RISK STRATIFICATION FOR REVASCULARISATION IN
ACUTE ISCHAEMIC SYNDROMES

Thesis submitted for the degree of Doctor of Medicine at the
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by

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INTRODUCTION
Acute Coronary Syndromes (ACS) is becoming the most common reason for acute medical admission in the Western World. Whereas the management of acute ST segment elevation myocardial infarction (MI) has been well defined for quite some time now that of non ST segment elevation MI has been the subject of debate in the recent years. It has emerged that an early invasive strategy with coronary angiography leading to early revascularisation by Percutaneous Coronary Intervention (PCI) or Coronary Artery Bypass Grafting (CABG) is the preferable management strategy for those felt to be at high risk. However, there is a need to accurately and individually assess patient risks from such revascularisation procedures in order to decide which revascularisation mode is more appropriate for a given patient, obtain informed consent and plan the peri-operative management of the patient in order to reduce the perceived risk as far as possible. Although several ‘Risk Scoring’ tests exist and are in use for CABG, there is no commonly accepted risk score for PCI. The aim of this thesis was to examine the background of current best management in non ST elevation ACS, and identify a way of risk stratifying patients undergoing PCI in such clinical settings.
ABSTRACT
Dr Savvas Sophocles Constantinides

"Risk stratification for revascularisation in acute ischaemic coronary syndromes"

Abstract:

Aim of study: PHASE I: To identify those clinical and simple anatomical variables that could predict early (30 days), medium (6 month) and late (1 year) mortality following Percutaneous Coronary Intervention (PCI) for non ST segment elevation Acute Coronary Syndromes (NSTEACS). To compare outcomes in a contemporary group undergoing Coronary artery Bypass Surgery (CABG) and to examine which clinical variables are related to early mortality. PHASE II: To develop a PCI risk score and apply it to the same database. To then apply the risk score to a separate cohort of patients for validation.

Methods: Data from 630 consecutive patients undergoing PCI for NSTEACS between January 1999 and December 2000 were analysed. Data from 522 patients who underwent CABG were also analysed for similar variables and outcomes were noted. The derived 8 variable PCI risk score was applied on the following 500 consecutive patients undergoing PCI for NSTEACS between January 2001 and August 2002.

Results: Age, partial revascularisation, peripheral vascular disease, diabetes mellitus and left ventricular impairment were found to be significant predictors of mortality following PCI for ACS. A ‘risk-score’ model including age, LV impairment, multi-vessel disease, diabetes, renal impairment, peripheral vascular disease and female sex was then tested on the same cohort and found to be good in predicting death following PCI. In the surgical study group higher rates of mortality were found with age, clinical features of heart failure, LV impairment, chronic airways disease and cerebrovascular disease. The derived PCI risk score was found on validation to be a good predictive tool for mortality.

Conclusion: Individualisation of risk stratification for patients undergoing revascularisation for acute coronary syndromes is not only possible but also simple using easily available clinical information by the bedside. The use of such a risk score should be considered when patients are being evaluated for such procedures.
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WORK PERFORMED PERSONALLY

All studies described in this thesis were conceived, organised and undertaken by myself.

Data were collected from the hospital database and managed, organised and analysed by myself. Statistical analyses were performed by myself with guidance from fellow research personnel from our institution.

The coronary artery bypass surgery substudy was conceived by myself but executed with the help of Drs Shane Gieowarsingh and Jay Shah who were fellow research registrars at the University Hospitals of Coventry and Warwickshire during the period of the study.
CONTRIBUTION TO THE MEDICAL LITERATURE

Publications in support of this thesis:

1. Savvas S. Constantinides, Faizel Osman, Amer Chit, Magdi Halim, Marin
   Been, Hardial Singh, Peter Glennon and Man Fai Shiu.
   A simple risk score for prediction of mortality in patients undergoing
   Percutaneous Coronary Intervention for Acute Coronary Syndromes.
   *American Heart Journal* (submitted)

2. S S Constantinides, G Gieowarsingh, M Halim, M Been, M F Shiu
   Predictors of mortality in patients with acute coronary syndromes undergoing
   percutaneous coronary intervention.
   *Heart* 2003; 89: 1245-1246.
Abstract Presentations:

   Predictors of mortality following Percutaneous Coronary Intervention in patients with Unstable Angina Pectoris or Non ST segment Elevation Myocardial Infarction.
   *British Cardiac Society, 2002.*

   Predictors of early mortality following urgent Percutaneous Coronary Intervention or Coronary Bypass Grafting amongst patients with unstable angina or Non-ST Elevation Myocardial Infarction.
   *British Cardiac Society, 2002.*

   Determinants of peri-operative mortality in patients with unstable angina pectoris undergoing coronary artery bypass grafting.
   *British Cardiac Society, 2002.*

   Predictors Of Mortality In Patients With Unstable Angina Pectoris Undergoing Percutaneous Coronary Intervention (PCI).
   *European Society of Cardiology, Cardiovascular Research Foundation, 2001.*
In the memory of my mother, Maria
CHAPTER 1:

BACKGROUND
DEFINITIONS OF ACUTE CORONARY SYNDROMES

*Acute Coronary Syndromes (ACS)* is a relatively recent term introduced to describe a group of conditions where acute changes in the rheology of coronary arteries lead to the development of a spectrum of clinical conditions. The changes in the rheology are usually a result of ongoing pathological changes in the atherosclerotic plaque with the resultant or concurrent activation of the coagulation cascade leading to intracoronary thrombosis. This, in addition to vasoactive changes, can lead to different degrees of acute or subacute coronary artery occlusion. The degree and duration of coronary occlusion is what determines the clinical manifestation of these syndromes.

Traditionally the term *unstable angina pectoris (UAP)* has been loosely used to describe acute coronary syndromes in the absence of obvious ECG ST segment elevation. With the use of serum cardiac troponins as sensitive markers of myocardial cell injury the use of this term has declined. Braunwald has classified unstable angina according to clinical severity but generally unstable angina is now described as worsening symptoms of angina over the preceding weeks (crescendo angina) or angina that occurs on minimal exertion or at rest, in the absence of any evidence of myocardial cell death (1).

*Non-ST segment Elevation Myocardial Infarction (NSTEMI)* is a recent term used to describe the clinical syndrome of myocardial damage due to varying degrees of cell necrosis as evidenced by elevation of serum markers such as creatinine kinase (CK) and its myocardial iso-enzyme (CK-MB) or the more recent and more sensitive and specific markers cardiac Troponin T or I (cTnT, cTnI) in the absence of
electrocardiographic persistent ST segment elevation (2). It is thought that this syndrome is caused by either a subtotal or transient coronary artery occlusion or recurrent distal platelet microembolisation from intracoronary atherothrombosis. It was previously described as non Q-wave myocardial infarction or subendocardial myocardial infarction.

*ST segment Elevation Myocardial Infarction (STEMI)* describes the clinical syndrome whereby persistent electrocardiographic elevation of the ST segment is associated with elevation of the serum markers of myocardial necrosis. It is, by and large, caused by complete atherothrombotic occlusion, permanent or transient, of the coronary artery involved and often results in 'transmural' myocardial wall necrosis or what was previously described as a Q-wave infarct characterised by the presence of pathological Q-waves on the electrocardiogram.
PATHOPHYSIOLOGY OF ACUTE CORONARY SYNDROMES

The atherosclerotic plaque: The development of the atherosclerotic plaque is the earliest event in the cascade that leads to the acute coronary syndromes. It starts as early as in childhood as evidenced by large post-mortem studies performed in the United States in the 1970s and 1980s (3).

Chronic minimal arterial endothelial injury is a physiological process and most commonly occurs at sites in the endovascular tree where turbulence of blood flow occurs at bending points and bifurcations (4). In addition to that and with passage of time the different known risk factors for the development of coronary artery disease contribute to the growth of the atherosclerotic plaque within the arterial wall.

Hypercholesterolaemia, advanced glycation end products in diabetes, chemical irritants in tobacco smoking, circulating vasoactive amines, immune complexes and perhaps infections lead to minimal endothelial injury and dysfunction which in turn leads to the accumulation of lipids and monocytes (macrophages) within the arterial wall. This process is facilitated by the chronic local shear forces employed on the endothelium by the blood flow and its dynamic changes, processes which are enhanced in hypertension (5).

The atherosclerotic lesion has been staged and its phases of progression have been characterised by the American Heart Association. The earliest atherosclerotic lesions or the ‘fatty streak’ which can be found in young children and infants, are included in types I-III (phase 1). The different types of fatty streaks (I and II) are based on the
relative numbers of smooth cells and macrophages and the amount of lipids contained in the lesions. Lesions type IV (phase 2) are characterised by diffuse intimal thickening consisting of smooth muscle cells and variable amounts of connective tissue. Lesions type V and VI (phase 3) include stenotic, fibrotic lesions (type V) which can rapidly progress to the complicated (type VI) lesion which can disrupt, thrombose and lead to acute ischaemia, myocardial infarction and even death (6).

The development of the atherosclerotic plaque is an ongoing dynamic process. The earliest atherosclerotic lesion, the ‘fatty streak’ or type III lesion represents a dynamic balance between the entry and exit of lipoprotein as well as the development of the extracellular matrix. A decrease in the lipoprotein entry, which can result from risk factor modification and therefore less endothelial injury, results in a predominance of lipoprotein exit and final scarring. However an increase of lipoprotein entry can result in the development of ‘vulnerable’ lipid-rich type IV and type V plaques that are prone to disruption (7).

The ‘vulnerable’ atherosclerotic plaque: Type IV and V atherosclerotic plaques usually consist of an abundant crescentic mass of lipids separated from the vessel lumen by a discrete component of extracellular matrix. Plaques with a large lipid pool and a thin fibrous cap are much more prone to rupture than those with a thick fibrous cap because a thick fibrous cap is more able to resist local mechanical stresses. The most important determinant of plaque stability is the composition of the fibrous cap in that a preponderance of inflammatory cells and a relative paucity of vascular smooth muscle cells leads to plaque rupture. These lesions which are ‘vulnerable’ to disruption and rapid progression to severe stenosis or occlusion are often seen as
‘mild stenoses’ on coronary angiography. In fact as much as two-thirds of acute coronary syndrome episodes are caused by disruption of such ‘mild’ angiographic stenoses (8).

The disruption of such ‘vulnerable’ plaques can be either a ‘passive’ or an ‘active’ process (9). ‘Passive’ plaque disruption is related to physical forces and occurs most frequently at the weakest point of the fibrous cap of the plaque where the cap is thin and heavily infiltrated by foam cells. Passive plaque vulnerability depends on firstly the circumferential wall stress or cap “fatigue”, secondly the location, size and consistency of the plaque core and finally blood-flow characteristics and in particular the impact of flow on the proximal aspect of the plaque (10).

‘Active’ plaque disruption is an active cellular process. Vulnerable plaques are very rich in macrophages and these cells are capable of degrading extracellular matrix by phagocytosis and the secretion of proteolytic enzymes such as plasminogen activators and metalloproteinases which weaken the fibrous cap and make it prone to rupture. Monocytes and macrophages seem to be initially recruited by endothelial adhesion molecules (VCAM-1), monocyte chemotactic proteins (MCP-1), monocyte colony stimulating factor (M-CSF) and interleukin-2 to protect the vessel wall from excess accumulation of lipoproteins. Eventually however they undergo apoptotic death which may in turn trigger the release of the metalloproteinases that lead to the exposure of prothrombotic substances on the endothelial cell surface (11-14).
Following the ‘disruption’ of the vulnerable plaque as outlined above, acute thrombosis and vasoconstriction complete the triad that leads to the rapid reduction in coronary blood flow responsible for the acute coronary syndrome.

Rupture or erosion of the fibrous cap of the atherosclerotic plaque exposes the highly thrombogenic collagenous matrix and lipid core to the circulation and leads inevitably to platelet accumulation and activation. This results to fibrin deposition and hence thrombus formation which can then lead to vessel occlusion. However, vessel occlusion is not inevitable and it has been shown that episodes of silent, subclinical plaque rupture occur frequently in patients with atherosclerosis. In one study up to 70% of plaques causing high grade stenosis had evidence of previous plaque rupture and repair in the absence of vessel occlusion or a corresponding clinical event (15). These episodes of non-occlusive plaque rupture result in the recruitment of new vascular smooth muscle cells under the influence of mitogens such as platelet derived growth factor and fibrin which are present in the thrombus (16). Thrombus also contains large quantities of transforming growth factor β which is a potent stimulator of vascular smooth muscle cell matrix synthesis. These factors therefore drive formation of new fibrous cap over the thrombus thereby increasing the size of the lesion. In other words, the size of the atherosclerotic lesions increases as a consequence of repeated episodes of rupture and repair.

The severity and hence the clinical sequelae of acute coronary thrombosis depends on a number of local and systemic factors (17). Local factors include the degree of plaque disruption and the composition of the plaque; deep fissuring or ulceration of a plaque with a rich lipid core would promote a much more severe thrombotic event.
than a superficial erosion of a fibrotic plaque. The geometry of the plaque and the
degree of stenosis would modify the effect on the flow of blood and less flow means
more thrombus accumulation. Platelet and thrombin activation may exacerbate the
already developing vasoconstriction. Tissue Factor (TF), a small molecular-weight
glycoprotein plays a pivotal role in the local initiation of the thrombotic cascade. It is
believed that TF initiates the extrinsic clotting cascade and is believed to be the major
regulator of coagulation, haemostasis and thrombosis (18).

Except from the above mentioned local factors, systemic factors that constitute a
generalised ‘hypercoagulable’ state play a role in the degree of coronary thrombosis.
There is evidence that circulating monocytes and white blood cells may be involved
in TF expression and thrombogenicity. That would explain the association between
elevated levels of C-reactive protein (CRP) and adverse medium term prognosis in
patients with coronary artery disease (19,20). Hypercholesterolaemia may trigger a
chronic hypercoagulable state and it has been shown that statins reduce the increased
blood thrombogenicity observed in the same patients under hyperlipidaemic
conditions (21). High catecholamine drive such as that observed in cigarette smokers
may also contribute to increased thrombogenicity. There is finally accumulating
evidence that systemic infections such as Chlamydia pneumoniae, cytomegalovirus
and Helicobacter pylori may be linked with atherothrombotic complications probably
by activating monocytes and white blood cells by activating tissue factor and platelet
interaction as well as raising fibrinogen concentrations (22).

*Vasoconstriction* also plays an important role in the pathogenesis of acute coronary
syndromes as demonstrated by Manseri and colleagues (23). In ACS, vasoconstriction
occurs as a response to a mildly dysfunctional endothelium near the culprit lesion or, more likely, may be a response to deep arterial damage or plaque disruption of the culprit lesion itself. In relation to culprit lesion related vasoconstriction, it seems that a predisposition exists for platelet-dependent and thrombin-dependent vasoconstriction at the site of plaque disruption and thrombosis that may be significant but transient. Therefore, platelet-dependent vasoconstriction, mediated by serotonin and thromboxane A$_2$ and thrombin-dependent vasoconstriction occur if the vascular wall has been damaged substantially with de-endothelialisation (24,25).

With regard to the pathobiology of acute coronary syndromes, in unstable angina a small fissuring of a lipid-rich plaque or a superficial erosion of a fibrotic plaque leads to an acute change in plaque geometry and the degree of stenosis with resultant reduction in coronary blood flow. Transient thrombotic episodes that spontaneously resolve may give rise to the pain at rest. This thrombus is usually labile and results in temporary vascular occlusion, perhaps lasting only 10-20 minutes. In addition, release of vasoactive substances by platelets such as serotonin and thromboxane together with the vasoactive effect of thrombin and vasoconstriction secondary to endothelial vasodilator dysfunction may also contribute to a reduction in coronary flow.

In NSTEMI, possibly more severe plaque disruption and less effective spontaneous lysis mechanisms lead to a more prolonged thrombotic vessel occlusion which often can last for up to an hour. After an hour, only $\frac{1}{4}$ of these patients have total vessel occlusion on coronary angiography. Spontaneous thrombolysis, resolution of vasoconstriction and opening up of collateral channels reduce the amount of myocardial damage that occurs by limiting the duration of myocardial ischaemia.
However, during the duration of thrombotic occlusion, platelet microemboli often embolise the distal microcirculation causing ‘islets’ of myocardial cell necrosis that accounts for release of cTnT in the circulation.

In STEMI larger plaque fissures lead to the formation of larger occlusive thrombus which then becomes fixed and persistent. This results in an abrupt, complete interruption of coronary perfusion which, when it persists for more than an hour, results in transmural necrosis of the involved myocardium (25). Some cases of sudden coronary death probably involve a rapidly progressive coronary lesion in which plaque disruption and resultant thrombosis lead to ischaemic and fatal ventricular arrhythmias in the absence of effective collateral flow.
EPIDEMIOLOGY OF ACUTE CORONARY SYNDROMES

The prevalence of acute coronary syndromes has been difficult to define. The ongoing development in the understanding of the pathophysiology of these coronary ischaemic syndromes, the improvement in the diagnostic tools and development of new, more sensitive and specific markers of myocardial cell injury and emergent new improved therapies have led to a change in the epidemiology of acute coronary syndromes. New definitions are not always universally and homogenously adopted by institutions and therefore diversity exists in the recording of these cases (26).

In addition, the epidemiology of acute coronary syndromes and the definitions of best management guidelines are based on clinical trials which do not represent 'real-life' patient cohorts. Clinical trial patients are a highly selected group of patients, which tend to belong to a lower risk category for their condition. National registries seem to be a more representative source of information however they are more useful in recording information on ST Elevation MI or ‘Q-wave’ infarcts than unstable angina or Non ST Elevation MI (27).

Because of these difficulties, prospective observational studies of large cohorts of patients make the best sources for the definition of epidemiology, outcomes and management strategies of patients with acute coronary syndromes. Several such studies have been reported recently.

The GRACE (Global Registry of Acute Coronary Events) study is a large scale multinational prospective registry that describes the epidemiology, management
practices and in-hospital outcomes of patients admitted with acute coronary syndromes (28). A total of 95 hospitals in 14 countries in North and South America, Europe, Australia and New Zealand enrolled 11,543 patients admitted with acute coronary syndromes between April 1999 and December 2000. The majority of these patients (64%, 7290/11453) were admitted with non ST elevation MI or unstable angina. The mean age of this subgroup was 65 with two thirds being men. A quarter was diabetics, two thirds had hypertension and about half were smokers. A sixth of these patients had undergone previous revascularisation.

Coronary angiography was used liberally in this cohort; 53% of the patients admitted with NSTEMI and 42% of those with unstable angina underwent coronary angiography prior to discharge. Percutaneous coronary intervention was performed in 28% of the NSTEMI patients and 18% of those with unstable angina during the index admission. Coronary artery bypass grafting was performed in 10% of those with NSTEMI and 5% of those with unstable angina. In hospital mortality was higher in those with NSTEMI (5%) compared to those with unstable angina (3%).

The Euro Heart Survey of Acute Coronary Syndromes (Euro Heart Survey ACS) is a prospective survey of the characteristics, treatments and outcomes of patients with acute coronary syndromes in Europe and the Mediterranean basin between 2000-2001 (29,30). In total 10 484 patients with a discharge diagnosis of acute coronary syndromes from 103 hospitals in 25 countries were enrolled. The discharge diagnosis was Q wave myocardial infarction in 32.8%, non-Q wave myocardial infarction in 25.3% and unstable angina in 41.9%.
The majority of these patients had no ST elevation (5367/10484 or 51%). Of this subgroup the majority had a discharge diagnosis of unstable angina (65.1%), non-Q wave MI in 26.9% and a Q-wave MI in 7.9%. Mean age was 65.8 with 64.4% males. Of these 23.5% were diabetics, 63.6% were hypertensive, 53.8% were or had been smokers in the past and 26.2% had a prior revascularisation procedure.

The in-hospital death rate for patients with no ST elevation was 2.4% and 1.4% had a re-infarction prior to discharge. By 30 days 3.5% of these patients had died. The rate of coronary angiography and revascularisation was similarly high to those in the GRACE study; 52% of these patients underwent in-patient coronary angiography. In this cohort one third of the patients admitted with non ST elevation ACS had an in-patient coronary angiogram as a routine. A quarter (25.4%) of these patients had pre-discharge percutaneous coronary intervention and 5.4% had bypass surgery. By 30 days 53.3% had coronary angiography followed by an angioplasty in 27.6% or bypass surgery in 9.6%.

