Identification of the High-Risk Patient in Primary Percutaneous Coronary Intervention: Development and Validation of a Novel Predictive Index

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Abstract

The aim of treatment in STEMI is to improve outcomes for patients in terms of mortality and quality of life. Mortality rates have improved with increased use of PPCI as first-line therapy however in-hospital mortality remains 5-8%. There are multiple therapies that may be beneficial for some patients, as adjuncts to PPCI. There is limited evidence for the use of these therapies and deciding which patients should receive them is challenging.

If operators could identify patients during the acute MI who may be at high risk of adverse outcomes, they may decide to administer adjunctive therapies or increase the length of critical care admissions, which could improve outcomes. Invasive methods, such as IMR, can identify patients with poor reperfusion following PPCI. However, clinical and angiographic variables that are easily recorded during PPCI could be used to risk assess patients, avoiding the need for extra invasive tests.

Clinical and angiographic variables that are readily available during PPCI were examined for associations with a composite outcome of 28-day mortality or subsequent severe impairment of left ventricular function (ejection fraction ≤35%). These variables included age, gender, culprit location, TIMI flow grade, myocardial blush grade, thrombus burden and corrected TIMI frame count. Variables with an association with the outcome were included in a multivariate logistic regression analysis to develop a predictive model – the Liverpool MI Risk Model.

Independent variables included in the Liverpool MI Risk Model were age, culprit vessel location and myocardial blush grade. The model accurately predicts the outcome of death within 28 days or subsequent severe impairment of left ventricular function (c statistic 0.79; 95% CI 0.75 to 0.83). External validation of the model using an independent cohort of patients showed good discrimination (c statistic 0.837; 95% CI 0.723 to 0.951) although the

model overestimated the risk of outcome events in the new cohort. The model was accurate in predicting adverse events in the validation cohort after simple recalibration.

The Liverpool MI Risk Model is a practical tool that uses information available during PPCI to accurately predict the occurrence of an adverse outcome. Using this model could help operators to make decisions regarding adjunctive therapies and duration of stay in critical care areas. External validation of the risk model overestimated the occurrence of an outcome in the validation cohort, prior to recalibration, likely due to differences in measurement methods, eligibility criteria and risk profiles between the two cohorts. A study including unselected STEMI patients using the same measurement methods as the derivation cohort should be used to validate the Liverpool MI Risk Model.

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Abbreviations List

BA: Bland-Altman

BARC: Bleeding Academic Research Consortium

BIDMC: Beth Israel Deaconess Medical Centre

CABG: Coronary artery bypass graft

CCU: Coronary care unit

CK-MB: Creatinine kinase-MB

CMR: Cardiac Magnetic Resonance

CMVO: Coronary microvascular obstruction

CRF: Clinical record form

CVA: Cerebrovascular accident

Cx: Circumflex

ECG: Clectrocardiogram

EF: Ejection fraction

EPV: Cvent per variable

ESC: European Society of Cardiology

FA: Femoral access

GPI: Glycoprotein 2b3a inhibitors

HEAT-PPCI: How effective are thrombolytics in primary percutaneous coronary intervention

HES: Hospital Episode Statistics

IABP: Intra-aortic balloon pump

ICC: Intra-class correlation coefficient

ICD-10: International Classification of Diseases 10th Revision

IMR: Index of Myocardial Resistance

ITU: Intensive care unit

LAD: Left anterior descending

LGE: Late gadolinium enhancement

LHCH: Liverpool Heart and Chest Hospital

LV: Left ventricular

MACE: Major adverse cardiovascular event

MBG: Myocardial blush grade

cTFC: Corrected TIMI frame count

MI: Myocardial infarction

MSI: Myocardial salvage index

NICE: National Institute for Health and Care Excellence

NPV: Negative predictive value

NSTEMI: Non-ST elevation myocardial infarction

PCI: Percutaneous coronary intervention

PISCO: Pressure-controlled intermittent coronary sinus occlusion

PLV: Posterior left ventricular

PPCI: Primary percutaneous coronary intervention

PPV: Positive predictive value

QALY: Quality-adjusted life year

RA: Radial access

RCA: Right coronary artery

RCT: Randomised controlled trial

SPECT: Single-photon emission computed tomography

SQL: Structured Query Language

STEMI: ST-elevation myocardial infarction

STR: ST resolution

TIMI: Thrombolysis in Myocardial Infarction trial

TMPG: TIMI myocardial perfusion grade

uTLR: Unplanned target lesion revascularisation

VBA: Visual Basic for Applications

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Thesis Outline

Primary percutaneous coronary intervention is the optimum treatment for acute reperfusion in STEMI. However, adverse events are still common despite timely reperfusion therapy. To improve outcomes in STEMI, operators need to identify patients who may benefit from adjunctive treatments, more intensive monitoring, and longer hospital stays as well as those who can be safely managed with a less aggressive approach. It may be possible to infer the subsequent clinical risk from information that is available at the time of index reperfusion.

In Chapter 1, I discuss the nature and magnitude of adverse events in STEMI and consider the potential methods by which an outcome may be improved. There are multiple therapies available as adjuncts to PPCI, however, the ideal patient population with potential for greatest gain at acceptable risk has not been well characterised. It is likely that the patients with most to gain from adjunctive therapies are those who experience poor microvascular reperfusion and may develop more substantial infarction damage as a result. Flow in the main coronary arteries does not always indicate good reperfusion at the level of the heart muscle tissue. 50% of patients with epicardial blood flow following PPCI demonstrate poor myocardial reperfusion on subsequent CMR and, therefore, patients with poor microvascular reperfusion following PPCI are less likely to be identified during the acute event. I examine methods of identifying poor myocardial reperfusion and how they can be applied during the acute MI. Several methods of identifying poor myocardial reperfusion have been developed, such as the index of myocardial resistance (IMR). However, this is an invasive test and adds time and cost to the procedure. It is possible that knowledge of these methods may help operators to identify patients with poor myocardial reperfusion during PPCI, and therefore aid decisions regarding adjunctive therapies and appropriate post-procedure surveillance.

HEAT-PPCI was a randomised trial of antithrombotic therapy in STEMI. The clinical and outcome data plus the angiograms from the trial were available for use in this thesis. In Chapter 2, I describe the methods used to assess the angiographic variables identified in Chapter 1, and the design of the database used for collecting relevant data on the variables.

The HEAT-PPCI database includes outcome data up to 28-days following STEMI. In Chapter 3, I explore the possibility of extending follow-up to 12 months for use in the Liverpool MI derivation study and evaluate the accuracy of Hospital Episode Statistics in identifying clinical outcomes by comparison with outcomes identified by medical notes review and independent physician adjudication.

The HEAT-PPCI database includes data on patient mortality up to 28 days following the index event. In Chapter 4, I evaluate mortality data up to 12 months following the index event and compare the mortality rate between the two treatment groups (randomised to either heparin or bivalirudin). In addition, I examine the causes of death of participants using data derived the death certificates of the patients.

Observational studies are often criticised because of the potential for unmeasured confounding affecting results. Operators' choice of access site is a potential confounder in the HEAT-PPCI trial. In Chapter 5, I examine the associations between the final access site used for the procedure, the default operator preference for access site and clinical outcomes. I also look at differences between operators when performing procedures via femoral access.

If the angiographic variables described in Chapter 2 are to be used by any operator performing PPCI, it is important to establish the agreement between repeat measurements to give an estimate of the reliability and reproducibility. In Chapter 6, I evaluate my ability to match my own assessments of each angiographic variable on repeat testing and compare

my assessments to those of a second observer, quantifying the intra- and inter-observer agreement.

In Chapter 7, I examine several clinical and angiographic variables that previous studies have shown to be associated with clinical outcomes in STEMI. I test each variable for associations with mortality and LV function with the aim of developing a risk prediction model. The initial purpose for developed this model was to identify high-risk patients during PPCI to aid operators' decisions regarding adjunctive treatments. However, given the lack of evidence for the use of adjunctive therapies in PPCI, this model may more usefully be used to categorise the low-risk patients, identifying those in whom a prolonged critical care stay may not be necessary and therefore, improving allocation of hospital resources.

All risk prediction scores should be externally validated. In Chapter 8, I test the predictive model on an independent cohort of STEMI patients. In Chapter 9, I explore the associations between the variables that are included in the model developed in Chapter 7 and infarct size quantified using cardiac magnetic resonance imaging.

Chapter 1: Contemporary management of acute myocardial infarction

1.1 Background

Coronary artery disease is the leading cause of death worldwide, causing 9.43 million deaths in 2016.[1,2]. Acute myocardial infarction (AMI) is a term used to describe the occurrence of symptoms and signs consistent with myocardial ischaemia with consequent evidence of myocardial injury.[3] AMI is divided into cases with or without persistent ST elevation on electrocardiogram (ECG).[4] ST-segment elevation indicates complete obstruction of an epicardial artery, whereas non-ST elevation myocardial infarction (NSTEMI) represents partial or transient obstruction of a coronary artery. Both result in a degree of ischaemic damage, demonstrated by a rise in cardiac enzymes. The management and outcomes of patients with ST-elevation myocardial infarction (STEMI) is the main topic of this thesis.

AMI is most frequently caused by the rupture or erosion of a coronary atherosclerotic plaque, resulting in thrombus formation and obstruction of the coronary artery.[5] This causes an acute reduction of coronary blood flow and insufficient oxygen supply to the myocardium. This then results in myocardial necrosis due to prolonged ischaemia.

The primary aim of treatment in STEMI is to restore blood flow to the myocardium as quickly as possible. Ischaemic time is defined as the time from symptom onset to initiation of treatment for STEMI and directly correlates with the extent of myocardial necrosis. Patient survival improves with shorter ischaemic time.[6,7] Options for reperfusion therapy in STEMI include percutaneous coronary intervention (PCI) (termed primary percutaneous coronary intervention (PPCI) when performed in the context of STEMI), or thrombolysis.

Patients presenting within 12 hours of symptom onset and with persistent ST-segment elevation should undergo pharmacological or mechanical reperfusion as early as possible.[8] In trials of prompt and high-quality PPCI versus thrombolysis, superior outcomes are shown with PPCI.[9] To reduce ischaemic times and system delays, PPCI services have become increasingly stream-lined: when a STEMI diagnosis is made in the pre-hospital setting patients will bypass the emergency department and be brought directly to the catheterisation laboratory. This practice is associated with a 20-minute saving in the ischaemic time.[3] Alternative treatment strategies such as pharmacological reperfusion using thrombolysis should be considered if this can be delivered within 120 mins of first medical contact and PPCI cannot be performed within 120 minutes of when thrombolysis would otherwise be administered.[3]

STEMIs comprise 39% of UK hospital admissions for AMI.[10] Mortality is approximately 12% in the 6 months following the event[11] but increases in patients with pre-existing conditions, such as heart failure and renal disease.[12] PPCI is the best treatment if it can be performed by an experienced centre and within a reasonable time-frame.[4] However, there is still a significant rate of adverse events following treatment. In-hospital mortality is around 5-8%[13] and a recent study showed that 3.5% of patients have a recurrent MI following PPCI in the 30 days following the procedure.[14] These statistics suggest there is scope to decrease mortality and complication rates in this group by improving their management.

1.2 Measuring and predicting outcomes in STEMI

The aim of treatment in STEMI is to improve outcomes for patients in terms of length and quality of life.[15] Examining outcomes in short- and long-term follow-up helps to establish the possible benefits of a new management strategy or treatment. Most cardiovascular trials will measure the rates of all-cause and cardiovascular mortality in follow-up.[15,16] In

addition, rates of important clinical events that are likely to increase mortality are often measured, such as stroke and myocardial infarction.[17] Other outcomes used with varying frequency include patient-reported outcomes, quality-of-life questionnaires, rates of hospitalisation and residual left ventricular (LV) function or infarct size.[15,16]

In clinical practice, patients at higher risk for poor long-term outcomes following STEMI can be identified using diagnostic tests: the magnitude of cardiac enzyme release and less favorable LV function are both used to help risk stratify patients and guide their management. Cardiac enzymes such as Troponin I and T and creatinine kinase-MB (CK-MB) are sensitive biomarkers for myocardial injury.[18] They are used in the diagnosis of AMI. The universal definition of acute myocardial injury states that the troponin value must be above the 99th percentile of the upper reference limit for the normal range of the assay used.[19] Troponin levels peak between 12-24 hours following the acute event. CK-MB is a cardiac-specific isoenzyme of creatinine kinase. It is highly sensitive and specific for cardiac tissue damage and begins to rise 4-6 hours after the onset of an acute MI.[20] It returns to baseline after 36-48 hours (troponin takes up to 2 weeks) and can therefore be used to accurately detect reinfarction. An increased CK-MB or troponin value reflects a greater size of infarct in patients following AMI.[21] It has also been shown to decrease with early reperfusion therapy in animal models, so can be useful in assessing the success of reperfusion therapy.[22] In STEMI, cardiac enzymes may not be available at the time of PPCI, but can be used after the acute event for risk stratification. The degree of enzyme release is predictive of the extent of myocardial injury and the size of the infarct.[23] Infarct size is a predictor of long-term mortality and heart failure in STEMI survivors.[3] Enzyme release can therefore be used, in combination with other clinical information, to predict mortality in patients with AMI.[11,24] Peak CK-MB values have been shown to predict in-hospital mortality with greater accuracy than peak troponin.[18]

International guidelines recommend assessment of the LV function and ejection fraction (EF) in all patients with STEMI prior to discharge.[3] LV dysfunction is a key prognostic factor in STEMI and is routinely measured using echocardiography.[19] Other imaging modalities such as cardiac magnetic resonance imaging (CMR) can be used if echocardiographic images obtained are poor quality. A measure of LV function reflects the extent of muscle damage following the acute event and is associated with infarct size and mortality.[25] Patients with a pre-discharge LV ejection fraction of <41% should be re-assessed 6-12 weeks following revascularisation to evaluate the need for further therapies such as an implantable cardioverter defibrillator.[3]

1.3 Measuring the success of PCI

The success of the PCI procedure is described by observing a return of normal flow in the culprit coronary artery. The predominant method currently used to characterise flow is the TIMI flow grade. This is a qualitative, visual, angiographic assessment divided into 4 grades depending on the observed speed of flow of radiographic contrast in the culprit artery (Table 1.1). The TIMI flow can be assessed in real time by the operator from the angiographic images produced during the procedure. It was first described by the TIMI trial group (in angiograms performed for trial purposes) to assess the efficacy of thrombolytic therapy in acute myocardial infarction.[26] Although TIMI flow was originally designed for use in thrombolysis trials, it has been used extensively in subsequent research to assess epicardial revascularisation after AMI. It is recommended practice to record the TIMI flow after all PCI procedures.[27] A TIMI flow grade of 2 or less indicates suboptimal flow through the vessel and poor myocardial perfusion, likely resulting in worse LV function and increased mortality.[28,29] A TIMI flow of 2 or less may occur despite successfully opening the culprit artery. This concept is known as “no-reflow” and is associated with less favourable

outcomes.[30] TIMI grade 3 is associated with lower rates of death at 30 days and improved LV function.[31,32] TIMI flow grade less than or equal to 2 is associated with worse symptoms of heart failure and a higher rate of in-hospital mortality.[33]

Grade 0 (no perfusion): There is no antegrade flow beyond the point of occlusion.
Grade 1 (penetration without perfusion): The contrast material passes beyond the area of obstruction but "hangs up" and fails to opacify the entire coronary bed distal to the obstruction for the duration of the cineangiographic filming sequence.
Grade 2 (partial perfusion): The contrast material passes across the obstruction and opacifies the coronary bed distal to the obstruction. However, the rate of entry of contrast material into the vessel distal to the obstruction or its rate of clearance from the distal bed (or both) are perceptibly slower than its entry into or clearance from comparable areas not perfused by the previously occluded vessel opposite coronary artery or the coronary bed proximal to the obstruction.
Grade 3 (complete perfusion): Antegrade flow into the bed distal to the obstruction occurs as promptly as antegrade flow into the bed proximal to the obstruction, and clearance of contrast material from the involved bed as rapid as clearance from an uninvolved bed in the same vessel or the opposite artery.

Table 1.1: Definitions of perfusion in the TIMI trial

1.4 Why are outcomes sometimes poor, despite "successful" PPCI?

Restoration of normal flow (TIMI flow grade 3) through the epicardial artery does not guarantee tissue reperfusion. Adequate patency and function of the microvasculature is

also required to ensure blood is then distributed to the capillary bed. A reduction of blood flow in the microvasculature of the heart is termed poor myocardial perfusion and can be identified on CMR as coronary microvascular obstruction (CMVO).

CMVO was described by a recent review using 4 interacting pathophysiological mechanisms:[34] 1: ischaemic-related injury which occurs when sustained ischaemia causes necrosis of myocytes and capillaries. 2: reperfusion injury then occurs when reperfusion is achieved but ischaemic duration was >3 hours. This is thought to occur because reperfusion potentiates ischaemic injury by stimulating the production of free radicals, causing cell swelling and cell disruption. The combination of these two mechanisms can cause myocardial oedema and haemorrhage as well as a generalized vascular inflammatory response. 3: distal embolisation of thrombi causing blockage of arterioles perpetuating an inflammatory response. 4: individual susceptibility of patients to developing CMVO caused by genetic factors. CMR is the best method for characterising the extent of myocardial damage in detail. Following the MI, areas of haemorrhage and oedema within the myocardium can be seen on CMR, confirming the presence of CMVO.

In a large proportion of STEMI patients, PPCI alone does not restore normal myocardial perfusion. A recent meta-analysis showed that over 50% of patients treated with PPCI have reduced microcirculatory blood flow on CMR following the acute event.[35] These patients have a higher risk of death, and survivors tend to have worse LV function.[36-39] Studies show that both infarct size and CMVO measured on CMR following PCI were good predictors of unfavourable LV remodelling and decreased LV function.[36,38,39] Reopening the obstructed artery restores blood flow in the visible epicardial vessels but may not restore normal blood flow in the microvasculature.

1.5 Adjunctive therapies in STEMI

There are multiple adjunctive therapies that can be used during PPCI or in the immediate post-procedural phase. In the next section, I discuss several adjunctive therapies that may improve myocardial reperfusion in the acute phase of MI, resulting in a decreased infarct size and improved long-term outcomes for patients. The list is not exhaustive but describes some of the treatments that could be considered by operators for use during or immediately after PPCI. Decisions to use adjunctive therapies must be carefully considered as each may have additional risks to the patient, as well as extra costs. Therapies may be expensive to purchase, require additional time from staff and increase demand for hospital resources, including longer stays in higher dependency areas. There is uncertainty about the most appropriate application for these adjunctive treatments.

1.5.1 Glycoprotein 2b3a inhibitors

Platelet activation and aggregation is central to the pathophysiology of ACS. The most recent guidance advises that all patients with STEMI should be treated with oral antiplatelet agents prior to PCI and intravenous anticoagulation during the procedure.[4] Glycoprotein 2b3a inhibitors (GPIs) are drugs that block the key receptor involved in the final common pathway of platelet aggregation. Administration of GPIs, therefore, results in rapid and potent inhibition of platelets aggregation. The European Society of Cardiology (ESC) guidelines reserve these agents for selective use in patients with STEMI, however they may play a role in patients with suboptimal reperfusion by preventing platelet aggregation and subsequent distal embolization of thrombi in myocardial capillaries.[4] GPIs, such as tirofiban and abciximab, are often used by operators as an adjunct to improve myocardial perfusion if there is evidence of poor coronary blood flow after the culprit vessel has been reopened or in cases with large thrombus burden. ESC guidance considers use of GPIs as “bailout” therapy to be considered when there is angiographic evidence of large thrombus, slow or

no-reflow following mechanical revascularisation. This is despite the absence of randomised trials in this area.[4] Recent National Institute for Health and Care Excellence (NICE) guidance advises the considered use of GPIs as an adjunct to PCI in patients with multi-vessel disease or diabetes.[40] Disadvantages to the use of GPIs include the cost of the drug and the extra time required by nursing staff to administer an intravenous medication. NICE estimates that when GPIs are used as an adjunct to PCI in high risk patients the base-case cost per quality-adjusted life year (QALY) is £25,811.[40] Side effects and adverse reactions must be considered such as thrombocytopenia and major bleeding which are listed as common side effects with a rate of at least 1%.[41]

1.5.2 Thrombolytics

Administration of fibrinolytic agents to achieve coronary reperfusion as the primary treatment in STEMI is only recommended in the event of a time delay in primary PCI. More recent research suggests there may be a role for fibrinolytic therapy given to patients directly into the coronary artery during PCI. Microthrombi within the myocardial capillaries have a mixed composition of both platelets and fibrin.[42] This suggests that a combination of anti-platelets agents and thrombolytics may improve myocardial perfusion. One study has demonstrated an improvement in myocardial reperfusion when streptokinase was given at the end of PCI.[43] However, a recent randomised trial comparing low-dose intracoronary alteplase versus placebo showed no difference in the extent of microvascular obstruction.[44] As with GPIs, thrombolytic use is associated with bleeding. Intracerebral and gastrointestinal bleeds are listed as common side effects with a rate of at least 1%. The cost of the medication must be considered with alteplase priced at £144 per 10mg.[45]

1.5.3 Vasodilators

Some guidance recommends use of intracoronary vasodilators to treat PCI-related no-reflow during PPCI.[27] Randomised controlled trials looking at intravenous adenosine in patients with acute myocardial infarction showed a reduction in infarct size measured on single-photon emission computed tomography (SPECT) in those receiving adenosine.[46,47] Studies looking at intracoronary adenosine in this setting showed a decreased incidence of no-reflow phenomenon.[48] One study showed benefit in giving intracoronary verapamil in improving coronary flow as measured by TIMI frame count.[49,50] Similar benefits have been shown in the administration of sodium nitroprusside in improving TIMI flow after mechanical revascularisation.[51] However, one study showed no benefit from this treatment so further research is needed in this area.[52] Furthermore, interpretation of the positive findings is complicated by the fact that both adenosine and sodium nitroprusside (via the generation of nitric oxide) inhibit platelet aggregation and inflammatory adhesion molecule function.[51,53,54] Risks with these drugs include their potential to cause hypotension, heart block and ventricular tachycardia. These need to be considered alongside the cost of the medication and the additional staff time required for each patient to receive an additional infusion.[48] Infusion time was up to 3 hours in some studies.

1.5.4 Intra-aortic balloon pump (IABP)

Intra-aortic balloon pumps (IABP) are invasive devices that are placed percutaneously via the femoral or axillary artery and advance to the descending thoracic aorta. They work by inflating a helium balloon in diastole, creating augmentation of diastolic pressure after aortic valve closure. The balloon deflates in systole, reducing afterload. This may increase coronary and systemic flow and can potentially improve myocardial recovery after STEMI. Intra-aortic balloon pumps have been advocated for use in patients with STEMI complicated by cardiogenic shock due to mechanical complications.[3] Recent trials looking at STEMI

patients treated with or without an intra-aortic balloon pump found no benefit in terms of 30-day survival or left ventricular function in patients without cardiogenic shock.[55,56] There could be an additional role for these devices in stable STEMI patients with suboptimal myocardial reperfusion following PCI however there is little evidence to support use in this setting. There are significant risks associated with this invasive procedure, with complication rates between 20-30%.[57] Costs of the device itself and the costs of extra staff time required for insertion and monitoring must be considered.

1.5.5 Deferred stenting

Deferred stenting is where primary stenting during PCI is not immediately performed in suspected STEMI. Instead the culprit artery is reperfused using either a guidewire, aspiration thrombectomy or a balloon catheter. The stent can then be implanted during a second procedure 1-3 days later, after antithrombotic treatment has been administered. This approach allows time for thorough assessment of the patient as well as optimisation of stent placement. During the acute phase, vessel diameter can be underestimated due to reduced flow-mediated dilatation and increase of factors that promote vascular spasm. The longitudinal extent of the underlying atheroma is more evident after removal of adherent thrombus, so the appropriate size of stent can be more accurately estimated. By allowing increased time for reduction in coronary thrombus burden prior to stenting, this strategy likely minimises distal emboli, reducing infarct size. However deferred stenting involves a second procedure with risks to the patient and costs in terms of staff time and prolonged hospital stay. The DEFER-STEMI trial showed that performing immediate balloon dilatation of the culprit vessel but delaying stent implantation in selected higher risk patients improved the myocardial salvage index and reduced no-reflow.[58] Subsequent trials investigating delayed stenting in patients without stratifying them into categories of risk showed no benefit in the patients randomised to deferred stenting.[59,60] This suggests a

possible role for deferred stenting in patients with multiple risk factors or who have indicators suggesting suboptimal myocardial reperfusion after PCI. There were concerns related to acute coronary reocclusion in these patients which occurred in 2-4% of cases.

1.5.6 Thrombus aspiration

Thrombus aspiration is sometimes performed in patients undergoing PCI for STEMI. The aim of thrombectomy in this setting is to restore patency of the culprit vessel and to prevent distal embolisation of thrombotic material and plaque debris into the microvasculature of the heart. Studies show that manual aspiration of thrombus is not indicated routinely during PCI for STEMI.[61,62] It may be beneficial as an adjunctive therapy to patients who are at risk of suboptimal reperfusion.[63]

1.5.7 Pressure-controlled intermittent coronary sinus occlusion

Pressure-controlled intermittent coronary sinus occlusion (PICSO) aims to improve myocardial reperfusion after PPCI. A balloon-tipped catheter is introduced into the coronary sinus to intermittently increase the pressure in the cardiac venous outflow tract. This technique has been hypothesized to enhance washout from the microcirculation and redistribute venous blood to the infarcted myocardium. This may reduce the extent of myocardial necrosis.[64] A recent trial showed that the technique is safe in the STEMI setting.[65] Observational trials aimed at evaluating the efficacy of PICSO as an adjunct to PPCI are currently ongoing.[66]

1.6 Identifying patients with poor myocardial reperfusion in the acute phase

No-reflow is not immediately apparent on angiographic review in all patients who are subsequently shown to have CMVO on CMR. Around 50% of patients with TIMI 3 flow after PCI may have reduced myocardial perfusion that is undetected in the acute phase.[34] These patients are, therefore, not considered for additional therapies or closer surveillance that could improve their outcome. Although CMR can accurately identify CMVO, it cannot be performed in-lab. It can only be used after the acute phase of STEMI once the patient has already missed the opportunity to benefit from adjunctive therapies that must be administered in-lab.

In our aim to improve outcomes in STEMI, we need to make informed decisions regarding the use of adjunctive therapies. To deliver therapies during the acute phase of STEMI, the risk of adverse outcomes must be estimated in the catheter lab. The current method of assessing myocardial perfusion, TIMI flow grade, does not identify a high proportion of patients who go on to develop CMVO and is therefore not likely to identify all high-risk patients. CMR or other imaging is useful but cannot easily be performed in-lab. There are several other methods that have been developed, aimed at identifying poor myocardial reperfusion in the acute phase of STEMI.

1.7 Invasive methods

1.7.1 Index of myocardial resistance (IMR)

At invasive angiography, it is possible to measure indices of coronary flow that may reflect tissue perfusion.[67] The index of microvascular resistance (IMR) gives a quantitative measurement of microvascular resistance down each epicardial vessel.[68] IMR is a coronary

guidewire-based measurement and provides information regarding microvascular function. IMR is calculated by multiplying the distal coronary pressure by the mean transit time of a saline bolus.[67] The mean transit time is calculated by measuring the temperature change of the saline bolus between two transistors on the guidewire. A thermistor located 3cm from the distal end of the coronary guidewire simultaneously measures pressure and temperature. Measurement of mean distal coronary pressures is performed at coronary hyperaemia induced by intravenous adenosine. An IMR <20 is considered normal, and an IMR >30 is elevated and indicates microvascular dysfunction. IMR has been shown to be an independent predictor of LV function at 3 months post-infarct. It is also a predictor of mortality in 3 year follow up.[69] A recent trial looked at the ability of IMR to predict CMVO on subsequent CMR.[70] IMR was measured at the end of PCI and CMR was performed several days later. This study found that IMR was a good predictor of CMVO, LV function and death. A trial performed in Oxford developed a scoring system that used clinical and angiographic variables to predict IMR cut-offs.[71] This trial used age, thrombus burden and pre-stenting IMR value to predict the post-stenting IMR value. This study showed that clinical and angiographic factors may add value in predicting poor myocardial perfusion.

IMR measurement requires an extra invasive diagnostic procedure and administration of IV vasodilators to achieve maximal hyperaemia.[72] This adds time and cost to each case. Operators are unlikely agree to perform IMR measurements in every patient with STEMI. This highlights the need for the development of non-invasive, inexpensive methods of characterising myocardial perfusion that can accurately predict outcomes.[73]

1.8 Clinical methods

When considering clinical characteristics that could predict outcomes following STEMI, I have examined factors that are likely to be known or estimable in all patients during the

acute phase. I have not included factors such as previous medical history or co-morbid conditions in this review because these may not be known during the time of primary reperfusion therapy, particularly in very unwell patients.

1.8.1 Age

Age is an important risk factor for mortality. As the age of a patient increases, their risk of death increases, and they have an increased risk of cardiovascular mortality following STEMI. The GRACE study showed that age is an independent predictor of risk in patients following AMI.[11] The well-known GRACE score predicts in-hospital and 6-month mortality in patients following AMI and includes age as a factor in the score. The TIMI risk score predicts death at 20-days following STEMI and also includes age in the score.[24] Other studies have shown that age is a good predictor of in-hospital and 30-day mortality.[74,75] Age can usually be estimated at diagnosis of STEMI even in patients who are very unwell or unable to communicate with medical staff during the acute event.

1.8.2 Gender

Although men tend to have larger infarcts, women experience poorer outcomes following STEMI, including a higher mortality rate.[76-78] The reasons for this are uncertain but studies have shown that differences often exist in baseline characteristics such as age and comorbidities as well as in presentation.[79] This mortality difference has decreased between the genders in the last 20 years, thought to be due to increased rates of reperfusion.[80] Mortality differences between men and women may simply be a result of confounders, such as comorbidities and presentation. This baseline information is not always available in the acute phase so gender could be a useful as a surrogate for other risk factors and could be used to predict adverse outcomes.

1.8.3 Killip classification

Signs of heart failure can be assessed and classified into the Killip classification system (Table 1.2).[81] Because the symptoms and signs of heart failure often occur as a result of poor left ventricular function, Killip classification is useful in identifying patients who are likely to have poor LV function and higher risk of death. Several studies have reported heart failure as a predictor of mortality.[82,83] The GRACE study demonstrated the association between heart failure and increased in-hospital and 6-month mortality in ACS patients and included Killip class in the GRACE risk score.[84]

Class I	No signs of congestion
Class II	S3 and basal rales on auscultation
Class III	Acute pulmonary oedema
Class IV	Cardiogenic shock

Table 1.2: Killip classification of heart failure

1.8.4 Ischaemic time

As discussed earlier in the chapter, ischaemic time is likely to predict poor outcomes in STEMI. This is because longer ischaemic times result in increased cardiac myocyte damage from prolonged ischaemia. Therefore, increasing ischaemic time is a useful predictor of poor outcomes in STEMI. A recent study showed that transmural necrosis, severe CMVO and poor LV function were directly related to increased ischaemic time.[85] One study showed a 37% increase in risk of transmural necrosis and a 21% increase in risk of severe CMVO with every 30 minute delay in reperfusion therapy.[86] Ischaemic time is recorded by

medical staff during the acute phase of STEMI. In most cases, accurate values of ischaemic time rely on the patient's recollection of the symptom-onset. If symptoms change or evolve over several hours, it may be difficult for the patient to determine the exact onset.

1.8.5 ECG changes before and after reperfusion treatment

The presence of pathological Q waves on ECG prior to PCI is found in 20% patients with STEMI. A recent study showed that STEMI patients with Q waves on ECG prior to PCI have a worse prognosis and a larger infarct size as well as increased CMVO on CMR post-infarct.[87] ST-resolution (STR) on post-PCI ECG is an indicator of the patency of the artery and the success of revascularisation. Early STR is a good prognostic marker in acute myocardial infarction[88] with some studies showing that increasing degrees of ST resolution following PCI are associated with reduced mortality rates and increased LV ejection fraction.[88-93] These studies often assessed the STR at multiple time points following the procedure, because STR may evolve for several hours following revascularisation. This makes STR an unhelpful parameter in the acute phase as it cannot be assessed with certainty during the PCI procedure. 12 lead ECG monitoring would be required to assess STR in-lab which is rarely standard practice.

1.9 Angiographic methods

There are several non-invasive measures of coronary flow and myocardial perfusion that can be evaluated by examining the primary PCI angiogram. Many of these methods have been validated in a research setting but are not routinely used in clinical practice. They have a distinct advantage over invasive methods because they use the angiographic images already obtained during PPCI. No extra equipment or medication is required and there is no

increased risk to the patient. The extra time needed to calculate the measures is minimal and they could be immediately implemented in clinical practice.

1.9.1 Thrombus burden

The TIMI thrombus grade gives a measure of the size of the thrombus in the culprit artery in terms of the length of the thrombus compared to the epicardial vessel diameter (Table 1.3).[94]

Grade 0: no cineangiographic characteristics of thrombus are present
Grade 1: possible thrombus is present, with such angiography characteristics as reduced contrast density, haziness, irregular lesion contour, or a smooth convex "meniscus" at the site of total occlusion suggestive but not diagnostic of thrombus
Grade 2: there is definite thrombus, with greatest dimensions ≤0.5 of the vessel diameter
Grade 3: there is definite thrombus but with greatest linear dimension >0.5 but <2 vessel diameters
Grade 4: there is definite thrombus, with the largest dimension >2 vessel diameters
Grade 5: there is total occlusion

Table 1.3: Definition of TIMI thrombus burden grades

It can be calculated from visual assessment of the angiographic images. There are few studies examining the prognostic value of thrombus burden in STEMI patients. One retrospective study found a higher thrombus grade to be an independent risk factor for major adverse cardiovascular events (MACE), including mortality.[95] Distal embolisation of thrombus is one of the pathophysiological mechanisms in CMVO. Studies have shown that

high thrombus burden in STEMI patients is associated with impaired post-procedure myocardial perfusion, higher rates of no-reflow and distal embolisation.[96,97] Therefore, measuring the thrombus burden may help to predict the degree of myocardial injury from this mechanism and therefore the subsequent infarct size, LV function and mortality.[98]

1.9.2 TIMI Frame count

The TIMI frame count (TFC) is another angiographic method used to give a quantitative measure that reflects the velocity of coronary blood flow. It was developed as an extension of the TIMI flow grade classification system. [99] If operators used TFC to assess angiographic flow in the coronary artery following PPCI this could help to eliminate the observer bias that may occur when estimating the TIMI flow grade. TIMI frame count uses the number of cineframes, acquired at a rate of 30 frames per second, needed for contrast to reach standardized landmarks to objectively reflect coronary blood flow velocity.[99] When adjusted for vessel length it becomes corrected TFC (cTFC). Because cTFC is a continuous variable, it is likely to detect borderline cases of poor myocardial perfusion where coronary flow may be deemed "normal" using TIMI flow grade. The original method describing cTFC advises increasing the count by a fixed number of frames if nitrates are used during the angiogram. TIMI frame count has been shown to have excellent reproducibility and rates of inter- and intra- observer agreement.[99] The ability of cTFC to predict adverse outcomes is uncertain. Some studies have shown that cTFC is a predictor of in-hospital mortality after thrombolysis, higher frame counts being associated with improved LV ejection fraction and LV wall motion,[100,101] but another showed that cTFC has no correlation to adverse outcomes, although in this study only two-thirds of available cinefilms were suitable for analysis of cTFC.[102,103]

1.9.3 Myocardial Blush Grade (MBG)

Myocardial blush grade (MBG) is a qualitative visual assessment of the amount of contrast filling areas of the microvasculature supplied by an epicardial artery.[104] This grading system was originally developed by van't Hof at al. and categorises the degree of myocardial blush into 4 grades, as illustrated in Table 1.4.

Grade 0: no myocardial blush
Grade 1: minimal myocardial blush
Grade 2: myocardial blush exists to a lesser extent and with less clearance than would be expected in a non-infarct related artery
Grade 3: normal myocardial blush

Table 1.4: Definitions of myocardial blush grade

MBG looks at blood flow into the microvasculature of the myocardium, which may be a useful additional measurement and may be independent of TIMI flow or TFC in cases of CMVO. Following PPCI, TIMI flow may be graded as normal, but a low blush grade may identify cases where microvascular dysfunction is limiting the passage of dye into the microcirculation. MBG can be calculated in-lab during PCI. In the first study describing MBG interobserver and intraobserver agreement was 90% and 97% respectively.[104] Decreased MBG correlates with an increased number of myocardial segments with transmural necrosis on CMR. In addition, the phenomenon of staining, classed as MBG 0, is associated with severe and persistent microvascular damage.[105] MBG of 0 or 1 was associated with an increased degree of unfavourable left ventricular remodelling and more frequent symptoms of heart failure.[106] MBG of 2 or 3 is associated with smaller infarct size, less

CMVO, improved LV ejection fraction and significantly lower mortality.[107,108,109] MBG 3 is a strong predictor of freedom from MACE at 5-year follow-up.[110]

1.9.4 TIMI Myocardial Perfusion Grade

The TIMI myocardial perfusion grade (TMPG) is calculated using a similar method to MBG.[111] TMPG assesses the filling and clearance of contrast from the myocardial vasculature rather than the density of myocardial blush as in MBG, and categorises this into 4 grades (Table 1.5).

Grade 0: No myocardial blush
Grade 1: Minimal blush and very slow clearing (e.g. present at beginning of next cine)
Grade 2: Good blush with slow clearing of myocardial contrast (present at end of cine but gone at beginning of next)
Grade 3: Good blush and normal clearing (ie. gone by end of cine)

Table 1.5: Definitions of TIMI myocardial perfusion grades

This is estimated from the ground-glass appearance of the contrast as it penetrates the microvasculature and then fades as it drains through the venous system. TMPG is an independent predictor of mortality.[111,112] TMPG is more complex to calculate than MBG. There is less evidence that it relates to LV function or adverse outcomes. The original method advises that each angiographic run used to assess TMPG must be at least three cardiac cycles long. This may be impractical in an acute setting and exposes the patient to increased radiation.

1.9.5 Culprit vessel

The location of the culprit lesion is often suspected from the ECG findings and subsequently confirmed on angiography. The culprit vessel is therefore a clinical and an angiographic variable. A recent study evaluating 10 PPCI trials showed that a LAD culprit is associated with a larger infarct and a higher risk of death following STEMI.[113] The location of the culprit lesion is associated with infarct size because a larger culprit vessel, or a culprit vessel supplying the anterior myocardium, will result in a larger infarct.[114]

1.10 Summary

The aims of treatment in STEMI are to improve survival rates and quality of life for patients. STEMI is associated with significant mortality and morbidity even if timely treatment with primary PCI is performed. The current method of determining PCI success, the TIMI flow grade, does not identify many patients with microvascular obstruction. It may be possible to identify more of these patients using clinical information and angiographic variables during PPCI. This would allow appropriate administration of adjunctive therapies which could improve myocardial perfusion, decreasing eventual infarct size and resulting in improved survival rates. However, evidence for the use of adjunctive therapies is weak. Therefore, using selected variables to identify low-risk patients may be of value and assist operators in making decisions regarding length of critical care stays and early discharge.

The development of a systematic and thorough approach to angiogram interpretation is likely to add information regarding the success of PPCI. The addition of well-validated angiographic grading systems could minimise the use of more invasive tests such as IMR. Core laboratories have developed guidance for systematic angiogram interpretation, but this is not applied frequently in clinical practice. These methods should be tested to ensure

their reproducibility, particularly using angiograms performed in emergencies that are likely to be of lower quality than those obtained during elective procedures.

Chapter 2: Selection and development of methods for angiographic analysis

2.1 Introduction

HEAT-PPCI was a single-centre, randomised controlled trial comparing unfractionated heparin versus bivalirudin in the treatment of patients with suspected STEMI, for planned management with PPCI (registered at clinicaltrials.gov NCT01519518).[115] The HEAT-PPCI database provided complete and extensive data on a large and unselected population of patients with suspected STEMI, undergoing PCI. The angiographic images obtained during the HEAT-PPCI trial, as well as the complete study database, were available for use in this thesis. This included the baseline characteristics of patients, the nature of the clinical presentation, details of the angiographic findings and any reperfusion intervention. The database also included estimates of infarct size from enzyme release, LV function from echocardiographic data, and surveillance for adverse events over the subsequent 28 days from the index event.

The aims, methods, analysis and results of each study that uses data from the HEAT-PPCI trial are described in detail in subsequent chapters. In the following chapter, I discuss the detail of the HEAT-PPCI trial, and the general methods used to collect clinical and angiographic data from the HEAT-PPCI angiograms.

2.1.1 How Effective are Antithrombotic Therapies in Primary Percutaneous Coronary Intervention: The HEAT-PPCI randomised controlled trial

Patients were randomised (1:1) at presentation to the Liverpool Heart and Chest Hospital and before entry into the catheterisation laboratory. Heparin was given as a bolus dose of 70U/kg bodyweight before the procedure with additional doses administered according to

activated clotting times measured during the procedure. Bivalirudin was given as a bolus of 0.75mg/kg followed by an infusion of 1.75mg/kg per hour for the duration of the procedure. Abciximab was allowed for selected use in both groups due to massive thrombus, no-reflow or a thrombotic complication. Participants were tracked during their index admission for clinical events, by careful review of the case notes, and followed-up for 28 days following randomisation. In addition, Hospital Episode Statistics (HES) data were obtained for participants at 28 days.

The primary efficacy outcome of the HEAT-PPCI trial was the proportion of patients who had at least one MACE at 28 days. MACE included all-cause mortality, cerebrovascular accident (CVA), reinfarction or additional unplanned target lesion revascularisation (uTLR). The primary safety outcome was the proportion of patients who had a major bleed by 28 days, classified as type 3-5 according to the Bleeding Academic Research Consortium (BARC).[115] All outcomes were adjudicated by a physician panel, blinded to the treatment allocation.

Recruitment took place from 7 February 2012 to 20 November 2013 and 1812 participants were included in the HEAT-PPCI final analysis. The results of the HEAT-PPCI trial showed that at least one MACE occurred in 79/905=8.7% patients in the bivalirudin group vs 52/907=5.7% in the heparin group (relative risk 1.52, 95% CI 1.09 to 2.13, p=0.01). This difference was mainly due to an increased number of reinfarction events in the bivalirudin group (relative risk 3.01 95% CI 1.36 to 6.66). There was no significant difference in all-cause mortality or cerebrovascular accident between the two groups.

2.2 Rationale for selection of grading systems

Angiographic grading systems were selected for use if they fulfilled the following criteria:

- Non-invasive - in that they did not require the application of additional equipment or software processing beyond the basic angiographic image acquisition and playback
- Previous research had shown an association with LV function and mortality
- They could be calculated, with relative ease, from the angiogram during the acute phase of MI reperfusion treatment

Some systems were excluded despite having the potential to predict poor outcomes. For example, TMPG was not included because it is very similar to MBG. Both measure the movement of contrast within the myocardium by grading the visible contrast density on the angiogram. However, MBG was preferred because it has been used in more studies and has a greater weight of evidence suggesting it can predict infarct size. In addition, TMPG requires the duration of the angiographic run to last at least 3 cardiac cycles to ensure complete washout of contrast is visualised, making practical application of TMPG more challenging, as well as increasing radiation exposure.

2.3 The angiographic core laboratory

I studied the literature that described the original methods used to apply each angiographic grading system and tested them on all angiograms from the HEAT-PPCI trial. The aim of this was to assess the practicality of deriving the grading scales from the existing angiograms and examine for technical issues in angiogram quality and acquisition that might compromise some estimation exercises. During this phase, I noted a significant proportion of angiograms where application of one or more of the grading scales was challenging due

to the quality of the angiogram. For example, grading MBG was difficult if there was inadequate image centring and run duration, whereas cTFC could not be confidently assessed in images where inadequate panning resulted in minimal views of the distal vessel. Prepared by this fastidious review of the angiographic records of more than 1400 patients, each comprised of multiple angiographic image runs, I was sufficiently acquainted with the core methods and problems associated with quantitative angiographic review.

To gain an understanding of how to apply the grading systems with more consistent quality I visited the Angiographic Core Lab at the Beth Israel Deaconess Medical Centre (BIDMC), Boston, MA. Angiographic core labs are the "gold standard" for angiographic analysis. It is common practice for research studies of coronary intervention to request angiographic core labs to analyse angiograms in clinical trials to ensure accuracy and consistency of interpretation and to limit bias.

The BIDMC core lab was run by the PERFUSE study group who developed the original methodology for TIMI flow, cTFC, TIMI thrombus burden and TMPG. I spent 5 days in Boston learning the methods of angiographic assessment used at the BIDMC core lab. I was able to refine the techniques as defined in the literature for application to a wider range of coronary anatomy and angiogram quality.

2.4 Accessing and reviewing the angiograms from the HEAT-PPCI trial

2.4.1 A "typical" PPCI procedure

The details of a PPCI procedure will vary depending on the underlying anatomy and pathology of the individual and any complications that arise during the procedure. The

following section describes a “typical” PPCI procedure and the process of acquisition of PPCI angiograms.

A patient with suspected STEMI is brought into the catheterisation laboratory (lab). The arterial access site, usually the right radial artery, is cleaned and infiltrated with local anaesthetic. The operator accessed the arterial system by introducing a sheath into the radial artery. Once the sheath is securely placed, the operator introduces a catheter into the sheath and manoeuvres the catheter through the arterial system to the ostia of the coronaries, under x-ray guidance. Contrast is injected along the length of the catheter to fill the target vessel and allow visualisation of the coronary arteries. Once the coronary arteries are visualised, the obstructed culprit artery is identified and treated. Treatment varied depending on the severity and location of the lesion but usually involved passing a wire along the obstructed artery and using other devices (usually balloons or hollow thrombus aspiration catheters) to restore blood flow. Stents might then be placed into the culprit segment to attempt to restore normal luminal geometry, to support areas of injury or dissection in the vessel lining, and aid successful reperfusion.

2.4.2 Obtaining angiograms

Each lab is fitted with an x-ray emitter and image intensifier which are attached to rotating arms and can be moved around the patient to view the coronary arteries at different angles. If a biplane lab is used, then two x-ray emitters and two image intensifiers are available and produce video images (cineruns) in two different planes for a given injection of contrast. The x-ray images are viewed on screens visible to the operator in the lab.

The operator views the coronaries on the screens and controls the acquisition of cineruns for storage and retrospective review. Selected cineruns that are saved for later review are obtained at a higher frame rate to increase the quality of the image.

2.4.3 Review of the angiograms

The angiograms from the HEAT-PPCI trial were reviewed using the viewing software Philips Xcelera version 3.2. Each cinerun was stored in chronologically order and could be retrospectively viewed and analysed in sequence.

