs cerebrovascular disease patients

As expected the proportion of patients which have had a prior cerebrovascular accident is very low, i.e. approximately 4%, this value remains fairly stable over the years.

3.6.27 Renal Dysfunction

Table 3.6.27 and Figure 3.6.27 represent those patients with renal dysfunction. This is classified as either chronic or acute renal failure, or abnormally high creatinine (i.e. ≥ 200 umol/L or < 200 umol/L but the estimated glomerular filtration rate, GFR < 60 mL/min). The remaining values not under the missing, normal, or renal disease dysfunction categories are functioning transplant patients (i.e. 8 overall, or 0.05%).

Table 3.6.27 – PCIs to renal dysfunction patients

Year	PCIs	Unknown	Normal	Renal Disease	Unknown (%)	Normal (%)	Renal dysfunction
2007	162	25	131	6	15.43%	80.86%	3.70%
2008	1708	167	1446	92	9.78%	84.66%	5.39%
2009	1980	338	1460	181	17.07%	73.74%	9.14%
2010	2303	805	1273	224	34.95%	55.28%	9.73%
2011	2440	657	1506	275	26.93%	61.72%	11.27%
2012	2351	65	1999	286	2.76%	85.03%	12.17%
2013	2198	697	1238	264	31.71%	56.32%	12.01%
2014	2260	455	1472	333	20.13%	65.13%	14.73%
2015	463	83	306	72	17.93%	66.09%	15.55%

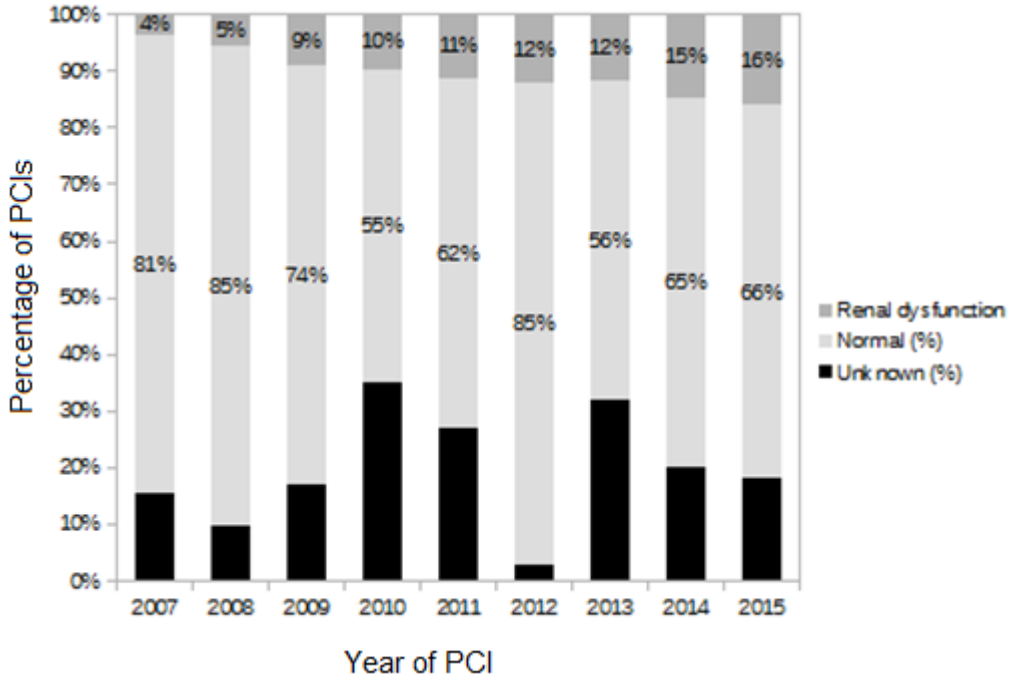


Figure 3.6.27 – PCIs to renal dysfunction patients

There is an almost (except for year 2013) year-on-year increase in the patients presenting with renal dysfunction over the years. This increases from 4% in 2007 to 16% in 2015. Those free from renal dysfunction make up approximately 65% of PCIs.

3.7 National PCI Information and Audit Data

The following information relates to the national audit PCI data, as reported by BCIS in their audit report of 2014 (BCIS, 2015). Information about national PCI activity in 2014 is listed here, and where possibly yearly trends. This is compared in 3.8, where available, to the corresponding ECTC PCI database listed in 3.6.

3.7.1 National PCI Activity

In 2014, there were 96,143 PCIs performed within 119 UK centres that performed PCIs. In 1991, there were fewer than 60 PCI centres. During this interval there has been a steady increase in almost every year, apart from a few years in which a PCI showed an apparent reduction (e.g. 1996, 2001, and 2013). Of these 119 PCI centres, 100 are provided by the NHS, and 19 are private. The number of centres, PCIs performed, and population estimates are broken down by country in Table 3.7.1. In mid-2014 figure for the entire UK was estimated as 64.5 million.

Table 3.7.1 – UK PCI activity by country in 2014

Country	NHS	Private	Population Estimate	Total PCIs	PCIs Rate (per population)
England	86	16	54.32 million	79,352	0.15%
Northern Ireland	4	0	1.84 million	4,235	0.23%
Scotland	6	2	5.35 million	8,499	0.16%
Wales	4	1	3.09 million	4,057	0.13%

There are 63 centres in UK which provide angiography services without performing PCI procedures. This is a reduction from approximately 90 centres in 2006. In 2014, angiography was performed 40,322 times in these 63 centres, and 207,041 times in the 119 PCI centres.

The number of interventional consultants increased from 621 in 2012, to 659 in 2014. Although not displayed, there is an expected general trend whereby the more consultants employed at a particular PCI centre, the higher the number of PCIs performed at that centre. The majority of the PCI centres in 2014 had less than 10 consultants and most of these centres performed less than 1500 PCIs. The average number of consultants per

NHS centre in 2014 was 7.3. In 2000, this was approximately 5.5. The average number of PCIs per operator was 123, in the three years prior to this (2011, 2012, and 2013) this was 127, 131, and 130, respectively.

From 2005 to 2013 there has been a year-on-year increase in the percentage of PCIs performed on acute patients from approximately 44% to 65.7% (in 2014 this reduced to 65.1%). Corresponding to this increase, the proportion of stable PCIs reduced from approximately 56% in 2005 to 34.4% in 2013. In 2014 there was a slight increase to 34.9%.

The indication for PCI is broken down by year in Figure 3.7.1.

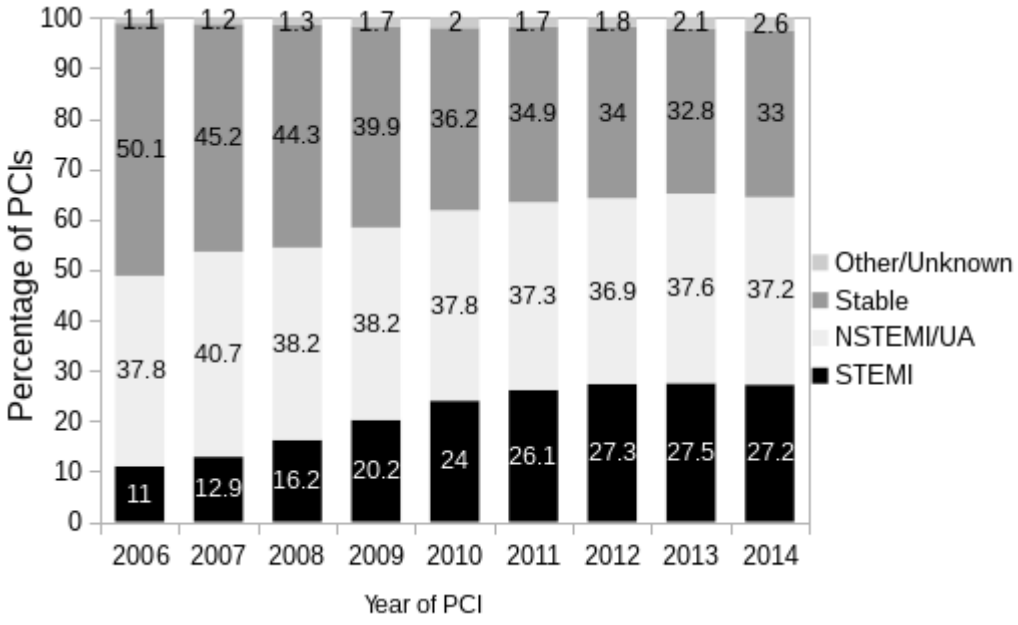


Figure 3.7.1- National Indication for PCI by year (BCIS, 2015)

As expected, the proportion of PCIs for STEMI has increased from only 11% in 2006, to 27.2% in 2014. Corresponding to this increase is a decrease in the proportion of stable patients from 50.1% in 2006, to 33% in 2014.

3.7.2 Demographics

In 2014, the average (mean) age of the patients that underwent a PCI procedure in the UK was 65.1. Approximately three quarters were male (74.3). Table 3.7.2 lists the basic national average demographic trends.

Table 3.7.2 – reported demographic figures from BCIS Audit Report (BCIS, 2015).

Year	**2007**	**2008**	**2009**	**2010**	**2011**	**2012**	**2013**	**2014**
Age (mean)	64.3	64.4	65.0	65.1	65.3	64.9	64.9	65.1
Male (%)	73.6%	73.8%	73.9%	74.0%	74.0%	74.1%	74.3%	74.3%
Previous MI	29.5%	30.2%	28.8%	28.4%	27.6%	26.8%	27.2%	27.4%
Previous PCI	18.6%	21.1%	22.3%	22.6%	22.7%	23.5%	24.7%	25.6%
Previous CABG	8.5%	9.1%	8.6%	8.4%	7.9%	8.9%	8.6%	8.4%
Pre-PCI ventilated (emergency only)	N/A	3.5%	3.9%	3.8%	4.5%	5.1%	5.5%	5.8%

Because it was known that female sex is a NWQIP model risk factor for in-hospital MACE following PCI, it was useful to further breakdown the patients by age and gender. It was hypothesised that in general women undergoing PCI were more elderly than men and hence why it was used as a risk factor. Table 3.7.3 displays the age group classification by gender breakdown (relative to the same gender only).

Table 3.7.3 – Age group distribution by gender in 2014 (BCIS, 2015).

Age (years)	**Male (%)**	**Female (%)**	**P Value**
≤ 50	9,856 (14.03%)	2,102 (8.64%)	*< 0.001*
51-60	18,189 (25.89%)	4,037 (16.60%)	*< 0.001*
61-70	21,005 (29.89%)	6,585 (27.08%)	*< 0.001*
71-80	15,185 (21.61%)	7,413 (30.48%)	*< 0.001*
≥ 81	6,031 (8.58%)	4,182 (17.20%)	*< 0.001*

The chi-square statistic was $\chi^2 = 2962.61$, $p < 0.001$ indicating significant differences in age groups between the two genders. As anticipated, female patients exhibit a much larger percentage of ages from ≥ 71 years (47.68%) compared to the male counterparts (30.19%).

3.7.3 Procedural Characteristics

The percentage of PCI procedures using stents has remained above 90% since 2003, with it being at 91.7% in 2014. As expected, in the 1990s it was low, which corresponds to an era when PCIs were primarily conducted using standard balloon angioplasties and did not involve stent insertion. The approximate rates in the years 1993, 1994, 1995, 1996, 1997 were 5%, 12.5%, 27.5%, 46%, and 60%, respectively. Figure 3.7.2 displays the mean percentage usage of drug-eluting stents (DES) for PCIs by each year.

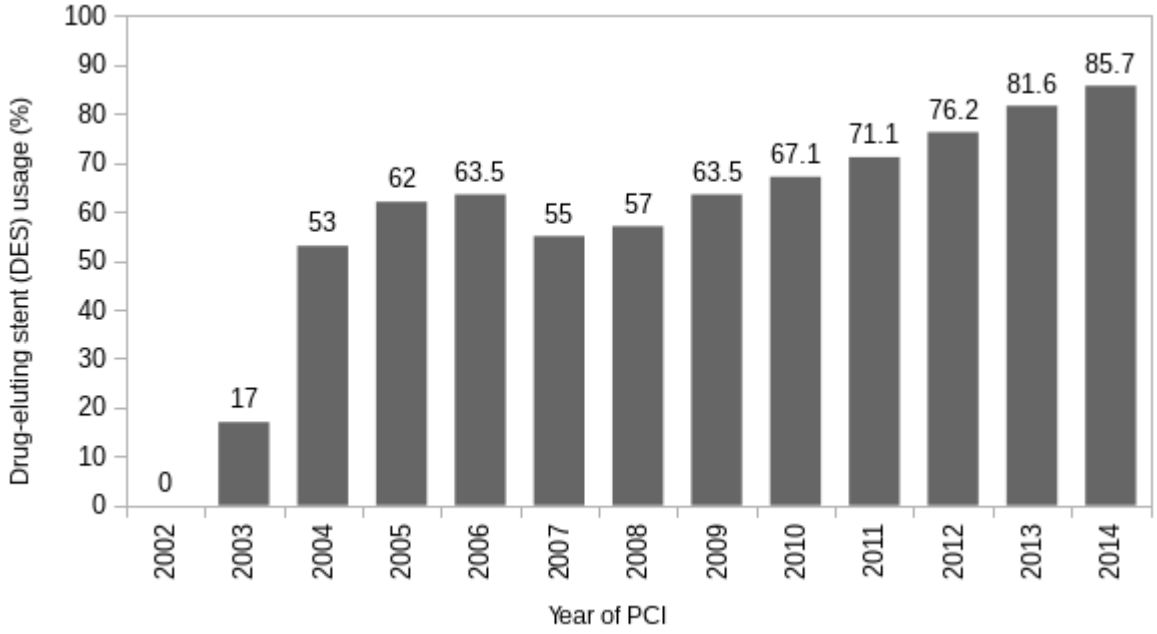


Figure 3.7.2 – mean DES usage by UK PCI centres (BCIS, 2015)

The breakdown of coronary vessel type treated by presenting syndrome (Stable, NSTEMI, or Primary PCI) is shown in Figure 3.7.3.

The LAD vessel is the most commonly treated for each syndrome (for Primary PCI, the RCA vessel is rounded up from 39.6%). For all syndromes, the 2nd most common vessel was the RCA, followed by the LCX.

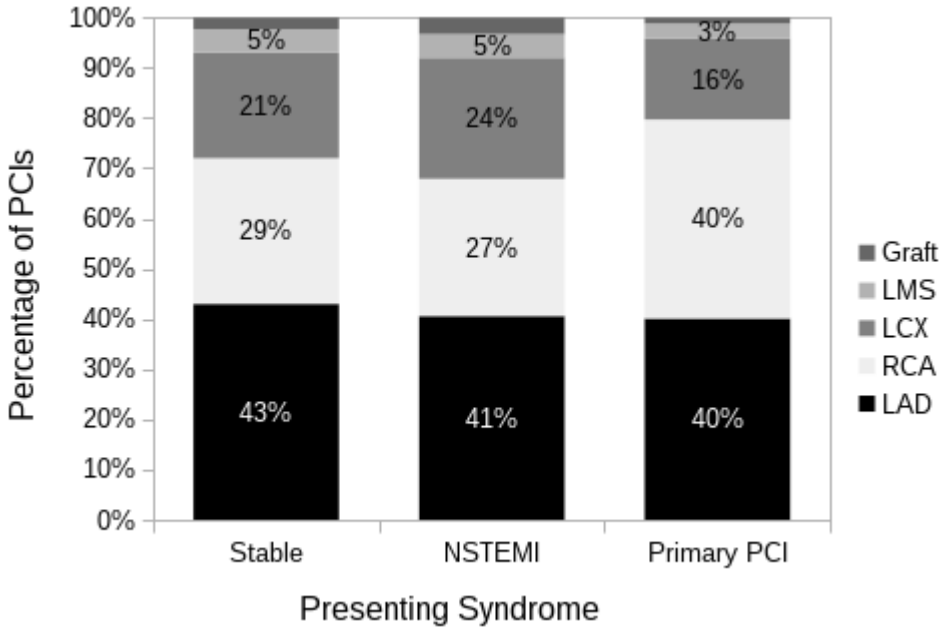


Figure 3.7.3 – coronary vessel type by presenting syndrome (BCIS, 2015).

3.8 Conclusions

From inspection of the ECTC PCI database and the national audit reports published by BCIS, it is apparent that the ECTC is one of the higher-volume PCI centres in the UK. In 2014, the majority of the national centres performed less than 1500 PCIs compared to the 2260 identified in the ECTC data. Both nationally, and at the ECTC there has been a general trend of increasing emergency PCI proportions, and hence a reduction in elective (stable) PCIs. In 2014, the most recent complete year for which both sets of data were available, the ECTC had a STEMI PCI percentage of 29.8% compared to the national average of 27.2%. As anticipated, and one of the justifications for externally validating the NWQIP on modern era, is the fact that the emergency proportions nationally have increased, therefore more operators are performing PCIs on patients that are at higher risk due to their coronary syndrome than previously.

Although the standard deviation was not reported in the latest BCIS audit report the previous years, the average (mean) age in years of patients has increased. In 2007 this was 64.3 years, and in 2014 it was 65.1 years. At the ECTC these figures were 64.5 and 65.7 years, respectively. There was no statistically significance difference in mean age over the years at the ECTC cohort.

As expected with the evolution of stent type, the percentage usage of DES used during PCIs has increased from approximately 34.6% in 2008 to 81.3% in 2014 at the ECTC. This increase is apparent nationally also, with a 57% usage in 2008 to 85.7% in 2014.

The three most commonly treated vessels for both the ECTC cohort and the national average were the LAD, RCA, and LCX, respectively. Almost half of all PCIs in both cohorts featured treatment to the LAD, followed by approximately one-third to the RCA, and approximately one-fifth to the LCX. Lesions to left main stem were treated in less than 3% of all PCIs at the ECTC, and 4% nationally. The graft vessels were the least treated type in both cases, in which the figures were less than 2.5% at the ECTC and 2% nationally.

Overall, the ECTC and national average exhibit similar trends over recent years, most notably from 2008 to 2014 in terms of patient demographics, clinical, and procedural characteristics. The similarity may allow any such risk prediction models for various outcomes constructed using the ECTC PCI cohort to be validated externally by other UK PCI centres to see if such incorporated risk factors are stable nationally, and hence verify

the authenticity of the model and possible subsequent adoption as a tool in clinical practice.

Addition demographic, clinical, and procedural characteristics for the ECTC cohort are reported in the three following study chapters (4, 5, and 6). The following studies investigate the different important clinical outcomes following PCI at the ECTC. They feature different inclusion/exclusion criteria for the entire dataset of 15,865 PCI records at the ECTC and hence why different values are reported across each of the three studies.

Chapter 4: External Validation of the North West Quality Improvement Programme (NWQIP) Risk Model

4.1 Introduction

The first published, peer-reviewed research, on in-hospital complications following percutaneous coronary intervention (PCI) in the UK was conducted by Grayson et al. (2006). Their research was conducted by a consortium of four cardiac centres/hospitals in the north-west of England in a time of predominantly high bare-metal stent (BMS) usage, and from this research a multivariate logistic regression model was developed, this being the North West Quality Improvement Programme (NWQIP) risk model. Before this, the majority of the published studies were conducted by researchers in the United States, which has a health care system with considerable differences to the UK. The NWQIP study utilised 9914 consecutive PCI patients in their analysis using PCI procedures from 1st August 2001 to 31st December 2003. The outcome of interest was in-hospital major adverse cardiac events (MACE), which is a composite outcome of death, Q-wave myocardial infarction, emergency coronary artery bypass graft (CABG) surgery, or a cerebrovascular accident. In some cases a patient may experience multiple components of MACE. A beneficial point about the NWQIP risk model is that the incorporated risk factors (age, female sex, cerebrovascular disease, cardiogenic shock, PCI priority, and LMS or graft lesion treatment) are all variables that are likely to have high data completion rates in UK PCI centres, especially with the advent of the minimum dataset specified by the British Cardiovascular Intervention Society (BCIS). These variables are also simple to identify, i.e. they can be recognised and recorded by staff fairly easily and the definition of them is likely to be consistent between different hospitals and different staff inputting the data. Of the independent risk factors within the NWQIP model, the presence of pre-procedural cardiogenic shock has the highest regression coefficient weighting and hence patients with this risk factor are as expected, at high risk of experiencing in-hospital MACE. The two other risk factors with high coefficients are emergency PCI and treatment to left main stem (LMS) lesions.

Grayson et al. (2006) reported an overall in-hospital MACE rate of 1.3% (129 patients). This was broken down into 0.7% (66) deaths, 0.4% (36) Q wave myocardial infarctions, 0.15% (15) emergency CABG surgeries, and 0.2% (20) cerebrovascular accidents. The discrimination performance was assessed using the area under the receiver operating characteristic (ROC) curve for which the value was 0.76, indicating a fair ability to discriminate between in-hospital MACE occurring or not occurring. When their PCI cohort were classified into one of eight risk groups based on the estimated probabilities of experiencing MACE, the Hosmer-Lemeshow goodness of fit statistic produced $p = 0.43$,

indicating only a small difference between estimated and observed MACE across the risk groups. The NWQIP model was then tested using 1786 consecutive PCIs from 1st January 2004 to 31st December 2004. The ROC curve for this validation set of PCIs was 0.72, which again represents a fairly good ability to discriminate. The patient demographics, clinical, and procedural characteristic were not reported for the validation PCI cohort, and hence it cannot be determined how closely these characteristic match the original 9914 patient.

The NWQIP risk model was more recently externally validated by Kunadian et al. (2008) using a PCI cohort of 5034 patients between September 2002 and August 2006. Their cohort reported an overall in-hospital MACE rate of 2.0% (104 patients). This was broken down into 1.3% (66) deaths, 0.22% (11) Q-wave myocardial infarctions, 0.20% (10) cerebrovascular accidents, and 0.14% (7) emergency CABG surgeries. Both studies reported similar rates for cerebrovascular accidents (0.20% and 0.20% respectively) and emergency CABG surgery (0.15% and 0.14% respectively) however there was a lower rate of death (0.7% versus 1.3%) which could be explained by the fact that the external study performed emergency PCIs in 17.6% relative to the 10.8% in the NWQIP study and hence more patients are at higher risk of dying. The ROC curve was 0.87 (95% confidence limits were 0.82 to 0.90) which indicates a better ability to discriminate than in the original NWQIP PCI cohort. The calibration of observed versus estimated MACE was $p = 0.95$, indicating an almost perfect fit among the different risk groups. In summary, it was found that the NWQIP model performed very well in terms of both discrimination and calibration for an external PCI cohort, and a different location (Midlands instead of north-west) within the UK and several years later than the original study.

4.1.1 Purpose

Despite the external validation of NWQIP (Kunadian et al., 2008) verifying the model's performance as a predictor for in-hospital MACE, in terms of discrimination and calibration, there are reasons why subsequent external validation of this model is required. These are described in section 1.1, but in addition, differences in characteristics are listed in Table 4.1.1. This shows the percentage of each characteristic between the ECTC, original NWQIP cohort (Grayson et al., 2006), and the external validation cohort (Kunadian et al., 2008). Such differences in characteristics along with technology evolution (i.e. higher modern DES usage), and increased numbers of cardiac centres and PCI operators are theorised to manifest as a performance alteration in the effectiveness of the NWQIP risk prediction model. Although the DES usage for both the NWQIP and external cohorts are not reported, the general usage of BMS in the UK in these era was low, i.e. less than 40% (BCIS, 2016).

Table 4.1.1 – prominent differences in characteristics between the ECTC, NWQIP, and external validation PCI cohorts

Characteristic	ECTC cohort	NWQIP cohort	External cohort	*p* Value
DES usage	68.5%	N/A	N/A	N/A
Age ≥ 70 years	38.8%	20.4%	26.4%	< 0.001
Diabetes mellitus	17.5%	13.2%	14.7%	< 0.001
Emergency PCI	30.0%	10.8%	17.6%	< 0.001
Previous PCI	22.3%	N/A	12.6%	< 0.001
Cardiogenic shock	2.9%	0.7%	1.7%	< 0.001
LMS lesions	2.2%	1.1%	N/A	< 0.001

In general, from the characteristics in Table 4.1.1, the ECTC cohort appear to be at higher risk, i.e. higher percentage of elderly, diabetic, emergency, cardiogenic shock, previous PCIs and LMS lesions. It may be the case however that higher proportions of non-stable patients means that the operators gain more experience in treating higher risk individuals and therefore gain the appropriate skills to treat such future patients with lower adverse outcome rates.

4.1.2 Hypothesis and Objectives

It is hypothesised that the NWQIP risk model will not perform as effectively as it did in the original or external validation studies. The theorised reason for the degradation of performance is that due to the combination of changes (specified in section 4.1.1) not all the incorporated risk factors (age, gender, PCI priority, cardiogenic shock, cerebrovascular disease, LMS lesions, or graft lesions) will exhibit significant associations with the outcome of in-hospital MACE, and therefore their incorporation into such a risk model is obsolete and thus affects the estimated probability.

The following objectives were created in order to test the hypothesis:

(1) Using the NWQIP risk model coefficients, generate the estimated probability of each patient experiencing in-hospital MACE based on the presence of the incorporated risk factors.

(2) To identify which patients experienced in-hospital MACE by extracting the relevant information from the mortality or complication data fields.

(3) Using the generated NWQIP probabilities and in-hospital MACE outcome data (from objective 1 and 2), Verify the NWQIP model performance (calibration and discrimination) by utilising the ECTC PCI cohort, which is based in a different location (south-east England) to the original NWQIP cohort (north-west England), and the external PCI cohort (Midlands), and also in a different era of stenting (i.e. a higher DES usage for PCIs).

(4) To attempt to explain the causative reasons for any performance changes in the NWQIP model for the ECTC PCI cohort relative to the original cohort (Grayson et al., 2006), or the external validation study (Kunadian et al., 2008).

4.2 Methods

4.2.1 Patient Data

The general PCI patient dataset available for this study is described in Chapter 3 (General Methods and Data). The entire range of PCIs (15,865) was considered for analysis (July 2007 to March 2015). The only PCI procedure records which were excluded from analysis were those missing crucial data from either: (1) an NWQIP model risk factor; (2) complication data. Cardiogenic shock (pre-procedural) was the only variable for which a blank field was assumed to be 'No', as recommended by consultant interventional cardiologists at the ECTC as this was stated that it was common practice to leave this field blank and only set it to 'Yes' if the patients were in cardiogenic shock.

The CVIS/ECTC dataset contained variables which represent all of the NWQIP risk factors, the risk factor and its corresponding field name and data type in the dataset are listed below in Table 4.2.1.

Table 4.2.1 – NWQIP risk factors and CVIS data fields

NWQIP Risk Factor	CVIS Data Field	CVIS Data Type	Example(s)
Age 70-79 years	Age	Integer (positive)	{71, 76}
Age ≥ 80 years	Age	Integer (positive)	{80, 89}
Female sex	Sex	Character	{M, F}
Cerebrovascular disease	Medical History	String	{Cerebrovascular event}
Cardiogenic shock	Cardiogenic Shock	String	{Yes, No}
Urgent PCI	Procedure Urgency	String	{Urgent}
Emergency PCI	Procedure Urgency	String	{Emergency}
LMS lesions treated	Vessels Attempted	String	{Lmain}
Graft lesions treated	Vessels Attempted	String	{Graft(s)}

Relating to the above NWQIP variables, and outcome data (procedural complications, status at discharge), the following records were excluded, as the estimated NWQIP probabilities of experiencing in-hospital MACE could not be calculated. The number of PCIs was 15,865.

Table 4.2.2 –NWQIP risk factor fields with missing data

Risk Factor	Missing (n)	Missing (%)
Age	0	0%
Sex	1	< 0.01%
Procedure Urgency	23	0.15%
Vessels Attempted	283	1.78%
Medical History	865	5.45%
Cardiogenic shock (pre-procedural)	1061	6.69%

The records with a 'Medical History' set to blank ('##') were excluded from analysis because it is unknown whether the patient may have had a previous cerebrovascular accident (stroke), and this could affect the performance testing of the NWQIP risk model had these records remained and were simply assumed as not having a prior stroke. Whilst not listed here, no significant differences were identified in the general characteristics for the records retained in the analysis versus those excluded because of missing NWQIP risk factors. The number of records missing one of the NWQIP risk factors, and hence excluded from analysis, totalled 978 (6.16%). The second group of data fields that were investigated for missing data were the complication/outcome fields as listed in table 4.2.3 below.

Table 4.2.3 – CVIS outcome/complication fields needed for the NWQIP model

Outcome Type	Missing (n)	Missing (%)
Post Procedure Complication	1716	10.82%
PCI Hospital Outcome	1448	9.13%
PCI Hospital Outcome or Post Procedure Complication	2132	13.44%

The records with missing risk factor or outcome/complication data in Tables 4.2.2 and 4.2.3 were not mutually exclusive. However, some records had multiple missing values for each. In total, including the valid NWQIP risk factor variables and the complication/outcome fields, there were 13,202 PCI records retained in the analysis, resulting in 2,663 (16.79%) of the records being omitted.

Because the complication/outcome information is scattered over multiple data fields in the CVIS database, the task of extracting the relevant data was broken down into the following sequence of steps. The fields checked were 'Post Procedural Complications' and 'PCI Hospital Outcome' respectively.

(1) Check of 'Post Procedural Complications' field is blank, if so invalidate the record.
(2) Check if 'PCI Hospital Outcome' field is blank; if so invalidate the outcome record.
(3) Check for 'Cerebrovascular accident' or 'CVA' MACE component.
(4) Check for 'Q-wave MI' MACE component.
(5) Check for 'In-hospital death' or 'death' for in-hospital death MACE component.
(6) Check for 'Pre-discharge emergency coronary surgery' or 'emergency CABG' MACE component.
(7) If either steps 3 to 6 are identified as present then set the current record to 'MACE'.

4.2.2 NWQIP Estimated Risk Calculation

The NWQIP risk model logistic regression coefficients (listed below in Table 4.2.4) that were reported by Grayson et al. (2006) were used to generate the estimated odds of each PCI patient experiencing in-hospital MACE. From these odds values, the estimated probabilities of MACE occurring was then generated

Table 4.2.4 - NWQIP risk factors and coefficient values (Grayson et al, 2006)

NWQIP Risk Factor	Coefficient
Age 70-79 years	0.7048
Age ≥ 80 years	1.0106
Female sex	0.4586
Cerebrovascular disease	0.8618
Cardiogenic shock	3.2636
Urgent PCI	0.4788
Emergency PCI	1.3625
LMS lesions treated	1.6502
Graft lesions treated	0.9101
(Intercept)	-5.4959

The estimated odds of experiencing MACE for a given patient were calculated using Equation 3, which utilises the logistic regression coefficients (Table 4.2.4).

(Equation 3. NWQIP calculation for odds of in-hospital MACE)

Odds = exp(-5.4959 + {age 70-79 years × 0.7048} + {age ≥ 80 years × 1.0106} + {female sex × 0.4586} + {cerebrovascular disease × 0.8618} + {cardiogenic shock × 3.2636} +

{urgent PCI × 0.4788} + {emergency PCI × 1.3625} + {LMS lesions treated × 1.6502} + {Graft lesions × 0.9101})

The estimated probability of a patient experiencing in-hospital MACE is then calculated using the odds value as shown in Equation 4.

(Equation 4. MACE percentage risk calculation from odds ratio)

MACE percentage = [odds / (1+odds)] ×100

The following examples of PCI patients and the presence of certain NWQIP risk factors show the generated odds and probabilities of experiencing in-hospital MACE.

Example 1: Female patient, 82 years old, emergency priority, PCI to graft lesions.

Odds = exp(-5.4959 + {female sex × 0.4586} + {age ≥ 80 years × 1.0106} + {emergency PCI × 1.3625} + {graft lesions × 0.9101}) = 0.173062.

Percentage probability of experiencing in-hospital MACE: [0.173062 / (1+0.173062)] ×*100* = ***14.75%***

Example 2: Male patient, 76 years old, cardiogenic shock, emergency priority, PCI to LMS.

Odds = exp(-5.4959 + {age 70-79 years × 0.7048} + {cardiogenic shock × 3.2636} + {emergency PCI × 1.3625} + {LMS lesions × 1.6502}) = 4.415848/

Percentage probability: [4.415848/(1+4.415848)] × 100 = **81.54%**

4.3 Results

4.3.1 Univariate Associations with in-hospital MACE

The patient demographic, clinical and procedural characteristics for the valid PCI procedures included in the analysis are listed in Tables 4.3.1 and 4.3.2 below. The percentages represented in the tables are relative to all data (i.e. including those missing). In total 13,202 records with a known MACE/non-MACE end-point were included in the analysis.

Table 4.3.1 – demographic and procedural univariate associations with in-hospital MACE

Risk Factor	Patients (%)	MACE (%)	OR (95% CI)	P Value
Age (years)				
< 50	10.5%	0.7%	**Reference**	*< 0.001*
50-59	20.0%	0.7%	0.987 (0.417 to 2.336)	0.977
60-69	30.6%	0.9%	1.206 (0.548 to 2.654)	0.642
70-79	25.6%	1.8%	2.442 (1.150 to 5.185)	*0.02*
>= 80	13.2%	3.5%	4.945 (2.329 to 10.492)	*< 0.001*
Gender				
Male	75.3%	1.1%	0.507 (0.363 to 0.710)	*< 0.001*
Female	24.7%	2.2%	**Reference**	
Priority				
Elective	40.3%	0.2%	**Reference**	*< 0.001*
Urgent	29.7%	0.5%	2.272(0.993 to 5.199	*< 0.001*
Emergency	30.0%	3.9%	18.971 (9.624 to 37.394	*< 0.001*
Cardiogenic shock				
No	97.1%	0.9%	**Reference**	
Yes	2.9%	17.1%	27.719 (15.109 to 31.221)	*< 0.001*
Prior CABG				
No	93.1%	1.5%	**Reference**	
Yes	6.9%	0.7%	0.485 (0.198 to 1.187)	0.106
Prior MI				
No	74.0%	1.5%	**Reference**	
Yes	26.0%	1.1%	0.735 (0.491 to 1.100)	0.133
Prior PCI				
No	77.7%	1.5%	**Reference**	
Yes	22.3%	1.0%	0.640 (0.405 to 1.011)	0.054
Cerebrovascular disease				
No	95.8%	1.2%	**Reference**	
Yes	4.2%	3.9%	3.244 (1.904 to 5.526)	*< 0.001*
Renal dysfunction				
No	95.1%	1.4%	**Reference**	
Yes	4.9%	1.3%	0.925 (0.406 to 2.110)	0.853
COPD				
No	95.8%	1.4%	**Reference**	
Yes	4.2%	1.2%	0.904 (0.368 to 2.221)	0.825

Valvular heart disease				
No	98.8%	1.4%	**Reference**	
Yes	1.2%	0.0%	0.986 (0.984 to 0.989)	0.211
peripheral vascular disease				
No	96.5%	1.3%	**Reference**	
Yes	3.5%	3.3%	2.546 (1.397 to 4.639)	*0.002*
Hypercholesterolaemia				
No	42.5%	1.6%	**Reference**	
Yes	57.5%	1.2%	0.747 (0.529 to 1.055)	0.096
Hypertension				
No	45.4%	1.6%	**Reference**	
Yes	54.6%	1.2%	0.763 (0.550 to 1.058)	0.103
Diabetes				
No	82.5%	1.4%	**Reference**	
Yes	17.5%	1.5%	1.140 (0.747 to 1.741)	0.544
Asthma				
No	96.6%	1.4%	**Reference**	
Yes	3.4%	0.6%	0.431 (0.106 to 1.750)	0.226
Renal disease				
No	86.2%	0.8%	**Reference**	
Yes	13.8%	1.6%	2.132 (1.244 to 3.652)	*0.005*
Dyspnoea class				
*I	37.6%	1.1%	**Reference**	0.779
II	29.8%	0.9%	0.825 (0.474 to 1.434)	0.495
III	13.8%	0.8%	0.763 (0.363 to 1.604)	0.476
IV	18.8%	0.8%	0.749 (0.385 to 1.459)	0.396
Angina class				
0	15.4%	1.7%	**Reference**	*0.017*
I	9.2%	1.4%	0.796 (0.373 to 1.700)	0.555
II	25.5%	0.7%	0.398 (0.202 to 0.787)	*0.008*
III	20.2%	0.7%	0.396 (0.190 to 0.823)	*0.013*
IV	29.7%	0.8%	0.442 (0.235 to 0.833)	*0.012*
Ventilated pre-op				
No	98.1%	1.3%	**Reference**	
Yes	1.9%	15.4%	14.210 (9.059 to 22.290)	*< 0.001*
Biomarkers raised				
No	15.9%	0.6%	**Reference**	
Yes	84.1%	1.0%	1.829 (0.555 to 6.028)	0.314

Table 4.3.2 – procedural univariate associations with in-hospital MACE

Risk Factor	Patients (%)	MACE (%)	OR (95% CI)	P Value
Ejection fraction				
< 30%	4.1%	6.9%	21.040 (10.569 to 41.889)	*< 0.001*
30-50%	32.1%	0.9%	2.660 (1.359 to 5.206)	*0.004*
>= 50%	63.8%	0.4%	**Reference**	*< 0.001*
Graft Lesion				
No	97.4%	1.4%	**Reference**	
Yes	2.6%	1.1%	0.788 (0.249 to 2.487)	0.683
LMS Lesion				
No	97.8%	1.4%	**Reference**	
Yes	2.2%	4.0%	3.016 (1.516 to 6.000)	*0.001*
Glycoprotein used				
No	86.5%	1.1%	**Reference**	
Yes	13.5%	3.4%	3.113 (2.190 to 4.426)	*< 0.001*

From both tables of associations (4.3.1. and 4.3.2) the risk factors which exhibit a statistically significant univariate association ($p < 0.05$) with in-hospital MACE are: age group; gender; PCI priority; cerebrovascular disease; peripheral vascular disease; renal disease; pre-operation ventilation; ejection fraction; LMS lesions; and glycoprotein inhibitor IIb/IIIa usage.

4.3.2 In-hospital MACE Outcomes

Of the 13,202 PCI records included in the analysis, 193 (1.46%) experienced in-hospital MACE. The breakdown of these MACE events is displayed in Table 4.3.3.

Table 4.3.3 – In-hospital MACE outcome events for ECTC patient cohort

MACE Component	Patients (n)	Patients (%)
Death	146	1.11%
Q-wave myocardial infarction	25	0.19%
Cerebrovascular accident	16	0.12%
Emergency CABG	12	0.09%

The majority of the patients which developed in-hospital MACE did only experience a single type, however as seen in Table 4.3.3 the total number of events is 199 meaning a few exhibited multiple MACE outcomes. Figure 4.3.1 displays the MACE rate by year of PCI procedure.

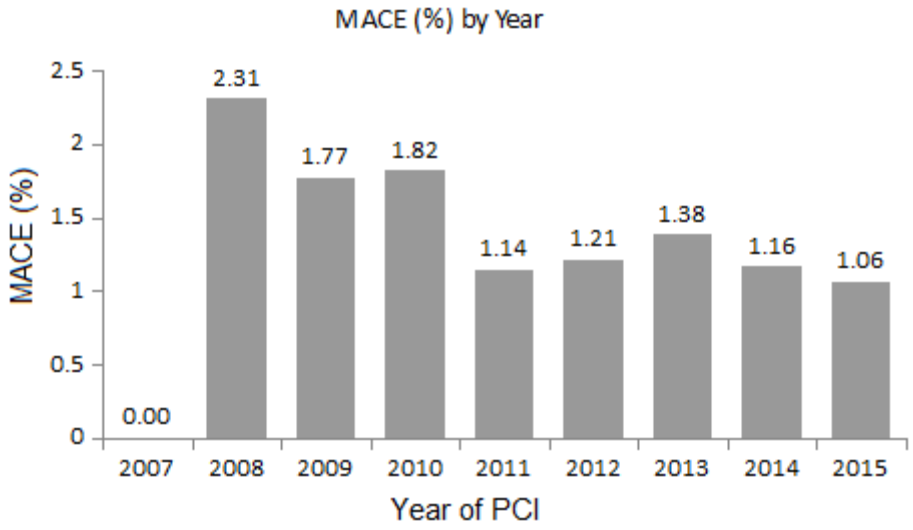


Figure 4.3.1 – ECTC MACE rate (%)

The MACE rate in 2007 was 0% because only 16 valid PCIs were performed during this year and most of these were stable patients and hence unlikely to experience adverse outcomes. From the BCIS Audit Report released in 2014 the national average MACE rates across each year (2007 to 2014) can only be seen by individual MACE components. These rates are displayed in Table 4.3.4.

