Clinical Outcomes after Percutaneous Coronary Interventions: Focusing on Selective Drug-eluting Stent Use

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Clinical Outcomes after Percutaneous Coronary Interventions: Focusing on Selective Drug-eluting Stent Use

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The introduction of DES has revolutionized interventional cardiology by reducing restenosis and thus target vessel revascularization (TVR) rates. Selective use of DES in those patients at highest risk of restenosis is a potentially attractive approach as it may allay concerns about the risk of late stent thrombosis (ST) and the need for compliance with dual anti-platelet therapy (DAPT), aspirin and clopidogrel for 1 year. Hence, clinical outcomes were examined after adoption of criteria for selective DES use at Liverpool Hospital, Sydney, Australia. Using these criteria which aimed for ~30% DES use in patients at high risk of restenosis, low TVR rates at 1 year of 4.9% were achieved, and rates of death and MI were comparable to those after BMS. Though the ST rate of 2% reflects 1st generation DES, whether similar findings occur with 2nd generation use remains to be determined.

In the emergent setting of STEMI, uncertainty about patients' ability to comply with 1year DAPT after DES is common, and thus selective BMS deployment could be an attractive strategy if this achieved low TVR rates in large IRAs. BMS deployment in STEMI patients with IRAs ≥3.5mm was associated with low rates of TVR (2.2%). Their use in this setting warrants comparison with 2nd generation DES deployment in future randomised clinical trials.

Rescue PCI is guideline-recommended as it improves outcomes after failed fibrinolytic therapy. However, these recommendations are based on data from an earlier era of pharmacotherapy and procedural techniques. Clinical outcomes following rescue PCI, with high utilization rates of glycoprotein IIb/IIIa inhibitors and stenting, were examined. Mortality rates were comparable to rates for contemporary primary PCI in patients without pre-PCI shock (3.2%), especially in early presenters. Whether rates of bleeding can be reduced by different pharmacotherapies and interventional techniques, need clarification in future studies. Prospective studies of future pharmaco-invasive strategies in STEMI patients are warranted.

As peri-procedural MI is an important early clinical outcome, its diagnosis based on cardiac marker levels and their prognostic significance are important. Evaluation of TnT criteria for periprocedural MI were performed, and the association of both TnT and creatine kinase MB level elevations on death and/or MI were examined in both stable coronary heart disease and acute coronary syndrome; post-PCI TnT levels were associated with event-free survival at one year only in patients with stable coronary heart disease. In patients with acute coronary syndrome and elevated TnT levels undergoing PCI several days later, criteria of ≥20% increases in TnT were more common than absolute increments of > 3XURL in TnT or creatine kinase-MB levels. Elevations of ≥ 20% above elevated pre-PCI levels detects any small peri-procedural MIs of questionable prognostic significance though this criteria has not been revised in the recently published revision of the universal definition of MI.

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Dedication

To my mother, Fatma and

loving memory of my father, Meloud

To my brothers

To my sisters

Publications from this Thesis

Shugman I, Diu P, Gohil J, Kadappu K, Leung M, Lo S, Leung D, Hopkins A, Juergens C, French J. Evaluation of troponin T criteria for peri-procedural myocardial infarction in patients with acute coronary syndromes. The American Journal of Cardiology. 2011;107:863-870

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Shugman I, Hee L, Mussap C, Diu P, Lo S, Hopkins AP, Nguyen P, Taylor D, Rajaratnam R, Leung D, Thomas L, Juergens CP, French JK. Bare-metal stenting of large coronary arteries in ST-elevation myocardial infarction is associated with low rates of target vessel revascularization. American Heart Journal.2013; 165:591-9

Shugman I, Idris H, Kadappu K K, Nguyen P, Taylor D, Rajaratnam R, Leung D, Hopkins AP, Lo S, Juergens CP, French JK. Evaluation of a policy of selective drug-eluting stent implantation for patients with high risk of restenosis. Heart Lung and Circulation. 2013 In Press

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Dhawan A, Parikh D, **Shugman I**, French J, Hallani H, Fernandes C, Juergens CP. Contrast induced nephropathy in patients with pre-existing renal impairment undergoing invasive coronary procedures — a long-term follow-up. Medical Journal of Australia 2011; 195:268-269.

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Abbreviations

ACC	American College of Cardiology
ACS	Acute Coronary Syndromes
AHA	American Heart Association
BASKET-LATE	Basel Stent Kosten Effektivitats Trial -Late Thrombotic events
BMS	Bare-Metal Stent (s)
CABG	Coronary Artery Bypass Graft
CHD	Coronary Heart Disease
CI	Confidence Intervals
CK	Creatine Kinase
CKMB	Creatine Kinase – Myocardial Band
DES	Drug Eluting Stent (s)
ECG	Electrocardiogram
ESC	European Society of Cardiology
GPIIb/IIIa	Glycoprotein IIb/IIIa
HORIZONS-AMI	Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction
LCx	Left Circumflex
LM	Left main coronary artery
MI	Myocardial Infarction
IV	Intravenous
LAD	Left Anterior Descending
NSTEMI	Non ST-segment Elevation Myocardial Infarction
IQR	Inter Quartile Range
IRA	Infarct Related Artery
OR	Odds Ratio

MRI	Magnetic Resonance Imaging
GPIIb/IIIa	Glycoprotein IIb/IIIa
HR	Hazards Ratio
PES	Paclitaxel-eluting Stents
PASSION	Paclitaxel-Eluting versus Conventional Stent in Myocardial Infarction with ST- segment Elevation trial
PCI	Percutaneous Coronary Intervention
RCA	Right Coronary Artery
PTCA	Percutaneous Transluminal Coronary Angioplasty
RR	Relative Risk
SES	Sirolimus- eluting Stents
ST	Stent thrombosis
STEMI	ST- segment Elevation Myocardial Infarction
TIMI	Thrombolysis In Myocardial Infarction
TNK	Tenecteplase
TRANSFER-AMI	Trial of Routine ANgioplasty and Stenting after Fibrinolysis to Enhance Reperfusion in Acute Myocardial Infarction
TYPHOON	Trial to Assess the Use of the Cypher Stent in Acute Myocardial Infarction Treated with Balloon Angioplasty
TnT	Troponin T
TnI	Troponin I
TLR	Target Lesion Revascularisation
TVR	Target Vessel Revascularisation
WHO	World Health Organisation

Abstract

The projects in this thesis aimed to examine issues of management of patients with coronary heart disease undergoing percutaneous coronary intervention (PCI). In particular the following were examined: clinical outcomes following PCI with selective drug-eluting stent (DES) use; clinical outcomes after bare-metal stent (BMS) deployment in large infarct-related arteries (IRA); clinical outcomes following rescue angioplasty for ST-elevation myocardial infarction (STEMI) with high utilisation rates of glycoprotein IIb/IIIa inhibitors; troponin T (TnT) criteria for periprocedural myocardial infarction (MI) and its association with late clinical outcomes.

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As peri-procedural MI is an important early clinical outcome, its diagnosis based on cardiac marker levels and their prognostic significance is important. Evaluation of TnT criteria for periprocedural MI was performed, and the association of both TnT and creatine kinase MB level elevations on death and/or MI was examined in both stable coronary heart disease and acute coronary syndrome; post-PCI TnT levels were associated with event-free survival at 1 year only in patients with stable coronary heart disease. In patients with acute coronary syndrome and elevated TnT levels undergoing PCI several days later, criteria of ≥20% increases in TnT were more common than absolute increments of > 3XURL in TnT or creatine kinase-MB levels. Elevations of ≥ 20% above elevated pre-PCI levels detect any small peri-procedural MIs of questionable prognostic significance, though this criterion has not been revised in the recently published revision of the universal definition of MI.

Overview of the Thesis

1.1.1. Overview of the Thesis

This thesis focuses on the evaluation of the clinical outcomes of patients with coronary heart disease (CHD) after percutaneous coronary intervention (PCI). In particular the following were examined: (a) clinical outcomes following strategies of selective use of stents (drug-eluting stents [DES] and bare-metal stents [BMS]) in the management of patients with coronary heart disease; (b) clinical outcomes following the use of BMS in large coronary arteries in ST-elevation myocardial infarction (STEMI); (c) clinical outcomes following selective stent use and high utilisation rates of glycoprotein IIb/IIIa inhibitors following rescue percutaneous coronary intervention for STEMI; and (d) evaluation of the criteria for the definition of periprocedural myocardial infarction and study the effects of troponin T and creatine kinase-MB elevations after PCI on late clinical outcomes.

1.1.2. Chapters description

Background and review of literature of the four main objectives of this thesis are included in Chapter 1. Chapter 2 provides an explanation of general methods used to address the three main objectives of this thesis. It also involves the definition of the study population and definitions used in the studies. The four main studies and their results, discussions and conclusions are presented in Chapters 3, 4, 5 and 6, respectively. Chapter 7 presents the final discussion and concluding remarks with future directions.

Chapter 1

Introduction and Literature Review

1.1. Epidemiology and Pathophysiology of Coronary Heart Disease

1.1.1. The epidemiology of cardiovascular diseases

Cardiovascular diseases are considered as significant causes of death in developed countries and increasingly in many developing countries. [1-3] Among these, coronary heart disease (CHD) is the most common cardiovascular disease and is associated with high disability and mortality. It is estimated that by the year 2020, CHD will become the leading cause of death worldwide. [2]

1.1.2. Pathophysiology and clinical classification of atherosclerotic coronary heart disease

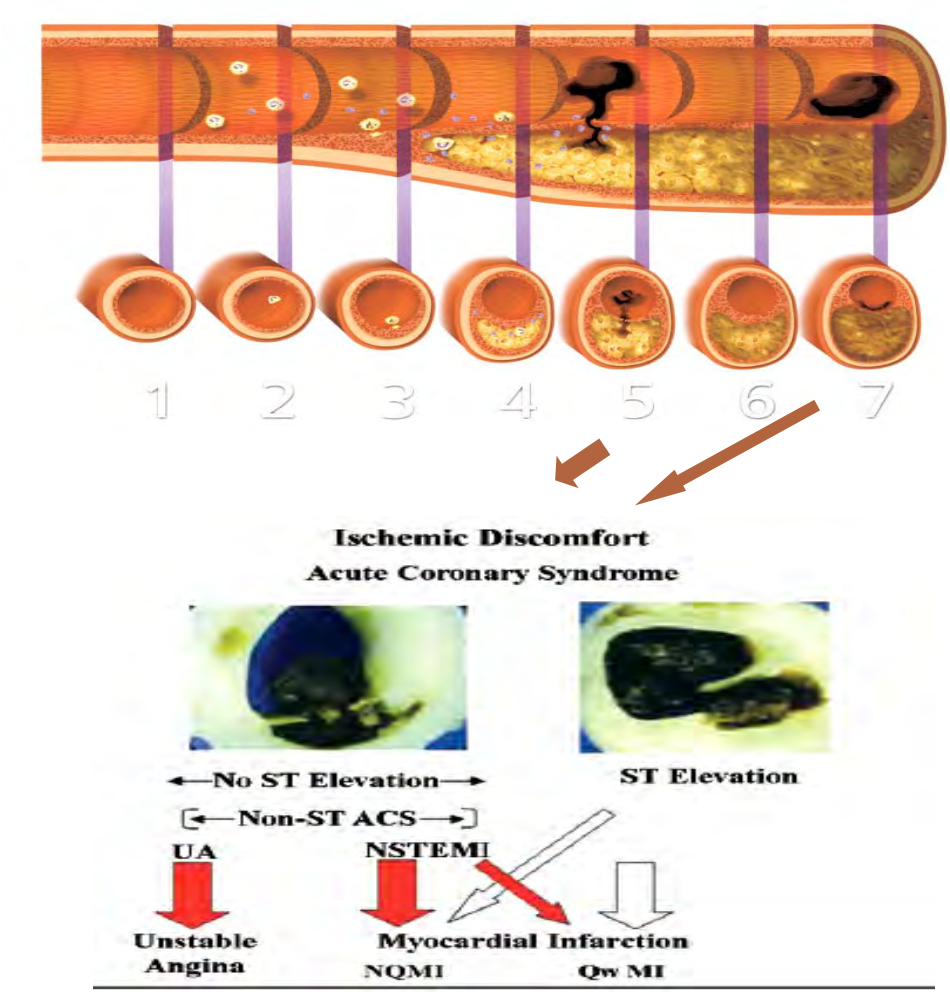
Coronary heart disease which is also called coronary artery disease is the clinical syndrome which refers to the failure of the coronary artery circulation to adequately maintain the balance between myocardial oxygen supply and consumption. The most common pathophysiological mechanism of CHD is atherosclerosis. At early stages of atherosclerotic lesion formation, extracellular lipids accumulate in the intima of the coronary arteries as a result of the activation of inflammatory leukocytes such as T lymphocytes and monocytes. This is followed by the fibrofatty changes stage and the formation of fibrous caps on the luminal aspect of the coronary arteries. This stage occurs as a result of the migration of monocytes to the lesion, formation of lipid-laden macrophage, secretion of inflammatory cytokines and growth factors, and the migration of smooth muscle cells. Atherosclerotic plaque growth and changes are shown in Figure 1.1. Either luminal superficial erosions or weakening of the fibrous cap by the secretion

of proteases with expression of procoagulant leads to the formation of vulnerable or high-risk plaque (Figure 1.1). [4] Vulnerable plaque is at high risk of rupture when it has one of the following features: an active inflammatory process, thin fibrous cap, large lipid content, surface fissuring, endothelial erosions with platelet activation and/or calcified nodules. [5] When the high-risk plaque undergoes disruption of the fibrous cap, stimulation of thrombogenesis causing thrombosis on occlusive or non-occlusive atherosclerotic plaque may occur. Resulting luminal thrombus depends on the local prothrombotic and fibrinolytic balance and can cause significant coronary flow reduction. In some cases thrombus resorption may be followed by collagen accumulation and smooth muscle cell growth. In a number of cases, occlusive and non-occlusive thrombi arise from the superficial erosion of the endothelial layer but not from rupture of the fibrous cap. As a result of plaque rupture and/or thrombus formation, coronary luminal reduction or complete occlusion may occur, which leads to myocardial underperfusion and a state of imbalance between the myocardial oxygen supply and oxygen consumption. [4]

The site and number of atherosclerotic plaques and their degree of change in size over time affects the degree of the coronary artery lumen obstruction. Depending on the degree and duration of the coronary artery lumen obstruction, presence of collateral myocardial vessels, and other factors that affect myocardial oxygen consumption such as an increase in heart rate and myocardial contractility following any physical or emotional activities may result in a state of imbalance between myocardial oxygen supply and oxygen consumption. [6] Patients may experience ischemic chest symptoms as a result of this imbalance especially when the atherosclerotic plaque leads to the reduction in the coronary lumen diameter to >50%.

Atherosclerotic plaques may cause narrowing in one or more of the coronary arteries. This will lead to symptoms of ischemia only after an increase in myocardial oxygen demand such as following exercise. As a result of this imbalance, a state of deficiency in the myocardium oxygen may present clinically as the spectrum of CHD depending on the degree and duration of this imbalance. Clinically, the spectrum of clinical presentations of CHD has been classified into chronic or stable CHD, acute coronary syndromes (ACS) and sudden death. [7] Chronic CHD includes silent ischemia and stable angina pectoris while the spectrum of ACS includes unstable angina pectoris and acute myocardial infarctions (MI). Along the spectrum, ACS is characterised by symptoms occurring acutely and may include unstable angina, non-ST-segment-elevation myocardial infarctions (NSTEMI) and ST-segment elevation myocardial infarctions (STEMI) (Figure 1.1). [8, 9] This is determined from the 12 lead electrocardiogram (ECG) and cardiac biomarker levels which include creatine kinase (CK), creatine kinase MB (CKMB) and/or the more specific and sensitive cardiac biomarkers, Troponins (Troponin T [TnT] or Troponin I [TnI]). [10] Within this range of ACS, STEMI represents the most severe form that may lead to mechanical instability, rhythm disturbance of the heart and/or sudden cardiac death, or long term morbidity.

Figure 1.1: Stages of Formation of Coronary Atherosclerotic Plaque and its Consequences



The upper section of the diagram represents the coronary artery (longitudinal and cross sections). It shows the stages of formation of the atherosclerotic plaque and its effect.

Labels are as following: (1) Cross section of normal artery, (2) Extracellular lipid accumulation in the coronary artery inner layer (intima), (3) Fibrofatty stage, (4) Lesion progression with weakening of the fibrous cap in addition to tissue factors and procoagulant expression, (5) Vulnerable or high-risk plaque undergoes rupture of the fibrous cap and stimulation of thrombogenesis that may lead to the development of thrombus depending on the balance between local prothrombotic and fibrinolytic activity; (6) Healing response with thrombus resorption and collagen accumulation and smooth muscle cell growth may follow.

(Reproduced from Libby, P; et al. [4]; Anderson, J.L; et al. [9]; and Davies, M.J. [11])

1.1.3. Pathology at the myocyte level

As a result of the marked reduction in coronary blood flow and the prolonged lack of oxygen and other nutrients at the myocyte level, cells quickly shift aerobic or mitochondrial metabolism to anaerobic glycolysis. This leads to a reduction in adenosine triphosphate (ATP) production which eventually leads to the inhibition of Na+/K+-ATPase and an increase in mitochondrial and cytosolic calcium which leads to osmotic overload and the activation of proteases that subsequently results in myocyte swelling. Finally, this may lead to contractile dysfunction and electrical disturbance of the affected myocytes that may result in arrhythmias. [6] The necrosis of myocytes may take several hours (2-4 hours) before it can be detected macroscopically by Computerised Tomography (CT) scan or magnetic resonance imaging (MRI) or even post-mortem microscopic examination. [10] The degree and extent of myonecrosis depends on the site of the affected coronary artery, the presence of collaterals and on the sensitivity of myocytes to the ischemia. Therefore, myonecrosis can be classified according to the size of the affected myocardium into microscopic or small myonecrosis (<10% of left ventricular myocardium), moderate (10-30% of left ventricular myocardium) or large myonecrosis (> 30% of left ventricular myocardium); and according to location of the affected myocardium. [10]

1.1.4. Risk factors for atherosclerotic coronary heart disease

There are many risk factors that may contribute to CHD and these can be divided into: a) modifiable risk factors which include hypercholesterolemia, smoking, diabetes mellitus, hypertension, a sedentary lifestyle and obesity; and b) non-modifiable risk factors which include age, male gender and family history of ischemic heart disease.

1.2. Evaluation and Management of Coronary Heart Disease

1.2.1. Chronic stable angina pectoris

Chronic stable angina pectoris is a clinical syndrome characterised by chronic symptoms attributable to myocardial ischemia such as central chest discomfort with or without radiation to the arms, back, jaw, neck or epigastrum; shortness of breath; weakness; diaphoresis; nausea and/or light headedness. These symptoms are aggravated by exercise or emotional stress, and are relieved by rest or nitroglycerin. [12] Patients with angina pectoris may progress to unstable angina pectoris, NSTEMI or STEMI.

1.2.1.1. Evaluation

After presentation of patients to the health care system with myocardial ischemic symptoms, a full medical history and examination are required. Laboratory investigations such as lipid profiles (high-density lipoprotein, low-density lipoprotein and triglycerides), fasting blood glucose level, full blood count (including haemoglobin and leukocyte count), and cardiac marker measurements if the clinical assessment shows some sign of instability should be performed. [12] These should be followed by non invasive testing such as a 12 lead ECG and when indicated, stress testing (stress ECG with or without imaging) to confirm the diagnosis. This may also be followed by invasive testing such as angiography. Figure 1.2 shows the steps for evaluation, diagnosis and management of patients with stable CHD and ACS.

1.2.1.2. Treatment

- Medical

The main aim of medical management is to improve prognosis, reduce symptoms and reduce death and MI. The medical management of stable-CHD involves the treatment and control of risk factors and control of plaque growth and prevention of thrombosis if the endothelial lining is dysfunctional or plaque becomes unstable. The management and control of plaque growth is carried out with aggressive cholesterol lowering treatment, and the prevention of thrombosis is carried out by the use of antiplatelet agents such as low doses of aspirin (75-150 mg /day). Management of risk factors includes: control of hypertension by anti-hypertensive agents such as angiotensin converting enzyme (ACE) inhibitors; advice and recommendations about quitting smoking; weight reduction for obese patients and regular exercise which may also play a role in the improvement of cardiovascular outcomes. The control of risk factors, the use of aspirin, cholesterol lowering agents, exercise and weight reduction have been shown to reduce the mortality associated with coronary disease. Figure 1.2 shows steps of evaluation and management of patients suspected of having coronary heart disease.

- Risk factor management

There are many risk factors that may contribute to CHD which can be divided into: a) modifiable risk factors which include hypercholesterolemia, smoking, diabetes mellitus, hypertension, a sedentary lifestyle and obesity; and b) non-modifiable risk factors which include age, male gender and family history of ischemic heart disease. Therefore, risk factor management focuses on the management of modifiable risk factors. Cessation of smoking and the control of diabetes with oral hypoglycaemic agents and insulin, the treatment of hypertension with antihypertensive agents and hypercholesterolemia with

lipid lowering agents, as well as weight reduction with regular exercise programs are all important aspects of the management of patients with CHD.

- Revascularization

Beyond medical therapies, there are three indications for further therapy with revascularization. The first is to alleviate symptoms and improve quality of life, the second is to prolong life and the third is to prevent non-fatal events. Both coronary artery bypass graft surgery (CABG) and percutaneous coronary intervention (PCI) are the main revascularization strategies. These are discussed in sections 1.3 and 1.4.

1.2.2. Acute coronary syndromes

Acute coronary syndromes are clinical syndromes which include UA, NSTEMI and STEMI. These syndromes are characterised by symptoms of chest discomfort with or without radiation to the arms, back, jaw, neck or epigastrum; or breathlessness; weakness; diaphoresis; nausea and/or light headedness. These symptoms are more severe, prolonged and more frequent than that of stable angina pectoris and also usually occur at rest. MI is characterised by more prolonged myocardial ischemic symptoms (> 30 minutes) and the occurrence of myocardial cell necrosis. [8, 9, 12]

1.2.2.1. Evaluation

At presentation to the health care system, clinical evaluation and characterisation of patients with ACS is important as their management is dependent on the differentiation of their types i.e. UA, NSTEMI or STEMI. [8, 9] A full medical history and examination are required. This is followed by recording a 12 lead ECG and blood test for myonecrosis markers including troponins (TnT or TnI), CKMB and/or CK. [9] In these clinical settings, UA is characterised by normal levels of myonecrosis markers with or without ECG changes, ST-segment depression, or prominent T-wave inversion.

NSTEMI is characterised by ECG changes, ST-segment depression or prominent T-wave inversion and positive /elevated levels of myonecrosis markers in the absence of persistent ST-segment elevation. STEMI is characterised by ECG changes with persistent ST-segment elevation or new left bundle branch block and positive/ elevated levels of markers of myonecrosis.

1.2.2.2. Treatment

- Medical

After the first medical contact, patients suspected of having ACS should receive 162-325 mg of acetyl salicylic acid tablets (chewable tablets are preferable as they quickly absorb through the bucal mucous membranes) unless contraindicated. Oxygen, heparin, glycoprotein IIb/IIIa (GPIIb/IIIa) inhibitors, nitroglycerin, morphine and beta-blockers may all be provided according to ACS presentation (Figure 1.2). [13]

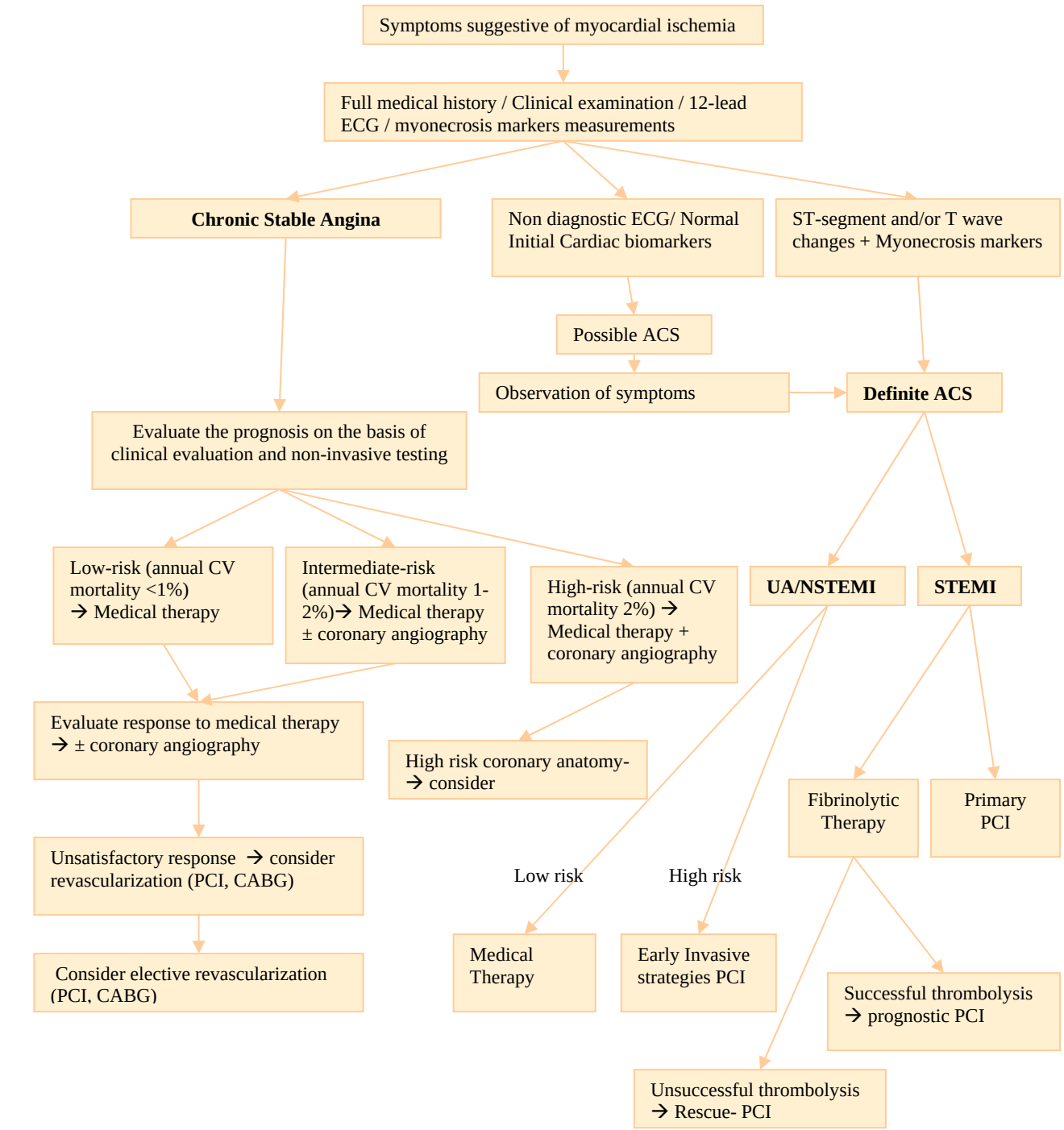
- Risk factor management

As discussed in the management of patients with stable-CHD in section 1.2.1.2.

- Revascularization

Beyond medical therapy, there are three indications for further therapy with revascularization. The first is to alleviate symptoms and improve quality of life, the second is to prolong life and the third is to prevent non-fatal events. CABG, PCI as well as pharmacological reperfusion for patients with STEMI are discussed later in sections1.3 and 1.4. There is considerable evidence that an invasive strategy improves outcomes in high risk NSTEACS.[9] Early stratification of patients by using clinical, ECG and cardiac markers parameters is essential. Figure 1.3 shows pathways in the management of patients with NSTEACS.

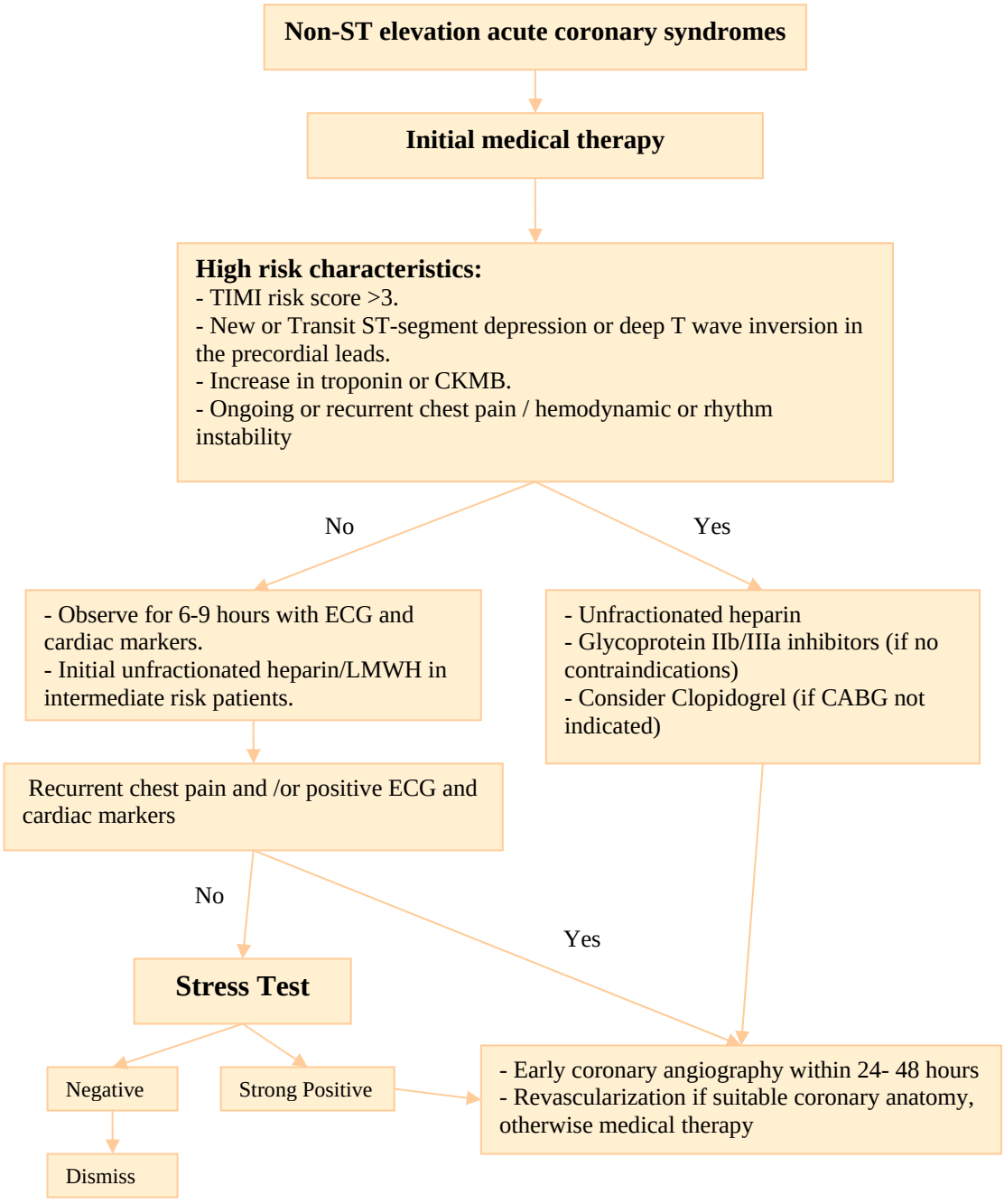
Figure 1.2: Algorithm for Evaluation and Management of Patients Suspected of having Coronary Heart Disease



ACS= acute coronary syndromes; CABG= coronary artery bypass grafting; ECG= electrocardiogram; NSTEMI= non-ST segment elevation myocardial infarction; PCI= percutaneous coronary intervention; STEMI= ST-segment elevation myocardial infarction; UA= unstable angina.

Modified from Anderson, J.L, et al. [9] *and Fox, K, et al.* [12]

Figure 1.3: Early Risk Stratification in the Management of Non-ST elevation Acute Coronary Syndromes



CABG= coronary artery bypass grafting; CKMB= creatine kinase- myocardial band; ECG= electrocardiogram; LMWH= low molecular weight heparin; PCI= percutaneous coronary intervention; TIMI= thrombolysis in myocardial infarction .

1.2.3. Clinical diagnosis of acute coronary syndromes and detection of myonecrosis

After a full medical history and examination, clinical detection of myocardial ischemia /necrosis includes the following investigations: 1) 12 lead ECGs; 2) measuring blood levels of myonecrosis markers; and 3) imaging.

1.2.3.1. Biochemical markers of myonecrosis

After the death of myocytes (cardiac muscle cells), various myocyte proteins are released into the circulatory system. These proteins are collectively called myonecrosis markers. These include: 1) myoglobin; 2) glutamine-oxaloacetic transaminase (GOT); 3) lactate dehydrogenase (LDH); 4) CK; 5) cardiac troponins (TnT and TnI); 6) CKMB, and other markers of myonecrosis. Of these clinically important biomarkers, CK , CKMB and troponins are commonly used clinically for diagnosis as well as prognostic assessment of the myonecrosis. For their high sensitivity and specificity for the detection of myonecrosis, troponins have become more widely used in recent years to detect early myocardial injury. [14].

Further discussion about cardiac markers and their clinical use as diagnostic tools for the detection of myonecrosis and as prognostic tools following PCI are detailed in section 1.8 of this Chapter.

1.3. Revascularization Strategies for Coronary Heart Disease

The main objectives of revascularization strategies in the management of CHD are to improve symptoms and prognosis and to prevent re-infarction, arrhythmias and heart failure.[15] Both revascularization procedures, PCI and CABG, are the most common procedures in the management of patients with CHD. The choice of revascularization strategies for specific patients' subsets depends on clinical and angiographic characteristics. In general, patients with three vessel disease or left main stenosis are recommended for CABG whereas the majority of patients with one or two vessel disease undergo PCI (see below).

1.3.1. Coronary artery bypass graft surgery

The first CABG surgery using a metal connector was performed successfully by Goetz in1960. [16] CABG was first established as an effective treatment of angina following randomised clinical trials in the1970s.[16] CABG has been studied extensively and compared with medical therapy and more recently with PCI through randomised clinical trials. Many randomised clinical trials have been published, which compare PCI, with or without stenting, with CABG. [17, 18]. The Bypass Angioplasty Revascularization Investigation (BARI) trial was a large randomised trial comparing percutaneous transluminal coronary angioplasty with CABG. [19] This trial included 1829 patients with multi-vessel disease that were randomly assigned to PCI or CABG. At 10 years, survival among the CABG group was 73.5% vs. 71.0 % among the PCI group (p = 0.18). Survival among the non-diabetic patients with the CABG group was 77.3% vs. 77.0 % among the PCI group (p = 0.59). While among diabetic patients, the CABG

group was associated with improved survival compared with the PCI group (57.8% vs. 45.5%, respectively, p= 0.025). Patients who underwent PCI had a higher revascularization rate than those who had CABG (76.8% vs. 20.3 % , respectively, p<0.001), but the angina rates did not differ.

Two large trials have compared PCI to CABG as revascularization strategies. The Synergy between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery (SYNTAX) trial compared CABG with PCI.[20] The SYNTAX score which is a new system for scoring complexity of the coronary artery disease on angiogram, identified patients with intermediate SYNTAX score (23-32) and higher SYNTAX scores (≥33) as being more likely to have further revascularization when assigned to PCI. However in the Future Revascularization Evaluation in patients with Diabetes mellitus: Optimal management of Multivessel disease (FREEDOM) trial , diabetic patients with multivessel disease has recently reported lower rates of death and MI among those assigned to CABG suggesting a left internal mammary artery graft to LAD is life saving.

In summary, over the years, the techniques of CABG and PCI have advanced leading to improvements of survival and quality of life for patients with CHD. The relative indications for PCI and CABG continue to evolve

1.3.2. Percutaneous coronary intervention

This is discussed in more details in the next section.

1.4. Percutaneous Coronary Intervention

1.4.1. Percutaneous coronary intervention

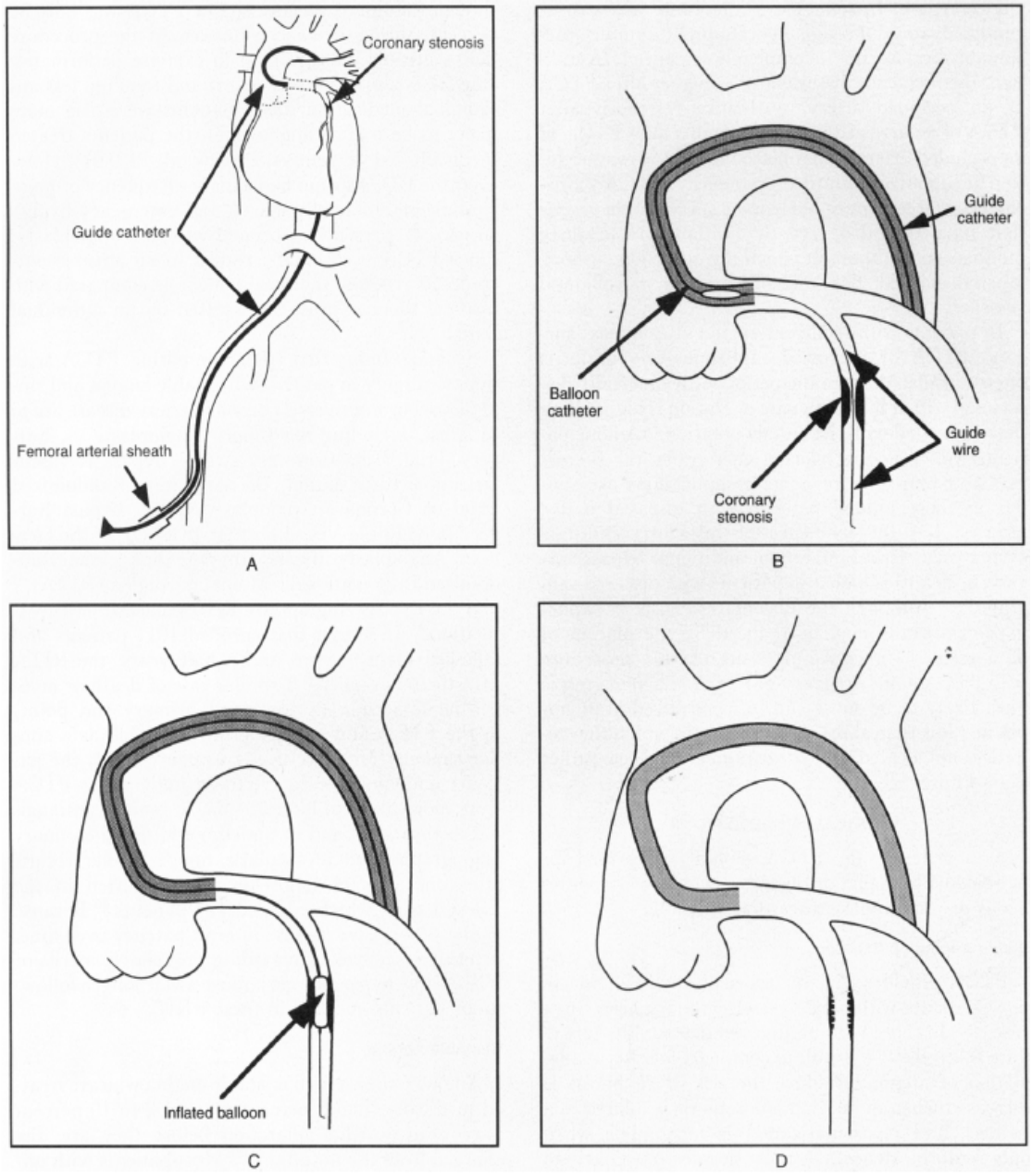
1.4.1.1. Principles of the procedure

Percutaneous coronary intervention (PCI) is also called percutaneous transluminal coronary angioplasty (PTCA), and is defined as follows: percutaneous means through the skin, coronary refers to the vessel name targeted, and intervention or angioplasty refers to the intervention technique used to widen the narrowed coronary arteries (Figure 1.4). PCI is a technique performed by introducing a luminal catheter, which is called a guiding catheter through the vascular access point, which is also known as an arterial sheath. The vascular access points include the femoral artery (in the groin) which has been historically the most commonly used vascular access point, the radial artery (in the wrist) or the brachial artery (in the elbow). The guiding catheter from the femoral, radial or brachial arteries is advanced to the ostium of the targeted coronary artery (right or left coronary artery). Firstly, a contrast material (dye) is injected through the catheter. Then an x-ray is generated from an x-ray machine to visualize the spread of the contrast material through the branches of the coronary arteries to determine the location of the diseased segment. This can be visualised through screen monitoring. After that, a flexible radio-opaque guide wire is introduced through the guiding catheter to the ostium of the affected coronary artery then to the diseased segment (occlusion or narrowing), and then to the distal segment of the affected coronary artery. This is followed by sliding a balloon catheter (which has radio-opaque marking) on the guide wire through the diseased segment. Angiographic films can be taken to determine the position of the guidewire and balloon catheter as both can be visualised with an x-ray.

Once the position of the balloon is determined to be at the level of the diseased segment, inflation of the balloon catheter is performed one or more times to open and/or dilate the culprit coronary artery lesion under controlled pressure. This is almost always followed by deployment of a stent which acts as a scaffold to prevent recoiling of the dilated segment. A few angiographic films are obtained after withdrawal of the balloon catheter to visualise and confirm the satisfactory final results, and the wire is withdrawn. [21]

Angioplasty using a balloon catheter is one of many techniques used during PCI. Different catheters/devices can also be used to treat the culprit lesion. These may include use of stents to keep the patency of the coronary arteries (described in the next sections, 1.4.2 and 1.4.3).These stents are delivered to the diseased segment by stent equipped catheters. Other devices can be used during PCI including: directional coronary atherectomy which includes using a catheter with a small mechanically driven cutter that cuts the coronary artery plaques into small particles; and other laser or rotating diamond burr equipped catheters to overcome the obstructed coronary arteries.

Figure 1.4 : Percutaneous Coronary Intervention



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1.4.1.2. History of percutaneous coronary intervention

The first percutaneous balloon coronary angioplasty was performed in May 1977 by Andreas Gruentzig and Myler during CABG surgery. [22-25] After this, Andreas Gruentzig performed the first coronary angioplasty of stenotic coronary artery as an alternative for CABG in September 1977 in Switzerland. [22, 23, 25, 26] He described the first five percutaneous coronary angioplasties performed on five patients with severe stenotic coronary artery lesions, as a non surgical method for revascularization of coronary arteries. [25] Of the first of 50 patients, PCI with balloon was successful in 32 (64%) patients, and 29 of them showed improvement in cardiac function on follow-up examination. An emergency CABG was required in 5 (10%) patients, and 3 (6%) showed evidence of MI based on the electrocardiogram.[26] They estimated that about 10-15% of candidates for surgical coronary intervention had lesions which were suitable for balloon coronary angioplasty. In the following years, many studies reported that balloon angioplasty could reduce the severity and diminish the ischemic manifestations caused by narrowed coronary artery. Early reports showed that the balloon mediated angioplasty decreased the severity of ischemic symptoms and reduced ischemic manifestation. [27, 28] In the first report from PCI registry of the National Heart, Lung and blood Institute (NHLBI) data was gathered from 34 centres performing coronary angioplasty in the United States and Europe since September 1977. The procedures were performed on 631 patients with a mean age of 51 years (range from 23 to76 years). Eighty percent had single vessel coronary disease and 17% had two or three vessel disease. PCI was successful (reduction by > 20 percent of coronary stenosis) in 59% of the stenosed coronary arteries (mean reduction in degree of stenosis was from 83% to 31%), and in 6% of them, emergency coronary bypass surgery was necessary. Myocardial infarction occurred in 4%. Among 65 patients with an initially successful

angioplasty, 83% had an improved situation compared with their situation before angioplasty. [27] As experience with PCI increased, its success rate improved to approximately 90%.[29]

Even though the success rate improved over time, complications after PCI with balloon persisted as a significant challenge of this procedure. In a considerable proportion of patients after successful PCI, symptoms of myocardium ischemia requiring management re-occurred. In the late 1980s-early 1990s, one of the major challenges was the early (acute) coronary vessel occlusion which occurred in 4%-8% of patients. This acute coronary vessels occlusion led to MI in 41% or required coronary surgery in 72% or it may lead to death in 4.9%.[23] Because the PCI could result in coronary artery occlusion, immediate access to bypass surgery was considered essential.[30]

The other challenge was the occurrence of restenosis of the culprit coronary arteries months after PCI. In a study by Nobuyoshi et al, [31] 229 patients were examined by angiographic follow-up at 1 month, 3 months, 6 months and 1 year after successful PCI. Over the follow-up period, the re-stenosis rate increased from 12.7% at 1 month, to 43.0% at 3 months, to 49.4% at 6 months and to 52.5% at 1 year respectively. [23] The occurrence of restenosis is affected by many mechanical, biochemical and histological factors following PCI with a balloon. Balloon dilation during PCI leads to stretching of the stenotic coronary vessel that may lead to intimal dissection, fissuring of the atheroma plaques and media tearing. These collectively may lead to activation of inflammatory responses within the wall of the affected segment of the coronary artery.[23]

Understanding the complications of PCI with balloon has led to improvements in equipment and procedural strategies to enhance the safety and efficacy of the procedures. In the 1980s, catheter based devices such as Directional Coronary

Atherectomy, Rotation Atherectomy and Excimer laser to remove atheromatous plaques and increase lumen diameter were introduced. However, because of their complications such as coronary artery perforation, higher restenosis rate (compared with PCI) and higher rates of sudden vessel closure and MI with Rotation Atherectomy devices, none of these devices were superior to PCI. [23, 32]

In summary, over the years, the success rate of PCI with balloon as a non surgical coronary intervention has improved, and this has improved patients' ischemic symptoms. However, despite the improved equipment and experience with PCI with balloon, the incidence of abrupt vessel closure that may require emergency CABG and occurrence of re-stenosis after balloon angioplasty, remain the main challenges for the clinicians. This led scientists and clinicians to think of alternative ways to maintain the coronary lumen diameter and reduce procedural complications.

1.4.2. Development of bare-metal stents in the management of coronary heart disease

The use of synthetic devices to maintain the lumen patency of the diseased blood vessels has been described by Dotter and Jerkins in 1964. [33, 34] Palmaz and his colleagues introduced the use of balloon angioplasty with stents in peripheral arteries in 1985. [34, 35] Schatz and his colleagues subsequently modified the Palmaz stent, which led to the development of the first successful coronary stent, called the Palmaz-Schatz stent. [36] Then Puel and Sigwart were the first to implant a stent in humans in March 1986; using a self expanding mesh device. Sigwart and colleagues were also the first to describe the use of this stent in 1987 for emergency vessel closure during balloon angioplasty. [37] In their study, 24 coronary self expanding stents were implanted in 19

patients (17 patients presented with restenosis, 4 with acute closure and 3 after venous bypass grafts).

In 1993, BMS were first approved in the United States to treat sudden and threatened vessel closure after failed balloon angioplasty. [23] After the introduction of BMS, many studies have been carried out to confirm the safety of using the stent to avoid emergency CABG surgery after failed balloon angioplasty. [23, 38] The two main trials, the Belgium Netherlands Stent Arterial Revascularization Therapies Study (BENESTENT) and the North American Stent Restenosis Study (STRESS), confirmed that coronary stenting significantly improved angiographic and clinical outcomes. Restenosis ($\geq$ 50%) rates decreased from 32% in the balloon angioplasty group to 22% in the stent group ($p = 0.02$) in the BENESTENT trial, and from 42% in the balloon angioplasty group compared to 32% in the stent group ($p = 0.046$) of the STRESS trial. The incidence of TVR rate decreased from 15% in the balloon angioplasty group to 10% with stenting in the STRESS trial. These trials have led to the establishment of stenting as an accepted standard in the management of coronary heart disease. [39, 40]

Despite these advancements and change in practice with the use of BMS, restenosis after BMS implantation continued to be a challenging problem as BMS only reduced the re-stenosis and did not eliminate restenosis. BMS are associated with a rate of 10-60% in-stent restenosis and about 60%-80% of restenotic coronary lesions require repeat revascularization. [41] The loss of the lumen in the stented segment is a combination of migration and proliferation of smooth muscle cells and myofibroblast from the media and adventitia to the intima, which results in intimal proliferation. This could happen as a result of reaction to the trauma caused by stent strut which stimulates migration of smooth muscle cells and fibroblasts from both the media and adventitia of the coronary vessel wall to the intima [41]. The presence of diabetes mellitus, coronary

artery lesion length, lesion complexity, culprit coronary vessel diameter and ostial lesions are factors that increase the incidence of restenosis. [41-46]

The other challenging issue associated with the early use of BMS was the occurrence of stent thrombosis (ST), especially within the first month after implantation of the BMS. Early trials of BMS reported the rate of early (≤ 30 days after stent implantation) ST in range of 16-24%. [23] This is a dangerous complication after stent deployment which led to STEMI in 90% of cases and in death in 20% [23]. The incidence of ST after BMS deployment has been reduced by improvement in the techniques of stent deployment to reduce the stent malapposition as well as the use of anticoagulation and antiplatelet therapies. Initially, anticoagulants in combination with aspirin were the main therapeutic modality used to reduce early thrombotic events. Further studies revealed that the combination of aspirin with the thienopyridine (ticlopidine) was superior to anticoagulants and aspirin where stents were optimally deployed using intravascular ultrasound. [47] As there were lower incidence of skin rash, less neutropenia and thrombotic thrombocytopenic purpura, and better safety with clopidogrel use (another thienopyridine), clopidogrel replaced ticlopidine. Thereafter dual antiplatelet therapy in the form of aspirin and clopidogrel become the standard therapy to reduce early thrombotic events following BMS deployment. All of these advancements in stent deployments techniques and combined antiplatelet therapies have reduced the incidence of ST to the rate of 1.2%. [23]

1.4.3. Development of drug-eluting stents and role of percutaneous coronary intervention with stenting in management of patients with coronary heart disease

Although BMS represented an important advancement compared with balloon angioplasty alone, significant restenosis because of intimal overgrowth continued to be

an important clinical challenge. On the basis of reducing the intimal proliferation and media hyperplasia which are the main histopathological features of restenosis following BMS deployment, the use of anti-mitotic agents on stents called drug eluting stents (DES) were developed to inhibit the restenotic process. DES has been developed from BMS by application of polymer containing antiproliferative drugs to prevent intimal proliferation and media hyperplasia, in order to decrease subsequent restenosis while maintaining coronary vessel patency. [23] The component of DES can be divided into a stent platform with variable design, coating or a carrier (usually polymer) and the drug to prevent restenosis. This structure of DES allows delivery of drug directly to the culprit lesion, therefore avoiding need for large systematic drug administration and thus inhibiting the local new intimal proliferation after stent insertion. Initially, the two main drugs used were sirolimus and paclitaxel. Sirolimus is an antifungal and immuno-suppressive agent while paclitaxel is an antineoplastic agent. Recently another two drugs have been approved, zotarolimus and everolimus. All these drugs are agents developed to inhibit cell division. These drugs elute and diffuse slowly into the wall of the coronary vessel to inhibit proliferation of the endothelium and smooth muscle cells. The use of DES was approved in Europe in 2002. In the United States, the USA Food and Drug Administration (FDA), an agency of the United States Department of Health and Human services approved sirolimus- eluting stents (SES) (Cypher) for use in April 2003 while paclitaxel-eluting stents (PES)(Taxus) were approved in 2004. Table 1.1 details the different types of BMS and DES in use in clinical practice.

Table 1.1: Types of Drug-eluting Stents and Bare-metal Stents

Stent	Company	Description
DES 1st generation		
Taxus Express2	Boston Scientific	DES (paclitaxel-eluting stents)
Cypher, Cypher Select	Cordis, and Johnson & Johnson	DES (sirolimus-eluting stents)
TAXUS Liberte	Boston Scientific	DES (paclitaxel-eluting stents)
DES 2nd generation		
Xience V	Abbott Vascular	DES (everolimus- eluting stents)
Endeavor Resolute	Medtronic	DES (zotarolimus-eluting stents)
BMS		
Liberte	Boston Scientific	BMS
PRO-Kinetic	BIOTRONIK	BMS
Driver	Medtronic	BMS
Express2	Boston Scientific	BMS
Tsunami Gold	Terumo	BMS
Gazelle	Biosensors International	BMS

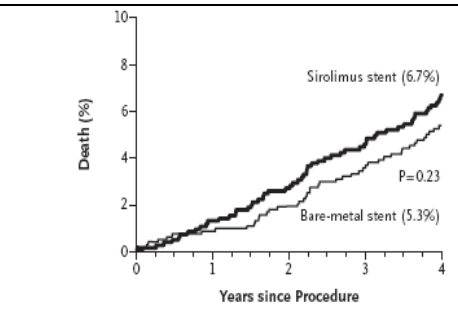
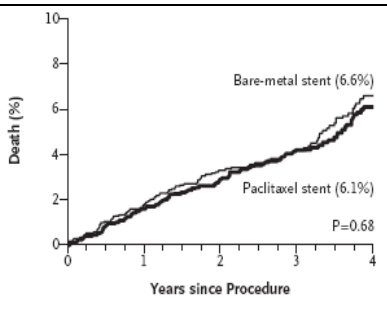
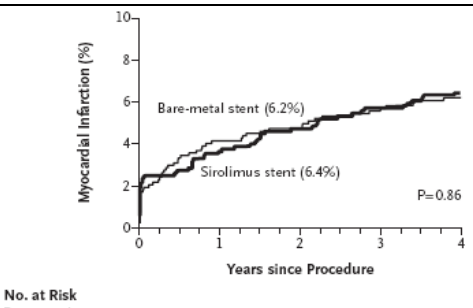
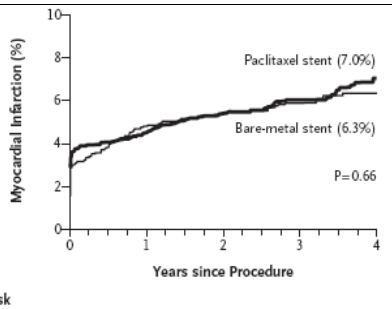
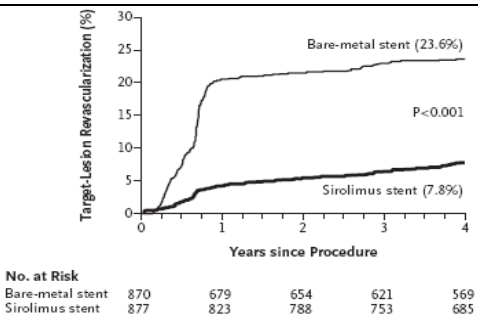
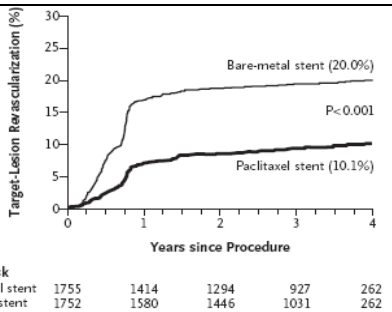
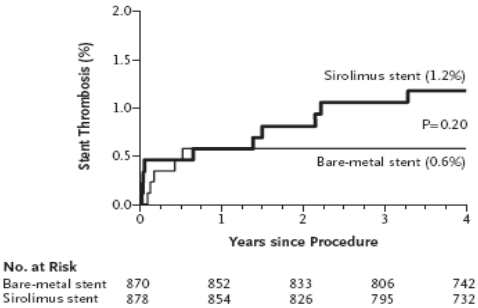
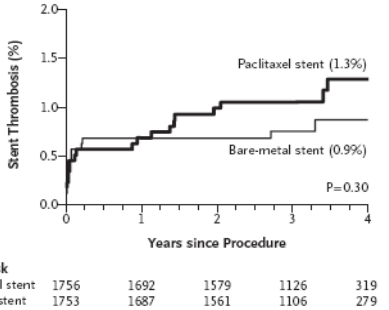
DES = drug eluting stent(s); BMS = bare-metal stent(s).

To evaluate and compare the effectiveness of both DES and BMS deployment during PCI in clinical studies, ischemic driven TVR and ischemic driven target lesion revascularization (TLR) have been used as surrogate. In addition to these, quantitative angiographic measurements of the coronary lumen have also been used to assess their effectiveness.

The first pivotal clinical studies that compared DES with BMS are the SIRIUS [48] and TAXUS-IV [49] trials which showed that DES reduced the rates of TVR compared with BMS. In the SIRIUS trial, which randomised 1058 patients with newly diagnosed native CHD in the United State to either sirolimus-eluting stents (n=533) or BMS (n=525), at 270 days the target lesion revascularization rate was 4.1% for patients who received sirolimus-eluting stents compared with 16.6% in patients who received BMS (<0.001). In this study, follow-up coronary angiography was performed in 350 patients assigned for sirolimus-eluting stents and in 353 patients assigned for BMS. At 240 days, mean in-segment (stent plus 5mm margins) minimal luminal diameter of the group with the sirolimus-eluting stents was 2.15± 0.61mm vs. 1.60 ± 0.72mm for BMS (p<0.001), with restenosis rates of 8.9% vs. 36.3% (p <0.001) respectively. [48] In the TAXUS-IV trial, 1314 patients were randomly assigned to receive either paclitaxel-eluting stents (n=662) or BMS (n=652). At nine months, the target lesion revascularization rate was 3% for patients who received paclitaxel-eluting stents compared with 11.3% in patients who received BMS (p<0.001). Follow-up coronary angiography was performed in 292 patients assigned to paclitaxel-eluting stents and in 267 patients assigned to BMS. The mean in-segment minimal luminal diameter of the group with paclitaxel-eluting stents at nine months was 2.03±0.55mm vs. 1.68±0.61mm for the BMS (p<0.001), with restenosis rates of 7.9% vs. 26.6% (p <0.001), respectively.[49] Stone et al performed

pooled analysis of nine randomised trials: four trials in which 1748 patients were randomly assigned to receive either sirolimus-eluting stents or BMS; and five trials in which 3513 patients were randomly assigned to receive either paclitaxel-eluting stents or BMS.[50] At 4 years follow-up, target lesion revascularization was significantly lower in both sirolimus-eluting stents and paclitaxel-eluting stents group compared with BMS groups (7.8% versus 23.6%, $p<0.001$; and 10% versus 20%, $p<0.001$, respectively) which can be seen in Figure 1.5. The rates of death and MI did not significantly differ between the either DES groups compared with BMS. The rate of ST at 4 years was 1.2% among patients with sirolimus-eluting stents compared with 0.6% among patients with BMS ($p=0.20$), and 1.3% among patients with paclitaxel-eluting stents compared with 0.9% among patients with BMS ($p=0.30$). In this pooled analysis, it has been noted that after 1 year, 5 events of ST occurred in patients with sirolimus-eluting stents compared with none among patients with BMS ($p=0.025$), and 9 events of ST among patients with paclitaxel-eluting stents compared with 2 among patients with BMS ($p=0.028$).

Figure 1.5: Results of Randomised Clinical Trials Comparing Drug-eluting Stents to Bare-metal Stents

	Sirolimus-eluting stents vs. BMS	Paclitaxel-eluting stents vs. BMS
Death	 No. at Risk Bare-metal stent 870 855 836 809 745 Sirolimus stent 878 859 832 801 738	 No. at Risk Bare-metal stent 1757 1699 1585 1129 320 Paclitaxel stent 1754 1692 1570 1113 285
MI	 No. at Risk Bare-metal stent 868 823 798 769 706 Sirolimus stent 873 827 797 765 704	 No. at Risk Bare-metal stent 1731 1624 1509 1073 301 Paclitaxel stent 1725 1619 1492 1053 269
TLR	 No. at Risk Bare-metal stent 870 679 654 621 569 Sirolimus stent 877 823 788 753 685	 No. at Risk Bare-metal stent 1755 1414 1294 927 262 Paclitaxel stent 1752 1580 1446 1031 262
ST	 No. at Risk Bare-metal stent 870 852 833 806 742 Sirolimus stent 878 854 826 795 732	 No. at Risk Bare-metal stent 1756 1692 1579 1126 319 Paclitaxel stent 1753 1687 1561 1106 279

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Following these trials, the practice experience of using DES has confirmed and reproduced the results of the clinical trials. This was addressed in the Rapamycin-Eluting Stent Evaluated At Rotterdam Cardiology Hospital (RESEARCH) registry. [51] A total of 508 consecutive patients with previously untreated coronary lesions, treated with sirolimus-eluting stents were compared with 450 patients who had received BMS in the period immediately preceding the introduction of DES. Patients who received sirolimus-eluting stents had a lower rate of adverse events (death, MI or TVR) at 1 year (9.7% vs. 14.8%, $p = 0.008$) with the differences largely being attributed to a reduction in clinically driven re-interventions (3.7% vs. 10.9%, $p < 0.001$). The results of this study at 2 years showed the adverse events in 15.4 % of the group who received sirolimus-eluting stents, as compared with 22% in the group who received BMS ($p = 0.01$). [52] A collaborative network meta-analysis of 38 trials was performed by Stettller et al. [53] This included 18023 patients treated with DES versus BMS, and sirolimus- versus paclitaxel- eluting stents with follow-up up to 4 years. A dramatic reduction in target lesion revascularization at 4 years of follow-up with DES was observed (SES vs. BMS: HR 0.30[0.24-0.37], $p<0.0001$; PES vs. BMS: HR 0.42[0.33-0.53], $p<0.0001$), with no significant differences in mortality or MI. Over time, deployment of DES has significantly reduced restenosis and the revascularization rate compared with BMS. This has also led to increased confidence with using PCI and extension of the treatment to more complex lesions which were previously treated with CABG.

Despite the advantages of DES in reducing revascularization rates, the concern about ST is a major issue with DES. Despite the ST rate being low and occurring with both DES and BMS, DES is more likely to be associated with very late ST. ST is discussed in more details in section 1.6 of this Chapter.