2.4.4 Quality of the angiograms

The images stored within Xcelera are compressed to allow multiple images to be stored on the hospital network. This is associated with some reduction in image quality when compared to the angiograms viewed in the lab during the procedure. In addition, the overall image quality can be affected by body habitus and positioning of the patient. Clear visualisation of the coronary artery anatomy is required for confident assessment of the grading systems.

2.5 Database creation

The aim was to create a database that allowed easy but structured data collection of the selected angiographic grading systems. A detailed description of the database design and creation is included in Appendix 1.

2.6 Methodology for assessing each angiographic grading system

2.6.1 TIMI flow grade

The TIMI flow grades were recorded as values between 0 and 3 (Chapter 1, Table 1.1).[26]

2.6.2 TIMI thrombus grade

TIMI thrombus grade was measured using the grading system originally developed by the TIMI study group (Chapter 1, Table 1.3).[94] To measure thrombus burden, I used the cinerun that displayed the first time-point at which dye flows distal to the occlusion. This view ensured the thrombus was fully visualised because the flow of contrast was able to outline the full mass before the thrombus was likely to be dislodged from the vessel wall. Displacement of the thrombus normally occurs after initial wire insertion or balloon dilatation of the culprit vessel. If initial wiring or ballooning did not allow blood flow distal to the thrombus, and the vessel remained totally occluded, then the thrombus burden was graded 5: total occlusion. If thrombus aspiration was performed, the thrombus burden was graded in the cinerun before thrombus aspiration. The thrombus burden was graded using a measuring tool within the angiogram viewing software (Figure 2.1). The size of the thrombus was measured relative to the vessel diameter, allowing calculation of the ratio of thrombus length to vessel diameter and an assessment of thrombus burden (Figure 2.2). A change in the angiographic projection angle can make a linear mass appear shorted. This can be a source of error. For consistency, measurements of thrombus were made from the view where the thrombus appeared to have the longest length.

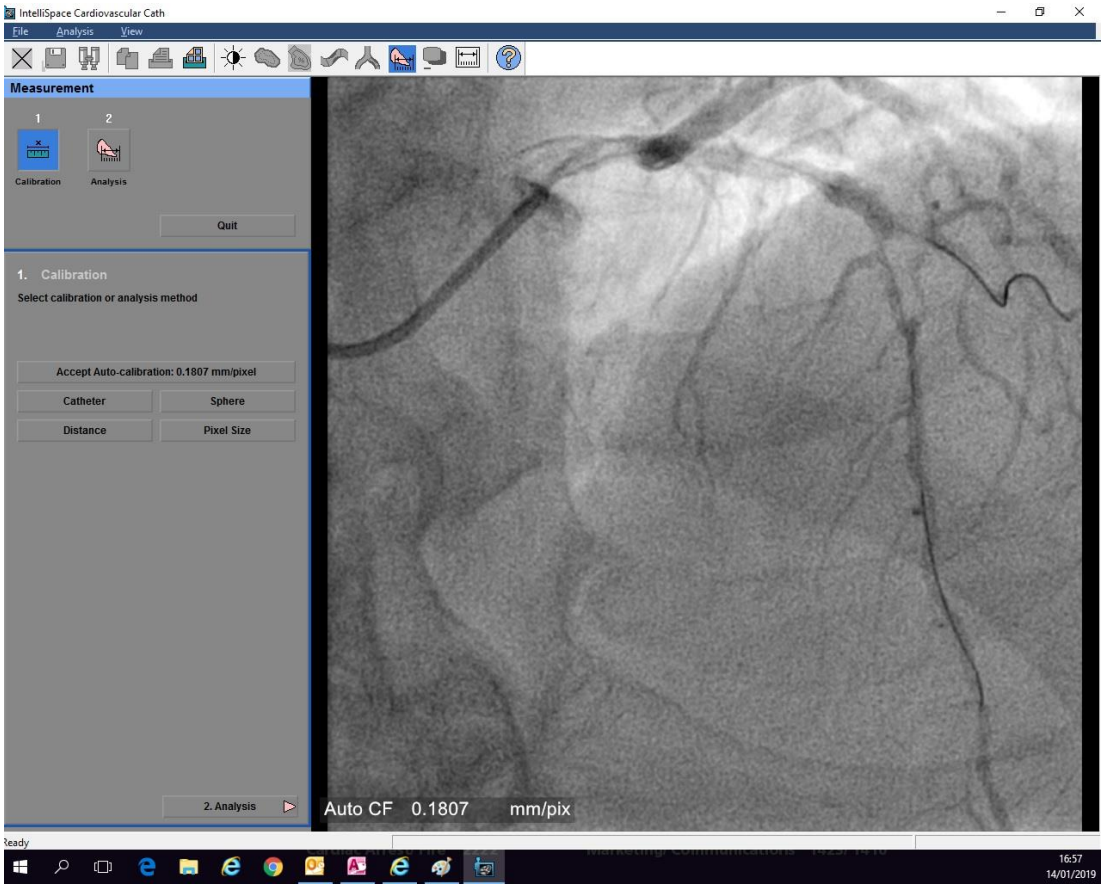


Figure 2.1: The measuring tool within the angiogram viewing software, Xcelera, used to measure the length of thrombus burden in the culprit artery

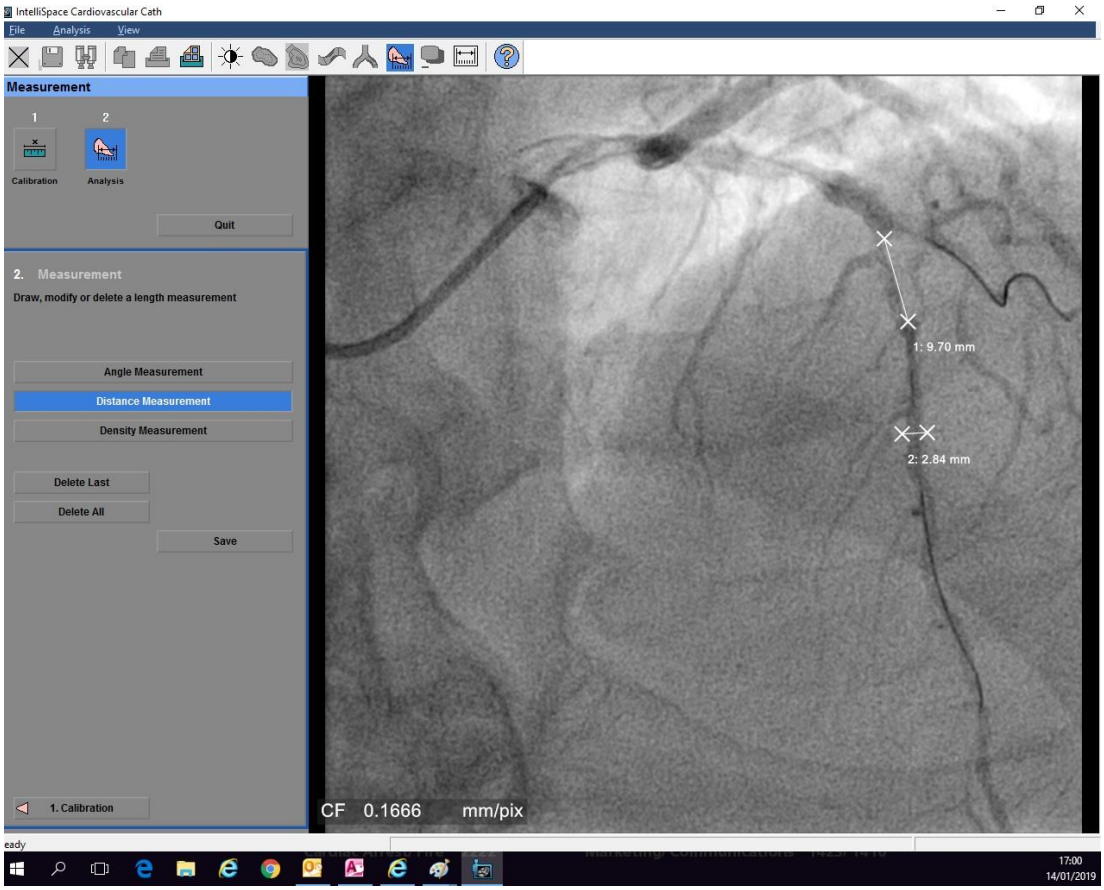


Figure 2.2: Using the measuring tool in Xcelera to compare the length of thrombus with the diameter of the culprit vessel to grade the thrombus burden

2.6.3 Corrected TIMI Frame Count (cTFC)

Corrected TIMI frame count (cTFC) was calculated using the method described in the TIMI 4 trial.[99] The cTFC estimates the speed of contrast moving down the coronary artery by counting the number of cineframes required for contrast to reach standardised distal coronary landmarks.

2.6.3.1 Selecting the initial frame for cTFC

The first frame used to calculate cTFC was the frame in which dye first fully enters the culprit artery after injection of contrast. This was defined when three criteria were met (Figure 2.3):

- A column of nearly full or fully concentrated dye must extend across the entire width of the origin of the artery.
- Dye must touch both borders of the origin of the artery.
- There must be antegrade motion to the dye

If the location of the vessel walls was not clear, then the frame where the width of dye across the vessel is at a maximum was used.

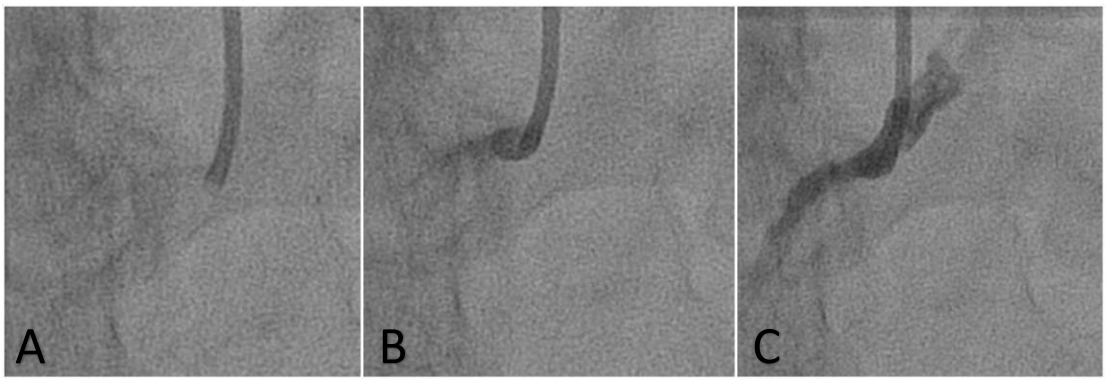


Figure 2.3: A: Frame -1, before dye injection B: Frame 0, dye has reached both sides of the vessel but there is no evidence of antegrade flow. C: Frame 1, there is clear demarcation of the vessel walls and evidence of antegrade flow. This is the initial frame.

If the LAD was subselectively engaged and the circumflex was being assessed, the first frame was counted from when the dye first touches both borders of the Cx.

2.6.3.2 Selecting the final frame for cTFC

The last frame was counted when dye first entered the distal landmark branch. Full opacification of the branch was not required; the initial opacification of the branch was counted as the final frame.

The distal landmark branches used for analysis:

- LAD: the distal bifurcation (i.e. the “pitchfork” or “whale’s tail”) (Figure 2.4 – image reproduced with permission – see Appendix 2).
- Circumflex: distal bifurcation of the segment with the longest total distance. If the circumflex was the culprit artery, then the longest distance that includes the culprit lesion was used (Figure 2.4).
- Right coronary artery: the first branch arising from the posterior lateral extension of the RCA after the origin of the posterior descending artery

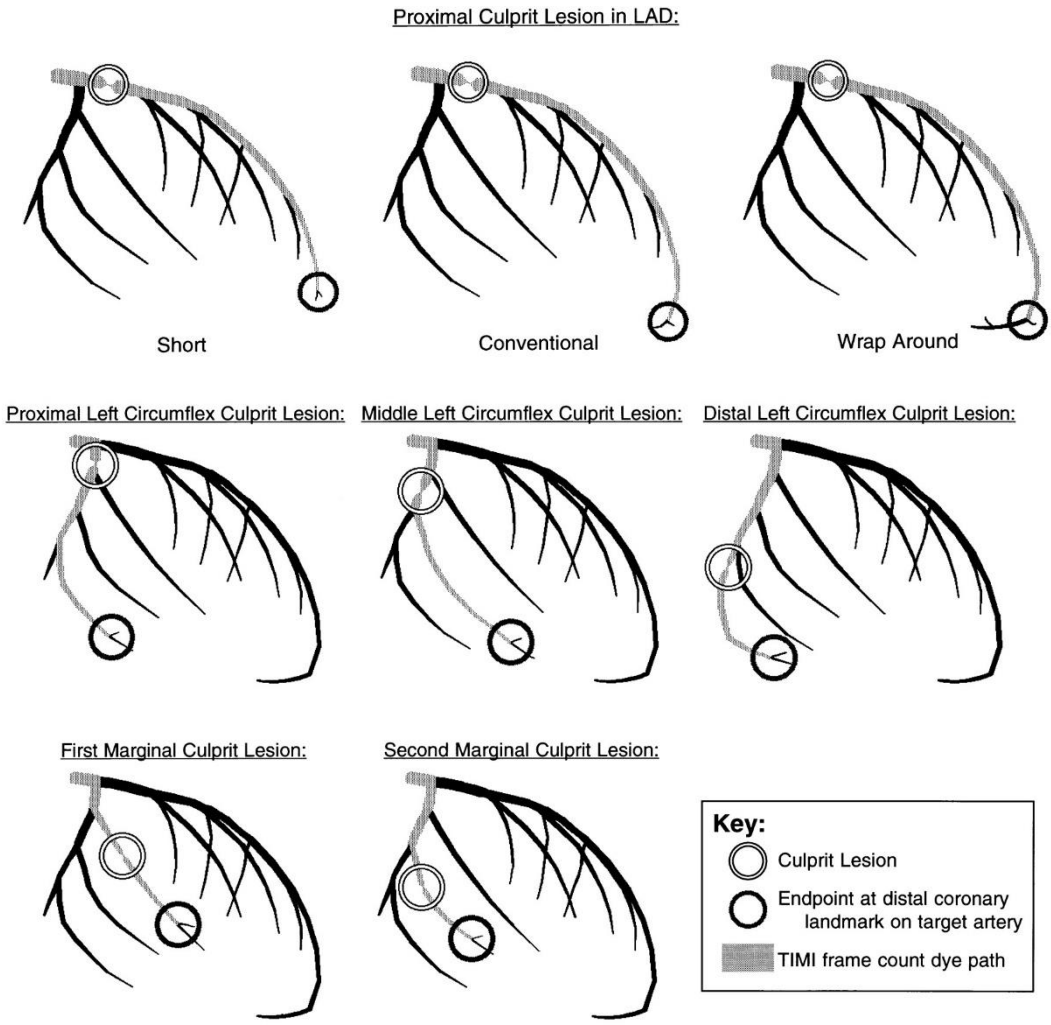


Figure 2.4: Anatomical landmarks used for TIMI frame counting in LAD and Cx vessels

For the final frame, the branch used must be present for more than one consecutive frame. This ensures that it is not a branch from another vessel (overlapping the region of interest) or artefact. To identify the final frame in all vessels except the RCA (and branches arising from the RCA), I used the branch that appears most distally along the vessel or on the vessel closest to the apex in the LAD. If a proximal branch fills after the most distal branch, then we used the proximal branch. This is because I was trying to measure the speed of blood flow and extent of myocardial perfusion, therefore the last vessel to fill should be the

final frame as this will give an approximation of the time taken to fill the smaller vessels and microvasculature.

2.6.3.3 Optimum angiographic views for assessing cTFC

When choosing the correct angiographic image to use for assessing the cTFC, circumflex vessels were best assessed in the right or left anterior oblique views with caudal angulation whereas the LAD was best assessed with cranial or lateral angulation. The RCA was best assessed in the left anterior oblique projection with steep cranial angulation.

2.6.3.4 Correcting for vessel length when assessing cTFC in the LAD.

The frame count does not differ significantly between the RCA and circumflex. However, the frame count in the LAD was significantly increased because the LAD is longer in length than the RCA or circumflex. Therefore, the frame count measured for the LAD was divided by 1.7 to calculate the final cTFC.

2.6.3.5 cTFC in wraparound LADs

A proportion of LAD arteries wrapped around the apex of the heart. When measuring the TFC in such vessels the aim was to measure the final frame at the frame contrast enters the branch that occurs closest to the apex. This vessel is best chosen by drawing a straight line from the ostium of the LAD to the apex and choosing the vessel closest to the line (Figure 2.5).

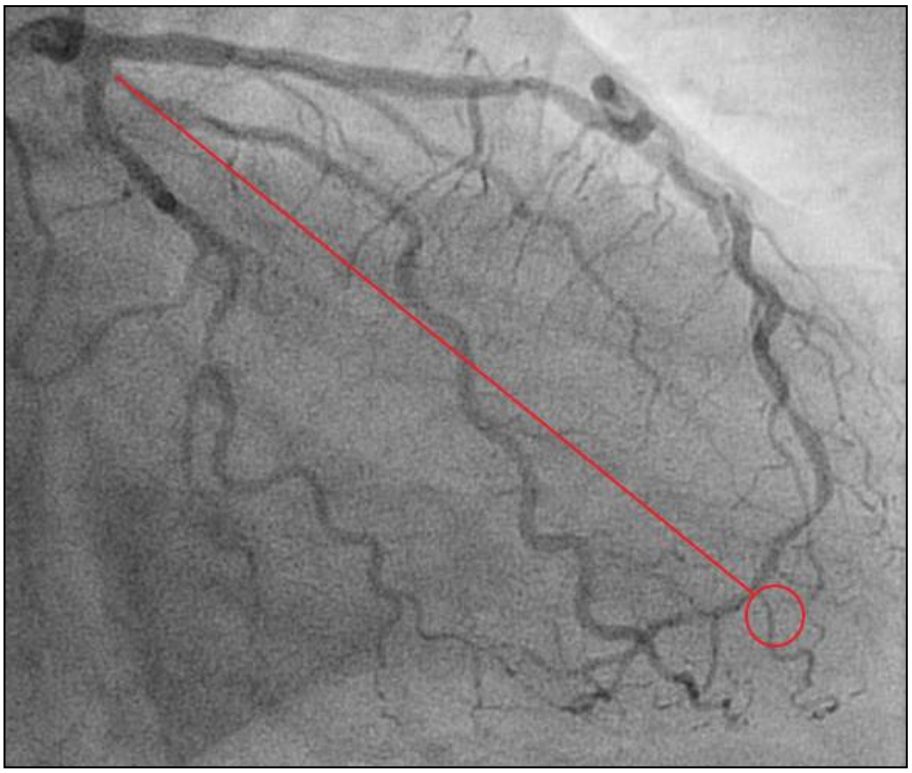


Figure 2.5: Selecting the branch closest to the apex for establishing the final frame for cTFC assessment of the LAD

2.6.3.6 Estimating cTFC when the full length of a vessel is not visualised

Some angiograms did not visualise the full length of the culprit vessel. In these cases, the vessel length was estimated based on looking at the length of the vessel in other runs and the cTFC was measured based on the visible fraction of the vessel on the angiogram. The cTFC was then estimated for total length of the vessel giving the "estimated cTFC."

2.6.3.7 Intermediate and diagonal culprit arteries

CTFC in intermediate and diagonal arteries was measured using the same method as in the circumflex artery: I counted the number of frames until contrast reached the most distal

bifurcation. If the culprit was the diagonal artery, the initial frame was counted from the ostium of the LAD.

2.6.3.8 Posterior left ventricular artery culprit

If the culprit lesion was the posterior left ventricular (PLV) artery, I recorded the final frame as the frame where the first branch of the PLV after the culprit lesion first appeared.
The original method of measuring cTFC in the RCA specifies counting cTFC to the first branch after the origin of the PDA. If the culprit is the PDA or interventricular branch, then the branch immediately distal to the culprit branch was used.

2.6.3.9 Frame speed

The cTFC is designed for angiograms acquired at 30 frames per second. Some angiograms during PPCI were acquired at 15 frames per second. To ensure the correct value for TFC was recorded, the number of frames counted was corrected for the frame rate, using 30 frames per second as the standard.

2.6.3.10 cTFC in an occluded culprit

If the culprit vessel was occluded, then the cTFC could not be calculated and the corresponding database field was left blank.

2.6.3.11 Use of nitrates

In HEAT-PPCI, the use of nitrates was not recorded, therefore cTFC was not corrected for nitrate use, as suggested in the original method.

2.6.4 Myocardial Blush Grade (MBG)

The MBG was calculated by examining the flow of contrast into the myocardium perfused by the culprit artery (either right or left), using the method developed by van't Hof et al.[104] Figure 2.6 illustrates an example of normal myocardial blush in the RCA.

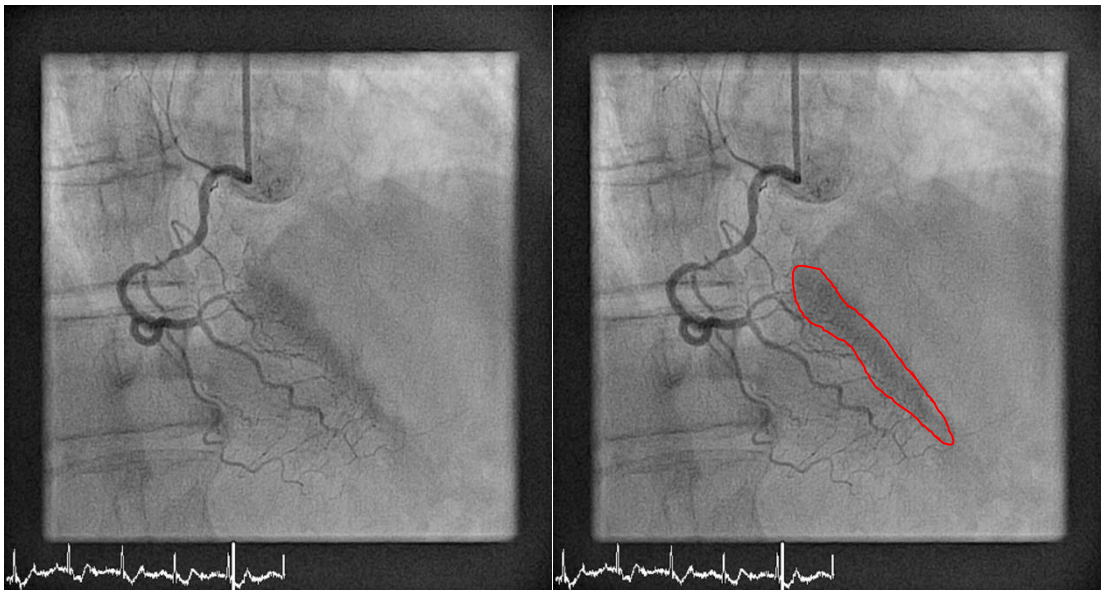


Figure 2.6: Normal grade 3 myocardial blush is demonstrated in the RCA. The region of myocardial blush is ringed in red in the right-hand image

Myocardial blush was graded as normal (grade 3) if the density of contrast appearing in the myocardium perfused by the culprit was equal to the density observed in the non-culprit side. If the density was less in the culprit side than the non-culprit side, MBG was graded as 1 or 2, according to the definitions in Chapter 1, Table 1.4. If no contrast appeared in the culprit side, MBG was graded 0. The run with the best projection was chosen to assess the myocardial region of the infarct-related coronary artery. Angiographic runs had to be sustained for long enough to allow some filling of the venous system. Backflow of contrast into the aorta should be present to be sure of adequate contrast filling into the epicardial coronary artery. If these criteria were not met, the MBG could not be calculated and the

corresponding database field was left blank. If myocardial blush is present before the injection of contrast, also known as “staining”, this was noted in the study database.

The method developed by van’t Hof et al. to assess the MBG involved all patients receiving the same dose of intracoronary nitroglycerin. In HEAT-PPCI there was no standardization of administration of IC nitroglycerin which may have affected the MBG grade.

2.7 Limitations

In the initial testing phase, I attempted to measure the grading systems as they were described in the literature. I found the original methods lacked detail to allow analysis of all angiograms in the HEAT-PPCI trial. I addressed these issues at the core lab and adopted their specific and proven methods of angiographic assessment. However, because the core labs do not publish their own methods of angiogram analysis there is likely to be variability between core labs as well as between research teams using these grading systems. A comprehensive method of assessing the grading systems should be published by the core labs to ensure the grades are comparable when used in different studies.

The accuracy of measurements is likely to differ across angiograms of varying quality. Our data was collected retrospectively, and the angiograms used were not obtained for the purpose of assessing the selected grading systems. In some cases, I was unable to assess a grading system because of poor angiographic quality. PPCI angiograms tend to be of poorer quality than those used in stable disease and this may impact the reproducibility of our methods between observers in the PPCI setting. I address the interobserver variability of the angiographic grading systems in Chapter 6.

Chapter 3: An examination of the use of Hospital Episode Statistics to identify outcomes in clinical trials

3.1 Introduction

The HEAT-PPCI trial tracked and recorded clinical outcomes for each patient up to 28 days following the acute STEMI event. This data could be used to explore possible associations between selected clinical and angiographic variables and outcomes. However, establishing outcomes for longer follow-up periods can perhaps better elucidate potential differences in efficacy between treatments as well as identify late complications.

Traditional methods of follow-up are often expensive and time-consuming, involving direct contact with each study participant over a prolonged period. The use of novel methods of trial follow-up, such as electronic databases, may reduce the cost, be more convenient for research staff and patients, and avoid loss to follow-up. I aimed to extend the follow-up for participants in HEAT-PPCI to 12 months following randomisation using Hospital Episode Statistics (HES) data. HES is a centralised database containing information for all patient care delivered in England in NHS facilities. HES is compiled from the coding data received from NHS trusts. Each episode of care is identified from the patients' hospital notes and recorded as a series of diagnostic and procedural codes. The diagnostic codes are taken from ICD-10 (International Classification of Diseases 10th Revision). Each code in HES is associated with a tariff that determines how much the hospital is paid per admission. Before I could plan a study using HES data to identify outcomes, I needed to establish the accuracy of HES in identifying clinical events when compared to traditional methods of follow-up.

The objective of this study was to compare the ability of HES data to identify the occurrence of trial-specific events declared by adjudication after examination of individual medical records. A second objective was to use the data from the HEAT-PPCI trial to compare ability

of the individual direct contact and HES methods to determine the incidence of confirmed readmission.

3.2 Methods

3.2.1 Patients and study design

The HEAT-PPCI trial is described in detail in Chapter 2. The primary objective of follow-up in HEAT-PPCI was to establish vital status and the occurrence of any pre-specified outcome measures. This involved the identification of all overnight admissions during the follow-up period and was achieved by direct patient contact (DC) at 4-6 weeks following randomisation. In addition, HES reports were examined for each patient to supplement the information obtained by DC. Suspected readmission events identified by HES were then confirmed by review of the medical notes.

3.2.2 Method of assessing the accuracy of DC and HES in identifying readmissions

Patients who had both a HES report and were tracked by direct contact were included in the analysis. The number of readmissions determined by the individual DC and HES methods were then compared to the total number of readmissions suggested by the two methods and then confirmed by review of the medical notes. When evaluating DC, if a readmission was not identified by DC but was identified by HES and subsequently confirmed by medical notes review, this was recorded as a false negative result. When evaluating the HES data, if a readmission was identified in the HES data but not confirmed by medical notes review, this was recorded as a false positive result. If a readmission was not identified by HES but was identified by DC and subsequently confirmed by medical notes review, this was recorded as a false negative result. From these data I could then

calculate the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of each method.

3.2.3 Method of assessing the diagnostic accuracy of HES data

The primary efficacy outcome of the HEAT-PPCI trial was the proportion of patients who had at least one MACE event at 28 days, as defined in chapter 2. The primary safety outcome was the proportion of patients who had at least one major bleed by 28 days, classified as BARC type 3-5. Key clinical information from each patient was reviewed by a blinded physician adjudication panel. This panel would then establish if outcome events had occurred in terms of the specific event definitions declared in the trial protocol.

The HES data obtained for the 28 days following randomisation were examined to identify ICD-10 codes that indicated the occurrence of any primary efficacy or safety outcome pre-specified in the HEAT-PPCI trial. All patients who were randomised, and for whom HES data was obtained, were included in this analysis. To identify key clinical events, the relevant ICD-10 codes were used to search the HES database (Tables 3.1 and 3.2). The events identified in the HES data were compared with those declared by physician adjudication. If a diagnosis was identified in HES that was not identified by physician adjudication, this was recorded as a false positive result. If a diagnosis was not identified in HES but was identified by physician adjudication, this was recorded as a false negative result.

ICD-10 codes used to identify recurrent myocardial infarctions	Decoded diagnosis
I210	ACUTE TRANSMURAL MYOCARDIAL INFARCTION OF ANTERIOR WALL
I211	ACUTE TRANSMURAL MYOCARDIAL INFARCTION OF INFERIOR WALL
I212	ACUTE TRANSMURAL MYOCARDIAL INFARCTION OF OTHER SITES
I213	ACUTE TRANSMURAL MYOCARDIAL INFARCTION, UNSPECIFIED
I214	ACUTE SUBENDOCARDIAL MYOCARDIAL INFARCTION
I219	ACUTE MYOCARDIAL INFARCTION, UNSPECIFIED
I220	SUBSEQUENT MYOCARDIAL INFARCTION OF ANTERIOR WALL
I221	SUBSEQUENT MYOCARDIAL INFARCTION OF INFERIOR WALL
I228	SUBSEQUENT MYOCARDIAL INFARCTION OF OTHER SITES
I229	SUBSEQUENT MYOCARDIAL INFARCTION OF UNSPECIFIED SITE
ICD-10 codes used to identify strokes	**Decoded diagnosis**
I606	SUBARACHNOID HAEMORRHAGE FROM OTHER INTRACRANIAL ARTERIES
I609	SUBARACHNOID HAEMORRHAGE, UNSPECIFIED
I611	INTRACEREBRAL HAEMORRHAGE IN HEMISPHERE, CORTICAL
I618	OTHER INTRACEREBRAL HAEMORRHAGE
I629	INTRACRANIAL HAEMORRHAGE (NONTRAUMATIC), UNSPECIFIED
I630	CEREBRAL INFARCTION DUE TO THROMBOSIS OF PRECEREBRAL ARTERIES
I633	CEREBRAL INFARCTION DUE TO THROMBOSIS OF CEREBRAL ARTERIES
I634	CEREBRAL INFARCTION DUE TO EMBOLISM OF CEREBRAL ARTERIES
I638	OTHER CEREBRAL INFARCTION
I639	CEREBRAL INFARCTION, UNSPECIFIED
I64X	STROKE, NOT SPECIFIED AS HAEMORRHAGE OR INFARCTION

Table 3.1: ICD-10 codes used to search the HES database and identify outcome events for stroke and recurrent myocardial infarction

ICD-10 codes used to identify bleeds	Decoded diagnosis
D500	IRON DEFICIENCY ANAEMIA SECONDARY TO BLOOD LOSS (CHRONIC)
H313	CHOROIDAL HAEMORRHAGE OR RUPTURE
H356	RETINAL HAEMORRHAGE
H431	VITREOUS HAEMORRHAGE
J942	HAEMOTHORAX
K226	GASTRO-OESOPHAGEAL LACERATION-HAEMORRHAGE SYNDROME
K25	GASTRIC ULCER
K26	DUODENAL ULCER
K27	PEPTIC ULCER
K28	GASTROJEJUNAL ULCER
K625	HAEMORRHAGE OF ANUS AND RECTUM
K920	HAEMATEMESIS
K921	MALAENA
K922	GASTROINTESTINAL HAEMORRHAGE, UNSPECIFIED
I60	SUBARACHNOID HAEMORRHAGE
I61	INTRACEREBRAL HAEMORRHAGE
I62	OTHER NON-TRAUMATIC INTRACRANIAL HAEMORRHAGE
N421	CONGESTION AND HAEMORRHAGE OF PROSTATE
R04	HAEMORRHAGE FROM RESPIRATORY PASSAGES
R58	HAEMORRHAGE, NOT ELSEWHERE CLASSIFIED
S064	EPIDURAL HAEMORRHAGE
S066	TRAUMATIC SUBDURAL HAEMORRHAGE
S065	TRAUMATIC SUBARACHNOID HAEMORRHAGE
T792	TRAUMATIC SECONDARY AND RECURRENT HAEMORRHAGE
T810	HAEMORRHAGE AND HAEMATOMA COMPLICATING A PROCEDURE
T812	ACCIDENTAL PUNCTURE AND LACERATION DURING A PROCEDURE

Table 3.2: ICD-10 codes used to search the HES database and identify outcome events for bleeding events

3.3 Results

3.3.1 Identifying readmissions

The HEAT-PPCI trial included 1812 patients. Following randomisation, 73 patients died in hospital before they were discharged from the index event and 39 participants remained inpatients at 28 days. Of the remaining 1700 with the potential to be re-admitted during the 28-day follow-up period, 1644/1700 = 96.7% were successfully followed up by both DC and HES (Figure 3.1). The method of direct contact used was recorded for all participants (Table 3.3).

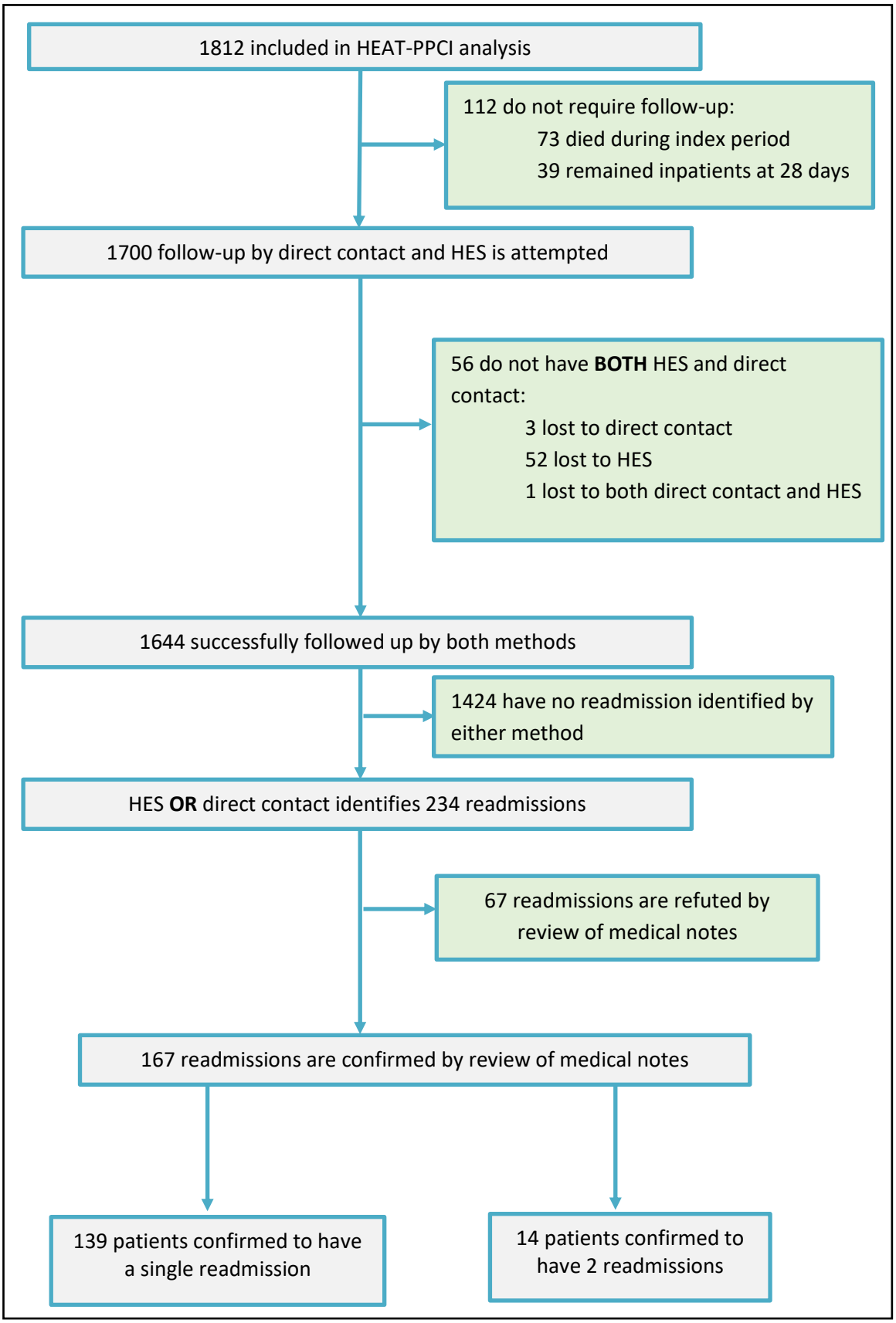


Figure 3.1: Flow diagram outlining the follow up obtained by direct contact and HES methodology for identifying readmissions

Method of direct contact used	Number of patients
Mail	1153 (70.1%)
Telephone	334 (20.3%)
Other direct patient contact (email, text message)	47 (2.9%)
GP or other primary care provider	48 (2.9%)
Outpatient clinic	44 (2.7%)
Inpatient	18 (1.1%)
Total	1644

Table 3.3: Methods of direct contact used to complete follow-up in HEAT-PPCI

The full results of the analysis of readmissions are presented in Table 3.4. HES identified 153/166 of confirmed readmissions (sensitivity: 153/166 = 92.2%; 95% CI 87.1% to 95.4%). HES missed 13 confirmed readmissions. All readmissions identified by HES were confirmed readmissions (specificity: 1492/1492 = 100%; 95% CI 99.7 to 100). During the follow-up period, 14 patients experienced 2 confirmed readmissions and 28/28 = 100% of these were identified in HES.

DC identified 144/166 confirmed readmissions (Sensitivity: 144/166 = 86.7%; 95% CI 80.7 to 91.1) and missed 22 confirmed readmissions. DC identified 66 suspected readmissions that were not found to be confirmed readmissions (Specificity: 95.6%; 95% CI 94.4 to 96.5). DC identified 16/28 readmissions in patients found to have 2 confirmed readmissions.

	Outcome from physician adjudication		Sensitivity (CI)	Specificity (CI)	PPV (CI)	NPV (CI)
	Readmission	No readmission				
HES detects readmission	**153**	**0**				
HES does not detect readmission	**13**	**1492**	92.2 (87.1 to 95.4)	100 (99.7 to 100)	100 (97.6 to 100)	99.1 (98.5 to 99.5)
	Readmission	No readmission				
DC detects readmission	**144**	**66**				
DC does not detect readmission	**22**	**1426**	86.7 (80.7 to 91.1)	95.6 (94.4 to 96.5)	68.6 (62.0 to 74.5)	98.5 (97.7 to 98.9)

Table 3.4: The readmissions confirmed by adjudication in the HEAT-PPCI trial are compared to the HES method and the direct contact method of identifying readmissions.

3.3.2 Identifying clinical events

Evaluable HES data was obtained for 1754 patients. Figure 3.2 describes the reasons why these data were not obtained for other trial subjects. The full results for this analysis are presented in Table 3.5.

During the index admission, HES correctly identified 1/29 = 3.4% (95% CI 0.6 to 17.2) of the recurrent MIs, 16/22 = 72.7% (95% CI 51.8 to 86.8) CVAs and 143/222 = 64.6% (95% CI 57.9 to 70.4) bleeding events. HES identified 15 recurrent MIs, 1 CVA and 175 bleeding events that were not confirmed by adjudication.

Following discharge, HES identified 2/3 = 66.7% (95% CI 20.8 to 93.9) of recurrent MIs, 4/5 = 80.0% (95% CI 37.6 to 96.3) CVAs and 15/31 = 48.4% (95% CI 31.9 to 65.2) bleeding events. HES incorrectly identified 46 recurrent MIs, 8 CVAs and 7 bleeding events that were not confirmed on adjudication.

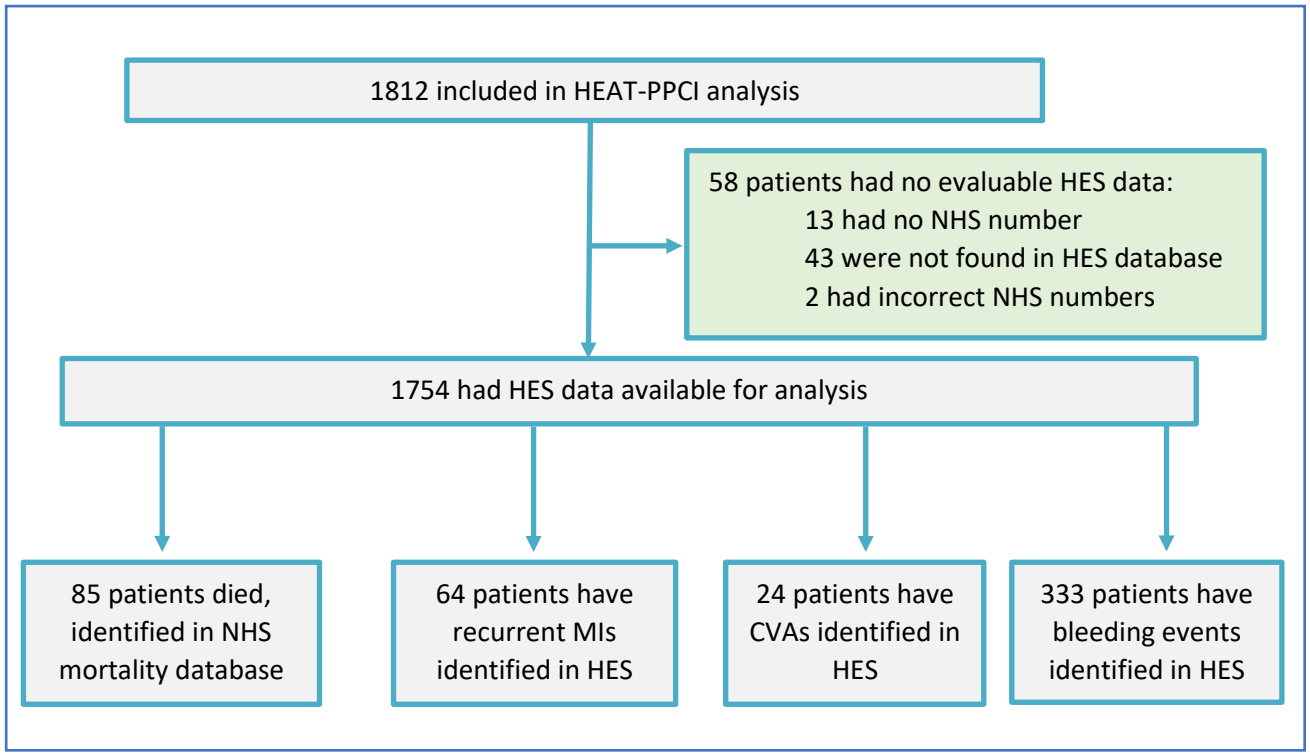


Figure 3.2: Flow diagram outlining the number of patients who were identified by HES as having a clinical event in the 28 days following randomisation

No. of patients with event during the index admission (prior to discharge)	Outcome from Physician Adjudication		Sensitivity (CI)	Specificity (CI)	PPV (CI)	NPV (CI)
	Recurrent MI	No recurrent MI				
HES detects recurrent MI	**1**	**15**				
HES does not detect recurrent MI	**28**	**1710**	3.4 (0.6 to 17.2)	99.1 (98.6 to 99.5)	6.2 (1.1 to 28.3)	98.3 (97.7 to 98.9)
	CVA	No CVA				
HES detects CVA	**16**	**1**				
HES does not detect CVA	**6**	**1731**	72.7 (51.8 to 86.8)	99.9 (99.7 to 99.9)	94.1 (73.0 to 98.9)	99.7 (99.2 to 99.8)
	Bleed	No bleed				
HES detects bleeding	**143**	**175**				
HES does not detect bleeding	**79**	**1357**	64.6 (57.9 to 70.4)	88.6 (86.7 to 90.0)	44.9 (39.6 to 50.5)	94.4 (93.2 to 95.6)
No. of patients with events after discharge						
	Recurrent MI	No recurrent MI				
HES detects recurrent MI	**2**	**46**				
HES does not detect recurrent MI	**1**	**1705**	66.7 (20.8 to 93.9)	97.4 (96.5 to 98.0)	4.2 (1.2 to 13.9)	99.9 (99.7 to 100)
	CVA	No CVA				
HES detects CVA	**4**	**8**				
HES does not detect CVA	**1**	**1741**	80.0 (37.6 to 96.4)	99.5 (99.1 to 99.8)	33.3 (13.8 to 60.9)	99.9 (99.7 to 100)
	Bleed	No bleeding				
HES detects bleeding	**15**	**7**				
HES does not detect bleeding	**16**	**1716**	48.4 (32.0 to 65.2)	99.6 (99.2 to 99.8)	68.2 (47.3 to 83.6)	99.1 (98.5 to 99.4)

Table 3.5: The diagnostic accuracy of the HES data in identifying patients with outcome events during the index admission and in any readmission in the follow-up period is compared to the standard provided by the adjudicated events. By assuming the adjudicated events are accurate, the sensitivity and specificity of each method can be calculated

3.4 Discussion

3.4.1 Main findings of this study

HES and DC are both effective methods of ascertaining readmission in a clinical trial. The results show that the most comprehensive information was obtained when both methods were used together. Compared to DC, HES demonstrated a trend towards better sensitivity and specificity. An analysis of HES coding does not result in rates for specific events that match those from adjudication, with limitations in both sensitivity and specificity.

3.4.2 What is already known on this topic

A recent study showed that the use of HES data in research has increased from 1 publication in 1996 to a total of 520 publications by 2014.[116] This trend may be due to advantages in using HES over more traditional methods of data collection. For instance, HES captures all events, diagnoses and procedures as perceived by the health service. It records what 'the system says has occurred' during a hospital admission. This information may better reflect the true societal impact, both clinical and fiscal, of the outcomes of trial patients. A study looking at the accuracy of using HES data to calculate inpatient costs found that data from HES was accurate when compared to data collected from medical notes review.[117] The mean difference in costs between the two methods was £899 with HES calculating 8% lower costs than medical records. HES data could, therefore, be useful in trials aiming to analyse the economic impact of treatments. Traditional trial follow-up pre-specifies the definitions of a clinical event using thresholds for confirming a diagnosis. This selective approach may not accurately reflect the patient experience or cost to the health service. A study looking at the non-fatal/non-MACE adverse events in a trial compared PCI to coronary artery bypass grafting (CABG) in patients with 2 or 3-vessel coronary artery disease.[118] The results showed that CABG was associated with a greater number of non-

MACE events despite the original trial publication favouring CABG because of a lower number of MACE adverse events.[119] MACE are commonly used as the primary outcome measures in trials of cardiovascular interventions. Since HES identifies any hospital admission, these data could be used in trials wishing to examine the broader physical and psychological impact of admission.