Table 4.3.4 – national average MACE component rates (BCIS Audit Report, 2014)

Year	Death	Q-wave MI	Cerebrovascular accident	Emergency CABG
2007	0.92%	0.15%	0.05%	0.08%
2008	1.03%	0.14%	0.08%	0.07%
2009	1.24%	0.11%	0.09%	0.08%
2010	1.5%	0.18%	0.12%	0.05%
2011	1.6%	0.13%	0.08%	0.05%
2012	1.9%	0.11%	0.09%	0.05%
2013	1.8%	0.09%	0.09%	0.05%
2014	1.9%	0.13%	0.09%	0.06%

The ECTC overall outcomes for years (2007 to 2015) as listed in Table 4.3.3 shows that the outcome rate for death (1.11%) is lower than the national average in all years from 2009 onwards. The Q-wave MI (0.19%), cerebrovascular accident (0.12%), and emergency CABG (0.09%) components see minor increases in the ECTC average cohort relative to each national average audit year.

Table (4.3.5) and Figure (4.3.2) display the breakdown of PCIs by year and priority. The figure was generated to ascertain whether fluctuations in MACE rate over the years (i.e. figure 4.3.1) could simply be explained by fluctuations in PCI priority.

Table 4.3.5 – ECTC PCIs by Priority

Year	Elective	Urgent	Emergency	TOTAL	Elective (%)	Urgent (%)	Emergency (%)
2007	11	5	0	16	68.75	31.25	0.00
2008	615	324	144	1083	56.79	29.92	13.30
2009	640	593	353	1586	40.35	37.39	22.26
2010	753	542	685	1980	38.03	27.37	34.60
2011	865	625	697	2187	39.55	28.58	31.87
2012	777	585	621	1983	39.18	29.50	31.32
2013	809	599	690	2098	38.56	28.55	32.89
2014	702	542	646	1890	37.14	28.68	34.18
2015	139	109	131	379	36.68	28.76	34.56

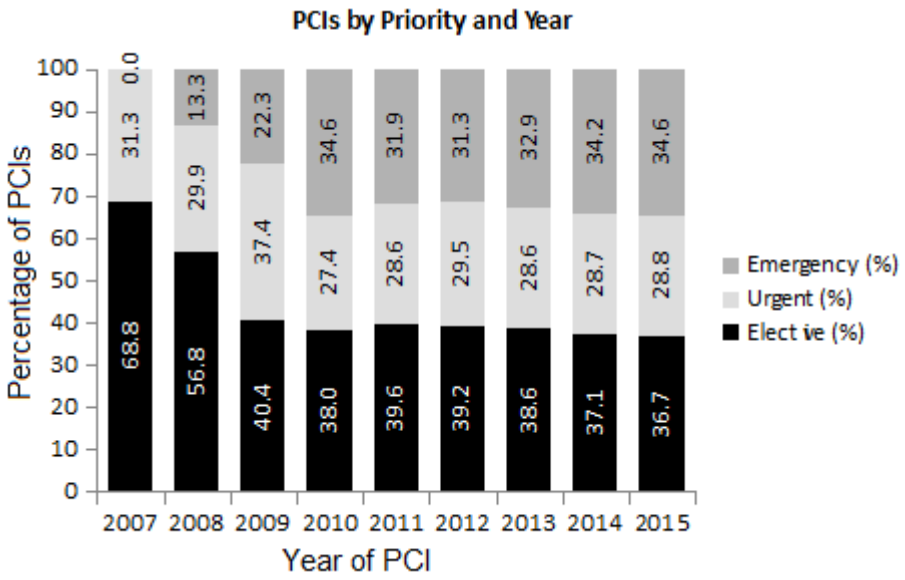


Figure 4.3.2 – ECTC PCIs by Priority

There is a general trend of decreasing proportion of elective PCIs over the years from approximately 69% in 2007 to 37% in 2015. A sudden rise in the number and hence proportion of emergency PCIs is seen in 2009 which can be explained by the ECTC activating its primary care pathway whereby out-of-hospital STEMI patients are treated directly at the ECTC instead of being treated elsewhere and then transferred to the ECTC as urgent patients. The emergency proportion has remained fairly stable from 2010 onwards and has been between 31.3% and 34.6%.

The estimated overall in-hospital MACE rate was obtaining by summing the NWQIP generated probabilities for each record. The summed probabilities of all 13,202 PCI records were 363.84. This represents the total number of predicted MACE outcomes for the 13,202 PCIs, expressed as a percentage this is 2.76%. The NWQIP model estimated MACE rate and observed MACE rate was 2.76% and 1.46% respectively. The standard deviation of the NWQIP probabilities was 7.6. Table 4.3.6 and Figure 4.3.3 show the observed and estimated MACE rates by year of PCI.

Table 4.3.6 – Observed and Estimated in-hospital MACE rates for ECTC PCI cohort

Year	Observed (%)	Estimated (%)
2007	0.00	0.75
2008	2.31	1.44
2009	1.77	2.31
2010	1.82	2.86
2011	1.14	3.18
2012	1.21	3.11
2013	1.38	2.84
2014	1.16	2.92
2015	1.06	2.45

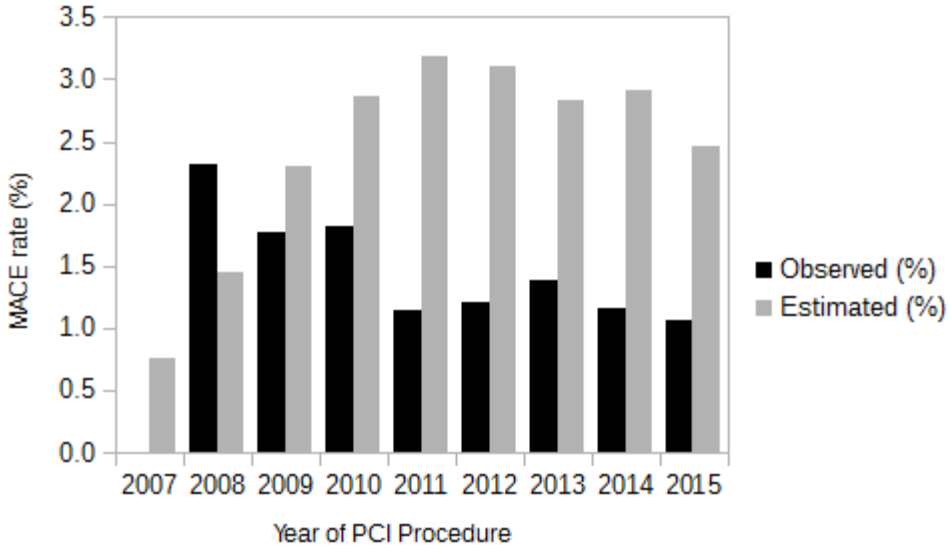


Figure 4.3.3 – Observed and Estimated in-hospital MACE rates for ECTC PCI cohort

4.3.3 Calibration of NWQIP

As detailed in Chapter 3 (General Methods and Data), the NWQIP was tested for its goodness of fit using the Hosmer-Lemeshow test. Eight risk groups were generated based on the record numbers and estimated probability distribution. The group information and statistics are listed in Table 4.3.8.The risk groups which exhibit the largest Hosmer-Lemeshow test statistic value correspond with the poorest fit of observed and expected in-hospital MACE rates. The degrees of freedom (df), chi-square value, and *p* value are listed in Table 4.3.7.

Table 4.3.7 – Hosmer-Lemeshow outcome measures for goodness of fit test

Measure	Calculation/Function	Value
Degrees of freedom	Number groups - 2	6
χ^2	Sum of group 1-8 H&L value	94.48
P Value	CHIDIST(94.48, DOF)	3.54×10^{-18}

Table 4.3.8 – Hosmer-Lemeshow Calibration testing for ECTC Cohort

Group	Obs. MACE	Obs. None	Obs. MACE (%)	Prob. MACE	Prob. None	Expected MACE	Expected None	H&L
1	7	2964	0.24%	0.45%	99.55%	13.4	2957.6	3.09
2	13	2816	0.46%	0.73%	99.27%	20.5	2808.5	2.79
3	7	1190	0.58%	1.15%	98.95%	13.8	1183.2	3.38
4	5	620	0.80%	1.35%	98.65%	8.4	616.6	1.4
5	15	2099	0.71%	1.59%	98.41%	33.7	2080.3	10.52
6	18	1426	1.25%	2.28%	97.72%	32.9	1411.1	6.93
7	23	1199	1.88%	3.98%	96.02%	48.7	1173.3	14.08
8	105	695	13.13%	24.05%	75.95%	192.4	607.6	52.28

The *p* value is below 0.05 indicating that there is a very large difference in at least one of the groups with regards to observed and estimated rates of in-hospital MACE, and hence because of this the model's suitability based on the calibration should be rejected. The poorest fitting groups based on the Hosmer-Lemeshow statistic are groups 5, 7, and 8 respectively as these show the biggest differences between observed and estimated MACE. The four highest groups also exhibit the poorest fits whereby groups 5 to 8 have much poorer fits than 1 to 4. This is shown in Figure 4.3.4.

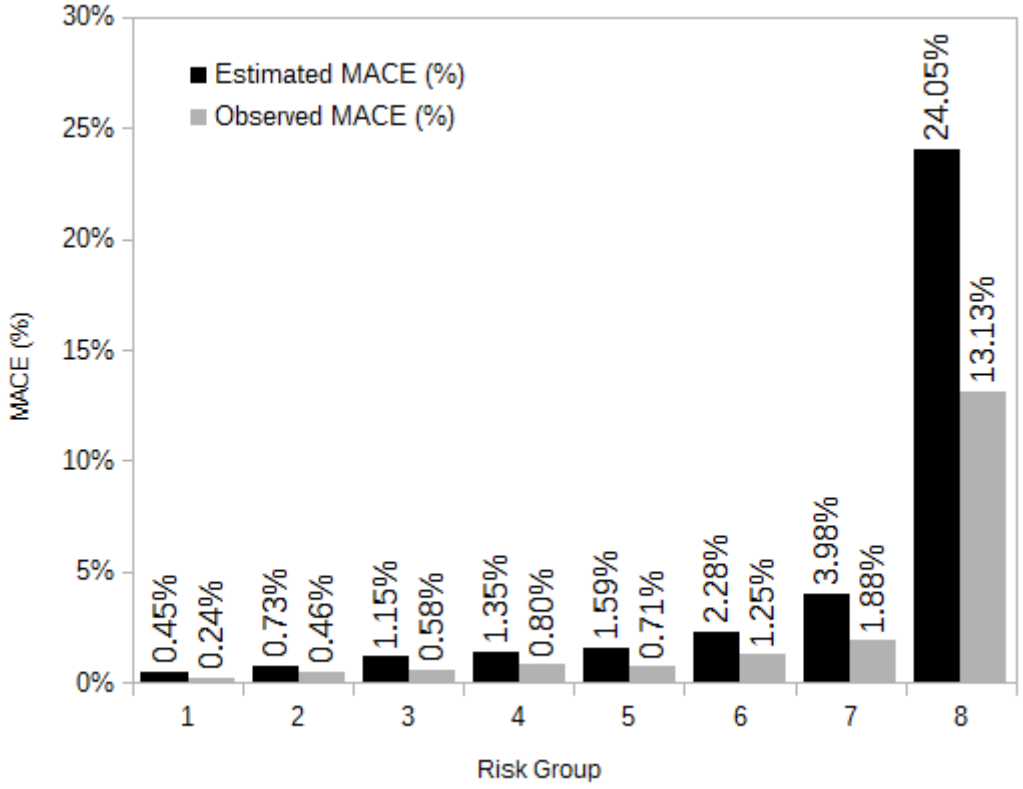


Figure 4.3.4 – MACE NWQIP estimated and observed rates (%)

An overestimation of approximately 50% (relative to the observed MACE %) can be seen in most of the eight risk groups. Following this, a subsequent calibration test (Table 4.3.9) was performed after having divided the estimated NWQIP % by 2, to identify how the calibration changes taking into account this 50% overestimation.

Table 4.3.9 – Hosmer-Lemeshow Calibration testing for ECTC Cohort dividing the estimated NWQIP risk by 2 to account for overestimation

Group	Obs. MACE	Obs. None	Obs. MACE (%)	Prob. MACE	Prob. None	Expected MACE	Expected None	H&L
1	7	2964	0.24%	0.23%	99.77%	6.7	2964.3	0.01
2	13	2816	0.46%	0.36%	99.64%	10.3	2818.7	0.73
3	7	1190	0.58%	0.58%	99.42%	6.9	1190.1	< 0.01
4	5	620	0.80%	0.67%	99.33%	4.2	620.8	0.15
5	15	2099	0.71%	0.80%	99.20%	16.8	2097.2	0.2
6	18	1426	1.25%	1.14%	98.86%	16.5	1427.5	0.14
7	23	1199	1.88%	1.99%	98.01%	24.3	1197.7	0.07
8	105	695	13.13	12.02%	87.98%	92.2	703.8	0.91

The Hosmer-Lemeshow test was non-significant ($\chi^2 = 2.23$, $p = 0.89$, df =6), meaning a good fit of estimated versus observed MACE is present. Each risk group still features the same patients hence the observed MACE is the same.

4.3.4 Discrimination Performance of NWQIP

The area under the ROC curve (AUROC) for the 13,202 PCIs in the ECTC cohort is shown in Figure 4.3.5. The discrimination input was the generated NWQIP probabilities and the outcome was the presence of in-hospital MACE.

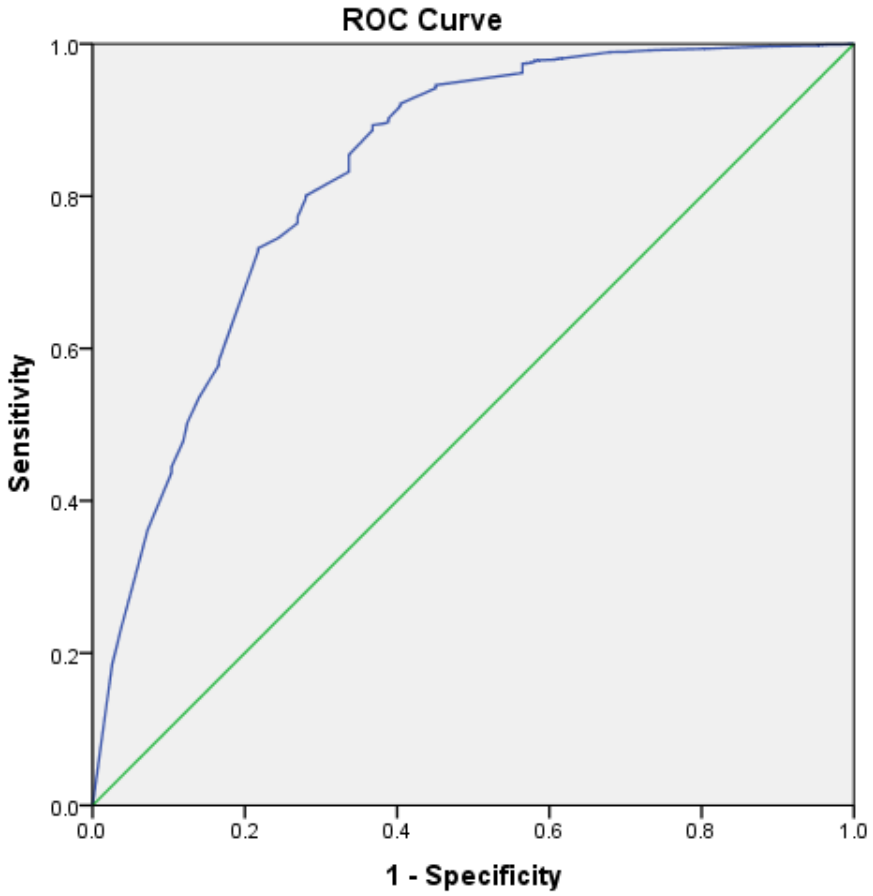


Figure 4.3.5 *– ROC curve for estimated NWQIP probability of MACE*

The AUROC was 0.83, the 95% confidence limits for this were 0.79 to 0.86 and the corresponding standard error was 0.017.

The AUROC was recalculated following the recalibration changes in Table 4.3.9, this was identical to the AUROC prior to recalibration (ROC = 0.83), as anticipated, as the patients are still in the same risk groups and hence the cut-off point during the sensitivity and specificity analysis for the ROC curve remains the same.

4.4 Discussion

The NWQIP risk prediction model was externally tested on the ECTC PCI cohort. This set of PCI procedures were performed in a different part of the UK (south-east) compared to the original NWQIP study and external validation study by Kunadian et al. (2008). The ECTC cohort is more recent compared to the original NWQIP study. Such differences in eras provide several important changes that can potentially alter adverse outcome rates amongst PCI patients. For example, modern cohorts are more likely to use a higher proportion of DES (and subsequent generations of DES) whereas in prior years there would have been a higher usage of BMS or, if you go back further in time, just standard balloon angioplasty with no stent insertion. Pharmacological therapy such as dual antiplatelet therapy (DAPT) may also be responsible. As reported in the BCIS Audit (2015) there has been an increase in the number of PCI centres and operators which could result in a faster treatment window for emergency patients. The ECTC cohort featured a much higher proportion of elderly patients, for example patients aged 70 years or above represented 38.8% overall compared to 20.4% in the original NWQIP study. The ECTC cohort also has an approximate additional 5% of male patients (at 75.3% relative to 70.9%). The ECTC cohort included more diabetic patients (17.5% relative to 13.7%) and of crucial importance, the ECTC involved more emergency patients (30.0% relative to 10.8%) and conversely a lower proportion of elective patients (40.3% relative to 56.3%). A lot of these characteristics would suggest that a higher rate of in-hospital MACE should be expected, but that was not observed.

The NWQIP risk model estimated an overall in-hospital MACE rate of 2.76% (364 patients) in the ECTC cohort of 13,202 PCIs, the actual MACE rate was only 1.46% (193 patients) however therefore suggesting that NWQIP overestimates the number of adverse outcomes by almost double. The majority of the eight risk groups seemed to feature this 50% increase in estimation. By dividing the estimated NWQIP probabilities by 2 (Table 4.3.9) and testing the calibration, the goodness of fit became non-significant, as expected with a $p = 0.89$, indicating close to a perfect fit, however it should be noted that this is essentially rescaling the estimated risk and does not yield any information whatsoever about which of the NWQIP risk factors have changed in terms of the association with in-hospital MACE. The readjustment of the NWQIP probabilities in this manner also does not change the low distribution of observed risk amongst the groups, i.e. risk groups 1 to 5 have the observed rates of 0.24%, 0.46%, 0.58%, and 0.80% respectively, thus distinguishing between a patient in risk group 2 with another in group 3 becomes difficult.

The area under the ROC curve was 0.83 which indicates a good ability to discriminate overall between patients experiencing/not experiencing MACE. However when the cohort of patients were ordered by estimated NWQIP risk of MACE and places into separate risk groups, the fit of estimated versus observed MACE was poor in most groups, especially the higher risk groups. The Hosmer-Lemeshow $\chi^2 = 94.48$ (df = 6) and the $p = 3.54\times10^{-18}$. A perfect calibration of observed and estimated MACE rates would be $p = 1$ and clearly the small p value suggests a very poor fit overall. Of the risk factors within the NWQIP model, only treatment to graft vessels no longer had a statistically significant univariate association with in-hospital MACE, this may be because operators are more experienced, or it may be due to operators not attempting to perform PCI to these vessels on given patients, as they may have done in the past. This suggests that it be omitted from future risk prediction models. The other variables in the NWQIP model, whilst significant, saw a reduction in the observed MACE race hence favouring recalibration of the coefficients.

Tables 4.3.3 and 4.3.4 show that the ECTC has a lower in-hospital death rate (1.11%) than the national average from years 2009 onwards, however, the Q-wave MI, cerebrovascular accident, and emergency CABG events exhibit slightly increased risks than the national average, this however, is likely to be explained by the fact that not all cardiac centres perform PCIs on high volumes of emergency patients like the ECTC does, this is consistent with the ECTC beginning its primary PCI treatment activation. Another possible explanation is that patients which exhibit a non-death MACE component at the ECTC, may have died had they been treated at a certain other cardiac centre, whereas at the ECTC they survived death but this resulted in another MACE component from occurring although this is not possible prove and it just a possible explanation. Overall, the MACE component rates are similar to the national averages across each year.

4.4.1 Limitations

A potential limitation is that it is assumed the staff (operators, consultants, and nurses) at the ECTC are appropriately skilled and trained to record complications correctly in the appropriate fields, i.e. if certain staff members are not storing all of the in-hospital MACE complications accurately this could lead to an underestimation of MACE events and hence influence the verification of the NWQIP model on the ECTC cohort. However, this potential limitation is minor would be present at every other cardiac centre and hospital. It was not possible to identify whether all staff were trained correctly or whether the complications, if any such occurred, were recognised. Clearly two of the four MACE components are easily recognisable, these being emergency CABG surgery and death,

but it may be the case that not all cerebrovascular accidents (stroke) or Q-wave MIs were recognised and hence recorded in the database.

4.4.2 Conclusions

The first hypothesis (section 1.3) in this thesis predicted that the NWQIP would not perform as effectively as it did on the original cohort (Grayson et al., 2006), or external validation study (Kunadian et al., 2008). This was proved to be true, despite the discrimination resulting in AUROC = 0.83, the calibration of observed and estimated groups was extremely poor ($\chi^2 = 94.48$, df = 6, $p = 3.54\times10^{-18}$) due to large differences in multiple risk groups. This negatively affects the usefulness of the model on the ECTC cohort. It is anticipated that subsequent external validation of the NWQIP model will confirm the findings of this study, that it may produce a satisfactory discrimination performance (i.e. AUROC = 0.8) but will also however exhibit a poor calibration for different risk groups.

Differences in the NWQIP estimated in-hospital MACE rate and the observed rates are difficult to ascertain the exact reason. It is however hypothesised that the cause is due to multiple reasons some of which have already been explained. In summary it anticipated that the following are all responsible however to isolate each them and to identify to what degree is difficult. Given the increase in certain characteristics predisposed to adverse outcomes such as in-hospital MACE it would be logical to assume higher risk estimation, as generated in the ECTC dataset using the NWQIP model, however a much lower observed risk was observed.

Firstly, the higher usage of DES may have a protective effect on complications. Typically it may be the case that smaller stents can be inserted into the coronary arteries than with BMS. Another reason may be that more PCI centres and registered operators means more emergency patients can be reach a PCI centre and subsequently be treated compared with previously where patients which had an out-of-hospital myocardial infarction could have been more likely to die before an ambulance reached them or if alive whilst an ambulance arrived, less likely to reach the PCI centre alive, because this data was not available for analysis it is difficult to verify. It may also be the case that operators are better trained now compared with previously, higher frequencies of patients receiving PCIs (of all priorities) may allow better training for junior doctors/operators and hence increase their efficiency and speed of performing PCI, this would obviously be of paramount importance in emergency procedures, as restoring blood flow to the tissues of the heart faster would result in less cardiac tissue dying.

The NWQIP risk model may benefit from recalibration of its incorporated risk factors. One approach would be simply to regenerate the logistic regression coefficients by using a modern PCI cohort. However a better solution may be to perform a completely new multivariate logistic regression analysis on a modern dataset, whilst utilising all available data fields, such as demographic, clinical, and procedural characteristics. Because of national bodies suggesting minimum dataset for PCIs and CABG surgery, modern PCI databases are more likely to be complete (i.e. little missing data) and have more data fields stored compared to the era when the NWQIP risk model was developed. By performing a new regression analysis it could potentially identify novel risk factors that had not previously been linked to adverse outcomes following PCI. It would be useful to also investigate whether increasing rates of comorbidities have an effect on elective patients, if previously diagnosed with cardiovascular disease a patient now may more likely be treated with pharmacological therapy (e.g. aspirin or clopidogrel) and hence only more seriously ill elective patients might go on to receive a PCI at the ECTC.

4.4.3 Future Work

In-hospital MACE rates occur at low frequencies, therefore for future work it would be beneficial if such data were available to extend the outcome period from in-hospital only to 30 day or one-year. Previous studies have suggested that if an emergency patient survives the first 30 days following their PCI procedure they have a good chance of surviving the near future. Unfortunately the dataset for this study did not have post-discharge complications available or the date at which they occurred. An issue with using in-hospital MACE as the outcome is that complications may not be recorded or recognised as easily, it is obvious that if a patient died or needs to undergo emergency CABG that these MACE components are easily known, but Q-wave myocardial infarctions and cerebrovascular accidents are more complicated to recognise and hence be recorded accurately in the database. It would be beneficial to see if robust and clear outcomes such as short to long-term mortality be investigated, this way high data completion rates would be expected and it can be assumed to be more accurate than complications fields, for example, some Q-wave myocardial infarction complications may be incorrectly recorded as non-Q-wave myocardial infarctions in the database and hence affecting the accuracy of risk prediction models. The benefit of looking at outcomes such as 30-day mortality, for example, is that some patients may survive the PCI procedure but exhibit complications shortly after they are transferred to another hospital. The useful outcome of 30 days bypasses this issue as regardless of where the patient dies, they will be reported as dead in ECTC database and hence provide a more robust and reliable outcome.

Chapter 5: 30-Day Mortality Prediction

5.1 Introduction

The analysis from Chapter 4, the evaluation of the North West Quality Improvement Programme (NWQIP) risk prediction model (Grayson et al, 2006), found that the NWQIP model could discriminate well using the outcome of in-hospital major adverse cardiac events (MACE) in a modern PCI cohort that was in a different geographical area (i.e. south-east England instead of north-west). The area under the receiver operating characteristic (ROC) curve was 0.83 (95% CI 0.79 to 0.86), this value is considered 'good' (Metz, 1978; Obuchowski, 2003; Ludemann et al., 2006). The calibration, which is a goodness of fit between observed and estimated in-hospital MACE rates amongst different risk groups based on ascending level of risk, was poor however ($\chi^2 = 94.4$, df = 6, $p < 0.001$). The small p value indicates that there were very large differences in at least one risk group with regards to observed and estimated rates. The analysis found that the four highest risk groups (out of a total of 8) had large differences between observed and estimated rates, thus affecting the risk models usefulness as a prediction tool for in-hospital MACE following PCI. There were many differences between the PCI characteristics (demographics, comorbidities, and procedural) of the original NWQIP cohort, the external validation study by Kunadian et al. (2008), and the ECTC PCI cohort. These differences are theorised to be responsible for the NWQIP risk model's calibration performance worsening on the modern ECTC cohort. In addition to these characteristics, differences in stenting technology (i.e. subsequent generations of drug-eluting stents, DES) and pharmacological therapies (dual antiplatelet and aspirin) are thought to be responsible.

Table 5.1.1 summarises the prominent differences between the three cohorts with regards to characteristics in the datasets.

Table 5.1.1 – Prominent characteristic differences between PCI cohorts

Characteristic	NWQIP (2006)	Kunadian (2008)	ECTC
Age ≥ 70 years	20.4%	26.4%	38.8%
Emergency PCI	10.8%	17.6%	26.9%
Prior PCI	NA	12.6%	20.1%
Diabetes	13.2%	14.7%	17.4%
Renal dysfunction	0.9%	1.6%	4.4%
Cardiogenic shock	0.7%	1.7%	2.5%
ACS/AMI	10.3%	16.1%	56.0%

It is anticipated that the manifestation of different comorbidity rates identified in modern UK populations may affect the adverse complication outcome rates, for example

increasing rates of diabetes mellitus, peripheral vascular disease (PVD), chronic obstructive pulmonary disease (COPD), renal disease etc.

As Chapter 4 determined in the analysis, graft lesions were no longer significant in their univariate association with in-hospital MACE, and that would suggest that recalibration of the NWQIP model using a modern PCI cohort is warranted. The NWQIP model overestimated the in-hospital MACE rate by predicting 2.76% when the actual rate was 1.46%. It could be the case than advances in interventional technology (i.e. higher usage of DES stents) or an increase in cardiac centres and hence more rapid revascularisation for emergency patients, be responsible for changes in adverse outcome rates.

By performing a multivariate logistic regression analysis on the contemporary ECTC PCI cohort of patients it may allow for improved discrimination and calibration in the modern era of PCI intervention, and thus provide a useful prediction tool for hospitals and cardiac centres, replacing the need for older models such as the NWQIP risk model which do not appear to be highly calibrated on the modern ECTC cohort. The in-hospital MACE outcome incorporates some components which occur at very low rates. These rates among the three PCI cohorts (original NWQIP training set, external validation cohort study, and the ECTC cohort) are listed in Table 5.1.2.

Table 5.1.2 – in-hospital MACE components (excluding death) for the NWQIP, external validation study and ECTC cohorts

MACE Component	NWQIP	Kunadian	ECTC
Emergency CABG	0.15%	0.14%	0.09%
Cerebrovascular disease	0.2%	0.20%	0.12%
Q-wave MI	0.4%	0.22%	0.19%

The in-hospital MACE components (apart from death) occur at such low rates it makes identifying statistically significant associations between them and certain characteristics difficult. Another issue with three of the MACE components (emergency CABG less so) is that they require accurate and timely identification of their occurrence, which inevitably will lead to some data inaccuracies. This is especially likely to occur when patients are transferred out of the ECTC to general hospitals following their PCI procedure. A more robust and informative outcome of interest is 30-day mortality, which is defined as death within 30 days of a patient's PCI procedure date, this does not factor length of stay (LOS) as patients of different priorities and conditions are likely to exhibit different LOS. The outcome of 30-day mortality is also more useful for patients and clinicians as the 30-day period has been defined as significant with regards to predicting recovery from the PCI procedure. In addition to these benefits of 30-day mortality versus in-hospital MACE, the

former is also likely to occur at a much higher rate thus increasing the statistical power and hence strength of univariate and multivariate associations.

The original NWQIP study was performed on a PCI cohort from August 2001 to December 2003, and consequently reports less variables tested for their univariate association than are typically recorded in modern PCI practice within the UK. The main reason for more variables and also increased data completeness is that the national audit body, the British Cardiovascular Intervention Society (BCIS), specify a minimum dataset which all PCI centres must provide (BCIS Dataset version 5.6.2). Identification of novel associations from previously untested characteristics may reveal several important new predictors of adverse outcomes which were discovered during the original NWQIP study era.

5.5.1 Hypothesis and Objectives

The hypothesis for this study is that a multivariate logistic regression model can be constructed to predict 30-day mortality. Due to the comprehensive ECTC PCI database, novel risk factors will be discovered 30-day mortality that were not present in the original NWQIP model, additionally, not all of the NWQIP risk factors will still be useful in predicting in-hospital MACE, or 30-day mortality and hence not required in modern risk prediction models. Usage of the 30-day mortality endpoint is predicted to be more robust (i.e. easily recognisable and hence recorded in the database) and hence it is anticipated that that risk models predicting this outcome could achieve good discrimination and calibration.

This study has the following objectives, which aim to test the specified hypothesis:

(1) Evaluate the NWQIP prediction model for 30-day mortality (i.e. instead of in-hospital MACE).
(2) Construct a prediction model for 30-day mortality using multivariate logistic regression analysis.
(3) Produce an integer-based scoring system for easy calculation of risk.
(4) Test the discrimination and calibration performance (training set).
(5) Verify the discrimination and calibration performance on an internal validation set.
(6) Identify the possible reasons behind any performance changes (for better or worse).
(7) Compare the predictors of the 30-day mortality analysis to existing published literature.

5.2 Methods

Many of the methods utilised in this study have been detailed in the General Methods and Data Chapter (3), but are also briefly described again here.

5.2.1 Database and Study Population

This study was a retrospective cohort study of data collected prospectively and recorded in the ECTC's comprehensive cardiovascular patient information management database (CVIS, Philips). The data was collected for all patients that have been to the ECTC for percutaneous coronary intervention (PCI) from 1st July 2007 to 31st January 2015. The entire database available for analysis comprises 13,938 consecutive PCI procedures featuring all levels of priority (elective, urgent, emergency, and salvage) and hence includes weekend and out of hours procedures. Within the entire set of 13,938 procedures, 3.9% (540 PCIs) contained missing data for a NWQIP risk factor (LMS lesion, graft lesion, cerebrovascular disease, or priority), a custom 30-day mortality independent predictor, or outcome data (i.e. in-hospital MACE or 30-day mortality) and consequently had to be excluded from analysis, otherwise comparing performance of NWQIP versus a custom prediction model would not be fair because different data would have been used to generate the performance metric results (discrimination and calibration). Repeat PCI procedures occurring within 30 days of the initial procedure were excluded.

The number of records retained in the final analysis was 13,398. This cohort of valid PCIs was further split into a training/development set and a validation set using a ratio of approximately 2:1, based on the date of the procedure. The date was chosen as the method of splitting over a random allocation because it would be more robust to future trends, for example, if a set of independent predictors are identified through the analysis of the training set and these are subsequently validated as predictors in the validation set then it proves they are robust to future trends/changes that may exist in the data. The training set contained 9279 PCIs from 1st July 2007 to 31st December 2012, and the validation cohort featured 4119 PCIs from 1st January 2013 to 31st January 2015.

The characteristics relating to the PCI procedures are listed in General Methods (Chapter 3) and Appendix B1. In brief, the following sets PCI characteristics were available for analysis, in addition to those recorded for MINAP (emergency/myocardial infarction).

Dates and Times

PCI operation, symptom onset (ACS only), arrival at first hospital (ACS only), arrival at PCI hospital (ACS only), first balloon inflation, admission, waiting list, arrival, discharge date, length of stay duration.

Staff Details

Consultant responsible, primary operation, primary operator status, second operator, consultant, reported by, reported by position, authorised by, authorised by position.

Demographic/History Characteristics

Age in years (time of procedure), sex, test reason, ethnic group, priority, intended and actual procedures, prior MI/CABG/PCI, renal disease history, LVEF category, diabetes status, medical history (e.g. Hypercholesterolaemia, hypertension, COPD, PVD, stroke etc.), cardiogenic shock (pre-procedure), stenosis percentages of LMS/LAD other/LAD proximal/RCA/LCX, number of grafts present, TIMI flow, clinical syndrome, indication for intervention, arterial access method, smoking status, BMI classification, CAD family history, renal problems.

Angiographic and Procedural Characteristics

Vessel(s) attempted, graft vessels attempted, number of CTOs attempted, number of lesions attempted, number of lesions successful, largest balloon/stent used, indication for stent, number restenoses attempted, number in-stent stenosis attempted, number stents used, number DES used, longest stented/treated segment, procedural complications, arterial complications, Post procedural complications, GP IIb/IIIa used during procedure, discharge status, drugs used, devices used, presenting ECG (ACS only), cardiac enzymes/markers raised, CCS angina status, NYHA dyspnoea status, ventilated pre-operation, rotablation, multivessel disease, pressure wire, IVUS, discharge location, ECG ischemia, heparin administered, bival administered.

Outcome/Complication Characteristics

Procedural complications, (e.g. coronary dissection, cardiac arrest), post-procedural complications, hospital outcome complications (e.g. blood transfusion, Q-wave MI), death (including patient date of death), and corresponding PCI procedure link.

5.2.2 External Validation of NWQIP

As detailed in Chapter 4, the reported logistic regression coefficients from the NWQIP risk model (Grayson et al, 2006) were used to calculate the predicted probability of in-hospital MACE for the training set, so that fair performance comparisons can be made between the NWQIP model and custom prediction model. Subsequent validation was performed using the AUROC (Hanley & McNeil, 1982) for assessing discrimination performance. The calibration, which is a fit between observed and predicted outcomes for different groups ordered by ascending risk, was assessed using the Hosmer-Lemeshow goodness of fit test (Hosmer & Lemeshow, 2013). First, the performance was tested using the in-hospital MACE outcome, defined as the occurrence of at least one of the following: in-hospital death (during the same admission of the PCI regardless of the cause); emergency CABG surgery; Q-wave MI, defined as a new pathological Q wave with creatine kinase (CK) more than twice the laboratory upper limit, or normal with elevated CK-MB or troponin T (BCIS Dataset, 2014); cerebrovascular accident (stroke). Second, the estimated probabilities were used with the 30-day mortality outcome, defined as death from any cause up to and including 30 days following the date of the PCI. For deaths which occurred following a patient's discharge, these were reported by a national data source, the linked HES-ONS (hospital episode statistics-office for national statistics; NHS Digital, 2017) mortality which tracks patients deaths and is updated internally on a monthly basis.

5.2.3 Statistical Methods

Continuous variables are represented using the mean and standard deviation (SD), and categorical/discrete variables such as procedure priority are expressed as a percentage. Univariate analysis was performed to identify the set of variables in the CVIS database that were significantly associated with 30-day mortality, the significance criteria for the univariate analysis was $p < 0.1$, this value is adopted in many studies including the original NWQIP analysis (Grayson et al., 2006) to identify potential predictors that may have low odds ratios (relative to emergency PCI for example), but do have a measurable effect. Subsequent regression analysis then only retains these predictors if $p < 0.05$ in the multivariate model (Bursac et al., 2008; Hannan et al., 2013). The nominal/categorical variables were analysed using chi-square test of Fisher's exact test where appropriate (i.e. variables which had small frequency counts), continuous data were tested using the Student's t-test. The odds ratios, 95% odds ratio confidence limits, and significance (*p*

value) were calculated for each variable with regards to their 30-day mortality association. The significant variables ($p < 0.1$) and those considered clinically important predictors were used as candidate variables for entry into the multivariate logistic regression analysis using forward selection. Following the regression analysis, the set of candidate predictors which exhibited a significance of $p < 0.05$ were retained and used in the final regression model. The bootstrap resampling technique (Efron & Tibshirani, 1986) was performed to generate 200 random samples with replacement from 70% of the training set population, this resampling allows relatively unbiased approximations of the predictive performance (discrimination), meaning it identifies whether the training set AUROC is stable.

In several PCI risk prediction models, such as the Toronto score (Chowdhary et al, 2009), and New York State Risk Score (Hannan et al, 2013), an additive integer score system was created as a simple tool for clinicians allowing an easier way of calculating a patient's risk without the need for a calculator or computer. In brief, a positive integer is assigned to each of the independent risk factors in the given multivariate regression model based closely on the odds ratio, often rounded to the nearest integer value. A similar scoring method has been adopted in the multivariate model developed for this study, utilising rounding up at .5. Patients were classified into one of five different risk groups based on the total integer score of their combined risk factors in the multivariate model (Table 5.2.1).

Table 5.2.1 – Integer risk score groups for multivariate 30-day mortality risk model

Risk Group	Integer Score (range)
Very low	0 to 9
Low	10 to 14
Moderate	15 to 19
High	20 to 24
Very high	$\geq$ 25

To detect possible multicollinearity between the risk factors within the custom multivariate logistic regression model, the variance inflation factor (VIF) and tolerance were calculated for each variable, a VIF of ≥ 4.0 and/or a tolerance of < 0.2 were considered thresholds/indicators for cause for concern (As described in 3.4).

Data were analysed using the statistical analysis software package SPSS for Windows release 20.0.0 (IBM Corporation, NY, USA).

5.3 Results

5.3.1 Outcomes following PCI

In the training set of 9279 PCI operations there were 128 (1.4%) in-hospital MACE complications. These are displayed in table 5.3.1 along with the corresponding validation set (4119 PCIs) outcomes. Within the MACE outcome there were: 96 (1.0%) in-hospital deaths; 20 (0.2%) Q-wave MIs; 10 (0.1%) emergency CABGs; and 6 (< 0.1%) cerebrovascular accidents.

Table 5.3.1 – in-hospital MACE and 30-day mortality outcomes for the ECTC training set (n = 9279) and validation set (n = 4119)

Outcome	Count	Percentage
Training Set (n = 9279)	-	-
In-hospital MACE total	128	1.4%
In-hospital death	96	1.0%
Q-wave MI	20	0.2%
Emergency CABG	10	0.1%
Cerebrovascular accident	6	< 0.1%
30-day mortality	197	2.1%
Validation Set (n = 4119)	-	-
In-hospital MACE total	45	1.1%
In-hospital death	31	0.8%
Q-wave MI	8	0.2%
Emergency CABG	4	0.1%
Cerebrovascular accident	2	< 0.1%
30-day mortality	84	2.0%

The in-hospital MACE complications reported above were not mutually exclusive. The majority of patients exhibiting in-hospital MACE did only develop a single component of MACE. The 30-day mortality count was 197 (2.1%) and within this end-point 101 (1.1%) died following discharge from the ECTC, but within the 30-day period. Of the 101 patients which survived to discharge, 36 of these died within seven days of their discharge date. The mean age (SD) of the training set cohort was 65.4 years (11.8), 74.7% of the patients were male. The most common indication for PCI as classified by the BCIS specification (BCIS Dataset, 2014) was stable angina (3869 patients, 41.7%), followed by 'Unstable angina/NSTEMI/convalescent STEMI' (2909, 31.4%), and Primary PCI (1984, 21.4%). The remaining 5.5% of indications comprise: rescue PCI, reinfarction PCI, unlisted/unspecified, bail out interventions. Table 5.3.2 reports the in-hospital MACE and 30-day mortality rates by priority of PCI for both the training and validation sets. As anticipated the highest adverse outcome rates are seen in the emergency priority PCI patients.