1.5. Role of Percutaneous Coronary Intervention with Stenting in Management of Patients with ST- segment elevation myocardial infarction

1.5.1. ST- segment elevation myocardial infarction (STEMI)

STEMI events represent a large proportion of ACS. There are approximately 865,000 person per year had acute myocardial infarction in the United States of which one third are caused by STEMI. [8] In the vast majority, it is caused by the sudden complete thrombotic occlusion of an epicardial coronary artery. [7, 8] STEMI are usually triggered by abrupt plaque rupture, erosion or fissuring of otherwise non-flow-limiting atherosclerotic plaques. These cause total cessation of blood flow and subsequent ischemia to the supplied microcirculation and myocardium. [7-9, 54-56] The resulting lack of oxygen and other nutrients quickly shifts aerobic or mitochondrial metabolism to anaerobic glycolysis. Restricted ATP production inhibits Na^+/K^+-ATPase, leading to osmotic overload and subsequent myocyte oedema and injury, associated with early contractile dysfunction. If the ischemia is severe and prolonged, irreversible ultra-structural cellular injury occurs and necrosis ultimately results, which progresses in a waveform fashion from the endocardium to the epicardium. [57, 58] Microembolization of microparticles from the acute coronary thrombus and necrotic plaque core to distal microvasculature can also cause arrhythmias, contractile dysfunction, micro-infarcts and reduced coronary reserve. [14, 59, 60]

Despite advances in clinical management, patients with STEMI continue to suffer from significant morbidity and mortality. Acute complications of STEMIs include arrhythmias, sudden cardiac death, cardiogenic shock, congestive heart failure, re-infarction, fibrinous pericarditis, cardiac free-wall rupture (VSD and MR) and mural

thrombus and embolisation. [58] Common longer-term complications that present later include heart failure and LV systolic dysfunction. [61] Mortality depends significantly on whether patients are able to access medical care, with 25-35% of all patients with MI dying before they reach a hospital. Also there are large mortality differences between those who can receive reperfusion therapy compared to those who do not. [62]

Rapid diagnosis is crucial to ensuring optimal management of patients presenting with STEMI. Effective targeted histories and physical examinations can promote rapid triage, along with prompt 12-lead ECG (serial if necessary). [8, 13] Oxygen, aspirin, heparin, glycoprotein IIb/IIIa (GPIIb/IIIa) inhibitors, nitroglycerin, morphine and beta-blockers may all be provided in the initial treatment of STEMI. [13] Prompt and complete coronary reperfusion is the gold standard in management of patients with STEMI. The main objective of reperfusion management for STEMI is to minimise ischemic time to preserve myocytes and minimise infarct size by restoring epicardial coronary blood flow. The main stay of clinical management is provided by reperfusion therapy, which is performed by pharmacological and/or mechanical reperfusion or both.

1.5.2. Reperfusion strategy in ST- segment elevation myocardial infarction

1.5.2.1. Pharmacological reperfusion

Pharmacological reperfusion strategies in STEMI include the administration of intravenous fibrinolytic and/or anti-thrombotic agents to open infarct-related coronary arteries and restore coronary blood flow. Various types of fibrinolytic therapies are available, all of which are plasminogen activators which directly or indirectly convert the plasminogen proenzyme to plasmin, which in turn degrades several proteins in thrombi, including fibrin, fibrinogen, prothrombin and factors V and VII. Streptokinase

was the first fibrinolytic to be isolated and used in a clinical field, and today is still commonly used due to its low cost. It has however been superseded in more recent times by newer genetically modified tissue plasminogen activators (tPA), particularly tenecteplase (TNK) and reteplase, which have higher plasma half-lives and better fibrin specificity, which confer greater efficacy in fibrinolysis, easier administration by bolus dosing and ultimately produce fewer bleeding complications. [63]

Fibrinolytics have been unequivocally shown to reduce mortality in STEMI patients. The GISSI study of 11,806 patients demonstrated the efficacy of intravenous streptokinase in reducing mortality within 21 day (10.7% vs. 13; RR=0.81; p=0.0002). [64] The Fibrinolytic Therapy Trialists' (FTT) collaborative group combined all trials of fibrinolytic therapies versus control prior to 1994, by randomising >1000 patients with suspected MI. This study showed that fibrinolytics reduced death by approximately 20-30 per 1000, with four extra strokes per 1000. [65]

1.5.2.2. Mechanical reperfusion

- Primary angioplasty compared with thrombolysis

Mechanical reperfusion in STEMI involves the use of a coronary guidewire and/or balloon with or without stent (i.e PCI) to mechanically initiate coronary blood flow. [54, 66-68] Given the superior safety and efficacy of primary angioplasty compared to thrombolytic therapy, this treatment is now the preferred reperfusion strategy when performed early by a skilled team. [54, 66-68] Several randomised clinical trials have evaluated the benefits of primary angioplasty as compared with thrombolysis and concluded that primary angioplasty is superior to thrombolysis in the treatment of STEMI in terms of death, re-infarction, and stroke.[54, 66, 67] A meta-analysis of 23 randomised trials has been performed, including 7739 thrombolytic eligible patients

with STEMI randomised to primary PCI (n = 3872) or thrombolytic therapy (n = 3867).[66] Among patients who received thrombolytic therapy, 76% received fibrin specific agents. Stents and GPIIb/IIIa inhibitors were used in 12 and 8 trials respectively. Primary PCI was superior to thrombolytic therapy in reducing overall short-term death (7% vs. 9%, p = 0.0002), nonfatal re-infarction (3% vs. 7%, p < 0.0001), and stroke (1% vs. 2%, p = 0.0004).

While randomised clinical trials and meta-analyses have shown that primary PCI maintains its advantage over fibrinolytics, the advantage of primary PCI in reduction of mortality decreases with increasing delay time (over local fibrinolytics),[69] particularly in patients who present within 120min of symptom onset.[55] Both PCI and fibrinolytic strategies can be combined.

1.5.2.3. Pharmaco-invasive strategies

Pharmaco-invasive strategies which entail the administration of fibrinolytics followed by emergent transfer for PCI within a short time window (6 hours), have shown greater promise for clinical benefit over more conservative strategies. The CARESS-in-AMI trial, [70] randomised 600 patients, aged ≤75 years, treated with half-dose reteplase, abciximab, heparin, and aspirin to immediate transfer for PCI (pharmaco-invasive) or to conservative management with rescue PCI if indicated. In the latter group, in-hospital angiography was performed on 36% and PCI on 30%. The primary outcome was a composite endpoint of death, reinfarction, and refractory ischemia at 30 days which occurred in 4.4% of the pharmaco-invasive group versus 10.7% of the standard care/rescue PCI group (HR 0.40; 95% CI 0.21-0.76; p = 0.004). Notably, this endpoint was driven by reduced refractory ischemia which occurred at 30 days, 0.3% in the pharmaco-invasive group versus 4.3% in the standard care/rescue PCI group (p = 0.003).

The results of the above trial were supplemented by the larger randomised control trial (Trial of Routine ANgioplasty and Stenting after Fibrinolysis to Enhance Reperfusion in Acute Myocardial Infarction [TRANSFER-AMI]). [71] In this trial 1059 high-risk patients with STEMI who received fibrinolytics were randomised, 528 patients were randomised to PCI performed within 6 hours after fibrinolysis (early pharmaco-invasive group) and 511 patients were randomised to standard treatment (defined as rescue PCI performed for clinically failed reperfusion and a recommendation that cardiac catheterization be performed in all patients within 2 weeks). The use of cardiac catheterization in the standard treatment group was consequently very high (89%). This was therefore essentially a trial of the timing of PCI after fibrinolysis which compared an early to a later pharmaco-invasive approach. The composite endpoint of 30-day death, re-infarction, congestive heart failure, severe recurrent ischemia, and shock occurred in 11.0% of the immediate PCI arm and 17.2% of the standard arm (RR 0.64; 95% CI: 0.47-0.87; p = 0.004). The difference in the two groups was also driven by recurrent ischemia (0.2% vs. 2.1%; relative risk 0.09; 95% CI: 0.01-0.68; p = 0.003) and re-infarction (3.4% vs. 5.7%; relative risk 0.57; 95% CI: 0.33-1.04; p = 0.06). The study concluded that the pharmaco-invasive approach of emergent transfer for PCI within 6 hours of fibrinolysis is safe and efficacious compared to standard treatment with thrombolytics and transfer for rescue PCI only.

The CAPTIM and WEST investigators recently reported retrospective pooled analyses of the subgroup presenting within 2 hours of symptom-onset, [72] revealed that a late mortality benefit occurred among those who received fibrinolysis (mostly pre-hospital, with a 25-30% rate of rescue PCI and about 70% in-hospital PCI), compared to primary PCI. The STREAM trial is prospectively evaluating a pharmaco-invasive strategy in STEMI patients presenting within 3 hours of symptom onset to non-PCI

centres. [73] In summary, the pharmaco-invasive strategies that entail “emergent” (<6h) or “routine” transfer for PCI after fibrinolytic therapy are safe and effective.

1.5.2.4. Rescue angioplasty for ST-elevation myocardial infarction

The advantage of thrombolysis as compared with primary angioplasty is that it can easily be administered early following diagnosis of STEMI out of hospital. While prompt primary PCI is a superior reperfusion strategy to fibrinolytic therapy alone, [66] for several reasons many patients world-wide receive fibrinolytic therapy as an initial reperfusion strategy. [74] However, the rate of failed reperfusion is observed in a relevant proportion of patients, ranging from 20% to 40%, according to the time of treatment.[65] The prognosis of these patients is worse as compared with those successfully reperfused. [65] PCI has gradually gained support in being utilised following failed fibrinolytic reperfusion therapy for STEMI. The use of PCI in such situations is called rescue PCI.

Several randomised trials have been conducted to establish the benefits of rescue angioplasty after failed reperfusion. In the Middlesbrough Early Revascularisation to Limit Infarction (MERLIN) trial, [75] a total of 307 patients, between 1999 and 2002, were randomised to conservative or invasive strategy. Despite the high success rate with rescue PCI in terms of Thrombolysis in myocardial infarction (TIMI) 3 flow grade and ST-segment resolution (61.4% vs. 50.5%, $p = 0.05$), no improved survival was observed by 30 days. The improvement in the overall outcome was mostly driven by a significant reduction in the need for subsequent revascularization. However, this benefit was counterbalanced by more strokes and bleeding complications. The results of this trial have strongly suggested a conservative policy in patients with failed thrombolysis. The results observed at 30 days were confirmed at a 3 years of follow-up, clearly demonstrating an absence of benefit in terms of survival.[76] However, several limitations

of this study should be noted, such as widespread use of non–fibrin-specific thrombolytic agent (streptokinase), and an underuse of proven contemporary interventions such as coronary stents and GPIIb/IIIa inhibitors. These considerations reduce the applicability of the results of the MERLIN trial to contemporary treatment of patients with failed thrombolysis, particularly in developed countries.

The REACT trial, [77] provided additional important data on rescue angioplasty. In this trial, a total of 427 patients with STEMI receiving thrombolysis with less than 50% ST-segment resolution after 90 minutes were randomised to conservative therapy, repeat thrombolytics, or rescue PCI. The event-free survival from the primary composite end point (death, recurrent MI, stroke, and severe heart failure) was significantly less in the rescue PCI group compared with both the conservative therapy (p= 0.004) and repeat thrombolysis group (p= 0.001). However, there were no significant differences in mortality.

A meta-analysis by Wijeysundera et al.[78] found that rescue PCI is associated with a relative risk reduction of 27% (RR=0.73, 95%CI 0.54-1.00, p=0.05) and 42% (RR=0.58, 95%CI 0.35-0.97, p=0.04) for heart failure and re-infarction respectively, and a trend towards significant association with mortality (RR=0.69, p=0.09).

Data is still lacking on the efficacy and safety of rescue PCI performed in the "real-world" setting, of the contemporary clinical practice with use of DES stents and GPIIb/IIIa inhibitors. In this context limited data is available from registries. Kunadian et al. studied 318 patients (1994-2005) who had rescue PCI.[79] In this study, only 14% received fibrin-specific lytics, 64% received stents, and 19% received GPIIb/IIIa inhibitors.

To identify the best strategy in these patients especially in the era of stenting and use of GPIIb/IIIa inhibitors, trials with a large sample size in this context are needed. In

addition, the non-invasive identification of patients with failed thrombolysis continues to complicate evaluation for further treatment. In fact, reduction in chest pain, decrease in ST-segment elevations, presence of arrhythmias, and trends of biochemical markers, although suggestive of reperfusion, may not be diagnostic.

In this context, Chapter 5 describes clinical outcomes after rescue PCI in the era of use of fibrin-specific lytics, higher rate of GPIIb/IIIa inhibitors, and stenting.

1.5.3. Drug-eluting stents and Bare-metal stents in management of patients with ST-segment elevation myocardial infarction

Since the introduction of DES to clinical practice, many clinical studies have been conducted on their use in the management of CHD. Many of these studies have been conducted in stable-CHD, UA and NSTEMI. [48, 49] The early clinical studies for the use of DES were performed on patients with stable-CHD. Both TAXUS-IV and SIRIUS trials revealed dramatic reductions in the rates of TVR compared with BMS. [48, 49] In addition to that, since BMS are as effective in STEMI as in stable-CHD, [80, 81] many assumed that a similar relation would exist for DES.

The first DES study that have been conducted on the patients with STEMI and supported their use in the treatment of STEMI came from the Rapamycin- Eluting stent Evaluated At Rotterdam Cardiology Hospital (RESEARCH) registry in 2004. [82] Lemos and his colleagues conducted a single centre observational study which compared 186 patients with STEMI treated with sirolimus-eluting stents to 183 patients with STEMI treated with BMS during a defined interval. At 30 days, there were no significant differences between the two groups in rates of death, non-fatal re-infarction, or TVR. Subacute angiographically documented ST (< 30 days) occurred in 3 patients treated with BMS versus none in the DES group. At 300 days, no differences were noted in rates of death or nonfatal re-infarction, but the DES group had a significantly lower rate of TVR (1.1% vs. 8.2%, $p < 0.01$). After adjusting for baseline and procedural characteristics, sirolimus-eluting stent placement was significantly associated with lower risk of death, nonfatal re-infarction or TVR (9.4%vs 17%, $p = 0.02$) (HR 0.53, 95% confidence interval 0.29-0.95, $p = 0.03$) at 300 days . [82]

This followed by another document which was published in 2005 , the randomised-controlled single High Dose Bolus Tirofiban and Sirolimus Eluting stent

versus Abciximab and Bare Metal stent in Myocardial Infarction (STRATEGY) study. [83] After these two studies DES were more frequently used in STEMI. In 2006, two large randomised trials of DES in STEMI, the Trial to Assess the Use of the Cypher Stent in Acute Myocardial Infarction Treated with Balloon Angioplasty (TYPHOON) trial [84] and the Paclitaxel-Eluting versus Conventional Stent in Myocardial Infarction with ST-segment Elevation trial (PASSION). [85] Both demonstrated a reduction in the revascularization rate among STEMI patients treated with DES.

The TYPHOON trial enrolled 712 patients with STEMI from 48 medical centres in 15 countries over a period of two years (October 2003 – October 2005). [84] Of note, patients who had received thrombolytics or previously had MI were excluded. Patients were randomised to primary PCI with either sirolimus- eluting stent, SES (DES) or BMS. The primary end-point was target-vessel failure (defined as target-vessel related death, recurrent MI, or TVR) at 1 year. Of note, 174 patients had routine angiographic follow-up at 8 months. At one year, the primary end-point was significantly lower in the DES arm (7.3% vs. 14.3%, $p = 0.004$) which was driven almost entirely by a lower rate of TVR (5.6% for DES vs. 13.4% for BMS, $p < 0.001$). There were no significant differences between groups in rates of death (2.3% for DES vs. 2.2 % for BMS, $p = 1.00$), re-infarction (1.1% for DES vs. 1.4 % for BMS, $p = 1.00$) or ST (3.4% for DES vs. 3.6 % for BMS, $p = 1.00$). The recommended duration of dual antiplatelet therapy was at least 6 months in both arms. Of note, ST included all cardiac deaths, a definition that may overestimate the thrombotic events in the STEMI population. Among the routine angiographic follow-up patients, the mean late luminal loss was significantly lower for the DES arm with an in-stent loss of 0.14 + 0.49mm compared to 0.83 + 0.52mm for the BMS arm ($p < 0.001$). Furthermore, the in-stent restenosis rates were

3.5% for DES and 20.3% for BMS (p = 0.001). This trial demonstrates that DES usage was safe and improved clinical outcomes at intermediate term follow-up.

Notably, also the Typhoon trial excluded patients with previously documented infarction and patients with overt acute heart failure and those with very low ejection fraction < 30%. Angiographic exclusion criteria were: previous PCI of the infarct related artery; excessive tortuosity or calcification; ostial or multiple lesion; massive thrombosis in the infarct related artery; bifurcation or left main coronary-artery disease; and severe multi-vessel coronary artery disease requiring surgical intervention and a target lesion of more than 30mm.

The PASSION trial randomised 619 patients with STEMI to primary PCI with either paclitaxel-eluting stents (DES) or BMS. [85] The primary end point was defined as a composite of cardiac death, recurrent MI, or target lesion revascularization at one year. While there was a trend in favour of DES, this trend was not statistically significant. The observed primary end point was 8.8 % for DES and 12.8 % for BMS (p = 0.09), the rate of all-cause mortality was 4.6% for DES and 6.5 % for BMS (p = 0.3), the rate of cardiac cause of death was 3.9% for DES and 6.2 % for BMS (p = 0.20), the rate of re-infarction was 1.7% for DES and 2.0 % for BMS (p = 0.74), the combined rate of cardiac death or re-infarction was 5.5% for DES and 7.2 % for BMS (p = 0.40) and the rate of target-lesion revascularization (TLR) was 5.3% for DES and 7.8 % for BMS (p = 0.23). In terms of safety outcome, the incidence of ST at 1 year was 1% for both groups. The exclusion criteria for this trial included: patients with cardiogenic shock; patients on mechanical ventilation; unsuitable coronary anatomy for stents and anticipated delay of more than 6 hours from the onset of the symptoms to the reperfusion.

The TYPHOON and PASSION trials had slightly different populations and selection criteria. The exclusion criteria was for high risk patients such as cardiogenic shock, patients after fibrinolytic therapy, and patients after resuscitation and high risk angiographic characteristics such as excessive tortuosity, calcification, ostial or multiple lesion, massive thrombosis in the infarct related artery, bifurcation, left main coronary-artery disease, and severe multi-vessel coronary artery disease requiring surgical intervention and target lesions of more than 30mm.

The differences in the statistical significance between TYPHOON and PASSION are not clearly understood. The absence of statistically significant differences observed in the studies outcome and in the rate of TVR may be due to the differences in types of the BMS that were used in the two studies, TYPHOON included any uncoated stents while PASSION included only one kind of BMS. This may explain the big differences in TVR for the BMS arm (7.8% for TYPHOON Study and 13.4% for PASSION study). Whether these differences in the TVR rates reflect the differences in the DES types, is uncertain. Hofma, [86] compared the outcomes of 136 consecutive STEMI patients treated with paclitaxel-eluting stents to 186 consecutive STEMI patients treated with sirolimus-eluting stents. No differences were found in this non-randomised comparison. The differences may also be explained by the use of angiographic follow-up in the TYPHOON trial, which may increase the rate of TVR by increasing the intervention without symptoms or objective evidence of ischemia.

The five years follow-up of patients in the PASSION trial revealed similar trends to the original study, [87] in that TLR with the PES (18.6% vs.21.8%, p = 0.28) and the incidence of definite and probable ST was 4.2% for PES group and 3.4 % for BMS (p=0.68). Table 1.2 summarises the important randomised clinical trials that compared DES with BMS in patients with STEMI.

Table 1.2 : Summary of Published Randomised Trials on the use of Drug-eluting Stents and Bare-metal Stents in ST-segment Elevation Myocardial Infarction

Study	Stent Type	Duration of Follow-up	Dual Antiplatelet treatment duration	GPIIb/IIIa inhibitor	Death (DES vs. BMS)	MI (DES vs. BMS)	TVR/TLR (DES vs. BMS)	ST (DES vs. BMS)
STRATEGY	SES (87) vs. BMS(88)	24 months	Aspirin indefinitely; clopidogrel for at least 3 months.	100%	8% vs. 9%, p = NS	7% vs. 9%, p = NS	TVR 7% vs. 20%, p = 0.01	0% vs. 2%, p = NS
TYPHOON[84]	SES (355) vs. Uncoated stent (357)	1 year	Aspirin (100 mg) indefinitely; Clopidogrel (75mg)/ Ticlopidine (250) for at least 6 months.	71.5%	2.3% vs. 2.2%, p = 1.00	1.1% vs. 1.4%, p = 1.00	TVR (Clinically driven) 5.6% vs. 13.4% , p < 0.001	3.4% vs. 3.6%, p = 1.00
PASSION[85]	PES (310) vs. Uncoated stent (309)	1 year	Aspirin (75-100mg) indefinitely; clopidogrel (75mg) for at least 6 months.	73.8%	4.6% vs. 6.5%, p = 0.3	1.7% vs. 2.0%, p = 0.74	TLR 5.3% vs. 7.8% , p = 0.23	1% vs. 1% , p = 0.99
SESAMI[88]	SES (160) vs. BMS (160)	12 months	Aspirin indefinitely; clopidogrel for at least 12months.	74.9%	1.8% vs. 4.3%, p = NS	1.8% vs. 1.8%, p = NS	5.0% vs. 13.1%, p = 0.015	4.3% vs. 4.3%, p = NS
SELECTION[89]	PES (40) vs. BMS(40)	7 months	Clopidogrel for 9 months	100%	2.5% vs. 7.5%, p = NS	0 % vs. 2.5% , p = NS	TLR 5% vs. 32.5%, p = 0.003	2.5% vs. 7.5%, p = NS
MISSION[90]	SES (158) versus BMS (152)	mean 12 months	Clopidogrel for 12 months	80%	1.3% vs. 2.6%, p = NS	5.7% vs. 9.2%, p = NS	TVR 12% vs. 23%, p = 0.01	1.3% vs. 2.0%, p = NS
DEDECATION	DES (313) [47%SES,40%PES,13%ZES] Vs. BMS (313)	mean 8 months	Clopidogrel for 12 months	97%	5.1% vs. 2.6% , p = NS	1.0% vs.1.9%, p = NS	TLR 5.1% vs. 13.1 p < 0.001	2% vs. 2.6% , p = NS
Diaz de la Llera	SES (60) vs. BMS(54)	mean 12 months	Clopidogrel for 1 month (BMS) and for 9 month (DES)	100%	5 % vs. 3.6%, p = NS	NOT REPORTED	TVR 0% vs. 5.7%, p = 0.064	1.7% vs. 0%, p = NS
MULTI-STRATEGY	SES (372) vs. BMS (372)	mean 8 months	Clopidogrel for 12 months	100%	3% vs. 4%, p = NS	3.2% vs. 4.6%, p = NS	TVR 3.2% vs. 10.2% p < 0.001	2.7% vs. 4%, p = NS
HORIZONS-AMI[91]	PES (2257) vs. BMS (749)	mean 12 months	Clopidogrel (> 6 months)	50%	3.5% vs. 3.5% , p = NS	3.7% vs. 4.5%, p = NS	TVR 5.8% vs. 8.7%, p = 0.006	3.1%vs. 3.4%, p = NS

The randomised-controlled single High Dose Bolus Tirofiban and Sirolimus Eluting stent versus Abciximab and Bare Metal stent in Myocardial Infarction (STRATEGY) [83, 92] study involved 175 patients with STEMI. Patients were randomised to PCI either with single high dose of Tirofiban followed by 18-24 hours infusion and sirolimus-eluting stent or to standard dose abciximab and BMS. The study was designed to address the efficacy of the sirolimus-eluting stent versus BMS in STEMI and to evaluate whether the higher cost of SES could be reduced by a less expensive GPIIb/IIIa inhibiter. The primary end points were freedom from death, non-fatal re-infarction or binary angiographic restenosis at 8 months. The binary restenosis rate was less in the SES arm (9%) than the BMS arm (36%, p = 0.002). At 2 years follow-up, the composite end point of death , MI or TVR was lower in the SES arm compared to BMS arm (24.2% vs. 38.6%, p = 0.038). This was driven largely by a reduction in TVR in the SES arm (9.8% vs. 25.5% p = 0.01). The rate of death was 11.5% for the SES arm and 13.6% for the BMS arm (p = 0.66) and MI was 8.0% for the SES arm and 9.0% for the BMS arm (p = 0.77). There were no differences in the rates of ST in this relatively small cohort at 2 years.

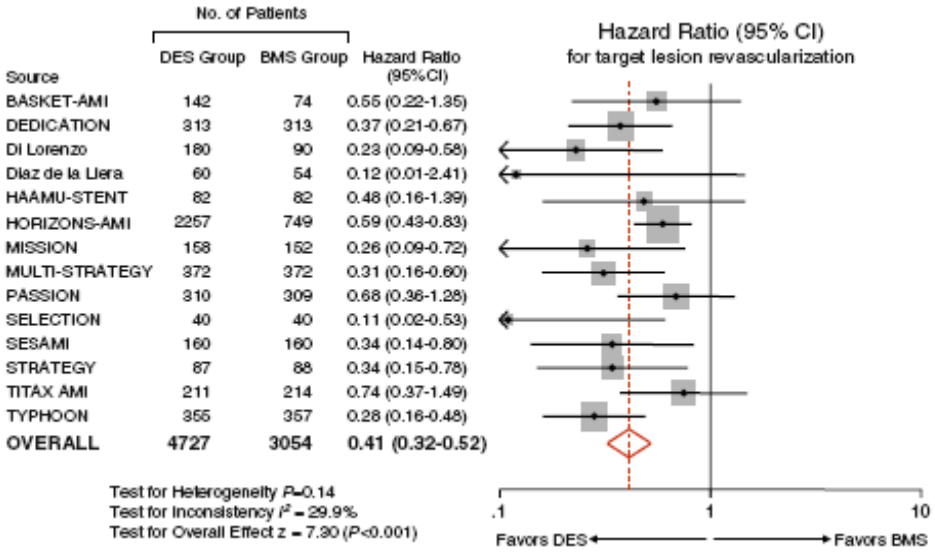
The largest randomised PCI trial on patients with STEMI was the Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction (HORIZONS-AMI) study.[91] This trial enrolled 3,006 patients with STEMI undergoing primary PCI in 11 countries, randomly assigned in a ratio of 3:1 (2257 patients treated with PES- DES and 749 patients treated with BMS). Angiographic data and clinical outcomes were reported at 13 and 24 months. At 13 months, there were significant reductions in in-stent late loss and binary restenosis with PES (10% vs. 22.9% with BMS, p<0.001) and in ischemia-driven TVR (5.8% for PES vs. 8.7% for BMS, p =0.006). [91] At 24 months of clinical follow-up, the use of PES was associated with

significant reductions in ischemia-driven TLR (8.3% for PES vs. 14.2% for BMS, p<0.001) and ischemia-driven TVR (11% for PES vs. 16.6% for BMS, p<0.001). In addition, there were no significant differences at 24 months between PES and BMS in all-cause mortality, cardiac death, re-infarction, or ST. [93]

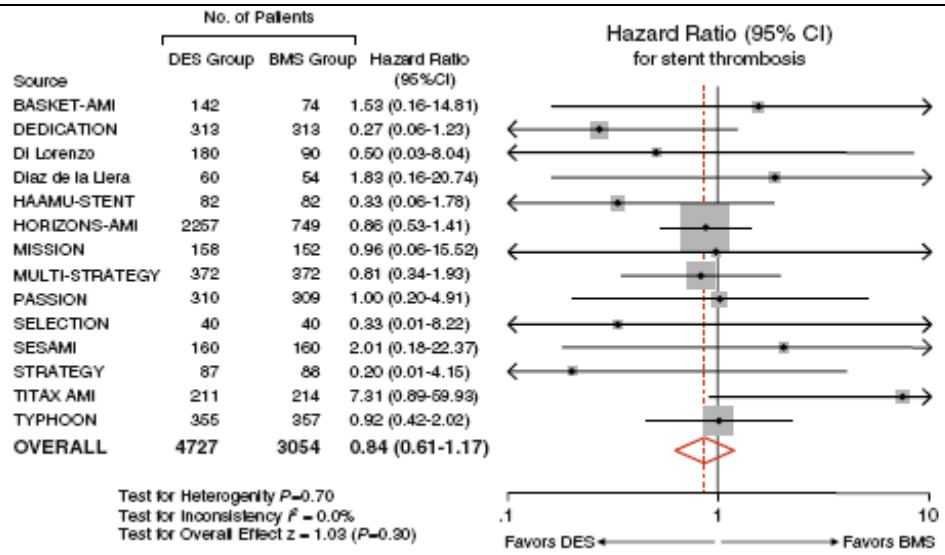
There have been few meta-analyses of randomised trials of DES in STEMI. [94-96] The meta-analysis by De Luca et al [96] included 11 trials, but not the HORIZONS-AMI trial. A total of 3,605 patients (1888 [52.3%] randomised to DES and 1719 [47.7%] randomised to BMS) were included in this meta-analysis. At 12 months follow-up, there was no significant difference in mortality (4.1% vs. 4.4%, OR 0.91 [95% CI: 0.66–1.27], p = 0.59, re-infarction (3.1% vs. 3.4%, OR 0.85 [95%CI: 0.58-1.23], p = 0.38) or ST (1.6% vs. 2.2%, OR 0.76 [95% CI: 0.47-1.23], p = 0.22), whereas DES were associated with a significant reduction in TVR (5.0% vs. 12.6%, OR 0.36 [95% CI:0.28-0.47], p < 0.0001). In another large meta-analysis included 14 randomised trials with 7781 patients (including the HORIZONS-AMI trial), at an average length of follow-up from 7-24 months, confirmed that DES reduces the risk of re-intervention in comparison with BMS (HR: 0.41[95%CI:0.32-0.52], p<0.001) without increasing the risk of death (HR: 0.90[95%CI:0.71-1.15], p=0.41) or ST (HR: 0.84[95% CI:0.61-1.17], p<0.001). [97] See Figure 1.6 and 1.7.

Figure 1.6 : Hazard Ratios of Target Lesion Revascularisation and Stent Thrombosis associated with Drug-eluting Stents versus Bare-metal Stents

(a) TLR



(b) ST

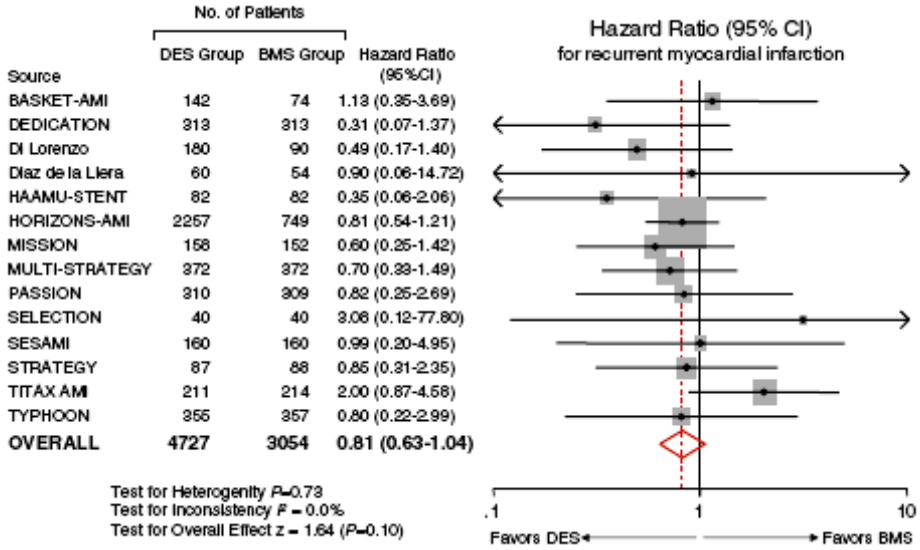


BMS = bare-metal stent; DES = drug-eluting stent; ST = stent thrombosis ; TLR = target lesion revascularization.

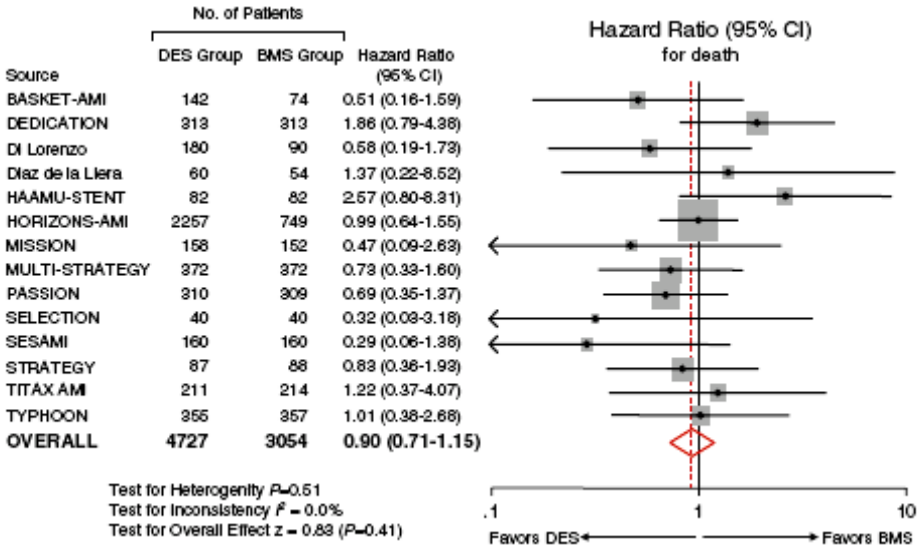
Reproduced with permission from Dibra, A., et al., Drug-eluting stents in acute myocardial infarction: updated meta-analysis of randomised trials. Clin Res Cardiol, 2010. 99(6): p. 345-57.[97]

Figure 1.7 : Hazard Ratios of Death and Myocardial Infarction Associated with Drug-eluting Stents versus Bare-metal Stents

(a) Death



(b) MI



BMS = bare-metal stent; DES = drug-eluting stent; MI = myocardial infarction.

Reproduced with permission from Dibra, A., et al., Drug-eluting stents in acute myocardial infarction: updated meta-analysis of randomised trials. Clin Res Cardiol, 2010. ***99****(6): p. 345-57.*[97]

Observational studies comparing DES with BMS in patients with acute MI have produced conflicting results. Newel, et al. (2006) [98] reported results of 306 consecutive STEMI patients who received DES (n=156) or BMS (n=150). Follow-up at 6 months revealed a significant reduction of mortality (1.9% vs. 10.1%, p = 0.003) and TVR (1.3% vs. 8.1%, p = 0.005) in favour of DES. On the other hand the Global Registry of Acute Coronary Events (GRACE) reported increased mortality with DES. [99]

In summary, studies comparing DES with BMS in patients with MI have shown that DES reduces rates of revascularization to treat restenosis when compared with BMS, but there were no significant differences between the two types of stents in the rates of death or subsequent MI.

1.6. Stent Thrombosis and Antiplatelet Therapies

1.6.1. Stent thrombosis

Stent thrombosis (ST) is a rare event that occurs after stent implantation with either DES or BMS. This thrombotic complication can lead to either partial or complete obstruction of the coronary arteries. Although it is rare, ST is the most dangerous complication after either DES or BMS stent deployment. It is estimated that ST might lead to STEMI in 90% of the cases and in 20% it may lead to death.[23] .

Many studies have used different definitions for ST. The Academic Research Consortium (ARC) have published a uniform definition for ST. [100] ST is classified into: (1) definite ST (proven by angiography or autopsy); (2) probable ST (including sudden cardiac death up to 30 days post stent implantation, as well as MI in the territories of the coronary artery after the site of implanted stent without angiographic confirmation ; and (3) possible ST (sudden cardiac death after 30 days of stent implantation). ST is also classified according to the time of occurrence after stent deployment into early, late and very late ST. Early ST occurs within 30 days after stent implantation and is subdivided into acute ST (≤24 hours) and subacute (>24 hours to ≤ 30 days). Late ST occurs between 30 days and 1 year while very late ST occurs after 1 year. [100]

With early trials of BMS, ST was observed to follow BMS especially within the first month after implantation, with reported rates of early ST (≤ 30 days after stent implantation) in the range of 16-24%. [23] The incidence of ST after BMS deployment has been reduced by improvement in the techniques of stent deployment to reduce the stent malapposition as well as the use of anticoagulation and antiplatelet therapies. In initial

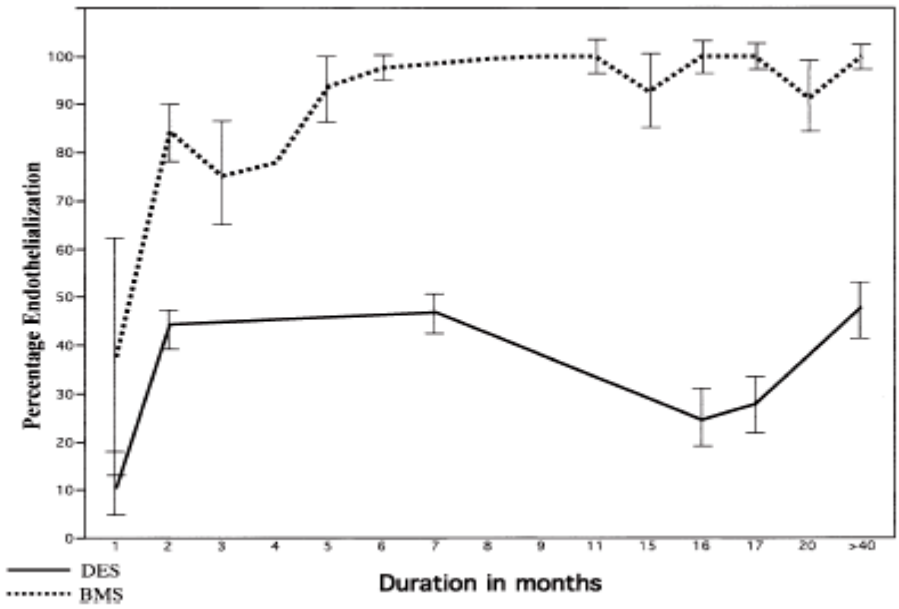
trials, the use of anticoagulant in combination with aspirin to reduce the early thrombotic events, was the main therapeutic modality used to reduce early thrombotic events. Further studies have shown that a combination of aspirin with Thienopyridine (ticlopidine) is superior to anticoagulation and aspirin. [47] Later clopidogrel replaced ticlopidine. Dual-antiplatelet therapy in the form of aspirin and clopidogrel became the standard therapy to reduce early thrombotic events following BMS deployment. All of theses advancements in the stent deployment techniques and combined antiplatelet therapies have reduced the incidence of ST to a rate of 1.2%. [23]

Early clinical trials of BMS did not find an increase in the rate of ST in patients with stable-CHD. Shortly after the introduction of DES, various case reports of theses adverse events were published, raising the concern that ST may limit the use of this technology due to this catastrophic complications. [101-103] Some of these events occurred during the first year while others occurred later after 1 year following stent implantation, raising the concern that DES posed risks far beyond the time intervals of most of the clinical trials. In several of theses cases the DES were used in ACS, increasing the concerns that DES implantation in STEMI may be particularly susceptible to this complication. It was proposed that the thrombotic milieu of acute coronary disease could lead to an increase rate of ST with DES compared with BMS. [104] A “firestorm” regarding late ST was raised at the European Society of Cardiology (ESC)/World Congress of Cardiology meeting and American College of Cardiology’s (ACC) 55th Annual scientific meeting in 2006 by the findings of two meta-analyses. These meta-analyses confirmed that late ST occurred more frequently than was previously reported in the randomised trials. The Basel Stent Kosten Effektivitats Trial - Late Thrombotic events (BASKET-LATE) study presented in March 2006 was conducted to identify the true incidence of death , MI and late ST in 746 patients

randomised to DES or BMS. Patients remained on clopidogrel therapy for 6 months and then followed for one year. Over the period of 6 months the patients had not experienced any events. After discontinuation of clopidogrel at 6 months, the patients were followed for a period of 1 year. It was found that late ST related events (death and MI) occurred about two times more frequently in patients who received DES than those with BMS (2.6% vs. 1.3%) and that late ST carried a four times higher risk of cardiac death /MI ($p < 0.001$)[104]

Procedural and technical factors play significant roles in the occurrence of early (acute and subacute) ST after both BMS and DES implantation, whereas late and very late ST seem to be influenced largely by the degree of endothelial coverage. [105] In autopsy studies, incomplete endothelialization over the stent with persistent fibrin deposition has been observed in relation to late ST (Figure 1.8). [106] In a recent study the link between persistent lack of strut coverage and late ST in DES has been assessed in vivo by using optical coherence tomography. [107] In this study, patients with late/very late ST (n=18) compared with control subjects (n=36, not experiencing ST for ≥3 years) had a higher percentage of uncovered struts.

Figure 1.8: Endothelialization following Drug-eluting Stents and Bare-metal Stents



BMS = bare-metal stent; DES = drug-eluting stent

Reproduced from Joner, M., et al., Pathology of drug-eluting stents in humans: delayed healing and late thrombotic risk. J Am Coll Cardiol 2006. ***48****(1): p. 193-202.* [106]

In addition to delayed healing, other pathological mechanisms of late and very late DES ST have been identified. Among these, incomplete stent apposition (defined as separation of stent struts from the arterial wall with evidence of blood flow behind the strut in the absence of a bifurcation) has been suggested to have a role in the pathogenesis of ST. [108]Additionally, late local hypersensitivity reactions to DES with extensive vasculitis of the intima, media, and adventitia, consisting of lymphocytes and eosinophils have also been described. [107, 109] Incomplete stent apposition may be the consequence of chronic inflammation and delayed healing, resulting in tissue necrosis and erosion around the stent. [107] Delayed re-endothelialization, impaired vasomotion, chronic inflammation, platelet adhesion, and low velocity flow between the stent and the aneurysmatic wall in the case of stent malapposition can all lead to ST. Finally, newly formed atherosclerotic changes within the neointimal tissue of stented segments can occur. [107] The incidence of any new atherosclerosis was observed more often in DES (31 %) than in BMS (16 %). [107] While the underlying processes responsible for the development of new atherosclerosis following stent implantation are likely to be multifactorial, this may involve the inability to maintain a fully functional endothelialized surface within the stent segment. [107]

Many reports have demonstrated that the greater risk of ST in the first year after DES deployment can occur after interruption of dual antiplatelet therapy. [110, 111] The early studies that established the efficacy of DES compared with BMS excluded patients with STEMI, while recently, a number of randomised trials have compared the outcomes of DES and BMS in patients with STEMI, confirming a favourable reduction in restenosis with DES. [84, 85, 88] These trials have generally excluded complex patients such as those in cardiogenic shock, rescue angioplasty patients and patients with complex lesions. Furthermore, there have been concerns among the interventional

community of using DES in patients presenting with STEMI, given the concern of delayed healing, lack of complete endothelialization and the thrombogenic environment of the necrotic plaque. [106, 112] The presence of a large thrombus burden, as is often the case during STEMI, has been shown to predict adverse events in patients treated with DES, with particular concern for late ST.[105 113]

In summary, ST risk can occur after both BMS and DES. The use of antiplatelet therapy has reduced both early and late ST over the years. However delayed endothelialization after DES deployment, likely result in very late ST.

1.6.2. Antiplatelet therapy

During normal stent deployment, significant trauma and damage to the endothelium occur. Initially, thrombogenic struts of the stent are exposed to passing coronary blood, creating the risk of early ST until the endothelium can re-grow. Anti-proliferative drugs of DES further delay endothelial growth. During this period of re-endothelialization, dual antiplatelet therapy in the form of aspirin and clopidogrel is needed. Patients with BMS or DES are typically recommended to usually continue clopidogrel for about 12 months and sometimes longer for more complicated lesions. All patients with stents should continue to take aspirin for life.

1.6.2.1.Thienopyridines

The thienopyridines include clopidogrel, ticlopidine, and prasugrel. Clopidogrel is the most common member of this class investigated and in clinical use. Ticlopidine is currently used infrequently, because of its high incidence of thrombotic thrombocytopenic purpura. A second generation of this drug, prasugrel, is of clinical use but still under approval. Clopidogrel is a prodrug which is converted to an active drug in the liver. It binds to and blocks the ADP receptor on platelets, a measurable

effect which lasts at least five days. An initial loading dose is necessary if rapid action is desired; otherwise a maintenance dose of three to seven days will be necessary before the platelet function is optimally reduced.

1.6.2.2. Glycoprotein IIb/IIIa inhibitors

The GPIIb/IIIa receptor is a major platelet integrin that plays a significant role in platelet aggregation. GPIIb/IIIa inhibitors bind to the receptors of activated platelets. Three intravenous GPIIb/IIIa inhibitors are currently available for clinical use: abciximab, tirofiban, and eptifibatide. Abciximab is a monoclonal antibody directed against the GPIIb/IIIa receptor. It is a nonspecific blocker. Tirofiban is a tyrosine derivative antagonist for the GPIIb/IIIa receptor and Eptifibatide is a cyclic heptapeptide.

Several randomised studies have evaluated the use of GPIIb/IIIa inhibitors in patients undergoing PCI.[114-117] Some trials focused on high-risk patients with MI or unstable angina undergoing PCI. [114, 115, 118] Other trials enrolled patients undergoing elective or urgent PCI with interventional devices such as angioplasty, atherectomy, or stenting. In almost all these trials the GPIIb/IIIa inhibitor was administered as a bolus immediately before coronary intervention, followed by infusions at 12 hours (abciximab) and 18 to 36 hours (eptifibatide or tirofiban). The primary outcome measured in these trials was a composite endpoint (death, nonfatal MI, or TVR) with major bleeding as a secondary safety endpoint.

In patients undergoing PCI, potent peri-procedural antiplatelet therapy with the GP IIb/IIIa antagonist reduces acute ischemic events, including MI and the need for urgent revascularization. The first trial that highlighted the central role of GPIIb/IIIa during PCI is the EPIC (Evaluation of 7E3 for the Prevention of Ischemic Complications) study. [118] This large well designed, prospective randomised double-bind

trial provided results which described the advantages and disadvantages of abciximab therapy as an adjunctive therapy for PCI. It included 2099 patients undergoing PCI who presented with high-risk clinical situations involving severe unstable angina, evolving MI, or high-risk coronary morphologic characteristics. At 30 days, treatment with a bolus plus infusion of the GP IIb/IIIa blocker, abciximab reduced the incidence of major adverse cardiac events (death, MI, or urgent revascularization) by 35% compared with placebo (8.3% vs.12.8%, p = 0.008). However, this was accompanied by an increase in the rate of thrombolysis in myocardial infarction (TIMI) major bleeding (14% vs. 7%, p = 0.001).

Another double-blind, placebo-controlled randomised trial of tirofiban in patients with acute coronary syndrome undergoing coronary interventions within 72 hours of presentation was the RESTORE (Randomised Efficacy Study of Tirofiban for Outcomes and REstenosis) trial.[114] Patients (n=2139) who received aspirin and heparin were randomised to receive tirofiban or placebo. The primary end point was composite of death, MI or coronary revascularization. At 2 days after angioplasty, the tirofiban group had a 38% relative reduction in the composite end point (p=0.005), and at 7 days there was a 27% relative reduction (p=0.022), largely because of a reduction in nonfatal MI and the need for repeat angioplasty. At 30 days, the primary composite end point was reduced from 12.2% in the placebo group to 10.3% in the tirofiban group, a 16% relative reduction (p=0.160). Thrombolysis In Myocardial Infarction (TIMI) major bleeding was 2.1% in the placebo group compared with 2.4% in the tirofiban group (p=0.662). In general the use of GPIIb/IIIa inhibitors improved clinical outcomes after PCI.

In the setting of STEMI, despite successful re-opening of the occluded coronaries, suboptimal myocardial re-perfusion may occur as a result of thrombotic re-

occlusion because of fibrinolysis induced platelet activation or distal embolization, resulting in adverse clinical outcomes. The interest in improving reperfusion success, while reducing hemorrhagic complications, has led to studies of GPIIb/IIIa inhibitors in the settings of STEMI management. This mainly included three different strategies in the use of GPIIb/IIIa inhibitors in management of patients with STEMI; as combined therapy during primary PCI; as combined therapy with low-dose fibrinolytic therapy alone; and as combined therapy with low-dose fibrinolytic therapy before PCI. Pharmaco-invasive strategies are discussed in sections 1.5.2.3 and 1.5.2.4.

1.7. Strategies of Selective Drug-eluting Stents and Bare-metal Stents Implantation

The introduction of DES has reduced late restenosis, and more importantly TVR. [39, 40] Since its introduction into clinical practice, the used of DES has dramatically increased, and has been incorporated into the clinical practice of many countries. This has been strengthened by many randomised trials and observational studies which have demonstrated that DES reduces clinical and angiographic restenosis compared with BMS use.[23, 48-50, 119] However there are still several concerns about the use of DES which can be summarized as follows: i) there are low but definite very late ST risk especially after 1st generation DES deployment , ii) patient compliance, particularly after emergency DES deployment, as 1 year of dual anti-platelet therapies recommended currently, [120-122] and as premature discontinuation of thienopyridine therapy is a major risk factor for ST; iii) the risk of bleeding is particularly high on triple therapy when systemic anticoagulation is also required; and iv) the economic impact particularly after DES use in multivessels disease. Therefore a strategy of selective DES use is attractive.

There is an inverse relationship between vessel size and TVR rate with the use of BMS.[123] The diameter of culprit lesion segments of diseased coronary artery is an important determinant of restenosis and TVR. [46, 93, 124-127 128] In this context, using BMS for those with lower restenosis risk and using DES in such patients at high risk for coronary restenosis, is an important approach, which will be further explored in Chapter 3 of this thesis. In previous studies, the definition of a “large” coronary artery is unclear with “cut-off points” of 3mm and 3.5mm. The efficacy of DES and BMS in large (≥ 3

mm in diameter) coronary arteries was evaluated in a large randomised trial, the Basel Stent Kosten Effektivitäts Trial Prospective Validation Examination (BASKET-PROVE) trial.[128] The results of the trial showed that in patients receiving stenting of large coronary arteries (≥ 3 mm), DES and BMS had equivalent rates of death and MI but experienced a significantly higher rate of TVR after BMS implantation. These results are different from some of the previous registry data regarding TVR in large vessels. This may be because of different cut-off points for defining large coronary arteries (3mm or 3.5 mm). In this context, Chapter 4 will examine the clinical outcomes after BMS deployment in large coronary arteries.

1.8. Cardiac Markers and Percutaneous Coronary Intervention

Myocardial cell death is accompanied by the release of various myocyte proteins into the circulatory system; these proteins are collectively called myonecrosis markers. These include Myoglobin, Glutamine-oxaloacetic transaminase (GOT), Lactate dehydrogenase (LDH), CK, CKMB, Cardiac troponins (TnT and TnI) and other markers of myonecrosis. Myoglobin, glutamine-oxaloacetic transaminase and lactate dehydrogenase are present in other parts of the body and therefore are less specific markers for myonecrosis than other available cardiac markers, therefore they are of less clinical use. Because myoglobin is a small molecular protein that releases early in cases of myonecrosis, it can be used in combination with more specific markers (CK, CKMB, troponins) to detect early myonecrosis. CK, CKMB and troponins are commonly used clinically for the diagnosis of myonecrosis as well as being used for their prognostic importance.[129] Kinetic profiles, timing, specificity and sensitivity of myonecrosis markers after myocardial cell injury are shown in Figure 1.9 and Table 1.3. [14]

1.8.1. Creatine kinase and Creatine kinase myocardial band

Creatine kinase is a dimer composed of two subunits types, M and B. The MB present in 20-30% of cardiac muscle while MM is predominantly found in skeletal muscle, and BB dimer is predominantly found in the brain and kidney. CK and CKMB are sensitive markers for myonecrosis and more specific than Myoglobin, Glutamine-oxaloacetic transaminase (GOT) or Lactate dehydrogenase (LDH). Because CK is present in large concentrations in other parts of the human body such as skeletal muscles, it has poor

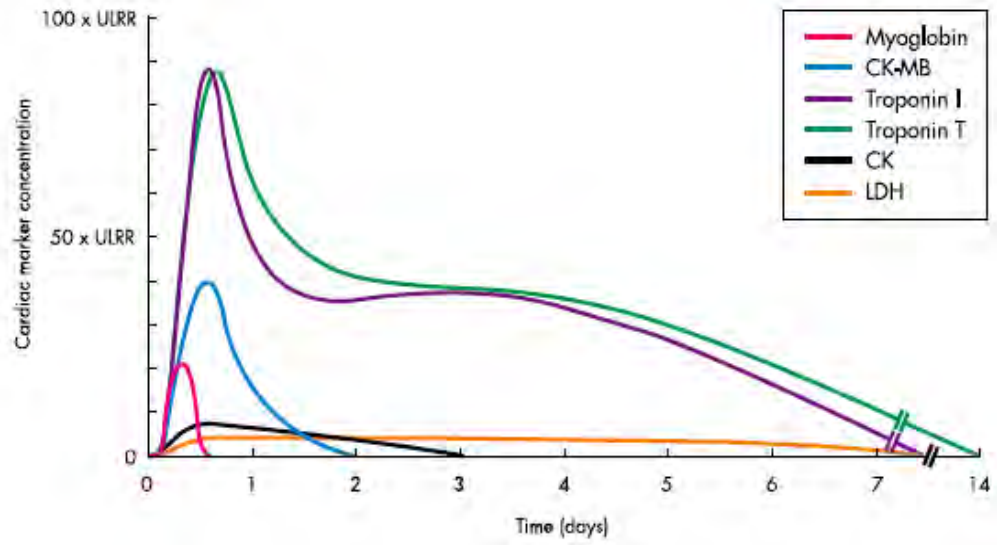
specificity. [129] On the other hand CKMB (which is an isoenzyme of CK) has better specificity than CK, because of its higher concentration in cardiac muscle cells than skeletal muscle cells. Of note, CKMB is also present in small amounts in other human body organs such as the uterus, prostate, and small intestine. Therefore, cardiac specificity may be impaired in some diseases affecting these organs.[129]

Measurements of CKMB include either measurement of enzymatic activity of different isoenzymes separated by electrophoresis or measurement of actual protein concentration (mass assays). The latter method allows measurement of lower amounts of CKMB with higher accuracy.

1.8.2. Troponins

Troponins are proteins that form complex structures that regulate calcium dependent interaction of myosin and actin in striated muscle. It has three distinct forms troponin C, I and T. Troponin C has limited clinical use because myocyte troponin C is identical to that of skeletal muscle troponin C, while TnI and TnT are more specific and sensitive cardiac biomarkers. After myocardial cell damage, troponins are released into the blood within 3-4 hours. Figure 1.9 shows different kinetic profiles for various cardiac biomarkers including CKMB and troponins.

Figure 1.9: Kinetic Profile of Myonecrosis Markers after Myocardial Infarction



CK = creatine kinase; CKMB = creatine kinase-myocardial band; LDH=Lactate dehydrogenase.

Reproduced from French, J.K. and White, H.D. [14]

Table 1.3 : Timing, Specificity and Sensitivity of Myonecrosis Markers

Myonecrosis marker	First detected*	Duration of detection	Sensitivity	Specificity
Myoglobin	1.5-2 hours	8-12 hours	+++	+
CKMB	2-3 hours	1-2 days	+++	+++
TnI	3-4 hours **	7-10 days	++++	++++
TnT	3-4 hours **	7-14 days	++++	++++
CK	4-6 hours	2-3 days	++	++
LDH	6-10 hours	5-7 days	++	+

TnT = troponin T; TnI = troponin I; CK = creatine kinase; CKMB = creatine kinase-myocardial band; LDH=Lactate dehydrogenase.

** hours after myocardial injury.*

*** high sensitivity troponin assays may detect elevations in troponin in peripheral blood early.*

Reproduced from French, J.K. and White, H.D. [14]

1.8.3. Cardiac biomarkers and periprocedural myonecrosis

Percutaneous coronary intervention can be associated with an incidence of procedural complications such as periprocedural myonecrosis. Periprocedural myonecrosis, which can range from a minor myocardial injury to a large MI, is commonly observed following PCI. As an early detection of MI following PCI is an important safety event and it is an important early clinical outcome that can occur after PCI, their detection have important clinical implications for patients.

Periprocedural myonecrosis can result from procedural complications such as distal embolisation, side branch occlusion, coronary dissection and disruption of collateral coronary blood flow. It can also occur silently after uncomplicated PCI procedures. Periprocedural myonecrosis can be detected by measuring cardiac biomarker elevations and the range of these elevations have been used to indicate the extent of myocardial injury during PCI.[130]

An elevation of cardiac biomarkers after coronary intervention is a common phenomenon, and can range from a minor to a large degree of elevation.[131] Cardiac biomarker elevations have also been recognised to occur after uncomplicated percutaneous coronary intervention for many years. [132] The frequency with which any periprocedural myocardial injury is detected has varied especially with the development of sensitive cardiac biomarkers and cardiac biomarker assays.[130] Elevations in CKMB levels above the upper limits of normal following an elective PCI can occur in about 30% of patients. [133] An elevation of cardiac troponin above the upper limits of normal following an uncomplicated PCI has been observed in about 40 % of patients undergoing elective PCI.[134] Cardiac troponins are more sensitive cardiac biomarkers than CKMB for minor degrees of myocardial damage and elevated values after PCI with or without stenting are more common than CKMB values. [131, 135, 136]

The clinical significance and long-term prognostic importance of periprocedural myonecrosis was uncertain in the early years of PCI. Early, small studies with short follow-up found no increased risk but subsequent large prospective trials have proved that higher elevation of markers of myonecrosis following PCI were clinically relevant. [131, 133] There was constant debate on the significance of elevated CKMB after percutaneous coronary intervention in the 1990s.

Although current guidelines recommend troponin as preferred to CKMB for diagnosis of myonecrosis in all circumstances, including periprocedural, the majority of studies that evaluated the prognostic significance of periprocedural biomarker elevation have used CKMB. Previous studies have suggested that only greater elevations of CKMB (> 5times the upper limit of normal [ULN]) independently correlates with mortality after elective PCI. [137-139] Stone et al, studied 7147 consecutive patients after elective PCI in which CKMB levels were systematically collected.[137] Peak CKMB levels increased to greater than 3 times ULN in 17.9% of patients, and Q-wave MI developed in 0.6% of patients. On multivariate analysis, the periprocedural development of new Q-wave MI and CKMB levels greater than 8 times ULN without Q-wave was a predictor of mortality (mortality rate at 2 years was 38.3%, HR: 9.9, $p < 0.0001$; and 16.3%, HR:2.2, $p < 0.0001$, respectively). Survival was unaffected by lesser degrees of CKMB elevation.

Smaller degrees of CKMB elevations (<3 times ULN) frequently occur after PCI and the impact of these minor degrees of periprocedural myonecrosis on late clinical outcomes cannot be neglected when compared with higher degrees of periprocedural CKMB elevations. In patients with lower levels of CKMB elevation (<3 times the URL) it may be difficult to find evidence of procedural complications and there is persistent debate about whether these enzyme rises are clinically significant. In a meta-analysis to

assess CKMB levels and survival, 23230 patients who underwent PCI from seven studies were included.[140] Nineteen percent of the patients had 1-5 times ULN of CKMB level elevation, while 6% had >5 times ULN elevation. Mean follow-up was 6-34 months per study. The mortality relative risks were 1.5 with 1-3 times ULN of CKMB level elevations, 1.8 with 3-5 times ULN elevations and 3.1 with >5 times ULN elevations. Thus, approximately 1 in 5 patients undergoing PCI will have an elevation of CKMB of 1-5 times, and 1 in 15 subjects will have an even larger increase. Any CKMB increase is associated with a potential increase in the subsequent risk of death during follow-up. One to three times CKMB elevations increase the risk of death by approximately 50%. The risk is increased by 80% with 3-5 times CKMB levels elevations and is tripled with over 5 times ULN of CKMB levels. [140]

Even in the era of stenting and statin therapy, there was a graded response for CKMB in predicting long-term mortality. In a study by Andron et al, [141] retrospective analyses of 3864 patients undergoing PCI with the deployment of at least one stent were performed. Periprocedural CKMB was independently associated with an increased risk of death (mean follow-up of 22 months) at an HR of 1.09 for every 10 units of CKMB. When compared to normal levels, CKMB ratios of 1-3 times elevated compared to a normal baseline were associated with an HR of 1.30, 3-5 times elevated with an HR of 1.76, and greater than five times with an HR of 2.26.

Following troponin introduction in the clinical field, many studies have investigated its prognostic significance. Some studies have shown that the serum concentration of cardiac troponin is an independent predictor of survival while others did not.[142-148] This variability is most likely to occur because of heterogeneity of inclusion criteria and variation in the sensitivity and specificity of the troponin assay used, difference sample size and difference in duration of follow-up.

The meta-analysis by Nienhuis et al, [142] included 20 studies (published between 1998 and 2007) involving 15,581 patients after elective PCI. The mean follow-up was 16.3 months (varied between 3 and 67 months). Overall, troponin was elevated after elective PCI in 32.9% of patients. Increased mortality was significantly associated with troponin elevation after PCI (4.4% vs. 3.3%, OR 1.35, p = 0.001), and combined death or nonfatal MI also occurred more often in patients with post procedural troponin elevation (8.1% vs. 5.2%, OR 1.59, p< 0.001). In another recent meta-analysis by Feldman et al, [143] to evaluate the impact of both TnI and TnT measured after elective PCI, 22,353 patients from 22 studies were included. The mean follow-up was 17.7 months (varied between 3 to 67 months). Post-procedural marker elevations were associated with an increase in mortality risk (5.8% vs. 4.4%, OR 1.45, 95 % CI, 1.22-1.72, p < 0.01) as well as the composite end point of all-cause mortality or MI (9.2% vs. 5.3%, OR:1.77[95 % CI, 1.48-2.11], p < 0.01).

Some other studies do not support a prognostic role of post procedural troponin elevations. In a study by Miller et al. [149] 2352 patients were studied in which TnT levels were measured before PCI and 8 and 16 h post-PCI. Patients with elevated baseline TnT levels had a higher overall cumulative 12-month rate of death or MI compared with those without elevated baseline levels (11.1% vs. 4.7%, p< 0.05). After adjustment for baseline risk factors, baseline TnT was a significant predictor of outcomes after PCI (HR, 1.14: 95% CI[1.07 -1.22]; p<0.001). Neither the timing nor the magnitude of post-procedural TnT elevations were predictive of long-term adverse events when baseline elevations were included in the analysis. This study was supported by another study by Prasad et al, [134] who analyzed 5487 patients undergoing elective PCI using a TnT assay (upper limit of normal <0.01 ng/mL). In patients with normal pre-PCI TnT levels, post-PCI elevation of TnT occurred in 43%. The 30-day mortality rate was 0.3% versus 2.3%

in those patients with pre-PCI TnT <0.01 compared to those who had an elevation of ≥0.01 ng/mL, respectively. Over a median follow-up of 28 months, an abnormal pre-PCI cTnT level was an independent predictor of death (HR: 1.79 [95%CI:1.35-2.39]; p <0.001), but the occurrence of PCI-related myonecrosis was not. The absolute risk of death from minor, isolated TnT elevations appears to be lower than when there is a pre PCI TnT elevation.