The accuracy of HES data may vary over time between institutions and is dependent on the quality of the clinical coding performed by each NHS trust. In 2013-14 an audit was performed of the clinical coding at 50 acute trusts assessing the accuracy of the ICD-10 codes allocated to each admission. The average error rate, defined as a change to the codes that would result in a change in the payment received by each trust, was 7%.[120] The lowest percentage error for a given trust was 1.1% and the highest 45.8%, demonstrating considerable variability in the accuracy of clinical coding across trusts. A systematic review performed in 2013 looked at studies of the accuracy of HES data when compared to clinical registries and case notes.[121] Although there is no consensus for an acceptable threshold of diagnostic accuracy, the median accuracy of the HES diagnostic codes was 80.3% when compared to notes review or clinical registry data.[122] This review also found that there has been an improvement in the diagnostic accuracy of HES data over time. A recent study by Wright-Hughes et al., assessing the accuracy of HES data in a trial investigating self-harm in adolescents, found that HES identified more than double the number of hospital attendances that were recorded by researchers.[123] In addition, HES identified 62% of self-harm diagnoses compared to diagnoses reported by researchers. This study concluded that HES data is useful in identifying hospital admissions but less accurate in identifying trial-specific clinical diagnoses.

3.4.3 What this study adds

In our study, 153/153 = 100% of the readmissions identified by HES were confirmed by medical notes review. In comparison, 66/210 = 31.4% of readmissions were identified incorrectly by DC. Using HES data removes the need to directly contact any trial patient and is likely to reduce the workload of a trial and, subsequently, the overall cost. When a patient reports a clinical event or readmission, this is thoroughly investigated by the research team, who must review the medical notes to confirm or refute the claim. If HES data is used, the reduction in workload may allow trial centres to divert resources from follow-up to trial recruitment activity.

This study showed that accuracy of HES in identifying clinical events is limited, in terms of the specific diagnostic thresholds that are the norm in clinical trials. The highly specific trial definitions of clinical outcomes in the HEAT-PPCI trial were not developed to be comparable to the ICD-10 codes used in HES. Therefore, the frequency of clinical events identified in HES is likely to differ when compared to physician adjudicated events. For instance, we were unable to stratify bleeding events into degrees of severity because this is not specified in any ICD-10 code. Therefore, regardless of severity, all bleeds were flagged as events. This demonstrates the limitations related to the number and complexity of diagnoses included in the ICD-10. For researchers planning to use HES in a clinical trial, one solution would be to tailor clinical outcomes to specific ICD-10 diagnoses. This would ensure that the pre-specified outcome measure can be identified in the HES database.

I was unable to perform analyses for the outcomes of unplanned target lesion revascularisation because I could not apply the usual range of trial qualifiers to the outcome of additional revascularisation. For example, the ICD-10 codes do not distinguish between planned and unplanned revascularisation. A possible solution would be to ensure future treatment intentions are recorded on the clinical record form of each patient

following the index event. This information could then be used with the HES database to establish if further intervention was planned or unplanned.

HES data only reports admissions that occur in hospitals in England. 2 of the 14 false negative readmission events in HES occurred outside this area. This limits the usefulness of HES data in tracking patients who move outside of England, or those who are admitted to hospitals when abroad. One solution would be to limit study inclusion to those with NHS numbers who are resident in England. However, this limits the recruitment and ability to generalise the results of the study and does not solve the issue of patients who are admitted to hospitals abroad or who live on the border of England and another UK home nation or the Republic of Ireland. There is an equivalent of HES data for Wales and Scotland, which also use ICD-10 codes and should be used in addition to the English HES database.

The use of the NHS number as an identifier is useful in trials with lengthy follow-up because the NHS number remains the same even if a patient moves or changes their name or phone number. However, patients without an NHS number will be missed. In this study, 58/1812 = 3.2% of patients did not return any data in the HES database. There were 13/58 = 22.4% patients who did not have an NHS number and an error was found in the NHS number of 2/58 = 3.4% so the HES database could not identify these patients. This error could be reduced by using a simple check digit code to ensure all NHS numbers are correct at the time of original recruitment. Using more meticulous methods of checking and rechecking the NHS number by the study team would also reduce errors.

3.4.4 Limitations of this study

This study reported very small numbers of clinical events prompting readmission following the index event. For example, only 5 strokes occurred after the index admission. It is therefore impossible to draw conclusions from such numbers. This study assessed

identification of recurrent MI, CVAs and bleeding events. Our assessment of the diagnostic accuracy of HES data is therefore limited to a small number of ICD-10 codes. This limits the generalisability of the results to studies looking at similar outcome measures. More studies should be performed to assess the accuracy of HES data across a wider range of diagnostic codes.

Data from medical notes and physician adjudication were used to confirm the occurrence of a readmission or clinical event. I, therefore, had to assume that the medical notes are accurate and complete. Any errors or omissions in the medical notes would have affected the results.

The adjudication seeks to ensure events are declared to match trial definitions. These may be different from “normal” clinical definitions and from the definitions used to code diagnoses in HES. Therefore, when using the same clinical information, there may be differences in the numbers of outcomes reported by each, creating perceived errors in the HES data.

Suspected readmissions identified by DC and HES were subsequently confirmed or refuted by medical notes review. For confirmation to occur, the suspected readmission had to be initially identified by either DC or HES. Therefore, any readmissions missed by both DC and HES would not have been identified in the HEAT-PPCI trial follow-up. To ensure all readmission events were identified, without using DC or HES, the medical notes of every patient in the HEAT-PPCI trial would have to be reviewed which was beyond the resources of this study.

3.5 Conclusion

A combination of HES and direct contact provides a comprehensive method of follow-up superior to either method alone. Using HES may reduce the resource burden and cost of follow-up in clinical studies. HES cannot accurately identify outcome measure events to match specific trial definitions tested by independent adjudication. However, the numbers of clinical events in this analysis are too small to draw definite conclusions about the accuracy of HES data when used for this purpose. A HES-based approach may also provide information about the general patient experience and total healthcare costs of a trial. Using HES may support patient recruitment and the completeness of follow-up by reducing the workload for both investigators and patients.

Chapter 4: 12-month follow-up from the HEAT-PPCI trial

4.1 Introduction

In Chapter 3, I examined the accuracy of HES data when used to identify non- fatal clinical events in an RCT. There are limitations in both the specificity and sensitivity of this method when compared to events identified and confirmed by review of medical notes. For these types of events, I concluded that using HES to extend follow-up to 12 months would not provide accurate information. In this Chapter, I aimed to identify the mortality rate at 12 months for patients in HEAT-PPCI and categorise cardiovascular and non-cardiovascular causes of death. The rationale for this was: 1) to complete the pre-specified follow-up for the HEAT-PPCI trial by recording the 12-month mortality 2) to use the mortality data as a clinical outcome in the derivation study for the Liverpool MI Risk Model.

4.2 Background

There is continuing debate about the relative safety and efficacy of unfractionated heparin and bivalirudin when used as the peri-procedural systemic anticoagulant at the time of PPCI for the acute reperfusion of myocardial infarction. Several clinical trials and meta-analyses have addressed this issue.[124-132] There is general agreement that the use of bivalirudin is associated with an increased rate of subsequent stent thrombosis but may induce less bleeding when compared to higher dose heparin regimes or the combined use of heparin and glycoprotein IIbIIIa receptor antagonist (GPI) agents.[124-126,130] Trials report conflicting results regarding potential advantages of either agent in terms of short- or medium-term mortality, although it is difficult to compare results because of differential use of GPIs between the treatment groups.

4.3 Methods

In HEAT-PPCI, patients were randomised to heparin (bolus 70U/kg) or bivalirudin (bolus 0.75mg/kg followed by an infusion 1.75mg/kg/h for the duration of the procedure). The design and 28-day results of the HEAT-PPCI trial have been published and discussed in earlier chapters.[115] The protocol for HEAT-PPCI specified an extended follow-up period for analysis of mortality at 12 months. This study reports the results of the pre-specified analysis and a post-hoc analysis for cardiovascular and non-cardiovascular cause of death.

Patients who had died between 28 days and 12 months following randomisation were identified using data from Demographics Batch Service, a national database controlled by NHS Digital. The cause of death for those who died during this period was then ascertained by obtaining death certificates from the national or local registry offices. The cause of death was classified as cardiovascular or non-cardiovascular by an adjudication panel, blinded to treatment allocation. The panel used to review the events was different from the panel used to adjudicate events at 28 days. Cardiovascular causes of death included: myocardial infarction, cardiac failure, arrhythmia, cerebrovascular accident, bleeding events, pulmonary embolism and dissection. All deaths that developed as a direct result of events originating from the index event were considered cardiovascular. Only deaths due to a clear, documented, non-cardiovascular cause (e.g. cancer, road-traffic accident) were classified as non-cardiovascular. Patients with an unknown or uncertain cause of death were counted as cardiovascular deaths for comparative analyses. Sudden death in the absence of a clear alternative diagnosis were declared as “unknown cause” and therefore classified as a cardiovascular death.

To investigate possible associations between 12-month mortality and events that occurred during the index admission, I examined the association between patients who had sustained at least one MACE at 28 days and subsequent mortality. I also compared the

procedural characteristics and hospital admission duration of the two randomised treatment groups.

4.4 Statistical analysis

All analyses were performed according to intention to treat. Data are presented as (n/d = p%) for categorical variables and as means (standard deviations) or medians (interquartile ranges) for continuous variables after testing for normality. I compared categorical data with the chi-squared test (or Fisher's exact test when the absolute number of observed events in any group was five or less). I compared continuous data with the t test (or the Wilcoxon test in the case of non-normal data). I used time-to-event curves to show the mortality data (patients were censored at the time of last follow-up). The protocol pre-specified comparison with the Cox proportional hazards model, unadjusted for other covariates, to calculate hazard ratios (HRs) and 95% confidence intervals. A p value of < 0.05 (2 sided) was considered statistically significant. SPSS version 24 (SPSS Inc., Chicago, IL, USA) was used for analyses.

4.5 Results

Between 7th February 2012 to 20th November 2013, 1829 patients were enrolled into the HEAT-PPCI trial. It was not possible to obtain consent in 13 cases, and in 4 cases participants refused to give, or withdrew consent (Figure 4.1). Therefore, 1812 patients were included in the initial analysis. Vital status at 12 months was obtained in 1805/1812, representing 99.6% of consented participants. Overall mortality at 12 months was 160/1805 = 8.9%. It was not possible to obtain death certificates for 3 subjects and in a

single additional case it was not possible to determine the cause of death from the information presented. For the purpose of this analysis, these cases were assumed to be cardiovascular deaths.

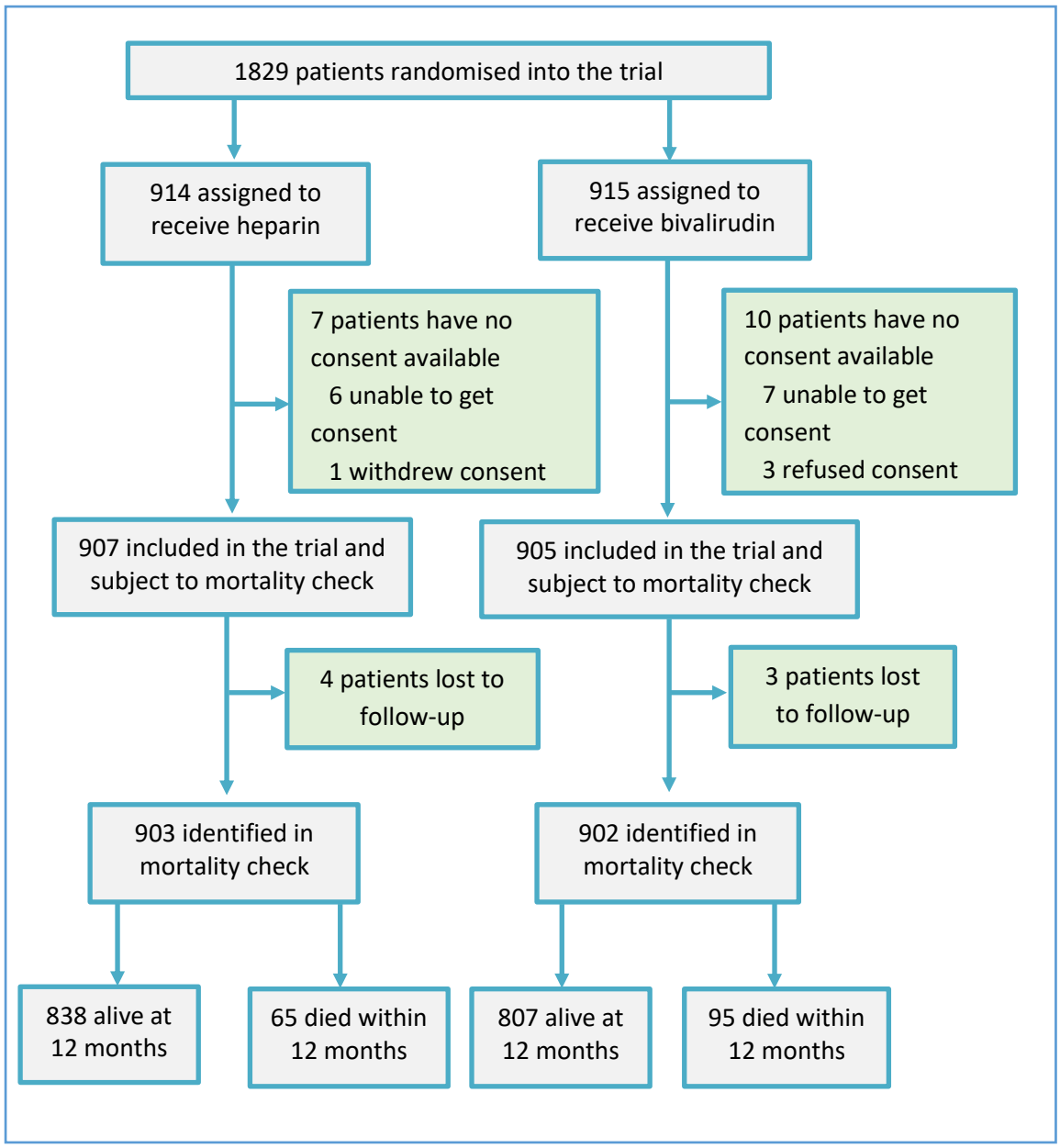


Figure 4.1: Flow diagram showing mortality rates at 12 months for participants in HEAT-PPCI

Table 4.1 illustrates the difference in all-cause, cardiovascular and non-cardiovascular mortality at 12 months between the two treatment groups, excluding patients lost to follow-up at 12 months. The rate of all-cause mortality at 12 months was significantly higher in the bivalirudin group compared to the heparin group (95/902=10.5% versus 65/903=7.2%, RR 1.46; 95% CI 1.08 to 1.98; p=0.013). The rate of cardiovascular mortality at 12 months was also higher, but the difference did not reach conventional levels of statistical significance (71/902 = 7.9% versus 53/903=5.9%; RR 1.34; 95% CI 0.95 to 1.88; p=0.092). The rate of non-cardiovascular mortality at 12 months was significantly higher in the bivalirudin group (24/902=2.7% versus 12/903=1.3%; RR 2.00; 95% CI 1.02 to 3.93; p=0.043).

Mortality at 12 months	Bivalirudin (n=902)	Heparin (n=903)	Absolute risk difference (95% CI)	Relative risk (95% CI)	p value
All-cause	95 (10.5%)	65 (7.2%)	3.33 (0.72 to 5.99)	1.46 (1.08 to 1.98)	0.013
Cardiovascular	71 (7.9%)	53 (5.9%)	2.00 (-0.33 to 4.38)	1.34 (0.95 to 1.88)	0.092
Non-cardiovascular	24 (2.7%)	12 (1.3%)	1.33 (0.04 to 2.73)	2.00 (1.02 to 3.93)	0.043

Table 4.1: All-cause and cardiovascular mortality rates at 12 months: the absolute risk and relative risk are displayed, excluding patients lost to follow-up at 12 months

Figures 4.2 and 4.3 show the event curves and hazard ratios for all-cause mortality and cardiovascular mortality for both treatment groups. The hazard for patients was highest during or immediately after the acute event, with 18/160=11.3% of all deaths over 12 months occurring on the day of randomisation (with an equal distribution between the treatment groups).

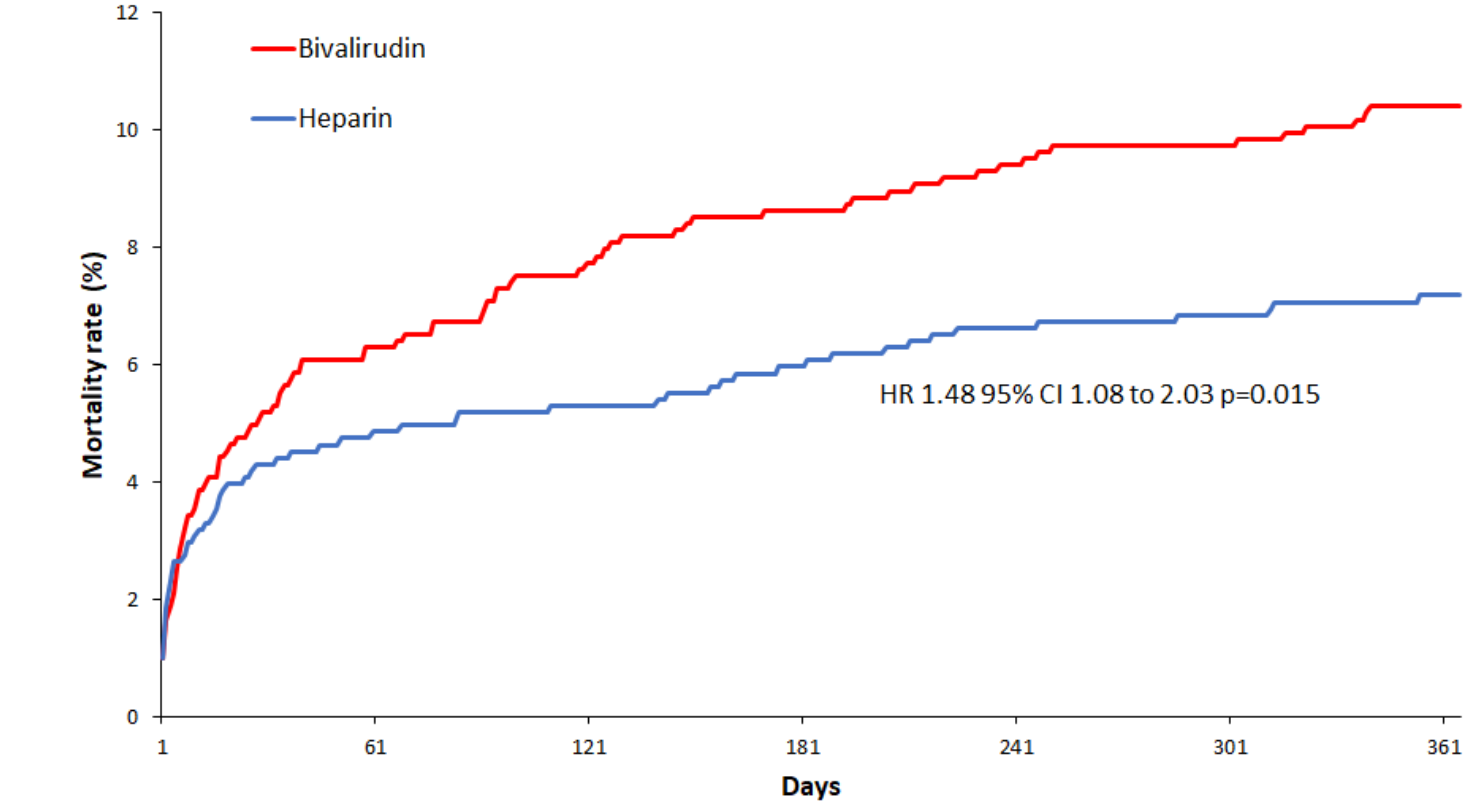


Figure 4.2: All-cause mortality over 12 months

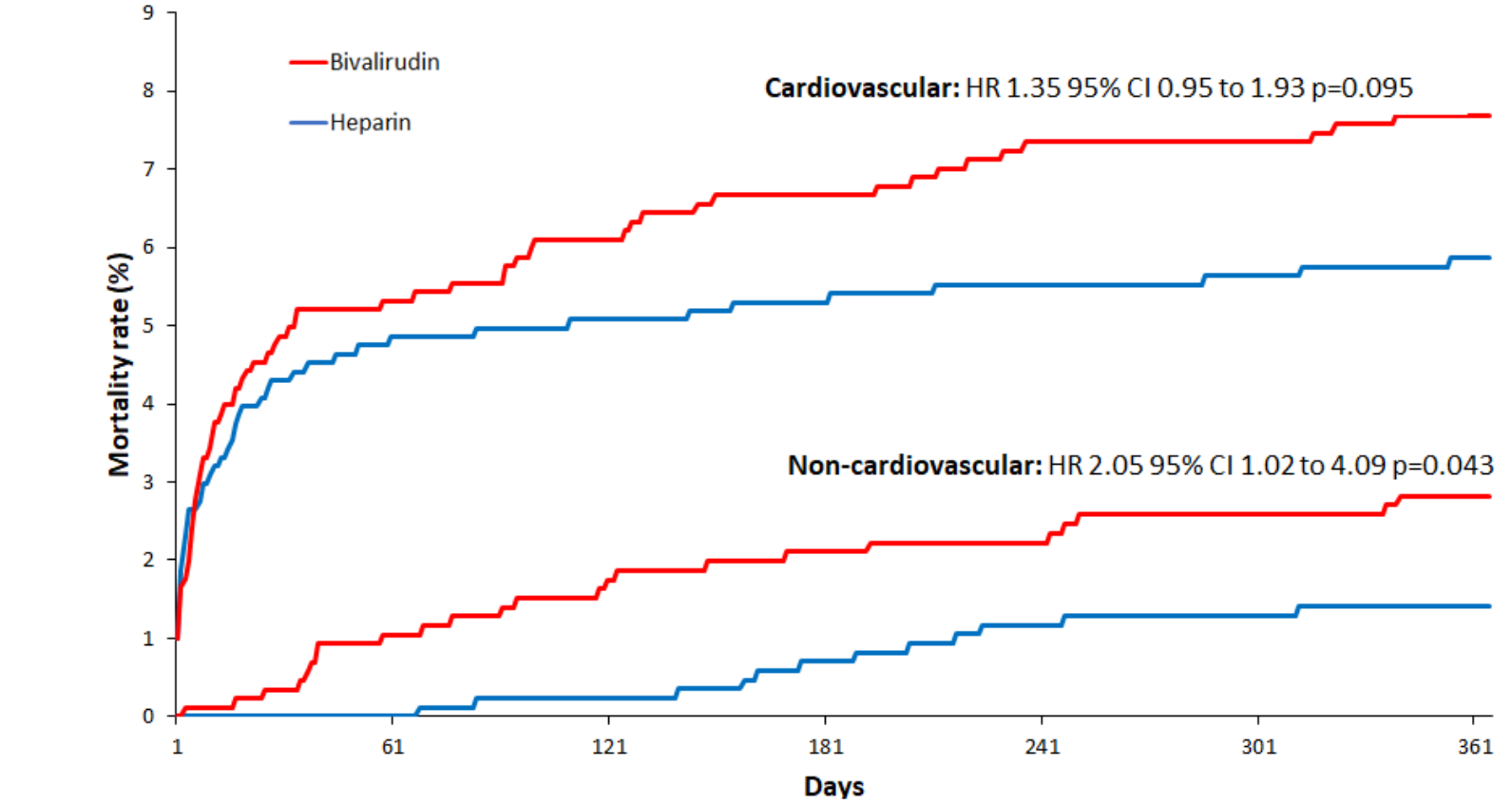


Figure 4.3: Cardiovascular and non-cardiovascular mortality over 12 months.

I wanted to investigate the association between occurrence of non-fatal MACE or major bleeding by 28 days and subsequent mortality. In total, 75 patients died during this 11-month period (49/75 = 65.3% in the bivalirudin group and 26/75 = 34.7% in the heparin group). Table 4.2 shows the number of these patients whose fatal event had been preceded by an adverse event in the index phase, both in terms of the number of all events observed and as a hierarchical analysis for individual patients. The absolute number of events and patients experiencing at least one event is very low and hence there is little evidence of an association between MACE or major bleeding at 28 days and subsequent mortality.

	All-cause mortality from 28 days to 12 months			
	Bivalirudin n=49		Heparin n=26	
	Hierarchical	All events	Hierarchical	All events
Non-fatal MACE at 28 days				
CVA	3 (6.1%)	3 (6.1%)	1 (3.8%)	1 (3.8%)
MI	1 (2.0%)	1 (2.0%)	0 (0.0%)	0 (0.0%)
uTLR	0 (0.0%)	1 (2.0%)	0 (0.0%)	0 (0.0%)
Total events	4 (8.2%)	5 (10.2%)	1 (3.8%)	1 (3.8%)
Bleeding outcomes				
Major bleeds	1 (2.0%)	1 (2.0%)	2 (7.7%)	2 (7.7%)
Non-fatal MACE or major bleed	4 (8.2%)	6 (12.2%)	2(7.7%)	3 (11.5%)

Table 4.2: Comparing rates of non-fatal MACE and bleeding in patients who died between 28 days and 12 months

As a surrogate for complexity of the clinical course during index management, I compared the rates of use of intra-aortic balloon pumps, inotropes, temporary pacing wires, and endo-tracheal intubation. There were no significant differences between the two randomised groups. When comparing the length of overall hospital admission or the time spent in high-dependency areas such as the intensive care unit (ITU) and the coronary care unit (CCU), there was no significant difference between the two groups (Table 4.3).

		Bivalirudin (n=905)	Heparin (n=907)	p value
Intra-aortic balloon pump use*		33/843 (3.9%)	26/843 (3.1%)	0.35
Temporary pacing wire insertion*		16/825 (1.9%)	15/845 (1.8%)	0.80
Inotropic support*		34/841 (4.0%)	31/845 (3.7%)	0.69
Intubation and ventilation*		11/842 (1.3%)	17/844 (2.0%)	0.26
Number of days in hospital: Total		3 (2.5 to 4)	3 (2.5 to 4)	0.25
	ITU†	0 (0 to 0)	0 (0 to 0)	0.73
	CCU‡	1 (0.5 to 1)	1 (0.5 to 1)	0.25
	Ward	2 (1.5 to 3)	2 (1.5 to 3)	0.41

*denominators used for these variables are lower than the total number of patients in the trial due to missing data.

Table 4.3: Additional interventions and admission lengths for the bivalirudin and heparin treatment groups.

4.6 Discussion

4.6.1 Main findings

In this single-centre, randomised trial, bivalirudin was compared to heparin in patients undergoing primary PCI. The rate of all-cause mortality at 12 months was significantly higher in the bivalirudin group. These results differ from other trials comparing heparin and bivalirudin in PPCI.[128,131,133,134]

4.6.2 What is known

The HORIZONS-AMI randomised trial compared bivalirudin monotherapy versus heparin plus a GPI.[131,134] The 3-year follow-up showed a lower rate of all-cause and cardiovascular mortality in the bivalirudin group (all-cause mortality: 5.9% vs. 7.7%; HR 0.75; 95% CI 0.58 to 0.97; p=0.03, cardiovascular mortality: 2.9% vs 5.1%; HR 0.56; 95% CI 0.40-0.80; p=0.001).[134] This trial reported lower rates of major bleeding in the bivalirudin group (6.9% vs 10.5%; HR 0.64; 95% CI 0.51-0.80; p=0.0001). Bleeding is an accepted risk factor for subsequent mortality so any increased bleeding rates may have an impact on mortality.[135]

The MATRIX trial, a large multi-centre RCT comparing bivalirudin monotherapy versus heparin plus discretional GPIs in STEMI and high-risk NSTEMI, also showed lower bleeding rates and lower mortality in the bivalirudin group.[132] (Bleeding events: 2.2% vs 3.3%; RR 0.68; 95% CI 0.51 to 0.91, all-cause mortality: 3.6% vs 4.6%; RR 0.79; 95% CI 0.63 to 0.99, cardiovascular mortality: 2.2% vs 3.0%; RR 0.74; 95% CI 0.55 to 0.99. P values were not reported.) Both HORIZONS-AMI and MATRIX involved differential use of GPIs between the treatment groups created at randomisation. This may have influenced outcomes, including bleeding and subsequent mortality, and makes it difficult to compare the independent effects of the antithrombotic agents under evaluation.

The BRIGHT randomised trial compared bivalirudin monotherapy with heparin monotherapy and with heparin plus GPIs in a three-arm design. This showed that 30-day bleeding rates was lowest in the bivalirudin arm and highest in the heparin plus GPI arm (4.1% vs 7.5% vs 12.3% p=<0.001) but there was no significant difference in mortality rates between the 3 arms at 1-year follow-up. Similarly, the EUROMAX randomised trial, comparing bivalirudin with heparin, with routine or optional use of GPI in the heparin arm, showed a lower rate of major bleeding at 30 days in the bivalirudin group (2.6% vs 6.0%; RR 0.43; 95% CI 0.28 to 0.66; p=<0.001). This may be related to the differential use of GPIs

between the groups (7% GPI use in bivalirudin cases vs 69.1% in heparin cases) but there was no significant difference in all-cause or cardiovascular mortality at 1 year (all cause: 2.7% in each group; RR 1.02; 95% CI 0.72 to 1.45; p=0.92, cardiovascular: 4.0% vs 4.3%; RR 0.93; 95% CI 0.63 to 1.39; p=0.74).[133]

The VALIDATE-SWEDEHEART trial is the largest and most recent trial evaluating bivalirudin versus heparin in PCI.[127] This multi-centre randomised registry-based study compared bivalirudin monotherapy with heparin monotherapy, excluding any patient treated with GPI in either group. The results of 180-day follow-up showed no difference in rates of major bleeding, all-cause mortality or cardiovascular mortality (major bleeding: 8.6% in each group; HR 1.00; 95% CI 0.84 to 1.19; p=0.98, all-cause mortality: 2.9% vs 2.8%; HR 1.05; 95% CI 0.78 to 1.41; p=0.76, cardiovascular mortality: 2.4% vs 2.3%; HR 1.04; 95% CI 0.75 to 1.45; p=0.80). However only 47% of eligible patients were enrolled in the trial and those not enrolled tended to be higher risk than those selected for inclusion. The NAPLES III trial randomised patients undergoing PCI to bivalirudin monotherapy or heparin monotherapy and compared rates of in-hospital major bleeding, showing no significant difference between the two groups (OR 0.78; 95%CI 0.35 to 1.72; p=0.54).[136] Several meta-analyses have been performed comparing heparin and bivalirudin in PCI.[124-126,129] The most recent, by Nührenberg et al., evaluates 12 RCTs comparing bivalirudin and heparin including VALIDATE-SWEDEHEART.[129] This analysis showed that there was no difference in mortality between the groups and the bleeding rates were similar with balanced use of GPI (OR 0.88; 95% CI 0.67 to 1.16; p = 0.35; p for heterogeneity < 0.01).

4.6.3 What this study adds

HEAT-PPCI remains the only trial of antithrombotic therapy in PPCI to achieve near 100% recruitment of all eligible patients. Exclusion criteria was minimal and all adult patients with suspected STEMI who had not previously been enrolled in the trial were included. The

study was more representative of typical practice and mortality rates were comparable to those reported by US and UK registries.[13,137] HEAT-PPCI compared bivalirudin with heparin with use of GPI as bailout only in both groups, resulting in 13% use in the bivalirudin group and 15% in the heparin group. The relative safety and efficacy of bivalirudin and heparin can only be reliably tested if the use of GPIs is similar in both groups.

This study appears to show increased all-cause mortality associated with the use of bivalirudin. If treatment with bivalirudin results in less favourable initial reperfusion during PPCI, or an increased rate of subsequent adverse events - like stent thrombosis - then we might expect that the increased mortality rate in the bivalirudin group would be attributable to cardiovascular causes. Cardiovascular mortality was higher with bivalirudin, but this difference did not reach conventional levels of statistical significance.

I looked at markers of infarct size such as LV function on echocardiography and CK-MB levels examined after the acute event. These were reported in the original publication and showed no significant differences between the treatment groups. In addition, there were no significant differences when we examined clinical markers of case complexity or adverse clinical course, including additional interventions performed or the length and nature of the hospital admission. There was no obvious association between non-fatal MACE and major bleeding at 28 days and subsequent mortality.

It is important to note that about 23% of all deaths were attributed to a non-cardiovascular cause. I observed a significant difference in non-cardiovascular mortality between the randomised groups and this is difficult to explain in terms of pharmacology or clinical plausibility. It is possible that this may represent the play of chance.

In Figure 4.3, the graph shows that the number of cardiovascular deaths increases, demonstrated by a steep curve, levelling off around day 30. This suggest that deaths

occurring in the 30 days after randomisation are most likely to experience a cardiovascular death, likely to be related to the index event. Therefore, 30-day mortality may be a more informative outcome than 12-month mortality because the deaths are more likely to occur due to the acute MI.

4.7 Limitations

The main limitations of HEAT-PPCI trial have been previously described.[115] There are some limitations of this study which should be mentioned. The trial was not powered for 12-month mortality. Therefore, there is poor precision in estimates of hazard ratio for 12-month mortality. Deaths that occurred between 28 days and 12 months following randomisation were determined as cardiovascular or not based on information from the death certificate alone. Medical notes were not available for these patients which may have affected the accuracy of the classification.

4.8 Conclusion

In patients undergoing PPCI for suspected STEMI, the rate of mortality at 12 months was significantly higher in patients treated with bivalirudin compared to heparin. There was a statistically significant difference in non-cardiovascular mortality between the treatment groups which is difficult to explain, raising the possibility that the difference in mortality may have occurred by chance.

30-day mortality may be a useful outcome for the Liverpool MI Risk Model because this outcome is likely to include a higher proportion of deaths that result from the acute event when compared to 12-month mortality.

Chapter 5: Radial versus femoral vascular access in ST-elevation myocardial infarction: the potential for confounding

5.1 Introduction

In developing the Liverpool MI Risk Model, the aim was to conduct an observational study, investigating possible associations between clinical and angiographic variables and outcomes such as death and LV function. I planned to use data from the RCT, HEAT-PPCI, to perform secondary observational studies. This type of work has the potential for confounding. In this chapter, I present an example of the potential for misleading results when considering the effects access site choice and default operator type on the outcomes of PPCI.

5.2 Background

Major bleeding after PCI is associated with increased mortality and major adverse cardiovascular events.[138] The choice of access site may influence the rate of complications and adverse events following primary PCI. Since the introduction of PPCI as the preferred treatment for reperfusion in the acute management of STEMI, there has been a shift in operator preference for radial over femoral access.[3,139,140] However recent trials comparing the two access sites in PPCI have shown conflicting results regarding the incidence of MACE and major bleeding.[141-144]

Previous trials comparing access sites do not consider the default preference of radial or femoral for each operator. Therefore, randomisation of the access site alone does not control for the varying experience of individual operators. The primary aim of this study

was to examine associations between default radial and default femoral operator type, irrespective of final access site chosen.

Despite the increase in radial access (RA) use, femoral access (FA) is still used in certain circumstances by all operators. It is, therefore, important to establish the safety of the FA when used by both femoral and radial operators. A secondary aim of this study was to analyse all FA cases to establish differences between default radial and default femoral operators.

5.3 Methods

The HEAT-PPCI trial recruited from the Liverpool Heart and Chest Hospital. For individual operators (defined as participants in the PPCI service, for the duration of the trial) the annual median PCI case volume was 218 cases (range: 158-283), based on data for the financial year 2013-14.

When patients were recruited into the HEAT-PPCI trial, they were treated by the operator who was assigned to PPCI activity by a rota system. Over time, this creates a near-random allocation of patient-types and risk profiles between operators. Operators in the study had established practice patterns for vascular access that allowed their categorisation as "default femoral" or "default radial" based on the access site used as their natural first preference, accounting for over 90% of all historic and trial-specific activity. The route of arterial access was determined by operator preference and recorded in the trial documentation. This allowed analysis of clinical outcomes by final arterial access site, defined as the route used for completion of the procedure, and by default operator type.

The primary efficacy and safety outcomes in HEAT-PPCI were 28-day MACE and major bleeds, as defined in Chapter 2. In this analysis, I examined the effect of access site and default operator type on 28-day MACE or major bleed, as well as LV function measured on echocardiogram and a single measurement of CKMB release during the index MI.

5.4 Statistical analysis

Data are presented as (n/ d = p%) for categorical variables and as means (standard deviations) or medians (interquartile ranges) for continuous variables after testing for normality. Comparisons between groups were made using chi-square test for categorical variables and unpaired t-test or Mann-Whitney U-test for continuous variables. A p value of < 0.05 (2 sided) was considered statistically significant. SPSS version 22 (SPSS Inc., Chicago, IL, USA) was used for analyses.

5.5 Results

Between 7th February 2012 to 20th November 2013, 1829 patients were enrolled into the HEAT-PPCI trial. It was not possible to obtain consent in 17 cases. Brachial artery was chosen as the final access site in 2 patients. Angiography was not attempted in 6 participants. Of the remaining 1804 cases, RA was used as the final access site in 1472/1804 = 81.6% cases and FA was used in 332/1804 = 18.4% cases (Figure 5.1). In patients where FA access was used, the access site was closed using an internal vascular closure device in 215/332 = 64.8% of cases, manual pressure was used in 105/332 = 31.6% of cases and 12/332 = 3.6% were not closed because the patient died during or shortly after the procedure. Table 5.1 details the baseline characteristics and

demographics of the participants categorised by final access site. There were significant differences between the two groups, with RA cases having a more favourable risk profile in term of younger age, higher systolic blood pressure, better renal function and a reduced incidence of previous MI/PCI/CABG. RA cases were also significantly less likely to have an intra-aortic balloon pump used during the procedure, to require venous access or receive glycoprotein IIb/IIIa inhibitors.

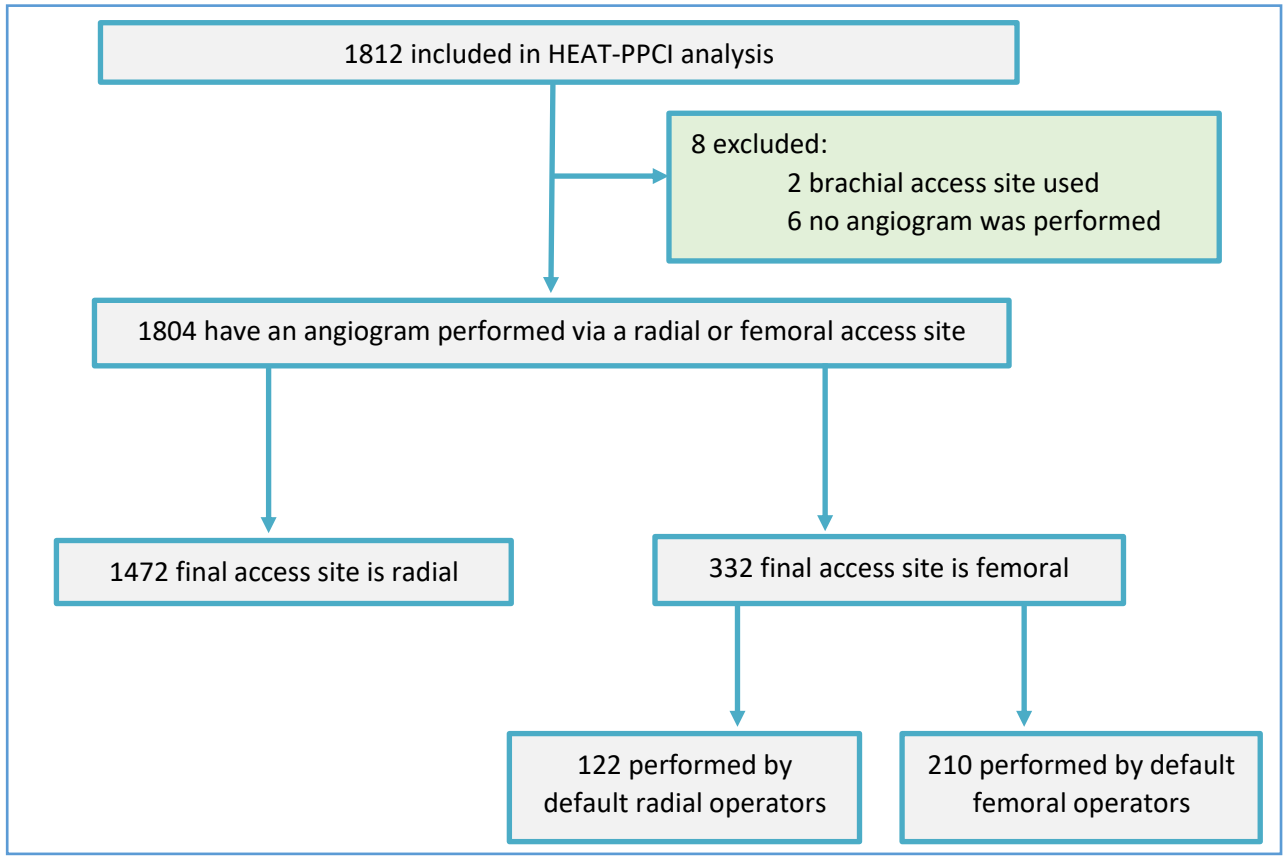


Figure 5.1: Flow diagram outlining the number of participants where radial and femoral access sites were used

	Radial Access	Femoral Access	
	(n=1472)	(n=332)	p value
Baseline Characteristics			
Age (years)	62.4+/-12.9	66.0+/-13.7	<0.001
Body weight (Kg)	80.5+/-17.9	77.7+/-18.4	0.016
SBP on admission (mmHg)	137.4+/-27.4	130.1+/-30.3	<0.001
eGFR (ml/kg/min)	76.0+/-16.0	69.8+/-20.1	<0.001
Haemoglobin (g/dl)	13.6+/-1.6	13.2+/-1.8	<0.001
Diabetes	195/1472 (13.2%)	53/332 (16%)	0.84
Previous MI	154/1472 (10.5%)	59/332 (17.8%)	<0.001
Previous CABG	16/1472 (1.1%)	26/332 (7.8%)	<0.001
Previous PCI	98/1472 (6.7%)	31/332 (9.3%)	<0.001
GPI Use	201/1471 (13.7%)	61/332 (18.4%)	0.03
Venous access Use	32/1472 (2.2%)	33/331 (10.0%)	<0.001
IABP Use	37/1373 (2.7%)	22/305 (7.2%)	0.001

Table 5.1: Baseline characteristics and demographics for radial and femoral access sites

5.5.1 Relationship between final access site and clinical outcomes

Table 5.2 illustrates the clinical outcomes by final access site. The primary efficacy outcome of MACE occurred in a significantly higher number of FA cases

vs. RA cases (36/332 = 10.8% vs. 91/1472 = 6.2% p = 0.003). The 28-day mortality was higher in the FA cases (27/332 = 8.1% vs. 55/1472 = 3.7% p=0.001). The number of major bleeding events was also significantly higher in the FA cases (22/332 = 6.6% vs. 38/1472 = 2.6% p=0.001). The proportion of patients with subsequent severe impairment of LV function was similar in both groups (131/1355 = 10.0% vs. 31/278 = 9.7% p=0.85). The median CKMB level in each group was similar (92 vs 94 p=0.42).

	Radial Access	Femoral Access	
	(n=1472)	(n=332)	p value
MACE	91/1472 (6.2%)	36/332 (10.8%)	0.003
Mortality	55/1472 (3.7%)	27/332 (8.1%)	0.001
Major Bleed	38/1472 (2.6%)	22/332 (6.6%)	0.001
Access site related	5/1472 (0.3%)	7/332 (2.1%)	<0.001
Minor Bleed	118/1472 (8%)	62/332 (18.7%)	<0.001
Access site related	59/1472 (4.0%)	55/332 (16.6%)	<0.001
Any Bleed	153/1472 (10.4%)	81/332 (24.4%)	<0.001
Severe LV function (EF ≤35%)	131/1355 (10.0%)	31/278 (9.7%)	0.85
CKMB	92 (33 to 182)	94 (36 to 201)	0.42

Table 5.2: 28-day clinical outcomes by final access site

5.5.2 Relationship between operator default access site and clinical outcomes

Individual default radial operators performed a similar number of procedures to default femoral operators but, as there were only two femoral operators, in total more radial than femoral procedures were performed, (1575/1804 = 87.3% vs. 229/1804 = 12.7%) (Figure 5.2). The baseline characteristics are detailed in Table 5.3. In procedures performed by femoral operators, there was a significantly higher incidence of previous CABG as well as a higher risk of requiring venous access or receiving GPIs.

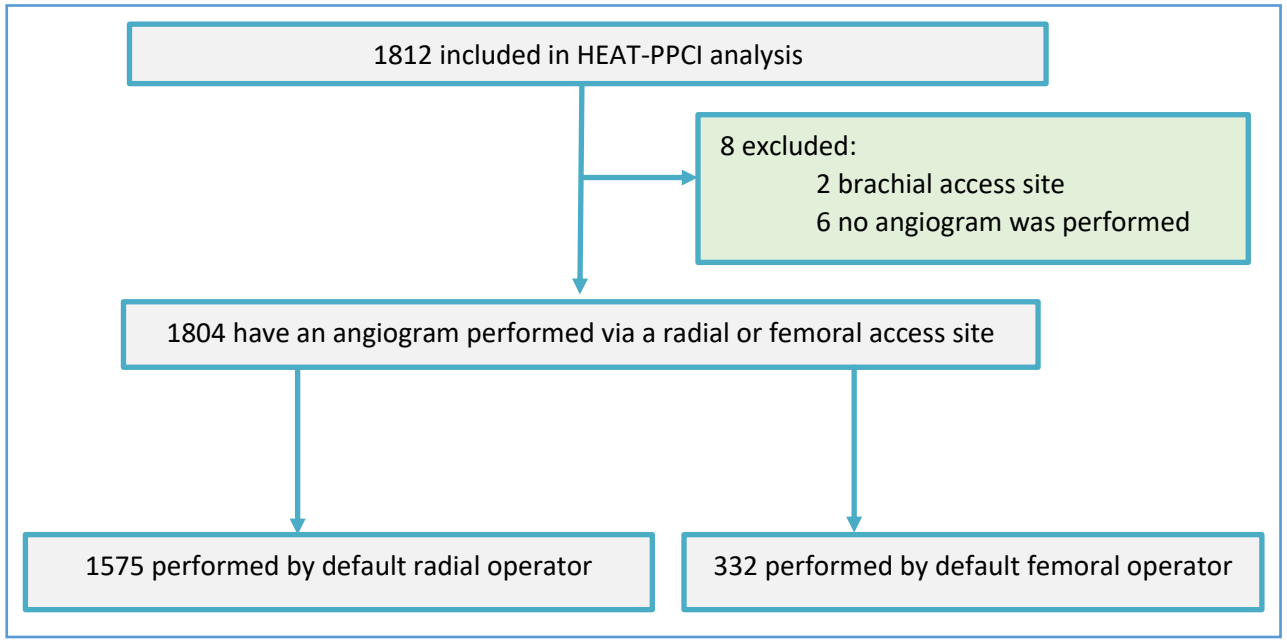


Figure 5.2: Flow diagram outlining the number of cases where access was gained by default femoral and default radial operators

	Default Radial Operators	Default Femoral Operators	
	(n=1575)	(n=229)	p value
Baseline Characteristics			
Age (years)	63.0+/-13.1	63.2+/-13.3	0.86
Body weight (Kg)	79.9+/-17.9	80.8+/-18.3	0.48
SBP on admission (mmHg)	136.0+/-28.1	136.1+/-28.0	0.92
eGFR (ml/kg/min)	75.0+/-16.9	73.8+/-17.4	0.32
Haemoglobin (g/dl)	13.5+/-1.6	13.6+/-1.5	0.59
Diabetes	213/1575 (13.5%)	35/229 (15.3%)	0.75
Previous MI	183/1575 (11.6%)	30/229 (13.1%)	0.66
Previous CABG	30/1575 (1.9%)	12/229 (5.2%)	0.006
Previous PCI	116/1575 (7.4%)	13/229 (5.7%)	0.48
GPI Use	219/1574 (13.9%)	43/229 (18.8%)	0.05
Venous access Use	61/1575 (3.9%)	16/228 (7.0%)	0.003
IABP Use	53/1469 (3.6%)	6/219 (2.7%)	0.47

Table 5.3: Baseline characteristics and demographics for default radial and default femoral operators

Table 5.4 illustrates the clinical outcomes by operators' default choice of access site. There was no significant difference in rates of MACE between procedures performed by default radial vs. default femoral operators (111/1575 = 7% vs. 16/229 = 7% p=0.97). The rate of occurrence of any bleeding event was higher if the procedure was performed by a femoral operator (48/229 = 21% vs 186/1575 = 11.8%), however, the rate of major

bleeding events was not significantly different between the two groups (49/1575 = 3.1% vs. 11/229 = 4.8% p=0.18). The proportion of patients in each group with subsequent severe impairment of LV function was not significantly different (148/1445 = 10.2% vs 14/219 = 6.4% p=0.073). There was no significant difference in the median CKMB release (91 vs 96 p=0.44).

