OPTIMISING CORONARY REPERFUSION IN ACUTE MYOCARDIAL INFARCTION: THE ROLE OF PRIMARY ANGIOPLASTY

A thesis submitted to the University of London for the degree of Doctor of Medicine

Elliot J Smith
BSc (Hons) 1991, University of London
MB BS 1994, University of London

Department of Cardiology, the London Chest Hospital UK and
Department of Clinical Pharmacology, Queen Mary University of London
ABSTRACT

Thrombolysis remains the predominant reperfusion strategy for ST segment elevation myocardial infarction (STEMI) in the United Kingdom. Although primary angioplasty may offer superior outcomes, the logistics of delivering this therapy in the UK have not been investigated. This thesis describes the development of a pilot primary angioplasty service in North East London. Outcomes are compared with the thrombolytic strategy, and platelet activation is explored as a possible biological mechanism determining reperfusion.

The impact of the thrombolytic strategy on revascularisation following STEMI in North East London was first investigated. Thrombolytic delivery was effective, but necessitated frequent early revascularisation, leading to prolonged hospital stay. A primary angioplasty service was developed at the cardiac centre, and expanded to serve six network hospitals. Within the limitations of a daytime pilot, the service improved clinical outcomes, and was associated with a substantial reduction in hospital stay.

Two admission strategies were compared - direct access to the cardiac centre following pre-hospital diagnosis by ambulance crews, and transfer of patients presenting to network emergency (A&E) departments after upstream administration of abciximab and clopidogrel. Direct access significantly reduced reperfusion times. Upstream anti-platelet therapy improved angiographic reperfusion prior to primary angioplasty, possibly compensating for inter hospital transfer delays.

A subgroup of STEMI patients underwent platelet activation studies. Lower baseline platelet monocyte aggregate (PMA) levels predicted improved angiographic reperfusion following primary angioplasty, supporting the concept that PMAs may reflect plaque rupture severity, and may promote microvascular
dysfunction. Early anti-platelet therapy reduced PMAs following intervention, which may explain the benefit of early abciximab observed in clinical trials.

In summary this thesis has demonstrated that primary angioplasty can be delivered safely and effectively in North East London. The efficacy of reperfusion may be determined by mechanisms involving platelet activation. Delivery of a 24 hour seven day service should now be addressed.
DECLARATION

The concept for the basis of this thesis was formulated jointly by myself and my supervisor, Professor Martin T Rothman. The studies contained in this thesis were designed by myself in collaboration with Professor Rothman and Dr. Anthony Mathur. The patient recruitment and data collection were performed by myself. The statistical analysis of the data was carried out by me with guidance from Jackie Cooper, medical statistician at the MRC Epidemiology and Medical care Unit at Charterhouse Square, and Dr. Ifty Khan in the Research and Development department, Barts and the London NHS Trust.

The copyright of this thesis rests with the author and no quotation from it or information derived from it may be published without the prior written consent of the author.

Elliot J Smith
CONTENTS

ABSTRACT......................................................................................................................... 2
DECLARATION .................................................................................................................... 4
ACKNOWLEDGEMENTS ..................................................................................................... 14
PUBLICATIONS ARISING FROM THIS THESIS ............................................................... 15
CHAPTER 1 INTRODUCTION ............................................................................................... 17
   1.1 Background ............................................................................................................. 18
   1.2 Pathophysiology of Acute Coronary Syndromes ..................................................... 20
      1.2.1 Coronary Thrombosis ..................................................................................... 20
      1.2.2 Mechanisms of plaque destabilisation ........................................................... 21
      1.2.3 Role of platelet activation in acute coronary syndromes ................................. 23
      1.2.4 Summary - Pathophysiology of Acute Coronary Syndromes ....................... 24
   1.3 Clinical Presentations of Acute Coronary Syndromes ............................................... 25
   1.4 Management of Acute Coronary Syndromes .......................................................... 25
      1.4.1 Pharmacological therapies for Acute Coronary Syndromes ............................ 26
   1.5 Medical Reperfusion Therapy for ST Elevation Myocardial Infarction ............... 30
      1.5.1 National Service Framework for Coronary Heart Disease and
           Reperfusion Therapy ......................................................................................... 31
      1.5.2 Limitations of Thrombolysis .......................................................................... 32
      1.5.3 Alternative Thrombolytic Strategies – Pre Hospital Thrombolysis,
           Failure to Reperfuse, and Rescue Angioplasty ................................................... 33
      1.5.4 Summary - Thrombolytic therapy in the United Kingdom ............................... 34
   1.6 Mechanical Reperfusion Therapy for ST segment Elevation Myocardial
       Infarction - Primary Angioplasty .............................................................................. 35
      1.6.1 Primary Angioplasty – Models of delivery ....................................................... 38
      1.6.2 Influence of Time to Reperfusion ................................................................... 40
FIGURES AND TABLES

Figures

Figure 1.1 Clinical Outcomes following Primary Angioplasty compared with Thrombolysis for the treatment of ST Segment Elevation Myocardial Infarction

Figure 1.2 Hypothetical construct of the relationship between symptom duration prior to reperfusion, mortality reduction, and the extent of myocardial salvage.

Figure 2.1 Map demonstrating the location of District Hospitals and the Regional Cardiac Centre within the North East London Cardiac Network.

Figure 2.2 Flow cytometry. Identification and gating of platelet events using forward and side scatter characteristics.

Figure 2.3. Flow cytometry. Histograms gated on platelet events demonstrating events fluorescing in the FL1 channel.

Figure 2.4 Flow cytometry. Measurement of platelet monocyte aggregates.

Figure 2.5 Enzyme linked immunosorbent assay.

Figure 3.1 Variation in referral rates for inpatient angiography at the regional cardiac centre from hospitals A to E.

Figure 3.2 The Invasive Management Pathway for patients presenting to centre E with STEMI.

Figure 3.3 Major Adverse Cardiac Events according to invasive or non invasive inpatient management strategy among 175 /192* patients admitted to Centre E

Figure 3.4 Major Adverse Cardiac Events following hospital discharge according to invasive or non invasive inpatient management strategy among 160 / 177* patients surviving beyond discharge from Centre E.

Figure 4.1 Map of North East London Cardiac Network demonstrating the expansion of the pilot primary angioplasty service.

Figure 4.2 Timing of presentation of patients admitted with STEMI within North East London 2001-2005.

Figure 4.3 Graph demonstrating the number of patients presenting to the Network Heart Attack Centre Recruitment during development of the pilot service.
Figure 4.4 Chronology of development of the North East London Pilot Primary Angioplasty Programme. .................................................................................................................. 118

Figure 5.1 Major adverse cardiac events (MACE) according to admission strategy............................................................................................................................ 141

Figure 6.1 Patient pathways for patients presenting with STEMI entered in platelet studies .................................................................................................................. 156

Figure 6.2 Comparison of platelet activation following primary angioplasty for STEMI (ruptured plaque angioplasty) and elective angioplasty for chronic stable angina (stable plaque angioplasty).................................................................................................................. 162

Figure 6.3 Influence of Early versus Late Anti-Platelet therapy with Clopidogrel and Abciximab on Platelet Activation following Primary Angioplasty for STEMI .............................................................................................................................. 173

Figure 6.4 Influence of abciximab on platelet activation and inflammation following elective coronary angioplasty for chronic stable angina .................................................. 177

Figure 7.1 Major Adverse Cardiac Events at median follow up 19 weeks ...... 196
Figure 7.2 Major adverse events among 101* STEMI patients presenting to the Network Heart Attack Centre (N-HAC) undergoing primary angioplasty: Influence of multi-vessel coronary disease .............................................................................................................................. 198

Figure 7.3 Major Adverse Events among patients with multivessel coronary disease undergoing primary angioplasty (n=46): Influence of culprit versus multi-vessel coronary angioplasty .............................................................................................................................. 199

Figure 7.4 Major Adverse Events among patients undergoing single vessel primary angioplasty (n=87): Influence of single vessel versus multi-vessel coronary disease .............................................................................................................................. 200

Figure 7.5 Emergency readmissions and unplanned cardiac catheterisation procedures at a median of 19 weeks follow up .............................................................................................................................. 202
Tables

Table 3.1 Percentage of patients receiving thrombolysis, and achieving NSF targets at each centre ........................................................................................................ 84

Table 3.2 Differences in duration of stay at the district hospital among patients admitted with STEMI referred and not referred for inpatient angiography .......... 86

Table 4.1 Patients Presenting to North East London Centres with ST Elevation Myocardial Infarction April 2003-4 .................................................................. 105

Table 4.2 Percentage of ACS patients with discharge diagnosis of ‘Myocardial Infarction (ST Elevation)’ April 2003-4 ......................................................... 106

Table 4.3 Inclusion and exclusion criteria for immediate transfer of STEMI patients from the community of A&E to a regional heart attack centre .......... 109

Table 4.4 Criteria for early discharge of uncomplicated patients following primary angioplasty for STEMI ........................................................................ 114

Table 5.1 Demographic details of patients with confirmed STEMI presenting to the N-HAC via ambulance transfer from local A&E departments (AET), and through direct LAS access (DA) ................................................... 128

Table 5.2 ECG and Clinical diagnosis following arrival at the N-HAC .......... 132

Table 5.3 Final diagnosis among patients delivered to the N-HAC that did not have STEMI .......................................................................................................... 133

Table 5.4 Comparison of reperfusion times according to access strategy .... 135

Table 5.5 Impact of pharmacological facilitation with abciximab - timing of therapy and Enzyme (CK) rise ............................................................... 136

Table 5.6 Abciximab facilitation and angiographic reperfusion pre and post procedure ........................................................................ 138

Table 5.7 Abciximab facilitation and ST segment resolution post procedure .. 139

Table 5.8 Abciximab facilitation and ST segment resolution pre procedure: comparison of AET+ and AET- patients .......................................................... 139

Table 6.1 Baseline demographic and procedural characteristics .................. 153

Table 6.2 Comparison of Platelet and Inflammatory markers at baseline sampling ........................................................................................................ 160
Table 6.3 The Influence of baseline platelet marker expression on epicardial and microvascular reperfusion following primary angioplasty ......................... 167
Table 6.4 Comparison of patients undergoing primary angioplasty receiving early versus late anti-platelet therapy with clopidogrel and abciximab .......... 169
Table 7.1 Baseline characteristics of study cohorts ........................................ 194
Table 7.2 Diagnosis following Emergency Readmission ................................. 203
Table 7.3 Cardiac catheter procedures performed during the index admission and during follow up ......................................................................................................................... 204
Table 7.4 Revascularisation procedures performed during the index admission and during follow up ......................................................................................................................... 205
Table 7.5 Analyses of hospital stay during index admission and following readmission .......................................................................................................................... 207
Table 7.6 Effect of early discharge on event rate among patients allocated to primary angioplasty ........................................................................................................................ 208
ACKNOWLEDGEMENTS

I am indebted to Professor Martin Rothman, my supervisor, for his guidance, support, time and effort throughout the period of this research and beyond. Without his wisdom, drive and inspiration the work contained in this thesis would not have been possible. I am also very grateful to Dr. Anthony Mathur for his guidance and support in developing the platelet studies within this thesis, and his time and effort in directing and moulding this research. I also wish to express my thanks to Professor Marion Macey at the Royal London Hospital who provided advice, training and support in performing flow cytometry, and to Professor Athol Johnston and Dr. Zamri Chik in the department of Clinical Pharmacology at Charterhouse Square, who assisted with the ELISA analyses. I also wish to thank Dr. Rebecca Anthony and Dr. Roxana Mo who assisted with platelet analyses under my supervision.

I wish to give special thanks to Melanie Preston and Laura Roberts for welcoming me into the research office at the London Chest Hospital, and providing advice and support ever since. I would also like to thank Dr. Ajay Jain for his assistance during this period. I am grateful to all the patients who agreed to participate in the studies that form the basis of this thesis, and to all of the Cardiologists, nurses, managers, A&E personnel, and London Ambulance Service personnel in North East London that have been instrumental in developing primary angioplasty at Barts and the London NHS Trust. In particular I am extremely grateful to Dr. Charles Knight for his guidance and advice in his capacity as Chair of the North East London Cardiac Network Board, and to Mr. Mark Whitbread, clinical lead for Primary Angioplasty at London Ambulance.

Finally I wish to thank my family, Lauren, Jamie, Dylan and Max, who have supported me throughout, and remain my inspiration.
PUBLICATIONS ARISING FROM THIS THESIS

Papers


Abstracts

EJ Smith, R Anthony, R Mo, MA Preston, KD McConnell, M Macey, MT Rothman, C Knight, A Mathur. Acute Myocardial Infarction In the Absence of Coronary Plaque Rupture Does not Activate Platelets.
Oral presentation British Cardiac Society April 2006.

EJ Smith, AK Jain, TR Keeble, MA Preston, A. Mathur, C J Knight, MT Rothman, The London Chest Hospital, London, United Kingdom. Facilitation With Abciximab Compensates For Delays In Transfer For Primary Percutaneous Intervention (PPCI). Oral presentation British Cardiac Society April 2006.

EJ Smith, R Mo, R Anthony, AK Jain, TR Keeble, MA Preston, KD McConnell, M Macey, MT Rothman, A Mathur.
Platelet Monocyte Aggregates Determine Efficacy of Reperfusion Following Primary Percutaneous Intervention (PPCI) For ST Segment Elevation Myocardial Infarction (STEMI), And Are Reduced By Early Anti-platelet Therapy.
Poster Presentation, Innovation in Intervention, ACC March 2006, Atlanta USA.

EJ Smith, AK Jain, SK Shukla, SP Ramdany, J Cooper, P Moss, A Mathur, AD Timmis, K Henderson, M Whitbread, CJ Knight, MT Rothman.
Pre Hospital ECG Diagnosis by Ambulance Crews Reduces Time to Reperfusion in ST segment Elevation Myocardial Infarction (STEMI) Patients Treated with Primary Angioplasty (PA).
Oral presentation British Cardiac Society May 2005.

CHAPTER 1 INTRODUCTION
1.1 Background

Acute Myocardial Infarction (AMI) is a major cause of morbidity and mortality worldwide. Recent data from the British Heart Foundation estimate the incidence of AMI in the United Kingdom to be 700 per 100,000 population per year, leading to an estimated 92,000 events (1). Furthermore, the coronary event mortality in two separate UK populations (Belfast and Glasgow 1983-1993 and 1985-1994 respectively) reported in the WHO MONICA (Monitoring Trends and Determinants in Cardiovascular Disease) Project (2) was 48%, and was thereby amongst the highest in Europe. Although the rate of cardiovascular death in the UK and around the world is falling, this trend is slowing, particularly in younger age groups. At present it is estimated that more than 1.2 million men and women living in the UK have suffered a heart attack (1).

It is also noteworthy that age standardised coronary heart disease mortality rates in North East London boroughs are amongst the highest in Britain, and commensurate with the high levels observed in Northern Scotland and Northern Ireland. It is possible that the high proportion of South Asians living in North East London may in part contribute to these statistics. It has been demonstrated that Indian, Bangladeshi, Pakistani and Sri Lankan individuals (who comprise up to 40% of the East London population) have a higher premature death rate from CHD than average, being 46% higher for men and 51% higher for women (1). Furthermore, this is the only ethnic group in which cardiovascular event rates are rising.

It is clear that direction of resources towards primary prevention of coronary events through education, lifestyle change, diet, exercise, and smoking cessation is warranted. Indeed the latter is represented as a key target mechanism to reduce CHD mortality within the National Service Framework for Coronary Heart Disease (3). However the size of the existing burden of acute
coronary events necessitates strategies to reduce morbidity and mortality following clinical presentation with these events.

This thesis investigates the management of patients presenting with ST segment myocardial infarction (STEMI). ST segment elevation on the ECG in association with chest pain commonly signifies acute coronary occlusion, and is thus the most severe acute coronary presentation. In this setting the immediate aim of therapy is to restore effective blood flow through the occluded epicardial artery as early as possible following presentation. This fundamental concept of reperfusion is based on the fact that ischaemia leading to necrosis is a progressive process, with irreversible injury of ischemic myocardium developing as a transmural wave front, occurring first in the subendocardium, and ultimately becoming transmural (4). Prompt reperfusion limits the degree of myocardial damage (4), and in turn improves prognosis (5). There are two traditional approaches to achieve coronary reperfusion. Medical reperfusion therapy involves the intravenous administration of a thrombolytic (fibrinolytic) agent in combination with aspirin. The mechanical reperfusion strategy involves immediate coronary angiography, followed by percutaneous intervention (PCI) to reopen the culprit vessel without antecedent thrombolysis. This strategy is referred to as primary angioplasty or primary PCI (PPCI). There is debate as to which should be the preferred reperfusion strategy for STEMI patients in the United Kingdom and around the developed world. This thesis examines the current provision of reperfusion therapy (thrombolysis) within a metropolitan United Kingdom population based in North East London, and studies the development, instigation, expansion and impact of a primary angioplasty service serving this population. The thesis also explores potential biological mechanisms that may determine the ultimate efficacy of reperfusion.

In this chapter the pathophysiology of the acute coronary syndromes is first discussed, with particular emphasis on the role of platelets in thrombosis, inflammation and coronary plaque destabilisation. This provides the background
for subsequent consideration of the management of STEMI, where the debate between medical (thrombolysis) and mechanical (primary angioplasty) reperfusion therapies is addressed in detail. The benefits and limitations of both strategies are discussed, highlighting both clinical and logistic issues that may determine which therapy delivers optimal reperfusion to individual patients. Finally the discussion of reperfusion therapy moves beyond the restoration of epicardial blood flow to achieving patency of the coronary microvasculature. The implications and mechanisms of microvascular dysfunction following reperfusion are considered, and once again the influence of platelets is highlighted.

1.2 Pathophysiology of Acute Coronary Syndromes

1.2.1 Coronary Thrombosis

Current understanding of the pathology of acute coronary events has been shaped by post mortem studies demonstrating the presence of coronary plaque fissuring in association with thrombosis in patients with ischaemic cardiac death (6). It has since been elucidated that over 90% of acute myocardial infarctions are characterised by the presence of an occlusive thrombus, but that the pathology of the underlying plaque varies (7). 65-75% of these thrombotic events occur as a result of rupture of an atheromatous plaque. These lesions are characterised by a necrotic core, thin fibrous cap, inflammatory cells (macrophages and T lymphocytes), and few smooth muscle cells (8). The remainder occur as a result of plaque erosion. These plaques are histologically quite different, with fewer inflammatory cells, more smooth muscle cells, and less necrosis in the core (9). While both situations are associated with coronary risk factors (smoking, cholesterol elevation, hypertension, diabetes and family history), plaque rupture is more closely linked to cholesterol levels (10), with erosion more common among younger patients, and females in particular (9). Interest has focused on the identification of thin cap fibroatheromas (TCFAs) as a precursor for plaque rupture. These lesions have many features in common
with ruptured plaques, including the thin cap (<65 μm), a necrotic core, macrophage and T cell infiltrates, and loss of smooth muscle cells (11). Despite these similarities, there is as yet no direct causal link between the so called ‘vulnerable’ plaque and rupture. Vascular, inflammatory and haematological mechanisms have been proposed, some or all of which may contribute (12).

Exposure of the damaged endothelial surface to the blood stream leads to platelet adhesion, the first step in the thrombotic process. The platelet glycoprotein (Gp) Ib/IX/V complex binds to sub-endothelial von Willebrand Factor (vWF) associated with collagen, which in turn leads to platelet activation. The glycoprotein (Gp) IIb/IIIa receptor complex [see 1.4.1 Pharmacological therapies for Acute Coronary Syndromes] is up-regulated and becomes activated allowing binding of fibrinogen and platelet aggregation resulting in a platelet rich ‘white’ thrombus. If allowed to progress, further fibrin deposition ultimately results in the trapping of red blood cells leading to formation of red thrombus. Tissue factor (TF) produced by macrophages and endothelial cells (ECs) further accelerates the formation of thrombus, and plasminogen activator inhibitor 1 (PAI-1) released from platelets inhibit fibrinolysis at the rupture site.

1.2.2 Mechanisms of plaque destabilisation

Endothelial dysfunction is a prerequisite for the development of coronary atherosclerosis. Changes in vascular endothelial function can be demonstrated early in the disease process, including increased permeability, expression of adhesion molecules, and loss of endothelium dependent vasodilatation. The expression of soluble intercellular adhesion molecule 1 (ICAM-1) is associated with risk of future myocardial infarction (13), and impaired endothelium dependent dilatation can be demonstrated in patients with acute MI in both culprit and unaffected coronary vessels (14). However it is unlikely that endothelial dysfunction in isolation is the primary cause of acute coronary thrombosis.
The role of inflammation in initiating plaque events has been studied extensively. Acute coronary syndromes are associated with systemic inflammation, with elevation of inflammatory markers (including CRP and IL6) at clinical presentation (15). Widespread inflammation is detectable throughout the coronary tree in patients with acute coronary syndromes (16). This is consistent with angiographic (17), angioscopic (18), and intravascular ultrasound (IVUS) studies (19) that have demonstrated the presence of multiple complex coronary plaques at locations remote from the culprit plaque in the same patient, although there is debate as to their prognostic importance (17;19;20). HMG co reductase inhibitors (statins) reduce inflammatory markers following ACS, suggesting that anti-inflammatory mechanisms may explain event reductions in patients treated with these agents, over and above their lipid lowering effect (21-24).

Inflammation may lead to plaque rupture via a number of mechanisms. Oxidised low density lipoprotein (LDL) leads to upregulation of cytokines, induction of tissue factor (TF), and macrophage over-expression of matrix metalloproteinases (MMPs) including MMP-1 and MMP-8, which digest collagen weakening the fibrous cap (25). Pro-inflammatory cytokines, including γ-interferon, Interleukin 1β and TNFα, cause cytotoxic breakdown of smooth muscle cells, reducing compensatory collagen production. The imbalance between overproduction of MMPs and underproduction of stabilising collagens increases the risk of rupture. It has recently been proposed that intra-plaque haemorrhage may be a key trigger for plaque destabilisation, due to the rich cholesterol content of erythrocyte membranes (26). Infection has also been proposed as a possible precursor to inflammation. However, although agents such as Chlamydia pneumoniae and Helicobacter pylori have been localised to coronary plaques, no aetiological link has been established (21).
1.2.3 Role of platelet activation in acute coronary syndromes

Increasing evidence supports the role of platelets as not only prothrombotic, but also pro-inflammatory particles with respect to acute coronary syndromes (ACS). The activation status of individual platelets can be measured using flow cytometry. P-selectin expression has until recently been the gold standard platelet activation marker (27). Levels are elevated in patients with acute MI (28;29), and it has been demonstrated that differences in P-selectin expression may predict the severity of ACS presentation (30). Michelson et al have since demonstrated that circulating platelet-monocyte aggregates (PMAs) may be more sensitive platelet activation markers than P-selectin (31). Importantly PMA elevation also predicts subsequent myocardial infarction in patients with chest pain (32). Whereas markers such as creatine kinase (CK) and troponin only rise following myocardial damage, PMAs may reflect the severity of plaque rupture before necrosis occurs. That platelet activation may be an early predictor of plaque behaviour in ACS may suggest that therapeutic intervention to reduce their activation might have a plaque stabilising effect, and could thereby improve clinical outcomes.

It is unclear however, whether platelet activation is a reactive process, or whether platelets may directly influence plaque behaviour. Recent evidence may suggest a potential mechanistic role of platelets in initiating plaque rupture. CD40 ligand (CD40L) is a pro-inflammatory cytokine of the tumour necrosis family that was first identified on cells of the immune system. CD40L is also present on vascular endothelial cells (ECs), smooth muscle cells, monocytes, and macrophages (33). Importantly it has now been demonstrated that the majority of human CD40L exists in platelet crypts (34). Following activation CD40L is rapidly translocated to the platelet surface, and soluble ‘sCD40L’ cleaved and released into the circulation by hydrolysis. CD40L has both thrombotic and inflammatory properties. It has a structural domain that allows binding to GpIIb/IIIa and stabilises arterial thrombi, a property retained by sCD40L (35). In addition, ligation of CD40 on ECs induces numerous
inflammatory responses including release of chemokines (e.g. IL6 and IL8) and expression of leukocyte adhesion molecules (34). It has already been demonstrated that interruption of CD40L signalling may reduce progression of stable atheromatous plaques in animal models (36;37), and that through induction of matrix metalloproteinase (MMP) expression (33) may be implicated as a mechanism of plaque rupture. Endothelial CD40 ligation can also impair EC migration by increasing production of reactive oxygen species (ROS) (38), another mechanism that may promote plaque instability. Observational clinical data support this concept. CD40L is elevated in ACS patients (39;40), with a higher ratio of sCD40L to membrane CD40L in acute MI compared with unstable angina (40), which may suggest a continuum of CD40L upregulation and hydrolysis related to the size of plaque rupture or thrombus burden.