In the United Kingdom, such a large prospective observational cohort registry of patients admitted with acute coronary syndromes was performed in 1998/1999. The Prospective Registry of Acute Ischaemic Syndromes in the U.K (PRAIS-UK) was set out to determine characteristics, practice patterns, outcomes and important markers of risk of patients admitted to a wide range of U.K. hospitals with acute coronary syndromes without ST elevation (31). A total of 56 U.K. hospitals participated enrolling a total of 1046 patients into the registry. The mean age at presentation in this cohort was 66 (+/-12) with 61% male. In addition, 16% had diabetes, 37% treated
hypertension, 23% were current smokers, 48% had prior MI and 23% had prior revascularisation (either PCI or CABG).

The rate of death in hospital was 1.5% and 7.4% at 6 months. In addition, 3.9% and 7.3% had a non-fatal MI in hospital and at 6 months respectively. By six months, 30% of these patients would have either died, had a new MI, refractory angina or readmitted to hospital with unstable angina. In this cohort, age seemed to be the most significant independent predictor of death with an odds ratio of 2.3 and 3.5 for the age strata 60-70 and >70 respectively compared to those <60. The elderly (age >70%) had a rate of death or new MI at 6 months of 17.3% compared to 11.7% and 5.7% in the 60-70 and <60 years of age respectively. In addition to age, presenting ECG changes (ST depression, Left Bundle Branch Block and T wave inversion in order of importance) were also independent predictors of adverse outcome along with male gender, presence of heart failure, and diabetes. It is of importance to note that most of the risk for major cardiac events occurred in the first 30 days following admission. This risk, however, continued through out the six months period especially for the composite outcome of death, MI, refractory angina and readmission with unstable angina.

The rate of coronary angiography and revascularisation for these high risk patients in the U.K has been, as evidenced in this study, exceedingly low in comparison to the previously mentioned registries. The overall rate of coronary angiography, PCI and CABG in hospital was 10%, 4% and 2% respectively. At six months it was 27%, 8% and 7% respectively.
It is evident that in comparison to the rest of Europe and the United States and taking into consideration the ‘North to South axis’ in the incidence of coronary artery disease, despite the similar epidemiology, management patterns in the United Kingdom have been different. This may be partly explained by the fact that the PRAIS-UK was an earlier study compared to the EuroHeart Survey ACS and the GRACE. It is certain that rates of coronary angiography and revascularisation have increased in the U.K. since the PRAIS-UK data were collected.

To summarise these studies, acute coronary syndromes without ST segment elevation comprise the majority of the hospital admissions with acute coronary syndromes. Two thirds of these are male and the average age is 65. It is of interest to note that in these registries over half the patients were older than 65, an age which is sometimes the ‘cut-point’ for exclusion in some of the large randomised clinical studies. Two thirds are hypertensive, a third is diabetic and about half are smokers. In-hospital mortality ranges between 2-5%. Management strategies vary in different countries but it appears that coronary angiography is becoming an integral part of the in-hospital management as about half of these patients are investigated for the need of revascularisation prior to their discharge from hospital. In the United Kingdom coronary angiography followed by revascularisation has previously been low.
DIAGNOSIS OF ACUTE CORONARY SYNDROMES

Clinical Presentation: The clinical presentation of acute coronary syndromes consists of a variety of clinical symptoms. Several clinical presentations of the typical ischaemic cardiac chest pain have been accepted as indicative of an acute coronary syndrome: prolonged (>20 minutes) anginal pain at rest, new onset severe angina or recent worsening of previously stable angina (crescendo angina) (32). However, atypical presentations of acute coronary syndromes are not uncommon, especially in the younger (<40) and older (>75) patients, as well as the diabetics and female patients. Atypical presentations include 'indigestion-like' or epigastric pain, progressive or acute onset dyspnoea, stabbing chest or pain with some pleuritic features. In one study, acute myocardial ischaemia was eventually diagnosed in 22% of patients presenting with sharp or ‘stabbing’ chest pains, 13% of patients presenting with pleuritic type chest pains and even 7% of those presenting with chest pain that was fully reproducible by palpation (33).

Physical examination: Physical examination is, more often than not, normal in patients presenting with acute coronary syndromes. The main purpose of the physical examination is to look for signs of haemodynamic instability, left ventricular failure or valvular dysfunction, and in particular measurement of heart rate and blood pressure, heart sounds and chest auscultation. In addition, to look for potential non-ischaemic causes of chest pain or any extra-cardiac conditions that could be contributing to the clinical presentation.
**Electrocardiogram:** The resting electrocardiogram is vital in the assessment of patients presenting with suspected acute coronary syndromes. It is of best value if recorded during an episode of chest pain, and if previous ECGs are available for comparison. It is useful as a screening tool especially in those with atypical presentation as it can give clues towards potential non-ischaemic syndromes such as pericarditis or pulmonary embolism. Clues towards pre-existent coronary artery disease such as Q-waves or left bundle branch block are also useful towards the potential cause of the presenting symptoms.

The electrocardiogram is most useful in the presence of ST segment shift (depression or elevation) and T wave changes. ST-segment elevation or depression of > 1mm in two or more contiguous leads is highly suggestive of high risk acute coronary syndromes. T wave inversion of > 1mm in leads with predominant R wave is also suggestive of acute coronary syndromes but less specific. It should however be noted that the resting electrocardiogram is often normal in patients presenting with acute coronary syndromes. In several studies, around 5% of patients with normal electrocardiograms who were discharged from the emergency department were ultimately found to have either an acute myocardial infarction or unstable angina (34-36).

**Biochemical markers of myocardial damage:** Cardiac troponin T and I have become the preferred markers of myocardial necrosis as they are more specific and more sensitive than the traditional cardiac enzymes such as creatinine kinase (CK) or its isoenzyme MB (CK-MB) in this setting. It is now established that elevation of cardiac troponin T or I reflects myocardial cell necrosis (2,37,38). In the setting of myocardial
ischaemia, as evidenced by the presence of ischaemic cardiac chest pain, ischaemic ECG changes or both, elevation of cardiac troponin T or I is now labelled as myocardial infarction. In these patients, an initial rise in troponins in peripheral blood is seen as soon as 3 to 4 hours after the onset of symptoms with persistent elevation up to two weeks. In order to demonstrate or exclude myocardial damage, repeated blood sampling and measurement are required during the first 6 to 12 hours after admission and after any further episodes of severe chest pains.

Risk assessment: An integral part of the diagnostic process in acute coronary syndromes is that of risk assessment. In those patients where the diagnosis is established, the management strategy to be selected in a particular patient depends on the perceived risk of progression to myocardial infarction or death. This evaluation of the perceived risk needs to be done early, at the time of initial diagnosis and admission to hospital and based on immediately available clinical information and easily obtainable laboratory data. Such include simple demographics such as age and gender, history of previous coronary artery disease and other risk factors such as diabetes mellitus, the nature of the presenting symptoms such as ongoing chest pain, ECG evidence of ischaemia, the results of laboratory tests such as biological markers of myocardial cell death, the assessment of left ventricular function by echocardiography or angiography and finally the coronary anatomy. Markers of risk can be divided in those of acute thrombotic risk and those of underlying or long-term disease. Markers of acute risk include:

1. Recurrence of chest pain
2. ST-segment depression
3. Dynamic ST-changes
4. Elevated levels of serum cardiac troponins
5. Presence of thrombus on coronary angiography

Markers of underlying disease include:

1. Age
2. History of prior MI
3. History of severe angina
4. Diabetes mellitus
5. Level of C-reactive protein (assessed by high sensitivity assays)
6. Left ventricular dysfunction
7. Extend of coronary disease

In addition to these, high risk features include also the presence of haemodynamic instability due to hypotension, ventricular arrhythmias or acute left ventricular failure.

The TIMI Risk Score for unstable angina/ Non-ST Elevation MI is a simple risk score containing 7 predictor variables which, when applied, can help categorising a patient’s risk of death or further events following a presentation of acute coronary syndrome (39). These 7 predictors are: age 65 years or older, at least 3 risk factors for coronary artery disease, prior coronary stenosis of 50% or more, ST-segment deviation on the electrocardiogram at presentation, at least 2 anginal events in prior 24 hours, use of aspirin in prior 7 days, and elevated serum markers of myocardial cell injury. The TIMI risk score was derived and validated in different subgroups of the TIMI 11B and ESSENCE trials that studied the efficacy of low molecular weight heparin for the treatment of unstable angina and NSTEMI. In the validation phase of the study, it was demonstrated that events increased significantly with increasing numbers of predictor variables present.
Coronary angiography: Patients that are assessed as being at medium or high risk during presentation and following risk stratification are best managed by performing coronary angiography to establish the coronary anatomy with a view to revascularisation, if possible, by either PCI or bypass surgery. Coronary angiography is also occasionally performed in those patients repeatedly admitted with presumed acute coronary syndromes and despite low risk features on non-invasive testing angiography provides conclusive evidence for the presence or absence of significant coronary artery disease.

To summarise, the diagnosis of the Acute Coronary Syndromes and their classification has changed since the wider use of troponins for their classification and risk stratification. Their diagnosis and classification is largely a clinical one, aided by simple bedside diagnostic tools such as the ECG and troponin levels. ECG ST segment Elevation Myocardial Infarction (STEMI) describes the syndrome of persistent ST elevation in association with cardiac type chest pain and subsequent elevation of markers of myocardial cell damage. Non ST Elevation MI (NSTEMI) describes the elevation of markers of myocardial cell damage in the absence of persistent ST segment elevation with or without the presence of typical cardiac sounding chest pain. Finally, the term unstable angina pectoris is now reserved for those presenting with symptoms of crescendo angina or angina at rest in the absence of ST segment elevation on the ECG or elevation of serum markers of myocardial cell injury.
PHARMACOLOGICAL TREATMENT OF ACUTE CORONARY SYNDROMES

The pharmacological management of acute coronary syndromes has been developing over the years. The growing knowledge and understanding of the pathophysiology of acute coronary syndromes has led to the development of various pharmacological therapies targeting different aspects of the pathophysiological process.

The pharmacological management can be categorised in a number of different ways. One way of understanding the mode of action of the different agents is by looking at the different pathophysiological processes and the agents that target them.

Traditionally coronary ischaemia has been seen as a ‘mismatch’ of coronary blood supply to the myocardial oxygen demand. The mismatch occurs, as outlined above, by an acute reduction of coronary blood flow caused by a sudden reduction in the diameter of the coronary artery. That in turn is caused by the prior chronic development of the atherosclerotic plaque and its sudden disruption leading to platelet aggregation, thrombin activation, platelet embolisation, inflammation and vasoconstriction.

To improve the ‘supply-demand mismatch’ beta blockade has been traditionally used to reduce myocardial oxygen demand by reducing contractility and heart rate. Theoretical benefit also occurs probably from the antiarrhythmic effects of these agents (40).
Calcium channel blockade has not been shown in clinical trials to have significant and consistent prognostic benefit. One small clinical trial suggested that diltiazem may have some benefit in those admitted with ‘non-Q wave’ myocardial infarction but has not been substantiated by further evidence (41). On the contrary, concerns have been raised regarding the safety of short acting dihydropyridine calcium channel blockers (nifedipine) and most guidelines do not recommend their use in the setting of acute coronary syndromes (42).

Nitrates, either short acting and administered intravenously or sublingually or long acting administered orally are recommended in the treatment of acute coronary syndromes for the reduction of ischaemia. Their benefit is mainly for symptom control as they have not been shown to influence the incidence of myocardial infarction or death in this setting (43). They act mainly by reducing ‘pre-load’ via their venodilatatory effect although some of the benefit is also derived from direct coronary vasodilatation and the reduction of ‘after-load’ through their weak vasodilatory effects.

Potassium channel activators (Nicorandil) have recently been increasingly used as second line agents for the treatment of stable angina and are increasingly more frequently used for the medical treatment of unstable angina. The IONA study (Impact of Nicorandil in Angina), a randomised double-blind placebo controlled trial in 5126 patients with stable angina showed that nicorandil reduced cardiovascular death, non-fatal MI and unplanned hospitalisation for angina by 17%, but it appeared that the reduction was mainly driven by the reduction in re-hospitalisation (44).
In the more recent years, efforts have been concentrated in reducing or preventing the thrombotic process in the coronary vessel, which is probably the most important element in the pathogenesis of the acute coronary syndromes.

The anti-platelet effects of aspirin achieved via the blockage of the cyclo-oxygenase pathway has now been known for some time. Its benefit was confirmed in the ISIS trials and its use in acute coronary syndromes is now well established (45).

Heparin in addition to aspirin has also been shown to reduce the incidence of myocardial infarction and death in patients with unstable angina. In a meta-analysis of 6 trials looking at the benefit of heparin in unstable angina, Oler et al demonstrated a 33% reduction in risk of MI or death in patients treated with aspirin plus heparin compared with those treated with aspirin alone (46).

Low molecular weight heparins, which are easier to administer and require less monitoring have been shown to be at least equally safe and efficient if not superior to the intravenously administered unfractionated heparin (47,48). Large trials such as the ESSENCE (Efficacy and safety of Subcutaneous Enoxaparin in Non Q wave Coronary Events) and TIMI 11B (Thrombolysis in Myocardial Infarction) studies have reported that twice daily enoxaparin was significantly more effective than a continuous infusion of unfractionated heparin in reducing the composite triple endpoint of death, MI or recurrent angina or urgent revascularisation (49,50). Low molecular weight heparin has now probably replaced unfractionated heparin in the treatment of acute coronary syndromes.
More recently, potent antithrombotic agents have been developed targeting the glycoprotein (GP) IIb/IIIa receptor, the most abundant receptor found on platelet membrane surfaces and an important pathway in platelet aggregation. Pioneering research by Coller and colleagues with a murine derived monoclonal antibody directed against the GP IIb/IIIa receptor led to the development of a chimeric monoclonal antibody Fab fragment compound known as c7E3 Fab or abciximab (Reopro) (51). Development of synthetic molecules of low molecular weight followed and two are commercially available, tirofiban (Aggrastat) and eptifibatide (Integrilin).

A number of studies have examined the possible benefit of GP IIb/IIIa inhibitors in the treatment of acute coronary syndromes, both as primary treatment but mainly in the context of percutaneous coronary intervention. The PRISM (Platelet Receptor Inhibition in Ischaemic Syndrome Management) and PRISM-PLUS (Platelet Receptor Inhibition in Ischaemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms) showed that those treated with tirofiban and heparin had significantly lower incidence of death, MI or refractory ischaemia or readmission for unstable angina at 30 days compared to those treated with heparin alone (52,53). The PURSUIT (Platelet glycoprotein IIb/IIIa in Unstable angina: Receptor Suppression Using Integrilin Therapy) demonstrated similar benefits whereas GUSTO IV ACS study showed no significant difference in the primary endpoint of death or myocardial infarction at 30 days between 24 hour abciximab, 48 hour abciximab and placebo in patients that did not undergo early PCI (54,55).

The benefit of GP IIb/IIIa inhibitors is much more evident in the context of percutaneous intervention for the treatment of acute coronary syndromes. In the
unstable angina sub-study of the EPIC trial (Evaluation of 7E3 in Preventing Ischaemic Complications) 62% reduction in death, myocardial infarction and urgent or repeat revascularisation was seen in those receiving abciximab compared to placebo (56). Similarly, the EPISTENT (Evaluation of Platelet IIb/IIla Inhibitor for Stenting) and CAPTURE (c7E3 Fab antiplatelet Therapy in Unstable Refractory angina) trials showed that treatment with abciximab in patients with refractory unstable angina reduced pre-procedural and peri-procedural events (57,58).

Overall, Glycoprotein IIb/IIla inhibitors have been a major pharmacological development in the management of coronary artery disease. Their value in reducing adverse cardiac events has been demonstrated not only during percutaneous coronary intervention for acute coronary syndromes with or without the presence of angiographically visible thrombus but also in complex high risk PCI for stable coronary syndromes especially in diabetics. In acute coronary syndromes they have an important role in treating high risk patients, especially those with evidence of myocardial cell injury. Their benefit is more evident in those undergoing revascularisation by PCI although some benefit is also offered for those treated with pharmacological therapy alone.

Clopidogrel, a platelet ADP receptor antagonist is another recently developed, orally administered potent antiplatelet agent initially developed for the treatment of patients who undergo stent implantation in combination with aspirin for the prevention of acute and sub-acute stent thrombosis. It is a thienopyridine derivative that inhibits platelet aggregation induced by adenosine diphosphate. Clopidogrel was shown in a large randomised placebo controlled study to prevent a composite of death from
cardiovascular causes, non-fatal myocardial infarction or stroke by 20% if added to aspirin compared to placebo and administered for an average of 9 months after initial presentation (59). Primary end-point was reached in 9.3% of the patients in the clopidogrel plus aspirin group compared to 11.4% in the aspirin alone group. However, this CURE (Clopidogrel in Unstable Angina to Prevent Recurrent Events) trial also demonstrated that this benefit was observed at the expense of an increased risk of major bleeding with clopidogrel, the majority of which, however, was not life threatening. The rate of major bleeding in the clopidogrel group was 3.7% compared to 2.7% in the placebo group. There was no statistical difference in the frequency of life-threatening bleeding between the two groups (2.1% v 1.8%, p=0.13). In other words, a 2.1% absolute risk reduction was observed at the expense of an absolute increase of 1% in the rate of major bleeding. That leaves an absolute risk reduction without major complications from treatment of just over 1%. It could be argued that the addition of clopidogrel to aspirin should be reserved for only those patients presenting with high risk features for progression to adverse cardiac events.

Other agents targeting the thrombotic cascade have also attracted attention but they have not established themselves for routine practice due to lack of convincing evidence for a favourable benefit:risk ratio. Direct thrombin inhibitors such as hirudin, bivalirudin and argatroban were developed to overcome the problems encountered with the indirect thrombin inhibitors such as heparin (60). Heparin has an unpredictable anticoagulant effect, the heparin/antithrombin complex is unable to inhibit fibrin-bound thrombin, an important trigger of thrombus growth and heparin is neutralised by platelet factor 4. All of these shortcomings are overcome by the direct thrombin inhibitors. However, despite their important pharmacokinetic and biological
advantages over heparin, direct thrombin inhibitors have failed, in randomised trials, to demonstrate a clear net clinical benefit compared with heparin because of a higher bleeding risk and only modest efficacy gain (61). Parenteral hirudin, bivalirudin and argatroban are currently licenced for use in North America and hirudin is considered by some as a therapeutic alternative in patients with heparin induced thrombocytopenia (62).

Finally, oral GP IIb/IIIa receptor inhibitors have also been developed but in four different trials (OPUS, TIMI14-EXCITE, SYMPHONY 1 and 2) not only showed no evidence of benefit but also in a meta analysis an increase in mortality was observed amongst patients receiving oral GP IIb/IIIa receptor blockers (63). Possible explanations for these disappointing results are either too high or too low levels of platelet inhibition. High levels of inhibition, similar to those reached with the intravenous agents, are not tolerable for chronic use because of the excess risk of bleeding. Low levels of inhibition seem to be insufficient to reduce recurrent thrombotic events and may even result in an increased risk of thrombotic events by inducing platelet activation and thrombin generation. The answer to this may be bedside monitoring of levels of inhibition and adjustment of dose but currently no such reliable assays are available. In the future, oral GP IIb/IIIa receptor inhibitors with more stable levels of inhibition and high affinity to the GP IIb/IIIa receptor may become available.
THE ROLE OF REVASCULARISATION IN THE TREATMENT OF ACUTE CORONARY SYNDROMES

The place of revascularisation alongside pharmacological therapies in the management of acute coronary syndromes has been fiercely debated in the last few years. Several randomised and observational studies have been reported to address the question of whether an aggressive strategy involving early coronary angiography and revascularisation should be routinely performed in patients who present with non-ST-segment elevation MI and unstable angina. There are now 5 randomised controlled trials that have compared the routine early invasive strategy with the selective invasive or ischaemia guided strategy.