	Default Radial Operators (n=1575)	Default Femoral Operators (n=229)	p value
Outcomes			
MACE	111/1575 (7%)	16/229 (7%)	0.97
Mortality	73/1575 (4.6%)	9/229 (3.9%)	0.63
Major Bleed	49/1575 (3.1%)	11/229 (4.8%)	0.18
Access site related	8/1575 (0.5%)	4/229 (1.7%)	0.055
Minor Bleed	142/1575 (9%)	38/229 (16.6%)	<0.001
Access site related	82/1575 (5.2%)	32/229 (14.0%)	<0.001
Any Bleed	186/1575 (11.8%)	48/229 (21%)	<0.001
Severe LV function (EF ≤35%)	148/1445 (10.2%)	14/219 (6.4%)	0.073
CKMB	91 (33 to 182)	96 (35 to 212)	0.44

Table 5.4: 28-day clinical outcomes by default radial and default femoral operators

5.5.3 Relationship between operator default access site and clinical outcomes in cases where FA was used

A total of 332/1804 cases were performed via FA, with 210/332 = 63.3% performed by default femoral operators and 122/332 = 36.7% performed by default radial operators. Table 5.5 illustrates the baseline characteristics of FA cases performed by radial operators and FA cases performed by femoral operators. Cases where FA was performed by default radial operators had a significantly higher risk profile in terms of more advanced age, lower systolic blood pressure, reduced renal function and increased incidence of previous MI and

PCI. FA cases performed by radial operators were significantly more likely to require venous access or have an IABP used during the procedure.

	Femoral Cases by Radial Operators (n=122)	**Femoral Cases by Femoral Operators** (n=210)	p value
Baseline Characteristics			
Age (years)	70.2+/- 13.8	63.7+/-13.0	<0.001
Body weight (Kg)	71.9+/-18.2	80.7+/-17.8	<0.001
SBP on admission (mmHg)	121.1+/-33.0	135.2+/-27.6	<0.001
eGFR (ml/kg/min)	63.6+/-22.8	73.8+/-19.4	<0.001
Haemoglobin (g/dl)	12.6+/-2.0	13.5+/-1.5	<0.001
Diabetes	22/122 (18%)	31/210 (14.8%)	0.19
Previous MI	32/122 (26.2%)	27/210 (12.9%)	0.002
Previous CABG	14/122 (11.5%)	12/210 (5.7%)	0.06
Previous PCI	19/122 (15.6%)	12/210 (5.7%)	0.003
GPI Use	21/122 (17.2%)	40/210 (19%)	0.68
Venous access Use	28/122(23.0%)	15/209 (7.2%)	<0.001
IABP Use	17/114 (14.9%)	5/191 (2.6%)	<0.001

Table 5.5: Baseline characteristics of participants where FA is used, by default operator type

Table 5.6 illustrates the clinical outcomes for the FA cases by default operator type. FA performed by default radial operators was associated with a significantly higher rate of MACE compared to FA performed by default femoral operators (22/122 = 18% vs. 14/210 = 6.7% p=0.003). Mortality rates at 28 days were significantly higher in the FA performed by radial operators. Major bleeding events occurred with more frequency in the FA cases

performed by RA operators (11/122 = 9% vs. 11/210 = 5.2% p<0.001). Rates of subsequent severe impairment of LV function were significantly higher in the FA cases performed by RA operators (18/107 = 16.8% vs 13/202 = 6.4% p=0.004). There was no significant difference in CKMB release between the two groups (96 vs 90 p=0.774).

	Femoral Access by Default Radial Operators (n=122)	Femoral Access by Default Femoral Operators (n=210)	p value
Outcomes			
MACE	22/122 (18%)	14/210 (6.7%)	0.003
Mortality	20/122 (16.4%)	7/210 (3.3%)	0.001
Major Bleed	11/122 (9%)	11/210 (5.2%)	<0.001
Access site related	3/122 (2.5%)	4/210 (1.9%)	0.71
Minor Bleed	24/122 (19.7%)	38/210 (18.1%)	0.72
Access site related	23/122 (18.9%)	32/210 (15.2%)	0.45
Any Bleed	33/122 (27%)	48/210 (22.9%)	0.39
Severe LV function (EF ≤35%)	18/107 (16.8%)	13/202 (6.4%)	0.004
CKMB	96 (35 to 206)	90 (37 to 184)	0.774

Table 5.6: 28-day clinical outcomes in cases where FA was used, by default radial and default femoral operators

5.6 Discussion

The results of this study suggest that there is no difference in outcomes of MACE (111/1575 = 7% vs 16/229 = 7% p=0.97), major bleeding (49/1575 = 3.1% vs. 11/229 = 4.8% p=0.18) or subsequent severe impairment of LV function (148/1445 = 10.2% vs 14/219 = 6.4% p=0.073) when comparing cases based on operator default preference.

Recent randomised controlled trials (RCTs) comparing radial and femoral access in PPCI show conflicting results. Three large trials have shown that use of RA in PPCI is associated

with lower mortality and fewer bleeding complications.[141,142,145] The largest and most recent trial, MATRIX (Minimising Adverse Haemorrhagic Events by Transradial Access Site and Systemic Implementation of angioX), randomised 8404 patients with acute coronary syndrome to radial or femoral access and reported a significant difference in all-cause mortality (1.6% vs 2.2%, RR 0.72, 95% CI 0.53-0.99; p=0.045) and major bleeding (1.6% vs 2.3%; RR 0.67, 95% CI 0.49-0.92; p=0.013).This has reinforced a trend towards increased RA. RA is now recommended as the preferred access site by ESC guidelines on management of STEMI.[3] Other trials have shown no difference in outcomes between RA and FA.[143,144] There are several possible reasons for these differing results. Firstly, recent advances in technology, such as use of vascular closure devices, have improved the safety of FA.[146] Secondly, RCTs often use different exclusion criteria, definitions of clinical outcomes and doses of antithrombotic medications which may affect the external validity of the results. Thirdly, randomising the access site does not consider the skill level of the operator. A recent observational trial of British Cardiovascular Intervention Society (BCIS) data showed total procedural volume and proportion of procedures undertaken radially by an operator was associated with lower mortality in patients undergoing PPCI via RA.[147] Therefore, the experience and familiarity of the operator is likely to affect the outcomes of the patient. For an RCT to compare the access sites in a useful way, operators would have to be similar and competence in using both RA and FA. Few operators meet this requirement and most RCTs do not consider operator or centre experience. Both MATRIX and RIVAL found that improvements in outcomes in RA cases were only significant when considering centres with high radial volume.[142,145]

Operators usually have a default access preference, with which they are more experienced.[115] This study compared outcomes by default operator type, reflecting real-world practice in a high-volume regional centre. Patients, therefore, benefitted from the clinical judgement exercised by the operator in their choice of access site. The results

showed no significant difference in clinical outcomes between radial and femoral operators, with comparable baseline characteristics in the two groups. Selection bias is likely to be minimal because patients were allocated to the operator at random, based on a rota system. The operator does not receive any clinical details of patients prior to their arrival at the PPCI centre and does not have any influence over patient referrals for PPCI, which are usually initiated by ambulance crews or physicians in local emergency departments. These results suggest that FA may not be associated with increased MACE when performed by experienced femoral operators. In trials where the access site is randomised, complications in FA cases could be overestimated because the operator may have to perform via an access site which they would not have chosen in normal clinical practice. As far as we know, this is the first study analysing outcomes by default operator type.

There have been multiple observational trials examining potential differences in outcomes when comparing access sites in PCI.[140,148,149] However, the circumstances and conduct of the HEAT-PPCI study afford a, possibly, unique opportunity to perform a comparison of the strategies of default femoral and radial access, free from much of the bias that normally confounds observational research. The data used in this study are from an RCT, with rigorous tracking of events and high-quality data collection. HEAT-PPCI used real-world, consecutive, unselected cases, making participant selection more reflective of routine practice.

A simple observational analysis of our data would suggest that the performance of PPCI cases with RA is associated with reduced incidence of mortality, MACE and major bleeding. However, examination of the baseline characteristics of patients grouped by final access site shows a less favourable risk profile in patients who had FA. Default radial operators only attempt femoral access in specific circumstances, many of which are associated with

higher risk. Such reasons include circulatory collapse resulting in an impalpable pulse; radial occlusion associated with previous procedures (a marker of chronic or advanced disease); a requirement to access bypass graft conduits and a need to access the groin for reasons of intra-aortic balloon pump insertion or placement of a temporary wire.

Some studies have suggested that procedures performed through FA by radial operators have higher complication rates.[150,151] This seems logical because increased experience with an access site leads to better outcomes.[147] However, a recent observational study showed that a reduction in the number and proportion of femoral cases is not associated with a loss of femoral proficiency.[152] This may be because although the radial operators are more experienced in RA in uncomplicated cases, in cases where the patient presents in cardiogenic shock or haemodynamically unstable, they perform PCI via FA and therefore maintain competency in the use of FA in complex cases. Our study shows that cases performed via FA had higher rates of MACE, major bleeding and severe LV function when performed by default RA operators, but the risk profile of these patients was less favourable. This suggests that the overall clinical condition of the patient may explain the increased incidence of MACE, major bleeding and poor LV function, rather than the access site used or access skills of the operator.

5.7 Limitations

The post-PPCI measurement of LV function does not consider the LV function of patients prior to the acute event. Patients who have had a previous MI or other cardiac event may have decreased LV function at baseline that is not a result of the index event. Therefore, the post-PPCI LV function may be misleading because we cannot assess the change in LV function that results from the index MI. Data for LV function was missing in 172/1804 =

9.5% patients. This may be because when a patient died early following randomisation, there was no opportunity to measure LV function, resulting in missing LV function data for that patient. The result of this missing data may be to mask any true difference in LV function between the two groups because patients with poor LV function are more likely to die early, before echocardiography can be performed.

The CK-MB measurement was not sampled at a consistent time interval from either symptom onset or hospital arrival and, therefore, it was not guaranteed that this measurement would capture the peak CK-MB release. The preferred method used in other trials is to take several measurements of CK-MB and select the peak CK-MB level as a surrogate marker of infarct size. Only one measurement of CK-MB was taken in HEAT-PPCI, limiting meaningful interpretation in this trial.

The number of cases performed by the default femoral operators (and the number of associated adverse events) is low and hence it is difficult to characterise results in this group with precision. There was no routine use of radiographic guidance, micropuncture or ultrasound imaging for femoral access during the trial. It is likely use of a more fastidious technique would improve outcomes for patients who have procedures performed via FA. This is an analysis of observational data and therefore cannot be used to infer a causal relationship between access site and outcomes. There may be a risk of unmeasured confounding. HEAT-PPCI was a single centre study so the results are not necessarily generalisable to all patient groups or operator experiences.

5.8 Conclusion

Default femoral operators achieved comparable outcomes compared to default radial operators. The less favourable outcomes observed in FA cases may result from its selective

use by radial operators in high risk cases. Further studies are required to establish the differences between RA and FA since the introduction of vascular closure devices and should compare the default operator type as this would better reflect real-world practice.

Chapter 6: Assessing the intra- and inter-observer agreement of angiographic grading systems

6.1 Introduction

In Chapter 2, I described the methods of assessing four selected angiographic variables: TIMI flow, thrombus burden, myocardial blush grade (MBG) and corrected TIMI frame count (cTFC). In this chapter, I evaluate my ability to match my assessments of the variables on repeat testing and compare my assessments against the assessments of a single other observer. I then quantify the intra- and interobserver agreement.

6.2 Methods

Using the random number generator function in Microsoft Excel, I identified a random sample of 100 participants with angiographic data in the HEAT-PPCI database. (See Appendix 3 for the power calculations used to define the sample size).

I analysed each angiogram (primary observer = SB) and assessed the variables at specific time points during the PPCI angiogram (Figure 6.1). On assessing each variable, I assessed the quality of the angiogram (as described in Chapter 2) and, from this, my ability to make an accurate quantitative judgement. When a variable could not be assessed with confidence and was marked as “estimated” or “unable to assess”, the datapoint was excluded from these analyses.

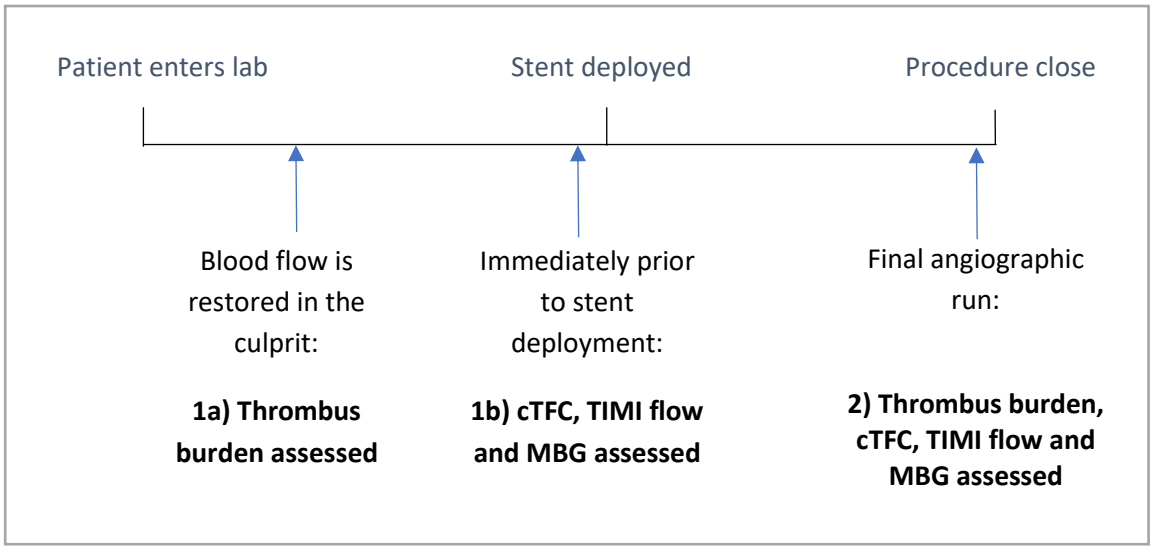


Figure 6.1: The time points when the grading systems were assessed: 1a) and 1b) pre-stent and 2) post-stent

6.2.1 Intraobserver agreement

I repeated an assessment of the variables 2 weeks after performing the initial assessment (primary assessment = SB1, repeat assessment = SB2). The repeat assessments were made on the same 100 angiograms using the same angiographic runs, blinded to the results of the initial assessment. The paired values of each variable were then compared (SB1 vs. SB2).

6.2.2 Interobserver agreement

The angiograms of the 100 participants were assessed a third time by a second observer (CP). CP undertook a period of training to ensure he was competent in assessing the variables as described in Chapter 2. CP reviewed the angiograms of the same 100 participants and assessed each variable using the same angiographic runs used by SB. The interobserver agreement was evaluated by comparing the paired assessments from each run made by the two observers (SB vs CP).

Because the "true" value of each variable was not known, I could not say whether measurements made by SB were more accurate on initial or repeat assessments, or whether assessments made by SB was more accurate than those made by CP. I, therefore, compared the differences between all three sets of paired values (SB1 vs SB2, SB1 vs CP, and SB2 vs CP).

6.3 Statistical analysis

Chapter 7 describes the development of the Liverpool MI risk model. This model was developed from the ordinal angiographic variables once they had been dichotomised into "normal" and "abnormal" assessments (Table 6.1). I also dichotomised the continuous variable cTFC according to an agreed cut-off for normal (<27).[99] The dichotomised variables were relevant to the Liverpool MI risk model, therefore, I assessed agreement based on the dichotomised variables instead of using the full range of grades. CTFC was also assessed as a continuous variable.

	TIMI	**TB**	**MBG**	**cTFC**
Normal	3	0	3	<27
Abnormal	0,1,2	1,2,3,4,5	0,1,2	≥27

Table 6.1: The values of each angiographic variable considered "normal" and "abnormal"

Dichotomous variables were assessed using percentage agreement, Cohen's kappa (k).

Continuous variables were assessed using intraclass correlation coefficient (ICC) and Bland-

Altman (BA) plots. Further explanation of the statistical analyses used in this chapter are detailed in Appendix 3.

6.4 Results

All 100 participants included in the study had an angiogram performed. Of these, 97/100 = 97% had a stent implanted during the PPCI procedure and therefore had two time-points assessed by each observer for TIMI flow, MBG and cTFC. All 100 angiograms had two assessments for thrombus burden because the initial assessment was performed regardless of whether a stent was inserted.

TIMI flow grade was assessed with confidence in 187/195 = 95.9% angiographic runs; thrombus burden 195/200 = 97.5%; cTFC 119/195 = 61.0%; MBG: 148/195 = 75.9%. Figure 6.2 describes the reasons for estimated or absent assessments for each grading system.

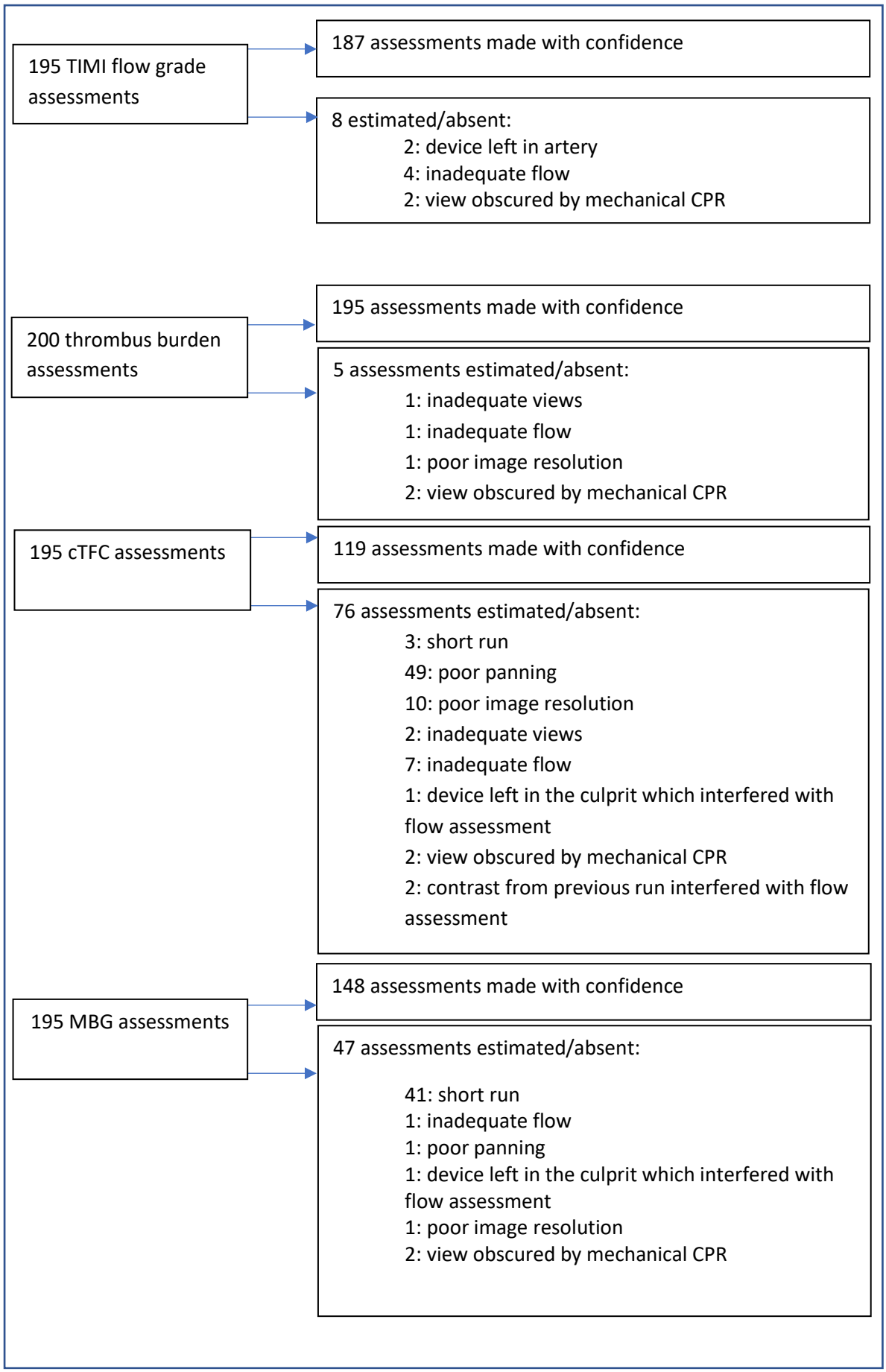


Figure 6.2: The quality of assessment of TIMI flow, TFC, thrombus burden and MBG.

6.4.1 Intraobserver agreement

6.4.1.1 TIMI flow

Table 6.2 and Figure 6.3 illustrate the agreement between assessments of TIMI flow made by SB1 and SB2. The observed agreement (P_o) was 92.5%, with a k statistic of 0.79 (95% CI 0.68 to 0.89), indicating good agreement.

TIMI flow (n=187)						
		SB2		P_o	P_e	k (95% CI)
		TIMI 3	TIMI 0 to 2	92.5%	64.4%	0.79 (0.68 to 0.89)
SB1	TIMI 3	137	2			
	TIMI 0 to 2	12	36			

Table 6.2: A crosstabulation table demonstrating the intraobserver agreement for TIMI flow (categorised as normal or abnormal), and associated k statistic

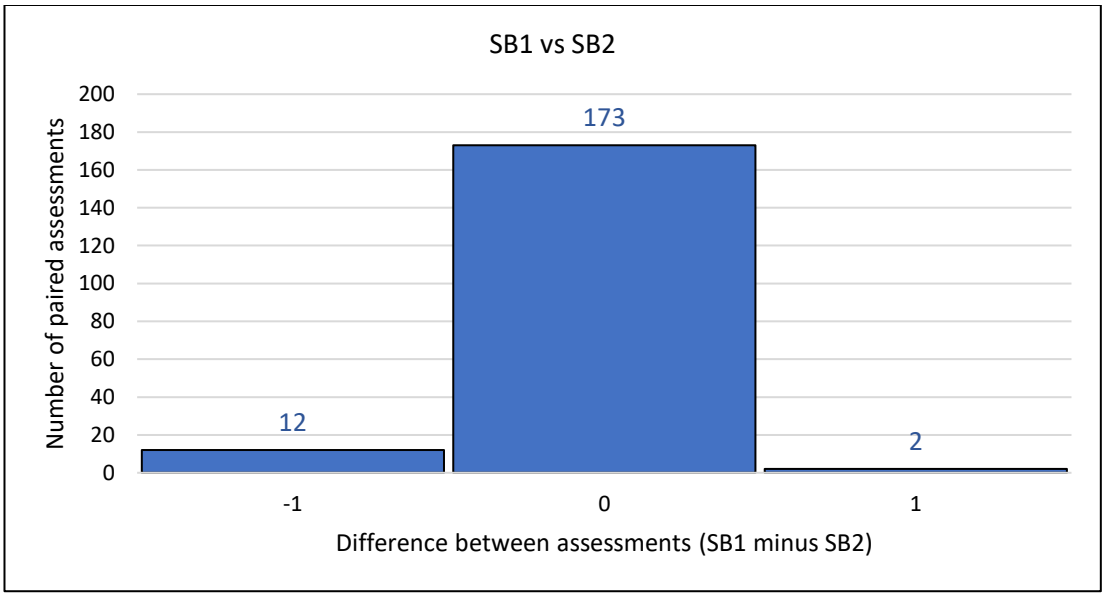


Figure 6.3: A histogram demonstrating the differences in assessments of TIMI flow made by SB1 and SB2

6.4.1.2 Myocardial blush grade

Table 6.3 and Figure 6.4 illustrate the agreement between assessments of MBG made by SB1 and SB2. P_o was 81.1%, with a kappa statistic of 0.40 (95% CI 0.22 to 0.58), indicating fair agreement.

MBG (n=148)						
		SB2		P_o	P_e	k (95% CI)
		MBG 3	MBG 0 to 2	81.1%	68.5%	0.40 (0.22 to 0.58)
SB1	MBG 3	105	12			
	MBG 0 to 2	16	15			

Table 6.3: A crosstabulation table demonstrating the intraobserver agreement for MBG (categorised as normal or abnormal), and associated k statistic

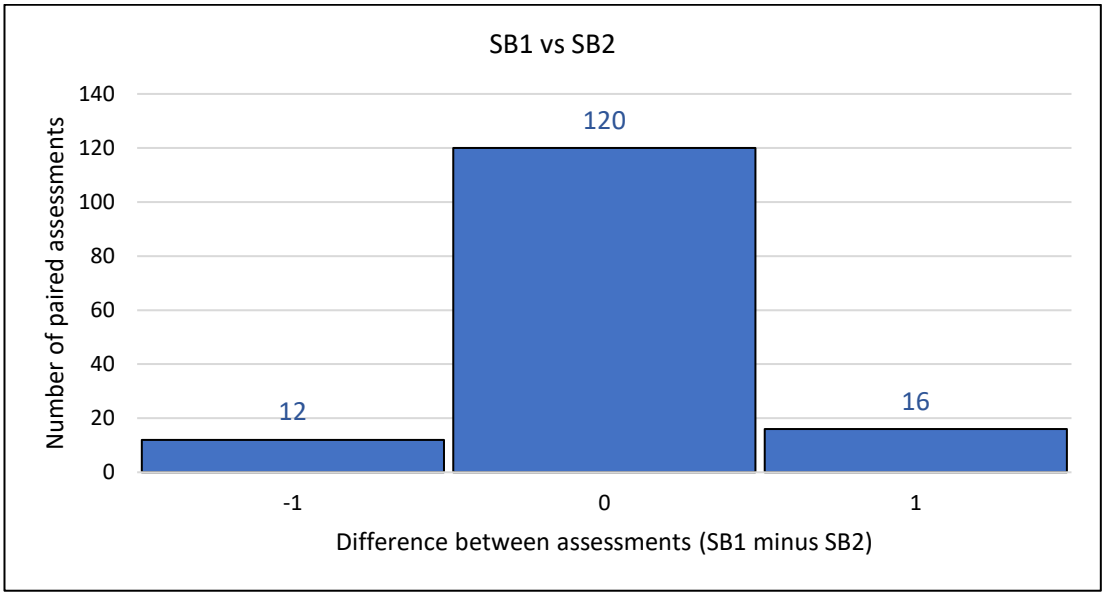


Figure 6.4: A histogram demonstrating the differences in assessments of MBG made by SB1 vs SB2

6.4.1.3 Thrombus burden

Table 6.4 and Figure 6.5 illustrate the agreement between assessments of thrombus burden made by SB1 and SB2. P_o was 97.9%, with a k statistic of 0.96 (95% CI 0.91 to 0.99), indicating excellent agreement.

Thrombus burden (n=195)						
		SB2		P_o	P_e	k (95% CI)
		TB 0	TB 1-4	97.9%	50.0%	0.96 (0.91 to 0.99)
SB1	TB 0	93	2			
	TB 1-4	2	98			

Table 6.4: A crosstabulation table demonstrating the intraobserver agreement for thrombus burden (categorised as normal or abnormal), and associated k statistic

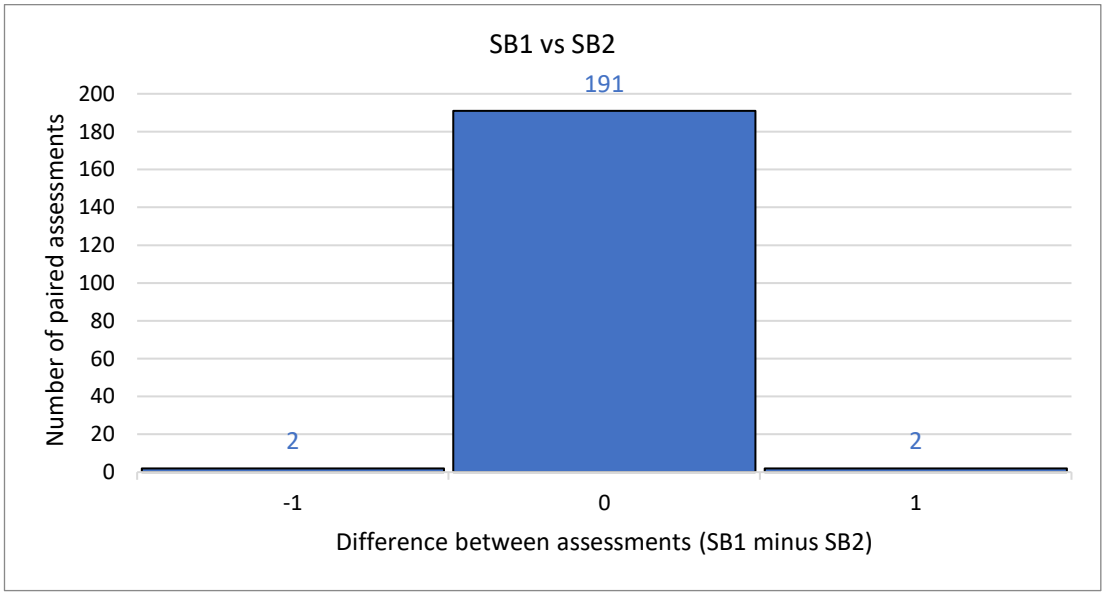


Figure 6.5: A histogram demonstrating the differences in assessments of thrombus burden made by SB1 vs SB2

6.4.1.4 cTFC: as a dichotomous variable

Table 6.5 and Figure 6.6 illustrate the agreement between assessments of cTFC made by SB1 and SB2, once dichotomised into normal (cTFC <27) and abnormal (cTFC ≤ 27). P_o was 95.8%, with a k statistic of 0.89 (95% CI 0.80 to 0.98), indicating excellent agreement.

cTFC (n=119)						
		SB2		P_o	P_e	k (95% CI)
		cTFC <27	cTFC ≥ 27	95.8%	60.3%	0.89 (0.80 to 0.98)
SB1	cTFC <27	84	1			
	cTFC ≥ 27	4	30			

Table 6.5: A crosstabulation table demonstrating the intraobserver agreement for cTFC (categorised as normal or abnormal), and associated k statistic

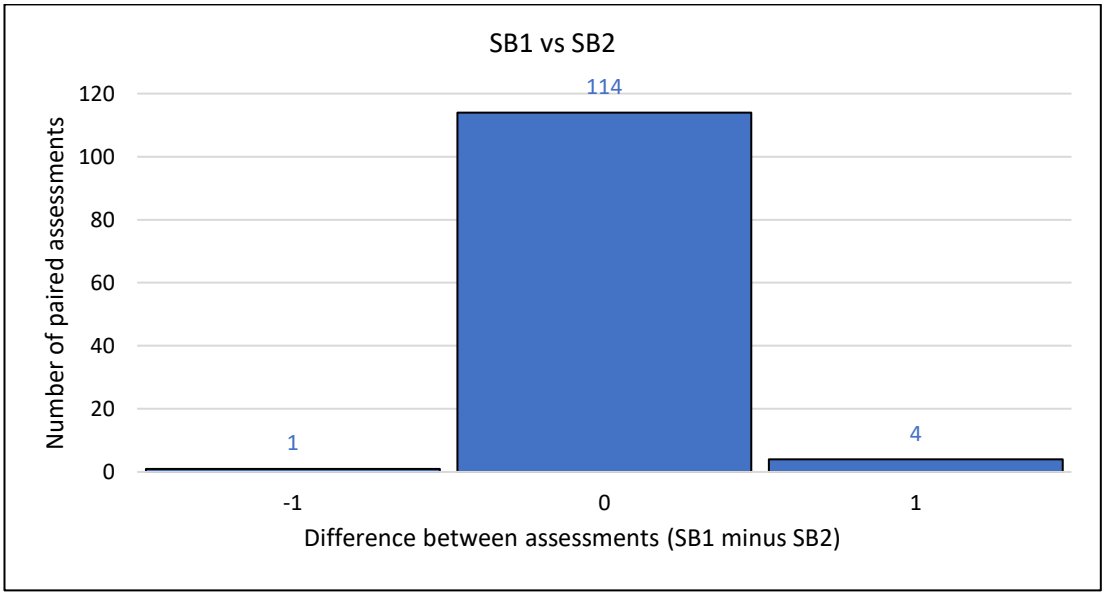


Figure 6.6: A histogram demonstrating the differences in assessments of dichotomised cTFC made by SB1 vs SB2

6.4.1.5 cTFC: as a continuous variable

The intraobserver agreement of cTFC as a continuous variable was assessed using ICC. Comparison of assessments made by SB1 and SB2 gave an ICC of 0.95 (95% CI 0.93 to 0.97) indicating excellent agreement (Table 6.6).

	Intra-class correlation coefficient (95% CI)
SB1 vs SB2	0.95 (0.93 to 0.97)

Table 6.6: The ICC for intraobserver agreement between assessments of cTFC

Figure 6.7 shows the Bland-Altman plot for the differences in assessments made by SB1 and SB2. The Bland-Altman analysis shows the limits of agreement are -7.06 to 8.98.

In our power calculation, I defined *a priori* that the paired measurements of cTFC performed by at different times or by different observers should be within +/- 8 of one another, for 95% of the paired measurements. For a cTFC of 20, this gives a SD of 4 and a mean difference of 0 (+-0.75). The mean difference when comparing SB1 vs SB2 was 0.95 (95 % CI -0.22 to 2.24) and the SD was 4.09. This demonstrates that the agreement is within the limits we considered acceptable for use in clinical practice.

The mean difference was close to zero, with a 95% CI that crossed the line of equality. This indicates a low possibility of bias between the repeated measurements. There are a similar number of values above and below the line of equality, suggesting a constant, random variability in errors of cTFC measurement i.e. differences appear to be independent of the absolute value of cTFC. There are several outliers that fall outside of the limits of agreement although these appear to be random errors, lying both above and below the line

of equality. There is no obvious trend showing a higher frequency of outliers for very high or very low values of cTFC.

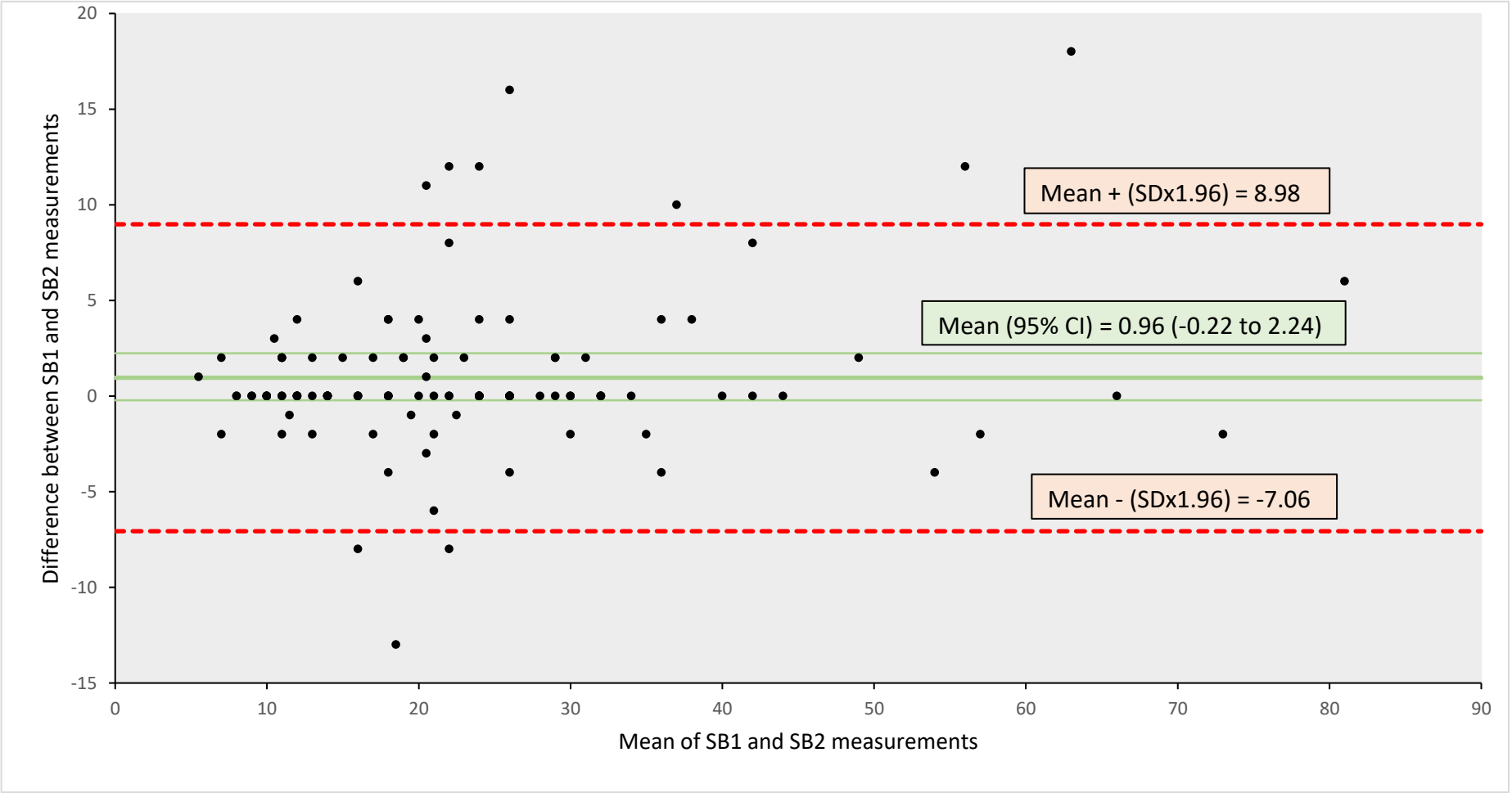


Figure 6.7: A Bland-Altman plot of cTFC measurements performed by SB1 and SB2

6.4.2 Interobserver agreement

6.4.2.1 TIMI flow

Table 6.7 and Figure 6.8 illustrate the agreement between assessments of TIMI flow made by SB1 and CP. P_o was 86.1%, with a k statistic of 0.61 (95% CI 0.48 to 0.75), indicating good agreement.

TIMI flow (n=187)						
		CP		**P_o**	**P_e**	**k (95% CI)**
		TIMI 3	TIMI 0 to 2	86.1%	63.9%	0.61 (0.48 to 0.75)
SB1	TIMI 3	130	9			
	TIMI 0 to 2	17	31			
		CP		**P_o**	**P_e**	**k (95% CI)**
		TIMI 3	TIMI 0 to 2	88.2%	66.9%	0.64 (0.51 to 0.78)
SB2	TIMI 3	137	12			
	TIMI 0 to 2	10	28			

Table 6.7: A crosstabulation table demonstrating the interobserver agreement for TIMI flow (categorised as normal or abnormal), and associated k statistic

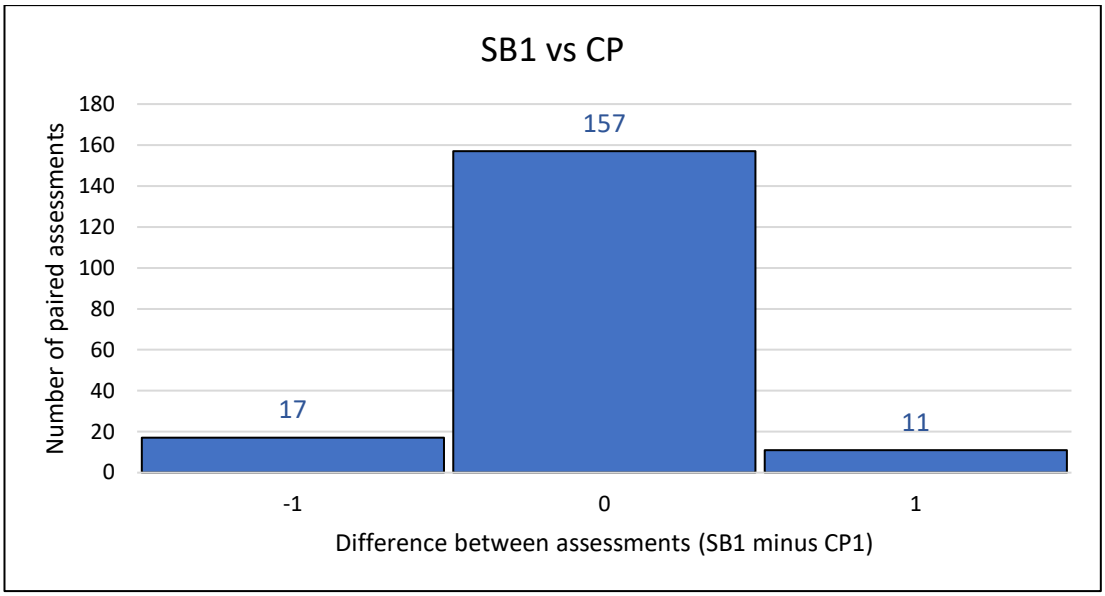


Figure 6.8: A histogram showing the differences in assessments of TIMI flow made by SB1 and CP

Table 6.7 and Figure 6.9 illustrate the agreement between assessments of TIMI flow made by SB2 and CP. P_o was 88.2%, with a k statistic of 0.64 (95% CI 0.51 to 0.78), indicating good agreement.

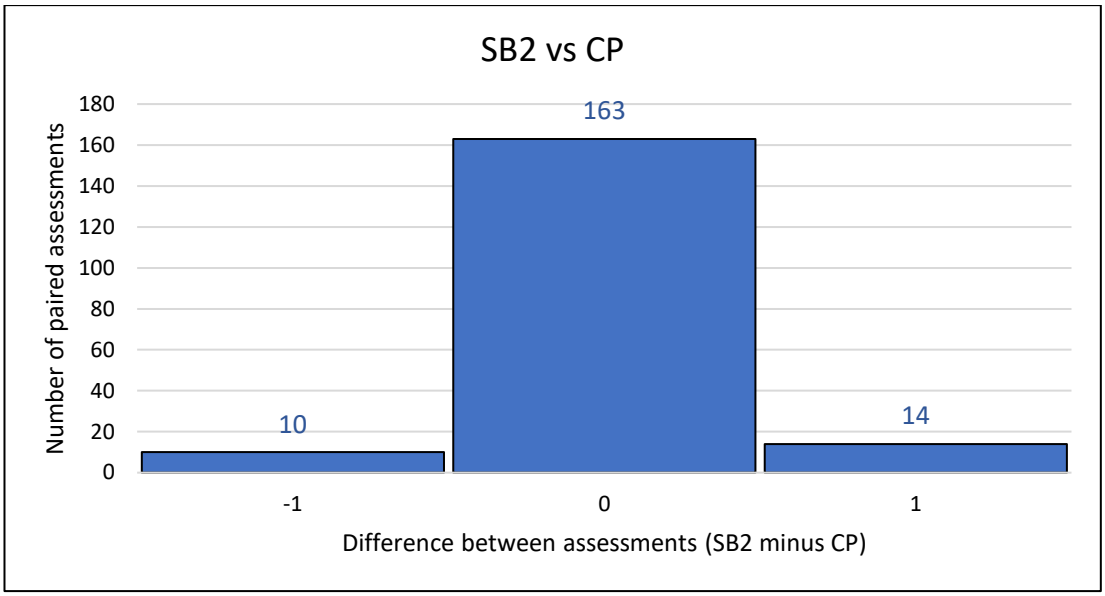


Figure 6.9: A histogram showing the differences in assessments of TIMI flow made by SB2 and CP

6.4.2.2 MBG

Table 6.8 and Figure 6.10 illustrate the agreement between assessments of MBG made by SB1 and CP. P_o was 79.1%, with a k statistic of 0.39 (95% CI 0.21 to 0.57), indicating fair agreement.