1.2.4 Summary - Pathophysiology of Acute Coronary Syndromes

Acute coronary syndromes result from coronary thrombosis. The majority of thromboses causing acute myocardial infarction occur as a result of plaque rupture. These lesions are characterised by a thin fibrous cap, a lipid rich necrotic core, and inflammatory cell infiltrates. Plaque erosion is less common. These lesions also lead to coronary thrombosis, though their histology may be quite different. The precise mechanisms leading to plaque rupture and erosion have not been fully elucidated. Pathological and clinical trial data support the role of plaque inflammation in initiating events, and in particular the presence of oxidised LDL. However, evidence is emerging that haematological factors rather than the vessel wall may instigate plaque events. Platelets possess both pro-thrombotic and pro-inflammatory properties that may have specific relevance. Markers of platelet activation (PMAs) may be early predictors of plaque behaviour in ACS. CD40 ligand expression also reflects platelet activation, but this molecule may also be mechanistic in the process of plaque destabilisation.
1.3 Clinical Presentations of Acute Coronary Syndromes

The clinical consequences of these plaque events depend predominantly upon whether the resulting thrombus becomes intermittently or persistently occlusive (although the impact of epicardial arterial occlusion may be modified by factors such as collateralisation and myocardial oxygen demand), and whether damage to cardiac myocytes ensues. ACS manifest with a spectrum of clinical presentations. These can be defined immediately at the time of presentation using the clinical history and 12-lead electrocardiogram (ECG), and then further refined according to subsequent biochemical evidence of myocardial necrosis in the hours and days following presentation. ST segment Elevation Myocardial Infarction (STEMI) represents the most severe acute presentation, with ST segment elevation on the ECG most commonly signifying complete coronary occlusion (41; 42). Recent data from the GRACE registry suggest that STEMI represents 25-30% of all ACS presentations (43). The remaining ACS are termed Non-ST segment Elevation Acute Coronary Syndromes (NSTE-ACS), and are further subdivided into Non-ST segment Elevation Myocardial Infarction (NSTEMI) and unstable angina (UA), differentiated by the presence or absence respectively of biochemical evidence of myocardial necrosis measured by cardiac specific troponins or enzyme release (e.g. creatine kinase), and evolution of ECG changes (44). These latter syndromes are not necessarily less benign, being associated with a range of clinical risk determined by demographic and clinical factors (including age, diabetes, hypercholesterolaemia, prior history) in addition to clinical investigations including the nature of the ECG changes, and the presence of cardiac specific troponin release (45;46). Clinical presentation with NSTE-ACS is less commonly associated with complete epicardial coronary arterial occlusion (47).

1.4 Management of Acute Coronary Syndromes

The goal of therapy for ACS is to prevent cardiac muscle damage, treat and prevent complications (including arrhythmia and heart failure), stabilise the
culprit plaque, and to prevent further cardiac events. There is universal acceptance that these syndromes necessitate a combination of chemotherapeutic agents, though debate continues as to the role of invasive investigation with cardiac catheterisation, and revascularisation, and further whether these interventions should be performed immediately, early (within hours to days), or delayed. The distinction between STEMI and NSTE-ACS is a critical step in determining not only the type of therapy administered, but also its timing. This thesis focuses on the immediate management of patients presenting with STEMI, where the immediate aim of therapy is the restoration of effective blood flow through the occluded coronary artery at the earliest opportunity. Before specifically considering reperfusion therapies, the role of relevant pharmacological and anti-platelet therapies will first be discussed.

1.4.1 Pharmacological therapies for Acute Coronary Syndromes

**Aspirin**
Aspirin is essential in the treatment of ACS. It prevents the synthesis of thromboxane A2, a strong platelet agonist, through the selective acetylation of the hydroxyl group of the serine residue at position 529 in the polypeptide chain of platelet prostaglandin H synthase (48). Aspirin therapy has independent prognostic value in the treatment of STEMI, similar to that of thrombolysis alone, with an additive benefit when administered in combination (49). Similarly aspirin has been demonstrated to improve prognosis in patients with NSTE-ACS (50-53).

**Beta Blockers**
Beta blocker therapy is sympatholytic, reducing cardiac workload and myocardial oxygen demand. Beta blockade reduces the risk of progression to acute MI in patients with unstable angina (54), and improves prognosis following acute MI, through reduction of arrhythmic death and possible protection against myocardial rupture (55).
**Statins**

The role of HMG co reductase inhibitors (statins) in reducing recurrent events following ACS is also firmly established (56-59). The pleiotropic effects of statin therapy may have particular relevance over and above their lipid lowering effect, and have been briefly discussed above [see 1.2.2 Mechanisms of plaque destabilisation]. The anti-inflammatory effects of atorvastatin 80mg were demonstrated in the MIRACL study, with an enhanced decline in C reactive protein (CRP) following discharge (though not interleukin-6) in the treatment group. In addition, high event rates associated with elevated plasma levels of soluble CD40L were abolished by atorvastatin (60;61).

**ACE-Inhibitors**

Angiotensin converting enzyme inhibitors (ACEI) were first demonstrated to reduce mortality following STEMI in the presence of clinical heart failure and with evidence of systolic LV dysfunction (62;63). However, STEMI patients without LV damage also benefit from ACEI therapy (63;64), and more recent data support their efficacy in improving clinical outcomes for a wide range of patients with established coronary disease, or risk factors such as diabetes (65;66).

Myocardial Infarction National Audit Project (MINAP) data demonstrate that between January and December 2003, at least 88% of people discharged from hospital following a heart attack in England and Wales were prescribed aspirin, 67% beta blockers, 83% statins and 73% ACE inhibitors (1). The role of these therapies in the setting of ACS is firmly established, and will not be directly investigated in this thesis. In contrast, new anti-platelet, anti-thrombotic, thrombolytic, and anti-inflammatory pharmacological strategies for ACS continue to evolve, and for both STEMI and NSTE-ACS the optimal therapeutic agents and combinations are as yet not fully defined.
Theinopyridines

The theinopyridines (ticlopidine and clopidogrel) irreversibly inhibit the binding of adenosine diphosphate (ADP) to the P2Y\textsubscript{12} receptor on the platelet surface. This interferes with platelet activation, degranulation, and inhibits the conformational change of the glycoprotein Gp\textsubscript{IIb/IIIa} receptor required for aggregation. Because of its superior side effect profile clopidogrel has become standard therapy in combination with aspirin for patients undergoing percutaneous coronary intervention with coronary stenting. This combination radically reduces the risk of acute vessel closure and subacute stent thrombosis (67;68). The role of clopidogrel in the medical treatment of NSTE-ACS is strongly supported by the CURE study, which demonstrated a reduction in event rates in patients randomised to the treatment arm for a period of 3-9 months (69). NSTE-ACS patients undergoing PCI also derived additional benefit over and above the use of clopidogrel to cover the intervention (70). Most recently, the addition of clopidogrel to aspirin with fibrinolysis has been proven effective in reducing the risk of death, or recurrent myocardial infarction (or an angiographically occluded infarct vessel) with no increment in bleeding (71). In addition to the inhibition of ADP binding, the clinical benefits of clopidogrel may be mediated by anti-inflammatory properties. It has recently been demonstrated that clopidogrel reduces platelet-leucocyte aggregate formation and sCD40L release in patients presenting with ACS (72).

Platelet glycoprotein IIb/IIIa receptor antagonists (GPRAs)

The glycoprotein IIb/IIIa receptor complex is the most densely expressed component of the platelet surface, with between 50 000 and 80 000 receptors on each individual platelet. 80% of Gp\textsubscript{IIb/IIIa} exists on the platelet surface in its resting state, with 20% internalized in the surface connecting system (SCS) and \(\alpha\)-granules. Upon stimulation Gp\textsubscript{IIb/IIIa} is exteriorized and undergoes conformational change to its active form. This allows binding of its primary ligand soluble fibrinogen. The process of fibrinogen bridging allows platelet-platelet co-adhesion, and is the final common pathway for platelet aggregation. As such,
inhibition of this receptor provides potent inhibition of aggregation. Abciximab is a monoclonal antibody fragment (Fab) directed against the receptor, directly blocking fibrinogen binding. Cross reactivity of abciximab with other integrins such as the α5β3 (vitronectin) receptor and the MAC-1 (CD11b/CD18) leucocyte receptor may provide additional anti-inflammatory mechanisms of action that may have relevance in the setting of ACS. Other GPRA therapies include the small molecule agents eptifibatide and tirofiban. Unlike abciximab these agents are competitive Gp IIb/IIIa inhibitors, and do not cross react with MAC-1 or α5β3 ((73;74).

GP IIb/IIIa receptor antagonists (GPRAs) have become established as adjuvant therapy following high-risk percutaneous interventions, with reductions in major adverse events in both elective and acute cases (75-78). In the setting of PCI for NSTE-ACS, significantly reduced event rates have been demonstrated with upstream GPRA therapy using either abciximab or tirofiban, although the benefit appears restricted to those patients with elevated cardiac troponins (79;80). While there is also some evidence to support the role of GPRA therapy as purely medical treatment for NSTE-ACS, the benefit is predominantly confined to those who then undergo a PCI (81), and indeed GPRAs are probably detrimental in low risk NSTE-ACS patients not undergoing intervention (82). In addition, there are data supporting the role of GPRA therapy for STEMI, facilitating primary PCI (83;84), with subgroup analysis of one study suggesting a greater benefit in those treated as early as possible prior to intervention (83) [see 1.6.4 Pharmacological facilitation of Primary Angioplasty].

As is the case with clopidogrel, the anti-platelet effects of GPRA therapy may not be limited to the prevention of platelet aggregation, but also may reduce platelet activation. GPRA agents have been demonstrated to inhibit the release of sCD40L in vitro (85;86). A recent study has now confirmed that GPRA therapy similarly reduces sCD40L release in vivo following PCI for NSTE-ACS patients (87). Furthermore, a retrospective analysis of the CAPTURE study
demonstrated that baseline elevation sCD40L predicted benefit from GPRA therapy (abciximab) independently of troponin in NSTE-ACS patients undergoing PCI (88). The effects of GPRA therapy on platelet-leucocyte aggregate formation have been more variable, with differential effects of GPRA agents (abciximab and eptifibatide) in vitro (89;90). However, the latest clinical data suggest that platelet leucocyte aggregates are also reduced in ACS patients undergoing PCI treated with both these GPRA agents (87). Importantly the reductions in both sCD40L and aggregate formation were independent of the effects of clopidogrel. The mechanisms for these effects are undetermined. Platelet-leucocyte interaction predominantly occurs through platelet P-selectin binding leucocyte PSGL-1. Secondary binding may also occur through fibrinogen cross-linking GpIIb/IIIa to leucocyte surface MAC-1, which would be affected by abciximab.

1.5 Medical Reperfusion Therapy for ST Elevation Myocardial Infarction

Intravenous thrombolysis remains the predominant reperfusion strategy for STEMI in the United Kingdom, and throughout the developed world. Large multi-centre randomised controlled trials in the 1980s and early 1990s have demonstrated that in combination with aspirin thrombolysis significantly improves mortality compared to aspirin alone (49;91-94). Since the advent of the first generation of thrombolytic agents whose efficacy were proven in these studies (including streptokinase and recombinant tissue plasminogen activator (rt-PA)) newer preparations (e.g. tenecteplase and reteplase) have been bioengineered to be more clot specific, and are also easier to administer (in bolus form). Superior angiographic infarct related artery (IRA) patency has been demonstrated with the use of these agents, although prognostic benefits have remained unchanged (95-97). 'Fibrin – platelet lysis' (the co-administration of a GPRA with a reduced dose of thrombolysis) reduced recurrent ischaemia, ST segment elevation, and improve IRA patency in the GUSTO V study, but again did not influence mortality (98;99).
1.5.1 National Service Framework for Coronary Heart Disease and Reperfusion Therapy

The National Service Framework (NSF) for Coronary Heart disease in England (3) has thus far supported the use of thrombolytic therapy as the preferred reperfusion strategy for STEMI, setting explicit ‘door to needle’ (DTN) and ‘call to needle’ (CTN) targets to ensure rapid drug delivery. The need for rapid access to pre-hospital care is emphasised in order to facilitate this.

Standard 4 of the NSF states:

‘Patients with symptoms of heart attack must receive help from trained personnel with access to defibrillation within 8 minutes of a call for help’.

Standard 5 states

‘People thought to be suffering from a heart attack should be assessed professionally and, if indicated, receive aspirin. Thrombolysis should be given within 60 minutes of calling for professional help.’

Standard 6 states:

‘NHS Trusts should put in place agreed protocols/systems of care so that people admitted to hospital with proven heart attack are appropriately assessed and offered treatments of proven clinical and cost effectiveness to reduce their risk of disability and death’.

The first report from the Royal College of Physicians Myocardial Infarction National Audit Project (MINAP) demonstrated that only 28% of hospitals supplying data treated the target 75% of eligible patients inside 30 minutes of arrival at hospital (100). However this has improved radically with each subsequent report such that delivery of thrombolytic therapy in the UK is now highly efficient, with 89% of hospitals now achieving the 30 minute target, which translates to 86% of all eligible patients receiving therapy within this time frame (101).
1.5.2 Limitations of Thrombolysis

The goal of reperfusion therapies is to restore normal flow in the infarct related artery. Thrombolysis in Myocardial Infarction (TIMI) flow grade describes reperfusion angiographically (102). TIMI grades 0 and 1 flow are characterised by little or no penetration of angiographic contrast beyond the culprit lesion, with TIMI 2 flow indicating complete opacification of the vessel with contrast, though less briskly than neighboring unaffected vessels. TIMI grade 3 describes optimal epicardial blood flow, where the culprit vessel can be completely opacified with contrast similarly to unaffected vessels. Achieving TIMI 3 flow is associated with improved short and long-term prognosis following reperfusion therapy for STEMI. French et al demonstrated that out to 12 years following randomisation to streptokinase, 72% of patients with TIMI 3, 67% of those with TIMI 2 and 54% of those with TIMI 0-1 flow survived (p = 0.023) (103).

However, prompt thrombolytic therapy in the setting of randomised controlled trials only achieves TIMI-3 flow in the IRA in 50-70% of patients receiving therapy (95;96;98). Furthermore, the rate of early re-occlusion remains high (6-13% early, and up to 30% by 30 days) (104;105). In addition, a significant proportion of patients in clinical practice are ineligible for treatment (through legitimate contraindications such as recent surgery, stroke, or bleeding diathesis), and perhaps more importantly, a significant number of eligible patients are denied treatment. The MIR and MITRA registries (21,092 patients) demonstrated that 48% of STEMI patients did not receive reperfusion therapy – 29% being ineligible, and 19% with no obvious contraindication (106). This finding is confirmed by more recent data from the GRACE registry (the largest international ACS registry to date including patients from 94 centres in 14 countries) demonstrating that up to 30% of STEMI patients still receive no reperfusion therapy at all (107).
1.5.3 Alternative Thrombolytic Strategies – Pre Hospital Thrombolysis, Failure to Reperfuse, and Rescue Angioplasty

Thrombolysis is most effective when administered early (5;108). This fact has led to the development and investigation of mechanisms to administer therapy prior to arrival at hospital. In the UK significant funds have been invested in equipping ambulance vehicles with 12-lead ECG and telemetry capabilities, alongside paramedic personnel training in ECG recognition and drug delivery. Early trials (109-111) demonstrated significant time savings can be achieved (median 30 -130 minutes) compared to hospital thrombolysis, though none translated the time saved into a mortality benefit. Earlier (pre hospital) thrombolytic administration does not avoid the problem posed by failure to achieve patency of the infarct related artery. The ‘Comparison of Angioplasty and Pre-hospital Thrombolysis in Acute Myocardial Infarction’ (CAPTIM) study (112) illustrates this issue. In 840 patients randomised to either pre-hospital thrombolysis or primary angioplasty the two strategies appeared equally efficacious. All patients in the study were taken by a physician-manned mobile intensive care unit directly to a cardiac centre with PCI facilities, where 26% of those randomised to thrombolysis underwent PCI specifically for failure to reperfuse. By 30 days, 70% of thrombolysis patients had undergone an unscheduled PCI, 33% undertaken as emergency procedures. Thus the pre-hospital thrombolysis strategy necessitated the backing of an emergency PCI strategy (termed ‘rescue angioplasty’) for those who failed to achieve clinical evidence of reperfusion.

The rescue strategy (angioplasty following thrombolysis where failure to reperfuse has been diagnosed) has been implemented to varying degrees in UK cardiac centres. However data supporting this strategy are limited. Of nine randomised rescue PCI trials prior to 2004, only 4 were prospective comparisons with conservative therapy, and these included only 368 patients (113). Across these studies the non-invasive criteria employed to diagnose failure to reperfuse were not uniform. In practice up to 40% of all patients
receiving thrombolysis fail to reperfuse following thrombolysis (113-115). This presents an important management dilemma.

Two recent randomised studies have now been performed in the UK, but have yielded contradictory results. In the Middlesborough Early Revascularisation to Limit Infarction (MERLIN) study (116), rescue PCI did not improve mortality, or left ventricular function at 30 days, and had a higher complication rate than a conservative approach (stroke 4.6% rescue vs. 0.6% conservative, P = 0.03, transfusion required 11.1% rescue vs. 1.3% conservative, p < 0.001). However, the need for unplanned revascularisation was significantly reduced (6.5% rescue vs. 20.5% conservative, p<0.01), again highlighting the necessity for early revascularisation in a significant proportion of patients receiving thrombolysis even when not performed immediately. In contrast 6-month data from the Rescue Angioplasty versus Conservative Treatment or Repeat Thrombolysis (REACT) study demonstrated that the rescue strategy did reduce the event rate (a composite of death, re-infarction, stroke, and severe heart failure) by half compared with a repeat dose of thrombolysis (TL), or heparin (HP) alone (31% TL and 30% HP respectively vs. 15% p=0.0009 and p=0.002 respectively) (117). Again there was no mortality benefit.

It is important to recognise that provision of rescue angioplasty for all patients with failure to reperfuse necessitates 24-hour PCI facilities for a sizeable proportion of STEMI patients. This infrastructure becomes relevant when comparing the thrombolytic strategy to alternative reperfusion strategies.

1.5.4 Summary - Thrombolytic therapy in the United Kingdom

Thrombolytic therapy is effective in the treatment of STEMI, with a marked reduction in mortality compared with aspirin alone. This therapy is the current preferred reperfusion strategy in the UK, with NSF targets directed towards rapid delivery of therapy. However, up to 30% of STEMI patients do not receive
therapy, only 50-70% of patients treated achieve effective reperfusion (TIMI 3 flow), and the rate of recurrent infarction may be high. There is no consensus as to the optimal therapy for those who fail to reperfuse following thrombolysis. Studies investigating the systematic use of rescue angioplasty have been equivocal. Importantly, these trials demonstrate a frequent requirement for invasive investigation and revascularisation following thrombolysis. At present revascularisation is not currently considered to be an integral part of the thrombolytic strategy for STEMI in the NSF guidelines. The extent of invasive investigation and revascularisation and their impact on resource utilisation has not been quantified in the NHS setting. This thesis addresses this issue.

1.6 Mechanical Reperfusion Therapy for ST segment Elevation Myocardial Infarction - Primary Angioplasty

Primary angioplasty is defined as immediate percutaneous intervention in the setting of STEMI, without administration of antecedent thrombolysis. This strategy can achieve IRA TIMI 3 flow in up to 95% of cases (118), and treats both the occlusive thrombus and the ruptured plaque. It is 12 years since the PAMI and Zwolle groups first demonstrated a mortality benefit and reductions in recurrent ischaemia and reinfarction respectively, in patients treated with primary angioplasty compared with thrombolysis (119;120). A quantitative review of the short-term results (between hospital discharge and 30 day follow up) of 10 randomised controlled trials conducted prior to 1997 demonstrated a mortality of 4.4% with angioplasty versus 6.5% using thrombolysis (p=0.02), with the composite endpoint of death or non fatal MI of 7.2% vs. 11.9% respectively (p<0.001) (121). Stroke was also significantly reduced (0.7% vs. 2.0%; P=.007). Long-term follow up data from ZWOLLE group (122) demonstrated an absolute mortality reduction of 11% (13% angioplasty vs. 24% streptokinase) after a mean of 5 years. There is consensus that primary angioplasty is the preferred reperfusion therapy in patients presenting with cardiogenic shock (123). The Shock study (Should we Emergently Revascularize Occluded Coronaries for
Cardiogenic Shock) demonstrated an absolute reduction in one-year mortality of 13.2% among STEMI patients presenting in cardiogenic shock receiving early revascularisation (46.7% survival compared with 33.6% in those treated with initial medical therapy, P<0.03) (124), although it should be recognised that only 55% of the revascularisation group actually underwent angioplasty, with 37.5% undergoing coronary bypass surgery. Importantly primary angioplasty is the only reperfusion strategy for those ineligible for thrombolysis.

Since the publication of these studies percutaneous coronary intervention (PCI) has evolved. Stenting following primary angioplasty reduces six month major adverse cardiac events (MACE) when compared with balloon angioplasty alone (POBA) through reductions in target vessel revascularisation (125), and further improvements in 30 day and 6 month mortality and non fatal myocardial infarction have been achieved with the addition of glycoprotein receptor antagonist (GPRA) therapy (126), without an associated increase in haemorrhagic stroke. A recent quantitative review of 23 trials comparing primary angioplasty and thrombolysis (127) included trials employing current interventional techniques (12 using stents and 8 using GPRA therapy). This suggested a significant mortality reduction following PCI compared with thrombolysis (whether or not cardiogenic shock patients were included), with significant reductions in stroke and non-fatal MI (figure 1.1). This was contemporary primary angioplasty in a wider group of patients than previously described.
Figure 1.1 Clinical Outcomes following Primary Angioplasty compared with Thrombolysis for the treatment of ST Segment Elevation Myocardial Infarction

Adapted from a quantitative review of 23 randomised trials demonstrating outcomes at 4-6 weeks (127).

* \( p=0.0002 \)

* \( p=0.0003 \)

† \( p<0.0001 \)

†† \( p=0.0004 \)
1.6.1 Primary Angioplasty – Models of delivery

These data support primary angioplasty as the preferred reperfusion strategy for STEMI. However, the majority of the studies included in these analyses performed primary PCI in experienced cardiac centres with on-site angioplasty facilities. In the United Kingdom (and elsewhere) the vast majority of STEMI patients do not present to cardiac centres, but district general hospitals (DGHs) without PCI facilities. Although models of primary angioplasty in district hospitals without on site surgery have been demonstrated safe and effective (128), they present logistic and clinical problems. While the number of UK district hospitals with cardiac catheterisation laboratories is increasing, only the minority have developed coronary intervention programmes. The number of district hospital labs performing diagnostic catheterisation increased by over 20% (to 83) from 2003-2004, while the total number of PCI centres rose by only 5% (to 77) during the same period (129). Most district centres would find it difficult to staff or fund a 24 hour service for their respective catchment populations. Furthermore, individually these centres could perform too low a volume of primary angioplasty procedures to ensure clinical effectiveness. Canto et al (130) introduced the concept almost 10 years ago that clinical outcomes may be compromised in low volume primary angioplasty centres in the United States. In-hospital mortality was 28% lower in high volume centres, although high volume itself was described as greater than 33 procedures per annum, and low volume varied between only 5 and 11 primary angioplasty procedures, which may have less relevance to current clinical practice.

The desire to deliver primary angioplasty as the preferred reperfusion strategy for all STEMI patients has resulted in the development and investigation of hospital network models of primary angioplasty, allowing systematic transfer of STEMI patients from centres without PCI facilities to a cardiac centre serving as a regional or network heart attack centre. A meta analysis of six randomised controlled trials investigating this approach concluded that even where transfer
is necessary PPCI remains superior to immediate on site thrombolysis (131),
driven predominantly by the reduction in non fatal MI, but with a trend towards
reduced mortality. Two of these studies in particular have focused attention on
the transfer strategy, and warrant further discussion.

The Danish Multicentre Randomized Trial on Thrombolytic Therapy versus
Acute Coronary Angioplasty in Acute Myocardial Infarction (DANAMI-2) study
(132) randomised both regional centre and DGH patients to on-site thrombolysis
with rt-PA or primary angioplasty with stenting in most cases (93%). This was a
high-risk group of patients with >4mm ST elevation and with symptoms for up to
12 hours. The composite endpoint of death, reinfarction, or stroke was
significantly reduced in the PCI group (13.7% versus 8.0% p=0.0003), driven
predominantly by the reduction in non fatal MI. Remarkably, this outcome was
observed even with transfer times (time from first presentation to arrival at the
cardiac centre) of up to 3 hours (although the majority (96%) were transferred
within two hours). The results are all the more striking as primary angioplasty
was not available in 2 of 5 participating centres prior to the study, and operators
were trained during a pilot period.