The earliest trial was the TIMI (Thrombolysis in Myocardial Infarction) IIIB, published in the Journal of the American College of Cardiology in 1995 (64). In this trial 1473 patients admitted with unstable angina or non-Q-wave MI were randomised to compare tPA versus placebo as initial therapy and an early invasive strategy (coronary angiography followed by revascularisation when anatomy was suitable) versus early conservative strategy (coronary angiography followed by revascularisation if initial medical therapy failed). At six weeks, the end-point for the comparison of the invasive and conservative strategies (death, myocardial infarction or an unsatisfactory symptom-limited exercise stress test) occurred in 18.1% of patients assigned to the early conservative strategy and 16.2% of patients assigned to the early invasive strategy. This difference was not statistically significant. The invasive strategy however led to a reduction in days of hospitalisation, need for re-hospitalisation and less need for anti-anginal medication. At 1 year, there was still no
difference in the incidence of death or MI between the conservatively and the invasively treated groups (10.8% vs. 12.0%, p=0.42). Fewer patients in the invasive group required re-hospitalisation (26% vs. 33%, p<0.001). A sub-analysis on the TIMI IIIB patient database performed by Solomon et al. however, demonstrated that once risk stratification was applied to the TIMI IIIB cohort, patients stratified as moderate or high risk had reduced incidence of death or MI both at six weeks and one year if treated using the early invasive strategy (65). In addition, at 42 days the difference in the rates of intervention between the two groups was only moderate (61% vs. 49%). Therefore, lack of risk stratification and lack of adequate separation of the two randomised groups in terms of management strategy may account for the neutral result of this study.

The second large trial addressing the same question of whether an early invasive strategy is superior to a more conservative approach for the treatment of NSTEMI is the VANQWISH (Veterans Affair Non-Q Wave Infarction Strategies in Hospital) trial (66). In this trial 920 patients admitted to hospital with NSTEMI were randomly assigned to either invasive management (462 patients) or conservative management (458 patients) defined as medical therapy followed by non-invasive testing and subsequent invasive management in those who developed spontaneous or inducible ischaemia. The results were very disappointing for the advocates of the invasive strategy. At discharge from hospital 7.8% of those in the invasive group reached the primary end-point of death or non-fatal infarction compared to 3.3% in the conservative group (p=0.004). The same trend was observed at one year when 24% in the invasive group compared to 18.6% in the conservative group had reached the primary end point. Overall mortality during follow-up (average of 23 months) did not
differ significantly between the two groups. It should be noted that there was, similar to TIMI IIIB, a large proportion of the patients in the conservative group crossing over to the invasive strategy group during the study leading to similar intervention rates in both the invasive and conservative groups (44% vs. 33% at one year). Also, on an ad hoc analysis of the VANQWISH data performed by Samaha et al, it was shown that once these patients are risk stratified on the basis of their clinical risk factors (the TIMI risk scores), only very low risk patients in the conservative arm had better outcomes than their invasive arm counterparts (67).

FRISC II (FRagmin and Fast Revascularisation during InStability in Coronary artery disease) was the first study that showed that the invasive may be the strategy of choice in the management of patients with unstable coronary artery disease (68). In this prospective multi-centre study 2457 patients in 58 Scandinavian hospitals were randomised to an ‘early-invasive’ or ‘non-invasive’ treatment strategy with placebo-controlled long-term low-molecular-mass heparin for 3 months. The upper age for inclusion was 75, with a mean age of those enrolled at 62, 70% of whom were male. Coronary angiography was performed within the first 7 days in 96% and 10% of the patients in the invasive and non-invasive groups respectively. Revascularisation by either PCI or CABG was performed within the first 10 days in 71% and 9% of the patients in the invasive and non invasive groups respectively. The proportion of patients undergoing PCI or CABG in both groups was almost equal. The primary end-point which was a composite of death or myocardial infarction at 6 months was reached in 9.4% in the invasive group compared to 12.1% in the non-invasive group. This 22% relative risk reduction was mainly due to a significant 23% reduction in the risk of myocardial infarction alone. There was a trend towards reducing mortality.
alone (relative risk reduction of 35%) which did not reach statistical significance. In addition, symptoms of angina and re-admission were halved by the invasive strategy. The importance of risk stratification was once again highlighted. Subgroup analyses showed that the benefit of the early invasive regimen on the risk of death or myocardial infarction was greater in patients with any indicator of higher risk at entry and especially those with ST segment depression on the presenting ECG or elevated markers of myocardial cell damage.

FRISC II was the first large randomised study that demonstrated the benefits of the early invasive strategy. The difference in the results of this study to the previous ones mentioned above might be explained by the differences in anti-anginal but mainly anti-thrombotic medication and especially the use of Glycoprotein IIb/IIIa receptor blockers in selected patients; the timing of the procedures; the large difference in the intervention rates in the two groups; the improved technology used in the procedures and especially the higher usage of intra-coronary stents in PCI and the low mortality associated with bypass surgery in this trial (69,70).

The next large trial that investigated the role of early revascularisation using the most recently available techniques was TACTICS-TIMI 18 (Treat Angina with Aggrastat and determine Cost of Therapy with Invasive or Conservative Strategy-Thrombolysis In Myocardial Infarction) (71). This study enrolled 2220 patients admitted with acute coronary syndromes without persistent ST-segment elevation. These were randomised to an early (2-48 hours) invasive strategy with routine coronary angiography followed by revascularisation when appropriate or to a more conservative strategy in which catheterisation was only performed in those who had objective evidence of ongoing
ischaemia or an abnormal stress test. Prior to discharge from hospital, 60% of those allocated to the invasive strategy underwent a revascularisation procedure compared to 36% of those allocated to the conservative arm of the study. The primary end-point of death, non-fatal MI or rehospitalisation for ACS at 6 months was reached in 19.4% of those in the conservative group compared to 15.4% of those in the invasive group, a relative risk reduction of 22%. The rate of death or myocardial infarction at 6 months was similarly reduced by 26%. As in the previous studies, the benefit was observed mainly in those with elevated cardiac troponin levels.

The most recently published trial comparing an interventional versus conservative treatment for patients with unstable angina or non-ST-elevation myocardial infarction is the British Heart Foundation RITA 3 (Randomised Intervention Trial of unstable Angina) randomised trial (72). This was a randomised U.K. based multi-centre trial that recruited 1810 patients admitted with non-ST-elevation acute coronary syndromes to 45 different hospitals in England and Scotland. Mean patient age was 62 years and 38% were women. Patients were assigned to an early interventional or conservative strategy. Of the patients assigned to the invasive strategy 44% underwent a revascularisation procedure during the index admission compared to 10% in the invasive group. By one year 57% of those in the invasive group had a revascularisation procedure compared to 28% in the conservative group. The majority of these revascularisation procedures were percutaneous coronary interventions. The primary end-point of death, non-fatal MI or refractory angina at 4 months was reached in 9.6% of the 895 patients in the invasive group compared to 14.5% of the 915 patients in the conservative group. This 34% relative risk reduction in the primary end-point was mainly due to halving of refractory angina in the intervention group.
Death or myocardial infarction was similar in both treatment groups at one year. Interestingly, subgroup analyses showed that the benefit observed in the invasively treated group was not evident in the female patients of the cohort. In addition, there was a trend of higher incidence of death or MI at one year in the invasively treated female patients.

In the RITA 3 trial, the lack of benefit in the reduction of myocardial infarction that was shown in FRISC II and TACTICS-TIMI 18 may be due to a number of reasons. Firstly, the risk profile of the RITA 3 patients was relatively low compared to the other studies due to the more lax inclusion criteria. Only 8.3% of conservatively treated patients in RITA 3 died or had a myocardial infarction compared with 14.1% in FRISC II and 12.2% in TIMI IIIB. Another possible explanation is the difference in the definitions of myocardial infarction. In FRISC II, myocardial infarction was diagnosed with a rise in cardiac enzymes twice the upper limit of normal in the conservatively treated group whereas a threefold increase following PCI or pathological Q waves after CABG were required for the diagnosis of myocardial infarction to be made in the invasive group. Similarly, in TACTICS-TIMI 18 although similar stringent criteria were applied for the definition of MI in the invasively treated group, any elevation above the upper limit of normal was sufficient for the diagnosis to be made in the conservative group. In contrast, the criteria for diagnosis of MI in RITA 3 were similar in both the invasive and conservatively treated groups. Thus, the more stringent criteria for inclusion of myocardial infarction after PCI might have amplified the differences between the groups in FRISC II and TACTICS-TIMI 18 with respect to the frequency of myocardial infarction, something that does not apply for RITA 3.
To summarise, the five studies mentioned above have given conflicting conclusions as to whether an early invasive strategy is superior to an early conservative ‘ischaemia driven’ strategy in the management of patients with non-ST-elevation acute coronary syndromes. TIMI IIIB that was reported in 1994 preceded the latest developments of modern intervention such as the routine use of stents and potent anti-thrombotic regimes and especially Glycoprotein IIb/IIIa receptor blockers. The VANQWISH trial suggested a hazard for those patients with non-ST-elevation myocardial infarction that underwent revascularisation but it should be noted that many of the deaths occurred in patients assigned for intervention but actually never had it done. In both of these trials there was only a modest difference in the frequency of interventions between the invasive and conservative groups. FRISC II, on the contrary that had well separated strategies and well defined inclusion criteria to recruit at least moderate but mainly higher risk ACS patients, showed a significant reduction in deaths by one year for the invasive strategy. TACTICS-TIMI-18 showed overall benefit in the composite cardiac end-points despite an apparent higher early mortality in the invasive group that balanced by 6 months (71). A composite analysis of all these trials suggests a risk reduction of 12% in death or MI on the borderline of significance (72). However, these and in combination with the most recently published RITA 3 suggest that the composite end-point of death, MI or refractory angina is significantly reduced with the invasive strategy. From the various studies’ subgroup analyses it appears that the benefit is more pronounced in the higher risk patients some of whom seem to derive benefit in reducing deaths and further myocardial infarction (73,74).

Thus, the importance of risk stratification in patients with acute coronary syndromes becomes paramount. This is reflected in all the guidelines published by the British
Cardiac Society, the American College of Cardiology and American Heart Association, and most recently by the European Society of Cardiology (75-77).

The British Cardiac Society guidelines for the management of acute coronary syndromes were published in 2001. The importance of risk stratification is emphasised. The following are mentioned as indicators of a higher risk for early adverse cardiac events: age >65, comorbidity and especially diabetes, prolonged (>15 min) episode of chest pain at rest, the presence of ischaemic ECG ST segment depression on admission or during episodes of pain, evidence of impairment of left ventricular systolic function, elevation of serum cardiac troponins and less so elevated C-reactive protein (measured with a high sensitivity assay) and ECG T wave inversion (less risk than in the presence of ST segment depression but higher risk than in the presence of normal ECG). High risk patients are defined as those with recurrent or refractory angina or any of those with elevated cardiac troponins, acute ischaemia associated with hypotension arrhythmia or heart failure or those with high risk features on their stress test results. These patients should, according to the guidelines, be treated with intravenous Glycoprotein Ilb/Ilia inhibitors for up to 96 hours or until revascularisation has taken place. It is recommended that they should all undergo coronary angiography with a view to the most appropriate revascularisation procedure. Intermediate risk patients or those without any of the high risk features and with a normal or moderately elevated cardiac troponin (cTnT 0.01-0.1 μg/l) should not necessarily undergo early coronary angiography and the decision of such an invasive strategy is left on the discretion of the individual cardiologist. Low risk patients or those with a negative cardiac troponins or low risk features on stress
testing can be managed from the outpatient setting and can be discharged according to the guidelines.

The most recently published guidelines are those from the European Society of Cardiology and were published at the end of 2002. In these guidelines, risk stratification markers are divided into markers of acute or thrombotic risk and those of underlying or long term risk. Markers identified for high acute risk include recurrence of chest pain, ST-segment depression, dynamic ST-segment changes, elevated levels of cardiac troponins and the presence of intra-coronary thrombus on angiography.

Markers of long-term risk include age, history of previous MI, prior CABG, diabetes, congestive heart failure, hypertension, renal dysfunction, raised inflammatory markers such as CRP, fibrinogen and IL-6 and the presence of LV dysfunction and extensive coronary artery disease. Patients considered at high risk for progression to myocardial infarction or death are defined as those with recurrent ischaemia, early post infarction unstable angina, elevated troponins, haemodynamic instability or major ventricular arrhythmias, diabetes mellitus or an ECG pattern that precludes the assessment of ECG changes. These patients are recommended to undergo early coronary angiography, preferably within the first 48 hours or at least during hospitalisation with a view to revascularisation. In patients considered to be at low risk from further events i.e. those with negative troponin levels, absence of ECG ST segment depression or elevation and who remained symptom-free during the initial observation period can be investigated by stress testing or other non-invasive tests such as stress echocardiography or stress myocardial perfusion scintigram. Only those with significant ischaemia on non-invasive testing will require further investigation with angiography.
PERCUTANEOUS CORONARY INTERVENTION (PCI): HISTORY AND CURRENT METHODS

The first to undertake scientific experimentation into the workings of the heart and vessels were the ancient Greeks. They experimented by putting air or water into the vascular system in an attempt to understand the function of the valves. The next milestone came from William Harvey centuries later who in 1628 described the blood circulation. Various scientists since then experimented by inserting various tubes and probes in the cardiac chambers to record pressures or electrical activity. It wasn’t though until 1929 that the first X-ray guided cardiac catheterisation in a living human heart was performed. Werner Forssman in Germany, and against the advice of his chief, exposed the left basilar vein of his own arm and introduced a urethral catheter into his venous system (78). Under fluoroscopic control and a mirror, he advanced the catheter to his right atrium and confirmed its position with a chest X-ray. Since then the procedure gradually evolved until 1967 Melvin Judkins introduced a percutaneous transfemoral technique to advance purposely shaped catheters into the coronary arteries that led to cardiac catheterisation as we know it today (79).

Melvin Judkins along with Charles Dotter was also the first person to envisage possible therapeutic applications of this newly developed technique. It involved a coaxial system of radio-opaque Teflon dilating catheters to improve blood flow in patients with peripheral vascular disease. This ‘Dotter technique’ failed to take off due to the high rate of complication (80).
The ‘father’ of percutaneous coronary intervention, however, is considered to be Andreas Gruntzig. In 1977, he read a remarkable paper to the American College of Cardiology meeting in Miami, Florida, USA. The paper was titled ‘Non-operative treatment of coronary artery disease’ and was received by a mixture of delight and astonishment (81). It described the idea of passing a fine, collapsed balloon across a coronary stenosis, inflating it to reduce the obstruction and then deflating it so that it can be removed. Following this initial breakthrough, Percutaneous Transluminal Coronary Angioplasty or ‘PTCA’ as it became widely known by, evolved with the evolution of different shaped catheters, and the use of a fine ‘guide’ wire that could be advanced across and beyond the coronary stenosis so that the inflatable balloon could be ‘threaded’ over it and positioned across the site of the stenosis.

The next revolutionary change in percutaneous coronary intervention came in 1987 when Dr Ulrich Sigwart of Lausanne, Switzerland, reported the first use of an intracoronary stent to reopen a vessel which had become occluded at the time of angioplasty (82). The idea of the stent, a tubular metal scaffold that is wrapped around the balloon and expands within the vessel at the lesion site to enlarge the lumen and support the vessel wall has been the ‘second wind of angioplasty’, as put by Professor Patrick Serruys, a leading Dutch interventionist. Stents have dramatically reduced the incidence of re-stenosis from around 30% to 10-15% at six months. They achieve that by resulting in a larger luminal gain and by reducing the immediate or early elastic recoil that occurs following plain balloon angioplasty. Also, they have been extremely useful in limiting coronary dissections following balloon stretching which can be complicated by early, abrupt vessel closure or late restenosis. In PCI for acute coronary syndromes in particular, the use of intra-coronary stents has reduced
the incidence of major adverse cardiac events (MACE) by helping to achieve prompt restoration of normal coronary flow and maximising the initial luminal gain, therefore having an immediate effect on improving left ventricular function especially in the presence of a totally occluded vessel. Some concern has been at times expressed on whether stents have contributed to an increase in the phenomenon of ‘no-reflow’ which is thought to be caused by the occlusion of the distal microvasculature due to embolisation of atherothrombotic material, although this has never been confirmed in clinical trials. Their advantages have been overwhelmingly greater and clinical trials suggest superiority to balloon angioplasty in all clinical settings so that their use has been well established in every level of PCI, including the acute coronary syndromes (83,84).

Although reducing, intra-coronary stents have been unable to eliminate the ‘curse’ of PCI, restenosis. It is argued that the larger the gain, the larger the trauma on the intima and the resulting hyperplasia leading to a substantial risk of restenosis. In-stent restenosis has, in fact, been the major caveat in making PCI inferior to bypass surgery as a result of a higher rate of need for repeat revascularisation procedures. To fight restenosis, stents continued to evolve and most recently, ‘drug-eluting’ stents have been described as the third large breakthrough in the evolution of percutaneous intervention. In an attempt to reduce restenosis, stents are now being coated with various cytotoxic or cytostatic pharmacological agents such as Rapamycin and Sirolimus. Slow release of these agents locally in the vascular wall arrests the cell division cycle and prevents the proliferation of fibroblasts and smooth muscle cell which, in response to the vascular injury sustained during angioplasty and stenting are largely responsible for the phenomenon of restenosis. Although early yet, the first
published data show that drug eluting stents can almost eliminate the processes of re-stenosis and therefore the need for repeat revascularisation procedures in a substantial proportion of patients undergoing percutaneous intervention. Ongoing evaluation and accumulating experience with ‘drug-eluting’ stents is hoped to confirm their safety and efficacy (85,86).

Percutaneous Coronary Intervention has continued to evolve since it was first described in 1977. Various intravascular devices have been developed in an attempt to prevent or deal with possible complications of the most traditional balloon dilatation and implantation of intracoronary stents. Intravascular ultrasound (IVUS), a small ultrasound probe at the tip of a specially designed catheter is being used to assess intravascular pathology including the composition and severity of the atherosclerotic plaque, the presence of intra-coronary thrombus or vessel dissection and the successful or not apposition of intracoronary stents in the endovascular lumen (87). Atherectomy devices, utilising rotational energy or laser techniques, are being used to ‘debulk’ the atherosclerotic plaque, especially in heavily calcified lesions, to allow the delivery of the balloon and stents.

Since the pathophysiology of acute coronary syndromes has been unravelled, the importance of in-situ intra-coronary thrombosis has been appreciated. The presence of intra-coronary thrombus at the time of intervention has been shown to be associated with a higher risk of death, myocardial infarction and recurrent ischaemia (88). It has also been suggested that intra-coronary thrombus at the time of intervention leads to higher re-stenosis rates (89). There are various reasons why the presence of thrombus during coronary intervention may be associated with a higher complication rate.
Distal embolisation of thrombotic material occurs following balloon dilatation often causing branch occlusion or the ‘no-reflow’ phenomenon. Balloon and stent expansion in the presence of thrombus may lead to the entrapment of thrombus which can act as a nidus for further, in-stent thrombosis. Furthermore it can obscure the geometry of the underlying lesion resulting in potential errors of stent choice, positioning and deployment.

Various thrombectomy devices have been developed to try and tackle this potential source of complication during PCI in acute coronary syndromes. The X-SIZER (EndiCOR Medical, San Clemente, California, USA) makes use of a helical rotational cutter and gentle suction to remove atherothrombotic debris during intervention. It is very simple to use, relatively atraumatic, and has been shown in clinical trials to be effective in thrombus removal and relatively safe (90-92). A randomised trial has shown that it can reduce myocardial damage that can occur as a result of intervention (93).

Other thrombectomy devices include the transluminal extraction catheter (TEC-Interventional Technologies, San Diego, California, USA), the Cordis endovascular hydrolyser thrombectomy system (Johnson and Johnson, Warren, New Jersey, USA) and the Angiojet (POSSIS Medical, Minneapolis, Minnesota, USA). The TEC device is another rotational cutting device with suction which has mostly been used for the treatment of vein grafts as it is more traumatic if used in the native vessels. The other two devices remove thrombi by the venturi effect from backwardly directed high velocity fluid jets (94-96).
A different approach in preventing the embolisation of thrombotic material during intervention involves the deployment of distal protection devices that can trap released debris and prevent it from dislodging into the distal vasculature. The use of such devices (PercuSurge, Medtronic, Minneapolis, Minnesota, USA) appears to be presently limited to saphenous vein grafts or non-occluded vessels with a length of normal distal vessel for placement of the capture device (97).
FACTORS THAT DETERMINE OUTCOMES AFTER PERCUTANEOUS CORONARY INTERVENTION

Despite the refinement of Percutaneous Coronary Intervention and its evolvement as the preferred treatment management in high risk patients presenting with Acute Coronary Syndromes and as for every invasive or surgical procedure, its potential benefits must be weighed against its potential risks. In PCI, balloon-induced baro-trauma damages the endothelium and often the media and adventitia of the coronary artery. Dissection of the arterial wall can be detected in up to 50 to 80% of patients after PCI. Plaque haemorrhage, platelet deposition or clot formation may result in lumen compromise (98,99). In addition, the higher prevalence of intra-coronary thrombus in acute coronary syndromes often results in distal embolisation of atherothrombotic material leading to necrosis of islets of myocardial cells or to the ‘no-reflow’ phenomenon that can lead to transmural myocardial infarction and even death.