Table 5.3.2 – in-hospital MACE and 30-day mortality outcomes by PCI priority

Outcome	Elective (n)	Urgent (n)	Emergency (n)
Training Set (n = 9279)	-	-	
In-hospital MACE total	0.5% (22)	0.6% (15)	3.6% (91)
30-day mortality	0.4% (17)	0.9% (25)	6.1% (155)
Validation Set (n = 4119)			
In-hospital MACE total	<0.1% (1)	0.9% (10)	2.4% (34)
30-day mortality	0.3% (4)	1.0% (11)	4.9% (69)

Stent usage was high at 93.4% with 30.7% (2852 PCIs) having DES stents exclusively inserted, and 62.5% (5824) underwent PCI with at least one BMS stent inserted, and 6.5% (603) did not have any stents used, i.e. just standard balloon angioplasty may have been used.

5.3.2 Univariate Associations with In-hospital MACE

Whilst the primary outcome of interest in this analysis was 30-day all-cause mortality, the in-hospital MACE univariate analysis produced the following significant univariate associations. Table 5.3.3 displays the characteristic, odds ratio, and corresponding *p* value.

Table 5.3.3 –significant univariate associations with in-hospital MACE (training set)

Characteristic	**Odds Ratio**	***P* Value**
Age group 70-79 years	2.94	0.008
Age group ≥ 80 years	5.97	< 0.001
Female gender	2.70	< 0.001
Peripheral vascular disease	2.94	< 0.001
Renal disease	2.13	0.004
Prior CABG	0.30	0.030
Emergency PCI Priority	7.87	< 0.001
Cerebrovascular disease	3.22	< 0.001
Cardiogenic shock	27.29	< 0.001
Pre-operation ventilation	19.10	< 0.001
LVEF 30-50%	2.78	0.002
LVEF < 30%	20.35	< 0.001
TIMI flow grade < 3	3.59	< 0.001
Left main stem lesions	2.75	0.008

5.3.3 Univariate Associations with 30-Day Mortality

The baseline characteristics (demographic, clinical and procedural) from the training set are displayed in tables 5.3.5 and 5.3.6, respectively. Both of the tables display the associations with 30-day all-cause mortality end-point, including the odds ratios, 95% confidence intervals, and *p* values. The patient percentage columns represent the percentage relative to the valid data, i.e. it excludes the missing records. The missing column represents the raw count of missing/blank records in the training set. The characteristics which exhibited a univariate association with 30-day mortality that had a significance of $p < 0.1$ were used as candidates for entry into the subsequent multivariate regression analysis. These characteristics were: age group (by decade); sex; PCI priority; diabetes mellitus; prior PCI; prior CABG; PVD; renal disease; cerebrovascular disease; cardiogenic shock (pre-procedural); COPD; pre-operation ventilation; LMS lesions; Despite TIMI flow grade, LVEF, and angina status classification (Canadian Cardiovascular Society) exhibiting significant relationships with 30-day mortality ($p < 0.001$; $p < 0.001$; and $p < 0.001$ respectively), these were excluded from the regression analysis because of the high percentage of missing data. TIMI flow grade and LVEF showed high odds ratios and contained 72.9% and 34.5% missing data respectively.

Table 5.3.4–significant univariate associations with 30-day mortality (training set) used as candidates for multivariate analysis

Characteristic	Odds Ratio	*P* Value
Age group 70-79 years	3.33	0.001
Age group ≥ 80 years	9.40	< 0.001
Female gender	2.23	< 0.001
Peripheral vascular disease	2.84	< 0.001
Renal disease	3.28	< 0.001
Prior CABG	0.47	0.044
Urgent PCI Priority	2.47	0.003
Emergency PCI Priority	16.18	< 0.001
Cerebrovascular disease	2.47	0.003
Cardiogenic shock	27.26	< 0.001
Pre-operation ventilation	24.66	< 0.001
LVEF 30-50%	4.78	< 0.001
LVEF < 30%	31.17	< 0.001
TIMI flow grade < 3	6.81	< 0.001
Left main stem lesions	2.87	< 0.001
Prior PCI	0.54	0.004
COPD	1.76	0.043
PVD	2.84	< 0.001

Table 5.3.5– univariate associations of 30-day mortality with ECTC training set (n = 9279) demographic and clinical characteristics

Variable	Patients (%)	IH-MACE (%)	30-Day (n)	OR (95% CI)	P Value	Missing (n)
Age (years)						0
< 50	1007 (10.4)	7 (0.7)	8 (0.8)	**Reference**		
50-59	1897 (19.6)	7 (0.4)	11 (0.6)	0.73 (0.29 to 1.82)	0.497	
60-69	3004 (31.1)	27 (0.9)	46 (1.5)	1.94 (0.91 to 4.13)	0.085	
70-79	2583 (26.7)	52 (2.0)	67 (2.6)	3.33 (1.59 to 6.95)	*0.001*	
≥ 80	1171 (12.1)	47 (4.0)	82 (7.0)	9.40 (4.53 to 19.53)	*< 0.001*	
Sex						2
Male	7232 (74.9)	74 (1.0)	122 (1.7)	**Reference**		
Female	2428 (25.1)	66 (2.7)	92 (3.8)	2.23 (1.74 to 3.02)	*< 0.001*	
Diabetes						299
No	7736 (82.6)	98 (1.3)	149 (1.9)	**Reference**		
Yes	1627 (17.4)	28 (1.7)	44 (2.7)	1.42 (1.01 to 1.99)	*0.045*	
Hypertension						375
No	4106 (44.2)	67 (1.6)	91 (2.2)	**Reference**		
Yes	5181 (55.8)	67 (1.3)	113 (2.2)	0.98 (0.74 to 1.30)	0.908	
PVD						375
No	8951 (96.4)	121 (1.4)	185 (2.1)	**Reference**		
Yes	336 (3.6)	13 (3.9)	19 (5.7)	2.84 (1.75 to 4.61)	*< 0.001*	
Renal Disease						1731
No	6943 (87.5)	60 (0.9)	77 (1.1)	**Reference**		
Yes	988 (12.5)	18 (1.8)	35 (3.5)	3.28 (2.18 to 4.91)	*< 0.001*	
Renal Dysfunction						375
No	8874 (95.6)	129 (1.5)	189 (2.1)	**Reference**		
Yes	413 (4.4)	5 (1.2)	15 (3.6)	1.73 (1.01 to 2.96)	*0.042*	
Prior CABG						98
No	8890 (93.0)	130 (1.5)	195 (2.2)	**Reference**		
Yes	674 (7.0)	3 (0.4)	7 (1.0)	0.47 (0.22 to 0.99)	*0.044*	
Prior MI						336
No	6801 (72.9)	91 (1.3)	143 (2.1)	**Reference**		
Yes	2525	35	49 (1.9)	0.92 (0.66 to 1.28)	0.624	

	(27.1)	(1.4)				
Prior PCI						
No	7605 (79.9)	112 (1.5)	175 (2.3)	**Reference**		144
Yes	1913 (20.1)	20 (1.0)	24 (1.3)	0.54 (0.35 to 0.83)	*0.004*	
Priority						0
Elective	4260 (44.1)	22 (0.5)	18 (0.4)	**Reference**		
Urgent	2802 (29.0)	16 (0.6)	29 (1.0)	2.47 (1.37 to 4.45)	*0.003*	
Emergency	2600 (26.9)	102 (3.9)	167 (6.4)	16.18 (9.92 to 26.37)	*< 0.001*	
Cerebrovascular disease						375
No	8927 (96.1)	119 (1.3)	186 (2.1)	**Reference**		
Yes	360 (3.9)	15 (4.2)	18 (5.0)	2.47 (1.51 to 4.06)	*< 0.001*	
Cardiogenic shock						0
No	9422 (97.5)	90 (1.0)	143 (1.5)	**Reference**		
Yes	240 (2.5)	50 (20.8)	71 (29.6)	27.26 (19.74 to 37.64)	*< 0.001*	
COPD						375
No	8907 (95.9)	129 (1.4)	190 (2.1)	**Reference**		
Yes	380 (4.1)	5 (1.3)	14 (3.7)	1.76 (1.01 to 3.05)	*0.043*	
VHD						375
No	9192 (99.0)	134 (1.5)	200 (2.2)	**Reference**		
Yes	95 (1.0)	0 (0.0%)	4 (4.2)	1.98 (0.72 to 5.43)	0.178	
Ventilated (pre-op)						0
No	9542 (98.8)	117 (1.2)	176 (1.8)	**Reference**		
Yes	120 (1.2)	23 (19.2)	38 (31.7)	24.66 (16.33 to 37.26)	*< 0.001*	
Coronary Syndrome						15
Stable	4248 (44.0)	22 (0.5)	18 (0.4)	**Reference**		
ACS/AMI	5399 (56.0)	118 (2.2)	196 (3.6)	8.85 (5.45 to 14.370)	*< 0.001*	

Table 5.3.6– univariate associations of 30-day mortality with ECTC training set (n = 9279) procedural characteristics

Variable	Patients (%)	IH - MACE (%)	30-Day (%)	OR (95% CI)	P Value	Missing
LVEF						3335
> 50%	4123 (65.2)	16 (0.4)	17 (0.4)	**Reference**		
30-50%	1959 (31.0)	21 (1.1)	38 (1.9)	4.78 (2.69 to 8.49)	< *0.001*	
< 30%	245 (3.9)	18 (7.3)	28 (11.4)	31.17 (16.80 to 57.81)	< *0.001*	
TIMI Flow						7044
3	1005 (38.4)	12 (1.2)	11 (1.1)	**Reference**		
< 3	1613 (61.6)	67 (4.2)	113 (7.0)	6.81 (3.65 to 12.71)	< *0.001*	
Graft lesions						17
No	9407 (97.5)	137 (1.5)	208 (2.2)	**Reference**		
Yes	238 (2.5)	2 (0.8)	6 (2.5)	1.14 (0.50 to 2.60)	0.749	
LMS lesions						0
No	9476 (98.1)	133 (1.4)	203 (2.1)	**Reference**		
Yes	186 (1.9)	7 (3.8)	11 (5.9)	2.87 (1.54 to 5.37)	< *0.001*	
Multivessel PCI						238
No	8043 (85.3)	112 (1.4)	178 (2.2)	**Reference**		
Yes	1381 (14.7)	26 (1.9)	30 (2.2)	0.98 (0.66 to 1.45)	0.924	
CTO						214
No	8763 (92.7)	123 (1.4)	194 (2.2)	**Reference**		
Yes	685 (7.3)	13 (1.9)	18 (2.6)	1.19 (0.73 to 1.94)	0.481	

5.3.4 External Validation of NWQIP

Using the ECTC training set (n = 9279), the NWQIP risk prediction model was validated for two outcomes of interest. Firstly, the outcome it was originally designed to predict (in-hospital MACE), and secondly the outcome of interest in this study, 30-day all-cause mortality. For in-hospital MACE the ROC curve (Figure 5.3.1) was 0.81 (standard error, SE = 0.022, 95% CI = 0.77 to 0.86). The Hosmer-Lemeshow goodness of fit test was significant, $p < 0.001$ ($\chi^2 = 58.06$, df = 6) this indicates a major difference between observed and estimated in-hospital MACE outcomes for the eight risk groups (number of groups = df + 2).

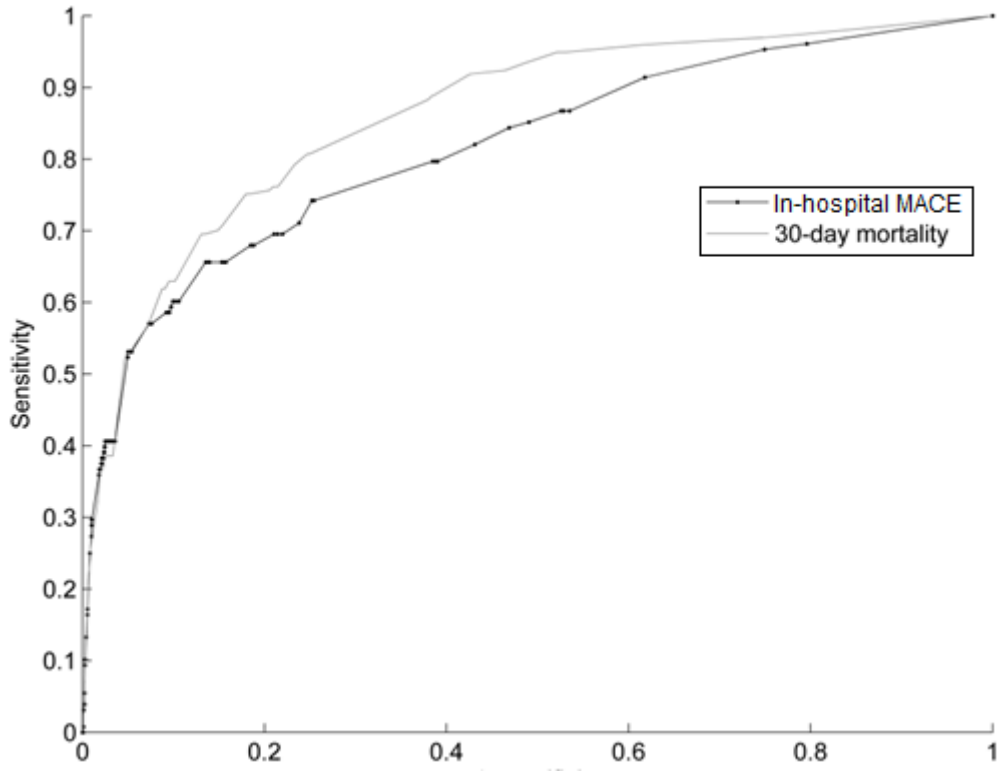


Figure 5.3.1 – ROC curve for NWQIP estimated probabilities for in-hospital MACE and 30-day mortality

For 30-day all-cause mortality the ROC curve (Figure 5.3.1) was 0.86 (SE = 0.014, 95% CI = 0.83 to 0.89). This improvement compared to in-hospital MACE (0.82) was not however statistically significant. The Hosmer-Lemeshow test was also significant, $p = 0.028$ ($\chi^2 = 14.20$, df = 6), again indicating a poor fit of observed and estimated outcomes. Despite both end-points showing good discrimination (ROC > 0.8), the NWQIP model is poorly calibrated when ordered by estimated risk from the regression probabilities.

The external validation study by Kunadian et al. (2008) assigned integer scores based on the odds ratio values, essentially rounding them to the closest integer. These values for each of the NWQIP risk factors are shown in Table 5.3.7.

Table 5.3.7– NWQIP risk factors and corresponding regression coefficients, odds ratios and integer score (as reported by Kunadian et al, 2008)

Variable	Coefficient	Odds Ratio	Integer Score
Age 70-79	0.7048	2.02	2
Age ≥ 80 years	1.0106	2.75	3
Female sex	0.4586	1.58	2
Urgent PCI	0.4788	1.61	2
Emergency PCI	1.3625	3.91	4
LMS lesion	1.6502	5.21	5
Graft lesion	0.9101	2.48	3
Cardiogenic shock	3.2636	26.14	26
Cerebrovascular disease	0.8618	2.37	3
Intercept	-5.4959	NA	NA

The calibration was additionally tested by using these reported integer scores. The patients were classified into one of five risk groups based on the total integer score of their risk factors. The five groups along with the integer score range, patient distribution and outcome rates are displayed in Table 5.3.8.

Table 5.3.8 – Integer score groups for the NWQIP risk model and corresponding In-hospital MACE and 30-day mortality rates

Group	Integer Score Range	Patients (%)	IH-MACE (%)	30-Day Mortality (%)
Very low	0 to 5	78.5%	0.52%	0.60%
Low	6 to 8	15.4%	1.47%	3.16%
Moderate	9 to 11	3.1%	6.19%	10.65%
High	12 to 14	0.5%	8.89%	15.56%
Very high	> 14	2.5%	20.09%	28.83%

The observed and NWQIP predicted/estimated outcome rates, along with the in-hospital MACE and 30-day mortality outcome rates are displayed below in Figure 5.3.2.

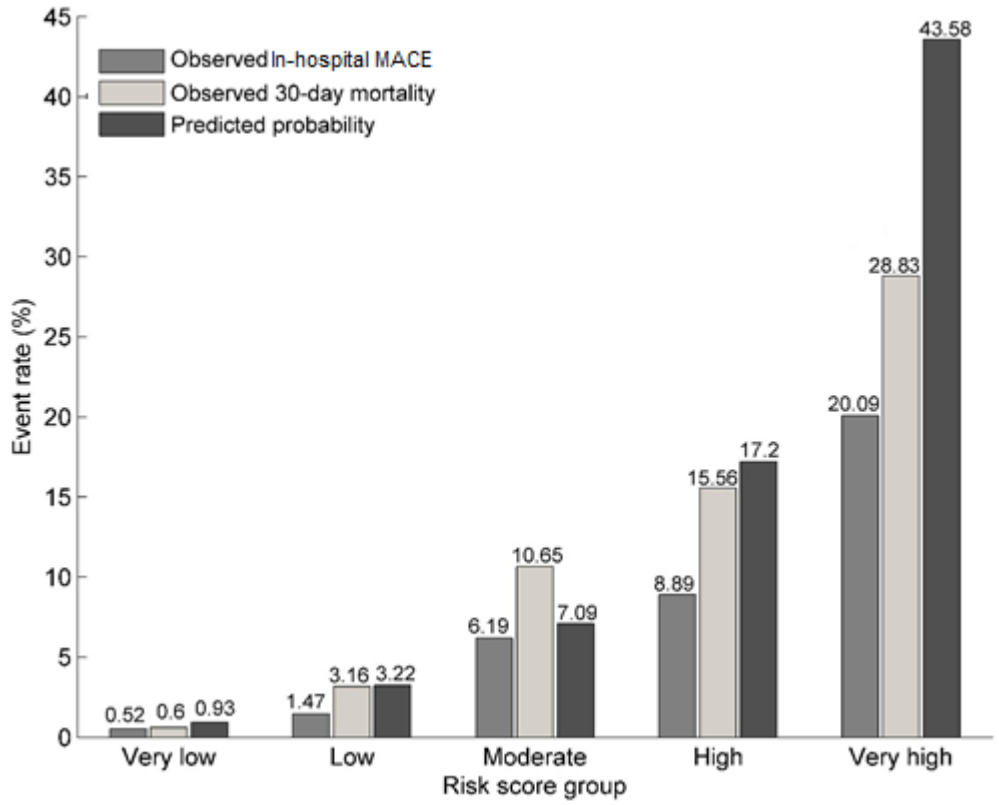


Figure 5.3.2 – NWQIP estimated outcome probabilities including observed in-hospital MACE and 30-day mortality rates

The 95% confidence limits for the predicted probabilities for each of the five groups are displayed in Table 5.3.9.

Table 5.3.9 – 95% confidence intervals for estimated NWQIP probabilities of in-hospital MACE

Group	95% CI Estimated NWQIP Probability
Very low	0.92% to 0.94%
Low	3.18% to 3.26%
Moderate	6.92% to 7.26%
High	15.97% to 18.43%
Very high	41.25% to 45.91%

For in-hospital MACE there was an overestimation within every risk group, and for 30-day mortality the 'Low' risk group was the only one within the 95% CI range. This suggests that the NWQIP model estimated probabilities are actually closer to the observed 30-day mortality rate than the in-hospital MACE rate.

5.3.5 Multivariate Predictors of 30-Day Mortality

The candidate variables which displayed a significance of at least $p < 0.1$ in the univariate association with 30-day mortality were used in the multivariate logistic regression analysis. Those which retained a statistical significance of $p < 0.5$ in the final multivariate prediction model are displayed in Table 5.3.10, also reported are the corresponding regression coefficients, odds ratios, 95% confidence intervals for the ORs, standard errors (SE), and *p* values. The vast majority of the ECTC PCI patients (91.4%, 8481) had an estimated probability of experiencing 30-day all-cause mortality of ≤ 5% and only a very small group (1.8%, 167) had an estimated probability of ≥ 20%.

Table 5.3.10 – multivariate predictors of 30-day all-cause mortality generated from logistic regression analysis

Risk Factor	Coefficient	SE	p Value	Odds Ratio	OR 95% CI	Integer Score
Age 60-69 years	1.102	.300	< *0.001*	3.011	1.67 to 5.42	3
Age 70-79 years	1.642	.292	< *0.001*	5.166	2.91 to 9.16	5
Age ≥ 80 years	2.452	.294	< *0.001*	11.607	6.53 to 20.65	12
Female sex	.453	.167	*.007*	1.573	1.13 to 2.18	2
Cardiogenic shock	1.990	.216	< *0.001*	7.314	4.79 to 11.18	7
Cerebrovascular disease	.733	.294	*.013*	2.082	1.17 to 3.70	2
Urgent PCI	.698	.318	*.028*	2.009	1.08 to 3.75	2
Emergency PCI	2.326	.268	< *0.001*	10.232	6.05 to 17.30	10
Peripheral vascular disease	.870	.306	*.004*	2.388	1.31 to 4.35	2
Ventilated (pre-op)	1.603	.296	< *0.001*	4.966	2.78 to 8.87	5
Intercept	-7.150					

The equation to calculate the estimated probabilities of 30-day mortality using the multivariate predictors in Table 5.3.10 is identical to that which was reported by Grayson et al. (2006) for in-hospital MACE, and this equation is listed in Chapter 4. Whilst not listed here, none of the predictors exhibited a variance inflation factor (VIF) or tolerance which would indicate high levels of multicollinearity.

The independent set of multivariate risk factors for 30-day mortality was similar to those reported in the NWQIP model for in-hospital MACE. Peripheral vascular disease (PVD) is a novel risk factor not present in the NWQIP model, and neither was pre-operation ventilation. Lesions in graft vessels or the left main stem (LMS) were not considered risk factors for 30-day mortality.

5.3.6 Performance of the Multivariate Model

The area under the ROC curve (Figure 5.3.3) was 0.88 (SE = 0.014, 0.85 to 0.91) indicating a very good ability to discriminate between those patients which died within 30 days of their PCI and those which were alive after 30 days. The Hosmer-Lemeshow goodness of fit test produced a non-significant *p* value ($p = 0.67$), $\chi^2 = 5.801$, df = 8. This indicates a good calibration of observed and estimated 30-day mortality rates across different risk groups.

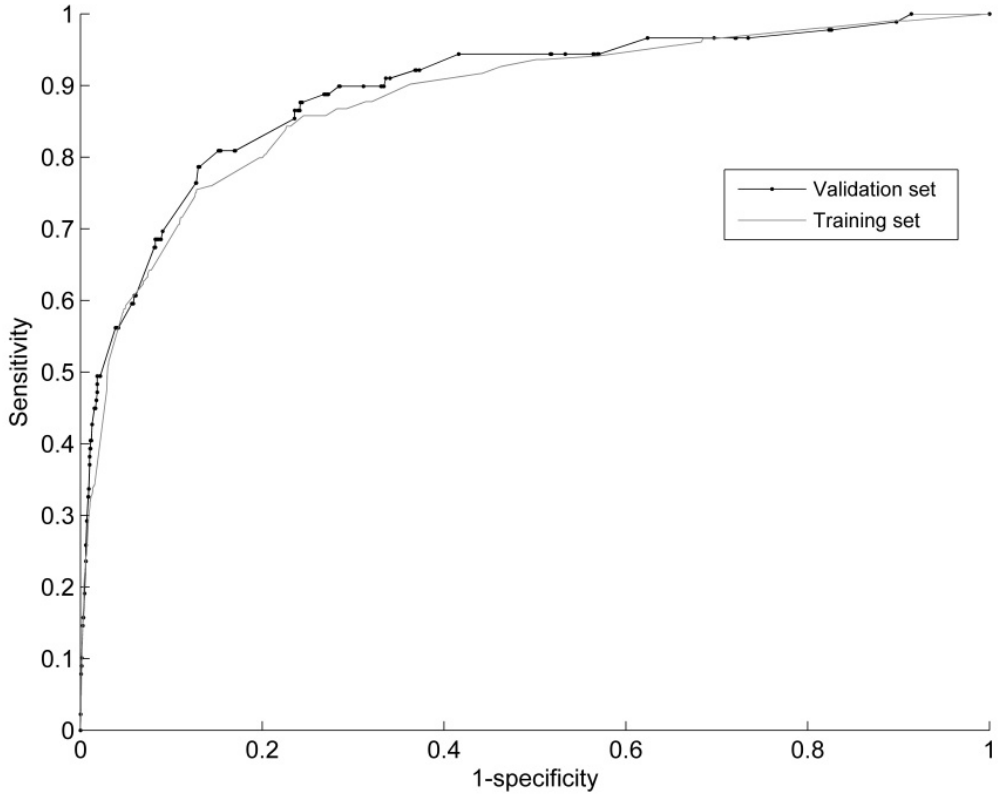


Figure 5.3.3 – receiver operating characteristic (ROC) curve for the 30-day risk prediction model using the training and validation datasets

5.3.7 Integer Scores for 30-Day Mortality Prediction

Each of the PCI patient records were classified into one of five risk groups (very low to very high) as done by Kunadian et al. (2008), the combined integer score of the risk factors identifies which of these groups they are classified under. The coefficients for the multivariate predictors (Table 5.3.9) are rounded to the closest integer and combined. The approximate risk score distributions across these five groups were 64% (5944), 21% (1921), 10% (903), 5% (427), and 0.1% (84) respectively as listed in Table 5.3.11.

Table 5.3.11 – Integer score risk groups with patient distribution and 30-day mortality rates

Risk Group	Patients (%)	30-Day Mortality (%)
Very low	5944 (64.06%)	23 (0.39%)
Low	1921 (20.70%)	28 (1.46%)
Moderate	903 (9.73%)	38 (4.21%)
High	427 (4.60%)	72 (16.86%)
Very High	84 (0.91%)	36 (42.86%)

The majority (64%) of the patients as expected are classified in the lowest risk that has a 30-day mortality rate of 0.39%, conversely a small proportion (0.91%) were classified into the highest risk group, however the 30-day mortality in this cohort was 42.86%.

5.3.8 Internal Validation of the 30-Day Mortality Model

The validation (n = 4119) PCI patient baseline characteristics (i.e. clinical, demographic, procedural) although they are not listed here they were similar to the training set (n = 9729). The majority of the characteristics had small deviations in rates compared to the two that were lower than 1.5%. The characteristics which exhibited the largest differences in rates in the validation set were renal disease (5.1% +), hypertension (1.7% +), prior MI (1.7% -), prior PCI (2.5% +), multi-vessel PCI (2.7% -), and PCI priority (elective 5.2% -; urgent 1.2% -; emergency 6.4% +).

In this set, 45 (1.1%) patients experienced in-hospital MACE and 84 (2.0%) died within 30 days of their PCI, of these, 53 died after discharge, with 19 of the 53 (35.8%) dying within seven days.

The bootstrap resampling (with replacement) technique was used on the training set and 200 samples were generated that contained a mean (SE) ROC curve of 0.879 (0.0153)

indicating a very good ability to discriminate between 30-day all-cause mortality occurring and not occurring. Following the generation of a stable average ROC curve, the multivariate logistic regression coefficients (Table 5.3.9) were used to generate the estimated probability of 30-day mortality for each record in validation set of 4119 PCI records. The ROC curve was 0.891 (SE = 0.021, 0.850 to 0.932), the improvement in discrimination compared to the training set was not statistically significant. The Hosmer-Lemeshow test was not significant, $p = 0.2682$ ($\chi^2 = 9.9553$, df = 8), indicating little departure from the perfect fit as shown in Figure 5.3.4.

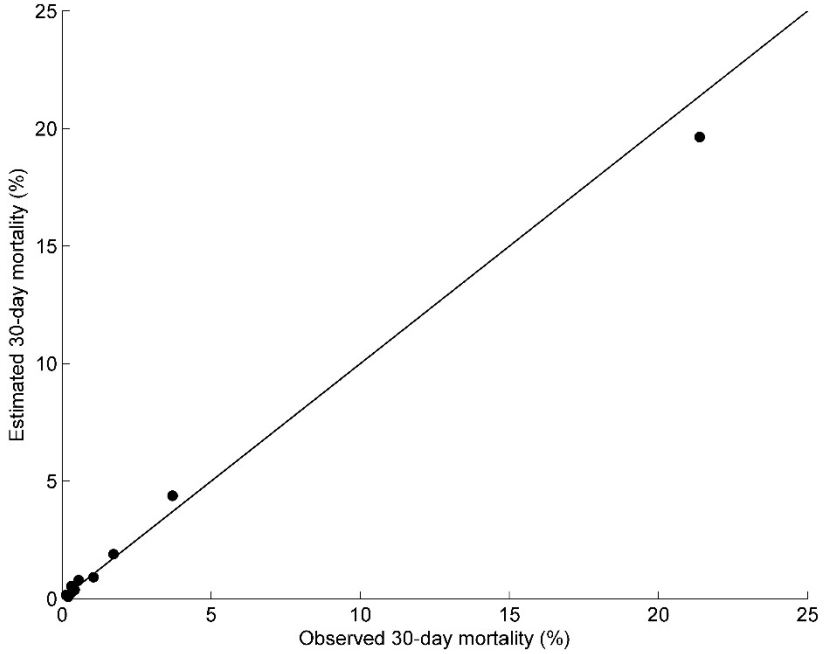


Figure 5.3.4 – calibration plot of observed and estimated 30-day mortality for the validation dataset (n = 4119, p = 0.27)

The integer score risk groups of observed and estimated 30-day mortality rates are displayed in Figure 5.3.5. The distribution of patients into these five risk groups was 56.5% (2325), 25.7% (1058), 11.6% (479), 4.7% (194), and 1.5% (63) respectively which compared to the training set distributions show an increased rate in all groups except for the 'very low' risk group, which sees a corresponding reduction from 64.1% to 56.5%.

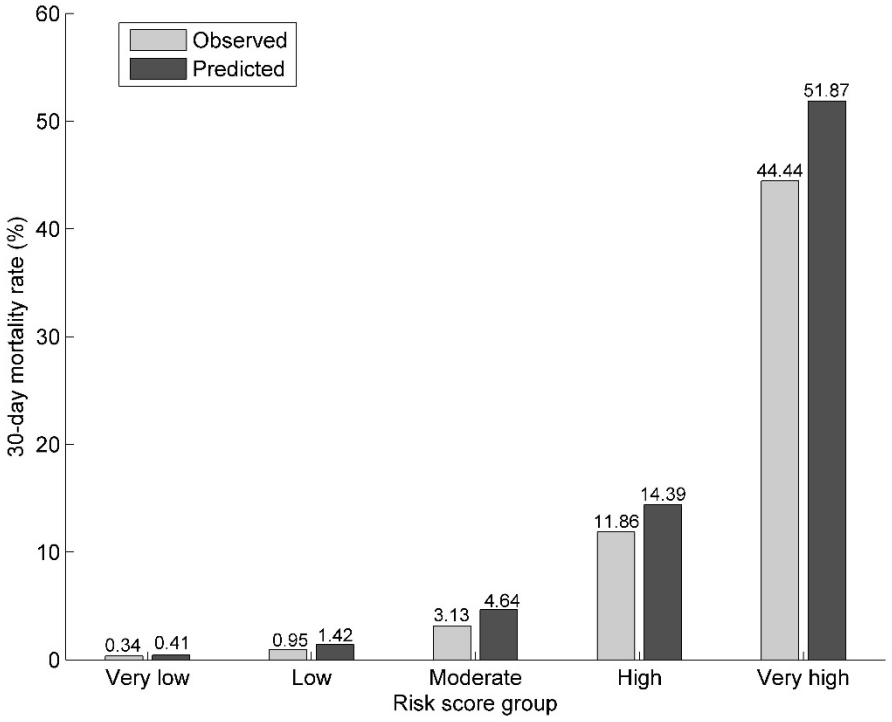


Figure 5.3.5 – observed and estimated 30-day mortality for the validation dataset (n = 4119)

There was a slight absolute overestimation for each of the five risk groups. The relative difference between the observed and predicted/estimated 30-day mortality rates for each group were 21%, 49%, 48%, 21%, and 17% respectively.

5.4 Discussion

As with the study in Chapter 4, this study showed that the NWQIP risk prediction model, originally designed for predicting in-hospital MACE, could discriminate more effectively that it did in its original setting (Grayson et al., 2006) the ROC curve was 0.81 (95% CI = 0.77 to 0.86), compared to the original ROC curve of 0.76. This improvement in discrimination for the NWQIP model on an external cohort of PCI patients was also reported by Kunadian et al. (2008), where the ROC curve was 0.86 (0.82 to 0.90).

When the NWQIP model was used as a tool for predicting 30-day all-cause mortality, there was a small increase in discrimination performance (ROC = 0.86, 0.83 to 0.89) although this improvement compared to in-hospital MACE was not statistically significant. Both the in-hospital MACE and 30-day mortality ROC curves suggest NWQIP continues to discriminate well despite being tested on: (i) a modern PCI cohort; (ii) different geographical location (south of England). It is suspected that the primary reason for this improvement in discrimination is the more robust nature of the outcome of 30-day mortality outcome compared to MACE. For in-hospital complications, the NWQIP model requires accurate and timely reporting of these events, and any such under-reporting in higher-risk cohorts could weaken the models ability to discriminate. Because the majority of the MACE events in our cohort (as in many other cohorts) was in-hospital death, it is not surprising that when focusing solely on 30-day death the model performs well, i.e. possibly suggesting that the other MACE events (Q-wave MI, stroke, emergency CABG) are less easy to predict, so, by removing these events as outcomes, the model becomes a stronger predictor.

The rate of in-hospital MACE in the ECTC PCI cohort (1.4%) was similar to the original NWQIP cohort (1.3%) despite the former exhibiting over a 12% increase in number of urgent and emergency patients reporting for PCI. If all other variables remained constant and there was an increase in non-stable PCIs it would be expected that the rate of MACE would increase as urgent/emergency patients are most at risk of adverse outcomes compared to stable (elective) patients. The similar in-hospital MACE rates seen between the two cohorts of PCI patients could possibly suggest that based on the same risk factors, fewer patients that underwent PCI almost a decade ago would now experience in-hospital MACE in the modern era of PCI practice.

The outcome of 30-day all-cause mortality is obtained from the hospital's patient administration system database following monthly updates from a national data source,

and hence is less likely to be wrong than MACE events. In the ECTC training and validation datasets the 30-day mortality rates were 2.0% and 2.1%, respectively. Table 5.4.1 lists the ECTC 30-day mortality rate across each year (training set: 2007-12, validation set: 2013-14), and the national average 30-day tracked mortality (via ONS-HES) for all PCIs for audit years 2007 to 2014 (BCIS Audit Report, 2015).

Table 5.4.1 – ECTC and national average 30-day mortality rates following PCI (BCIS Audit Report, 2015)

Year	**2007**	**2008**	**2009**	**2010**	**2011**	**2012**	**2013**	**2014**
National 30-day mortality	1.5%	1.6%	2.0%	2.1%	2.4%	2.7%	2.7%	2.8%
ECTC 30-day mortality	0%	1.6%	1.8%	2.6%	2.6%	2.1%	2.2%	2.0%

In 2007, the ECTC opened and therefore the majority of procedures were stable (elective) hence the 30-day mortality rate of 0%. In 2010 there is a sudden increase at the ECTC to 2.6% (from 1.8% in 2009), the cause of this is believed to be due to the ECTC activating the primary care pathway, and hence the beginning of more emergency patients being treated, and hence a much higher risk of 30-day mortality relative to stable patients. From 2012 onwards the ECTC rate remains lower than the national average rate.

The other metric for assessing performance, calibration, a fit of observed versus predicted outcomes across multiple groups ordered by ascending risk, did not perform well. The *p* values for NWQIP with the in-hospital MACE and 30-day mortality outcomes were $p < 0.001$, and $p < 0.028$ respectively, in both cases this represents a very large difference in observed versus predicted rates in at least one of the risk groups.

The cause of a poor calibration performance is likely due to changing patient demographics and an increase in the proportion of emergency PCIs performed on critically ill patients such as those presenting with STEMI, and pre-procedural cardiogenic shock and ventilation. The ECTC cohort of PCI patients in general exhibited a greater proportion of high-risk procedural and clinical characteristics than both the original NWQIP study (Grayson et al, 2006) and the external validation study by Kunadian et al. (2008). In the ECTC cohort, 12.1% of the patients were classified as octogenarians (aged 80 to 89 years) or nonagenarians (aged 90-99 years) which is a very high proportion relative to the other studies (2.1% and 3.8% respectively). It is known that the life expectancy is increasing in the UK, thus in the future the figure may increase beyond 12.1%. It is also commonly known that elderly patients in general recover more slowly than their younger counterparts to treatment. The percentage of emergency PCIs in the ECTC cohort also represents a larger proportion (26.9%) of procedures relative to the other two studies of

10.8% and 17.6% respectively. Other increases in characteristics considered to be important include renal dysfunction, which is 4.4% compared to 0.9% and 1.6% respectively. Diabetes mellitus increased slightly to 17.4% compared to 13.2% and 14.7% respectively. Of the patients reporting for PCI at the ECTC, 20.1% had prior PCI (either at the ECTC or another hospital/cardiac centre) compared to 12.6% in the Kunadian study (2008), the prior PCI percentage was not reported in the original NWQIP study although it is anticipated to be lower than both the ECTC and Kunadian cohorts. Pre-procedural cardiogenic shock was more prominent in the ECTC cohort at 2.5% compared to 0.7% and 1.7% respectively it would be anticipated that a larger proportion of emergency PCIs should correspond with a relative increase in cardiogenic shock patients.

The multivariate logistic regression analysis identified two additional risk factors that were significantly associated with 30-day mortality, which were not present in the original NWQIP risk prediction model. These were peripheral vascular disease (PVD), also reported by Peterson et al. (2010) and hence incorporated into their NCDR CathPCI Risk Score System, and pre-operation ventilation. The pre-operation ventilation figures were not reported in either the original NWQIP study or the external study. It is however possible that this was either not reported or tested as a potential risk factor of in-hospital MACE because of the high percentage of elective patients (at 56.3%), i.e. almost no elective patients would be ventilated before their PCI, as pre-operation ventilator usage is largely associated with patients that experience out-of-hospital cardiac arrest following a myocardial infarction.

PVD was present in a smaller proportion of patients in the ECTC cohort at 3.6% compared to 6.3% and 7.5% respectively. PVD was identified as a multivariate predictor by Kunadian et al. (2008) and showed similar odds ratios to the model developed using the ECTC data for the 30-day mortality outcome (2.135, $p = 0.013$; and 2.388, $p = 0.004$ respectively).

This multivariate analysis has confirmed that certain risk factors for adverse outcomes following PCI, such as advanced age, female gender, urgent/emergency priority, cerebrovascular disease and pre-procedural cardiogenic shock, have remained useful predictors over the last decade, at least in a UK clinical setting. It is also important to note that some of these predictors have similar univariate and adjusted multivariate odds ratios. In the custom multivariate model constructed from the ECTC cohort, the patient age group 60-69 years old became a significant predictor and hence was incorporated into the final model. The age group did become a more powerful multivariate predictor in the custom prediction model compared to the NWQIP model for in-hospital MACE, i.e. for

NWQIP the odds ratios for 70-79 years, and ≥ 80 years was 2.02 and 2.75 respectively compared to 5.17 and 11.07 respectively.

Unlike the NWQIP model, PCI to the left main stem (LMS) lesions or graft lesions were not significant predictors for either in-hospital MACE or 30-day mortality, for the former outcome Kunadian also did not list these in their multivariate predictor table. It can only be speculated as to the reason why these are no longer significant predictors of adverse short-term outcomes following PCI, but it could be that interventional cardiologists have greater experience in treating LMS disease, due to increasing levels of PCIs being performed. It is also possible than an improvement in stenting technology, the usage of intravascular medical imaging and embolic protection devices, and more effective pharmacological therapy has contributed to a dramatic reduction in risk associated with treating LMS and graft lesions.

The multivariate prediction model for 30-day mortality exhibits very good discrimination (ROC = 0.88) and calibration of observed versus predicted outcomes of different risk groups (p = 0.67), this performance was confirmed using the internal validation set from the ECTC cohort data (ROC = 0.89, p = 0.26). From the five integer score groups (very low, low, moderate, high, very high), the internal validation did exhibit relative overestimates of 21%, 49%, 48%, 21%, and 17% respectively. However, because the frequencies of 30-day mortality are very small relative to the entire dataset size (4119) this is likely to occur when classifying patients into multiple risk groups on an outcome that occurs at a low rate. The actual frequencies of 30-day mortality in these five groups were: 23; 28; 38; 72; and 36. Certain characteristics currently not recorded or measured by hospitals or cardiac centres may improve the overall calibration, for example, quality of life, diet, and exercise. In the future, genetic characteristics may be easily used as risk factors, for example identification of genetic differences related to the development (speed) of lesions, effectiveness of drugs (aspirin, clopidogrel etc.).

5.4.1 Limitations

The primary outcome of interest in this study was 30-day all-cause mortality, but both the original NWQIP study (Grayson et al, 2006) and the corresponding external validation study (Kunadian et al, 2008) did not report this outcome and therefore straightforward comparisons between some elements of this analysis cannot be made to these prior studies.