The PRAGUE-2 study (133) randomised DGH patients only to on-site
thrombolysis with streptokinase or transfer for PCI. The combined end-point of
death, reinfarction or stroke at 30 days occurred in 15.2% of the thrombolysis
(TL) group vs. 8.4% of the PCI group (P<0.003). Although the mortality reduction
(10% TL vs. 6.8% PCI) was not significant across all patients, it became
significant in patients who presented greater than 3 hours following onset of
symptoms (15.3% TL versus 6% PCI P<0.02). This is in keeping with data from
the Zwolle group demonstrating an exponential increase in mortality following
thrombolysis with increasing symptom duration, which was significantly
attenuated in patients undergoing primary PCI (134).
1.6.2 Influence of Time to Reperfusion

DANAMI-2 and PRAGUE 2 have already influenced clinical practice in Europe and the United States. In Denmark and the Czech Republic where the two landmark trials were performed, thrombolytic therapy is no longer utilised for the majority of STEMI patients. However, the systematic transfer of unselected patients for primary angioplasty inevitably prolongs the time to reperfusion. In PRAGUE-2 the transfer strategy was highly efficient. The median time from randomisation to reperfusion (balloon inflation) was 94 minutes, including transport duration of 48 minutes. In contrast the time from randomisation to administration of thrombolysis was only 12 minutes. Allowing for the fact that reperfusion may not occur for up to 60 minutes following administration of thrombolysis, the transfer strategy still delayed reperfusion by 22 minutes in this trial. Similarly in DANAMI-2 the time from randomisation at a DGH to balloon inflation was 116 minutes, compared with randomisation to thrombolysis of 20 minutes, causing a reperfusion delay of 36 minutes. Despite allowing longer transfer times by protocol, the actual median transfer time in DANAMI-2 was only 32 minutes. Although the DANAMI-2 trialists concluded that an initial strategy of transfer for primary PCI should be superior to thrombolysis 'when transfer time is less than 3 hours', it is conceivable that longer transfer times could disadvantage patients that would have received prompt thrombolysis. This raises a question as to whether there may be a time limit to the efficacy of the systematic transfer strategy, or whether there is a need for adjunctive therapy in transferred patients.

An analysis (135) of 21 trials included in the quantitative review by Keeley et al (127) has explored the impact of transfer delay. It concluded that the mortality benefit of primary PCI may be lost if the delay to the invasive strategy (defined as the time difference between the administration of on site thrombolysis and that of primary angioplasty, or 'door to balloon minus door to needle time (DTB – DTN)) exceeds 60 minutes. In terms of MACE (death, reinfarction or stroke), the two strategies reached equivalence when DTB-DTN was 93 minutes. The
analysis has some caveats. The relation between time delay and outcome was assessed on a group basis for each study rather than by individual patients, the analysis did not include trials with prolonged (DTB-DTN > 60 minutes) transfer delays, and importantly the authors assumed a linear association between delay and outcome. Nevertheless this finding has had a direct impact on health policy. The most recent published ACC/AHA Guidelines for the Management of Patients With ST-Elevation Myocardial Infarction (136) state that thrombolysis should be the preferred treatment where DTB-DTN is expected to exceed 60 minutes.

1.6.3 Influence of Symptom Duration

It is possible however that this guideline is over simplistic, as the relationship between the time delay to primary angioplasty and outcome is likely to be non-linear. Gersh and Anderson (108) have constructed a theoretical model demonstrating the relationship between mortality reduction, myocardial salvage and time from onset of symptoms to reperfusion (figure 1.2). This has an initial time-dependent phase within the first 2-3 hours where the potential percentage mortality reduction and myocardial salvage following reperfusion therapy is high, but then falls rapidly. Subsequently, a mortality benefit is still present but of decreasing magnitude over time such that treatment delay may exert less influence on outcomes. Importantly, this model suggests that delaying definitive reperfusion therapy through transfer to another centre may disadvantage patients presenting within the first few hours of pain, such that they are on the flat part of the curve by the time that primary angioplasty is performed (figure 1.2). This hypothetical construct is further complicated by the fact that the duration of the early time dependent period may vary for individual patients as a result of multiple factors including the duration of coronary occlusion, the intermittency of the occlusion, the presence of collateral circulation, and myocardial oxygen demand.
Figure 1.2 Hypothetical construct of the relationship between symptom duration prior to reperfusion, mortality reduction, and the extent of myocardial salvage

Adapted from Gersh et al, JAMA 2005 (137).

- The mortality benefit of reperfusion therapy is maximal in the first 2-3 hours following onset of symptoms, as a result of myocardial salvage. After this period the mortality benefit is reduced, and as the curve flattens, the time to reperfusion is less critical.

- If successful reperfusion at a non PCI centre could be achieved with thrombolysis at point A, transfer for primary angioplasty may be harmful if this achieves reperfusion at points B or C. For a patient undergoing primary angioplasty at point C, pharmacological facilitation may have the potential to significantly improve mortality if reperfusion can be achieved at point A, but not at point B.
The influence of symptom duration at the time of presentation is therefore highly relevant to the delivery of primary angioplasty. In the Controlled Device Investigation to Lower Late Angioplasty Complications (CADILLAC) study shorter DTB times had the greatest impact in patients presenting within the first two hours of symptoms (138). Meanwhile, as discussed earlier, the mortality benefit of transfer for PPCI over thrombolysis in PRAGUE-2 was confined to those presenting beyond 3 hours from symptom onset (133). In addition, in the CAPTIM study mortality was reduced in patients receiving pre-hospital thrombolysis within 2 hours of symptoms compared to PCI, but thereafter the trend favoured primary angioplasty. Finally the Myocardial Infarction Triage Intervention (MITI) trial (139) demonstrated that the mortality of patients treated with thrombolysis in the first 70 minutes following symptom onset was 1.2% compared with 8.7% thereafter. Infarction size was limited to 4.9% vs. 11.2% of the left ventricle.

The implication of these data is that thrombolysis and primary angioplasty are both highly effective in the first few hours following onset of symptoms, and that the speed of delivery may be more important than the therapy delivered during this period. However, beyond the first 2-3 hours, during which period up to 60% of patients may present (140) the time to reperfusion is less critical, and therefore primary angioplasty becomes more effective, owing to its superiority in achieving epicardial patency.

1.6.4 Pharmacological facilitation of Primary Angioplasty

Thrombolysis and primary angioplasty are not necessarily mutually exclusive. Facilitated primary angioplasty in the setting of STEMI describes a strategy of initial therapy with a thrombolytic agent or a glycoprotein IIb/IIIa receptor antagonist (either alone or in combination) followed by immediate angiography and angioplasty where appropriate. The rationale for this approach is to achieve reperfusion at the earliest opportunity before definitive mechanical treatment.
TIMI grade 3 flow prior to primary angioplasty may be expected spontaneously in 15-20% of cases, and is associated with improved procedural success, reduced LV dysfunction and reduced mortality (141;142).

Despite the intuitive value of this approach, early trials comparing routine angioplasty following thrombolytic therapy with a conservative ischaemia driven revascularisation strategy were disappointing, with no demonstrable improvement in left ventricular function (143-146), trends toward increased mortality (145), and significantly more bleeding (144). However, these studies predated the use of stents, smaller arterial sheaths, and low profile guiding catheters, and may therefore be less relevant to current clinical practice. In addition the trials were performed at a time when adjuvant anti-thrombotic therapies were evolving, prior to the routine use of theinopyridines, and in an era where high dose of heparin was routinely prescribed.

A series of more recent small studies investigating facilitated primary angioplasty have combined contemporary PCI techniques with reduced dose thrombolytic regimens. In the Plasminogen Activator Angioplasty Compatibility Trial (PACT), facilitation with half dose rt-PA increased pre procedural TIMI-3 flow from 15% (without thrombolysis) to 33% pre procedure, but had little effect on clinical outcomes (114). The Bavarian Reperfusion Alternatives (BRAVE) study (147) randomised DGH patients to facilitation with half dose reteplase in combination with a GPRA (abciximab) versus abciximab alone, followed by transfer to a PCI centre (147). There was no difference in the primary endpoint of left ventricular infarct size (using myocardial perfusion imaging), and no difference in MACE, although there was a non significant increase in bleeding in those receiving combined therapy.

The BRAVE study was successful in terms of efficient service delivery. The median DTN time for pre transfer therapy was 30 minutes (combined reteplase and abciximab) and 24 minutes (abciximab alone), and the median transfer time...
was 35 minutes in both the groups. However, median symptom duration at presentation was 130 and 140 minutes respectively, meaning that drugs were administered approximately 2.5 hours following symptoms, and may have only achieved reperfusion by 3 - 3.5 hours. The lack of clinical benefit may therefore have been the result of missing the early ‘time dependent’ window for reperfusion discussed above (Figure 1.2).

The use of upstream GPRA therapy alone to facilitate primary angioplasty has also been explored. These agents are already established in reducing MACE following high risk PCI (75;78), and have been proven more effective when administered prior to intervention in the setting of NSTE-ACS (148). The ADMIRAL study provided support for upstream abciximab prior to primary angioplasty with stenting (83), demonstrating that administration of abciximab prior to primary angioplasty with stenting improved TIMI flow grades pre and post procedure, with lower six month MACE (7.4% abciximab vs.15.9% placebo, p=0.02), and improved LV recovery. Importantly, the 25% of patients in the abciximab arm who received the drug earlier (in a mobile intensive care unit or the emergency department) derived the greatest benefit. In contrast however, tirofiban (a small molecule GPRA) did not have any impact on either TIMI 3 flow pre procedure or clinical and angiographic outcomes in the Ongoing Tirofiban in Myocardial Infarction Evaluation (On-TIME) trial (149).

Thus at present, the key questions of whether, and which therapy should be utilised to facilitate primary angioplasty remain unanswered. As yet the ability to achieve improved patency before intervention has not translated into clinical benefit. However, the studies to date have occurred in parallel with the evolution of percutaneous technologies and adjunctive pharmacology. In addition the trials have been small. A number of ongoing studies may provide answers to this question including the Facilitated Intervention with Enhanced Reperfusion Speed to Stop Events (FINESSE) study, and the Assessment of the Safety and Efficacy of a New Thrombolytic (ASSENT IV) trial. However, the results of these
will need to be interpreted in the context of symptom duration at the time of presentation.

1.6.5 Summary – Primary Angioplasty

Primary Angioplasty has been proven superior to thrombolysis in 23 randomised controlled trials. It offers improved infarct related arterial patency treating both the thrombus and the culprit plaque. It is the preferred treatment for STEMI with cardiogenic shock, and the only reperfusion option for patients with contraindications to thrombolysis. However, results vary with operator experience, and the majority of patients present to centres without PCI facilities. The systematic transfer of DGH patients with STEMI to a cardiac centre for primary PCI is safe and feasible. However, the time to reperfusion may be prolonged compared to on site thrombolysis. Data suggest that the transfer strategy could lose its efficacy when the delay to PPCI exceeds 60 minutes (DTB-DTN > 60 minutes), and have been incorporated into clinical guidelines. However, this may be over simplistic as clinical outcomes are more closely related to the duration of symptoms at the time of presentation than the speed of delivery of therapy. Furthermore this relationship is non linear, such that the speed of delivery may be more relevant for patients presenting early, and indeed this subgroup may be disadvantaged if transfer for PPCI prolongs reperfusion time. This provides a rationale for the pharmacological facilitation of primary angioplasty, to achieve reperfusion at the earliest opportunity in all patients. However, as yet the questions of both the optimal combination and timing of therapy remain undetermined, with the results of ongoing clinical trials awaited.

The challenge faced by health providers is to deliver the optimal therapy for all STEMI patients. While it is clear that a PCI strategy is a necessity in treating STEMI (even where thrombolysis is the preferred first line treatment), the model, mechanism and timing may need to vary within STEMI populations. To date there has been no National Service Framework or National Health Service
strategy to investigate the provision of optimal reperfusion therapy with primary angioplasty in the United Kingdom.

1.7 Optimising Reperfusion

1.7.1 The Concept of Microvascular Perfusion

In comparing treatment strategies for STEMI, the discussion thus far has been based on the supposition that early restoration of optimal epicardial patency (TIMI grade 3 flow) is the primary objective of reperfusion therapy. However TIMI-3 flow does not guarantee perfusion at tissue level. Up to 40% of patients do not regain microvascular and myocyte perfusion despite achieving TIMI-3 flow in the infarct related artery (118;150).

The concept of the 'no-reflow' phenomenon has been demonstrated in animal models of ischaemia and reperfusion, and describes impaired tissue perfusion in the territory of the infarct related vessel despite restoration of epicardial flow (151). This impairment of microvascular flow does not occur until the duration of ischaemia is sufficient to cause myocardial necrosis, but increases thereafter as ischaemia is prolonged. In the experimental setting, where ischaemia and reperfusion are achieved using ligatures of non-diseased animal coronary vessels, the anatomical area of no-reflow is confined to areas of already irreversibly damaged myocardium. In clinical practice this process is more complex. Plaque disruption and thrombus formation in the epicardial artery lead to the risk that following reperfusion (particularly with primary angioplasty but also following thrombolysis) athero-thrombotic material may be propagated to the distal coronary bed (152). As the restored blood flow is preferentially diverted to areas of lower vascular resistance, this process may result in reperfusion related damage to myocardium that may not have been affected if the vessel had remained occluded.
1.7.2 Assessment of microvascular perfusion following STEMI

Experimental models of ischaemia and reperfusion predict that the degree of microvascular dysfunction should correlate with the extent of myocardial damage, and clinical measures of microvascular perfusion following reperfusion therapy have confirmed this finding (153-156). Microvascular injury is associated with adverse left ventricular remodelling (150;157;158), heart failure (154;158) and worse prognosis (159;160), relationships which persist even when controlling for infarct size (161). Angiographic no-reflow (or ‘slow-reflow’) is a severe manifestation of microvascular dysfunction in the setting of STEMI, and describes the persistence of contrast in the epicardial vessel despite removal of the initial obstruction. However this refers only to one extreme of a spectrum of microvascular injury. Numerous clinical methods for quantifying the extent of microvascular compromise following myocardial infarction have been described, including ECG ST segment analysis (153;155;156;160), angiographic blush scores (154;158-160), coronary flow velocity (160;162;163), myocardial contrast echocardiography (MCE) (150;157), nuclear perfusion imaging and magnetic resonance imaging (MRI) (161). At present there is no gold standard for the clinical measurement of microvascular perfusion, and only the minority of these modalities are applicable in routine clinical practice.

Myocardial blush grade (MBG) is an angiographic method of grading microvascular patency, by scoring the density and persistence of contrast in the myocardial territory of the infarct related artery. As such it can be measured immediately following percutaneous intervention, but cannot determine the subsequent evolution of microvascular function (without serial cardiac catheter studies). Nevertheless, it is well validated, has strong prognostic value, and is readily available in clinical practice (154;159;160).

The analysis of ST segment resolution (STR) is a surrogate measure for microvascular perfusion. However, its clinical and prognostic value has been proven repeatedly since its introduction (153;159;160). Whereas angiographic
blush measures microvascular patency, ST resolution reflects cell membrane integrity and myocyte function (164). This technique is simple, reproducible, and again readily available at the time of reperfusion and throughout the post reperfusion period. Its prognostic value is additive to angiographic blush scores (158;159), and a recent study suggests that ST resolution has the greater independent long term prognostic value (160).

1.7.3 Mechanisms of Microvascular Dysfunction in STEMI

Microcirculatory dysfunction following reperfusion is caused by a number of mechanisms including ischaemia induced loss of endothelial integrity, red blood cell extravasation, neutrophil plugging, platelet microembolisation, and vascular spasm. Ischaemic endothelial injury impairs production of endothelium derived vasodilators such as nitric oxide, while vasoconstrictors such as endothelin and oxygen free radicals may be produced in excess. In addition reperfusion itself may cause a paradoxical worsening of cardiac function (165), damaging not only the cardiac myocytes, but also microvascular endothelial cells (166). This process of reperfusion injury is also characterised by an exacerbation of the imbalance between production of reactive oxygen species and nitric oxide (NO) (167). In addition reperfusion is associated with recruitment of neutrophils into the infarct zone (168), which leads to microvascular plugging (169;170). The recruited neutrophils are also another major source of reactive oxygen species, which cause further direct myocyte and endothelial toxicity (168). Platelet microembolisation has been the target of pharmacological anti-platelet therapies (83;84) and mechanical anti-embolic strategies (171;172) aimed at improving outcomes following PPCI. Post mortem studies support the importance of this mechanism of microvascular compromise, with a high incidence of platelet aggregates found in the small intra myocardial vessels of patients suffering sudden ischaemic cardiac death (173). Finally, cellular oedema (of myocytes and endothelial cells) in response to the insults of both ischaemia and reperfusion may result in extrinsic capillary compression.
1.7.4 Prevention and Treatment of Microvascular Dysfunction

Clinical strategies for treating microvascular dysfunction have targeted a number of the contributory mechanisms discussed above. Pharmacological therapies investigated include potassium channel (K\text{ATP}) opening with NO donation (nicorandil) (174;175), calcium channel inhibition (verapamil) (176), complement inhibition and neutrophil adhesion antagonism (anti-CD18) (177;178). While adenosine and nicorandil have shown some promise, the clinical benefits have not been sufficient for these therapies to enter routine clinical practice.

In the context of primary angioplasty anti-embolic strategies have dominated clinical studies directed at improving microvascular perfusion, including pharmacological anti-platelet therapy (glycoprotein Gp Ilb/Illa receptor antagonists (GPRAs)), and mechanical prevention of distal embolisation using thrombectomy catheters and distal protection devices. The role of GPRAs has been discussed earlier, both as adjuvant therapy for all high risk ACS [see 1.4.1 Pharmacological therapies for Acute Coronary Syndromes], and in the context of facilitated primary angioplasty for STEMI specifically [see 1.5.4 Summary - Thrombolytic therapy in the United Kingdom]. The clinical benefits of GPRAs may be partly mediated by improved microvascular perfusion. This has been demonstrated in studies employing angiographic perfusion scores, invasive coronary flow, and myocardial contrast echocardiography (163;179), although a recent post hoc analysis of myocardial blush scores in 1301 patients randomised to primary angioplasty with or without abciximab was less supportive (180). The precise mechanism for this benefit remains uncertain. GPRAs may reduce distal micro emboli, and inhibit the formation of platelet micro-particles that can be deleterious to the microvasculature through endothelial binding (181). In the case of abciximab, additional cross-reactivity with the $\alpha_5\beta_3$ (vitronectin) receptor may also contribute to the reduction in platelet-endothelial binding (181).
The use of mechanical distal protection and thrombectomy devices for STEMI is not yet clearly defined. While they have the potential to prevent deterioration in microvascular perfusion, none have yet delivered an improvement in clinical outcome. In the EMERALD study (Enhanced Myocardial Efficacy and Removal by Aspiration of Liberated Debris) the PercuSurge GuardWire distal protection system (Medtronic, Santa Rosa, CA, USA) used during PPCI less than 6 hours after presentation with STEMI did not improve angiographic perfusion scores, ST segment resolution, final infarct size or clinical endpoints when compared to the results from a randomized control group (171). More concerning are the results of the recently presented AIMI study (172) where rheolytic thrombectomy (Angiojet, Possis) not only failed to improve the quality of reperfusion (despite a prior supportive study (182)), but was also associated with a significant increase in mortality when compared with routine PPCI alone.

A number of explanations could account for the disappointing results of microvascular treatment strategies. Pathophysiologically, thrombus removal from the epicardial vessel may not be sufficient to improve microvascular dysfunction as this process does not affect the endothelial damage, oedema, neutrophil interactions, and release of vasoactive factors that contribute to the insult. Clinical study design may also be relevant. Neither AIMI nor EMERALD specifically selected patients with angiographically evident thrombus, a design which may have been more intuitive. However, it is likely that any effort to improve microvascular perfusion will be influenced by the duration of symptoms prior to reperfusion, and that the therapeutic time window may be narrow. Patients who present early (within 3 hours) have an excellent prognosis with minimal microvascular injury and are therefore unlikely to benefit from additional microvascular therapies. Those who present later sustain more microvascular injury, but may have less myocardium to salvage and the microvascular damage may not be reversible, such that the measurable benefit may be minimal (183).
1.7.5 Summary Microvascular Perfusion

Epicardial infarct artery patency (TIMI grade 3 flow) does not guarantee perfusion at tissue level. Damage to the coronary microvasculature is associated with larger infarct size, adverse left ventricular remodeling and worse prognosis. The microvascular insult is mediated by a combination of platelet and atherothrombotic embolisation, ischaemic endothelial damage, neutrophil plugging, vasospasm, and cellular oedema. While there is no gold standard method to assess the coronary microvasculature, angiographic myocardial blush grade and ST segment resolution on the ECG are well validated reproducible techniques that provide complementary information, and are readily available at the time of coronary intervention.

Among the 90% of patients achieving TIMI-3 flow following primary angioplasty only half achieve complete ST resolution and angiographic microvascular patency (myocardial blush grade 2 or 3) (184). Thus there is a need to find strategies to further optimise microvascular perfusion following primary angioplasty. To date adjunctive therapies targeting the microvasculature have been disappointing, although study design and a narrow therapeutic time window could explain these results. Of all these microvascular strategies, anti-platelet agents (specifically glycoprotein Gp IIb/IIIa receptor antagonists (GPRAs)) have been most promising, though their precise mechanism of action with respect to microvascular dysfunction is not determined.

1.8 Platelet Activation, Primary Angioplasty, and Microvascular Perfusion

The role of platelet activation in the pathogenesis of acute coronary syndromes has been discussed above [see 1.2.3 Role of platelet activation in acute coronary syndromes]. Platelet activation is associated with an increased risk of developing an ACS, and the degree of activation may determine the type of clinical presentation. Enhanced platelet monocyte aggregate (PMA) formation predicts the extent of subsequent myocardial damage before it occurs (32)
which may suggest that PMAs directly affect plaque behaviour. Similarly it has also been discussed that CD40L may be implicated in the process of plaque rupture (33). The prothrombotic and pro-inflammatory properties of CD40L (including thrombus stabilisation, interaction with ECs, expression of leucocyte adhesion molecules, release of chemokines, induction of reactive oxygen species) (185) make it attractive as a potential mediator of microvascular compromise and reperfusion injury. To date the effects of platelet activation on the efficacy of reperfusion and microvascular function following primary angioplasty for STEMI have not been investigated.

It is important to note that the interaction between platelet activation and reperfusion is likely to be reciprocal. Reperfusion itself may further activate platelets. Re-oxygenation of anoxic platelets in response to reperfusion increases platelet aggregation, and induces the production of reactive oxygen species from the platelets themselves, mediating further microvascular and myocyte damage (168;186;187). In addition there appears to be a reciprocal interaction whereby platelets activate neutrophils and vice versa (188). Activated platelets also enhance the production of reactive oxygen species by neutrophils (189).

Primary angioplasty will itself influence platelet activation, which may in turn also affect the success of reperfusion. As the primary angioplasty process includes a combination of aspirin, clopidogrel, abciximab, and heparin in addition to the procedure itself, the consequences for platelet activation will be the sum of all their effects. Elective PCI (with or without stenting) enhances platelet expression of activation markers (31;190;191). To date however, there has been only one study of platelet activation in STEMI patients undergoing primary angioplasty (29). Platelet activation measured by P-selectin expression fell 4-8 hours following the procedure, returning at 24-48 hours - a finding that was not apparent in elective patients. There was an associated fall in platelet count and micro-particles were generated following primary angioplasty, which may signify
platelet sequestration rather than deactivation. This study may not be relevant to current practice, predating the use of coronary stents and GPRAs, and the availability of more sensitive measures of platelet activation. Nevertheless the study did demonstrate a significant difference between platelet behaviour following elective and primary angioplasty that may reflect differences in plaque pathology. Whereas elective PCI disrupts a stable plaque enhancing platelet activation, in the setting of STEMI an inflammatory and thrombotic process is already established at the site of the culprit plaque prior to intervention.

The influences of GPRAs therapy and clopidogrel on platelet activation have also been discussed above [see 1.4.1 Pharmacological therapies for Acute Coronary Syndromes]. GPRAs therapy appears to reduce sCD40L release and platelet-leucocyte aggregate formation in patients undergoing PCI following a NSTE-ACS, an effect which is independent of clopidogrel (87). It is possible to speculate that the modification of platelet activation (measured by PMA formation and CD40L) may also provide a mechanism for the benefit of GPRAs therapy in improving microvascular dysfunction following primary angioplasty. To date these markers have not been investigated in patients with STEMI undergoing primary angioplasty, and their relation to microvascular perfusion has not been explored. This thesis examines the influence of primary angioplasty on platelet activation measured by P-selectin expression, CD40L expression, sCD40L release, and platelet-monocyte aggregate formation. In addition, the influence of these activation markers on microvascular perfusion (measured by ST resolution and myocardial blush grade) is addressed.

1.9. Summary

ST segment elevation myocardial infarction is a severe and frequent acute coronary presentation, usually signifying a freshly occluded epicardial coronary artery due to thrombosis. Plaque rupture is the precipitating event in the majority of cases, with plaque erosion accounting for most of the remainder. The mechanisms determining these processes continue to be the subject of intense
investigation. While platelets are critical to the development of thrombosis, recent evidence suggests that platelet activation may be mechanistic in initiating plaque events.