MBG (n=148)						
		CP		**P_o**	**P_e**	**k (95% CI)**
		MBG 3	MBG 0 to 2	79.1%	65.7%	0.39 (0.21 to 0.57)
SB1	MBG 3	100	17			
	MBG 0 to 2	14	17			
		CP				
		MBG 3	MBG 0 to 2	**P_o**	**P_e**	**k (95% CI)**
	MBG 3	104	17	81.8%	67.2%	0.44 (0.27 to 0.62)
SB2	MBG 0 to 2	10	17			

Table 6.8: A crosstabulation table demonstrating the interobserver agreement for MBG (categorised as normal or abnormal), and associated k statistic

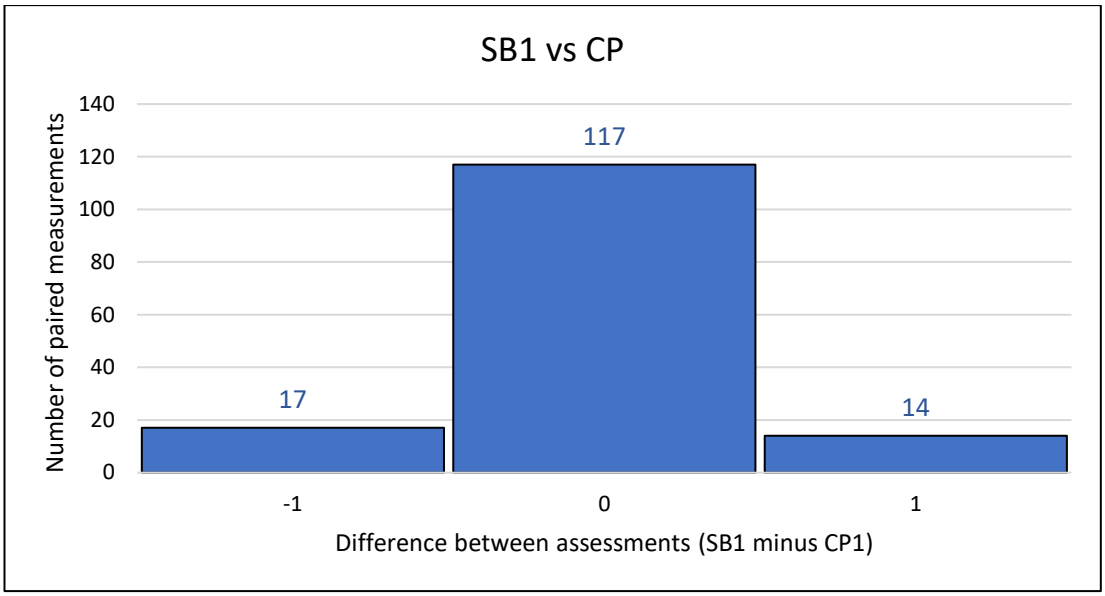


Figure 6.10: A histogram showing the differences in assessments of MBG made by SB1 and CP

Table 6.8 and Figure 6.11 illustrate the agreement between assessments of MBG made by SB2 and CP. P_o was 81.8%, with a k statistic of 0.44 (95% CI 0.27 to 0.62), indicating moderate agreement.

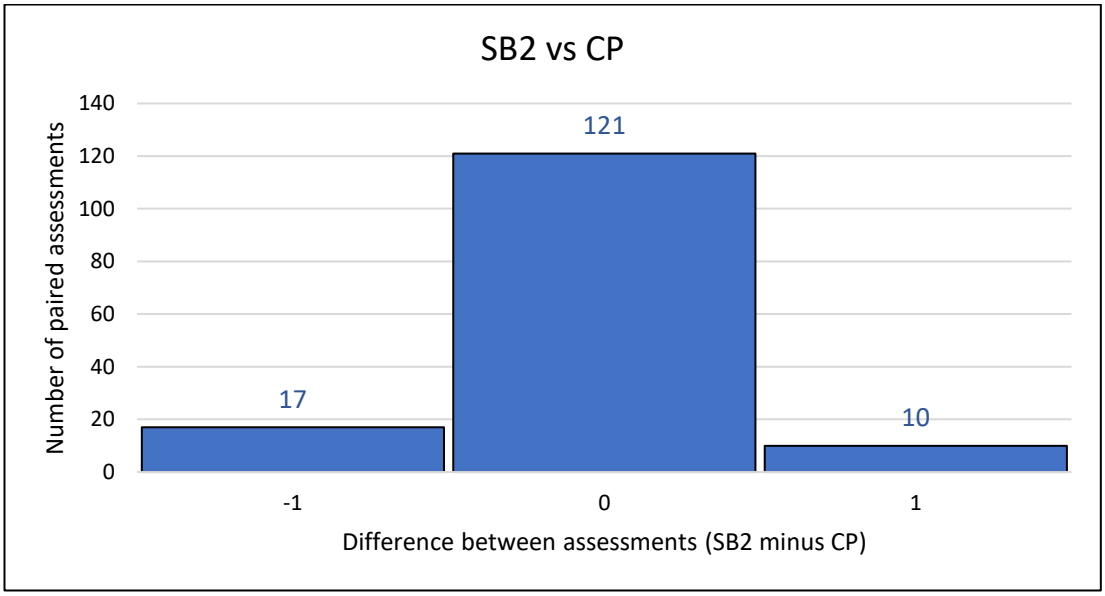


Figure 6.11: A histogram showing the differences in assessments of MBG made by SB2 and CP

6.4.2.3 Thrombus burden

Table 6.9 and Figure 6.12 illustrate the agreement between assessments of thrombus burden made by SB1 and CP. P_o was 97.4%, with a k statistic of 0.95 (95% CI 0.90 to 0.99), indicating excellent agreement.

Thrombus burden (n=195)						
		CP		**P_o**	**P_e**	**k (95% CI)**
		TB 0	TB 1-4	97.4%	50.1%	0.95 (0.90 to 0.99)
SB1	TB 0	92	3			
	TB 1-4	2	98			
		CP				
		TB 0	TB 1-4	**P_o**	**P_e**	**k (95% CI)**
SB2	TB 0	91	4	96.4%	50.0%	0.93 (0.88 to 0.98)
	TB 1-4	3	97			

Table 6.9: A crosstabulation table demonstrating the interobserver agreement for thrombus burden (categorised as normal or abnormal), and associated k statistic

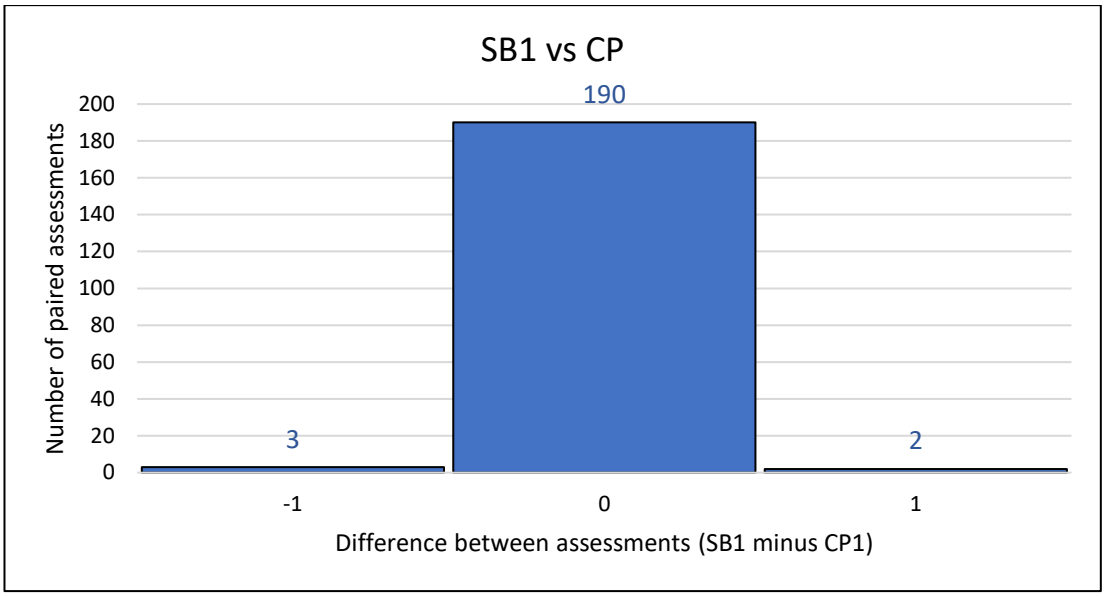


Figure 6.12: A histogram showing the differences in assessments of thrombus burden made by SB1 and CP

Table 6.9 and Figure 6.13 illustrate the agreement between assessments of thrombus burden made by SB2 and CP. P_o was 96.4%, with a k statistic of 0.93 (95% CI 0.88 to 0.98) indicating excellent agreement.

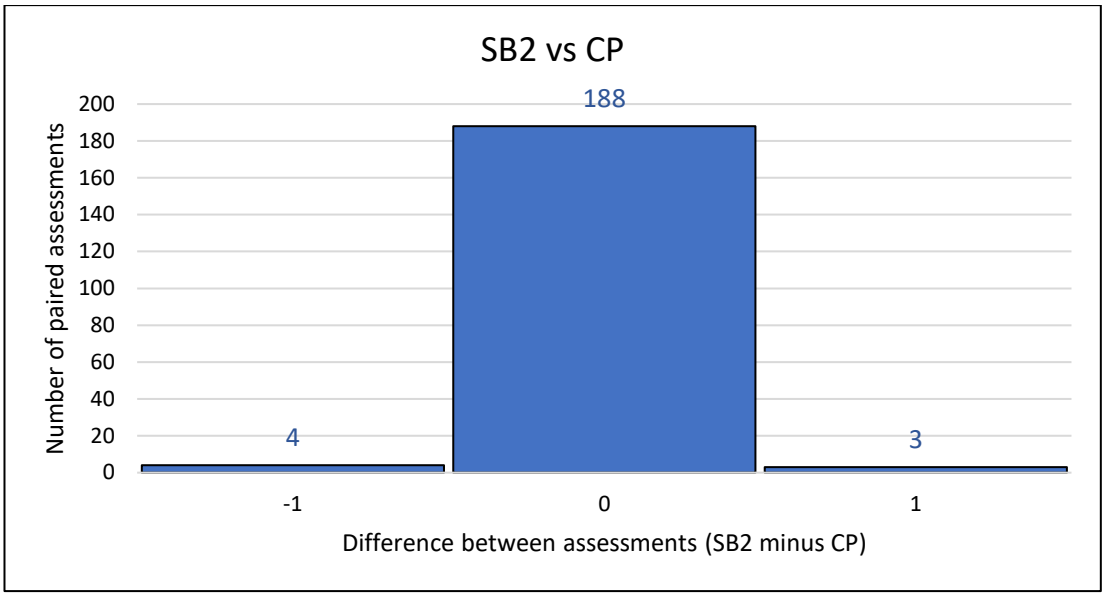


Figure 6.13: A histogram showing the differences in assessments of thrombus burden made by SB2 and CP

6.4.2.4 cTFC as a dichotomous variable

Table 6.10 and Figure 6.14 illustrate the agreement between assessments of cTFC made by SB1 and CP. P_o was 89.9%, with a k statistic of 0.76 (95% CI 0.63 to 0.89), indicating good agreement.

cTFC (n=119)						
		CP		**P_o**	**P_e**	**k (95% CI)**
		cTFC <27	cTFC ≥ 27	89.9%	57.7%	0.76 (0.63 to 0.89)
SB1	cTFC <27	77	8			
	cTFC ≥ 27	4	30			
		CP				
		cTFC <27	cTFC ≥ 27	**P_o**	**P_e**	**k (95% CI)**
SB2	cTFC <27	79	9	90.8%	58.7%	0.78 (0.65 to 0.90)
	cTFC ≥ 27	2	29			

Table 6.10: A crosstabulation table demonstrating the interobserver agreement for cTFC (categorised as normal or abnormal), and associated K statistic

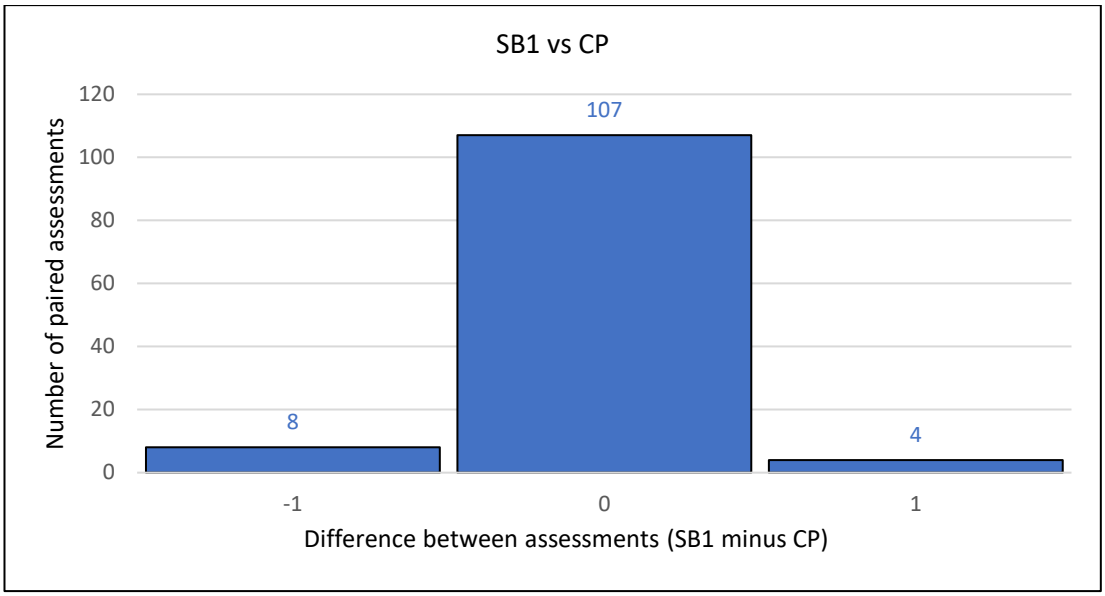


Figure 6.14: A histogram showing the differences in assessments of cTFC made by SB1 and CP

Table 6.10 and Figure 6.15 illustrate the agreement between assessments of cTFC made by SB2 and CP. P_o was 90.8%, with a k statistic of 0.78 (95% CI 0.65 to 0.90) indicating good agreement.

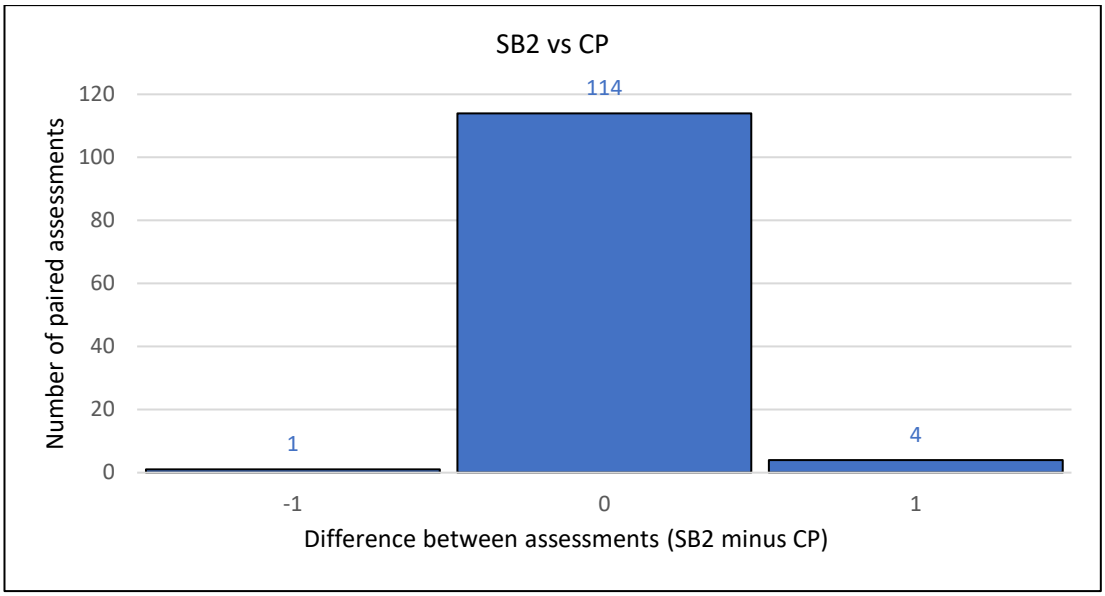


Figure 6.15: A histogram showing the differences in assessments of cTFC made by SB2 and CP

6.4.3.1 cTFC as a continuous variable

The interobserver agreement of cTFC as a continuous variable was assessed using ICC. Comparison of assessments made by SB1 vs CP gave an ICC of 0.81 (95% CI 0.73 to 0.86). SB2 vs CP gave an ICC of 0.80 (95% CI 0.70 to 0.86), indicating good agreement (Table 6.11).

	Intra-class correlation coefficient (95% CI)
SB1 vs CP	0.81 (0.73 to 0.86)
SB2 vs CP	0.80 (0.70 to 0.86)

Table 6.11: The ICC for interobserver agreement between assessments of cTFC

Figure 6.16 shows the Bland-Altman plot for the differences in assessments made by SB1 and CP. The Bland-Altman analysis shows the limits of agreement are -22.86 to 17.45.

The mean difference when comparing assessments made by SB1 vs CP was -2.61. The 95% CI was -4.58 to -0.92 and the SD was 10.24. This demonstrates that the agreement is outside of the limits I considered acceptable for use in clinical practice.

The mean difference was -2.61, with a 95% CI that did not cross the line of equality. This indicates the presence of bias, with CP measuring cTFC values an average of 2.61 higher than measurements made by SB1.

When values of cTFC are less than 40, the variability in errors appears to be random, with values of SB1-CP appearing both above and below the line of equality. However, when the cTFC is above 40, the majority of differences are negative (appear below the line of equality). This indicates that as the value of cTFC increases, CP is consistently measuring

higher values of cTFC than SB1. Two outliers, lying outside of the limits of agreement, occur when CP records values that are significantly higher than those recorded by SB1.

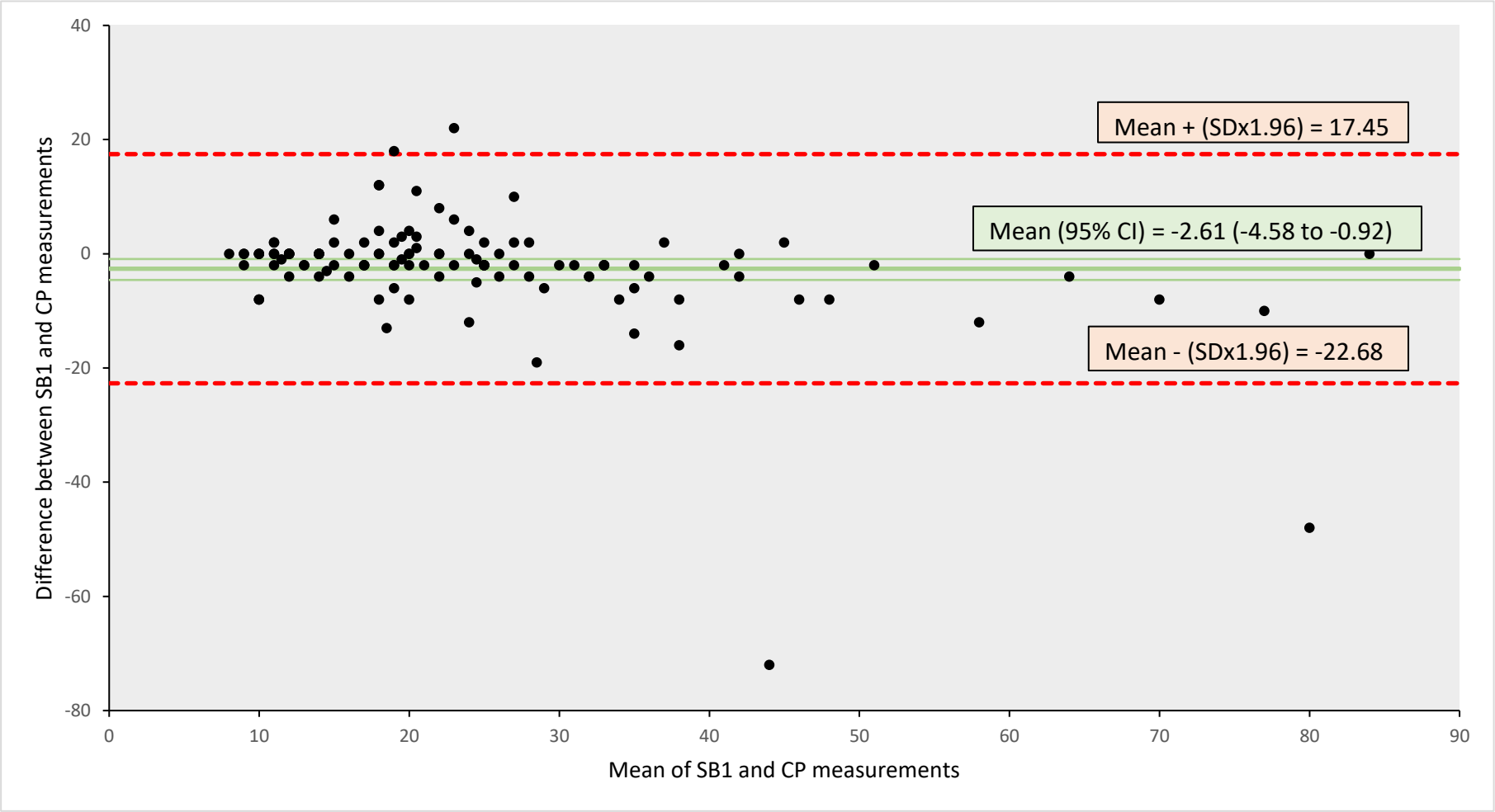


Figure 6.16: A Bland-Altman plot of cTFC measurements performed by SB1 and CP.

Figure 6.17 shows the Bland-Altman plot for the differences in assessments made by SB2 and CP, showing a similar pattern of differences to the BA plot in Figure 6.16 (SB1 vs CP). The Bland-Altman analysis shows the limits of agreement are -23.10 to 15.95.

The mean difference when comparing SB2 vs CP was -3.51 (95 % CI -1.97 to -5.47) and the SD was 9.96. Similar to SB1 vs CP, this demonstrates that the agreement is outside of the limits considered acceptable for use in clinical practice.

The mean difference was -3.51, with a 95% CI that does not cross the line of equality, indicating the presence of significant bias, with CP measuring values an average of 3.51 higher than measurements made by SB2. When the mean of the paired measurements is between 10 and 40, the differences appear above and below the line of equality. However, as the mean cTFC increases, the differences increase and are negative values. This suggests that as the mean cTFC increases, CP consistently measures higher values of than SB2.

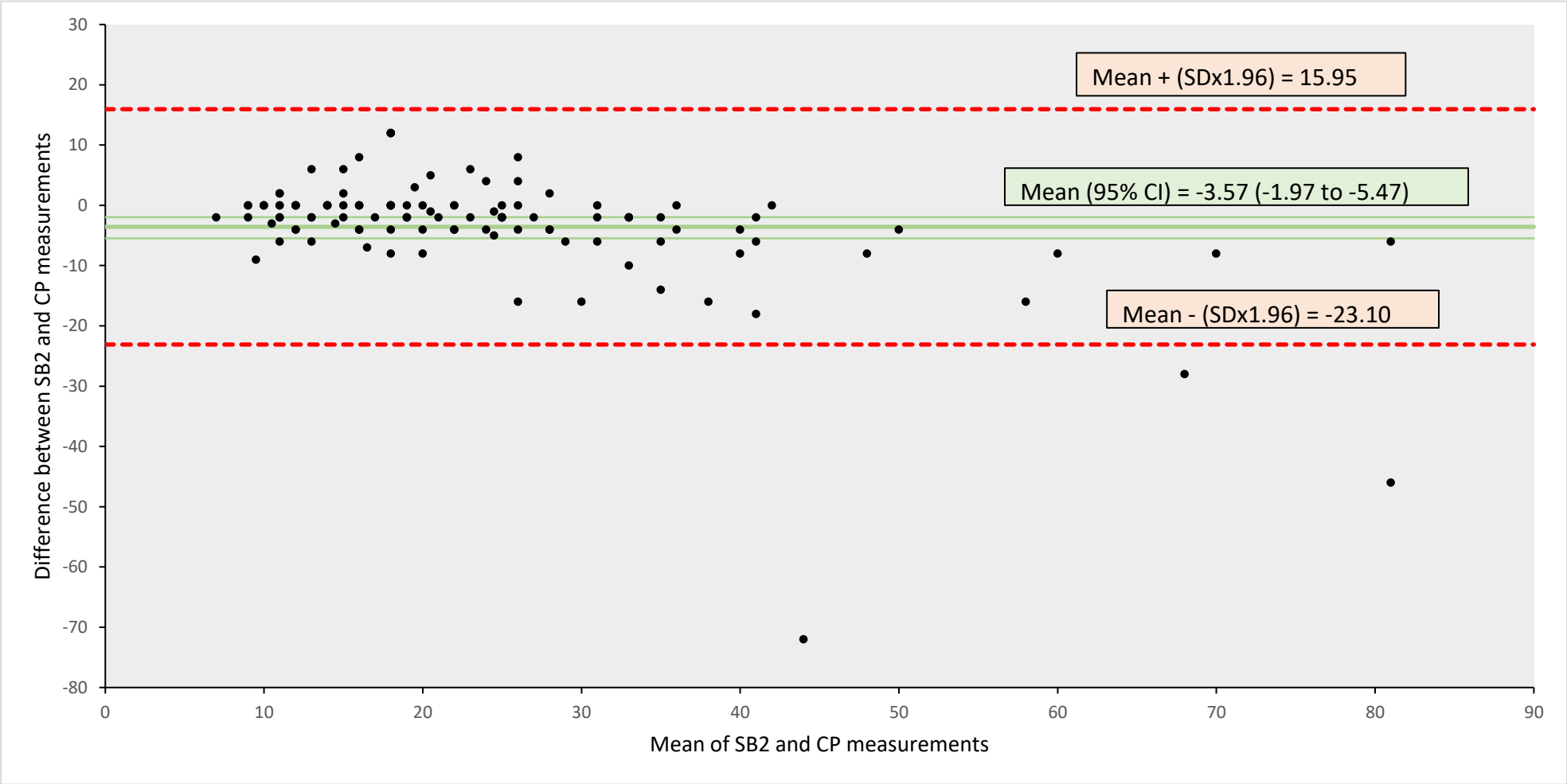


Figure 6.17: A Bland-Altman plot of measurements performed by SB2 and CP.

6.5 Discussion

6.5.1 Main findings

TIMI flow showed good intra- and interobserver agreement (intra: k =0.79; inter: k=0.61 and k=0.64), with a better agreement in the intra- than interobserver analysis. MBG showed fair agreement, with similar k values for both intra- and interobserver analyses (intra: k=0.40; inter: k=0.39 and k=0.44). Thrombus burden showed excellent agreement in both analyses (intra: k=0.96; inter: k=0.95 and k=0.93). Dichotomised cTFC showed good agreement, with better agreement in the intraobserver analysis (intra: k=0.89, inter k=0.76 and k=0.78).

Intraobserver agreement of cTFC as a continuous variable showed excellent agreement when evaluated using ICC and BA analysis (ICC: 0.95; limits of agreement: -7.06 to 8.98; mean difference: 0.95; 95 % CI -0.22 to 2.24) Interobserver analysis showed good agreement when evaluated using ICC (0.81 and 0.80) but did not show clinically acceptable limits of agreement in the BA analyses (-22.86 to 17.45 and -23.10 to 15.95). There was also evidence of bias between observers in the interobserver analyses (mean difference: -3.51; 95 % CI -1.97 to -5.47 and -2.61; 95 % CI -4.58 to -0.92).

6.5.2 What is known from other studies?

Several studies have assessed reproducibility and agreement of TIMI flow, thrombus burden, MBG and cTFC, showing good agreement for all 4 angiographic grading systems.

6.5.2.1 TIMI flow

Although the original authors of the TIMI flow grade did not assess reproducibility between observers, this has been done in several subsequent studies.[26,153] Gibson et al. used Cohen's k to assess agreement in TIMI flow measurements between the study centre and core lab, reporting 89% interobserver agreement and a k statistic of 0.59.[99]

6.5.2.2 Myocardial blush grade

Van't Hof et al. published the original method for assessing myocardial blush.[104] In their paper they report estimations of inter- and intraobserver agreement as percentage agreement (intra: 90%, inter: 97%). Several other studies describe the intra- and interobserver agreement in MBG using percentage agreement alone, with values ranging from 85% to 95% total agreement.[107,110,154] Assessing the percentage agreement alone risks an overestimation because chance agreement is not considered. For example, if we consider that there are 2 grades used to assess the dichotomous variables (normal and abnormal), there is a 1 in 2 chance of selected a single observer selected a grade by chance. The probability that a pair of assessments taken by 2 different observers will agree is 0.50 x 0.50 = 0.25. If there is equal prevalence of each grade within the data, the assessments will agree in 25% of cases simply due to chance. Therefore, reporting k statistics alongside percentage agreement is preferred to reporting percentage agreement alone. Some more recent studies used Cohen's k to quantify agreement between MBG measurements, reporting k values between 0.82 to 0.92.[93,155,156]

6.5.2.3 cTFC

Cohen's k was used by Gibson et al. to assess repeatability between injections of contrast performed minutes apart in the measurement of cTFC. [99] No assessment was made of reliability between different observers. Other studies comparing cTFC measurements have

also used the k statistic, reporting k values between 0.84 and 0.85, as well as reporting the mean difference +- standard deviation of paired measurements of cTFC.[102,103,157]

6.5.2.4 Thrombus burden

The original publication describing thrombus burden also does not report levels of agreement between observers.[94] Several subsequent trials have assessed agreement of thrombus burden using Cohen's k but none have used the original TIMI thrombus grading system that I have used in this thesis.[95,96,158]

6.5.3 What does this study add?

The k values for intra- and inter-observer agreement for MBG are disappointing when compared to k values of the other variables. By examining the distribution of the grades of MBG in the comparison of SB1 and SB2 (Table 6.3) I can see that the decision made by observers to choose normal or abnormal MBG results in a similar number of assessments where the grades agree (SB1 = SB2: 15) and disagree in both directions (SB1<SB2: 17; SB1>SB2: 12). This is likely because the "true" value of MBG is on the border of normal and abnormal, creating errors when one observer decides the blush is normal whereas the other observer decides it is abnormal. The assessments disagree even though both observers thought the blush was on the border of normal and abnormal. This demonstrates how quantisation - splitting up into ordinal categories - creates artefact and noise on the category boundaries. If MBG could be assessed using a continuous scale this would avoid categorising and creating arbitrary boundaries that have little clinical meaning. A continuous measure of MBG would likely improve both the intra- and interobserver agreement as well as the predictive ability of the variable.

As shown in the methods section, the prevalence of each grade within the dataset will affect the k statistic, with high prevalence resulting in a lower k value. Therefore, when interpreting a k statistic we must consider the frequency that each grade occurs. Individual grades within each grading system are likely to occur with differing frequencies depending on the variable, which will influence the k statistics. This makes comparisons of k statistics in between the variables more challenging. To mitigate this limitation, I included assessments from multiple time points throughout the angiogram. Assessments of coronary flow, myocardial perfusion and thrombus burden are likely to change before and after intervention. Therefore, by including assessments of each variable at these two time points, the underlying disease state is likely to be more varied, increasing the heterogeneity of the data. To the best of our knowledge, this is the only study that examines the agreement of the grading systems at more than one time-point on the angiogram.

6.5.3.1 ICC

Using ICC demonstrated excellent reliability in intra- and interobserver measurements of cTFC. ICC is a good measure of reliability when assessing continuous data because it reflects both the degree of correlation and the agreement between measurements.[159] A limitation of ICC is that it is affected by both sample size and sample heterogeneity. Therefore, a small sample with a lack of variability among subjects would result in a lower ICC.

6.5.3.2 BA plots

Several studies use mean difference and 95% confidence intervals to assess agreement for cTFC.[93,102,103] BA analysis has the advantage of displaying the mean difference at different magnitudes of the measured cTFC. Calculating the limits of agreement gives a visual impression of the variability of 95% of the mean differences.[160]

The BA analysis performed to evaluate interobserver agreement (SB1/CP, SB2/CP) showed less than clinically acceptable agreement. For SB1 vs CP, the limits of agreement were -17.45 to 22.68. This is a significantly larger limit than the stated acceptable limits of +/- 8. This variability indicates that the measurements made by the two observers are significantly different and not interchangeable. This disagreement between observers is unlikely to be due to the underlying method of measuring cTFC because the intraobserver analysis shows acceptable agreement on repeat measurements. It is possible that further training for operators who plan measure cTFC during PPCI may improve the interobserver agreement.

The interobserver agreement will have been affected by presence of outliers within the data. The distribution of mean differences in all three distributions of cTFC (SB1/SB2, SB1/CP, SB2/CP) is non-normal, likely in part because of complete agreement (mean difference = 0) making up a high percentage of differences (SB1/SB2: 60/119 = 51%). BA plots can be used for non-normal distributions as they are still likely to have around 95% of observations within 2 standard deviations of the mean.[161] However, several outliers in the data will have contributed to the non-normal distribution and may be responsible for wide limits of agreement, skewing the data and resulting in a mean difference moving away from 0.

For example, when comparing SB1/CP there are 3/119 paired measurements that give mean differences >40 frames, with 116/119 paired measurements giving a mean difference <23 frames. Once the 3 anomalous results were removed from the data, the mean difference (95% CI) becomes -1.28 (-2.29 to -0.22) with a SD of 5.7 and the limits of agreement decrease (-12.46 to 9.89), indicating that when anomalies are removed, the overall agreement is improved.

These outliers are likely to result from the variability between observers in selection of the coronary branch used for the final frame calculation. PPCI angiograms tend to be limited in quality when compared to angiograms performed during elective procedures. This is because the aim of the procedure is to reduce infarct size by delivering timely revascularisation, therefore, the quality of the angiogram obtained may be compromised in favour of delivering speedy treatment. Reduced angiogram quality makes it more challenging to identify the distal branch that should be used for assessing the final frame in the cTFC measurement. Therefore, when it is unclear which branch should be used, or there is more than one suitable branch identified, different observers may select different branches. This results in large differences in paired measurements of cTFC which, in turn, produces a wide standard deviation and limits of agreement on BA analysis. This occurs despite a high percentage total agreement because the anomalies skew the data. When assessing cTFC in future studies, observers should make a note of angiograms where two possible branches could be used for the final frame calculation and employ a third observer to assess cTFC in that run.

A limitation of BA plots is the assumption that the mean of the two values is the “true” value. The error of each observer from the true value is therefore assumed to be the same. One observer may be closer to the true value than the other and the BA plot may give an inaccurate view of the error of each observer. The method of BA analysis defines the limits of agreement but does not determine whether this limit is clinically acceptable, therefore acceptable limits of agreement should be set prior to data analysis.

6.5.4 Limitations of the study design

Sample size was a limitation in this study. For dichotomous variables, I decided a kappa coefficient of the sample population could differ up to 20% from the "true" value of kappa

in the population. If a more accurate value for kappa was required, the sample size would have to be increased.

Only two observers were used in this analysis, limiting interpretation of the agreement to these two observers. If I wanted to generalise the results to a wider population of observers, more observers would need to be trained and included in the study.

A proportion of assessments for each angiographic grading system were excluded due to poor angiographic quality leading to estimated values for the variable. These exclusions will have limited the sample size. Using angiograms that were obtained specifically for the purpose of assessing the selected grading systems would have increased the quality of the angiograms, increased sample size and likely improved agreement between observers.

6.6 Conclusion

The TIMI flow grade, thrombus burden and dichotomised cTFC show good intra- and interobserver variability. MBG showed less agreement than other variables, although this should not result in the exclusion of this variable from predictive models because the percentage agreement was good and kappa statistics have limitations. cTFC as a continuous variable did not show adequate interobserver agreement, with evidence of systematic bias between observers. There is potential for this to improve if observers undergo further training in assessing cTFC.

Chapter 7: Evaluating the association between clinical and angiographic factors, and mortality at 28-days or poor LV function: the development of the Liverpool MI Risk Model

7.1 Introduction

Several scores have been developed to help risk-stratify patients with STEMI, but few can be calculated during the acute event. Development of a risk model that could be applied during PPCI may aid operators' decisions regarding adjunctive reperfusion therapies or additional post-procedure monitoring. This could improve patient outcomes and be cost effective for hospitals. Current ESC guidelines on management of STEMI recommend all patients be admitted to CCU or ITU for a period of monitoring following revascularisation.[3] However, a recent registry study showed that only 16% of STEMI patients develop a complication that requires admission to the ITU.[162] Risk stratifying patients during the acute event could help operators decide which patients are most likely to benefit from admission to ITU, and decide the optimal length of stay in critical care areas.

The aim of this study was to evaluate whether clinical and angiographic variables, recorded during the acute event, could predict a composite outcome of 28-day mortality or subsequent severe impairment of LV function. Any associations could then be used to create a practical tool linking the selected variables with the clinical outcome for use by operators during PPCI.

7.2 Methods

7.2.1 Source of data

This study was a prospective design, conducted on data collected during the HEAT-PPCI trial at the Liverpool Heart and Chest Hospital. Specific information was collected by structured review of existing angiograms. Clinical data on participants were obtained from the existing HEAT-PPCI database.

7.2.2 Participants

Patients recruited into the HEAT-PPCI trial were eligible for the study if they fulfilled the following inclusion criteria:

7.2.2.1 Inclusion criteria

- Angiography performed during the HEAT-PPCI trial.
- Angiographic evidence of MI decided by the operator.
- PCI attempted, defined as the use of a guidewire, balloon catheter, thrombus aspiration catheter or stent

7.2.2.2 Exclusion criteria

- Patients with coronary artery bypass grafts
- Patients identified on angiography as having more than one culprit lesion
- Patients who experienced a recurrent MI within 28 days following the acute event
- Patients who experienced in-lab MACE or require emergency surgery prior to PCI completion
- Patients where the culprit vessel was the RV branch

7.2.3 Clinical outcomes

Clinical outcomes collected in HEAT-PPCI included all-cause mortality at 12 months, MACE at 28 days, LV function prior to discharge and CK-MB release. The primary outcome used in this study was a composite of subsequent severe impairment of LV function (defined as an ejection fraction ≤ 35%) or all-cause mortality at 28 days following randomisation.

LV function was included in the composite outcome because it is an important prognostic marker, with a decreased ejection fraction (EF) predicting mortality after STEMI.[25,163-165] LV function also predicts infarct size following MI and is one of the diagnostic criteria for heart failure.[25,166] When accompanied by symptoms of heart failure, patients with poor LV EF report severe impairment of quality of life, although several trials show that LV EF alone is not an independent predictor.[167-171]

LV function was measured in 95.1% participants. LV function was measured using transthoracic echocardiography and recorded as the following categories of ejection fraction (%):

- Normal: ≥55
- Mild impairment: 45-54
- Moderate impairment: 36-44
- Severe impairment: ≤35

All-cause mortality was recorded for HEAT-PPCI participants up to 28 days. In Chapter 4, I extended follow-up and explored the cardiovascular and non-cardiovascular deaths in the HEAT-PPCI trial up to 12 months. I noted that the hazard was highest immediately following the acute event, and most cardiovascular deaths occurred during the first 28 days. Hence, I selected 28-day mortality as the outcome measure in this study. The use of death certificates gave an indication as to the cause of death in patients who survived to 28 days

but had died by 12 months, however, it had limitations as a method of determining cause of death. I, therefore, chose to use all-cause mortality at 28 days as the outcome.

Major adverse cardiovascular events (MACE) were recorded at 28-days following the index procedure. These included all-cause mortality, stroke, recurrent MI and unplanned revascularisation. Stroke, recurrent MI and unplanned revascularisation are unlikely to be associated with infarct size during the acute event and were therefore not included as outcome measures.

An increased CK-MB value reflects a greater size of infarct in patients following AMI.[21] CK-MB was measured in 94.8% patients with confirmed MI on angiography but, as discussed in Chapter 5, was not sampled at a consistent time interval and was unlikely to consistently capture the peak CK-MB release. The available data on CK-MB was unlikely to be a reliable surrogate marker for infarct size and was not used as an outcome in this study.

7.2.4 Selection of predictors

Table 7.1 illustrates the clinical and angiographic variables that were considered potential predictors for inclusion in the study.

Clinical variables:	Angiographic variables:
Age	TIMI flow
Gender	cTFC
Culprit vessel	Thrombus burden
	MBG

Table 7.1: Variables considered for use in the study

7.2.4.1 Clinical variables

Data regarding the clinical variables (age, gender, culprit vessel) were taken from the HEAT-PPCI database.

7.2.4.2 Angiographic variables

The angiographic variables included in this study were TIMI flow, thrombus burden, cTFC and MBG, all as dichotomous variables. The PPCI angiogram of each eligible participant was analysed and the angiographic variables assessed in the final angiographic run at the end of the PPCI procedure (Figure 7.1). The methods of assessing the angiographic grading systems that were used in this study are described in Chapter 2.

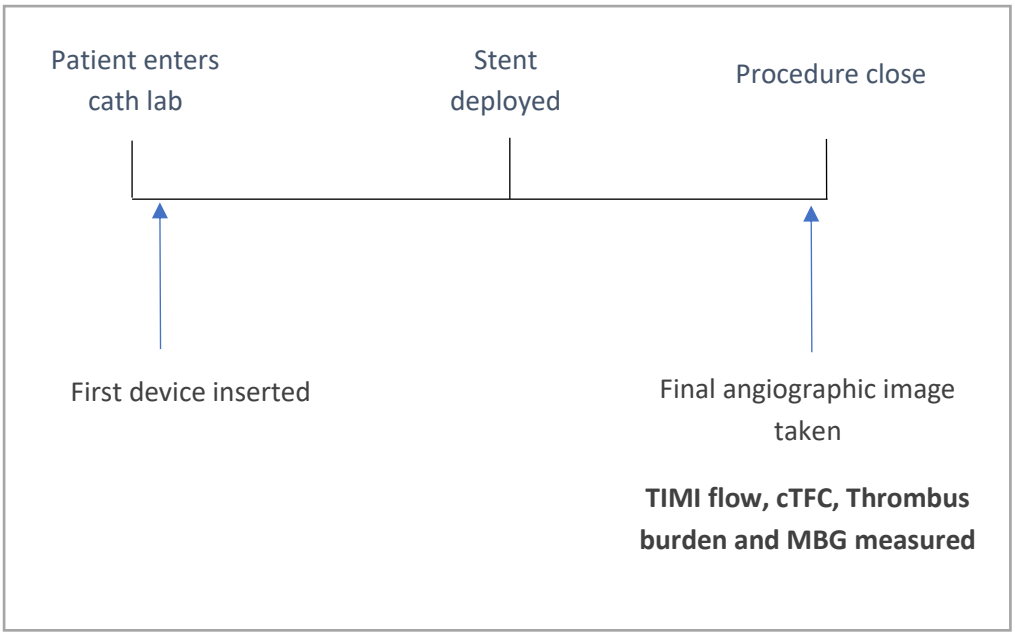


Figure 7.1: A timeline of the index procedure in HEAT-PPCI demonstrating the time-point for assessment of angiographic variables.

When recording the data on the angiographic variables, I was blinded to associated clinical characteristics and clinical outcomes for a given participant. It was not possible to blind results of other angiographic variables as I frequently used the same angiographic runs to assess more than one variable.

For each angiographic variable assessed, I made a judgement on the quality of the assessment and recorded this in the database.

7.2.5 Sample size

The sample size in HEAT-PPCI was powered to uncover differences between antithrombotic medications in PPCI which is not relevant to this study. Therefore, I needed to check that the sample size in HEAT-PPCI would be large enough for the purposes of this study. HEAT-PPCI included 1812 patients in their analysis, 1803/1812 = 99.5% had an angiogram performed for suspected STEMI.

An accepted "rule-of-thumb" when developing a risk model is to use the event per variable (EPV) ratio to determine the sample size.[172] The EPV is the number of events in the data divided by the number of regression coefficients in the risk model. One study suggests that an EPV of 10 or more is needed to avoid overfitting the risk model. Therefore, a dataset should contain complete data on at least 10 times the number of patients who experience an event as the number of predictors in the model. I estimated at least 1000 complete datasets would be available from HEAT-PPCI and patient records. HEAT-PPCI reported a rate of all-cause mortality or subsequent severe impairment of LV function in 215/1812 = 11.8% patients. Therefore, our outcome event will occur in approximately 120 patients, giving good statistical power for up to 12 predictors.

7.3 Statistical Analysis

Categorical data was compared using the chi-square test. Continuous variables are presented as median and interquartile ranges and were compared using the Mann-Witney-U test. For all analyses a two-sided $p < 0.05$ was considered statistically significant. I identified 7 potential predictors (3 clinical and 4 angiographic) for inclusion in the study, however, it did not seem practical for operators to have to calculate 7 variables during an emergency procedure. The inclusion of too many variables can lead to a complex model

which is overfitted to the specific features of the sample, rather than reflecting the general population.[172] Therefore, I aimed to reduce the tool to include only the minimum number of predictors that would still provide an accurate estimate of the outcome. Selected clinical and angiographic variables were examined by univariate logistic regression analysis for their relation to the outcome. TIMI flow, thrombus burden, culprit location, cTFC and MBG were dichotomized and treated as binary variables. Values for angiographic variables were only included in the analysis if they had been assessed "with confidence". Significant univariate predictors of the outcome, using an accepted arbitrary cut-off of p=0.25, were selected for the final multivariate logistic regression analysis used to derive the risk prediction model.[173]

7.4 Results

1812 patients entered the lab in the HEAT-PPCI trial. Of these, 1479 had confirmed MI on angiography, with 1410 receiving a completed PCI procedure with no other exclusion criteria (Figure 7.2). A total of 1371/1410 = 97.2% patients had complete information on the composite outcome of death at 28 days or subsequent severe impairment of LV function.

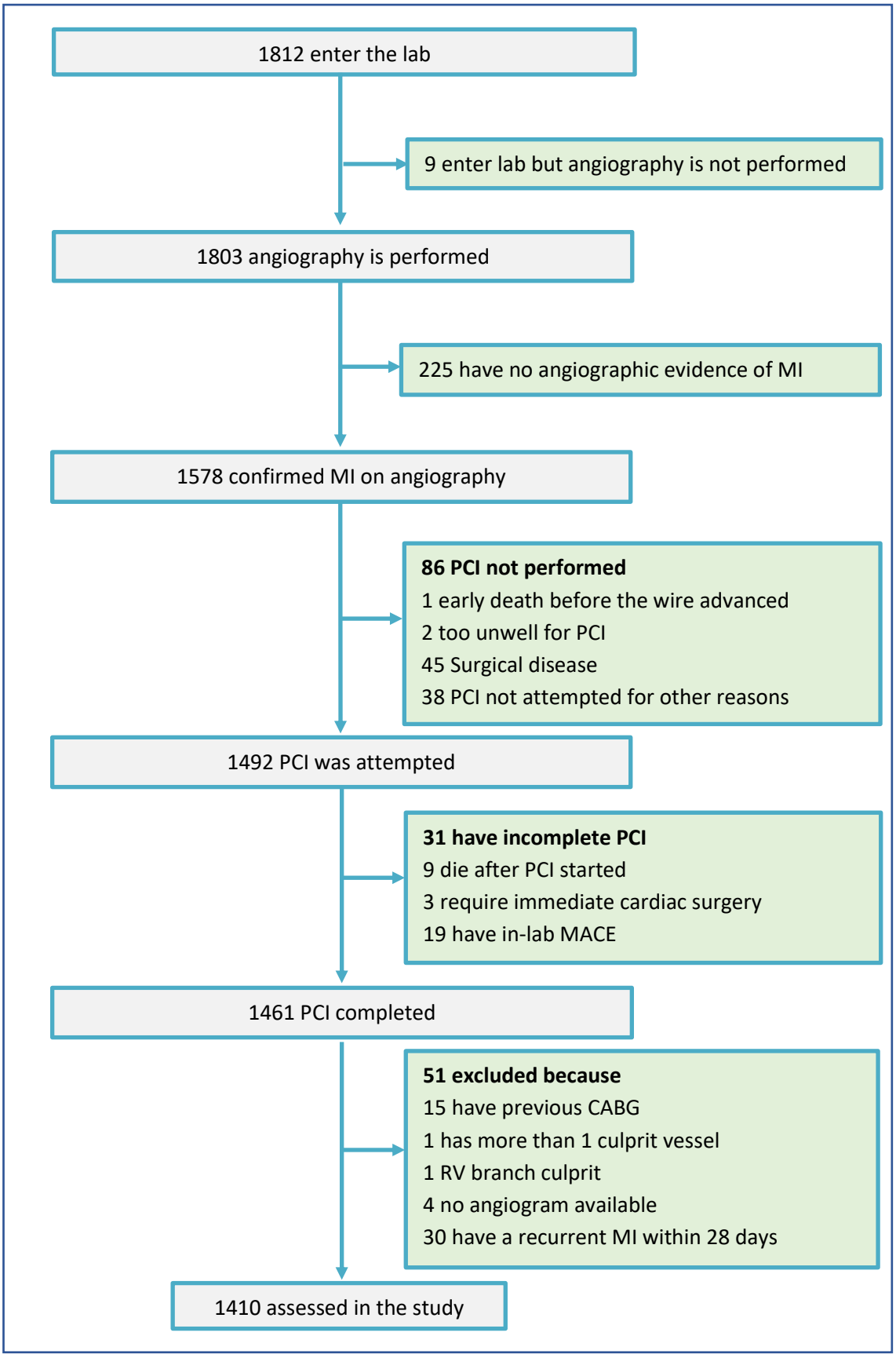


Figure 7.2: Flow diagram for the inclusion of participants in the study

7.4.1.1 Age

The median age of all patients was 63 (53 to 73) (Table 7.2). The median age was significantly different between those patients who experienced the composite outcome and those who did not (71 vs 62, p <0.001) (Table 7.2).