The rate of in-hospital MACE and 30-day mortality should be low, at any well-established PCI centre in the developed world, as such it would have been beneficial to have access to a larger sample size of PCIs available for analysis, especially considering certain comorbidities such as diabetes mellitus ($p = 0.072$), renal disease ($p < 0.001$), and COPD ($p = 0.071$) were identified as good candidates from the univariate association analysis with 30-day mortality using a significant threshold of $p < 0.1$. Researchers in the US in particular have been able to take advantage of larger datasets for either development of risk prediction models, or external testing. For example, a study by Singh et al. (2008) utilised 370,793 CABG procedures for externally validating a PCI mortality prediction model. This limitation warrants other PCI centres in the UK, especially to externally validate the multivariate model developed in this study.

Approximately 4% of the PCIs in the ECTC cohort contained missing data for either a NWQIP risk factor, custom multivariate model risk factor, or event outcome data (in-hospital MACE or 30-day mortality) and therefore had to be omitted from analysis. The missing data for clinically important risk factors should however become less frequent in future practice due to more rigorous data completion policies and protocols being enforced.

5.4.2 Conclusions

The final hypothesis (section 1.3) stated that logistic regression analysis could identify useful predictors for other important outcomes following PCI. This study proved it to be true by the construction of a risk prediction model for 30-day all-cause mortality. It identified novel predictors, not incorporated in the NWQIP model (pre-operation ventilation and peripheral vascular disease), and also found that graft lesions and LMS lesions were not significant predictors and thus could be omitted from a new risk model. The model was internally tested using a validation dataset and found to have both stable calibration and discrimination.

In the current era of PCI practice the NWQIP risk prediction model for in-hospital MACE continues to provide good discrimination performance, however, this study demonstrated that the risk model requires considerable recalibration to render the model useful for individual patients. Matheny et al. (2005) also identified improvements in discrimination but poor calibration in other published risk prediction models when applied to their cohort of PCI patients. In this study the model has been refined by including two novel risk

factors, not present in the NWQIP model, most notably pre-procedural ventilation, which is clearly extremely important given its strong association with 30-day mortality (odds ratio = 23.7, $p < 0.001$). Ventilation prior to a PCI procedure is largely a surrogate marker for out-of-hospital cardiac arrest, and it is therefore not surprising that critically ill patients have a higher probability of an adverse outcome. This study has confirmed the ability of the custom multivariate risk model to predict the 30-day mortality outcome in a contemporary UK population at a cardiac centre performing a high rate of emergency PCI procedures. It is hoped that the proposed multivariate prediction model for 30-day mortality will prove useful for comparing performance of operators, cardiac centres, and for clinically assessing the risk of individual patients that undergo PCI.

5.4.3 Future Work

External validation of the risk prediction model should be conducted using a contemporary cohort of patients (i.e. high DES usage era) preferably outside of the South East of England to verify the geographic stability of the incorporated risk factors, meaning does it generalise to the other geographic locations within the UK. This analysis also identifies the importance of including comorbidities in future risk prediction model design, this will be more applicable when referral systems improve, meaning such comorbidities are diagnosed prior to a patient's first PCI.

Additionally, it would be interesting and useful to investigate other important outcomes, especially those appropriate for elective (stable) patients. Both the in-hospital MACE events and 30-day mortality occurred at very low rates in the ECTC cohort, as shown in Table 5.4.2

Table 5.4.2 – in-hospital MACE and 30-day mortality rates for the ECTC training and validation PCI cohorts

Outcome	**Overall**	**Elective**	**Emergency**
Training set (n = 9279			
In-hospital MACE	1.4%	0.5%	3.6%
30-day mortality	2.1%	0.4%	6.1%
Validation set (n = 4119)			
In-hospital MACE	1.1%	0.1%	2.4%
30-day mortality	2.0%	0.3%	4.9%

The outcome rates occur at extremely low rates, especially for elective patients and hence would not provide much useful information for these low-risk patients. Identification of adverse outcomes which occur at higher frequencies should be investigated. Such outcomes may include long-term mortality, i.e. three years instead of 30 days, or the likelihood that a patient may require a future coronary revascularisation procedure. Such outcomes are useful for predicting the future workload of cardiac centres, and for informing patients of likely outcomes, i.e. what is the probability they will require another PCI in the next three years.

Chapter 6: Three-Year Repeat Revascularisation or Death in Elective PCI Patients

6.1 Introduction

6.1.1 Background

The 30-day mortality study conducted in Chapter 5 analysed the following popular end-points of interest after PCI. In-hospital complications in the form of major adverse cardiac events (MACEs) – a composite outcome of at least one of the following: (i) all-cause death; (ii) Q-wave myocardial infarction; (iii) emergency CABG surgery; and (iv) cerebrovascular accident. The second outcome was 30-day all-cause mortality, which is defined as death within 30 days of a patient's index PCI procedure. Both of these end-points are important for both clinicians and patients for justifying whether revascularisation by PCI should be performed, and for educating patients on the risk of adverse outcomes should they proceed with the PCI procedure. Table 6.1.1 displays the overall rates of in-hospital MACE and 30-day all-cause mortality were identified in the Chapter 5.

Table 6.1.1 – In-hospital MACE and 30-day mortality rates for ECTC training and validation sets

Outcome	Rate (%)	Dataset	Total PCIs
In-hospital MACE	1.4%	Training (1/7/07 to 31/12/12)	9279
30-day mortality	2.1%	Training (1/7/07 to 31/12/12)	9279
In-hospital MACE	1.1%	Validation (1/1/13 to 31/1/15)	4119
30-day mortality	2.0%	Validation (1/1/13 to 31/1/15)	4119

As seen in Table 6.1.1 both the in-hospital MACE and 30-day mortality end-points exhibit low rates in both the training and validation sets generated from the ECTC cohort. When focussing solely on elective PCI patients the rate of both MACE and 30-day mortality as expected is much lower. Table 6.1.2 displays the elective cohort rates for both outcomes and datasets.

Table 6.1.2 – In-hospital MACE and 30-day mortality rates for elective patients within the ECTC dataset

Outcome	Rate (%)	Dataset	Total PCIs
In-hospital MACE	0.54%	Training (1/7/07 to 31/12/12)	4070
30-day mortality	0.42%	Training (1/7/07 to 31/12/12)	4070
In-hospital MACE	0.06%	Validation (1/1/13 to 31/1/15)	1556
30-day mortality	0.26%	Validation (1/1/13 to 31/1/15)	1556

6.1.2 Motivation

The previous analysis, described in section 6.1.1, investigated the outcomes in-hospital MACE and 30-day mortality. Due to both of these outcomes occurring at very low rates among patients of elective priority, it is necessary to consider other important outcomes which are useful for clinicians and patients but occur at higher rates as this may allow better prediction models to be designed for elective patients.

6.1.3 Hypothesis and Objectives

The hypothesis for this study is that risk factors in the form of comorbidities will be identified following via the logistic regression analysis. As described in Chapter 2, certain studies (depending on the outcome of interest following PCI) have identified comorbidities as risk factors, especially relating to mortality, such as diabetes, COPD, PVD, and renal disease etc. Therefore, because death is a component of interest, at least one of these comorbidities will be identified as a significant multivariate predictor.

The main objective of this study was to identify the demographics, clinical, or procedural characteristics and hence patient subgroups which are most at risk of experiencing either: (i) all-cause death; or (ii) repeat revascularisation. Both of these end-points are within three years. This is for a given patient's first elective PCI procedure at the ECTC. By identifying the set of important factors associated with this 3-year end-point it could allow a prediction model to be constructed to estimate the approximate risk of a given patient of similar characteristics experiencing an adverse outcome within 3 years. The characteristics determined to have a significant multivariate relationship with repeat revascularisation or death can then be compared to those found in similar studies, most notably conducted in the US clinical setting to determine if existing literature is consistent both over time and in the UK.

6.2 Methods

6.2.1 Patient Database

As detailed in section 3.2, the entire ECTC database comprised 15,865 PCI records, and also included 3,339 coronary artery bypass graft (CABG) surgery records. The date of these interventional procedures was performed ranges from July 2007 to March 2015. A number of these records however were excluded from analysis following certain exclusion criteria (described in section 6.2.3) being applied due to the choice in the outcome of interest.

6.2.2 Definitions

Repeat revascularisation (RR) is defined as any subsequent coronary revascularisation procedure on a patient which has had an initial PCI at the ECTC. The subsequent revascularisation procedure (if applicable to a given patient) may be in the form of another PCI, CABG surgery (alone), or CABG surgery combined with valve surgery (e.g. aortic or mitral valves). The three-year event includes any repeat revascularisation within three years of the initial PCI, and also includes all-cause mortality.

A staged procedure is a subsequent revascularisation, most likely to be a PCI whereby the procedure itself is planned prior to the execution of an initial PCI. For example, an elective patient may have multiple coronary vessels diseased and hence require multiple stents to be inserted. Some operators will insert the stents over two PCI procedures rather than one. It may be that one vessel requires immediate revascularisation and another can be delayed for several weeks when the patient has had time to recover, or the operations may be also be split to reduce the radiation dosage administered. Because these staged procedures are already known to occur to both the cardiologists and patients the need to predict there occurrence is obsolete and hence this is why they are excluded from analysis.

Staged procedures are not consistently labelled in the CVIS database, some are identified via a ‘Test Reason’ field, and others are defined in an ‘Indication for Intervention’ field. It is known from operator experience that many staged procedures exist but are not defined using either of these two data variables. Some of these staged procedures can be identified from the discharge letters however a lot of procedures, especially those from

2007 to 2008 did not contain any discharge letters in the CVIS database. Rather than having to manually search, load, read potentially thousands of discharge letters (if they at all existed) the following criteria was applied to flag up likely staged procedures. A lot of the records which are not correctly listed as staged have been labelled as 'Stable angina' in the test reason and/or indication for intervention fields. If the subsequent PCI was classified as both of the following then they were classified as 'Staged' in this study.

(1) Elective Priority

(2) Interval (in days)s between the initial PCI discharge date and the next PCI waiting list date was one week or less then it is an indication of staged.

In total for the three-year outcome, 60 additional PCI repeat revascularisations were flagged as staged procedures using the above criteria that were not labelled as such in the test reason or indication for intervention fields.

6.2.3 Inclusion/Exclusion Criteria

This analysis investigates the repeat revascularisation or death outcomes within three-years for patients which have had an elective initial PCI only. Patients which have had an initial urgent or emergency priority PCI are excluded from analysis. However urgent and emergency procedures are included in the subsequent repeat revascularisation procedure. As listed in the definitions, staged procedures were not included as repeat revascularisation procedures.

6.2.4 Repeat Revascularisation Search Program

The code which performs the task of analysing the database of PCI and CABG procedures for the next repeat revascularisation was written using Visual Basic for Applications (VBA), the source code is listed in Appendix C. In summary, the code iterates through each PCI record and firstly identifies whether it is a valid record for analysis. If valid, it looks for all other PCIs for the same patient (using an anonymised ID unique to patient), and determines whether a match is found. If a match is detected then the base/index PCI has the repeat revascularisation PCIs details copied to its row for

subsequent analysis (i.e. procedure ID, procedure Date, procedure priority, vessels attempted etc.).

The VBA code makes use of a data structure called a 'Dictionary', which is an array of keys and values. In this scenario each key of the dictionary represents the patient ID, and the corresponding value represents the spreadsheet row number in the Excel document that the first valid record is stored on. By using this data structure it allows almost instantaneous lookup of whether a patient exists, this lookup is performed at a later stage of the analysis. Two dictionaries were used, one for PCI procedures and one for CABG surgery procedures.

The following represents tasks performed by the VBA code prior to searching for repeat revascularisations. The code has two input parameters which will alter the type of repeat revascularisations being searched for.

Search Type – this can be set to find any 'repeat revascularisations' as in this study, or it can be limited to only search for subsequent 'target vessel revascularisations', the latter represents revascularisation procedures that are performed on at least one of the coronary vessels treated during the patient's initial/index PCI at the ECTC.

Priority Filter – This input parameter controls whether the base/index/initial PCI is (i) elective; (ii) all priorities (elective, urgent, or emergency). In this analysis the priority filter is set to elective PCIs only, therefore urgent/emergency initial PCIs were excluded from analysis.

The Excel file with the procedure data contains two sheets which represent PCI procedures (BCIS) and CABG surgery (SCTS), each sheet has been initially manually sorted by (i) Patient ID; and (ii) Date of operation. The sorting resulted in every patient having all their PCI procedures clustered together (if they had more than one procedure) and ordered by date of their PCIs from earliest to most recent. This sorting was performed to make the subsequent processing faster and allowed debugging/verification that the VBA code was working correctly by avoiding the need to scroll to different locations within the spreadsheet.

Processing Steps

The following tasks are performed by the VBA code in order to find the occurrence of repeat revascularisations.

Task 1: Iterate through each PCI record in the BCIS (PCI) data sheet, upon a patient's first elective PCI, insert the patient ID (and row number) into the PCI dictionary data structure. In total, there were 6,115 unique patients that had at least one elective PCI at the ECTC.

Task 2: Iterate through each CABG record in the SCTS data sheet, upon a patient's first CABG procedure, insert the ID (and row number) into the CABG dictionary data structure.

In total, there were 3,335 unique patients that had at least one CABG procedure at the ECTC.

Task 3: Iterate through each unique patient in the PCI dictionary data structure (6,115 in total).
Task 3.1: Exclude the record from analysis if 'vessel attempted' for the index/next PCI are missing.

Task 3.2: Start on the next row number (+1) of the patient's base record, if it is a different patient then restart the search on the next patient in the dictionary data structure, as no subsequent PCI procedures were found for this patient.

Task 3.3: If the same patient ID is found, check the PCI is not 'Staged'. If it is then skip to the next patient.

Task 3.4: For the vessels attempted column (index PCI and next PCI) convert the 'LADproximal' and 'LADother' into a single 'LAD' vessel. This is because the CVIS database represents them as two distinct vessels, yet for analysis they are considered a single vessel only.

Task 3.6: Copy the next (non-staged) PCI details to the index/base elective PCI row. The following information is copied across, for subsequent analysis.

- Operation date
- Indication for Intervention
- Test Reason
- Vessels attempted
- Priority of the repeat revascularisation PCI
- Repeat revascularisation PCI procedure ID

Once the first repeat revascularisation PCI has been found the VBA code then repeats the same sequence of steps for the remaining unique patients in the PCI dictionary data structure.

Task 4: This group of tasks are concerned with looking for any intermediate CABG surgery procedure which occurs between the index/base elective PCI and the next PCI recorded (if such a PCI was found previously). The details of any valid intermediate CABG replace the next PCI details.

Task 4.1: Iterate through each unique patient in the CABG dictionary data structure and check whether the patient has had a PCI at the ECTC (regardless of the operation date). This checks whether the same patient also exists in the PCI dictionary data structure. If no match is found, then the code moves on to the next patient in the CABG dictionary data structure. If a match is found the next task is performed (4.2).

Task 4.2: Check whether the base/index PCI has been populated with a repeat revascularisation PCI, if no such PCI is found then skip to the next patient in the CABG dictionary. If such a PCI is found then the next task is performed (4.3).

Task 4.3: Iterate through each CABG record for the same unique patient (starting with earliest procedure date) and check whether the CABG operation date is between the base/index PCI and the date of the repeat revascularisation PCI. If the date is not within the range then move on to the next CABG for this patient (if multiple exist) and repeat the comparison. If the date is within the range then perform the next task (4.4).

Task 4.4: Populate the index/base PCI record with the CABG details (i.e. the CABG replaces the next revascularisation PCI details). The following CABG procedure data is copied across.

- CABG Procedure Date
- CABG Procedure ID
- CABG Priority
- CABG vessel(s)
- CABG type: (i) CABG alone; (ii) CABG and Valve surgery within the same procedure

Task 5: This set of tasks is responsible for populating the index/base PCI records which have not had a subsequent PCI; or hence been replaced by an intermediate CABG.

Task 5.1: Iterate through each unique patient in the PCI dictionary data structure and if a patient has no repeat revascularisation (PCI or CABG) currently populated then check whether the patient has a CABG recorded in the CABG dictionary data structure. If a CABG has been found and it occurs after the date of the base/index PCI procedure then populate the CABG details into the base/index PCI record.

- CABG Procedure Date
- CABG Procedure ID
- CABG Priority
- CABG vessel(s)
- CABG type: (i) CABG alone; (ii) CABG and Valve surgery within the same procedure.

6.2.5 Custom Spreadsheet Formulas

The following formulas were used following the completion of the VBA code execution. The formulas listed here calculate useful information for working out which PCIs count as a repeat revascularisation and death outcome, or those that require excluding from analysis.

Interval to Revascularisation

The interval to the repeat revascularisation was calculated as the number of days from the index/base elective PCI procedure date to the date of the repeat revascularisation PCI or CABG procedure.

```
=DATEDIF([Index PCI Date], [Repeat Revascularisation Date], "D")
```

Days to Cut-off

This was calculated in order to censor/exclude patients which had not seen the full time period for the outcome. For example, for all patients which did not have a repeat revascularisation procedure or die within the three year time period, were excluded if the 'Days to cut-off' exceeded three years. These patients could not be included for analysis because the time period has not been reached for them.

=DATEDIF("12/03/15", [Index PCI Date], "D")

Days to Death

This represented the number of days from the index/base PCI procedure date to the date of death (if the patient did indeed die). This was calculated to ascertain whether the patient survived the analysis period of three years or not.

```
=DATEDIF([Index PCI Date], [Date of Death], "D")
```

6.3 Results

Of the entire 15,865 consecutive PCI procedures performed at the ECTC between July 2007 and March 2015 there were 3,568 (22.5%) records that remained in the analysis as they met the following criteria: (i) elective priority; (ii) determined to be non-staged procedures; (iii) the patients' first elective revascularisation procedure at the ECTC; (iv) not missing vital details such as vessel attempted; and (v) non censored due to the breaking the cut-off period of three years. Figure 6.3.1 shows the number of PCIs excluded from analysis and the final number retained. Some of the procedures excluded may have been omitted for multiple exclusion criteria; this is why the total figure of the five criteria is greater than 12,137.

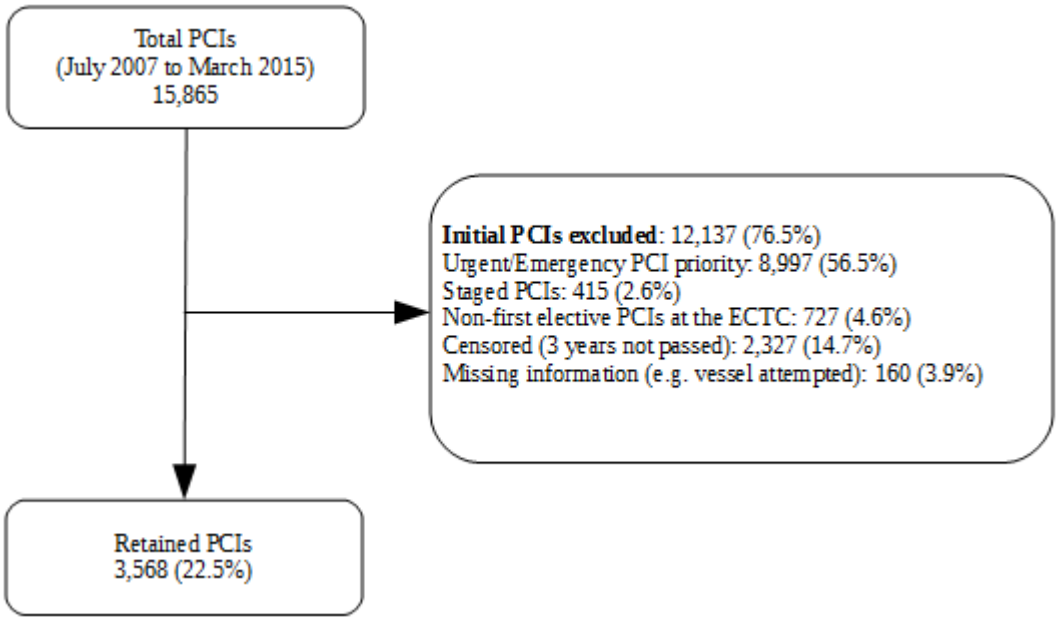


Figure 6.3.1 – flow diagram showing excluded and the retained PCIs

6.3.1 Three-year Outcomes

The primary outcome or endpoint of interest was three-year repeat revascularisation or death (RRD). Of the 3,568 unique patients that underwent an initial elective PCI at the ECTC, there were 522 (14.6%) combined events within three years of the initial elective PCI. This figure is broken down into 374 (10.5% overall) repeat revascularisations and 148 (4.1%) deaths. It should be noted that some of these patients which underwent a repeat revascularisation may have also died within the three-year period but the event would only be counted as a repeat revascularisation. Figure 6.3.2 displays the breakdown of the three-year events by repeat revascularisation type (PCI or CABG), PCI procedure priority, and median number of days until the event. The percentages displayed are relative to the overall data (i.e. not just the parent node).

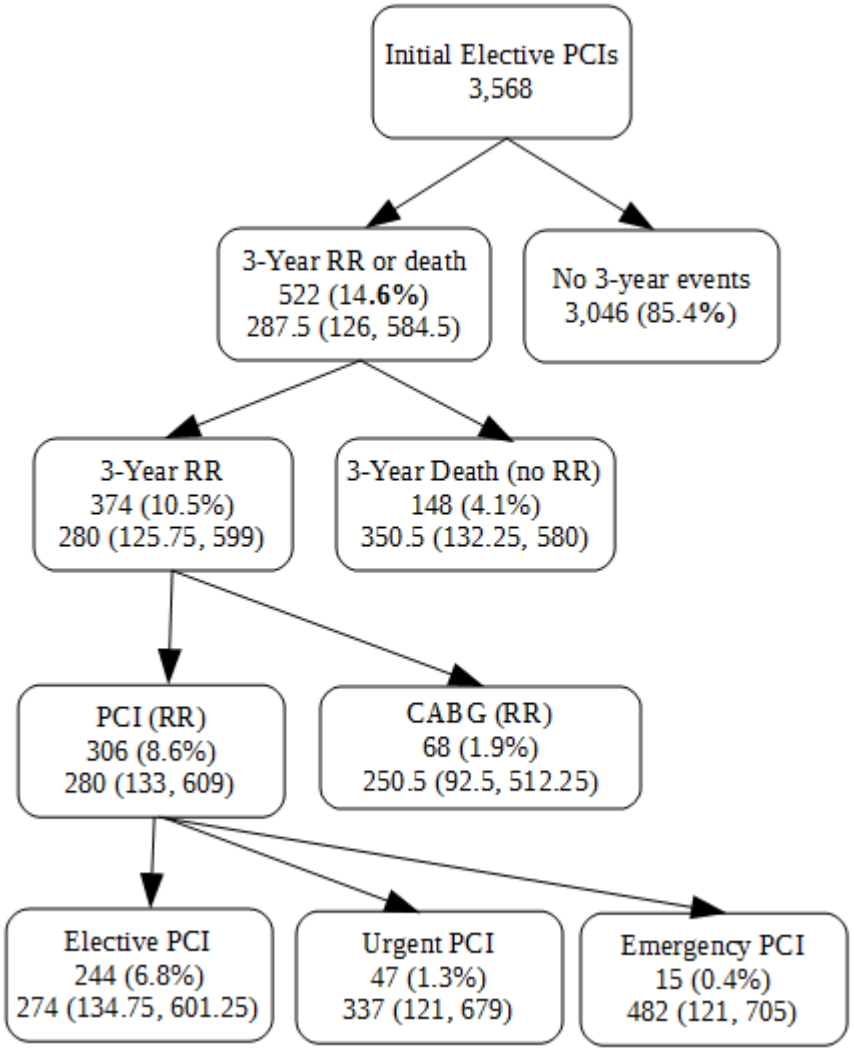


Figure 6.3.2 – three-year event breakdown by procedure and priority type.

The rate at which the RRD events occur by months since the date of the initial PCI is shown in Figure 6.3.3. After three years (36 months) the overall rate is at 14.6% (522 events).

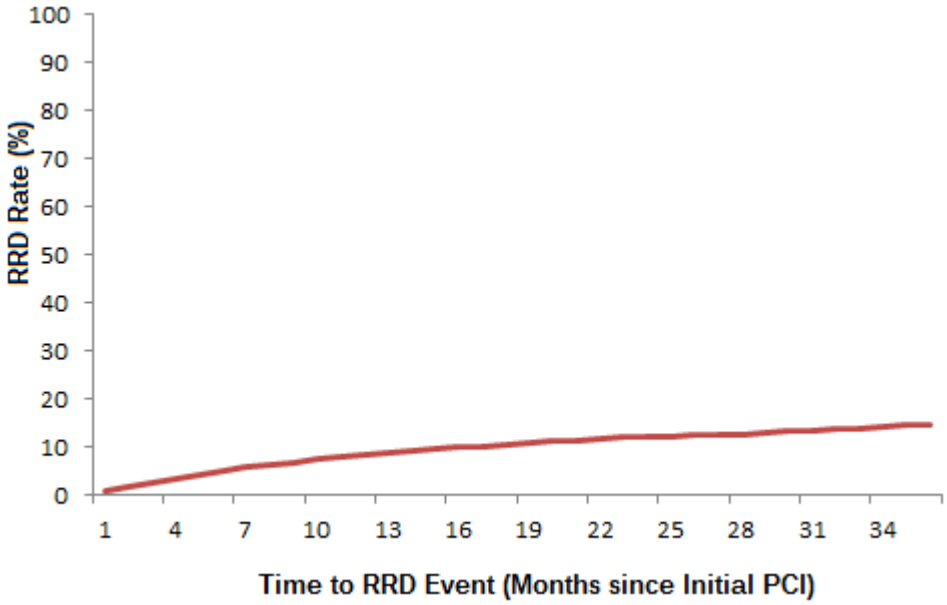


Figure 6.3.3 – Cumulative RRD event rates over three years

The breakdown of the RRD events by each yearly quarter (three month periods) is show below in Figure 6.3.4.

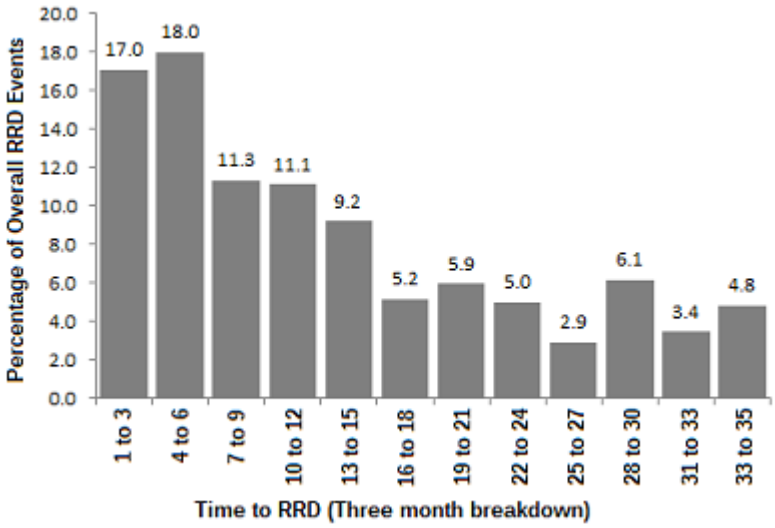


Figure 6.3.4 – Breakdown of Time to RRD events by three-month periods

As shown above the three-month period which shows the highest percentage of RRD events is from the fourth to sixth months following the initial elective PCI procedure. The

combined total of RRD events within the first nine months is 46.3 % (242 of 522 events). The overall rate of RRD within this same time period is 6.8% (252/3,568).

6.3.2 Univariate Associations with 3-Year RRD

Table 6.3.1 lists the univariate associations of the three-year repeat revascularisation or death (RRD) outcome with the demographic, clinical, and procedural characteristics of each of the initial elective PCI included in the ECTC 3,568 valid cohort. The percentage values displayed in the table represent the valid percent of non-missing data. The number of missing values (if any) is displayed in the final column of the table.

Table 6.3.1 – Univariate associations with 3-year repeat revascularisation or death (RRD)

Characteristic	Patients n = 3046 (%)	RRD n = 522 (%)	*P* Value	OR (95% CI)	Missing
Age Group (years)	-	-	*< 0.001*		0
< 50	266 (7.5)	39 (14.7)	-	**Reference**	
50-59	664 (18.6)	83 (12.5)	0.378	0.83 (0.55 to 1.25)	
60-69	1227 (34.4)	142 (11.6)	0.163	0.76 (0.52 to 1.11)	
70-79	1095 (30.7)	188 (17.2)	0.326	1.20 (0.83 to 1.75)	
≥ 80	316 (8.9)	70 (22.2)	*0.022*	1.65 (1.07 to 2.54)	
Gender					1
Male	2704 (75.8)	403 (14.9)		**Reference**	-
Female	863 (24.2)	119 (13.8)	0.420	0.91 (0.73 to 1.13)	-
BMI Classification			0.632		1913
Normal	292 (17.6)	37 (12.7)	-	**Reference**	
Overweight	715 (43.2)	109 (15.2)	0.293	1.24 (0.83 to 1.85)	
Obese Class 1	421 (25.4)	58 (13.8)	0.669	1.10 (0.70 to 1.71)	
Obese Class 2	179 (10.8)	20 (11.2)	0.629	0.86 (0.48 to 1.54)	
Obese Class 3	48 (2.9)	7 (14.6)	0.715	1.17 (0.49 to 2.81)	
Smoking Status			0.785		899
Never Smoked	957 (35.9)	146 (15.3)	-	**Reference**	
Ex-Smoker	1364 (51.1)	203 (14.9)	0.804	0.97 (0.77 to 1.22)	
Current Smoker	348 (13.0)	57 (16.4)	0.621	1.08 (0.77 to 1.52)	
Family History of CHD					577
No	1,398 (46.7)	204 (14.6)		**Reference**	
Yes	1,593 (53.3)	217 (13.6)	0.447	0.92 (0.75 to 1.1)	
Previous PCI	858 (24.6)				81
No	2629 (75.4)	372 (14.1)		**Reference**	
Yes	858 (24.6)	133 (15.5)	0.329	1.11 (0.89 to 1.38)	
Previous CABG					56
No	3193 (90.9)	440 (13.8)		**Reference**	
Yes	319 (9.1)	70 (21.9)	*< 0.001*	1.75 (1.32 to 2.33)	

Previous MI					200
No	2169 (64.4)	282 (13.0)		**Reference**	
Yes	1199 (35.4)	212 (17.7)	*< 0.001*	1.43 (1.18 to 1.74)	
Hypertension					137
No	1286 (37.5)	177 (13.8)		**Reference**	
Yes	2125 (62.5)	326 (15.2)	0.250	1.12 (0.92 to 1.36)	
Hypercholesterolaemia					137
No	1258 (36.7)	183 (14.5)		**Reference**	
Yes	2173 (63.3)	320 (14.7)	0.886	1.01 (0.83 to 1.23)	
Diabetes					111
No	2800 (81.0)	377 (13.5)		**Reference**	
Yes	657 (19.0)	122 (18.6)	0.001	1.46 (1.17 to 1.83)	
COPD					137
No	3308 (96.4)	475 (14.4)		**Reference**	
Yes	123 (3.6)	28 (22.8)	0.010	1.75 (1.14 to 2.70)	
PVD					137
No	3280 (95.6)	472 (14.4)		**Reference**	
Yes	151 (4.4)	31 (20.5)	0.037	1.53 (1.02 to 2.30)	
VHD					137
No	3384 (98.6)	496 (14.7)		**Reference**	
Yes	47 (1.4)	7 (14.7)	0.964	1.01 (0.45 to 2.28)	
Cerebrovascular disease					137
No	3284 (95.7)	477 (14.5)		**Reference**	
Yes	147 (4.3)	26 (17.7)	0.289	1.26 (0.81 to 1.95)	
Renal Disease					137
No	3270 (95.3)	465 (14.2)		**Reference**	
Yes	161 (4.7)	38 (23.6)	*0.001*	1.86 (1.27 to 2.71)	
Rotablation					0
No	3491 (97.8)	500 (14.3)		**Reference**	
Yes	77 (2.2)	22 (28.6)	*< 0.001*	2.39 (1.44 to 3.95)	
CTO					109
No	3104 (89.7)	440 (14.2)		**Reference**	
Yes	355 (10.3)	71 (20.0)	*0.003*	1.51 (1.14 to 2.00)	
Atorvastatin					0
No	2804 (78.6)	414 (14.8)		**Reference**	
Yes	764 (21.4)	108 (14.1)	0.663	0.95 (0.75 to 1.19)	
GP 2b/3a usage					31
No	3,235 (91.5)	487 (15.1)		**Reference**	
Yes	302 (8.5)	32 (10.6)	*0.036*	0.67 (0.46 to 0.98)	
Heparin					491
No	3,068 (99.7)	440 (14.3)		**Reference**	
Yes	9 (0.3)	0 (0.0)	0.220	- (N/A)	
Bival usage					491
No	168 (5.5)	25 (14.9)		**Reference**	
Yes	2,909 (94.5)	415 (14.3)	0.825	0.95 (0.6 to 1.47)	
Multivessel PCI					74

No	2696 (77.2)	382 (14.2)		**Reference**	
Yes	798 (22.8)	119 (14.9)	0.599	1.06 (0.85 to 1.32)	
Stent Type			*< 0.001*		113
None	192 (5.6)	72 (37.5)		**Reference**	
≥ 1 BMS	1043 (30.2)	175 (16.8)	*< 0.001*	0.33 (0.24 to 0.46)	
DES exclusive	2220 (64.3)	259 (11.7)	*< 0.001*	0.22 (0.16 to 0.30)	
Stent Length (mm)			0.175		0
< 15	402 (15.1)	43 (10.7)	-	**Reference**	
15-19	785 (29.4)	106 (13.5)	0.168	1.30 (0.89 to 1.90)	
20-24	375 (14.0)	60 (16.0)	0.030	1.59 (1.05 to 2.42)	
> 24	1109 (41.5)	142 (12.8)	0.270	1.23 (0.85 to 1.76)	
Stent Diameter (mm)			0.575		0
2.25	217 (8.1)	20 (9.2)	-	**Reference**	
2.50	593 (22.2)	75 (12.6)	0.181	1.43 (0.85 to 2.40)	
2.75	493 (18.5)	70 (14.2)	0.068	1.63 (0.96 to 2.76)	
3.00	772 (28.9)	106 (13.7)	0.080	1.57 (0.95 to 2.59)	
3.50	477 (17.9)	60 (12.6)	0.200	1.42 (0.83 to 2.42)	
4.00	105 (3.9)	17 (16.2)	0.069	1.90 (0.95 to 3.81)	
4.50	8 (0.3)	2 (25)	0.162	3.28 (0.62 to 17.36)	
5.00	6 (0.2)	1 (16.7)	0.545	1.97 (0.22 to 17.70)	
Stent Diameter (mm)					0
≤ 2.75	1303 (48.8)	165 (12.7)		**Reference**	
> 2.75	1368 (51.2)	186 (13.6)	0.475	1.09 (0.87 to 1.36)	
Coronary Vessel					0
Left main	74 (2.1)	17 (23.0)	*0.040*	1.76 (1.01 to 3.05)	
LCx	949 (26.6)	130 (13.7)	0.343	0.90 (0.72 to 1.11)	
RCA	1222 (34.2)	195 (16.0)	0.105	1.17 (0.96 to 1.42)	
LAD	1877 (52.6)	253 (13.5)	*0.040*	0.82 (0.68 to 0.92)	
Graft vessel	81 (2.3)	21 (25.9)	*0.004*	2.08 (1.25 to 3.46)	

The characteristics which were identified as having a significant association ($p < 0.05$) with the three-year RRD outcome were: stent type group; glycoprotein inhibitor IIIb/IIa usage; rotablator usage; presence of a chronic total occlusion (CTO); renal disease; age (≥ 80 years); prior bypass graft surgery (CABG); prior myocardial infarction (MI); diabetes mellitus; chronic obstructive pulmonary disease (COPD); peripheral vascular disease (PVD); and treatment to the left main stem or a graft vessel.

Whilst the association was not significant, the body mass index (BMI) classification of the 'Overweight' group exhibited a higher RRD rate (15.2%) than the highest 'Obese' class (14.6%. class 3). However many records were not recorded for height and weight therefore the BMI could not be calculated for many procedures. As expected patients that were currently smoking had a higher rate of RRD (16.4%) versus the non-smoker counterparts (15.3%).

The stent length and diameter in Table 6.3.1 are for the single-vessel PCI procedures.

6.3.3 Stent and Vessel Characteristics

As shown in Table 6.3.2 the classification of the 3,568 (minus the 113 missing) initial PCI procedures by stent type (None used; at least one BMS; DES exclusively) reveals that very few procedures occurred without the insertion of a stent (5.6%), almost a third (30.2%) involved the insertion of at least one BMS stent, and the majority (64.3%) involved exclusive DES usage. As expected the BMS and to a further degree DES seem to function as a protective mechanism versus no stent insertion. The drop from the rate for no stents (37.5% RRD) to the DES rate (11.7%) is quite large.

The majority of the initial elective PCIs were single-vessel procedures with this being 2,973 in total (83.3%). The detailed analysis of these PCIs has been performed in the results section 6.3.5. For the multi-vessel procedures, totalling 595 (16.7%), the highest overall rate for any combination of vessels treated was only 5.0% (180 PCIs) representing almost one third of the multi-vessel PCIs. The vessels representing 5.0% was the LAD and LCX arteries. Closely followed were the LAD and RCA vessels for which 145 PCIs (4.1%) were performed on this combination. This was followed by the RCA and LCX vessels (114 PCIs) for which the rate was 3.2%.

The stent type group usage across the year of the initial elective PCI procedure is shown in Figure 6.3.5, and as expected shows the following: (i) increase across the year of DES insertion from 31% in 2007 to 77.5% in 2012; (ii) a general decrease in BMS usage from 65.5% in 2007 to 18.8% in 2012. The percentage of procedures featuring no stents remains low with the latest rate being 3.8% in 2012.

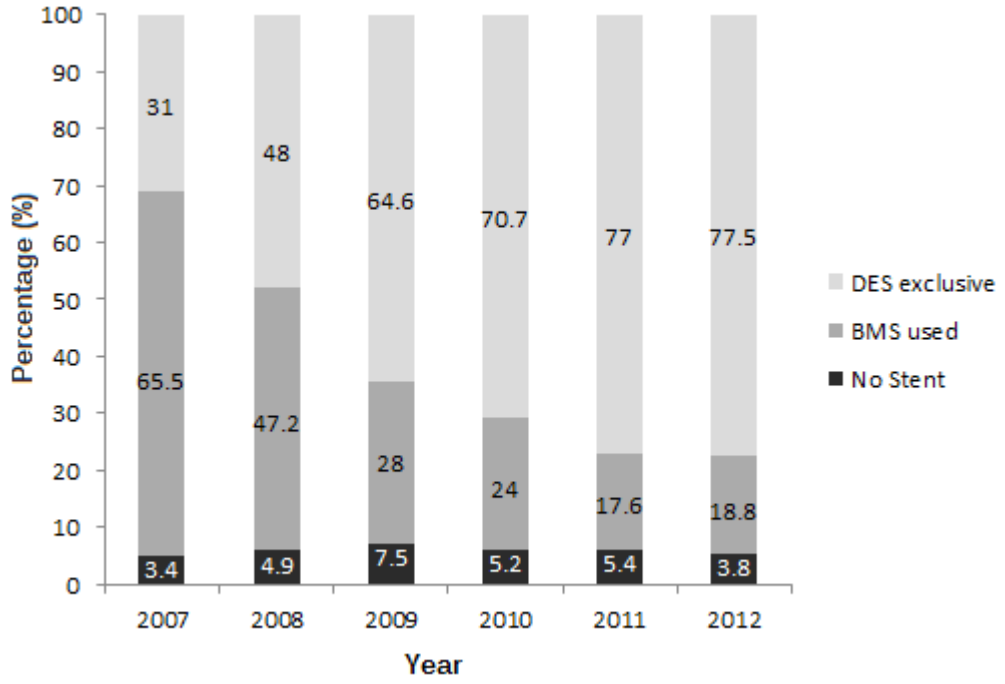


Figure 6.3.5 – Stent usage versus tear of initial elective procedure

Table 6.3.2 displays the breakdown of stent type against the mean and median (25th and 75th percentiles) number days to the 3-year RRD.

Table 6.3.2 – PCI Stent group type versus mean and median days until RRD

Stent Group	Count (%)	RRD (%)	Mean (SD)	Median (25th/75th)
None	192 (5.6%)	72 (37.5%)	255.4 (301.0)	140 (54.25, 254.25)
BMS used	1043 (30.2%)	175 (16.8%)	360.9 (290.3)	281 (121, 538)
DES exclusive	2220 (64.3%)	259 (11.7%)	430.7 (301.4)	370 (168, 665)

As expected, in addition to a decrease in event rates from the 'no stent' group to the DES exclusive group, there is also an increase in both the mean and median number of days to the RRD events. For the patients that did not have a stent inserted, of those that experienced 3-year RRD, it occurred to half within approximately 4.6 months (140 days), and for those that received DES stents exclusively, half of the RRD patients experienced it in just over one year (370 days).