In summary, cardiac biomarker elevations after PCI are common. The studies on CKMB post PCI reported that periprocedural cardiac markers elevations is common after PCI, and in most of the cases it is limited to low level elevations. Most studies have suggested that the degree of subsequent risk of mortality correlates with the extent of rise of CKMB levels elevations. On the other hand, an increase of troponin after PCI is also common and that controversies exists about their minor elevations following PCI and that pre-PCI troponins level may have more prognostic significance.

The influence of post-PCI TnT and CKMB elevations and their effect on late clinical outcomes for patients with ACS, and in those with stable CHD is studied in Chapter 6 of this thesis.

1.8.4. Detection of myonecrosis and diagnostic criteria for periprocedural myocardial infarction

Traditionally, the World Health Organisation (WHO) definition of MI was the first definition to be implemented in clinical practice. Following this, a task force was convened, which led to the establishment of the clinically oriented consensus document for universal definitions of MI in 2000, 2007 and more recently in 2012.[10, 150, 151] These universal definitions of MI have highlighted the importance of biomarkers of myocardial injury (CKMB or Troponin) as a central role in the diagnosis of MI and

highlighted the importance of patterns of elevation of blood levels of cardiac biomarkers above the 99th percentile upper reference limit (URL).

Because of its specificity and sensitivity, CKMB had an important impact on the diagnosis of patients with CHD in the past. Even though, the development of CKMB mass assays improved both the clinical sensitivity and specificity of CKMB for myocardial injury compared with the measurement of enzyme activity, its specificity and sensitivity can be decreased in other conditions such as skeletal muscle injury. This has led to implementation of more sensitive and specific cardiac biomarkers, cardiac troponins (I or T). Because of the higher specificity and sensitivity of cardiac troponins, [135, 136, 152, 153] their measurement is preferred to CKMB for diagnosis of MI. [10, 150, 152, 154] Troponins have become an integral part of the most recent universal definition of MI. In addition, advances in assay technology have led to the development of high-sensitivity cardiac troponin assays, which enable the detection of cardiac troponin concentrations that are lower by a factor of 10 than those measureable using conventional assays.[155]

The definition of periprocedural MI is a matter of debate and varies between clinical trials. The consensus definition of MI published in 2000 initially defined MI, including periprocedural MI, as any rise and fall in cardiac biomarkers (CKMB or troponin) above the ULN.[150] After that, the consensus document published in 2007, the universal definition of MI, defined PCI-related MI as an increase of biomarkers (CKMB or troponin) greater than 3 times ULN classified as MI (type 4a), and considered elevations of cardiac biomarkers between 1 and 3 times ULN as indicative of peri-procedural myocardial necrosis but not infarction.[10] This definition applies for patients with normal baseline biomarkers. If the biomarker levels are elevated and rising prior to PCI, the universal myocardial infarction consensus documents (the 2000, 2007 and the 2012) acknowledge that there are insufficient data to recommend biomarker criteria for

the diagnosis of PMI. [10, 150, 151] If the biomarker levels are stable or falling, recurrent infarction is diagnosed if there is ≥20% increase of a previously stable or falling elevated levels (troponin or CKMB).[10] However, the 2007 universal MI definition recommended using different amounts of elevation of cardiac markers (TnT or CKMB) depending on the clinical situation, either spontaneous MI or post-PCI. Two cardiac marker levels, preferably troponin, one immediate and a second 6 hours later, and an increase of ≥ 20 % TnT above stabilized or falling elevated pre-PCI levels are necessary for cardiac marker based post-PCI re-MI definition, in addition to ECG or imaging. [10, 156] Table 1.4 details clinical classification of the different types of myocardial infarction as defined in the universal definition of MI. [10]

Table 1.4 : Clinical Classification of Different Types of Myocardial Infarction

Type	Definition
Type 1	Spontaneous myocardial infarction related to ischaemia due to a primary coronary event such as plaque erosion and/or rupture, fissuring or dissection
Type 2	Myocardial infarction secondary to ischaemia due to either increased oxygen demand or decreased supply: for example, coronary artery spasm, coronary embolism, anaemia, arrhythmias, hypertension or hypotension
Type 3	Sudden unexpected cardiac death, including cardiac arrest, often with symptoms suggestive of myocardial ischaemia, accompanied by presumably new ST-elevation, or new left bundle branch block, or evidence of fresh thrombus in a coronary artery by angiography and/or at autopsy, but death occurring before blood samples could be obtained or at a time before the appearance of cardiac biomarkers in the blood
Type 4 a	Myocardial infarction associated with PCI
Type 4 b	Myocardial infarction associated with stent thrombosis as documented by angiography or at autopsy
Type 5	Myocardial infarction associated with coronary artery bypass grafting

PCI= percutaneous coronary intervention.

Cardiac troponins T (TnT) and I (TnI) have long half-lives and are detectable in blood for up to 10-14 days post-MI, whereas CKMB levels remain elevated in the circulation for only 2-3 days post-MI. [14, 157] Because of these differences in kinetic profiles, the measurement of CKMB levels was recommended in the 2000 MI redefinition for the diagnosis of early re-infarction, including post- PCI when troponin levels were elevated. [150] However, the 2007 universal MI definition recommended using different amounts of elevation of cardiac markers (TnT or CKMB) depending on the clinical situation, either spontaneous MI or post-PCI. Two cardiac marker levels, preferably troponin, one immediate and a second 6 hours later, and an increase of $\geq$ 20 % TnT above stabilized or falling elevated pre-PCI levels are necessary for cardiac marker based post-PCI re-MI definition, in addition to ECG or imaging. [10, 156]

Because there are relatively few data to support the troponin-based definition of re-infarction, especially post-PCI in patients with elevated pre-PCI TnT levels, [158, 159] cardiac marker levels in such patients warrant further evaluation. Chapter 6 of this thesis evaluates the cardiac marker criteria for periprocedural MI using TnT and CKMB.

Chapter 2
General Methodology

2.1. Aims and Hypotheses

Study 1: Aims to determine whether the selective policy of DES utilisation during PCI at our institution achieves an acceptably low TVR rate.

Hypothesis: We hypothesized that PCI with the selective use of DES criteria targeting the lesions with high risk of restenosis, could be an effective approach with an acceptable efficacy and safety profile for patients who present with CHD. This study is included in Chapter 3.

Study 2: The aim of this study is to examine clinical outcomes of consecutive, unselected patients with STEMI undergoing PCI with BMS, in particular infarct related artery (IRA) of ≥3.5mm in diameter.

Hypothesis: We hypothesized that in these patients with large IRAs of ≥3.5mm, BMS deployment may be associated with low TVR rates. This study is included in Chapter 4.

Study 3: The aim of this study is to examine safety and clinical outcomes following rescue PCI, in particularly with high utilization rates of GPIIb/IIIa inhibitors and stenting, which may provide the basis for prospective studies of future pharmaco-invasive strategies in STEMI patients.

Hypothesis: We hypothesized that PCI with high utilisation rate of GPIIb/IIIa inhibitors after failed fibrinolysis may be effective and safe and achieve acceptable clinical

outcomes that may be comparable to the outcomes after primary PCI. This study is included in Chapter 5.

Study 4: The aims of this study are to evaluate the TnT and CKMB criteria of peri-procedural myocardial infarction, and to examine the effect of post-PCI TnT and CKMB elevations on late clinical outcomes for patients with ACS and in those with stable CHD.

Hypothesis: We hypothesize that there might be significant differences between relative increase in cardiac marker when compared with absolute change in TnT or CKMB, and that post-PCI prognostic values of these markers may be different according to the type of CHD. This study is included in Chapter 6.

2.2. Methods

2.2.1. Study population

The population of the 4 studies included consecutive patients within the South Western Sydney Local Health District. They presented locally or were transferred from referral hospitals for angiography and /or angioplasty at the Cardiac Catheterisation Laboratory, cardiology department, Liverpool Hospital, Sydney, NSW, Australia. These included transfers from non PCI hospitals in South Western Sydney Area Health Services (SWSAHS) including Campbelltown, Fairfield, Bowral, Camden and Bankstown hospitals. Therefore the Cardiac Catheterisation Laboratory at Liverpool Hospital, serving the needs of a population of about 900,000 people.

From January 2004, Liverpool Hospital commenced a 24 hours 7day/week Cardiac Catheterisation Laboratory interventional roster and commenced primary PCI for STEMI patients who presented to Liverpool Hospital during working hours. From June 2006, Liverpool Hospital had a 24 hours/7 days a week primary PCI roster.

All consecutive patients undergoing angiography and /or angioplasty have had their clinical and procedural characteristics entered prospectively in the Cardiology Reporting System (CRS) database since 1994 by trained nurses and/or clinicians at the time of presentation to Cardiac Catheterisation Laboratory at Liverpool Hospital. These were entered on a standard case report form in the cardiology database with standard definitions for all fields. The demographic data includes patients' age, gender and body mass index (BMI). Patients' risk factors for ischemic CHD such as cigarette smoking, hyperlipidemia, diabetes mellitus, and family history of CHD is also included. Procedural data include indications for angioplasty, which included: non ST-segment

elevation myocardial infarction, unstable angina and STEMI, here combined as ACS. Patients with angina (classes II-III) and other stable manifestations of CHD were classified as stable CHD. Other relevant procedural data in relation to each study were collected according to their relevance in each study.

Audit activity of the database performed at about 6 month interval by the cardiologist supervised the database (A.H) and when necessary notification to the scientific officers, nurses and/or cardiologist about any amendment and clarification required. In addition, during data collection from these database, each variable was reviewed and those with entry errors or biologically implausible, were cross checked with other medical records and corrected in the database. In addition cross checking of random cases for their accuracy with files and other databases were performed.

As the approval of DES use by the Food and Drug Administration was in early 2003, in October 2003, Cardiac Catheterisation Laboratory adopted specific criteria for DES use targeting patients with high risks of restenosis. Therefore, consecutive patients with CHD undergoing PCI who presented locally or were transferred to the Cardiac Catheterisation Laboratory at Liverpool Hospital after 1 October 2003 were studied. Consecutive patients with CHD over the period from 1 October 2003 to 31 October 2006 were included in the study in Chapter 3, and the study in Chapter 4 included consecutive patients with STEMI who presented or were transferred to Liverpool Hospital over a longer time frame, between 1 October 2003 and March 2010. In the study included in Chapter 5, consecutive patients who underwent rescue PCI in the era of stenting and GPIIa/IIIb inhibitors use were included from the period from January 2002 through to December 2009. For the study in Chapter 6, all consecutive patients who had angioplasty in the same period from 1 October 2003 to 31 October 2006 were

screened and, only those with available cardiac markers before and after PCI were included.

2.2.2. Ethics approval

The 4 studies include in Chapters 3, 4, 5 and 6 are part of the analysis for quality improvement and analysis of outcomes after Percutaneous Coronary Intervention and were approved by the Sydney South West Area Health Service Human Research Ethics Committee (Project No: QA2008/034).

2.2.3. Data collection

The demographic, clinical and procedural data of the consecutive patients were collected and screened for their accuracy from the electronic medical records and the patient's notes, and the other databases such as Power Chart and Hoslab databases at Liverpool hospital, Sydney, Australia. Data were collected and stored using Microsoft Excel database and each patient was coded with a study number.

2.2.4. Definitions

- Definitions of diagnosis

- Stable CHD was defined as coronary artery disease with symptoms mainly on exercise.
- Unstable angina was defined as a clinical syndrome with myocardial ischemia in the absence of MI.
- MI was defined according to the World Health Organisation (WHO) definition which require two of the three criteria: a clinical presentation with symptoms consistent with myocardial ischemia, which included a history of ischemic chest pain lasting more than 30 minutes and unrelieved by sublingual nitrates, and/or

typical 12 lead ECG changes, showing at least 2mm of ST-segment elevation in two or more contiguous chest leads or at least 1mm in two or more contiguous limb leads, and or pattern of cardiac marker elevations.

- The definition of cardiogenic shock at presentation is based on the clinical criteria for cardiogenic shock which require hypotension (a systolic blood pressure of less than 90 mmHg for at least 30 minutes or the need for supportive measures to maintain a systolic blood pressure of greater than or equal to 90 mmHg), end-organ hypoperfusion (cool extremities or a urine output of less than 30 ml/h, and a heart rate of greater than or equal to 60 beats per minute). The hemodynamic criteria are a cardiac index of no more than 2.2 l/min per square metre of body-surface area and a pulmonary-capillary wedge pressure of at least 15 mmHg.

- Definitions of risk factors

Risk factors in each patient were determined and classified by treating physicians as following:

- Hypertension: hypertension as documented by a blood pressure greater than 140 mmHg systolic or 90 mmHg diastolic on at least 2 occasions, history of hypertension diagnosed and treated with medication, diet, and/or exercise, and /or current use of antihypertensive pharmacological therapy.
- Dyslipidemia: history of dyslipidemia diagnosed and/or treated by a physician include documentation of the following: total cholesterol greater than 200 mg/dl (5.18 mmol/l); or low-density lipoprotein greater than or equal to 130 mg/dl (3.37 mmol/l); or, high-density lipoprotein less than 40 mg/dl (1.04 mmol/l); or initiation of treatment if low-density lipoprotein is greater than 100 mg/dl (2.59 mmol/l) in patients with known coronary artery disease.

- Family history of premature CHD: defined as any direct blood relatives (parents, siblings, children) who have had any of the following at age less than 55 years: Angina, MI, Sudden cardiac death without obvious cause.
- Smoking: history confirming cigarette smoking.
- Diabetes mellitus: either newly diagnosed or treated diabetes mellitus

2.2.5. Pre-angioplasty treatment

All patients with MI were treated with aspirin (300mg/day) at first medical contact. Heparin was administered according to the appropriate hospital guideline. The guidelines for patients receiving fibrin-specific fibrinolytic therapy for STEMI recommend administration of weight-adjusted heparin (60U/kg bolus for a maximum of 4000U followed by 12U/kg/h [maximum 1000U/h]) adjusted to maintain an APTT 50 to 70s for 48h. [8]

Eligibility for fibrinolytic therapy for STEMI was determined by the absence of contraindications, including absolute contraindications of previous stroke and recent head trauma and relative contraindications of poorly controlled hypertension, gastrointestinal bleeding, or current Warfarin use, as well as the informed written consent of the patient to the therapy (where possible). Fibrinolytic therapy was administered according to the guideline specific to each regimen. [8]

The administration of other pharmacologic agents, including nitrates, antithrombotic agents (Warfarin, Enoxaparin), beta-blockers, calcium channel antagonists and analgesics was at the discretion of the attending physician or cardiologist.

2.2.6. Technique and definitions of angioplasty

2.2.6.1. Angioplasty technique

Diagnostic angiography and/or angioplasty were performed according to the standard clinical guidelines. [160-162]A clopidogrel loading dose (300mg or 600mg) was given before or during PCI procedures. Percutaneous approaches were either via femoral or radial artery. Either 6 or 7 French femoral sheaths were inserted into the femoral artery using the Seldinger technique. An intra-arterial heparin at 100 units per kg body weight (70 units/kg if a GPIIb/IIIa inhibitor was administered) was given. The administration of GPIIb/IIIa inhibitors (tirofiban or abciximab) was at the discretion of the interventional cardiologist. An intra arterial radio-opaque guidewire was then inserted through the femoral or radial sheath to the coronary artery to cross the coronary artery lesion. This was followed by insertion of balloon tipped catheter guided by the guide wire. This was followed by inflation of the balloon at the lesion site then insertion of a stent. The choice between using balloon catheter or stent-balloon catheter for direct stenting depends on the cardiologist's choice and severity of the lesion. Post stenting balloon dilatation was recommended in the most of the procedures.

Since October 2003, Cardiac Catheterisation Laboratory at Liverpool Hospital predefines specific criteria for deployment of DES in patients based on a perceived increase risk of restenosis. Patients were eligible to receive a DES if they satisfied one or more DES use criteria described below. Over the study period, BMS used were Liberte, PRO-Kinetic, Driver, Tsunami Gold and Gazelle; and DES used were 1st generation (TAXUS Liberte, Cypher Select), and 2nd generation (Xience V and Endeavor Resolute). These are summarized in Table 2.1. Routine angiographic follow-up for asymptomatic patients was not mandatory. Indefinite continuation of oral aspirin was encouraged while clopidogrel were prescribed to be taken for about 6 -12 months.

Table 2.1: Types of Drug-eluting and Bare-metal Stents		
Stent	**Company**	**Description**
DES 1st generation		
Taxus Express2 (~ 2003-2005)	Boston Scientific	DES (paclitaxel- eluting stents)
Cypher, Cypher Select (~2005-2008)	Cordis, and Johnson& Johnson	DES (sirolimus- eluting stents)
TAXUS Liberte (2005-2008)	Boston Scientific	DES (paclitaxel- eluting stents)
DES 2nd generation		
Xience V 2008/2010 (~ 2009-2010)	Abbott Vascular	DES (everolimus- eluting stents)
Endeavor Resolute (~2008-2010)	Medtronic	DES (zotarolimus- eluting stents)
BMS		
Liberte (~2003-2010)	Boston Scientific	BMS
PRO-Kinetic (~2003-2010)	BIOTRONIK	BMS
Driver (`2003-2010)	Medtronic	BMS
Express2 (2003-2006)	Boston Scientific	BMS
Tsunami Gold (2003-2010	Terumo	BMS
Gazelle (2008-20010)	Biosensors International	BMS

DES = drug eluting stent(s); BMS = bare-metal stent(s).

2.2.6.2. Criteria used for deployment of DES in lesions at high risk of restenosis

Since October 2003, specific clinical criteria for use of DES were instituted and displayed in Cardiac Catheterisation Laboratory at Liverpool Hospital. Because of financial limitations, these criteria aim to limit the use of DES to 25-30% of patients considered at highest risk of restenosis, and are follows:

- Presence of a lesion in the left main coronary artery.
- Presence of diabetes mellitus with reference target coronary vessel diameter ≤ 3 mm.
- Presence of ostial lesions in any of the main coronary vessels (right coronary artery [RCA], left anterior descending coronary artery [LAD], and left circumflex [LCX]).
- Presence of lesion(s) in the proximal third of LAD.
- In target lesions ≥ 20 mm in length where the reference target segment diameter is ≤ 3.0 mm.
- Lesions where the reference vessel segment diameter is ≤ 2.5 mm.
- In-stent restenosis.

The choice between pre-dilatation of the culprit lesion with balloon or direct stenting and post-dilation of the stent with balloon angioplasty was left to the interventional cardiologist's opinion. Details of the angiography and PCI procedure were recorded on the "Cardiac Catheterisation Worksheet". These include angiographic and lesion characteristics and stent types.

2.2.6.3. Definition of primary percutaneous coronary intervention

Primary angioplasty for STEMI included PCI on patients diagnosed with STEMI who presented directly or transferred to Liverpool hospital .This was after consultation with the interventional cardiologist at Liverpool Hospital Cardiac Catheterisation Laboratory.

2.2.6.4. Definition of referral for rescue percutaneous coronary intervention

Referral for emergency angiography with a view to urgent revascularisation after failed fibrinolysis for STEMI was decided upon consultation with the consultant cardiologist at the Liverpool Hospital Cardiac Catheterisation Laboratory.

Failed fibrinolysis was defined by lack of complete resolution of the ST-segment from baseline elevation (i.e. < 50% recovery), with or without the persistence of ischemic clinical symptoms, as determined at approximately 60 minutes after the administration of fibrinolytics.

2.2.6.5. Definition of referral for routine (prognostic) percutaneous coronary intervention

This indicates the use of PCI as a routine (prognostic) procedures following successful thrombolysis and/or after delayed presentation.

2.2.6.6. Percutaneous coronary intervention for non-ST-segment elevation myocardial infarctions

This indicates the use of PCI for NSTEM.

2.2.6.7. Percutaneous coronary intervention for stable coronary heart disease

This indicates the use of PCI for stable CHD

2.2.6.8. Definitions of angiographic parameters

- Coronary artery anatomy: determined and classified angiographically and clinically as the following: a)native which included left main coronary artery (LM), left anterior descending coronary artery (LAD), left circumflex (LCx) and right coronary artery (RCA); and b) grafts which included either an arterial or venous bypass).

- Culprit coronary artery (symptoms related to the coronary artery) was defined as the primary coronary vessels which were considered to be responsible for the coronary events based on cardiologist assessment of the ECG and angiographic data. [163] In cases in which this is difficult to determine, the vessel supplying the largest territory of myocardium was selected (LM, LAD, LCx, RCA, graft [vein or artery]).

- Culprit lesion site: classified based on the lesion site inside the coronary artery into lesion at origin of the coronary artery, lesion at proximal or mid or distal third of the culprit coronary artery.

- Lesions were classified as A, B and C according to American College of Cardiology / American Heart Association (ACC/AHA) guidelines. [160] This is explained in Table 2.2

- Stent diameter or nominal diameter of the post-dilatation balloon was used as a surrogate for target vessel diameter.

- Culprit coronary artery blood flow was assessed pre- and post-angioplasty. TIMI flow grades were determined in the culprit vessel according to official TIMI Study Group definitions (Figure 2.1), [164, 165] by an experienced interventional cardiologists who was blinded to the patients' clinical characteristics and outcomes.

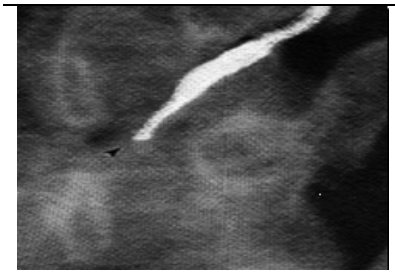
- Angiographically successful procedures were defined as final post-PCI minimum stenosis diameter reduction to $\leq$ 20% in cases with stenting or $\leq$ 50% in balloon angioplasty in the presence of grade 3 Thrombolysis In Myocardial Infarction (TIMI) flow. [161, 162]

Table 2.2 : American College of Cardiology/American Heart Association (ACC/AHA) Lesion Classification

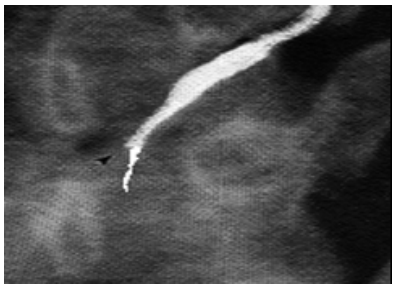
Lesion type:	Characteristics	
Type A (Lesions with anticipated success rate≥85%)	➢ Discrete (< 10mm in length) ➢ Concentric ➢ Readily accessible ➢ Located in non angulated segment (< 45˚) ➢ Smooth contour	➢ Little or no calcification ➢ Not totally occlusive ➢ Not ostial in location ➢ No major branch involvement ➢ Absence of thrombus
Type B* (Lesions with anticipated success rate 60-85%)	➢ Tubular in shape(10-20 mm in length) ➢ Eccentric ➢ Moderate touristy of proximal segment ➢ Located in moderately angulated segments (> 45˚, <90˚) ➢ Irregular contour	➢ Ostial in location ➢ Bifurcation lesions requiring double guide wires ➢ Some thrombus ➢ Moderate to heavy calcification ➢ Total occlusion less than three months old ➢ And / or bridging collaterals
Type C (Lesions with anticipated success rate < 60%)	➢ Diffuse (> 20 mm in length) ➢ Excessive touristy of proximal segment ➢ Located in extremely angulated segments (> 90˚)	➢ Total occlusion more that three months old ➢ Inability to protect major side branches ➢ Degenerated vein graft with friable lesions

** Type B1 = one type of B lesion characteristic; Type B2 = more than one type of B lesion characteristic)*

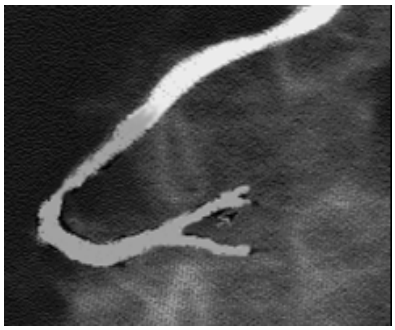
Figure 2.1: Images and Explanations of Thrombolysis In Myocardial Infarction (TIMI) flow grades



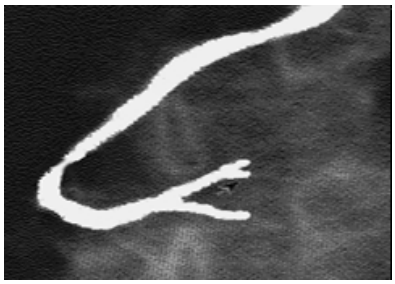
TIMI flow grade 0 (no perfusion):
There is no antegrade flow beyond the point of occlusion.



TIMI flow 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.



TIMI flow 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 – e.g. the opposite coronary artery or the coronary bed proximal to the obstruction



TIMI flow 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.

Reproduced from TIMI Study group, 2003, [166] & Chesebro et al., Circulation. 1987;76(1):142-154.[164]

2.2.7. Post-angioplasty treatment

Post-discharge, dual antiplatelet therapy consisting of oral aspirin (75- 100 mg/day) and oral clopidogrel (75mg/day) was recommended to all patients unless there was a contraindication. Oral aspirin was prescribed lifelong (75- 100 mg/day) while oral clopidogrel (75mg/ day) was prescribed for at least 12 months, unless there was a contraindication. Smoking cessation was encouraged where appropriate. Reduction of blood low-density lipoprotein to below 2.0mmol/L by statin therapy was suggested. The use of ACE-Inhibitors, angiotensin-receptor blockers, and β blockers were prescribed according to the indication for patients, unless contraindicated.

2.2.8. Clinical outcomes

In-hospital clinical outcomes were obtained by reviewing patient of medical records including the data from Liverpool Hospital Cardiac Catheterisation Laboratory's Cardiology Reporting System (CRS) database. In-hospital clinical events were recorded until the time of discharge.

For late clinical follow-up, patients undergoing angioplasty at Liverpool hospital Cardiac Catheterisation Laboratory have routine telephone follow-up which was conducted by trained research staff (either nurses or doctors) for quality assurance at between 8-12 months post-PCI to determine occurrence of cardiac clinical events. These included cardiac symptoms requiring cardiac hospitalization, hospitalization for coronary revascularization or MI and death. Information regarding deceased patients was obtained from family members, physicians and/or medical records and death registry. Where telephone contact was not available, patients' clinical files and database results were searched and local treating physician of patients were contacted for evidence of clinical follow-up. Medical records were also reviewed for repeated

procedures and ST events. These methods were used to determine the majority of patients' late outcomes. Definitions of clinical outcomes were as following:

- Non fatal re-infarction was determined by the development of further chest pain lasting more than 30 minutes and accompanied by new electrocardiographic changes (new Q waves > 0.04s or ST-segment elevation > 0.1mV in two leads for more than 30 minutes), further enzyme rise (creatine kinase > 2 times normal or TnT), or both. [77] Re-infarction included both ST-elevation and non-ST-elevation myocardial infarction.

- Target vessel revascularization (TVR) was defined as any repeat revascularization of the infarct related artery including repeat PCI or CABG irrespective of whether the procedure was clinically or angiographically driven. [100] The target vessel was defined as the entire major coronary vessel proximal and distal to the target lesion, which includes upstream and downstream branches and the target lesion itself.

- Target lesion revascularization(TLR) was defined as any repeat PCI of the target lesion including the stent, or within 5 mm of the proximal or distal stent edges; or CABG of the infarct related artery (IRA) .[100]

- Stent thrombosis (ST) was defined based on the Academic Research Consortium (ARC), see Table 2.3. [100] Only patients with definite (angiographically proven) ST were included in this study. ST was judged to have occurred if Thrombolysis in myocardial infarction (TIMI) flow grade 0 with occlusion originating in peri-

stent region was seen, or grade 1, 2 or 3 in the presence of thrombus originating in the peri-stent region. This was assessed by 3 interventional cardiologists. Angiographic evidence of thrombus was defined as a discrete, intraluminal filling defect with defined borders and separated from the vessel wall. In addition to that at least one of the following criteria had to be met: acute ischemic symptoms (typical chest pain with duration > 20 minutes), ischemic ECG changes (ST- segment elevation in territory of implanted stent, ST-segment depression or T-wave inversion in territory of implanted stent); typical rise and fall in cardiac biomarkers. All cases of angiographically proven ST were confirmed by an interventional cardiologist. ST was also categorized according to timing of its occurrence into early, late and very late (Table 2.4).

Table 2.3: Classifications of Stent Thrombosis

Classification	Explanation
Definite ST	- Acute coronary syndrome with angiographic or autopsy evidence of thrombus or occlusion
Probable ST	- Acute myocardial infarction in target vessel territory without angiographic confirmation or unexplained death within 30 days of index procedure
Possible ST	- All unexplained deaths occurring at least 30 days from index procedure

ST= Stent thrombosis

Table 2.4: Timing of Stent Thrombosis

- Early ST	0- 30 days after stent implantation
. Acute ST	0- 24 hours after stent implantation
. Subacute ST	> 24 hours to 30 days after stent implantation
- Late ST	> 30 days to 1 year after stent implantation
- Very Late ST	> 1 year after stent implantation

ST= Stent thrombosis

- Death included all cause mortality, cardiac deaths during follow-up were considered cardiac unless a non-cardiac cause was determined.

- The composite major adverse cardiac events were defined as the occurrence of one or more of the following: death, re-infarction or target vessel revascularisation (TVR).

2.2.9. Statistical analysis

Statistical analysis was performed using Statistical Package for Social Sciences software (SPSS, Inc, Chicago, Illinois, USA) version 14.0 and 17.0. Categorical variables were expressed as numbers and percentages per group and the continuous variables were expressed as mean ± standard deviation (SD) for normally distributed variables or medians (inter-quartile range [IQR]) for skewed variables. For the comparisons, unpaired categorical variables were compared by chi-square (χ^2) testing or Fisher's exact testing as appropriate; and McNemar's test was used to compare paired categorical variables. Parametric continuous variables were compared by unpaired (independent samples) student's t-tests for comparison of means, while non-parametric continuous variables were compared by Mann-Whitney U testing. Paired continuous and ordinal data was compared by Wilcoxon signed rank test. One-way ANOVA with post-hoc Bonferroni test were used to compare more than two groups.

Univariable and multivarible analyses were conducted to establish factors associated with clinical outcomes. All variables were tested for association with clinical outcomes, with those showing association on univariable analysis at $p > 0.20$ included in multivariable analysis.

Forward stepwise logistic regression method was used for multivariate analysis. Independent variables were selected by criteria of clinical relevance and evidence of significance or trends towards significance on univariable analysis. These models were developed to predict the likelihood of reaching the late mortality and composite clinical endpoints. “Goodness of fit” of the model compared to the observed data was evaluated by calculating the Hosmer-Lemeshow statistic, where low χ^2 values and high corresponding p values indicate that the data can adequately be modelled into a logistic function. [167]

Kaplan-Meier method of analysis was used to generate survival event free-survival curves and Log rank test was used to compare the statistical significance. All p values (2-sided where appropriate) of less than 0.05 were considered statistically significant for all analyses.

Statistical analysis for each study is explained more in each chapter.

2.2.10. Specific methodology

All specific methodologies to individual studies in this thesis will be discussed within the relevant Chapters.

Chapter 3

Evaluation of Clinical Outcomes Following Selective Stents Deployment According Patients Risk of Restenosis

3.1. Introduction

The deployment of BMS during percutaneous coronary intervention (PCI) is associated with a reduction in rates of restenosis compared to balloon angioplasty.[40] The use of drug-eluting stents (DES) has further reduced TVR rates.[48-50, 119] Clinical trials and registries have generally compared DES with BMS in all patients with CHD without specifically addressing DES use based on the patient's perceived risk of TVR. [48, 49, 119] Low TVR rates have been reported following BMS deployment, in patient subsets with certain clinical and/or lesion characteristics such as non-diabetics, and shorter lesions in large diameter arteries, [168, 169] though randomised trials have not specifically evaluated their use in such circumstances. [93] Identification of specific patient subsets with low TVR rates post-BMS deployment, may minimize concerns about the risk of late ST and the need for compliance with dual antiplatelet therapy with aspirin and clopidogrel for 1 year, and may have a favourable economic impact.[170] Thus we aimed to determine such patient subsets by examining clinical outcomes in the first 3 years after commencing our selective DES use criteria.

3.2. Methods

3.2.1. Study population

The study population consisted of consecutive patients undergoing PCI at the cardiac catheterization laboratories of Liverpool Hospital (Sydney, Australia) from October 2003 (when our institutional selective criteria for DES use started) to October 2006 (Figure 3.1). All patients had baseline clinical and angiographic data recorded prospectively in the cardiology department database as previously described (as

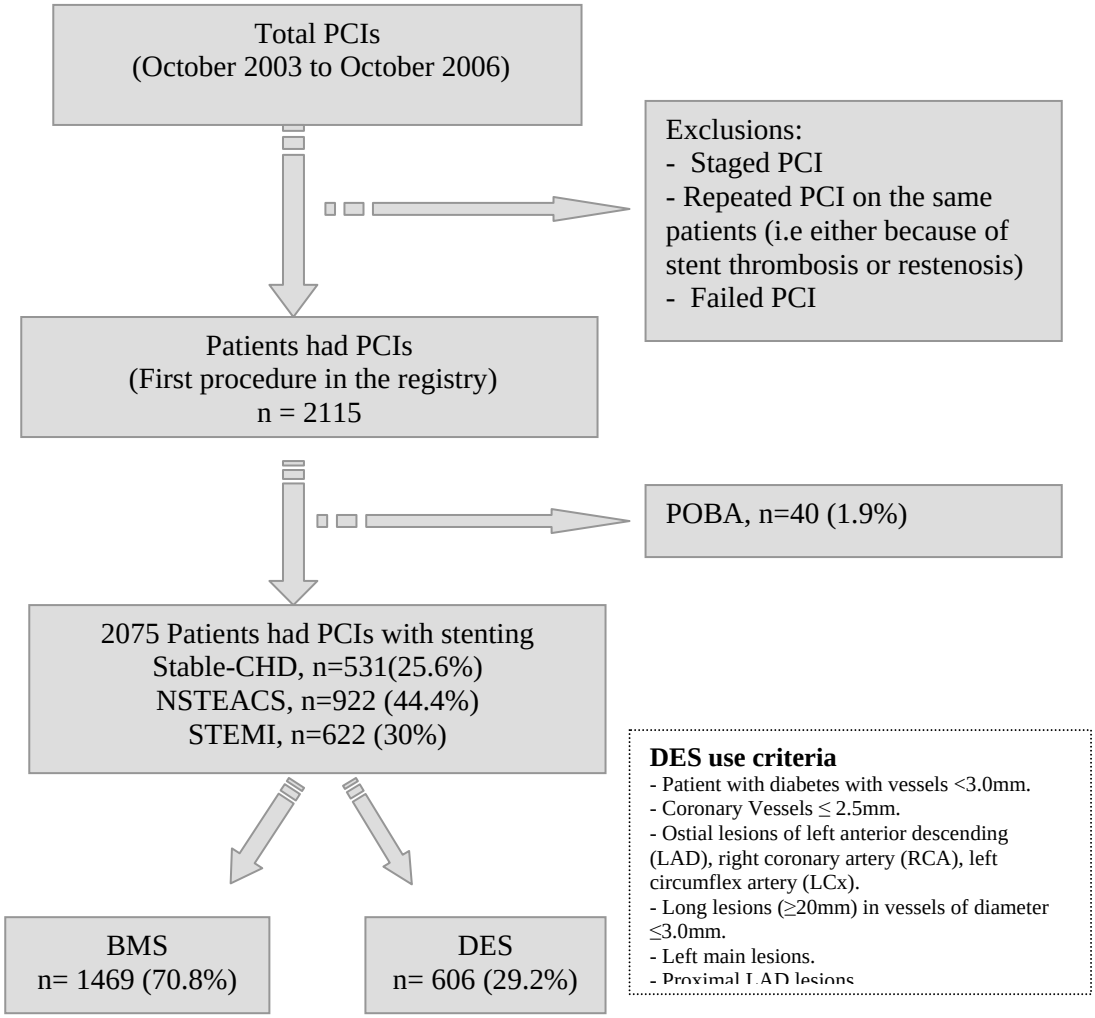
described in Chapter 2) .[169] The study was approved by South Western Sydney Local Health District human research ethics committee (no.QA2008/034).

3.2.2. Percutaneous coronary intervention procedures

Percutaneous coronary intervention procedures were performed with standard techniques. Unless contraindicated, aspirin (300mg) was given before PCI and continued indefinitely thereafter as 100-150mg/day, clopidogrel loading dose of 300mg or 600mg was given either before, at the time of PCI or immediately after PCI and prescribed at dose of 75mg/day post-PCI for at least 12 months. A bolus of unfractionated heparin (60-100 U/Kg) was given at the start of PCI procedures. The use of intravenous GPIIb/IIIa inhibitors, either tirofiban or abciximab, was at the operator's discretion. All angiographic and procedural data are reported and coded on the cardiology database prospectively.

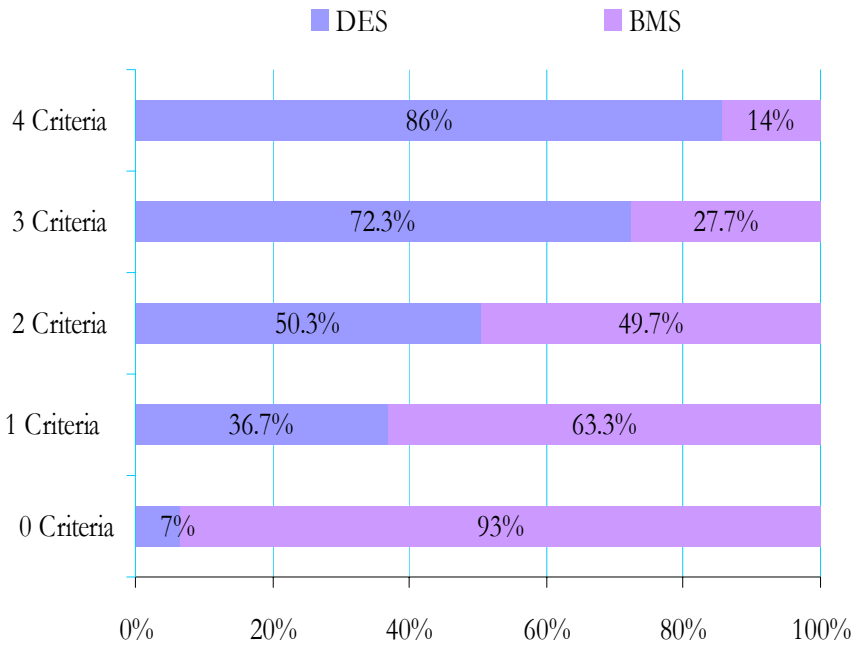
The selective DES use criteria shown in Figure 3.1,[169] aimed to achieve 30% DES use. The adherence to these criteria was assessed independently (Figure 3.2) to clinical outcomes and among patients who received DES, there was 92% criteria compliance. The DES included 1st generation stents: TAXUS Liberte (Boston Scientific, USA), TAXUS Express2 (Boston Scientific, USA), Cypher (Cordis Johnson and Johnson, USA), Cypher Select (Johnson and Johnson, USA). The BMS used were: Express2 and Liberte (Boston Scientific, USA), Multilink-Vision (Abbott Vascular, USA), PRO-Kinetic (Biotronik, Switzerland), Driver (Medtronic, USA), and Tsunami Gold (Terumo, Japan). Angiographic success was defined as a final post-PCI minimum stenosis diameter reduction to < 20% with stenting or <50% with balloon and grade 3 TIMI flow. Patients were classified according to stent type: DES or BMS only. Either nominal diameter of the post-dilation balloon, or nominal stent size if no post-dilation was performed, was taken to correspond to the final target coronary artery diameter.

Figure 3.1: Study population



CABG= coronary artery bypass grafting; CHD= coronary heart disease; DES = drug-eluting stents; BMS = bare-metal stents; NSTEACS = non ST- segment elevation acute coronary syndromes; PCI= percutaneous coronary intervention; POBA= plain old balloon angioplasty; STEMI= ST- segment elevation myocardial infarction. Late follow-up was obtained in 2040 patients 98.3% (98% among patients with DES and 98.4% among patients with BMS, p= 0.505)

Figure 3.2 : Drug-eluting Stents and Bare-metal Stents According to the Number of Criteria Satisfied



BMS= bare-metal stents; DES= drug-eluting stents

3.2.3. Clinical follow-up and definitions

Clinical follow-up was performed by trained clinical staff (nurses and/or doctors). Patients, their next of kin or primary physicians were contacted by phone and were asked about recurrent cardiac symptoms requiring hospitalization, need for coronary revascularization, or MI, and these were confirmed and recorded in the database. Data regarding mortality was obtained from medical records, physicians, next of kin and state death registry. Other clinical outcomes such as repeated procedures for ST and restenosis were independently verified.

The clinical outcomes were determined at 30 days and 1 year and defined as following: (1) death include all cause mortality, (2) MI is defined by chest pain lasting ≥30 minutes and accompanied by new ECG changes (Q waves >0.04s or ST-segment elevation >0.1mV) and/or further biomarker rise (creatine kinase [>2x URL],CKMB [>URL] or TnT [>URL]) (3) TVR was defined as ischemia-driven repeat revascularization of the infarct-related artery, requiring repeat PCI or CABG; (4) target lesion revascularization (TLR) was defined as repeat PCI of the stented segment within 5mm of the proximal and/or distal stent edge; or CABG. We report definite ST confirmed by angiography, as defined by the Academic Research Consortium.[100]

3.2.4. Data analysis

All statistical analyses were performed using SPSS (Inc, Chicago) version 17.0. Categorical variables are expressed as numbers and percentages, and continuous variables as mean ± standard deviations (SD) or medians with 25th and 75th percentile. For group comparisons Pearson's chi square (χ^2) test or Fisher's exact test were used as appropriate for unpaired categorical variables. The student's t tests or the Mann-Whitney U tests (for skewed distribution) were used for continuous variables. Propensity score analysis were performed using a multivariable logistic regression

analysis for use of DES versus BMS to compensate for the study's nonrandomised design; the rationale and methods have been previously described. [171] Clinical and angiographic variables which were significant ($p<0.05$) on univariate analysis among the two treatment groups (DES vs. BMS) were included in propensity score analysis model. These included age (≥75years), BMI, diabetes, hyperlipidemia, hypertension, smoking, prior aspirin use, type of presentation (stable-CHD/ACS), site of culprit lesion (left main, proximal LAD, RCA and LCx), lesions at bifurcations, calcified lesion, ostial lesions, reference vessel diameter, lesion length ≥20mm and type B2 and C ACC/AHA lesion class. The propensity score for each patient was calculated and ranged from 0.03 to 0.93. The propensity score was then incorporated into the regression analysis as a covariate with stent type (DES vs. BMS) and was then used to adjust the clinical outcomes.

Clinical outcomes were also displayed using Kaplan-Meier methodology, and were compared with Log Rank test. All p-values <0.05 (2 sided) were considered statistically significant.

Analysis was also performed using the restenosis risk score from the Revascularization and Stents in Acute Myocardial Infarction (HORIZONS-AMI) trial. [93] This included three risk variables for restenosis, Diabetes Mellitus, lesion length ≥ 30mm and vessel diameter ≤3mm . One point was assigned to each of the 3 risk variables, and patients with 0, 1, and ≥2 points of these 3 risk factors were classified as low, intermediate, or high risk for restenosis respectively. Then TLR rates for DES and BMS were assessed according to the above risk score.

3.3. Results

3.3.1. Clinical and procedural characteristics

From October 2003 to October 2006, 2115 consecutive patients with CHD underwent PCI, in which 2075 (98%) patients had successfully received at least one stent and 40 (1.9%) patients had balloon angioplasty alone. Among the patients who received stents, 1469 (71%) patients received BMS, and 606 (29%) patients received at least one DES (Figure 3.1). Patient baseline characteristics according to the type of stents are shown in Table 3.1. Among these, 622 patients (30%) had ST-segment elevation MI, 922 patients had non-ST segment elevation acute coronary syndromes and 531 patients (26%) had stable-CHD. There were more patients with stable CHD among the DES group (31% vs. 23%, p <0.0001). Patients who received DES were more likely to have diabetes (31% vs.18%, p <0.0001), hypertension (56% vs.49%, p=0.002) and hyperlipidemia (74% vs. 69%, p=0.014). Angiographic and procedural details are shown in Table 3.2. Patients who received DES were more likely to have culprit lesions in the proximal LAD (41% vs. 16%, p< 0.0001), and left main coronary artery (2.6% vs. 0.7 %, p=0.002), while patients who received BMS were more likely to have culprit lesions in the RCA and LCx (40% vs. 16%, p<0.0001 and 22% vs. 17%, p<0.004 respectively). Patients who received DES had more bifurcation culprit lesions (33% vs. 16%, p<0.0001), more B2 and C ACC/AHA class lesions (76% vs. 66%, p<0.0001), more ostial lesions (13.4% vs. 4.1%, p<0.0001) and longer lesion lengths (median 18[13-25] vs. 16[12-24], p <0.0001) compared with patients who received BMS. Post-procedural TIMI-3 flow was achieved in 99% of the patients (100% in patients with DES vs. 98.7% in patients with BMS, p= 0.006). GPIIb/IIIa inhibitors were used in 30% of patients (28.4% in patients with DES vs. 30.5% in patients with BMS, p= 0.339).

Table 3.1: Baseline Clinical Characteristics

	All patients (n= 2075)	Patients with drug-eluting stents (n= 606)	Patients with bare-metal stents (n=1469)	*P* value
Age (mean ± SD) (years)	62.8(11.9)	62.7 (±11.3)	62.9 (±12)	0.740
Age ≥65 years, n (%)	950 (45.8%)	275(45.4%)	675 (45.9%)	0.813
Age ≥75 years, n (%)	371(17.9 %)	93(15.3%)	278(18.9%)	0.053
Male gender, n (%)	1555(74.9%)	444(73.3%)	1111(75.6 %)	0.259
Body mass index (kg/m^2)	27.45[25-31]	27.7[25-31]	28.0[25-31]	0.023
Diabetes mellitus, n (%)	450(21.7 %)	187(30.9 %)	263(17.9%)	<0.0001
Hypertension, n (%)	1051(50.7 %)	339(55.9 %)	712(48.5%)	0.002
Previous aspirin use, n (%)	1266(61.1 %)	343(56.6%)	923(63.0%)	0.007
Hyperlipidemia § , n (%)	1454(70.1 %)	448(73.9%)	1006(68.5%)	0.014
Smoking, n (%)	480(23.1 %)	104 (17.2%)	376(25.6%)	<0.0001
Family history of CHD, n (%)	453(21.8 %)	129(21.3%)	324(22.1%)	0.700
Previous PCI, n (%)	113(5.4 %)	38(6.3 %)	75(5.1 %)	0.288
Previous CABG, n (%)	135(6.5 %)	44(7.3 %)	91(6.2 %)	0.371
- Stable CHD, n (%)	531(25.6 %)	187(30.9 %)	344(23.4%)	<0.0001
- ACS, n (%)				
a - NSTEACS, n (%)	922(44.5 %)	295(48.7 %)	627(42.7%)	0.012
b - STEMI, n (%)	622(30.0 %)	124(20.5%)	498(33.9%)	<0.0001
Cardiogenic shock pre-PCI, n (%)	53(2.6 %)	13(2.1 %)	40(2.7 %)	0.448

ACS = Acute Coronary Syndromes; CHD=Coronary Heart Disease; NSTEACS = non ST- segment elevation acute coronary syndromes; PCI = Percutaneous coronary intervention; STEMI= ST-segment elevation myocardial infarction

§ Hyperlipidemia defined as previous diagnosis of hypercholesterolemia, including treatment with lipid-lowering agents or fasting low-density lipoprotein cholesterol of ≥130 mg/dl or total cholesterol of ≥200 mg/dl.

Table 3.2: Angiographic and Procedural Characteristics

	All patients (n= 2075)	Patients with drug-eluting stents (n= 606)	Patients with bare-metal stents (n=1469)	*P* value
Culprit coronary artery, n (%)				
- Left Main	27(1.3%)	16 (2.6%)	11 (0.7%)	0.001
- Left anterior descending artery	872(42.0 %)	380 (62.7%)	492 (33.5%)	<0.0001
- Left circumflex coronary artery	426(20.5 %)	100 (16.5%)	326 (22.2%)	0.004
- Right coronary artery	680(32.8 %)	95 (15.7%)	585 (39.8%)	<0.0001
- Bypass graft	70(3.4 %)	15 (2.5 %)	55(3.7%)	0.146
Lesion type (ACC/AHA), n (%)				
- A	102(4.9%)	20(3.3 %)	82(5.6 %)	0.029
- B1	543 (26.2 %)	124(20.5 %)	419(28.6%)	<0.001
- B2	816(39.4 %)	252(41.7 %)	564(38.4 %)	0.174
- C	611(29.5%)	209(34.5%)	402(27.4%)	0.001
-B2/C	1427(68.9%)	469(76.2%)	966(65.8%)	<0.0001
Lesions at Proximal LAD, n (%)	490(23.6%)	249(41.1 %)	241(16.4%)	<0.0001
Culprit lesions at bifurcation, n (%)	431(20.8 %)	201 (33.2%)	230 (15.7%)	<0.0001
Culprit lesions calcifications, n (%)	317(15.3 %)	126(20.8%)	191(13.0%)	<0.0001
Ostial lesions, n (%)	141(6.8 %)	81(13.4 %)	60(4.1 %)	<0.0001
Culprit lesion length (mm)*	16[12-24]	18[13-25]	16[12-24]	<0.001
Culprit lesion length ≥ 20mm, n (%)	841(40.5%)	297 (49.0%)	544(37.1%)	<0.001
Total stented length (mm) *	20[16-28]	20[16-28]	20[15-28]	0.307
Stent diameter (mm) *				
- < 3 mm, n (%)	730(35.2 %)	285 (47.0%)	445(30.3 %)	<0.0001
- ≥ 3 mm- 3.49 mm, n (%)	644(31.0 %)	193(31.8%)	451(30.7 %)	0.608
- ≥ 3.5 mm, n (%)	701(33.8 %)	128(21.1%)	573(39.0%)	<0.0001
> 1 stent, n (%)	616(29.7 %)	185(30.5%)	431(29.3%)	0.590
Maximal deployment pressure (atm)*	16[16-20]	18[16-20]	16[16-20]	0.141
Maximal duration of deployed pressure (sec) *	30[23-30]	30[25-30]	30[22-30]	0.501
Glycoprotein IIb/IIIa inhibitor, n (%)	620(29.9%)	172(28.4%)	448(30.5%)	0.339
- Tirofiban	369(17.8 %)	102(16.8 %)	267(18.8 %)	
- Abciximab	238 (11.5 %)	68 (11.2 %)	170 (11.6 %)	
- Eptifibatide	13 (0.6%)	2 (0.3 %)	11(0.7%)	
TIMI flow grad after PCI, n (%)				0.006
3	2015(99.1 %)	595(100%)	1420(98.7%)	
≤ 2	18(0.9 %)	0(0 %)	18(1.3%)	
Percent of coronary artery stenosis*				
Pre-PCI	90[80-98]	90[80-95]	90[80-99]	0.016
Post-PCI	0[0-0]	0[0-0]	0[0-0]	0.192
Angiographic success, n (%)	2057(99.1 %)	606(100 %)	1451(98.8 %)	0.006
Procedural success, n (%)	2072(99.9 %)	606(100 %)	1466(99.8%)	0.266

ACC/AHA=American college of cardiology/American heart association; PCI=Percutaneous coronary intervention; TIMI=Thrombolysis In Myocardial Infarction.

** median [IQR]*

3.3.2. Clinical outcomes

At 30 days, overall mortality, MI and TVR rates were 1.9%, 1.4% and 1.3% respectively. The rate of death / MI was 3.1%. Among patients who received DES compared with BMS, mortality was 1.2% vs. 2.1% (p= 0.143), MI was 1.5% vs. 1.4 % (p= 0.819) and the TVR rate was 1.9 % vs. 1.1% (p= 0.181). Clinical outcomes including TVR rates at 30 days and 1 year are shown in Table 3.3. The rate of early definite ST was 0.8 % (1.5% for DES vs. 0.5% for BMS, p=0.025).

At 1 year, the overall rates of mortality, MI, TVR, composites of death /MI, and death/MI/TVR were 4.2%, 2.6%, 5.7%, 6.5% and 10.5% respectively. Among patients who received DES compared with BMS mortality was 3.9% vs. 4.4% (p= 0.621), MI was 2.9% vs. 2.5% (p=0.631), the TVR rate was 4.9% vs. 6.1% (p= 0.288). The overall rates of definite ST (early and late) were 2% for DES vs. 0.6% for BMS (p= 0.002). Kaplan-Meier curves (Figure 3.3) over 2 years showed no differences in event rates between DES and BMS except for ST. Kaplan-Meier curves for death or MI over 2 according stents type are shown in Figure 3.4.

After propensity score adjustment, DES significantly reduced TVR rate at 1 year compared with BMS (OR: 0.46 95% CI [0.28-0.74], p=0.001), with no significant differences in other clinical outcomes (Table 3.3). After adjustments, the significant differences noted in death, and death /MI at 30days were not significant at 1 year (Table 3.3).

Analysis of the study cohort according to diabetic status and the diameter of deployed stent(s) revealed that: (a) in diabetic patients, TVR rates with BMS vs. DES were 9.6% vs. 6% (p= 0.172); whereas in non-diabetics they were 5.3% vs. 4.4% respectively (p= 0.458), Figure 3.5; (b) among patients who received BMS ≥3.5mm in diameter, the 1 year TVR rate was 3.6%, whereas patients who received intermediate or

small sized BMS had respective TVR rates of 7.2% and 8.2% (p=0.005). Kaplan-Meier curves for TVR over 2 years among patients who received BMS of ≥3.5mm in diameter was lower than those who received intermediate- or small-sized BMS (Figure 3.6).

Analysis using the restenosis risk score (low, intermediate and high risk) from the HORIZONS-AMI trial showed that among patients who had none of the 3 risk factors for restenosis (low risk, 27%), there were no differences in TLR at 12 months in those who receiving BMS compared with DES (2.5% and 1.9% respectively, p = 0.99). The overall TLR rate among patients progressively increased with an increase risk score of restenosis from low, intermediate to high risk (2.4% vs. 4.4% vs. 6.4%, p= 0.007). The TLR rate in patients who received BMS progressively increased with an increase risk score of restenosis from low, intermediate to high risk (2.5% vs. 4.4% vs. 8.4%, p= 0.001), Figure 3.7.

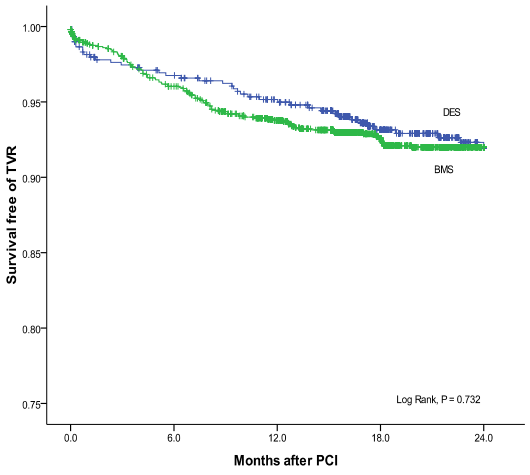
Table 3. 3: Clinical Outcomes Following Percutaneous Coronary with Selective Drug-eluting Stents Use Policy.

	All patients (n=2040)	**Patients with drug-eluting stents (n= 594)**	**Patients with bare-metal stents (n=1446)**	***P* value**	***Propensity score Adjusted OR (95% CI) (DES vs. BMS)***	***P* value**
30 days						
Death, n (%)	38(1.9%)	7(1.2%)	31(2.1%)	0.143	0.28(0.12-0.69)	0.006
MI, n (%)	29(1.4%)	9(1.5%)	20(1.4%)	0.819	0.71(0.30-1.72)	0.449
TVR, n (%)	27(1.3%)	11(1.9%)	16(1.1%)	0.181	1.00(0.42-2.38)	0.996
TLR, n (%)	20(1.0%)	10(1.7%)	10(0.7%)	0.039	1.5(0.56-4.11)	0.407
ST, n (%) - Acute - Sub-acute	16(0.8%) 5(0.2%) 11(0.5%)	9(1.5%) 2(0.3%) 7(1.2%)	7(0.5%) 3(0.2%) 4(0.3%)	0.025	2.32(0.76-7.13)	0.142
Death/MI, n (%)	63(3.1%)	15(2.5%)	48(3.3%)	0.346	0.43(0.23-0.82)	0.011
Death/MI/TVR, n (%)	69(3.4%)	18(3.0%)	51(3.5%)	0.573	0.49(0.27-0.89)	0.020
1 year						
Death, n (%)	86(4.2%)	23(3.9%)	63(4.4%)	0.621	0.63(0.37-1.08)	0.093
MI, n (%)	53(2.6%)	17(2.9%)	36(2.5%)	0.631	0.86 (0.45-1.66)	0.652
TVR, n (%)	117(5.7%)	29(4.9%)	88(6.1%)	0.288	0.46(0.28-0.74)	0.001
TLR, n (%)	89(4.4%)	23(3.9%)	66(4.6%)	0.487	0.52(0.31-0.90)	0.018
ST, n (%)	20(1%)	12(2%)	8(0.6%)	0.002	2.53(0.92-6.96)	0.073
Death/MI, n (%)	133(6.5%)	38(6.4%)	95(6.6%)	0.886	0.72(0.47-1.12)	0.141
Death/MI/TVR, n (%)	214(10.5%	53(8.9%)	161(11%)	0.139	0.52(0.36-0.74)	< 0.001

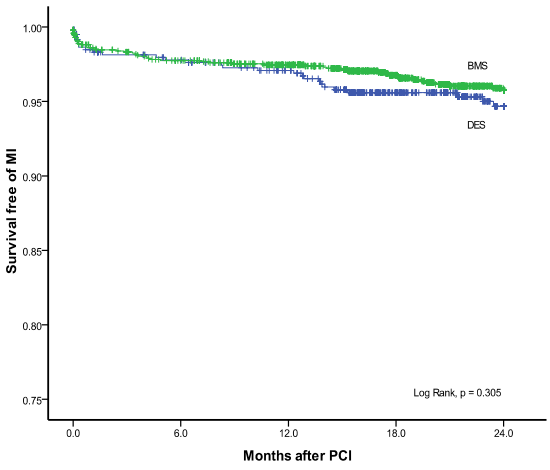
MI= myocardial infarction; TLR= target lesion revascularization; TVR= target vessel revascularization; ST= stent thrombosis.

Figure 3.3: Kaplan-Meier Curve for Target Vessel Revascularization, Death, Myocardial Infarction and Stent Thrombosis According to the Type of Stents

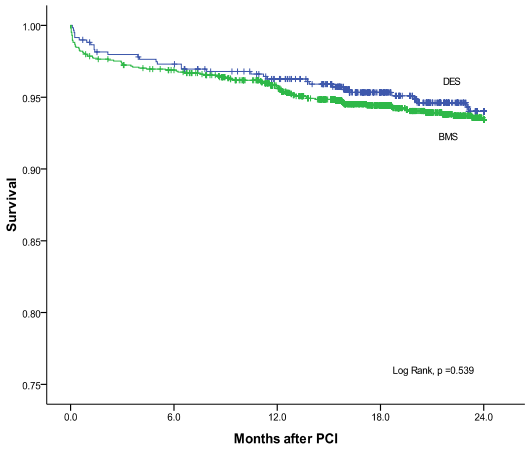
TVR



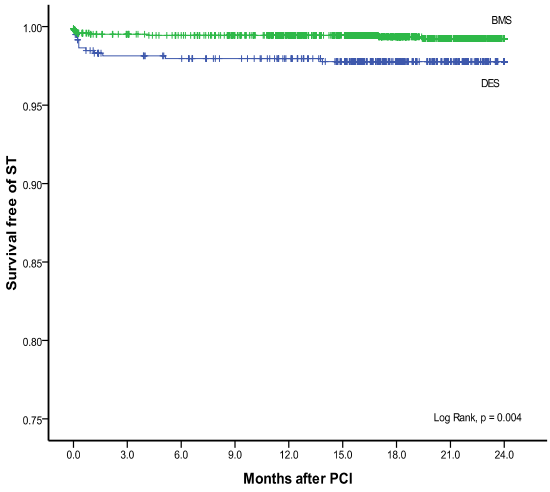
Myocardial infarction



Death



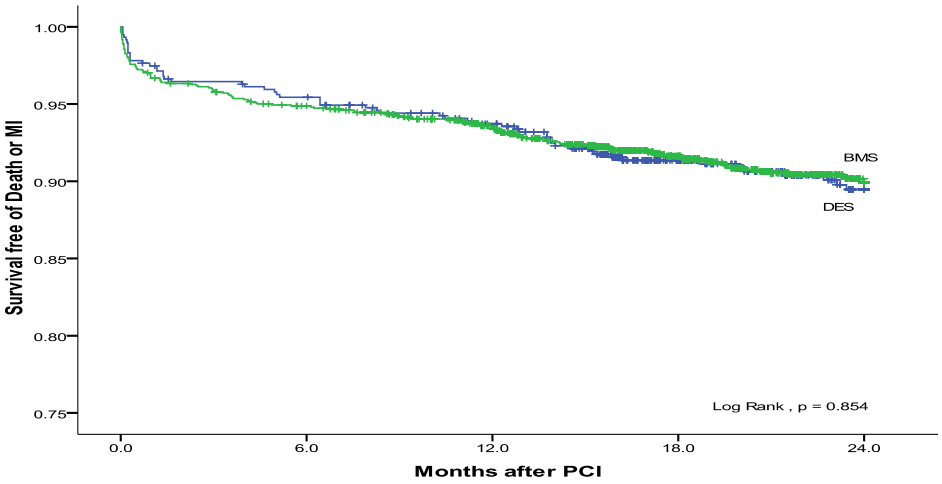
Stent Thrombosis



Death, myocardial infarction (MI), target vessel revascularization rate (TVR) and stent thrombosis (ST) rates are shown according stent type bare metal stent (BMS) or drug-eluting stents (DES).