	All patients n=1410	Alive at 28 days and LV EF > 35%	Died at 28 days or LV EF ≤ 35%	p value
Age	63 (54 to 73)	62 (54 to 73)	71 (60 to 80)	<0.001
Gender				
Male	1025/1410 (72.7%)	898/1001 (89.7%)	103/1001 (10.3%)	0.57
Female	385/1410 (27.3%)	328/370 (88.6%)	43/370 (11.4%)	
Culprit location				
LAD	531/1410 (37.7%)	415/521 (79.7%)	106/521 (20.3%)	<0.001
LMS	13/1410 (0.9%)	9/13 (69.2%)	4/13 (30.8%)	
RCA	632/1410 (44.8)	581/607 (95.7%)	26/607 (4.3%)	
Cx	206/1410 (14.6%)	196/202 (97.0%)	6/202 (3.0%)	
Dx	28/1410 (2.0%)	25/28 (89.3%)	3/28 (10.7%)	

Table 7.2: Clinical variables categorised according to the occurrence of the outcome

7.4.1.2 Gender

Male patients accounted for 1025/1410 = 72.7% of participants (Table 7.2). Comparing the proportion of men vs women who experienced the composite outcome did not show a significant difference between the two groups (103/1001 = 10.3% vs 43/370 = 11.4%; p=0.57) (Table 7.2).

7.4.1.3 Culprit vessel

The culprit vessel was most frequently the RCA (632/1410 = 44.8%) and the LAD (531/1410 = 37.7%) (Table 7.2). The LMS made up only 13/1410 = 0.9%, Cx 206/1410 = 14.6% and Dx 28/1410 = 2.0%. Table 7.2 demonstrates significant differences in the culprit vessel when comparing patients who experienced the composite outcome compared to those who did not (LAD culprit: 106/521 = 20.3% vs 415/521 = 79.7%; p=<0.001). To increase the predictive power of culprit location, I dichotomised this variable into the LAD or LMS vs. any other culprit vessel prior to performing further analyses.

7.4.1.4 TIMI flow

An assessment of TIMI flow was made in 1410/1410 = 100% patients, with 1395/1410 = 98.9% made with confidence (Figure 7.3). TIMI flow grade 0 accounted for 17/1395 = 1.2% of confident assessments; Grade 1: 12/1395 = 0.9%; Grade 2: 184/1395 = 13.2%; Grade 3: 1182/1395 = 84.7% (Table 7.3). Comparing TIMI flow grades in patients who experienced an outcome showed a significant difference (p=0.002) (Table 7.4).

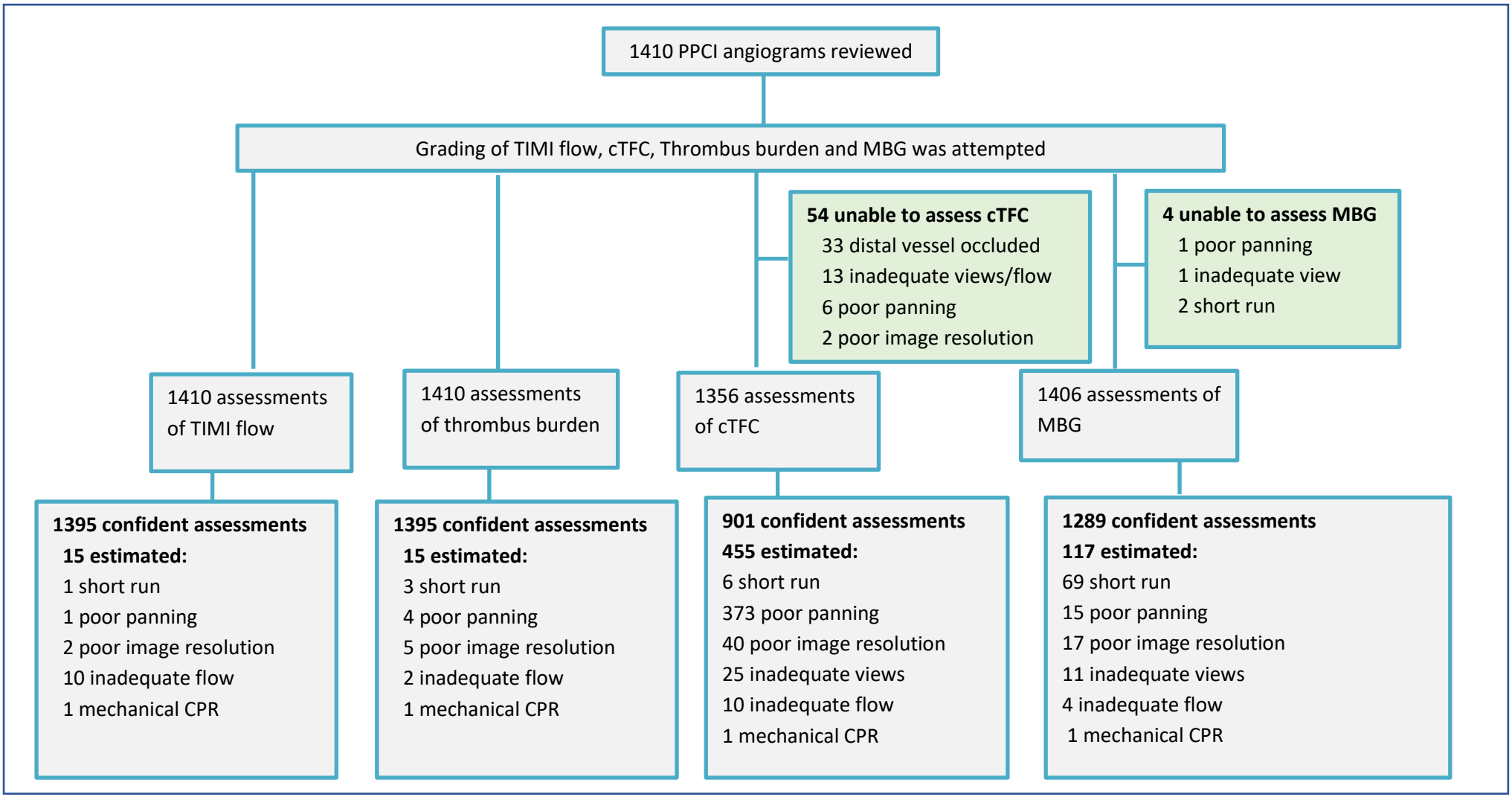


Figure 7.3: A flow diagram showing the quality of assessments made using the 4 angiographic grading systems

		Assessments made with confidence
TIMI flow		
	0	17/1395 (1.2%)
	1	12/1395 (0.9%)
	2	184/1395 (13.2%)
	3	1182/1395 (84.7%)
	0	1318/1395 (94.5%)
	1	17/1395 (1.2%)
	2	2/1395 (0.1%)
	3	13/1395 (0.9%)
	4	27/1395 (1.9%)
	5	18/1395 (1.3%)
MBG		
	0	20/1289 (1.6%)
	1	34/1289 (2.6%)
	2	135/1289 (10.5%)
	3	1100/1289 (85.3%)
cTFC		
	All	20 (14 to 30)
	≤27	620/934 (66.4%)
	>27	314/934 (33.6%)

Table 7.3: Distribution of assessments made with confidence for angiographic variables

	Alive at 28 days and	Died at 28 days or LV EF ≤ 35%	p value

	LV EF > 35%		
TIMI flow			
0	11/16 (68.8%)	5/16 (31.3%)	0.002
1	7/10 (70.0%)	3/10 (30.0%)	
2	155/181 (85.6%)	26/181 (14.4%)	
3	1043/1150 (90.7%)	107/1150 (9.3%)	
Thrombus burden			
0	1159/1287 (90.1%)	128/1287 (9.9%)	0.015
1	13/16 (81.3%)	3/16 (18.8%)	
2	2/2 (100%)	0/1 (0%)	
3	10/12 (83.3%)	2/12 (16.7%)	
4	20/26 (76.9%)	6/26 (23.1%)	
5	11/16 (68.8%)	5/16 (31.3%)	
MBG			
0	13/19 (68.4%)	6/19 (31.6%)	<0.001
1	23/34 (67.6%)	11/34 (32.4%)	
2	107/130 (82.3%)	23/130 (17.7%)	
3	980/1075 (91.2%)	95/1075 (8.8%)	
cTFC			
All	20 (14 to 30)	20.5 (14 to 28)	0.92
≤27	567/602 (94.2%)	35/602 (5.8%)	
>27	274/301 (91.0%)	27/301 (8.9%)	

Table 7.4: Angiographic variables of included participants categorised according to the occurrence of the outcome

7.4.1.5 Thrombus burden

An assessment of Thrombus burden was made in 1410/1410 = 100% patients, with 1395/1410 = 98.9% made with confidence (Figure 7.3). Thrombus burden grade 0 made up

1318/1395 = 94.5% of confident assessments; Grade 1: 17/1395 = 1.2%; Grade 2: 2/1395 = 0.1%; Grade 3: 13/1395 = 0.9%; Grade 4: 27/1395 = 1.9%; Grade 5: 18/1395 = 1.3% (Table 7.3). Comparing thrombus burden grades in patients who experienced an outcome showed a significant difference in the distribution of the grades (p=0.015) (Table 7.4).

7.4.1.6 Myocardial blush grade

An assessment of MBG was made in 1406/1410 = 99.7% patients, with 1395/1410 = 98.9% made with confidence (Figure 7.3). MBG 0 accounted for 20/1289 = 1.6% of confident assessments; MBG 1: 34/1289 = 2.6%; MBG 2: 135/1289 = 10.5%; MBG 3: 1100/1289 = 85.3% (Table 7.3). Comparing MBG in patients who experienced an outcome showed a significant difference in the distribution of the grades (p=<0.001) (Table 7.4).

7.4.1.7 cTFC

An assessment of cTFC was made in 1356/1410 = 96.1%, with 901/1356 = 66.4% made with confidence (Figure 7.3). The median cTFC for all assessments was 20 (13 to 29) and the median for cTFC made with confidence was 20 (14 to 30) (Table 7.3). cTFC could not be assessed in vessels where there was distal obstruction present (TIMI flow 0), regardless of angiogram quality. Therefore, I dichotomised the cTFC variable into assessments less than or equal to 27 (normal flow) and assessments greater or equal to 27 (abnormal flow). In the group of patients with abnormal cTFC, I included those where the cTFC could not be assessed due to distal obstruction. 1356/1410 = 96.1% cTFC assessments were completed with 934/1410 = 66.2% made with confidence (Table 7.3). Comparing cases based on the composite outcome showed no significant difference between the groups (35/602 = 5.8% vs 27/301 = 8.9%; p=0.06) (Table 7.4).

Table 7.4 demonstrates small numbers in the lower grades for all angiographic grading systems. To increase the power of the predictive model and to ensure easy calculation of

the resulting risk prediction score, ordinal variables were dichotomised prior to performing the univariate analysis (see Table 6.1 in Chapter 6). Dichotomising continuous variables is not recommended in logistic regression, therefore, age and cTFC remained as continuous variables.[174-176]

7.4.2 Selection of variables for the multivariate analysis

Table 7.5 shows the results of the logistic regression analysis performed for each variable to assess the univariate association with the composite outcome. Increasing age, LAD or LMS culprit location, abnormal TIMI flow, abnormal thrombus burden and abnormal MBG all demonstrated a significant association with the occurrence of the composite outcome, with age, culprit location and MBG identified as the strongest predictors. Variables that were statistically significant predictors, defined using the arbitrary cut-off of p=0.25, were then included in the multivariate analysis.[173]

	Odds ratio	**95% CI**	**p value**
Age	1.04	1.02 to 1.05	<0.001
Male gender	0.896	0.612 to 1.31	0.571
LMS/LAD culprit	5.945	3.992 to 8.852	<0.001

Abnormal TIMI flow (<3)	1.916	1.261 to 2.910	0.002
Abnormal Thrombus burden (>0)	2.587	1.442 to 4.643	0.001
Abnormal MBG (<3)	2.886	1.917 to 4.343	<0.001
cTFC	1.005	0.989 to 1.022	0.530

Table 7.5: Results from the univariate analysis

7.4.3 Results of the multivariate analysis

The multivariate analysis was performed by Dr Antonio Eleuteri, University of Liverpool, and the author. The variables included in this analysis were culprit vessel location (CV), TIMI flow (TF), thrombus burden (TB), MBG (all dichotomised as previously described) and Age (as a continuous variable). A total of 1271 patients had complete data on the predictors included in this analysis. Of these, 30/1271 = 2.4% had data missing for the composite outcome.

7.4.3.1 The model

A logistic regression model was fitted to the data to estimate the probability of the outcome event (outcome=1) conditional on the vectors of factors X. The model expressing the log-odds of the event as a function of the factors is shown in equation (7.1):

$$log\left(\frac{Pr\{\text{Outcome}=1|X\}}{1-Pr\{\text{Outcome}=1|X\}}\right) = \beta_0 + \beta_1\text{Age} + \beta_2\text{CV} + \beta_3\text{TF} + \beta_4\text{TB} + \beta_5\text{MBG} \qquad (7.1)$$

We assume the regression model is linear in the parameters β, however we do not make any linearity assumption about Age (the other predictors are binary, so non-linearity is not relevant). We estimated Spearman's ρ^2 statistic[177] to assess the strength of the marginal

relationship between the outcome and age; this informs us about the complexity of the (possibly non-monotonic) relationship. The ρ^2 statistic is 0.03 (p value <0.0001). Since it is small, Age will enter linearly in the model.

The total Wald statistic for the model is 105.8 (5 d.f., p<0.0001). In Table 7.6, the Wald statistics for each factor, and the attendant odds ratio with 95% confidence limits are shown.

Factor	**Odds ratio (95% CI)**	**χ^2 (p value)**
Age	2.07 (1.55 to 2.78)	23.82 (<0.0001)
Culprit location	6.16 (4.00 to 9.47)	68.42 (<0.0001)
TIMI Flow	1.21 (0.70 to 2.09)	0.48 (0.49)
Thrombus burden	1.57 (0.74 to 3.32)	1.37 (0.24)
MBG	2.32 (1.39 to 3.88)	10.39 (0.0013)

Table 7.6: Logistic regression model statistics

Internal validation was performed using bootstrapping (1000 repetitions) and the discrimination and calibration performance of the model were assessed.[177] In Figure 7.4 are reported the apparent, ideal and bias-corrected calibration graphs. The model tends to overestimate the probability of the event when it's larger than 0.4. The maximum absolute error in predicted probability is estimated to be 0.02. The estimated shrinkage factor is 0.96 (this is the likelihood the model will reliably predict new observations).

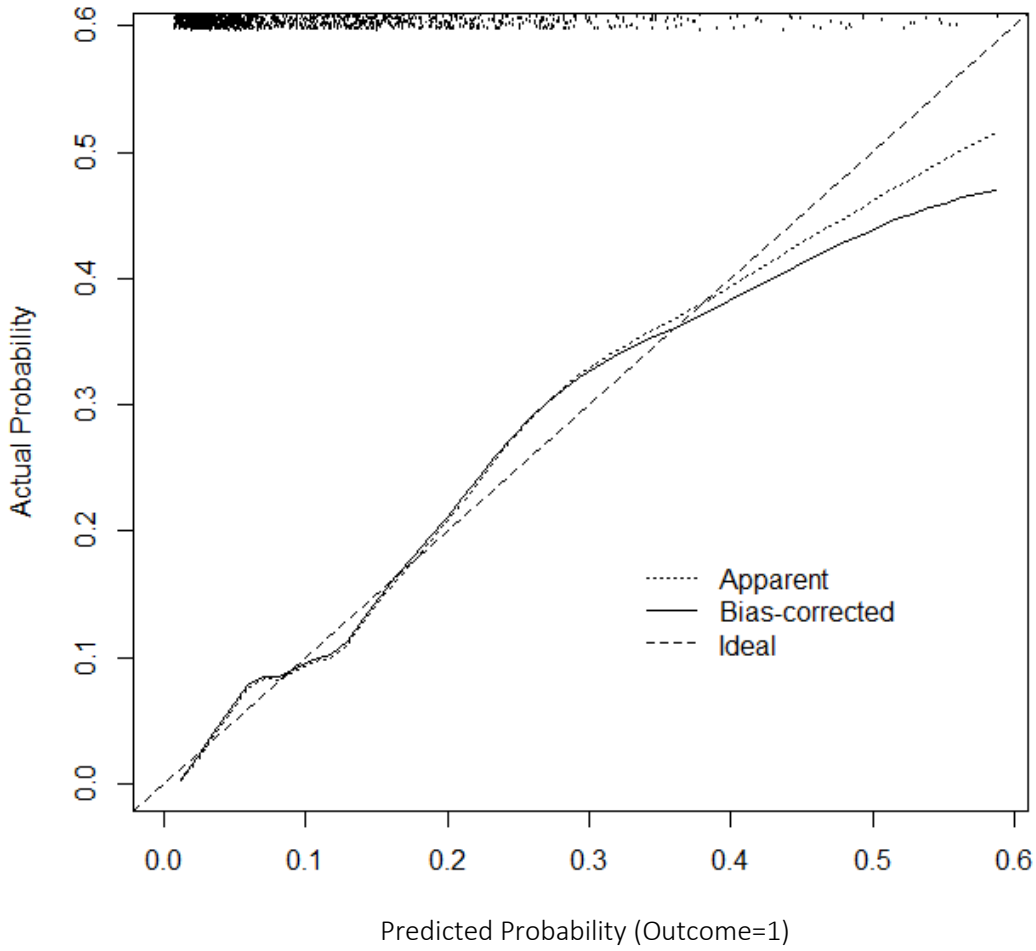


Figure 7.4: Calibration performance. The rug plot at the top of the graph shows the observed data. (Outcome = 1 denotes the occurrence of the outcome)

The model's discrimination (AUC) is 0.79 (0.75 to 0.83), with an upward estimated bias of 0.014. In Figure 7.5 the ROC curve is shown.

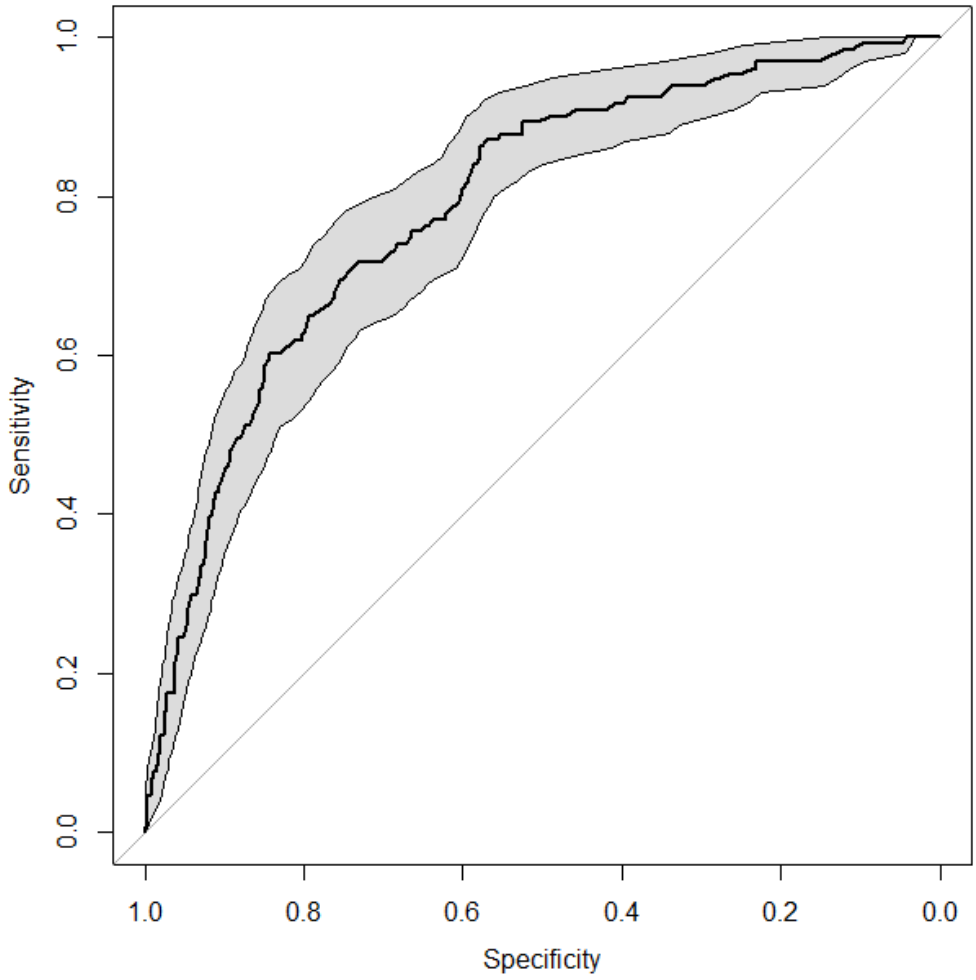


Figure 7.5: ROC curve with 95% bootstrapped confidence interval (1000 repetitions)

7.4.3.2 Approximating the full model

Step-down variable selection via Akaike Information Criterion (AIC)[177] was also performed with bootstrap resampling. 54% of the models selected Age, Culprit Location and MBG as relevant factors (in agreement with the statistics in Table 7.7). 36% of the models also considered Thrombus Burden as relevant. 8% of the models considered all the factors relevant, and 2% of the models only Age and Culprit Location.

A parsimonious model is of interest for clinical practice, so approximations can be developed that can predict the outcomes of the full model with high accuracy.[177] The

simplification is done using a fast backward step-down against the full model predicted values. Table 7.7 shows the factors, the cumulative AIC and cumulative R^2. The simpler model with highest accuracy is the one that includes all factors excluding Thrombus Burden and TIMI flow, with R^2=0.987. Note that adding Thrombus Burden only marginally improves the accuracy, to R^2=0.997.

Deleted factor	**AIC**	**R^2**
Culprit location	1499.2	0
Age	514.12	0.654
MBG	165.49	0.886
Thrombus burden	15.44	0.987
TIMI flow	2.38	0.997

Table 7.7: Step-down model selection

The variance matrix of the coefficients of the reduced model differs from the variance matrix of the original model, and it accounts for the selection procedure so that the statistics are "honest".[177] The ratios of the variances of the reduced model to the variances of a reduced model fitted against the actual outcomes, range from 1.0030 to 1.0096, so the variability of the coefficients does not increase appreciably.

The total Wald statistic for the reduced model is 103.9 (3 d.f., p<0.0001). The Wald statistics for the factors are shown in Table 7.8.

Factor	**χ^2 (p value)**
Age	25.69 (<0.0001)

Culprit location	68.14 (<0.0001)
MBG	18.77 (<0.0001)

Table 7.8: Reduced model statistics

The statistics are similar to those reported in Table 7.7 for the full model. This would not be the case had deleted variables been very collinear with retained variables.

The equation for the simplified model is as follows:

$$log\left(\frac{Pr\{\text{Outcome}=1|X\}}{1-Pr\{\text{Outcome}=1|X\}}\right) = -5.96 + 0.0395 \cdot \text{Age} + 1.81 \cdot \text{CV} + 1.01 \cdot \text{MBG} \quad (7.2)$$

A logistic regression model, termed the Liverpool MI Risk Model, was developed to predict the outcome (outcome=1) conditional on observed patient Age, Culprit location and MBG. The model exhibits good discrimination (AUC 0.79 95% CI: 0.75 to 0.83) and calibration (maximum absolute error 0.02, shrinkage 0.96) properties.

Using equation (7.2), we can predict the outcome for any values of the predictors using the Liverpool MI Risk Model. We created a risk prediction chart that could be used to look-up predictions of the outcome for categories of age (Figure 7.6). This form is more practical for use during PPCI compared to entering the values of each predictor into a computer or calculator.

	LAD or LMS culprit		**Other culprit**	
	Myocardial Blush Grade		**Myocardial Blush Grade**	
Age	Abnormal (<3)	Normal (3)	Abnormal (<3)	Normal (3)
<20	8.4	3.2	1.5	0.5
21-30	12.4	4.9	2.3	0.8
31-40	17.4	7.1	3.3	1.2
41-45	20.3	8.5	4.0	1.5
46-50	23.8	10.2	4.9	1.8
51-55	27.5	12.2	5.9	2.2
56-60	31.6	14.4	7.0	2.7
61-65	36.1	17.0	8.5	3.3
66-70	40.7	20.0	10.1	3.9
71-75	45.6	23.4	12.1	4.8
76-80	50.5	27.1	14.3	5.7
81-85	55.4	31.2	16.9	6.9
86-90	60.2	35.5	19.9	8.2
91-95	64.9	40.2	23.2	9.9
96-100	69.2	45.0	26.9	11.8

% risk of death at 28-days or LV EF ≤ 35%

Figure 7.6: Risk prediction chart for the occurrence of 28-day death or subsequent severe impairment of LV function following PPCI

7.5 Discussion

7.5.1 Main findings of the study

The main findings of this study showed that the composite outcome of 28-day mortality or subsequent severe impairment of LV function can be accurately predicted by a combination of age, abnormal MBG and LAD/LMS culprit lesions. Using these results, we developed the Liverpool MI Risk Model.

7.5.2 What is known?

There is a large amount of research into the associations between clinical and angiographic variables and outcomes following STEMI.[178] Here, I discuss studies that have created practical tools and scoring systems aimed for use in clinical practice to identify high-risk patients undergoing PPCI.

7.5.2.1 Risk scores that use clinical factors only

There have been several studies that use clinical characteristics alone to develop scores to predict outcomes following STEMI. Clinical variables have been developed into risk scores in thrombolysis trials where PPCI was not routine therapy, therefore, angiographic data were not available.[179] PPCI is now the preferred treatment for reperfusion in STEMI and the majority of patients in recent trials will have angiographic data available for inclusion in a risk score.

The GRACE score is used to predict risk of in-hospital and 6-month mortality.[11] This score includes age, heart rate, blood pressure, serum creatinine, Killip class, cardiac arrest on admission, ST-segment deviation on ECG and elevated cardiac enzymes. This shows excellent discrimination (c statistic for STEMI patients: 0.82 derivation, 0.83 validation). However, this score cannot always be used by operators during PPCI because it includes

results from bloods tests which may not be available in time for review during the acute event.

The PAMI risk score was developed from the data of 3252 patients who underwent PPCI for STEMI.[179] The score included age, Killip class, heart rate, diabetes and anterior myocardial infarction, and was predictive of 6-month mortality (c-statistic 0.78). No external validation of the score was performed. The aim of the score was to enable risk assessment of patients prior to reperfusion therapy, therefore, angiographic variables were not included.

Andrews et al. developed a risk score that predicts 30-day mortality in patients undergoing PPCI for STEMI.[180] This required only 4 variables: age, call-to-balloon time, cardiogenic shock and heart failure. This model showed excellent discrimination (c statistic: 0.87 derivation, 0.86 validation). Like PAMI, this study aimed to develop a score that could risk stratify patients prior to any reperfusion therapy and, therefore, angiographic variables were excluded.

7.5.2.2 Risk scores that use angiographic factors

The CADILLAC score incorporated post-procedural TIMI flow as well as clinical variables.[181] This study showed good discrimination and accurately predicts 30-day and 1-year mortality based on age, Killip class, ejection fraction based on left ventriculography during PPCI, TIMI flow post-procedure, anaemia, renal insufficiency and the presence of triple vessel disease (c-statistics for 30-day mortality: 0.83 derivation 0.81 validation; 1-year mortality: 0.79 derivation, 0.78 validation). However, this score is complex, and it is unlikely operators will be able to easily calculate it during the acute event. It also requires results from blood tests that may not be available. Performing left ventriculography adds cost to the procedure as well as risk to the patient from increased contrast and radiation exposure. It is not routinely performed by operators during PPCI.

De Luca et al. derived a score aimed at identifying low-risk patients for early discharge, predicting 30-day mortality.[182] This included age, anterior infarction, Killip class, ischaemic time, post-procedural TIMI flow grade and the presence of multivessel disease. This score could identify 73.4% of low-risk patients (score ≤3) with good discrimination (c statistic 0.907).

The angiographic perfusion score developed by Gibson et al. includes TIMI flow grade and TIMI myocardial perfusion grade measured before and after PCI.[183] This gives a single score that indicates successful reperfusion. This score was associated with 30-day mortality and infarct size measured on SPECT, but no predictive model was developed. Although this score is simple and can easily be calculated by the operator during PPCI, inclusion of simple clinical factors would likely improve discrimination.

A small study (n=253) by Haager et al. showed that the addition of abnormal MBG and persistent ST-elevation post-intervention (STE) increased the predictive power of clinical characteristics when predicting 30-day mortality following STEMI.[93] A combination of STE and MBG demonstrated good discrimination (c statistic 0.71). Like our results, this study demonstrated that cTFC was not an independent predictor of mortality. This study did not develop a risk score from the results or externally validate the model.

7.5.2.3 Risk scores that use additional invasive measurements

The ATI score was developed with an aim to predict the risk of microvascular impairment using factors that could be assessed at the time of coronary reopening.[71] The score aimed to predict the IMR cut-off of >40 (indicating microvascular obstruction). The score included age, pre-stenting IMR and thrombus burden. These factors accurately predicted the final dichotomised IMR value (c statistic: 0.87 derivation, 0.81 validation). However, this score gives no information regarding subsequent mortality or infarct size. The inclusion of pre-

stenting IMR limits the practical use of the ATI score as operators would have to perform the additional invasive test for all STEMI patients. This would add cost and time to the procedure as well as additional risk to the patient from further instrumentation to the coronaries.

7.5.3 What our study adds

7.5.3.1 Inclusion criteria

HEAT-PPCI represents unselected, real-world population, with minimal exclusion criteria. The risk score is, therefore, generalisable to a wide demographic of PPCI patients. This differs from other risk scores, such as the CADILLAC score, where patients with cardiogenic shock, or any comorbidities that were judged to affect their prognosis (likely to die within a year) were excluded.[181]

7.5.3.2 Choice of clinical factors

Although there are multiple clinical characteristics that are associated with increased infarct size and mortality, the included variables must be available, or at least estimable, in the catheter lab during PPCI. For example, estimating the age of an unconscious or very unwell patient may be possible whereas eliciting their past medical history and risk factors is likely to be more challenging in an emergency setting. Therefore, some clinical factors, such as diabetes and ischaemic time, were excluded from the study because unwell patients may not be able to relay the required information to hospital staff.

ECG changes were not included as a variable because often only a 3-lead ECG is available prior to PPCI. A 3-lead ECG would not allow proper evaluation of degrees of ST-elevation or ST-elevation resolution.

7.5.3.3 Choice of angiographic factors

All angiographic variables included in our analysis could be measured from information already obtained from the PPCI angiogram. No additional tests, equipment or time was required to calculate the variables. The risk model could, therefore, be implemented immediately by any operator performing PPCI, and provide valuable information without adding time, expense or risk.

7.5.3.4 Using a univariate analysis

We performed a univariate analysis to select variables for inclusion in the multivariate analysis. Performing a univariate analysis is widely used for developing risk models and has the advantage of utilising all available data for each variable. Multivariate analyses require complete datasets for every variable if a participant is to be included, which reduces the sample size. However, performing univariate analyses prior to multivariate analysis has been criticised because it may wrongly reject potentially important variables when the relationship between the outcome and a risk factor is confounded.[175,176]

7.6 Limitations

Use of LV function as a clinical outcome has limitations. LV function prior to the acute event is not known, therefore, some patients may have poor LV function as a result of a previous cardiac event. In these cases, the LV function will not give reliable information regarding an estimation of the infarct size resulting from the acute event.

Killip class has been included in several similar risk scores and is a good predictor of poor LV function and mortality, and easily assessed in patients with suspected STEMI. I could not include Killip class in our analysis because this was not recorded in the HEAT-PPCI trial.

The HEAT-PPCI angiograms were reviewed in retrospect, therefore, the images were not obtained with consideration of the measurement of the angiographic variables. This may account for the high proportion of estimated assessments in the study, resulting in a smaller number of complete datasets for use in the analysis.

7.7 Conclusions

The simple addition of MBG in the assessment of the PPCI angiogram gives valuable information to the operator regarding risk of adverse outcome. The Liverpool MI risk model developed from the HEAT-PPCI database is simple and practical. It can be calculated in-lab during PPCI and accurately predicts the composite outcome of 28-day mortality or subsequent severe impairment of LV function (EF ≤ 35%). This model could aid operators in risk-stratifying patients and identifying those who could be considered for shorter stays in critical care areas or early discharge.

Chapter 8: External validation of the Liverpool MI Risk Model

8.1 Introduction

Chapter 7 describes the development of the Liverpool MI risk model. This model was derived using data from the HEAT-PPCI trial and includes the predictors of age, culprit location and MBG measured at the end of the procedure. It produces a percentage risk of death at 28-days or poor LV function following PPCI. HEAT-PPCI was a single-centre trial and, therefore, there are limits on the generalisability of the risk model to other hospitals or patient groups.

Risk prediction scores should be validated internally and externally.[184] We have performed internal validation of the Liverpool MI risk model using bootstrapping described in Chapter 7. However, external validation involves assessing the model in a new but similar cohort of patients. It is the strongest test of a risk model, although rarely done.[185] External validation assesses the generalisability of a model to ensure it performs well in other groups and can then be used in clinical practice.[185] It can be performed in a different geographical area and over different time periods.[176] A good model should retain clinical utility proven by good statistical performance in the new dataset.

In this study, we aimed to externally validate the Liverpool MI risk model using an independent cohort of PPCI patients from another UK centre.

8.2 Methods

8.2.1 Study design

The Detection and Significance of Heart Injury in ST Elevation Myocardial Infarction (BHF MR-MI) was a single-centre, prospective, cohort study.[186] BHF MR-MI recruited 324 patients with STEMI at the Golden Jubilee National Hospital, Glasgow. The study recorded clinical and angiographic variables including age, culprit location and TMPG. In the Liverpool MI Risk Model, we collected data on MBG. The main difference between the two grading systems is that the TMPG measures the clearance of contrast from the myocardium whereas the MBG measures the maximum density of contrast.[104,111] We chose to use the MBG because this can be calculated on shorter cineruns without the need to continue the run until all contrast has cleared from the myocardium.

By assuming the TMPG is equivalent to the MBG (see Table 8.1), we were able to include the TMPG assessments taken in the BHF MR-MI study for use in the validation of the Liverpool MI Risk Model.

	Myocardial blush grades (MBG)	TIMI myocardial perfusion grades (TMPG)
Grade 0	No myocardial blush	No myocardial blush
Grade 1	Minimal myocardial blush	Minimal blush and very slow clearing (e.g. present at beginning of next cine)
Grade 2	Myocardial blush exists to a lesser extent and with less clearance than would be expected in a non-infarct related artery	Good blush with slow clearing of myocardial contrast (present at end of cine but gone at beginning of next)
Grade 3	Normal myocardial blush	Good blush and normal clearing (ie. gone by end of cine)

Table 8.1: Grade equivalents for myocardial blush grades and TIMI myocardial perfusion grades

The BHF MR-MI study recorded LV function on CMR following the acute event and all-cause mortality up to a minimum follow-up of 3 years. This data set contained all the variables and outcomes required for application of the Liverpool MI Risk Model. It was, therefore, possible to use this data set for external validation of the model.

8.2.2 Participants

324 patients with a diagnosis of acute STEMI were enrolled in the trial between 11th May 2011 and 22nd November 2012.

8.2.2.1 Inclusion criteria

- a diagnosis of acute STEMI.

8.2.2.2 Exclusion criteria

- Major systemic illness (e.g. cancer limiting survival < 6 months)
- Metallic implant or metallic foreign body (contraindications to CMR)
- Pregnancy

8.2.3 Clinical outcomes

The BHF MR-MI measured several clinical outcomes. The primary outcome was myocardial salvage measured on CMR at baseline and 6 months after index hospitalisation. Secondary outcomes included CMR measurements of myocardial salvage index, final infarct size, myocardial haemorrhage, microvascular obstruction, area-at-risk and left ventricular ejection fraction. Other outcome measures included recurrent myocardial infarction within 6 months, MACE defined as cardiac death, non-fatal MI or hospitalisation for heart failure over 12 months, and all-cause death or hospitalisation for heart failure.

We used the composite outcome of 28-day death or poor LV function (defined as EF $\leq$35%) measured on CMR for use in the validation of the Liverpool MI Risk Model.

8.2.4 Statistical analysis

The statistical analysis was performed by Dr Antonio Eleuteri, University of Liverpool in collaboration with the author. To validate the model, we followed a model-based framework for calibration.[187] Specific details of the statistical analysis are included in Appendix 4.

8.3 Results

The external validation data set is comprised of 305/324 = 94.1% complete observations; 19 observations were excluded from the analysis because of missing data. The number of outcome events is 12/305 = 3.7%. In the Liverpool data, 131/1241 = 11% outcome events were observed. A two-sided test to compare the proportions of events in the two populations rejects the null hypothesis of equality; the 95% confidence interval on the difference between proportions is 3.9% to 9.7% with a p-value of 0.0002. There is therefore evidence of a higher risk of outcome events in the Liverpool population.

Table 8.2 illustrates the clinical and procedural characteristics of the Liverpool derivation cohort compared with the Glasgow validation cohort. There are significant differences between the two groups, with the Glasgow cohort having a more favourable risk profile in terms of renal function (a lower proportion of patients with eGFR <60), reduced incidence of hypertension, hyperlipidaemia and less likely to be smokers. The Glasgow cohort were significantly more likely to have normal TIMI flow at the end of the procedure, despite having a higher risk of abnormal MBG.

The renal function between the two cohorts was compared by examining the proportion of patients with an eGFR <60 because in the BHF MR-MI trial, the cut-off for quantifying eGFR was ≥60 (in Liverpool the cut-off was >90). Therefore, I considered a normal eGFR as ≥60 in both cohorts for the purpose of this analysis.

	Liverpool derivation cohort (n=1410)	Glasgow validation cohort (n=324)	p value
Age	63.5 (12.8)	59.3 (11.5)	<0.001
Male gender	1025/1410 = 72.8%	237/324 = 73.1%	0.869
Hypertension	572/1409 = 40.6%	105/324 = 32.4%	0.006
Hyperlipidaemia	522/1402 = 37.2%	94/324 = 29.0%	0.005
Diabetes	180/1404 = 12.8%	34/324 = 10.5%	0.252
Smoker	985/1391 = 70.8%	196/324 = 60.5%	<0.001
Previous MI	136/1410 = 9.6%	25/324 = 7.7%	0.281
Previous PCI	92/1410 = 6.5%	18/324 = 5.6%	0.519
Systolic BP	134 (118 to 153)	134 (118 to 150)	0.956
Heart rate	75 (62 to 88)	77 (65 to 89)	0.133
eGFR <60	180/1116 = 16.1%	26/324 = 8.0%	<0.001
	MBG	**TMPG**	
3	1160/1406 = 82.5%	65/309 = 21.0%	<0.001
2	176/1406 = 12.5%	157/309 = 50.8%	
1	49/1406 = 3.5%	17/309 = 5.5%	
0	21/1406 = 1.5%	70/309 = 22.6%	
Final TIMI flow			
0	21/1410 = 1.5%	0/324 = 0%	<0.001
1	15/1410 = 1.1%	3/324 = 0.9%	
2	192/1410 = 13.6%	20/324 = 6.2%	
3	1194/1410 = 84.7%	301/324 = 92.9%	

Table 8.2: Characteristics of the Liverpool and Glasgow cohorts.

8.3.1 Validation of the risk model

We applied equation (7.2) derived in Chapter 7 for the Liverpool MI Risk Model to create a risk score (s) for each participant in the Glasgow cohort. We then plotted a ROC curve to establish the discrimination of the model for Glasgow participants (Figure 8.1). This showed good discrimination with an AUC of 0.837 (95% CI 0.723 to 0.951).

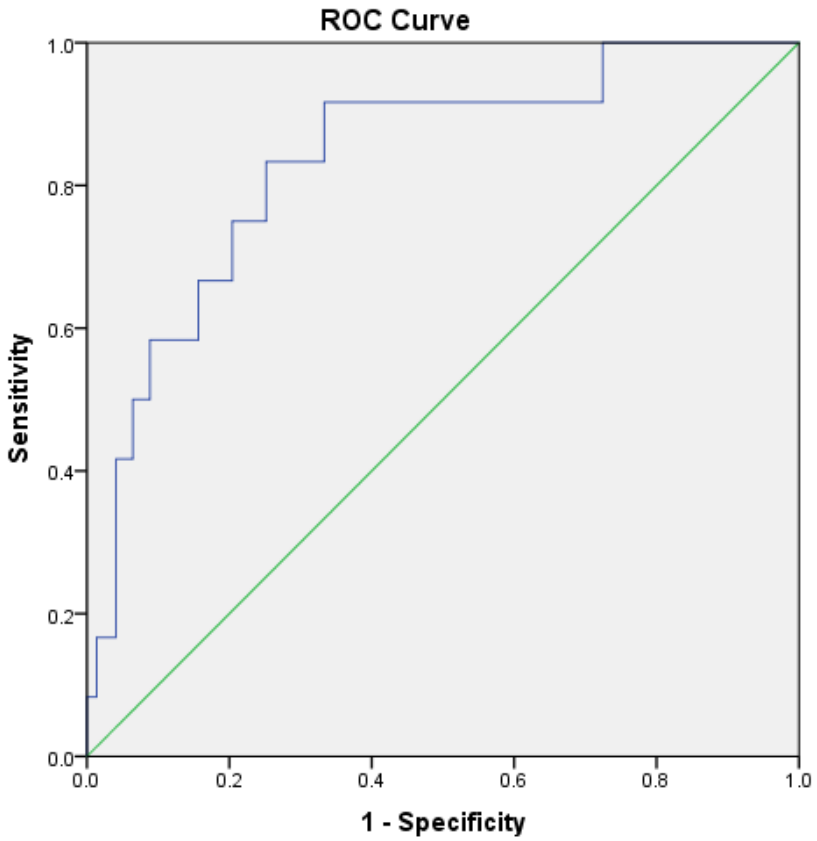


Figure 8.1: ROC curve for the Liverpool MI Risk Model when applied to the Glasgow cohort

We fitted the three logistic regression models. These showed that the Liverpool MI Risk Model consistently overestimates the risk of an outcome in the Glasgow cohort. The results of this analysis are detailed in Appendix 4.

The Liverpool MI Risk Model was recalibrated to accurately predict outcome events in the Glasgow cohort using the following equation:

$$r = 1.433s - 1.06 \quad (8.1)$$

r is the recalibrated risk score and s is the risk score derived from the Liverpool MI Risk Model. Table 8.3 shows a risk prediction chart developed from the model after calibration. This can be used in clinical practice when assessing patients similar to those in the Glasgow cohort.

	LAD or LMS culprit		**Other culprit**	
	Myocardial Blush Grade		**Myocardial Blush Grade**	
Age	Abnormal (<3)	Normal (3)	Abnormal (<3)	Normal (3)
<20	1.1	0.3	0.08	0.02
21-30	2.1	0.5	0.2	0.04
31-40	3.6	0.9	0.3	0.1
41-45	4.7	1.1	0.4	0.1
46-50	6.1	1.5	0.5	0.1
51-55	8.0	2.0	0.6	0.2
56-60	10.3	2.6	0.9	0.2
61-65	13.3	3.5	1.1	0.3
66-70	16.8	4.5	1.5	0.4
71-75	21.2	5.9	2.0	0.5
76-80	26.3	7.7	2.6	0.6
81-85	32.1	10.0	3.4	0.8
86-90	38.6	12.9	4.5	1.1
91-95	45.5	16.4	5.9	1.4
96-100	52.5	20.6	7.6	1.9

Table 8.3: Risk prediction chart for the occurrence of 28-day death or subsequent severe LV function recalibrated for use in Glasgow patients

8.4 Discussion

The Liverpool MI Risk Model shows good discrimination when tested on the Glasgow cohort (c statistic 0.873; 95% CI 0.723 to 0.951). However, the Liverpool MI Risk Model predicts an overall higher risk on the Glasgow data, as reflected in the simple comparison of the percentage of outcome events in the two populations. The model can be recalibrated to provide accurate predictions on the Glasgow population. The need for recalibration highlights the existence of unknown variables that affect the risk that are not included in the model.

Some risk models may over- or underestimate the number of outcome events on validation because the design or methods used are deficient, for example, if the model is overfitted or an important predictor has not been included.[185] Poor performance in external validation can also result if the validation cohort show significant differences in the patient characteristics, measurement methods of variables or treatments delivered. The Liverpool MI Risk Model overestimates the occurrence of outcome events when tested on the Glasgow validation dataset.

One reason for this may be differences in the measurement methods of MBG. The proportion of assessments of normal MBG following PPCI in each cohort is significantly different (Liverpool: 1160/1406 = 82.5% vs Glasgow: 65/309 = 21.0%; $p<0.001$). These results suggest that reperfusion was better in the Liverpool cohort which could be accounted for simply due to differences in procedure success and operator skills. If this were true, we would expect improved outcomes for the Liverpool patients. However, the Liverpool patients were at higher risk of adverse events compared to the Glasgow patients. Therefore, the differences in the distributions of MBG grades in the two cohorts is more likely to be due to differences in the measurement method of myocardial blush grade.