The goal of therapy for STEMI is the rapid restoration of arterial patency. There is debate as to the optimal reperfusion strategy. The National Service Framework for Coronary Heart Disease supports the widespread use of thrombolysis, and delivery of this therapy has improved across the UK since its publication. However, up to 30% of patients do not receive therapy, and only 50% of patients treated achieve optimal reperfusion. In addition, reperfusion failure, reinfarction and recurrent ischaemia lead to a frequent need for revascularisation, often urgent. Primary angioplasty has been proven more effective than thrombolysis, provided that it can be performed rapidly in an experienced centre. In practice however, the majority of patients do not present to a hospital that can provide this treatment. This necessitates transfer mechanisms to deliver patients to a distant cardiac centre, which may prolong the time to reperfusion, and thereby lose the benefit. Pharmacological therapy may be administered prior to transfer to achieve earlier or more effective reperfusion. However, it is as yet undetermined whether and which therapy should be administered. At present there is no NSF revascularisation strategy for patients presenting with STEMI, and the logistics of providing primary angioplasty for the majority of UK patients has not been addressed.

Prognosis following reperfusion therapy for STEMI is determined by the quality of blood flow in the epicardial artery. In those achieving complete epicardial patency (TIMI-3 flow), outcome is further influenced by patency of the microvascular circulation, which can be assessed at the time of reperfusion using angiographic and ECG analyses. The causes of microvascular dysfunction following reperfusion are multifactorial. To date, therapies directly targeting microvascular perfusion have demonstrated limited clinical benefit. Of these, anti-platelet strategies (specifically with glycoprotein IIb/IIIa receptor
antagonists) have proven most effective, though the precise mechanisms are unclear. Thrombo-inflammatory platelet activation markers may be implicated in the development of microvascular dysfunction following reperfusion. The influence of platelet activation on microvascular reperfusion following primary angioplasty has not previously been investigated.

This research involves the analysis of the existing UK reperfusion strategy (thrombolysis) as applied to a metropolitan population based in North East London, and describes the development and instigation of a primary angioplasty service serving a network of district hospitals. The logistics and efficacy of two simultaneous patient transfer strategies are investigated, in tandem with the influence of pharmacological facilitation with glycoprotein IIb/IIIa receptor antagonist therapy. In addition to clinical outcomes, the impact of these strategies on microvascular perfusion is examined. The potential role of platelet activation in determining epicardial microvascular perfusion is studied, and in turn the effect of the primary angioplasty process on platelet activation is explored.

1.10 Aims of the Thesis

- To determine the extent and impact of invasive investigation and revascularisation following thrombolysis for ST segment Elevation Myocardial Infarction in North East London

- To describe the process of development and instigation of a pilot primary angioplasty service in North East London, using a network heart attack centre model

- To compare a strategy of pre-hospital ECG diagnosis and direct ambulance access to the network heart attack centre with that of inter-
hospital patient transfer in delivering primary angioplasty within a network of hospitals without PCI facilities

- To investigate the influence of platelet activation on epicardial and microvascular perfusion following primary angioplasty for ST segment Elevation Myocardial Infarction

- To investigate the effect of the primary angioplasty process on platelet activation in patients presenting with ST segment Elevation Myocardial Infarction

- To compare clinical outcome and resource utilisation following the instigation of a the pilot primary angioplasty service with outcomes following the thrombolytic strategy in North East London

1.11 Central Hypotheses

- Primary Angioplasty can be delivered safely and effectively in a United Kingdom population, with improved efficiency and clinical outcomes compared with thrombolysis.

- The efficacy of reperfusion following primary angioplasty can be determined by the degree of platelet activation at presentation
CHAPTER 2 METHODS
2.1 Subjects

This research involves the comparison of reperfusion strategies for patients presenting with ST segment elevation myocardial infarction (STEMI) in North East London. STEMI was defined in accordance with the consensus document of The Joint European Society of Cardiology/American College of Cardiology Committee for the redefinition of myocardial infarction (44) as follows: Ischaemic symptoms in association with new or presumed new ST segment elevation at the J point in two or more contiguous leads with the cut-off points 0.2 mV in leads V1, V2, or V3 and 0.1 mV in other leads, and a rise in a biochemical marker of myocardial necrosis (CK or troponin) according to the local reference range.

2.1.1 Thrombolysis

Data were collected from consecutive patients allocated to the thrombolytic reperfusion strategy following presentation with confirmed STEMI to five district hospitals within the North East London Cardiac Network (April 2003 - January 2005) (Figure 2.1, hospitals A-E). Data collection was prospective and non randomised using dedicated databases at each centre. In addition data from a historical cohort of STEMI patients admitted to hospital E between October 2001 and October 2002 were also included to enable comparison of outcomes prior to the instigation of a daytime pilot primary angioplasty service initiated at the regional cardiac centre (Figure 2.1) within the same NHS Trust. In hospital outcomes were recorded for all network patients. Follow up data post discharge were obtained from both historical and contemporaneous patient cohorts allocated to the thrombolytic strategy presenting to centre E, through outpatient clinics, recurrent admissions, and contact with general practitioners [see chapter 3.3 METHODS].
Figure 2.1 Map demonstrating the location of District Hospitals and the Regional Cardiac Centre within the North East London Cardiac Network

Key

The London Chest Hospital (Barts and the London NHS Trust). Regional cardiac centre functioning as a pilot Network Heart Attack Centre (N-HAC)

District General Hospital with Accident and Emergency Department
A Newham University Hospital
B Whipps Cross University Hospital
C King George Hospital, Ilford
D Oldchurch Hospital
E The Royal London Hospital
F Homerton University Hospital
2.1.2 Primary Angioplasty
Data were collected from unselected consecutive patients presenting with suspected STEMI to a regional cardiac centre functioning as a pilot network heart attack centre (N-HAC) between April 2003 and May 2005, utilising primary angioplasty as the preferred reperfusion strategy (Figure 2.1). Data collection was prospective and non randomised. Demographic, clinical, haematological and biochemical data were recorded and stored on a dedicated database using SPSS software (SPSS Inc. Chicago Illinois). In hospital outcomes were recorded in those patients with confirmed ST segment elevation myocardial infarction. Follow up data were recorded through designated outpatient clinics, recurrent admissions and contact with general practitioners.

2.2 Interventions
2.2.1 Thrombolysis
The thrombolytic strategy included the administration of 300mg aspirin orally and intravenous thrombolysis in standard doses (streptokinase, recombinant tissue plasminogen activator (alteplase – rTPA), reteplase or tenecteplase) for eligible patients, administered according to local and National Service Framework (NSF) guidelines (3). Patients could be transferred emergently for coronary angiography if thrombolysis was contraindicated, for recurrent or persistent ST elevation, or for ongoing ischaemia according to local physician preference. In addition patients could be transferred non-emergently for angiography during the index admission at the discretion of the admitting physician.

2.2.2 Primary Angioplasty
The development, mechanism of operation, and expansion of the network pilot primary angioplasty protocol is described in Chapter 4. Patients identified with suspected STEMI were admitted directly to the N-HAC cardiac catheter laboratory via two routes. London Ambulance Service (LAS) crews making an
independent pre-hospital diagnosis were permitted to bring unselected patients directly to the N-HAC, bypassing the nearest Accident and Emergency department (A&E) ('direct access'). Patients initially presenting to one of the participating network A&E departments could also be transferred urgently by ambulance to the N-HAC ('A&E transfer'). Patients identified by LAS crews or A&E physicians were transferred to the N-HAC without consultation with local physicians or the N-HAC itself. The N-HAC was notified of arrival by London Ambulance Control.

All patients allocated to the primary angioplasty strategy received 300mg aspirin orally, theinopyridine therapy (clopidogrel 300mg orally), and intravenous glycoprotein Gp IIb/IIIa receptor antagonist therapy (abciximab) prior to angiography. Aspirin was administered by London Ambulance Service (LAS) crews in those presenting via that route, or at the first hospital of presentation. Clopidogrel and abciximab were administered as soon as possible following arrival in the N-HAC cardiac catheter lab ('direct access' admissions), or prior to transfer from A&E ('A&E transfers').

Patients were assessed, and where appropriate taken directly to the catheter lab and angiography performed according to local protocol [see Angiographic analyses]. Cardiac catheterisation procedures were performed via the femoral or radial route using 6F or 8F catheters. Culprit vessel angioplasty and stent implantation were performed in all cases (where appropriate), with non-culprit intervention performed at the operator's discretion.
2.3. Platelet Studies

2.3.1 Subjects

The platelet studies presented in this thesis compare platelet activation in three groups of subjects:

1. Patients with confirmed STEMI undergoing immediate angiography with a view to primary angioplasty. Patients were consented shortly following arrival at the N-HAC prior to coronary angiography.

2. Patients with chronic stable angina admitted to the N-HAC for elective coronary angioplasty. Subjects with a history of an acute coronary syndrome within the preceding six weeks were excluded.

3. A control group of subjects with no symptoms or prior history of ischaemic heart disease recruited through advertisement. Subjects taking aspirin or other anti-platelet therapy within a week prior to the study were excluded.

Ethical approval was obtained from the North East London Regional Ethics Committee (reference number P/03/024).

2.3.2 Blood Sampling, Preparation and Analysis

Samples were drawn from the antecubital fossa with minimal stasis using a 21-gauge needle prior to entering the cardiac catheter lab, at 2 hours following balloon inflation and at 18-24 hours following coronary angioplasty among those undergoing intervention.

Flow Cytometry

Flow cytometry (FACS Scan, BD Biosciences, USA) was performed in the Department of Haematology at the Royal London Hospital, and data analysed using Cellquest (version 3.1, BD Biosciences, USA) and Summit (version 4.0 DakoCytomation, USA) software.
Blood was collected into EDTA, and then transferred into a tube (protected from light) containing citrate-theophylline-adenosine-dipyridamole (CTAD). The combined EDTA / CTAD tube was stored at 4°C and analysed within 6 hours. 5µl of blood were incubated for 5 minutes at 4°C with 5µl of anti-sera, then diluted in 90µl Tyrode's salt solution. This has previously been demonstrated to be a reliable method of sample preparation and analysis for ex vivo platelet and leucocyte activation assessment (192).

**Platelet Surface markers**

P-selectin expression was measured using fluorescein isothiocyanate (FITC) conjugated anti-CD62P (Beckman Coulter UK, IgG1 mouse antibody, clone: CLB-Thromb/6). CD40L expression was measured using phycoerythrin (PE)-conjugated anti-CD154 (Beckman Coulter UK, IgG1 mouse antibody, clone: MR1). The platelet gate was identified using forward and side scatter characteristics, with positive events identified using histograms of count against fluorescence intensity (Figure 2.2). The boundary between negative and positive events was determined using FITC / PE conjugated isotype controls. 10,000 platelet events were counted (Figure 2.3).
Figure 2.2 Flow cytometry. Identification and gating of platelet events using forward and side scatter characteristics.

A dot plot of side scatter versus forward scatter characteristics of a whole blood sample during flow cytometry. A dark cloud of erythrocytes and white blood cell lines appear in the upper right quadrant, being of relatively larger size (forward scatter) and granularity (side scatter) than the platelet cloud which appears below and the left. A gate has been drawn around the platelet cloud as indicated.
Figure 2.3. Flow cytometry. Histograms gated on platelet events demonstrating events fluorescing in the FL1 channel.

Figure 2.3a. The boundary between positive and negative events is first determined using FITC conjugated isotype control antibody, with a cut off of 0.1% in region R6.

A whole blood sample is analysed for CD62P (P selectin) expression. The sample is first incubated with an isotype control antibody linked to the fluorophore FITC to assess fluorescence resulting from non-specific antibody binding. The histogram plot above demonstrates count versus fluorescence intensity in the FL-1 channel for events occurring within the platelet gate demonstrated in figure 2.2. A region (R6) is created to determine the boundary between positive and negative events, which by convention includes 0.1% of events using the isotype control antibody.
Figure 2.3b. The experiment is repeated using FITC conjugated test antibody (in this case anti-CD62P). The percentage of positive events in R6 determines the percentage expression of membrane P-selectin (2.7%).
Platelet Monocyte Aggregates (PMA)

Using PE conjugated anti-CD14, (Beckman Coulter UK, IgG2a mouse antibody, clone RMO52) the monocyte gate was identified on a dot plot of side scatter against PE (FL2) fluorescence. Platelet positive monocyte events were identified using FITC-anti Gp IX (CD42a), which is constitutively expressed on all platelets (Beckman Coulter UK, IgG2a mouse antibody, clone: SZ1). A plot of FL2 versus FL1 demonstrated dual positive events denoting aggregates (figure 2.4). Non-specific antibody binding was excluded using FITC-IgG2a isotype controls. 1000 monocyte events were counted. Quantification of PMA formation was quoted as a percentage using the ratio of dual positive events (aggregates) to all CD14 positive events (monocytes).

All analyses were repeated in triplicate by convention. Results with a coefficient of variation greater than 10% were re-prepared and re-analysed. Where the coefficient of variation was greater than 10% on two separate analyses, the sample was excluded from data analysis.
Figure 2.4 Flow cytometry. Measurement of platelet monocyte aggregates

**Left panel:** Dot plot of side scatter (SSC-H) vs. FL2 fluorescence. The gated area demonstrates monocytes as a population of CD14-PE positive events.

**Right panel:** Dot plot of FL2 vs. FL1 fluorescence demonstrating platelet monocyte aggregates (PMAs) as a population of dual positive events in the right upper quadrant. These are quantified as the percentage of the total monocyte population (right upper quadrant + left upper quadrant)
**Plasma Assays**

Citrated plasma samples were taken onto ice, and immediately centrifuged for 15 minutes at 1000g at 4°C. The supernatant was removed and centrifuged again for 10 minutes at 10,000g at 4°C to remove excess platelets. The plasma was aliquotted into cryovials and stored at -80°C. All samples were defrosted only once. Where necessary, repeat sample analysis was always performed using a separate cryovial from the same patient.

Soluble P-selectin, high sensitivity soluble CD40 ligand (sCD40L), and interleukin 6 (IL-6) were measured using enzyme-linked immunosorbent assay (ELISA) according to manufacturers instructions (Bender Medsystems, UK).

Briefly, sample plasma was added to the immunosorbent surface in the ELISA plate wells, fixed and then washed. A detection antibody to the antigen (sCD40L, P-selectin, or IL-6 as appropriate) was added. Plates were washed again to remove unbound antibody. A secondary antibody conjugated to a substrate specific enzyme was then added, and plates washed again. Finally the specific substrate was added, eliciting a chromogenic response.

All samples were analysed in duplicate according to conventional methodology. In addition to sample plasma, reagents of standard concentrations supplied by the manufacturer and six additional internal control samples were included on each plate. Optical density was recorded using a GENios microplate reader (Tecan, Austria) using a 450nm filter. Samples returning a coefficient of variation in optical density greater than 10% were repeated. Repeat samples returning a coefficient of variation greater than 10% were excluded from analysis. Standard curves were generated using Microsoft XL software (Microsoft, USA), allowing derivation of concentrations (Figure 2.5).
Serum creatine kinase (CK) level was measured as a marker of myocardial infarct size on admission and at 18-24 hours in the biochemistry department at the Royal London Hospital. The highest level was recorded as the peak CK.

**Figure 2.5 Enzyme linked immunosorbent assay.**

Optical density vs. concentration of P-selectin (ng/ml): An example of a standard curve generated using a P-selectin ELISA plate (Bender Medsystems, UK)

The graph demonstrates optical density against concentration (in ng/ml) for an ELISA plate assaying soluble P selectin. The points are derived using reagents of standard concentrations supplied by the manufacturer, and an equation derived to obtain the P selectin concentration for a given optical density.
2.4 ECG analyses

ST segment resolution on the 12 lead ECG was used as a surrogate marker of microvascular reperfusion (155;184). ST segment analysis was performed on all patients assigned to the primary angioplasty strategy, where the ECG was interpretable.

The 12 lead ECG was performed by the ambulance crew (in those presenting via this route), on arrival at the first hospital of presentation, at the heart attack centre prior to primary angioplasty, at 60 to 90 minutes post procedure on the coronary care unit, and at 18-24 hours. The location and extent of maximum ST segment elevation was recorded. Recordings were copied and anonymised.

The ST segments were measured 20ms after the J-point to the nearest 0.25mm using calipers by a trained independent observer blinded to the clinical details. The summed ST segment recovery (ΣSTR) was calculated according to the validated method employed by Schroeder et al (155) as follows: The difference between the sum of ST segment elevation (ΣSTE) (in leads V1-V6, I and aVL for anterior and II, III, aVF, V5, V6 for non-anterior infarction) at baseline and immediately following primary angioplasty was expressed as a percentage of the baseline ΣSTE. This was repeated for an ECG at 18-24 hours. The pre-procedural ECG (if different to baseline) was also measured to assess spontaneous and pharmacologically facilitated reperfusion.

2.5 Angiographic analyses

A full diagnostic study was performed on all patients undergoing primary angioplasty as per local protocol. Angiography of the target vessel was performed to demonstrate the culprit lesion(s) in at least 2 orthogonal views for the right coronary artery and 3 for the left coronary artery (at least 60° of rotation or angulation between views) following administration of intracoronary nitrate.
Image acquisition for angiographic perfusion imaging was performed to demonstrate the myocardial infarct territory with minimal overlap of non-infarcted regions. Runs were acquired to demonstrate arterial opacification and contrast washout (with filling of the coronary venous system or for 3 cardiac cycles following cessation of contrast injection). Intracoronary isosorbide dinitrate (1-2mg) was injected prior to initial and final acquisitions to standardise coronary vasomotor tone. Image acquisition was performed using a digital image system (GE Healthcare, USA) at a rate of 15 frames per second.

Angiographic perfusion views were obtained on all patients undergoing primary angioplasty immediately pre and post procedure, and analyses performed by two independent observers blinded to the clinical data. Epicardial flow was assessed using the TIMI flow grade (102), and microvascular perfusion was assessed using the myocardial blush grade and corrected TIMI frame count (cTFC) in the territory of the infarct related artery, as described by Van't Hof et al (193), and Gibson et al (194) respectively, as explained below. TIMI thrombus burden in the index vessel was also assessed prior to intervention (195).

2.5.1 TIMI Flow Classification

**TIMI 0**  No perfusion.

**TIMI 1**  Penetration of angiographic contrast with minimal perfusion. Contrast fails to opacify the entire bed distal to the stenosis for the duration of the cine run.

**TIMI 2**  Partial perfusion. Contrast opacifies the entire coronary bed distal to the stenosis. However, the rate of entry and/or clearance is slower in the coronary bed distal to the obstruction than in comparable areas not perfused by the dilated vessel.

**TIMI 3**  Complete epicardial perfusion. Filling and clearance of contrast equally rapid in the coronary bed distal to stenosis as in other coronary beds.
2.5.2 Myocardial Blush Grade (MBG)

<table>
<thead>
<tr>
<th>MBG 0</th>
<th>no contrast density or persistent staining of the myocardium with contrast.</th>
</tr>
</thead>
<tbody>
<tr>
<td>MBG 1</td>
<td>minimal contrast density</td>
</tr>
<tr>
<td>MBG 2</td>
<td>moderate contrast density, but less than that obtained during angiography of a non infarct related artery.</td>
</tr>
<tr>
<td>MBG 3</td>
<td>normal contrast density comparable to that obtained during angiography of a non infarct related artery.</td>
</tr>
</tbody>
</table>

2.5.3 Corrected TIMI Frame Count

The number of frames taken for contrast to reach standardised distal landmarks was counted. The first frame was counted when contrast fully entered the infarct related artery antegrade, with a column of contrast visualised to extend across the entire width of the artery. The last frame was counted when dye first appeared at the predefined distal landmark. For the left anterior descending artery (LAD) this was the distal bifurcation at the apex. For the right coronary artery (RCA) the landmark was the first branch of the postero-lateral extension after the bifurcation. For the circumflex (Cx) this was the distal bifurcation of the vessel where dye travels the furthest but also passes through the culprit lesion. The total number of frames counted was multiplied by 2 for standardisation with the initial method described (30 frames per second), as has been recently validated for use in a modern digital cardiac catheter lab (196). LAD values were divided by 1.7 to control for the longer length of the LAD as described in the original paper by Gibson et al (194).
2.5.4 Angiographically evident thrombus (AET)
A patient was considered to have AET if TIMI thrombus grades 2 to 5 are present.

**TIMI thrombus grade 0**
no angiographic characteristics of thrombus are present

**TIMI thrombus grade 1**
possible thrombus is present, with such angiography characteristics as reduced contrast density, haziness, irregular lesion contour, or a smooth convex "meniscus" at the site of total occlusion suggestive but not diagnostic of thrombus

**TIMI thrombus grade 2**
there is a definite filling defect consistent with thrombus, with greatest dimensions ≤1/2 the vessel diameter

**TIMI thrombus grade 3**
there is a definite filling defect consistent with thrombus but with greatest linear dimension >1/2 but <2 vessel diameters

**TIMI thrombus grade 4**
there is a definite filling defect consistent with thrombus, with the largest dimension ≥2 vessel diameters; and in

**TIMI thrombus grade 5**
there is total occlusion.
2.6 Clinical Outcomes

2.6.1 Mortality
Cardiac death was defined as death due to any of the following:

- Acute myocardial infarction.
- Cardiac perforation/pericardial tamponade.
- Arrhythmia or conduction abnormality.
- Death due to complication of the procedure, including bleeding, vascular repair, transfusion reaction, or bypass surgery.
- Any death in which a cardiac cause cannot be excluded.

Non-cardiac death was defined as a death not due to cardiac causes (as defined above).

2.6.2 Major Adverse Cardiac Events
A major adverse cardiac event (MACE) was defined as death, myocardial infarction (Q wave and non-Q wave), cerebrovascular accident, or emergency revascularisation.

Non fatal myocardial infarction was defined as typical chest pain with a new increase in troponin I or T, with or without ECG changes.

Emergency revascularisation following discharge was defined as revascularisation driven by ischaemic chest pain necessitating recurrent hospital admission, with or without a rise in troponin or ECG changes.

Revascularisation during the index admission and elective revascularisation for exercise induced ischaemia following discharge were recorded, but were not included in the composite MACE endpoint.
2.7 Statistics

Statistical analyses specific to each chapter are documented in their respective methods section. Normally distributed continuous variables are presented as means and standard deviations. Skewed distributions are presented as medians and inter quartile ranges. All statistical analyses were performed using SPSS software version 11.5 (SPSS Inc. Chicago Illinois). A p value of less than 0.05 was considered statistically significant.
CHAPTER 3 The Burden of Revascularisation following the Thrombolytic Strategy for the Treatment of ST Segment Elevation Myocardial Infarction
3.1 ABSTRACT

Thrombolysis remains the predominant reperfusion strategy for ST segment Elevation Myocardial Infarction (STEMI) in the United Kingdom with National Service Framework targets directed towards delivery of this therapy. Primary angioplasty can improve outcomes, but has been perceived to be prohibitively expensive, due to the potential increase in revascularisation activity. This chapter investigates the existing extent of coronary angiography and revascularisation following STEMI treated using the thrombolytic strategy in North East London, and its impact on resource utilisation measured by duration of hospital stay.

Subjects: 993 patients with ST segment Elevation Myocardial Infarction admitted to five district hospitals without on site coronary intervention within North East London. Data collection was prospective and non-randomised.

Methods: Inter hospital transfers for inpatient coronary angiography (IPA) and duration of hospital stay were measured at all centres. A subgroup of 192 subjects admitted to one centre (centre E) was further investigated with respect to inpatient revascularisation and clinical outcome. This cohort was followed for a median (IQR) of 20 (10 - 41) weeks. Major Adverse Cardiac Events (MACE) included death, non-fatal myocardial infarction (NIFMI), stroke, and emergency revascularisation post discharge. Hospital readmissions, outpatient catheter studies and planned revascularisations were also recorded.

Results: 851 (86%) patients received thrombolytic therapy. 50% (492) were transferred for IPA, although there was significant variation between centres (36% - 61%, p<0.001). Of these 16% were transferred urgently within the first 24 hours of admission. Inpatient stay at the district hospital was prolonged by a median of 2 days in patients referred for non urgent IPA (median [IQR] 6 [4-11] vs. 8 [5-15] days, p<0.001). 54% (103) of the subgroup presenting to centre E
were transferred for IPA, leading to inpatient revascularisation in 38% (73), 88% performed percutaneously (PCI). MACE was elevated among patients discharged without angiography compared to those transferred for IPA (37% vs. 10%, p=0.001). Mortality and stroke were both significantly elevated (18% vs. 5% IPA, p=0.004; 7% vs. 1%, p=0.035 respectively) though this is likely to reflect patient selection. NFMI and emergency revascularisation following discharge were both higher in those not undergoing IPA, though not reaching significance (10% vs. 4% IPA p=0.15; 10% vs. 4% IPA, p=0.15 respectively). 30% of those not undergoing IPA underwent angiography during follow up, 15% following emergency readmission. At the time of follow up 65% had undergone angiography, and 45% revascularisation (85% PCI).