PCI = percutaneous coronary intervention.

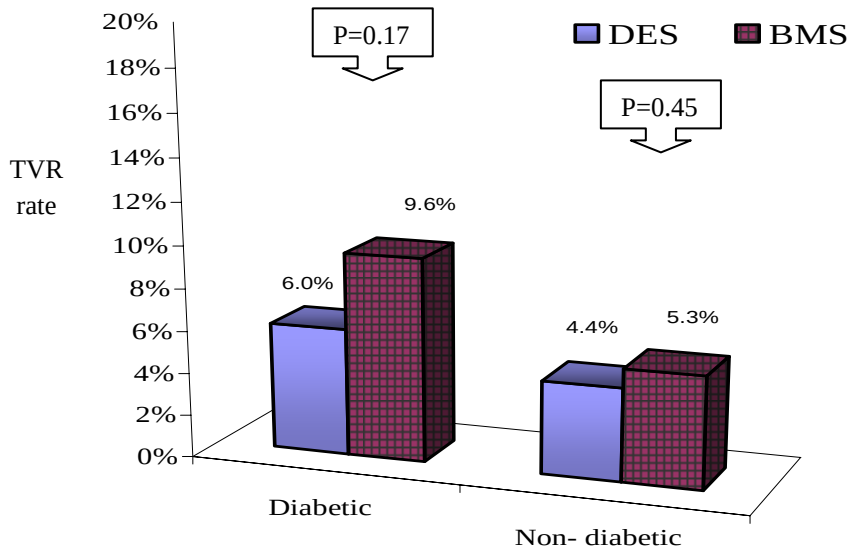
Figure 3.4: Kaplan-Meier curve for Death or Myocardial infarction



Death or myocardial infarction (MI) rates are shown according stent type bare metal stent (BMS) or drug-eluting stents (DES).

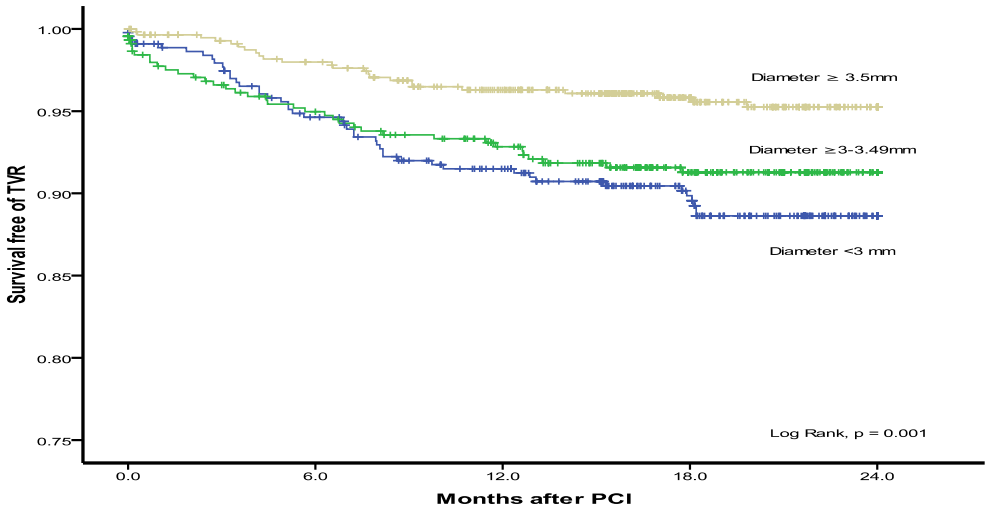
PCI = percutaneous coronary intervention.

Figure 3.5 : Target Vessel Revascularization Rates at 1 Year Distinguished by Diabetics State



TVR= target vessel revascularization; DES = drug-eluting stent; BMS = bare-metal stent.

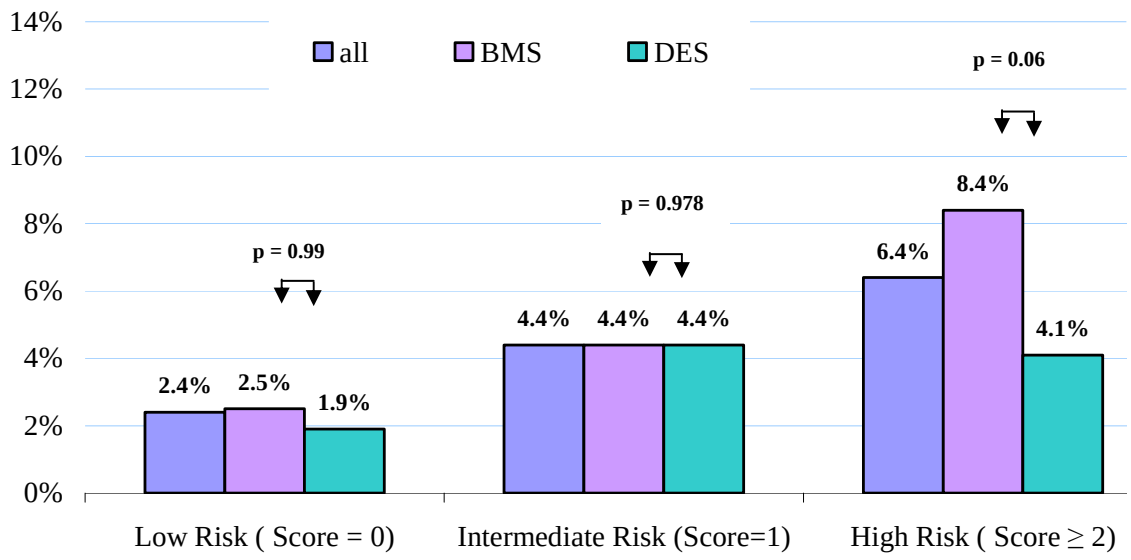
Figure 3.6: Kaplan-Meier curve for target vessel revascularization according to vessel size after BMS deployment



Target vessel revascularization rate (TVR) rates are shown with bare metal stent deployment according to stent sizes 1) <3mm; 2) 3.0-3.49mm and 3) ≥3.5mm. Among those who received BMS, TVR for those with lesion length <20mm versus 20-29mm versus ≥30 mm were 6.6% vs. 7.8% vs. 10.3% respectively (p=0.160).

PCI = percutaneous coronary intervention.

Figure 3.7: Target lesion revascularization rate at 1 year based on restenosis risk score



Target lesion revascularization rate according to HORIZONS-AMI trial risk score for restenosis. Three risk factors for restenosis (insulin-requiring diabetes, reference vessel diameter ≤3mm, and lesion length ≥30mm) were used in the HORIZONS-AMI trial to classify patients into three risk groups, low (none of the above risk factors), intermediate (one risk factor) and high risk (≥2 risk factors).

3.4. Discussion

This study reports clinical outcomes of consecutive patients undergoing PCI in the first 3 years after adoption of selective criteria for DES deployment and which were instituted to control costs associated with the adoption of this new technology. These criteria aimed to deploy DES in ~30% patients at highest risk of restenosis. DES were deployed in 29% of PCI patients and 92% of these patients met the institution's selective use criteria. These selective DES use criteria are the probable explanation for similar clinical outcomes including TVR rates in patients with DES and BMS. The TVR rate at 1 year in low risk patients with BMS is lower than that reported in randomised trials and lower than that from registries without selective DES use.[49, 50] The TVR rate among patients receiving BMS in large diameter coronary arteries (≥3.5mm) was low at 3.6%.

Randomised clinical trials demonstrated that the use of DES compared to BMS reduces revascularization rates, [48-50, 119] whereas registries tend to reflect outcomes after individual clinician's decision about stent choice rather than specific criteria for DES such as reported here. Similar criteria were later adopted by the NSW Department of Health and the National Institute for Clinical Excellence in UK.[172, 173]

In the Ontario Registry, [174] TVR rates at 1 year for BMS and DES were 8.6% and 5.2% respectively, which are similar to those reported here. In the Melbourne Interventional Group (MIG) registry in which comparable DES were used [175], the TVR rates were 7.4% and 6.4% for BMS and DES respectively. More recently, a report from the Temporal Analysis of the Multicenter Evaluation of Drug Eluting Stents and

Ischemic Events (EVENT) registry reported overall TVR rates at 1 year during two eras, firstly liberal DES use (92%, 2004-2006) and secondly "somewhat restrictive" DES use (68%, 2007), of 5.6% and 6.5% respectively. These rates were comparable with our overall TVR rate of 5.7% with selective DES criteria targeting patients with perceived high risk of restenosis (29% DES use). Recently published results from the Swedish Coronary Angiography and Angioplasty Registry (SCAAR) have shown lower rates of both restenosis and stent thrombosis with use of second generation DES, compared with first generation DES use.[176] Although these results are reassuring, further study is needed to confirm this finding.

In the HORIZONS-AMI trial, three risk factors for restenosis (insulin-requiring diabetes, reference vessel diameter ≤3mm, and lesion length ≥30mm) were used to classify patients into three risk groups, low, intermediate and high risk for TLR. Among patients who had none of these 3 risk factors (32%), there were no differences in event rates between patients receiving BMS and DES with TLR rates at 12 months of 3.3% and 3.2% respectively.[93] We applied this score to our study, and we found 27% of our patients had none of these three factors and among such patients the TLR rates were 2.5% and 1.9% for BMS and DES respectively.

In the Basel Stent KostenEff ektivitäts trial (BASKET), DES significantly reduced non-MI-related TVR compared with BMS in patients with small coronary arteries (<3mm) and this was not significantly different in (large) coronary arteries ≥3mm. [126, 127] We observed a low TVR rate (3.6%) following deployment of BMS in large (≥3.5mm) coronary arteries, whereas patients who received small or intermediate size BMS had TVR rates of 8.2% and 7.2% respectively. The study of Steinberg et al. found a TLR rate of 3.5% at 1 year after deployment of BMS of ≥3.5mm in diameter, which was comparable to 3.4% TLR following DES deployment in arteries of ≥3.5mm

in diameter. [125] Thus we consider that vessels of ≥3.5mm rather than ≥3mm should be considered large in the context of BMS use. Given these low TVR rates, BMS deployment in arteries ≥3.5mm should be compared with newer generation DES in a randomised clinical trial with extended follow-up.

Our study has certain limitations. Because of our selective DES use criteria,[169] patients with CHD who received DES (29%) were at higher perceived risk of restenosis, inferences cannot be drawn about the magnitude effect of DES on TVR rates, compared with that with BMS. To account for the effect of these factors, propensity scoring analyses for stent selection strategy (DES versus BMS) were performed and included in the adjustment for clinical outcome analysis. [171] Unrecorded factors may have resulted in BMS use in patients with co-morbidities, assumed bleeding risk, and anticipated non-compliance with dual anti-platelet therapy, all of which potentially may have lead to underestimation of the safety of BMS in this study. As routine quantitative coronary angiography and intravascular imaging was not available inaccuracy in assessment of vessel size may have occurred.

3.5. Conclusion

It is possible to use selective criteria for DES deployment while maintaining 'acceptably' low TVR rates. Clinical outcomes including TVR rates were similar with BMS and DES using these selective criteria. The TVR rates following BMS deployment among patients with large coronary arteries (≥3.5mm) and among non-diabetics were low. Comparison of selective versus routine DES use especially newer generation DES in patients with coronary arteries ≥3.5mm in diameter should be undertaken in future randomised clinical trials.

Chapter 4

Bare-metal Stenting of Large Coronary Arteries in ST-Elevation Myocardial Infarction

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4.1. Introduction

Primary PCI is the preferred reperfusion strategy for patients presenting with STEMI when performed in a timely manner by a skilled cardiac catheterization laboratory team [66, 67, 177]. Patients with STEMI without access to primary PCI undergo angiography and usually PCI at some stage during their initial hospitalization. [178, 179] Randomised clinical trials in selected populations and registries of STEMI patients have shown that drug-eluting stents (DES) reduce restenosis and TVR rates compared to BMS. [83-85, 88, 91, 180] Decisions about stent selection, either DES or BMS, in the emergency setting of STEMI are complicated by patients' relative inability to provide informed consent. [181] In particular, clinicians have concerns about patient compliance with 1 year of dual anti-platelet therapy recommended currently after DES deployment. [120-122] as premature discontinuation of thieno-pyridine therapy is a major risk factor for stent thrombosis. [111] The diameter of culprit lesion segments of infarct-related arteries (IRA) is an important determinant of restenosis and TVR. [46, 93, 124, 125]

In this study, we examined clinical outcomes of consecutive, unselected patients with STEMI undergoing PCI with BMS, as we considered that IRAs ≥3.5mm in diameter may be common. Furthermore we hypothesized that in these patients with large IRAs of ≥3.5mm, BMS deployment may be associated with low TVR rates.

4.2. Methods

4.2.1. Study population

In this study, among 1282 consecutive patients with STEMI undergoing PCI at Liverpool Hospital (Sydney, Australia) during their index hospitalization between October 2003 to March 2010, were studied, 1059 (83%) received BMS (see figure 4.1). Until May 2006, primary PCI was performed only on STEMI patients who presented to Liverpool Hospital emergency department during working hours. From June 2006, a 24 hour primary PCI service was offered to all patients presenting directly to Liverpool Hospital. Patients from referral hospitals, underwent either rescue PCI or PCI after successful fibrinolysis. All patients had clinical, angiographic and procedural data recorded prospectively in the cardiology department database at Liverpool Hospital as previously described (as described in Chapter 2). [182] STEMI was defined as chest pain of ≥30 minutes and ST-segment elevation ≥1mm in two contiguous leads (or ≥ 2mm in two contiguous leads V1-V3) or new LBBB, together with elevated levels of cardiac biomarkers (creatine kinase [> 2x URL], creatine kinase-MB [>URL] or TnT [> URL]). The study protocol was approved by South Western Sydney Local Heath District human research ethics committee (QA2008/034).

4.2.2. Percutaneous coronary intervention procedures

Unless contraindicated, aspirin (300mg) was given immediately at presentation or pre-PCI and continued indefinitely thereafter as 100-150mg/day. Clopidogrel loading dose of 300mg or 600mg was given either upstream or at the time of PCI and continued at 75mg/day post-PCI and recommended for at least 12 months. A bolus of unfractionated heparin (60-100 U/Kg) was given at the start of PCI procedures. The use of BMS (or

DES) was according to previously reported criteria (as descried in Chapter 2) .[169] The use of intravenous GP IIb/IIIa inhibitors, either tirofiban or abciximab, was at operator discretion. Statins, ACE-Inhibitors, angiotensin-receptor blockers, and β blockers were recommended, unless contraindicated.

The DES included 1st generation devices: TAXUS Liberte (Boston Scientific, MA, USA), TAXUS Express2 (Boston Scientific, MA, USA), Cypher (Cordis Johnson and Johnson, NJ, USA), Cypher Select (Cordis Johnson and Johnson, NJ, USA). The 2nd generation DES was XIENCE V (Abbott Vascular, USA). The BMS used were: Express2 and Liberte (Boston Scientific, MA, USA), Multilink-Vision (Abbott Vascular, USA), PRO-Kinetic (Biotronik, Switzerland), Driver (Medtronic, MN, USA), and Tsunami Gold (Terumo, Japan).

BMS diameter defined as the nominal diameter of the post-dilatation balloon, or nominal stent size if no post-dilation was performed, and was taken to correspond with the reference diameter of the IRA. Stent diameters were divided into three groups: <3mm (small), ≥3-<3.5mm (intermediate), and ≥3.5mm (large).

4.2.3. Definitions and clinical follow-up

Cardiogenic shock was defined as refractory hypotension (systolic blood pressure <90mm Hg lasting ≥1 hour), and end-organ hypo-perfusion, with or without mechanical support. Significant angiographic coronary stenoses were ≥70%. Lesions were classified according to ACC/AHA criteria. [160] Angiographically successful PCI was defined as <20% final lumen diameter post-stenting, or <50% post-balloon angioplasty, and TIMI 3 flow. [161]

Clinical follow-up was performed by research staff (nurses and/or doctors). Patients, their next of kin or primary physicians were contacted by phone and were

asked about recurrent cardiac symptoms requiring hospitalization, need for coronary revascularization, or MI. Data regarding mortality was obtained from medical records, physicians, next of kin and the state death registry. Other clinical outcomes such as repeated procedures for stent thrombosis (ST) and restenosis were independently verified. Clinical outcomes were defined as follows: (1) death, (2) non-fatal re-infarction defined by chest pain lasting ≥30 minutes and accompanied by new ECG changes (Q waves >0.04s or ST-segment elevation >0.1mV) and/or further biomarker rise (creatine kinase [>2x URL],CKMB [>URL] or TnT [>URL]) [10]; (3) TVR defined as ischemia-driven repeat revascularization of the IRA, requiring repeat PCI or CABG; [100] (4) target lesion revascularization (TLR) defined as repeat PCI of the stented segment within 5mm of the proximal and/or distal stent edge; or CABG. [100] We report definite ST confirmed by angiography, as defined by the Academic Research Consortium. [100]

4.2.4. Data analysis

All statistical analyses were performed using SPSS (Inc, Chicago) version 17.0. Categorical variables are presented as numbers and percentages, continuous variables as mean ± standard deviations (SD) or medians with 25th and 75th percentile. For group comparisons, Pearson's chi square (χ^2) test or Fisher's exact test were used as appropriate for unpaired categorical variables, and the student's t test or the Mann-Whitney U test were used for continuous variables. One-way ANOVA with post-hoc Bonferroni test were used to compare more than two groups. Univariable and multivariate analyses were performed to determine predictors of TVR and death/ MI among patients with BMS. Univariable analysis included the following variables: age, male gender, body mass index, diabetes mellitus, current smoking, hypertension, previous PCI, hyperlipdemia, pre-PCI cardiogenic shock, presentation for primary,

rescue PCI or PCI after successful thrombolysis, culprit lesion at (left main, proximal LAD , LCx and RCA), lesions at bifurcations, lesion classification, ostial lesions, lesion length ≥20mm, IRA diameter (<3.5mm, ie small or intermediate stents), type B2 and C ACC/AHA lesion class, use of GPIIb/IIIa inhibitors and multivessel disease (defined as ≥ 70% stenosis in ≥2 major epicardial vessels [LAD, LCx and RCA] or ≥50% stenosis of left main coronary artery [defined as 2 vessel disease]). Variables which were significant at p<0.2 on univariable analysis were included in multivariable stepwise logistic regression analysis model. TVR and death/MI were also displayed using Kaplan-Meier analysis, and were compared with Log Rank test. All *p*-values <0.05 (2 sided) were considered statistically significant.

4.3. Results

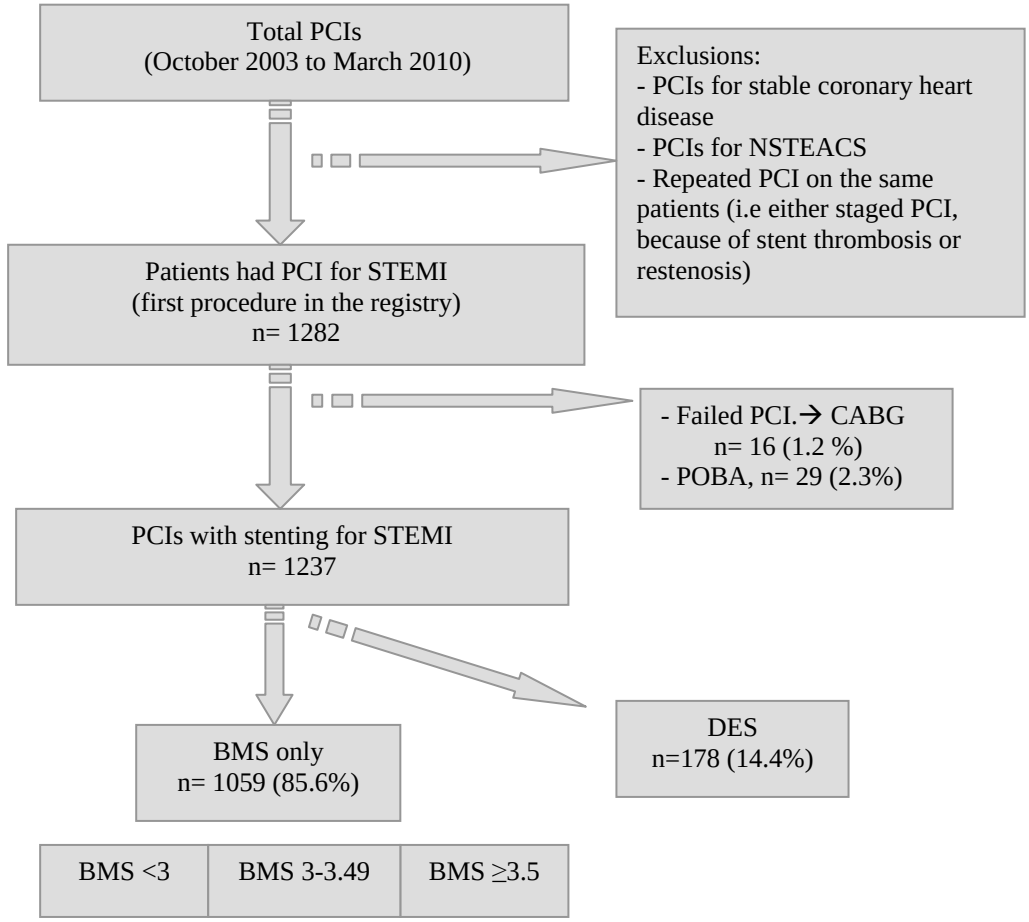
4.3.1. Clinical and procedural characteristics

From October 2003 to March 2010, 1282 consecutive patients with STEMI underwent PCI, of whom 1059 (83%) patients received BMS (<3mm, n=214; 3-3.49mm, n=333; and ≥3.5mm, n=512) (Figure 4.1); 178 (14%) received DES. Overall, the rate of large IRAs (≥3.5mm) stented was 45%. Patient baseline characteristics according to the BMS size, and stent type, are shown in Table 4.1. Among patients who received BMS, those who received large BMS compared with intermediate and small BMS were younger (57.8±12 vs. 59.6±12vs. 59.8±13, p=0.042); more likely to be males (85.4% vs. 79.9% vs.72.4%, p<0.001) and have larger body mass index (28.7±6 vs. 27.5±5vs. 27.1±5, p<0.001).

Angiographic and procedural details are shown in Table 4.2. Among patients who received BMS, post-procedural TIMI-3 flow was achieved in 98% of the patients; GPIIb/IIIa inhibitors were used in 47%. Among patients who received large BMS

compared with intermediate and small BMS were less likely to have culprit lesions in LAD artery (28.3% vs. 49.5% vs. 47.7%, p<0.001), and LCx artery (5.7% vs. 13.5% vs. 16.4%, p<0.001), but more likely RCA lesions (61.9% vs. 31.8% vs.17.8%, p<0.001). Patients who received large BMS had less bifurcation culprit lesions (11% vs. 18% vs. 23%, p<0.001), and shorter culprit lesion length (median 16[12-24] vs. 18[13-24] vs. 20[15-28], p=0.015).

Figure 4.1: Study Population



BMS= bare-metal stents; CABG= coronary artery bypass grafting; DES= drug-eluting stents (169 (95%) 1st generation); NSTEACS= Non ST- segment elevation acute coronary syndromes; PCI= percutaneous coronary intervention; POBA= plain old balloon angioplasty; STEMI= ST-segment elevation myocardial infarction.

Table 4.1: Baseline Clinical Characteristics

	Patients with bare-metal stents					Patients with drug-eluting stents
	All (n=1059)	**<3mm (n= 214) (20.2%)**	**3-3.49 mm (n= 333) (31.4%)**	**≥3.5mm (n= 512)* (48.3%)**	***P* Value †**	**All (n=178)**
Age (mean ± SD) (years)	58.8±12	59.8±12.7	59.6±11.7	57.8±12	0.042	60.6±12
Age ≥65 years, n (%)	324(30.6%)	74(34.6%)	110(33%)	140(27.3%)	0.079	67(37.6%)
Male gender, n (%)	858(81%)	155(72.4%)	266(79.9%)	437 (85.4%) ‡	< 0.001	138(77.5%)
Body mass index (kg/m^2, mean ± SD)	27.98±5.3	27.1±5	27.5±4.7	28.7±5.7‡§	<0.001	27.8±5.9
Diabetes mellitus, n (%)	142 (13.4%)	32(15.0%)	45(13.5%)	65(12.7%)	0.716	48 (27%) ‖
Hypertension, n (%)	365 (34.5%)	81(37.9%)	116(34.8%)	168(32.8%)	0.422	83 (46.6%) ‖
Previous aspirin use, n (%)	570 (53.9%)	113(52.8%)	193(58.1%)	264(51.7%)	0.172	95 (53.4%)
Hyperlipidemia ¶, n (%)	520 (49.1%)	101(47.2%)	168(50.5%)	251(49%)	0.758	113 (63.5%) ‖
Current Cigarette Smoker, n (%)	352 (33.2%)	62(29.0%)	110(33.5%)	180(35.2%)	0.271	57 (32%)
Family history of CHD, n (%)	183 (17.3%)	40(18.7%)	51(15.3%)	92(18%)	0.505	41 (23%)
Previous PCI, n (%)	30(2.8%)	5(2.3%)	10(3%)	15(2.9%)	0.885	2 (1.1%)
Cardiogenic shock pre-PCI, n (%)	60 (5.7%)	14(6.5%)	21(6.3%)	25(4.9%)	0.563	13(7.3%)
- Primary PCI, n (%)	452(42.7%)	91(42.5%)	132(39.6%)	229(44.7%)	0.344	48 (27%) ‖
- Rescue PCI, n (%)	206 (19.5%)	39(18.2%)	60(18%)	107(20.9%)	0.515	35(19.7%)
- PCI after successful thrombolysis, n (%)	401(37.9%)	84(39.3%)	14(42.3%)	176(34.4%)	0.059	95(53.4%) ‖
Thrombolytic use, n (%)	607 (57.3%)	123(57.5%)	201(60.4%)	283(55.3%)	0.344	130 (73%) ‖

CHD=Coronary Heart Disease; PCI=Percutaneous coronary intervention.

** 10 patients had prior CABG (in total 12 patients).*

† p value for comparison across BMS subgroups (<3mm vs. 3-3.49mm vs. ≥3.5mm) using one-way ANOVA , if significant post hoc test was performed to indicate significance within BMS subgroups.

‡ p value <0.05 for comparison between BMS ≥3.5mm and <3mm.

§ p value <0.05 for comparison between BMS ≥3.5mm and 3-3.49mm.

‖ p value <0.05 for comparison between BMS (all) and DES (all).

¶ Hyperlipidemia defined as previous diagnosis of hypercholesterolemia, including treatment with lipid-lowering agents or fasting low-density lipoprotein cholesterol of ≥130 mg/dl or total cholesterol of ≥200 mg/dl.

Table 4.2: Angiographic and Procedural Characteristics

	Patients with bare-metal stents					Patients with drug-eluting stents
	All (n=1059)	**<3mm (n= 214)**	**3-3.49mm (n= 333)**	**≥3.5mm (n= 512)**	***P* Value †**	**All (n=178)**
Culprit coronary artery, n (%)						
- Left Main	6(0.6%)	2(0.9%)	0(0%)	4(0.8%)	0.243	7(3.9%) ‖
- Left anterior descending artery	412(38.9%)	102(47.7%)	165(49.5%)	145 (28.3%) ‡§	<0.001	125(70%) ‖
- Left circumflex coronary artery	109 (10.3%)	35(16.4%)	45(13.5%)	29(5.7%) ‡§	<0.001	13(7.3%)
- Right coronary artery	461(43.5%)	38(17.8%)	106(31.8%)	317(61.9%) ‡§	<0.001	25(14%) ‖
- Bypass graft	13(1.2%)	0(0%)	2(0.6%)	11(2.1%) ‡	0.026	1(0.6%)
- Other coronary branches	58(5.5%)	37(17.3%)	15(4.5%)	6(1.2%) ‡	<0.001	7(3.9%)
Lesion type (ACC/AHA), n (%)						
- B	628 (59.4%)	130(60.7%)	211(63.4%)	287(56.3%)	0.111	100 (56.2%)
- C	390 (36.9%)	74(34.6%)	112(33.6%)	204(40%)	0.127	72 (40.4%)
Lesions at Proximal LAD, n (%)	257(24.3%)	42(19.6%)	107(32.1%)	108(21.1%) ‡	<0.001	81(45.5%) ‖
Culprit lesions at bifurcation, n (%)	166(15.7%)	49(22.9%)	60(18%)	57(11.1%) ‡§	<0.001	50(28.1%) ‖
Culprit lesions calcifications, n (%)	86(8.1%)	20(9.3%)	26(7.8%)	40(7.8%)	0.764	28(15.7%) ‖
Ostial lesions, n (%)	44 (4.2%)	9(4.2%)	15(4.5%)	20(3.9%)	0.913	26 (14.6%)
Culprit lesion length (mm)*	18[14-25]	16[12-24]	18[13-24]	20[15-28] ‡	0.015	20[14-30]
Culprit lesion length ≥ 20mm, n (%)	510(48.2%)	87(40.7%)	145(43.5%)	278(54.3%) ‡§	<0.001	94(52.8%)
Total stented length (mm) *	21[16-30]	20[15-30]	20[16-30]	23[18-32] ‡	0.028	23.5[16-33]
Stent diameter (mm) *	3[2.75-3.5]	-	-	-	-	2.75[2.5-3] ‖
> 1 stent, n (%)	302 (28.5%)	59(27.6%)	87 (26.1%)	156 (30.5%)	0.371	56 (31.5%)
Maximal deployment pressure (atm) *	18[16-20]	16[14-18]	18[16-20]	18[16-20] ‡§	<0.001	18[16-20]
Maximal duration of deployed pressure (sec) *	25[20-30]	25[20-30]	25[20-30]	25[20-30]	0.984	29[20-30]
Number of diseased vessles #					0.145	
- 1 vessel disease	636(60.1%)	117(54.7%)	199 (59.8%)	320 (62.5%)	0.148	109(61.2%)
- 2 vessel disease	311(29.4%)	72 (33.6%)	102 (30.6%)	137 (26.8%)	0.734	46(25.8%)
- 3 vessle disease	112 (10.6%)	25 (11.7%)	32 (9.6%)	55 (10.7%)		23 (12.9%)
Glycoprotein IIb/IIIa inhibitor, n (%)					0.707	
- Tirofiban	314(29.7%)	66(30.8%)	102 (30.6%)	146(28.5%)		55(30.9%)
- Abciximab	164(15.5%)	25(11.7%)	48(14.4%)	91(17.8%)		29(16.3%)
- Eptifibatide	14(1.3%)	3(1.4%)	7 (2.1%)	4 (0.8%)		1(0.6%)
TIMI flow grad after PCI, n (%)						
3	1035 (97.7%)	212(99.1%)	326(97.9%)	497(97.1%)	0.250	177(99.4%)
2	21(2%)	1(0.5%)	6(1.8%)	14(2.7%)	0.130	1 (0.6%)
0-1	3(0.3%)	1(0.5%)	1(0.3%)	1(0.2%)	0.819	0 (0%)
Percent of coronary artery stenosis Pre-PCI *	95%[90-100]	95%[90-100]	95%[90-100]	95%[90-100]	0.738	90%[90-100]
Angiographic success, n (%)	1032 (97.5%)	210(98.1%)	326(97.9%)	496(96.9%)	0.509	177 (99.4%)
Procedural success, n (%)	1013 (95.7%)	206(96.3%)	319(95.8%)	488(95.3%)	0.839	175 (98.3%)

- ACC/AHA=American college of cardiology/American heart association; PCI=Percutaneous coronary intervention; TIMI=Thrombolysis In Myocardial Infarction.

** median [IQR]*

† p value for comparison across BMS subgroups (<3mm vs. 3-3.49mm vs. ≥3.5mm) using one-way ANOVA , if significant post hoc test was performed to indicate significance within BMS subgroups.

‡ p value <0.05 for comparison between BMS ≥3.5mm and <3mm.

§ p value <0.05 for comparison between BMS ≥3.5mm and 3-3.49mm.

‖ p value <0.05 for comparison between BMS (all) and DES (all).

 # Multi vessels disease defined as ≥ 70% stenosis in ≥2 major epicardial vessels (left anterior descending, left circumflex and right coronary arteries) or ≥50% stenosis of left main coronary artery(which is defined as 2 vessel disease).

4.3.2. Clinical outcomes

At 30 days, mortality rates among patients who received large BMS compared with intermediate and small BMS were 3.2% vs. 5.2% vs.6.2% respectively (p=0.152) and for non-fatal MI, the respective rates were 0.6% vs. 2.8% vs.1.0%, p=0.027 and for TVR the rates were 0.4% vs. 2.5% vs.1.9%, p=0.033. At 1 year, mortality among patients who received large BMS compared with intermediate and small BMS were 4.4% vs. 8.0% vs.7.6%, p=0.0.072, and death/MI rates were 6.6% vs. 11.7% vs.9.0%, p=0.042; the respective TVR rates were 2.2% vs. 9.2% vs.9.0%, p<0.001. The rates of definite stent thrombosis were 0.2% vs. 1.8% vs. 0.5%, p=0.027 for large, intermediate and small BMS, respectively. Clinical outcomes are shown in Table 4.3, and Kaplan-Meier analysis for TVR and death/MI according to the size of BMS are shown in Figure 4.2.

On multivariate analysis, the independent predictors of TVR at 12 months after BMS deployment were: IRA diameter <3.5mm (OR 4.39 [95% CI:2.24-8.60], p<0.001), proximal LAD lesion (OR 1.89 [95% CI:1.08-3.31], p=0.027), hypertension (OR 2.01 [95% CI:1.17-3.438], p=0.011) and prior PCI (OR 3.46[95% CI:1.21-9.85], p=0.02); diabetes was not associated with TVR. The independent predictors of death/MI at one year after BMS deployment were: pre-PCI cardiogenic shock (OR 8.16 [95% CI:4.16-16.01], p<0.001), age ≥ 65years (OR 2.63 [95% CI:1.58-4.39], p<0.001), LAD lesions (OR 1.95 [95% CI: 1.19-3.21], p=0.008), female gender (OR 1.93 [95% CI: 1.12-3.32], p=0.019), ACC/AHA lesion classes B2 and C (OR 2.17 [95% CI: 1.10-4.27], p=0.026) and hyperlipidemia (OR 0.59 [95% CI: 0.35-0.98], p=0.04); multivessel disease was not associated (p=0.22).

Table 4.3: Clinical Outcomes

	Patients with bare-metal stents					Patients with drug-eluting stents
	All (1035)	<3mm (n= 210)	3-3.49mm (n= 326)	≥3.5mm (n= 499)	*P* Value †	All (173)
30 days						
Death, n (%)	46(4.4%)	13(6.2 %)	17(5.2 %)	16(3.2%)	0.152	6(3.5%)
MI, n (%)	14(1.4%)	2(1.0 %)	9(2.8 %)	3(0.6 %) *§*	0.027	3(1.7%)
TVR, n (%)	14(1.4%)	4(1.9 %)	8(2.5 %)	2(0.4 %) *§*	0.033	3(1.7%)
TLR, n (%)	11(1.1%)	3(1.4 %)	7(2.1 %)	1(0.2 %) *§*	0.024	3(1.7%)
ST, n (%)	8(0.8%)	1(0.5%)	6(1.8 %)	1(0.2%) *§*	0.027	3(1.7%)
Death/MI, n (%)	57(5.5%)	14(6.7%)	24(7.4%)	19(3.8 %)	0.065	8(4.6%)
Death/MI/TVR, n (%)	60(5.8%)	16(7.6 %)	25(7.7 %)	19(3.8%)	0.030	9(5.2%)
1 year						
Death, n (%)	64(6.2%)	16(7.6%)	26(8.0%)	22(4.4%)	0.072	10(5.8%)
MI, n (%)	30(2.9%)	4(1.9%)	15(4.6%)	11(2.2%)	0.084	5(2.9%)
TVR, n (%)	60(5.8%)	19(9.0%)	30(9.2%)	11(2.2%) *‡§*	<0.001	9(5.2%)
TLR, n (%)	52(5.0%)	15(7.1%)	27(8.3%)	10(2.0%) *‡§*	<0.001	8(4.6%)
ST, n (%)	8(0.8%)	1(0.5%)	6(1.8%)	1(0.2%) *§*	0.027	4(2.3%)
Death/MI, n (%)	90(8.7%)	19(9.0%)	38(11.7%)	33(6.6%) *§*	0.042	13(7.5%)
Death/MI/TVR, n (%)	130(12.6%)	34(16.2%)	58(17.8%)	38(7.6%) *‡§*	<0.001	19(11.0%)

MI= myocardial infarction; ST= stent thrombosis; TLR= target lesion revascularization; TVR= target vessel revascularization.

† p value for comparison across BMS subgroups (<3mm vs. 3-3.49mm vs. ≥3.5mm) using one-way ANOVA, if significant post hoc test was performed to indicate significance within BMS subgroups.

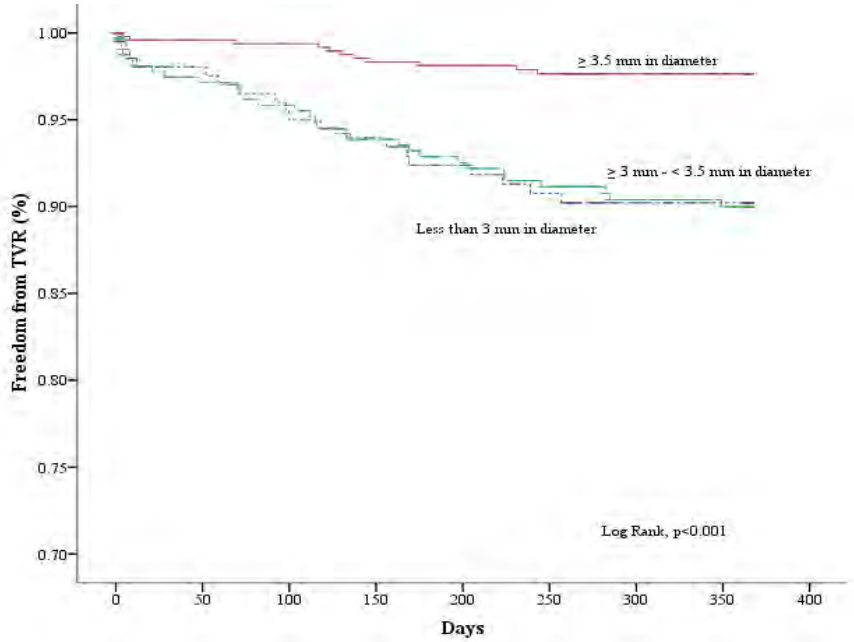
‡ p value <0.05 for comparison between BMS ≥3.5mm and <3mm.

§ p value <0.05 for comparison between BMS ≥3.5mm and 3-3.49mm.

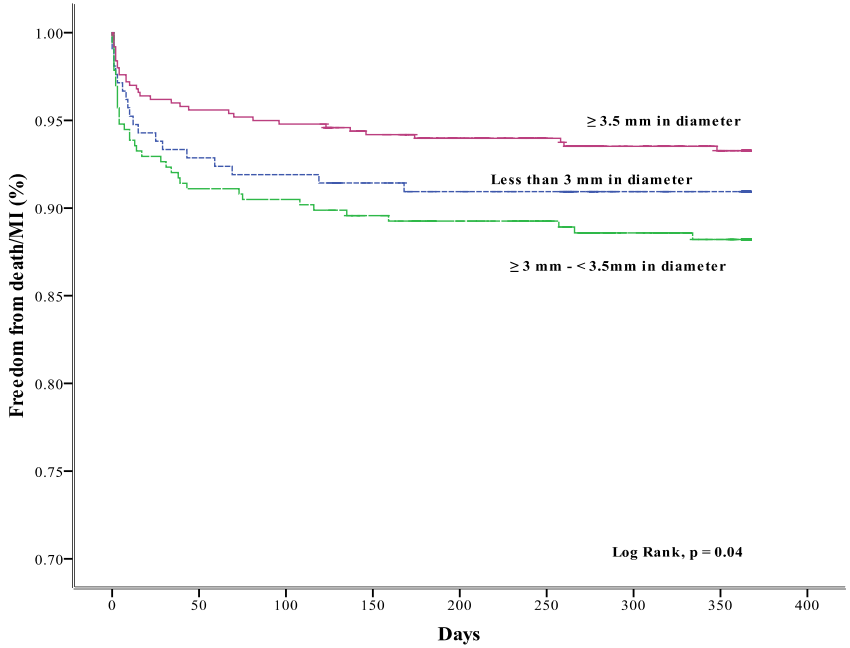
‖ p value <0.05 for comparison between BMS (all) and DES (all).

Figure 4.2: Kaplan-Meier Curve for Target Vessel Revascularization and Death/MI According to the Size of Bare-metal stents

(A) TVR



(B) Death/MI



Late target vessel revascularization rate (panel A) and death /MI rates (panel B) are shown according to bare metal stent (BMS) sizes 1) <3mm; 2) 3.0-3.49mm and 3) ≥3.5mm. Among those who received BMS, TVR for those who received stents ≥3mm, compared to stents <3mm, were 5% vs. 9% (p=0.024). The TVR rates with respect to nominal stent diameter were 9.1% (<3mm), 6.8% (3-3.49mm) and 1.9% (≥3.5mm), p <0.0001. Among the patients who received DES ≥3.5mm (n=42), 3.0-3.49 mm (n=65), and <3mm (n=66), respective TVR rates at 1 year were 2.4% vs. 6.2% vs. 6.1%, p= 0.639.

4.4. Discussion

This study examines clinical outcomes after PCI performed during the index hospitalization in STEMI patients, and demonstrates that BMS use in large (≥3.5mm) coronary arteries is associated with low rates of TVR (2.2%). Large IRAs occurred in ~ 45% of STEMI patients, and in this circumstance BMS deployment was associated at 1 year with lower rates of TVR, and death/re-infarction, compared to smaller IRAs, including vessels of 3-3.49mm in diameter.

The definition of a "large" coronary artery lacks uniformity with "cut-points" of 3mm and 3.5mm in previous reports.[125, 128] In our study, approximately 45% of STEMI patients had PCI to an IRA of ≥3.5mm in diameter. BMS use in this context was associated with a low TVR (2.2%). We observed significantly higher TVR rates for BMS in intermediate arteries of 3 to <3.5mm, and small arteries (<3mm), both ~9%, suggesting the use of 3mm as a cutpoint for large IRAs is too low at least in the context of BMS. Our overall TVR rate for STEMI treated with BMS was 5.8%, which was somewhat lower than the 8.7% rate in HORIZONS-AMI [91, 93], possibly due to our selective use of DES in those at highest risk of re-stenosis.

In the HORIZONS-AMI trial about 32% of patients had none of the 3 risk factors associated with re-stenosis, (insulin-requiring diabetes, reference vessel diameter ≤3mm, and lesion length ≥30mm), there were no differences in event rates between patients receiving BMS and DES with TLR rates at 12 months of 3.3% and 3.2% respectively. [93] Our study found a comparable rate of patients with none of these 3 risk factors (36%), and TLR rate in this subgroup was 2.5% for BMS.

In the BASKET study, which recruited patients with stable-CHD as well as ACS, the significant benefit of DES compared with BMS in reducing non-MI-related TVR was seen in patients with small coronary arteries (<3mm) but was not significantly different in large coronary arteries (≥3mm). [126, 127] In another study, with a similar mix of stable and acute CHD patients, the TLR rate at 1 year after deployment of BMS (≥3.5mm in diameter) was 3.5% and this was comparable to 3.4% following DES deployment in arteries of ≥3.5mm in diameter. [125] In BASKET-PROVE study which also recruited patients with stable as well as acute CHD , following BMS deployment in coronary arteries ≥3mm, the TVR rate was 10.3% at 2 years. [128] This included stenting of intermediate coronary arteries (3-3.49mm in diameter). As we have observed a high TVR rate following BMS deployment in the group with intermediate size coronary arteries (3-3.49mm in diameter), vessels with a diameter ≥3.5mm should be considered 'large' in the context of BMS selective use.

In our study, the rate of death/MI at 1 year was 8.7% for all patients receiving BMS, whereas in the HORIZONS-AMI trial the death/MI rate at 1 year was 6.8% (7.0% for BMS and 6.8% for DES, p= NS). [91] The death/MI rate in our highly selected patients receiving DES was 7.5%. The lower death/MI rate of 6.6% among patients in our study with IRAs ≥3.5mm is probably due to differences in other characteristics including more younger patients, less women and fewer LAD IRAs. Of note in BASKET, among all patients with coronary arteries ≥3mm, receiving DES compared to BMS, the cardiac death/MI rate at 18months was slightly higher (HR=2.07, p=0.05). [126] At 3 year follow-up HORIZONS-AMI demonstrated similar rates of death/MI, 11.5% for BMS and 11.8% for DES (p=NS). [183] We found a rate of death/MI of 11.9% for BMS, among the small proportion of patients who had 3 years follow-up.

Our study has certain limitations. Firstly, whether prior PCI as predictor of TVR at one year, was due to stent thrombosis, re-stenosis, or disease progression in a previously non-stented arterial segment was not recorded. Because of our institutional criteria for selective use of DES which targets patients at highest risk of re-stenosis including those with smaller arteries, [169] only 14% of these patients with STEMI received DES. As many patients with diabetes selectively received a DES, this is probably explains why diabetes was not a predictor of TVR after BMS deployment. Furthermore, as our selective DES use criteria allows DES use in vessels ≥3 mm in the proximal LAD, and a large proportion of our patients the IRAs were of ≥3.5mm in diameter, our ability to directly compare outcomes after BMS and DES deployment was compromised. Unrecorded factors may have resulted in BMS use in patients with co-morbidities, assumed bleeding risk, and anticipated non-compliance with dual anti-platelet therapy, all potentially affecting stent choice in those undergoing emergent stenting.

Also, intravascular imaging modalities such as intravascular ultrasound and optical coherence tomography, are the most accurate methods for measuring coronary artery reference diameter [184, 185], but were beyond the scope of the present study. Quantitative coronary angiography requires specialized post-processing software and was not routinely available at our institution. Therefore, for this study, used the nominal stent/balloon diameter as a surrogate for the reference diameter of the culprit coronary artery segment in the absence of preferred quantitative tools; this may have introduced small measurement errors. Our single-centre registry does not routinely collect data regarding patient's compliance with dual anti-platelet therapy and other adjunctive therapies. Finally, cost effectiveness analysis following selective use of DES, as recently reported, [170] was beyond the scope of the current study.

4.5. Conclusion

We report that nearly half the STEMI patients undergoing PCI had an IRA ≥ 3.5mm in diameter. We categorize such arteries as “large” and observed that BMS use in these vessels achieved low TVR rates and had low rates of stent thrombosis. As our DES use was selective, no inferences can be made about comparative rates of TVR in this context. Comparison of TVR rates between BMS and 2nd generation DES in large (≥ 3.5mm) coronary arteries in patients with STEMI requires further randomised trials.

Chapter 5

Safety and efficacy of rescue angioplasty for ST-elevation myocardial infarction with high utilisation rates of glycoprotein IIb/IIIa inhibitors

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5.1. Introduction

The aim of reperfusion strategies for patients with STEMI is to minimise ischemic time to maximise preservation of myocytes, and minimise infarct size by restoring antegrade coronary blood flow. [67, 186, 187] While prompt primary percutaneous coronary intervention (PCI) is a superior reperfusion strategy to fibrinolytic therapy alone, [66] for several reasons many patients world-wide receive fibrinolytic therapy as an initial reperfusion strategy. [74] In fact, early pre-hospital fibrinolysis may achieve as good as, or better, late clinical outcomes than primary PCI if appropriately high rates of rescue PCI and in-hospital PCI occur. [72 178 188]

Fibrinolytic-treated patients are recommended for immediate angiography and if indicated rescue PCI, if they have failed to reperfuse, as five randomised clinical trials have shown improved outcomes compared to conservative management. [74, 75, 77, 78] However, these trials, and more recent reports from registries, have included significant proportions of patients who did not receive fibrin-specific therapies, stents (including drug-eluting) or GPIIb/IIIa antagonists. [75, 77, 78, 189, 190] As patients treated at Cardiac Catheterisation Laboratory at Liverpool Hospital and undergoing rescue PCI have received high rates of these therapies, we studied consecutive patients to identify factors that influence clinical outcomes, so these insights may provide the basis for prospective studies of future pharmaco-invasive strategies in STEMI patients.

5.2. Methods

5.2.1. Study Population

We prospectively collected clinical, demographic and angiographic data on consecutive patients undergoing rescue PCI at Cardiac Catheterisation Laboratory at Liverpool Hospital (Sydney, Australia); details of the Cardiac Catheterisation Laboratory database has recently been reported (as described in Chapter 2). [191]

During the study period from January 2001 to December 2009, patients in the area of our Cardiac Catheterisation Laboratory service (~900,000 population) with STEMI with 12 hours symptom onset, without contra-indications and received fibrinolytic therapy and intravenous heparin were treated with aspirin (usually 300mg) at first medical contact, until May 2006 (except for those presenting to Liverpool Hospital during working hours when primary PCI was usually performed). From June 2006 a 24 hour primary PCI service was offered to patients presenting directly to Liverpool Hospital. Failed pharmacologic reperfusion was defined < 50% ST-segment recovery compared to baseline ST elevation at ~ 60-90 minutes. Patients with transient ST recovery but subsequently persistent ST segment re-elevation (< 12 hours post-STEMI) were also included. Assessment of outcomes after PCI was approved by the Sydney South West Area Health Service Human Ethics Research Committee (Project No: QA2008/034).

5.2.2. Procedural Techniques

Rescue PCI was performed via the femoral approach in 99% of patients using unfractionated heparin, administered according to the pre-procedural ACT levels. Clopidogrel loading with 300-600mg (and 75mg daily for 12 months) was given if not administered ‘upstream’. The use of GPIIb/IIIa receptor inhibitors (tirofiban or

abciximab) was at the discretion of the referring physicians and/or interventionists. Deployment of DES was based on our Cardiac Catheterisation Laboratory selective use criteria, adopted in October 2003 (applying to 89% of patients reported here) and were as follows: left main lesions; ostial lesions in major epicardial arteries; proximal LAD lesions; lesions length ≥20mm in vessels ≤3mm; any lesion in vessels ≤2.5mm, any lesion in diabetic patients with vessels <3.0mm; and in-stent restenosis. Infarct artery Thrombolysis In Myocardial Infarction (TIMI) flow grading and corrected TIMI frame counts (CTFC) pre-PCI and post-PCI including imputation of a CTFC of 100 for TIMI 0-1 flow were assessed by two cardiologists who were blinded to the patients' history and outcomes. [165]

5.2.3. Electrocardiographic analyses

Analysis of ECGs prior to and 60-90 minutes post fibrinolytic therapy, prior to and after rescue PCI, and prior to discharge was performed with callipers, by 5 clinicians trained in ST-segment recovery analysis (herein called ST recovery), blinded to outcomes. ST recovery was characterised as: 1) complete (≥ 70%), 2) partial (> 30% to < 70%) and 3) no recovery (≤ 30%). [192, 193] Infarct size estimation by Selvester QRS scoring used the 32-point system (each point represents ~ 3% of the left ventricular myocardium). [194, 195] The myocardial salvage was determined by subtracting infarct size from myocardium at risk (maximal scores of baseline ST-elevation), and dividing this difference by the at-risk score. [196]

5.2.4. Clinical outcomes

Outcomes were examined at 30 days and ~1 year and included all-cause mortality, non-fatal MI, TVR, stroke and TIMI major bleeding. [77] TVR was defined as repeat revascularization (PCI or CABG) of the infarct artery including proximal and distal to

the target lesion. Clinical outcome data were obtained by reviewing patients' medical records, and trained research staff (nurses or doctors) contacting patients, their next of kin or local physicians or cardiologists by telephone. Data regarding mortality was obtained from medical records, physicians, family members and the death registry and all patients had follow-up to 30 days and 8 (3%) lost follow-up at 12 months.

5.2.5. Data analyses

Categorical variables are reported as numbers (%), and compared by χ^2 test or Fisher's exact test as appropriate, and continuous variables are reported as medians and IQR. Normally distributed continuous variables were compared by unpaired student t-tests for comparison of means, while skewed continuous variables were compared by Mann-Whitney U tests. Paired continuous and ordinal data was compared by Wilcoxon sign rank tests.

Univariable and multivariable analyses to determine factors associated with clinical outcomes included the following variables: age, female gender, body mass index, diabetes mellitus, current smoking, prior MI, prior aspirin use, hypertension, hyperlipidemia, prior PCI, cardiogenic shock, TIMI major bleeding, symptom-onset-to-door, symptom-onset-to-lytic, door-to-balloon, anterior MI, post-PCI TIMI flow grade, post-PCI CTFC, incomplete (< 70%) ST recovery (maximal leads and sum of leads), at-risk myocardium salvaged < 50% and < 70%, final QRS score > 4, multi-vessel disease, GPIIb/IIIa inhibitors, DES use and total stent length; those with $p < 0.2$ were included in multivariate analysis. Multivariate Cox regression was used to identify independent factors associated with late clinical outcomes. Odds ratios (OR) and 95% confidence intervals (CI) are reported. All statistical analyses were performed using Statistical Package for Social Sciences version 17.0 software (SPSS Inc, Chicago, Illinois). All p values < 0.05 (2 sided) were considered statistically significant.

5.3. Results

5.3.1. Clinical and procedural characteristics

Between January 2001 and December 2009, of 241 patients undergoing rescue PCI (189 patients [78%] after inter-hospital transfer); 36 (15%) patients had PCI performed prior to 1st January 2004, 102 (42.3%) had procedures between 1st January 2004- 31st May 2006, and 103 (42.7%) had rescue PCIs after 1st June 2006. These patients had a median age of 55 [IQR:48-65] years, were hospitalized for 4 [IQR:3-5.5] days, and 24 (10%) had cardiogenic shock prior to rescue PCI; other patient characteristics are shown in Table 5.1. Median symptom-onset-to-door time was 1.2 h [IQR 0.8-2.2], median symptom-onset-to-'lytic time was 2h [IQR:1.3-3.2], median 'lytic-to-balloon time was 3.85h [IQR:3-5] and median door-to-balloon time was 4.7h [IQR:3.6-6.1]. Among patients with symptom onset to fibrinolytic times ≤120 minutes, the median fibrinolytic therapy to balloon times were 240 minutes [IQR: 185-318] compared to 227 minutes [IQR:186-333] in those receiving fibrinolysis at > 120 minutes (p = 0.763). Among the study cohort, 235 (98%) received a fibrin-specific fibrinolytic (93% tenecteplase), 230 (95%) patients had ≥ 1 stent deployed (11.6% DES) and 187 (78%) patients received GPIIb/IIIa inhibitors (56% tirofiban and 22% abciximab). At angiography, 99 (41%) patients had initial infarct-artery TIMI-3 flow and 87 (36.1%) patients had TIMI 0-1 flow, whereas post-PCI TIMI-3 flow was achieved in 218 (91%) patients, p < 0.001. Table 5.2 shows angiographic and procedural characteristics.

Table 5.1: Baseline Clinical Characteristics

	All patients n=241	Symptom onset-to-lytic time		*p* value
		≤ 120 minutes n=125	> 120 minutes n=116	
Age (years), median [IQR]	55[48-65]	54[47-62]	57[49-66]	0.076
Age ≥65 years	61(25.3%)	26(20.8%)	35(30.2%)	0.095
Female gender	43(17.8%)	20(16%)	23(19.8%)	0.438
Body mass index	27.4[24.6-30.5]	27.8[25.7-31.5]	26.1[24.2-29.4]	0.003
Hypertension	98(40.7%)	47(37.6%)	51(44%)	0.315
Diabetes Mellitus	43(17.8%)	20 (16%)	23(19.8%)	0.438
Hyperlipidemia	96 (39.8%)	48(38.4%)	48(41.4%)	0.637
Current (< 12mth) cigarette smoking	127(52.7%)	71(56.8%)	56(48.3%)	0.185
Family history of coronary artery disease	66(27.4%)	38(30.4%)	28(24.1%)	0.276
Prior myocardial infarction	19(7.9%)	12(9.6%)	7(6.0%)	0.305
Prior PCI	11(4.6%)	7(5.6%)	4(3.4%)	0.424
Prior CABG	4(1.7%)	2(1.6%)	2(1.7%)	0.999
Prior aspirin use	44 (18.3%)	27(21.6%)	17(14.7%)	0.163
Transfer from non-PCI centres	189(78.4%)	102(81.6%)	87(75%)	0.213
Fibrin-specific fibrinolytic given	235(97.5%)	122(97.6%)	113(97.4%)	0.999
Symptom-onset-to-door time (minutes)	74[46-133]	50[34.5-65]	137[98.5-277]	< 0.001
Symptom-onset-to-lytic time (minutes)	120[79-192]	80[61-95.5]	203[147.3-367.5]	< 0.001
Symptom-onset-to-balloon time (minutes)	379[291-522]	305[260-396.5]	458.5[355.5-727.25]	< 0.001
Door-to-balloon time (minutes)	279[217-364]	254[209-354.5]	296[230.3-389.3]	0.018
Lytic-to-balloon time (minutes)	232[185-312]	240[185-318]	227[186-300]	0.763
Cardiogenic shock pre-PCI	24(10%)	9(7.2%)	15(12.9%)	0.138
Anterior infarction	128(53.1%)	65(52%)	63(54.3%)	0.720

CABG=Coronary artery bypass grafting; PCI=Percutaneous coronary intervention.

Categorical variables are shown as count (%) and continuous variables are shown as median [interquartile range].

Table 5.2: Angiographic and Procedural Characteristics

	All patients n=241	Symptom onset-to-lytic time		*p* value
		≤ 120 minutes n=125	> 120 minutes n=116	
Infarct-related coronary artery				0.998
- Left Main	3(1.2%)	1(0.8%)	2(1.7%)	
- Left anterior descending artery	122(50.6%)	63(50.4%)	59(50.9%)	
- Left circumflex coronary artery	9(3.7%)	5(4.0%)	4(3.4%)	
- Right coronary artery	95(39.4%)	50(40.0%)	45(38.8%)	
- Bypass graft	2(0.8%)	2(1.6%)	0	
- Other coronary branches	10(4.1%)	4(2.3%)	6(5.2%)	
Number of diseased vessels				0.731
1	145(60.2%)	75(60%)	70(60.3%)	
2	65(27%)	31(24.8%)	34(29.3%)	
3	31(12.9%)	19(15.2%)	12(10.3%)	
Lesion classification (ACC/ AHA)				
- B2	98(40.8%)	49(39.5%)	49(42.2%)	0.668
- C	78(32.5%)	42(33.9%)	36(31%)	0.639
Culprit lesion length	16[13-24]	18[14.3-24.7]	16[12.3-24.0]	0.224
Culprit lesion length ≥20mm	104(43.3%)	55(44.4%)	49(42.2%)	0.741
Coronary artery stenosis pre-PCI (%)	95%[90-100]	95%[90-100]	95%[90-100]	0.893
Stenting	230(95.4%)	122(97.6%)	108(93.1%)	0.095
- ≥ Drug eluting stent	28(11.6%)	10(8%)	18(15.5%)	0.069
- ≥ Bare-metal stent	202(83.8%)	112(89.6%)	90(77.6%)	0.011
Stent length (mm)	18[14-24]	18[14-24]	18[14.25-24]	0.406
Stent diameter (> 3mm)	188(81.7%)	107(87.7%)	81(75%)	0.013
Stent diameter (> 3.5mm)	117(50.9%)	74(60.7%)	43(39.8%)	0.002
basline TIMI flow grade				0.356
3	99(41.1%)*	49(39.2%)	50(43.1%)	
2	55(22.8%)	27(21.6%)	28(24.1%)	
0-1	87(36.1%)	49(39.2%)	38(32.7%)	
TIMI flow grade after PCI				0.633
3	218(90.5%)*	112(89.6%)	106(91.4%)	
2	20(8.3%)	11(8.8%)	9(7.8%)	
0-1	3(1.2%)	2(1.6%)	1(0.9%)	
- Initial corrected TIMI frame counts	30[16-100]†	38[16-100]	25[16-100]	0.221
- Initial CTFC > 40	105(43.9%)	61(48.8%)	44(38.6%)	0.112
- Post-PCI corrected TIMI frame counts	14[9-20]†	14[10-23]	14[8-19]	0.204
- Post-PCI CTFC > 40	12(5.0%)	9(7.2%)	3 (2.6%)	0.106
Glycoprotein IIb/IIIa inhibitor use	187(77.6%)	102(81.6%)	85(73.3%)	0.121
- Tirofiban	134(55.6%)	76(60.8%)	58(50%)	
- Abciximab	53(22%)	26(20.8%)	27(23.2%)	
Length of hospital stay (days)	4[3-5.5]	4[3-5]	4[2-6]	0.906
Successful PCI procedure	237(98.3%)	125(100%)	112(96.6%)	0.052

ACC/AHA=American college of cardiology/American heart association; CTFC=Corrected TIMI frame counts; PCI=Percutaneous coronary intervention; TIMI=Thrombolysis In Myocardial Infarction.

Categorical variables are shown as count (%) and continuous variables are shown as median [interquartile range].

** † p value for comparison is < 0.001*

5.3.2. Electrocardiographic analysis

The median ST recovery prior to PCI was 22% [IQR -24 to +54%], while the median ST recovery after PCI was 66.7% [IQR:50-82%]. Post-PCI, complete ST recovery (≥ 70%) occurred in 109 (48.4%) patients and partial ST recovery occurred in 83 (36.9%) patients, while in 33 (15%) ST recovery was < 30%. Of patients without ST recovery at 60-90 minutes post-fibrinolysis, 13% (31 patients) achieved ST recovery during transfer. Prior to angiography of patients who had ST recovery < 70%, 77% had initial TIMI 0-1. After PCI, of those who achieved ≥ 70% ST recovery, 94% had post-PCI TIMI-3. The median at-risk myocardium determined by QRS scoring was 11 [IQR:7-15] (~33% of the myocardium) and the median final QRS score was 4 [IQR:2-6], (~12% of the myocardium). The median myocardium salvage index was 0.58 [IQR:0.37-0.78], (Appendix A and B).