Table 6.3.3 displays the mean stent dimensions for across the cohorts and stent group type. This includes the total stent length, minimum stent diameter and longest stent used, all measured in millimetres (mm).

Table 6.3.3 – PCI Stent group type versus total stent length and minimum stent diameter

Characteristic	All	None	BMS	DES
Total Stent Length (mm)				
All	31.36 (20.63)	27.50(16.16)	26.67 (18.89)	33.60(21.11)
No-RRD	31.30 (20.58)	29.59(18.58)	26.25 (18.24)	33.54(21.20)
RRD	31.72 (20.94)	23.67 (9.99)	28.69 (21.76)	34.06(20.40)
Minimum Stent Diameter (mm)				
All	2.88 (0.45)	2.94 (0.67)	3.14 (0.48)	2.76 (0.38)
No-RRD	2.88 (0.45)	2.86 (0.63)	3.15 (0.48)	2.76 (0.38)
RRD	2.91 (0.46)	3.06 (0.75)	3.11 (0.50)	2.77 (0.36)

The dimension values for the 'no stent' group in Table 6.3.3 represent either the intended stent dimensions, or if the PCI was a standard balloon angioplasty, then balloon dimensions.

The RRD rate over different years of the initial elective PCI separated by the number of native vessels treated is show below in figure 6.3.6. Overall the single-vessel PCIs represented 83.3% of the PCIs, and multi-vessel PCIs represented the remaining 16.7%.

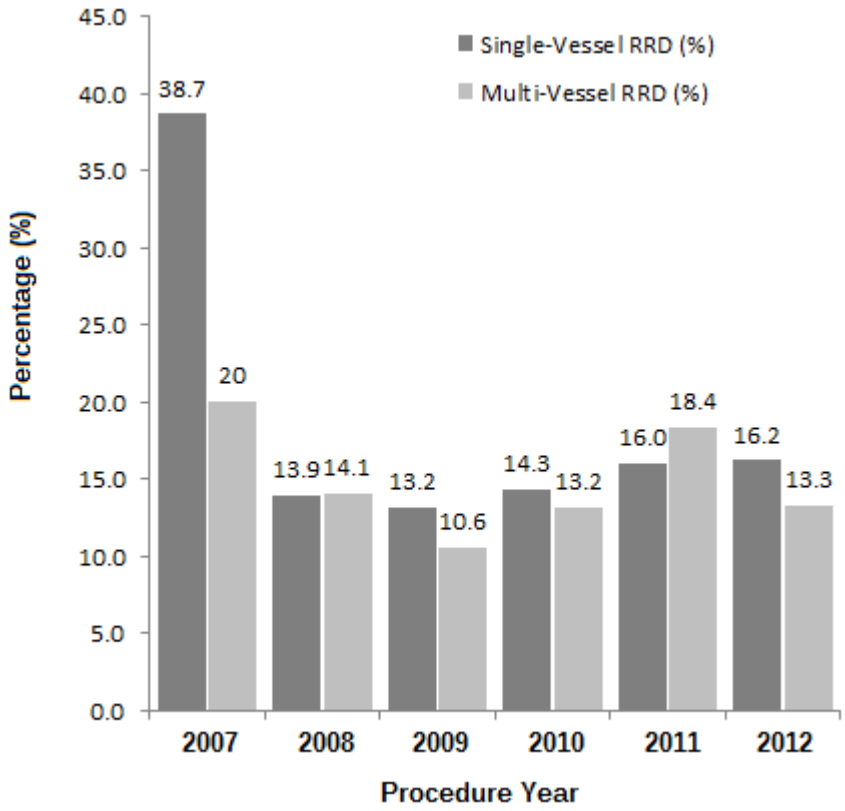


Figure 6.3.6 – RRD rates by year and single/multi-vessel PCI

6.3.4 Multivariate Predictors of RRD

The characteristics which exhibited a significant univariate relationship with three-year RRD as reported in section 6.3.2 were used candidate variables for entry into the multivariate logistic regression model. This was to determine which of reported risk factors were still significant when combined with the other significant univariate characteristics and after having been controlled for multicollinearity.

Table 6.3.4 – Multivariate predictors of 3-year repeat revascularisation or death (RRD)

Characteristic	Coefficient	SE	P Value	Adjusted OR (95% CI)
Age ≥ 80 years	0.502	0.16	*0.002*	1.65 (1.21 to 2.27)
Prior CABG	0.445	0.16	*0.006*	1.56 (1.13 to 2.15)
Prior MI	0.259	0.11	*0.017*	1.30 (1.05 to 1.60)
COPD	0.634	0.24	*0.007*	1.89 (1.19 to 2.99)
BMS used	-1.120	0.19	*< 0.001*	0.33 (0.23 to 0.47)
DES used (only)	-1.529	0.18	*< 0.001*	0.22 (0.15 to 0.31)
Diabetes	0.414	0.12	*0.001*	1.51 (1.19 to 1.93)
Intercept	-0.797	NA	NA	NA

The risk factor with the highest adjusted odds ratio (1.89) was COPD. It is apparent that co-morbidities including diabetes and chronic obstructive pulmonary disease (COPD) have higher rates of RRD. The type of stent (whether a BMS was used or DES exclusively) acted as a protective effect hence the odds ratios below 1.0.

The Hosmer-Lemeshow goodness of test (χ^2 = 2.622, with 5 degrees of freedom) was performed to assess the calibration (match of predicted RRD against actual RRD), this was a good fit amongst different risk groups with the *p* = 0.76, indicating there were no significant differences between the observed and estimated groups. The area under the ROC curve was 0.65 (95% CI 0.62 to 0.68, SE = 0.015). The value of 0.65 is regarded as fairly poor for discriminating between RRD and no RRD, with 0.50 being randomly guessing the outcome and 1.0 being a perfect score. This ROC curve is shown in Figure 6.3.7.

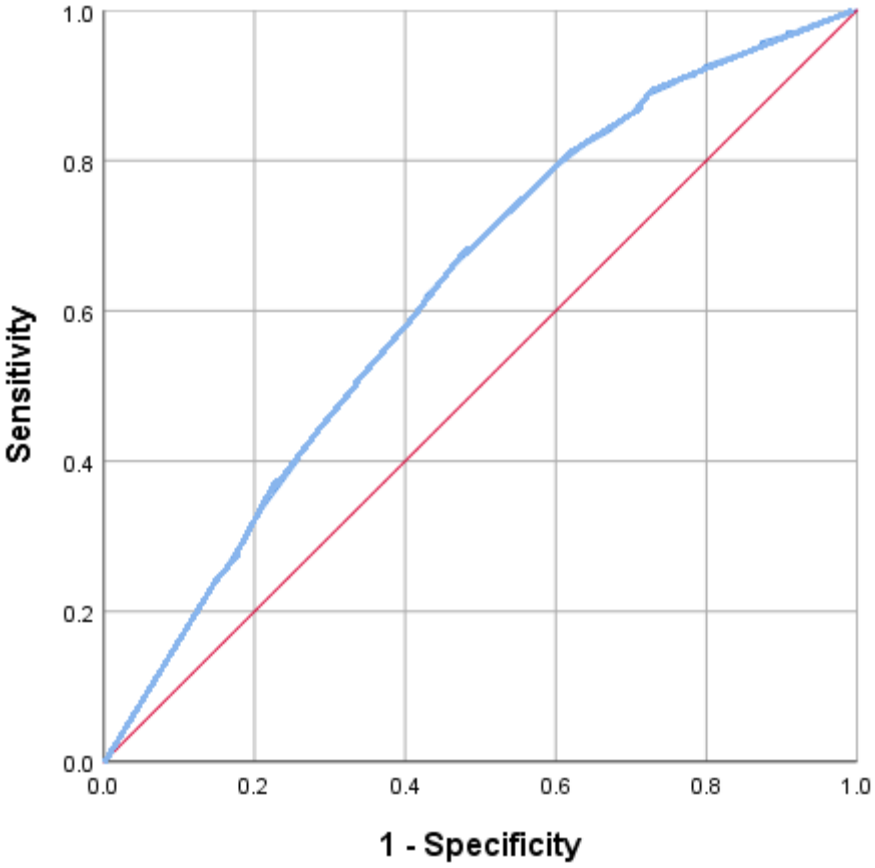


Figure 6.3.7 – Area under the ROC curve for the 3-Year RRD Prediction Model

6.3.5 Single-vessel PCI Analysis

The following analysis was conducted on a subset of the main 3,568 PCI cohort, namely that which features the initial PCI to a single vessel only. This was performed to identify whether any strong associations exist which were masked, or hidden when multiple coronary arteries were investigated in the previous sections. The aim was identify whether any particular vessels in isolation are predisposed to the adverse outcome of 3-year repeat revascularisation or death (RRD). Another reason for investigating single-vessel PCIs was that it is known with certainty which vessel given devices are applied to. For the entire cohort of PCIs (3,568) on multiple-vessel PCIs, the data is not available with certainty to show which stent is applied to which coronary artery. Obviously, this problem does not exist if only a single vessel is being treated.

There were 2,973 (83.3%) single-vessel PCI procedures amongst the total valid cohort. There were 436 (14.7) RRD events. Of the 436 events, 317 (10.7%) of these were repeat revascularisations and the remaining 119 (4.0%) died.

The single-vessel PCIs were defined as planned PCI treatment to a single coronary vessel, as broken down into one of the following five categories.

- right coronary artery (RCA)
- left circumflex artery (LCX)
- left anterior descending artery (LAD)
- left main stem (LMS)
- graft vessel (from a previous bypass graft surgery)

Table 6.3.5 lists the breakdown of events by the type of coronary vessel treated in the initial elective PCI. The percentage represented by the repeat revascularisation (RR) endpoint and death endpoint is relative to the overall event rate. The *p* value represents whether there is a significant difference in RRD rate for whether a specific vessel was treated or not. The rows are ordered by descending percentage of the treated coronary artery.

Table 6.3.5 – Three-Year RRD breakdown by coronary vessel (single-vessel PCIs)

Vessel	**All PCIs (2,973)**	**RRD (436)**	**RR (317)**	**Death (119)**	***P* Value**	**OR**
LAD	1,427 (48.0%)	186 (13.0%)	133 (9.3%)	53 (3.7%)	*0.016*	0.78
RCA	904 (30.4%)	149 (16.5%)	112 (12.4%)	37 (4.1%)	0.064	1.23
LCX	557 (18.7%)	80 (14.4%)	58 (10.4%)	22 (3.9%)	0.823	0.97
Graft	65 (2.2%)	17 (26.2%)	10 (15.4%)	7 (10.8%)	*0.008*	2.10
LMS	20 (0.7%)	4 (20.0%)	4 (20%)	0 (0%)	0.499	1.46

The most frequently treated coronary vessel was the LAD with almost half of all the single-vessel PCIs (48%) involving lesions in this vessel. The second most commonly treated artery was the RCA (30.4%) followed by the LCX (18.7%), graft vessels (2.2%), and the LMS (0.7%) respectively.

Table 6.3.5 reveals two significant factors relating to the association of coronary vessels with the 3-year RRD end-point for single-vessel PCI. Firstly, that if the lesions being treated are located in the left anterior descending artery (LAD) it produces a protective effect, hence the odds ratio being lower than 1.0, when compared to treatment of any other coronary vessel type. Secondly, although the sample size is very small, for treatment of lesions in previously grafted vessels, there is a higher risk of RRD, hence the odds ratio being 2.1. Whilst treatment to the left main stem shows the highest risk of RRD (20%), the sample size is very small, with only four events occurring in the cohort, and is not considered statistically significant (p = 0.499).

Table 6.3.6 shows the RRD rate and the corresponding mean (SD), and median (25^{th} and 75^{th} percentiles respectively) number of days until the event for each coronary vessel type treated.

Table 6.3.6 – Single-vessel PCI days to RRD versus coronary vessel treated.

Vessel	**All PCIs (2,973)**	**RRD (436)**	**Mean (SD)**	**Median**	**Median (25^{th} and 75^{th} percentile)**
LAD	1,427 (48.0%)	186 (13.0%)	406.9 (306.7)	308.5	152.5, 629.5
RCA	904 (30.4%)	149 (16.5%)	364.0 (311.0)	238.0	104.5, 634.0
LCX	557 (18.7%)	80 (14.4%)	406.5 (311.3)	360	140.5, 626.3
Graft	65 (2.2%)	17 (26.2%)	468.5 (377.4)	427.0	114.5, 885.5
LMS	20 (0.7%)	4 (20.0%)	270.8 (130.2)	287.5	141.0, 383.8

Of the five vessel types, the highest median number of days to a repeat revascularisation or death outcome within 3-years is graft vessels with 427 days. However, the 25^{th} and 75^{th} percentiles for this were 114.5 and 885.5 which shows there is a large difference in time for the graft vessel RRD events. The vessel with the lowest median number of days until an RRD event was the right coronary artery (RCA). This was 238 days with the 25^{th} and 75^{th} percentiles being 104.5 and 634 respectively.

Of the 317 (10.7%) repeat revascularisation procedures within three years for single-vessel initial PCIs, Table 6.3.7 lists the initial single-vessel treated and the frequency of corresponding repeat revascularisation vessel(s). Those of low frequencies are grouped in the 'Other' RR Vessel category. The individual percentage of each vessel(s) in the 'Other' category is smaller than the percentage of the lowest named vessel.

Table 6.3.7 – Single-vessel PCI days to RRD versus coronary vessel treated

Vessel	RR Vessel	Count (%)
LAD	LAD	61 (45.9%)
	RCA	27 (20.3%)
	LCX	19 (14.3%)
	LCX and LAD	13 (9.8%)
	Other	13 (9.8%)
RCA	RCA	43 (38.4%)
	LAD	27 (24.2%)
	LCX	16 (14.3%)
	LAD and RCA	9 (8.1%)
	Other	17 (15.2%)
LCX	LCX	19 (32.8%)
	LAD	16 (27.5%)
	RCA	9 (15.5%)
	LCX, LAD and RCA	7 (12.1%)
	Other	7 (12.1%)
LMS	LMS	1 (25%)
	Graft	1 (25%)
	Graft, LCX	1 (25%)
	LX, LAD	1 (25%)
Graft	LAD	3 (30%)
	Graft and LAD	2 (20%)
	Other	5 (50%)

Target Vessel Revascularisation (TVR)

Table 6.3.8 displays the repeat revascularisation by vessel type for a single classification only. The TVR rates which represent the revascularisation of the initial coronary vessel in the repeat revascularisation can be present in multiple categories (e.g. RCA to RCA, RCA to LAD and RCA). The rates were as follows in Table 6.3.8.

Table 6.3.8 – TVR rates by type of coronary vessel treated in the initial PCI

Vessel	Count (%) within RR	TVR rate overall (%)	TVR vessel rate (%)
LAD	84/133 (74.3%)	2.83%	84/1,427 (5.89%)
RCA	65/112 (58.0%)	2.19%	65/904 (7.19%)
LCX	30/58 (51.7%)	1.01%	30/557 (5.39%)
Graft	4/10 (40.0%)	0.13%	4/65 (6.15%)
LMS	1 / 4 (25.0%)	0.03%	1/20 (5.0%)

6.3.5.1 Stent Characteristics

Of the 2,973 single-vessel PCIs the breakdown into the stent type group (No stent, BMS used, and DES exclusive) is shown in table 6.3.9. Of the 2,973 single-vessel cohort, 96 PCIs were missing (leaving 2,877) detailed device information on the stent type, so were omitted from the following table as it could not be determined if they were under the BMS or DES classification. The percentage represented is relative to the non-missing data.

Table 6.3.9 – Single-vessel PCIs by Stent Type and number of days to an RRD event (mean and median)

Stent Group	Count (%)	RRD (%)	Mean (SD)	Median (25^{th}/75^{th})
None	181 (6.3%)	67 (37.0%)	240.7 (285.0)	140 (53, 243)
BMS used	862 (30.0%)	141 (16.4%)	374.7 (291.1)	301 (133, 567)
DES exclusive	1834 (63.7%)	215 (11.7%)	458.2 (313.9)	392 (175, 714)

As anticipated, the median number of days to a RRD event increases from 140 in the no stent group to 392 days in the DES exclusive group. From investigating these rates between different stent type groups, it was crucial to ensure that these rates were not simply caused by specific vessels being more likely to receive a certain stent type. Tables 6.3.10 to 6.3.15 display the breakdown of stent type by coronary vessel, RRD events and stent dimensions (such as the average minimum stent diameter and average total stent length).

No Stent Group

Of the valid 2,973 single-vessel PCIs, 6.3% (181) of these procedures did not involve the insertion of a stent. This group would include standard balloon angioplasty or procedures for which a stent was intending to be used but wasn't inserted. The percentage is relative to the overall counts for the group.

Table 6.3.10 – No Stent PCIs versus coronary vessel

Vessel	Count (%)	RRD (%)	Mean (SD)	Median (25^{th}/75^{th})
LAD	67 (37.0%)	26 (38.8%)	257.9 (284.9)	155 (90, 268.8)
RCA	79 (43.6%)	30 (38.0%)	262.7 (298.5)	140 (51.8, 533.8)
LCX	31 (17.1%)	10 (32.3%)	144.5 (260.3)	48.5 (40.3, 136.5)
Graft	3 (1.7%)	0 (0.0%)	-	-
LMS	1 (0.6%)	1 (100%)	97 (-)	97 (97, 97)

Table 6.3.11 –No Stent PCIs versus minimum stent diameter and total stent length

Characteristic	RRD	No RRD	*P* Value
Total Stent Length (mm)			
LAD	22.40 (8.44)	29.50 (12.13)	0.299
RCA	20.00 (9.51)	24.29 (13.65)	0.561
LCX	36.00 (8.49)	28.33 (27.10)	0.72
Graft	-	30.00 (-)	-
LMS	-	-	-
Minimum Stent Diameter (mm)			
LAD	3.10 (0.82)	3.33 (0.94)	0.676
RCA	3.20 (0.86)	2.79 (0.39)	0.281
LCX	2.63 (0.18)	2.75 (0.32)	0.625
Graft	-	2.50 (-)	-
LMS	-	-	-

The number of PCIs in the 'No stent' group missing balloon dimension data for the coronary vessels was 21, 25, 8, 0, and 1 respectively

BMS Group

Table 6.3.12 – BMS PCIs versus coronary vessel

Vessel	Count (%)	RRD (%)	Mean (SD)	Median (25^{th}/75^{th})
LAD	346 (40.1%)	51 (14.7%)	402.8 (290.4)	339 (154, 583)
RCA	307 (35.6%)	51 (16.6%)	333.1 (296.7)	238 (108, 478)
LCX	172 (20.0%)	26 (15.1%)	421.5 (270.0)	399.5 (178, 614.8)
Graft	30 (3.5%)	12 (40.0%)	338.9 (331.6)	157.5 (93.8, 698.3)
LMS	7 (0.8%)	1 (14.3%)	273 (273)	273 (273, 273)

Table 6.3.13 – BMS PCIs versus minimum stent diameter and total stent length

Characteristic	RRD	No RRD	*P* Value
Total Stent Length (mm)			
LAD	22.26 (16.96)	21.58 (13.35)	0.749
RCA	30.80 (24.30)	24.93 (18.86)	0.108
LCX	19.48 (13.46)	21.76 (12.44)	0.405
Graft	22.50 (9.53)	27.39 (16.58)	0.365
LMS	9.00 (-)	11.20 (3.35)	0.581*
Minimum Stent Diameter (mm)			
LAD	3.12 (0.42)	3.15 (0.42)	0.652
RCA	3.20 (0.46)	3.30 (0.47)	0.165
LCX	2.98 (0.35)	3.13 (0.46)	0.070
Graft	3.60 (0.85)	3.32 (0.64)	0.304
LMS	3.50 (-)	4.20 (0.57)	0.325*

The number of missing stent dimensions for the BMS group was 35, 42, 15, 2, and 0 respectively.

DES Group

Table 6.3.14 – DES PCIs versus coronary vessel

Vessel	Count (%)	RRD (%)	Mean (SD)	Median (25^{th}/75^{th})
LAD	966 (52.7%)	104 (10.8%)	446.7 (309.0)	371 (175, 684)
RCA	491 (26.8%)	64 (13.0%)	439.5 (313.2)	381.5 (157.3, 717.5)
LCX	337 (18.4%)	41 (12.2%)	478.5 (320.8)	414 (217, 783.5)
Graft	30 (1.6%)	5 (16.7%)	779 (310.1)	945 (442.5, 1034)
LMS	10 (0.5%)	1 (10.0%)	411 (-)	411 (411,411)

Table 6.3.15 – DES PCIs versus minimum stent diameter and total stent length

Characteristic	RRD	No RRD	*P* Value
Total Stent Length (mm)			
LAD	30.95 (17.10)	28.71 (16.19)	0.187
RCA	33.89 (20.36)	37.56 (24.80)	0.267
LCX	25.46 (11.41)	26.04 (17.94)	0.840
Graft	27.20 (8.64)	26.84 (13.13)	0.954
LMS	18.00 (-)	12.89 (4.28)	0.291*
Minimum Stent Diameter (mm)			
LAD	2.72 (0.30)	2.77 (0.35)	0.153
RCA	2.97 (0.42)	2.89 (0.42)	0.172
LCX	2.70 (0.31)	2.62 (0.30)	0.147
Graft	3.40 (0.55)	3.06 (0.54)	0.208
LMS	2.75 (-)	3.58 (0.53)	0.174*

The number of missing stent dimensions for the DES exclusive group was 8, 2, 2, 0, and 0 respectively.

6.3.5.2 Stenosis Information

In the available data for this study, information relating to the approximate percentage that the lesion occludes a given coronary artery was available. However, this was not accessible for graft vessels. This unfortunately was missing from many records because it is not a mandatory field. However, an analysis into the data for which stenosis percentages was performed. This was also performed to test the hypothesis of whether disease severity (% occlusion of the vessel) is highly associated with RRD.

Table 6.3.16 – PCI procedure stenosis percentages for coronary arteries

Vessel	Total (%)	RRD (%) by sub group	RRD (%) by vessel
LAD (proximal)			
0 to 49%	426 (36.0%)	49 (24.0%)	35.4%
50 to 74%	125 (17.9%)	16 (12.8%)	11.1%
75 to 94%	349 (29.8%)	45 (12.9%)	31.2%
95 to 99%	221 (18.9%)	23 (10.4%)	16.0%
100%	49 (4.2%)	9 (18.4%)	6.2%
LAD (other)			
0 to 49%	402 (34.9%)	37 (9.2%)	26.1%
50 to 74%	124 (10.8%)	20 (16.1%)	14.1%
75 to 94%	364 (31.6%)	54 (14.8%)	38.0%
95 to 99%	192 (16.7%)	17 (8.9%)	12.0%
100%	70 (6.1%)	14 (20.0%)	9.9%
RCA			
0 to 49%	9 (1.3%)	2 (22.2%)	1.6%
50 to 74%	29 (3.9%)	5 (17.2%)	4.0%
75 to 94%	274 (37.2%)	36 (13.1%)	29.0%
95 to 99%	327 (44.4%)	64 (19.6%)	51.6%
100%	98 (13.3%)	17 (17.3%)	13.7%
LCX			
0 to 49%	1 (0.2%)	0 (0.0%)	0%
50 to 74%	19 (4.0%)	6 (31.6%)	9.0%
75 to 94%	227 (47.7%)	32 (14.1%)	47.8%
95 to 99%	196 (41.2%)	21 (10.7%)	31.3%
100%	33 (6.9%)	8 (24.2%)	11.9%
LMS			
0 to 49%	2 (13.4%)	1 (25.0%)	25%
50 to 74%	3 (20.0%)	2 (66.7%)	50%
75 to 94%	8 (53.3%)	1 (12.5%)	25%
95 to 99%	2 (13.3%)	0 (0.0%)	0%
100%	0 (0.0%)	0 (0.0%)	0%

6.3.5.3 Univariate Associations with 3-Year RRD

An analysis was performed (as with table 6.3.1) on the cohort of single-vessel initial PCIs. Whilst not reported here, the list of significant ($p < 0.05$) characteristics which were associated with three-year RRD are displayed in Table 6.3.17 along with the corresponding rates, *p* values, and odds ratios (95% confidence intervals).

Table 6.3.17 –significant univariate associations with 3-Year RRD

Characteristic	Patients (n = 2,973)	RRD (n = 436)	*P* Value	Odds Ratio (95% CI)	Missing
Age Group (years)			*< 0.001*		0
< 50	230 (7.7%)	37 (16.1%)		Reference	
50-59	556 (18.7%)	61 (11.0%)	0.050	0.64 (0.41 to 1.00)	
60-69	1,037 (34.9%)	123 (11.9%)	0.082	0.70 (0.47 to 1.05)	
70-79	898 (30.2%)	160 (17.8%)	0.538	1.13 (0.77 to 1.67)	
≥ 80	252 (8.5%)	55 (21.8%)	< 0.001	1.46 (0.92 to 2.31)	
Prior CABG	266 (9.1%)	59 (22.2%)	*< 0.001*	1.78 (1.31 to 2.43)	49
Prior MI	1006 (35.9%)	182 (18.1%)	*< 0.001*	1.50 (1.21 to 1.85)	171
Diabetes	543 (18.9%)	103 (19.0%)	*0.001*	1.51 (1.18 to 1.93)	95
COPD	100 (3.5%)	22 (22.0%)	*0.034*	1.68 (1.04 to 2.73)	116
Renal Disease	140 (4.9%)	33 (23.6%)	*0.002*	1.87 (1.25 to 2.80)	116
Rotablation	69 (2.3%)	19 (27.5%)	*0.002*	2.27 (1.32 to 3.88)	0
CTO	286 (9.9%)	56 (19.6%)	*0.017*	1.46 (1.07 to 1.97)	90
LAD vessel treated	1,427 (48.0%)	186 (13.0%)	*0.016*	0.78 (0.63 to 0.95)	0
Graft Vessel treated	65 (2.2%)	17 (26.2%)	*0.008*	2.10 (1.20 to 3.70)	0
Stent Type			*< 0.001*		96
None	181 (6.3%)	67 (37.0%)		Reference	
≥ 1 BMS	862 (30.0%)	141 (16.4%)	*< 0.001*	0.34 (0.23 to 0.47)	
DES exclusive	1,834 (63.7%)	215 (11.7%)	*< 0.001*	0.23 (0.16 to 0.32)	

The single-vessel significant univariate characteristics were similar to those for the entire cohort (3,568 initial PCIs including multi-vessel procedures), apart from: the omission of treatment to left main stem (LMS) for which the odds ratio and *p* value were 1.46 and 0.50 respectively; peripheral vascular disease (PVD) for which the values were 1.28 and 0.320 respectively; and glycoprotein inhibitor usage which were 0.70 and 0.101 respectively.

6.3.5.4 Multivariate Predictors of 3-Year RRD (Single-Vessel)

The list characteristics with a significant univariate association ($p < 0.05$) with 3-Year RRD for single-vessel initial PCI procedures were used as candidates for entry into a multivariate logistic regression analysis to identify the list of significant multivariate predictors, after controlling for multicollinearity. The multivariate predictors are listed below in table 6.3.18.

Table 6.3.18 – Multivariate Predictors of 3-Year RRD for Single-Vessel PCI Procedures

Characteristic	Coefficient	SE	P Value	Odds Ratio (95% CI)	Integer score
Age ≥ 80 years	0.479	0.2	*0.008*	1.62 (1.14 to 2.30)	2
Prior CABG	0.412	0.2	*0.021*	1.51 (1.07 to 2.14)	2
Prior MI	0.271	0.1	*0.022*	1.31 (1.04 to 1.66)	1
COPD	0.597	0.3	*0.025*	1.82 (1.08 to 3.06)	2
BMS used	-1.112	0.2	*< 0.001*	0.33 (0.22 to 0.48)	1
DES used (only)	-1.503	0.2	*< 0.001*	0.22 (0.16 to 0.32)	0
Diabetes	0.441	0.1	*0.001*	1.55 (1.19 to 2.03)	2
Intercept	-8.19	NA	NA	NA	NA

The risk factor with highest adjusted odds ratio for the single-vessel PCIs was also COPD. The set of multivariate predictors as anticipated was identical to the entire cohort (3,568 PCIs), the inclusion of multi-vessel PCIs did not 'hide' or mask any potential risk factors that were only present for single-vessel prediction of RRD.

The Hosmer-Lemeshow goodness of fit statistic was $\chi^2 = 2.532$ with df = 5, and $p = 0.77$, again indicating a good fit of observed RRD versus estimated RRD across different risk groups. The area under the ROC curve was again similar to the entire cohort, with AUROC = 0.66 (95% CI 0.63 to 0.69, SE = 0.016). The ROC curve is shown in Figure 6.3.8.

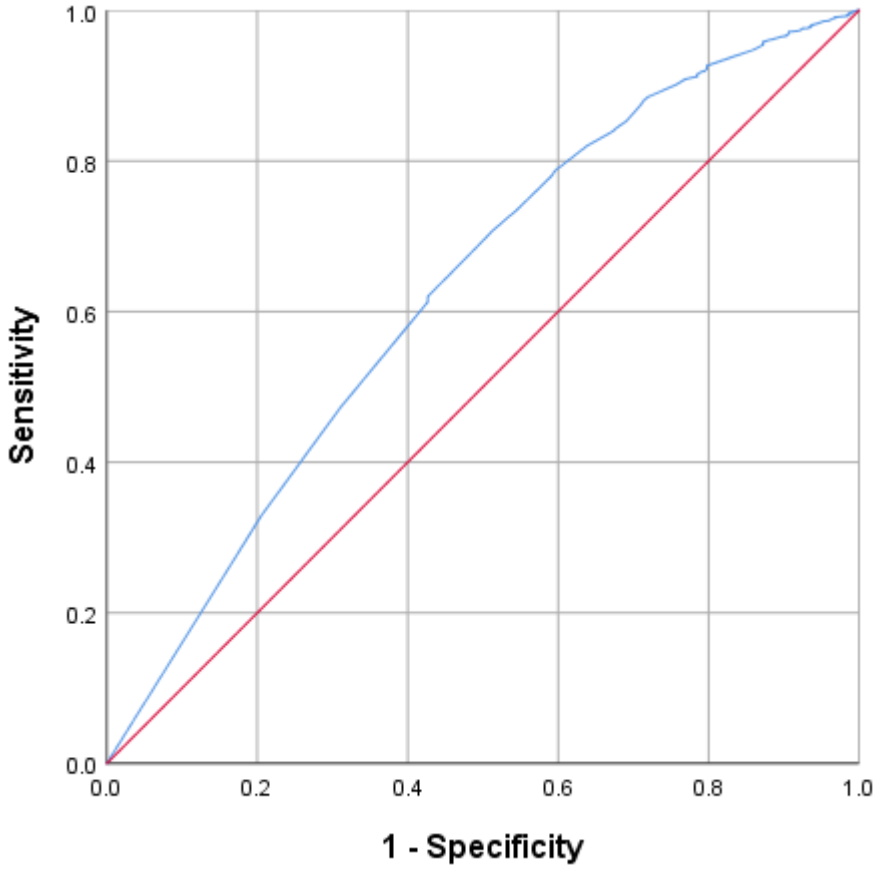


Figure 6.3.8 – ROC curve for multivariate predictors of 3-Year RRD (single-vessel PCIs)

6.3.6 BMS and DES Procedures

The results from the investigation in 6.3.5 reveal that the number of PCIs which did not feature the insertion of a stent was low, at 6.3%. A subsequent analysis was performed on the single-vessel cohort to investigate the PCIs which featured the insertion of a stent (BMS or DES).

In total, after excluding the 'no stent' group, there were 2696 valid PCIs in the remaining cohort. The breakdown by type is displayed in Table 6.3.19.

Table 6.3.19 – PCIs with either a BMS or DES inserted (n=2696)

Stent Type	No RRD (%)	RRD (%)	Total (%)
BMS	721 (83.6)	141 (16.4)	862 (32.0)
DES	1619 (88.3)	215 (11.7)	1834 (68.0)

The overall rate RRD in for both stent types was 13.2% (356 events). The majority of the PCIs (68%) used a drug-eluting stent (DES). The BMS group had the higher rate of RRD at 16.4% versus 11.7% in the DES group. The characteristics identified as potential candidate variables for multivariate analysis are displayed in Table 6.3.20.

Table 6.3.20 – Univariate associations of single-vessel PCIs featuring BMS or DES insertion, with 3-year RRD

Characteristic	Patients (%)	RRD (%)	P value	Odds Ratio	OR 95% CI
Prior MI	885	148 (16.7%)	< 0.001	1.55	1.23 to 1.96
Prior CABG	238	52 (21.8%)	< 0.001	2.01	1.44 to 2.80
Diabetes	488	91 (18.6%)	< 0.001	1.73	1.33 to 2.25
Renal Disease	120	30 (25.0%)	< 0.001	2.30	1.50 to 3.53
COPD	94	19 (20.2%)	0.042	1.70	1.01 to 2.85
Rotablator	61	14 (23.0%)	0.023	1.20	1.09 to 3.67
Age ≥ 80	225	50 (22.2%)	< 0.001	2.02	1.44 to 2.83
Graft treated	60	17 (28.3%)	< 0.001	2.68	1.51 to 4.75
LAD treated	1312	155 (11.8%)	0.038	0.79	0.63 to 0.99
Age					
< 50	213	30 (14.1)	< 0.001	**Reference**	
50-59	494	47 (9.5)	0.075	0.64	0.39 to 1.05
60-69	949	98 (10.3)	0.115	0.70	0.45 to 1.09
70-79	815	131 (16.1)	0.477	1.17	0.76 to 1.79
>= 80	225	50 (22.2).	0.029	1.74	1.06 to 2.877
Stent Length					
< 15mm	402	43 (10.7)	0.175	**Reference**	
15-19mm	785	106 (13.5)	0.168	1.30	0.89 to 1.90

20-24mm	375	60 (16.0)	0.030	1.59	1.045 to 2.420
> 24mm	1109	142 (12.8)	0.270	1.23	0.854 to 1.761
Stent Diameter					
2.25	217	20 (9.2)	0.575	**Reference**	
2.50	593	75 (12.6)	0.181	1.43	0.85 to 2.40
2.75	493	70 (14.2)	0.068	1.63	0.96 to 2.76
3.00	772	106 (13.7)	0.080	1.57	0.95 to 2.59
3.50	477	60 (12.6)	0.200	1.42	0.83 to 2.42
4.00	105	17 (16.2)	0.069	1.90	0.95 to 3.81
4.50	8	2 (25)	0.162	3.28	0.62 to 17.36
5.00	6	1 (16.7)	0.545	1.97	0.22 to 17.70
Stent Diameter					
<= 2.75mm	1303	165 (12.7)	0.475	**Reference**	
> 2.75mm	1368	186 (13.6)		1.09	0.87 to 1.36

The majority of the candidates exhibiting a significant univariate association with three-year RRD are the same as those identified in the cohort that included the PCIs with no stent. In this analysis however, treatment to the LAD vessel appears to show a lower rate of RRD compared to any other vessel treated (i.e. graft, RCA, LCx, LMS).

The candidates were then used for entry into the multivariate model. The stent type was included as a candidate as prior knowledge suggested this was a risk factor (table 6.3.19). The variables that remained significant predictors in the final multivariate model are listed in Table 6.3.21

Table 6.3.21 – Multivariate Predictors of 3-Year RRD for Single-Vessel PCI Procedures for BMS/DES stent insertion

Characteristic	Coefficient	SE	P Value	Odds Ratio (95% CI)	Integer score
Age ≥ 80 years	0.561	0.19	*0.003*	1.75 (1.22 to 2.52)	2
Prior CABG	0.529	0.19	*0.004*	1.70 (1.18 to 2.44)	2
Prior MI	0.312	0.13	*0.014*	1.37 (1.07 to 1.75)	1
COPD	0.591	0.27	*0.029*	1.81 (1.06 to 3.07)	2
DES used	-0.386	0.13	*0.002*	0.68 (0.53 to 0.87)	-1
Diabetes	0.507	0.14	*< 0.001*	1.66 (1.26 to 2.19)	1
Renal Disease	0.472	0.23	*0.044*	1.60 (1.01 to 3.07)	1
Intercept	-2.026	NA	NA	NA	NA

The multivariate predictors in Table 6.3.21 are similar to those reported in Table 6.3.18, which included the ‘no stent’ cohort. The only addition risk factor identified in 6.3.21 was renal disease.

The Hosmer-Lemeshow goodness of fit test was non-significant, χ^2 = 1.166, df = 5, and *p* = 0.95, indicating a good fit between observed and estimated 3-year RRD. The calibration plot is displayed in Figure 6.3.9.

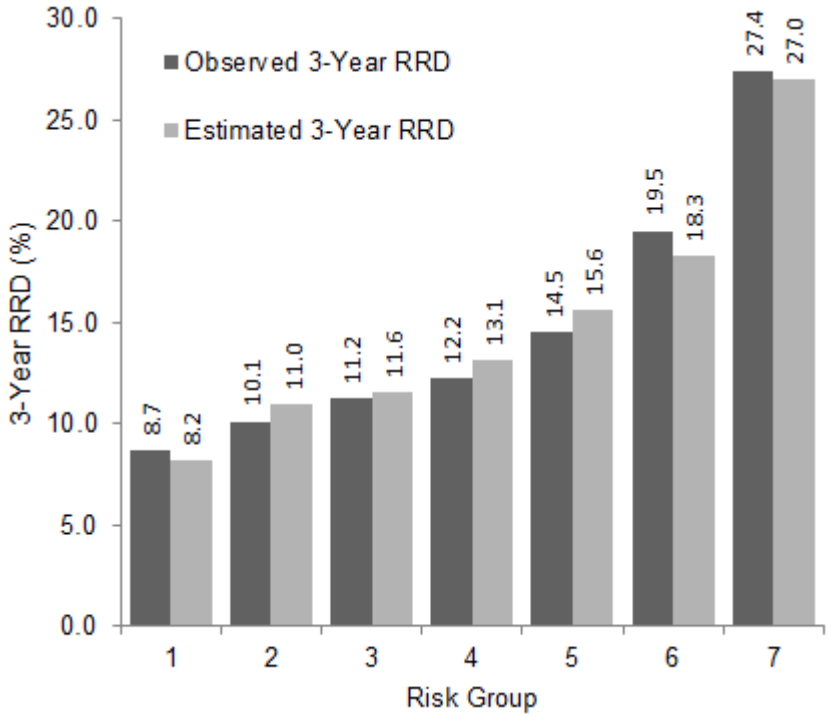


Figure 6.3.9 – Observed versus estimated 3-year RRD for BMS and DES insertion cohort

Despite a good fit between the observed and estimated rates amongst each group, the area under the ROC curve (AUROC) was 0.63 (0.59 to 0.66), indicating a poor ability to discriminate, as also seen in the model developed including the 'no stent' cohort.

6.4 Discussion

6.4.1 Outcomes

The primary motivation for this study was to identify which demographic, procedural, or clinical characteristics, if any, are highly associated (i.e. statistically significant, $p < 0.05$) with RRD. As documented in Chapter 2 (Literature Review) and identified in the previous chapter which investigated 30-day all-cause mortality rates at the ECTC, it has been widely established that elective PCI patients (at least any acceptably performing hospital or cardiac centre) exhibit low rates of popular outcomes, such as in-hospital major adverse cardiac events (MACEs) or mortality, short-term MACE or mortality (i.e. 30 days following a procedure).

This study investigated the rate of the composite endpoint, or outcome of a non-staged repeat revascularisation or all-cause mortality (RRD) within three-years of a patient's first elective PCI at the Essex Cardiothoracic Centre (ECTC). The repeat revascularisation events included any subsequent coronary revascularisation procedure for a given patient, whether this is a subsequent PCI or a CABG.

The overall three-year RRD rate was 14.6% (522 events), as expected the majority of these (374) were repeat revascularisations (10.5% overall) and the remaining 148 (4.1%) events were deaths. From 2008 (the first full calendar year of procedures at the ECTC) onwards, the RRD rate remains similar between single-vessel and multi-vessel initial PCI procedures with the largest difference being only 2.9%, occurring in 2012 (single-vessel = 16.2% and multi-vessel = 13.3% RRD). The majority (81.8%) of the repeat revascularisation patients were referred for a PCI in their subsequent procedure resulting in only 18.2% undergoing a bypass graft (CABG). Of the 306 patients returning within three years for another PCI, most were elective (244, 79.7%) with the remaining 62 (20.3%) requiring urgent or emergency PCI. Almost half of the events (46.3%) occurred within the first nine months following the date of the procedure.

As expected, the highest rate of RRD is seen in the 'No stent' group with 37.5% of patients experiencing RRD, followed by 16.8% in the BMS group, and 11.7% in the DES group. These rates were very similar for the single-vessel PCI analysis, at 37.0%, 16.4%, and 11.7% respectively.