Conclusions: Despite effective delivery of thrombolysis, the majority of STEMI patients in North East London require coronary angiography. Of those who undergo revascularisation, the majority is performed percutaneously. Inpatient transfer for angiography significantly prolongs hospital stay at the non interventional centre. Those not transferred for IPA are more frequently readmitted with recurrent events leading to further emergency catheterisation and revascularisation procedures. The existing burden of revascularisation following STEMI necessitates reassessment of the approach to reperfusion therapy in North East London, including consideration of primary angioplasty.
3.2 INTRODUCTION

The superiority of primary angioplasty over thrombolysis as reperfusion therapy for ST segment elevation myocardial infarction (STEMI) has been demonstrated by multiple randomised controlled trials (127). In spite of this there has been a perception in the United Kingdom that the benefits of this therapy are not sufficient to overcome the financial cost of revascularisation and the logistics of treating the majority of STEMI patients that present to hospitals without on-site coronary intervention. Recent studies have established that transfer of STEMI patients for primary angioplasty from district hospitals to a ‘regional heart attack centre’ (RHAC) with interventional facilities is safe, and may be more effective than immediate on-site thrombolytic therapy (132;133). Additionally, STEMI patients treated at non interventional centres utilising thrombolysis may also require inpatient transfer for coronary angiography at a cardiac centre for failure to reperfuse, recurrent ischaemia, if there are contraindications to thrombolysis, or high risk features including an early positive exercise test. The aim of this study was to investigate the extent of angiography and revascularisation following presentation with STEMI within a network of hospitals in North East London all utilising the thrombolytic reperfusion strategy. Comparison was made between referral practice between centres, and the impact of transfer on bed utilisation was assessed.

3.3 METHODS

Patients

The study included 993 patients with ST segment Elevation Myocardial Infarction admitted to five district hospitals without on site coronary intervention within North East London. Data collection was prospective and non-randomised. Consecutive STEMI patients were entered on separate dedicated databases at each centre. Each hospital dataset was collected independently, and then combined for analysis. Data from four hospitals (A, B, C and D) relate to consecutive admissions between April 2003 and January 2005. Centre E was the district general hospital located geographically closest to and within the
same NHS Trust as a tertiary cardiac centre serving all five district hospitals (Figure 2.1). Data from hospital E included 192 patients; 105 admitted consecutively between October 2001 and October 2002 prior to the instigation of a daytime (0800-1700) pilot primary angioplasty service, and 87 patients admitted between April 2003 and April 2004 presenting outside the operating hours of the pilot primary angioplasty service.

Interventions

Eligible patients were treated with thrombolysis according to National Service Framework (NSF) guidelines (3). Inpatient coronary angiography was performed following inter-hospital transfer to the regional cardiac centre. The decision to refer patients for inpatient angiography was based on local guidelines and physician preference. Transfer within 24 hours of admission was used as a surrogate for emergency catheterisation for failure to reperfuse or early recurrent ischaemia. Inpatient revascularisation was performed according to operator preference. Patients were discharged according to local physician preference.

Outcome Measures

The rate of in-patient angiography and hospital stay were recorded at all centres. Hospital stay excluded hospitalisation at the cardiac centre. In-patient revascularisation was recorded in 192 patients presenting to hospital E. This cohort were followed for a median (IQR) of 20 (10-41) weeks. In hospital mortality was 8% (15). Data were available for 160/177 (90%) patients alive at discharge, through outpatient clinics, inpatient episodes, and general practitioner or patient telephone interview where necessary. Of the 17 patients lost to follow up, 3 left the country leaving no forwarding address. The remainder were not traceable due to incorrect or inconsistent personal and or general practitioner details. Major adverse cardiac events (MACE) included a composite of death, non fatal myocardial infarction, stroke, and emergency revascularisation following discharge. Non fatal infarction was defined as typical chest pain with a new increase in troponin I, with or without ECG changes. Emergency
Revascularisation following discharge was defined as revascularisation driven by ischaemic chest pain necessitating recurrent hospital admission, with or without a rise in troponin or ECG changes. Revascularisation during the index admission and elective revascularisation for exercise induced ischaemia following discharge were recorded, but were not included in the composite MACE endpoint.

Statistics
Due to the skewed distribution of data, comparisons of duration of hospital stay and rates of referral for inpatient angiography were performed using non parametric tests. Mann Whitney U tests were used to compare duration of hospital stay between patients transferred and not transferred for inpatient angiography. Variation in referral rates for inpatient and urgent angiography and length of stay between more than two centres was assessed using Kruskal-Wallis tests. Comparison of event rates between patients transferred for angiography and those not transferred was assessed using Chi squared tests.

3.4 RESULTS
Thrombolytic therapy
851 (86%) patients received thrombolytic therapy. Table 3.1 demonstrates that prescription and delivery of thrombolysis at participating centres was uniformly high.

Transfer for inpatient angiography
50% (492) were transferred for inpatient cardiac catheterisation during the index admission. Of these 16% were transferred urgently within the first 24 hours of admission (Figure 3.1). There was significant variation between centres both in referral for inpatient angiography (36% centre D - 61% centre C, p<0.001), and urgency of transfer (6% centre B - 25% centre D, p<0.001).
Table 3.1 Percentage of patients receiving thrombolysis, and achieving NSF targets at each centre

<table>
<thead>
<tr>
<th></th>
<th>% Thrombolysis</th>
<th>% DTN&lt;30*</th>
<th>% CTN&lt;60*</th>
</tr>
</thead>
<tbody>
<tr>
<td>A n=141</td>
<td>78</td>
<td>90</td>
<td>65</td>
</tr>
<tr>
<td>B n=141</td>
<td>81</td>
<td>80</td>
<td>44</td>
</tr>
<tr>
<td>C n=260</td>
<td>89</td>
<td>83</td>
<td>59</td>
</tr>
<tr>
<td>D n=168</td>
<td>94</td>
<td>90</td>
<td>53</td>
</tr>
<tr>
<td>E n=192</td>
<td>87</td>
<td>97</td>
<td>86</td>
</tr>
<tr>
<td>Mean</td>
<td>86</td>
<td>88</td>
<td>61</td>
</tr>
</tbody>
</table>

DTN < 30 – percentage of patients receiving therapy within 30 minutes of arrival at the referring centre

CTN < 60 – percentage of patients receiving therapy within 60 minutes of the first call for professional help

*Data do not directly relate to the cohorts investigated in this study. Data supplied from each centre are for the study period, as reported in the fourth Myocardial Infarct National Audit Project (MINAP) report June 2005 (101).
Figure 3.1 Variation in referral rates for inpatient angiography at the regional cardiac centre from hospitals A to E

- No Transfer for Angiogram
- Transfer for Inpatient Angiogram WITHIN 24 hours
- Transfer for Inpatient Angiogram AFTER 24 hours

P<0.001

A n=141  B n=232  C n=168  D n=260  E n=192  Total n=993
Hospital Stay

There were significant differences in median hospital stay between centres (Table 3.2) ranging from 5 days (centres A and E) to 8 days (centre B), P<0.001. Inpatient stay at the district hospital was prolonged by a median of 2 days in patients transferred for angiography beyond the first 24 hours of admission. Once again there was significant variation in hospital stay for this subgroup of patients between centres such that hospital stay was not prolonged at centre E, but was prolonged by 6 days at centre D, with an 8 day difference in median stay between these two centres, suggesting differential access to the tertiary centre between hospitals.

Table 3.2 Differences in duration of stay at the district hospital among patients admitted with STEMI referred and not referred for inpatient angiography.

<table>
<thead>
<tr>
<th>Hospital</th>
<th>Hospital Stay all patients</th>
<th>Hospital Stay No IPA</th>
<th>Hospital Stay IPA &gt; 24hr</th>
<th>P (Mann-Whitney)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A n= 141</td>
<td>5 [4-9]</td>
<td>5 [4-6]</td>
<td>8 [5-18]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>B n= 232</td>
<td>8 [5-12]</td>
<td>7 [5-10]</td>
<td>10 [7-14]</td>
<td>0.002</td>
</tr>
<tr>
<td>C n= 168</td>
<td>7 [5-11]</td>
<td>6 [4-8]</td>
<td>9 [6-15]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>D n= 260</td>
<td>7 [5-12]</td>
<td>7 [6-10]</td>
<td>13 [6-23]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>E n=192</td>
<td>5 [3-7]</td>
<td>5 [4-8]</td>
<td>5 [3-7.5]</td>
<td>0.12</td>
</tr>
<tr>
<td>Total 993</td>
<td>6 [4-11]</td>
<td>6 [5-9]</td>
<td>8 [5-15]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>P (Kruskal-Wallis)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

IPA Inpatient angiogram
IPA>24hr Transferred for inpatient angiography beyond 24 hours following presentation
Inpatient cardiac catheterisation and revascularisation (Centre E)

Figure 3.2 demonstrates the invasive management pathway for patients presenting to centre E. 54% (103/192) were transferred for inpatient angiography, leading to revascularisation in 38% (73/192), of which 88% (64/73) was performed percutaneously (PCI).

Cardiac Catheterisation and revascularisation procedures during follow up

Patients discharged without undergoing inpatient angiography:
Follow up data were available for 69/76 patients discharged without undergoing inpatient transfer for cardiac catheterisation. 30% (21) subsequently underwent angiography, 11 following emergency readmission with an acute presentation. 17% (13) underwent revascularisation (9 PCI, 4 CABG) of which 9 were performed as emergencies (6 PCI, 3 CABG).

Patients discharged following inpatient angiography:
Follow up data were available for 91/101 patients discharged having undergone cardiac catheterisation during the index admission. 11 required a repeat catheter study, 4 following emergency readmission. 6/59 (10%) of patients undergoing PCI during the index admission required a repeat revascularisation procedure during follow up, 3 (5%) for target vessel failure (TVF). 5 patients underwent PCI, 1 CABG. 2 (3%) procedures were performed as emergencies (1 CABG, 1 PCI). Of 9 patients allocated to CABG following inpatient angiography, only 3 were performed during the index admission. 1 patient died in hospital prior to CABG being performed. 5 patients were discharged pending planned readmission for CABG, one of whom was readmitted and revascularised as an emergency prior to the date planned.

At a median (IQR) of 20 (10-41) weeks follow up, 65% of patients had undergone cardiac catheterisation, and 45% revascularisation (85% PCI).
Patients Lost to Follow up

17 patients (9%) were lost to follow up. 3/17 returned overseas following the index admission and could not be contacted. The remaining 14 patients could not be traced for follow up through clinics, the general practitioner, or contact addresses. 5/14 were of South Asian origin, a reflection of the local East London catchment population of centre E. Some are not British citizens visiting from overseas or illegal immigrants. Some may present with different names (or spellings), or with varying dates of birth. Many are not registered with a General Practitioner. Finally, there is an additional daily daytime population of up to 200,000 people visiting or working in the City of London that falls within the catchment population of centre E. These factors may have contributed to the loss to follow up. It is not known whether patients lost to follow up may have had major adverse events.
Figure 3.2 The Invasive Management Pathway for patients presenting to centre E with STEMI

192 STEMI

Index admission

103 (54%)
Transfer cardiac catheter

89 (46%)
Not Transferred

65 PCI
9 CABG
30 medical

Deaths

1 (<24hrs)

63 PCI
8 CABG
30 medical

13 deaths (6-24hrs)

lost to follow up

5

58 PCI
8 CABG
25 medical

7 lost to follow up

Follow up

Angio

9 (16%)
0
2 (8%)

All Revascularisation

5 PCI (9%)
1 CABG (2%)
1 CABG

21 (26%)

All Revascularisation

9 PCI (11%)
4 CABG (5%)

Emergency Revascularisation

1 PCI (2%)
1 CABG (2%)

6 PCI (7%)
3 CABG (4%)

TOTAL AT FOLLOW UP: 65% angiography; 45% revascularised (85%PCI)

* 3/8 patients stratified to CABG following inpatient angiography were discharged pending elective revascularisation

** 3/5 repeat PCI procedures were for target vessel failure, the remainder were for de novo disease.
Major Adverse Cardiac Events

Figure 3.3 demonstrates that the composite event rate was significantly elevated among patients that were not transferred for inpatient angiography relative to those who were. The endpoints of death and stroke reached independent significance. The rate of non fatal MI and emergency revascularisation following discharge without inpatient angiography was more than double that observed among those that had been transferred for an angiogram, although not reaching significance. Figure 3.4 demonstrates events following hospital discharge. There was no significant difference in mortality or stroke among patients surviving beyond discharge. Non fatal MI and emergency revascularisation almost invariably occurred following discharge, driving a persistently significant difference in overall MACE between those that underwent inpatient angiography compared with those that did not.

Cardiac Readmissions

In total 37 patients were readmitted with chest pain, 11 with non fatal MI as defined above. The rate of readmission was lower in those referred for angiography than those discharged without an angiogram (17% vs. 25%, p=NS).
Figure 3.3 Major Adverse Cardiac Events according to invasive or non-invasive inpatient management strategy among 175/192* patients admitted to Centre E

* 17 patients lost to follow up excluded from analysis
Figure 3.4 Major Adverse Cardiac Events following hospital discharge according to invasive or non-invasive inpatient management strategy among 160 / 177* patients surviving beyond discharge from Centre E

* 17 patients lost to follow up excluded from analysis
3.5 DISCUSSION

Transfer for angiography and hospital stay

This study demonstrates that 50% of patients admitted with STEMI across the North East London sector are transferred for coronary angiography during the index admission. This occurred despite the proportion of patients receiving thrombolytic therapy being substantially higher than that observed in the GRACE registry (107), and surpassing current NSF delivery targets. There was significant variation in the rate of transfer for angiography from the referring centres. Hospital stay also varied between centres, and was significantly prolonged for patients requiring non urgent transfer in 4 out of 5 centres investigated, suggesting delay in access to the cardiac centre. The extent of delay also varied significantly between centres, indicating inequity of access. The greatest prolongation of inpatient stay occurred at the centre referring the lowest proportion of patients, raising the possibility that delay in access to the cardiac centre may itself have been a disincentive to refer patients. That hospital stay following acute MI may be unnecessarily prolonged in the UK and in East London specifically has previously been demonstrated (197;198). However the finding that the need for invasive investigation is a significant contributor to this process has important implications to service delivery. Transfer of patients with non ST elevation syndromes for inpatient cardiac catheterisation has already been identified as a cause of prolonged hospitalisation in patients with acute coronary syndromes (199;200), but has not previously been highlighted in the setting of STEMI.

Comparison with published data

It is also noteworthy that the rate of cardiac catheterisation, and the proportion transferred within the first 24 hours of admission were both lower than would be predicted by published data. 55% of patients enrolled in the GUSTO-1 thrombolytic study underwent emergency, elective or protocol cardiac catheterisation (201). This trial excluded patients ineligible for thrombolysis or with cardiogenic shock, both indications for emergency angiography that would
be expected to increase this proportion (202). In addition, up to 40% of patients who receive thrombolytic therapy demonstrate ECG evidence of failure to reperfuse (persistent ST segment elevation 60-90 minutes following therapy) (113-115), in whom emergency transfer for rescue angioplasty should be considered. In the CAPTIM study (comparing pre-hospital thrombolysis and primary angioplasty), 26% of patients randomised to thrombolysis underwent urgent PCI for this indication (112). The present study did not record the indication for transfer or assess ST segment resolution. Thus the actual number of patients eligible for rescue cannot be calculated. However, given the expected frequency of failure to reperfuse, these data suggest that the majority of patients with failed reperfusion were not referred to the cardiac centre. This could have been a consequence of equivocal trial data relating to the role of rescue angioplasty (113;116). However, more recent randomised controlled trial data have emerged definitively favouring the rescue strategy (117). Another explanation may have been a lack of specific guidance governing the indications for emergency angiography following STEMI treated with thrombolysis throughout the network. Indeed, at present there is no National Service Framework guideline governing the treatment of failure to reperfuse. The present study suggests that implementation of such guidance would dramatically increase the number of urgent catheterisations and revascularisations at the tertiary cardiac centre.

Revascularisation and MACE
Subgroup analysis of patients presenting to centre E demonstrated that following transfer for angiography the majority of patients required revascularisation, most performed percutaneously. Event rates at follow up were significantly lower in those transferred for inpatient angiography compared to those treated conservatively. The significant differences in death and stroke are likely to have been a consequence of appropriate selection rather than the treatment strategy per se. Some patients will have been moribund at presentation or unsuitable for invasive management due to significant
comorbidity, and patients developing a disabling stroke following thrombolysis would not have been transferred. 13 of 16 deaths among those not transferred for angiography occurred in hospital, 6 within the first 24 hours of admission. Furthermore, there was no mortality difference between strategies among patients surviving beyond hospital discharge. In contrast, the trend towards a significant reduction in both non fatal MI and emergency revascularisation does suggest a benefit for performing invasive investigation during the index admission. These findings are in keeping with the reduction in unplanned revascularisations observed in the GRACIA study among patients randomised to a strategy of systematic angiography within 24 hours of thrombolysis when compared with an ischaemia driven approach (203). In the Merlin study, although rescue angioplasty did not improve mortality, there was a significant reduction in MACE, driven by the reduction in unplanned revascularisations following discharge (116).

Limitations
This study does have a number of important limitations. The comparison of referral rates for angiography between participating centres assumes that the populations compared have similar risk characteristics. However, this was not investigated. In fact the degree of ethnic diversity and deprivation may have been higher in two of the inner city populations examined (E and A), with a higher proportion of South Asian patients relative to the others. This population specifically has a higher incidence of coronary disease, may be treated less effectively in the acute setting of STEMI due to atypical presentation (204), and may require a higher rate of subsequent invasive investigation (205). Nevertheless, cohorts with similar population characteristics (C and D) still had significantly different rates of transfer for angiography.

It is proposed that the prolongation of hospital stay at the non interventional centres was the result of delay in access to tertiary cardiology. However this may have occurred as a result of delayed referral at the district hospital. It is also
possible that the need for transfer itself selected out a high risk group requiring longer hospitalisation, although hospital stay was not prolonged at centre E, and this would not explain differences in prolongation of stay between centres.

Subgroup analysis of cohort E was used to assess revascularisation practice and clinical outcomes following STEMI, but for the reasons stated above may not have been representative of the entire North East Sector. Importantly, the combination of a historical cohort of patients with a more contemporary cohort presenting exclusively outside working hours may also have altered the risk profile of the population studied, and the approach to treatment. Although the rate of transfer for angiography was similar between these cohorts (55% 2001/2 vs. 51% 2003/4, p=0.43), the rate of transfer within 24 hours was significantly lower in the out of hours population (34% 2001-2 vs. referral 14% (p=0.019), suggesting a possible bias against urgent transfer out of hours. This warrants further investigation, with comparison of urgent transfer activity during working and non-working hours at all centres within the network.

Implications to Service delivery in North East London
At present NSF targets remain focused on the delivery of thrombolytic therapy. However, concentration on immediate infarct management may take the emphasis away from subsequent hospital care and clinical outcomes. It is clear from this study that effective delivery of thrombolysis does not ensure effective patient management. The thrombolytic strategy necessitates prompt access to angiography and revascularisation for the majority of patients. In order to improve STEMI management while continuing to use thrombolysis, it is necessary to improve equity of access to early invasive investigation across the North East London sector. In addition, evidence based practice dictates that the number of patients transferred should increase, with provision of urgent access for up to 40% of patients receiving thrombolysis that fail to reperfuse, and those ineligible for therapy. This will itself demand the availability of 24 hour angioplasty facilities, with the necessary infrastructure to allow rapid transfer
between centres. This questions the concept that adopting primary angioplasty as the preferred reperfusion strategy for STEMI would require a substantial increase in revascularisation activity beyond that already required.

3.6 CONCLUSIONS

Despite effective delivery of thrombolysis, the majority of patients presenting within North East London require coronary angiography. Of those undergoing revascularisation, the vast majority is performed percutaneously. Half of all patients admitted are transferred to the cardiac centre during the index admission, leading to prolonged hospitalisation at the non-interventional centre. There is inequity of both referral and access to tertiary cardiac services between centres. Furthermore, the proportion of STEMI patients transferred, and in particular the rate of emergency transfer is substantially lower than trial data would predict. Those that are not referred for inpatient angiography are more frequently readmitted with recurrent events, necessitating further emergency catheterisation and revascularisation procedures. The existing burden of revascularisation following presentation with STEMI necessitates reassessment of the delivery of reperfusion therapy in North East London, including consideration of primary angioplasty.
CHAPTER 4 Delivering Primary Angioplasty in North East London: Development and Instigation of a Pilot Programme
4.1 ABSTRACT

Randomised controlled trial data support the use of primary angioplasty as the preferred reperfusion strategy for ST segment Elevation Myocardial Infarction (STEMI). However, the majority of STEMI patients do not present to a cardiac centre with interventional capabilities. Models of immediate transfer from non cardiac centres have been suggested, but have not been investigated in the United Kingdom. This chapter describes the development of a pilot primary angioplasty programme in North East London, with the objective of investigating the feasibility of delivering optimal evidence based therapy to the majority of patients presenting with STEMI within a hospital network. The rationale for the service model chosen is described, with key innovations highlighted. The mechanisms of service instigation and expansion are described, with emphasis on the importance of collaboration with ambulance services and Accident and Emergency partners at an early stage. Finally the fundamental outcome measures for service evaluation and future directions are described.
4.2 INTRODUCTION

Randomised controlled trial data support the use of primary angioplasty as the preferred reperfusion strategy for ST segment Elevation Myocardial Infarction (STEMI) (127). Although the majority of STEMI patients do not present to a cardiac centre with interventional capabilities, recent studies have established that transfer of STEMI patients from district hospitals to a regional cardiac centre with interventional facilities may be more effective than immediate on-site thrombolytic therapy (132;133). Application of this model of infarct care has not been investigated in the United Kingdom. At present National Service Framework (NSF) targets remain directed towards the administration of thrombolytic therapy, and successive Myocardial Infarction National Audit Project (MINAP) reports have demonstrated highly effective delivery of this therapy across England and Wales (100;101). However, it has been demonstrated in Chapter 3 that there is also a significant requirement for transfer for invasive investigation and revascularisation following the thrombolytic strategy in North East London, which is in keeping with trial data (112;116;203). At present revascularisation is not recognised as an integral part of the thrombolytic strategy for STEMI in NSF guidelines. Designing a primary angioplasty service may therefore be challenging in an atmosphere where national targets are currently being achieved, and as yet there is no additional government funding. This chapter describes the development, instigation and expansion of a pilot primary angioplasty programme serving North East London. The background, logistics, and service model are discussed, in addition to the mechanisms and chronology of service expansion. The outcome measures necessary for service evaluation and future directions for the service are considered.
4.3 BACKGROUND

4.3.1 Objectives
The aim of developing a pilot primary angioplasty service in North East London was to investigate the feasibility of delivering optimal evidence based therapy to the majority of patients presenting with STEMI within a hospital network. A key objective was to provide equity of access to emergency specialist care for all patients irrespective of postcode or hospital of first presentation.

4.3.2 Structure of Existing Invasive Cardiac Services in North East London
The North East London Cardiac Network includes six hospitals with emergency departments admitting unselected patients with acute coronary syndromes, and without on site coronary intervention facilities. These centres are served by two dedicated tertiary cardiac centres without accident and emergency departments (A&E), performing elective and emergency percutaneous and surgical revascularisation, both based within the same NHS Trust in central London. Six Primary Care Trusts (PCTs) fund services provided by five NHS Trusts within the network for an estimated population of 1.8 million inhabitants (Figure 4.1).

In addition to providing elective and emergency cardiac services to the hospitals within the North East London Network, the cardiac centres also provide services to an additional five hospitals in Essex, increasing their referring catchment population to 3.8 million.
Figure 4.1 Map of North East London Cardiac Network demonstrating the expansion of the pilot primary angioplasty service. District Hospitals and their respective PCTs are shown.

FIGURE 4.1 Key

A  Newham University Hospital  
B  Whipps Cross University Hospital  
C  King George Hospital, Ilford  
D  Oldchurch Hospital  
E  The Royal London Hospital  
F  Homerton University Hospital
Figure 4.1 Key Continued

Network heart Attack centre

Regional Cardiac Centre not functioning as heart attack centre

Referring District General Hospital

AREA 1: 'Local' Catchment
Apr 2003 – Aug 2003
Popn 0.25m

AREA 2: 'East Central' catchment
Aug 2003- Dec 2004
Popn 0.75m

AREA 3: North East London catchment
Jan 2005- present
Total Popn 1.8m

AREA 1: Tower Hamlets PCT
AREA 2: Newham PCT
City and Hackney PCT
AREA 3: Barking, Dagenham, and Redbridge PCT
Havering PCT
Waltham Forest PCT
4.3.3 STEMI presentations within North East London Network per annum

Table 4.1 demonstrates the number of ‘Definite’ Myocardial Infarction patients presenting to each hospital within the network for the year 1st April 2003 to 31st March 2004, derived from pooled MINAP data returns from each centre. The number of patients identified as a ‘definite’ myocardial infarction on arrival is always less than or equal to the total with a final diagnosis of ‘myocardial infarction (ST Elevation)’. Although STEMI patients with a classical history and ECG changes represent the majority, not all cases are clear at presentation. This therefore provides an estimated range of expected presentations per year (535 – 694), with a mean of 615, equating to 342 STEMI presentations per million population.