5.3.3. Clinical outcomes

Mortality at 30-days was 6.2% (15 patients), of whom 8 patients had pre-PCI cardiogenic shock and 2 had TIMI major bleeding; 7 (3.2%) patients died among 217 patients without pre-PCI cardiogenic shock. Bleeding events occurred in 59 (25%) patients, 16 (6.6%) patients suffered TIMI major bleeding and 23 (9.5%) patients received blood transfusions, 2 (0.8%) patients suffered a non-fatal haemorrhagic stroke, and 2 had other non-fatal strokes. Bleeding events among those who received GPIIb/IIIa inhibitors, compared with those not receiving these agents were 26.2% vs. 18.5% (p = 0.285), while TIMI major bleeding were 6.4% vs. 7.4% (p = 0.761) and bleeding events requiring transfusion were 9.1% vs.11.1% (p = 0.656). Re-infarction occurred in 8 (3.3%) patients, and 7 (2.9%) patients required TVR; 4 patients had PCI and 3 had CABG (Table 5.3). The only outcome difference between patients treated ≤ and, > 120

minutes of symptom-onset-to-lytic was severe congestive heart failure at 30 days (8.8%vs. 17.2%, p = 0.05) (Table 5.3).

Mortality rate at 1 year (median 11.3 [IQR:5.8-16.8] months) was 8.2% (19 patients), and among those without pre-PCI shock was 5.3% (11 patients), Table 5.3. Also, 5.2% (12 patients) had re-infarction. The TVR rate was 6.4% (15 patients), and among the 230 stented patients was 5.4% (3.7% DES vs. 5.6% BMS; p = 0.560). The TVR rate was 2.6% among those with stents diameter (s) ≥3.5mm compared to 8.3% among patients with stents < 3.5mm (p = 0.063); the TVR rates in those with stent diameters ≥3mm and < 3mm were 4.4% and 9.5% respectively (p = 0.246). Among the 17 patients who had DES with diameter (s) ≥3mm, none had TVR.

Table 5.3: 30 Days and 1 Year Clinical Outcomes

	All patients n=241	Symptom onset-to-lytic time		*p* value	Patients without pre-PCI cardiogenic shock n=217
		≤ 120 minutes n=125	> 120 minutes n=116		
30 days					
Death	15(6.2%)	6(4.8%)	9(7.8%)	0.342	7(3.2%)
Nonfatal stroke	4(1.7%)	3(2.4%)	1(0.9%)	0.623	3(1.4%)
Bleeding*	59(24.5%)	28(22.4%)	31(26.7%)	0.435	50(23%)
TIMI major bleeding*	16(6.6%)	7(5.6%)	9(7.8%)	0.501	11(5.1%)
Transfusion*	23(9.5%)	11(8.8%)	12(10.3%)	0.683	17(7.8%)
Severe congestive cardiac failure (NYHA Class III-IV)†	31(12.9%)	11(8.8%)	20(17.2%)	0.05	19(8.8%)
Re-MI	8(3.3%)	6(4.8%)	2(1.7%)	0.284	6(2.8%)
Target vessel revascularisation (TVR)	7(2.9%)	4(3.2%)	3(2.6%)	0.999	6(2.8%)
- PCI	4(1.7%)	3(2.4%)	1(0.9%)	0.623	3(1.4%)
- CABG	3(1.2%)	1(0.8%)	2(1.7%)	0.610	3(1.4%)
Death, re-MI, TIMI major bleeding or Nonfatal stroke	31(12.9%)	16(12.8%)	15(12.9%)	0.976	19(8.8%)
1 year					
Death	19(8.2%)	7(5.8%)	12(10.6%)	0.182	11(5.3%)
Re-MI	12(5.2%)	9(7.5%)	3(2.7%)	0.094	10(4.8%)
Target vessel restenosis	18(7.7%)	10(8.3%)	8(7.1%)	0.720	16(7.7%)
TVR	15(6.4%)	8(6.7%)	7(6.2%)	0.883	13(6.2%)
Severe congestive cardiac failure (NYHA Class III-IV)	34(14.6%)	13(10.8%)	21(18.6%)	0.094	22(10.5%)
Death or re-MI	27(11.6%)	14(11.7%)	13(11.5%)	0.969	19(9.1%)
Death, re-MI or TVR	36(15.5%)	18(15.0%)	18(15.9%)	0.845	27(12.9%)
Death, re-MI, TVR or nonfatal stroke	38(16.3%)	19(15.8%)	19(16.8%)	0.840	28(13.4%)
Death, re-MI, TVR, nonfatal stroke or severe CCF	59(25.3%)	27(22.5%)	32(28.3%)	0.307	44(21.1%)

** Bleeding events among those who received glycoprotein IIb/IIIa inhibitors, compared with those not receiving these agents were 26.2% vs. 18.5% (p = 0.285), while TIMI major bleeding were 6.4% vs. 7.4% (p = 0.761) and bleeding events requiring transfusion were 9.1% vs.11.1% (0.656).*

† Severe congestive cardiac failure as an outcome was defined as congestive cardiac failure that was present post-rescue PCI procedure, which included cardiogenic shock.

Amongst all 241 patients, 24 patients developed cardiogenic shock prior to catheterisation; of these, 13 patients' cardiogenic shock resolved post-PCI, while 11 patients' cardiogenic shock persisted.

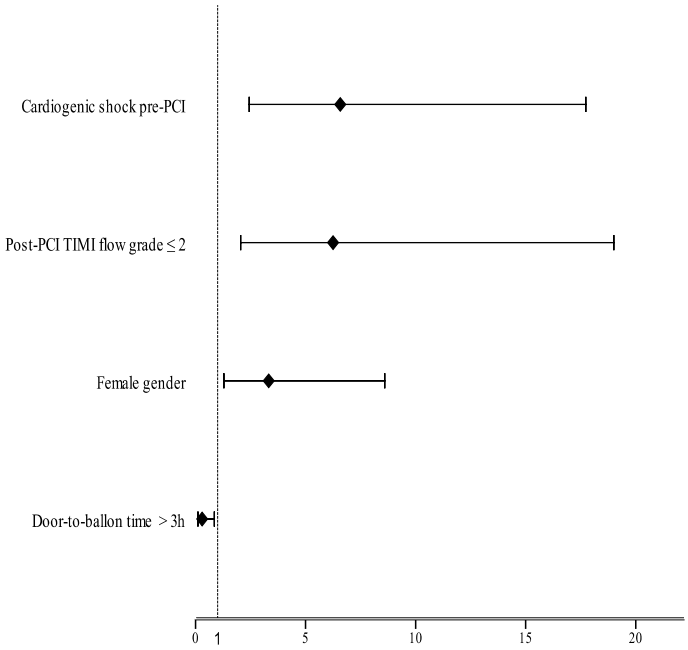
Amongst the 217 patients without pre-PCI cardiogenic shock, 7 developed cardiogenic shock after their PCI procedure.

5.3.4. Predictors of adverse outcomes:

Significant factors associated with TIMI major bleeding within hospitalization period on univariable analysis were female gender (p = 0.012), pre-PCI cardiogenic shock (p = 0.013) and age ≥ 65 years (p = 0.012). On multivariable analysis, the independent factors associated with TIMI major bleeding were, female gender (OR 3.194 [95% CI:1.063-9.597], p = 0.039) and pre-PCI cardiogenic shock (OR 3.619 [95% CI:1.073-12.207], p = 0.038). The use of GPIIb/IIIa inhibitors was not associated with TIMI major bleeding.

Predictors of late mortality on univariable analysis were: age ≥65 years (p = 0.011), female gender (p = 0.011), pre-PCI cardiogenic shock (p < 0.001), post-PCI TIMI flow grade ≤ 2 (0.027) and TIMI major bleeding within the index hospitalization (p = 0.031). Conversely, current smoking (or ceased < 12mth) and door-to-balloon times > 3h were associated with low late mortality (p = 0.016 and p = 0.039 respectively). On Cox multivariate analysis, the independent factors associated with high late mortality included female gender (OR 3.323 [95% CI: 1.284-8.600], p = 0.013), post-PCI TIMI flow grade ≤2 (OR 6.249 [95% CI: 2.054-19.009], p = 0.001) and pre-PCI cardiogenic shock (OR 6.578 [95% CI: 2.440-17.735], p < 0.001) (figure 5.1).

Figure 5.1: Independent Factors Associated with Mortality at 1 Year



	OR (95% CI)	p value
Cardiogenic shock pre-PCI	6.578(2.440-17.735)	< 0.001
Post-PCI TIMI flow grade ≤ 2	6.249(2.054-19.009)	0.001
Female gender	3.323(1.284-8.600)	0.013
Door-to-ballon time > 3h	0.300(0.106-0.852)	0.024

5.4. Discussion

For patients with STEMI treated by fibrinolytic therapy, including those being managed by a pharmaco-invasive strategy, 25-30% will have indications for rescue PCI. [71, 188] In our study, three quarter of patients who underwent rescue PCI had presented to hospital within 2 hours of symptom-onset. In such early presenting patients, a pharmaco-invasive strategy may have benefit due to early successful rescue PCI enhancing myocardial salvage and reducing mortality. [72, 186] The CAPTIM and WEST investigators recently reported retrospective pooled analyses of the subgroup presenting within 2 hours of symptom-onset, [72] a late mortality benefit occurred among those who received fibrinolysis (mostly pre-hospital, with a 25-30% rate of rescue PCI and ~70% in-hospital PCI), compared to primary PCI. The STREAM trial is prospectively evaluating a pharmaco-invasive strategy in STEMI patients presenting within 3 hours of symptom onset to non-PCI centres. [73]

We report mortality rates, 3.2% and 5.3% at day-30 and 1 year respectively are comparable to those reported for primary PCI in patients (> 50% with anterior MI) without pre-PCI shock similar to mortality in the APEX AMI trial. [197] When patients with cardiogenic shock were included, 30-day mortality was 6.2%; 3 other rescue PCI registries have reported 30-day mortality rates in the range of 5.2%-10.7%. [189, 190, 198]

Most reports of rescue PCI outcomes have included at most a few hundred patients, so comparisons of mortality rates are likely to be confounded with insufficient power. However post hoc analysis of the REACT trial showed patients randomised to rescue angioplasty compared with conservative management and further fibrinolysis, had a late survival benefit. [77, 78] In the MERLIN trial which recruited patients between

February 1999 and June 2002, mortality was 9.8% at 30 days and 14.4% at one year. Mortality was 4.9% at 30 days and 7.6% at 1 year in the REACT trial which randomised patients from December 1999 to March 2004. [75, 76, 199, 200] Several factors may have influenced a lower mortality rate in our study compared to those reported in REACT and MERLIN trials, such as higher rates of use of tenecteplase (94%), stenting (95%) and GPIIb/IIIa inhibitors (78%).

Measurement of final infarct size can determine a significant factor for attributable mortality risk, easily performed by calculation of Selvester QRS scores from 12-lead ECG. A myocardial salvage index of 0.58 reported here is similar to that measured by STOP-AMI investigators using nuclear scanning in those who had successful reperfusion. [201] Cardiac MRI is a more sensitive technique for assessing final infarct size, though achieving a second post-hospitalization MRI scan even in a clinical trial setting can be problematic.

The use of GPIIb/IIIa inhibitors after fibrinolytic therapy in the setting of PCI in the early hours after symptom onset has been contentious given clinician concerns about balancing bleeding risks with risks of recurrent ischemic events. In our study of rescue PCI, there was an ~80% rate of GPIIb/IIIa inhibitor use which were not associated with an increased bleeding risk. Some small non-randomised studies on GPIIb/IIIa use in this setting, [202-205] have reported TIMI major bleeding of 6.9% and 12% among patients who underwent rescue PCI and received GPIIb/IIIa inhibitors. [203, 204] Several factors may have contributed to the differences in the bleeding rate after rescue PCI compared with older studies, such as the use of smaller arterial sheath calibre, and improvements in pharmaco-therapies including lower heparin doses associated with lower activated clotting times. Whether lower rates of bleeding occur in this setting, using thrombin inhibition with bivalirudin, compared to unfractionated heparin and GPIIb/IIIa

inhibitors, as occurred in different groups of acute coronary syndrome patients in ACUITY and the Revascularization and Stents in Acute Myocardial Infarction (HORIZONS-AMI) trial is under investigation.

Recent trials have reported lower TVR rates after STEMI following DES deployment compared to BMS among unselected patients, including arteries ≥3 mm, though TVR rates may be heterogeneous, dependent on various angiographic and clinical factors.[93] In our study ~ 50% of patients underwent rescue PCI for STEMI had a culprit lesion segment ≥ 3.5mm in diameter, and among these patients the TVR rate was 2.6% after BMS deployment, compared to 8.3% among patients with stents < 3.5mm; the later similar rate to 8.7 % reported from HORIZONS-AMI.[91, 93] Also in Basket-Prove study, in patients with stable and acute CHD, after BMS deployment in coronary arteries > 3mm, had TVR rate of 10.3% at 2 years.[128] Thus the reduction of TVR rates with BMS in STEMI appears to occur in arteries ≥3.5mm. Because the ability of patients to appreciate the necessity of prolonged dual anti-platelet therapy in the setting of acute STEMI may be compromised, [181] and the low TVR rates with BMS in vessels ≥3.5mm in diameter, future studies should specifically address the necessity of DES use in this setting.

This study has limitations inherent in an observational study, and there may have been unappreciated referral biases at non-PCI hospitals, so deaths prior to and during inter-hospital transfer were not recorded. We found a paradoxical survivor benefit among those with door to balloon times > 3 hours which may represent lower risk group of younger patients and lower rates of pre-PCI cardiogenic shock and referral bias whereas in the FAST-MI registry a higher mortality was observed in those undergoing rescue PCI treated ≥220 minutes compared to those at ≤ 128 minutes after fibrinolysis.[178] We report low rates of radial access in comparison to some other studies

which may have influenced our rates of bleeding. While the RIVAL trial reports that in a subgroup of patients with STEMI, radial access reduces the incidence of the primary outcome of death, MI, stroke or major bleeding and the secondary outcomes of death, MI, or stroke, and overall mortality within 30 days compared with femoral approach. This subgroup analysis warrants future trial confirmation.[206] Additionally, we did not routinely collect data on rates of "upstream" clopidogrel administration.

5.5. Conclusions

The mortality rate of 3.2% in unselected patients without prior shock undergoing rescue PCI in the era of liberal use of stents and GPIIb/IIIa inhibitors, is similar to that of STEMI patients treated with primary PCI. These data suggest that a pharmaco-invasive approach to STEMI with rescue PCI especially among those presenting at < 2 hours is a reasonable strategy when there is not expeditious access to primary PCI, especially in early presenting patients. Finally, the very low TVR rate with BMS in coronary arteries ≥3.5mm in this STEMI setting should be compared to DES use in a trial with appropriate size.

Chapter 6

Evaluation of troponin T criteria for peri-procedural myocardial infarction in patients with acute coronary syndromes

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6.1. Introduction

The importance of patterns of elevation of blood levels of markers of myonecrosis has been emphasised in the 2000 and 2007 universal definitions of MI. [10, 150, 156] Because of the higher specificity and sensitivity of cardiac troponins, [135, 136, 152, 153] their measurement has become preferred to CKMB for diagnosis of MI. [10, 150, 152, 154] Cardiac troponins T (TnT) and I (TnI) have long half-lives and are detectable in blood for up to 10-14 days post-MI, whereas CKMB levels remain elevated in the circulation for only 2-3 days post-MI. [14, 157] Because of these differences in kinetic profiles, the measurement of CKMB levels was recommended in the 2000 MI redefinition for the diagnosis of early re-infarction, including post-percutaneous coronary intervention (PCI) when troponin levels were elevated. [150] However, the 2007 universal MI definition recommended using different amounts of elevation of cardiac markers (TnT or CKMB) depending on the clinical situation, either spontaneous MI or post-PCI. Two cardiac marker levels, preferably troponin, one immediate and a second 6 hours later , and an increase of $\geq$ 20 % TnT above stabilized or falling elevated pre-PCI levels are necessary for cardiac marker based post-PCI re-MI definition, in addition to ECG or imaging. [10, 156]

Because there are relatively few data to support the troponin-based definition of re-infarction especially post-PCI in patients with elevated pre-PCI TnT levels, [158, 159] we examined cardiac marker levels in such patients. Initially we examined relations between levels of CKMB and TnT in patients with acute coronary syndromes (ACS) and stable-CHD to develop an algorithm for absolute increases in TnT levels above the

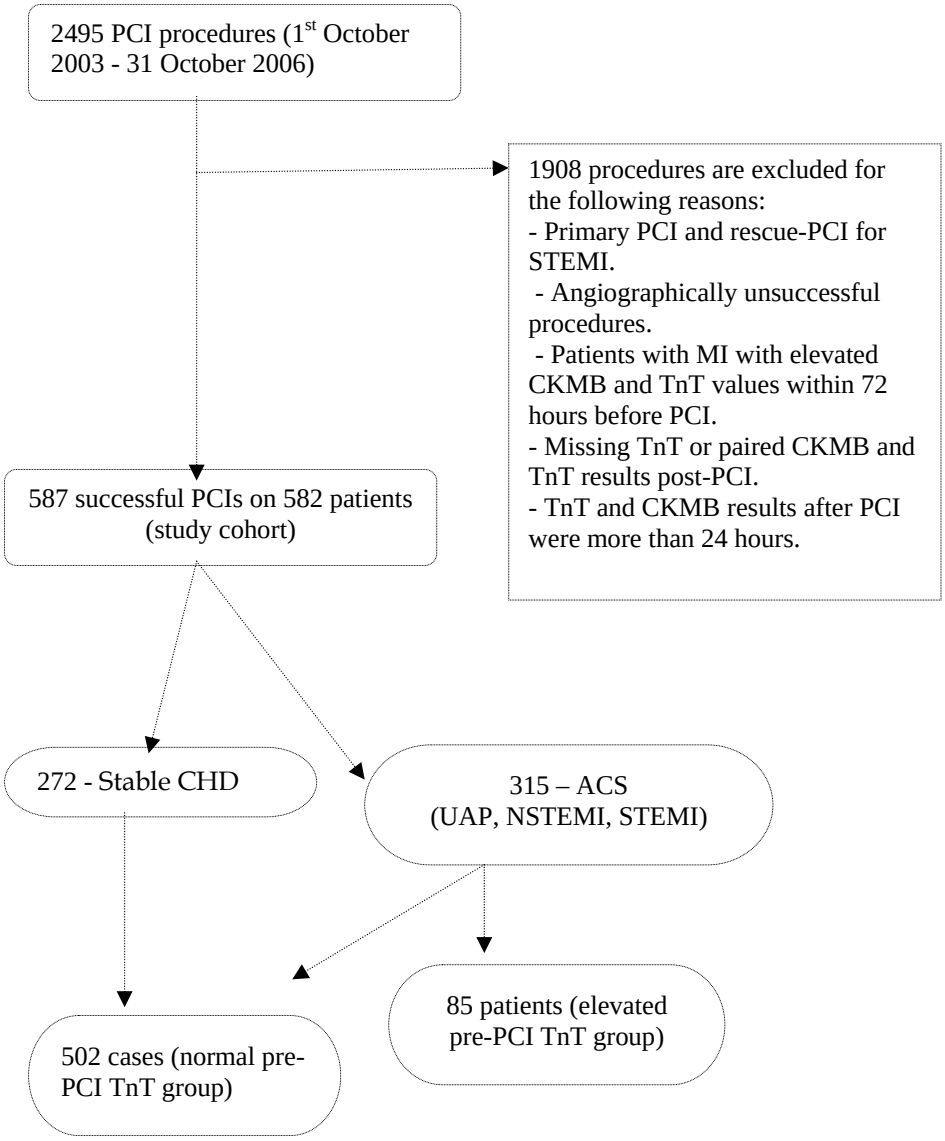
upper reference limit (URL). We used this algorithm in ACS patients with elevated pre-PCI TnT levels, but normal CKMB levels, to compare percentage and absolute increases in peri-procedural cardiac marker levels. The influence on late outcomes of TnT and CKMB elevations post-PCI for patients with ACS, compared to those with stable CHD was also examined.

6.2. Methods

6.2.1. Study population

All patients undergoing PCI have clinical, angiographic and procedural data recorded prospectively in the cardiology database at the Liverpool Hospital cardiac catheterisation laboratory in Sydney, Australia. This data includes procedural indications, patient demographics, the use of pharmacologic agents, angiographic and lesion characteristics, and stent types such as drug-eluting stents. Procedural indications were categorized as: non ST-segment elevation ACS and STEMI, here combined as "ACS"; patients with angina (classes II-III) and other stable manifestations of CHD were classified as "stable CHD". Among patients undergoing PCI during the study period, 587 PCIs performed on 582 unique patients (5 had staged PCIs) had sufficient cardiac marker data for inclusion (Figure 6.1). This study was approved from Liverpool Hospital ethics committee as part of a quality assurance project (QA2008/034).

Figure 6.1: Study population



The diagram shows the patients from the total angioplasty cohort. Also the reasons for inclusion in and exclusion from the current study for those who underwent PCI in the study period are shown. (UAP = unstable angina pectoris; NSTEMI= non-ST segment elevation myocardial infarction; STEMI= ST-segment elevation myocardial infarction)

6.2.2. Percutaneous coronary intervention procedures

Aspirin (unless contraindicated), clopidogrel (300mg or 600mg) and a bolus of un-fractionated heparin was given at the start of PCI procedures. Intravenous GPIIb/IIIa inhibitors were administered according to the interventional cardiologist's discretion. Stent deployment and rotational arterectomy were performed according to the standard practice. Angiographically successful procedures were defined as final post-PCI minimum stenosis diameter reduction to < 20% in cases after stenting or to < 50% following balloon angioplasty in the presence of grade 3 Thrombolysis In Myocardial Infarction (TIMI) flow. [161, 162]

Clinical follow-up was obtained by trained research staff (either nurses or doctors) at 8-12 months post-PCI. Patients, their relatives or local physicians were contacted by phone and were questioned as to the recurrence of cardiac symptoms requiring hospitalization, particularly coronary revascularization, or MI. Information regarding death was obtained from family members, physicians, medical records and death registry. Other clinical outcomes such as repeated procedures for stent thrombosis and restenosis were also documented in our database.

6.2.3. Cardiac myonecrosis marker measurements

Venous blood samples for measurement of TnT and CKMB (mass) levels (both Roche, Mannheim, Germany), were obtained before and after PCI; post-PCI samples were obtained at a median of 18 hours (IQR: 16-20 hours). Further markers measurements were obtained when an ischemic event was suspected, or according to physician discretion. Only patients with TnT and CKMB levels measured concurrently and within 24 hours post-PCI were included in the analysis of the relationship between TnT and

CKMB levels. A cohort of 85 patients with ACS underwent delayed PCI due to scheduling (Figure 6.1), who had normal CKMB and elevated TnT levels that were either stable or falling (post peak). The upper reference limit (URL) for TnT was 0.03μg/L (defined as the level at the coefficient of variation [CV] of ≤ 10%), using The 3rd generation TnT assay was used prior to 15 January 2006 and the 4th generation TnT assay thereafter. The URL for CKMB (mass) was 4.9μg/L for males and 2.9μg/L for females. The gender specific levels were in all analyses.

6.2.4. Data analysis

Predominantly performed based on the indication for PCI and TnT levels prior to PCI. Statistical analysis was performed using SPSS (SPSS Inc, Chicago) version 14.0. Categorical variables were expressed as numbers and percentages per group and the continuous variables as mean ± standard deviation (SD) for normally distributed variables or medians and IQR for skewed variables. For the group comparisons Pearson's chi square (χ^2) test or Fisher's exact test were used for unpaired categorical variables, and McNemar's test was used for paired categorical variables. The student's t tests or the Mann-Whitney U tests (for skewed variables) were used for continuous variables. The relationship between post-PCI TnT and post-PCI CKMB were modelled using linear regression with logarithmic transformations of TnT and CKMB levels. We included a term to account for severe pre-PCI renal impairment (defined here as estimated pre-PCI glomerular filtration rate [eGFR] < 30 ml/min/1.73 m^2, using the MDRD formula [eGFR = 186.3 x $SerumCr^{-1.154}$ x $age^{-0.203}$ x 0.742 (if female)]). [207] Forward stepwise logistic regression analyses were performed to determine independent predictors of TnT level elevations post-PCI and late events (death or nonfatal MI). Age (≥70 years old), ACC/AHA class B2 and C lesions, lesions in saphenous vein grafts

(SVG), diabetes mellitus, duration of PCI (as dichotomous variable at median PCI duration = 59 minutes), maximum balloon pressure and duration were included in the model for prediction of post-PCI TnT level elevations. Clinical indications for PCI (ACS and stable CHD), Age (≥ 70 years old), diabetes mellitus, PCIs on patients with culprit lesions in SVG, PCIs on patients with culprit lesions at coronary artery bifurcation, post-PCI CKMB level elevations (> 3XURL), post-PCI TnT level elevations (> 3XURL) and patients with pre-PCI eGFR < 30 ml/min/1.73 m^2 were included in prediction models for late death or MI. Comparisons of frequencies of death or nonfatal MI between groups were performed using Kaplan-Meier analyses and log rank testing. P values < 0.05 were considered statistically significant; the 5 patients with staged procedures were only included once.

6.3. Results

6.3.1. Patients clinical and procedural characteristics

Among patients who underwent successful PCI during the study period, October 2003 – October 2006, 587 procedures were performed on 582 patients (5 had staged procedures), who met this study's inclusion criteria (Figure 6.1); 315 PCIs were performed on patients with ACS and 272 PCIs on patients who had stable CHD. The baseline demographic and angiographic characteristics of patients according to the clinical indication for PCI and the pre-PCI TnT levels are shown in Tables 1 and 2. Peri-procedural GPIIb/IIIa inhibitors were used in 20.4% (12.9% tirofiban; 7.5% abciximab), and in 98% of PCIs at least one stent was deployed (35% had ≥ 1 drug-eluting stent). 3 patients had rotational atherectomy.

The rates of peri-PCI MI for all 587 PCI procedures based on TnT and CKMB levels elevations (both > 3XURL) as recommended by the 2007 universal definition of MI are 23.9% and 16.7% respectively. Independent predictors of TnT level elevations post-PCI on multivariable regression analysis were: Age (≥ 70 years old) (OR 1.683: 95% CI [1.124-2.519], p = 0.011), duration of PCI (as dichotomous variable at 59 minutes) (OR 1.586: 95% CI [1.069-2.352], p = 0.022) and ACC/AHA class B2 and C lesions (OR 1.54 : 95% CI [1.001-2.368], p = 0.049).

Table 6. 1: Baseline Clinical Characteristics

	Pre-PCI TnT level			Clinical indication for PCI		
	TnT < 0.03 µg/L (stable CHD and ACS) (n =502)	**TnT > 0.03 µg/L (ACS) (n = 85) ***	**p-value**	**ACS (n = 315)**	**stable CHD (n = 272)**	**p-value**
Age (mean ± SD) years	64.3 (10.8)	62 (12.7)	0.11	63 (11.6)	65 (10.3)	0.028
Male gender	378 (75.3)	65 (76.5)	0.816	245 (77.8)	198 (72.8)	0.162
Diabetes mellitus	101 (20.1)	13 (15.3)	0.298	63 (20)	51 (18.8)	0.703
Smoking	64 (12.7)	25 (29.4)	<0.0001	72 (22.9)	17 (6.3)	<0.0001
Hypertension	278 (55.4)	45 (52.9)	0.676	179 (56.8)	144 (52.9)	0.346
Family history of CHD	100 (19.9)	22 (25.9)	0.21	65(20.6)	57 (21)	0.924
Hyperlipidemia	340(67.7)	55(64.7)	0.583	224 (71.1)	171 (62.9)	0.034
Previous PCI	44 (8.8)	1 (1.2)	0.015	16 (5.1)	29 (10.7)	0.011
Previous CABG	28 (5.6)	4 (4.7)	0.495	15 (4.8)	17 (6.3)	0.428
eGFR < 60†	103 (20.6)	21 (24.7)	0.392	62 (19.7)	62 (23)	0.33
eGFR < 30†	8 (1.6)	4 (4.7)	0.082	9 (2.9)	3 (1.1)	0.137

ACS= acute coronary syndrome; CABG= coronary artery bypass grafting; CHD = coronary heart disease; CKMB = creatine kinase-MB; eGFR= estimated glomerular filtration rate; n = number; PCI=percutaneous coronary intervention; SD= standard deviation; TnT= troponin T.

Data represent number (%) unless otherwise stated.

* *CKMB returned to normal before PCI (The median time from admission to PCI were 5 days (IQR, [3-7])*

† *ml/min/1.73 m^2.*

Table 6.2 : Angiographic and Procedural Characteristics

	Pre-PCI TnT level			Clinical indication for PCI		
	TnT < 0.03 µg/L (stable CHD and ACS) (n =502)	**TnT > 0.03 µg/L (ACS) (n = 85)**	**p-value**	**ACS (n = 315)**	**Stable CHD (n =272)**	**p-value**
PCI duration (min)*	59[43-80]	69[52-88]	0.01	64[45-83]	55[42-80]	0.087
Site of Culprit lesion						
LAD	193 (38.4)	27 (31.8)	0.239	119 (37.8)	101 (37.1)	0.872
RCA	131 (26.1)	26(30.6)	0.387	90 (28.6)	67 (24.6)	0.282
LCX	83 (16.5)	23(27.1)	0.020	59 (18.7)	47 (17.3)	0.649
Lesion classification (ACC/			0.457†			0.028†
AHA)	179(35.7)	38(44.7)	0.113	126(40)	91(33.6)	0.109
- B2	152(30.3)	22(25.9)	0.406	98(31.1)	76(28)	0.418
- C						
Culprit lesion at bifurcation	133(26.5)	23(27.1)	0.921	95(30.2)	61(22.5)	0.037
Culprit Lesion length (mm)*	16[12-24]	16[15-24]	0.633	16[16-25]	16[12-23]	0.351
Total stented length (mm) *	20[15-28]	20[16-25]	0.567	20[16-28]	20[16-26]	0.934
Stent diameter (mm) *	3[2.5-3]	3[2.5-3]	0.485	3[2.5-3]	2.75[2.5-3]	0.003
DES	181 (36)	27(31.8)	0.444	113(35.9)	95(34.9)	0.811
BMS	309 (61.6)	58(68.2)	0.239	200(63.5)	167(61.4)	0.662
Inflation pressure max (atm)*	18[16-20]	16[16-20]	0.952	18[16-20]	16[15-18]	0.027
GPIIb/IIIa inhibitor			0.292			< 0.0001
Tirofiban	65 (12.9)	11(12.9)		56 (17.8)	20(7.4)	
Abciximab	34 (6.8)	10 (11.8)		35 (11.1)	9 (3.3)	

- ACC/AHA = American college of cardiology/American heart association; ACS = acute coronary syndrome; atm = atmospheric pressure; BMS = bare-metal stent; CHD = coronary heart disease; DES = drug eluting stent; IQR = interquartile range; LAD = left anterior descending coronary artery; LCX = left circumflex coronary artery; n = number; PCI = percutaneous coronary intervention; RCA = right coronary artery; SD = standard deviation; TnT= troponin T.

- Data represent number (%) unless otherwise stated.

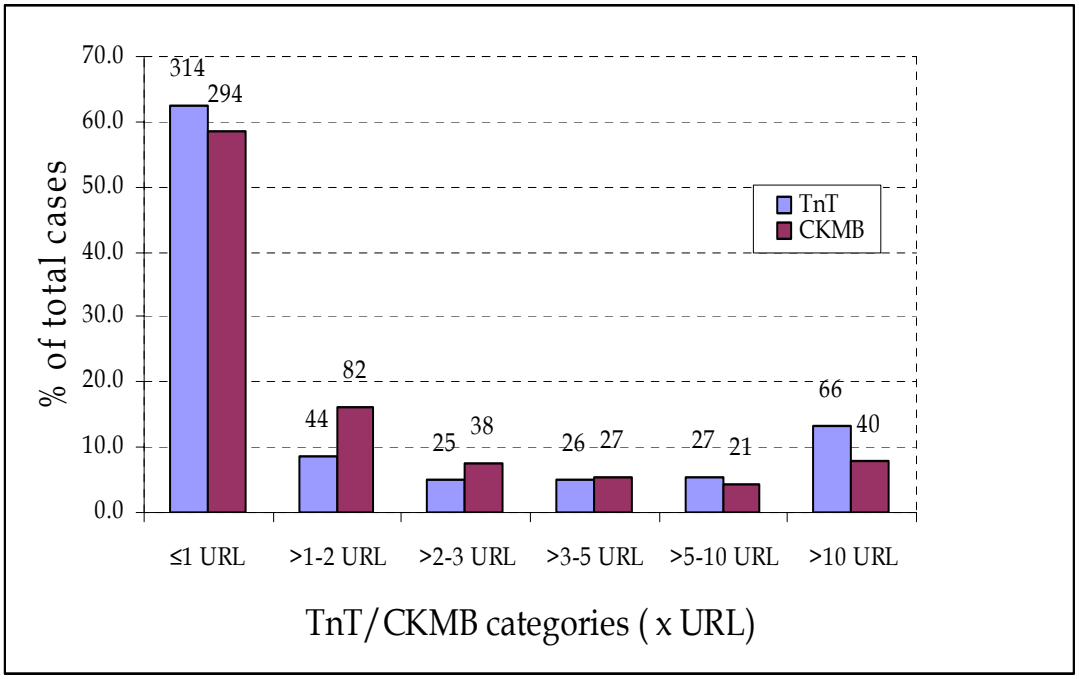
** median [IQR]*

† p-value for combined ACC/AHA class B2 and C lesions

6.3.2. Relation between troponin T and CKMB levels post-PCI in patients with normal pre-PCI levels

Among the 502 PCIs performed on patients who had normal pre-PCI TnT levels (Figure 6.1), elevation of post-PCI TnT levels to above the URL occurred in 188 cases (37.5%; 34.6% in stable CHD and 40.9% in ACS), median level 0.145 μg/L [IQR: 0.07 - 0.65 μg/L], and elevation in post-PCI CKMB levels to above the URL occurred in 208 cases (41.4%; 37.9% in stable CHD and 45.7% in ACS), median level 13 μg/l [IQR: 7 – 37.8 μg/L]. Based on elevations of CKMB levels to > 3XURL , peri-procedural MI occurred in 88 cases (17.5%), whereas TnT levels > 3 XURL (> 0.09 μg/L) peri-procedural MI occurred in 119 cases (23.7%) ($p < 0.0001$). The relationships between post-PCI TnT and CKMB levels for patients with normal baseline pre-PCI TnT levels are shown in Figure 6.2. Of those with elevated post-PCI TnT levels, 13.3% had normal CKMB levels. In patients without pre-PCI TnT elevations, significantly higher elevations in post-PCI TnT levels occurred in ACS patients compared to stable CHD patients (median 0.27 μg/L [IQR: 0.08 - 3.97μg/L] versus median 0.12μg/L [IQR: 0.06 - 0.283μg/L] , $p = 0.002$).

Figure 6.2: Levels of CKMB and Troponin T Post-PCI in Patients who had Normal troponin T Levels Pre-PCI

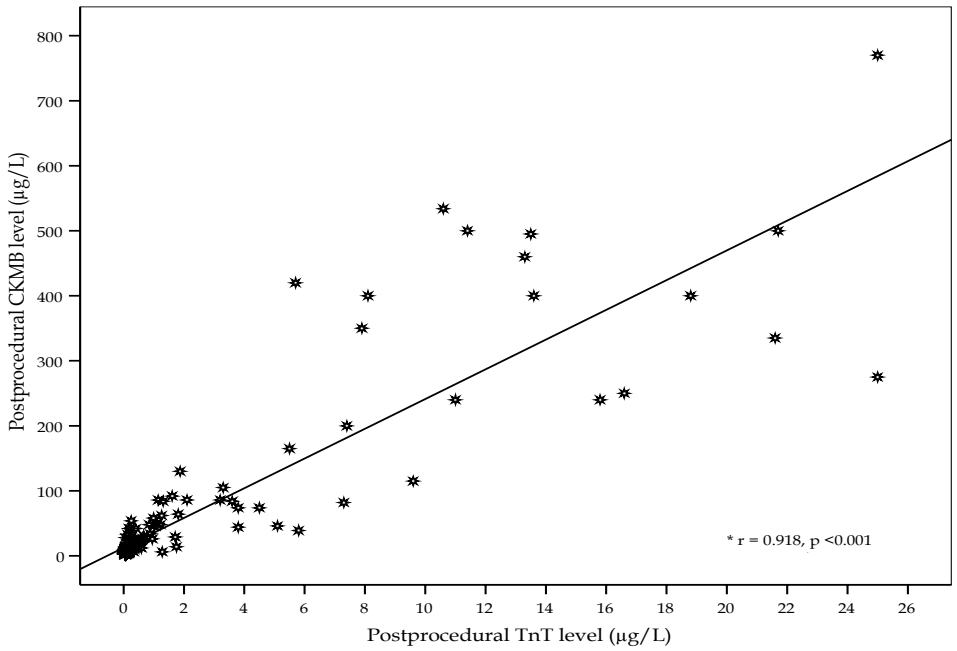


Patients with stable CHD (n=272), ACS (n=230); URL = upper reference limit; URL for TnT = 0.03µg/L; URL for CKMB = 4.9µg/L for males and 2.9µg/L for females. Numbers on top of each bar represents the number of cases in each category.

There is a high correlation (r = 0.918: 95% CIs [0.892 to 0.938], p < 0.001) between the amount of elevation of TnT and CKMB levels post-PCI when pre-PCI TnT levels were normal (Figure 6.3). The regression equation describing the association was:

TnT (μg/L) = $\mathbf{e}^{[(1.202\ (\text{In CKMB μg/L})) - 4.693 + 0.264\ (\text{if eGFR} < 30)]}$, **e** = 2.718. Using this equation and assuming eGFR > 30 ml/min/1.73 m^2, CKMB levels elevations to 3XURL (14.7 μg/L for males and to 8.7 μg/L for females) correspond to TnT levels of 0.23 μg/L and 0.12 μg/L respectively. Prediction of CKMB levels from measured TnT levels can be obtained from the equation: CKMB level (μg/L) = $*\mathbf{e}^{[3.737+ (0.701\ (\text{In TnT μg/L})) - 0.261\ (\text{if eGFR} < 30\ )]}$, * **e**= 2.718. It should be noted that there was no significant correlation when either of these biomarker level elevations post-PCI were to < 2XURL (both r < 0.11, p > 0.40)

Figure 6.3: The Association Between Elevated CKMB and TnT Levels Post-PCI



This shows patients with normal CKMB and normal TnT levels pre-PCI; patients with post-PCI values in the normal range are not included.

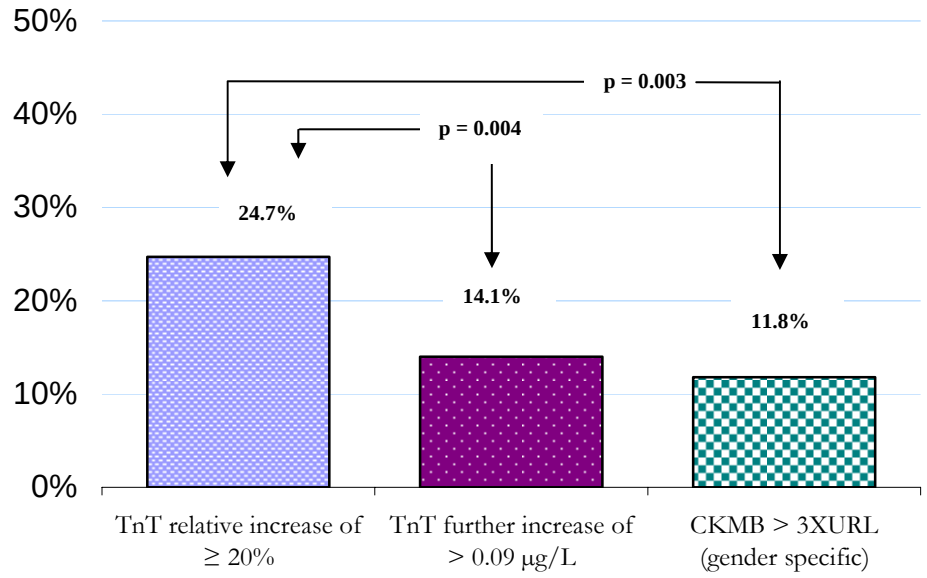
** Pearson's correlation coefficient (measured after logarithmic transformations of TnT and CKMB levels).*

6.3.3. Detection of post-PCI myonecrosis in ACS patients when pre-PCI TnT levels were elevated but CKMB levels were normal

There were 85 patients with ACS who underwent PCI at a median time of 5 days [IQR, 3-7] and had normal pre-PCI CKMB levels but elevated TnT levels (median level 0.30 μg/L, [IQR: 0.09 – 0.855 μg/L]) (table 6.3). Of these, 28 patients (32.9%) had further elevations in TnT levels post-PCI (median increase in TnT level 0.31 μg/L [IQR: 0.13 - 0.8 μg/L]) and 21 patients (24.7%) had post-PCI TnT level elevations of ≥ 20% above the elevated pre-PCI TnT levels. Of these 21 patients meeting the 2007 cardiac marker based definition of peri-procedural MI (none had peri-procedural ECG changes), 9 patients had CKMB elevations > 3XURL post-PCI; 8 had CKMB level elevations < 3XURL, and 4 had no CKMB elevation (a further patient had > 3XURL CKMB but no TnT elevation), so 10/85 (11.8%) met the 2000 re-MI definition (24.7% vs. 11.8%, p = 0.003), Figure 6.4. A further absolute increase in post-PCI TnT levels of > 0.09μg/L (~ 3XURL) occurred in 12/85 (14.1%) (24.7% vs. 14.1%, p = 0.004), Figure 6.4. Of 57 patients with no further TnT elevation post-PCI, 13 (22.8%) had an elevation in CKMB levels to above the URL (table 6.3).

The correlation coefficient between the absolute increases in TnT levels and CKMB levels (r = 0.752: 95% CIs [0.526 to 0.878], p < 0.0001), and the equation describing this relationship is: further TnT elevation (μg/L) = $\mathbf{e}^{[(1.103\ (\text{In CKMB μg/L})) - 4.821 + 0.406\ (\text{if eGFR} < 30)]}$, e= 2.718.

Figure 6.4: Detection of Periprocedural Myocardial Infarction in Patients with Acute Coronary Syndromes when Pre-PCI TnT Levels were Elevated but CKMB Levels were Normal



CKMB = creatine kinase-MB; TnT= troponin T; URL = upper reference limit.

Table 6.3: The relationship between post-PCI CKMB and TnT levels in patients with elevated pre-PCI TnT and normal CKMB levels pre-PCI

	TnT			
		TnT elevation (%)*		
	No further TnT elevation	< 20% elevation	≥ 20% elevation	Number
CKMB ≤ URL	44	2	4	50
CKMB > URL - ≤ 2XURL	10[†]	5	7	22
CKMB > 2XURL - ≤ 3XURL	2[‡]	0	1	3
CKMB > 3XURL	1[§]	0	9	10
Total	57	7	21	85

CKMB = creatine kinase-MB; TnT= troponin T; URL = upper reference limit.

** Percent of post-PCI TnT elevation from the elevated baseline pre-PCI TnT levels*

[†] The mean post-PCI CKMB level elevation for 10 patients was 5.3 (SD 1.7) μg/L.

[‡] The TnT for this patient drop from 0.68μg/L pre-PCI to 0.51μg/L post-PCI while CKMB post-PCI was elevated (11μg/L). Pre-PCI CK results for this patient were 57U/L and post-PCI CK level was 124U/L.

[§] The Pre-PCI TnT for this patient was 1.14μg/L which was dropped to 0.95μg/L post-PCI while CKMB become elevated from 2.9μg/L pre-PCI to 28μg/L post-PCI.

6.3.4. Late clinical outcomes

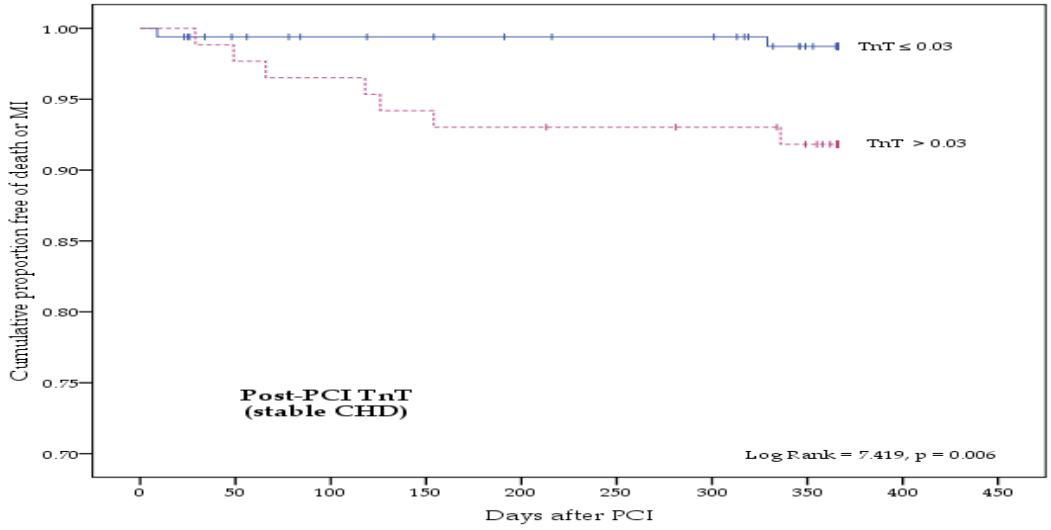
During the follow-up period (~ 1 year) for patients with normal pre-PCI TnT levels, who underwent PCI for stable CHD and ACS, death occurred in 14 patients (9 patients with ACS [4%] vs. 5 patients with stable CHD[2%], p = 0.141), late nonfatal MI occurred in 9 patients (5 patients with ACS [2.3%]vs. 4 patients with stable CHD [1.6%], p = 0.416), and early and late stent thrombosis occurred in 6 patients (3 patients with ACS [1.4%] vs. 3 patients with stable CHD [1.2%] , p = 0.59).

Among patients with stable CHD who had post-PCI TnT levels and/or CKMB levels > URL, 1 year survival free of death or nonfatal MI was lower than in those without post-PCI TnT and/or CKMB level elevations(92% vs. 98.8% for TnT, p = 0.006; 92.6% vs. 98.7% for CKMB, p = 0.012 [Log rank]), whereas among patients with ACS and either normal or elevated pre-PCI TnT and/or CKMB levels there were no differences in event-free survival irrespective of post-PCI cardiac markers levels (94.5% vs. 93% for TnT, p = 0.691 ; 94.1% vs. 93.2% for CKMB, p = 0.810 [Log rank]) as shown in Figure 6.5 (A, B, C and D).

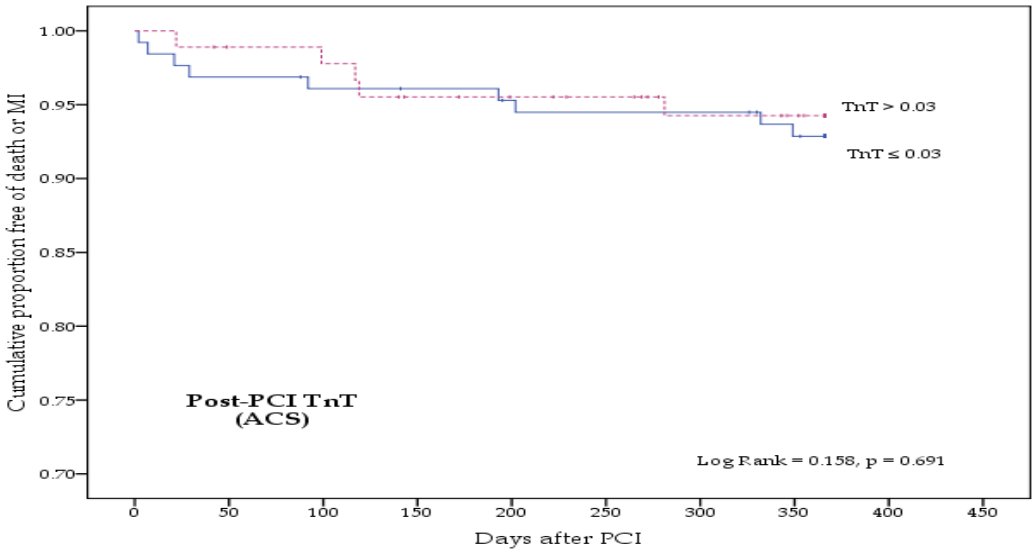
Among patients with stable CHD who had post-PCI TnT levels and/or CKMB levels > 3XURL, 1 year survival free of death or nonfatal MI was lower than in those without such elevations (87.5% vs. 98.5% for TnT, p < 0.001; 83.9% vs. 98.2% for CKMB, p < 0.001[Log rank]), whereas among patients with ACS and normal pre-PCI TnT and CKMB levels there were no differences in event-free survival for those who had post-PCI TnT and/or CKMB elevations (> 3XURL) compared to those without such elevations (95.2 % vs. 92.9% for TnT, p = 0.555 ; 94.3% vs. 93.4% for CKMB, p = 0.822 [Log rank]).

Figure 6.5: (A and B): Survival Free of Death or Nonfatal Myocardial Infarction After PCI According to Troponin T Status Post-PCI

(A)



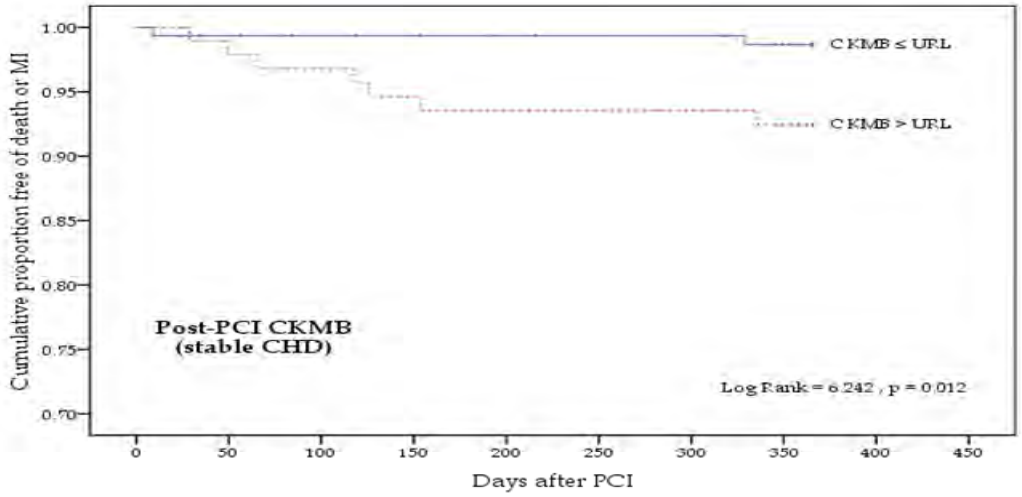
(B)



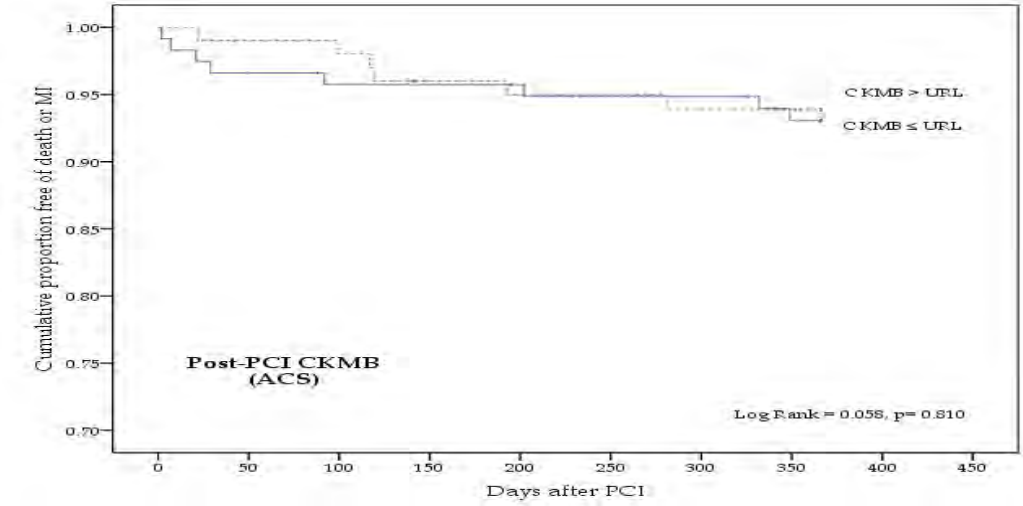
The Kaplan-Meier survival curves are shown according to post-PCI myonecrosis marker levels in patients with stable CHD and ACS with normal pre-PCI myonecrosis markers. Panels A and B show patients with stable CHD and ACS respectively, with respect to TnT levels.

Figure 6.5: (C and D). Survival Free of Death or Nonfatal Myocardial Infarction After PCI According to CKMB Status Post-PCI

(C)



(D)



The Kaplan-Meier survival curves are shown according to post-PCI myonecrosis marker levels post-PCI in patients with stable CHD and ACS with normal pre-PCI myonecrosis markers. Panels C and D show patients with stable CHD and ACS respectively with respect to CKMB levels.

Among patients with ACS who had elevated pre-PCI TnT, survival free of death or nonfatal MI at 1 year for those with post-PCI TnT elevations ≥20% compared to elevation < 20% was 95% vs. 95% (p = 0.89 [Log rank]).

On multivariable analysis, independent predictors of death or nonfatal MI at 1 year were: Diabetes Mellitus (OR 3.188: 95% CI [1.331-7.635], p = 0.009) and post-PCI CKMB level elevation > 3XURL (OR 3.029: 95% CI [1.202-7.637], p = 0.019).

6.4. Discussion

The 2007 universal definition of MI requires ≥ 2 pre-procedural troponin levels 6 hours apart, and then a relative (≥20%) increase in post-PCI TnT levels is also required to define post-PCI MI. We consider at 5 days following admission for ACS will rarely be performed, either in routine practice or in clinical trials. An important aspect of our study was the inclusion of patients with ACS, who had delay in PCI largely due to inter-hospital transfer and scheduling, and who had elevated TnT but normal CKMB levels prior to PCI. This provided an opportunity to measure further absolute increases in TnT levels post-PCI and correlate these with CKMB levels.

We found a high degree of correlation between post-PCI CKMB and TnT levels when both markers levels were elevated to > 2XURL in stable CHD patients, a finding similar to a previous report. [208] We also found a significant association between an absolute increase in TnT levels above the stable pre-PCI elevated levels and the absolute increase in CKMB levels above the URL. While we did not examine associations between peak levels of CKMB and TnT , which occur at differing times after infarct onset, [14] we consider that our reported association of these marker levels at a median of 18 hours (the morning after PCI) will be useful in clinical practice. Furthermore, we found that when there were minor elevations in pre-PCI TnT levels, the 2007 universal definition of MI lead to small further elevations of ≥20% in TnT levels being diagnosed as (small) re-infarctions that (understandably) did not meet

CKMB re-infarction criteria. Conversely, when the pre-PCI TnT level was > 0.8μg/L or 20-30 fold above URL quite large absolute increases in post-procedural TnT levels did not meet ≥20% increased in TnT re-infarction criteria , though the > 3XURL CKMB elevation re-MI criteria were met.

Our results confirm that even using earlier generations of assays, TnT is a sensitive myonecrosis marker. With the ongoing development of TnT assays, there has been evolution in the reference ranges and the level which is considered > 3XURL. [209] when our study commenced, elevated levels were locally reported as > 0.03μg/L; also the level of the 10% CV was 0.035μg/L. [209] While it is now appreciated that TnT levels ≥0.01μg/L, detectable by the3rd and 4th generation TnT assays are biologically abnormal, [134] we choose > 0.09μg/L using these TnT assays, which represents > 3XURL, the definition post-procedural MI when pre-PCI cardiac marker levels were normal.

We were not able to examine pre-PCI and post-PCI TnT levels in the range 0.01-0.03μg/L (or even lower levels) using the high sensitivity TnT assay as recently reported. [134] The use of this assay would have been unlikely to have influenced our major findings which focused on detection of (larger) peri-procedural TnT elevations measured by the 3rd and 4th generation assays. Also, as indicated in a recent editorial by Morrow, [155] the major utility of minor elevations of these sensitive markers is in identifying more high risk patients who may benefit from an early invasive strategy. Furthermore, the prognostic significance of minor increases in post-PCI TnT levels which meet the new re-MI criteria of ≥20%, when pre-PCI TnT levels are ≤0.03μg/L and are detected by high sensitivity assays.

The prognostic significance of peri-procedural elevations of CKMB > 3XURL has been known for over a decade, [131, 210] and subsequently similar evidence has been

reported for troponin. [142] The detection of early re-infarction including, peri-procedural re-MI, using TnT- and TnI-based definitions has been confounded by the kinetic profiles of these cardiac markers with prolonged duration of level elevations.

Many investigators have reported the prognostic significance of elevated levels of CKMB post-PCI on mortality. [210, 211] However, minor CKMB elevations which reflect small areas of myonecrosis identified on contrast enhanced magnetic resonance imaging, [212] have also been shown to have a relationship with survival. In the current study, patients who underwent PCI for stable CHD and had any post-PCI TnT and/or CKMB levels elevations had a reduced rate of survival free of death or nonfatal MI at 1 year compared with those without post-PCI marker elevations.

The post-PCI TnT and CKMB level elevations were higher in the ACS group when compared with the stable CHD group, which may be explained by higher frequency of ACC/AHA class B2 and C and bifurcation lesions. Data recently reported from Mayo Clinic, [134] which showed that among patients with ACS undergoing PCI, only elevated pre-PCI, and not post-PCI, cardiac marker levels affected the survival. Also peri-procedural MI in patients with ACS in the ACUITY trial, [213] did not influence late events though pre-PCI marker levels did. However, in the ACUITY trial a significant fraction of patients had angiography and angioplasty within 12 -18 hours of presentation, and though there were explicit criteria for clinical events committee for adjudication of MI, [213] a proportion of these potential early peri-procedural events may not have been confirmed because of uncertainty about early elevation profiles in marker levels. In contrast, because of the cardiac marker selection criteria for our study, we did not include patients who had ‘early’ angiography and angioplasty. Also, whether the ACUITY investigators made gender–specific adjustments for CKMB reference ranges

is not clear, though as in our study because most CHD patients are male, the salient findings are unlikely to be altered by this adjustment.

Our study has limitations. Although this is a single centre study in which the PCI data was collected prospectively, the cardiac marker data was analysed retrospectively which may have lead to an unappreciated bias. Secondly, as both cardiac markers were not measured for all stable CHD patients prior to PCI, we may have occasionally erroneously assumed normality of pre-PCI markers. Other illnesses confounding causes of TnT level elevations other than renal impairment were not evaluated in the current study, [14] though most patients were stable at the time of PCI. Also, as a relatively small number of patients were in the group with ACS and elevated TnT levels but normal CKMB levels, there was insufficient power to determine any (potentially modest) influence of further post-PCI TnT elevations on 1 year outcomes. Finally, we examined the composite late clinical outcome of death and (non-procedural) nonfatal MI as our sample size had limited power to examine associations between late mortality and marker levels as reported from the Mayo Clinic. [134]

6.5. Conclusion

The diagnosis of peri-procedural MI, in ACS patients with elevated pre-PCI TnT levels, was more frequent when a ≥20% increase post-PCI was used as criteria, compared to either a > 3XURL for either TnT (≥ 0.09μg/L) or CKMB. As we confirmed previous reports that elevations in post-PCI TnT levels influenced event-free survival at 1 year only in patients with stable CHD, but not for those post-ACS. Thus with the increase use of troponins, new universal definition of re-infarction based on marker elevations of ≥ 20% above elevated pre-PCI levels will detect any small peri-procedural MIs of questionable prognostic significance suggesting this criteria may need reconsideration.

Chapter 7

General Discussion and Concluding Remarks

Given the improvement in the management of CHD, and advances in PCI, it is important that clinical outcomes are evaluated. Clinical trials are the corner-stone in assessing the effects of these improvements in technology such as the use of different types of stents and antiplatelet therapies. On the other hand, retrospective analysis of registry data from high volume PCI centres can demonstrate the effect of this advancement in “real world” settings. Such analyses are important to detect any unanticipated effects of new technologies.

As PCI has lead to improvements in health outcomes including mortality, in this thesis factors affecting outcomes after PCI were studied in different clinical circumstances. The focus of this thesis has mainly been on: (i) clinical outcomes after selective strategies of DES and BMS use in the management of patients undergoing PCI for various manifestations of CHD, (ii) the clinical outcomes after BMS deployment in large infarct-related coronary arteries, (iii) clinical outcomes following rescue-PCI with higher usage rate of GPIIb/IIIa inhibitors, and selective stent use, and (iv) TnT and CKMB levels in relation to PCI, and late outcomes of death or MI.

The findings of this project are summarised in the following: Firstly, it is possible to use selective criteria for DES / BMS while maintaining relatively low TVR rates and that clinical outcomes including death, MI and TVR rate were comparable between BMS / DES following the application of the selective policy. However, over the first 3 years, first generation DES, used selectively, had more frequent stent thrombosis. Secondly, nearly half of the STEMI patients undergoing PCI had a “large” IRA $\geq$ 3.5mm in diameter and that BMS use in these arteries achieved low TVR rates and had low rates of stent thrombosis. Thirdly, in the era of liberal use of stents and GPIIb/IIIa inhibitors, a mortality rate of 3.2% in unselected patients without pre-PCI

cardiogenic shock, undergoing rescue PCI, is comparable to reported mortality rates of STEMI patients treated with primary PCI. The TVR rate is low with selective strategies of DES in this group of patients. Finally, the diagnosis of peri-procedural MI in ACS patients with elevated pre-PCI TnT levels, was more frequent when a ≥20% increase in levels post-PCI was used as a criterion, compared to either a > 3XURL increase in either TnT (≥ 0.09µg/L) or CKMB. Further, post-PCI TnT levels influenced event-free survival at 1 year only in patients with stable CHD, but not for those following ACS.