6.4.1.1 Univariate Predictors of RRD

The univariate predictors of RRD which exhibited this highest odds ratios were rotablator usage (2.4), treatment to a previously grafted coronary vessel (2.1), renal disease (1.9), closely followed by prior CABG, COPD, and LMS treatment with an approximate odds ratio of 1.8. The other univariate risk factors were old age (≥ 80 years), diabetes, PVD, presence of a CTO, and a prior myocardial infarction. The two characteristics with apparent protective effects (i.e. odds ratios below 1.0) were glycoprotein inhibitor usage and the BMS/DES stent groups. It should be noted that prior CABG and graft vessel treatment are related and therefore would only exhibit univariate associations. T multivariate logistic regression process eliminates the multicollinearity from the final model. The rate of RRD in PCIs to a previously grafted vessel is high. However, the median time to RRD is longer than any other native coronary vessel. None of these characteristics are surprising, especially as elderly patients are more likely to have a higher chance of dying (one of the two RRD components) as well as having other (unrecorded) comorbidities being linked to mortality. The classification of angina, although not listed, was analysed, but as anticipated because this cohort were stable, elective patients it is not surprising that this would not be identified as a predictor due to unstable angina being more associated with urgent patients.

6.4.1.2 Multivariate Predictors of RRD

The final set of multivariate predictors, after having controlled for multicollinearity was identical for the entire PCI cohort (3,568 procedures) and for the single-vessel cohort (2,973). These were in descending order of adjusted odds ratio: COPD (1.9); age ≥ 80 years (1.7); prior CABG (1.6); diabetes (1.5); prior MI (1.3); and the protective effects were BMS (0.33) and DES (0.22) both relative to the 'No stent' group. The single-vessel multi-vessel predictors exhibited similar values for the corresponding odds ratios. Rotablator usage, presence of a CTO, PVD, and renal disease were used as candidates for entry into a multivariate analysis as they exhibited a significant univariate relationship with RRD, however after controlling for multicollinearity these characteristics were no longer significant in the final multivariate model. It could be the case that elderly, diabetic, and patients with severe previously documented coronary heart disease exhibit higher rates of PVD and renal disease, and similarly those with prior myocardial infarctions and those which needed prior bypass grafts also exhibited tougher, more calcified coronary lesions, hence having a high multicollinearity. It is also highly likely that CTO or rotablator usage was more prominent in the 'No stent' group, such that a stent could not be successfully inserted due to a CTO or hard lesions.

6.4.1.3 Single-vessel Initial PCI Analysis

Of the 3,568 initial PCI procedures, 83.3% of these were PCI to either a single native coronary vessel or previously grafted coronary vessel. The overall RRD rate was 14.7%, broken down into 10.7% repeat revascularisations and 4.0% deaths. These procedures were additionally investigated in isolation to determine whether any different significant predictors could be identified that was hidden when combined with multi-vessel PCIs. The stent group usage (from None, BMS, to DES) was 6.3%, 30.0% and 63.7% respectively with the corresponding median days to RRD being 140, 301, and 392 respectively.

The left anterior descending vessel (LAD) was treated, or at least attempted in 48% of all single-vessel PCIs, the next highest rate was the right coronary artery (RCA) which was involved in 30.4% of procedures. The treatment of the left main stem (LMS) was not a significant univariate risk factor, this is likely to be because of the low sample size (20) and the fact the most of the PCIs involving LMS treatment were in the multi-vessel procedure cohort. The LAD vessel was involved in 74.3% of the repeat revascularisations, closely followed by the RCA in 58%. The RCA showed the lowest median days to RRD (238), and the highest as expected was CABG at 427.

Single-Vessel to Single-vessel Repeat Revascularisation Events

For procedures featuring a repeat revascularisation to a single vessel, the LAD exhibited the highest percentage whereby almost half (45.9%) involved target vessel revascularisation of the LAD, however this figure could be high because the proximal and other branches are combined within the LAD.

For most coronary vessels a TVR (same corresponding vessel) was the highest treated vessel on the repeat revascularisation as stated above this was 45.9% for the LAD, 38.4% for the RCA, and 32.8% for the LCX, therefore there is a higher chance of the same vessel needing revascularisation in future than any other vessel when fixing the initial PCI to a single vessel only. It is unknown simply whether it is a problem with the stent failing or restenosis, such that the conditions which resulted in the specific coronary artery becoming stenotic in the first place are simple repeating.

Stent Type breakdown by Vessel Attempted

For the 'No stent' group, the vessel with the highest attempted rate was the RCA (43.6%) followed by the LAD (37.0%). Interestingly the LCX exhibited the lowest number of median

days to a RRD event (49). There were no significant different between any of the balloon (or attempted stent, if it indeed failed) dimensions.

For the PCIs using a BMS stent, the LAD vessel had the highest attempted rate with 40.1%, closely followed by the RCA (35.6%). Interestingly in this stent group, the LCX had the highest median days to repeat revascularisation (400). There were no significant differences between any of the stent dimensions for the RRD patients versus the no-RRD counterparts. Although not significant (p = 0.07) the mean minimum stent diameter for the LCX vessel was larger for the no-RRD group at 3.13mm (SD = 0.46) versus 2.98 mm (0.35), thus a very slight increased risk of RRD if a smaller stent diameter is used. The logical assumption here would be that the smaller the vessel would become more easily occluded.

The DES cohort (as did the BMS) showed the LAD as the highest vessel attempted rate (52.7%) followed by the RCA (26.8%). The lowest median days to RRD was for the LAD at 371 days. Also as shown with the BMS group, the DES didn't not have any significant differences but the mean minimum stent diameter was higher (2.77mm, SD = 0.35) for the no-RRD group versus the RRD group (2.72mm, SD = 0.30), the p value was 0.153.

Stenosis Percentages for Attempted Vessels

The treatment of the LAD was identified as a significant univariate predictor of RRD, it reported a protective effect (odds ratio 0.78) if this vessel was treated compared to PCIs where it was not. A likely reason for this was that, compared to the LCX and RCA arteries, the LAD patients were treated for a much lower percentage stenosis in their vessels. For example, LCX and RCA had 41.2% and 44.4% of patients with 95-99% stenosis, the LAD proximal and other vessels exhibited high rates of 0-49% stenosis, at 36.0% and 34.9% respectively. The RCA also exhibited a very high percentage of 100% stenosis (13.3%) compared to the LCX (6.9%), LAD proximal (4.2%), and LAD other (6.1%).

PCIs Including BMS or DES Insertion

The final analysis within this study excluded the PCIs which did not feature a stent insertion (i.e. balloon angioplasty), thus retaining only the BMS and DES procedures. This allowed comparisons to be made between the BMS and DES cohort, i.e. to verify whether certain predictors reported by others (Wilson et al., 2011; Wang et al., 2012; Taniwaki et al., 2014) were useful in predicting three-year RRD in the ECTC cohort. Previously, the BMS and DES patients were only compared to the reference variable, ‘no stent group’, and not directly with each other. After exclusion of the ‘no stent’ group, an additional risk

factor was identified, this being renal disease. The stent diameter and stent length was investigated, as existing research reported (Hess et al., 2014) these as predictors for 1-year target vessel revascularisation (TVR). It was unknown whether this also features as a risk factor in the combined outcome of 3-year RRD. Following testing, it was found that neither the minimum stent diameter or stent length in the overall BMS and DES cohorts were significant predictors of 3-year RRD. The exact reason for this is unknown. It may be the case that the significance of the predictor is effectively diluted by the non-TVR PCIs for the repeat revascularisation events, because the present study combined the BMS and DES cohort, it may be that further investigation into BMS and DES stent dimension thresholds, reveals they become significant (e.g. stent type BMS and diameter ≤ 2.75 mm versus DES ≤ 2.75), this would have been interesting to investigate had a larger database been available. One of the main difficulties in comparing BMS and DES subgroups is that the characteristics are changing, and so have the indications as to why each stent was used. In modern PCI procedures, a DES will almost always be used. The majority of the BMS cohort present was from PCIs performed in earlier years at the ECTC. Therefore direct comparisons are problematic.

The discrimination performance when excluding the ‘no stent’ group was also poor (AUROC = 0.63, 0.59 to 0.66). This verifies that the usage of longer-term predictors, such as 3-year RRD, are less effective than those identified at the short-term, as identified in the 30-day morality prediction model developed in Chapter 5. When the stent type is DES, this acts as a ‘protective’ effect relative to BMS, the DES usage is a predictor in the multivariate model (OR = 0.68 , p = 0.002), this is consistent with other literature (Wilson et al., 2011).

6.4.2 Other Literature

Whilst, at the time of conducting this study, no other literature could be found using the same endpoint, some similarities were identified in predictors for repeat revascularisation. Wu et al. (2004) identified diabetes as a predictor of repeat revascularisation by CABG. Their study, however, identified multi-vessel disease as a predictor which, was not found to be significant in this study. More interestingly, the total (or 'maximum') stent length (per mm longer) was also. Their repeat revascularisation rate was 16.2% compared to 10.5% present. Similarly to this study, Wu et al. also identified prior CABG as a predictor although their repeat revascularisation outcome for this predictor was limited to PCI only (not CABG). When they fixed their outcome to repeat revascularisation by CABG only (i.e. excluding PCI) they found that prior CABG and MI were predictors but surprisingly were associated with lower outcomes and subsequent risk of CABG.

In a study by Wang et al. (2012) that focussed on obesity in repeat revascularisation within DES PCI patients, they identified hypercholesterolaemia and diabetes as multivariate predictors, however their outcome was limited to non-target lesion revascularisations, whereas this study identified a rate of target vessel revascularisation (TVR) which could be why hypercholesterolaemia was identified as a predictor in this cohort.

In the 4-year study of repeat revascularisation in new-generation DES patients by Taniwaki et al. (2014) similar predictors were found. However, their study focussed on target lesion revascularisation (TLR) rates amongst different DES stent types. Like this study it was found that age, diabetes (insulin-treated however), and although high rates were found in this present study but not statistically significant, the treatment of the right coronary artery (RCA) was associated with a higher risk of TLR. Interestingly, also identified was that treatment to the LAD vessel operates as a protective effect versus treatment not involving the LAD. This was identified as a significant univariate predictor, offering a similar protective effect (OR = 0.78, p = 0.03), in the ECTC cohort after the ‘no stent’ group was excluded, however during the multivariate analysis it was found not to be significant. This could be due to other incorporated risk factors having a higher likelihood of the LAD being treated relative to other coronary vessels. Treatment to saphenous grafts were also identified as a significant predictor however in the available database for the present study the breakdown of graft vessel type was not performed. The study by Taniwaki et al., in addition to TLR predictors also identified the list of predictors for any revascularisation. Younger age was identified as protective (odds ratio 0.98, 95% CI 0.97

to 0.99). Diabetes as also found in the ECTC cohort was a predictor (OR = 1.38, 1.08 to 1.76). Whilst the present study exhibited a non-significant lower minimum stent diameter (surrogate for vessel diameter) as having a higher rate of RRD, Taniwaki et al. found that a smaller reference vessel diameter was associated with a lower rate (0.76, 0.62 to 0.93). It's possible that using the combined outcome of death and repeat revascularisation affected this finding and, that if limited to repeat revascularisation only, it may be significant.

6.4.3 Limitations

Not all of the PCI procedures that were planned, or 'Staged', may have been detected during this analysis, and hence some of the 374 (10.5%) repeat revascularisation events may have in reality been initially planned by a cardiologist during the time of the patient's initial PCI. This possible limitation is due to the PCI procedures not necessarily being recorded or identified as such in the CVIS database correctly by operators, or other staff following completion of a patient's procedure. If recorded correctly, the information used to identify staged procedures can be located in one of four fields within the database: (i) 'Indication for Intervention'; (ii) 'Test Reason'; (iii) 'Medical Notes'; (iv) discharge letters. The adopted solution to detect likely staged procedures not recorded correctly as such, was recommended by an experienced interventional cardiologist and CVIS user within the ECTC. It was made apparent that all staged procedures would be both elective, and the interval in days between the patient's initial PCI discharge and date of entry onto the subsequent waiting list would be less than one week.

As previously discussed in Chapter 6 (The all-cause 30-day mortality study), the cause of death for patients was not available, therefore patients that died within three years of their initial PCI procedure, may have died from causes completely unrelated to their cardiovascular disease. It is therefore not viable to predict whether the initial elective PCI had a positive or negative effect on the patient’s survival.

A minor limitation encountered is that the actual lesion dimensions (i.e. segment length or width) are not recorded anywhere in the CVIS database. Only the dimensions of the stent(s) and balloon(s) used in the procedure were available, however these act as surrogates for the former, and assume that the interventional cardiologists would have selected the optimum stent length and width to treat the stenotic coronary vessel most appropriately.

A possible limitation (although unknown) as that data completeness could be masking out comorbidities or diagnosis information. In the earlier years of the ECTC operation detailed information is more likely to be missing than compared to modern times. If a field or medical history was blank in the past it might not necessarily mean the condition did not exist, but simply that is was not known about or tested for. Thus trends in demographic and patient characteristics could simply be better explained by data completeness.

As also previously discussed in the other studies, a limitation exists relating to patients that may have relocated outside of the Essex region within the three-year period, and thus would have likely undergone a subsequent revascularisation procedure at another cardiac centre or hospital, if such a procedure was required. This could also result in mortality notifications not being transferred to the CTC. Because of limitations with ethical approval and data access, patient primary care records at other hospitals or cardiac centres was not available in this study. It is therefore possible that the rates reported in this study are underestimated, and this would subsequently impede the performance of risk prediction. It may however be argued that given old age (≥ 80 years) is a multivariate risk factor, these patients are less likely to relocate than their younger counterparts.

6.4.4 Conclusions

The final hypothesis in section 1.3 was tested and determined to be true. Certain novel risk factors were identified in the construction of the multivariate models for predicting 3-year RRD. The risk factors, not present in the NWQIP risk model, were: prior CABG; prior MI; COPD; BMS or DES insertion; and diabetes mellitus. Additionally, it was discovered that as with the 30-day mortality model, treatment to lesions in the LMS or graft vessels, were not significant. It might be the case that going forward, these two NWQIP risk factors might not be useful predictors of other adverse outcomes either, possibly due to more experienced operators knowing how to treat these vessels, than was previously the case during the original NWQIP cohort era.

The discriminatory testing of the multivariate models in this study produced an area under the ROC curve considered fairly poor (0.65 and 0.66 respectively), thus limiting the usefulness of these predictors in a model that would be accepted elsewhere. Because of the composite outcome of repeat revascularisation and death within three years, it is anticipated that differing characteristics may limit the predictive accuracy of events, i.e. the patient characteristics that experience such events are too different and thus when

combined into a single composite outcome the usefulness or accuracy of any one such endpoint is diminished. It does however identify certain predictors which allows certain subgroups to be given more care and planning to.

The composite outcome of three-year RRD reported here can be extremely useful for interventional cardiologists, care nurses, and patients in terms of planning future operations and informed decision making. By knowing the core set of multivariate risk factors which exhibit strong relationships with the RRD outcome, it can assist in making caring for the most vulnerable patients more efficient, or in simple terms allocate resources more effectively. This study also revealed the relationship breakdown between stenosis percentage group and RRD rate. The lower rates of RRD seen in procedures treating the left anterior descending arteries (proximal or other) can be explained due to lower vessel occlusion, or 'stenosis percentage' when compared to other coronary arteries, especially the right coronary artery (RCA).

There may be a cancellation effect occurring relating to the similar RRD rates over the years the ECTC has been active. The increase in higher risk elective patients, such as those with comorbidities including diabetes, hypertension, hypercholesterolaemia, peripheral vascular disease (PVD), and chronic obstructive pulmonary disease (COPD) is apparent and would likely increase the risk of both repeat revascularisation and death. However, the increased percentage usage of DES stents and corresponding reduction of BMS insertion, could act as a preventative measure thus lowering the RRD rates so in essence combining these two factors cancels out any differences in the RRD rate over time.

It should be noted that when drawing conclusions from the three-year RRD event reported in this study, some patients that underwent a repeat revascularisation may have also died following the subsequent procedure but still within the three-year period. Therefore, the only event reported in this instance would be the repeat revascularisation procedure.

6.4.5 Future Work

Other cardiologists at cardiac centres similar to the ECTC could investigate the RRD rates in their cohorts in ascertain whether the multivariate predictors as identified in this study are also prominent predictors in their cohort of initial elective PCIs.

For future investigation into adverse outcomes, including repeat revascularisation and long-term mortality, it would be useful to have a framework in place which could track patients nationally rather than being limited to a single cardiac centre. This would directly address the limitation of patients potentially relocating to a different area and limit the chance of event rates being underestimated.

This study combined PCI procedures regardless of the type of stent embedded, i.e. the cohort included procedures featuring (i) standard balloon angioplasty; (ii) bare-metal stent (BMS) insertion; (iii) different generations of drug-eluting stent (DES) usage. Due to the decreasing percentage of PCIs using BMS, as displayed in this cohort (65.5% in 2007 falling to 18.8% in 2012), and corresponding increase in DES usage (31% in 2007 rising to 77.5% in 2012), it should warrant a prediction model or analysis that looks at DES in isolation, or at least separates BMS and DES into different models, the only slight negative point would be the complexity of having operators use multiple algorithms to estimating risk. It would have been interesting to investigate specific subgroups of DES patients, such as those with diabetes, or more specifically, diabetic patients with small stent diameters, and whether this subgroup exhibits higher rates versus non diabetic patients. Had a larger database of PCIs been available, this would have been investigated. As with this study, by utilising a single prediction model that incorporates the stent type (none, BMS usage, DES exclusive) it allows all patients to be compared using the same risk prediction system.

It would be beneficial to provide additional training to any staff members, whether this be interventional cardiologists, coders, or nurses, to populate patient procedure data into the CVIS database. It should be made clear that more complete datasets regarding patient demographics, procedural aspects, comorbidities, and other clinical characteristics are beneficial for investigating which subgroups of patients are at higher risk of experiencing various important clinical outcomes. By not leaving important data fields blank such as 'Test Reason' or 'Indication for Intervention', it could have perhaps improved upon identifying various associations between patients and rates of RRD. As previously discussed, identification of whether successive PCI procedures for a given patient were staged or not could be addressed rather than having to check in several different database fields or manually read thousands of medical notes fields. Clearer labels and descriptions could be utilised such "*Does this patient need to return for another cardiac revascularisation procedure (PCI/CABG)?*" if users have trouble understanding.

Chapter 7: Conclusions

7.1 Summary of Studies

The three studies (Chapters 4, 5, and 6) investigated important adverse outcome rates of three main endpoints following percutaneous coronary intervention (PCI) at the Essex Cardiothoracic Centre (ECTC). In total the number of valid PCIs available for analysis was 15,865 and these procedures were performed on patients of all priorities (elective, urgent, and emergency) between July 2007 and March 2015.

7.1.1 Main Findings

From conducting the three studies (Chapters 4, 5, and 6) to meet the thesis objectives stated in section 1.5, the following was learned:

- The NWQIP risk model for predicting in-hospital MACE did not perform as effectively as it did in the original study (Grayson et al., 2006), or the external validation study (Kunadian et al., 2008), the calibration, which is a measure of estimated and observed MACE rates amongst different risk groups exhibited large differences and hence the NWQIP model overestimated MACE rates.
- Treatment to lesions in the LMS or graft vessels is not significant multivariate predictors of in-hospital MACE, or 30-day mortality, in the ECTC cohort.
- The 30-day all-cause mortality rate in the ECTC cohort was 2.1% in the training set and 2.0% in the validation set (including all PCI priorities).
- Multivariate predictors of 30-day mortality in the ECTC cohort were verified using an internal validation set. These predictors (odds ratios; and P values) were: ages 60-69 (3.01; < 0.001); 70-79 (5.17; < 0.001); age ≥ 80 years (11.61; < 0.001); female sex (1.57; 0.007); cardiogenic shock (7.31; < 0.001); cerebrovascular disease (2.08; 0.013); urgent PCI (2.01; 0.028); emergency PCI (10.23; < 0.001); peripheral vascular disease (2.39; 0.004); and pre-operation ventilation (4.97; < 0.001).
- The discrimination (AUROC = 0.89, SE = 0.021) and calibration ($\chi 2 = 9.955$, $p = 0.27$, and df = 8) were verified using the validation set.
- Some of the 30-day mortality risk factors identified in Chapter 5 have also been reported in two recently published risk models for 30-day mortality (McAllister et al, 2016; Wall et al, 2017), thus verifying their importance as predictors on other cohorts within the UK. These were cardiogenic shock, age, PCI priority, and cerebrovascular disease (in the McAllister study).

- For elective PCI patients, the rate of three-year repeat revascularisation or death (RRD) was 14.6% (10.5% were repeat revascularisations and 4.1% were patient deaths).
- Multivariate predictors of 3-year RRD were: age ≥ 80 years (1.65; 0.002); prior CABG (1.56; 0.006); prior MI (1.3; 0.017); COPD (1.89; 0.007); BMS insertion (0.33; < 0.001); DES exclusive insertion (0.22; < 0.001); and diabetes (1.51; 0.001). When excluding PCIs that did not use a stent, renal disease was identified as a risk factor (OR = 2.29, $p < 0.001$). When utilising a BMS and DES cohort, the stent dimensions (diameter and length) were not significant predictors of 3-year RRD.
- The performance of the 3-year RRD risk model was quite poor in terms of discrimination, i.e. the AUROC = 0.65 (SE = 0.015), and the calibration was $\chi 2 = 2.622$ (P = 0.76, df = 5). Therefore suggestion that using such a long endpoint (three years) weakens associations of risk factors and that other characteristics not currently recorded in the ECTC database may yield better associations with the outcome and hence be more useful in a prediction model. Such characteristics may include diet, and sedentary lifestyle, or premature cessation of dual anti-platelet therapies (DAPT).

7.1.2 Hypothesis

The three hypotheses stated in the Introduction chapter (1.3) in brief were:

Hypothesis 1: The NWQIP risk model is outdated and will not perform as effectively in a modern PCI cohort.

Hypothesis 2: Not all of the NWQIP risk factors will be significant predictors of in-hospital MACE in a modern PCI cohort and hence some would no longer be used in a modern risk prediction model.

Hypothesis 3: Multivariate logistic regression analysis on a modern PCI cohort could allow novel risk factors to be identified that have significant associations with adverse outcomes following PCI (i.e. in-hospital MACE, mortality, repeat revascularisation).

These hypotheses were tested in the analysis of each of the three main studies within this thesis, and were found to be true, or at least true for the ECTC PCI cohort. Firstly for hypothesis 1, it was found in Chapter 4 that the NWQIP model is poorly calibrated and

large differences are present between the observed and estimated MACE rates amongst different risk groups. For hypothesis 2, it was found that treatment to LMS or graft lesions were no longer significant predictors of MACE or 30-day mortality. Lastly, for hypothesis 3, two novel risk factors were identified for the outcome of 30-day mortality. These were peripheral vascular disease (PVD) and pre-operation ventilation. These two risk factors, in addition to several other variables (some of which are present in the NWQIP model) were incorporated into a 30-day mortality prediction model and internally validated to verify the performance.

7.2 In-hospital MACE

In-hospital MACE is a composite endpoint comprising the occurrence of at least one of the following: death; Q-wave myocardial infarction; emergency coronary artery bypass graft (CABG) surgery; or a cerebrovascular accident (stroke). This composite outcome was investigated because it was chosen as the outcome of the UK's first major risk prediction model following PCI (Grayson et al, 2006). By investigating this outcome it could be determined whether MACE rates had differed over time which also equates to changes in intervention technology, by geographical location within the UK (i.e. north-west relative to the south-east where the ECTC is located).

Another reason to externally validate the NWQIP model and the MACE outcome was that it had already been externally validated on a PCI cohort a few years after the original study (Kunadian et al, 2008), for which this cohort was based in the Midlands (as opposed to the north-west of England). They found that the NWQIP risk model performed better for predicting MACE in their cohort than it did in the original cohort. The performance metrics for these two studies and the analysis using the ECTC cohort are listed below in Table 7.1.1.

Table 7.1.1 – summary of NWQIP risk model performance testing across different PCI cohorts

PCI Cohort	Patients	Date	MACE (%)	ROC	HL p Value
NWQIP original	9914	01/2001 to 12/2003	129 (1.30%)	0.76	0.43
NWQIP validation	1786	01/2004 to 12/2004	N/A	0.72	N/A
External validation	5034	09/2002 to 08/2006	104 (2.07%)	0.86 (0.82 to 0.90)	0.95
ECTC	13202	07/2007 to 03/2015	193 (1.46%)	0.83 (0.79 to 0.96)	< 0.01

By revalidating the NWQIP model and the MACE outcome on the ECTC cohort it could determine how reliable the model is at estimating MACE rates on a modern cohort despite many changes (as mentioned) in technology, demographics, comorbidities etc. The discrimination (area under the ROC curve) saw an improvement in both the Kunadian (2008) study and in the ECTC cohort. The calibration, i.e. the goodness of fit between observed and estimated MACE amongst different risk groups was excellent (p = 0.95) in the Kunadian cohort, bearing in mind a p value of 1.0 would indicate a perfect calibration, i.e. a 100% match of observed and estimated MACE in every risk group. The calibration in

the ECTC cohort however was extremely poor ($p < 0.01$) indicating there were large differences in multiple risk groups. In the eight different risk groups it was found that the large differences between observed and estimated MACE were present in the four highest risk groups. The exact reason behind this poor calibration could be explained by certain NWQIP risk factors such as treatment to left main stem (LMS) lesions or graft lesions no longer being such a high-risk during modern PCI procedures. Faster revascularisation, especially for emergency patients i.e. those presenting with ST-elevation myocardial infarction (STEMI) stemming from more UK PCI centres and operators could mean than in modern times critically ill patients have faster door-to-balloon times and whereas previously they may have died in the operating theatre (hence the in-hospital death MACE component) but now they survive. The study found that in the ECTC cohort, lesions in graft vessels no longer exhibited a univariate or hence multivariate relationship with MACE as the $p = 0.68$.

7.3 30-Day Mortality

The outcome of all-cause 30-day mortality following PCI was chosen because the in-hospital MACE end-point occurs at very low rates in any respectably performing hospital or cardiac centre. The rates in the three studies as displayed in Table 7.1.1 were 1.3%, 2.07%, and 1.46% respectively. This outcome is clearly especially low in stable (elective) PCI patients. As reported in Chapter 4, the majority of the MACE events are due to in-hospital death, for example out of the 193 MACE events identified in the ECTC cohort, 146 (75.5%) were due to death. Such low rates of the other three MACE components (Q-wave MI, cerebrovascular accident, and emergency CABG) result in low statistical power when performing a univariate analysis with the characteristics in the PCI dataset. Because death is such an important component, and is easily recognisable and recorded correctly in cardiac centre databases, this outcome was analysed for the second study (Chapter 5). The overall in-hospital death rate was 1.11% (146 events from 13,202 PCIs), whilst this is an clearly an important outcome, this also occurs at a very low rate. Despite the ability to predict in-hospital MACE being useful for operators, consultants, and patients (for informed consent of risk), more useful outcomes would be long-term, for example a given patient might have a relatively low risk of dying during their hospitalisation, but they may have a higher risk of dying three weeks following their discharge. Clearly being able to identify longer-term outcomes is of equal importance. As detailed in Chapter 2 (Theoretical Background), some research has suggested than the 30 day window following a PCI procedure is important for assessing recovery from the PCI, i.e. the highest risk to those PCI patients comes within the first several weeks of their operation. This was largely the justification for the choice of 30-day mortality, and the fact that it is robust and easily recognisable. Former ECTC patients which died have their death date updated in the PAS database and this is linked to the ECTC CVIS database usually it is updated within 30 days. The all-cause mortality outcome had to be used because the exact cause of death information was not available or recorded in the CVIS database.

In Chapter 5 (30-Day Mortality Prediction), a multivariate logistic regression analysis was performed to construct a 30-day mortality risk prediction model for PCI patients. The entire ECTC cohort of PCIs was divided into a training set, used to develop the risk model, and a validation set, used to internally validate the model's performance. The outcomes of 30-day all-cause mortality and in-hospital MACE are listed in Table 7.1.2 for both the training set (n = 9279) and validation set (n = 4119).

Table 7.1.2 – ECTC training set and validation set outcomes for in-hospital MACE and 30-day mortality by priority of PCI

Outcome	Elective (n)	Urgent (n)	Emergency (n)	Total (n)
Training Set (n = 9279)	-	-		
MACE	0.5% (22)	0.6% (15)	3.6% (91)	1.4% (128)
30-day mortality	0.4% (17)	0.9% (25)	6.1% (155)	2.1% (197)
Validation Set (n = 4119)				
MACE	<0.1% (1)	0.9% (10)	2.4% (34)	1.1% (45)
30-day mortality	0.3% (4)	1.0% (11)	4.9% (69)	2.0% (84)

As expected the rates for both outcomes in elective and urgent patients are very low. It can be argued that the MACE (3.6%, 2.4%) and 30-day mortality (6.1%, 4.9%) are still very low respectively. The training set performance produced an ROC of 0.88 (0.85 to 0.91) which suggests very good discrimination, and the Hosmer-Lemeshow goodness of fit test produced $p = 0.67$ indicating little departure of a perfect fit across different risk groups for observed versus estimated outcomes. When this prediction model was tested on the validation PCI cohort (n = 4119) it produced a similar ROC curve of 0.89 (0.85 to 0.93) and a goodness of fit of $p = 0.26$, again both metrics suggest the model performed for discrimination and calibration respectively.

The risk factors in the 30-day mortality risk prediction model incorporated some of those present in the NWQIP model for MACE prediction such as age, female sex, cardiogenic shock, PCI priority, and cerebrovascular disease however the two novel risk factors were pre-operation ventilation, often a surrogate marker of out-of-hospital cardiac arrest, and peripheral vascular disease (PVD).

Comparison with other models

Since the 30-day mortality model, using the ECTC cohort(Chapter 5), was developed, two studies featuring the development of a 30-day mortality logistic regression model have been published by other researchers in the UK (McAllister et al, 2016; Wall et al, 2017). It is important to consider the similarities and differences between these models and the one developed using the ECTC cohort. Following the publication of these studies, it allows interesting comparisons to be made within the UK, as previously, the majority of risk score models where developed outside of the UK (e.g. United States). The US in particular is known to contain differences in population and hence patient characteristics reporting for PCI.

McAllister et al., (2016) utilised a very large database of PCI data for procedures performed in the whole of England and Wales from 2007-2011. Scotland and Northern

Ireland were excluded due to issues of reliability for 30-day mortality tracking from the Office for National Statistics (ONS). In total, their training database featured 336,433 PCI procedures. They validated their model using data from 76,804 PCI procedures performed in 2012 across England and Wales. The 30-day mortality for training and validation cohorts was 1.70% and 2.09% respectively. The increased mortality rate in the validation cohort is consistent with increasing proportions of emergency priority PCIs performed over recent years. The binary predictors in the final model were: female sex (OR = 1.07 per year, 1.07 to 1.08), diabetes (OR = 1.69, 1.56 to 1.83), prior MI (OR=1.17, 1.10 to 1.25), cerebrovascular event (OR=1.54, 1.39 to 1.71), cardiogenic shock (OR=45.47, 30.72 to 67.31). The other predictors were procedure urgency (classified into five groups), age (OR=1.07, 1.07 to 1.08), renal disease based on creatinine (OR=2.71, 2.38 to 3.09) and dialysis (OR=3.09, 2.56 to 3.73). Two predictors based on age-shock and age-diabetes interaction were also incorporated into their regression equation.

In 2017, Wall et al., developed and validated a model using a cohort of 6522 patients from the South Yorkshire Cardiothoracic Centre between January 2007 and September 2013, in the north of England. Their model was validated both internally and externally, at Manchester Royal Infirmary, using a database of 3290, and 3239 PCIs respectively. The external validation cohort comprised PCIs from January 2012 to December 2014. The 30-day mortality rates were for training, internal validation, and external validation cohorts were 2.3%, 2.3%, and 2.0% respectively. Five risk factors were identified in their univariate analysis and used their model, the odds ratios and corresponding 95% CIs were: cardiogenic shock (OR =20.1, 11.6 to 35.1), emergency PCI (OR=10.5, 5.8 to 19.0), history of renal disease (OR=5.0, 2.6 to 9.5), diabetes (OR=1.6, 1.1 to 2.4), and age (OR=1.1 per year, 1.0 to 1.1).

The reported characteristics of the training set for each of the three studies are displayed in Table 7.1.3.

Table 7.1.3 – Characteristics for the ECTC, McAllister, and Wall training cohorts used to develop their respective 30-day mortality models

Characteristic	ECTC	McAllister (2016)	Wall (2017)
Mean age (SD)	65.4 (11.8)	64.7 (N/A)	62.5 (11.6)
Male sex	74.9%	74.19%	71.8%
Cardiogenic shock	2.5%	1.4%	0.9%
PCI Priority			
Elective	44.1%	41.73%	31.9%
Urgent	29.0%	35.64%	32.0%
Emergency	26.9%	22.42%	36.1%
Diabetes	17.4%	17.73%	14.3%
Prior CABG	7.0%	8.24%	N/A
Prior MI	27.1%	25.2%	27.4%
Prior PCI	20.1%	20.63%	N/A
Cerebrovascular event	3.9%	3.67%	N/A
History of Renal Disease	12.5%	2.19%	1.6%

Whilst there is some variation in the date ranges of each training cohort, all of the PCIs began in 2007. The latest date was featured in the Wall cohort, ending in 2013. As seen from Table 7.1.3, the ECTC cohort featured the highest percentage (2.5%) of patients with cardiogenic shock, which is known to be one of, if not, the strongest predictors of adverse events (MACE and 30-day mortality) following PCI. There was also a large difference between renal disease in the ECTC cohort compared to both external cohorts. This was 12.5%, 2.19%, 1.6%. The reason for this is unknown. It may be the case that district hospitals send renal disease patients to the ECTC for PCI at an earlier stage in the patients' cardiovascular disease than other PCI centres. Hence, the patients may get treated as elective whereas other centres treat renal disease patients with emergency PCI at a later stage instead. It could also be an issue of data reliability at the ECTC. The ECTC cohort had similar rates to the cohort used by McAllister (national England and Wales PCIs), and/or Wall across several characteristics, these were: mean age, male gender, elective proportion, diabetes, prior CABG, prior MI, prior PCI, and cerebrovascular events.

Risk factors

Each of the three models retains three of the NWQIP risk factors, as predictors, these are age, cardiogenic shock, and procedure priority. The presence and strength of cardiogenic shock as a major predictor in all models, is no surprise, given that patients exhibiting this are considered critically ill. The ECTC and McAllister models also included female sex and cerebrovascular events as predictors. The omission of female sex from the Wall model is surprising, however because this risk factor exhibits the lowest odds ratios (of any binary independent predictor) in the ECTC and McAllister models (1.57 and 1.12 respectively), it may be the case that the Wall cohort (based in Sheffield) perform treatment on a higher proportion of younger female patients, which could explain the lower association with 30-day mortality. The univariate odds ratio however, for female sex and 30-day mortality was not reported by Wall, so the degree of the relationship with the outcome cannot be verified. The female patients in the Wall cohort represented 28.2% of all PCIs, whereas this was only 25.1% (ECTC) and 25.8% (McAllister) in the other studies. The omission of cerebrovascular events as a predictor in the Wall cohort should also be noted. The reason for this not being a risk factor in their cohort is unknown, it may be the case that this subgroup are less likely to undergo PCI, and instead be given pharmacological therapy to treat their symptoms. All three models were consistent with the omission of two of the NWQIP risk factors, these being treatment to graft lesions and to the left main stem (LMS). The reason for this, as described in Chapters 4 and 5, may simply be due to increasing operators and PCI Centres, or by operators having more experience with these vessels. By having an increased number of PCI centres performing primary PCI, it may be the case that faster transport to the centres for emergency patients exists now than did previously.

The ECTC model, unlike both the McAllister and Wall models, did not incorporate renal disease or diabetes as predictors in the final model. Given the inclusion in both external models and some other published literature (external to the UK), it is important to consider why they were not present in the ECTC model. A possible explanation is that they exhibited high multicollinearity with other predictors in the model, such as age, hence why they were dropped. It may also be that their presence in the model did not increase the amount of explained statistical variance in the relationship with 30-day mortality, and hence include did not increase the discrimination or calibration performance.

Another possible explanation is that the older PCI records in the ECTC cohort are less likely to contain medical history for the patients, especially emergency. The ECTC is a tertiary cardiac centre, meaning elective patients are referred there by hospitals in the

local county, this means the patients' medical history (e.g. diabetes and renal disease) may not correctly be linked and recorded at the ECTC. This is especially more likely for older PCI records. However, given the importance in recent years for submission to the national audit body, the data completion and accuracy rates are likely to improve. For emergency patients especially, access to their medical history may be limited, especially if the patient has never undergone a prior PCI or CABG at the ECTC. This could be a possible explanation as diabetes and renal disease information may simply be recorded as negative, rather than missing, hence affecting the association with 30-day mortality during the regression analysis.

The two external studies did not report data on peripheral vascular disease (PVD), as this was identified as a risk factor in the ECTC model. It is difficult to therefore to consider the reasons for its omission without looking at the odds ratios. It may be the case that the medical history is not easily obtained either from referral hospitals, or that increasing proportions of emergency PCI patients means that detailed history was not available and hence was not identified as a significant predictor. Pre-operation ventilation patients were excluded from the McAllister study, so comparisons cannot be made to their cohort with regards to it being a predictor of 30-day mortality in the ECTC model.

Performance

Table 7.1.4 displays the performance metrics for each model, including the area under the ROC curve (AUROC), and the Hosmer-Lemeshow (H&L) goodness of fit calibration test. These values, unless unavailable (N/A), are listed for both the training and validation cohorts used for the ECTC and the two recently published models.

Table 7.1.4 – Performance metrics for the ECTC, McAllister, and Wall cohorts

Model	Dataset	AUROC (95% CI)	H&L test
ECTC	Training	0.88 (0.85 to 0.91)	*P = 0.67*
	validation	0.89 (0.85 to 0.93)	*P* = 0.27
McAllister et al (2016)	Training	0.84 (N/A)	N/A
	Validation	0.85 (N/A)	N/A
Wall et al (2017)	Training	0.82 (0.79 to 0.85)	*P* = 0.32
	Validation (internal)	0.81 (0.76 to 0.86)	P = 0.39
	Validation (external)	0.90 (0.87 to 0.93)	P = 0.07

The calibration in the model developed by Wall, when applied on an external cohort, was p = 0.07, although considered non-significant, this is close to exhibiting large differences between observed and predicted 30-day mortality.

When visually inspecting the calibration plots of observed versus estimated risk for each of the three models, they all exhibit a similar characteristic whereby clustering amongst the lower several risk groups is seen, i.e. the percentages of both estimated and observed 30-day mortality, for these groups are very close. Despite the omission of both diabetes and renal disease, the ability to discriminate and the fit of observed versus estimated 30-day mortality remains similar. The similarities in performance despite the differences in which risk factors are used, could be due to the fact that the certain risk factors (present in all), e.g. cardiogenic shock, PCI priority, and increasing age, carry a strong association with the 30-day outcome, and risk factors that are not present in the ECTC (e.g. diabetes and renal disease), carry weaker ones that their inclusion does not necessarily increase performance by a large amount.

Future Recommendations

Clearly all three models can discriminate well between those patients that die within 30 days of PCI and those which did not, as evident by the range of the AUROC values (0.81 to 0.90). When each model was validated, whether this is using an internal or external cohort, the ability to discriminate well was maintained. The calibration of observed and estimated 30-day mortality rates was also verified on their respective validation cohorts.

As previously mentioned, for the outcome 30-day mortality, across all three of these UK models, the lower risk groups are clustered closely together, i.e. there are only small percentage differences between for example, a patient in risk 2 and a patient in risk group 3. This is especially a problem for such models because the frequency of adverse rates in these groups is low, and hence overestimation or underestimation during model construction is more likely.

The outcome of 30-day mortality across each model was classified as all-cause, i.e. those including both cardiac and non-cardiac death. It may be the case that many patient deaths are not related to patient's cardiovascular disease and hence this would weaken any associations for risk factors. In an ideal scenario, it would be beneficial to obtain the cause of death for each patient, to determine if it was cardiac related in origin. The multivariate regression analysis could then be performed again to yield useful insights for risk factors associated with cardiac death in the UK. The risk factors associated with cardiac death may exhibit stronger relationships and hence allow patients to be classified into risk

groups more appropriately, thus allowing better risk prediction to be achieved. Currently, access to the cause of death is not available for analysis, unless the patient experienced a complication resulting in death during their index procedure.

In the future, using ECTC data, it would beneficial to test the performance of both the McAllister and Wall models. To verify whether the selection of risk factors identified in their models, aid in increasing discrimination or calibration performance. The McAllister model was developed using a large database of PCI from across England and Wales, and hence could reveal interesting information about how closely the national average PCI characteristics used to develop the model, relate to the ECTC cohort.