The BHF MR-MI research group collected data on the TIMI myocardial perfusion grade (TMPG) rather than the MBG.[70,186] Table 8.1 shows how the MBG grades used in the Liverpool cohort were mapped to the TMPG grades used in the Glasgow cohort. However, this is an approximation and differences in the different methods of measuring blush grades may affect the performance of the model on validation.

If the measurement methods of blush in the two studies differed significantly, we can estimate which method was more accurate by comparing the distributions of MBG in other studies in a PPCI setting. Table 8.4 shows the proportion of normal and abnormal MBG grades assessed post-PPCI in 8 studies. We can see that there is significant variation between the studies, with an increased proportion of normal MBG in the more recently published studies. This may be due to improved treatment and the development of streamlined PPCI services over the past decade. Because of the wide variation in the proportions of normal MBG, it is difficult to determine whether the Glasgow or Liverpool cohorts more closely reflect the results from other studies. These studies use MBG rather than TMPG to measure blush.

	MBG grades 0/1/2	MBG grade 3
Mahmoud et al., 2019[188]	27/100 (27.0%)	73/100 (73.0%)
Badjaoui et al., 2019[189]	59/160 (36.8%)	101/160 (63.1%)
Groot et al., 2017[190]	113/376 (30.1%)	263/376 (69.9%)
Di Vito et al., 2016[191]	53/128 (41.4%)	75/128 (58.5%)
Kampinga et al., 2010[108]	1305/2118 (61.6%)	813/2118 (38.3%)
Kaya et al., 2007[110]	59/103 (57.3%)	44/103 (42.7%)
Haager et al., 2003[93]	174/253 (68.8%)	79/253 (31.2%)
Stone et al., 2002[154]	125/173 (72.2%)	48/173 (27.7%)

Table 8.4: This table compares the distribution of MBG grades across several studies of PPCI

For the Liverpool MI Risk Model, I dichotomised MBG into normal (grade 3) and abnormal (grades 0,1,2). However, it may be that errors are occurring when operators are asked to distinguish between grade 2 and grade 3. Therefore, it is reasonable to think that dichotomising the grades as grades 0 and 1 vs grades 2 and 3 may be more useful when comparing the Liverpool and Glasgow cohorts. Table shows that the difference in the proportion of participants with "normal" MBG decreases when we dichotomise the grades as 0/1 and 2/3 (see Table 8.5).

Dichotomisation of MBG	Liverpool derivation cohort	Glasgow validation cohort	p value
Original model			
Grade 3	1160/1406 = 82.5%	65/309 = 21.0%	<0.001
Grades 0/1/2	246/1406 = 17.5%	244/309 = 79.0%	
New model			
Grades 2/3	1336/1406 = 95.0%	222/309 = 71.8%	
Grades 0/1	70/1406 = 5.0%	87/309 = 28.2%	<0.001

Table 8.5: The distribution of grades when MBG is dichotomised for the original model (grade 3 vs grades 0/1/2) and in the new model (grades 2/3 vs grades 0/1)

We can test whether this has an impact on the outcome by creating a risk model using the same three variables as in the Liverpool MI Risk Model but dichotomising MBG as normal (grades 2/3) and abnormal (grades 0/1). If the Glasgow cohort validates well on this new risk model, this would indicate that errors in distinguishing between grade 3 and the other grades of MBG could be the reason for overestimation of outcome events when applying the Liverpool MI Risk Model to the Glasgow cohort. Table 8.6 shows the logistic regression analysis when changing the cut-offs for dichotomising the MBG.

	B	SE_B	Wald	df	p value	Exp(B)	95% CI for Exp (B)
Age	0.04	0.008	26.680	1.00	<0.001	1.041	1.025 to 1.057
Culprit Location	1.797	0.218	68.088	1.00	<0.001	6.033	3.937 to 9.245
MBG	1.259	0.363	12.029	1.00	0.001	3.522	1.729 to 7.123
Constant	-5.880	0.570	106.515	1.00	<0.001	0.003	

Table 8.6: Result of the logistic regression analysis predicting an adverse event when MBG is dichotomised into grades 0/1 vs 2/3

The discrimination of the new model is similar to the original model (AUC 0.78; 95% CI 0.74 to 0.82). Table 8.7 shows that the new model predicts the total number of events in the Liverpool cohort to a good approximation (mean percentage predicted events is 11.9% vs observed events is 10%.) When applied to the Glasgow cohort, the mean percentage predicted events is 11.9% but the observed events is 3.7%. This shows that changing the dichotomised cut-offs for MBG does not improve the ability of the Liverpool Risk Model to predict outcome events in the Glasgow cohort.

	Liverpool cohort	Glasgow cohort
Predicted events (%)	11.9	11.8
Observed events (%)	10.3	3.8

Table 8.7: Predicted vs observed total events using the new model when MBG is dichotomised by grades 0/1 vs 2/3

Even if the categorisation of MBG had accounted for some of the differences between the cohorts, it does not explain why the total number of events in the Liverpool is significantly higher than in Glasgow (131/1241 = 11% vs 12/305 =3.7%; p value 0.0002). One possible explanation is the use of different eligibility criteria for patient recruitment. In the BHF MR-MI study, patients who were deemed to have a major systemic disease or poor prognosis (likely to die within 6 months) were not eligible to participate in the study. In contrast, HEAT-PPCI included all adults who had not previously been recruited into the study and did not exclude patients with a poor prognosis. This may explain the more favourable risk profile and lower risk of outcome events seen in the Glasgow cohort.

In addition, HEAT-PPCI employed a strategy of delayed consent to allow recruitment of patients who were too unwell to consent to participation in the study. BHF MR-MI did not employ this strategy and it is likely that patients who were unable to consent prior to PPCI due to severe illness or incapacity were excluded from the study. This would result in exclusion of patients who are more likely to have a less favourable risk profile and a higher risk of experiencing an outcome event.

The primary outcome in BHF MR-MI was myocardial salvage measured on CMR 6 months after the acute event. The study, therefore, aimed to recruit patients who were likely to survive for at least 6 months following PPCI to allow data collection for the primary outcome. However, excluding patients with major systemic illness or a poor prognosis decreases the generalisability of the study. We can demonstrate this by examining the national statistics for mortality and comparing them to the risks predicted for patients in the Glasgow cohort. Table 8.4 shows that the predicted risk of an outcome event in Glasgow patients who are 85 years old could be as low as 0.8% if patients have a normal MBG and an RCA/Cx/Dx culprit (compared to 6.9% in the Liverpool cohort). Between 2015

and 2017, the Office of National Statistics reported the number of registered UK deaths in people aged 80-84 was 5.9%.[192] The Glasgow cohort is, therefore, unlikely to be generalisable because the risk of an outcome event (which includes death at 28 days) is lower than that seen in the general population.

We explored the differences in patient recruitment for each study by examining the total number of PPCI procedures performed by each centre and comparing this to the number of participants recruited into each study. The Golden Jubilee Hospital in Glasgow performed 650 PPCI procedures in 2016 (650/12 = 54 per month).[13] The BHF MR-MI study recruited 324 participants over 16 months. We do not have access to the screening log for BHF MR-MI so we do not know the proportion of patients who had a PPCI and were excluded due to major illness or poor prognosis. Therefore 324/(54 x 16) = 324/864 =37.5% of the likely PPCI procedures performed over 16 months were recruited into the study. In comparison, HEAT-PPCI reported near 100% recruitment of all eligible patient. The study population represented 97% of all patients who were managed with angiography in the context of suspected STEMI. The high proportion of patients recruited into the HEAT-PPCI is likely to result from a combination of broad eligibility criteria, using a strategy of delayed consent and setting out with an aim to collect data on different primary outcomes that did not require patients to survive at least 6 months following PPCI.

Glasgow patients had a more favourable risk profile in terms of better renal function, reduced incidence of hypertension, hyperlipidaemia and less likely to be smokers (Table 8.2). The difference in risk profiles of the two cohorts may have contributed to the observed difference in the percentage of outcomes events.

Following validation, the Liverpool MI Risk Model should be tested using an impact study, where we assess the effect of the model on physician behaviour, patient outcome and cost effectiveness of care when compared to usual care without the model.[176]

8.5 Limitations

The Glasgow cohort consisted of 324 participants. This is a reasonable sample size if the percentage of outcomes events was approximately 10%, matching that in the Liverpool cohort (and national registries). As discussed in chapter 7, The recommended rule of thumb for a model is 10 events per variable (EPV). There were three variables included in the Liverpool MI Risk Model so to accurately validate the model required at least 30 events in the Glasgow dataset. However, the event rate in the Glasgow cohort was 3.7%, with 12 events in total. A further cohort with at least 30 events should be used to validate the model.

The BHF MR-MI study was not designed to be used as a validation cohort for the Liverpool MI Risk Model. This is an important limitation of our study. Therefore, we must expect the observed differences in baseline demographics and risk of outcome events because the aim of BHF MR-MI was to collect 6-month CMR data, and not to report the outcome of 28-day death or subsequent severe LV function. A study was designed to report the composite outcome used in the Liverpool MI Risk Model would likely perform better if used for external validation of the model.

8.6 Conclusions

This study shows that age, MBG and culprit location create a similar gradient of risk in an external cohort of STEMI patients. When tested on the Glasgow cohort, the Liverpool MI Risk Model shows good discrimination (c statistic 0.873). The model overestimates the risk of an outcome event in the Glasgow cohort; however, the model can make accurate predictions after simple recalibration. Differences between the two studies that provided the derivation and validation cohorts may account for the need to recalibrate the model after initial testing. These differences include eligibility criteria, strategies to obtain

consent, primary outcome measures and measurement methods of myocardial blush. A study of unselected STEMI patients, using the standardised method of measuring MBG, should be used to validate the model. Further studies should then assess the impact of using the model in clinical practice.

Chapter 9: The BHF MR-MI database: CMR insights into infarct size in STEMI

9.1 Introduction

The Liverpool MI Risk Model uses age, culprit location and myocardial blush grade to predict the risk of death or subsequent severe impairment of LV function. LV function was measured on echocardiography in the HEAT-PPCI trial and on CMR in the BHF MR-MI study. LV function may reflect larger infarct size, with a lower LV ejection fraction indicating a larger infarct. CMR allows direct visualisation and measurement of the area of infarcted myocardium. It is considered the gold standard in quantifying infarct size, although not routinely performed in all STEMI patients.[193] In this chapter, I used data from the BHF MR-MI to conduct an exploratory study, examining possible associations between three variables (age, culprit location and TIMI myocardial perfusion grade) and the outcome of infarct size measured on CMR in STEMI survivors.

9.2 Quantifying infarct size using CMR

Infarct size is quantified on CMR by late gadolinium enhancement.[194] In normal cardiomyocytes, the contrast agent, gadolinium chelate, cannot cross cell membranes. Following myocardial necrosis, the cell membranes rupture allowing the contrast into the cells. Therefore, the infarct size can be determined by the percentage volume of the total LV mass where gadolinium is present and visible on CMR.[193] The myocardial tissue at risk, frequently termed “area-at-risk” is the myocardial territory supplied by the culprit artery and includes the myocardium that is reversibly damaged as well as the myocardium that is infarcted. “myocardial salvage” can be calculated by subtracting the infarct size from the area-at-risk. The “myocardial salvage index” refers to the ratio of myocardial salvage to the

area-at-risk.[193] The myocardial salvage index is, therefore, useful in quantifying the success of revascularisation therapy because it records the volume of myocardium salvaged from infarction as a proportion of the potential volume that might have infarcted had revascularisation not been performed or if there was no blood supply from collateral or adjacent vessels.

In Chapter 1, I introduced the concept of microvascular obstruction (CMVO), which can be measured on CMR. CMVO is identified on CMR as a dark hypo-intense core within areas of hyper-enhancement on early or late gadolinium enhancement (termed early or late CMVO respectively).[193] The presence of CMVO is associated with decreased LV function and increased mortality.[36,38,39]

9.3 Methods

The BHF MR-MI study was a single-centre prospective cohort study described in detail in Chapter 8.[186] The study recruited STEMI patients who had a CMR performed at baseline and 6 months following the acute event.

9.3.1 Clinical outcomes

The BHF MR-MI study measured several clinical outcomes. The primary outcome was myocardial salvage measured on CMR at baseline and 6 months after index hospitalisation. Secondary outcomes included CMR measurements of myocardial salvage index, final infarct size, myocardial haemorrhage, microvascular obstruction, area-at-risk and LV ejection fraction. Other outcome measures included recurrent myocardial infarction within 6 months, MACE (defined as cardiac death, non-fatal MI or hospitalisation for heart failure over 12 months), and all-cause mortality.

For this study the primary outcome was:

- Percentage late gadolinium enhancement (%LGE): The myocardial mass of late gadolinium (grams) was quantified with computer-assisted planimetry. The territory of infarction was delineated with the use of a signal intensity threshold of >5 SD above a remote reference region and expressed as a percentage of total LV mass % (LGE).[70]

Secondary outcomes included:

- Myocardial salvage index (MSI)
- Any microvascular obstruction (CMVO)

9.3.2 Statistical analysis

Data are presented as (n/d = p%) for categorical variables and as means (standard deviations) or medians (interquartile ranges) for continuous variables after testing for normality. Comparisons between groups were made using a chi-squared test for categorical variables and unpaired t-test or Mann-Whitney U-test for continuous variables. A p value of < 0.05 (2 sided) was considered statistically significant. Multivariate analyses were performed to evaluate the degree of variation in a dependent variable (LGE, MSI and CMVO) that could be explained by the independent variables (age, culprit location and TMPG). Standard multiple regression was performed if the dependent variable was continuous, and binomial logistic regression if the variable was dichotomous. SPSS version 24 (SPSS Inc., Chicago, IL, USA) was used for analyses.

9.4 Results

In the BHF MR-MI study, 324/324 = 100% of patients had a CMR performed 2-3 days following the acute event and 299/324 = 92.2% had a follow-up CMR performed at 6 months.

9.4.1 % LV on late gadolinium enhancement

Of the included patients, 322/324 = 99.4% had values for LGE. Any association between Age and LGE was evaluated by visual inspection of a scatter plot of the two variables (Figure 9.1). This showed no clear correlation, confirmed by calculating the Pearson's R correlation coefficient for age vs LGE, which was 0, indicating no correlation between the two variables.

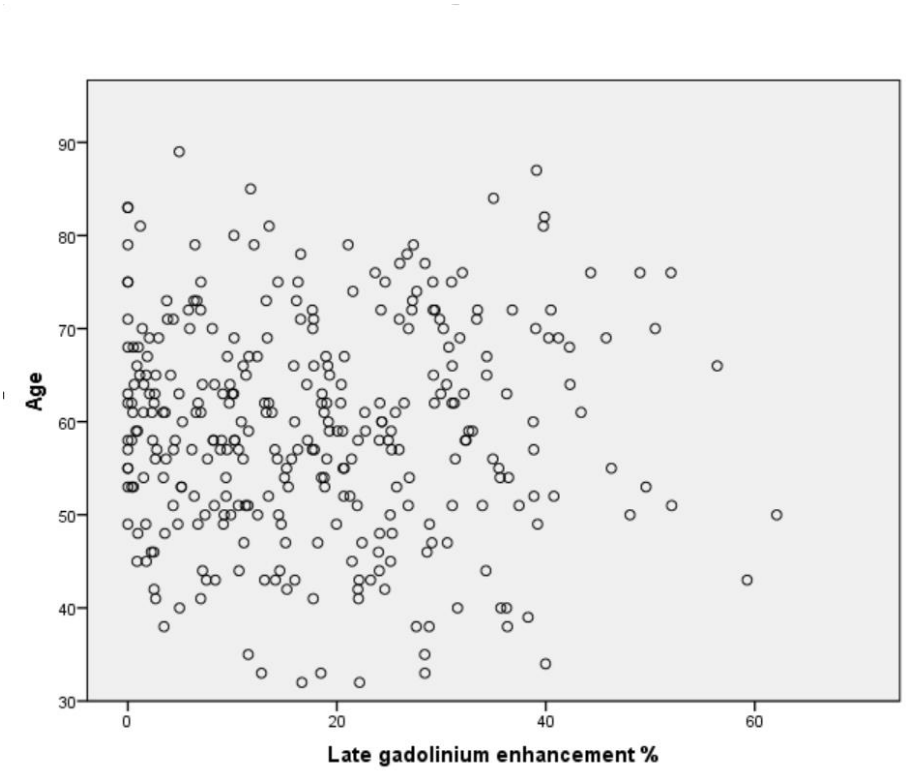


Figure 9.1: A scatterplot demonstrating the lack of correlation between age and LGE

The difference in median LGE was compared for the dichotomised culprit location. This showed a statistically significant difference in the median LGE in LAD/LMS culprits compared to other culprit locations (Table 9.1). The difference in median LGE was compared for normal and abnormal TMPG. This showed there was a difference, although it did not reach conventional levels of statistical significance.

	LGE (%)	p value
Culprit location		
LAD/LMS	26.4 (12.9 to 36.3)	<0.001
Other	12.4 (4.4 to 21.9)	
TMPG		
Normal	13.3 (4.8 to 25.2)	0.162
Abnormal	17.7 (7.2 to 28.2)	

Table 9.1: The median (IQR) LGE % according to culprit lesion and TMPG

A multiple regression analysis was run to evaluate the degree of variation in LGE due to the culprit location and TMPG. Age was excluded because there was no correlation between age and LGE, and, therefore, age failed the assumption of linearity required for multiple regression. The model was significantly better than the mean model (the mean of all values of LGE) (p=<0.001) and the R squared for the overall model was 17.3%, with an adjusted R square of 16.7%.[195] Therefore, the addition of culprit location and TMPG explained 16.7% of the variability in LGE measurements compared to the mean model. The coefficients for the model are demonstrated in Table 9.2, with both variables adding significantly to the model to predict LGE (culprit location: p<0.001, TMPG: p=0.039).

Variable	B	SE_B	Beta	p value	95% CI for B
Intercept	10.978	1.648		<0.001	7.74 to 14.22
Culprit location	11.366	1.452	0.41	<0.001	8.51 to 14.22
TMPG	3.56	1.713	0.109	0.039	0.19 to 6.93

B = unstandardised regression coefficient; SEB = Standard error of the coefficient; Beta = standardised coefficient

Table 9.2: Results of the multiple regression analysis for predicting LGE from culprit location and TMPG

9.4.2 Myocardial salvage index

295/324 = 91.0% patients had values for myocardial salvage index (MSI). Figure 9.2 demonstrates no correlation between age and MSI. Pearson's R correlation coefficient for age vs MSI was 0.031, confirming a lack of correlation.

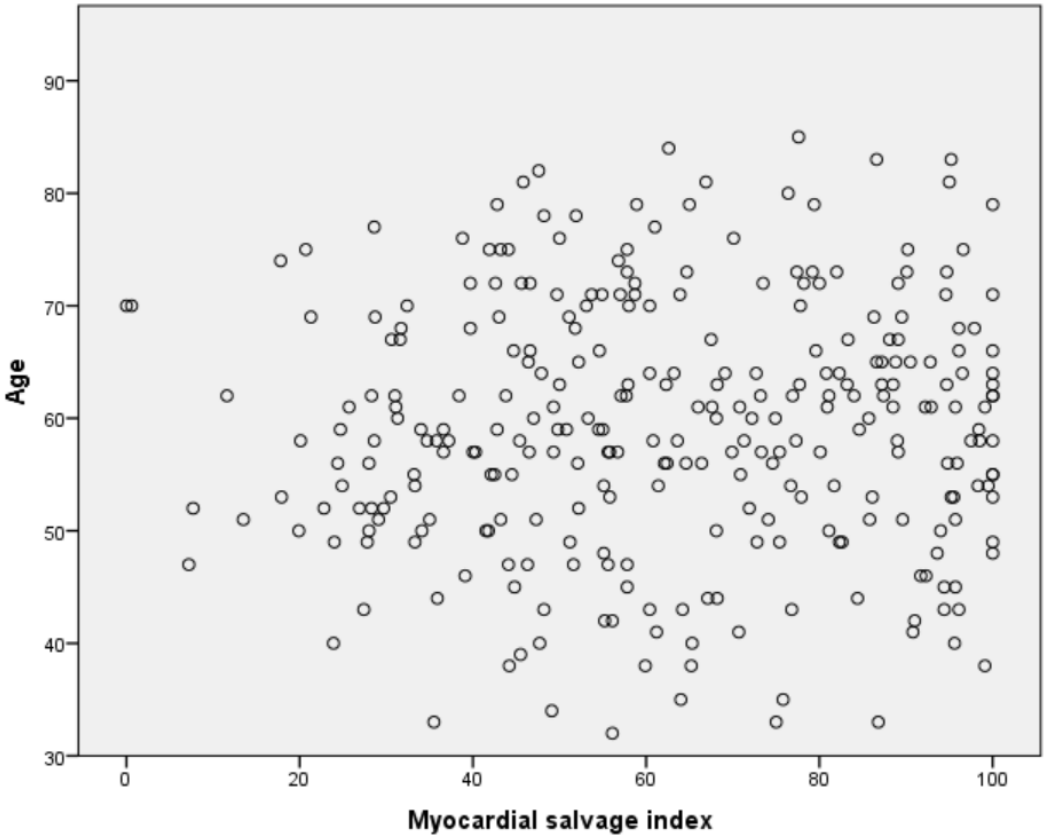


Figure 9.2: A scatterplot of age vs MSI

The difference in median MSI was compared for the dichotomised culprit location and normal/abnormal TMPG (Table 9.3). This showed a difference in the median MSI in LAD/LMS vs other culprit lesions which was not statistically significant (57.5 vs 64.8 p=0.167). The difference in median LGE was compared for normal and abnormal TMPG, showing a statistically significant difference (68.1 vs 60.4 p=0.009).

	MSI	p value
Culprit location		
LAD/LMS	57.5 (42.4 to 81.1)	0.167
Other	64.8 (46.6 to 86.3)	
TMPG		
Normal	68.1 (51.2 to 93.3)	0.009
Abnormal	60.4 (42.3 to 81.1)	

Table 9.3: The median (IQR) MSI according to culprit lesion and TMPG

A multiple regression analysis was performed to evaluate the degree of variability in MSI measurements due to culprit location and TMPG. Age was excluded because there was no relationship between age and MSI. The multiple regression model statistically significantly predicted MSI (R squared = 3.1 %; adjusted R squared = 2.4%; p=0.013). Therefore, the addition of culprit location and TMPG explained 2.4% of the variability in MSI measurements. The coefficients for the model are demonstrated in Table 9.4, with TMPG adding significantly to the model, although culprit location did not (TMPG: p=0.007, culprit location: p=0.137).

Variable	B	SE_B	Beta	p value	95% CI for B
Intercept	71.758	3.435		<0.001	64.99 to 78.52
Culprit location	-4.515	3.026	-0.089	0.137	-10.47 to 1.44
TMPG	-9.689	3.557	-0.162	0.007	-16.69 to -2.69

B = unstandardised regression coefficient; SEB = Standard error of the coefficient; Beta = standardised coefficient

Table 9.4: The results of the multiple regression analysis to predict MSI from culprit location and TMPG

9.4.3 Coronary microvascular obstruction (CMVO)

Of the patients recruited into the study, 324/324 = 100% had an assessment of CMVO on CMR. When comparing age, culprit location and TMPG by presence or absence of CMVO, there was no significant differences between the two groups (Table 9.5).

	Presence of CMVO		
	Yes	**No**	**p value**
Age	59 (11.7)	59 (11.2)	0.589
Culprit location			
LAD/LMS	75/118 (63.6%)	43/118 (36.4%)	0.118
Other	112/205 (54.6%)	93/205 (45.4%)	
TMPG			
Normal	32/65 (49.2%)	33/65 (50.8%)	0.11
Abnormal	147/244 (60.2%)	97/244 (39.8%)	

Table 9.5: Comparing age, culprit location and TMPG by presence of CMVO

In a multiple logistic regression analysis, age, culprit location and TMPG were not significant predictors of CMVO (p=0.157). The full model is demonstrated in Table 9.6.

	B	**SE_B**	**Wald**	**df**	**p value**	**Exp(B)**	**95% CI for Exp (B)**
Age	-0.01	0.01	0.46	1.00	0.499	0.99	0.97 to 1.01
Culprit Location	0.36	0.25	2.15	1.00	0.143	1.43	0.89 to 2.32
TMPG	0.50	0.28	3.06	1.00	0.080	1.65	0.94 to 2.88
Constant	0.21	0.65	0.10	1.00	0.752	1.23	

Table 9.6: Result of the logistic regression analysis predicting CMVO using age, culprit location and TMPG

9.5 Discussion

9.5.1 Main findings

This study showed that both culprit location and TMPG are predictors of LGE. In multiple regression analysis, these predictors account for 16.7% of the variability in measurements of LGE (adjusted R squared = 16.7%; p=<0.001). Culprit location and TMPG are associated with MSI, accounting for 2.4% of the variability (Adjusted R squared = 2.4%, p=0.013). Age has no clear association with LGE or MSI. (R = 0.0 and 0.013). Age, culprit location and TMPG did not predict presence of CMVO on binomial logistic regression analysis (full model p=0.157; age p=0.499; culprit location p=0.143; TMPG p=0.080).

9.5.1.1 Exploration of %LGE

Age does not have a clear association with LGE, suggesting that increased age is not related to an increased infarct size. In multiple regression analysis, the culprit location and TMPG explain 16.7% of the variability seen in LGE compared to the mean model. This suggests that a LAD/LMS culprit location is associated with an increased infarct size. Coronary arteries supply different sized areas of myocardium. LAD or LMS occlusion is likely to result in a larger infarct than any occlusion in any other artery because the LAD usually supplies a larger area of myocardium, therefore a larger area-at-risk. This is supported by a previous study of patients with STEMI treated with thrombolysis, that showed larger infarcts on CMR with anterior location of the infarct.[196]

For the purposes of this discussion, we assume that MBG and TMPG are equivalent, as defined in Chapter 8, Table 8.1. Abnormal TMPG is predictive of increased LGE. TMPG quantifies the contrast clearance from the myocardium, indicating the degree of blood flow reaching the microvasculature. A larger infarct will result in a lower blush grade/abnormal blush grade. This has been shown in a previous study: the INFUSE-AMI study compared

infarct size measured on CMR with MBG in a trial of STEMI patients managed with thrombolysis.[109] This study showed that a higher % infarcted LV mass was associated with MBG of 0 or 1 (19.5% vs 16.7%; p=0.002).

These results support the choice of variables used in the Liverpool MI Risk Model, as both culprit lesion and TMPG are predictive of infarct size measured on CMR. The addition of age is likely to add important information simply because increasing age results in an increased risk of death, although the results suggests that the effect of age is independent of reperfusion impact.

9.5.2 MSI

MSI is a measure of the success of revascularisation, reporting the ratio of salvaged myocardium and area-at-risk. Culprit location and TMPG explain 2.4% of the variability seen in MSI measurements whereas age had no clear association with MSI. Anatomical location of the occlusion cannot be altered by reperfusion therapy and therefore is a constant predictor of infarct size and less likely to predict MSI.

TMPG may be related to MSI because successful PPCI is more likely to result in good blood flow in the microvasculature of the myocardium, visible as increased contrast density and improved clearance in the culprit territory i.e. normal blush. However, blush grades do not consider the salvaged myocardium or area-at-risk so is more likely to have an association with infarct size.

Several risk scores have been developed and validated that use anatomical information from the angiogram to predict potential infarct size or area-at-risk.[197,198] One study showed that initial TIMI flow grade, presence of >1 collateral vessel and time-to-reperfusion were independent predictors of MSI.[199] Therefore, the addition of these predictors to a model using MBG and culprit location may increase the ability of the model to predict MSI.

9.5.3 CMVO

Age, TMPG and culprit location were not predictive of presence of CMVO. A study showed that a risk score comprising of Killip class, diabetes status, age, ST-elevation on ECG, and delayed presentation of STEMI (>3hrs) could be used to predict the presence of CMVO (c-statistic 0.904).[200] The study also showed that a proximal anterior LAD culprit was also predictive of MVO but did not improve discrimination when added to the model. Although, this analysis did not find the combination of age, culprit vessel and MBG was predictive of CMVO, however this does not exclude the possibility that these variables are predictive when combined in a model with other variables. This is a common phenomenon, known as Simpson's paradox, whereby the associations between variables may change with the addition of other variables.[201]

9.6 Limitations

The limitations of the BHF MR-MI study are discussed in full in Chapter 8. This was an analysis of observational data and therefore cannot be used to infer a causal relationship between variables as there may be a risk of unmeasured confounding. The assumptions that TMPG and MBG are equivalent and equal has limitations, as discussed previously in Chapter 8.

9.7 Conclusion

Culprit location and TMPG are associated with infarct size quantified as % LGE of the LV mass on CMR. This supports the inclusion of culprit location and MBG in the Liverpool MI Risk Model where they likely contribute to the predictive power of the model because of associations with subsequent LV function, a surrogate for infarct size. Age was not

associated with LGE and likely adds predictive power to the Liverpool model because of the association with increased risk of death.

Final word

The aim of this thesis was to explore possible methods of improving outcomes for STEMI patients. STEMI is associated with significant mortality and morbidity even if timely treatment with primary PCI is performed. The 12-month mortality follow-up in the HEAT-PPCI trial showed a mortality rate of 8.9%. This result reflects the rates of national registries and highlights the potential to improve mortality rates in STEMI.

Current assessment of the PPCI angiogram includes a statement of the final TIMI flow grade and a description of the luminal geometry of the treated culprit. However, there are several well-validated angiographic grading systems that can be assessed on the PPCI angiogram. These include thrombus burden, myocardial blush grade and corrected TIMI frame count. The development of a systematic approach to angiogram interpretation, including assessment of these additional variables, is likely to add information regarding the success of PPCI and possibly identify more patients with poor myocardial reperfusion. To recommend the use of the variables in clinical practice I attempted to establish the reliability of the variables on repeat assessment. The TIMI flow grade, thrombus burden and dichotomised cTFC showed good intra- and interobserver variability, with MBG showing moderate agreement.

Several risk scores have been developed to help risk-stratify patients with STEMI, but few can be calculated during the acute event. If patients who are more likely to experience an adverse event following STEMI could be identified during PPCI they may benefit from timely administration of adjunctive therapies or longer surveillance in critical care. The Liverpool MI Risk Model combined an assessment of the MBG with age and culprit vessel location to accurately predict 28-day death or subsequent severe impairment of LV function (ejection fraction ≤35%).

All risk models should be validated on an external cohort of patients. I used data from the BHF MR-MI study to validate the Liverpool MI Risk Model. The discrimination of the model on validation was similar to the derivation cohort (c statistic: 0.837; 95% CI 0.723 to 0.951), however, the model overestimated the number of adverse events in the validation cohort. This is likely due to differences in the method of measuring myocardial blush used by each study as well as significant differences in eligibility criteria, strategies to obtain consent, and primary outcome measures. A study of unselected STEMI patients should be used to validate the Liverpool MI Risk Model. Following validation, an impact study should be performed to assess the effect of using the Liverpool MI Risk Model on patient outcomes.

MBG is a well-known grading system for assessing contrast density in the myocardium and reflects the degree of microvascular reperfusion achieved. However, in the UK, it is not routine practice to assess MBG. The results from the Liverpool MI Risk Model show that the simple addition of MBG to the assessment of a PPCI angiogram could help operators risk stratify patients adding minimal extra time to the procedure. In clinical practice, the Liverpool MI Risk Model could be used during PPCI to help operators identify low-risk patients. These patients could then be directed to lower intensity clinical areas, facilitating earlier discharge and improving resource utilisation.

10.1 Appendix 1: Database creation

10.1.1 Aim

The original HEAT-PPCI database was created in Microsoft Access. I used the same software to develop the database and associated data collection form which allowed the data collection form to be more easily populated by the existing data from HEAT-PPCI database. Access provides for full Structured Query Language (SQL) database functionality in a product that is practical to learn as a junior researcher. I was able to develop a secure application that was efficient to use yet also involved computer code for date entry checks and automated calculation.

10.1.2 Flat versus relational database

Relational databases have advantages over flat databases because they can record multiple episodes/vessels/admissions/events per patient. Using a relational database would allow entry of data into several distinct tables. Therefore, one patient could have several episodes which were linked to their unique clinical record form (CRF) number (see Figure 10.1). However, I was using a database where the number of events was already known from the previous data collection during the HEAT-PPCI trial. I, therefore, used a flat design because I was not adding extra episodes per patient, but was adding additional procedural information to pre-existing episodes. Theoretically, if a patient had more than one admission for STEMI during the trial, they could have more than one episode entered the database. This did not apply to the HEAT-PPCI trial, as patients who presented with a STEMI and had already been enrolled in the trial were excluded and, therefore, I did not have to examine multiple episodes during data collection.

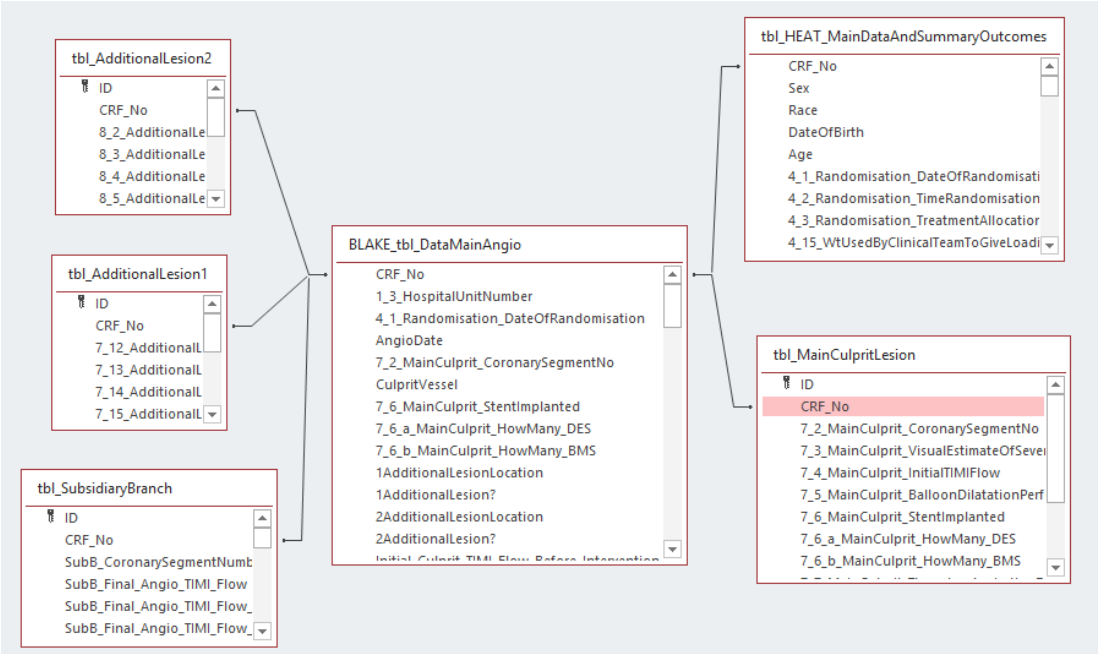


Figure 10.1: Example of one-to-many relationships within the database

10.1.3 The data collection form

Figure 10.2 shows the data collection form. This includes the fields populated by existing data from the HEAT-PPCI database as well as data filled during this analysis of the HEAT-PPCI angiograms. The angiographic grading systems were assessed from several cineruns selected from each angiogram and the grades recorded in the form. This form then automatically populated a database table. The fields used for data collection are listed in Figure 10.3.

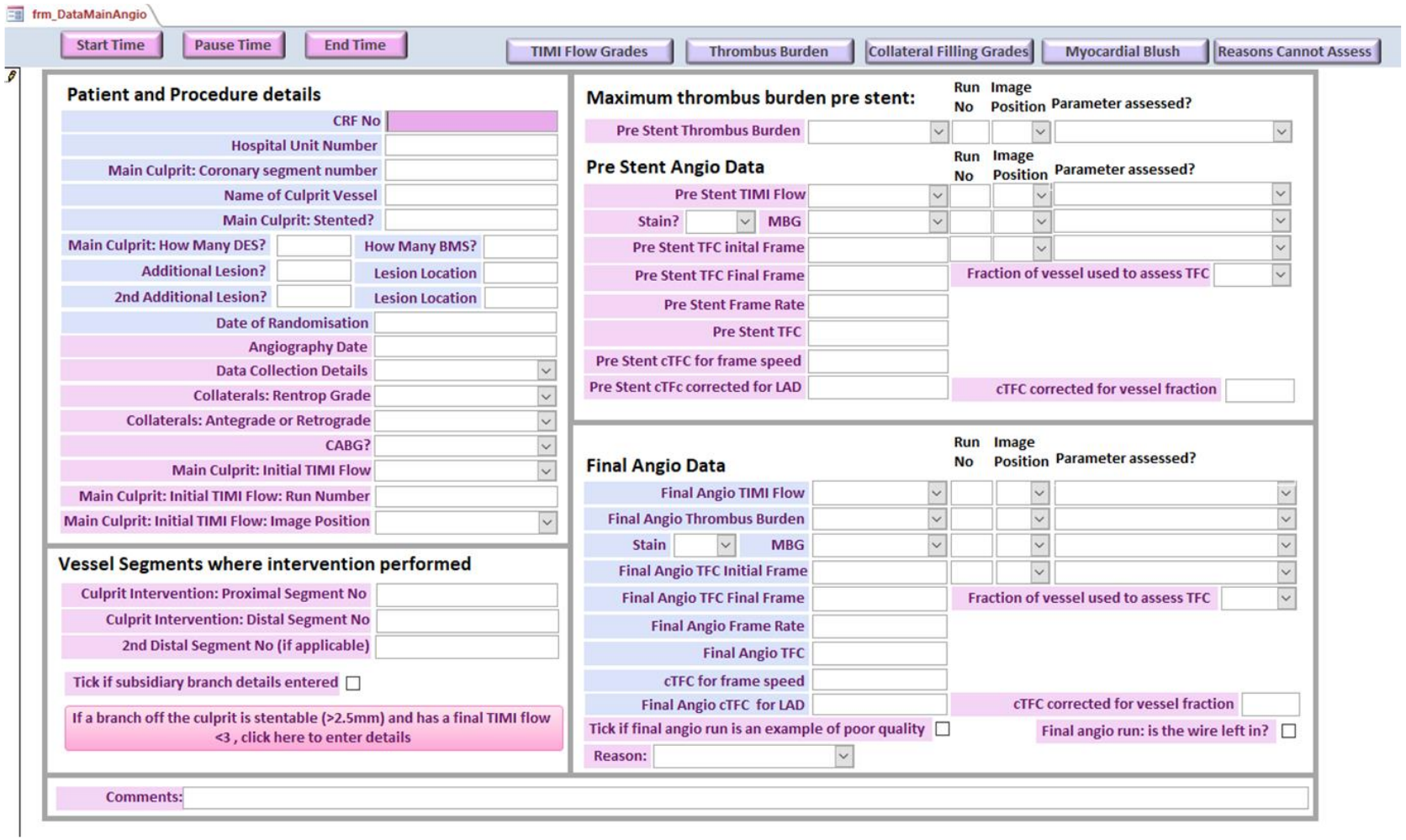


Figure 10.2: The form designed in Microsoft Access to collect data on each angiographic grading system

Columns

Name	Type	Size
CRF_No	Long Integer	4
1_3_HospitalUnitNumber	Text	50
4_1_Randomisation_DateOfRandomisation	Date/Time	8
AngioDate	Date/Time	8
7_2_MainCulprit_CoronarySegmentNo	Integer	2
CulpritVessel	Text	4
7_6_MainCulprit_StentImplanted	Text	25
7_6_a_MainCulprit_HowMany_DES	Integer	2
7_6_b_MainCulprit_HowMany_BMS	Integer	2
1AdditionalLesionLocation	Text	255
1AdditionalLesion?	Text	255
2AdditionalLesionLocation	Text	255
2AdditionalLesion?	Text	255
Initial_Culprit_TIMI_Flow_Before_Intervention	Text	255
Initial_culprit_TIMI_Flow_Run_Number_in_Excelera	Long Integer	4
Initial_culprit_TIMI_Flow_Position_Lateral_Frontal	Text	255
Pre_Stent_TIMI_Flow	Text	255
Pre_Stent_TIMI_Flow_Run_Number_in_Excelera	Long Integer	4
Pre_Stent_TIMI_Flow_Position_Lateral_Frontal	Text	255
Pre_Stent_TIMI_Flow_Assessment_Quality	Text	255
Pre_Stent_Thrombus_Burden	Text	255
Pre_Stent_Thrombus_Burden_Run_Number_in_Excelera	Long Integer	4
Pre_Stent_Thrombus_Burden_Position_Lateral_Frontal	Text	255
Pre_Stent_Thrombus_Burden_Assessment_Quality	Text	255
Pre_Stent_Thrombus_Burden_Run_Number_in_Excelera	Long Integer	4
Pre_Stent_Thrombus_Burden_Position_Lateral_Frontal	Text	255
Pre_Stent_Thrombus_Burden_Assessment_Quality	Text	255
Pre_Stent_TFC_inital_Frame	Long Integer	4
Pre_Stent_TFC_Assessment_Quality	Text	255
Pre_Stent_TFC_Final_Frame	Long Integer	4
Pre_Stent_TFC	Integer	2
Pre_Stent_Frame_Rate	Long Integer	4
Pre_stent_TFC_Run_Number_in_Excelera	Long Integer	4
Pre_Stent_TFC_Position_Lateral_Frontal	Text	255
Pre_Stent_cTFC_corrected_for_frame_speed	Long Integer	4
Pre_Stent_cTFC_corrected_for_LAD	Long Integer	4
Pre_Stent_cTFC_corrected_for_vessel_fraction	Long Integer	4
Pre_Stent_Fraction_vessel_TFC	Single	4
Pre_Stent_Stain	Text	255
Pre_Stent_MBG	Text	255
Pre_Stent_MBG_Run_Number_in_Excelera	Long Integer	4
Pre_Stent_MBG_Position_Lateral_Frontal	Text	255
Pre_Stent_MBG_Assessment_Quality	Text	255
Final_Angio_TIMI_Flow	Text	255
Final_Angio_TIMI_Flow_Run_Number_in_Excelera	Long Integer	4
Final_Angio_TIMI_Flow_Position_Lateral_Frontal	Text	255
Final_Angio_TIMI_Flow_Assessment_Quality	Text	255
Final_Angio_Thrombus_Burden	Text	255
Final_Angio_Thrombus_Burden_Run_Number_in_Excelera	Long Integer	4
Final_Angio_Thrombus_Burden_Position_Lateral_Frontal	Text	255
Final_Angio_Thrombus_Burden_Assessment_Quality	Text	255
Final_Angio_TFC_Initial_Frame	Long Integer	4
Final_Angio_TFC_Assessment_Quality	Text	255
Final_Angio_TFC_Final_Frame	Long Integer	4
Final_Angio_TFC	Integer	2
Final_Angio_Frame_Rate	Long Integer	4

Final_Angio_TFC_Run_Number_in_Excelera	Long Integer	4
Final_Angio_TFC_Position_Lateral_Frontal	Text	255
Final_Angio_cTFC_corrected_for_frame_speed	Long Integer	4
Final_Angio_cTFC_corrected_for_LAD	Long Integer	4
Final_Angio_cTFC_corrected_for_vessel_fraction	Long Integer	4
Final_Angio_Fraction_vessel_TFC	Single	4
Final_Angio_Stain	Text	255
Final_Angio_MBG	Text	255
Final_Angio_MBG_Run_Number_in_Excelera	Long Integer	4
Final_Angio_MBG_Position_Lateral_Frontal	Text	255
Final_Angio_MBG_Assessment_Quality	Text	255
Final_Angio_Quality_Poor	Yes/No	1
Final_Angio_wire_left_in	Yes/No	1
Final_Angio_Quality_Poor_reason	Text	255
DataCollectionDetails	Text	25
Collateral_Rentrop_Grade	Text	255
Collaterals_AntegradeRetrograde	Text	255
CABG	Text	255
Treated_culprit_segment_starts	Long Integer	4
Treated_culprit_segment_ends	Long Integer	4
Treated_culprit_segment_ends2	Long Integer	4
Time_to_fill_form	Long Integer	4
Comments:	Text	255
SubBranch_entered	Yes/No	1

Figure 10.3: Database documenter showing the fields used to collect data

10.1.4 Using data from the HEAT-PPCI trial database

Selected data from the HEAT-PPCI trial were linked to the form and populated the relevant fields. These fields were used to identify the correct angiogram within the viewing software as well as the culprit segment and type of coronary intervention performed. The culprit segment and the segments where intervention was performed were defined using a numbering system detailed in Figure 10.4.

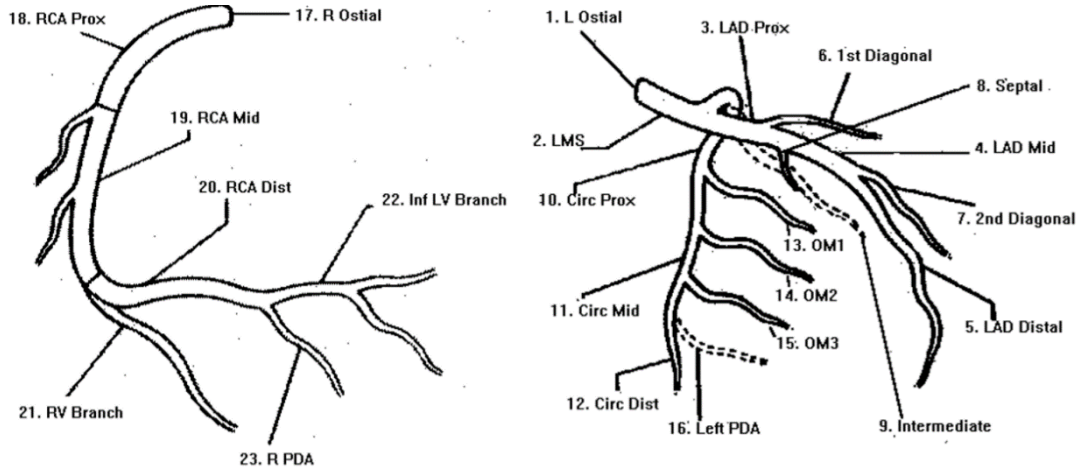


Figure 10.4: Labelling of coronary segments in the HEAT-PPCI trial

10.1.5 Collecting data from the angiograms

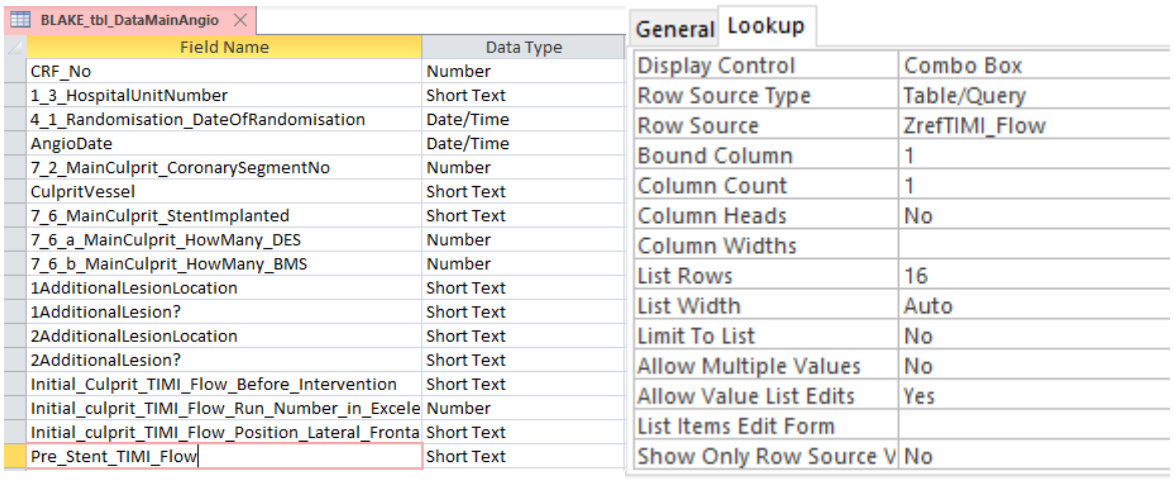
Data was collected from the angiograms that described the overall procedure, such as the treated coronary segments, collateral grade and angiographic quality. I also collected data on the selected angiographic grading systems. These were assessed prior to stent insertion (if one or more stents were implanted during the procedure) and in the final angiographic cinerun, once all intervention was complete. Throughout the thesis I refer to these time-points as “pre-stent” and “post-stent”. The thrombus burden prior to stent insertion was calculated at an earlier time point (referred to as “pre-stent”). In addition to the value for each angiographic system, the cinerun as numbered in Xcelera, was also recorded. If the angiogram was acquired in a biplane lab, the plane (lateral or frontal) was recorded. This allowed easy re-review of the cinerun used for data collection to check data quality.