7.1. The Diagnostic and Prognostic Significance of Periprocedural Cardiac Markers Elevations

Periprocedural myonecrosis following PCI is an important early clinical outcome that can occur after PCI, and its detection has significant clinical implications for patients. Periprocedural myonecrosis detected by an elevation of cardiac biomarkers after coronary intervention is a common phenomenon. These elevations can range from minor to larger degree elevations.[131] Larger elevations in cardiac biomarkers indicates a greater extent of myonecrosis.

The frequency with which any periprocedural myocardial injury is detected has varied especially with the development of sensitive cardiac biomarkers and cardiac biomarkers assays.[130] Cardiac troponins are a more sensitive cardiac biomarker than CKMB for minor degrees of myocardial damage. Elevated values after PCI with or without stenting are more common than increases in CKMB. [131, 135, 136]

The clinical significance and long-term prognostic importance of periprocedural myonecrosis was uncertain in the early years of PCI. Originally, small studies with short follow-up found no increased risk but subsequent large prospective trials have proved

that higher elevation of markers of myonecrosis following PCI are clinically relevant. [131, 133]

The clinical studies on CKMB post PCI reported that periprocedural cardiac markers elevations are common after PCI, and in most of the cases it is limited to low level elevations. Most studies have suggested that the degree of subsequent risk of mortality correlates with the extent of rise in CKMB levels. There has been debate on the significance of elevated CKMB after percutaneous coronary intervention in 1990s. Previous studies have suggested that only greater elevations of CKMB levels (> 5 times the upper limit of normal [ULN]) independently correlates with mortality after elective PCI. [137-139] Lower levels of CKMB elevations (<3 times ULN) occur more frequently after PCI and the impact of minor degrees of periprocedural myonecrosis on late clinical outcomes cannot be neglected when compared with higher degrees of periprocedural CKMB elevations. In patients with lower levels of CKMB elevations (<3 times the URL) it may be difficult to find evidence of procedural complications and there is persistent debate about whether these enzyme rises are clinically significant. In meta-analysis to assess CKMB levels and survival,[140] 1 to 3 times CKMB elevations increase the risk of death by approximately 50%. The risk is increased by 80% with 3-5 times CKMB elevations and is tripled with over 5 times ULN of CKMB levels. [140] Even in the era of stenting and statin therapy, there was a graded response for CKMB in predicting long-term mortality. [141]

Troponin is a more sensitive and specific myonecrosis biomarkers than other cardiac biomarkers. Following its introduction in the clinical field, many studies have investigated its prognostic significance. Some studies have shown that the serum concentration of cardiac troponin is an independent predictor of survival while other did not.[142-148] This variability is most likely because of heterogeneity of inclusion criteria,

variation in the sensitivity and specificity of the troponin assay used, different sample size and difference in duration of follow-up.

An increase of troponin after PCI is also common and controversies exists about their minor elevations following PCI and that pre-PCI troponins levels may have more prognostic significance. In recent 2 meta-analyses, [142] [143] an increased mortality was significantly associated with troponin elevation after PCI, and combined death or nonfatal MI also occurred more often in patients with post procedural troponin elevation. On the other hand, some other studies do not support the prognostic role of post-procedural troponin elevations and indicate that pre-PCI troponins level may have more prognostic significance. In a study by Miller et al [149], patients with elevated baseline TnT levels had a higher overall cumulative 12-month rate of death or MI compared with those without elevated baseline levels (11.1% vs. 4.7%, $p< 0.05$). After adjustment for baseline risk factors, baseline TnT was a significant predictor of outcomes after PCI (HR, 1.14: 95% CI[1.07 to 1.22], $p<0.001$). Neither the timing nor the magnitude of post-procedural TnT levels elevations were predictive of long-term adverse events when baseline elevations were included in the analysis.

The finding of this study are also supported by another study by Prasad et al, [134] who analyzed 5487 patients undergoing elective PCI using a TnT assay (ULN<0.01 ng/mL). Those with normal pre-PCI TnT levels, post-PCI elevation of TnT occurred in 43% of patients. The 30-day mortality rate was 0.3% versus 2.3% in those patients with pre-PCI TnT <0.01 compared with those who had an elevation of ≥0.01 ng/mL, respectively. Over a median follow-up of 28 months, an abnormal pre-PCI cTnT level was an independent predictor of death (HR: 1.79 [95%CI:1.35–2.39], $p <0.001$), but the occurrence of PCI-related myonecrosis was not. The absolute risk of death from minor, isolated TnT elevations appears to be lower than when there is a pre PCI TnT elevation.

In Chapter 6 of this thesis post-PCI TnT and CKMB elevations and their effect on late clinical outcomes for patients with ACS, and in those with stable CHD were studied. The results from Chapter 6 of this study confirmed previous reports that an elevation of post-PCI TnT and/or CKMB levels for patients with stable CHD had a reduced rate of survival free of death or nonfatal MI at 1 year compared with those without post-PCI marker elevations. [140-143] In patients with ACS undergoing PCI in this project, an elevation of post PCI TnT/CKMB did not influence survival free of death or MI at one year. These support results reported by Prasad, et al [134] which showed that among patients with ACS undergoing PCI, only elevated pre-PCI, and not post-PCI, cardiac marker levels affected the survival rates. Also peri-procedural MI in patients with ACS in the ACUITY trial, [213] did not influence late events, though pre-PCI marker levels did. However, in the ACUITY trial a significant fraction of patients had angiography and angioplasty within 12 -18 hours of presentation. Although there were explicit criteria for clinical events committee for adjudication of MI, [213] a proportion of these potential early peri-procedural events may not have been confirmed because of uncertainty about early elevation profiles in marker levels.

In contrast, because of the cardiac marker selection criteria for this study, we did not include patients who had 'early' angiography and angioplasty. Also, whether the ACUITY investigators made gender–specific adjustments for CKMB reference ranges is not clear. However, as in our study because most CHD patients are male, the salient findings are unlikely to be altered by this adjustment.

The definition of periprocedural MI is a matter of debate and varies between clinical trials. The consensus definition of MI published in 2000 initially defined MI, including periprocedural MI, as any rise and fall in cardiac biomarkers (CKMB or troponin) above the ULN.[150] This was followed by a consensus document published in

2007 know as the universal definition of MI. It defined PCI-related MI as an increase of biomarkers (CKMB or troponin) greater than 3 times ULN classified as MI (type 4a). The definition also considered elevations of cardiac biomarkers between 1 and 3 times ULN as indicative of peri-procedural myocardial necrosis but not infarction.[10] This definition applies to patients with normal baseline biomarkers. If the biomarkers levels are elevated and rising prior to PCI, the above document acknowledges that there are insufficient data to recommend biomarker criteria for the diagnosis of PMI. If the biomarkers' levels are stable or falling, recurrent infarction is diagnosed if there is an ≥20% increase of a previously stable or falling elevated levels (troponin or CKMB).[10] However, the 2007 universal MI definition recommended using different levels of elevation of cardiac markers (TnT or CKMB) depending on the clinical situation, either spontaneous MI or post-PCI. Two cardiac marker levels, preferably troponin, one immediate and a further 6 hours later, and an increase of ≥ 20 % TnT above stabilized or falling elevated pre-PCI levels are necessary for cardiac marker based post-PCI re-MI definition, in addition to ECG or imaging. [10, 156]

Troponins are preferred markers for detection of myonecrosis because of their higher specificity and sensitivity compared with CKMB, [135, 136, 152, 153] and their use are now preferred to CKMB for diagnosis of MI, [10, 150, 152, 154] which was confirmed in this thesis (Chapter 6).

Chapter 6 of this thesis also evaluated cardiac marker criteria for periprocedural MI and found that among patients with ACS with elevated pre-PCI TnT levels, diagnosis of periprocedural MI was more frequent when a ≥20% increase post-PCI was used as the criterion, compared to either a > 3XURL for either TnT (≥ 0.09µg/L) or CKMB. Further, when there were minor elevations in pre-PCI TnT levels, the 2007 universal definition of MI lead to small further elevations of ≥20% in TnT levels being

diagnosed as (small) re-infarctions that (understandably) did not meet CKMB re-infarction criteria. Conversely, when the pre-PCI TnT level was > 0.8μg/L or 20-30 fold above URL, quite large absolute increases in post-procedural TnT levels did not meet ≥20% increased in TnT re-infarction criterion, though the > 3XURL CKMB elevation re-MI criterion was met.

The results of this study also support the results of study by Lim et al, [214] published in the same period, which showed that there is differentiation issues in evaluating periprocedural MI by using CKMB and troponins. Troponin thresholds may need to be adjusted to differentiate infarction from periprocedural myonecrosis. At present, there is no established cut-off value for troponin that accurately defines periprocedural MI (especially if the baseline troponin is elevated). In this context, CKMB would still appear to be an appropriate criterion for defining PMI. The more recently published third universal definition of myocardial infarction raise the threshold for troponin in defining periprocedural MI to > 5 times URL (arbitrary defined).[151]

An improvement in the technical safety of coronary stent procedures, second-generation DES, and adjunctive pharmacological therapies may lead to reduction of the periprocedural myonecrosis. An analysis from a trial comparing everolimus-eluting versus paclitaxel-eluting stents found no impact of periprocedural myocardial enzyme elevation, [215] whether a historic or an updated definition, on mortality at 30 days, 1 year, or 2 years. However, this study had low overall mortality rates and excluded high-risk patients along with patients with pre-procedural cardiac enzyme elevations.

The just published new universal definition of MI appears to loosen the post-PCI MI definition compared to the previous version.[10, 151] Of the 38% patients who had post PCI 4th generation TnT levels >0.03 μg/l, ~3/4 of these (29%) had TnT levels >0.07 μg/l, which equates approximately to an HS TnT level of >5X the upper reference limit

(>70ng/l). In our study most of these did not have ischaemic ECG changes, periprocedural imaging (invasive or non-invasive) abnormalities detected, and their procedural chest pain could be ascribed to stent deployment. Thus we consider the number patients defined as having peri-procedural MI is likely to markedly reduce in both routine practice and clinical trials. What implications this definition change may have in terms of the prognostic significance of post PCI marker elevations in stable CHD patients, both described here and by others,[134, 213] should be the subject of future studies.

Finally, It would be interesting to see what the effects would be when high-sensitivity troponin assays,[155] now used in many centres, are adopted by the ESC and ACC to define periprocedural MI. This could further complicate differentiating minor periprocedural myonecrosis from large infarction.

7.2. Clinical Outcomes after Drug-eluting and Bare-metal Stents

The introduction of BMS has reduced acute obstruction rates and thus periprocedural MI and late restenosis and more importantly TVR. [39, 40] While DES have further reduced TVR rate, [48-50, 119] problems with ST, prolonged dual antiplatelet therapy, and safety and costs of DES, particularly in public hospitals are concerns among cardiologists. [111, 170, 172, 173, 216-218] Paralleling this technolgy evolution has been the evolving elements of stenting in urgent constraints for ACS.

Current clinical practice guidelines recommend 12 months of dual antiplatelet therapy after placement of a DES in patients who are not at high risk of bleeding. However longer concerns about occurrence of ST after 12 months and duration of dual antiplatelet therapy beyond 12 months is uncertain.

The premature discontinuation of clopidogrel therapy is associated with a marked increase in the risk of stent thrombosis and it is the leading independent predictor for stent thrombosis. In a large observational cohort study of patients treated with DES, overall stent thrombosis rate was 1.3%.[111] It occurred in 29% of patients in whom antiplatelet therapy was discontinued prematurely. This discontinuation of antiplatelet therapy was in independent predictor of stent thrombosis. [110, 111 104]

Another concern about use of dual antiplatelet therapy is the bleeding risk. There have been concerns about the risk of bleeding when using clopidogrel in addition to aspirin. When compared with aspirin, clopidogrel is associated with lower risk of gastrointestinal bleeding.[219] However, when clopidogrel was combined with aspirin and administered for prolonged duration (up to 28 months), randomised trials demonstrated an absolute increase (ranging from 0.4% to 1.0%) in major bleeding, compared with aspirin alone.[219]

Stent selection (either DES or BMS) in emergency setting of STEMI can be affected by the informed consent of the patients as many physicians have concern about the compliance with dual antiplatelet therapy following stent deployment. Informed consent especially for compliance with dual antiplatelet therapy following DES is needed to facilitate the decision about stent selection. However in emergency settings of STEMI, patient's relative ability to comprehend information in relation to consent about the compliance with dual antiplatelet therapy might be impaired by factors such as anxiety, fear, pain, and the effects of morphine. [181]

In addition to the above, the presence of diabetes mellitus, coronary artery lesion length, lesion complexity, culprit coronary vessel diameter and ostial lesions are factors associated with high restenosis rate and therefore high TVR rate. [41-46] These factors suggest that strategies of selective DES use to minimize the harm and maximize benefit

from reduction of restenosis is potentially attractive approach. These strategies also have an impact on the cost of using DES, particularly in public hospital.[170]

Chapter 3 of this thesis examined clinical outcomes after adoption of selective criteria for DES deployment. DES were deployed in 29% of patients at highest risk of restenosis and 92% of these patients met the institution's selective use criteria. Selective DES use criteria could be an explanation for similar clinical outcomes including TVR rates in patients with DES and BMS. The TVR rate at 1 year in low risk patients with BMS is lower than that reported in randomised trials and lower than that from registries without selective DES use, [49, 50] whereas registries tend to reflect outcomes after individual clinician's decision about stent choice rather than specific criteria for DES such as reported here. Similar criteria were later adopted by the NSW Department of Health in Australia and the National Institute for Clinical Excellence in United Kingdom.[172, 173]

From the results of Chapter 4 of this thesis, following DES use criteria, overall TVR rate for STEMI patients treated with BMS was 5.8%, which was somewhat lower than the 8.7% rate reported in HORIZONS-AMI trial in which there were no DES use criteria [91, 93]. In the HORIZONS-AMI trial about 32% of patients had none of the 3 risk factors associated with re-stenosis, (insulin-requiring diabetes, reference vessel diameter ≤3mm, and lesion length ≥30mm), there were no differences in event rates between patients receiving BMS and DES with TLR rates at 12 months of 3.3% and 3.2% respectively [93]. A comparable rate of patients with none of these 3 risk factors (36%) among patients with STEMI were observed in this project, and the TLR rate in this subgroup was 2.5% for BMS. (Chapter 4)

Continued improvement in DES technology, in terms of drugs, polymers, and delivery platforms, has resulted in newer generations of DES which achieve better

clinical results, with clinically lower rates of restenosis and stent thrombosis. [176, 220] The restenosis rate and thus TVR rates are expected to be reduced further. While the risks of stent thrombosis appear lower with newer generation of DES compared with BMS, uncertainties regarding the risks of very late stent thrombosis still exist , which may continue to occur after the first years after stent implantation. Further data is required in large RCTs to confirm whether bio-absorbable stents may be the solution to this.

A recent report from the Temporal Analysis of the Multicenter Evaluation of Drug Eluting Stents and Ischemic Events (EVENT) registry reported overall TVR rates at 1 year during two eras, firstly liberal DES use (92%, 2004-2006) and secondly "somewhat restrictive" DES use (68%, 2007), of 5.6% and 6.5% respectively. These rates were comparable to the overall TVR rate of 5.7% with selective DES criteria targeting patients with perceived high risk of restenosis (29% DES use), as noted in Chapter 3. Recently published results from the Swedish Coronary Angiography and Angioplasty Registry (SCAAR) have shown lower rates of both restenosis and stent thrombosis with the use of second generation DES, compared with first generation DES use.[176] Given these results, it will be interesting to know what effect of newer generation DES on the TVR rate with both restrictive and liberal use approaches.

The selective criteria for DES deployment aimed to use ~30% DES and maintain 'acceptably' low TVR rates. The analyses and follow-up of the entire 9 year cohort of patients (~7500) who underwent PCI after the introduction of the selective DES use policy described here, would allow modelling of various scenarios of potentially acceptable TVR rates such as 3%, 4%, 5% to refine criteria for DES use in the future. These criteria may varied slightly depending on the patient's indication for PCI, STEMI, NSTEACS or stable CHD. While we may speculate from our data that somewhat more liberal selective DES use criteria (~50-60% use) may lead to lower

overall TVR rates, analyses of our larger cohort would help identify what that proportion of patients should be. Such analyses could facilitate refinement of a "risk score for TVR" such as reported from HORIZONS-AMI.[93]

When patients tolerate and adhere to the prescribed dual antiplatelet therapy, DES should be the treatment of choice for patients who are at high risk of restenosis. In patients with lower risk of restenosis and those in whom prolonged dual-antiplatelet therapy may be problematic, BMS deployment can be an alternative. Comparison of selective versus routine DES use especially with the newer generation DES should be undertaken in future randomised clinical trials.

7.3. Bare-metal Stent Use in Large Infarct Coronary Arteries

The introduction of BMS has reduced late restenosis and more importantly TVR. [39, 40] While DES have further reduced the TVR rates, [48-50, 119] problems with ST and prolonged dual antiplatelet therapy and DES safety and costs particularly in public hospitals are concerns among clinicians. [111, 170, 172, 173, 216-218] Because of these issues, use of BMS in certain situations such as in large coronary arteries is worth investigation.

There is an inverse relationship between vessel size and TVR rate with the use of BMS.[123] The diameter of culprit lesion segments of diseased coronary artery is an important determinant of restenosis and TVR [46, 93, 124-127 128].

In the previous studies, the definition of a "large" coronary artery is unclear with "cut-off points" of 3mm and 3.5mm. [125-128] From the results of the project in Chapter 4, among patients with STEMI, 45% had PCI to the coronary arteries of ≥3.5mm in diameter and the TVR in this group was low. In addition to this, there were significantly higher TVR rates for BMS in intermediate arteries of 3 to <3.5mm, and small arteries

(<3mm) were also observed, both ~9%. It appeared that the use of 3mm as a cut-off point for large coronary arteries is too low at least in the context of BMS. In contrast to trials exploring cut points of vessel size at 3mm in diameter in relation to restenosis rates, our data suggests that restenosis rate following BMS deployment approach DES rates at vessel size of ≥3.5mm in diameter, and lesion length was not as powerful approach of restenosis.

In Chapter 4 of this thesis, clinical outcomes after PCI performed during the index hospitalization in STEMI patients were studied, particular after BMS deployment in large coronary arteries. The result of this study demonstrated that BMS use in large (≥3.5mm) coronary arteries is associated with low rates of TVR (2.2%) compared to smaller coronary arteries, including vessels of 3-3.49mm in diameter.

It is important that the other risks of restenosis, other than vessel size for example diabetic mellitus, lesion complexity and lesion length should be considered.[93] In these context, using DES in such patients at high risk for coronary restenosis and using BMS for those with lower restenosis risk is an important approach, as discussed in Chapter 3 and also discussed in the section above.

It will be important to evaluate the efficacy of newer DES versus newer BMS under the treatment of newer antiplatelet regimens in large coronary arteries, as there is still no evidence on this issue. Therefore, comparison of TVR rates between newer BMS and newer generation DES in large (≥ 3.5mm) coronary arteries in patients with STEMI requires further randomised trials with appropriate sample size.

7.4. Rescue PCI in the Era of Liberal Use of Stents and GPIIb/IIIa Inhibitors

The main goal in the treatment of patients with STEMI is to restore oxygenated coronary blood flow to myocytes. While primary PCI is a superior reperfusion strategy to fibrinolytic therapy alone, [66] for several reasons many patients world-wide receive fibrinolytic therapy as an initial reperfusion strategy. [74] Because the rate of failed reperfusion is observed in a significant proportion of patients, ranging from 25% to 30%, according to the time of treatment, [65, 71, 188] the prognosis of these patients is worse as compared with those successfully reperfused. [65]

Pharmaco-invasive strategies which entail the administration of fibrinolytics followed by emergent transfer for PCI within a short time window (6 hours), have shown greater promise for the clinical benefit over more conservative strategies. [70, 71] Fibrinolytic-treated patients should be recommended for immediate angiography and if indicated rescue PCI if they have failed to reperfuse. Five randomised clinical trials have shown improved outcomes compared to conservative management. [74, 75, 77, 78] .

Among early presenting patients, a pharmaco-invasive strategy may have benefit. This may be because an early successful rescue PCI enhance myocardial salvage and lower mortality. [72, 186] The CAPTIM and WEST investigators recently reported retrospective pooled analyses of the subgroup presenting within 2 hours of symptom-onset. [72] A late mortality benefit occurred among those who received fibrinolysis (mostly pre-hospital, with a 25-30% rate of rescue PCI and ~70% in-hospital PCI), compared to primary PCI. The STREAM trial is prospectively evaluating a pharmaco-invasive strategy in STEMI patients presenting within 3 hours of symptom

onset to non-PCI centres. [73] In the rescue PCI study (Chapter 5), ~75% of patients who underwent rescue PCI had presented to hospital within 2 hours of symptom-onset.

Several randomised trials have been conducted to establish the benefits of rescue angioplasty after failed reperfusion. [75-78] However these trials, and more recent reports from registries,[75, 77-79, 189, 190] have included significant proportions of patients who did not receive fibrin-specific therapies, stents (including DES) or GPIIb/IIIa antagonists. Data is still lacking on the efficacy and safety of rescue PCI performed in a "real-world" setting, in the contemporary clinical practice with use of DES stent and GPIIb/IIIa inhibitor.

In this context, Chapter 5 of this thesis studies clinical outcomes after rescue PCI in the era of use of fibrin-specific lytics, higher rate of GPIIb/IIIa inhibitors, and stenting, and found that the mortality rate of 3.2% in unselected patients without prior shock undergoing rescue PCI is low and comparable to that of STEMI patients treated with primary PCI. The mortality rates of 3.2% and 5.3% at day-30 and 1 year respectively are comparable to those reported for primary PCI in patients without pre-PCI shock similar to mortality in the APEX AMI trial. [197] These data suggest that a pharmaco-invasive approach to STEMI with rescue PCI is a reasonable strategy when expeditious access to primary PCI is not avilable, especially in early presenting patients.

The risk of serious bleeding has been concern among clinician performing PCI, in the first few hours after full-dose fibrinolytic therapy, including rescue PCI. There was an increased risk of minor bleeding associated with rescue PCI in the meta-analysis by Wijeysundera et al. [78] However, the REACT trial found no differences in major bleeding rates in the rescue PCI and conservative arms.[77] Although the radial artery approach to rescue PCI has been reported to be associated with low rates of transfusion

compared with those reported with the femoral approach, bleeding risk after rescue-PCI is still a concern.

The use of GPIIb/IIIa inhibitors after fibrinolytic therapy in the setting of PCI in the early hours after symptom onset has been contentious, given clinician concerns about balancing bleeding risks with risks of recurrent ischemic events. Some small non-randomised studies on GPIIb/IIIa use in this setting, [202-205] have reported TIMI major bleeding of 6.9% and 12% among patients who underwent rescue PCI and received GPIIb/IIIa inhibitors. [203, 204] In this context in Chapter 5, there was approximately 80% rate of GPIIb/IIIa inhibitor use with rescue PCI. This was not associated with an increased bleeding risk.

Several factors may have contributed to the differences in the bleeding rate after rescue PCI among older studies, such as the use of smaller arterial sheath calibre, and improvements in pharmaco-therapies including lower heparin doses associated with lower activated clotting times. Whether lower rates of bleeding occur in this setting, using thrombin inhibition with bivalirudin, compared to unfractionated heparin and GPIIb/IIIa inhibitors, as occurred in different groups of acute coronary syndrome patients in ACUITY and HORIZONS-AMI trials is under investigation.

To identify the best strategy among patients after fibrinolytic therapy, especially in the era of stenting and use of GPIIb/IIIa inhibitors, further trials with a large sample size in this context are needed. In addition, the non-invasive identification of patients with failed thrombolysis continues to complicate evaluation for further treatment. In fact, reduction in chest pain, decrease in ST-segment elevations, presence of arrhythmias, and trends of biochemical markers, although suggestive of reperfusion, may not be diagnostic.

7.5. Final Concluding Points and Future Directions

- It is possible to use selective criteria for DES / BMS while maintaining low TVR rates, and that clinical outcomes including death, MI, and TVR rate were comparable between BMS and DES following this selective policy. Comparison of selective versus routine DES use especially with the newer generation DES should be considered in further randomised clinical trial. More liberal selective DES use criteria (~50-60% use) may lead to lower overall TVR rates, analyses of our larger cohort would help identify what that proportion of patients should be. Such analyses could facilitate refinement of a "risk score for TVR" such as reported from HORIZONS-AMI.

- Nearly half the STEMI patients undergoing PCI had a "large" IRA ≥ 3.5mm in diameter and that BMS use in these vessels achieved low TVR rates and had low rates of stent thrombosis. Comparison of TVR rates between BMS and 2nd generation DES especially in large (≥ 3.5mm) with newer antiplatelet regimens in patients with STEMI requires further randomised trials with appropriate sample size.

- In the era of liberal use of stents and GPIIb/IIIa inhibitors, a mortality rate of 3.2% in unselected patients without pre-PCI cardiogenic shock undergoing rescue PCI is comparable to that of STEMI patients treated with primary PCI. The TVR rate is also acceptably low using selective strategies of DES in this group. These data suggest that a pharmaco-invasive approach to STEMI with rescue PCI is a reasonable strategy when expeditious access to primary PCI is

unavailable, especially among patients presenting early. Further trials with a large sample size in this context are needed.

- The diagnosis of peri-procedural MI, in ACS patients with elevated pre-PCI TnT levels, was more frequent when a ≥20% increase post-PCI was used as criterion, compared to either a > 3XURL for either TnT (≥ 0.09µg/L) or CKMB, and that post-PCI TnT levels influenced event-free survival at 1 year only in patients with stable CHD, except for those following ACS. Thus with the increased use of troponins, new universal definition of re-infarction based on marker elevations of ≥ 20% above elevated pre-PCI levels will detect any small peri-procedural MIs of questionable prognostic significance suggesting. This criteria may need reconsideration.

7.6. Summary

This thesis has examined issues of management of patients undergoing PCI specifically with selective DES use criteria and thus requirements for a year of dual antiplatelet therapy. While an 'acceptably' low TVR rate has been observed with this selective stent use policy and with use of BMS in infarct related coronary arteries ≥3.5mm in diameter, using 30% DES is probably too low given the TVR rate in 3mm arteries, so more liberal criteria may be needed. Further, with high rates GPIIb/IIIa inhibitors with stenting among those undergoing rescue PCI for STEMI, comparable rates of mortality to those with primary PCI, especially patients presenting early, suggesting that a pharmaco-invasive approach to STEMI with rescue PCI in early presenters is a reasonable strategy when there is not ready access to primary PCI. Further clinical trials with a large sample

size in this context are needed. Finally, the prognostic importance of periprocedural MI in elective PCI needs further clarification especially given the recent altered universal definition of MI.

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Appendix

A - Data Collection.

B - Publications.

1- Data collected for studies in chapters 3 and 4 (DES/BMS /CHD /PCI Studies)

Identification:

Name: _____ Gender: M □ F □

DOB: ___/___/___ Age: _____ CRSID:_____ MRN: _____

PCI date: ___/___/___ Weight: _____kg Height: _____cm BMI:_____

Risk factors:

DM □ Smoking □ HT □ Family History of IHD □ Hyperlipidemia □ Previous Aspirin use □

Previous PCI □ Date of prior PCI: _____/ ___/____

Previous CABG □ Date of prior CABG: _____/ ___/____

Presentation:

Stable CHD □

UA □

NSTEMI□

STEMI□ Primary□ / Rescue□ / Prognostic □

Cardiogenic Shock before PCI □

PCI data:

PCI date: ___ /____ / ____ PCI time: Start ____ (am/pm) Finish ___ (am/pm)

Access site: Femoral □ Radial □ Brachial□

Culprit vessel	Site of the lesion	% of sten.prePCI	% of sten. post-PCI
- LM □	ostial□ / proximal□/mid□ /distal□	___	___
- LAD □	ostial□ / proximal□/mid□ /distal□	___	___
- LCx □	ostial□ / proximal□/mid□ /distal□	___	___
- RCA □	ostial□ / proximal□/mid□ /distal□	___	___
- Arterial Graft □	ostial□ / proximal□/mid□ /distal□	___	___

- Venus Graft □ ostial□ / proximal□/mid□ /distal□ ___ ___

Number of Diseased Vessels SVD □ DVD □ TVD □

Number of treated Vessels _____

Lesion length _____ mm

Lesion Class (ACC/AHA Classification) A □ B1 □ B2 □ C □

Lesion Classification □ Lesion at Bifurcation □

Rotablation □

Intervention /Type of stent used:

DES □ stent name _____, Diameter _____ mm , length _____

BMS □ stent name _____, Diameter _____ mm , length _____

DES and BMS □ stent names_____, Diameter _____ mm , length _____

POBA only □ Met DED criteria: Yes □ No □

Number of stents _____

Total stented length _____

Largest Balloon diameter size used for dilatation _____mm

Maximum pressure used _____ atm

Maximum duration of applied pressure _____ sec

Dissection □

TIMI flow grade after intervention: I □ II□ III□

Complications □ _____

Antiplatelet:

Aspirin □

Clopedogrile loading □ Dose _____ mg

GPIIb/IIIa inhibitors Tirofiban □ Abciximab□ Ebtifibatide□

Clinical outcomes:

Date of follow-up: _____/____/_____

Death Yes □ No □ _____/____/_____

Cause of death _____ (Cardiac □ Non-Cardiac □)

Instent restenosis : Yes □ No □ Date: _____/____/_____

Stent thrombosis: Yes □ No □ Date: _____/____/_____Time: _____

Target Vessel Revascularization: Yes □ No □

Date: _____/____/_____ CABG □ Repeat PCI □

Target lesion Revascularization: Yes □ No □

Date: _____/____/_____ CABG □ Repeat PCI □

Myocardial Infarction: Yes □ No □ Date: _____/____/_____

Comments: _____

_____

_____

2- Data collected for the study in chapter 5 (Rescue-PCI Study)

Identification:

Name: _____ Gender: M □ F □

DOB: ___/___/___ Age: _____ CRSID: _____ MRN: _____

PCI date: ___/___/___ Weight: _____kg Height: _____cm BMI:_____

Risk factors:

DM □ Smoking □ HT □ Family History of IHD □ Hyperlipidemia □ Previous Aspirin use □ Previous MI □

Previous PCI □ Date of prior PCI: _____/ ___/____

Previous CABG □ Date of prior CABG: _____/ ___/____

Presentation:

STEMI□ Rescue□

Cardiogenic Shock before PCI □

Cardiogenic Shock after PCI □

Date of Chest pain onset: _____ Time of onset: _____

Date of presentation to ED: _____ Time of presentation to ED: _____

Date of cardiology referral: _____ Time of cardiology referral: _____

Date of patient leaving ED: _____ Time of patient leaving ED: _____

Date of arrival at LDH CCL: _____ Time of arrival at LDH CCL: _____

Date of 1st balloon inflation: _____ Time of 1st balloon inflation: _____

Date of completion of PCI: _____ Time of completion of PCI: _____

PCI data:

PCI date: ___ /____ / ____ PCI time: Start ____ (am/pm) Finish ___ (am/pm)

Access site: Femoral □ Radial □ Brachial□

Culprit vessel	Site of the lesion	% of sten.prePCI	% of sten. post-PCI
- LM □	ostial□ / proximal□/mid□ /distal□	___	___
- LAD □	ostial□ / proximal□/mid□ /distal□	___	___

- LCx □ ostial□ / proximal□/mid□ /distal□ ___ ___

- RCA □ ostial□ / proximal□/mid□ /distal□ ___ ___

- Arterial Graft □ ostial□ / proximal□/mid□ /distal□ ___ ___

- Venus Graft □ ostial□ / proximal□/mid□ /distal□ ___ ___

Number of Diseased Vessels SVD □ DVD □ TVD □

Number of treated Vessels _____

Lesion length _____ mm

Lesion Class (ACC/AHA Classification) A □ B1 □ B2 □ C □

Lesion Classification □ Lesion at Bifurcation □

Rotablation □

Intervention /Type of stent used:

DES □ stent name _____, Diameter _____ mm , length _____

BMS □ stent name _____, Diameter _____ mm , length _____

DES and BMS □ stent names_____, Diameter _____ mm , length _____

POBA only □

Number of stents _____

Total stented length _____

Largest Balloon diameter size used for dilatation _____mm

Maximum pressure used _____ atm

Maximum duration of applied pressure _____ sec

Dissection □

TIMI flow grade after intervention: I □ II□ III□

Complications □ _____

Antiplatelet:

Aspirin □

Clopedogrile loading □ Dose _____ mg

GPIIb/IIIa inhibitors Tirofiban □ Abciximab□ Ebtifibatide□

ECG data:

ECG on presentation□ date: _____ time: _____

ECG prior to PCI/ EST □ date: _____ time: _____

ECG post PCI/ EST □ date: _____ time: _____

ECG on discharge □ date: _____ time: _____

Clinical outcomes:

Stroke: Yes □ No□ date _____/____/_____ Hemorrhagic □ Infarction □

Bleeding: Yes □ No□ date _____/____/_____ TIMI: major □ minor □

Transfusion Yes □ No□ date _____/____/_____

No. of units transfused: _____

Heart failure: Yes □ No □ date _____/____/_____ NYHA class: _____

Death Yes □ No □ date _____/____/_____

Cause of death _____ (Cardiac □ Non-Cardiac □)

Instent restenosis : Yes □ No □ Date: _____/____/_____

Stent thrombosis: Yes □ No □ Date: _____/____/_____Time: _____

Target Vessel Revascularization: Yes □ No □

Date: _____/____/_____ CABG □ Repeat PCI □

Target lesion Revascularization: Yes □ No □

Date: _____/____/_____ CABG □ Repeat PCI □

Myocardial Infarction: Yes □ No □ Date: _____/____/_____

Follow-up date : _____/____/_____

Comments: _____

_____

_____

3- Data collected for the study in chapter 6 (Cardiac Biomarkers/PCI Study)

Identification:

Name _____ Gender: M □ F □

DOB ___/___/___ Age _____ CRSID_____ MRN _____

PCI date: ___/___/___ Weight: _____kg Height: _____cm BMI_____

Risk factors:

DM □ Smoking □ HT □ Family History of IHD □ Hyperlipidemia □ Previous Aspirin use □

Previous PCI □ Date of prior PCI: _____/ ___/____

Previous CABG □ Date of prior CABG: _____/ ___/____

Presentation:

Stable CHD □

UA □

NSTEMI□

STEMI□

Cardiogenic Shock before PCI □

PCI data:

PCI date: ___ /____ / ____ PCI time: Start ____(am/pm) Finish ___ (am/pm)

Access site: Femoral □ Radial □ Brachial□

Culprit vessel	Site of the lesion	% of sten. prePCI	% of sten. post-PCI
- LM □	ostial□ / proximal□/mid□ /distal□	___	___
- LAD □	ostial□ / proximal□/mid□ /distal□	___	___
- LCx □	ostial□ / proximal□/mid□ /distal□	___	___
- RCA □	ostial□ / proximal□/mid□ /distal□	___	___
- Arterial Graft □	ostial□ / proximal□/mid□ /distal□	___	___
- Venus Graft □	ostial□ / proximal□/mid□ /distal□	___	___

Number of Diseased Vessels SVD □ DVD □ TVD □

Number of treated Vessels _____

Lesion length _____ mm

Lesion Class (ACC/AHA Classification) A □ B1 □ B2 □ C □

Lesion Classification □ Lesion at Bifurcation □

Rotablation □

Intervention /Type of stent used :

DES □ stent name _____, Diameter _____ mm , length _____

BMS □ stent name _____, Diameter _____ mm , length _____

DES and BMS □ stent names_____, Diameter _____ mm , length _____

POBA only □

Number of stents _____

Total stented length _____

Largest Balloon diameter size used for dilatation _____mm

Maximum pressure used _____ atm

Maximum duration of applied pressure _____ sec

Dissection □

TIMI flow grade after intervention: I □ II□ III□

Complications □ _____

Antiplatelet:

Aspirin □

Clopedogrile loading □ Dose _____ mg

GPIIb/IIIa inhibitors Tirofiban □ Abciximab□ Ebtifibatide□

ECG data:

ECG prior to PCI □ date: _____ time: _____

ECG post PCI □ date: _____ time: _____

Laboratory Data:

- Pre-PCI Creatinine value: _____ Date: _____ Time: _____

- Pre-PCI eGFR value: _____ Date: _____ Time: _____

- Post-PCI Creatinine value: _____ Date: _____ Time: _____
- Post-PCI eGFR value: _____ Date: _____ Time: _____
- Pre-PCI Hb value: _____ Date: _____ Time: _____
- Post-PCI Hb value: _____ Date: _____ Time: _____
- Pre-PCI WBC value: _____ Date: _____ Time: _____
- Post-PCI WBC value: _____Date: _____ Time: _____
- Pre-PCI Platelet value: _____ Date: _____ Time: _____
- Post-PCI Platelet value: _____ Date: _____ Time: _____
- Pre-PCI CK value: _____ Date: _____ Time: _____
- Post-PCI CK value: _____ Date: _____ Time: _____
- Pre-PCI CKMB value : _____Date: _____ Time: _____
- Post-PCI CKMB value: _____Date: _____ Time: _____
- Pre-PCI TnT value : _____ Date: _____ Time: _____
- Post-PCI TnT value: _____ Date: _____ Time: _____

Clinical outcomes:

Death Yes □ No □ date _____/____/_____

Cause of death _____ (Cardiac □ Non-Cardiac □)

Instent restenosis : Yes □ No □ Date: _____/____/_____

Stent thrombosis: Yes □ No □ Date: _____/____/_____Time: _____

Target Vessel Revascularization: Yes □ No □

Date: _____/____/_____ CABG □ Repeat PCI □

Target Lesion Revascularization: Yes □ No □

Date: _____/____/_____ CABG □ Repeat PCI □

Myocardial Infarction: Yes □ No □

Date: _____/____/_____

Follow-up date : _____/____/_____

Comments: _____

_____

_____

Bare-metal stenting of large coronary arteries in ST-elevation myocardial infarction is associated with low rates of target vessel revascularization

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Background During percutaneous coronary intervention (PCI) performed in the emergent setting of ST-segment elevation myocardial infarction (STEMI), uncertainty about patients' ability to comply with 12 months dual antiplatelet therapy after drug-eluting stenting is common, and thus, selective bare-metal stent (BMS) deployment could be an attractive strategy if this achieved low target vessel revascularization (TVR) rates in large infarct-related arteries (IRAs) (≥3.5 mm).

Methods and results To evaluate this hypothesis, among 1,282 patients with STEMI who underwent PCI during their initial hospitalization, we studied 1,059 patients (83%) who received BMS, of whom 512 (48%) had large IRAs ≥3.5 mm in diameter, 333 (31%) had IRAs 3 to 3.49 mm, and 214 (20%) had IRAs <3 mm. At 1 year, TVR rate in patients with BMS was 5.8% (2.2% with large BMS [≥3.5 mm], 9.2% with BMS 3-3.49 mm [intermediate], and 9.0% with BMS <3.0 mm [small], $P < .001$). The rates of death/reinfarction among patients with large BMS compared with intermediate BMS or small BMS were lower (6.6% vs 11.7% vs 9.0%, $P = .042$). Among patients who received BMS, the independent predictors of TVR at 1 year were the following: vessel diameter <3.5 mm (odds ratio [OR] 4.39 [95% CI 2.24-8.60], $P < .001$), proximal left anterior descending coronary artery lesions (OR 1.89 [95% CI 1.08-3.31], $P = .027$), hypertension (OR 2.01 [95% CI 1.17-3.438], $P = .011$), and prior PCI (OR 3.46 [95% CI 1.21-9.85], $P = .02$). The predictors of death/myocardial infarction at 1 year were pre-PCI cardiogenic shock (OR 8.16 [95% CI 4.16-16.01], $P < .001$), age ≥65 years (OR 2.63 [95% CI 1.58-4.39], $P < .001$), left anterior descending coronary artery culprit lesions (OR 1.95 [95% CI 1.19-3.21], $P = .008$), female gender (OR 1.93 [95% CI 1.12-3.32], $P = .019$), and American College of Cardiology/American Heart Association lesion classes B2 and C (OR 2.17 [95% CI 1.10-4.27], $P = .026$).

Conclusion Bare-metal stent deployment in STEMI patients with IRAs ≥3.5 mm was associated with low rates of TVR. Their use in this setting warrants comparison with second-generation drug-eluting stenting deployment in future randomized clinical trials. (Am Heart J 2013;165:591-9.)

Primary percutaneous coronary intervention (PCI) is the preferred reperfusion strategy for patients presenting with ST-segment elevation myocardial infarction (STEMI) when performed in a timely manner by a skilled cardiac catheterization laboratory team.[1-3] Patients with STEMI without access to primary PCI undergo angiography and usually PCI at some stage during their initial hospitalization.[4,5] Randomized clinical trials in selected populations and registries of STEMI patients have shown that drug-eluting stents (DES) reduce restenosis and target vessel revascularization (TVR) rates compared with bare-metal stents (BMS).[6-11] Decisions about stent selection, either DES or BMS, in the emergency setting of STEMI are complicated by patients' relative inability to provide informed consent.[12] In particular, clinicians have concerns about patient compliance with 1 year of dual antiplatelet therapy recommended currently after DES deployment,[13-15] as premature discontinuation of thienopyridine therapy is a major risk factor for stent thrombosis.[16] The diameter of culprit lesion segments of infarct-related arteries (IRA) is an important determinant of restenosis and TVR.[17-20]

In this study, we examined clinical outcomes of consecutive, unselected patients with STEMI undergoing

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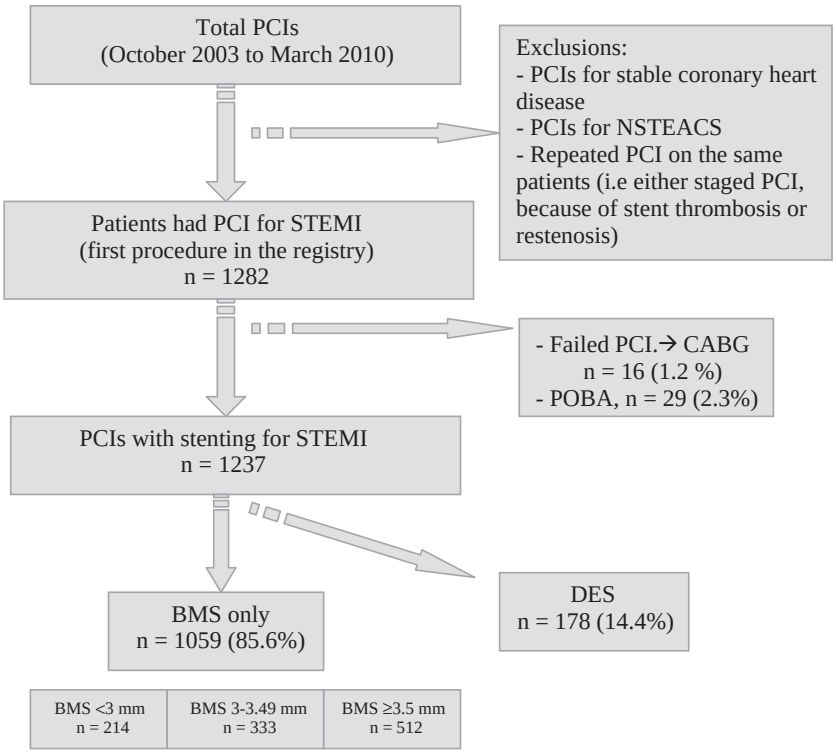
Figure 1



Study population. DES, drug-eluting stents (169 [95%] first generation); NSTEACS, non–ST-segment elevation acute coronary syndromes; POBA, plain old balloon angioplasty.

PCI with BMS, as we considered that IRAs ≥3.5 mm in diameter may be common. Furthermore, we hypothesized that, in these patients with large IRAs of ≥3.5 mm, BMS deployment may be associated with low TVR rates.

Methods

Study population

In this study, among 1,282 consecutive patients with STEMI undergoing PCI at Liverpool Hospital (Sydney, Australia) during their index hospitalization between October 2003 to March 2010 were studied; 1,059 (83%) received BMS (see Figure 1). Until May 2006, primary PCI was performed only on STEMI patients who presented to Liverpool Hospital emergency department during working hours. From June 2006, a 24-hour primary PCI service was offered to all patients presenting directly to Liverpool Hospital. Patients from referral hospitals underwent either rescue PCI or PCI after successful fibrinolysis. All patients had clinical, angiographic, and procedural data recorded prospectively in the cardiology department database at Liverpool Hospital as previously described.[21] *ST-segment elevation myocardial infarction* was defined as chest pain of ≥30 minutes and ST-segment elevation ≥1 mm in 2 contiguous leads (or ≥2 mm in 2 contiguous leads V_1-V_3) or new left bundle-branch block, together with elevated levels of cardiac biomarkers (creatine kinase [>2× Upper reference limit (URL)], creatine kinase-MB [>URL], or troponin T [>URL]). The study protocol was approved by South Western Sydney Local Heath District human research ethics committee (QA2008/034).

Percutaneous coronary intervention procedures

Unless contraindicated, aspirin (300 mg) was given immediately at presentation or pre-PCI and continued indefinitely thereafter as 100 to 150 mg/d. Clopidogrel loading dose of 300 or 600 mg was given either upstream or at the time of PCI and continued at 75 mg/d post-PCI and recommended for at least 12 months. A bolus of unfractionated heparin (60-100 U/kg) was given at the start of PCI procedures. The use of BMS (or DES) was according to previously reported criteria.[22] Postdilatation of the stents performed in 69% of patients. Over the study period, the usual approach in the management of patients with multivessel disease, in the absence of cardiogenic shock, was to treat the culprit lesion only at the time of the acute event (unless with inferior myocardial infarction [MI], when there was uncertainty regarding right coronary artery [RCA] and left circumflex coronary artery [LCx] lesions being the culprit). Staged PCI to nonculprit lesions were usually performed at ~1 month. The use of intravenous glycoprotein IIb/IIIa inhibitors, either Tirofiban or Abciximab, was at operator discretion. Statins, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and β-blockers were recommended, unless contraindicated.

Bare-metal stent diameter was defined as the nominal diameter of the postdilatation balloon, or nominal stent size if

Table I. Baseline clinical characteristics

	Patients with BMS					Patients with DES
	All (n = 1059)	**<3 mm (n = 214) (20.2%)**	**3-3.49 mm (n = 333) (31.4%)**	**≥3.5 mm (n = 512)* (48.3%)**	***P*†**	**All (n = 178)**
Age (mean ± SD) (y)	58.8 ± 12	59.8 ± 12.7	59.6 ± 11.7	57.8 ± 12	.042	60.6 ± 12
Age ≥65 y, n (%)	324 (30.6%)	74 (34.6%)	110 (33%)	140 (27.3%)	.079	67 (37.6%)
Male gender, n (%)	858 (81%)	155 (72.4%)	266 (79.9%)	437 (85.4%)‡	<.001	138 (77.5%)
Body mass index (kg/m^2, mean ± SD)	27.98 ± 5.3	27.1 ± 5	27.5 ± 4.7	28.7 ± 5.7‡,§	<.001	27.8 ± 5.9
Diabetes mellitus, n (%)	142 (13.4%)	32 (15.0%)	45 (13.5%)	65 (12.7%)	.716	48 (27%)‖
Hypertension, n (%)	365 (34.5%)	81 (37.9%)	116 (34.8%)	168 (32.8%)	.422	83 (46.6%)‖
Previous aspirin use, n (%)	570 (53.9%)	113 (52.8%)	193 (58.1%)	264 (51.7%)	.172	95 (53.4%)
Hyperlipidemia,¶ n (%)	520 (49.1%)	101 (47.2%)	168 (50.5%)	251 (49%)	.758	113 (63.5%)‖
Current cigarette smoker, n (%)	352 (33.2%)	62 (29.0%)	110 (33.5%)	180 (35.2%)	.271	57 (32%)
Family history of CHD, n (%)	183 (17.3%)	40 (18.7%)	51 (15.3%)	92 (18%)	.505	41 (23%)
Previous PCI, n (%)	30 (2.8%)	5 (2.3%)	10 (3%)	15 (2.9%)	.885	2 (1.1%)
Cardiogenic shock pre-PCI, n (%)	60 (5.7%)	14 (6.5%)	21 (6.3%)	25 (4.9%)	.563	13 (7.3%)
Primary PCI, n (%)	452 (42.7%)	91 (42.5%)	132 (39.6%)	229 (44.7%)	.344	48 (27%)‖
Rescue PCI, n (%)	206 (19.5%)	39 (18.2%)	60 (18%)	107 (20.9%)	.515	35 (19.7%)
PCI after successful thrombolysis, n (%)	401 (37.9%)	84 (39.3%)	14 (42.3%)	176 (34.4%)	.059	95 (53.4%)‖
Thrombolytic use, n (%)	607 (57.3%)	123 (57.5%)	201 (60.4%)	283 (55.3%)	.344	130 (73%)‖

Abbreviation: *CHD*, Coronary heart disease.
*Ten patients had prior CABG (in total 12 patients).
† *P* value for comparison across BMS subgroups (<3 vs 3-3.49 vs ≥3.5 mm) using 1-way ANOVA, if significant post hoc test was performed to indicate significance within BMS subgroups.
‡ $P < .05$ for comparison between BMS ≥3.5 and <3 mm.
§ $P < .05$ for comparison between BMS ≥3.5 and 3 to 3.49 mm.
‖ $P < .05$ for comparison between BMS (all) and DES (all).
¶ Hyperlipidemia defined as previous diagnosis of hypercholesterolemia, including treatment with lipid-lowering agents or fasting low-density lipoprotein cholesterol of ≥130 mg/dL or total cholesterol of ≥200 mg/dL.

no postdilation was performed, and was taken to correspond with the reference diameter of the IRA. Stent diameters were divided into 3 groups: <3 mm (small), ≥3 to <3.5 mm (intermediate), and ≥3.5 mm (large).

Definitions and clinical follow-up

Cardiogenic shock was defined as refractory hypotension (systolic blood pressure <90 mm Hg lasting ≥1 hour) and end-organ hypoperfusion, with or without mechanical support. Significant angiographic coronary stenoses were ≥70%. Lesions were classified according to American College of Cardiology/American Heart Association (ACC/AHA) criteria.[23] Angiographically, successful PCI was defined as <20% final lumen diameter poststenting or <50% post–balloon angioplasty and thrombolysis in myocardial infarction (TIMI) 3 flow.[24]

Clinical follow-up was performed by research staff (nurses and/or physicians). Patients, their next of kin, or primary physicians were contacted by telephone and were asked about recurrent cardiac symptoms requiring hospitalization, need for coronary revascularization, or MI. Data regarding mortality were obtained from medical records, physicians, next of kin, and the state death registry. Other clinical outcomes such as repeated procedures for stent thrombosis (ST) and restenosis were independently verified. *Clinical outcomes* were defined as follows: (1) death, (2) nonfatal reinfarction defined by chest pain lasting ≥30 minutes and accompanied by new electrocardiographic changes (Q waves >0.04 seconds or ST-segment elevation >0.1 mV) and/or further biomarker rise (creatine kinase [>2× URL], creatine kinase-MB [>URL], or troponin T [>URL])[25]; (3) TVR defined as ischemia-driven repeat revascularization of the IRA, requiring repeat PCI or coronary artery bypass graft surgery (CABG)[26]; (4) target lesion revascularization (TLR) defined as repeat PCI of the stented segment within 5 mm of the proximal and/or distal stent edge or CABG.[26] We report definite ST confirmed by angiography, as defined by the Academic Research Consortium.[26]

Data analysis

All statistical analyses were performed using SPSS version 17.0 (SPSS, Inc, Chicago, IL). Categorical variables are presented as numbers and percentages; continuous variables, as mean ± SDs or medians with 25th and 75th percentile. For group comparisons, Pearson χ^2 test or Fisher exact test was used as appropriate for unpaired categorical variables, and the Student *t* test or the Mann-Whitney *U* test was used for continuous variables. One-way analysis of variance (ANOVA) with post hoc Bonferroni test was used to compare more than 2 groups. Univariable and multivariate analyses were performed to determine predictors of TVR and death/ MI among patients with BMS. Univariable analysis included the following variables: age, male gender, body mass index, diabetes mellitus, current smoking, hypertension, previous PCI, hyperlipidemia, pre-PCI cardiogenic shock, presentation for primary, rescue PCI or PCI after successful thrombolysis, culprit lesion (left main, proximal left anterior descending coronary artery [LAD], LCx, and RCA), lesions at bifurcations, lesion classification, ostial lesions, lesion

Table II. Angiographic and procedural characteristics

	Patients with BMS					Patients with DES
	All (n = 1059)	<3 mm (n = 214)	3-3.49 mm (n = 333)	≥3.5 mm (n = 512)	P*	All (n = 178)
Culprit coronary artery, n (%)						
Left main	6 (0.6%)	2 (0.9%)	0 (0%)	4 (0.8%)	.243	7 (3.9%)†
LAD	412 (38.9%)	102 (47.7%)	165 (49.5%)	145 (28.3%)‡,§	<.001	125 (70%)†
LCx	109 (10.3%)	35 (16.4%)	45 (13.5%)	29 (5.7%)‡,§	<.001	13 (7.3%)
RCA	461 (43.5%)	38 (17.8%)	106 (31.8%)	317 (61.9%)‡,§	<.001	25 (14%)†
Bypass graft	13 (1.2%)	0 (0%)	2 (0.6%)	11 (2.1%)‡	.026	1 (0.6%)
Other coronary branches	58 (5.5%)	37 (17.3%)	15 (4.5%)	6 (1.2%)‡	<.001	7 (3.9%)
Lesion type (ACC/AHA), n (%)						
B	628 (59.4%)	130 (60.7%)	211 (63.4%)	287 (56.3%)	.111	100 (56.2%)
C	390 (36.9%)	74 (34.6%)	112 (33.6%)	204 (40%)	.127	72 (40.4%)
Lesions at proximal LAD, n (%)	257 (24.3%)	42 (19.6%)	107 (32.1%)	108 (21.1%)‡	<.001	81 (45.5%)†
Culprit lesions at bifurcation, n (%)	166 (15.7%)	49 (22.9%)	60 (18%)	57 (11.1%)‡,§	<.001	50 (28.1%)†
Culprit lesions calcifications, n (%)	86 (8.1%)	20 (9.3%)	26 (7.8%)	40 (7.8%)	.764	28 (15.7%)†
Ostial lesions, n (%)	44 (4.2%)	9 (4.2%)	15 (4.5%)	20 (3.9%)	.913	26 (14.6%)
Culprit lesion length (mm)‖	18 (14-25)	16 (12-24)	18 (13-24)	20 (15-28)‡	.015	20 (14-30)
Culprit lesion length ≥20 mm, n (%)	510 (48.2%)	87 (40.7%)	145 (43.5%)	278 (54.3%)‡,§	<.001	94 (52.8%)
Total stented length (mm)‖	21 (16-30)	20 (15-30)	20 (16-30)	23 (18-32)‡	.028	23.5 (16-33)
Stent diameter (mm)‖	3 (2.75-3.5)	–	–	–	–	2.75 (2.5-3)†
>1 stent, n (%)	302 (28.5%)	59 (27.6%)	87 (26.1%)	156 (30.5%)	.371	56 (31.5%)
Maximal deployment pressure (atm)‖	18 (16-20)	16 (14-18)	18 (16-20)	18 (16-20)‡,§	<.001	18 (16-20)
Maximal duration of deployed pressure (s)‖	25 (20-30)	25 (20-30)	25 (20-30)	25 (20-30)	.984	29 (20-30)
No. of diseased vessles¶						
1-vessel disease	636 (60.1%)	117 (54.7%)	199 (59.8%)	320 (62.5%)	.145	109 (61.2%)
2-vessel disease	311 (29.4%)	72 (33.6%)	102 (30.6%)	137 (26.8%)	.148	46 (25.8%)
3-vessel disease	112 (10.6%)	25 (11.7%)	32 (9.6%)	55 (10.7%)	.734	23 (12.9%)
Glycoprotein IIb/IIIa inhibitor, n (%)					.707	
Tirofiban	314 (29.7%)	66 (30.8%)	102 (30.6%)	146 (28.5%)		55 (30.9%)
Abciximab	164 (15.5%)	25 (11.7%)	48 (14.4%)	91 (17.8%)		29 (16.3%)
Eptifibatide	14 (1.3%)	3 (1.4%)	7 (2.1%)	4 (0.8%)		1 (0.6%)
TIMI flow grade after PCI, n (%)						
3	1035 (97.7%)	212 (99.1%)	326 (97.9%)	497(97.1%)	.250	177 (99.4%)
2	21 (2%)	1 (0.5%)	6 (1.8%)	14 (2.7%)	.130	1 (0.6%)
0-1	3 (0.3%)	1 (0.5%)	1 (0.3%)	1 (0.2%)	.819	0 (0%)
Percentage of coronary artery stenosis pre-PCI‖	95% (90-100)	95% (90-100)	95% (90-100)	95% (90-100)	.738	90% (90-100)
Angiographic success, n (%)	1032 (97.5%)	210 (98.1%)	326 (97.9%)	496 (96.9%)	.509	177 (99.4%)
Procedural success, n (%)	1013 (95.7%)	206 (96.3%)	319 (95.8%)	488 (95.3%)	.839	175 (98.3%)

* *P* value for comparison across BMS subgroups (<3 vs 3-3.49 vs ≥3.5 mm) using 1-way ANOVA, if significant post hoc test was performed to indicate significance within BMS subgroups.
† $P < .05$ for comparison between BMS (all) and DES (all).
‡ $P < .05$ for comparison between BMS ≥3.5 and <3 mm.
§ $P < .05$ for comparison between BMS ≥3.5 and 3 to 3.49 mm.
‖ Median (IQR).
¶ Multivessels disease defined as ≥70% stenosis in ≥2 major epicardial vessels (LAD, LCx, and RCA) or ≥50% stenosis of left main coronary artery (which is defined as 2-vessel disease).

length ≥20 mm, IRA diameter (<3.5 mm, ie, small or intermediate stents), type B2 and C ACC/AHA lesion class, use of glycoprotein IIb/IIIa inhibitors, and multivessel disease (defined as ≥70% stenosis in ≥2 major epicardial vessels [LAD, LCx, and RCA] or ≥50% stenosis of left main coronary artery [defined as 2-vessel disease]). Variables, which were significant at $P < .2$ on univariable analysis, were included in multivariable stepwise logistic regression analysis model. Target vessel revascularization and death/MI were also displayed using Kaplan-Meier analysis and were compared with log rank test. All *P* values <.05 (2 sided) were considered statistically significant.

Analysis was also performed using the restenosis risk score from the HORIZONS-AMI trial.[20] This included 3 risk variables for restenosis, diabetes mellitus, lesion length ≥30 mm, and vessel diameter ≤3 mm. One point was assigned to each of the 3 risk variables, and patients with 0, 1, and ≥2 points of these 3 risk factors were classified as low, intermediate, or high risk for restenosis, respectively. Then TLR rates for DES and BMS were assessed according to the above risk score.

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Table III. Clinical outcomes

	Patients with BMS					Patients with DES
	All (1035)	**<3 mm (n = 210)**	**3-3.49 mm (n = 326)**	**≥3.5 mm (n = 499)**	***P****	**All (173)**
30 d						
Death, n (%)	46 (4.4%)	13 (6.2 %)	17 (5.2 %)	16 (3.2%)	.152	6 (3.5%)
MI, n (%)	14 (1.4%)	2 (1.0 %)	9 (2.8 %)	3 (0.6 %)‡	.027	3 (1.7%)
TVR, n (%)	14 (1.4%)	4 (1.9 %)	8 (2.5 %)	2 (0.4 %)‡	.033	3 (1.7%)
TLR, n (%)	11 (1.1%)	3 (1.4 %)	7 (2.1 %)	1 (0.2 %)‡	.024	3 (1.7%)
ST, n (%)	8 (0.8%)	1 (0.5%)	6 (1.8 %)	1 (0.2%)‡	.027	3 (1.7%)
Death/MI, n (%)	57 (5.5%)	14 (6.7%)	24 (7.4%)	19 (3.8 %)	.065	8 (4.6%)
Death/MI/TVR, n (%)	60 (5.8%)	16 (7.6 %)	25 (7.7 %)	19 (3.8%)	.030	9 (5.2%)
1 y						
Death, n (%)	64 (6.2%)	16 (7.6%)	26 (8.0%)	22 (4.4%)	.072	10 (5.8%)
MI, n (%)	30 (2.9%)	4 (1.9%)	15 (4.6%)	11 (2.2%)	.084	5 (2.9%)
TVR, n (%)	60 (5.8%)	19 (9.0%)	30 (9.2%)	11 (2.2%)†,‡	<.001	9 (5.2%)
TLR, n (%)	52 (5.0%)	15 (7.1%)	27 (8.3%)	10 (2.0%)†,‡	<.001	8 (4.6%)
ST, n (%)	8 (0.8%)	1 (0.5%)	6 (1.8%)	1 (0.2%)‡	.027	4 (2.3%)
Death/MI, n (%)	90 (8.7%)	19 (9.0%)	38 (11.7%)	33 (6.6%)‡	.042	13 (7.5%)
Death/MI/TVR, n (%)	130 (12.6%)	34 (16.2%)	58 (17.8%)	38 (7.6%)†,‡	<.001	19 (11.0%)

All *P* values for comparing BMS (all) with DES (all) were not significant.
* *P* value for comparison across BMS subgroups (<3 vs 3-3.49 vs ≥3.5 mm) using 1-way ANOVA, if significant post hoc test was performed to indicate significance within BMS subgroups.
† $P < .05$ for comparison between BMS ≥3.5 and <3 mm.
‡ $P < .05$ for comparison between BMS ≥3.5 and 3 to 3.49 mm.