Attempts to identify those factors that are associated with adverse outcomes following PCI in general were mainly performed in the United States in the early 1990’s. This was by and large a ‘pre-stent era’ and the refinement of adjunctive pharmacological therapy with agents like Glycoprotein IIb/IIIa antagonists had not yet taken place.

Perhaps the most widely known work was done by Hannan et al in 31 New York State hospitals between 1991 and 1994 (100). All 62,670 patients that underwent PCI during that period were identified and studied for those factors that are associated with a higher probability of death or same stay CABG surgery rates. The overall in-
hospital mortality was 0.9% and same stay CABG surgery rate was 3.43%. This work led to the development of the New York State PTCA mortality model. It identified the following factors as important in dictating outcomes after PTCA: Age, female sex, reduced left ventricular ejection fraction, history of congestive heart failure, previous MI at various time points up to 7 days, the presence of haemodynamic instability, cardiogenic shock, renal failure, femoro-popliteal disease, diabetes mellitus, the need for the insertion of an intra-aortic balloon pump, multi-vessel angioplasty and previous open heart surgery; previous angioplasty appeared to have a protective effect. It is also of interest to note that in this database it was shown that both hospital PTCA volume and cardiologist PTCA volume are significantly inversely related to in-hospital mortality rate and same stay CABG surgery rate for patients undergoing PTCA. Patients undergoing PTCA by cardiologists having annual PTCA volumes of less than 75 or in hospitals with annual PTCA volumes of 400 or less had significantly higher incidence of death or same-stay CABG surgery compared to higher volume operators or hospitals. It is important to note that this risk prediction model was developed amongst patients undergoing PTCA for any indication and clinical severity and included the full spectrum of coronary artery disease clinical syndromes from stable angina to acute myocardial infarctions with cardiogenic shock. The order of stent usage in this cohort was less than 20% and Glycoprotein IIb/IIa inhibitors were then not yet available.

The value of the New York State PTCA Mortality Model and its applicability in the ‘post-stent’ era has since been studied by other investigators. Holmes et al applied this model to all patients undergoing stenting at the Mayo Clinic from 1995 to 1998 (101). In this study 3761 patients undergoing 4063 procedures were analysed for risk factors
known to predict adverse outcomes following PCI including the New York Model risk score. In this cohort, in-hospital death rate was 1.6% and at mean follow up of 1.2+/−1.0 year the death rate was 4.1%. The New York model risk score in a logistic regression model was the most significant factor associated with in-hospital mortality (OR 1.86; P<0.001). The New York model was also predictive of death at late follow up. In addition, multivariate analysis also identified diabetes, prior cardiac surgery, prior shock, renal failure, and left ventricular systolic ejection fraction of less than 40% as significant independent indicators of post-discharge mortality.

A different study at the Mayo clinic was carried out by Rihal et al (102). An analysis carried out on 3387 patients who underwent 3830 PCI procedures between 1995 and 1997. The risk score derived from the New York State Model was again found to be highly predictive of death. The expected in-hospital mortality rate of 2.32% was indeed very close to the observed mortality of 2.38%. In this study, the contribution of lesion characteristics which is not included in the New York State Model was found to be less important than clinical and demographic parameters in determining outcome. The presence of calcium, thrombus or type C lesion was only modestly associated with death.

In another study, O’Connor et al also sought to identify risk factors associated with in-hospital death among patients undergoing percutaneous coronary interventions (103). Data were collected on 15,331 patients undergoing percutaneous coronary intervention between 1994 and 1996 in six clinical centres in Northern New England and Massachusetts, USA. Logistic regression analysis was used to identify predictors of in-hospital death. Older age, congestive heart failure, peripheral or cerebrovascular
disease, increased creatinine levels, lowered ejection fraction, treatment of cardiogenic shock, treatment of an acute myocardial infarction, urgent or emergent priority, pre-procedure insertion of an intra-aortic balloon pump and PCI of a type C atheromatous lesion on coronary angiography were variables associated with an increased risk of in-hospital mortality following the procedure.

The largest study to identify a minimum set of variables for interventional cardiology that carried the most statistical weight for predicting adverse outcomes was carried out by Block et al (104). A working group with expertise in epidemiology, biostatistics and coronary intervention analysed 158,273 cases from eight cardiac databases in the USA from the mid-80's to the mid-90's. Univariate followed by multivariate analysis using a multivariate regression model were used to distinguish predictors of in-hospital death, in-hospital CABG and Q-wave myocardial infarction. In-hospital death in the various databases ranged from 0.4 to 3.5%. Here 29 variables were found to have the strongest statistical association with adverse outcome after PCI with the most powerful ones being measures of haemodynamic instability, disease severity, demographics and comorbid conditions. In particular, for in-hospital death, age, reduced LVEF, number of diseased vessels, congestive cardiac failure, acute indication for the procedure, cardiogenic shock, the use of an intra-aortic balloon pump and the presence of diabetes and renal failure were most commonly found to be associated with adverse outcomes. The association of angiographic characteristics of the coronary anatomy was again found to be less powerful in predicting adverse outcomes.
An attempt to devise a simple, easily applicable risk index for predicting patients risk for major complications defined as in-hospital death, emergency bypass surgery as a result of the procedure or enzymatic myocardial infarction was reported by Kimmel et al in 1995 (105). This group analysed data that was collected prospectively for the Registry of the Society for Cardiac Angiography and Intervention in the United States for 1992. Multivariable logistic regression was used to determine which variables were independently associated with complications in 10,622 angioplasty procedures. Predictors of major complications were multi-vessel disease, unstable angina, recent myocardial infarction, type C lesion or left main stem angioplasty, cardiogenic shock, and age. Certain geographic areas in the United States or Canada were found to be associated with higher risk for complications whereas previous coronary artery bypass surgery was found in this group to be protective. The derived predictive index consisted of these six parameters plus aortic valve disease. This index was then validated in 10,030 procedures performed in the following year and collected from the same sources. Risk scores were classified into four risk classes: low (none of the above risk factors present), moderate (one or two risk factors present), high (three risk factors) and very high (more than three risk factors present). The discriminatory ability of this predictive index was found to be only moderate (ROC 0.70).

In a more recent American study, Moscucci et al reported the analysis of 10,796 procedures performed in a consortium of 8 hospitals between 1997 and 1999 (106). Predictors of in-hospital mortality were identified by the use of multivariate logistic regression analysis. In-hospital mortality in this cohort was 1.6%. Acute myocardial infarction, cardiogenic shock, history of cardiac arrest, renal insufficiency, low ejection fraction, peripheral vascular disease, lesion characteristics and especially the
presence of intra-coronary thrombus, female sex and advanced age were all found to be independent predictors of death. An additive risk prediction score was devised based on the coefficients of the logistic regression model and then validated on an independent dataset of 5863 consecutive procedures performed between 1999 and 2000. The model was found to have excellent discrimination (ROC 0.90) and was accurate for prediction of mortality among different subgroups.

The next group to research this area was that of Shaw et al who sought to develop and evaluate a risk adjustment model for in-hospital mortality following percutaneous coronary intervention procedures using data from a large multi-centre registry (107). Data on 100,253 PCI procedures collected at the American College of Cardiology-National Cardiovascular Data Registry were analysed for factors associated with increased risk for PCI related mortality. Those found to be associated with higher risk of mortality included cardiogenic shock, age, salvage, urgent and emergent PCI, use of an intra-aortic balloon pump, reduced left ventricular function, presentation with an acute myocardial infarction, diabetes mellitus, renal failure, chronic lung disease, recent use of a thrombolytic agent, use of (non-stent) devices during PCI, left main disease, proximal left anterior descending artery disease and lesion characteristics. The area under the ROC curve of 0.89 signified a good predictive value of this long, rather cumbersome predictive model. Interestingly, patient factors were more predictive in the MI model while lesion and procedural factors were more predictive in the analysis of non-MI patients.

Perhaps one of the best known attempts to develop a ‘PCI Risk Score’ came from the Mayo Clinic in the United States. Singh et al published his work in an effort to
identify clinical and angiographic factors associated with major cardiovascular complications of PCI including in-hospital death, Q-wave myocardial infarction, urgent or emergent coronary artery bypass surgery and stroke (108). Their main aim was to construct a simple risk score for risk stratification following PCI. Data on 5,463 PCI procedures performed between 1996 and 1999 were analysed and the emergent risk model was validated on all the PCI procedures performed in the same institution during the year 2000. A relatively simple 8-point risk score was devised including the following 8 variables: cardiogenic shock, left main stem disease, severe renal disease, urgent or emergent procedure, congestive heart failure NYHA class III or higher, presence of angiographically evident thrombus, multivessel disease and older age. Again it should be noted that the majority of these variables were clinical (5) as opposed to angiographically derived data (3). On validation, the area under the ROC curve was 0.782 signifying a useful predictive tool. Although this model is relatively simple and probably applicable by the bedside, it does not concentrate on patients with acute coronary syndromes who are at highest risk from such interventional procedures.

The same group of researchers who developed this prediction model which became best known as the Mayo Clinic PCI Risk Score, went on to compare it with the American College of Cardiology/American Heart Association (ACC/AHA) lesion classification to predict complications following PCI (109). Both were applied on a dataset of 5,193 patients who underwent PCI between 2000 and 2003 at the same institution. Their ability to predict death, Q-wave MI, stroke and emergency CABG was compared. The ability of the Mayo clinic risk score was significantly better in predicting adverse outcome after PCI compared to the ACC/AHA lesion classification.
(area under ROC curve 0.78 compared to 0.67). However, lesion classification by ACC/AHA score was better than the Mayo risk score for predicting angiographic failure, although its absolute ability was modest (area under the ROC curve 0.58). Therefore, this study also supports the hypothesis that clinical characteristics are more important in predicting adverse outcomes after PCI compared to angiographic lesion characteristics.

Qureshi et al also sought to develop a simplified scoring system based on pre-intervention clinical characteristics to predict in-hospital mortality after PCI (110). This was also a single centre study where data on 9,954 PCI procedures over a 3 year period (1996-1998) were collected and analysed for predictors of in-hospital mortality. The factors with the highest univariate odds for dying following PCI were myocardial infarction within the last 14 days, elevated creatinine, multivessel disease and age > 65. Although simple, this prediction model is rather oversimplified and fails to identify and use well documented predictors of mortality following PCI such as left ventricular function and diabetes mellitus.

The only U.K. study thus far on the subject was published by the King’s Healthcare London group in the Heart in 2001 (111). de Belder et al attempted to create a risk model for predicting death, myocardial infarction or urgent bypass surgery following PCI by using available computer software that can predict probabilities of events using the Bayes’s theorem. A Bayes’s table was created on the first 1,500 patients who underwent PCI in 1995 and then validated on the subsequent 1,000 patients on the same database. Age, sex, left ventricular function on left ventriculography, American Heart Association classification of lesion morphology, clinical presentation
(stable, unstable angina, primary PCI for AMI, salvage PCI or cardiogenic shock), previous CABG, diabetes mellitus, hypertension, renal failure and multi-vessel PCI were assessed to determine their influence on the incidence of complications. Of those only presentation with cardiogenic shock, ejection fraction <30%, thrombolysis given within the last 24 hours, renal impairment (creatinine > 200 μmol/l) and age > 76 were found to be significant predictors of major complications. On validation, the model was found to be moderately good in its ability to predict major adverse events (ROC 0.76).

It is evident from the above mentioned studies that the vast majority of information on the subject of identifying those demographic, clinical or anatomical factors that determine outcomes after percutaneous coronary intervention originated in the United States in the early 1990’s. This was an era when stent usage was low and the use of the modern adjunctive pharmacological agents that in certain subgroups have dramatic impact in reducing complications was non-existent. It is not known whether the findings in the US populations with their individual patient characteristics and different health care systems apply to the European or British populations.

It is also important to note that these studies were conducted for all PCI procedures encompassing the full spectrum of clinical presentation of coronary artery disease. They included patients with stable and unstable angina, acute myocardial infarction in the context of primary or salvage PCI and even cardiogenic shock. The large diversity of clinical presentation in these studies does not allow for these predictive models to concentrate on different patient subgroups and presentations. Their ability to predict is diluted by the low incidence of complications in those patients undergoing the
procedure for stable angina. It has, after all, been suggested that complications following PCI are more likely to be driven mainly by the underlying pathology and extend of coronary artery disease rather than the procedure itself, especially in the medium and long term (106,112).

Interestingly, and in support of the above comment, in most of these studies the most powerful parameters for predicting adverse events following PCI are related to the demographic and clinical characteristics of the patients rather than their anatomical or angiographic features of their coronary artery disease.
In the practice of modern medicine and in particular in the management of acute coronary syndrome, risk stratification is of paramount importance. Risk stratification is important in two vital levels of the patient care. First of all, it is important in the initial assessment of the patient’s presentation. Risk stratification at presentation will allow the clinician to decide on the need to employ certain management strategies in an attempt to modify the perceived risks and to reduce the possibility of adverse clinical outcomes. This has been extensively studied in the area of the acute coronary syndromes and based on these studies all published guidelines on the management of these patients emphasises the importance of applying risk stratification based on clinical and early investigational characteristics to categorise patients into high, medium or low risk.

Based on this level of stratification, management then takes the course of simple risk factor management and pharmacological therapy or that of invasive investigation followed by aggressive pharmacological and invasive revascularisation strategies.

At this point the second level of risk stratification comes to play. In any invasive procedure the risks involved as a result of the procedure will depend on the patient’s characteristics and their clinical condition. Risk stratification at this point seems to be better applied by our surgical colleagues than us the physicians. Interventional cardiology in the management of coronary artery disease but in particular of acute coronary syndromes has now largely become a ‘surgical specialty’ in the sense that invasive revascularisation strategies, often high risk, are employed in the management
of these patients. Risk stratification at this level should involve the assessment of the risk of a given procedure, in this instance percutaneous coronary intervention, for individual patients, but should also take into account the risk of the patient suffering adverse clinical events if this therapy is not employed. This will of course allow the clinician to make more appropriate decisions in the management of these patients.

Risk stratification is also important during the process of obtaining consent for these revascularisation procedures. In the current days of open doctor and patient relationship where all knowledge should be shared and made available to the patient this has become even more vital. Most of medico-legal cases nowadays involve failure of adequate consent that led to a misunderstanding on the perceived risks by the patients and their relatives (3). Because of this, consent should be individualised. This can only be done with careful and validated risk stratification of both the patient’s clinical risk of undergoing a certain management strategy (e.g. PCI) but also the risks of employing alternative treatment strategies (in this case medical therapy or bypass graft surgery).

Effective risk stratification in the context of PCI would finally allow the clinician to be prepared for those high risk situations that will necessitate employing management strategies before, during and after the procedure. Such could include Glycoprotein IIb/IIIa inhibitors, intra-aortic balloon counter-pulsation or longer hospital stay in an attempt to try to reduce that perceived clinical risk as much as possible.
AIM OF THE STUDY: PHASE I AND PHASE II

Identifying predictors of mortality and developing a simple, ‘user-friendly’ risk-score for predicting death following PCI in patients with acute coronary syndromes is very important for a number of reasons.

Individualising patient risk is useful when discussing the perceived benefits and risks of a given procedure and the comparative advantages or disadvantages of alternative management strategies. This is particularly important when obtaining consent from patients that are about to undergo percutaneous coronary intervention.

Identifying high risk patients should prompt the clinician to use new and expensive adjuvant therapies in an attempt to reduce the predicted risk. Because of the need of rationalising resources these new expensive adjuvant therapies are only available for a small group of high risk patients.

In the current era of clinical governance and on-going performance audits, having a unifying risk assessment system will allow more accurate comparisons between individual operators and different institutions. Allowing for differences in the case mix makes the comparison more meaningful and allows for those institutions or operators that are faced with more high risk cases to be assessed with that in consideration.

These issues are particularly important in those patients undergoing PCI for acute coronary syndromes. Intervention in stable coronary artery disease overall carries a
low mortality and allows time for planning management strategies and obtain consent. For the treatment of STEMI, revascularisation has to be imminent and PCI is increasingly becoming the treatment of choice in some countries although in the UK the lack of resources has not allowed this indication to expand yet. Thrombolysis remains the gold-standard whereas bypass surgery is not offered because of the high risks involved.

Unstable angina pectoris and NSTEMI are increasingly becoming the most common indications for percutaneous coronary intervention. In addition, this group of patients are more likely to suffer complications and the contribution of different clinical risk factors are amplified under these acute circumstances.

AIM OF PHASE I
The aim of this part of the study to analyse data from a two year PCI database from a cardiothoracic tertiary referral centre and identify which clinical and simple anatomical parameters, when present, are associated with higher risk of complications. This two year period was chosen because a uniformity of practice had been achieved in our institution. By that time, the rate of stent usage had reached a plateau and a policy on the anti-thrombotic regime was established.

In addition and out of interest, an equivalent database of patients who underwent coronary artery bypass grafting in the same institution and during the same study period was performed in order to compare outcomes and identify those risk factors that are associated with adverse outcomes when the surgical strategy is employed. This was done in order to try and understand whether it is possible to speculate which
treatment strategy is more appropriate in certain groups of patients that present with acute coronary syndromes.

AIM OF SECTION II

The aim of PHASE II of the study was to devise an easily applicable clinical ‘risk-score’ to enable identification of patients at high risk from complications. This risk score should involve parameters that are easily available, easily characterised, factors that are not subject to individual clinicians’ opinions and are easily reproducible. It should be possible to apply it on the bedside, preferably without the assistance of a computer. Once such an easily applicable risk score was devised, it should be tested on the same cohort that it was developed in (the ‘development’ cohort) to assess its ability to predict mortality. If found useful, to then perform an initial validation of the derived risk score in the same institution but on a separate cohort of patients (the ‘validation’ cohort). The following consecutive 500 patients undergoing PCI over a 20 month period for the same indications as in phase I were selected for this latter purpose.
CHAPTER 2:

STUDY METHODS AND

RESULTS: PHASE I
SETTING

The study was conducted at the Cardiology Department of Walsgrave Hospital, University Hospitals of Coventry and Warwickshire, United Kingdom (90). Walsgrave Hospital is a large district General Hospital of almost 1,000 beds and covers an area whose catchment population is in the order of 300,000. The Cardiology and Cardiothoracic Units are staffed by 5 Consultant Cardiologists and 5 Consultant Cardiothoracic Surgeons with their teams of Specialist Registrars, Staff Grade Physicians and Senior House Officers. It is one of the three major tertiary referral centres in the West Midlands and treats patients from the whole of the Warwickshire area and from some areas of South and East Birmingham. All operators are high volume interventionists with equivalent approaches to their interventional practice.

Coventry has a large Asian community and a significant number of patients treated originate from the Indian subcontinent. As a result of that there is a significant burden of premature coronary artery disease and diabetes in the catchment population.

A significant proportion of patients treated for acute coronary syndromes either by PCI or by surgery is out of hospital transfers from the referring hospitals in the area. About a third of those undergoing PCI and half of those who underwent surgery were transfers from referring hospitals. Inter-hospital transfers in the UK, as is well known, are invariably associated with delays mainly by the lack of hospital beds to accommodate them. Patients can wait anything from two days up to two weeks but most patients that are transferred initially for coronary angiography have their
procedures done and if necessary followed by PCI within 7 days. Waiting times for inpatient surgery are worse and most patients have to wait an average of two weeks.
SUBJECTS

Patients that were screened for this study were all those admitted directly to our institution or transferred from the regional referring hospitals for percutaneous coronary intervention for a period of 2 years between the beginning of January 1999 and end of December 2000. Patients who were in cardiogenic shock at the time of the procedure, those having the procedure as primary or salvage PCI for an acute myocardial infarction or had an AMI within 24 hours prior to the procedure were excluded from the study. In addition all those who were electively admitted or had the procedure for stable angina pectoris were excluded. Patients included were those who had the procedure done on an urgent basis and during their index admission for any acute coronary syndrome other than ST segment elevation MI. These were patients with Unstable Angina Pectoris (UAP), Unstable Post-Infarct Angina (UPIA) and Non-ST-segment Elevation Myocardial Infarction (NSTEMI). It should be noted that at that time at our Institution cardiac troponins were not routinely available therefore only those patients with creatinine kinase levels above twice the upper limit of normal and without persistent ECG ST segment elevation were labelled as NSTEMI. It is most likely that with the use of cardiac troponins and the new WHO definitions for myocardial infarction a substantial percentage of patients with UAP would actually have had a NSTEMI. Only first time procedures were included. This was a hypothesis generating exercise over a 2 year period so no power calculations were performed to determine the number of patients necessary to prove the hypothesis. The number of patients was determined by the time limits set for the study. In total 630 patients were included. Their characteristics are described in the ‘Patient Characteristics’ section below.
DATA COLLECTION

Data were collected at our institution for local and national audit purposes since 1996. A database was created that logged every coronary interventional procedure and included information on demographics, clinical and anatomical characteristics, procedural characteristics and outcomes.