10.1.6 Drop-down menus

The possible inputs for a given field were limited using drop-down menus to create structured data entry. Each option was labelled with a number code. By allowing selection of a data input option by simply typing the number code into the field, I aimed to increase

the speed of data entry, reduce errors and erroneous free text. This also allowed for easier searching within the database during data analysis.

To create a drop-down menu, I created a separate table, termed ZRef, and created a link in the “lookup” function (Figure 10.5).



BLAKE_tbl_DataMainAngio

Field Name	Data Type
CRF_No	Number
1_3_HospitalUnitNumber	Short Text
4_1_Randomisation_DateOfRandomisation	Date/Time
AngioDate	Date/Time
7_2_MainCulprit_CoronarySegmentNo	Number
CulpritVessel	Short Text
7_6_MainCulprit_StentImplanted	Short Text
7_6_a_MainCulprit_HowMany_DES	Number
7_6_b_MainCulprit_HowMany_BMS	Number
1AdditionalLesionLocation	Short Text
1AdditionalLesion?	Short Text
2AdditionalLesionLocation	Short Text
2AdditionalLesion?	Short Text
Initial_Culprit_TIMI_Flow_Before_Intervention	Short Text
Initial_culprit_TIMI_Flow_Run_Number_in_Excele	Number
Initial_culprit_TIMI_Flow_Position_Lateral_Fronta	Short Text
Pre_Stent_TIMI_Flow	Short Text

General | Lookup

Display Control	Combo Box
Row Source Type	Table/Query
Row Source	ZrefTIMI_Flow
Bound Column	1
Column Count	1
Column Heads	No
Column Widths	
List Rows	16
List Width	Auto
Limit To List	No
Allow Multiple Values	No
Allow Value List Edits	Yes
List Items Edit Form	
Show Only Row Source V	No

Figure 10.5: The process of creating a drop-down menu for data entry

I populated the ZRef look-up table “ZrefTIMI_Flow” with the options listed in Figure 10.6. These options were then the only data that could be entered into that field. The drop-down menu can be seen in the data collection form in Figure 10.7.

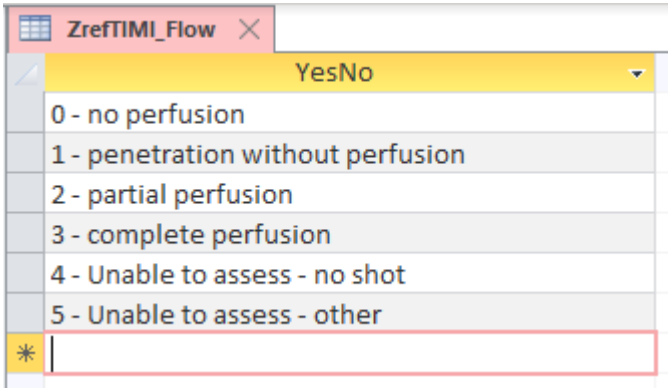


Figure 10.6: An example of a Zref table used to create drop-down menus for data entry

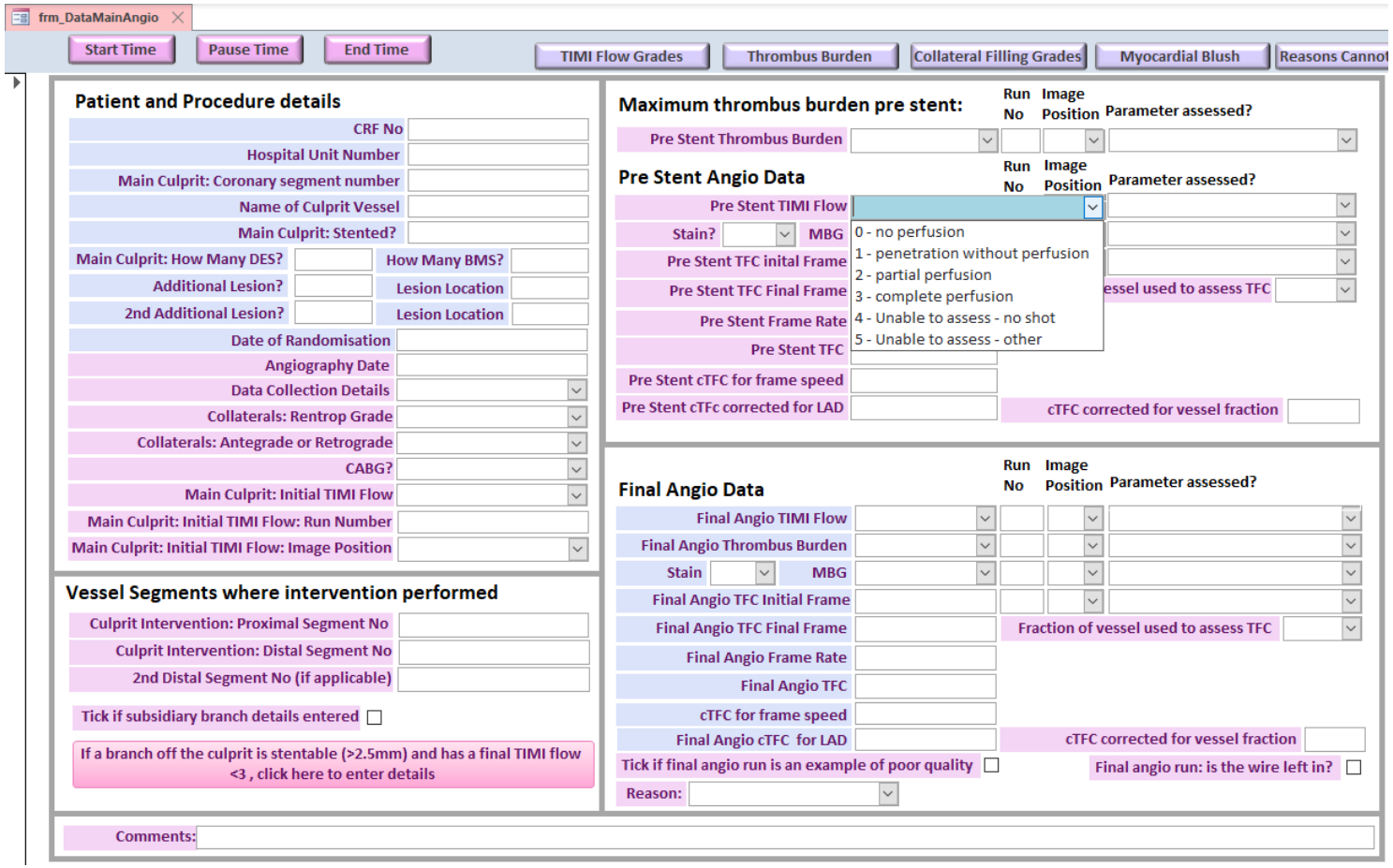


Figure 10.7: An example of a drop-down menu with pre-set options for data-entry

Buttons and associated pop-up windows were also available for thrombus burden grades, myocardial blush grades and Rentrop collateral grades. These could be used as quick reminders of the definitions of each grading system (Figure 10.8).

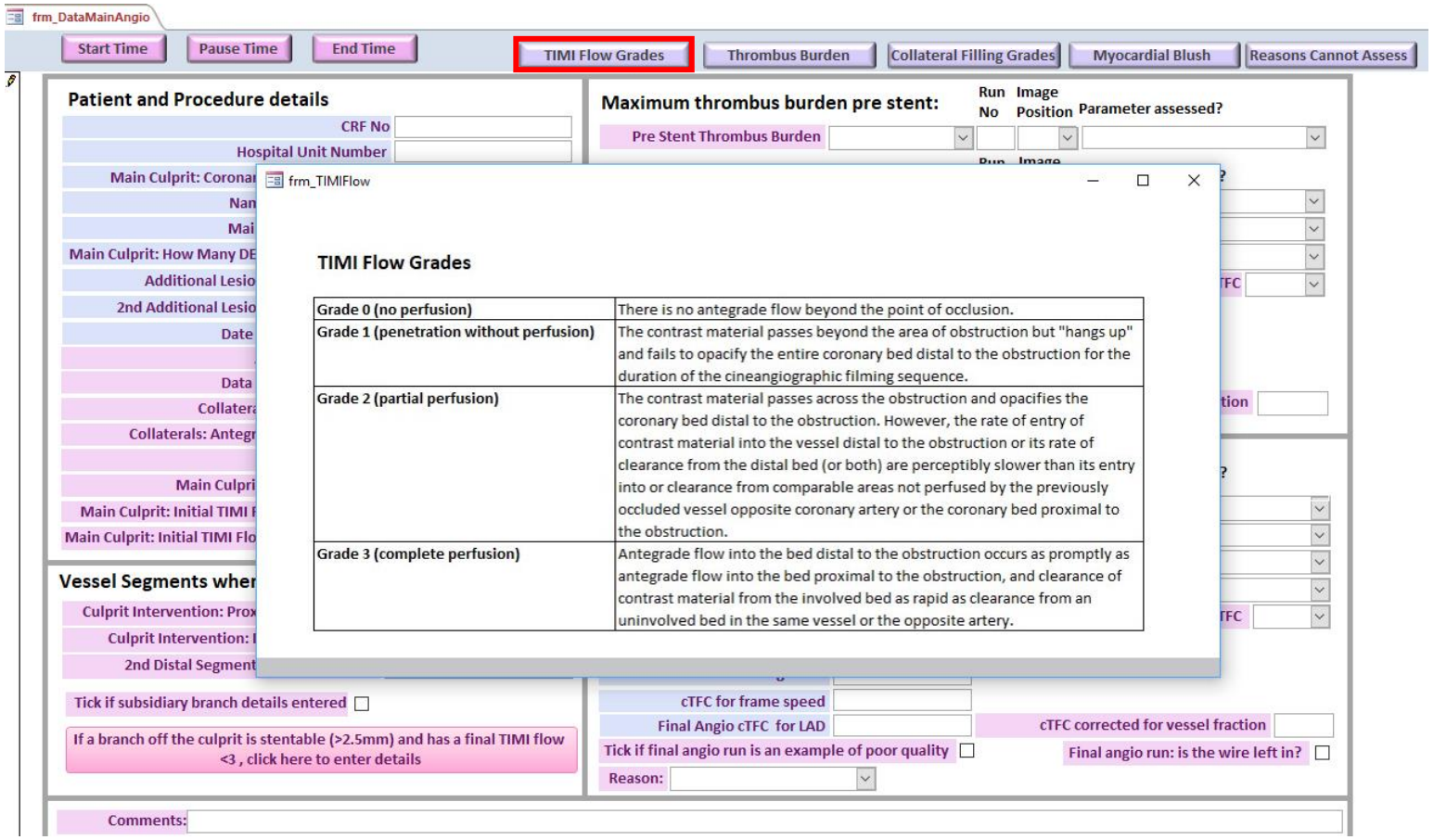


Figure 10.8: Example of the TIMI flow grade button (outlined in red) programmed to display a pop-up window of the TIMI flow grading system for quick reference during data collection

If I judged that the angiographic grade could not be confidently assessed, a data field was filled describing the degree of uncertainty in the assessment and the reason for selecting this option (Figure 10.9). Common reasons included poor angiographic image resolution, poor angiographic panning, and cineruns that were too short to allow confident assessment of a grading system. An assessment of confidence was made each time a value was recorded for each system, at each time point.

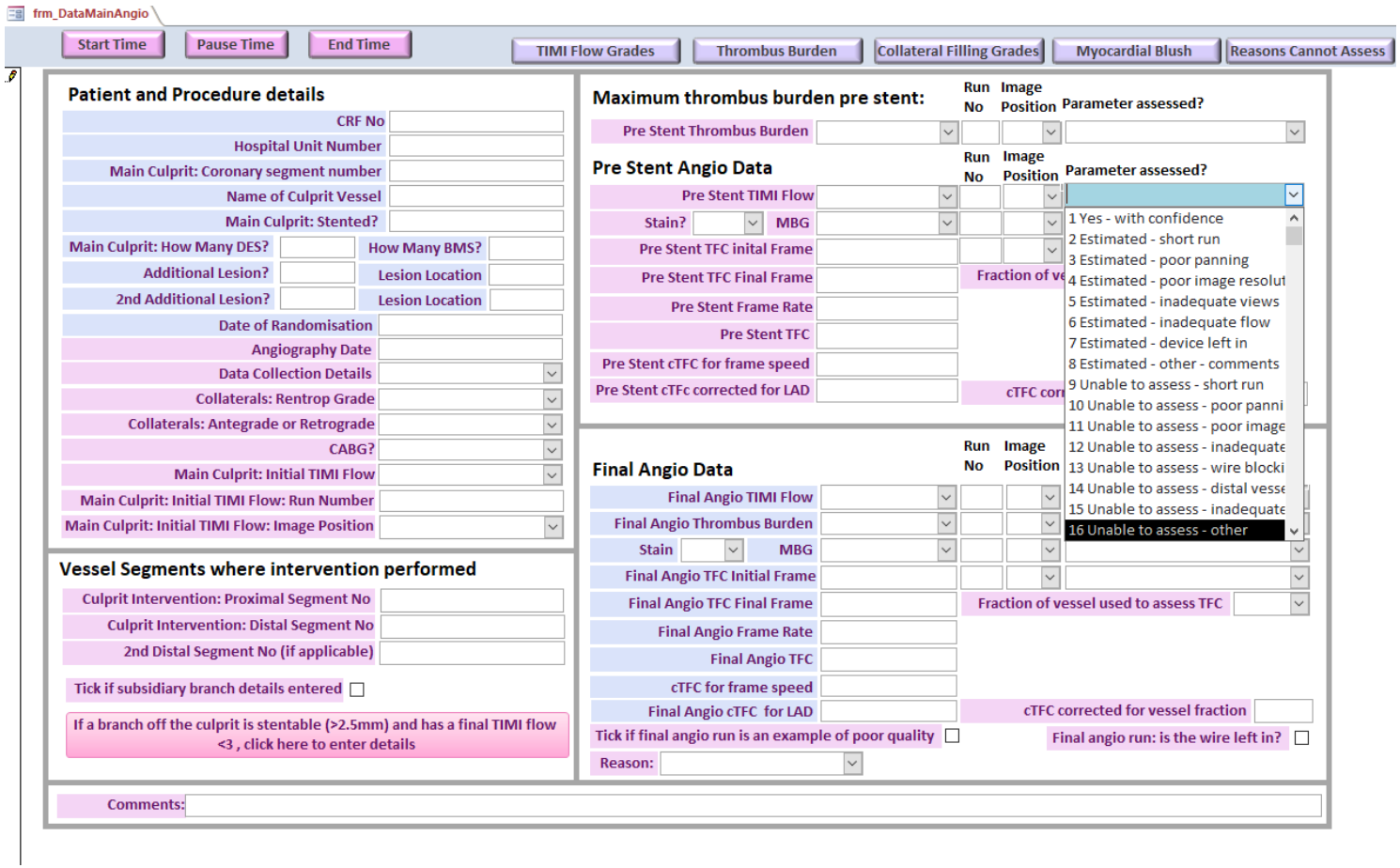


Figure 10.9: The drop-down options for recording the level of confidence in the assessment of a variable and the reason the input has been either estimated or not assessed

10.1.7 Programming automated values to fill the database

Several fields were programmed to automatically fill when data was manually entered into other related fields in the database. This was to increase the speed and accuracy of data collection. Visual Basic for Applications (VBA) was used to programme the automated calculation.

According to the original published method of calculating cTFC, assessment of the left anterior descending (LAD) artery differs from the circumflex (Cx) or right coronary artery (RCA) due to the longer mean length of the LAD.[99] To ensure the frames counted were corrected for longer LAD length, the database was programmed to automatically divide the frames counted by 1.7 if the culprit vessel was the LAD.

The frame rate of the cinerun (frames per second) was recorded and entered into the corresponding field in the database. The database was programmed to automatically correct the frames counted according to the frame rate, using 30 frames per second as the standard, as per the published method.

When initially testing the methods on the HEAT-PPCI angiograms, a high proportion of the angiographic runs did not display the full length of the culprit vessel. This made assessment of the cTFC more challenging. I, therefore, estimated the true length of the culprit vessel by calculating the cTFC in the visible section as a fraction of the estimated true vessel length. The cTFC calculated from the visible section was then multiplied by the visible section as a fraction of the estimated total length of the vessel. This allowed an estimate of the true cTFC to be made. This process was recorded in the "Parameter assessed?" field as "2. Estimated – poor panning". When both the estimated vessel fraction and the cTFC from the visible section were recorded in the form, the cTFC was automatically calculated and recorded in the corresponding field.

The field labelled “cTFC corrected for vessel fraction” contained the frame count, once it had been corrected for frame rate, LAD length (if the LAD was the culprit) and vessel fraction (if the full length of the culprit vessel was not visualised on the angiogram). I have termed this value the “estimated cTFC”. Recording the estimated cTFC in the database gave the option to use these values in addition to the cTFC, assessed with confidence, increasing the amount of data I could use in the final analysis.

The time taken to complete one data form was recorded in the database. A timer was programmed into the form using VBA and is illustrated in Figure 10.10.

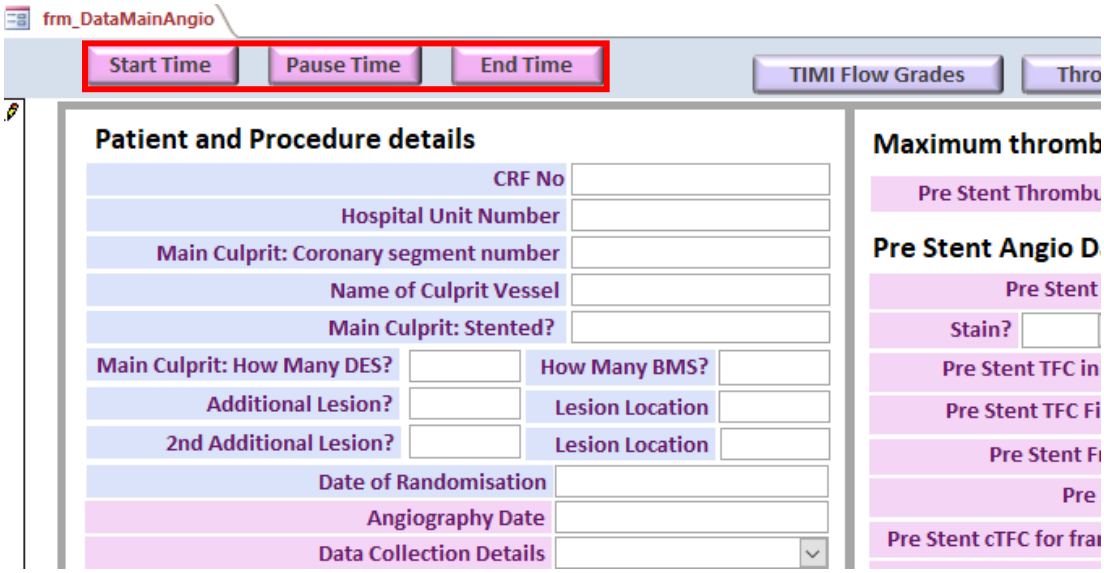


Figure 10.10: Buttons programmed to measure the time it takes to fill the form (outlined in red)

Figure 10.2 shows a button in the bottom left-hand corner of the data form labelled “if the branch off the culprit is stentable (>2.5mm) and has a final TIMI flow <3, click here to enter details”. On pressing this button, a further form appears as illustrated in Figure 10.11. This

form is then filled with the details of the stentable branch. The fields used for data collection using the “stentable branch” form are listed in full in Figure 10.12.

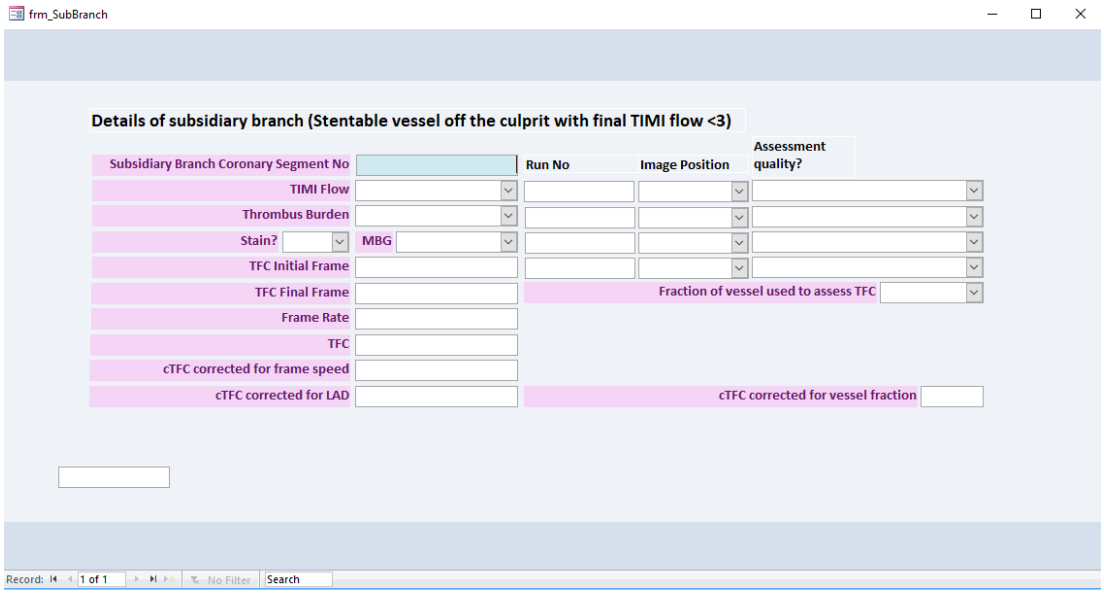


Figure 10.11: Figure illustrating the pop-up form for identifying and assessing any subsidiary branch of the culprit vessel that has poor flow at the end of the procedure

\\LHCH-FS01\users$\sblak\My Documents\Myocardial Reperfusion MD - Data Collection Databases\Current\AngioDataTable20180720TIMIFlow1462.accdb 22 May 2019

Table: tbl_SubsidiaryBranch Page: 1

Columns

Name	Type	Size
ID	Long Integer	4
CRF_No	Integer	2
SubB_CoronarySegmentNumber	Long Integer	4
SubB_Final_Angio_TIMI_Flow	Text	255
SubB_Final_Angio_TIMI_Flow_Run_Number_in_Excelera	Long Integer	4
SubB_Final_Angio_TIMI_Flow_Position_Lateral_Frontal	Text	255
SubB_Final_Angio_TIMI_Flow_Assessment_Quality	Text	255
SubB_Final_Angio_Thrombus_Burden	Text	255
SubB_Final_Angio_Thrombus_Burden_Run_Number_in_Excelera	Long Integer	4
SubB_Final_Angio_Thrombus_Burden_Position_Lateral_Frontal	Text	255
SubB_Final_Angio_Thrombus_Burden_Assessment_Quality	Text	255
SubB_Final_Angio_TFC_Initial_Frame	Long Integer	4
SubB_Final_Angio_TFC_Final_Frame	Long Integer	4
SubB_Final_Angio_TFC	Integer	2
SubB_Final_Angio_Frame_Rate	Long Integer	4
SubB_Final_Angio_TFC_Run_Number_in_Excelera	Long Integer	4
SubB_Final_Angio_TFC_Position_Lateral_Frontal	Text	255
SubB_Final_Angio_cTFC_corrected_for_frame_speed	Long Integer	4
SubB_Final_Angio_cTFC_corrected_for_LAD	Long Integer	4
SubB_Final_Angio_cTFC_corrected_vessel_fraction	Long Integer	4
SubB_TFC_Assessment_Quality	Text	255
SubB_Fraction_Vessel_TFC	Single	4
SubB_Final_Angio_Stain	Text	255
SubB_Final_Angio_MBG	Text	255
SubB_Final_Angio_MBG_Run_Number_in_Excelera	Long Integer	4
SubB_Final_Angio_MBG_Position_Lateral_Frontal	Text	255
SubB_Final_Angio_MBG_Assessment_Quality	Text	255

Figure 10.12: Database documenter displaying the fields used in the "stentable branch" data collection form

10.1.8 Queries

I used the query function in Microsoft Access to access data results. Simple select queries were used to retrieve data from one table. Complex select queries allowed linking if data between tables and were used to answer questions that involved data from more than one table.

10.1.8.1 Simple queries

Using simple select queries, I could count the number of events from a single table. For example, to count the number of patients who had TIMI 3 flow at the end of PPCI I created a 2-column query and used the count function to identify the proportion of each TIMI flow grade (Figure 10.13).

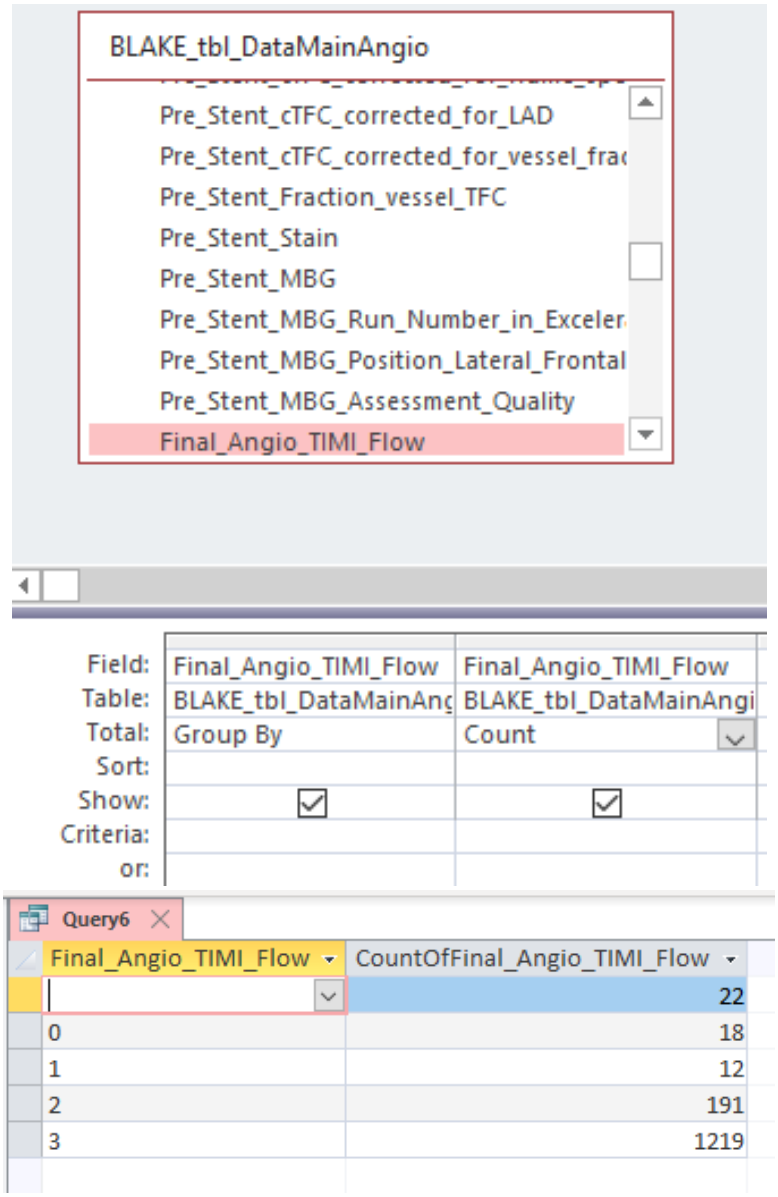


Figure 10.13: A 2-column query used to identify the counts of each TIMI flow grade

10.1.8.2 Complex queries

Queries that required data from more than one table were more complex. The unique CRF number assigned to each study participant allowed me to link tables within the database and display data from several tables within one query. I could then examine the associations between the outcome data collected in the HEAT-PPCI trial data table (tbl_HEAT_MainDataAndSummaryOutcomes) and the angiographic variables recorded into the study data collection form (BLAKE_tbl_DataMainAngio). For example, I wanted to retrieve data on the mortality rate at 28 days in patients with abnormal MBG. I linked the two required tables (Figure 10.14) and created a 2-column query with the final MBG grade and death. Using the "criteria" function in the Final_Angio_MBG field I could then specify only patients with MBG <3.

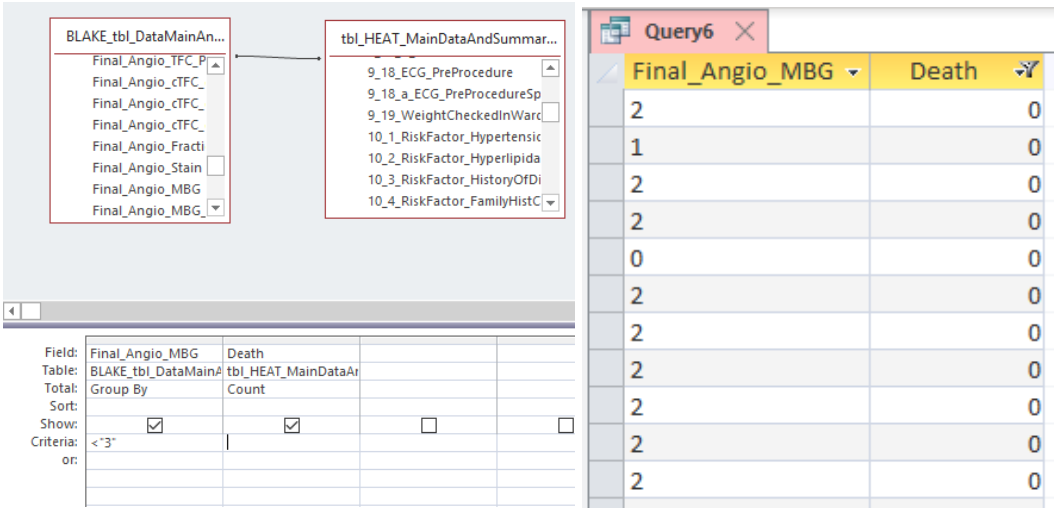


Figure 10.14: Complex query showing occurrence of death and MBG grade <3

Once retrieved from simple and complex queries, I exported the data to IBM SPSS Version 24 for statistical analysis.

10.2 Appendix 2: Copyright agreement for reproduction of cTFC figures

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Jan 09, 2019

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10.3 Appendix 3: Assessing intra- and inter-observer agreement: statistical analysis

10.3.1 Dichotomous variables

To determine the agreement between two assessments of a dichotomous variable, I calculated the percentage agreement or the proportion of cases where the assessments agree. This gives a measure called the overall proportion of agreement.[202] However, this measure does not take into account the chance agreement, defined as the proportion of agreement you would expect from the two assessments based on chance alone. We, therefore, used Kappa (k) statistics to assess agreement for all dichotomous variables.

10.3.1.1 Cohen's Kappa (k)

Cohen's k was developed to measure agreement between observers whilst considering any agreement due to chance.[203] Cohen's k is represented by the following equation:[204]

$$k = \frac{P_o - P_e}{1 - P_e} \tag{10.1}$$

P_o is the observed agreement and P_e is the agreement expected to occur by chance. k is therefore dependent on the prevalence of disease in the population. If disease prevalence is high, P_e increases and the k statistic decreases.

A value for k can range from -1 to +1. A negative value for k indicates that the agreement is less than that expected due to chance. A value of 0 indicates that the observed agreement was no better than that due to chance. A value increasing above 0 represents agreement that is better than that expected to occur by chance. The classification of k values is shown in Table 10.1.

Value of k	**Strength of agreement**
<0.20	Poor
0.21-0.40	Fair
0.41-0.60	Moderate
0.61-0.80	Good
0.81-1.00	Excellent

Table 10.1: Classification of k values

10.3.2 Continuous variables

For continuous variables, intra-class correlation coefficient (ICC) estimates and their 95% confidence intervals were calculated based on a single-rater, absolute-agreement, 2-way random effects model for interobserver reliability (SB1 vs CP or SB2 vs CP) and a single-rater, absolute agreement, 2-way mixed effects model for intraobserver reliability (SB1 vs SB2). Bland-Altman plots were used to display agreement between observers.

10.3.2.1 Intra-class correlation coefficient

The intra-class correlation co-efficient (ICC) was designed to assess the degree of correlation and agreement between measurements. ICC assesses reliability, defined as a ratio of true variance over true variance plus error variance. There are many types of ICC and selecting the correct type is essential for an accurate assessment of reliability.[159] There are several decisions that must be made to allow selection of the correct type of ICC for the specific analysis. For the interobserver analysis I used a two-way random effects model. This model assumes the observers used in the study are randomly selected from a wider population of similar observers, allowing generalisation of the results to any observers who possess similar characteristics to the observers used in the study. For example, I assumed that other observers will be trained to the same standard of assessing cTFC as SB and CP. A one-way random effects model would be used if every assessment of cTFC was assessed by a different set of observers randomly selected from a general population of observers. A two-way mixed-effect model should be used if the same observers are used and these are the only observers of interest i.e. the results do not need to be generalised to a larger population of observers. When assessing intraobserver reliability (SB1 vs SB2), the two-way mixed effects model is appropriate because I cannot assume that the results from only one observer can be generalised to a population. The calculation is the same as for the two-way random effects model so the statistics do not change.[159]

Another variation between ICC types depends on the application of the measure. For example, in clinical practice the cTFC is likely to be assessed by one operator in the cath lab, therefore, I use a “single measure” ICC. If the cTFC was assessed by taking the mean of several measures of cTFC from several operators, I would use an “average measures” ICC.

I then had to decide if I used absolute agreement or consistency in our assessment of ICC. Consistency is the degree to which the grade assessed by one observer can be equated to other observer's grade plus a systematic error. Absolute agreement concerns the extent to which one assessment equals the other.

For this analysis I used the absolute agreement of two-way random effects model and assumed the following model:

$$x_{ijk} = \mu + r_i + s_j + \varepsilon_{ijk} \tag{10.2}$$

In this model, x_{ijk} is the k^{th} measurement on the j^{th} subject by the i^{th} observer; μ is the overall population mean of the measurements; s_j is the difference from μ of the j^{th} subject's so-called true score (i.e. the mean over repeated measurements on the j^{th} subject); r_i is the difference from μ of the i^{th} observer's measurement; and ε_{ijk} is the random error in the kth measurement on the j^{th} subject by the i^{th} observer.

We assumed that r_i and s_j vary normally with zero mean and variances respectively σ_r^2 and σ_s^2. The error terms are assumed to be independently and normally distributed with zero mean and variance σ_ε^2.[205]

The ICC can be expressed as the variance ratio:

$$\rho_{\text{inter}} = \frac{\sigma_s^2}{\sigma_s^2 + \sigma_r^2 + \sigma_\varepsilon^2}. \tag{10.3}$$

An ICC approaching 1.0 indicates excellent reliability, whereas an ICC of less than 0.5 indicates poor reliability.[206]

10.3.2.2 Bland-Altman plots

Bland-Altman (BA) plots examine the potential for bias between the mean differences of paired measurements and were used to demonstrate the magnitude of the difference between observers over the range of cTFC measurements. BA plots quantify the "agreement interval" within which 95% of the observed differences fall:

$$\text{Limits of agreement} = \text{mean difference} \pm 1.96 \times \text{standard deviation} \quad (10.4)$$

For this analysis, the difference between the two paired values of cTFC and the mean of the two values were plotted against one another.[161] The limits of agreement considered acceptable were decided *a priori* and are explained in the power calculation in section 6.3.3.2. Bias was defined as the consistent tendency for the cTFC measured at one time point to exceed the measurement made at the second time point or by the second observer.[161] This was evaluated by both a visual assessment of the BA plot and calculating the mean difference plus 95% CI. If measurement error was truly random then the mean of all the differences in the sample should be close to 0, with a 95% CI that crosses the line of equality (the line all points would lie on if the two assessments always gave exactly the same measurement).[161]

10.3.3 Defining the sample size

10.3.3.1 Dichotomous variables

Because I was estimating the interobserver reliability coefficient (Cohen's $\boldsymbol{k}$) of a population from a sample, I aimed to ensure the coefficient did not differ by more than 20% (an arbitrary value frequently chosen by researchers) from the "true" coefficient of the population. Therefore, it was important to use a sample size that would give an estimate that differs no more than 20% from the "true" value. Gwet et al. proposed a solution to this for use when estimating kappa-like agreement coefficients.[207]

For all kappa-like coefficients, the required number of subjects (n) depends on the relative error (r) and the difference between the observed agreement (P_o) and the chance-agreement (P_e) as follows:

$$n = \frac{n*}{1+n*/N} \qquad \text{where} \quad n* = \frac{1}{r^2(P_o - P_e)^2} \tag{10.5}$$

N is the number of subjects in the entire population. If a sample size is obtained using equation (10.5), the difference between the calculated coefficient and its "true" value will not exceed r (the probability will be less than 0.05). This equation shows that if the relative error is to be decreased, the sample size must be increased. The smaller the difference between P_o and P_e, the larger the required sample size. Table 10.2 shows the magnitude required for n for different values of relative error and agreement probability differences. If we assume that the chance agreement probability is 0, this will give us a minimum sample size requirement. Therefore if we conservatively assumed that the observers are likely to agree at least 50% of the time with a relative error of 20%, our sample size should be 100.[207]

$P_o - P_e$	Relative error		
	20%	30%	40%
0.1	2500	1111	625
0.2	625	278	156
0.3	278	123	69
0.4	156	69	39
0.5	100	44	25
0.6	69	31	17
0.7	51	23	13
0.8	39	17	10
0.9	31	14	8
1.0	25	11	6

Table 10.2: The number of subjects required by relative error and probability difference from Gwent et al.

10.3.3.2 Continuous variables

To decide a sample size for the study, I chose an acceptable level of variability for the cTFC as an observed difference +/- 8 frames or less of the absolute value of the arithmetic mean of the two individual observations, for 95% of the paired comparisons. The acceptable difference between measurements was a clinical judgement based on preliminary measurements of cTFC made while testing the methods. The sample size required for a precise estimation of agreement between measurements of the cTFC was determined by assuming a mean difference between observers of 0 and a standard deviation of 4. If the SD was 4 and 100 subjects were included, for a typical cTFC of 20, the mean difference is 0 (95% CI: 0.78 to -0.78). I assumed that 100 patients would each have an average of 2 cTFC assessments, with 60% made with confidence, yielding 120 measurements.

10.4 Appendix 4: External validation of the Liverpool MI Risk Model: Statistical Analysis

The following statistical analysis was performed for the validation of the Liverpool MI Risk Model:

Let s be the linear predictor for each subject using the original model coefficients:

$$s = \beta_0 + \beta_{Age}Age + \beta_{CV}CV + \beta_{MBG}MBG$$

We then fit the following set of logistic regression models:

$$E[y] = f(\gamma_0 + s) \tag{10.6}$$

$$E[y] = f(\gamma_0 + \gamma_1 s) \tag{10.7}$$

$$E[y] = f(\gamma_1 \text{group}_1 + \gamma_2 \text{group}_2 + \cdots + \gamma_k \text{group}_k + s) \tag{10.8}$$

where $E[\,]$ is the expectation operator (expected value), y is the binary outcome (event/no event) and $f()$ is the logistic function.

The parameter γ_0 from model (10.6) is the calibration-in-the-large (a comparison of the mean of all predicted risks with the mean observed risk). The group variables in model (10.8) are used to categorize p into deciles of predicted risk, to assess the relevance of risk groups. The parameter γ_1 from model (10.7) is the calibration slope and appears as a coefficient of the predictor p. The usefulness of these parameters stems from their interpretability as Standardised Incidence Ratios (SIR), calculated as the ratio of observed number of outcome events to the expected number of outcome events.

In models (10.6) and (10.8), the linear predictor s acts as an offset, without an attached parameter i.e. they are obtained from parameters that do not appear as coefficients of the predictor s. In models (10.6) and (10.7), $exponent(\gamma_0)$ estimates the ratio of observed events in the validation data set to the number predicted by the model, either globally

(model 10.6: calibration-in-the-large) or by risk groups (model 10.8). A value of $exponent(\gamma_0)$ close to 1 indicates that the model is a good predictor of events in the validation population.

From model (10.7), $exponent(\gamma_1)$ describes the impact of a unit increase of predictor s in terms of increased risk i.e. how many more events we can expect in the original population vs. the validation population per unit increase of predictor s. A value of $exponent(\gamma_1)$ close to 0 indicates that the model performs well in the validation population.

The validation process is described by all three models; however, we use model (10.7) to recalibrate the model to make it useful in a new population.

In model (10.8) we used two groups (since the number of events in the validation data set is small.) The two groups are defined by the median (2.3) of the predicted risk score in the Glasgow data.

The following table shows the SIRs estimated from the three models, with 95% robust confidence intervals.[177]

Model (10.6)	0.22 (0.12, 0.39)
Model (10.7)	4.2 (1.9, 9.1)
Model (10.8), group 1 (score ≤ 2.3)	0.11 (0.016, 0.81)
Model (10.8), group 2 (score > 2.3)	0.24 (0.13, 0.44)

Table 10.3: SIRs with 95% confidence intervals

The SIRs for models (10.6) and (10.8) are significantly less than 1, with 95% CI that do not include 1 (Table 10.7). This indicates that the Liverpool MI Risk Model tends to predict more events than observed in the Glasgow data, both globally (model 10.6) and when divided into risk groups (model 10.8). The SIR for model (10.7) is 4.2 (95% CI 1.9 to 9.1) suggesting that for each unit increase in the risk predictor p, we can expect the SIR to increase by a factor of at least 1.9 and up to 9.1, with 95% confidence. These results confirm the previous observation that the Liverpool population exhibits a higher proportion of adverse events with respect to the Glasgow population.

In Table 10.4 we show the actual observed and expected number of events in the two risk groups defined in model (10.8). Using model (10.7) we recalibrated the predictions of the Liverpool model, and calculated the recalibrated expected number of events. The recalibrated model accurately predicts the observed number of events. See also Figures 10.15 and 10.16 for a graphical representation.

	Observed	**Expected**	**Recalibrated expected**
Group 1 (score ≤ 2.3)	1	8.9	0.95
Group 2 (score > 2.3)	11	46	11

Table 10.4: Observed and expected event counts

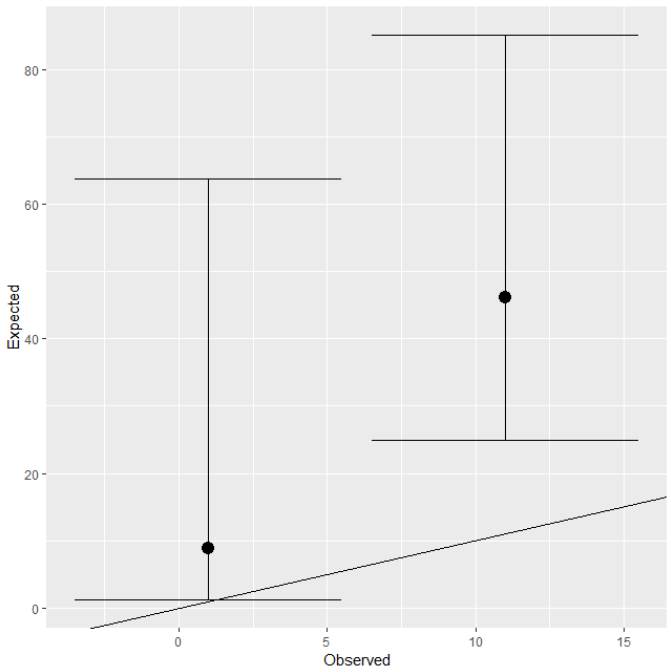

Figure 10.15: Observed vs. Expected number of events in Groups 1 and 2, with 95% confidence intervals. The black line is the identity line (where x=y).

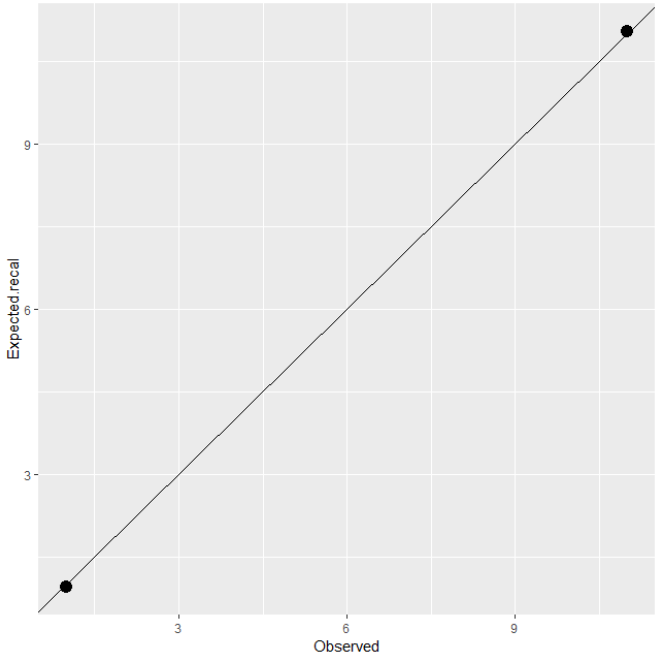

Figure 10.16: Observed vs. Recalibrated expected number of events. The black line is the identity line.

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