Results

Clinical and procedural characteristics

From October 2003 to March 2010, 1,282 consecutive patients with STEMI underwent PCI, of whom 1,059 patients (83%) received BMS (<3 mm, n = 214; 3-3.49 mm, n = 333; and ≥3.5 mm, n = 512) (Figure 1); 178 (14%) received DES. Overall, the rate of large IRAs (≥3.5 mm) stented was 45%. Patient baseline characteristics according to the BMS size and stent type are shown in Table I. Among patients who received BMS, those who received large BMS compared with intermediate and small BMS were younger (57.8 ± 12 vs 59.6 ± 12 vs 59.8 ± 13, $P = .042$), more likely to be males (85.4% vs 79.9% vs 72.4%, $P < .001$), and have larger body mass index (28.7 ± 6 vs 27.5 ± 5 vs 27.1 ± 5, $P < .001$).

Angiographic and procedural details are shown in Table II. Among patients who received BMS, postprocedural TIMI 3 flow was achieved in 98% of the patients; glycoprotein IIb/IIIa inhibitors were used in 47%. Among patients who received large BMS compared with intermediate and small BMS were less likely to have culprit lesions in LAD artery (28.3% vs 49.5% vs 47.7%, $P < .001$) and LCx artery (5.7% vs 13.5% vs 16.4%, $P < .001$) but more likely RCA lesions (61.9% vs 31.8% vs 17.8%, $P < .001$). Patients who received large BMS had less bifurcation culprit lesions (11% vs 18% vs 23%, $P < .001$) and shorter culprit lesion length (median 16 [12-24] vs 18 [13-24] vs 20 [15-28], $P = .015$).

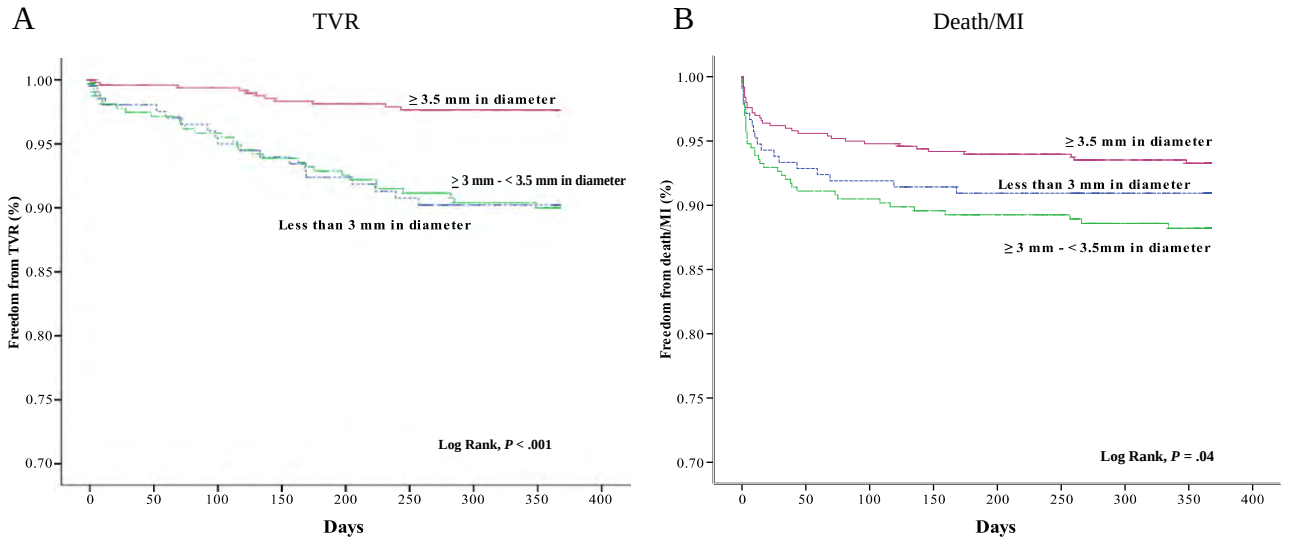
Clinical outcomes

At 30 days, mortality rates among patients who received large BMS compared with intermediate and small BMS were 3.2% versus 5.2% versus 6.2%, respectively ($P = .152$), and for nonfatal MI, the respective rates were 0.6% versus 2.8% versus 1.0% ($P = .027$), and for TVR, the rates were 0.4% versus 2.5% versus 1.9% ($P = .033$). At 1 year, mortality among patients who received large BMS compared with intermediate and small BMS was 4.4% versus 8.0% versus 7.6%, $P = .072$, and death/MI rates were 6.6% versus 11.7% versus 9.0%, $P = .042$; the respective TVR rates were 2.2% versus 9.2% versus 9.0%, $P < .001$. The rates of definite stent thrombosis were 0.2% versus 1.8% versus 0.5%, $P = .027$, for large, intermediate, and small BMS, respectively. Clinical outcomes are shown in Table III, and Kaplan-Meier analysis for TVR and death/MI according to the size of BMS is shown in Figure 2.

Analysis using the HORIZONS-AMI trial restenosis risk score (low, intermediate, and high risk) showed that this score was associated with TLR in our study cohort (Figure 3). Thirty-five percent of patients had none of the 3 risk factors for restenosis. Target lesion revascularization rates at 1 year were 2.8% with BMS and 3.3% with DES; $P = .594$. The TLR rate increased in patients who received BMS with an increasing restenosis risk score (2.8% vs 5.8% vs 8.1%, $P = .02$) but did not among those receiving DES (3.3% vs 4.9% vs 4.8%, $P = .93$) (Figure 3).

On multivariate analysis, the independent predictors of TVR at 12 months after BMS deployment were the following: IRA diameter <3.5 mm (odds ratio [OR] 4.39 [95% CI 2.24-8.60], $P < .001$), proximal LAD lesion (OR 1.89 [95% CI 1.08-3.31], $P = .027$), hypertension (OR 2.01 [95% CI 1.17-3.438], $P = .011$), and prior PCI (OR 3.46 [95% CI 1.21-9.85], $P = .02$); diabetes was not associated

Figure 2



Kaplan-Meier curve for TVR and death/MI according to the size of BMS. Late TVR rate (panel **A**) and death /MI rates (panel **B**) are shown according to BMS sizes (1) <3 mm, (2) 3.0 to 3.49 mm, and (3) ≥3.5 mm. Among those who received BMS, TVR for those who received stents ≥3 mm, compared with stents <3 mm, was 5% versus 9% ($P = .024$). The TVR rates with respect to nominal stent diameter were 9.1% (<3 mm), 6.8% (3-3.49 mm), and 1.9% (≥3.5 mm), $P < .0001$. Among the patients who received DES ≥3.5 mm (n = 42), 3.0 to 3.49 mm (n = 65), and <3 mm (n = 66), respective TVR rates at 1 year were 2.4% versus 6.2% versus 6.1%, $P = .639$.

with TVR. The independent predictors of death/MI at 1 year after BMS deployment were the following: pre-PCI cardiogenic shock (OR 8.16 [95% CI 4.16-16.01], $P < .001$), age ≥65years (OR 2.63 [95% CI 1.58-4.39], $P < .001$), LAD lesions (OR 1.95 [95% CI 1.19-3.21], $P = .008$), female gender (OR 1.93 [95% CI 1.12-3.32], $P = .019$), ACC/AHA lesion classes B2 and C (OR 2.17 [95% CI 1.10-4.27], $P = .026$), and hyperlipidemia (OR 0.59 [95% CI 0.35-0.98], $P = .04$); multivessel disease was not associated ($P = .22$).

Discussion

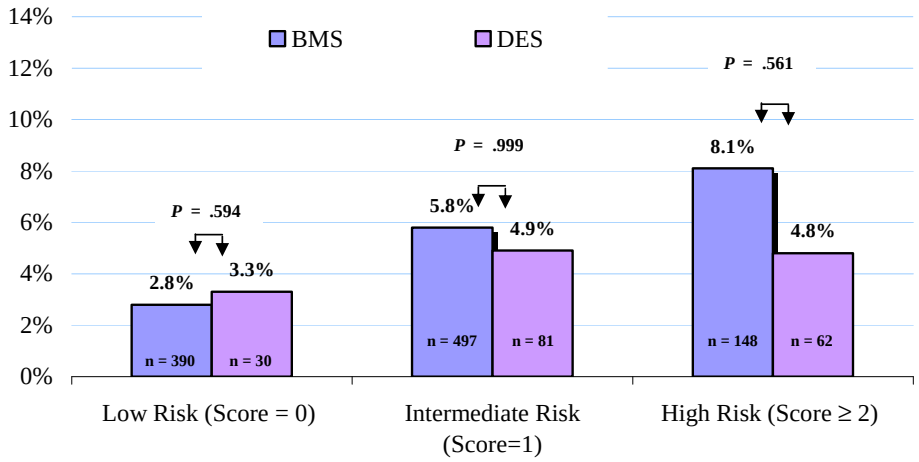
This study examines clinical outcomes after PCI performed during the index hospitalization in STEMI patients and demonstrates that BMS use in large (≥3.5 mm) coronary arteries is associated with low rates of TVR (2.2%). Large IRAs occurred in ~45% of STEMI patients, and in this circumstance, BMS deployment was associated at 1 year with lower rates of TVR and death/reinfarction, compared with smaller IRAs, including vessels of 3 to 3.49 mm in diameter.

The definition of a "large" coronary artery lacks uniformity with "cut-points" of 3 and 3.5 mm in previous reports.[19,27] In our study, approximately 45% of STEMI patients had PCI to an IRA of ≥3.5 mm in diameter. Bare-metal stent use in this context was associated with a low TVR (2.2%). We observed significantly higher TVR rates for BMS in intermediate arteries of 3 to <3.5 mm and small arteries (<3 mm), both ~9%, suggesting the use of 3 mm as a cut point for large IRAs is too low at least in the context of BMS. Our overall TVR rate for STEMI treated with BMS was 5.8%, which was somewhat lower than the 8.7% rate in HORIZONS-AMI,[10,20] possibly due to our selective use of drug eluting stents in those at highest risk for restenosis.

In the HORIZONS-AMI trial, approximately 32% of patients had none of the 3 risk factors associated with restenosis (insulin-requiring diabetes, reference vessel diameter ≤3 mm, and lesion length ≥30 mm); there were no differences in event rates between patients receiving BMS and DES with TLR rates at 12 months of 3.3% and 3.2%, respectively.[20] Our study found a comparable rate of patients with none of these 3 risk factors (35%), and TLR rate in this subgroup was 2.9% for BMS.

In the BASKET study, which recruited patients with stable coronary heart disease as well as acute coronary syndromes, the significant benefit of DES compared with BMS in reducing non–MI-related TVR was seen in patients with small coronary arteries (<3 mm) but was not significantly different in large coronary arteries (≥3 mm).[28,29] In another study, with a similar mix of stable and acute coronary heart disease patients, the TLR rate at 1 year after deployment of BMS (≥3.5 mm in diameter) was 3.5%, and this was comparable with 3.4% following DES deployment in arteries of ≥3.5 mm in diameter.[19] In

Figure 3



Target lesion revascularization rate at 1 year based on restenosis risk score. Target lesion revascularization rate according to HORIZONS-AMI risk score for restenosis. Three risk factors for restenosis (diabetes, reference vessel diameter ≤3 mm, and lesion length ≥30 mm) were used in the HORIZONS-AMI trial to classify patients into 3 risk groups, low (none of the above risk factors), intermediate (one risk factor), and high risk (≥2 risk factors). The TLR rates among patients progressively increased with an increasing restenosis risk score from low, intermediate, to high risk (2.9% vs 5.7% vs 7.1%, $P = .034$).

BASKET-PROVE study, which also recruited patients with stable as well as acute coronary heart disease, following BMS deployment in coronary arteries ≥3 mm, the TVR rate was 10.3% at 2 years.[27] This included stenting of intermediate coronary arteries (3-3.49 mm in diameter). As we have observed a high TVR rate following BMS deployment in the group with intermediate size coronary arteries (3-3.49 mm in diameter), vessels with a diameter ≥3.5 mm should be considered "large" in the context of BMS selective use.

In our study, the rate of death/MI at 1 year was 8.7% for all patients receiving BMS, whereas in the HORIZONS-AMI trial, the death/MI rate at 1 year was 6.8% (7.0% for BMS and 6.8% for DES, *P* nonsignificant).[10] The death/MI rate in our highly selected patients receiving DES was 7.5%. The lower death/MI rate of 6.6% among patients in our study with IRAs ≥3.5 mm is probably due to differences in other characteristics including more younger patients, less women, and fewer LAD IRAs. Of note in BASKET, among all patients with coronary arteries ≥3 mm, receiving DES compared with BMS, the cardiac death/MI rate at 18 months was slightly higher (hazard ratio 2.07, $P = .05$).[28] At 3-year follow-up, HORIZONS-AMI demonstrated similar rates of death/MI, 11.5% for BMS and 11.8% for DES (*P* nonsignificant).[30] We found a rate of death/MI of 11.9% for BMS, among the small proportion of patients who had 3-year follow-up.

Our study has certain limitations. Firstly, whether prior PCI as predictor of TVR at 1 year was due to stent thrombosis, restenosis, or disease progression in a previously nonstented arterial segment was not recorded. Because of our institutional criteria for selective use of DES, which targets patients at highest risk for restenosis including those with smaller arteries,[22] only 14% of these patients with STEMI received DES. As many patients with diabetes selectively received a DES, this probably explains why diabetes was not a predictor of TVR after BMS deployment. Furthermore, as our selective DES use criteria allow DES use in vessels ≥3 mm in the proximal LAD and a large proportion of our patients the IRAs were of ≥3.5 mm in diameter, our ability to directly compare outcomes after BMS and DES deployment was compromised. Unrecorded factors may have resulted in BMS use in patients with comorbidities, assumed bleeding risk, and anticipated noncompliance with dual antiplatelet therapy, all potentially affecting stent choice in those undergoing emergent stenting.

In addition, intravascular imaging modalities such as intravascular ultrasound and optical coherence tomography are the most accurate methods for measuring coronary artery reference diameter[31,32] but were beyond the scope of the present study. Quantitative coronary angiography requires specialized postprocessing software and was not routinely available at our institution. Therefore, for this study, used the nominal stent/balloon diameter as a surrogate for the reference diameter of the culprit coronary artery segment in the absence of preferred quantitative tools; this may have introduced small measurement errors. Our single-center registry does not routinely collect data regarding patient's compliance with dual antiplatelet therapy and other adjunctive therapies. Finally, cost-effectiveness analysis following

selective use of DES, as recently reported,[33] was beyond the scope of the current study.

In conclusion, we report that nearly half the STEMI patients undergoing PCI had an IRA ≥3.5 mm in diameter. We categorize such arteries as "large" and observed that BMS use in these vessels achieved low TVR rates and had low rates of stent thrombosis. As our DES use was selective, no inferences can be made about comparative rates of TVR in this context. Comparison of TVR rates between BMS and second-generation DES in large (≥3.5 mm) coronary arteries in patients with STEMI requires further randomized trials.

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Disclosures

There are no conflicts of interest to disclose.

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Safety and efficacy of rescue angioplasty for ST-elevation myocardial infarction with high utilization rates of glycoprotein IIb/IIIa inhibitors

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Background Fibrinolytic therapies remain widely used for ST-elevation myocardial infarction, and for "failed reperfusion," rescue percutaneous coronary intervention (PCI) is guideline recommended to improve outcomes. However, these recommendations are based on data from an earlier era of pharmacotherapy and procedural techniques.

Methods and Results To determine factors affecting prognosis after rescue PCI, we studied 241 consecutive patients (median age 55 years, interquartile range [IQR] 48-65) undergoing procedures between 2001 and 2009 (53% anterior ST-elevation myocardial infarction and 78% transferred). The median treatment-related times were 1.2 hours (IQR 0.8-2.2) from symptom onset to door, 2 hours (IQR 1.3-3.2) from symptom onset to fibrinolysis (93% tenecteplase), and 3.9 hours (IQR 3.1-5.2) from fibrinolysis to balloon. Procedural characteristics were stent deployment in 95% (11.6% drug eluting) and 78% glycoprotein IIb/IIIa inhibitor use, and Thrombolysis In Myocardial Infarction (TIMI) 3 flow rates pre-PCI and post-PCI were 41% and 91%, respectively ($P < .001$). At 30 days, TIMI major bleeding occurred in 16 (6.6%) patients, and 23 (9.5%) patients received transfusions; nonfatal stroke occurred in 4 (1.7%) patients (2 hemorrhagic). Predictors of TIMI major bleeding were female gender (odds ratio 3.194, 95% CI 1.063-9.597; $P = .039$) and pre-PCI shock (odds ratio 3.619, 95% CI,1.073-12.207; $P = .038$). Mortality at 30 days was 6.2%, and 3.2% in patients without pre-PCI shock. One-year mortality was 8.2% (5.3% in patients without pre-PCI cardiogenic shock), 5.2% had reinfarction, and the target vessel revascularization rate was 6.4% (2.6% in arteries ≥3.5 mm in diameter). Pre-PCI shock, female gender, and post-PCI TIMI flow grades ≤2 were significant predictors of 1-year mortality on multivariable regression modeling, but TIMI major bleeding was not.

Conclusions Rescue PCI with contemporary treatments can achieve mortality rates similar to rates for contemporary primary PCI in patients without pre-PCI shock. Whether rates of bleeding can be reduced by different pharmacotherapies and interventional techniques needs clarification in future studies. (Am Heart J 2012;163:649-656.e1.)

The aim of reperfusion strategies for patients with ST-elevation myocardial infarction (STEMI) is to minimize ischemic time to maximize preservation of myocytes and minimize infarct size by restoring antegrade coronary blood flow.[1-3] Although prompt primary percutaneous coronary intervention (PCI) is a superior reperfusion strategy to fibrinolytic therapy alone,[4] for several reasons, many patients worldwide receive fibrinolytic therapy as an initial reperfusion strategy.[5] In fact, early prehospital fibrinolysis may achieve as good as, or better, late clinical outcomes than primary PCI if appropriately high rates of rescue PCI and in-hospital PCI occur.[6-8]

Fibrinolytic-treated patients are recommended for immediate angiography and, if indicated, rescue PCI, if they have failed to reperfuse, as 5 randomized clinical trials have shown improved outcomes compared with conservative management.[5,9-11] However, these trials, and more recent reports from registries, have included significant proportions of patients who did not receive fibrin-specific therapies, stents (including drug eluting), or glycoprotein IIb/IIIa (GPIIb/IIIa) antagonists.[9-13] Because patients treated at our cardiac catheterization laboratory (CCL) and undergoing rescue PCI have received high rates of these therapies, we studied consecutive patients to identify factors that influence clinical outcomes, so these insights may provide the basis for prospective studies of future pharmacoinvasive strategies in STEMI patients.

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Methods

Study population

We prospectively collected clinical, demographic, and angiographic data on consecutive patients undergoing rescue PCI at CCL at Liverpool Hospital (Sydney, Australia); details of the CCL database has recently been reported.[14]

During the study period from January 2001 to December 2009, patients with STEMI with 12 hours symptom onset, without contraindications, received fibrinolytic therapy and intravenous heparin were treated with aspirin (usually 300 mg) at first medical contact, in the area of our CCL service (~900,000 population) except for those presenting to Liverpool Hospital during working hours when primary PCI was usually performed until May 2006. Subsequently, a 24-hour primary PCI service was offered to patients presenting directly to Liverpool Hospital. Failed pharmacologic reperfusion was defined <50% ST-segment recovery compared with baseline ST elevation at approximately 60 to 90 minutes. Patients with transient ST recovery but subsequently persistent ST-segment reelevation (<12 hours post-STEMI) were also included. Assessment of outcomes after PCI was approved by the Sydney South West Area Health Service Human Research Ethics Committee (project no. QA2008/034). No extramural funding was used to support this work.

Procedural techniques

Rescue PCI was performed via the femoral approach in 99% of patients using unfractionated heparin, administered according to the preprocedural activated clotting time. Clopidogrel loading with 300 to 600 mg (and 75 mg daily for 12 months) was given if not administered "upstream." The use of GPIIb/IIIa receptor inhibitors (tirofiban or abciximab) was at the discretion of the referring physicians and/or interventionists. Deployment of drug-eluting stents (DES) was based on our CCL selective use criteria, adopted in October 2003 (applying to 89% of patients reported here) which were as follows: left main lesions, ostial lesions in major epicardial arteries, proximal left anterior descending lesions, lesions length ≥20 mm in vessels ≤3mm, any lesion in vessels ≤2.5 mm, any lesion in diabetic patients with vessels <3.0mm, and in-stent restenosis. Infarct artery Thrombolysis In Myocardial Infarction (TIMI) flow grading and corrected TIMI frame counts (CTFC) pre-PCI and post-PCI including imputation of a CTFC of 100 for TIMI 0 to 1 flow were assessed by 2 cardiologists who were blinded to the patients' history and outcomes.[15]

Electrocardiographic analyses

Analysis of electrocardiographs (ECGs) before and 60 to 90 minutes after fibrinolytic therapy, before and after rescue PCI, and before discharge were performed with callipers by 5 clinicians trained in ST-segment recovery analysis (herein called ST recovery), blinded to outcomes. ST recovery was characterized as (1) complete (≥70%), (2) partial (>30% to <70%), and (3) no recovery (≤30%).[16,17] Infarct size estimation by Selvester QRS scoring used the 32-point system (each point represents ~3% of the left ventricular myocardium).[18,19] The myocardial salvage was determined by subtracting infarct size from myocardium at risk (maximal scores of baseline ST elevation) and dividing this difference by the at-risk score.[20]

Clinical outcomes

Outcomes were examined at 30 days and approximately 1 year and included all-cause mortality, nonfatal myocardial infarction (MI), target vessel revascularization (TVR), stroke, and TIMI major bleeding.[10] *Target vessel revascularization* was defined as repeat revascularization (PCI or coronary artery bypass graft surgery [CABG]) of the infarct artery including proximal and distal to the target lesion. Clinical outcome data were obtained by reviewing patients' medical records and by trained research staff (nurses or doctors) contacting patients, their next of kin, or local physicians or cardiologists by telephone. Data regarding mortality were obtained from medical records, physicians, family members, and the death registry; all patients had follow-up to 30 days, and 8 (3%) were lost to follow-up at 12 months.

Data analyses

Categorical variables are reported as numbers (%) and were compared by χ^2 test or Fisher exact test as appropriate; continuous variables are reported as medians and interquartile ranges (IQR). Normally distributed continuous variables were compared by unpaired Student *t* tests for comparison of means, whereas skewed continuous variables were compared by Mann-Whitney *U* tests. Paired continuous and ordinal data were compared by Wilcoxon signed rank tests.

Univariate and multivariate analyses to determine factors associated with clinical outcomes included the following variables: age, female gender, body mass index, diabetes mellitus, current smoking, prior MI, prior aspirin use, hypertension, hyperlipidemia, prior PCI, cardiogenic shock, TIMI major bleeding, symptom onset to door, symptom onset to lytic, door to balloon, anterior MI, post-PCI TIMI flow grade, post-PCI CTFC, incomplete (<70%) ST recovery (maximal leads and sum of leads), at-risk myocardium salvaged <50% and <70%, final QRS score >4, multivessel disease, GPIIb/IIIa inhibitors, DES use, and total stent length; those with $P < .2$ were included in the multivariate analysis. Multivariate Cox regression was used to identify independent factors associated with late clinical outcomes. Odds ratios (OR) and 95% CIs are reported. All statistical analyses were performed using Statistical Package for Social Sciences version 17.0 software (SPSS, Inc, Chicago, IL). All *P* values < .05 (2 sided) were considered statistically significant.

The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the manuscript, and its final content.

Results

Clinical and procedural characteristics

Between January 2001 and December 2009, of 241 patients undergoing rescue PCI (189 patients [78%] after interhospital transfer), 36 (15%) patients had PCI performed before January 1, 2004, 102 (42.3%) had procedures between January 1, 2004, and May 31, 2006, and 103 (42.7%) had rescue PCIs after June 1, 2006. These patients had a median age of 55 (IQR 48-65) years and were hospitalized for 4 (IQR 3-5.5) days; 24 (10%) had cardiogenic shock before rescue PCI. Other patient

Table I. Baseline clinical characteristics

	All patients, n = 241	Symptom-onset–to–lytic time		P
		≤120 min, n = 125	>120 min, n = 116	
Age (y), median (IQR)	55 (48-65)	54 (47-62)	57 (49-66)	.076
Age ≥65 y	61 (25.3%)	26 (20.8%)	35 (30.2%)	.095
Female gender	43 (17.8%)	20 (16%)	23 (19.8%)	.438
Body mass index	27.4 (24.6-30.5)	27.8 (25.7-31.5)	26.1 (24.2-29.4)	.003
Hypertension	98 (40.7%)	47 (37.6%)	51 (44%)	.315
Diabetes mellitus	43 (17.8%)	20 (16%)	23 (19.8%)	.438
Hyperlipidemia	96 (39.8%)	48 (38.4%)	48 (41.4%)	.637
Current (<12 m) cigarette smoking	127 (52.7%)	71 (56.8%)	56 (48.3%)	.185
Family history of coronary artery disease	66 (27.4%)	38 (30.4%)	28 (24.1%)	.276
Prior myocardial infarction	19 (7.9%)	12 (9.6%)	7 (6.0%)	.305
Prior PCI	11 (4.6%)	7 (5.6%)	4 (3.4%)	.424
Prior CABG	4 (1.7%)	2 (1.6%)	2 (1.7%)	.999
Prior aspirin use	44 (18.3%)	27 (21.6%)	17 (14.7%)	.163
Transfer from non-PCI centers	189 (78.4%)	102 (81.6%)	87 (75%)	.213
Fibrin-specific fibrinolytic given	235 (97.5%)	122 (97.6%)	113 (97.4%)	.999
Symptom-onset–to–door time (min)	74 (46-133)	50 (34.5-65)	137 (98.5-277)	<.001
Symptom-onset–to–lytic time (min)	120 (79-192)	80 (61-95.5)	203 (147.3-367.5)	<.001
Symptom-onset–to–balloon time (min)	379 (291-522)	305 (260-396.5)	458.5 (355.5-727.25)	<.001
Door-to-balloon time (min)	279 (217-364)	254 (209-354.5)	296 (230.3-389.3)	.018
Lytic-to-balloon time (min)	232 (185-312)	240 (185-318)	227 (186-300)	.763
Cardiogenic shock pre-PCI	24 (10%)	9 (7.2%)	15 (12.9%)	.138
Anterior infarction	128 (53.1%)	65 (52%)	63 (54.3%)	.720

Categorical variables are shown as n (%) and continuous variables are shown as median (IQR).

characteristics are shown in Table I. Median symptom-onset–to–door time was 1.2 hours (IQR 0.8-2.2), median symptom-onset–to–lytic time was 2 hours (IQR 1.3-3.2), median lytic-to-balloon time was 3.85 hours (IQR 3-5), and median door-to-balloon time was 4.7 hours (IQR 3.6-6.1). Among patients with symptom-onset–to–fibrinolytic times ≤120 minutes, the median fibrinolytic-therapy–to–balloon times were 240 minutes (IQR 185-318) compared with 227 minutes (IQR 186-333) in those receiving fibrinolysis at >120 minutes (P = .763). Among the study cohort, 235 (98%) received a fibrin-specific fibrinolytic (93% tenecteplase), 230 (95%) patients had ≥1 stent deployed (11.6% DES), and 187 (78%) patients received GPIIb/IIIa inhibitors (56% tirofiban and 22% abciximab). At angiography, 99 (41%) patients had initial infarct-artery TIMI 3 flow, and 87 (36.1%) patients had TIMI 0 to 1 flow, whereas post-PCI, TIMI 3 flow was achieved in 218 (91%) patients, P < .001 (Table II).

Electrocardiographic analysis

The median ST recovery before PCI was 22% (IQR −24% to +54%], whereas the median ST recovery after PCI was 66.7% (IQR 50%-82%). Post-PCI, complete ST recovery (≥70%) occurred in 109 (48.4%) patients, and partial ST recovery occurred in 83 (36.9%) patients, whereas in 33 (15%), ST recovery was <30%. Of patients without ST recovery at 60 to 90 minutes postfibrinolysis, 13% (31 patients) achieved ST recovery during transfer. Before angiography of patients who had ST recovery <70%, 77% had initial TIMI 0 to 1. After PCI, of those who achieved ≥70% ST recovery, 94% had post-PCI TIMI 3. The median at-risk myocardium determined by QRS scoring was 11 (IQR 7-15) (~33% of the myocardium), and the median final QRS score was 4 (IQR 2-6) (~12% of the myocardium). The median myocardium salvage index was 0.58 (IQR 0.37-0.78) (online Appendix A and B).

Clinical outcomes

Mortality at 30 days was 6.2% (15 patients), of whom 8 patients had pre-PCI cardiogenic shock and 2 had TIMI major bleeding; 7 (3.2%) patients died among 217 patients without pre-PCI cardiogenic shock. Bleeding events occurred in 59 (25%) patients, 16 (6.6%) patients had TIMI major bleeding and 23 (9.5%) patients received blood transfusions, 2 (0.8%) patients had a nonfatal hemorrhagic stroke, and 2 had other nonfatal strokes. Bleeding events among those who received GPIIb/IIIa inhibitors, compared with those not receiving these agents, were 26.2% versus 18.5% (P = .285), whereas TIMI major bleeding were 6.4% versus 7.4% (P = .761), and bleeding events requiring transfusion were 9.1% versus11.1% (P = .656). Reinfarction occurred in 8 (3.3%) patients, and 7 (2.9%) patients required TVR; 4 patients had PCI and 3 had CABG (Table III). The only outcome difference between patients treated ≤ and, >120 minutes

Table II. Angiographic and procedural characteristics

	All patients, n = 241	Symptom-onset–to–lytic time		P
		≤120 min, n = 125	>120 min, n = 116	
Infarct-related coronary artery				.998
Left main	3 (1.2%)	1 (0.8%)	2 (1.7%)	
Left anterior descending artery	122 (50.6%)	63 (50.4%)	59 (50.9%)	
Left circumflex coronary artery	9 (3.7%)	5 (4.0%)	4 (3.4%)	
Right coronary artery	95 (39.4%)	50 (40.0%)	45 (38.8%)	
Bypass graft	2 (0.8%)	2 (1.6%)	0	
Other coronary branches	10 (4.1%)	4 (2.3%)	6 (5.2%)	
No. of diseased vessels				.731
1	145 (60.2%)	75 (60%)	70 (60.3%)	
2	65 (27%)	31 (24.8%)	34 (29.3%)	
3	31 (12.9%)	19 (15.2%)	12 (10.3%)	
Lesion classification (ACC/AHA)				
B2	98 (40.8%)	49 (39.5%)	49 (42.2%)	.668
C	78 (32.5%)	42 (33.9%)	36 (31%)	.639
Culprit lesion length	16 (13-24)	18 (14.3-24.7)	16 (12.3-24.0)	.224
Culprit lesion length ≥20mm	104 (43.3%)	55 (44.4%)	49 (42.2%)	.741
Coronary artery stenosis pre-PCI (%)	95% (90-100)	95% (90-100)	95% (90-100)	.893
Stenting	230 (95.4%)	122 (97.6%)	108 (93.1%)	.095
≥DES	28 (11.6%)	10 (8%)	18 (15.5%)	.069
≥BMS	202 (83.8%)	112 (89.6%)	90 (77.6%)	.011
Stent length (mm)	18 (14-24)	18 (14-24)	18 (14.25-24)	.406
Stent diameter (>3 mm)	188 (81.7%)	107 (87.7%)	81 (75%)	.013
Stent diameter (>3.5 mm)	117 (50.9%)	74 (60.7%)	43 (39.8%)	.002
Baseline TIMI flow grade				.356
3	99 (41.1%)*	49 (39.2%)	50 (43.1%)	
2	55 (22.8%)	27 (21.6%)	28 (24.1%)	
0-1	87 (36.1%)	49 (39.2%)	38 (32.7%)	
TIMI flow grade after PCI				.633
3	218 (90.5%)*	112 (89.6%)	106 (91.4%)	
2	20 (8.3%)	11 (8.8%)	9 (7.8%)	
0-1	3 (1.2%)	2 (1.6%)	1 (0.9%)	
Initial CTFC	30 (16-100)†	38 (16-100)	25 (16-100)	.221
Initial CTFC >40	105 (43.9%)	61 (48.8%)	44 (38.6%)	.112
Post-PCI CTFC	14 (9-20)†	14 (10-23)	14 (8-19)	.204
Post-PCI CTFC >40	12 (5.0%)	9 (7.2%)	3 (2.6%)	.106
GPIIb/IIIa inhibitor use	187 (77.6%)	102 (81.6%)	85 (73.3%)	.121
Tirofiban	134 (55.6%)	76 (60.8%)	58 (50%)	
Abciximab	53 (22%)	26 (20.8%)	27 (23.2%)	
Length of hospital stay (d)	4 (3-5.5)	4 (3-5)	4 (2-6)	.906
Successful PCI procedure	237 (98.3%)	125 (100%)	112 (96.6%)	.052

ACC/AHA, American College of Cardiology/American Heart Association.
Categorical variables are shown as n (%) and continuous variables are shown as median (IQR).
*†*P* value for comparison is < .001.

of symptom onset to lytic was severe congestive heart failure at 30 days (8.8% vs 17.2%, *P* = .05) (Table III).

Mortality rate at 1 year (median 11.3, IQR 5.8-16.8 months) was 8.2% (19 patients), and among those without pre-PCI shock, it was 5.3% (11 patients) (Table III). In addition, 5.2% (12 patients) had reinfarction. The TVR rate was 6.4% (15 patients), and among the 230 stented patients, it was 5.4% (3.7% DES vs 5.6% bare-metal stents [BMS]; *P* = .560). The TVR rate was 2.6% among those with stents diameter(s) ≥3.5 mm compared with 8.3% among patients with stents <3.5 mm (*P* = .063); the TVR rates in those with stent diameters ≥3 mm and <3 mm were 4.4% and 9.5%, respectively (*P* = .246). Among the 17 patients who had DES with diameter(s) ≥3 mm, none had TVR.

Predictors of adverse outcomes

Significant factors associated with TIMI major bleeding within hospitalization period on univariable analysis were female gender (*P* = .012), pre-PCI cardiogenic shock (*P* = .013), and age ≥65 years (*P* = .012). On multivariable analysis, the independent factors associated with TIMI major bleeding were female gender (OR 3.194, 95% CI 1.063-9.597; *P* = .039) and pre-PCI cardiogenic shock (OR 3.619, 95% CI, 1.073-12.207; *P* = .038). The

Table III. Thirty-day and 1-year clinical outcomes

	All patients, n = 241	Symptom-onset–to–lytic time		P	Patients without pre-PCI cardiogenic shock, n = 217
		≤120 min, n = 125	>120 min, n = 116		
30 d					
Death	15 (6.2%)	6 (4.8%)	9 (7.8%)	.342	7 (3.2%)
Nonfatal stroke	4 (1.7%)	3 (2.4%)	1 (0.9%)	.623	3 (1.4%)
Bleeding*	59 (24.5%)	28 (22.4%)	31 (26.7%)	.435	50 (23%)
TIMI major bleeding*	16 (6.6%)	7 (5.6%)	9 (7.8%)	.501	11 (5.1%)
Transfusion*	23 (9.5%)	11 (8.8%)	12 (10.3%)	.683	17 (7.8%)
Severe CHF (NYHA class III-IV)†	31 (12.9%)	11 (8.8%)	20 (17.2%)	.05	19 (8.8%)
Re-MI	8 (3.3%)	6 (4.8%)	2 (1.7%)	.284	6 (2.8%)
Target vessel revascularization (TVR)	7 (2.9%)	4 (3.2%)	3 (2.6%)	.999	6 (2.8%)
PCI	4 (1.7%)	3 (2.4%)	1 (0.9%)	.623	3 (1.4%)
CABG	3 (1.2%)	1 (0.8%)	2 (1.7%)	.610	3 (1.4%)
Death, re-MI, TIMI major bleeding, or nonfatal stroke	31 (12.9%)	16 (12.8%)	15 (12.9%)	.976	19 (8.8%)
1 y					
Death	19 (8.2%)	7 (5.8%)	12 (10.6%)	.182	11 (5.3%)
Re-MI	12 (5.2%)	9 (7.5%)	3 (2.7%	.094	10 (4.8%)
Target vessel restenosis	18 (7.7%)	10 (8.3%)	8 (7.1%)	.720	16 (7.7%)
TVR	15 (6.4%)	8 (6.7%)	7 (6.2%)	.883	13 (6.2%)
Severe CHF (NYHA class III-IV)	34 (14.6%)	13 (10.8%)	21 (18.6%)	.094	22 (10.5%)
Death or re-MI	27 (11.6%)	14 (11.7%)	13 (11.5%)	.969	19 (9.1%)
Death, re-MI, or TVR	36 (15.5%)	18 (15.0%)	18 (15.9%)	.845	27 (12.9%)
Death, re-MI, TVR, or nonfatal stroke	38 (16.3%)	19 (15.8%)	19 (16.8%)	.840	28 (13.4%)
Death, re-MI, TVR, nonfatal stroke, or severe CHF	59 (25.3%)	27 (22.5%)	32 (28.3%)	.307	44 (21.1%)

CHF, Congestive heart failure; NYHA, New York Heart Association.
Among all 241 patients, 24 patients developed cardiogenic shock before catheterization; of these, 13 patients' cardiogenic shock resolved post-PCI, whereas 11 patients' cardiogenic shock persisted.
Among the 217 patients without pre-PCI cardiogenic shock, 7 developed cardiogenic shock after their PCI procedure.
* Bleeding events among those who received GPIIb/IIIa inhibitors compared with those not receiving these agents were 26.2% versus 18.5% ($P = .285$), whereas TIMI major bleeding were 6.4% versus 7.4% ($P = .761$) and bleeding events requiring transfusion were 9.1% versus11.1% (0.656).
† Severe congestive heart failure as an outcome was defined as congestive heart failure that was present post–rescue PCI procedure, which included cardiogenic shock.

use of GPIIb/IIIa inhibitors was not associated with TIMI major bleeding.

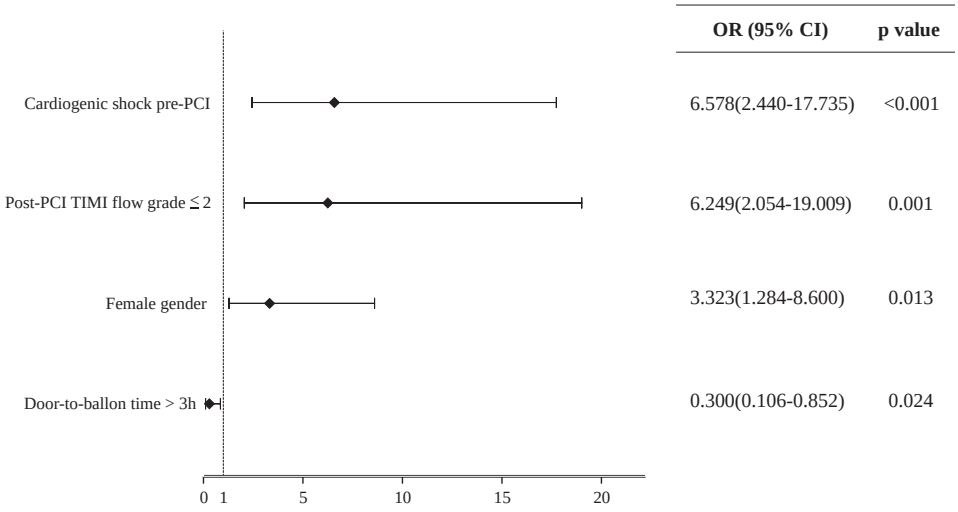
Predictors of late mortality on univariable analysis were age ≥65 years ($P = .011$), female gender ($P = .011$), pre-PCI cardiogenic shock ($P < .001$), post-PCI TIMI flow grade ≤2 (0.027), and TIMI major bleeding within the index hospitalization ($P = .031$). Conversely, current smoking (or ceased <12 months) and door-to-balloon times >3 hours were associated with low late mortality ($P = .016$ and $P = .039$, respectively). On Cox multivariate analysis, the independent factors associated with high late mortality included female gender (OR 3.323, 95% CI 1.284-8.600; $P = .013$), post-PCI TIMI flow grade ≤2 (OR 6.249, 95% CI, 2.054-19.009; $P = .001$), and pre-PCI cardiogenic shock (OR 6.578, 95% CI 2.440-17.735; $P < .001$) (Figure 1).

Discussion

For patients with STEMI treated by fibrinolytic therapy, including those being managed by a pharmacoinvasive strategy, 25% to 30% will have indications for rescue PCI.[7,21] In our study, three fourth of patients who underwent rescue PCI had presented to hospital within 2 hours of symptom onset. In such early presenting patients, a pharmacoinvasive strategy may have benefit because of early successful rescue PCI enhancing myocardial salvage and have lowering mortality.[1,8] The CAPTIM and WEST investigators recently reported retrospective pooled analyses of the subgroup presenting within 2 hours of symptom onset[8]; a late mortality benefit occurred among those who received fibrinolysis (mostly prehospital, with a 25%-30% rate of rescue PCI and ~70% in-hospital PCI), compared with primary PCI. The STREAM trial is prospectively evaluating a pharmacoinvasive strategy in STEMI patients presenting within 3 hours of symptom onset to non-PCI centers.[22]

We report mortality rates of 3.2% and 5.3% at day 30 and 1 year, respectively, which are comparable with those reported for primary PCI in patients (>50% with anterior MI) without pre-PCI shock similar to mortality in the APEX AMI trial.[23] When patients with cardiogenic

Figure 1



Independent factors associated with mortality at 1 year.

shock were included, 30-day mortality was 6.2%; 3 other rescue PCI registries have reported 30-day mortality rates in the range of 5.2% to 10.7%.[12,13,24]

Most reports of rescue PCI outcomes have included at most a few hundred patients, so comparisons of mortality rates are likely to be confounded with insufficient power. However, post hoc analysis of the REACT trial showed that patients randomized to rescue angioplasty compared with conservative management and further fibrinolysis had a late survival benefit.[10,11] In the MERLIN trial, which recruited patients between February 1999 and June 2002, mortality was 9.8% at 30 days and 14.4% at 1 year. Mortality was 4.9% at 30 days and 7.6% at 1 year in the REACT trial, which randomized patients from December 1999 to March 2004.[9,25-27] Several factors may have influenced a lower mortality rate in our study compared with those reported in REACT and MERLIN trials, such as higher rates of use of tenecteplase (93%), stenting (95%), and GPIIb/IIIa inhibitors (78%).

Measurement of final infarct size can determine a significant factor for attributable (mortality) risk, easily performed by calculation of Selvester QRS scores from 12-lead ECG. A myocardial salvage index of 0.58 reported here is similar to that measured by STOP-AMI investigators using nuclear scanning in those who had successful reperfusion.[28] Cardiac magnetic resonance imaging is a more sensitive technique for assessing final infarct size, although achieving a second post-hospitalization magnetic resonance imaging scan even in a clinical trial setting can be problematic.

The use of GPIIb/IIIa inhibitors after fibrinolytic therapy in the setting of PCI in the early hours after symptom onset has been contentious given clinician concerns about balancing bleeding risks with risks of recurrent ischemic events. In our study of rescue PCI, there was an approximately 80% rate of GPIIb/IIIa inhibitor use, which were not associated with an increased bleeding risk. Some small, nonrandomized studies on GPIIb/IIIa use in this setting[29-32] have reported TIMI major bleeding of 6.9% and 12% among patients who underwent rescue PCI and received GPIIb/IIIa inhibitors.[30,31] Several factors may have contributed to the differences in the bleeding rate after rescue PCI compared with older studies, such as the use of smaller arterial sheath caliber, and improvements in pharmacotherapies including lower heparin doses associated with lower activated clotting times. Whether lower rates of bleeding occur in this setting, using thrombin inhibition with bivalirudin, compared with unfractionated heparin and GPIIb/IIIa inhibitors, as occurred in different groups of acute coronary syndrome patients in ACUITY and HORIZONS-AMI trial is under investigation.

Recent trials have reported lower TVR rates after STEMI after DES deployment compared with BMS among unselected patients, including arteries ≥3 mm, although TVR rates may be heterogeneous, dependent on various angiographic and clinical factors.[33] In our study, approximately 50% of patients who underwent rescue PCI for STEMI had a culprit lesion segment ≥3.5 mm in diameter, and among these patients, the TVR rate was 2.6% after BMS deployment, compared with 8.3% among patients with stents <3.5mm; the latter similar rate to 8.7% reported from HORIZONS-AMI.[33,34] Also in the Basket-Prove study, patients with stable and acute coronary heart disease, after BMS deployment in coronary arteries >3 mm, had TVR rate of 10.3% at 2 years.[35] Thus, the reduction of TVR rates with BMS in STEMI appears to occur in arteries ≥3.5 mm. Because the ability of patients

to appreciate the necessity of prolonged dual antiplatelet therapy in the setting of acute STEMI may be compromised,[36] and the low TVR rates with BMS in vessels ≥3.5 mm in diameter, future studies should specifically address the necessity of DES use in this setting.

This study has limitations inherent in an observational study. There may have been unappreciated referral biases at non-PCI hospitals, so deaths before and during interhospital transfer were not recorded. We found a paradoxical survivor benefit among those with door-to-balloon times >3 hours, which may represent a lower risk group of younger patients and lower rates of pre-PCI cardiogenic shock and/or referral bias as in the FAST-MI registry, a higher mortality was observed in those undergoing rescue PCI treated ≥220 minutes compared with those at ≤128 minutes after fibrinolysis.[6] We report low rates of radial access in comparison with some other studies, which may have influenced our rates of bleeding. Although the RIVAL trial reports that, in a subgroup of patients with STEMI, radial access reduces the incidence of the primary outcome of death, MI, stroke, or major bleeding and the secondary outcomes of death, MI, or stroke, and overall mortality within 30 days compared with femoral approach, this subgroup analysis warrants future trial confirmation.[37] In addition, we did not routinely collect data on rates of "upstream" clopidogrel administration.

In conclusion, the mortality rate of 3.2% in unselected patients without prior shock undergoing rescue PCI in the era of liberal use of stents and GPIIb/IIIa inhibitors is similar to that of STEMI patients treated with primary PCI. These data suggest that a pharmacoinvasive approach to STEMI with rescue PCI especially among those presenting at <2 hours is a reasonable strategy when there is no expeditious access to primary PCI, especially in early presenting patients. Finally, the very low TVR rate with BMS in coronary arteries ≥3.5 mm in this STEMI setting could be compared with DES use in an appropriately sized trial.

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Disclosures

Conflict of Interest: None declared.

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Appendix A. Electrocardiographic analyses

Selvester QRS scoring for infarct size estimation was undertaken on 194 (81%) patients with first MIs; 19 patients had prior MI; 16 had conduction disorders including bundle-branch block, ventricular hypertrophy, and artificially paced rhythms; and 12 had indecipherable or missing ECGs. The median at-risk myocardium-determined potential QRS score was 11 (IQR 7-15) (~33% of the myocardium), and the median final QRS score was 4 (IQR 2-6), (~12% of the myocardium) (Table A1). The median salvage index of at-risk myocardial was 68% (IQR 37%-78%); 61% had <70% salvage of at-risk myocardium. The median final QRS score for those who received GPIIb/IIIa inhibitors was 4 (IQR 2-6) (~12% of the myocardium) and 5 (IQR 2.5-7) (15% of the myocardium) in those who did not receive GPIIb/IIIa inhibitors, $P = .129$.

Table A1. Electrocardiographic characteristics

		Symptom-onset–to–lytic time		
	All patients, n = 241	**≤120 minutes, n = 125**	**>120 minutes, n = 116**	***p***
At-risk myocardium Potential QRS score*	11 (7-15)†	11 (7-15)	11 (7-15)	.721
Final infarct size assessment Final QRS score*	4 (2-6)†	4 (2-6)	4 (2-7)	.922
At-risk and salvaged myocardium analysis				
Percent at-risk myocardium salvaged, median (IQR)	58.3% (37.2%-77.8)	–	–	–
Patients with <50% at-risk myocardium salvaged	73 (37.6%)			
Patients with <70% at-risk myocardium salvaged	123 (63.4%)			

*Each point awarded by the Selvester QRS scoring system corresponds to approximately 3% of myocardium.
*Number of patients were eligible for Selvester QRS scoring (n = 194), exclusions (n = 19 had previous infarctions, n = 16 had conduction disorders [BBB, hypertrophy, artificially paced rhythms], and n = 12 had indecipherable/missing ECGs).
†*P* value for comparison is <.001.

Appendix B. ST-segment recovery and TIMI flow grade

Table B1. ST segment recovery and TIMI flow grade

	Pre-PCI ST-recovery in lead with maximum deviation at baseline		
	Median (IQR), 22 (–24 to 54)		
	No recovery (<30%)	**Partial recovery (≥30 to <70%)**	**Complete recovery (≥70%)**
All	59.1% (127)	28.4% (61)	12.6% (27)
Baseline TIMI			
TIMI 0-1	37.8% (48)	39.3% (24)	25.9% (7)
TIMI 2	22.0% (28)	24.6% (15)	29.6% (8)
TIMI 3	40.2% (51)	36.1% (22)	44.4% (12)
	Post-PCI ST-recovery in lead with maximum deviation at baseline		
	Median (IQR), 67 (50-82)		
	No recovery (<30%)	**Partial recovery (≥30 to <70%)**	**Complete recovery (≥70%)**
	14.7% (33)	36.9% (83)	48.4% (109)
Post-PCI TIMI flow			
TIMI 0-1	0% (0)	1.2% (1)	0% (0)
TIMI 2	6.1% (2)	9.6% (8)	6.4% (7)
TIMI 3	93.9% (31)	89.2% (74)	93.6% (102)

Evaluation of Troponin T Criteria for Periprocedural Myocardial Infarction in Patients With Acute Coronary Syndromes

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In patients with acute coronary syndromes undergoing percutaneous coronary intervention (PCI), the diagnosis of periprocedural myocardial infarction is often problematic when the pre-PCI levels of cardiac troponin T (TnT) are elevated. Thus, we examined different TnT criteria for periprocedural myocardial infarction when the pre-PCI TnT levels were elevated and also the associations between the post-PCI cardiac marker levels and outcomes. We established the relation between the post-PCI creatine kinase-MB (CKMB) and TnT levels in 582 patients (315 with acute coronary syndromes and 272 with stable coronary heart disease). A post-PCI increase in the CKMB levels to 14.7 μg/L (3× the upper reference limit [URL] in men) corresponded to a TnT of 0.23 μg/L. In the 85 patients with acute coronary syndromes and normal CKMB, but elevated post peak TnT levels before PCI (performed at a median of 5 days, interquartile range 3 to 7), the post-PCI cardiac marker increases were as follows: 21 (24.7%) with a ≥20% increase in TnT, 10 (11.8%) with an CKMB level >3× URL, and 12 (14%) with an absolute TnT increase of >0.09 μg/L (p <0.005 for both). In the patients with stable coronary heart disease and post-PCI cardiac markers >3× URL compared to those without markers elevations, the rate of freedom from death or nonfatal myocardial infarction was 88% for those with TnT elevations versus 99% (p <0.001, log-rank) and 84% for those with CKMB elevations versus 98% (p <0.001, log-rank). Of the patients with acute coronary syndromes, the post-PCI marker levels did not influence the outcomes. In conclusion, in patients with acute coronary syndromes and elevated TnT levels undergoing PCI several days later, ≥20% increases in TnT were more common than absolute increments in the TnT or CKMB levels of >3× URL. Also, periprocedural cardiac marker elevations in patients with acute coronary syndromes did not have prognostic significance. **(Am J Cardiol 2011;107:863–870)**

The importance of the patterns of elevation in the blood levels of markers of myonecrosis has been emphasized in the 2000 and 2007 universal definitions of myocardial infarction (MI).[1–3] When the troponin levels are elevated before percutaneous coronary intervention (PCI), to meet the recurrent MI criteria, 2 cardiac marker levels are required, preferably troponin, the first immediate and the second 6 hours later.[2,3] Also, an increase of ≥20% in troponin levels greater than stabilized or decreasing elevated pre-PCI levels is needed. Changes on the electrocardiograms or imaging findings, together with biomarkers, contribute to the recurrent MI criteria.[2,3] Because few data are available to support this troponin-based definition of reinfarction,[4,5] we examined the cardiac marker levels in such patients. Initially, we examined the relations between the levels of creatine kinase-MB (CKMB) and troponin T (TnT) in patients with acute coronary syndromes and stable coronary heart disease to develop an algorithm for the absolute increases in TnT levels greater than the upper reference limit (URL). We used this algorithm in patients with acute coronary syndromes with elevated pre-PCI TnT levels, but normal CKMB levels, to compare the percentage and absolute increases in periprocedural cardiac marker levels. We also examined the influence of TnT and CKMB elevations after PCI on the late outcomes in patients with acute coronary syndromes compared to those with stable coronary heart disease.

Methods

All patients undergoing PCI have had clinical, angiographic, and procedural data recorded prospectively in the cardiology database at the Liverpool Hospital cardiac catheterization laboratory (Sydney, Australia). These data included procedural indications, patient demographics, medications, angiographic and lesion characteristics, and stent type, such as drug-eluting stents. The procedural indications were categorized as acute coronary syndromes with or without ST-segment elevation. Those with angina (class II-III) and other stable manifestations of coronary heart disease

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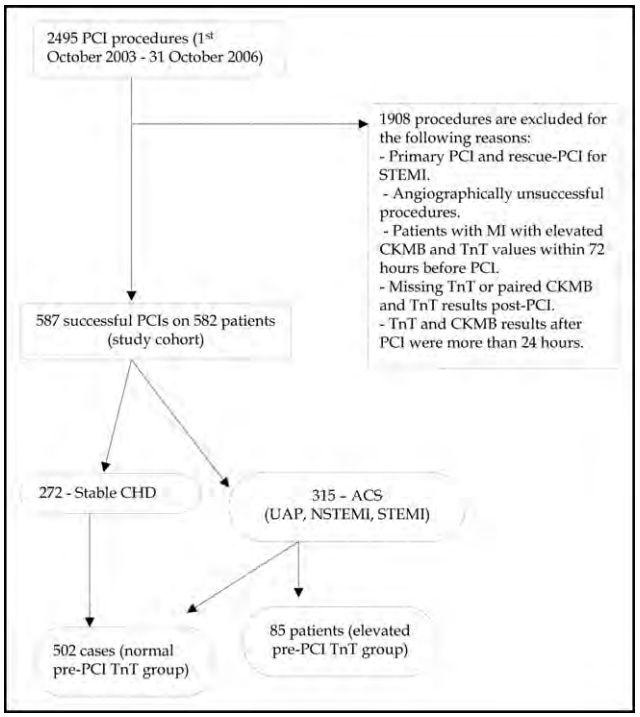

Figure 1. Patient flow diagram showing patients from total angioplasty cohort and reasons for inclusion in, and exclusion from, the present study for those who underwent PCI during study period. ACS = acute coronary syndromes; CHD = coronary heart disease; NSTEMI = non–ST-segment elevation myocardial infarction; STEMI = ST-segment elevation myocardial infarction; UAP = unstable angina pectoris.

were classified as having "stable coronary heart disease." During the study period, 587 PCIs were performed on 582 unique patients (5 underwent staged PCI) who had sufficient cardiac marker data for inclusion (Figure 1). The Liverpool Hospital ethics committee approved the present study as a part of a quality assurance project (QA2008/034).

Aspirin (unless contraindicated), clopidogrel (300 or 600 mg), and a bolus of unfractionated heparin were given at the start of PCI. The use of intravenous glycoprotein IIb/IIIa inhibitors was at the interventional cardiologist's discretion. Stent deployment and rotational atherectomy were performed according to standard practice. Angiographically successful procedures were defined as a final post-PCI minimum stenosis diameter reduction to <20% after stenting or to <50% after balloon angioplasty in the presence of grade 3 Thrombolysis In Myocardial Infarction flow.[6,7]

The clinical follow-up data were obtained by trained research staff (nurses or doctors) 8 to 12 months after PCI. The patients, their relatives, or local physicians were interviewed by telephone and asked about recurrent cardiac symptoms requiring hospitalization, in particular, coronary revascularization or MI. Data regarding death were obtained from the family members, physicians, medical records, and death registry. Other clinical outcomes such as repeated procedures for stent thrombosis and restenosis were also documented in our database.

Venous blood samples for assays of TnT and CKMB (mass) levels (Roche, Mannheim, Germany) were obtained before and after PCI. The post-PCI samples were obtained at a median of 18 hours (interquartile range 16 to 20). Additional marker levels were obtained when an ischemic event was suspected or according to physician discretion. Only patients with TnT and CKMB levels measured concurrently and within 24 hours after PCI were included in the analysis of the relation between the TnT and CKMB levels. A cohort of 85 patients with acute coronary syndromes underwent delayed PCI because of scheduling (Figure 1). These patients had had normal CKMB and elevated TnT levels that were either stable or decreasing (after peak). The URL for TnT using the third- and fourth-generation assays (used before and after January 15, 2006, respectively) was 0.03 μg/L, defined as the level at ≤10% of the coefficient of variation. Gender-specific CKMB (mass) levels were used in all analyses. The URL was 4.9 μg/L for men and 2.9 μg/L for women.

Statistical analysis was performed using the Statistical Package for Social Sciences, version 14.0 (SPSS, Chicago, Illinois). The categorical variables are expressed as numbers and percentages per group, continuous variables as the mean ± SD for normally distributed variables, and skewed variables as the median and interquartile range. For group comparisons, Pearson's chi-square test or Fisher's exact test was used for unpaired categorical variables. McNemar's test was used for paired categorical variables. The Student *t* test or Mann-Whitney *U* test (for skewed variables) was used for continuous variables. The relation between the post-PCI TnT and post-PCI CKMB were modeled using linear regression analysis with logarithmic transformations of TnT and CKMB levels, accounting for the pre-PCI estimated glomerular filtration rate <30 ml/min/1.73 m^2, using the Modification of Diet in Renal Disease formula (estimated glomerular filtration rate = $186.3 \times \text{serum creatinine}^{-1.154} \times \text{age}^{-0.203} \times 0.742$, if female).[8] Forward stepwise logistic regression analysis was performed to determine the predictors of TnT elevation after PCI and late events (death or nonfatal MI). Age (≥70 years), American College of Cardiology/American Heart Association class B2 and C lesions, lesions in saphenous vein grafts, diabetes mellitus, duration of PCI (as a dichotomous variable at a median PCI duration of 59 minutes), maximum balloon pressure, and duration were included in the model for prediction of the post-PCI TnT elevations. The clinical indications for PCI (acute coronary syndromes and stable coronary heart disease), age (≥70 years), diabetes mellitus, PCI of culprit lesions in saphenous vein grafts, PCI of patients with culprit lesions at coronary bifurcations, post-PCI CKMB elevations (>3× URL), post-PCI TnT elevations (>3× URL), and patients with a pre-PCI estimated glomerular filtration rate <30 ml/min/1.73 m^2 were included in prediction models for late death or nonfatal MI. Comparisons of the frequencies of death or nonfatal MI between the groups were performed using Kaplan-Meier analyses and log-rank testing. p Values <0.05 were considered statistically significant; the 5 patients with staged procedures were included once.

Results

Of the patients who had undergone successful PCI during the study period, October 2003 to October 2006, 587 PCIs were performed on 582 patients (5 underwent staged

Table 1
Baseline clinical characteristics

Variable	Pre-PCI TnT Level			Clinical Indication for PCI		
	TnT <0.03 μg/L (stable CHD and ACS; n = 502)	TnT >0.03 μg/L (ACS; n = 85)*	p Value	ACS (n = 315)	Stable CHD (n = 272)	p Value
Mean age ± SD (years)	64.3 ± 10.8	62 ± 12.7	0.11	63 ± 11.6	65 ± 10.3	0.028
Men	378 (75%)	65 (77%)	0.816	245 (78%)	198 (73%)	0.162
Diabetes mellitus	101 (20%)	13 (15%)	0.298	63 (20%)	51 (19%)	0.703
Smoker	64 (13%)	25 (29%)	<0.0001	72 (23%)	17 (6%)	<0.0001
Hypertension	278 (55%)	45 (53%)	0.676	179 (57%)	144 (53%)	0.346
Hyperlipidemia†	340 (68%)	55 (65%)	0.583	224 (71%)	171 (63%)	0.034
Previous percutaneous coronary intervention	44 (9%)	1 (1%)	0.015	16 (5%)	29 (11%)	0.011
Previous coronary bypass	28 (6%)	4 (5%)	0.495	15 (5%)	17 (6%)	0.428
Estimated glomerular filtration rate (ml/min/1.73 m^2)						
<60	103 (21%)	21 (25%)	0.392	62 (20%)	62 (23%)	0.33
<30	8 (2%)	4 (5%)	0.082	9 (3%)	3 (1%)	0.137

* CKMB returned to normal before PCI (median interval from admission to PCI 5 days, interquartile range 3–7).

† Hyperlipidemia defined as previous diagnosis of hypercholesterolemia, including treatment with lipid-lowering agents or fasting low-density lipoprotein cholesterol of ≥130 mg/dl or total cholesterol of ≥200 mg/dl.

ACS = acute coronary syndromes; CHD = coronary heart disease.