The same dataset demonstrates that STEMI represented 29% of all patients discharged with a diagnosis of an acute coronary syndrome during that period (including all patients coded as STEMI, Non STEMI, acute coronary syndrome troponin positive or negative, and unstable angina) (Table 4.2). This proportion is consistent with that predicted by international registry data (43).
Table 4.1 Patients Presenting to North East London Centres with ST Elevation Myocardial Infarction April 2003-4

Data from a North East London Strategic Health Authority report 2004 (206).

<table>
<thead>
<tr>
<th>Hospital</th>
<th>No. of Patients with Admission Diagnosis of 'Definite' Myocardial Infarction</th>
<th>No. of Patients with Discharge Diagnosis of 'Myocardial Infarction (ST Elevation)'</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>69</td>
<td>98</td>
</tr>
<tr>
<td>B</td>
<td>90</td>
<td>129</td>
</tr>
<tr>
<td>C</td>
<td>118</td>
<td>118</td>
</tr>
<tr>
<td>D</td>
<td>154</td>
<td>201</td>
</tr>
<tr>
<td>E</td>
<td>72</td>
<td>94</td>
</tr>
<tr>
<td>F</td>
<td>32</td>
<td>54</td>
</tr>
<tr>
<td>Total</td>
<td>535</td>
<td>694</td>
</tr>
</tbody>
</table>
Table 4.2 Percentage of ACS patients with discharge diagnosis of 'Myocardial Infarction (ST Elevation)' April 2003-4.
Data from a North East London Strategic Health Authority report 2004 (206).

<table>
<thead>
<tr>
<th>Hospital</th>
<th>All ACS</th>
<th>STEMI</th>
<th>% STEMI</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>392</td>
<td>98</td>
<td>25%</td>
</tr>
<tr>
<td>B</td>
<td>321</td>
<td>129</td>
<td>40%</td>
</tr>
<tr>
<td>C</td>
<td>466</td>
<td>118</td>
<td>25%</td>
</tr>
<tr>
<td>D</td>
<td>582</td>
<td>201</td>
<td>35%</td>
</tr>
<tr>
<td>E</td>
<td>390</td>
<td>94</td>
<td>24%</td>
</tr>
<tr>
<td>F</td>
<td>222</td>
<td>54</td>
<td>24%</td>
</tr>
<tr>
<td>Total</td>
<td>2373</td>
<td>694</td>
<td>29%</td>
</tr>
</tbody>
</table>

4.4 SERVICE MODEL DEVELOPMENT
4.4.1 Tailoring the Service Model to the target population
Published trial data support a number of models for delivering primary angioplasty, either based on transfer of patients from a non-interventional centre to a heart attack centre (HAC) (132; 133), or in a district catheter lab without on-site surgical cover (128) [see 1.6.1 Primary Angioplasty — Models of delivery]. It was clear from the outset that the latter model would not be appropriate to the North East London population. This would require substantial investment in new cardiac catheter facilities by individual Trusts, with associated staffing and training. Importantly, each separate centre would perform too few primary angioplasty procedures per year (Table 4.1), a predictor of adverse outcomes (130).

While the HAC model was ostensibly more applicable, utilising existing resources at the regional cardiac centres, this strategy also has limitations that
are relevant to service design. It has been proposed that the mortality benefit of primary angioplasty over thrombolysis may be lost if the delay to the invasive strategy (defined as the time difference between the administration of on site thrombolysis and that of primary angioplasty, or ‘door to balloon minus door to needle time (DTB – DTN)) exceeds 60 minutes (135) [see 1.6.2 Influence of Time to Reperfusion]. In the DANAMI-2 study (132), the door (of the hospital of first presentation) to balloon times for patients transferred from distant centres were comparable to and in some cases shorter than those presenting directly to a cardiac centre. Notably patients in that study initially presenting to a cardiac centre were first admitted to its A&E, whereas those transferred from distant centres were admitted directly to the cardiac catheter laboratory. Thus while these data suggest that rapid transfer is achievable, it is also evident that presentation to the A&E may itself delay access to reperfusion. Therefore our own perspective was that the key to providing the earliest possible reperfusion would be to combine pre-hospital diagnosis with delivery of patients directly to the cardiac catheter lab bypassing the A&E completely wherever possible.

4.4.2 Pre hospital Diagnosis by London Ambulance Service Crews
Prior to the consideration of a pilot primary angioplasty service, London Ambulance Service (LAS) crews in North East London had already undertaken considerable training in ECG recognition, demonstrating reliable diagnosis of STEMI using on-board 12-lead ECG equipment (207). The NHS plan and the NSF have emphasised the critical role of ambulance services in the management of acute MI with a commitment to the development of pre hospital thrombolysis through paramedic training (3). However, the density of the metropolitan population served by LAS in inner city areas of East London was such that the mean transit time from the community to the A&E was 6.4 minutes (208), suggesting that pre hospital administration of thrombolysis may not significantly improve (and could potentially delay) access to reperfusion therapy. There was however an opportunity to utilise both the diagnostic skills and rapid transit times of LAS in delivering patients diagnosed in the community directly to
the cardiac catheter laboratory of the regional cardiac centre rather than A&E, with a view to immediate angiography. The 'direct access' model was consequently developed in collaboration with LAS, cultivating a close working relationship from the outset.

4.4.3 Referral Mechanism
A key element of the protocol developed was that autonomy would be given to referring LAS crews. In order to facilitate rapid access to reperfusion, the decision was taken to accept patients without consultation with medical staff at the receiving centre or ECG transmission. Inclusion and exclusion criteria are shown in table 4.3. Notable exclusions were cardiac arrest and left bundle branch block (LBBB) on the ECG. Only patients with established cardiac arrest of uncertain aetiology at the time of arrival of an ambulance crew to the scene were excluded. Patients going into cardiac arrest following a diagnosis of STEMI on route could be taken directly to the HAC. LBBB was excluded based on previous local audit data demonstrating that less than half all patients receiving thrombolysis for LBBB locally had a discharge diagnosis of STEMI (data not shown). Patients with cardiogenic shock were excluded from immediate transfer without referral, but could be accepted following consultation with the on call physician at receiving centre.

A dedicated emergency telephone was installed in the cardiac catheter lab, receiving calls only from the LAS control room, alerting staff to the expected time of arrival. The receiving centre made a commitment to accept and treat all patients received. In doing so it was understood that there would be occasions where patients with non cardiac pathology might be received. The facility to transfer patients from the cardiac centre to the nearest A&E was therefore agreed for cases where emergency non cardiac care may be necessary.
Table 4.3 Inclusion and exclusion criteria for immediate transfer of STEMI patients from the community of A&E to a regional heart attack centre.

<table>
<thead>
<tr>
<th>INCLUSION CRITERIA</th>
<th>EXCLUSION CRITERIA</th>
</tr>
</thead>
<tbody>
<tr>
<td>· Symptom onset &lt; 12 hours</td>
<td>· Cardiogenic Shock*</td>
</tr>
<tr>
<td>· ST segment Elevation MI on ECG</td>
<td>· Intubated / ventilated</td>
</tr>
<tr>
<td>· Orientated, conscious</td>
<td>· Established Cardiac Arrest</td>
</tr>
<tr>
<td>· No age limit</td>
<td>· Confused / reduced conscious level</td>
</tr>
<tr>
<td></td>
<td>· Previous Stroke with dense hemiplegia</td>
</tr>
<tr>
<td></td>
<td>· Left Bundle Branch Block</td>
</tr>
</tbody>
</table>

* Patients with cardiogenic shock were included following physician consultation
4.4.4 Choice of Site
In collaboration with the London Ambulance Service it was decided that there should be one receiving cardiac centre, to avoid the need for individual crews to consult a rota prior to deciding which centre was open for primary angioplasty on any given day or week. The centre chosen was that which was geographically more accessible to crews from the catchment population (Figure 4.1).

4.4.5 Estimating Workload
The key initial issue facing the cardiac centre was the volume and potential impact of the incremental interventional activity on existing resources. Beyond addressing the quantity of additional procedures required, there were concerns that a radical increase in preferential acute revascularisation for STEMI patients may be performed at the expense of elective procedures (for which waiting times were already under scrutiny, and themselves NSF targets (3)), and patients with Non ST segment elevation acute coronary syndromes (NSTE-ACS), who were waiting up to two weeks for inpatient transfer for angiography and revascularisation. Moreover, the increased activity within North East London could disadvantage patients requiring elective and emergency interventions from Essex centres, which were not included in the primary angioplasty proposal.

These concerns were partially addressed by the observation that 50% of patients presenting with STEMI within North East London were already being transferred for coronary angiography during the index admission, with almost all subsequent revascularisation being performed percutaneously [Chapter 3]. Moreover, this was occurring at the cost of prolonged hospital stay, and frequent readmissions with recurrent events leading to further inpatient revascularisations. Finally the existing rate of inter hospital transfer following STEMI was itself falling short of evidence based standards, such that an increment in coronary intervention for this cohort of patients would become inevitable.
That the cardiac centre was already delivering an invasive strategy to the majority of STEMI patients led to the understanding that a primary angioplasty programme would not represent a completely new interventional workload, but that invasive management would be moved forward in the treatment pathway. It also led to the hypothesis that the impact of undertaking additional immediate angiography at the time of acute infarction for all STEMI patients may be offset by bed day savings, and a reduction in readmissions, recurrent events and emergency revascularisations. Furthermore, removal of the burden of inter hospital transfers resulting from the STEMI cohort may be expected to reduce rather than exacerbate transfer delays for patients with NSTE-ACS.

4.5 MECHANISM OF INSTIGATION

4.5.1 Stepwise approach

The move from separate hospitals independently administering thrombolysis to treating all STEMI patients with a network wide primary angioplasty service required a stepwise approach. It was evident that an immediate 24-hour protocol would necessitate considerable initial investment and radical changes in working practice, in advance of demonstrating safety and efficacy locally. An independent report by the North East London Strategic Health Authority (206) showed that 48% of all STEMI admissions within the North East sector (April 2001-September 2004) presented within working hours (0800 and 1700) (Figure 4.2). This was consistent with data from the Zwolle group, which demonstrated not only that the majority of STEMI presentations occurred during working hours, but also that the outcome following primary angioplasty was significantly better when performed within that period (209). It was therefore accepted that the protocol would initially be provided as a daytime weekday service only, with a view to providing proof of concept. In addition the service would initially be offered to LAS crews within the local population only, in order for those crews with the most extensive ECG training, a greater working knowledge of the cardiac centre, and short transit times to gain experience with the protocol and give feedback during the early pilot phase. However it was imperative that the
protocol lend itself to future application to a wider population on a 24-hour seven-day basis.

Audit data (October 2001-2002) from the initial catchment population (250,000 inhabitants, 105 STEMI per annum) prior to commencement of the pilot demonstrated that 82.5% of STEMI patients arrived at hospital via LAS, predicting that 2 – 3 patients per month would be delivered to the cardiac centre during the hours of operation of the pilot service (Appendix Ia)

Figure 4.2 Timing of presentation of patients admitted with STEMI within North East London 2001-2005
Data from a North East London Strategic Health Authority report 2004 (206).
4.5.2 Protocol Following Arrival at the Cardiac Centre

The protocol was designed so that the incoming LAS crew would be greeted at the entrance to the hospital by a designated team consisting of a specialist registrar, nurse, technician and senior house officer and the patient taken directly into the catheter lab resuscitation area. The aim was to assess, examine, and consent the patient rapidly, aiming for the patient to be on the catheter lab table within 15 minutes. Within this period aspirin (if not already administered), clopidogrel and upstream intravenous abciximab would be administered prior to entering the lab. Following coronary angiography, culprit vessel angioplasty with stenting wherever possible would be performed, with further revascularisation of non culprit vessels at the operator's discretion. Following the procedure patients would be monitored on the coronary care unit for a period of 24 hours. Evidence supports discharge of uncomplicated patients as early as 3 days following admission (201; 210). There are further data suggesting that the event rate for patients who are free from arrhythmic and other complications within the first 48 hours remains relatively constant out to 30 days, such that additional hospitalisation may be unnecessary (211). A decision was therefore taken to investigate the safety of feasibility of very early discharge at 48 hours for uncomplicated patients (table 4.4) during the pilot period. These patients would return to a specifically designed clinic within one week for medical review, further education and cardiac rehabilitation. All patients would be reviewed medically at 6-8 weeks following discharge.
Table 4.4 Criteria for early discharge of uncomplicated patients following primary angioplasty for STEMI

- Age <75
- Successful culprit vessel revascularisation
- Moderate or good LV function on left ventricular angiogram or echocardiogram
- Freedom from
  - recurrent ischaemia
  - clinical heart failure
  - ventricular arrhythmia
- Reviewed by cardiac rehabilitation team

4.6 EARLY EXPERIENCE - DEVELOPMENT OF PHASE 1

The programme commenced in April 2003. Figure 4.3 demonstrates the number of patients received via the primary angioplasty protocol at the cardiac centre per month from April 2003 to May 2005 inclusive. Only four patients were delivered to the cardiac centre during the first four months of operation of the protocol, less than half that predicted. This was caused by unnecessary service closures (for international conferences, internal audit and training days, or technical problems in the cardiac catheter lab). This in turn had a significant effect on LAS crews, who lost confidence in whether the service would be running on a given day, and delaying the necessary learning curve for LAS crews and catheter lab staff to become fully conversant with the protocol. Importantly, patients self-presenting to the local A&E were being excluded. To fully address these issues, a renewed commitment to avoid closures at the cardiac centre was required, in addition to the modification of the protocol to include patients presenting directly to A&E.
Figure 4.3 Graph demonstrating the number of patients presenting to the Network Heart Attack Centre Recruitment during development of the pilot service.

The arrows demonstrate commencement of the A&E transfer protocol from district hospitals A-F. At the time of writing hospital D had not commenced A&E transfer.

4.6.1 Structured Critical Ambulance Transfer (SCATS) from Accident and Emergency

A rapid transfer protocol from the local A&E was therefore developed (Appendix 1b). This allowed patients initially presenting to the A&E department and fulfilling entry criteria (table 4.3) to be transferred immediately to the cardiac centre, again without ECG transmission or physician consultation. However, prior to the instigation of this protocol patients waiting (even for emergency) inter hospital transfer were given a lower priority by ambulance services than a category A (highest priority - 8 minute response) 999 call from the community, as they were deemed to be under existing medical care. This therefore necessitated the development of a ‘Structured Critical Ambulance Transfer System’ (SCATS) by LAS. A SCATS transfer request would commit LAS to an 8 minute target response time for STEMI patients in A&E, avoiding unnecessary transfer delays.
to reperfusion, and providing equity of access with patients diagnosed by LAS crews in the community.

This protocol had a substantial benefit to recruitment (Figure 4.3), not only in transferring walk-in patients, but also allowing LAS crews a safety net whereby uncertain or complex cases would not automatically be excluded if taken to A&E. It also fostered a close working relationship with local A&E personnel.

4.6.2 Pharmacological facilitation prior to transfer from Accident and Emergency
Immediate transfer from A&E also afforded the opportunity to administer concomitant anti platelet therapy at an earlier opportunity. Pharmacological facilitation with initial thrombolytic therapy or a glycoprotein IIb/IIIa receptor antagonist (GPRA) prior to transfer may achieve earlier reperfusion prior to definitive mechanical treatment, though at the expense of increased bleeding post procedure (144;145) [see 1.6.4 Pharmacological facilitation of Primary Angioplasty]. At present the optimal combination of therapy is undetermined. The ADMIRAL study supports the use of upstream abciximab prior to primary angioplasty with stenting (83), with the greatest benefit in those patients receiving the drug earlier, either in a mobile intensive care unit or the emergency department rather than on arrival in the catheter lab. Recent meta analysis data provide further support for this concept (126). Therefore prior to transfer from the A&E department it was decided that a bolus of abciximab in addition to aspirin and clopidogrel would be administered, provided this did not delay the transfer process.

The utilisation of the A&E transfer protocol in conjunction with upstream anti-platelet therapy required additional training for A&E medical and nursing staff. This was provided in a series of didactic lectures and practical sessions provided by the N-HAC team, with repeat sessions provided at times of changeover of junior medical staff.
4.7 GEOGRAPHICAL EXPANSION OF THE SERVICE

4.7.1 East Central Sector

The combined direct access and A&E transfer protocols increased recruitment and experience prompting further expansion to the catchments of another two district hospitals in East Central London during the same hours of operation (Figure 4.3 and Figure 4.4; Appendix Ic). This necessitated further protocol refinement.

4.7.1.1 Implications to LAS

With geographical expansion, in order to continue utilising the direct access protocol, LAS crews making a pre-hospital diagnosis required clearance to bypass the nearest A&E in favour of delivery to the N-HAC catheter lab. This represented a fundamental change in working practice by LAS. A wider programme of ECG training was required to educate crews at the additional stations before the expansion could go live. This was undertaken internally by LAS. Once trained, it was important to inform staff at the N-HAC that expansion to a wider catchment may involve patients presenting directly from further distances brought initially by potentially less experienced crews, such that a reduction in diagnostic accuracy may be expected. Expansion to direct admissions from the East Central Sector was completed in October 2003 (Figure 4.3, Figure 4.4).
Figure 4.4 Chronology of development of the North East London Pilot Primary Angioplasty Programme.

<table>
<thead>
<tr>
<th>Event</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presentation of concept to Tower Hamlets PCT</td>
<td>Oct 2002</td>
</tr>
<tr>
<td>Pilot proposal sent to Network Cardiologists (Appendix Ia)</td>
<td>2003</td>
</tr>
<tr>
<td>Multidisciplinary Planning meetings at HAC</td>
<td>Apr 2003</td>
</tr>
<tr>
<td>A&amp;E transfer Proposal published (Appendix Ib)</td>
<td></td>
</tr>
<tr>
<td>East central sector expansion proposal published (appendix Ic)</td>
<td>2004</td>
</tr>
<tr>
<td>Presentations to East Central A&amp;Es (A,E,F)</td>
<td>Oct 2003</td>
</tr>
<tr>
<td>Presentations to East Central PCTs</td>
<td></td>
</tr>
<tr>
<td>First report to North East London Cardiac Network Board</td>
<td>Apr 2004</td>
</tr>
<tr>
<td>First business case for 24 hour service submitted</td>
<td></td>
</tr>
<tr>
<td>First Primary Angioplasty Live Case training day hosted at the N-HAC</td>
<td>Oct 2004</td>
</tr>
<tr>
<td>Second report to North East London Cardiac Network Board (Appendix Ie)</td>
<td></td>
</tr>
<tr>
<td>Proposal for expansion of service to North East London Cardiac Network (Appendix Ie)</td>
<td>2005</td>
</tr>
<tr>
<td>Presentations to Network A&amp;Es (B,C,D)</td>
<td></td>
</tr>
<tr>
<td>Final business case for 24 hour service submitted</td>
<td>Jun 2005</td>
</tr>
<tr>
<td>Invitation to participate in DoH / BCS Pilot National Infarct Angioplasty Programme (NIAP)</td>
<td></td>
</tr>
<tr>
<td>Presentation to CEOs for Network PCTs</td>
<td>Jan 2006</td>
</tr>
<tr>
<td>Funding Agreed for 24 hour Network Primary Angioplasty Service</td>
<td>April 2006</td>
</tr>
<tr>
<td>Service Development</td>
<td>Service Expansion</td>
</tr>
</tbody>
</table>

Landmark dates in service expansion are demonstrated on the right side of the figure. Landmark dates in service development are demonstrated on the left.
4.7.1.2 Implications to Network Hospitals

From September 2003 – February 2004, following the commencement of the local A&E transfer protocol, half of all patients delivered were transferred from A&E. It was therefore essential to enable the two additional A&E departments within the East Central sector to participate in the transfer protocol. This involved further network collaboration with A&E physicians, general physicians and cardiologists across three NHS Trusts (Figure 4.4). Discussions were held with all clinical stakeholders including local general physicians, and specific training was arranged for A&E medical and nursing staff.

4.7.1.3 Logistics of Expansion and Funding

A primary angioplasty working group was convened at the HAC to oversee the expansion programme, with the role of directing policy, disseminating information within the HAC and the network, and protocol development and implementation. Members included a lead consultant cardiologist, a lead specialist registrar, the clinical director for cardiac services at the HAC, the general manager and finance director for cardiac services at the HAC, the chair of the North East London Cardiac Network, and a senior representative from LAS with a special interest in cardiology.

Separate presentations on behalf of the HAC working group were made to cardiac representatives from the individual participating PCTs within the East Central Sector, and also to healthcare commissioners through the forum of the North East London Cardiac Network Board (Figure 4.4). It was made clear that the process did not require additional funding during the pilot stage, but had been designed to inform future investment in the management of STEMI patients, and revascularisation. All stakeholders were updated with the progress of the programme through the Cardiac Network Board.
This process enabled the pilot protocol to function as a network service for the first time, although still within the restrictions of a daytime service. This completed phase 1 of the pilot development process.

4.7.2 North East London Cardiac Network (Phase 2)
The protocol gained momentum with increasing recruitment from within East Central London (Figure 4.3). In October 2004 phase 2 of the pilot was proposed (Appendix Ie), whereby the service would be expanded to serve the entire North East London Network, accepting direct LAS admissions and offering the immediate transfer protocol to the three additional A&E departments (Figure 4.4). This expansion added further complexity to the service.

4.7.2.1 Implications to LAS
LAS crews traveling from the outskirts of the sector could now be asked to pass three separate A&E departments with an acute STEMI patient on board, travelling a distance of up to 22 miles, taking up to 30 minutes before gaining access to specialist reperfusion therapy. This would represent a considerable change in attitude and methodology for the participating crews. Importantly, the movement of ambulance vehicles over larger distances, and out of their locality had the potential to leave those areas short of operational cover, which could compromise response times to other emergencies. However LAS agreed to continue the learning process within the confines of daytime hours of operation. Once more an extended training program was undertaken by LAS, with the direct access protocol commencing across the Network in January 2005.
4.7.2.2 Implications to Network Hospitals

Following the publication of the initial proposal for network expansion of the pilot protocol in October 2004 (Appendix le), Accident and Emergency physicians and cardiologists working in the furthest A&E departments required substantial reassurance from the N-HAC working group and LAS that transfer times within published guidelines were achievable (136;212). These legitimate concerns were also communicated to the respective PCTs. A process of consultation between members the N-HAC team, physicians at all three additional centres, and representatives of one of the PCTs, took place commencing in December 2004, culminating in unanimous agreement from all departments in April 2005. Simultaneously, the A&E education and training process commenced at two of the three centres (Figure 4.4) while discussions were in progress, and in addition these centres applied for local clearance to administer pre transfer clopidogrel and abciximab therapy. At the time of writing, five out of six A&E departments within the sector are utilising the immediate transfer protocol, with the final centre expected to commence in January 2006. LAS continue to provide direct access for patients diagnosed pre hospital from all areas of the sector.

4.8 SERVICE EVALUATION

In tandem with the evolution of the pilot protocol, key targets were identified to allow ongoing critical appraisal and evaluation of the service. In terms of service delivery it would be necessary to demonstrate that access to immediate angiography and reperfusion with primary angioplasty could be satisfactorily achieved within the limits of accepted published guidelines, and that clinical outcomes are similar to or better than those observed in clinical trials and large published registries. Furthermore it would be necessary to establish improvements in service delivery and patient experience compared to patients treated with thrombolysis within North East London. Specifically, in the light of the data presented in Chapter 3, the service would aim improve the patient
pathway, leading to a reduction in hospital stay, recurrent admissions, and emergency revascularisations. These measures aimed to determine the ultimate direction of the service, and in particular whether it should be adopted in its current form as a permanent 24 hour network wide service.

The service design also included key innovations that may inform future practice not only within the boundaries of the North East London Network service, but may also have implications to other metropolitan populations intending to adopt a regional heart attack centre model for delivering primary angioplasty. Firstly, the direct access protocol is the first of its kind to offer ambulance crews immediate access to interventional cardiology without physician consultation or ECG transmission. Chapter 5 compares this access strategy with that of A&E transfer (with GPRA facilitation), presenting the impact of each strategy on diagnostic accuracy, time to reperfusion, quality of reperfusion, myocardial infarct size, and clinical outcome. Secondly the discharge of uncomplicated patients at 48 hours following intervention represents the earliest discharge of STEMI patients described to date. The safety and efficacy of this strategy during the pilot period is presented in Chapter 7.

The move from a pilot to a substantive service would constitute the final phase of the programme (phase 3). Construction of a business case for this service was developed from January 2004 (Appendix 1d) utilising data from the pilot phase presented in this thesis (chapters 3, 5, and 7). A finalised business case was submitted in April 2005 and approved in November 2005, with a planned implementation date of April 2006 (Figure 4.4).