The study database was created based on the information collected for these purposes. Information on demographics, clinical characteristics such as the presence of risk factors, clinical presentation and indication for the procedure, anatomical variables as characterised by the coronary angiogram findings, procedural details and procedural and clinical outcomes. This information was collected at the end of the procedure by filling-in a pre-designed form. The form was completed by the operator and the information and its completeness then checked by the audit department of the Cardiac Services.

Information logged during data collection following PCI is summarised in Table 1. That included the mode of admission and whether the procedure was routine (patient admitted from the waiting list), emergency (performed during an acute admission) or a transfer from a referring hospital. Clinical indications were defined either as stable angina pectoris, unstable angina pectoris, acute myocardial infarction as a primary or salvage procedure, post-infarct angina or non-Q wave myocardial infarction. Further information was requested on the timing of any recent or same admission MI. Demographic data included date of birth and age, gender and ethnicity (white, black or asian).
The commonly used clinical risk factors for coronary artery disease were recorded:

- Hypertension defined by the prior use of antihypertensive agents by the patient;

- Diabetes mellitus, either insulin treated, treated with oral hypoglycaemic agents or just diet controlled.

- The presence of family history of coronary artery disease in first degree relatives.

- Current or previous smoking.

- Hypercholesterolaemia defined as either a random cholesterol level of > 5.0 mmol/Lt during the index admission or prior use of cholesterol lowering drugs.

- Renal impairment defined by a serum creatinine of > 200 μmol/Lt during the index or a recent (within 6 months) investigation.

- Previous myocardial infarction as evidenced by either the patient’s medical records, the presence of pathological Q-waves on the ECG or regional wall motion abnormalities on either echocardiography or left ventriculography.

- Any comorbidity that was felt to be significant in terms of prognosis, concurrent medication or the risk of complications.

- Chronic Obstructive Pulmonary Disease (COPD) as evidenced by the need for the use of bronchodilating drugs or diagnostic abnormalities on spirometry if available.
• Peripheral vascular disease causing either symptoms of claudication, Transient Ischaemic Attacks (TIAs) or previous stroke, doppler studies confirming haemodynamically significant stenoses in either the carotid or peripheral vascular system, prior surgery for peripheral vascular disease or carotid endarterectomy or obvious difficulties in gaining vascular access during the angiographic procedure.

Information obtained from the diagnostic coronary angiogram includes number of main epicardial coronary arteries with a stenosis of > 70% severity, the location of the stenosis and the left ventricular ejection fraction calculated from the difference in the end-diastolic and end-systolic left ventricular volumes on ventriculography.

Information on the interventional procedure included the number and location of the vessels treated, the type and dimension of the balloon used to dilate them and the number, location, make and dimensions of the intracoronary stents deployed. 'Partial revascularisation' was defined as a 'mismatch' between the number of vessels diseased and the number of vessels treated with PCI. The use of adjuvant pharmacological therapies such as Glycoprotein IIb/IIIa inhibitors was also documented as well as the use of any additional interventional tools such as rotational atherectomy or thrombectomy with the X-SIZER rotational thrombectomy catheter system.
Table 1: Information included during data collection following PCI

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Clinical indications</th>
<th>Risk factors</th>
<th>Coronary angiogram</th>
<th>PCI</th>
<th>Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Name</td>
<td>SAP</td>
<td>Hypertension</td>
<td>No vessels diseased</td>
<td>Balloons-types/dimensions</td>
<td>Death</td>
</tr>
<tr>
<td>Age</td>
<td>UAP</td>
<td>Diabetes</td>
<td>LMS</td>
<td>Stents-types/dimensions</td>
<td>VF</td>
</tr>
<tr>
<td>Gender</td>
<td>MI primary</td>
<td>Family Hx IHD</td>
<td>LAD</td>
<td>Deployment-location/pressures</td>
<td>Pacing</td>
</tr>
<tr>
<td>Ethnicity</td>
<td>MI salvage</td>
<td>Smoking</td>
<td>LCx</td>
<td>Glycoprotein IIb/IIIa inhibitors</td>
<td>No reflow</td>
</tr>
<tr>
<td>PIA</td>
<td>Hypercholesterolaemia</td>
<td>RCA</td>
<td>Rotational atherectomy</td>
<td>Tamponade</td>
<td></td>
</tr>
<tr>
<td>NQWMI</td>
<td>Renal impairment</td>
<td>SVG</td>
<td>Thrombectomy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MI current admission</td>
<td>LVEF-Normal</td>
<td></td>
<td>Distal protection devices</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Comorbidity</td>
<td>LVEF-Mild</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>COPD</td>
<td>LVEF-Moderate</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PVD</td>
<td>LVEF-Severe</td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

Procedural success was defined as achieving luminal gain resulting in < 50% residual stenosis. Any intra-procedural complications were logged at the end of the procedure.

In-hospital complications were logged at the time they occurred and survival status was documented at the time of discharge. Thirty day, six month and one year all cause mortality was collected using the Patient Analysis and Tracking System (PATS). Events, especially those occurring after discharge, were validated by telephone communication or correspondence with the relevant general practitioners.
COMPARATIVE SURGICAL SUBSTUDY

In order to compare and to try and identify whether coronary artery bypass surgery (CABG) outcomes in a similar setting are driven by the same or different factors we performed a parallel sub-study looking at patients undergoing CABG for acute coronary syndromes (113).

The enrolment period was similar to the main study. Data on 522 consecutive patients who underwent a first CABG procedure for unstable angina pectoris, non-ST segment elevation MI or unstable post-infarct angina were analysed. These patients underwent CABG either during the index admission or during a scheduled readmission within 1-4 weeks of discharge. Patients with cardiogenic shock or those who underwent emergency surgery as a result of a PCI complication directly from the Catheterisation Laboratory were excluded. Demographic, clinical and anatomical characteristics and outcomes were collected routinely for every patient undergoing CABG and obtained from the PATS database. Patient characteristics are described below in the PHASE I results section.

Univariate analysis was performed to identify potential predictors of peri-operative mortality (in-hospital death) and independent determinants were subsequently ascertained by analysing these using multiple logistic regression.

Variables that were looked at include the following:

- age
- gender
• ethnicity
• transfer status
• pulmonary disease
• smoking
• diabetes mellitus
• presence of peripheral or cerebrovascular disease
• renal impairment
• dyspnoea status (New York Heart Association NYHA grade)
• history of previous myocardial infarction or previous PCI
• number of vessels diseased
• left ventricular function
• hypertension (>140/90 or on antihypertensive therapy) and
• pre-operative medication.

Parsonnet or EUROSCORE values were not analysed as these are well validated risk prediction models for cardiac surgery with no equivalent models in wide use for PCI.
STATISTICAL METHODS

All the statistical analyses were performed using the SPSS 10.0 (1996 SPSS Inc.) statistical program. Data were transported from the original database to an SPSS format. The database was simplified to contain as many categorical variables as possible. Thirty day, six month and one year mortality, ethnicity, hypertension, diabetes mellitus, family history of ischaemic heart disease, smoking, hypercholesterolaemia, renal impairment (serum creatinine > 200 µmol/l), previous myocardial infarction, serious comorbidity, chronic obstructive pulmonary disease, peripheral vascular disease, multivessel (> 2) disease, partial revascularisation (mismatch between number of vessels diseased and number of vessels treated by PCI) were all expressed as simple categorical data.

Age was initially looked at as a continuous variable. Thirty day, six month and one year mortality was evaluated in patient quartiles of 4 almost equal age groups: ≤ 56 years, n=158; 57-66 years, n=158; 67-74 years, n=169 and ≥ 75 years, n=145. For simplicity, patients were then evaluated into 4 age groups as follows: A < 55 (mean 48.1), n=118; B 55-64 (mean 59.9), n=174; C 65-74 (mean 69.5), n=193; and D ≥ 75 (mean 79.5), n=145. This allowed age to be analysed as a categorical variable.

Left ventricular function was also analysed as a categorical variable by dividing patients into those with normal ejection fraction (LVEF > 70% or LVEF type 1), those with mild LV dysfunction (LVEF 50-70% or LVEF type 2), moderate LV dysfunction (LVEF 30-50% or LVEF type 3) and severe LV dysfunction (LVEF < 30% or LVEF type 4). Further analysis was done by simplifying these categorical data.
even further into 2 groups, those with an ejection fraction of $>50\%$ and those with $<50\%$.

All data were present for the total number of patients in the cohort except from LV function which was missing from the angiographic data when left ventriculography was not done during diagnostic angiography in 226/630 (35.9\%) of the cases. All the analyses were performed initially excluding those cases where data were missing. Further analyses were performed assuming normal LV function for those missing. By using this method, the significance of the given variable (in this case LV function) would, if anything, be underestimated. In addition, in order to account for the missing data, analyses were made by randomly assigning LV function for those with missing data or LV function was estimated using already existent information. It was assumed to be impaired in the presence of either previous history of myocardial infarction or multi-vessel disease.

A univariate analysis was firstly performed looking at which demographic, simple anatomical and clinical variables were associated with increased risk of mortality at 30 days, 6 months and 1 year. Those found to be statistically significant ($p \leq 0.1$, Chi square test) were then entered into a multiple logistic regression (forward linear) model in order to identify those variables that could help predict early (30 days), medium (6 months) or late (1 year) death. Significant independent predictors of early, medium or late mortality were taken as those with a statistical significance ($p$ value) of less than 0.05.
PATIENT CHARACTERISTICS

In total 630 patients were included (Table 2: Patient characteristics). The discharge diagnosis was UAP in 72.5% (457/630), UPIA in 24.6% (155/630) and only 2.9% (18/630) had NSTEMI. This low rate for NSTEMI is due to the fact that at the time of the study, sensitive markers of myocardial cell injury (TnT or Tnl) were not in routine use at our institution. Of the total 72% (455/630) were male. The vast majority, 88.1%, were White Europeans (556/630) and 11.7% (74/630) were of Asian descent. There was one Afrocarribean Black. Of the total number of patients 23.0% (145/630) were over the age of 75, 30.6% (193/630) were between 65 and 74, 27.6% (174/630) were aged 55-64 and 18.0% (118/630) were age less than 55. The rate of stent usage in this cohort was 91.3% (575/630). The overall use of Glycoprotein IIb/IIIa receptor antagonists (REOPRO) was 21.3% (134/630). Of the total cohort 12.8% (81/630) were diabetic, 28.7% (181/630) were diagnosed hypertensive patients (on treatment) and 51% (322/630) had hypercholesterolaemia; 28.8% (182/630) were current smokers. Also, 3.5% (22/630) had documented renal impairment with serum creatinine levels > 200 µmol/l and 4.0% (25/630) had peripheral or cerebro-vascular disease sufficient to cause symptoms, require treatment or pose access problems during intervention. One third or 33.9% (214/630) had sustained a previous myocardial infarction whereas 9.5% (60/630) had any other significant comorbidity including diseases of the gastrointestinal, peripheral and central nervous system or disorders of the blood.

On coronary angiography, 35.8% (226/630) had single vessel disease, 30.7% (194/630) had two vessels disease and 33.4% (211/630) had triple vessel disease. The
proportion of patients with multi-vessel disease increased, as expected, with age. 
More than half of the patients aged over 75 had triple vessel disease (76/146, 52.4%).

Systolic function was assessed by means of left ventriculography at the time of coronary angiography in 405/630 (64.2%). 50.6% (205/630) had normal left ventricular ejection fraction (LVEF > 70%), 30.1% (122/630) had mild left ventricular systolic impairment (LVEF 50-70%), 14.1% (57/630) had moderate impairment (LVEF 30-50%) whereas 5.2% (21/630) of those who had it checked had severe left ventricular impairment (LVEF < 30%). This observation is probably biased to underestimate the prevalence of severe left ventricular dysfunction. Patients who are clinically unwell or have clinical signs of heart failure are less likely to be subjected by the operator to left ventriculography which can precipitate worsening of the heart failure and lead to the development of acute pulmonary oedema on the table.

Further sub-analyses were performed in these 4 age subgroups and are outlined in Table 2.
### Table 2: Patient characteristics

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>Group A</th>
<th>Group B</th>
<th>Group C</th>
<th>Group D</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (%)</td>
<td>630(100)</td>
<td>118(18.0)</td>
<td>174(27.6)</td>
<td>193(30.6)</td>
<td>145(23.0)</td>
<td></td>
</tr>
<tr>
<td>Male:Female</td>
<td>2.6:1</td>
<td>4.6:1</td>
<td>4.1:1</td>
<td>2.2:1</td>
<td>1.4:1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>181(28.7)</td>
<td>27(22.9)</td>
<td>44(25.3)</td>
<td>56(29.0)</td>
<td>53(36.6)</td>
<td>0.06</td>
</tr>
<tr>
<td>Hypercholesterolaemia</td>
<td>322(51.0)</td>
<td>64(54.2)</td>
<td>105(60.3)</td>
<td>98(50.8)</td>
<td>54(37.2)</td>
<td>0.01</td>
</tr>
<tr>
<td>Clin. Diagnosis: UAP</td>
<td>457(72.5)</td>
<td>75(63.6)</td>
<td>126(72.4)</td>
<td>130(67.4)</td>
<td>126(86.9)</td>
<td>0.001</td>
</tr>
<tr>
<td>UPIA</td>
<td>155(24.6)</td>
<td>39(33.1)</td>
<td>44(25.3)</td>
<td>55(28.5)</td>
<td>17(11.7)</td>
<td>0.001</td>
</tr>
<tr>
<td>NSTEMI</td>
<td>18(2.9)</td>
<td>4(3.4)</td>
<td>4(2.3)</td>
<td>8(4.1)</td>
<td>2(1.4)</td>
<td>0.001</td>
</tr>
<tr>
<td>Comorbidity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>81(12.8)</td>
<td>7(5.9)</td>
<td>23(13.2)</td>
<td>32(16.6)</td>
<td>19(13.1)</td>
<td>0.06</td>
</tr>
<tr>
<td>Ethnic origin: White</td>
<td>555(88.1)</td>
<td>100(84.7)</td>
<td>151(86.7)</td>
<td>170(88.1)</td>
<td>134(92.4)</td>
<td>0.4</td>
</tr>
<tr>
<td>Asian</td>
<td>74(11.7)</td>
<td>18(15.3)</td>
<td>23(13.2)</td>
<td>22(11.4)</td>
<td>11(7.6)</td>
<td>0.4</td>
</tr>
<tr>
<td>Black</td>
<td>1(0.2)</td>
<td>0(0)</td>
<td>0(0)</td>
<td>1(0.5)</td>
<td>0(0)</td>
<td>0.4</td>
</tr>
<tr>
<td>LVEF: Not done</td>
<td>226(35.8)</td>
<td>41(34.7)</td>
<td>61(35.1)</td>
<td>65(33.7)</td>
<td>58(40)</td>
<td>0.4</td>
</tr>
<tr>
<td>Normal (&gt;70%)</td>
<td>205(50.6)</td>
<td>45(38.1)</td>
<td>60(34.5)</td>
<td>58(30.1)</td>
<td>42(29.0)</td>
<td>0.4</td>
</tr>
<tr>
<td>Mild (50-70%)</td>
<td>122(30.1)</td>
<td>25(21.2)</td>
<td>30(17.2)</td>
<td>42(21.8)</td>
<td>25(17.2)</td>
<td>0.4</td>
</tr>
<tr>
<td>70%</td>
<td>57(14.1)</td>
<td>5(4.2)</td>
<td>18(10.3)</td>
<td>19(9.8)</td>
<td>15(10.3)</td>
<td>0.4</td>
</tr>
<tr>
<td>50%</td>
<td>21(5.2)</td>
<td>2(1.7)</td>
<td>5(2.9)</td>
<td>9(4.7)</td>
<td>5(3.4)</td>
<td>0.4</td>
</tr>
<tr>
<td>Severe (&lt;30%)</td>
<td>226(35.8)</td>
<td>65(55.1)</td>
<td>70(40.2)</td>
<td>63(32.6)</td>
<td>28(19.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>No. of vessels dis. 1</td>
<td>193(30.7)</td>
<td>36(30.5)</td>
<td>55(31.8)</td>
<td>61(31.6)</td>
<td>41(28.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>2</td>
<td>211(33.4)</td>
<td>17(14.4)</td>
<td>49(28.2)</td>
<td>69(35.8)</td>
<td>76(52.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Peripheral vasc. disease</td>
<td>25(4.0)</td>
<td>1(0.8)</td>
<td>3(1.7)</td>
<td>11(5.7)</td>
<td>11(7.6)</td>
<td>0.01</td>
</tr>
<tr>
<td>Previous MI</td>
<td>214(33.9)</td>
<td>35(29.7)</td>
<td>56(32.2)</td>
<td>71(36.8)</td>
<td>52(35.9)</td>
<td>0.5</td>
</tr>
<tr>
<td>Renal impairement</td>
<td>22(3.5)</td>
<td>0(0)</td>
<td>3(1.7)</td>
<td>8(4.1)</td>
<td>11(7.6)</td>
<td>0.04</td>
</tr>
<tr>
<td>Partial revasc.</td>
<td>352(55.8)</td>
<td>44(37.3)</td>
<td>90(51.7)</td>
<td>119(61.7)</td>
<td>98(67.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Smoking</td>
<td>182(28.8)</td>
<td>60(50.8)</td>
<td>56(32.2)</td>
<td>44(22.8)</td>
<td>22(15.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Glycoprotein IIb/IIIa use</td>
<td>134(21.3)</td>
<td>22(18.6)</td>
<td>37(21.3)</td>
<td>33(17.1)</td>
<td>42(29.0)</td>
<td>0.05</td>
</tr>
</tbody>
</table>

**Group A = age < 55**

**Group B = age 55 – 64**

**Group C = age 65 – 74**

**Group D = age > 75**

UAP = Unstable Angina Pectoris

UPIA = Unstable Post Infarct Angina

NSTEMI = Non ST segment Elevation Myocardial Infarction

MI = Myocardial Infarction

LVEF = Left Ventricular Ejection Fraction
Patient characteristics for the parallel surgical group were also looked at: about 55% (290/522) were over the age of 65 with 87 being the maximum and 35 the minimum age at operation. 66.5% (374/522) were male. 80% (417/522) were white caucasians, 19% (100/522) were Indian subcontinent Asians and 1% (5/522) were afrocarribeans.

Two thirds of the cohort patients (341/522, 65%) were transferred from peripheral referring hospitals. 6% (28/522) had sustained a previous myocardial infarction, 13% (67/522) had a previous PCI and 21% (110/522) were diabetic. 8% (43/522) were current smokers and 15% (78/522) had a history of lung disease, mainly Chronic Obstructive Pulmonary Disease (COPD).

Clearly, this surgical cohort is not comparable to the main study cohort that underwent PCI. Patients referred for surgery have more extensive, multi-vessel coronary artery disease that is deemed not suitable for PCI or had previously failed PCI. Patients who had emergency surgery as a result of an acute PCI complication were excluded from this study. On the other hand, patients who are felt to be of too high an anaesthetic risk due to very poor left ventricular function, respiratory or severe carotid disease and those with extensive comorbidity especially due to age are often referred for PCI.
OUTCOME MEASURES-PHASE 1

The 1 year all cause mortality for the whole series was 6.8% (43/630). The 30 days and 6 months mortality was 3.5% (22/630) and 5.4% (34/630) respectively. Mortality was increased, as expected, with age which was more marked in the over 75. One year mortality was as follows in the various age groups: Group A (<55) 0.8% (1/118); Group B (55-64) 1.1% (2/174); Group C (65-74) 6.2% (12/193) and Group D (≥75) 19.3% (28/145).