7.4 Three-Year RRD

Three-Year Repeat Revascularisation or Death (RRD) is defined as all-cause death or any unplanned/non-staged coronary revascularisation, whether this be a PCI or CABG within three years of a patient's initial elective PCI at the ECTC. The justification for this outcome was that even 30-day mortality following PCI occurs at low rates, i.e. in the ECTC training set and validation set these rates were 2.1% and 2.0% respectively. Most importantly these rates were very low (as one would expect) in elective patients for which the rates were 0.4% and 0.3% respectively. What cardiology consultants, interventional operators and patients would be more interested in are the prediction of important outcomes following elective PCI procedures, knowing the risk for an emergency patient may in most cases be irrelevant for two main reasons (1) the patient is in a critical state and cannot effectively make decisions about whether to have the procedure and (2) the alternative to a patient not having a PCI make be death

The end-points of the first two studies (Chapters 4 and 5), whilst important outcomes to investigate, are very short-term and do not provide useful information for the elective patient's prognosis over longer periods of time. Whilst the 30-day period may be useful for identifying whether a patient has recovered from the PCI procedure it says nothing about the risks of future adverse events. These factors favoured investigating two other important outcomes which were reportedly known to occur at higher rates as described in Chapter 2 (Theoretical Background), and anticipated to occur at much higher rates for elective patients than simply analysing in-hospital MACE and 30-day mortality. The outcomes were combined into a composite end-point that was investigated in the third study within this Thesis (Chapter 6, Three-Year Repeat Revascularisation or Death), these were the occurrence death or repeat revascularisation within three years. The three year time period is useful because it extended the analysis window for mortality from 30 days and the repeat revascularisation component was important because it allows informed consent to patients, i.e. elective patients may opt against going through with a PCI if they know there is a high risk of death, or high risk that they might require another PCI within three years. This outcome also allows operators, consultants and cardiology staff to better allocate their resources to the patients at the highest risk, and also plan future workload. By looking at past repeat revascularisation rates it can provide expectations of how many patients they would expect to see back at the ECTC for another revascularisation procedure. Identifying these end-points with anticipated high rates in the

PCI cohort, would allow a higher statistical power and hence strong univariate and multivariate association analysis.

The event rates in the three-year RRD analysis that featured 3,568 valid PCIs are listed below in Table 7.1.5.

Table 7.1.5 – Three-Year RRD outcome rates (n = 3,568) following elective PCI at the ECTC

Outcome	Patients (n)	Patients (%)
RRD	522	14.6%
Repeat Revascularisation	374	10.5%
Death	148	4.1%

Overall 14.6% (522 patients), almost one elective patient in every seven experienced either death or a return to the ECTC for subsequent coronary revascularisation procedure. Not surprisingly the majority of the repeat revascularisations (10.5%, 374 patients) were subsequent PCI procedures (8.6%, 306 patients). Of these 306 PCIs the majority were elective (79.7%, 244), which is important an important point to consider, because the vast majority are elective it would suggest that the patient's initial elective PCI could have been protective, i.e. if an elective patient had been previously seen by cardiology consultants and subsequently underwent elective PCI it would be extremely detrimental if that elective patient then went on to have a subsequent myocardial infarction, because treating an elective patients cardiovascular disease it clearly the primary aim so they are free from such adverse outcomes as future heart attacks.

It was discovered that when investigating the time-to-event for Three-Year RRD, 57.4% of these events occurred within one year following the initial elective PCI. To further break down the 12 months, 35% of the events occurred within six months. Investigating the differences in events over time was an important consideration from the beginning of this study as it can identify whether the typical cessation period of 12 months where patients usually stop taking dual-antiplatelet therapy (DAPT) yields any sudden clustering of death or repeat revascularisation events, this was identified in this study.

The multivariate predictors for 3-Year RRD were advanced age (i.e. ≥ 80 years), prior CABG, prior MI, COPD and diabetes. Two 'protective' characteristics (i.e. odds ratios below 1.0) were incorporated in the model, these being BMS insertion and DES insertion, clearly the insertion of DES acts as the biggest protective effect (i.e. lower risk) relative to BMS. The BMS characteristic was incorporated because this is relative to either standard balloon angioplasty or a failed PCI, such as where the lesions were too calcified to

penetrate and hence the coronary vessel was not treated effectively. Both of these factors suggest BMS/DES usage in the risk model act as surrogates for failed PCI/balloon angioplasty which can be seen as beneficial especially in cardiac databases where failed PCIs are difficult to determine. The other factors are not surprising, firstly elderly patients are clearly more at risk of dying than their younger counterparts, and also are likely to have more frail coronary vessels and weaker hearts. Diabetes and COPD have been linked to adverse outcomes and higher rates of death for many years (as identified in Chapter 2, theoretical background) so it is not surprising these comorbidities are considered significant risk factors. Patients with prior CABGs were found to have higher risks of 3-Year RRD, the exact reasoning behind this may be difficult to prove but it is hypothesised that CABG patients would have undergone the graft surgery because their cardiovascular disease was complex (i.e. multi-vessel, complex lesion characteristics such as location within the artery), the CABG may have effectively provided complete revascularisation and hence blood flow to the coronary vessel but the patient's lifestyle, diet, lack of exercise which predisposed them to cardiovascular disease in the first place may not have change since their CABG and hence the reformation of lesions may have occurred, or another explanation is that other coronary vessels not treated by the CABG have become occluded and they are the causative reason behind the repeat revascularisation.

Prior myocardial infarction was also a risk factor incorporated into the risk model, the likely explanation behind this again relates to the patient’s susceptibility to cardiovascular disease manifestation, myocardial infarction patients may be more likely to develop lesions faster and these lesions may be more complex relative to stable patients.

The 3-Year RRD risk model developed in Chapter 6 utilised to entire utilised the entire ECTC PCI (not counting exclusion criteria) and hence there was only a training set. The three-year end-points of mortality and repeat revascularisation would have meant that the training and validation sets if both were used, would be very small. Therefore it was decided to use the entire available cohort for development of the risk model, and in the future test it with subsequent ECTC PCI after a sufficient time period has occurred, additionally it would be beneficial for external PCI centres to test the model on their PCI cohorts. The discrimination, i.e. area under the ROC curve was 0.65 (0.62 to 0.68) indicating a fairly poor performance level especially relative to the NWQIP model for MACE (ROC = 0.83) and the 30-day mortality risk model (ROC = 0.88). The model was however calibrated well with the Hosmer-Lemeshow goodness of fit test producing p =

0.76, indicating an excellent fit of observed versus predicted 3-Year RRD across different risk groups.

The reduction in discriminatory power as described above, relative to the original NWQIP model and the 30-day mortality model developed in Chapter 5 could be explained by the fact that all the multivariate predictors in the logistic regression model exhibit much lower estimated odds ratios and hence regression coefficients compared to the other two models for the MACE and 30-day mortality outcomes. Because this model uses a three-year window and the others use in-hospital and 30-day (respectively) it is likely that time weakens these associations and other characteristics either not currently recorded in the database, or not easily/economically measured be responsible. One of these characteristics is likely to be diet, i.e. cholesterol/fat intake can affect the rate and probability of plaque/lesions building up in either the same coronary arteries or other non-treated coronary arteries. Secondly, lack of exercise and sedentary lifestyle which results in a weaker heart as opposed to an athletic individual with a strong heart is an important factor to consider. Currently genetic predisposition and DNA sequencing is expensive and a very low number of patients would have ever had their DNA analysed, in the future with cheaper sequencing technology and more available testing methods it may be the case that genetic single nucleotide polymorphisms (SNPs) be identified relating to the formation of lesions in coronary vessels, however this is just a hypothesis at this stage, and clearly it is unlikely cardiac centres will stored patient's DNA data for analysis.

7.5 Limitations

An important point to consider during the analysis of the ECTC PCI data in all three of the studies incorporated in this Thesis was that it was unknown how accurate the recorded data is, this is especially important for the end-points, i.e. in-hospital complication data fields, and mortality. For example the two factors to consider are: (1) are complications (most notably Q-wave MI, and cerebrovascular accidents) accurately recognised by hospital staff, and if they are do the staff input into the CVIS database for every patient PCI procedure in which they occur; (2) Do the patients which die out-of-hospital all correctly get reported in the CVIS/ECTC database, or are the some patients that have died (e.g. within three years) that the CVIS database does not know about. These two factors could result in an underestimation of actual outcomes and hence mean the risk models developed exhibit regression coefficients and odds ratios that have weaker associations than they truly should be. It is anticipated that because the UK centres are under a homogeneous structure, i.e. the National Health Service (NHS), any such limitation in this area would at the very least be consistent across different cardiac centre databases and thus would have little overall effect on the risk model if used in another UK centre. Given more stringent data completion policies, especially those created by the British Cardiovascular Intervention Society (BCIS), it is anticipated that going forward this type of limitation would be less of a problem, especially with better staff training and diagnosis equipment.

A limitation related the 30-day mortality and 3-Year RRD risk models is that the death outcome component was all-cause, hence not only would this outcome comprise of patients that died from a cardiac cause, but could also include patients that died from a completely unrelated cause such as a car crash, or non-related disease such as cancer. Because tracking patients after they have left hospital is extremely difficult and beyond the ethical clearance of this Thesis, cause of death information was not available. Many other studies and risk models, not just limited to outcomes following PCI but many other types of procedures and surgeries, still use all-cause death. But clearly it would be useful to cardiology consultants, PCI operators, and patients to identify the rate of total deaths that responsible related to the patient's cardiovascular disease state. High rates of cardiac-related deaths could indicate a failure in treating the patient effectively, as obviously the primary aim of coronary intervention is to reduce mortality and morbidity amongst cardiovascular disease patients. If it was found that despite a PCI procedures, patients were still dying from their cardiovascular disease this could cause ramifications for

nationally funding PCI procedures, i.e. why would the NHS spend money on these procedures if it did not make patient's cardiovascular disease state improve.

Similarly to tracking the patient's death after they have been discharged from the ECTC, it is also not known if the patient relocates to an area outside of Essex that they have undergone a subsequent coronary revascularisation (PCI or CABG) at another cardiac centre. Because of this a possible underestimation of three-year RRD rates could be present.

Relating to data accuracy, it is also unknown how well certain patients have been previously diagnosed for certain comorbidities known to be risk factors of adverse complications (e.g. PVD, COPD, diabetes etc.). Patients in the CVIS database which do not have anything present for the Medical History data field may not necessarily be free from known medical issues, it may just be the case that they have not been diagnosed at that current stage, if in the future they are diagnosed with any such comorbidity, the prior PCI procedure record is not updated retrospectively, they would only have their medical history data field updated with such a comorbidity in future PCI procedures. It is unknown how accurately patients are diagnosed and hence the strength of various univariate and multivariate relationships with outcomes should be considered.

7.6 Final Conclusions

The five objectives specified in section 1.5 were completed during the undertaking of the three studies. Objective 1 was completed by investigating the outcomes following PCI in all three studies. Objective 2 was completed in the Chapter 4 study. Objectives 3 and 4 were completed in Chapters 4 and 5. Objective 5 was completed in Chapter 6. In completing these objectives, all three of the specified hypotheses were tested and determined to be true.

The three research studies within this thesis (Chapters 4, 5, and 6) provide a useful insight into important adverse event rates in PCI patients within the south-east of England. It was found than changing demographics, stenting technology, and comorbidities in a modern era all seem to play a role in the worsening performance of the established NWQIP risk model for predicting in-hospital MACE. It was found that NWQIP overestimated these adverse outcome rates and the ECTC cohort was no longer at as high risk for patients who exhibited the NWQIP risk factors.

The more robust outcome of 30-day mortality was investigated which previously, to the Author's knowledge had not been done, or even reported by Grayson et al. (2006) or Kunadian et al. (2008). As previously discussed in Chapter 7.3, two new models were published in the UK by other researchers (McAllister et al, 2016; Wall et al, 2017), featuring the outcome of 30-day mortality, this allowed findings to be compared between the three models. The model developed in Chapter 5 identified two additional risk factors (not present in the NWQIP model) that were pre-operation ventilation (a surrogate for out-of-hospital cardiac arrest), and peripheral vascular disease (PVD), the latter of which was also determined to be a predictor by Peterson et al. (2010). This risk model was internally validated by a PCI cohort of 4119 patients and was shown to be stable, i.e. produce a similar performance to the training set used to construct it. The discrimination and calibration performance was similar compared to the other two UK 30-day mortality models recently developed.

It was found that even extending in-hospital death to 30 days following the date of the PCI procedure, the rates were still very low relatively speaking, and this was even more apparent for elective patients. The findings in this study provided the justification for investigating outcomes for elective (low risk) patients that would be useful to operators, consultants, and patients, such outcomes were repeat revascularisation or death within three years of the patients PCI. Previous studies as detailed in the Theoretical

Background (Chapter 2) used either repeat revascularisation or death but they were not used as composite outcomes over a period of three years. In addition to these, all of these studies were conducted outside of the UK national health care setting and thus the findings and rates are questionable when applied to a UK PCI cohort.

It was found that COPD, diabetes, age, stent insertion (BMS or DES), prior CABG, and prior MI were all predictors of 3-Year RRD, and that the majority of these events (57.4%) occurred within the first year following a patient's initial elective PCI at the ECTC. The discrimination performance however was weaker than that found using the NWQIP model (for in-hospital MACE) or the 30-day mortality risk model (Chapter 5). Such weakening of associations and hence discrimination performance could suggest that these recorded risk factors diminish over time and over characteristics either not currently known or recorded come into play and explain the associated variance. Despite this reduction in performance, along with the 30-day mortality risk model it would be beneficial to validate these for: (1) future PCI patients at the ECTC – to test how stable the model is, and how it adapts to trends in comorbidities and stent types; (2) external PCI cohorts to the ECTC but still within the UK. If such validation certifies the stability of the risk models as useful predictors of their associated outcomes, then the models could further be tested in clinical settings external to the UK. Because of the PCI dataset specification (BCIS dataset 5.6.2), it is known that UK based cardiac centres will have data fields for all of the risk factors within both the 30-day mortality model, and the 3-Year RRD model. So it is not anticipated this model would be too complex for any external entity to validate.

Overall these three studies contribute to the prediction of outcomes following PCI in UK cardiac centres. Apart from the two recent studies described, there has been limited, published, peer-reviewed studies conducted in a UK setting, and the combination of the analysis performed in this thesis has provided useful insights not previously known.

7.7 Summary of Original Contributions

At the time of writing this and to the knowledge of the author, the research within this thesis provides three main original contributions to the field of adverse outcomes following PCI procedures performed in the UK, and more specifically, in the county of Essex.

This was the first UK study (Chapter 4) to assess the performance of the NWQIP risk prediction model (for in-hospital MACE following PCI) in a modern era which features many differences as described in Chapter 1, compared to the original NWQIP study era (Grayson et al., 2006) and the external validation study era (Kunadian et al., 2008). It was found that NWQIP no longer performs as well as it did in its original setting over a decade ago. The model overestimates the risk of in-hospital MACE in the ECTC PCI cohort, and exhibits prominent differences between the observed and estimated risk amongst different risk groups. This suggested that the model should be recalibrated and/or investigation into novel risk factors should be performed. It was discovered that treatment to the LMS and graft lesions were no longer significant predictors and hence their usage in modern prediction models should be reconsidered.

Secondly, a multivariate prediction model for 30-day mortality (Chapter 5) following PCI was developed. Several of the predictors were also present in the NWQIP model (age, female sex, cardiogenic shock, cerebrovascular disease, and PCI priority) thereby reconfirming their importance as predictors in the modern era. Additionally, peripheral vascular disease (PVD) and pre-operation ventilation were identified. The prediction model was internally tested using a validation cohort to verify the stable discrimination and calibration performance. Comparisons to the recent UK studies were made and similar predictors were featured in all models (namely age, cardiogenic shock, and PCI priority).

The third study within this thesis (Chapter 6) was the first to investigate the outcome of 3-year repeat revascularisation or death (RRD) in elective patients following PCI in the UK. Elective patients have very low rates for short-term adverse outcomes such in-hospital MACE and 30-day mortality. Investigation into risk factors for these patients over a longer time period was therefore warranted. The multivariate predictors identified were: age, prior CABG; prior MI; stent type (BMS/DES); and diabetes. This confirmed that certain comorbidities over time, e.g. diabetic patients will have increased risk of adverse events. The performance of the model was poor however. It is hypothesised that other characteristics not currently available in the PCI database, such as sedentary lifestyle, diet, and cessation of dual anti-platelet therapy (DAPT) could enhance risk prediction.

7.8 Recommendations for Future Research

Clearly an important point to consider with data analysis studies that have a primary aim to identify the strength of relationships between certain characteristics/risk factors and adverse outcomes is data completeness. Having high data completeness rates would allow a better analysis to be performed and yield more accurate relationships amongst the data. It is anticipated that with more effective staff training and data completion policies put forward by national bodies (e.g. BCIS) that better data analysis could be undertaken on adverse outcomes following PCI in the future.

With regards the database/dataset available for analysis in these three studies, it would be beneficial to make staff more aware of what to input into certain data fields. For example when analysis the vessels attempted during the PCIs at the ECTC it was discovered that some procedures on lesions inside previously grafted vessels were simply listed as 'Graft(s)' in this field, and did not have the name of the coronary vessel that had been grafted, this had to be located under a more difficult process of analysing an 'Event' data field manually (which was obviously time consuming and not very efficient). Some of these PCIs did have the correct graft vessel listed in addition to the 'Graft(s)' value in the vessels attempted field. The discrepancy between these two is that they do not mean the same, for example, a procedure with PCI to a RCA graft vessel may in one record be listed as 'RCA, Graft(s)', but in another simply Graft(s). In addition to this other PCI records indicated that the RCA vessel and the graft vessel were separate, i.e. multi-vessel PCI, when in reality the graft vessel may have been the left circumflex (LCx) artery. Modifications and more efficient and clear PCI procedural characteristics such as graft vessel vein type, and the native vessel it was grafted onto could better recorded. Not all procedures were correctly marked when they failed, for example, some basics fields indicate the number of lesions attempted and number of lesions treated yet when manually reviewing the Events data field, it was noticed that some of these PCIs failed and it would not be known from looking at the former fields. These instances were manually corrected however this was time consuming and obviously not efficient for future analysis especially in a digital age.

Due to the inability to track patients once they were discharged from the ECTC, unless they returned to the ECTC for any type of cardiac procedure, the true rates of adverse outcomes were difficult to know and hence underestimation of rates could occur. Whilst

such a framework may be expensive, in future it would be extremely beneficial to have a better patient tracking mechanism in place so that various UK cardiac centres and hospitals can follow a patient's future care, i.e. future revascularisations (at different cardiac centres), future visits to general practitioners (GPs) for chest pain and other indicators of cardiovascular disease. Currently, it is not known how these patients lives are affected after their PCI, i.e. are they able to resume activities such as walking, running, cycling they the manifested disease previously prohibited them from doing, or does the PCI provided not have any effect of their quality of life (QoL), or worst of all does make their life worse, i.e. are they confined to their home for the rest of their life. A possible solution to tracking their QoL would be for cardiac rehabilitation teams to request questionnaires to be completed (e.g. the Short-Form 36 QoL).

Another interesting line of research for future work would be to distinguish outcomes rates between the different generations of drug-eluting stents (i.e. 1st, 2nd, and 3rd generation DES) and identify whether the additional costs to the NHS of successive generations is justified by any reduction in adverse event rates. In the future further analysis of bioabsorbable and biodegradable stents, following the current development of the second generation by Abbot Laboratories, if adopted for commercial usage, could then be compared to the various DES generations at the ECTC. A small point related to DES PCIs especially relevant to the 3-Year RRD study is that despite recommendations being provided to patients about taking dual antiplatelet therapy (DAPT) or aspirin alone, the exact period of time the patients continue to these pharmacological therapies us unknown and may have an effect of 3-Year RRD rates. It was identified that a lot of the pharmacological therapy information was stored in a free text 'Patient Notes', perhaps in the future a more efficient medicine component could be built into PCI/patient databases that tracks all known medicines a patient is taken along with the start/end periods.

As detailed in the Theoretical Background (Chapter 2) some researchers have focussed on developing multiple risk models to better assess strengths of certain relationships. For example separate risk models for BMS and DES PCI procedures, or separate risk models for different priorities or indications, i.e. one model for stable/elective patients and another model for emergency/STEMI patients. This could be beneficial but also has the drawback of increased complexity, i.e. operators, audit reports, consultants, and patients would have to juggle multiple risk models instead of just one which incorporates these differences as risk factors, i.e. single models would typically have emergency PCIs as a predictor, and indeed the 3-Year RRD model developed (Chapter 6) uses the stent types (BMS, or DES) as 'protective' risk factors.

The final point relating to datasets or how the data is recorded is the identification of staged PCIs, in the 3-Year RRD analysis especially, staged procedures were not easily identified and multiple data fields were interrogated, along with free-text notes fields to determine whether a procedure was truly staged. The aim was to identify unplanned/non-staged procedures so a lot of the records had to be manually assessed by eye for whether or not they were staged. A simple data field rather than having to consult four separate fields and a discharge letter document would be highly beneficial for future analysis. It is unknown how effectively staged procedures are recorded at other UK cardiac centres, but there is no reason to believe the ECTC would be any different to them.

As for future work to be conducted by other research utilising PCI cohort databases external to the ECTC, the two risk models developed (Chapter 5, 30-day mortality and Chapter 6, 3-Year RRD) should be externally validated to assess how well they perform using other patient populations, if such external validation provides a good performance for discrimination and calibration this could would indicate that the risk models could be adopted for usage at UK PCI centres for predicting such adverse outcomes or at least be used as an audit tool for comparing operators or hospitals with each other. The two recently published UK models could also be verified on new ECTC PCI procedures to assess how stable their discrimination and calibration performance is, and how this compares to the ECTC 30-day mortality model, developed in Chapter 5.

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Appendices

Appendix A:
Bootstrap Resampling Code

```
% [Script: Bootstrap Resampling for ROC AUC value]
% [Author: L Webster]
% [Last updated: 20/02/14]
Clc
clear
I = load('bstrap-NWQIPMACE.txt');
p = I(:,1); % probabilities
y = I(:,2); % real 30-day mortality outcome
n_rows = size(I,1); % get number of rows.
n_replacement = round(n_rows * 0.7); % no. of picks for each sample
disp(['Total rows: ' num2str(n_rows) ', replacement: ' num2str(n_replacement)]);
AUC_samples = [];
randomz = [];

for bSample=1:200 % iterate 10 samples (change to 200)
iSamples = [];
for i=1:n_replacement

r = randi([1,n_rows]);
iSamples(end+1,1) = p(r);
iSamples(end,2) = y(r);
end
[X,Y,T,AUC] = perfcurve(iSamples(:,2), iSamples(:,1),1);
AUC_samples(end+1) = AUC;
plot(X,Y);
hold on
disp(['Finished generating sample: ' num2str(bSample)]);
end
disp(['Average AUC: ' num2str(mean(AUC_samples))]);
std(AUC_samples)
```

Appendix B: Cardiovascular Database Fields

This section lists the variables available and subsequently considered for analysis as significant risk factors for predicting various outcomes (in-hospital MACE, 30-day mortality, repeat revascularisation, and target vessel revascularisation). The exact field names have been removed because they are confidential. It should be noted that the 'Example Types' column of a specific variable may not necessarily list all types represented in the database. For example, the variable 'Test Reason' features 607 unique values and therefore many are omitted, and only the most frequently populated values are displayed here. 'D/T' represents 'Date and Time'. Some of the fields are calculated, for example there is a field 'History of neurological disease' which lists specific diseases/disorders, and another field 'History of neurological dysfunction' which is a Yes/No field that looks are any value in the former field.

Appendix B1: PCI Fields from the BCIS Dataset

Field	Example Types/Description/Units
Sex	Male, female, unknown
Referral source	Ambulance, DGH, CTC internal, GP, other, ward
Test Reason	STEMI-acute (possible PPCI), stable angina, chest pain, NSTEMI-stabilised on medical therapy, ACS, CAD, NSTEMI – on going instability, inferior MI, MI, unstable angina, …etc.
Intended Procedure	Left Heart Catheter +/- PCI, PCI standard, Pressure Wire +/- PCI, PCI Rotablation, Left Heart Catheter with LV angiogram, …etc.
Priority	Elective in-patient, planned inter-hospital transfer, emergency direct admission (PPCI), elective daycase, emergency interhospital transfer (PPCI), emergency PPCI admission, Day Case, Elective New, …etc.
Actual Procedure	Aortogram, Coronary graft angiography, LV Angiogram, percutaneous coronary intervention, coronary angiogram and LV study, …etc.
Operation Date and Time	[*date and time of procedure*]
Consultant Responsible	-
Primary Operator	-
Primary Operator Status	-
Second Operator	-
Previous MI	Yes, No, Unknown, Missing
Previous CABG	Yes, No, Unknown, Missing
Previous PCI	Yes, No, Unknown, Missing
History: Renal Disease	Acute failure (dialysis), chronic failure: dialysis/haemodialysis/peritoneal dialysis, missing, unknown, normal, GFR 30 to 50 ml/min, transplant, abnormal creatinine levels (3)
LVEF Category	Good (>50%), Moderate (30-50%), Poor (<30%), Unknown, Missing
Diabetes	Not Diabetic, Type 2 (oral/insulin/diet controlled), Type 1, Unknown, Missing, Unknown – data awaited, impaired glucose tolerance, newly diagnosed diabetes.
Medical History	Asthma, cerebrovascular event, COPD, Diabetes, Hypercholesterolaemia, hypertension, non-coronary cardiac surgery, PVD, renal problems, valvular heart disease, unknown, missing.
Cardiogenic shock	[*pre-procedure*]
LMS stenosis	Unknown/missing, 0%, 1-49%, 50-74%, 75-94%, 95-99%, 100%
LAD proximal stenosis	Unknown/missing, 0%, 1-49%, 50-74%, 75-94%, 95-99%, 100%
LAD other stenosis	Unknown/missing, 0%, 1-49%, 50-74%, 75-94%, 95-99%, 100%
RCA stenosis	Unknown/missing, 0%, 1-49%, 50-74%, 75-94%, 95-99%, 100%
Cx stenosis	Unknown/missing, 0%, 1-49%, 50-74%, 75-94%, 95-99%, 100%
Num. grafts present	
Num. grafts patent	
IRA Flow Grade	TIMI 0, TIMI 1, TIMI 2, TIMI 3, missing, unknown
D/T symptom onset	[*PCI; ACS only*]
D/T arrival first hospital	[*ACS only*]
D/T arrival at PCI hospital	[*ACS only*]
D/T of first balloon inflation	[*PCI*]
Clinical syndrome	Acute Coronary Syndrome (ACS/AMI), Stable, Unknown, Missing
Indication for Intervention	Stable – angina, ACS – UA/NSTEMI/convalescent STEMI, ACS – Primary PCI for AMI (no lysis), Staged procedure, ACS – Rescue PCI for AMI, …etc.
Procedure Urgency	Elective, Urgent, Emergency, Salvage, Unknown, Missing
Arterial access	Arterial, Venous, Arterial & Venous, Missing

Vessel(s) attempted	Graft(s), LADother, LADprox, LCX, LMain, RCA, Missing
Num. vessels attempted	[*Not epicardial territories*]
Num. Chronic occlusions	[*Number of chronic occlusions attempted*]
Num. lesions attempted	[*Number of lesions attempted*]
Num. lesions successful	[*Number of lesions successfully treated*]
Largest balloon/stent	[*Largest balloon/stent used*]
Indication for stent	Stent used – elective/sub optimal result/bail out, not applicable, stent not used – other/lesion too long/small vessel/side branch or bifurcation/danger of losing side branch/tortuous artery
Left main stem protected	Yes, No, Missing
Num. restenoses	[*Number of restonoeses attempted*]
Num. Instent stenoses	[*Number of instent stenoses attempted*]
Num. stents used	
Num. DES used	[*Number of Drug-eluting stents used*]
Longest stented/treated	[*Longest stented/treated segment*]
Procedural complications	None, missing, coronary dissection, cardiac arrest/arrythmia – VF, …etc.
Arterial complications	None, missing, haemorrhage, arterial dissection, unlised, …etc.
Post-proc complications	None, missing, in-hospital death, access site haematoma, unlisted, …etc.
PCI Hospital Outcome	No complications, missing, death, unlisted, arterial complication, …etc.
GP IIb/IIIa drug(s) used	Abciximab,tirofiban,eptifibitide,unlisted/missing/none [*during procedure*]
Date Discharge	
Status at discharge	Alive, Dead, missing, unknown
Drugs	Lignocaine, Heparin, Isoket, Verapamil, Diazemuls, …etc.
Devices	[*Make and dimensions of balloon/catheter/BMS/DES, and other used*]
Presenting ECG (ACS only)	ST elevation/LBBB, T wave changes, Normal Sinus Rhythm, ST depression, no acute changes, unknown, other acute changes, missing
Cardiac enzymes/marker	[*Cardiac Enzymes/Markers Raised: yes/no*]
Angina Status Class	[*CCS – Canadian Cardiovascular Society classification, pre-proc and stable*]
Dyspnoea Status Class	[*NYHA classification*]
ECG ischaemia	On resting ECG, No, Unknown/missing, On nuclear perfusion, …etc.
Discharged To	[Hospital DGH], Home, Referring Centre, Carers home, ward, surgery, …etc.
Arterial management	LBA, LFA, LFV, LRA, Other, RBA, RFA, RFV, RRA, missing
Ventilated pre-op	[*Pre-operation ventilator usage*]
Consultant	
Age at procedure	
D/T Arrival	
D/T Admission	
D/T Waiting list	
Angiogram	Yes/No
Pressure Wire	Yes/No
IVUS	
Unprotected LMS	
Rotablation	
CTO	[*Chronic total occlusion*]
Graft PCI	
Multivessel PCI	
Primary PCI admission	
Primary PCI procedure	
NWQIP risk score	

NWQIP risk %	
Epicardial territories	[*Epicardial territories stented*]
Height	
Weight	
Smoking Status	Ex smoker, Unknown, Smokes, Never Smoked, 5-10 per day, …etc.
Family History of CAD	Yes, No, Unknown, Missing
Radiation dose	
Fluoroscopy time	
Contrast Medium	Visipaque, ultravist, omnipaque, optiray, omnipaque 350, iomeron, (blank)
Contrast Medium Dose	
Drugs at Procedure	Lignocaine, Heparin, Isoket etc.
Ethnic Group	White British, Bangladeshi, Black African, Not known, …etc.
Post Op Medicine	Aspirin, Atorvastatin, Clopidogrel, Ramipril, …etc.
Drug therapy PreOp	
Why no IIb/IIIa given	[*during procedure*] recent lysis, good result in low risk patient, …etc.
History of Hypertension	No history of hypertension, history of hypertension, blank
Event notes	[Balloon, stent inserted, details and location etc.]
Mechanical ventilation	Yes, No, Blank
Thrombolysis	Yes, No, Unknown, Yes - < 1 day, Yes – 1-7 days, Yes > 7 days
LVEF (Percentage)	
Recent lysis (ACS only)	Yes, No, Unknown, Yes - < 1 day, Yes – 1-7 days, Yes > 7 days
Num. grafts post-op	
Q Wave on ECG	Yes, No, Unknown, Blank
D/T call for help (STEMI)	
Admission route	Interhospital transfer, direct to cardiac centre, out patient referral, …etc.
Cholesterol	
IRA flow PostOp	TIMI 0, TIMI 1, TIMI 2, TIMI 3, Unknown, Blank

Appendix B2: Cardiac Surgery Fields from the SCTS Dataset

Field	Example Types/Description/Units
Test Reason	CAD, ACS, IHD, aortic valve disease, breathlessness, STEMI, NSTEMI, …etc.
Priority	Emergency (Interhospital transfer/inpatient), elective, …etc.
D/T admission	
Referral	Urgent via wards, elective, emergency via (wards/ITU/A&E), ..etc.
Operation Type	CABG, CABG + Valve, Valve, blank
D/T Surgery Start	[*Two separate fields representing (1) Date, and (2) Time*]
D/T Surgery Finish	[*Two separate fields representing (1) Date, and (2) Time*]
D/T Leave Theatre	[*Two separate fields representing (1) Date, and (2) Time*]
Cardiac procedure	CABG alone, CABG + valve, CABG + other, CABG + valve + other, …etc.
Sex	Male, Female
History of hypertension	Treated/BP > 140/90 on > 1 occasion prior to admission, None, Unknown
Ventilated Pre-Op	Yes, No, Blank
Cardiogenic shock	[*Pre-Op*] Yes, No, Blank
Intended procedure	CABG, aortic valve replacement and CABG, mitral valve replacement, …etc.
Haemoglobin	
Staff Details	[*Multiple fields: requestor/2nd consultant/2nd assistant, anesthetist, ...etc*]
Pre-op cardiac massage	Yes, No, Blank
Pump	Yes, No, Blank
D/T return to ITU	
Oxygenator	Avant, Eos, Affinity, ECC.O, RX 15, blank
Arterial pump	Roller, centrifugal, blank

Num. previous MIs	One, two or more, none, unknown, blank
D/T last PCI	[*Date of last PCI performed, includes non-CTC PCIs, i.e. pre 2007*]
Interval surgery & last MI	No previous MI, 1-30 days, 31-90 days, 6-24 hours, < 6 hours, blank
Diabetes management	Not diabetic, oral therapy, insulin, diet
Smoking status	Current smoker, ex smoker, never smoked, blank
[H] neuro dysfunction	[*History of neurological dysfunction*] Yes, No, blank
[H] neuro disease	None, TIA/RIND, CVA full recovery, Parkinson's, multiple sclerosis, …etc.
D/T last catheterisation	
Pre-op heart rhythm	Sinus rhythm, atrial fibrillation, ventricular fibrillation/tachycardia, …etc.
Status at discharge	Alive, Died in cardiac unit/ward/theatre
Discharge destination	Home, same hospital (other spec.), other hospital, convalescence, blank
D/T discharge/death	[*Combined field of either discharge date of date of death in hospital*]
Graft site	"RCA-PDA, OM1, Mid LAD", "Mid LAD", "Mid LAD, OM1, RCA-PDA", …etc.
Euroscore additative	0-20, blank
Euroscore logistic	0-100%, blank
Cardiopulmonary bypass	Yes, No, Blank
BMI	[*Body mass Index*]
BSA	
Height	(Metres)
Weight	(Kilograms)
Operative urgency	Elective, Urgent, Salvage, Emergency, Blank
D/T Anaesthetic	
LVEF Category	Good (>50%), Fair (30-49%), Poor (<30%), not measured,

	blank
LVEF percentage	
Carotid Bruits	Yes, No, blank
Angina Status pre-op	[*Canadian Cardiovascular Society classification*]
Dyspnoea status pre-op	[*NYHA classification*]
Renal disease (surgery)	None, CKD stage 3, creatinine > 200 micro mol/l, unknown, …etc.
Pulmonary disease	None, COAD/emphysema, asthma, long term bronchodilator, …etc.
Primary incision	Median/right sternotomy, left/right thoracotomy
D/T Procedure	
Sub procedure name	CABG, aortic valve replacement and CABG, mitral valve repair, …etc.
Theatre bloods	1-13, blank
Theatre FPP	1-9, blank
Theatre platelets	1-7, blank
OIR ITU bloods	1-33, blank
ITU FPP bloods	1-19, blank
ITU platelets bloods	1-14, blank
L/R heart catheterisation	This admission, previous admission, No, blank
PA systolic	30-85, blank
Creatinine (pre-op)	18-1320, blank
Multisystem failure	Yes, no, Blank
Other risk factors	No, until operation, within one week of operation, blank
Extent of vessel disease	2 vessels > 50% stenosis, 3 vessels > 50% stenosis, 1 vessel > 50%, …etc.
LMS Disease	Not investigated, LMS > 50% stenosis, no LMS or LMS < 50% stenosis
Claudication	Yes, No, blank
Carotid Occlusion	Yes, no, blank

Previous planned surgery	Yes, No, blank
Active endocarditis	Yes, No, blank
Creatinine	
IV nitrates/heparin	Until operation, No, blank, within one week of operation
IV inotropes prior anaes.	No, Yes, Blank,
Any Complications	Recovery without post op complication, complications occurred, blank
D/T Discharge Surgery	
No CABG	
D/T Death	
Other cardiac procedures	Other not listed, no other, blank, …etc.
Infection complications	None, chest infection, superficial sternal wound infection, …etc.
Other vascular complic.	[*complications*] None, deep venous thrombosis, other, …etc.
Aorta details	Blank, asc. Aneurysm interposition tube graft, …etc.
Valve details	[*Uniques*] aortic stenosis replace mechanical, …etc.
Other Thor. Vasc. Procs.	[*thoracic vascular procedures*] None, aortic or peripheral vascular, …etc.
GI tract	None, other, hepatic failure, jaundice, prolonged ileus, …etc.
Re-operation	Bleeding/tamponade, cardiac problems, graft problems, …etc.
Intra-aortic balloon pump	No, blank, pre-operation, intra-operation
Reason for ^ IAB pump	Unstable angina, haemodynamic instability
Category	CTC inpatient, CTC out patient, DGH, DGH outpatient, ECTC surgery, …etc.
Graft conduit	Long SV, free LIMA, pedicle LIMA, …etc.

Bypass Time	
Mitral Aortic	Aortic, Mitral, Both, Neither
Length of Stay (LOS)	
Waiting Days	
Waiting Working Days	
Time in minutes (ward)	

Appendix B3: Myocardial Infarction Fields from the MINAP Dataset

Field	Example Types/Description/Units
Gender	Male, Female, Unknown
Ethnic Group	White British, White, Not Known, Black African, Pakistani, …etc.
Pickup Postcode	
D/T Test	
Smoking Status	Current smoker, never smoked, ex smoker, unknown, non smoker ?, …etc.
Diabetes	Diabetes (dietary/insulin/oral medicine), not diabetic, insulin + oral, …etc.
D/T symptom onset	
D/T call for help	
D/T arrival 1st responder	
Serum gluclose	[*Get measurement from John/Stewart*]
D/T arrival ambulance	
D/T arrival hospital	
Statin use	Yes, No, Unknown, Blank
Ejection Fraction %	0-100, -1
Cardiac enzymes raised	Yes, No, Unknown, Blank.
Place 1st 12 lead ECG	[*Performed*] Ambulance, other facility, unknown, in hospital

D/T reperfusion treat.	[*treatment*]
Delay before treatment	No, awaiting cath lab team, cath lab compromised, unexplained delay, other, cardiac arrest, ambulance procedural delay, …etc.
Cardiac rehabilitation	Yes, No, Not indicated, unknown, patient declined
Smoking cessation advice	Yes, no, unknown, planned in rehab, not applicable
Dietary advice given	Yes, no, unknown, planned in rehab, not applicable
D/T Procedure	
Source	Paramedic ambulance, IHT A&E (DGH), CTC clinic, IHT ward (DGH)
Cardiac arrest location	A&E, no arrest, CCU, cath lab, ward, elsewhere hospital, after arrival, …etc.
Intervention	Not performed, angioplasty, CABG, planned after discharge, blank, …etc.
D/T discharge	
D/T arrival non intervent.	[*interventional hospital*]
Death in hospital	Blank, unknown, from MI, other cardiac/non-cardiac, …etc.
Initial diagnosis	ACS, definite MI, other initial diagnosis, chest pain, blank
D/T MCCU	
Where was aspirin/antiplatelet given	Not given, unknown, out of hospital, after arrival in hospital, already on drug, contraindicated
Peak troponin	
Discharged Beta blocker	Yes, no, not indicated, unknown, …etc.
ACE inhibitor or ARB	Yes, no, not indicated, unknown, …etc.
Discharged on statin	Yes, no, not indicated, unknown, …etc.
Discharged ACE/ARB	Yes, no, not indicated, unknown, …etc.
Discharge destination	Home, Other hospital, unknown, convalescence, other speciality, blank

Initial reperfusion treat.	[*treatment*] Primary PCTA, reperfusion not attempted, …etc.
Discharge diagnosis	MI (ST-e), ACS/NSTEMI, PCI related MI, MI (unconfirmed), …etc.
Presentation comments	[*Unique details on case presentation*]
Ambulance trust	East of England, East Midlands, London ambulance, north west, blank
Angio performed	Blank, N/A, other, patient died, diagnosis not ACS, …etc.
Coronary angiography	N/A, blank, not performed, symptom driven this hospital, …etc.
Bleeding complications	None, unknown, intracranial bleed, …etc.
Outcome of interest	Blank, unknown, discharged (no neurologic deficit), another hospital, …etc.
Reason no reperfusion	Other, none, too late, elective decision, ineligible ECG, …etc.