4.9 MULTIDISCIPLINARY APPROACH

The key to the progression of the pilot primary angioplasty service has been collaboration. From its conception, all members of the cardiac catheter lab team were involved in developing the protocol, prior to its commencement. Since its
instigation, acute coronary syndrome training days have been attended simultaneously by catheter lab staff, ambulance crews, A&E and ward staff to promote the team approach. In addition dedicated training days have been devised to familiarise LAS crews with angioplasty procedures and the catheter lab environment. All stakeholders, including PCTs, commissioners, A&E departments and cardiac staff have been updated with progress reports and have been involved in the expansion of the service. Data have been fed back to the North East London Cardiac Network board (Figure 4.4, Appendix 1e), with each stage in the evolution of the protocol receiving scrutiny before backing. Importantly the programme has relied heavily on service innovations and adaptations made by the London Ambulance Service, who have been prepared to change practice radically to meet the needs of this population.

4.10 CONCLUSIONS

This chapter has described the process and chronology of development of a pilot primary angioplasty service serving patients presenting with ST segment elevation myocardial infarction based in North East London. A heart attack centre model was developed utilising two access strategies; immediate transfer from district hospitals to the cardiac centre, and direct access to the centre from trained ambulance crews making an independent pre-hospital diagnosis. The service involves multidisciplinary collaboration, crossing traditional geographical and organisational boundaries. This service needs to demonstrate safety and efficacy, improving both service delivery and patient experience. If this can be achieved the protocol readily lends itself to temporal expansion to a 24-hour seven-day programme.
CHAPTER 5 Service delivery, reperfusion and clinical outcomes following Direct Ambulance Access versus Accident and Emergency Transfer for Primary Angioplasty in North East London
5.1 ABSTRACT

Delays in transfer of ST Segment Elevation Myocardial Infarction (STEMI) patients from district hospital Accident and Emergency (A&E) departments may negate the benefit of primary angioplasty. Pharmacological facilitation may provide a bridge to mechanical reperfusion, though data supporting this approach are equivocal. Direct access to the cardiac catheter lab bypassing A&E has the potential to reduce reperfusion times, and may therefore be preferable. This chapter compares a direct access (DA) strategy utilising prehospital ECG diagnosis by ambulance crews, with transfer from A&E departments (AET) for primary angioplasty. Facilitation with a glycoprotein IIb/IIIa receptor antagonist is investigated.

Methods: 144 consecutive suspected STEMI patients within a network of 6 hospitals were delivered to a heart attack centre catheter lab without physician consultation or ECG transmission (66 DA, 78 AET). DA allowed bypass of the nearest A&E if necessary with patients receiving aspirin only at the time of diagnosis. AET included self presentations, and non DA ambulance patients. These patients were treated with aspirin, clopidogrel, and a glycoprotein IIb/IIIa receptor antagonist prior to transfer. 105 patients with confirmed STEMI underwent coronary angiography. 103 underwent culprit vessel angioplasty with stenting. All patients received abciximab prior to intervention.

Outcome measures

Accuracy of clinical diagnosis by ambulance crews and A&E departments was compared. In those undergoing primary angioplasty, reperfusion times were measured from symptom onset (pain to balloon - PTB), call for specialist help (call to balloon – CTB), and first hospital arrival (door to balloon - DTB). Peak creatine kinase (CK) was measured as a marker of infarct size. Epicardial and microvascular blood flow were assessed in each group (TIMI flow grade, myocardial blush grade (MBG), corrected TIMI frame count (cTFC)), and ECG ST segment resolution. MACE included death, non fatal myocardial infarction,
stroke, and emergency revascularisation at a median follow up of 16 (9-28) weeks. Incidence of bleeding was recorded.

Results
Diagnostic accuracy for STEMI was lower among patients brought directly via LAS. DA significantly improved all reperfusion times (PTB, CTB, DTB) compared to AET. Peak CK was similar in both groups. TIMI flow, MBG, and cTFC were all significantly better prior to intervention in those receiving early abciximab, though flow post procedure was similar. ST segment resolution post procedure was also similar in both groups. There were no differences in MACE between the two groups.

Conclusions
Pre hospital diagnosis with direct ambulance catheter lab access significantly reduces time to reperfusion although there is scope to improve diagnostic accuracy. Both strategies were similar with respect to infarct size and clinical outcome, which may be explained by improved epicardial and microvascular blood flow prior to intervention in the AET group. These data suggest that early facilitation with abciximab may compensate for inter hospital transfer delays when this strategy cannot be avoided. The optimal strategy may be to combine these approaches, with ambulance crews administering pre hospital abciximab, or similar therapy.
5.2 INTRODUCTION

Transfer of ST Segment Elevation Myocardial Infarction (STEMI) patients from a district hospital Accident and Emergency (A&E) department for primary angioplasty at a heart attack centre has been demonstrated safe and effective. However, it has already been discussed that transfer delays may negate the benefit of this strategy [see 1.6.2 Influence of Time to Reperfusion]. Pharmacological facilitation may improve patency of the infarct related artery prior to intervention providing a bridge to definitive mechanical reperfusion, though data supporting this approach are equivocal, and at present the optimal therapy remains uncertain. In order to avoid delays in reperfusion we designed a pilot primary angioplasty service providing direct access (DA) to the cardiac catheter lab for ambulance crews making a pre hospital diagnosis [Chapter 4], allowing vehicles to bypass the nearest A&E where necessary. Service delivery, efficacy of reperfusion and clinical outcomes were compared with a strategy of transfer from A&E departments (AET) with utilisation of pharmacological facilitation with a glycoprotein IIb/IIIa receptor antagonist (abciximab, ReoPro®, Eli Lilly and Company).

5.3 METHODS

5.3.1 Subjects

144 consecutive patients were delivered to a network heart attack centre (N-HAC) between April 2003 and May 2005, from within the North East London Cardiac Network. Patients were recruited from within the local catchment of the N-HAC (April 2003-August 2003), the East central catchment (August 2003-December 2004), and from the entire North East catchment (January 2005-May 2005) as described in the preceding chapter [see Chapter 4; Figure 4.1]. 66 (46%) were admitted directly from the community (DA) via London ambulance Service (LAS) crews, and 78 (54%) via transfer from five A&E departments participating in the pilot programme (AET). AET patients included self presentations to the local A&E, patients developing ST elevation in the A&E department, and patients arriving via LAS crews where there was uncertainty of
ECG diagnosis. Patients were accepted at the N-HAC without physician consultation or ECG transmission. Data collection was prospective and non randomised.

105 (73%) patients were diagnosed with STEMI, 42 (40%) DA, 63 (60%) AET. 103 underwent primary angioplasty. Of those not treated with primary angioplasty, one patient was referred for bypass surgery, and the other was treated medically (TIMI grade 3 flow with no residual stenosis). Demographic details of the AET and DA STEMI groups were similar, although there was a higher prevalence of previous myocardial infarction and prior percutaneous intervention (PCI) in the DA cohort (Table 5.1).

Table 5.1 Demographic details of patients with confirmed STEMI presenting to the N-HAC via ambulance transfer from local A&E departments (AET), and through direct LAS access (DA)

<table>
<thead>
<tr>
<th></th>
<th>AMBULANCE DIRECT ACCESS (DA)</th>
<th>A&amp;E TRANSFER (AET)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N= 42</td>
<td>N=63</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>58 (13)</td>
<td>58 (12)</td>
<td>NS</td>
</tr>
<tr>
<td>Sex</td>
<td>36 Male (86%)</td>
<td>44 Male (70%)</td>
<td>NS (0.06)</td>
</tr>
<tr>
<td>Smoker</td>
<td>26 (62%)</td>
<td>47 (75%)</td>
<td>NS</td>
</tr>
<tr>
<td>Hypercholesterolaemia</td>
<td>9 (21%)</td>
<td>19 (30%)</td>
<td>NS</td>
</tr>
<tr>
<td>Diabetic</td>
<td>8 (19%)</td>
<td>11 (17.5%)</td>
<td>NS</td>
</tr>
<tr>
<td>Hypertensive</td>
<td>20 (48%)</td>
<td>23 (37%)</td>
<td>NS</td>
</tr>
<tr>
<td>Prior MI</td>
<td>6 (14%)</td>
<td>2 (3.2%)</td>
<td>0.034</td>
</tr>
<tr>
<td>Prior PCI</td>
<td>4 (9.5%)</td>
<td>0</td>
<td>0.012</td>
</tr>
<tr>
<td>Prior CABG</td>
<td>1 (2%)</td>
<td>1 (1.5%)</td>
<td>NS</td>
</tr>
</tbody>
</table>
5.3.2 Interventions
Loading with oral clopidogrel (300mg) and an intravenous bolus of abciximab were administered prior to coronary intervention in all cases. Culprit vessel angioplasty with stenting was performed in all cases, with further revascularisation of non culprit vessels at the operator's discretion.

4/5 participating A&E departments administered clopidogrel 300mg and a bolus of abciximab prior to transfer (AET'). The remaining centre (hospital F; see Chapter 4; Figure 4.1) administered clopidogrel only, with abciximab administered on arrival at the N-HAC (AET'). This centre was 2.1 miles away from the N-HAC, with a journey time of 15 minutes.

5.3.3 Outcome Measures
Service Delivery
Service delivery was compared by assessment of the accuracy of clinical diagnosis among all patients delivered to the N-HAC, and by the time to reperfusion in STEMI patients undergoing primary angioplasty.

ST segment elevation on the ECG was confirmed by the receiving cardiologist in the presence of ≥ 2mm in two contiguous anterior leads, and ≥ 1mm in non-anterior leads [chapter 2]. A final diagnosis of STEMI was confirmed at discharge in the presence of ST elevation at presentation and any of the following: a culprit lesion at angiography in the anatomical territory of the ECG changes, a regional wall motion abnormality in the anatomical territory of the ECG changes, or a rise in troponin I or CK.

Reperfusion times were measured from symptom onset (pain to balloon - PTB), call for specialist help (call to balloon – CTB), and first hospital arrival (door to balloon - DTB). The door to needle time (DTN) was defined as the time from first hospital arrival until the abciximab bolus was administered.
Efficacy of Reperfusion

Efficacy of reperfusion was assessed by coronary angiography and ST segment resolution on the ECG among patients undergoing primary angioplasty. Comparison was made between 41 DA patients, 52 AET+ patients receiving abciximab facilitation, and 10 AET- patients receiving abciximab at the N-HAC following transfer.

Angiographic epicardial and microvascular blood flow were assessed in all patients using the TIMI flow grade (102), myocardial blush grade (MBG) (154), and corrected TIMI frame count (cTFC) (194). Angiographically evident thrombus was assessed using the TIMI thrombus score (213) [see Chapter 2; 2.5 Angiographic analyses].

ECG data sufficient for assessment of ST segment resolution were available for 80/105 STEMI patients (33 (79%) DA and 47 (75%) AET) at presentation, post procedure and at 18-24 hours following admission. 21/37 AET+ patients and 8/10 AET- patients had sufficient ECG data available for analysis prior to angiography both before transfer and on arrival at the N-HAC. ST segment resolution was calculated according to the method described by Schroeder et al (214) [see Chapter 2; 2.4 ECG analyses].

Clinical outcome

Peak creatine kinase (CK) was measured as a marker of infarct size. Major adverse cardiac events (MACE) including death, non fatal myocardial infarction, stroke, and emergency revascularisation were recorded after a median follow up period of 16 (9-28) weeks. Major bleeding was defined as any of the following: a fall in haemoglobin (Hb) > 4g/dl; overt bleeding with a fall in Hb > 3g/dl; the requirement for a blood transfusion of 2 or more units; retroperitoneal or intracranial haemorrhage. Minor bleeding was defined as overt bleeding not meeting the criteria for a major bleed.
5.3.4 Statistics
Comparison of continuous variables between cohorts was assessed using non-parametric tests where the distribution of data was skewed (Mann Whitney U and Kruskal-Wallis tests). Normally distributed variables were compared independent samples T-tests. Chi square and Fisher's exact test were used to compare categorical variables.

5.4 RESULTS

5.4.1 Accuracy of Diagnosis
105/144 patients presenting via the protocol had a final diagnosis of confirmed STEMI [see 2.1 Subjects]. Table 5.2 demonstrates ECG findings, invasive management, and the final clinical diagnosis made at the N-HAC for DA and AET groups. Diagnostic accuracy was significantly higher among patients transferred from ME compared with those admitted via LAS directly.

A total of 39 subjects did not have confirmed STEMI (24 DA, 15 AET) (table 5.3). Of these 46% did have ST segment elevation on the presenting ECG which was ultimately of another aetiology. 62% of patients without a final diagnosis of STEMI underwent an inpatient cardiac catheterisation procedure, and 18% underwent a PCI procedure. 15% (6) had a final diagnosis of myocarditis or pericarditis. The discrepancy in diagnostic accuracy was related to an excess of patients with both Non-ST segment elevation acute coronary syndromes (NSTE-ACS) and non-ischaemic cardiac presentations in the DA group (table 5.3). The majority of NSTE-ACS patients were troponin positive, and would ultimately have required invasive coronary investigation at the cardiac centre. Those with non-ischaemic cardiac pathology had either acutely decompensated left ventricular function in the setting of chronic heart failure, or a pre-existing cardiomyopathy with ST elevation but no cardiac pain. No subject required transfer for acute non-cardiac intervention.
Table 5.2 ECG and Clinical diagnosis following arrival at the N-HAC

<table>
<thead>
<tr>
<th></th>
<th>Direct Access DA n=66</th>
<th>A&amp;E Transfer AET n=78</th>
<th>P value ($\chi^2$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECG ST segment elevation</td>
<td>51 (77%)</td>
<td>72 (98%)</td>
<td>0.011</td>
</tr>
<tr>
<td>Final diagnosis STEMI</td>
<td>42 (64%)</td>
<td>63 (81%)</td>
<td>0.021</td>
</tr>
<tr>
<td>Cardiac Catheter</td>
<td>54 (82%)</td>
<td>64 (82%)</td>
<td>NS</td>
</tr>
<tr>
<td>Percutaneous intervention (all)</td>
<td>45 (68%)</td>
<td>63 (81%)</td>
<td>0.021</td>
</tr>
<tr>
<td>Primary Angioplasty for STEMI</td>
<td>41 (62%)</td>
<td>62 (79%)</td>
<td>0.034</td>
</tr>
</tbody>
</table>
### Table 5.3 Final diagnosis among patients delivered to the N-HAC that did not have STEMI

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Direct Access (n=24)</th>
<th>A&amp;E Transfer (n=15)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NSSTE-ACS troponin positive</strong></td>
<td>7 (29%)</td>
<td>2 (13%)</td>
</tr>
<tr>
<td><strong>NSSTE-ACS troponin negative</strong></td>
<td>2 (8%)</td>
<td>3 (20%)</td>
</tr>
<tr>
<td><strong>Pericarditis / Myocarditis</strong></td>
<td>1 (4%)</td>
<td>5 (33%)</td>
</tr>
<tr>
<td><strong>Other Cardiac</strong></td>
<td>8 (33%)</td>
<td>1 (7%)</td>
</tr>
<tr>
<td>- LVF</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>- DCM</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>- HCM</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>- Arrhythmia</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>- ACHD</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td><strong>Other Non Cardiac</strong></td>
<td>6 (25%)</td>
<td>4 (27%)</td>
</tr>
<tr>
<td>- Non cardiac chest pain</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>- Collapse cause unknown</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>- Subdural haematoma</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>- Asymptomatic</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

**INVESTIGATION and MANAGEMENT**

<table>
<thead>
<tr>
<th>Investigation</th>
<th>Direct Access (n=24)</th>
<th>A&amp;E Transfer (n=15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECG ST segment elevation</td>
<td>9 (37.5%)</td>
<td>9 (60%)</td>
</tr>
<tr>
<td>Cardiac Catheter</td>
<td>13 (54%)</td>
<td>11 (73%)</td>
</tr>
<tr>
<td>Percutaneous Intervention</td>
<td>4 (17%)</td>
<td>3 (20%)</td>
</tr>
</tbody>
</table>

**Key**
- LVF: Acute Left ventricular failure
- DCM: Dilated Cardiomyopathy
- HCM: Hypertrophic Cardiomyopathy
- ACHD: Adult Congenital Heart Disease
5.4.2 Time to reperfusion

Among those patients with confirmed STEMI, the duration of symptoms at the time of first presentation was similar in both groups (table 5.4). The DA strategy reduced all reperfusion times (PTB, CTB and DTB), with a significantly higher proportion achieving both the 2 hour target DTB time recommended by the European task force for primary percutaneous intervention and the 90 minute target recommended by ACC/AHA Guidelines for the Management of Patients With ST-Elevation Myocardial Infarction [1.6.2 Influence of time to reperfusion] (table 5.4) (136;212). Median (IQR) transfer time (time from arrival at the first centre to arrival at the N-HAC) was 69 (51-88) minutes.
Table 5.4 Comparison of reperfusion times according to access strategy

<table>
<thead>
<tr>
<th>All Patients</th>
<th>DIRECT ACCESS (DA) N=42</th>
<th>A&amp;E TRANSFER (AET) N=63</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptom duration at presentation (min)</td>
<td>112 [62-236]</td>
<td>105 [53-175</td>
<td>NS</td>
</tr>
<tr>
<td>Symptom duration at presentation &lt;180</td>
<td>63%</td>
<td>79%</td>
<td>NS</td>
</tr>
<tr>
<td>Transfer time (min)</td>
<td>NA</td>
<td>69 (51-88)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Patients Undergoing Primary Angioplasty</th>
<th>DIRECT ACCESS (DA) n=41</th>
<th>A&amp;E TRANSFER (AET) n=62</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain to balloon PTB (min)</td>
<td>172 [102-256]</td>
<td>216 [170-349]</td>
<td>0.01</td>
</tr>
<tr>
<td>Call to balloon CTB (min)</td>
<td>83 [70-105]</td>
<td>135 [120-163]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Door to balloon DTB (min)</td>
<td>40 [32-48]</td>
<td>106 [93-133]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>door to balloon &lt;120</td>
<td>99%</td>
<td>65%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Door to balloon &lt;90</td>
<td>94%</td>
<td>22%</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
5.4.3 Abciximab facilitation

Symptom duration at presentation was similar between DA patients, and both AET+ and AET- groups (Table 5.5). Despite the prolongation of pain to balloon time in AET+ cohort relative to DA (58 minutes), the peak CK was similar in both these groups. The door to needle time (time from arrival at the first centre to administration of abciximab) was significantly longer in the AET+ group than at the N-HAC (DA). Nevertheless there was still a significant difference (53 minutes) in the time from abciximab administration to balloon inflation (needle to balloon time - NTB) between AET+ and DA patients. It is also noteworthy that the median transfer time was 23 minutes shorter among the 10 AET- patients. This may have been a result of the proximity of this centre to the N-HAC relative to the other referring centres [see Chapter 4; Figure 4.1], but could also imply that delays were incurred at other centres in administering abciximab. Peak CK was also higher in this cohort, although this did not reach significance in this small subgroup.

Table 5.5 Impact of pharmacological facilitation with abciximab - timing of therapy and Enzyme (CK) rise

<table>
<thead>
<tr>
<th></th>
<th>Direct Access (DA) N=41</th>
<th>A&amp;E Transfer Abciximab pre transfer (AET+) N=52</th>
<th>A&amp;E Transfer Abciximab post transfer (AET-) N=10</th>
<th>P (DA vs. AET+)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptoms</td>
<td>112 (62-236)</td>
<td>100 (58-174)</td>
<td>135 (33-356)</td>
<td>NS</td>
</tr>
<tr>
<td>Door to needle</td>
<td>18 (10-35)</td>
<td>37 (19-63)</td>
<td>71 (41-83)</td>
<td>0.002</td>
</tr>
<tr>
<td>Pain to needle</td>
<td>153 (74-251)</td>
<td>142 (90-251)</td>
<td>191 (117-443)</td>
<td>NS</td>
</tr>
<tr>
<td>Transfer time</td>
<td>-</td>
<td>74 (57-102)</td>
<td>51 (43-65)</td>
<td>0.02*</td>
</tr>
<tr>
<td>Needle to balloon</td>
<td>21 (1-33)</td>
<td>74 (65-86)</td>
<td>21 (11-38)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pain to balloon</td>
<td>172 (102-256)</td>
<td>230 (172-337)</td>
<td>198 (120-483)</td>
<td>0.009</td>
</tr>
<tr>
<td>Peak CK</td>
<td>721 (370-1451)</td>
<td>800 (423-1887)</td>
<td>1239 (743-1735)</td>
<td>NS</td>
</tr>
</tbody>
</table>

* P value = AET+ vs. AET-
5.4.4 Angiographic reperfusion and ST segment resolution

TIMI flow grade, myocardial blush grade (MBG), and corrected TIMI frame count (cTFC) prior to intervention were superior among AET+ patients relative to DA (Table 5.6). There was no difference in angiographic thrombus burden between groups. Among the AET+ patients the rates of TIMI 3 flow, and TIMI grades 2 or 3 flow prior to intervention were almost identical to those of the DA group, although when compared with the AET+ the difference was not significant (owing to the small AET- sample size). This observation suggests that improved patency prior to intervention in AET+ patients was likely to be the result of abciximab therapy rather than spontaneous recanalisation occurring during the period of transfer. There was no difference between cohorts in epicardial or microvascular flow following intervention.

There were no differences between patient groups in ST resolution post procedure, or at 18-24 hours, in keeping with the angiographic data. Although not reaching statistical significance, there was a trend (p=0.08) towards improved ST resolution pre procedure in those AET patients pre treated with abciximab (AET+ vs. AET-), which would be consistent with the angiographic findings (Table 5.7 and Table 5.8).
Table 5.6 Abciximab facilitation and angiographic reperfusion pre and post procedure

<table>
<thead>
<tr>
<th></th>
<th>Direct Access (DA) N=41</th>
<th>A&amp;E Transfer + abciximab pre transfer (AET+) N=52</th>
<th>A&amp;E Transfer + abciximab post transfer (AET-) N=10</th>
<th>P (DA vs. AET+)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PRE PCI</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TIMI 3</td>
<td>8 (19%)</td>
<td>22 (42%)</td>
<td>2 (20%)</td>
<td>$\text{Chi}^2 0.019$</td>
</tr>
<tr>
<td>TIMI 2/3</td>
<td>16 (38%)</td>
<td>31 (58%)</td>
<td>4 (40%)</td>
<td>$\text{Chi}^2 0.048$</td>
</tr>
<tr>
<td>MBG 2/3</td>
<td>8 (20%)</td>
<td>24 (46%)</td>
<td>3 (30%)</td>
<td>$\text{Chi}^2 0.007$</td>
</tr>
<tr>
<td>Mean TIMI Thrombus burden</td>
<td>3.8 (1.7)</td>
<td>3.4 (1.7)</td>
<td>3.1 (2.1)</td>
<td>NS</td>
</tr>
<tr>
<td>Median cTFC</td>
<td>100 (43-100)</td>
<td>45 (18-100)</td>
<td>79 (32-100)</td>
<td>$0.03 \text{MW-U}$</td>
</tr>
<tr>
<td><strong>POST PCI</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TIMI 3</td>
<td>36 (86%)</td>
<td>51 (96%)</td>
<td>9 (90%)</td>
<td>$\text{Chi}^2 \text{NS (0.07)}$</td>
</tr>
<tr>
<td>TIMI 2/3</td>
<td>39 (93%)</td>
<td>53 (100%)</td>
<td>10 (100%)</td>
<td>$\text{Chi}^2 0.048$</td>
</tr>
<tr>
<td>MBG 2/3</td>
<td>25 (64%)</td>
<td>35 (70%)</td>
<td>4 (40%)</td>
<td>NS</td>
</tr>
<tr>
<td>Mean TIMI Thrombus burden</td>
<td>0.1 (0.2)</td>
<td>0.1 (0.7)</td>
<td>0.1 (0.3)</td>
<td>NS (0.057)</td>
</tr>
<tr>
<td>Median cTFC</td>
<td>14 (12-24)</td>
<td>15 (10-21)</td>
<td>14 (10-20)</td>
<td>NS</td>
</tr>
</tbody>
</table>
Table 5.7 Abciximab facilitation and ST segment resolution post procedure

<table>
<thead>
<tr>
<th></th>
<th>Direct Access (DA) N=33/41</th>
<th>A&amp;E Transfer Abciximab pre transfer (AET+) N=35/52</th>
<th>A&amp;E Transfer Abciximab post transfer (AET-) n=10/10</th>
<th>P (DA vs. AET+)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>60-90 min</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>STR median (IQR)</td>
<td>68% (41-84)</td>
<td>69% (49-83)</td>
<td>70% (33-77)</td>
<td>NS</td>
</tr>
<tr>
<td>STR &gt; 50%</td>
<td>22 (67%)</td>
<td>25 (71%)</td>
<td></td>
<td>NS</td>
</tr>
<tr>
<td>STR &gt; 70%</td>
<td>16 (48%)</td>
<td>18 (51%)</td>
<td></td>
<td>NS</td>
</tr>
<tr>
<td><strong>18-24 hours</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>STR median (IQR)</td>
<td>79% (50-89)</td>
<td>75% (58-89)</td>
<td>75% (48-86)</td>
<td>NS</td>
</tr>
<tr>
<td>STR &gt; 50%</td>
<td>26 (79%)</td>
<td>29 (83%)</td>
<td></td>
<td>NS</td>
</tr>
<tr>
<td>STR &gt; 70%</td>
<td>22 (67%)</td>
<td>22 (63%)</td>
<td></td>
<td>NS</td>
</tr>
</tbody>
</table>

**Key**

STR: ST Segment Resolution

Table 5.8 Abciximab facilitation and ST segment resolution pre procedure: comparison of AET+ and AET- patients

<table>
<thead>
<tr>
<th></th>
<th>A&amp;E Transfer Abciximab pre transfer (AET+) n=21/35</th>
<th>A&amp;E Transfer Abciximab post transfer (AET-) n=8/10</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>STR median (IQR)</strong></td>
<td>43 (-8 to 79)</td>
<td>17 (-7 to 28)</td>
<td>NS</td>
</tr>
<tr>
<td><strong>STR &gt; 50%</strong></td>
<td>10</td>
<td>1</td>
<td>NS (0.08)</td>
</tr>
<tr>
<td><strong>STR &gt; 70%</strong></td>
<td>5</td>
<td>1</td>
<td>NS</td>
</tr>
</tbody>
</table>
5.4.5 Clinical Outcomes

Bleeding
There were two major bleeding complications (both in AET⁺ patients). One patient required a transfusion of 2 units. This patient had a background of chronic anaemia due to gastric angiodysplasia. The patient remained haemodynamically stable. A second patient developed a small haemorrhagic stroke (confirmed by CT scan) following a fall in platelet count (< 20x10⁹), characterised by transient confusion but no persistent neurology.