The excess mortality in the over 75 occurred early i.e. within 30 days. Early mortality in the various age groups was as follows: Group A 0% (0/118), Group B 0% (0/174), Group C 2.1% (4/193) and Group D 12.4% (18/145).

Medium term (6 months) mortality was also, as expected, higher in the elderly: Group A 0.8% (1/118), Group B 0.6% (1/174), Group C 5.7% (11/193) and Group D 14.5% (21/145). A summary of the total cohort and individual age group early, medium and late mortality is seen in Figure 1.
Figure 1: Bar chart showing 30 day, 6 month and 1 year mortality for the total cohort and for the different age groups.

For the age quartiles, mortality trends were as follows:

≤ 56: 0% (0/158), 0.6% (1/158) and 1.3% (2/158) for 30 day, 6 month and 1 year mortality respectively;

57-66: 0% (0/158), 0.6% (1/158) and 0.6% (1/158) for 30 day, 6 month and 1 year mortality respectively;

67-74: 2.4% (4/169), 6.5% (11/169) and 6.5% (11/169) for 30 day, 6 month and 1 year mortality and finally

≥ 75: 12.4% (18/145), 14.5% (21/145) and 19.3% (28/145) for 30 day, 6 month and 1 year mortality.
Univariate analysis showed the following to affect 30 day mortality: age > 65 (p<0.001), multi-vessel (three vessel) disease (p=0.03), history of previous MI (p=0.08), partial revascularisation (p=0.015) and smoking (p=0.05). Six month mortality was affected by age > 65 (p<0.001), impaired Left Ventricular (LV) systolic function (ejection fraction < 50%) (p=0.05), multi-vessel disease (p=0.003), renal impairment (p=0.02), peripheral vascular disease (p=0.03), partial revascularisation (p=0.001) and smoking (p=0.05). One year mortality was influenced by the following: age > 65 (p<0.001), hypercholesterolaemia (>5mmol/l) (p=0.05), diabetes mellitus (p=0.01), impaired LV systolic function (p<0.001), multi-vessel disease (p<0.001), previous MI (p=0.05), peripheral vascular disease (p=0.007), renal impairment (p=0.004) and partial revascularisation (p=0.001).

When the above parameters were respectively entered into multiple logistic regression models to determine which of those are independent predictors for early, medium and late death, we found that age > 65 (OR 8.0, 95% CI 3.8-17.1, p<0.001), impaired LV systolic function (OR 2.3, 95% CI 1.01-5.4, p=0.05), peripheral vascular disease (OR 3.1, 95% CI 1.02-9.4, P=0.05), partial revascularisation (OR 3.1, 95% CI 1.2-7.8, p=0.02) and diabetes mellitus (OR 2.7, 95% CI 1.2-6.3, p=0.02) were all independent predictors of death 1 year after the PCI for unstable angina. Six months after the procedure the only independent predictors of mortality were age > 65 (OR 6.8, 95% CI 3.0-15.0, p<0.001) and partial revascularisation (OR 3.6, 95% CI 1.8-9.7, p=0.01). For early (30 day) death following PCI for unstable angina, the only independent predictor of mortality was age (OR 18.9, 95% CI 5.5-64.5, p<0.001). The results of univariate and multivariate (multiple regression model) analyses are summarised in Tables 3, 4 and 5.
Table 3: Results of univariate analysis (only statistically significant factors shown) and multivariate (multiple logistic regression) analysis for 30 day mortality.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariate analysis</th>
<th>Multivariate analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>P value</td>
<td>OR (CI), p value</td>
</tr>
<tr>
<td>Age &gt; 65</td>
<td>p &lt; 0.001</td>
<td>18.9 (5.5-64.5), p &lt; 0.001</td>
</tr>
<tr>
<td>Multivessel (3) disease</td>
<td>p = 0.03</td>
<td>NS</td>
</tr>
<tr>
<td>Previous MI</td>
<td>p = 0.09</td>
<td>NS</td>
</tr>
<tr>
<td>Partial revascularisation</td>
<td>p = 0.01</td>
<td>NS</td>
</tr>
<tr>
<td>Smoking</td>
<td>p = 0.05</td>
<td>NS</td>
</tr>
</tbody>
</table>

Table 4: Results of univariate (only statistically significant factors shown) and multivariate (multiple logistic regression) analysis for 6 months mortality.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariate analysis</th>
<th>Multivariate analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>P value</td>
<td>OR (CI), p value</td>
</tr>
<tr>
<td>Age &gt; 65</td>
<td>p &lt; 0.001</td>
<td>6.8 (3.0-15.0), p &lt; 0.001</td>
</tr>
<tr>
<td>Comorbidity</td>
<td>p = 0.02</td>
<td>NS</td>
</tr>
<tr>
<td>LVEF &lt; 50 %</td>
<td>p = 0.05</td>
<td>NS</td>
</tr>
<tr>
<td>Multivessel (3) disease</td>
<td>p = 0.003</td>
<td>NS</td>
</tr>
<tr>
<td>Renal impairment</td>
<td>p = 0.02</td>
<td>NS</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>p = 0.03</td>
<td>NS</td>
</tr>
<tr>
<td>Partial revascularisation</td>
<td>p = 0.001</td>
<td>3.6 (1.8-9.7), p = 0.01</td>
</tr>
<tr>
<td>Smoking</td>
<td>p = 0.05</td>
<td>NS</td>
</tr>
</tbody>
</table>

Table 5: Results of univariate analysis (only statistically significant factors shown) and multivariate (multiple logistic regression) analysis for 1 year mortality.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariate analysis</th>
<th>Multivariate analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>P value</td>
<td>OR (CI), p value</td>
</tr>
<tr>
<td>Age &gt; 65</td>
<td>p &lt; 0.001</td>
<td>8.0 (3.8-17.1), p &lt; 0.001</td>
</tr>
<tr>
<td>Comorbidity</td>
<td>p = 0.004</td>
<td>NS</td>
</tr>
<tr>
<td>LVEF &lt; 50%</td>
<td>p = 0.01</td>
<td>2.3 (1.0-5.4), p = 0.05</td>
</tr>
<tr>
<td>Multivessel (3) disease</td>
<td>p &lt; 0.001</td>
<td>NS</td>
</tr>
<tr>
<td>Renal impairment</td>
<td>p = 0.01</td>
<td>NS</td>
</tr>
<tr>
<td>Partial revascularisation</td>
<td>p &lt; 0.001</td>
<td>3.1 (1.2-7.8), p = 0.02</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>p = 0.01</td>
<td>2.7 (1.2-6.3), p = 0.02</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>p = 0.004</td>
<td>3.1 (1.0-9.4), p = 0.05</td>
</tr>
</tbody>
</table>
OR = Odds Ratio
CI = 95% Confidence Interval
MI = Myocardial Infarction
NS = Not (statistically) Significant
COMPARATIVE SURGICAL SUBSTUDY RESULTS

The total in-hospital mortality for the 522 patients in the surgical cohort was 9.6% (50/522). Average time to death was 5.6 days, however, the data were largely skewed to the left with the majority of deaths (42%) occurring on the day of surgery. In-hospital mortality was as follows in the various age groups: Age < 55 (n=79) 8%, age 55-64 (n=153) 4%, age 65-74 (n=182) 9% and age ≥ 75 (n=108) 19%.

Univariate analysis showed the following variables to be associated with the in-hospital mortality: age (p<0.001), transfer from another hospital (p=0.03), the presence of cerebrovascular disease (p=0.003), hypertension (p=0.02), renal impairment (p=0.006), impaired left ventricular function (p<0.001), left main stem artery involvement (p=0.03), chronic airways disease (p=0.02) and clinical symptoms of congestive heart failure (NYHA Classification) (p=0.001).

Multivariate analysis showed the following variables to be independent predictors of in-hospital mortality following CABG surgery for acute coronary syndromes: age (p=0.01), chronic airways disease (p=0.02, OR 2.6, CI 1.1-6.1), cerebrovascular disease (p=0.04, OR 2.8, CI 1.1-7.4), clinical symptoms of heart failure (p=0.08, OR 5.3, CI 1.6-17.9) and left ventricular systolic impairment (p=0.04, OR 4.4, CI 1.6-12.1). These results are summarised in Table 6:
Table 6: Results of the univariate and multivariate analysis for factors predictive of in-hospital death following CABG for acute coronary syndromes.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariate analysis</th>
<th></th>
<th>Multivariate analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>P value</td>
<td></td>
<td>P value</td>
</tr>
<tr>
<td></td>
<td>OR (CI)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>&lt; 0.001</td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td>Chronic airways disease</td>
<td>0.02</td>
<td>0.02</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2.6 (1.1-6.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>0.003</td>
<td>0.04</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2.8 (1.1-7.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NYHA class</td>
<td>0.001</td>
<td>0.08</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5.3 (1.6-17.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LV impairment</td>
<td>&lt;0.001</td>
<td>0.04</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4.4 (1.6-12.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transfer status</td>
<td>0.03</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Renal impairment</td>
<td>0.006</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Left main stem disease</td>
<td>0.03</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.02</td>
<td>NS</td>
<td></td>
</tr>
</tbody>
</table>
CHAPTER 3:

DISCUSSION OF RESULTS:

PHASE I
As life expectancies continue to increase, Cardiologists will increasingly be faced by the difficult clinical dilemma of caring for elderly patients with acute coronary syndromes. This is difficult because the very elderly are often excluded from the large randomised clinical trials that determine best clinical practice. This, as a rule has unfortunately not spared the landmark studies that have determined the modern management strategy of NSTEMI that often involves aggressive invasive investigation and management. For example, the FRISC II trial, one of the landmark studies supporting an early invasive approach to the treatment of acute coronary syndromes, excluded patients aged over 75. It is a well known fact that clinical trial circumstances often vary greatly from day to day clinical practice (114). This tends to be more important when it comes to applying clinical trial results to the elderly.

In our study, it is evident that age plays a major role in the clinical outcome of PCI for acute coronary syndromes. The finding that age is the only independent predictor of mortality at 30 days is indicative of its importance in determining early or procedural related outcome after PCI in acute coronary syndromes. It may also, however, reflect the relatively small number of patients in the study.

Elderly patients had substantially higher early or procedure related mortality as well as higher late mortality. One month mortality was 2.1% in those aged 65-75 whereas it rose to 12.4% in those aged > 75. While it is customary to attribute 30 days mortality to the procedure, for this age group the high prevalence of extensive arterial disease and other co-morbidities such as diabetes, multi-vessel disease and impaired left ventricular function clearly play a role. A few deaths may be related to a degree of
interaction between the procedure and pre-procedural mortality whereas a small proportion will be secondary to the procedure alone.

Medium (6 months) and late (1 year) mortality was, as expected, again higher in the older age group and in particular in those over 75. This probably represents the higher prevalence of not only cardiovascular related comorbidity in the elderly but also the higher prevalence of other conditions such as cancer. It is difficult to find comparable data in published series as the elderly, as mentioned above, are usually excluded from randomised trials.

Having said that, this study need not necessarily, discourage physicians from opting for an invasive revascularisation procedure by PCI where appropriate, for those high risk patients presenting with non ST elevation acute coronary syndromes including those over the age of 75. PRAIS-UK, a prospective registry carried out at the U.K. looking at clinical outcomes and practice patterns of unstable angina and NSTEMI highlighted the poor prognosis of this condition especially in the > 70 years old with a 6 month rate of death or MI at 17.3% compared to 5.7 and 11.7% in the < 60 and 60-70 years old respectively (31). This ongoing registry showed a very low revascularisation rate in this cohort with only 4% undergoing in-patient PTCA and even less having bypass surgery.

Older patients often have an acceptable procedural risk but their medium term risk for death is much higher than in the younger patients. Is it their disease and comorbidity? Does PCI, despite the risks, improve on the natural history?

The answers can only come with a properly planned trial that includes the over 75’s. The recent TIME study addressed the question of how to best manage patients over the age of 75 with intractable symptoms due to coronary artery disease (115). Best
medical therapy was compared against an invasive approach that led to revascularisation, by PCI mainly, in those whose coronary anatomy was deemed suitable for either PCI or surgery. Both quality of life and 1 year mortality were better in the invasive group despite a higher early mortality in that group.

At the other end of the spectrum of coronary artery disease, advanced age alone has not been found to be a contraindication to an aggressive approach to the treatment of acute ST segment elevation myocardial infarction. In a study reported by Singh et al in 1999, primary percutaneous intervention in octogenarians was shown to be not only feasible but also reasonably safe (116,117). Although the mortality associated with primary angioplasty for acute myocardial infarction in octogenarians remained high despite the significant improvement in clinical success rate over the years (21% in hospital mortality in those aged over 80), the long-term prognosis following a successful angioplasty was no different from that in age- and sex-adjusted U.S. white population.

These results are obviously encouraging and the next step would be to examine if the same applies for those elderly patients presenting with non ST segment elevation acute coronary syndromes.

To conclude, it should be remembered that in all observational randomised clinical trials, the elderly are associated with increasingly poor outcomes within 6 months after an episode of acute coronary syndrome irrespective of treatment strategy (118). Although the patient’s age is naturally expected to affect long-term outcome among patients with coronary artery disease, the age of the patient with acute coronary syndrome is a strong predictor of short-term outcome as well. And that this is a
THE ROLE OF PARTIAL REVASCULARISATION

The second most important determinant of mortality in this study was found to be partial revascularisation. Partial or incomplete revascularisation is defined as the management strategy whereby only some of the significant flow-limiting coronary artery stenoses are treated in a given patient. That usually involves identifying the ‘culprit vessel’ that is thought to be the vessel in which plaque rupture and thrombosis has occurred and therefore led to the development of the index event that led to the patient’s admission to hospital. Then, within that vessel, if more than one lesions are present, the ‘culprit lesion’ is identified angiographically by its severity, complexity or the presence of thrombus and targeted for angioplasty and stenting.

Identifying ‘culprit vessels’ and ‘culprit lesions’ is not always a straightforward exercise. ‘Culprit vessels’ are usually identified by extrapolating information on the areas of myocardial ischaemia from non-invasive testing. Most commonly that is obtained from resting ECG changes but occasionally stress ECG, myocardial perfusion scanning or dobutamine stress echocardiography. However, the resting ECG in acute coronary syndromes is often normal and, even when not, it is not always easy to determine which coronary artery is responsible for supplying a certain myocardial territory. This problem is more common when trying to identify the culprit vessel in inferior, posterior and lateral territory ischaemia where the right coronary artery, circumflex and diagonal vessels could all be incriminated.

Culprit lesions are identified on coronary angiography. These lesions are usually high grade lesions with B2 or C characteristics i.e. often eccentric, hazy looking lesions with evidence of intracoronary thrombus present. However, it is a well known fact
that plaque activation and rupture is an active on-going process, and not uncommonly acute coronary syndromes result from thrombosis on mild, non-flow limiting plaques which can, by the time of coronary angiography, resolve to their original status and therefore be difficult to identify (119).

Partial revascularisation was undertaken in 55.8% of our cases in the context of the ‘culprit vessel’ only being dealt by angioplasty and stenting. This strategy is acceptable and indeed advisable when the risk of bypass surgery or multi-vessel stenting is perceived to be high during the early stages of an acute coronary syndrome. Therefore, a lower risk, single vessel PCI is performed initially instead of multi-vessel stenting or bypass graft surgery. This strategy is mostly used in the context of ST elevation acute coronary syndromes, in acute coronary syndromes associated with haemodynamic instability or cardiogenic shock and in those patients where comorbidity is expected to increase the risk from a prolonged multi-vessel revascularisation procedure. These patients, often, tend to be the elderly. In the U.K. setting, partial revascularisation has also sometimes become necessary due to the potentially longer waiting times for transfer to cardiac surgical centres for bypass surgery, in some patients who become more unstable while waiting for transfer or where PCI is considered to offer a reasonable alternative as a bridge to surgery as part of a ‘staged’ procedure strategy.

Partial revascularisation is usually sufficient to reduce the immediate risk of adverse cardiac events in these patients. However, planned complete revascularisation should ideally take place, where possible, at a later stage in order to avoid medium or long term cardiac events. Of course, the decision to proceed to full revascularisation will be made on an individual patient basis. There is little doubt that reluctance for further
procedures once the acute event has passed is more common in the older age group. This would certainly explain some of the late mortality.

Why should the performance of partial revascularisation be associated with an adverse clinical outcome and increased mortality at 6 and 12 months? One possible explanation would be that the ‘culprit’ lesions and vessels are often wrongly identified as the ones responsible for the index event and as being at the highest risk for causing adverse clinical events. But a more likely explanation is that patients treated with this strategy are often rendered asymptomatic for a while which makes it difficult to insist on further procedures. This results in leaving possibly a number of vulnerable lesions untreated that can give rise to adverse cardiac events, further acute coronary syndrome episodes, myocardial infarction and ultimately death.

This area is in obvious need of a properly conducted randomised clinical trial involving the elderly as well as the younger patients. No such trials have thus far been performed in the setting of acute coronary syndromes. One small observational trial reported by Glazier et al in 1992 addressed the issue of ‘incomplete revascularisation’ defined as balloon dilatation of ‘ischaemia producing’ coronary stenoses only in the presence of more anatomically significant stenoses on coronary angiography (120). It failed to show any adverse clinical events at one year in those treated with this strategy.
THE ROLE OF COMORBIDITY

The finding that poor left ventricular systolic function, peripheral vascular disease, and diabetes mellitus are associated with adverse prognosis following PCI are also in agreement with previous large studies of risk factor analysis in PCI for stable angina as well as acute coronary syndromes (100-106). These risk factors as well as the dramatic effect of age were also shown to be predictors of adverse prognosis in patients presenting with acute coronary syndromes (121,122).

Although these risk factors, in addition with others and mainly that of renal impairment and left ventricular dysfunction were shown to affect outcome after PCI in the large observational studies performed in the States in the early and mid-nineties, in our study they do not feature as independent predictors of early or ‘procedure-related’ mortality. The fact that in our study their importance comes to play only for determining survival outcomes at 1 year may be not only a reflection of the relatively small number of patients. It may also reflect the fact that their importance lies with their contribution to the natural progression of atherothrombotic vascular disease as opposed to having a direct effect on procedural outcome itself (123-125). It is probably most likely that the more severe the impairment of left ventricular systolic function or renal dysfunction is, the more significant the direct effect on the procedural related mortality is.

All large observational studies on risk stratification of patients presenting with acute coronary syndromes have shown that left ventricular function and diabetes mellitus are associated with adverse prognosis irrespective of the treatment strategy (invasive or conservative) employed.
Therefore, the interaction of these risk factors, all of which are of course more common in the elderly, in the natural history of acute coronary syndromes and their contribution to procedure related mortality following PCI is interesting but rather complex. The issue becomes more complex if one considers that, as shown from most registries on the management of acute coronary syndromes, those patients with multiple comorbidities presenting with acute coronary syndromes and who are often older, are treated conservatively. There is therefore a selection bias towards selecting young patients who tend to have less comorbidities for aggressive invasive treatments and those usually have a better prognosis irrespective of treatment strategy. On the contrary, those elderly patients with multiple risk factors and comorbidities are often treated conservatively and are only selected for invasive investigation and therapy if conservative therapy fails. This, by definition, would classify them at an even higher risk from their acute coronary syndromes. These patients therefore, not surprisingly, have a higher risk of suffering complications following interventional procedures.

Risk stratification by clinicians should, as mentioned above, take place at two different levels of patient management. Initial risk stratification based on initial presentation, clinical characteristics, ECG findings and biochemical evidence of myocardial necrosis should initially stratify patients into low, medium and high risk for progression to myocardial infarction and death. At that point and after repeat evaluation on initial response to medical therapy the decision is taken on the need for an invasive investigational strategy by means of coronary angiography. A clinical risk score tool such as the TIMI risk score would help clinicians take such decisions (121). Once coronary angiography has been performed, but even prior to it and based on the clinical information available, the clinician should re-stratify the patient on their perceived risk from undergoing either PCI or CABG or continued medical therapy.
Our proposed PCI risk score and the already established risk scores for cardiac surgery such as the Parsonnet and EUROSCORE should help the risk stratification process at this stage and aim decision making and consent to treatment processes (126-131).
THE ROLE OF BYPASS SURGERY

Coronary Artery Bypass Surgery has been an established mode of therapy for coronary artery disease for a few years now. In line with PCI, it has continuously evolved so that the method is now safer with better cardioplegia, associated with less peri-operative complications, better and longer lasting arterial conduits are now used and is becoming increasingly less invasive with the advent of the MIDCAB (Minimally Invasive Direct Coronary Artery Bypass) and methods of operating on the ‘beating heart’ without the need for cardiopulmonary bypass (132). However, it remains a major operation with significant associated morbidity and often mortality. It probably offers a better long term outcome compared to PCI mainly because of less need for repeat revascularisation procedures however medium term mortality remains similar to PCI at least for stable angina pectoris (132-136).