Table 2
Angiographic and procedural characteristics

Variable	Pre-PCI TnT Level			Clinical Indication for PCI		
	TnT <0.03 μg/L (stable CHD and ACS; n = 502)	TnT >0.03 μg/L (ACS; n = 85)	p Value	ACS (n = 315)	Stable CHD (n = 272)	p Value
Percutaneous coronary intervention duration (minutes)			0.01			0.087
Median	59	69		64	55	
Interquartile range	43–80	52–88		45–83	42–80	
Site of culprit coronary narrowing						
Left anterior descending artery	193 (38%)	27 (32%)	0.239	119 (38%)	101 (37%)	0.872
Right coronary artery	131 (26%)	26 (31%)	0.387	90 (29%)	67 (25%)	0.282
Left circumflex coronary artery	83 (17%)	23 (27%)	0.020	59 (19%)	47 (17%)	0.649
Lesion classification (ACC/AHA)			0.457*			0.028*
B2	179 (36%)	38 (45%)	0.113	126 (40%)	91 (34%)	0.109
C	152 (30%)	22 (26%)	0.406	98 (31%)	76 (28%)	0.418
Culprit lesion at bifurcation	133 (27%)	23 (27%)	0.921	95 (30%)	61 (23%)	0.037
Culprit lesion length (mm)			0.633			0.351
Median	16	16		16	16	
Interquartile range	12–24	15–24		16–25	12–23	
Total stented length (mm)			0.567			0.934
Median	20	20		20	20	
Interquartile range	15–28	16–25		16–28	16–26	
Stent diameter (mm)			0.485			0.003
Median	3	3		3	2.75	
Interquartile range	2.5–3	2.5–3		2.5–3	2.5–3	
Stent type						
Drug-eluting stent	181 (36%)	27 (32%)	0.444	113 (36%)	95 (35%)	0.811
Bare metal stent	309 (62%)	58 (68%)	0.239	200 (64%)	167 (61%)	0.662
Maximum inflation pressure (atm)			0.952			0.027
Median	18	16		18	16	
Interquartile range	16–20	16–20		16–20	15–18	
Glycoprotein IIb/IIIa inhibitor						
Tirofiban	65 (13%)	11 (13%)	0.999	56 (18%)	20 (7%)	<0.001
Abciximab	34 (7%)	10 (12%)	0.106	35 (11%)	9 (3%)	<0.001

* p Value for combined American College of Cardiology/American Heart Association (ACC/AHA) class B2 and C lesions.

procedures), who met the present study's inclusion criteria (Figure 1). Of these 587 PCIs, 315 were performed in patients with acute coronary syndromes and 272 in patients with stable coronary heart disease. The demographic and angiographic characteristics of the patients according to the clinical indication for PCI and the pre-PCI TnT levels are

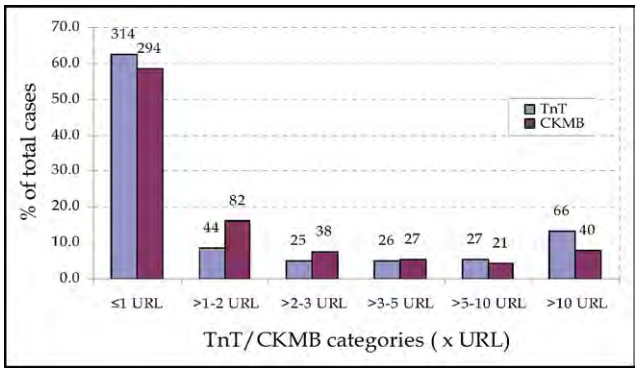

Figure 2. CKMB and TnT levels after PCI in patients with normal TnT levels before PCI. Stable coronary heart disease, n = 272; acute coronary syndromes, n = 230. URL for TnT = 0.03 μg/L; URL for CKMB = 4.9 μg/L for men and 2.9 μg/L for women. Numbers on top of each bar represent number of patients in each category.

listed in Tables 1 and 2. Periprocedural glycoprotein IIb/IIIa inhibitors were used in 20% (12.9% tirofiban and 7.5% abciximab). In 98% of PCIs, ≥1 stent was deployed (35% had ≥1 drug-eluting stent); 3 patients underwent rotational atherectomy. The rate of peri-PCI MI for all 587 PCI procedures, as determined by elevated TnT and CKMB levels (both >3× URL), as recommended by the 2007 universal definition of MI, was 23.9% and 16.7%, respectively. The independent predictors of TnT elevation after PCI on multivariate regression analysis were age (≥70 years; odds ratio [OR] 1.68, 95% confidence interval [CI] 1.12 to 2.52, p = 0.011), duration of PCI (as a dichotomous variable at 59 minutes; OR 1.59, 95% CI 1.07 to 2.35, p = 0.022), and American College of Cardiology/American Heart Association class B2 and C lesions (OR 1.54, 95% CI 1.00 to 2.37, p = 0.049).

Of the 502 PCIs performed in patients with normal pre-PCI TnT levels, elevated TnT levels after PCI to greater than the URL occurred in 188 patients (38%; 35% of patients with stable coronary heart disease and 41% of patients with acute coronary syndromes). The median level was 0.15 μg/L (interquartile range 0.07 to 0.65). Elevated CKMB levels after PCI to greater than the URL occurred in 208 patients (41%; 38% with stable coronary heart disease and 46% with acute coronary syndromes). The median CKMB level was 13 μg/L (interquartile range 7 to 38). According to the increased CKMB levels to >3× URL, periprocedural MI occurred in 88 patients (18%). In contrast, TnT levels >3× URL (>0.09 μg/L) indicated that periprocedural MI had occurred in 119 patients (24%; p <0.0001). The relations between the post-PCI TnT and CKMB levels for patients with normal baseline pre-PCI TnT levels are shown in Figure 2. Of those with elevated post-PCI TnT levels, 13% had normal CKMB levels. In patients without pre-PCI elevated TnT, significantly greater elevations in the post-PCI TnT levels occurred in the patients with acute coronary syndromes compared to those with stable coronary heart disease (median 0.27 μg/L, interquartile range 0.08 to 3.97 vs median 0.12 μg/L, interquartile range 0.06 to 0.28, respectively; p = 0.002).

A high correlation (r = 0.92, 95% CI 0.89 to 0.94, p <0.001) was seen between the elevated levels of TnT and CKMB after PCI when the pre-PCI TnT levels were normal (Figure 3). The regression equation describing this association is TnT (μg/L) = $e^{[(1.202[\ln \text{CKMB}\,\mu g/L]) - 4.693 + 0.264(\text{if estimated glomerular filtration rate} < 30)]}$, e = 2.718. Using this equation and assuming an estimated glomerular filtration rate >30 ml/min/1.73 m^2, CKMB elevations to 3× URL (14.7 μg/L for men and to 8.7 μg/L for women) corresponded to TnT levels of 0.23 μg/L and 0.12 μg/L respectively. The prediction of CKMB levels from the measured TnT levels can be obtained from the equation: CKMB level (μg/L) = $e^{[3.737 + (0.701\ [\ln \text{TnT}\ \mu g/L]) - 0.261\ (\text{if estimated glomerular filtration rate} < 30)]}$, e = 2.718. No significant correlation was seen when either of these biomarker level elevations after PCI were <2× URL (r <0.11, p >0.40 for both).

A total of 85 patients with acute coronary syndromes who underwent PCI at a median interval of 5 days (interquartile range 3 to 7) who had normal pre-PCI CKMB levels but elevated TnT levels (median level 0.30 μg/L, interquartile range 0.09 to 0.86 μg/L; Table 3). Of these, 28 patients (33%) had additional increases in the TnT levels after PCI (median increase in TnT level 0.31 μg/L, interquartile range 0.13 to 0.8 μg/L). With respect to the post-PCI biomarker elevations, 21 patients (24.7%) had a ≥20% additional elevation in TnT level, 12 patients (14%) had an additional elevation in TnT level of >0.09 μg/L (~3× URL), and 10 patients (11.8%) had a CKMB elevation >3× URL (p = 0.004 and p = 0.003 comparing ≥20% TnT increases, respectively). Of the 21 patients with a ≥20% additional TnT elevation (Table 3), none of whom had had periprocedural electrocardiographic changes, 9 had a CKMB elevation >3× URL after PCI, 8 had a CKMB elevation <3× URL, and 4 had no CKMB increase (an additional patient had a >3× URL CKMB but no TnT increase). Of the 57 patients with no additional TnT elevation after PCI, 13 (23%) had an elevation in CKMB levels to greater than the URL.

The correlation coefficient between the absolute increases in the TnT and CKMB levels is 0.75 (95% CI 0.53 to 0.88, p <0.0001), and the equation describing this relation is as follows: additional TnT elevation (μg/L) = $e^{[(1.103[\ln \text{CKMB}\,\mu g/L]) - 4.821 + 0.406\ (\text{if estimated glomerular filtration rate} < 30)]}$, e = 2.718.

During ~1 year of follow-up, of the patients with normal pre-PCI TnT levels, 14 died (9 with acute coronary syndromes [4%] and 5 with stable coronary heart disease [2%], p = 0.14), 9 had late nonfatal MI (5 with acute coronary syndromes [2.3%] and 4 with stable coronary heart disease [1.6%], p = 0.416), and 6 developed early and late stent thrombosis (3 with acute coronary syndromes [1.4%] and 3 with stable coronary heart disease [1.2%], p = 0.59).

Of the patients with stable coronary heart disease who had post-PCI TnT levels and/or CKMB levels greater than the URL, the 1-year rate of freedom from death or nonfatal MI was lower than in those without post-PCI TnT and/or CKMB elevations (92% vs 98.8% for TnT, p = 0.006; 93% vs 99% for CKMB, p = 0.012, log-rank). Of the patients with acute coronary syndromes and either normal or elevated pre-PCI TnT and/or CKMB levels, no differences were seen in event-free survival, irrespective of the post-PCI cardiac marker levels (95% vs 93% for TnT, p = 0.69, and 94% vs 93% for CKMB, p = 0.81, log-rank; Figure 4).

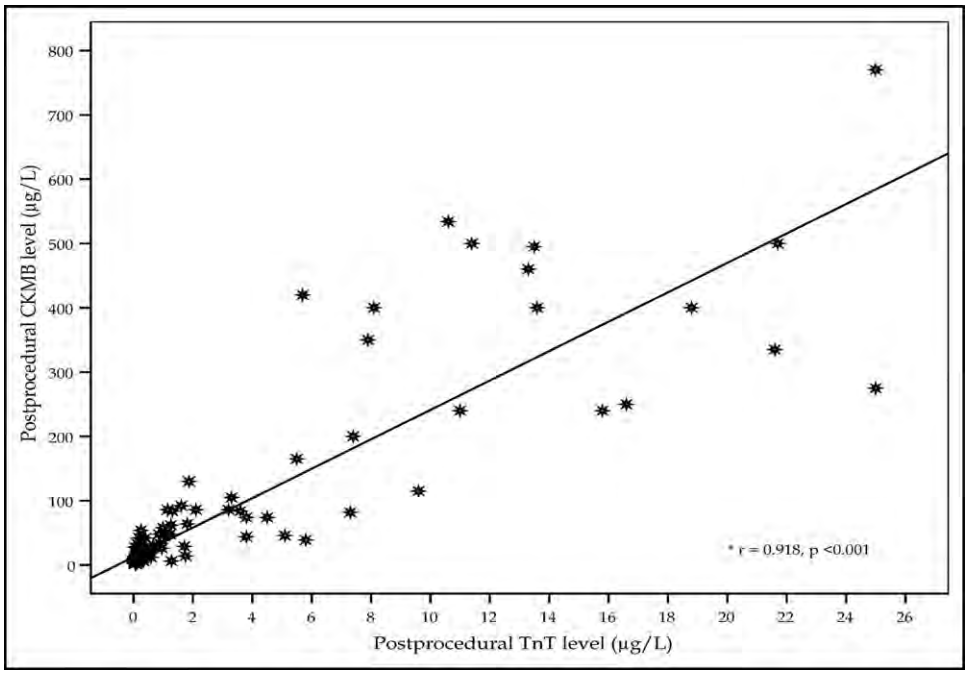

Figure 3. Association between elevated CKMB and TnT levels after PCI showing patients with normal CKMB and normal TnT levels before PCI. Patients with post-PCI values in normal range not included. *Pearson's correlation coefficient (measured after logarithmic transformations of TnT and CKMB levels).

Table 3
Relation between postpercutaneous coronary intervention (PCI) creatine kinase-MB (CKMB) and troponin T (TnT) levels in patients with elevated prepercutaneous coronary intervention (PCI) troponin T (TnT) and normal creatine kinase-MB (CKMB) levels

Variable	TnT			Patients (n)
	No Additional Elevation	Additional Elevation (%)*		
		<20% Elevation	≥20% Elevation	
Creatine kinase-MB at or less than upper reference limit	44	2	4	50
Creatine kinase-MB greater than upper reference limit but ≤2× upper reference limit	10†	5	7	22
Creatine kinase-MB >2× upper reference limit but ≤3× upper reference limit	2‡	0	1	3
Creatine kinase-MB >3× upper reference limit	1§	0	9	10
Total	57	7	21	85

* Percentage of post-PCI TnT elevation from elevated baseline pre-PCI TnT levels.
† Mean post-PCI CKMB level elevation for 10 patients was 5.3 ± 1.7) µg/L.
‡ TnT decreased from 0.68 µg/L before PCI to 0.51 µg/L after PCI and CKMB after PCI had increased to 11 µg/L.
§ Pre-PCI TnT was 1.14 µg/L and had decreased to 0.95 µg/L after PCI; CKMB increased from 2.9 µg/L before PCI to 28 µg/L after PCI.

Of the patients with stable coronary heart disease who had post-PCI TnT levels and/or CKMB levels >3× URL, the 1-year rate of freedom from death or nonfatal MI was lower than in those without such elevations (88% vs 99% for TnT, p <0.001, and 84% vs 98% for CKMB, p <0.001, log-rank). In contrast, among the patients with acute coronary syndromes and normal pre-PCI TnT and CKMB levels, no differences were seen in event-free survival for those who had post-PCI TnT and/or CKMB elevations (>3× URL) compared to those without such elevations (95% vs 93% for TnT, p = 0.56, and 94% vs 93% for CKMB, p = 0.82, log-rank).

On multivariate analysis, the independent predictors of death or nonfatal MI at 1 year were diabetes mellitus (OR 3.19, 95% CI 1.33 to 7.64, p = 0.009) and post-PCI CKMB level elevation >3× URL (OR 3.03, 95% CI 1.20 to 7.64, p = 0.019).

Discussion

The 2007 universal definition of MI requires ≥2 pre-PCI troponin levels 6 hours apart and a relative (≥20%) increase in the post-PCI TnT level to define post-PCI MI. An important aspect of our study was the inclusion of patients with acute coronary syndromes, who had experienced a delay in PCI largely because of interhospital transfer and scheduling, and who had elevated TnT but normal CKMB levels before PCI. This allowed us to measure further the absolute increases in TnT levels after PCI and correlate these with the CKMB levels. We considered at 5 days after admission for acute coronary

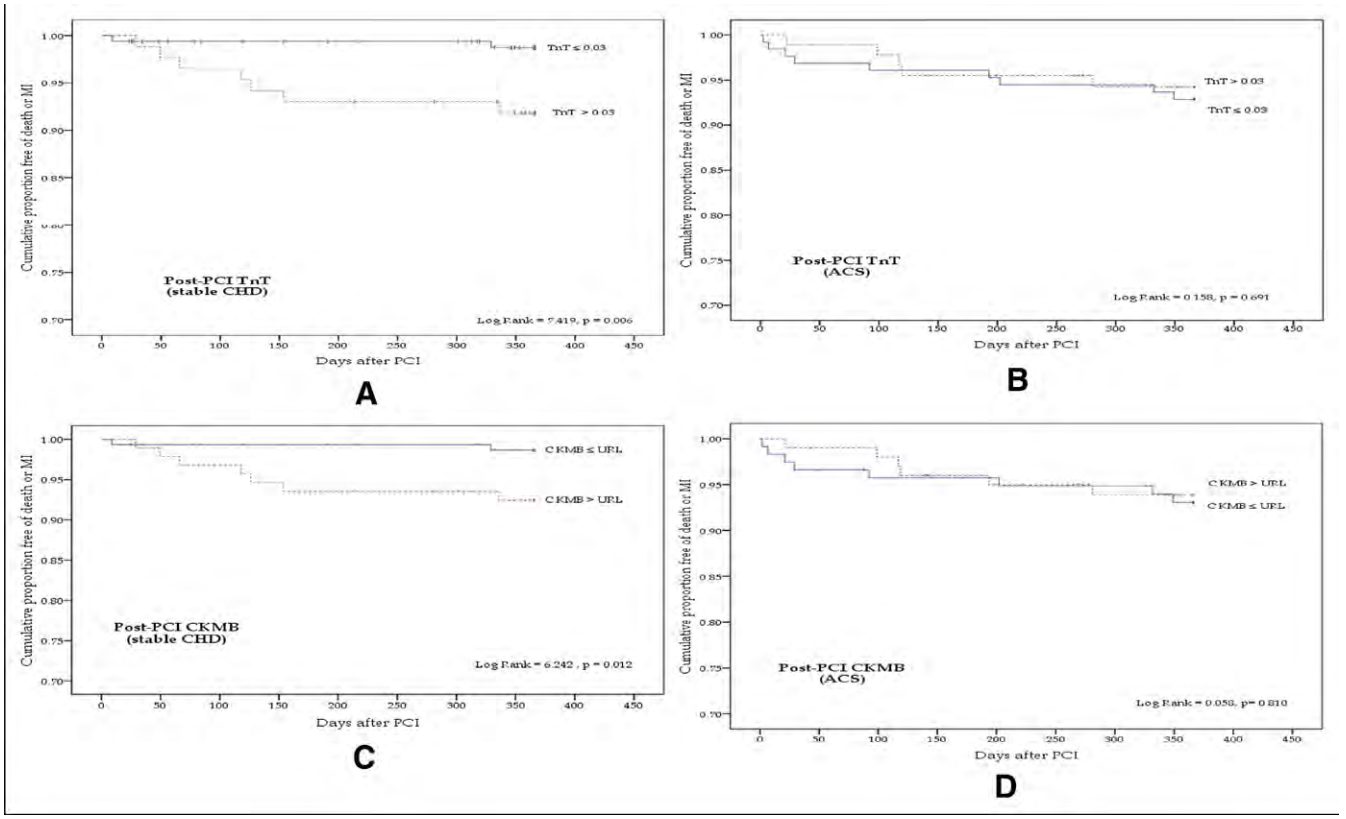

Figure 4. Freedom from death or nonfatal MI after PCI according to myonecrosis marker status after PCI. Kaplan-Meier survival curves shown according to myonecrosis marker levels after PCI in patients with stable coronary heart disease (CHD) and acute coronary syndromes (ACS) with normal pre-PCI myonecrosis markers. *(A,C)* Patients with stable coronary heart disease with respect to TnT and CKMB levels. *(B,D)* Patients with acute coronary syndromes with respect to TnT and CKMB levels. Among patients with acute coronary syndromes and elevated pre-PCI TnT, rates of freedom from death or nonfatal MI at 1 year for those with post-PCI TnT elevation of ≥20% compared to <20% were 95% and 95%, respectively (p = 0.89, log-rank).

syndromes that PCI would now be uncommonly performed in either routine practice or trials.

We found a high degree of correlation between the post-PCI CKMB and TnT levels when both markers levels were elevated to >2× URL in patients with stable coronary heart disease, a finding similar to that from a previous report.[9] We also found a significant association between an absolute increase in the TnT level to greater than the stable pre-PCI elevated level and the absolute increase in CKMB level to greater than the URL. Although we did not examine the associations between the peak levels of CKMB and TnT, which occur at different points after infarct onset,[10,11] we considered that our reported association of these marker levels at a median of 18 hours (the morning after PCI) will be useful in clinical practice. Furthermore, if minor elevations were present in the pre-PCI TnT levels, the 2007 universal definition of MI would lead to small additional elevations of ≥20% in TnT levels being diagnosed as (small) reinfarctions that (understandably) did not meet the CKMB reinfarction criteria. In contrast, when the pre-PCI TnT level was >0.8 μg/L or 20- to 30-fold greater than the URL, quite large absolute increases in postprocedural TnT levels did not meet the ≥20% increase in TnT reinfarction criteria, although the >3× URL CKMB elevation reinfarction criteria had been met.

Our results have confirmed that even using earlier generations of assays, TnT is a sensitive myonecrosis marker. With the ongoing development of TnT assays, an evolution has occurred in the reference ranges and the level considered >3× URL.[12] When our study began, elevated levels were locally reported as >0.03 μg/L; also, the level of the 10% coefficient of variation was 0.035 μg/L.[12] Although it has now been appreciated that TnT levels ≥0.01 μg/L, detectable using the third- and fourth-generation TnT assays are biologically abnormal,[13] we chose >0.09 μg/L using these TnT assays, representing >3× URL, the definition of postprocedural MI when the pre-PCI cardiac marker levels were normal.

We were not able to examine the pre-PCI and post-PCI TnT levels in the range of 0.01 to 0.03 μg/L (or even lower levels) using the high-sensitivity TnT assay, as recently reported.[13] The use of this assay would have been unlikely to have influenced our major findings, which focused on the detection of (larger) periprocedural TnT elevations measured by the third- and fourth-generation assays. Also, as indicated in a recent editorial by Morrow,[14] the major utility of minor elevations of these sensitive markers is in identifying more high-risk patients who might benefit from an early invasive strategy. Furthermore, the prognostic significance of minor increases in post-PCI TnT levels that meet the new recurrent MI

criteria of ≥20%, when the pre-PCI TnT levels are ≤0.03 μg/L and are now detected by high-sensitivity assays requires clarification.

The prognostic significance of periprocedural elevations of CKMB >3× URL has been known for more than a decade,[15,16] and, subsequently, similar evidence has been reported for troponin.[17] The detection of early reinfarction, including periprocedural recurrent MI, using TnT- and troponin I-based definitions has been confounded by the kinetic profiles of these cardiac markers with prolonged duration of elevation.[10,11]

Many investigators have reported the prognostic significance of elevated levels of CKMB after PCI.[15,18] However, minor CKMB elevations, which reflect small areas of myonecrosis identified on contrast-enhanced magnetic resonance imaging,[19] have also been shown to have a relation to survival. In the present study, the patients who underwent PCI for stable coronary heart disease and had any post-PCI elevated TnT and/or CKMB level had a reduced rate of freedom from death or nonfatal MI at 1 year compared to those without post-PCI marker elevations.

The post-PCI TnT and CKMB level elevations were greater in the acute coronary syndromes group compared to the stable coronary heart disease group, which could be explained by the greater frequency of American College of Cardiology/American Heart Association class B2 and C and bifurcation lesions. The data recently reported from the Mayo Clinic,[13] which showed that among patients with acute coronary syndromes undergoing PCI, only elevated pre-PCI, and not post-PCI, cardiac marker levels affected survival. Also periprocedural MI in patients with acute coronary syndromes in the Acute Catheterization and Urgent intervention Triage Strategy (ACUITY) trial[20] did not influence late events, although pre-PCI marker levels did. However, in the ACUITY trial, a significant fraction of patients underwent angiography and angioplasty within 12 to 18 hours of presentation. Also, although explicit criteria were in place for the clinical events committee for adjudication of MI,[20] a proportion of these potential early periprocedural events might not have been confirmed because of uncertainty about the early elevation profiles in marker levels. In contrast, because of the cardiac marker selection criteria for our study, we did not include patients who had undergone "early" angiography and angioplasty. Also, whether the ACUITY investigators made gender-specific adjustments for CKMB reference ranges is not clear, although, as in our study, because most patients with coronary heart disease are men, the salient findings would likely be unaltered by this adjustment.

Our study had limitations. Although this was a single-center study in which the PCI data were collected prospectively, the cardiac marker data were analyzed retrospectively, which might have led to an unappreciated bias. Second, because both cardiac markers were not measured for all patients with stable coronary heart disease before PCI, we might have occasionally erroneously assumed the normality of the pre-PCI marker levels. Other illnesses as confounding causes of TnT elevations other than renal impairment were not evaluated in the present study,[10] although most patients were stable at PCI. Also, because a relatively small number of patients were in the group with acute coronary syndromes and elevated TnT levels but normal CKMB levels, the power was insufficient to determine any (potentially modest) influence of additional post-PCI TnT elevations on the 1-year outcomes. Finally, we examined the composite late clinical outcome of death and (nonprocedural) nonfatal MI because our sample size had limited power to examine associations between late mortality and marker levels, as reported from the Mayo Clinic.[13]

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Original Article

Evaluation of a Policy of Selective Drug-eluting Stent Implantation for Patients at High Risk of Restenosis

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Drug-eluting stent (DES) deployment during percutaneous coronary intervention (PCI) has reduced target-vessel revascularisation rates (TVR). The selective use of DES in patients at highest risk of restenosis may allay concerns about universal compliance of dual antiplatelet therapy for one year, and potentially reduce costs. If this strategy achieved acceptably low TVR rates, such an approach could be attractive.

Late clinical outcomes were examined in 2115 consecutive patients (mean age 63 ± 12 years, 75% male, 22% diabetics) who underwent PCI in the first three years from October 2003, after commencing the following selective criteria for DES use: left main stenosis; ostial lesions of major epicardial arteries; proximal LAD lesions; lesions ≥ 20 mm in length with vessel diameter ≤ 3.0 mm; lesions in vessels ≤ 2.5 mm; diabetics with vessel(s) ≤ 3.0 mm; and in-stent restenosis. Among patients undergoing PCI, 2075 (98%) patients received stents (29% ≥ 1 DES and 71% bare metal stent [BMS]), and among those who received DES, there was a 92% compliance with these criteria. There were no differences in clinical outcomes between the two stent groups except for definite stent thrombosis, which occurred in 2% after DES, and 0.6% after BMS at one year ($p = 0.002$). With BMS, large coronary arteries (≥3.5 mm), intermediate (3–3.49 mm) and small arteries (<3 mm) in diameter had a TVR rate at one year of 3.6%, 7.2% and 8.2% respectively ($p = 0.005$).

It is possible to use selective criteria for DES while maintaining low TVR rates. The TVR rate with BMS was low in those with stent diameters ≥ 3.5 mm. The higher DES stent thrombosis rate reflects first generation DES use, though whether routine second generation DES use reduces these rates needs confirmation.

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Keywords. Percutaneous coronary intervention; Drug-eluting stents; Bare-metal stents; Selective drug-eluting stents use criteria; Target vessel revascularisation

Introduction

The deployment of bare-metal stents (BMS) during percutaneous coronary intervention (PCI) is associated with a reduction in rates of restenosis compared to balloon angioplasty [1]. The use of drug-eluting stents (DES) has further reduced target-vessel revascularisation (TVR) rates [2–5]. Clinical trials and registries have generally compared DES with BMS in all patients with coronary heart disease without specifically addressing DES use based on the patient's perceived risk of TVR [2,3,5]. Low TVR rates have been reported following BMS deployment in patient subsets with certain clinical and/or lesion characteristics such as non-diabetics, and shorter lesions in large diameter arteries [6,7] though randomised trials have not specifically evaluated their use in such circumstances [8]. Identification of specific patient subsets with low TVR rates post-BMS deployment, may minimise concerns about the risk of late stent thrombosis and the need for compliance with dual antiplatelet therapy with aspirin and clopidogrel for one year, and may have a favourable economic impact [9]. Thus we aimed to determine such patient subsets by examining clinical outcomes in the first three years after commencing our selective DES use criteria.

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Methods

Study Population

The study population consisted of consecutive patients undergoing PCI at the cardiac catheterisation laboratories of Liverpool Hospital (Sydney, Australia) from October 2003 (when our institutional selective criteria for DES use started) to October 2006 (Fig. 1). All patients had baseline clinical and angiographic data recorded prospectively in the cardiology department database as previously described [7]. The study was approved by South Western Sydney Local Health District human research ethics committee (no. QA2008/034).

Percutaneous Coronary Intervention Procedures

Percutaneous coronary intervention procedures were performed with standard techniques. Unless contraindicated, aspirin (300 mg) was given before PCI and continued indefinitely thereafter as 100–150 mg/day, Clopidogrel loading dose of 300 mg or 600 mg was given either before, at the time of PCI or immediately after PCI and prescribed at dose of 75 mg/day post-PCI for at least 12 months. A bolus of unfractionated heparin (60–100 U/kg) was given at the start of PCI procedures. The use of intravenous glycoprotein IIb/IIIa inhibitors, either Tirofiban or Abciximab, was at the cardiologists' discretion. All angiographic and procedural data are reported and coded on the cardiology database prospectively.

The selective DES use criteria shown in Fig. 1 [7], aimed to achieve 30% DES use. The adherence to these criteria was assessed independently of clinical outcomes. The DES included first generation stents: TAXUS Liberte (Boston Scientific, USA), TAXUS Express2 (Boston Scientific, USA), Cypher (Cordis Johnson and Johnson, USA), Cypher Select (Cordis Johnson and Johnson, USA). The BMS used were: Express2 and Liberte (Boston Scientific, USA), Multilink-Vision (Abbott Vascular, USA), PRO-Kinetic (Biotronik, Switzerland), Driver (Medtronic, USA), and Tsunami Gold (Terumo, Japan). Angiographic success was defined as a final post-PCI minimum stenosis diameter reduction to <20% with stenting or <50% with balloon and grade 3 TIMI flow.

Patients were classified according to stent type: DES or BMS only. Either nominal diameter of the post-dilation balloon, or nominal stent size if no post-dilation was performed, was taken to correspond to the final target coronary artery diameter.

Clinical Follow-up and Definitions

Clinical follow-up was performed by trained clinical staff (nurses and/or doctors). Patients, their next of kin or primary physicians were contacted by phone and were asked about recurrent cardiac symptoms requiring hospitalisation, need for coronary revascularisation, or myocardial infarction (MI), and these were confirmed and recorded in the database. Data regarding mortality was obtained from medical records, physicians, next of kin and state death registry. Other clinical outcomes such as repeated procedures for stent thrombosis (ST) and restenosis were independently verified.

The clinical outcomes were determined at 30 days and one year and defined as following: (i) death including all cause mortality, (ii) myocardial infarction as defined by chest pain lasting $\geq$30 min and accompanied by new ECG changes (Q waves > 0.04 s or ST-segment elevation > 0.1 mV) and/or further biomarker rise (creatine kinase [>2× URL], CKMB [>URL] or troponin T [>URL]), (iii) TVR was defined as ischaemia-driven repeat revascularisation of the infarct-related artery, requiring repeat PCI or coronary artery bypass graft surgery (CABG), and (iv) target lesion revascularisation (TLR) was defined as repeat PCI of the stented segment within 5 mm of the proximal and/or distal stent edge; or CABG. We report definite ST confirmed by angiography, as defined by the Academic Research Consortium [10].

Data Analysis

All statistical analyses were performed using SPSS Inc. (Chicago) version 17.0. Categorical variables are expressed as numbers and percentages, and continuous variables as mean $\pm$ standard deviations (SD) or medians with 25th and 75th percentile. For group comparisons Pearson's chi square (χ^2) test or Fisher's exact test were used as appropriate for unpaired categorical variables. The student's *t*-tests or the Mann–Whitney *U*-tests (for skewed distribution) were used for continuous variables. Propensity score analysis was performed using a multivariable logistic regression analysis for use of DES versus BMS to compensate for the study's nonrandomised design; the rationale and methods have been previously described [11]. Clinical and angiographic variables which were significant on univariate analysis among the two treatment groups (DES vs. BMS) were included in propensity score analysis model. These included age ($\geq$75years), BMI, diabetes, hyperlipidaemia, hypertension, smoking, prior aspirin use, type of presentation (stable-CHD/ACS), site of culprit lesion (left main, proximal left anterior descending [LAD], right coronary artery [RCA] and left circumflex artery [LCx]), lesions at bifurcations, calcified lesion, ostial lesions, reference vessel diameter, lesion length $\geq$ 20 mm and type B2 and C (ACC/AHA) lesion class. The propensity score for each patient was calculated and ranged from 0.03 to 0.93. The propensity score was then incorporated into the regression analysis as a covariate with stent type (DES vs. BMS) and was then used to adjust the clinical outcomes.

Clinical outcomes were also displayed using Kaplan–Meier methodology, and were compared with Log Rank test. All *p*-values < 0.05 (2 sided) were considered statistically significant.

Analysis was also performed using the restenosis risk score from the Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction (HORIZONS-AMI) trial [8]. This included three risk variables for restenosis, diabetes mellitus, lesion length $\geq$ 30 mm and vessel diameter $\leq$ 3 mm. One point was assigned to each of the three risk variables, and patients with 0, 1, and $\geq$2 points of these three risk factors were classified as low, intermediate, or high risk for

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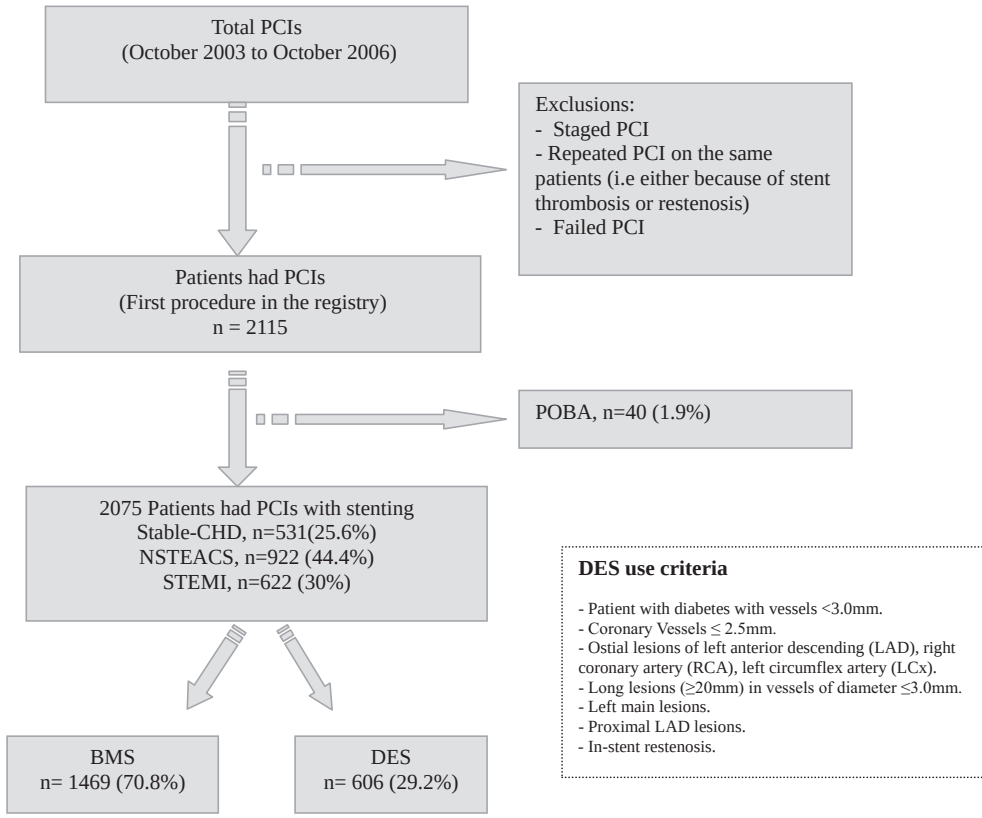

Figure 1. *Study population. CABG, coronary artery bypass grafting; CHD, coronary heart disease; DES, drug-eluting stents; BMS, bare-metal stents; NSTEACS, non ST- segment elevation acute coronary syndromes; PCI, percutaneous coronary intervention; POBA, plain old balloon angioplasty; STEMI, ST-segment elevation myocardial infarction. Late follow-up was obtained in 2040 patients 98.3% (98% among patients with DES and 98.4% among patients with BMS, p = 0.505).*

restenosis respectively. Then TLR rates for DES and BMS were assessed according to the above risk score.

Results

Clinical and Procedural Characteristics

From October 2003 to October 2006, 2115 consecutive patients with CHD underwent PCI, in which 2075 (98%) patients had successfully received at least one stent and 40 (1.9%) patients had balloon angioplasty alone. Among the patients who received stents, 1469 (71%) patients received BMS, and 606 (29%) patients received at least one DES (including 61 patients who received both DES and BMS) (Fig. 1). Among patients who received DES, there was 92% criteria compliance. Patient baseline characteristics according to the type of stents are shown in Table 1. Among these, 622 patients (30%) had ST-segment elevation MI, 922 patients (44.4%) had non-ST segment elevation acute coronary syndromes and 531 patients (26%) had stable coronary heart disease (stable-CHD). There were more patients with stable CHD among the DES group (31% vs. 23%, $p < 0.0001$). Patients who received DES were more likely to have diabetes (31% vs.18%, $p < 0.0001$), hypertension (56% vs.49%, $p = 0.002$) and hyperlipidaemia (74% vs. 69%, $p = 0.014$).

Angiographic and procedural details are shown in Table 2. Patients who received DES were more likely to have culprit lesions in the proximal LAD (41% vs. 16%, $p < 0.0001$), and left main coronary artery (2.6% vs. 0.7%, $p = 0.002$), while patients who received BMS were more likely to have culprit lesions in the RCA and LCx (40% vs. 16%, $p < 0.0001$ and 22% vs. 17%, $p < 0.004$ respectively). Patients who received DES had more bifurcation culprit lesions (33% vs. 16%, $p < 0.0001$), more B2 and C ACC/AHA class lesions (76% vs. 66%, $p < 0.0001$), more ostial lesions (13.4% vs. 4.1%, $p < 0.0001$) and longer lesion lengths (median 18 [13–25] vs. 16 [12–24], $p < 0.0001$) compared to patients who received BMS. Post-procedural TIMI-3 flow was achieved in 99% of the patients (100% in patients with DES vs. 98.7% in patients with BMS, $p = 0.006$). Glycoprotein IIb/IIIa inhibitors were used in 30% of patients (28.4% in patients with DES vs. 30.5% in patients with BMS, $p = 0.339$).

Clinical Outcomes

At 30 days, overall mortality, MI and TVR rates were 1.9%, 1.4% and 1.3% respectively. The rate of death/MI was 3.1%. Among patients who received DES compared to BMS, mortality was 1.2% vs. 2.1% ($p = 0.143$), MI was 1.5% vs. 1.4% ($p = 0.819$) and the TVR rate was 1.9% vs.

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Table 1. *Baseline Clinical Characteristics.*

	All Patients ($n = 2075$)	Patients with Drug-eluting Stents ($n = 606$)	Patients with Bare-Metal Stents ($n = 1469$)	*P* Value
Age (mean ± SD) (years)	62.8 (±11.9)	62.7 (±11.3)	62.9 (±12)	0.740
Age ≥ 65 years, *n* (%)	950 (45.8%)	275 (45.4%)	675 (45.9%)	0.813
Age ≥ 75 years, *n* (%)	371 (17.9%)	93 (15.3%)	278 (18.9%)	0.053
Male gender, *n* (%)	1555 (74.9%)	444 (73.3%)	1111 (75.6%)	0.259
Body mass index (kg/m^2)	27.45 (25–31)	27.7 (25–31)	28.0 (25–31)	0.023
Diabetes mellitus, *n* (%)	450 (21.7%)	187 (30.9%)	263 (17.9%)	<0.0001
Hypertension, *n* (%)	1051 (50.7%)	339 (55.9%)	712 (48.5%)	0.002
Previous aspirin use, *n* (%)	1266 (61.1%)	343 (56.6%)	923 (63.0%)	0.007
Hyperlipidaemia[a], *n* (%)	1454 (70.1%)	448 (73.9%)	1006 (68.5%)	0.014
Smoking, *n* (%)	480 (23.1%)	104 (17.2%)	376 (25.6%)	<0.0001
Family history of CHD, *n* (%)	453 (21.8%)	129 (21.3%)	324 (22.1%)	0.700
Previous PCI, *n* (%)	113 (5.4%)	38 (6.3%)	75 (5.1%)	0.288
Previous CABG, *n* (%)	135 (6.5%)	44 (7.3%)	91 (6.2%)	0.371
Stable CHD, *n* (%)	531 (25.6%)	187 (30.9%)	344 (23.4%)	<0.0001
ACS, *n* (%)				
(a) NSTEACS, *n* (%)	922 (44.5%)	295 (48.7%)	627 (42.7%)	0.012
(b) STEMI, *n* (%)	622 (30.0%)	124 (20.5%)	498 (33.9%)	<0.0001
Cardiogenic shock pre-PCI, *n* (%)	53 (2.6%)	13 (2.1%)	40 (2.7%)	0.448

ACS, acute coronary syndromes; CHD, coronary heart disease; NSTEACS, non ST-segment elevation acute coronary syndromes; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction.
[a] Hyperlipidaemia defined as previous diagnosis of hypercholesterolaemia, including treatment with lipid-lowering agents or fasting low-density lipoprotein cholesterol of ≥130 mg/dl or total cholesterol of ≥200 mg/dl.

1.1% ($p = 0.181$). Clinical outcomes including TVR rates at 30 days and one year are shown in Table 3. The rate of early definite ST was 0.8% (1.5% for DES vs. 0.5% for BMS, $p = 0.025$).

At one year, the overall rates of mortality, MI, TVR, composites of death/MI, and death/MI/TVR were 4.2%, 2.6%, 5.7%, 6.5% and 10.5% respectively. Among patients who received DES compared to BMS mortality was 3.9% vs. 4.4% ($p = 0.621$), MI was 2.9% vs. 2.5% ($p = 0.631$), the TVR rate was 4.9% vs. 6.1% ($p = 0.288$). The overall rates of definite ST (early and late) were 2% for DES vs. 0.6% for BMS ($p = 0.002$). Kaplan–Meier curves (Fig. 2) over 2 years showed no differences in event rates between DES and BMS except for stent thrombosis.

After propensity score adjustment, DES significantly reduced the TVR rate at one year compared with BMS (OR: 0.46 95% CI [0.28–0.74], $p = 0.001$), with no significant differences in other clinical outcomes (Table 3). After adjustments, the significant differences noted in death, and death/MI at 30 days were not significant at one year (Table 3).

Analysis of the study cohort according to diabetic status and the diameter of deployed stent(s) revealed that: (i) in diabetic patients, TVR rates at one year with BMS vs. DES were 9.6% vs. 6% ($p = 0.172$); whereas in non-diabetics they were 5.3% vs. 4.4% respectively ($p = 0.458$), and (ii) among patients who received BMS ≥ 3.5 mm in diameter, the one year TVR rate was 3.6%, whereas patients who received intermediate or small sized BMS had respective TVR rates of 7.2% and 8.2% ($p = 0.005$). Kaplan–Meier curves for TVR over two years among patients who received BMS of ≥3.5 mm in diameter was lower than those who received intermediate- or small-sized BMS (Fig. 3).

Analysis using the restenosis risk score (low, intermediate and high risk) from the HORIZONS-AMI trial showed that among patients who had none of the three risk factors for restenosis (low risk, 26%), there were no differences in TLR at one year in those who receiving BMS compared with DES (2.5% and 1.9% respectively, $p = 0.99$). The overall TLR rate among patients progressively increased with an increase risk score of restenosis from low, intermediate to high risk (2.4% vs. 4.4% vs. 6.4%, $p = 0.007$). The TLR rate in patients who received BMS progressively increased with an increase risk score of restenosis from low, intermediate to high risk (2.5% vs. 4.4% vs. 8.4%, $p = 0.001$) (Fig. 4).

Discussion

This study reports clinical outcomes of consecutive patients undergoing PCI in the first three years after adoption of selective criteria for DES deployment, which were adopted at our hospital to control costs associated with the adoption of this new technology. These criteria aimed to deploy DES in ∼30% patients undergoing PCI at

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Table 2. *Angiographic and Procedural Characteristics.*

	All Patients ($n = 2075$)	Patients with Drug-eluting Stents ($n = 606$)	Patients with Bare-Metal Stents ($n = 1469$)	*P* Value
Culprit coronary artery, *n* (%)				
Left main	27 (1.3%)	16 (2.6%)	11 (0.7%)	0.001
Left anterior descending artery	872 (42.0%)	380 (62.7%)	492 (33.5%)	<0.0001
Left circumflex coronary artery	426 (20.5%)	100 (16.5%)	326 (22.2%)	0.004
Right coronary artery	680 (32.8%)	95 (15.7%)	585 (39.8%)	<0.0001
Bypass graft	70 (3.4%)	15 (2.5%)	55 (3.7%)	0.146
Lesion type (ACC/AHA), *n* (%)				
A	102 (4.9%)	20 (3.3%)	82 (5.6%)	0.029
B1	543 (26.2%)	124 (20.5%)	419 (28.6%)	<0.001
B2	816 (39.4%)	252 (41.7%)	564 (38.4%)	0.174
C	611 (29.5%)	209 (34.5%)	402 (27.4%)	0.001
B2/C	1427 (68.9%)	469 (76.2%)	966 (65.8%)	<0.0001
Lesions at proximal LAD, *n* (%)	490 (23.6%)	249 (41.1%)	241 (16.4%)	<0.0001
Culprit lesions at bifurcation, *n* (%)	431 (20.8%)	201 (33.2%)	230 (15.7%)	<0.0001
Culprit lesions calcifications, *n* (%)	317 (15.3%)	126 (20.8%)	191 (13.0%)	<0.0001
Ostial lesions, *n* (%)	141 (6.8%)	81 (13.4%)	60 (4.1%)	<0.0001
Culprit lesion length (mm)[a]	16 [12–24]	18 [13–25]	16 [12–24]	<0.001
Culprit lesion length ≥ 20 mm, *n* (%)	841 (40.5%)	297 (49.0%)	544 (37.1%)	<0.001
Total stented length (mm)[a]	20 [16–28]	20 [16–28]	20 [15–28]	0.307
Stent diameter (mm)[a]				
<3 mm, *n* (%)	730 (35.2%)	285 (47.0%)	445 (30.3%)	<0.0001
≥3–3.49 mm, *n* (%)	644 (31.0%)	193 (31.8%)	451 (30.7%)	0.608
≥3.5 mm, *n* (%)	701 (33.8%)	128 (21.1%)	573 (39.0%)	<0.0001
>1 stent, *n* (%)	616 (29.7%)	185 (30.5%)	431 (29.3%)	0.590
Maximal deployment pressure (atm)[a]	16 [16–20]	18 [16–20]	16 [16–20]	0.141
Maximal duration of deployed pressure (s)[a]	30 [23–30]	30 [25–30]	30 [22–30]	0.501
Glycoprotein IIb/IIIa inhibitor, *n* (%)	620 (29.9%)	172 (28.4%)	448 (30.5%)	0.339
Tirofiban	369 (17.8%)	102 (16.8%)	267 (18.8%)	
Abciximab	238 (11.5%)	68 (11.2%)	170 (11.6%)	
Eptifibatide	13 (0.6%)	2 (0.3%)	11 (0.7%)	
TIMI flow grad after PCI, *n* (%)				0.006
3	2015 (99.1%)	595 (100%)	1420 (98.7%)	
≤2	18 (0.9%)	0 (0%)	18 (1.3%)	
Percent of coronary artery stenosis[a]				
Pre-PCI	90 [80–98]	90 [80–95]	90 [80–99]	0.016
Post-PCI	0 [0–0]	0 [0–0]	0 [0–0]	0.192
Angiographic success, *n* (%)	2057 (99.1%)	606 (100%)	1451 (98.8%)	0.006
Procedural success, *n* (%)	2072 (99.9%)	606 (100%)	1466 (99.8%)	0.266

ACC/AHA, American College of Cardiology/American Heart Association; PCI, percutaneous coronary intervention; TIMI, thrombolysis in myocardial infarction.
[a] Median [IQR].

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Table 3. *Clinical Outcomes.*

	All Patients ($n = 2040$)	Patients with Drug-eluting Stents ($n = 594$)	Patients with Bare-Metal Stents ($n = 1446$)	*P* Value	Propensity Score Adjusted OR (95% CI) (DES vs. BMS)	*P* Value
30 days						
Death, *n* (%)	38 (1.9%)	7 (1.2%)	31 (2.1%)	0.143	0.28 (0.12–0.69)	0.006
MI, *n* (%)	29 (1.4%)	9 (1.5%)	20 (1.4%)	0.819	0.71 (0.30–1.72)	0.449
TVR, *n* (%)	27 (1.3%)	11 (1.9%)	16 (1.1%)	0.181	1.00 (0.42–2.38)	0.996
TLR, *n* (%)	20 (1.0%)	10 (1.7%)	10 (0.7%)	0.039	1.5 (0.56–4.11)	0.407
ST, *n* (%)	16 (0.8%)	9 (1.5%)	7 (0.5%)	0.025	2.32 (0.76–7.13)	0.142
Acute	5 (0.2%)	2 (0.3%)	3 (0.2%)			
Sub-acute	11 (0.5%)	7 (1.2%)	4 (0.3%)			
Death/MI, *n* (%)	63 (3.1%)	15 (2.5%)	48 (3.3%)	0.346	0.43 (0.23–0.82)	0.011
Death/MI/TVR, *n* (%)	69 (3.4%)	18 (3.0%)	51 (3.5%)	0.573	0.49 (0.27–0.89)	0.020
1 year						
Death, *n* (%)	86 (4.2%)	23 (3.9%)	63 (4.4%)	0.621	0.63 (0.37–1.08)	0.093
MI, *n* (%)	53 (2.6%)	17 (2.9%)	36 (2.5%)	0.631	0.86 (0.45–1.66)	0.652
TVR, *n* (%)	117 (5.7%)	29 (4.9%)	88 (6.1%)	0.288	0.46 (0.28–0.74)	0.001
TLR, *n* (%)	89 (4.4%)	23 (3.9%)	66 (4.6%)	0.487	0.52 (0.31–0.90)	0.018
ST, *n* (%)	20 (1%)	12 (2%)	8 (0.6%)	0.002	2.53 (0.92–6.96)	0.073
Death/MI, *n* (%)	133 (6.5%)	38 (6.4%)	95 (6.6%)	0.886	0.72 (0.47–1.12)	0.141
Death/MI/TVR, *n* (%)	214 (10.5%)	53 (8.9%)	161 (11%)	0.139	0.52 (0.36–0.74)	<0.001

MI, myocardial infarction; TLR, target lesion revascularisation; TVR, target vessel revascularisation; ST, stent thrombosis.

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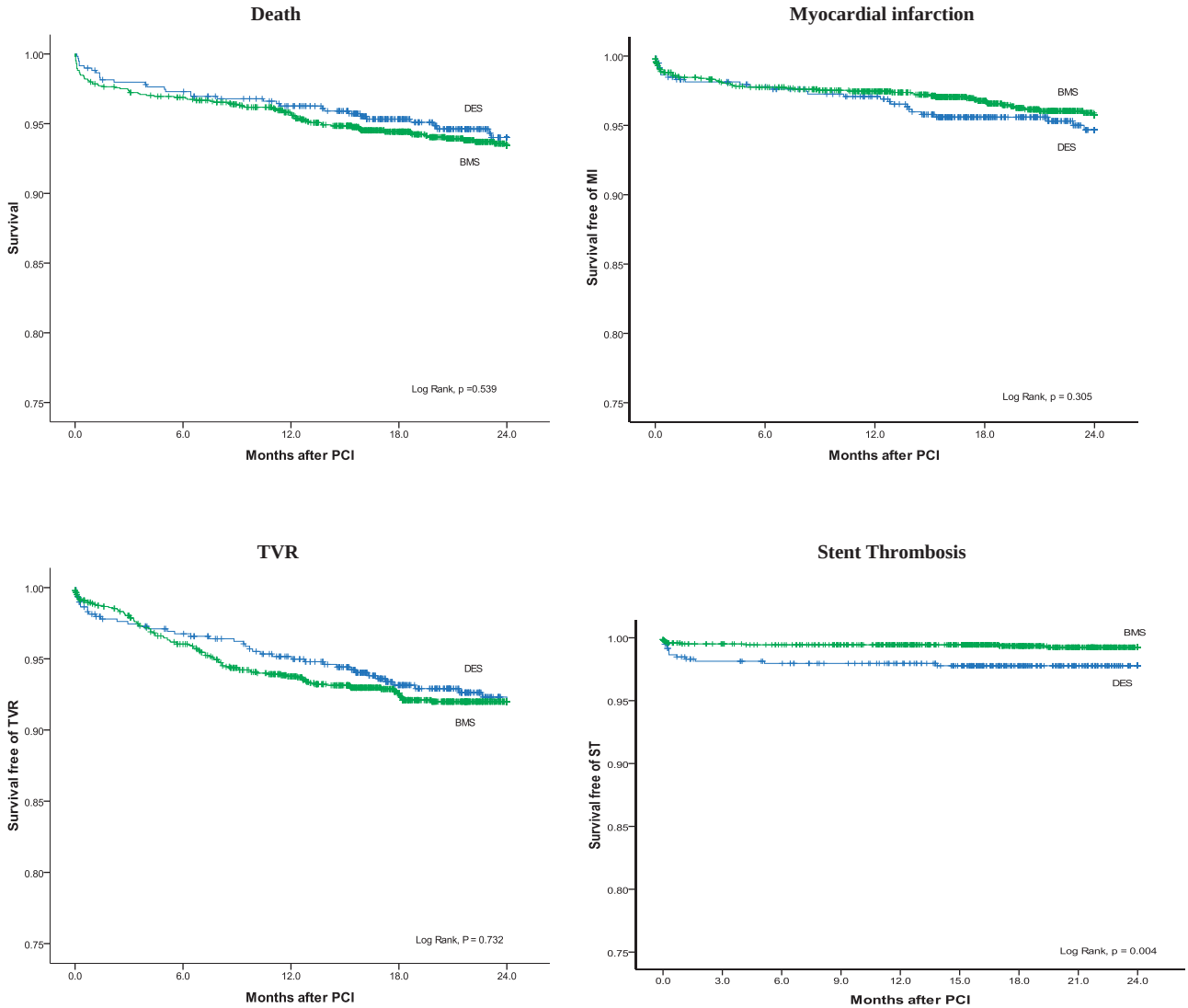

Figure 2. *Kaplan–Meier curve for target vessel revascularisation, death, myocardial infarction and stent thrombosis according to the type of stents. Death, myocardial infarction (MI), target vessel revascularisation rate (TVR) and stent thrombosis (ST) rates are shown according stent type bare metal stent (BMS) or drug-eluting stents (DES).*

highest risk of restenosis. DES were deployed in 29% of PCI patients and 92% of these patients met the institution's selective use criteria. These selective DES use criteria are the probable explanation for similar clinical outcomes including TVR rates in patients with DES and BMS. The TVR rate at one year in low risk patients with BMS is lower than that reported in randomised trials and lower than that from registries without selective DES use [3,4]. The TVR rate among patients receiving BMS in large diameter coronary arteries (≥3.5 mm) was low at 3.6%.

Randomised clinical trials demonstrate that the use of DES compared to BMS reduces revascularisation rates [2–5], whereas registries tend to reflect outcomes after individual clinician decisions about stent choice rather than specific criteria for DES such as reported here. Similar criteria to our institutions were later adopted by the NSW Department of Health, Australia and the National Institute for Clinical Excellence in UK [12,13].

In the Ontario Registry [14], TVR rates at one year for BMS and DES were 8.6% and 5.2% respectively, which are similar to those reported here. In the Melbourne Interventional Group (MIG) registry in which comparable DES were used [15], the TVR rates were 7.4% and 6.4% for BMS and DES respectively. More recently, a report from the Temporal Analysis of the Multicenter Evaluation of Drug Eluting Stents and Ischemic Events (EVENT) registry from the USA reported overall TVR rates at one year during two eras, firstly liberal DES use (92%, 2004–2006) and secondly "somewhat restrictive" DES use (68%, 2007), of 5.6% and 6.5% respectively. These rates were comparable with our overall TVR rate of 5.7% with selective DES criteria targeting patients with perceived high risk of restenosis (29% DES use). Recently published results from the Swedish Coronary Angiography and Angioplasty Registry (SCAAR) have shown lower rates of both restenosis and stent thrombosis with use of second generation DES,

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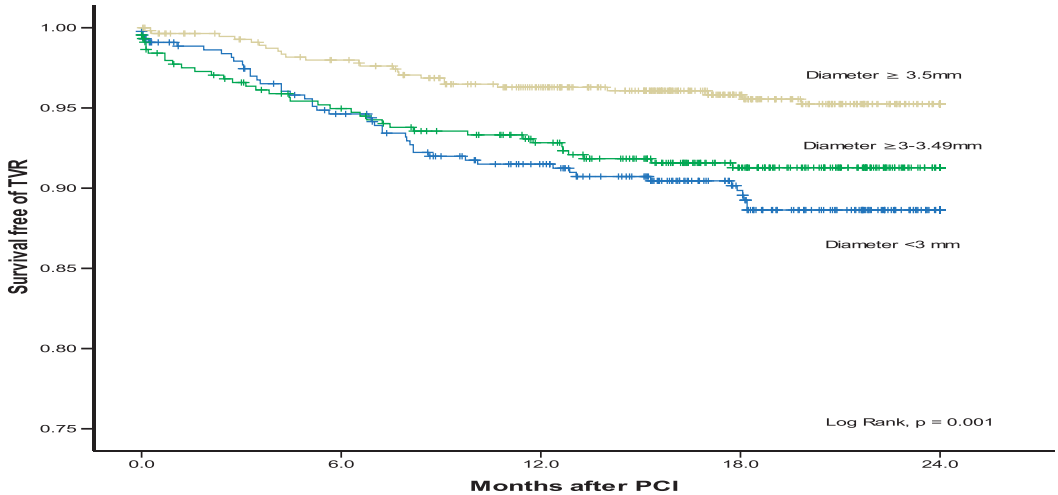

Figure 3. *Kaplan–Meier curve for target vessel revascularisation according to vessel size after bare-metal stent deployment. Target vessel revascularisation rate (TVR) rates are shown with bare metal stent deployment according to stent sizes (1) <3 mm; (2) 3.0–3.49 mm and (3) ≥3.5 mm. Among those who received BMS, TVR for those with lesion length < 20 mm versus 20–29 mm versus ≥30 mm were 6.6% vs. 7.8% vs. 10.3% respectively (p = 0.160).*

compared with first generation DES use [16]. Although these results are reassuring, further study is needed to confirm these findings.

In the HORIZONS-AMI trial, three risk factors for restenosis (insulin-requiring diabetes, reference vessel diameter ≤ 3 mm, and lesion length ≥ 30 mm) were used to classify post STEMI patients into three risk groups, low, intermediate and high risk for TLR. Among patients who had none of these three risk factors (32%), there were no differences in event rates between patients receiving BMS and DES with TLR rates at one year of 3.3% and 3.2% respectively [8]. We applied this score to our study, and we found 26% of our patients had none of these three factors and among such patients the TLR rates were 2.5% and 1.9% for BMS and DES respectively.

In the Basel Stent KostenEff ektivitäts trial (BASKET), DES significantly reduced non-MI-related TVR compared with BMS in patients with small coronary arteries (<3 mm) and whereas TVR rates were not significantly different in coronary arteries ≥ 3 mm [17,18]. We observed a low TVR rate (3.6%) following deployment of BMS in large (≥3.5 mm) coronary arteries, whereas patients who received small or intermediate size BMS had TVR rates of 8.2% and 7.2% respectively. The study by Steinberg et al. [19] found a TLR rate of 3.5% at one year after deployment of BMS of ≥3.5 mm in diameter, which was comparable

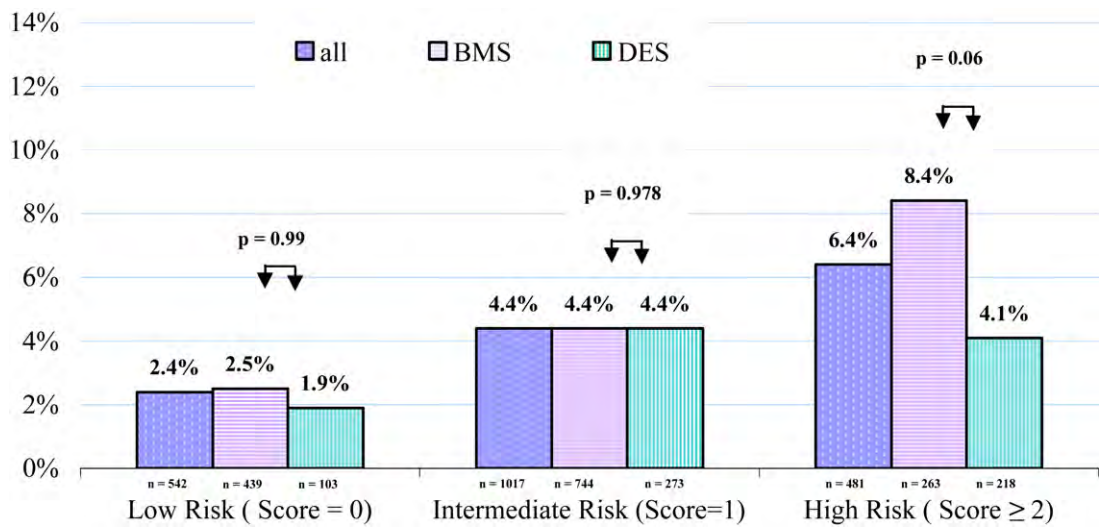

Figure 4. *Target lesion revascularisation rate at 1 year based on restenosis risk score. Target lesion revascularisation rate according to HORIZONS-AMI risk score for restenosis. Three risk factors for restenosis (insulin-requiring diabetes, reference vessel diameter ≤ 3 mm, and lesion length ≥ 30 mm) were used in the HORIZONS-AMI trial to classify patients into three risk groups, low (none of the above risk factors), intermediate (one risk factor) and high risk (≥2 risk factors).*

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to 3.4% TLR following DES deployment in arteries of ≥3.5 mm in diameter. Thus we consider that vessels of ≥3.5 mm rather than ≥3 mm should be considered large in the context of BMS use. Given these low TVR rates, BMS deployment in arteries ≥ 3.5 mm should be compared with newer generation DES in a randomised clinical trial with extended follow-up.

Our study has certain limitations. Because of our selective DES use criteria [7], patients with coronary heart disease who received DES (29%) were at higher perceived risk of restenosis, inferences cannot be drawn about the magnitude effect of DES on TVR rates, compared with that with BMS. To account for the effect of these factors, propensity scoring analyses for stent selection strategy (DES versus BMS) were performed and included in the adjustment for clinical outcome analysis [11]. As there may be greater endothelial dysfunction and thus more difficulty in determining "true vessel diameter" in patients with STEMI, utilisation of the HORIZONS-AMI predictor for TLR may have limitations in those patients with NSTEACS and stable CHD. Unrecorded factors may have resulted in BMS use in patients with co-morbidities, assumed bleeding risk, and anticipated non-compliance with dual anti-platelet therapy, all of which potentially may have lead to underestimation of the safety of BMS in this study. As we excluded failed PCI procedures and that the reported TIMI flow was determined by the proceduralists (except for rescue PCI), TIMI-3 flow rates could be overestimated. As routine quantitative coronary angiography and intravascular imaging was not available some inaccuracy in the assessment of vessel diameter may have occurred.

Conclusion

It is possible to use selective criteria for DES deployment while maintaining 'acceptably' low TVR rates. Clinical outcomes including TVR rates were similar with BMS and DES using these selective criteria. The TVR rates following BMS deployment among patients with large coronary arteries (≥3.5 mm) and among non-diabetics were low. Comparison of selective versus routine DES use especially newer generation DES in patients with coronary arteries ≥ 3.5 mm in diameter should be undertaken in future randomized clinical trials.

Conflicts of interest

There are no conflicts of interest to disclose.

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