Appendix C: Excel VBA Reintervention Code

The following code was developed to identify the repeat revascularisation and target vessel revascularisation index PCI records, and there subsequent valid procedure. The main purpose of this code is to identify the revascularisation procedure (PCI or CABG) and obtain the procedure ID number and date so that subsequent analysis can be performed.

```
Private Sub findRevascularisations(SEARCHTYPE As Integer, PRIORITY_FILTER
As String)
' Main procedure to search for RR/TVR procedures (PCIs or CABGs)
' SEARCHTYPE 0 = RR (any)
' SEARCHTYPE 1 = TVR (only)
' PRIORITY_FILTER = text to filter if we want to ignore records
' ...added handling of PCI to Graft vessels.
' Last updated: 02/11/15

Dim numRowsBCIS, numRowsSCTS, i, j, numFound As Integer
Dim dictPCI As Dictionary ' hold PCI IDs/row numbers
Dim dictCABG As Dictionary ' hold CABG SCTS IDs/row numbers
Dim startTimer As Double
Dim xxxx As String

Dim secondsElapsed As Double
Dim str_VesselAttempted As String
Dim str_NextVesselsAttempted As String
Dim date_operation, date_operation_nested, date_operation_scts,
date_waiting_nested As Date
Dim str_BasePriority, str_graftsite, str_LPI_bcis, str_lpi_bcis_nested,
str_previousLPI, str_SurgeryType, str_NextTestReason,
str_NextStagedLookup, strTVRcheck As String
Dim col_NextRevascDate, col_NextProcID, col_NextRevascType,
col_NextPriority, col_Interval2Revasc, col_Interval2Death As Integer
Dim col_scts_graftsite, col_stagedNext, col_LPI_bcis, col_PROCID_bcis,
col_LPI_scts, col_PROCIID_scts, col_Date_bcis, col_Date_scts,
col_NextDate, col_Staged, col_SurgeryType, col_VesselAttempted,
col_priority_bcis, col_priority_scts, col_waitingdate,
col_NextTestReason, col_priorRevasc, col_StagedLookup As Integer
Dim str_BaseGraftVessels As String
Dim str_NextGraftVessels As String
Dim str_CABGvessels As String
Dim filterElectiveOnly As Boolean
Dim index As Integer
filterElectiveOnly = False
' Increase performance by temporarily disabling some features...
Application.ScreenUpdating = False
Application.DisplayStatusBar = False
Application.EnableEvents = False


Worksheets("BCIS Data").Activate ' load the PCI/BCIS worksheet
numRowsBCIS = ActiveSheet.Range("A65536").End(xlUp).Row
numRowsSCTS = Worksheets("SCTS Data").Range("A65536").End(xlUp).Row
```

```
Set dictPCI = New Dictionary
Set dictCABG = New Dictionary

' ***[Set Column Lookup Numbers]***
col_priorRevasc = ColumnNum("PriorRevasc", "BCIS Data")
col_LPI_bcis = ColumnNum("1_02 Local Patient Identifier", "BCIS Data")
col_PROCID_bcis = ColumnNum("PROC_ID", "BCIS Data")
col_LPI_scts = ColumnNum("1_02 Local Patient Identifier", "SCTS Data")
col_PROCID_scts = ColumnNum("PROC_ID", "SCTS Data")
col_Date_bcis = ColumnNum("3_01 Date and time of operation", "BCIS Data")
col_Date_scts = ColumnNum("0_63 Surgery Start Date", "SCTS Data")
col_Staged = ColumnNum("2_02 Indication for Intervention", "BCIS Data")
col_SurgeryType = ColumnNum("0_39 Operation Type", "SCTS Data")
col_VesselAttempted = ColumnNum("3_09 Vessels attempted", "BCIS Data")
col_priority_bcis = ColumnNum("2_03 Procedure Urgency", "BCIS Data")
col_priority_scts = ColumnNum("2_35 Operative urgency", "SCTS Data")
col_waitingdate = ColumnNum("0_1 Waiting List Date", "BCIS Data")
col_NextTestReason = ColumnNum("0_2 Test Reason", "BCIS Data")
strPreviousLPI = "Nothing" ' dummy value
col_stagedNext = ColumnNum("StagedNext", "BCIS Data")
col_StagedLookup = ColumnNum("StagedLookup", "BCIS Data")
col_scts_graftsite = ColumnNum("3_15 Graft Site", "SCTS Data")
col_graftvesselsattempted = ColumnNum("Graft Vessels attempted", "BCIS
Data") 'get PCI to which graft vessels
col_GraftMappingCustom = ColumnNum("Graft Mapping Custom", "SCTS Data") '
SCTS grafts to native names

' ***[END]***
colx_RunTime = ColumnNum("RunTime", "BCIS Data")
colx_RRType = colx_RunTime + 1
colx_LPI = colx_RunTime + 2
colx_BaseProcID = colx_RunTime + 3
colx_NextProcID = colx_RunTime + 4
colx_BaseDate = colx_RunTime + 5
colx_NextRevascDate = colx_RunTime + 6
colx_NextRevascType = colx_RunTime + 7
colx_NextPriority = colx_RunTime + 8
colx_Interval2Revasc = colx_RunTime + 9
colx_Interval2Death = colx_RunTime + 10
colx_BaseVessels = colx_RunTime + 11
colx_NextVessels = colx_RunTime + 12
colx_NextIndication = colx_RunTime + 13
colx_NextTestReason = colx_RunTime + 14
colx_VesselDetails = colx_RunTime + 15 ' Stores info such as S:S, S:M,
M:S, M:S etc.
colx_NextWaitingDate = colx_RunTime + 16

If SEARCHTYPE = 0 Then
    Debug.Print "Search: Repeat Revascularisation (any)"
ElseIf SEARCHTYPE = 1 Then
    Debug.Print "Search: Target Vessel Revascularisation (TVR only)"
End If

If PRIORITY_FILTER = "Elective,Urgent,Emergency" Then
    Debug.Print "Filter: None - including all base PCI priorities"
    filterElectiveOnly = False
ElseIf PRIORITY_FILTER = "Elective" Then
    Debug.Print "Filter: Elective PCI priorities only"
    filterElectiveOnly = True
End If
```

```
'...::::[Begin PCI Dictionary]::::....
startTime = Timer
last_PCI = "" ' set to blank first time...

For i = 2 To numRowsBCIS
    str_LPI_bcis = ActiveSheet.Cells(i, col_LPI_bcis).Value
    str_BasePriority = ActiveSheet.Cells(i, col_priority_bcis).Value


    If str_LPI_bcis = last_PCI Then
        'already loaded first into dictionary so skip

    Else
        ' Might need to change this if want all priorities [!?]
        If filterElectiveOnly = True And str_BasePriority = "Elective"
Then
            dictPCI.Add str_LPI_bcis, i
            last_PCI = str_LPI_bcis

        ' Handle if we include ALL first PCI priorities, NOT just
elective.
        ElseIf filterElectiveOnly = False Then
            dictPCI.Add str_LPI_bcis, i
            last_PCI = str_LPI_bcis
        End If
    End If
Next i

Debug.Print "Unique PCI Patients: " + Str(dictPCI.count)
'...::::[END PCI dictionary]::::....

'...::::[Begin CABG Dictionary]::::....
Debug.Print "Loading PCIs into Dictionary..."

last_CABG = "" ' set to blank first time...

For i = 2 To numRowsSCTS
    str_LPI_scts = Worksheets("SCTS Data").Cells(i, col_LPI_scts).Value

    If str_LPI_scts = last_CABG Then
        'already loaded first into dictionary so skip
    Else
        dictCABG.Add str_LPI_scts, i
        last_CABG = str_LPI_scts
    End If

Next i

Debug.Print "Unique CABG Patients: " + Str(dictCABG.count)
'...::::[END PCI dictionary]::::....

' Iterate through PCI patients
Debug.Print "Looking for next PCI records..."
For Each patient In dictPCI.Keys

    str_BasePriority = ActiveSheet.Cells(dictPCI.Item(patient),
col_priority_bcis).Value
    nextFound = False
        ' proceed to analyse code.
        exclusionReason = "" ' string for holding exclusion reason
```

```
        excludeRecord = False ' string for deciding if record should be
excluded
        isVesselLAD = False ' for combining LAD other and proximal
vessels into single LAD later on!
        str_LPI_bcis = ActiveSheet.Cells(dictPCI.Item(patient),
col_LPI_bcis).Value ' get LPI value of row, have as key name anyway
        nextFound = 0
        str_VesselAttempted = ActiveSheet.Cells(dictPCI.Item(patient),
col_VesselAttempted).Value
        str_priorRevasc = ActiveSheet.Cells(dictPCI.Item(patient),
col_priorRevasc).Value
        ActiveSheet.Cells(dictPCI.Item(patient), colx_RunTime).Value =
Now()
        If SEARCHTYPE = 0 Then
            ActiveSheet.Cells(dictPCI.Item(patient), colx_RRType).Value =
"Any"
        ElseIf SEARCHTYPE = 1 Then
            ActiveSheet.Cells(dictPCI.Item(patient), colx_RRType).Value =
"TVR"
        End If

        If str_VesselAttempted = "" Or str_VesselAttempted = "##" Then
            ActiveSheet.Cells(dictPCI.Item(patient),
colx_BaseVessels).Value = "Missing"
            excludeRecord = True
            GoTo SkipToNextRow
        End If

        samePatient = True ' check if same patient
        str_LastLPI = str_LPI_bcis
        index = 1 ' hold increment for while loop
        Do While str_LastLPI = str_LPI_bcis
            str_lpi_bcis_nested = ActiveSheet.Cells(dictPCI.Item(patient)
+ index, col_LPI_bcis).Value ' Get LPI of nested (next PCI + 1)
            If str_lpi_bcis_nested <> str_LPI_bcis Then
                ' Next Patient
                GoTo SkipToNextRow
            Else
                ' Same Patient
                ' Amend so checks if valid before populating other revasc
columns
                isTVR = False ' identify whether a TVR
                isTVRgraft = False ' if PCI to graft lesion(s)
                ' Verify whether procedure is staged or not...
                str_NextStagedLookup =
ActiveSheet.Cells(dictPCI.Item(patient) + index, col_StagedLookup).Value
                If str_NextStagedLookup <> "Staged" Then
                    str_NextVesselsAttempted =
ActiveSheet.Cells(dictPCI.Item(patient) + index,
col_VesselAttempted).Value
                    ' set TVR to false if base/next vessels are missing
                    If str_NextVesselsAttempted = "" Or
str_NextVesselsAttempted = "##" Or str_VesselAttempted = "##" Or
str_VesselAttempted = "" Then
                        ' cannot consider TVR because we do not know at
least one of base/next vessels being treated
                        excludeRecords = True
                        exclusionReason = exclusionReason +
";BaseOrNextVesselMissing"
                        GoTo SkipToNextRow
                    Else
```

```
                        ' Both the Base/Next vessels ARE known
                        ' Combine LADprox and LADother into single LAD
vessel
                        If InStr(str_VesselAttempted, "LADprox") <> 0
Then
                            str_VesselAttempted =
Replace(str_VesselAttempted, "LADprox", "LAD")
                        End If
                        If InStr(str_VesselAttempted, "LADother") <> 0
Then
                            str_VesselAttempted =
Replace(str_VesselAttempted, "LADother", "LAD")
                        End If
                        If InStr(str_NextVesselsAttempted, "LADprox") <>
0 Then
                            str_NextVesselsAttempted =
Replace(str_NextVesselsAttempted, "LADprox", "LAD")
                        End If
                        If InStr(str_NextVesselsAttempted, "LADother") <>
0 Then
                            str_NextVesselsAttempted =
Replace(str_NextVesselsAttempted, "LADother", "LAD")
                        End If
                        ' /END LAD proximal and other unification.

                        strTVRcheck = ""
                        ' Check if both base/next NOT grafts = easy to
handle
                        If InStr(str_VesselAttempted, "Graft") = 0 And
InStr(str_NextVesselsAttempted, "Graft") = 0 Then
                            strTVRcheck =
CheckVessels(str_VesselAttempted, str_NextVesselsAttempted)
                            If InStr(strTVRcheck, "TVR") <> 0 Then
                                'TVR detected!
                                isTVR = True
                            End If ' /END TVR check
                        End If ' /END non-graft both check

                       ' Handle if base OR next has graft(s) being
treated with PCI
                        If InStr(str_VesselAttempted, "Graft") <> 0 Or
InStr(str_NextVesselsAttempted, "Graft") <> 0 Then
                            str_BaseGraftVessels =
ActiveSheet.Cells(dictPCI.Item(patient), col_graftvesselsattempted).Value
                            str_NextGraftVessels =
ActiveSheet.Cells(dictPCI.Item(patient) + index,
col_graftvesselsattempted).Value

                            ' check if the graft vessels are missing or
present
                            ' [Update: 16/11/15] Fix graft vessel not
being detected for TVR, e.g. base LCX (non-graft) and next LCX Graft

                            ' Allow base to be missing and just raw-
vessel but next is graft
                            ' Only check if graft vessel missing is being
treated

                            Dim combinedNextVessels As String
                            Dim combinedBaseVessels As String
                            combinedNextVessels = ""
```

```
                            combinedBaseVessels = ""
                            '[1] Permutation: Base not-graft but valid,
and next has graft.
                            If InStr(str_VesselAttempted, "Graft") = 0
And str_VesselAttempted <> "-1" And str_VesselAttempted <> "##" And
InStr(str_NextVesselsAttempted, "Graft") <> 0 Then
                                ' Base is valid but not graft, but next
is graft!
                                ' combine next VA/graft...

                                combinedNextVessels =
str_NextVesselsAttempted + "," + str_NextGraftVessels
                                strGraftTVRcheck =
CheckVessels(str_VesselAttempted, combinedNextVessels) ' instead of base
graft

                                If InStr(strGraftTVRcheck, "TVR") <> 0
Then
                                    'TVR detected - strange because base
not listed as graft but revasc IS
                                    isTVRgraft = True
                                End If

                            ElseIf InStr(str_VesselAttempted, "Graft") <>
0 And InStr(str_NextVesselsAttempted, "Graft") = 0 Then
                                combinedBaseVessels = str_VesselAttempted
+ "," + strBaseGraftVessels ' new variable
                                strGraftTVRcheck =
CheckVessels(combinedBaseVessels, str_NextVesselsAttempted)
                                If InStr(strGraftTVRcheck, "TVR") <> 0
Then
                                    ' TVR detected!
                                    isTVRgraft = True
                                End If

                            ElseIf str_BaseGraftVessels = "##" Or
str_BaseGraftVessels = "-1" Or str_NextGraftVessels = "##" Or
str_NextGraftVessels = "-1" Then
                                isTVR = False
                                strTVRcheck = "MissGraft"
                                strGraftTVRcheck = "MissGraft"
                            Else

                                If InStr(str_VesselAttempted, "Graft") <>
0 And (str_BaseGraftVessels <> "##" And str_BaseGraftVessels <> "-1")
Then
                                    ' populate base graft vessel column
                                    combinedNextVessels = "" ' hold
vessel attempted + graft vessel info
                                    combinedNextVessels =
str_NextVesselsAttempted + "," + str_NextGraftVessels
                                    strGraftTVRcheck =
CheckVessels(str_BaseGraftVessels, combinedNextVessels)

                                    If InStr(strGraftTVRcheck, "TVR") <>
0 Then
                                        ' TVR detected on graft
                                        isTVRgraft = True
                                    End If
                                End If '/END Graft validation check
```

```
                            End If '/END Base/Next vessel validation
check
                        End If '/END at least one graft base OR next
present

                        ' Handle whether RR or TVR
                        If SEARCHTYPE = 0 Or (SEARCHTYPE = 1 And isTVR =
True) Or (SEARCHTYPE = 1 And isTVRgraft = True) Then
                            ' It is a valid revascularisation record so
populate/extract necessary data
                                str_indication =
ActiveSheet.Cells(dictPCI.Item(patient), col_Staged).Value ' termed
staged but set to indication for intervention
                                str_indication_nested =
ActiveSheet.Cells(dictPCI.Item(patient) + index, col_Staged).Value
                                str_NextTestReason =
ActiveSheet.Cells(dictPCI.Item(patient) + index,
col_NextTestReason).Value

                                date_operation =
ActiveSheet.Cells(dictPCI.Item(patient) + index, col_Date_bcis).Value
                                ActiveSheet.Cells(dictPCI.Item(patient),
colx_NextRevascDate).Value = date_operation            'next date
                                ActiveSheet.Cells(dictPCI.Item(patient),
colx_NextVessels).Value = str_NextVesselsAttempted     'next vessels
                                ActiveSheet.Cells(dictPCI.Item(patient),
colx_BaseVessels).Value = str_VesselAttempted          'base vessels
                                ActiveSheet.Cells(dictPCI.Item(patient),
colx_NextPriority).Value = ActiveSheet.Cells(dictPCI.Item(patient) +
index, col_priority_bcis).Value   'next priority
                                ActiveSheet.Cells(dictPCI.Item(patient),
colx_NextProcID).Value = ActiveSheet.Cells(dictPCI.Item(patient) + index,
col_PROCID_bcis).Value 'next Proc ID
                                ActiveSheet.Cells(dictPCI.Item(patient),
colx_NextIndication).Value = str_indication_nested 'next indication
                                Worksheets("BCIS
Data").Cells(dictPCI.Item(patient), colx_Interval2Revasc).Value =
ActiveSheet.Cells(dictPCI.Item(patient) + index, col_waitingdate).Value
                                ActiveSheet.Cells(dictPCI.Item(patient),
colx_NextWaitingDate).Value = ActiveSheet.Cells(dictPCI.Item(patient) +
index, col_waitingdate).Value 'next Waiting Date
                                ActiveSheet.Cells(dictPCI.Item(patient),
colx_LPI).Value = str_LPI_bcis ' LPI
                                ActiveSheet.Cells(dictPCI.Item(patient),
colx_BaseDate).Value = ActiveSheet.Cells(dictPCI.Item(patient) + index,
col_Date_bcis).Value 'base Date
                                ActiveSheet.Cells(dictPCI.Item(patient),
colx_NextRevascType).Value = "PCI"
                                ActiveSheet.Cells(dictPCI.Item(patient),
colx_Interval2Death).Value = strTVRcheck + ";" + strGraftTVRcheck
                                ActiveSheet.Cells(dictPCI.Item(patient),
colx_BaseProcID).Value = ActiveSheet.Cells(dictPCI.Item(patient),
col_PROCID_bcis).Value
                                 ActiveSheet.Cells(dictPCI.Item(patient),
colx_BaseDate).Value = ActiveSheet.Cells(dictPCI.Item(patient),
col_Date_bcis).Value

                                strPreviousLPI = str_LPI_bcis ' not sure
if correct...
                                nextFound = 1
```

```
                                    ''''''''''''''Exit For ' not sure if
Exit For or do nothing!

                        End If '/END TVR/RR SEARCHTYPE filter check
                    End If '/END blank/missing vessel check for base
                End If '/END Staged lookup check!
            End If '/END LPI, same patient match!


            index = index + 1
        Loop
SkipToNextRow:
            If nextFound = 0 Then
                ' No new PCI detected
                ActiveSheet.Cells(dictPCI.Item(patient),
colx_BaseDate).Value = ActiveSheet.Cells(dictPCI.Item(patient),
col_Date_bcis).Value 'base Date
                ActiveSheet.Cells(dictPCI.Item(patient),
colx_NextRevascDate).Value = "No new Identified"
            End If

'    End If '/END Priority filter
Next
Debug.Print "Finished PCI Dictionary While"

'...:::::[CABG Inbetween PCI-PCI]::::.....
' Iterate through first CABG records and see if falls inbetween PCI-PCI
date
Dim counterCABGreplacePCI As Integer
Dim filter As String
counterCABGreplacePCI = 0
strPreviousLPI = "blar"
index = 0 ' start from zero instead of 1 this time, because want to test
first CABG, not from 2nd
For Each patient In dictCABG.Keys

    nextFound = 0
    ' [1] Check if CABG Patient exists in BCIS PCIs (first elective
only!)
    If dictPCI.Exists(patient) Then
        ' Only proceed to check IF a next PCI has populated the base PCI
record.
        filter = ActiveSheet.Cells(dictPCI.Item(patient),
colx_NextRevascDate).Value

        If filter <> "No new Identified" And filter <> "" Then ' changed
to blank!
            ' Patient exists in BCIS/PCI so iterate through all CABGs of
same patient (if multiple exist)
            index = 0
            Do While patient = Worksheets("SCTS
Data").Cells(dictCABG.Item(patient) + index, col_LPI_scts).Value
                date_operation = ActiveSheet.Cells(dictPCI.Item(patient),
colx_BaseDate).Value  ' Base date
                date_operation_nested =
ActiveSheet.Cells(dictPCI.Item(patient), colx_NextRevascDate).Value '
Next PCI date

                str_LPI_bcis = ActiveSheet.Cells(dictPCI.Item(patient),
col_LPI_bcis).Value
```

```
                str_LPI_scts = Worksheets("SCTS
Data").Cells(dictCABG.Item(patient) + index, col_LPI_scts).Value

                date_operation_scts = Worksheets("SCTS
Data").Cells(dictCABG.Item(patient) + index, col_Date_scts).Value
                str_SurgeryType = Worksheets("SCTS
Data").Cells(dictCABG.Item(patient) + index, col_SurgeryType).Value
                str_graftsite = Worksheets("SCTS
Data").Cells(dictCABG.Item(patient) + index, col_scts_graftsite).Value
                str_CABGvessels = Worksheets("SCTS
Data").Cells(dictCABG.Item(patient) + index,
col_GraftMappingCustom).Value ' September - load  CABG vessels mapped to
native names.
                isTVRgraft = False

                ' Check if date inbetween base PCI and next PCI
                If date_operation_scts > date_operation And
date_operation_scts < date_operation_nested And (str_SurgeryType = "CABG"
Or str_SurgeryType = "CABG + Valve") Then
                    ' Date IS inbetween the base PCI and next PCI so
replace the PCI with the current CABG
                    str_VesselAttempted =
ActiveSheet.Cells(dictPCI.Item(patient), col_VesselAttempted).Value
                    str_BaseGraftVessels =
ActiveSheet.Cells(dictPCI.Item(patient), col_graftvesselsattempted).Value
                    ' Combine the LADother and LADproximal into single
LAD vessel
                    If str_VesselAttempted = "##" Or str_VesselAttempted
= "" Then
                        ' Cannot consider TVR...
                    Else
                        If InStr(str_VesselAttempted, "LADprox") <> 0
Then
                            str_VesselAttempted =
Replace(str_VesselAttempted, "LADprox", "LAD")
                        End If
                        If InStr(str_VesselAttempted, "LADother") <> 0
Then
                            str_VesselAttempted =
Replace(str_VesselAttempted, "LADother", "LAD")
                        End If

                    End If
                    '/END Combine...

                    str_VesselAttempted = Replace(str_VesselAttempted,
"Graft(s)", "")
                    If str_BaseGraftVessels <> "##" And
str_BaseGraftVessels <> "-1" Then
                        ' Graft Vessel Known...
                        str_VesselAttempted = str_VesselAttempted + "," +
str_BaseGraftVessels
                    End If
                    If str_CABGvessels <> "-1" And str_VesselAttemped <>
"##" And str_VesselAttempted <> "" Then
                        strTVRcheck = CheckVessels(str_VesselAttempted,
str_CABGvessels)

                        If InStr(strTVRcheck, "TVR") <> 0 Then
                            ' We have TVR
                            isTVRgraft = True
```

```
                            ' MsgBox ("TVR graft Detected")
                        End If
                    End If

                    If SEARCHTYPE = 0 Or (SEARCHTYPE = 1 And isTVRgraft =
True) Then
                        ActiveSheet.Cells(dictPCI.Item(patient),
colx_NextRevascDate).Value = date_operation_scts
                        ActiveSheet.Cells(dictPCI.Item(patient),
colx_NextProcID).Value = Worksheets("SCTS Data").Cells(dictCABG(patient)
+ index, col_PROCID_scts).Value
                        ActiveSheet.Cells(dictPCI.Item(patient),
colx_NextPriority).Value = Worksheets("SCTS
Data").Cells(dictCABG(patient) + index, col_priority_scts).Value
                        ActiveSheet.Cells(dictPCI.Item(patient),
colx_NextTestReason).Value = "-"
                        ActiveSheet.Cells(dictPCI.Item(patient),
colx_NextWaitingDate).Value = "-"
                        ActiveSheet.Cells(dictPCI.Item(patient),
colx_NextIndication).Value = "-"
                        ActiveSheet.Cells(dictPCI.Item(patient),
colx_NextVessels).Value = str_CABGvessels
                        nextFound = 1
                        counterCABGreplacePCI = counterCABGreplacePCI + 1

                        If str_SurgeryType = "CABG" Then
                            ActiveSheet.Cells(dictPCI.Item(patient),
colx_NextRevascType).Value = "CABG replace"
                        ElseIf str_SurgeryType = "CABG + Valve" Then
                            ActiveSheet.Cells(dictPCI.Item(patient),
colx_NextRevascType).Value = "CABG + Valve replace"
                        End If
                    End If '/END SEARCHTYPE check TVR check

                    GoTo SkipToNextCABGPatient
                Else
                        ' No intermediate match for this CABG so skip -
Do not goto because another CABG with SAME patient may exist
                End If '/END date operation match inbetween

            index = index + 1 ' increment next CABG record.
            Loop
        End If '/END Patient exists but does have PCI check
    End If '/END patient does not exist.

SkipToNextCABGPatient:
Next
Debug.Print "Finished CABG Intermediate search"
'....::::[END CABG between PCI-PCI]::::....

'....::::[Start CABG no PCI search]::::....
Debug.Print "Starting CABG no PCI search"

For Each patient In dictCABG.Keys
    nextFound = 0
    ' [1] Check if CABG patient exists in BCIS/PCIs (first elective only)
    index = 0
    If dictPCI.Exists(patient) Then
        ' Patient exists in BCIS, only proceed if no PCI/CABG exists.
        filter = ActiveSheet.Cells(dictPCI.Item(patient),
colx_NextRevascDate).Value
```

```
        ' check if set to 'No new Identified'!
        If filter = "No new Identified" Then
            ' Loop through multiple, could be that first CABG is before
PCI
            Do While patient = Worksheets("SCTS
Data").Cells(dictCABG.Item(patient) + index, col_LPI_scts).Value
                date_operation = ActiveSheet.Cells(dictPCI.Item(patient),
colx_BaseDate).Value
                date_operation_scts = Worksheets("SCTS
Data").Cells(dictCABG.Item(patient) + index, col_Date_scts).Value
                str_SurgeryType = Worksheets("SCTS
Data").Cells(dictCABG.Item(patient) + index, col_SurgeryType).Value
                ' check date of CABG is after the base PCI date...
                If (str_SurgeryType = "CABG" Or str_SurgeryType = "CABG +
Valve") And date_operation_scts > date_operation Then
                    str_VesselAttempted =
ActiveSheet.Cells(dictPCI.Item(patient), col_VesselAttempted).Value
                    str_BaseGraftVessels =
ActiveSheet.Cells(dictPCI.Item(patient), col_graftvesselsattempted).Value
                    isTVRgraft = False
                    str_LPI_scts = Worksheets("SCTS
Data").Cells(dictCABG.Item(patient) + index, col_LPI_scts).Value
                    str_graftsite = Worksheets("SCTS
Data").Cells(dictCABG.Item(patient) + index, col_scts_graftsite).Value
                    str_CABGvessels = Worksheets("SCTS
Data").Cells(dictCABG.Item(patient) + index,
col_GraftMappingCustom).Value
                    ' Combine LADother and LADproximal into single LAD
vessel...
                    If InStr(str_VesselAttempted, "LADprox") <> 0 Then
                            str_VesselAttempted =
Replace(str_VesselAttempted, "LADprox", "LAD")
                    End If
                    If InStr(str_VesselAttempted, "LADother") <> 0 Then
                        str_VesselAttempted =
Replace(str_VesselAttempted, "LADother", "LAD")
                    End If
                    If InStr(str_NextVesselsAttempted, "LADprox") <> 0
Then
                        str_NextVesselsAttempted =
Replace(str_NextVesselsAttempted, "LADprox", "LAD")
                    End If
                    If InStr(str_NextVesselsAttempted, "LADother") <> 0
Then
                        str_NextVesselsAttempted =
Replace(str_NextVesselsAttempted, "LADother", "LAD")
                    End If
                    '/END LAD other and proxminal unification

                    str_VesselAttempted = Replace(str_VesselAttempted,
"Graft(s)", "")
                    If str_BaseGraftVessels <> "##" And
str_BaseGraftVessels <> "-1" Then
                        ' Graft Vessel Known...
                        str_VesselAttempted = str_VesselAttempted + "," +
str BaseGraftVessels
                    End If
                    If str_CABGvessels <> "-1" And str_VesselAttemped <>
"##" And str_VesselAttempted <> "" Then
                        strTVRcheck = CheckVessels(str_VesselAttempted,
str_CABGvessels)
```

```
                        If InStr(strTVRcheck, "TVR") <> 0 Then
                            ' We have TVR
                            isTVRgraft = True
                            'MsgBox ("TVR graft Detected")
                        End If
                    End If
                    ' Check TVR/SEARCHTYPE
                    If SEARCHTYPE = 0 Or (SEARCHTYPE = 1 And isTVRgraft =
True) Then
                        ActiveSheet.Cells(dictPCI.Item(patient),
colx_NextRevascDate).Value = date_operation_scts
                        ActiveSheet.Cells(dictPCI.Item(patient),
colx_NextProcID).Value = Worksheets("SCTS
Data").Cells(dictCABG.Item(patient) + index, col_PROCID_scts).Value
                        ActiveSheet.Cells(dictPCI.Item(patient),
colx_NextPriority).Value = Worksheets("SCTS
Data").Cells(dictCABG.Item(patient) + index, col_priority_scts).Value
                        ActiveSheet.Cells(dictPCI.Item(patient),
colx_NextTestReason).Value = "-"
                        ActiveSheet.Cells(dictPCI.Item(patient),
colx_NextWaitingDate).Value = "-"
                        ActiveSheet.Cells(dictPCI.Item(patient),
colx_NextIndication).Value = "-"
                        ActiveSheet.Cells(dictPCI.Item(patient),
colx_NextVessels).Value = str_CABGvessels
                        nextFound = 1

                        If str_SurgeryType = "CABG" Then
                            ActiveSheet.Cells(dictPCI.Item(patient),
colx_NextRevascType).Value = "CABG no PCI"
                        ElseIf str_SurgeryType = "CABG + Valve" Then
                            ActiveSheet.Cells(dictPCI.Item(patient),
colx_NextRevascType).Value = "CABG+Valve no PCI"
                        End If

                    End If '/END SEARCHTYPE TVR check
                End If '/END surgerytype/date check

            index = index + 1
            Loop



        End If '/END filter no new identified
    End If '/END patient check exists in BCIS


Next

Debug.Print "Finished CABG no PCI search"
'...:::::[END CABG no PCI search]::::....

secondsElapsed = Round(Timer - startTime, 2)
Debug.Print "...finished in: " + Str(secondsElapsed)

Application.ScreenUpdating = True
Application.DisplayStatusBar = True
Application.EnableEvents = True
End Sub
```

Appendix D: Excel VBA Devices Extraction Code

The purpose of the following code is to extract the list of BMS and DES stents from the Devices field, so that the exact stent dimensions (length and diameter) can be identified for subsequent analysis. This code makes use of two separate BMS and DES tables featuring all stents used and their details such as name, manufacturer, diameter, and length.

```
Private Sub cmdExtractDevices_Click()
' Procedure: extracts all BMS and DES stents from the Devices field by
using
' ...a table of BMS and DES stents on their own sheets.
'
' Last Updated: 24/6/15
Application.ScreenUpdating = False

Dim numRows As Integer
Dim numStentsBMS As Integer
Dim numStentsDES As Integer
Dim numRowsBMS As Integer
Dim numRowsDES As Integer

Dim TEMPstrDevices As String ' temp var for replacement call

Dim lengthTotalBMS As Double
Dim lengthTotalDES As Double
Dim widthSmallestBMS As Double
Dim widthSmallestDES As Double
Dim widthLargestBMS As Double
Dim widthLargestDES As Double

Dim i As Integer ' main BCIS looping variable
Dim j As Integer ' loop through stents fields
Dim k As Integer ' loop through devices array

Dim colDevices As Integer ' hold col num of Devices
Dim colProcID As Integer

Dim DEVICES() As String ' main devices array *obsolete
Dim strDevices As String ' main devices string
Dim strProcID As String
Dim xLength As Integer

Worksheets.Add.Name = "VBA_Devices"

Worksheets("BCIS Data").Activate
numRows = ActiveSheet.Range("A65536").End(xlUp).Row
numRowsBMS = Worksheets("Stents BMS").Range("A65536").End(xlUp).Row
numRowsDES = Worksheets("Stents DES").Range("A65536").End(xlUp).Row

colDevices = ColumnNum("DEVICES", "BCIS Data")
colProcID = ColumnNum("PROC_ID", "BCIS Data")

' [Loop thru BCIS rows/Device]
```

```
For i = 2 To numRows
    numStentsBMS = 0
    numStentsDES = 0
    lengthTotalBMS = 0
    lengthTotalDES = 0
    widthSmallestBMS = 0
    widthSmallestDES = 0
    widthLargestBMS = 0
    widthLargestDES = 0

    strDevices = ActiveSheet.Cells(i, colDevices).Value ' main devices
string
    strProcID = ActiveSheet.Cells(i, colProcID).Value

    ' [Loop thru BMS stent table]
    For j = 2 To numRowsBMS
        If InStr(strDevices, Worksheets("Stents BMS").Cells(j, 1).Value)
Then
            ' [Check if same stent (dimensions) used more than once! copy
as original destroyed]
            TEMPstrDevices = ActiveSheet.Cells(i, colDevices).Value
            xLength = Len(TEMPstrDevices) - Len(Replace(TEMPstrDevices,
Worksheets("Stents BMS").Cells(j, 1).Value, ""))
            yLength = Len(Worksheets("Stents BMS").Cells(j, 1).Value)

            If (xLength / yLength) > 1 Then
                If (xLength / yLength) > 2 Then
                    'MsgBox "Proc ID: " & strProcID & ", has same BMS
multiple times: " & (xLength / yLength)
                End If
                numStentsBMS = numStentsBMS + (xLength / yLength)
                ' (add dimension information)
                lengthTotalBMS = lengthTotalBMS + ((xLength / yLength) *
Worksheets("Stents BMS").Cells(j, 5).Value)
                '[largest width]
                If widthLargestBMS = 0 Then
                    widthLargestBMS = Worksheets("Stents BMS").Cells(j,
4).Value
                Else
                    ' replace if smaller
                    If widthLargestBMS < Worksheets("Stents
BMS").Cells(j, 4).Value Then
                        widthLargestBMS = Worksheets("Stents
BMS").Cells(j, 4).Value
                    End If
                End If
                '[end largest width]
                '[smallest width]
                If widthSmallestBMS = 0 Then
                    widthSmallestBMS = Worksheets("Stents BMS").Cells(j,
4).Value
                Else
                    'replace if larger
                    If widthSmallestBMS > Worksheets("Stents
BMS").Cells(j, 4).Value Then
                        widthSmallestBMS = Worksheets("Stents
BMS").Cells(j, 4).Value
                    End If
                End If
                '[end smallest width]
            Else
```

```
            ' stent exists in Devices only once (same dimensions)
                numStentsBMS = numStentsBMS + 1
                ' [add dimension information]
                lengthTotalBMS = lengthTotalBMS + CDbl(Worksheets("Stents
BMS").Cells(j, 5).Value)
                If widthSmallestBMS = 0 Then
                    widthSmallestBMS = CDbl(Worksheets("Stents
BMS").Cells(j, 4).Value)
                Else
                    'replace if smaller
                    If widthSmallestBMS > CDbl(Worksheets("Stents
BMS").Cells(j, 4).Value) Then
                        widthSmallestBMS = CDbl(Worksheets("Stents
BMS").Cells(j, 4).Value)
                    End If
                End If
                ' [largest width]
                If widthLargestBMS = 0 Then
                    widthLargestBMS = CDbl(Worksheets("Stents
BMS").Cells(j, 4).Value)
                Else
                    ' replace if smaller
                    If widthLargestBMS < CDbl(Worksheets("Stents
BMS").Cells(j, 4).Value) Then
                        widthLargestBMS = CDbl(Worksheets("Stents
BMS").Cells(j, 4).Value)
                    End If
                End If
                ' [end largest width]
            End If
        End If
    Next j
    ' [... END Stents BMS loop]

    ' Write  Devices sheet headers
    Worksheets("VBA_Devices").Cells(1, 1).Value = "PROC_ID"
    Worksheets("VBA_Devices").Cells(1, 2).Value = "BMS Stents"
    Worksheets("VBA_Devices").Cells(1, 3).Value = "DES Stents"
    Worksheets("VBA_Devices").Cells(1, 4).Value = "BMS Total Length (mm)"
    Worksheets("VBA_Devices").Cells(1, 5).Value = "BMS Smallest diameter
(mm)"
    Worksheets("VBA_Devices").Cells(1, 6).Value = "BMS Largest diabeter
(mm)"
    Worksheets("VBA_Devices").Cells(1, 7).Value = "DES Total Length (mm)"
    Worksheets("VBA_Devices").Cells(1, 8).Value = "DES Smallest diameter
(mm)"
    Worksheets("VBA_Devices").Cells(1, 9).Value = "DES Largest diameter
(mm)"
    ' end  devices headers

    ' Write BMS details to new Devices sheet
    Worksheets("VBA_Devices").Cells(i, 1).Value = ActiveSheet.Cells(i,
colProcID).Value
    Worksheets("VBA_Devices").Cells(i, 2).Value = numStentsBMS
    Worksheets("VBA_Devices").Cells(i, 4).Value = lengthTotalBMS
    Worksheets("VBA_Devices").Cells(i, 5).Value = widthSmallestBMS
    Worksheets("VBA_Devices").Cells(i, 6).Value = widthLargestBMS
    ' end BMS details

    ' [*] Same calculations again for DES stents
    For j = 2 To numRowsDES
```

```
    If InStr(strDevices, Worksheets("Stents DES").Cells(j, 1).Value) Then
        TEMPstrDevices = ActiveSheet.Cells(i, colDevices).Value
        tmpDevice = Worksheets("Stents DES").Cells(j, 1).Value

        xLength = Len(TEMPstrDevices) - Len(Replace(TEMPstrDevices,
Worksheets("Stents DES").Cells(j, 1).Value, ""))
        yLength = Len(Worksheets("Stents DES").Cells(j, 1).Value)

        If (xLength / yLength) > 1 Then

            numStentsDES = numStentsDES + (xLength / yLength)
            lengthTotalDES = lengthTotalDES + ((xLength / yLength) *
Worksheets("Stents DES").Cells(j, 5).Value)
            '[largest width]
            If widthLargestDES = 0 Then
                widthLargestDES = Worksheets("Stents DES").Cells(j,
4).Value
            Else
                ' replace if smaller
                If widthLargestDES < Worksheets("Stents DES").Cells(j,
4).Value Then
                    widthLargestDES = Worksheets("Stents DES").Cells(j,
4).Value
                End If
            End If
            ' end largest width
            If widthSmallestDES = 0 Then
                widthSmallestDES = Worksheets("Stents DES").Cells(j,
4).Value
            Else
                ' replace if smaller
                If widthSmallestDES > Worksheets("Stents DES").Cells(j,
4).Value Then
                    widthSmallestDES = Worksheets("Stents DES").Cells(j,
4).Value
                End If
            End If
        Else
        ' Stent exists only once
        numStentsDES = numStentsDES + 1

        lengthTotalDES = lengthTotalDES + CDbl(Worksheets("Stents
DES").Cells(j, 5).Value)
        If widthSmallestDES = 0 Then
            widthSmallestDES = CDbl(Worksheets("Stents DES").Cells(j,
4).Value)
        Else
            ' replace if smaller
            If widthSmallestDES > CDbl(Worksheets("Stents DES").Cells(j,
4).Value) Then
                widthSmallestDES = CDbl(Worksheets("Stents DES").Cells(j,
4).Value)
            End If
        End If
        ' largest width
        If widthLargestDES = 0 Then
            widthLargestDES = CDbl(Worksheets("Stents DES").Cells(j,
4).Value)
        Else
            ' replace if smaller
```

```
            If widthLargestDES < CDbl(Worksheets("Stents DES").Cells(j,
4).Value) Then
                widthLargestDES = CDbl(Worksheets("Stents DES").Cells(j,
4).Value)
            End If
        End If
        ' end largest width
    End If
    End If

    Next j

    ' Write DES details to new Devices sheet
    Worksheets("VBA_Devices").Cells(i, 3).Value = numStentsDES
    Worksheets("VBA_Devices").Cells(i, 7).Value = lengthTotalDES
    Worksheets("VBA_Devices").Cells(i, 8).Value = widthSmallestDES
    Worksheets("VBA_Devices").Cells(i, 9).Value = widthLargestDES
    ' end DES details

    Debug.Print (i)

Next i
' [...END BCIS loop]

Worksheets("VBA_Devices").Activate

Application.ScreenUpdating = True
End Sub
```