The place of bypass graft surgery in the treatment of acute coronary syndromes remains somehow controversial. It has long been recognised that bypass grafting in the setting of an acute ST segment elevation myocardial infarction is detrimental to the patient. However, and following the studies for the invasive therapies of acute non-ST elevation coronary syndromes and especially FRISC II, TACTICS-TIMI 18 and RITA-3, a large majority, often up to 40% of the patients randomised to the ‘invasive-revascularisation’ strategy actually underwent bypass surgery as opposed to PCI. Like any other invasive therapy, the feasibility and the risk of a given therapy have to be weighted against the potential benefits before the decision to proceed with such therapy is taken.
We therefore felt it would be useful to run a parallel study to the main study group to allow some comparison between those patients undergoing surgery for acute coronary syndromes with those undergoing PCI and their outcomes.

Although no direct comparison can take place as this was not a randomised clinical trial, some useful conclusion and guidelines can be drawn from the results.

The surgical sub-study ran in parallel to the main study, at the same institution and during approximately the same period. For this part 522 consecutive patients either admitted directly from our institution or transferred from referring hospitals (about two-thirds of the total) for first-time coronary artery bypass grafting for acute coronary syndromes, excluding those who needed surgery directly as a result of PCI complications. Compared to the main study PCI group, there were more female patients than male (33.5% in the surgical group compared to 28% in the PCI group).

There was similar proportional representation of the elderly age groups in both cohorts; 56% were over the age of 65 and 21% over the age of 75 in the surgical group and 58% were over the age of 65 and 23% over the age of 75 in the angioplasty group. As far as comorbidity was concerned, again, there was similar representation in both cohorts. Although more patients who underwent surgery were diabetic compared to those undergoing PCI (21% v 13%), many more patients undergoing PCI had suffered a previous MI compared to those undergoing surgery (34% v 6%). At least moderate LV dysfunction was observed in a larger proportion of the patients who underwent surgery compared to those who underwent PCI (47% v 20%). In addition and as one would expect double the proportion of the surgically treated groups had triple vessel disease compared to the angioplasty treated group (73% v
33%). These differences between the parallel PCI and surgical groups are summarised in Table 7.

*Table 7: Comparative rates of important parameters in the PCI and CABG parallel groups*

<table>
<thead>
<tr>
<th>Parameters</th>
<th>PCI</th>
<th>CABG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>28 %</td>
<td>33.5 %</td>
</tr>
<tr>
<td>Age&gt;65</td>
<td>58 %</td>
<td>56 %</td>
</tr>
<tr>
<td>Age&gt;75</td>
<td>23 %</td>
<td>21 %</td>
</tr>
<tr>
<td>Diabetes</td>
<td>13 %</td>
<td>21 %</td>
</tr>
<tr>
<td>Previous MI</td>
<td>34 %</td>
<td>6 %</td>
</tr>
<tr>
<td>Impaired LV function</td>
<td>20 %</td>
<td>47 %</td>
</tr>
<tr>
<td>3 vessel disease</td>
<td>33 %</td>
<td>73 %</td>
</tr>
</tbody>
</table>

Within the different age groups however, the most elderly patients (those aged >75) who underwent PCI tended to have a similar, if not heavier co-morbidity load compared to their surgically treated equivalents; 13% of the angioplasty treated elderly patients were diabetic compared to 9% of the surgically treated elderly patients. Peripheral or cerebrovascular disease was observed in 8% of the elderly angioplasty group compared to 5% in the elderly surgical group. On the contrary, triple vessel disease was observed more commonly in the surgically treated elderly group (82% v 52%). Significantly impaired LV function was present much more commonly in the surgical >75 group (5.4% in the PCI group compared to 58% in the CABG group). This difference however may be amplified as patients with surgical disease more often undergo ventriculography whereas patients who have ‘follow-on’ PCI procedures are less likely to have one in order to try and reduce the amount of contrast used.
Perhaps one should expect a higher early mortality in the surgically treated group compared to the PCI group. In-hospital mortality for the whole surgical cohort was 9% compared to the 3.5% 30 day mortality in the angioplasty cohort. However, one should observe the large difference in procedure related mortality (almost threefold) with some interest. The difference in mortality becomes even more interesting when one looks at the difference in mortality in the two cohorts according to age. In the youngest patients (those aged less than 55) no early mortality was observed in the angioplasty group compared to 8% mortality in the surgical group. In those aged 55-64, a zero mortality again compares favourably to a 4% mortality in the surgically treated equivalent age group. In those aged 65-74, the surgical mortality was 9% compared to 2% in the PCI group whereas at the extreme of age (>75) the mortality in the PCI group remained considerably lower than in the surgical group (12% compared to 19%).

Several comments can be made in relation to this observation. Firstly, the fact that the early mortality is higher in the surgical group compared to the angioplasty group is not a surprise finding. It has been shown in most large studies comparing percutaneous to surgical revascularisation for coronary artery disease. What is surprising however, is the scale of the difference; it is more profound in the younger age groups (<65) where there was no PCI mortality compared to a substantial mortality in the surgical group (5%). In the more elderly (>65) the difference is less dramatic yet still remains substantial and almost double in the surgical group (13%) compared to the PCI group (6.4%).

Some additional variables were shown from the multiple regression analysis to be significant independent predictors for early mortality following bypass surgery.
compared to PCI. Although in our main study only age was found to be an
independent predictor of early death, for the surgically treated patients in addition to
age, the presence of cerebrovascular disease, left ventricular impairment, clinical
symptoms of heart failure and chronic respiratory disease were also shown to be
independent predictors of early death.

It is therefore evident from this observation that short term survival after
revascularisation for acute coronary syndromes is better following PCI than bypass
surgery. However, one should remember that we have not looked at medium or long
term mortality in the surgical group. In addition, it is a well known fact that with
current practice, PCI is associated with a higher incidence of adverse cardiac events
mainly because of the need for target vessel revascularisation within the first few
months after the procedure.

It may be that the best policy for these patients is to treat the index event, if possible,
with percutaneous coronary intervention and then follow with complete
revascularisation within the next few weeks with either surgery or further PCI
procedures. This would probably apply more for the elderly patients who also suffer
from chronic respiratory disease, have evidence of cerebrovascular disease and have
clinical or objective evidence of left ventricular failure. That of course could be the
subject of a properly designed randomised controlled trial to compare the strategy of
initial partial revascularisation followed by early complete revascularisation versus
early complete revascularisation with bypass surgery for multi-vessel disease in the
setting of acute coronary syndrome. Of interest in relation to this will also be the
results of the clinical trials that are under way comparing surgery to multi-vessel
stenting using drug eluting stents.
Finally, it should be noted that this is an observational comparison of two relatively small groups of patients undergoing the procedures in a single unit over a two year period. Any conclusions therefore made in relation to comparing these groups and their outcomes should be made with a great deal of caution.

Previously reported similar studies also identified diabetes and LV impairment as a predictor of early mortality following surgical revascularisation for acute coronary syndromes. However, they concentrated more on technical aspects of the procedures such as aortic cross-clamp time, method of cardioplegia and the use of an intra-aortic balloon pump (137-139). These are often not known until during or after the procedure which makes their value in deciding revascularisation strategies less useful at the time of choice.

The choice of the most appropriate revascularisation procedure for a given patient presenting with an acute coronary syndrome is a complex process. There are those patients where PCI is the obvious choice, such as those with single or double vessel discrete lesions, and those where CABG seems to be the best option such as those with distal bifurcation or trifurcation left main disease. A large number of patients however fall into a ‘grey-zone’ which, since the arrival of the drug-eluting stents, seems to be ever-expanding. The choice of PCI or surgery then largely depends on the perceived risk of surgery versus the perceived likelihood of a successful full revascularisation with an acceptable risk for restenosis by multivessel stenting.
CHAPTER 4:
DEVELOPMENT AND VALIDATION OF A PCI RISK SCORE: STUDY METHODS AND RESULTS PHASE II
Perhaps the most important aim of the study was to devise a simple, easily applicable clinical risk score that could predict mortality in patients with acute coronary syndromes undergoing percutaneous coronary intervention. The cardiological community has for a while now recognised the need for such a PCI risk score.

A good risk score is one that is easily applicable and can even be used on the bedside by the physicians without the need for a computer. It should be easily reproducible and contain variables that are objective and not subject to individual opinion. It should have a good predictive value and be applicable across different institutions with different case mix and procedure protocols.

One of the scopes of this project was to device a risk score that would fulfil the above criteria as much as possible. The risk score was devised taking into consideration the work of previous investigators as outlined in previous sections and the results of our own experience. Variables included where mainly those that were found to be significant in our multiple regression model and the weighted risk score was largely based on the odds ratios in that analysis. Certain variables that did not reach statistical significance in our study but faiired in most of the other research projects dealing with predicting outcomes after PCI were included. Such variables were female sex and renal impairment. Female gender was not associated with adverse outcomes in our study and renal impairment was found to be significant in the univariate but not the multivariate analysis. In addition, although partial revascularisation was found to be a significant independent predictor of mortality in our study it is a novel variable and not previously used by any other investigator in the larger studies on the subject as
mentioned previously. In the context of PCI, partial revascularisation is invariably associated with multi-vessel disease which is a most widely used variable and therefore this was included in the risk score instead. In general, variables included were simple demographic and simple anatomical variables as used in our study. Complicated anatomical variables such as site and type of lesion were not used as these are more subject to individual interpretation. In addition, it was not the scope of this study to examine their significance. It is evident from previous studies that clinical risk factors carry more weight in determining mortality outcomes than lesion characteristics.

Based on this, two risk scores were devised. Risk score 1 contained 8 variables all carrying the same weight of 1 and is therefore an unweighted score. Age features twice because in our study was found to be the single most significant variable determining outcomes in these patients. This risk score is as outlined below:

*Risk Score 1*

- Age \(\geq 65\) 1
- Age \(\geq 75\) 1
- LVEF < 50% 1
- Renal impairment 1
- Multi-vessel disease 1
- Peripheral or cerebro-vascular disease 1
- Diabetes mellitus 1
- Female sex 1

Max. Score 8
Risk score 2 is a weighted score where more weight is given to variables that were felt to be more significant in determining poor outcomes. How much weight each variable would carry was decided by taking into account the odds ratios from our multiple logistic regression and the experience from published data from larger multi-centre studies performed in the past. Score 2 is as outlined below:

**Risk Score 2:**

- Age > 65 5
- Age > 75 5
- LVEF < 50% 4
- Renal impairment 3
- Multi-vessel disease 3
- Peripheral or cerebro-vascular disease 2
- Diabetes mellitus 2
- Female sex 1

Max Score 25

In both risk scores, if LVEF is not known on left ventriculography or echocardiography, could be assumed abnormal if there is a history of previous myocardial infarction and the presence of pathological Q waves on resting ECG.

Renal impairment is defined as a serum creatinine of $\geq 200$ mmol/Lt during index admission. Multi-vessel disease was taken as triple vessel disease. Peripheral vascular disease diagnosed on the basis of definite clinical history of intermittent claudication, previous surgery, vascular access difficulties during coronary angiography or
objective evidence of vascular obstruction on Doppler ultrasound studies or peripheral angiography. Diabetes mellitus was diagnosed if patients required diet adjustment, oral hypoglycaemic agents or insulin for the treatment of abnormal blood glucose levels.
Once the two risk scores were devised, they were first tested on the original 'development' cohort to confirm a good predictive value. First, they were entered in a forward linear multiple regression model to ensure that they are both independent predictors of early (30 day) and late (1 year) mortality. The risk score values were individually calculated for every patient in the cohort and then patients were re-grouped according to their risk score value. Mortality was then calculated for every risk score value subgroup.

To determine the value of the prognostic fit of each model, receiver operating curves (ROC) were plotted for each risk score in predicting mortality at 30 days, 6 months and 1 year. The ROC curve is a widely accepted statistical method of determining the predictive value of any prognostic model. The resultant curve, plotted on axes representing Sensitivity against 1-Specificity gives a measure of the model’s predictive value by calculating the area under it. An area of 0.5 under the curve or if the curve is a straight line at any point equidistant from either axis signifies a prognostic model of no value where each occurrence can be attributed purely to chance. On the other hand, an area of 1.0 under the curve signifies a perfect prognostic fit where each occurrence can be accurately predicted by the model. In real life, most prognostic models lie somewhere in-between these two extremes. Most statisticians accept that an area under an ROC curve of 0.7 or above signifies a useful prognostic model for predicting events. The closer the area becomes to 1.0, the better the prognostic value of the model becomes (140-141).
To assess the value of the proposed risk prediction models in this study we attempted to validate the models in a separate cohort of patients. For this purpose, the following 500 consecutive patients undergoing PCI at the University Hospitals of Coventry & Warwickshire for the same indications as in PHASE I or ‘development’ phase (UAP, NSTEMI, UPIA) were chosen. All patients undergoing PCI in our institution were screened using the same inclusion and exclusion criteria as in PHASE I and the first 500 were recruited over a 20 month period (January 2001 – August 2002). Both risk scores were applied to individual patients and grouped according to their risk score values. Mortality was then calculated for each subgroup as was done for the main ‘development’ cohort. Multiple regression analysis was once again used to determine that both risk scores are independent predictors of 30 day and 1 year mortality. Finally, ROC curves were then plotted for both risk scores to test their ability to predict mortality at 30 days and 1 year.
APPLICATION OF THE RISK SCORE

Both risk scores were retrospectively applied on the study cohort to investigate the relationship between the different scores and 30 day and 1 year mortality. 30 day mortality increased, as expected, with increasing values on either risk score. Thirty days mortality varied according to the following tables for each risk score:

Table 8: Thirty days mortality according to Risk Score 1 (unweighted) values.

<table>
<thead>
<tr>
<th>Score value</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
</tr>
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<tbody>
<tr>
<td>n=630</td>
<td>141</td>
<td>183</td>
<td>165</td>
<td>94</td>
<td>37</td>
<td>10</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>30 days death</td>
<td>0</td>
<td>2</td>
<td>11</td>
<td>4</td>
<td>4</td>
<td>1</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>n (%)</td>
<td>(0)</td>
<td>(1.1)</td>
<td>(6.7)</td>
<td>(4.3)</td>
<td>(10.8)</td>
<td>(10.0)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

It is evident form this table that a Risk Score 1 value of 0-1 was associated with very low risk of mortality (1% or less). Values of 2-3 are associated with a moderate 30 day mortality of around 5% whereas in those with a Risk Score 1 value of 4-5 or more the risk of 30 day mortality is high at around 10% or more.

For Risk Score 2 findings were similar. Risk Score 2 values were grouped in aliquots of 5 and the 30 days mortality was as follows:
Risk Score 2, as one might expect, gives a more linear relationship between the Risk Score value and 30 days mortality. Values 0-5 were associated with very low mortality of less than 1%, 6-10 with a moderate mortality of around 3%, scores 11-15 with a high mortality of around 10% and scores higher than 16 with a very high mortality of up to around 15% or more. It should be noted in these mortality figures that they become less reliable at the higher score values as the absolute numbers of patients diminishes with increasing score values.

Similar analyses were applied for mortality 1 year after PCI for acute coronary syndromes. One year mortality varied according to Risk Score 1 values as follows:

Table 9: Thirty days mortality according to Risk Score 2 (weighted) values.

<table>
<thead>
<tr>
<th>Score value</th>
<th>0-5</th>
<th>6-10</th>
<th>11-15</th>
<th>16-20</th>
<th>21-25</th>
</tr>
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<tbody>
<tr>
<td>N=630</td>
<td>n=319</td>
<td>n=153</td>
<td>n=117</td>
<td>n=39</td>
<td>n=2</td>
</tr>
<tr>
<td>30 days death n</td>
<td>1</td>
<td>5</td>
<td>11</td>
<td>5</td>
<td>-</td>
</tr>
<tr>
<td>(%)</td>
<td>(0.3)</td>
<td>(3.3)</td>
<td>(9.4)</td>
<td>(12.8)</td>
<td>-</td>
</tr>
</tbody>
</table>
Table 10: One year mortality according to Risk Score 1 (unweighted) values.

<table>
<thead>
<tr>
<th>Score Value</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=630</td>
<td>n=141</td>
<td>n=183</td>
<td>n=165</td>
<td>n=94</td>
<td>n=37</td>
<td>n=10</td>
<td>n=0</td>
<td>n=0</td>
<td>n=0</td>
</tr>
<tr>
<td>1 year death n</td>
<td>0</td>
<td>4</td>
<td>14</td>
<td>11</td>
<td>10</td>
<td>4</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>(%)</td>
<td>(0)</td>
<td>(2.2)</td>
<td>(8.5)</td>
<td>(11.7)</td>
<td>(27.0)</td>
<td>(40.0)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

One year mortality again increases, as expected with increasing values of the Risk Score 1. One year mortality was low for those with scores 0-1 and less than 3%, scores 2-3 with a mortality of around 10% whereas those with risk values of 4 or more had mortality rates of around 30% or more.

For Risk Score 2, one year mortality varied as follows:

Table 11: One year mortality according to Risk Score 2 (weighted) values.

<table>
<thead>
<tr>
<th>Score Value</th>
<th>0-5</th>
<th>6-10</th>
<th>11-15</th>
<th>16-20</th>
<th>21-25</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=630</td>
<td>n=319</td>
<td>n=153</td>
<td>n=117</td>
<td>n=39</td>
<td>n=2</td>
</tr>
<tr>
<td>1 year death n</td>
<td>2</td>
<td>13</td>
<td>16</td>
<td>11</td>
<td>1</td>
</tr>
<tr>
<td>(%)</td>
<td>(0.6)</td>
<td>(8.4)</td>
<td>(13.7)</td>
<td>(28.2)</td>
<td>(50)</td>
</tr>
</tbody>
</table>
Again, one year mortality varied according to, as expected, increasing values of the weighted risk score. Risk Score 2 values 0-5 were associated with very low one year mortality of around or less than 1%. Mortality then rises steeply to between 5-10% for values of 6-10, then to 10-15% for values 11-15, and then to around 30% or more for values of 16-20 or higher.

What is evident is that both the unweighted Risk Score 1 and the weighted Risk Score 2 can have a good predictive value for early as well as long term death following PCI for acute coronary syndromes. What is clearly needed is a larger scale prospective evaluation of these risk scores in a temporally and geographically distant cohort of patients to the one that the score was originally developed. That would of course provide more solid evidence regarding the predictive values of these risk scores.

Receiver operating characteristic (ROC) curves were plotted for both risk scores in order to determine their discriminatory value in predicting mortality both at 30 days and one year. These ROC curves are shown below:
ROC curve for the ability of Risk score 1 (unweighted) to determine the risk for 30 day mortality. The area under the curve is 0.738 (95% CI 0.658-0.818) which signifies a moderate predictive value.
**ROC curve** for the ability of *Risk Score 2 (weighted)* to predict mortality at 30 days. The area under the curve is 0.818 (95% CI 0.758-0.879) which again signifies a good predictive value.
ROC curve for the ability of Risk Score 1 (unweighted) to predict death after PCI at 1 year. The area under the curve is 0.797 (95% CI 0.737-0.856) which signifies a moderate predictive value.
**ROC curve** for **Risk Score 2 (weighted)** for the prediction of death *1 year* after PCI. The area under the curve is 0.831 (95% CI 0.784-0.878) which signifies a good predictive value.
VALIDATION OF THE RISK SCORES

The validation phase of the study was a retrospective application of the two prediction models derived from the 'development' phase. It included the following 500 consecutive patients undergoing PCI for NSTEACS at the University Hospitals of Coventry & Warwickshire over a 20 month period between January 2001 and August 2002. Selection criteria were the same as in the development period and patients were evaluated in the same 4 age groups: group A <55 (n=110), group B 55-64 (n=141), group C 65-74 (n=141) and group D ≥75 (n=108). The rate of use of Glycoprotein IIb/IIIa receptor antagonists in the validation cohort was 66.8% (334/500) and the rate of stent usage was similar to that in the 'development' phase (460/500 or 92%).

Overall mortality was lower in the 'validation' group (n=500) compared with the main study or 'development' group (n=630). Thirty day mortality was 2.4% (12/500) and again as expected increased with advancing age: age <55 years, 0%; age 55-64, 0.7% (1/141); age 65-74, 3.5% (5/141) and age ≥75, 5.6% (6/108). Thirty day, 6 month and 1 year mortality in this 'validation' cohort and the different age groups is summarised in Figure 2:
Figure 2: 30 day, 6 month and 1 year mortality in the total cohort and different age groups (<55 years, 55-64 years, 65-74 years and ≥75 years) in the ‘validation’ group.

Multivariate regression analysis in the ‘validation’ group revealed that both the simple, ‘unweighted’ group and the more complex ‘weighted’ one were independent predictors of mortality at 30 days, 6 months and 1 year mortality (p<0.001). Thirty day, 6 month and 1 year mortality according to risk score values for both risk scores is shown in Table 12 and 13.
Table 12: Incidence of 30 day, 6 month and 1 year mortality according to risk score 1 (unweighted) values.

<table>
<thead>
<tr>
<th>Score value</th>
<th>0 (n=500)</th>
<th>1 (n=106)</th>
<th>2 (n=137)</th>
<th>3 (n=122)</th>
<th>4 (n=83)</th>
<th>5 (n=31)</th>
<th>6 (n=18)</th>
<th>8 (n=3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>30-day mortality n, (%)</td>
<td>0 (0)</td>
<td>1 (0.7)</td>
<td>1 (0.8)</td>
<td>4 (4.8)</td>
<td>3 (9.7)</td>
<td>3 (16.7)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>6-month mortality n, (%)</td>
<td>0 (0)</td>
<td>1 (0.7)</td>
<td>3 (2.5)</td>
<td>8 (9.6)</td>
<td>4 (12.9)</td>
<td>4 (22.2)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>1-year mortality n, (%)</td>
<td>0 (0)</td>
<td>3 (2.2)</td>
<td>5 (4.1)</td>
<td>9 (10.8)</td>
<td>4 (12.9)</td>
<td>4 (22.2)</td>
<td>0 (0)</td>
<td></td>
</tr>
</tbody>
</table>

Table 13: Incidence of 30 day, 6 month and 1 year mortality according to risk score 2 (weighted) values.

<table>
<thead>
<tr>
<th>Score value</th>
<th>0-5 (n=500)</th>
<th>6-10 (n=269)</th>
<th>11-15 (n=130)</th>
<th>16-20 (n=74)</th>
<th>21-25 (n=26)</th>
<th>21-25 (n=1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>30-day mortality n, (%)</td>
<td>1 (0.4)</td>
<td>4 (3.1)</td>
<td>2 (2.7)</td>
<td>5 (19.3)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>6-month mortality n, (%)</td>
<td>1 (0.4)</td>
<td>6 (4.6)</td>
<td>7 (9.5)</td>
<td>6 (23.1)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>1-year mortality n, (%)</td>
<td>3 (1.1)</td>
<td>8 (6.2)</td>
<td>8 (10.8)</td>
<td>6 (23.1)</td>
<td>0 (0)</td>
<td></td>
</tr>
</tbody>
</table>
ROC curves were plotted to examine the value of both of these predictive model to accurately predict mortality at 30 days and 1 year.

ROC curve for the ability of Risk score 1 (unweighted) to determine the risk for 30 day mortality. The area under the curve is 0.835 (95% CI 0.731-0.938) which signifies a good predictive value.
**ROC curve** for the ability of *Risk score 2 (weighted)* to determine the risk for *30 day* mortality. The area under the curve is 0.799 (95% CI 0.677-0.922) which signifies a good predictive value.
ROC curve for the ability of Risk score 1 (unweighted) to determine the risk for 1 year mortality. The area under the curve is 0.774 (95% CI 0.693-0.855) which signifies a moderate predictive value.
ROC curve for the ability of Risk score 2 (weighted) to determine the risk for 1 year mortality. The area under the curve is 0.787 (95% CI 0.708-0.866) which signifies a moderate predictive value.
CHAPTER 5:

CONCLUSIONS
SUMMARY

Revascularisation is becoming the preferred treatment option for managing patients at high risk from unstable angina pectoris or non ST segment elevation myocardial infarction. However, the potential benefit of either surgery or PCI has to be weighted against its potential risks. In addition, highlighting the potential risks of a given procedure for a given patient has become an important component of good clinical practice. It is therefore vital to be able to risk stratify patients not only for the perceived risk of their medical condition and its presentation but also for the predicted risk from a proposed treatment or procedure for that condition.

It is not always feasible to extrapolate results of clinical trials to every day clinical practice. Quoting risks of procedures from published clinical trials is not always justified as it is a known fact that trial circumstances vary greatly from day to day clinical practice (114).

It is evident from our study that age plays a major role in the outcome of PCI for acute coronary syndromes. Partial revascularisation was also shown to be an independent significant predictor of mortality after PCI for acute coronary syndromes. Partial revascularisation was undertaken in almost two thirds of our cases and in the context of the ‘culprit’ vessel only being dealt with by angioplasty and stenting. In our series, it appeared to be the second most important predictor of death after age. The finding that poor systolic left ventricular function, peripheral vascular disease and diabetes mellitus are associated with adverse prognosis following PCI are also in agreement with previous large studies of risk factor analysis in PCI for stable as well as unstable angina pectoris and acute coronary syndromes.
It was therefore possible to develop a simple clinical risk score in order to be able to risk stratify acute coronary syndrome patients according to their likelihood of suffering complications following PCI. We developed two such a risk scores, a weighted one and an unweighted one. The latter is easier to apply and contains clinical and simple angiographic variables that are reproducible and easily available. Both risk scores were shown in our study to have a reasonably good predictive value in identifying those patients more likely to die following PCI for acute coronary syndromes.

Finally, a parallel study looking at those characteristics affecting early outcome of patients undergoing bypass graft surgery is reported. This lends itself for comparison with the outcomes from the main study or SECTION I of this thesis. Although this comparison should be made with caution as these were both parallel observation studies in different study groups and with different selection criteria and patient characteristics, it appears that the elderly with poor left ventricular function and respiratory and cerebrovascular disease do worse initially after surgery than their counterparts undergoing percutaneous revascularisation.
THE VALUE OF ‘RISK SCORES’

It is evident that risk scores have a useful role to play at various crucial points on the patient’s journey from clinical presentation and admission to hospital to treatment and clinical outcomes.

Risk scores are important in the initial risk stratification of patients presenting with acute coronary syndromes. High risk patients will thus be identified and put forward for aggressive medical therapy followed by early invasive investigation and treatment. Such a risk score is the ‘TIMI Risk Score’, a clinical risk score designed to identify high risk patients from a number of readily available clinical information and simple investigation results.

The next important level of risk stratification is at the point of making the decision whether to revascularise or not, and if yes by which method, percutaneous or surgical. For one to be able to do that effectively and safely, there is a need for a predictive tool that can predict which patients are of higher risk of adverse clinical events following the procedure. This would allow patients that are of a high risk to be considered for adjunctive therapies that would aim to reduce that risk, for the consent to be made more accurately or even to consider the alternative therapies. Our surgical colleagues are armed with a number of such predictive tools, with the ‘Parsonnett Risk Score’ and the ‘EUROSCORE’ being the most widely used. Both of these risk scores have been extensively validated, and have been shown to have a reasonable predictive value in the U.K. populations even though they were developed elsewhere. No such risk score currently exists in wider use for the prediction of risk for patients undergoing PCI.
So why is it so important to produce such a risk score for PCI and in particular for those patients undergoing the procedure for acute coronary syndromes? Although PCI under normal circumstances is associated with a low mortality risk, patients undergoing the procedure for acute coronary syndromes exhibit a different pathophysiological milieu which puts them at a higher risk of early or late adverse events. Firstly, it is important to have such a predictive tool in discussing with patients and their relatives the possible risks when they are about to consent to undergo PCI. Rather than presenting patients with the average risk of complication for all patients undergoing PCI, derived from large clinical trials where practice circumstances always differ from day to day clinical practice, a physician can tell patients which risk stratum they are in and approximate probability of having a major complication. This results in an improvement of the process of informed consent. Secondly, such a tool can be useful in identifying which patients should receive new and expensive adjuvant therapies. Thirdly, interventional cardiologists and individual laboratories can compare their overall results with the probability of complications predicted by applying the risk score to their individual populations. This would facilitate the process of auditing and quality assurance and comparisons can be made from year to year or after a change in practice. In addition, a universally applied risk score would allow a fair comparison between institutions taking into account the different ‘case mix’ in each centre (142).

Such a risk score, in order to be good, should be easy to implement, preferably by the bedside; it should contain variables that can be objectively defined with no inter-observer variability and that are readily available for most patients being investigated or treated for the given condition; it should be robustly validated for the same condition for which it was originally developed; and it should be reviewed
periodically or after changes in clinical practice to re-validate its ability to predict outcomes.

Assessing the accuracy of a multivariate prediction tool is not straightforward. The predictive equations provide an estimated risk of mortality which lies anywhere between 0 and 100% for an individual patient based on their incidence of the various risk factors that make up the risk score. However, a patient either dies or does not therefore direct comparisons between predicted and observed outcomes for individual patients are not a useful measure of the efficacy of the predictive tool. The area under the ROC curve is believed to be a more appropriate statistical measure of the ability of the model to predict what it intends to do. The ROC curve is a plot of sensitivity versus 1-specificity and the area under it is a useful summary measure of the diagnostic accuracy of the tool. An area of 1 suggests a perfect predictor and a value of 0.5 is a test of no value. Areas of between 0.5 and around 0.7 represent a rather low accuracy – the true positive proportion is not much greater than the false positive one. Values between 0.7 and 0.9 indicate tests which are useful with a moderate predictive value. Values higher than 0.9 represent tests with high predictive accuracy. ROC curves have now been widely used for evaluating the accuracy of risk prediction models.

The overall predictive ability of the risk prediction models suggested by the current thesis (‘Risk Score 1’ and ‘Risk Score 2’) indicated by the areas under the ROC curves which ranged between 0.74 – 0.84 is at least moderate and makes these predictive tools useful in current clinical practice. However, further validation is required in geographically and chronologically separate populations to the ones that they were originally developed before they can be widely applied in current clinical
practice. This was the aim of the validation phase of this thesis. Having said that, the simplicity of these risk predictive models and the easy availability of the parameters that comprise them should at least make it easy to further validate initially and then apply for general use.

No such risk predictive model currently exists in wide use. Most risk prediction models for PCI were developed in high volume single centres in the United States in the early and mid-nineties before stents and Glycoprotein IIb/IIIa inhibitors which have been shown to have a large impact in risk reduction following PCI were in wide use. Most of these simply contain the odds ratios from the multiple logistic regression analyses in a rather complicated manner that probably require information technology for their application. Perhaps the best known attempt in producing such a score was the ‘New York State PTCA Mortality Model’, developed in the early nineties by Hannan et al. This risk score was developed in the ‘pre-stent’ and ‘pre-GlycoproteinIIb/IIIa inhibitors era’, in a very large cohort of patients undergoing PCI for all indications and included patients with stable as well as unstable/acute coronary disease. Although it has been well validated it remains rather complicated to apply, it is now out of date and is therefore not in general use, at least not on this side of the Atlantic.

What is required is a simple, easily applicable validated risk prediction model that can be used by the bedside by physicians deciding on patients management and during discussion with patients and their relatives at the time of consent. It could be argued that such risk scores are the ones proposed by this thesis.
STUDY LIMITATIONS

The main study of this thesis is a retrospective analysis of a single centre database on the outcomes of patients treated with percutaneous coronary intervention for acute coronary syndromes excluding those undergoing primary intervention for acute ST elevation MI or a salvage procedure for failed thrombolysis. These patients are a highly selective group of patients who were thought to be of moderate or high risk from their presenting symptoms and other tools used for risk stratification such as ECG findings and cardiac Troponin T (cTnT) levels. It is likely that the threshold to proceed to coronary angiography and intervention is lower in the younger age group. In these lower risk groups, the low event rate makes the analysis of comorbidities more difficult. At the other end of the spectrum, the older the patient the higher the threshold for coronary angiography. In other words, the older age group patients are likely to have more severe or ongoing symptoms than the younger ones. Ideally we could have examined a full consecutive series of patients with acute coronary syndromes from presentation through to discharge irrespective of coronary angiography or PCI procedures. In the setting of a tertiary referral centre with patients transferred from a wide geographic area this would be extremely difficult.

The number of the patients is small compared to previous studies as this is the experience from a single centre over a period of 2 years. Restricting the study to a single centre and a relatively short period of time avoids confounding factors of differences in practice. The unit had a coherent policy between operators and in the 2 years studied there was no significant change in stent or drug administration policy.
Our relatively low use of Glycoprotein IIb/IIIa receptor antagonists may explain a higher than published mortality but except from patients with diabetes mellitus the effect on procedural and long term mortality would have been very small. It is of interest to note that our Glycoprotein IIb/IIIa usage was in fact appropriately higher in the higher risk (elderly) patients. Differential Glycoprotein IIb/IIIa receptor blockers usage in the different age groups cannot therefore logically explain the difference in mortality between the age groups. Since the study period funding for these drugs at the University Hospitals of Coventry & Warwickshire has become more relaxed. This was evidenced by the higher rate of Glycoprotein IIb/IIIa inhibitors usage in the validation phase of this thesis.

In this study we have concentrated only on those patients having their procedure in the context of acute coronary syndromes. This was because both published series and our own experience showed exceedingly low mortality in patients undergoing PCI for stable angina pectoris. Including these patients would dilute the impact of all risk factors in an understanding of the role of PCI in acute coronary syndromes. We have not looked at the rate of MI following these procedures as cardiac Troponin T (cTnT) and Creatinine Kinase (CK) data were not routinely collected after the procedure. ECG features were not examined in this study. Likewise we have not used cTnT as these are now mainly being used to risk stratify patients during their assessment for the need for diagnostic angiography.

Although peri-procedural CK or cTnT elevations have been shown in some studies to be associated with adverse short and long term outcomes it would be difficult to interpret in the context of an acute coronary syndrome and unlikely to determine
outcome after PCI in this setting (143,144). These parameters are probably more important markers of disease activity and plaque instability in this clinical setting.

The lack of information on LV function on about a third of the patients is due to the practice of not routinely performing an LV angiogram during cardiac catheterisation for acute coronary syndromes. It is a significant predictor of 6 month and 1 year mortality when analysing only those patients whose data were available. Therefore and in order to use all the data collected to keep the power of the study at reasonable levels we chose to analyse all data including those where LV function information was missing. In order to do that we assumed normal LV function for those where data was missing. This is an acceptable method of dealing with missing data when the given variable if present is expected to affect outcomes. By assuming normal values then the given valuable is underestimated in its importance to determine outcomes. If despite that assumption the analysis shows this factor to be a significant predictor of outcomes then it can be concluded that the variable is a truly significant predictor of outcomes. This, of course, is not the only acceptable way of dealing with missing data. Alternatively one could randomly assign the presence or absence of the missing variable but then the power of the study regarding the given variable is probably adversely affected and the reliability of the analysis outcomes is less convincing. Perhaps a better approach would be to do an ‘educated guess’ approach to missing data and try to estimate the presence or absence of the variable by taking into account other known variables that could affect it. For example, for missing LV function data in this study, one could assume the presence of significant LV dysfunction in the presence of triple vessel disease and/or with a history of previous myocardial infarction. This, of course, would not always be true. We therefore chose to assume normality of the missing data as this would tend to underestimate the power of the
missing variable. Despite doing so, LV function was found to be a significant
predictor of 1 year mortality. We feel that in a study of this nature it is probably best
to underestimate the power of a given variable than to overestimate its importance.
Our analysis of LV function significance is in agreement with previous studies and
probably reflects that it is also an important factor for short as well as long term
survival.

The 'Risk Scores' were devised by analysing this limited single centre database and
applying previous knowledge based on previous large multi-centre studies. Our
variables were more or less in agreement with previous investigators' experiences
except perhaps that of female sex and renal impairment which did not appear to reach
significance in the multiple regression model of our study. This may simply reflect the
smaller numbers in our study. However we decided to include these in our risk scores
due to their overwhelming representation as important outcome factors in previous
studies. Especially renal impairment features in all previous studies as an important
predictor of adverse outcomes. In fact it was statistically significant as an indicator for
adverse outcomes in our study on univariate analysis.

In our study, partial revascularisation was shown to be a significant independent
predictor of mortality following PCI for acute coronary syndromes but multi-vessel
was not. It is, however, likely that partial revascularisation and multi-vessel disease
are interchangeable terms in this setting. Most often than not, in the setting of acute
coronary syndromes, in the presence of multi-vessel disease usually only the 'culprit
vessel' is tackled with angioplasty. Because of that and the fact that multi-vessel
disease is a more uniformly accepted term that is readily understood and more
objectively defined, we felt that for the purposes of a ‘risk-score’ multi-vessel disease would be a better variable to include.

We applied the ‘risk-scores’ to the original database from which they were developed and there, perhaps as one would expect, were found to have a reasonably good predictive value in predicting mortality. Ideally the ‘risk-score’ should be validated in a chronologically and geographically distant database including larger number of patients, preferably prospectively, to establish whether it would be more generally applicable. Initial steps towards this have been taken in validating the risk scores in the following 500 patients undergoing PCI for NSTEACS.

The next step is to apply it prospectively in other centres and when well validated to examine the possibility of extending its use to patients undergoing PCI for stable angina pectoris as well.
The main aim of this thesis was to identify those risk factors that when present increase the likelihood of mortality in patients undergoing Percutaneous Coronary Intervention (PCI) for Acute Coronary Syndrome (ACS). The aim of the study was to identify simple readily available demographic, clinical and investigational characteristics of patients, which, if present in the clinical setting of ACS independently increase mortality after PCI. We identified 5 such variables: age, Left Ventricular (LV) impairment, diabetes mellitus, peripheral vascular disease and partial revascularisation. Other factors also play a role such as renal impairment, multi-vessel disease and peripheral vascular disease.

These variables were then combined into a clinical ‘risk-score’ format that would be easily applicable by the bedside to estimate the mortality risk of patients undergoing PCI for ACS. Two such risk score were devised, both including the same 8 variables (age>65, age>75, female sex, LV impairment, renal impairment, diabetes mellitus, multi-vessel disease and peripheral or cerebrovascular disease). One was weight adjusted and the other a simpler, single point score. Both scores were shown to be at least moderately useful in predicting death after PCI when applied retrospectively to the same cohort that this was developed and when validated in a different cohort of patients.

A parallel sub-study over the same period of time was performed looking at outcomes following emergent Coronary Artery Bypass Grafting (CABG) for patients with acute coronary syndromes. The outcomes were loosely compared with those of PCI and the clinical variables that determine mortality were identified. Age was again found to be
an independent predictor of early mortality following surgery together with chronic respiratory disease, cerebrovascular disease, clinical symptoms of heart failure and impaired left ventricular ejection fraction.

With the ever increasing role of Percutaneous Coronary Intervention in the treatment of Acute Coronary Syndromes it has become vital to be able to readily individualise patients' risk from such procedures. This could be done by establishing a well validated simple to use clinical risk score. What is now required for the risk scores put forward by the current thesis are to be evaluated and validated on a nationwide basis so that they can be used in clinical practice. The validation process could begin regionally and would invariably involve possible re-adjustments and fine tuning to improve its predictive ability and its general applicability. Such adjustments could for example include reducing the creatinine levels to include lower levels as abnormal or even perhaps stratifying different creatinine levels, same as with age, to make the model more sensitive. Such changes could only come with further testing. In addition, it would also be useful to compare the value of this U.K. derived risk score to one of the American PCI risk scores such as the Mayo Clinic score or the New York State PTCA risk prediction model in their ability to predict outcomes after PCI in U.K. populations.

Finally, it is required to establish by means of a properly conducted clinical trial the value of 'culprit-only' partial revascularisation in the setting of acute coronary syndromes and the role for early full revascularisation and 'hybrid' (PCI followed by CABG) revascularisation procedures.
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