3 other patients developed thrombocytopenia (1 with a platelet count < 20x10⁹, 2 <50x 10⁹). 1 of these subjects developed minor bleeding (a small femoral haematoma). 4 other patients developed small femoral haematomas. There was no other minor bleeding.

Major Adverse Cardiac Events
Major adverse event rates at follow up were similar among AET and DA patients (Figure 5.1), with overall MACE for both cohorts falling within the boundaries of previously published randomised and registry data (127;215). Although there may appear to be an excess of deaths driving a higher event rate in the direct access group, the small sample size makes further interpretation of these data unsafe. There were in total only 4 deaths among these patients, 3 occurring in the direct access group.
Figure 5.1 Major adverse cardiac events (MACE) according to admission strategy

All P values non significant

Key

CVA  Cerebrovascular accident
MACE  Major Adverse Cardiac Event
5.5 DISCUSSION

5.5.1 Service Delivery

This study demonstrates effective delivery of primary angioplasty using two separate access strategies within a metropolitan population. The proportion of patients with confirmed ST segment elevation on the ECG, and a final diagnosis of STEMI were lower among patients presenting directly via LAS crews. A small study undertaken locally prior to commencement of the pilot service had established that recognition of ST segment elevation by trained paramedics was similar to that of senior house officers in A&E (207). The present study demonstrated that the reduction in diagnostic accuracy was not the result of failure to recognise ST elevation, but predominantly due to an excess of patients delivered with evidence of coronary ischaemia but no ST segment elevation. This is likely to have been the consequence of a number of factors. The distinction between ST elevation as a mechanism of diagnosing a heart attack, and ST elevation as a pre requisite for deriving a benefit from primary angioplasty may not initially have been made clear. Thus there may have been a desire among some crews to bring all patients diagnosed with possible AMI. The geographical expansion of the service [chapter 4] will have further compounded this training issue, as each sector embarked on its own learning curve with the immediate referral protocol. Also, given the number of crews operating in the North East LAS sector, and the hours of operation of the pilot service, the opportunity for individual crews to gain repeated exposure to the protocol will have thus far been limited. While it is clear that ongoing training and direct feedback in the catheter lab environment are essential, it is also reassuring that the majority of DA patients without STEMI did have a cardiac diagnosis, and would ultimately have required invasive investigation. This demonstrates that LAS crews are sufficiently skilled to diagnose acute coronary syndromes independently and without consultation, but that dissemination of the specifics of the protocol with respect to ST elevation must be improved. In tandem with this, alternative strategies including ECG telemetry could also be considered in order
to avoid unnecessary mobilisation of the STEMI team in future, particularly with expansion to a 24 hour protocol.

The advantage of the DA strategy was the significant reduction in the time to reperfusion. The majority of patients in both groups achieved reperfusion times (DTB) within the recent European task force recommendations (212). However, the majority of AET patients fell outside the 90 minute target specified in the most recent North American guidelines (136). While the latter was not specifically targeted at patients transferred from distant centres, this highlights the disparity between strategies. Notably the median time from admission to A&E to arrival at the N-HAC was over an hour, which may have been longer than expected given the relatively short distances to travel [see chapter 4; figure 4.1]. It is possible that there may have been delays waiting for ambulance transfer from the A&E departments, although the finding that door to needle time was significantly prolonged in AET compared with DA suggests that delays may have been incurred prior to requesting ambulance transfer ('SCATS') [chapter 4]. While more detailed audit of the referral and transfer process prior to arrival at the N-HAC is warranted with ongoing service development, there does appear to be scope to improve the efficiency of A&E transfer. This may have particular relevance as the symptom duration at the time of presentation was less than 3 hours in 79% of AET patients. As discussed in chapter 1 [1.6.3 Influence of Symptom Duration] this patient subgroup did not derive a mortality benefit from transfer for primary angioplasty in the PRAGUE-2 study when compared with on site thrombolysis (133). Nevertheless the median delay to primary angioplasty (DTB-DTN) in this study was 69 minutes, which is only narrowly beyond the 60 minute target in the North American guidelines (136), and well inside the 93 minutes required to derive a benefit in MACE, as described in the original analysis of transfer delay by Nallamothu et al (135).
5.5.2 Pharmacological facilitation

Despite the delay in transfer, clinical outcomes and infarct size measured by peak CK rise were similar utilising both strategies. This finding is of interest considering that as stated above, the majority of patients presented within the first 3 hours of symptom onset, the period where the outcome following reperfusion is most time dependent (216). It is tempting to speculate that the administration of abciximab to the majority of AET patients prior to transfer could have compensated for transfer delay. However, it is important to recognise that this small study was not sufficiently powered to detect differences in clinical outcome.

Previous studies have demonstrated improved outcomes among patients receiving abciximab during primary angioplasty (126), with superior microvascular perfusion post procedure compared to those treated without a GPRA. In addition the ADMIRAL study (83) demonstrated further benefit among patients receiving therapy earlier. All patients in this study received abciximab prior to intervention, and therefore the finding that reperfusion following the procedure was similar in both AET+ and DA groups may have been intuitive. However, epicardial and microvascular patency were significantly improved prior to intervention among those receiving abciximab prior to transfer (AET+) compared with DA patients. Earlier reperfusion may account for the benefit of very early abciximab therapy observed in studies such as ADMIRAL. Whether this effect of early therapy compensates for transfer delay could only be addressed with a randomised study of pre transfer abciximab versus abciximab on arrival specifically in patients transferred to the HAC from distant centres. It should be noted however that thrombolytic agents also improve arterial patency prior to intervention when used to facilitate primary angioplasty, but have not thus far demonstrated improved clinical outcomes [see chapter 1; 1.6.4 Pharmacological facilitation of Primary Angioplasty]. Indeed the recently presented ASSENT 4 study (217) demonstrated that administration of tenecteplase (TnK) prior to primary angioplasty was inferior to primary
angioplasty alone, with increased mortality in the TnK arm that was not explained by bleeding complications. Additional anti-platelet and anti-inflammatory mechanisms may therefore be relevant, and are the subject of further investigation in chapter 6 of this thesis.

The potential benefit of early administration of abciximab observed among AET patients does not exclude the possibility that DA patients might also derive additional clinical benefit with pre hospital abciximab therapy if it were available. A randomised study comparing pre hospital paramedic administration of clopidogrel and abciximab with therapy on arrival at the N-HAC specifically among DA patients could be designed to answer this question. While this strategy would necessitate further training for LAS crews, proof of concept for paramedic drug delivery has already been provided by successful programs of pre hospital thrombolysis elsewhere in the UK (218;219).

5.5.3 Limitations
The data presented here reflect outcomes of a developing rather than an established service. The non randomised nature of this study raises the possibility of selection bias. Although demographics were similar, it is possible for example that self presentation to A&E may select a lower risk cohort with less severe presentations than patients presenting directly via ambulance, such that transfer delay may have had less impact. In addition, the study was not designed to directly compare the 10 AET$^-$ patients transferred from one institution with the remaining AET$^+$ patients, and cannot provide an indication of the efficacy of abciximab facilitation per se. Finally these results cannot be generalised to patients presenting outside working hours, when potential transfer delays in real world practice may be exacerbated. However, the data can serve to inform future development of a 24 hour service.
5.6 CONCLUSIONS

Pre hospital diagnosis with direct ambulance catheter lab access (DA) significantly reduces time to reperfusion among STEMI patients undergoing primary angioplasty compared with Accident and Emergency transfer (AET). However, there is scope to improve the diagnostic specificity of ambulance crews, and the efficiency of abciximab administration and transfer from participating A&Es. Both strategies were similar with respect to infarct size and clinical outcome, which may be explained by improved epicardial and microvascular blood flow prior to intervention in the AET group. These data suggest that early facilitation with abciximab may compensate for inter hospital transfer delays when this strategy cannot be avoided. The optimal future strategy may be to combine these approaches, with ambulance crews administering pre hospital abciximab.
CHAPTER 6 Platelet Activation and its Relation to Outcome following Primary Angioplasty for ST Segment Elevation Myocardial Infarction
6.1 ABSTRACT

Platelet monocyte aggregates (PMA) and CD40 ligand (CD40L) are platelet activation markers that possess thrombotic and pro-inflammatory properties. These may influence the effectiveness of reperfusion therapy for ST segment elevation myocardial infarction (STEMI). This chapter describes the effect of the primary angioplasty process on platelet activation, and investigates the influence of platelet activation on reperfusion following primary angioplasty. The impact of early facilitation with anti-platelet therapy is also examined.

Subjects

25 STEMI patients underwent immediate cardiac catheterisation at a network heart attack centre (N-HAC). 23 underwent primary angioplasty. All received aspirin (ASA), clopidogrel (CLP) and abciximab (ABX) prior to intervention. Aspirin was administered by ambulance crews. 15 patients transferred from district hospitals received CLP and ABX prior to transfer to the N-HAC ('early therapy' - ET). 10 patients brought directly to the N-HAC by ambulance from the community received CLP and ABX on arrival but prior to catheterisation ('late therapy' -LT). Median time from CLP and ABX therapy to balloon inflation was 70 min (63-90) ET vs. 33 min (20-43) LT, p=0.004. Ischaemia duration was similar in the two groups. Results were compared with 23 patients with chronic stable angina (CSA) of whom 21 underwent elective coronary angioplasty, and a control group of 11 subjects with no history of coronary disease (CTL).

Methods

PMA, P-selectin and CD40L surface expression were measured by flow cytometry in peripheral venous blood on arrival (T=0), 2 and 24 hours post balloon inflation. Plasma P-selectin, soluble sCD40L, and IL-6 were measured by ELISA. Peak creatine kinase (CK) within 24 hours was measured for infarct size. TIMI flow grade, Myocardial Blush Grade (MBG), corrected TIMI frame count (cTFC), and thrombus scores were assessed pre and post primary angioplasty. ECG ST segment resolution was measured post procedure.
Results

Baseline PMA levels were significantly elevated among STEMI patients relative to CSA and CTL (26.4% ± 4.4 vs. 16.2% ± 2.1 and 16.7% ± 1.5 respectively, p=0.042). Levels remained elevated 2 hours following coronary intervention in STEMI patients, but fell by 49% and 32% (p=0.006 and 0.036) to similar levels by 24 hours in both STEMI and CSA cohorts. PMA levels fell more rapidly after intervention (by 35% at 2 hours, p=0.001) in CSA patients. P-selectin expression also fell significantly by 24 hours following intervention in both STEMI and CSA cohorts, with no significant differences between the two groups. CD40L and sCD40L remained unaffected by the angioplasty process in both settings. IL-6 increased significantly at each time point in both angioplasty groups.

PMA expression < 20% (median) at presentation was associated with TIMI grade 3 flow (9/9 vs. 4/8, p=0.015) and MBG 3 (7/9 vs. 2/8, p=0.03) post procedure, but not ST segment resolution. Peak CK was lower in patients with PMA < 20% (500 [283-1015], 1462 [837-1945] p=0.046). No association was demonstrated between CD40L or P-Selectin and reperfusion.

PMA fell by 34% at 2 hours following primary angioplasty (p=0.013) in the ET cohort, but remained elevated in the LT group. P-selectin increased significantly at 2 hours in the LT group (by 118%, p=0.012). CD40L and IL-6 were unaffected by the timing of anti-platelet therapy.

Conclusions

Primary angioplasty for ST segment elevation myocardial infarction did not increase platelet activation. Low PMA levels at presentation predicted improved reperfusion, supporting the concept that PMAs reflect the severity of plaque rupture, and may promote microvascular dysfunction. Early anti-platelet therapy reduced platelet activation 2 hours following intervention. This mechanism may contribute to the clinical benefits of early anti-platelet therapy in STEMI patients treated with primary angioplasty described in clinical trials.
6.2 INTRODUCTION

Thus far this thesis has discussed the rationale and mechanism for the delivery of primary angioplasty as the preferred reperfusion strategy for patients presenting with ST segment elevation myocardial infarction (STEMI) in North East London. In the preceding chapter, effective clinical outcomes have been demonstrated utilising two complementary access strategies – direct access to the catheter laboratory by ambulance crews following pre-hospital diagnosis, and transfer from the accident and emergency departments of district hospitals following administration of pre-transfer anti-platelet therapy. It has been proposed that early administration of adjuvant anti-platelet therapy may compensate for prolongation of ischaemia in patients transferred from district centres.

Platelet activation plays a key role in the pathogenesis of acute myocardial infarction. Platelet activation measured by P-selectin expression increases in patients with acute coronary syndromes (ACS), and differences in expression may predict the severity of clinical presentation (30). Platelet monocyte aggregates (PMA) and CD40 ligand (CD40L) may be more sensitive markers of platelet activation (31;34), and are themselves associated with plaque instability, thrombus formation and inflammation (33;220). These properties may influence the effectiveness of reperfusion therapy, and may also implicate these markers as therapeutic targets. This chapter investigates whether the outcome following primary angioplasty may be determined by mechanisms involving platelet activation.

6.3 Aims

1. As discussed in Chapter 1 [1.8 Platelet Activation, Primary Angioplasty, and Microvascular Perfusion], coronary angioplasty in the setting of a stable atheromatous plaque may itself activate platelets (31;191;221;222). This study aims to compare platelet activation following coronary angioplasty in the setting of plaque rupture (primary angioplasty
for STEMI) with platelet activation following stable plaque angioplasty (elective angioplasty for chronic stable angina).

2. To investigate the influence of platelet activation at presentation on epicardial and microvascular reperfusion following primary angioplasty for STEMI

3. To investigate the effect of early administration of combined anti-platelet therapy with clopidogrel and abciximab on platelet activation following primary angioplasty for STEMI

6.4 Hypotheses

1. Coronary angioplasty in the setting of plaque rupture does not lead to further platelet activation

2. The degree of platelet activation at presentation predicts reperfusion following primary angioplasty for STEMI

3. Early administration of anti-platelet therapy improves outcome following primary angioplasty through a reduction in platelet activation.

6.5 METHODS

6.5.1 Subjects

The study was a prospective observational investigation of platelet activation among patients undergoing coronary intervention at the N-HAC. The timing, doses and choice of anti-platelet therapy, as well as the timing and extent of revascularisation in each study group were determined by clinical protocol and/or operator preference at the N-HAC and were not designed specifically for platelet studies. The logistics of performing flow cytometry within six hours of venesection at multiple time points (detailed below) in addition to restricted availability of access to flow cytometry limited sample sizes to those presented
in this chapter. The results of these studies must therefore be viewed in the context of these limitations.

Of 105 confirmed STEMI patients presenting to the Network Heart Attack Centre (N-HAC) during the study period (January 2004 – May 2005), 25 patients were recruited on arrival at the N-HAC into the platelet study. 23/25 underwent primary angioplasty with stenting, 1 was listed for coronary artery bypass surgery (CABG), and 1 was treated medically (TIMI grade 3 flow at presentation with no residual coronary stenosis).

During the same study period, 23 patients with a history of chronic stable angina (CSA) were recruited into the platelet study, prior to a planned elective angioplasty and stenting procedure. 21/23 actually underwent angioplasty (1 underwent angiography only and did not proceed to PCI, and the other had a failed attempt at opening a chronic total occlusion without balloon inflation). Subjects with a history of ACS within 6 weeks of the study were excluded.

A control group of 11 volunteers with no prior history of ischaemic heart disease were also recruited through advertisement (CTL). This latter group was recruited from among health care professionals and other NHS workers as it was deemed unethical by the North East London Regional Ethics Committee to approach unaffected relatives and friends of the patients recruited. As a result the CTL group was not matched for age and sex with the two angioplasty groups which may be a confounding factor. However existing data suggest that gender and age do not affect either platelet aggregation (223) or activation (measured using soluble CD40L) (224) in healthy subjects. Baseline demographic and procedural characteristics are demonstrated in table 6.1.
### Table 6.1 Baseline demographic and procedural characteristics

<table>
<thead>
<tr>
<th></th>
<th>STEMI (n=25)</th>
<th>CSA (n=23)</th>
<th>P value (STEMI vs. CSA)</th>
<th>CTL (n=11)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age mean (sd)</td>
<td>60 (12)</td>
<td>65 (7)</td>
<td>NS</td>
<td>47 (17)</td>
</tr>
<tr>
<td>Male Sex</td>
<td>68%</td>
<td>79%</td>
<td>NS</td>
<td>36%</td>
</tr>
<tr>
<td>Smoker</td>
<td>84%</td>
<td>53%</td>
<td>0.026</td>
<td>55%</td>
</tr>
<tr>
<td>Diabetic</td>
<td>17%</td>
<td>12%</td>
<td>NS</td>
<td>9%</td>
</tr>
<tr>
<td><strong>Procedure</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abciximab</td>
<td>100%</td>
<td>48%</td>
<td>&lt;0.001</td>
<td>-</td>
</tr>
<tr>
<td>Number of</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>vessels treated</td>
<td>1.1 (0.5)</td>
<td>1.2 (0.5)</td>
<td>NS</td>
<td>-</td>
</tr>
<tr>
<td>Mean (sd)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of</td>
<td>1.4 (0.8)</td>
<td>1.2 (0.6)</td>
<td>NS</td>
<td>-</td>
</tr>
<tr>
<td>lesions treated</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (sd)</td>
<td>1.75 (1.1)</td>
<td>1.5 (1.0)</td>
<td>NS</td>
<td>-</td>
</tr>
<tr>
<td>Number of</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>stents used</td>
<td>1.75 (1.1)</td>
<td>1.5 (1.0)</td>
<td>NS</td>
<td>-</td>
</tr>
<tr>
<td>Mean (sd)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Key**

- **STEMI**: ST segment Elevation Myocardial Infarction
- **CSA**: Chronic Stable Angina
- **CTL**: Control
6.5.2 Interventions

Primary angioplasty for STEMI

All STEMI patients were treated with aspirin, clopidogrel and GpIb/IIa receptor antagonist (GPRA) therapy (abciximab) prior to coronary intervention. Aspirin 300mg was administered orally in all cases at the earliest opportunity (either in the ambulance or at the first hospital of presentation). 15/25 patients were transferred to the network heart attack centre (N-HAC) from the A&E departments of 5 district hospitals within a hospital network, having received ‘early’ anti-platelet therapy (ET) with oral clopidogrel 300mg and a weight adjusted intravenous bolus of abciximab prior to transfer. The remaining 10 patients were admitted to the N-HAC directly from the community following pre hospital diagnosis by the ambulance crew. Ambulances could bypass the nearest network A&E department in favour of admission to the N-HAC. These patients received ‘late’ clopidogrel and abciximab therapy (LT) immediately following arrival at the N-HAC cardiac catheter lab, but prior to coronary intervention. Figure 6.1 demonstrates the patient pathway, and the timing of administration of anti-platelet therapy in each group.

Elective coronary angioplasty for chronic stable angina

All patients received an oral loading dose of clopidogrel 300mg greater than 6 hours prior to intervention, and were already established on aspirin 75-300mg daily according to the standard elective angioplasty protocol at the N-HAC. Importantly adjuvant GPRA therapy with abciximab was used in 48% of elective cases, administered during or immediately after (but never before) the procedure according to operator preference (table 6.1). GpIb/IIa antagonists (abciximab, eptifibatide and tirofiban) have been reported to inhibit the release of sCD40L in vitro (85;86) and abciximab also inhibits agonist-induced formation of monocyte platelet aggregates in vitro (90). In vivo GPRA therapy has been demonstrated to reduce both sCD40L and PMA formation in ACS patients undergoing PCI (87). In addition GPRAs reduced circulating PMAs in stable patients undergoing PCI (225) although that study did not have a non-GPRA
control arm. Therefore the administration of abciximab to a proportion of patients in the CSA group may be an important confounding factor when comparing platelet responses following angioplasty in the setting of CSA relative to STEMI. This issue is specifically addressed in section 6.6.4 [6.6.4 Influence of abciximab therapy on platelet activation following elective coronary angioplasty for chronic stable angina].
Figure 6.1 Patient pathways for patients presenting with STEMI entered in platelet studies

Key

PCI | Percutaneous intervention
TIMI Flow | TIMI angiographic flow grade
MBG | Myocardial Blush Grade
CTFC | Corrected TIMI Frame Count
STR | ST segment Resolution
T | Time in minutes
† | Median time difference between administration of early and late anti-platelet therapy (see table 6.4b)
†† | Median ‘pain to balloon’ times (see table 6.4b)
6.5.3 Blood sampling

Peripheral venous blood samples were obtained using a standardised sampling protocol [see Chapter 2; 2.3.2 Blood Sampling, Preparation and Analysis]. Samples were taken on arrival at the N-HAC among STEMI patients or immediately prior to entering the catheter lab for chronic stable angina patients (t=0), and then at 2 hours following balloon inflation (t=2) and 18-24 hours following balloon inflation (t=24). PMA, CD40L and membrane P-selectin expression were measured by whole blood flow cytometry, and plasma sCD40L and P-selectin were measured by enzyme linked immunoassay (ELISA). Peak CK within the first 24 hours of admission was measured as a marker of myocardial infarct size. Plasma Interleukin 6 (IL-6) was measured by ELISA as a marker of inflammation. Among the STEMI cohort, ET patients had received abciximab and clopidogrel at the time of initial sampling (t=0) whereas LT patients always received therapy after the first sample had been taken.

Complete data for all biomarkers were available for analysis from all chronic stable angina (CSA) and control (CTL) patients (n=23 CSA, n=21 undergoing elective angioplasty, n=11 CTL).

Complete ELISA data were available from all STEMI patients (sCD40L, soluble P-selectin, IL-6) (n=25 STEMI, n=23 undergoing primary angioplasty).

Complete flow cytometric data were available from 21/25 STEMI patients for membrane P-selectin and CD40L (n=21 STEMI, n=19 undergoing primary angioplasty).

Complete flow cytometric data were available from 18/25 STEMI patients for PMAs (n=18 STEMI, n=17 undergoing primary angioplasty). The remaining samples were excluded from analysis as a result of either insufficient data (too few monocyte events counted), or inconsistent results (coefficient of variability > 10% on more than 2 separate analyses of the same sample).
6.5.4 Outcome measures

Hypothesis 1
Comparison of platelet activation markers at baseline was made between the three patient cohorts (STEMI, CSA and CTL). Serial changes in platelet activation following intervention were analysed in those STEMI patients undergoing a primary angioplasty procedure and chronic stable angina patients (CSA) undergoing elective angioplasty between sampling time points (0-2 hours, 0-24 hours, 2-24 hours).

Hypothesis 2
Platelet parameters were correlated with epicardial and microvascular perfusion at initial angiography in all STEMI patients, and post reperfusion therapy in those undergoing primary angioplasty. Angiographic measures included TIMI flow grade, Myocardial Blush Grade (MBG), TIMI thrombus burden and corrected TIMI frame count (cTFC) [see Chapter 2; 2.5 Angiographic analyses]. Angiographic data were available for all patients. ST segment resolution on the 12 lead ECG was assessed pre and post procedure and additionally at 18-24 hours [see Chapter 2; 2.4 ECG analyses]. ECG data were available for 18/25 subjects.

Hypothesis 3
Platelet parameters were compared between STEMI patients undergoing primary angioplasty treated with early and late anti-platelet therapy. All STEMI patients received aspirin, clopidogrel and abciximab therapy prior to intervention. Platelet responses in CSA patients treated with or without glycoprotein GpIIb/IIIa receptor antagonist therapy were also compared.

6.5.5 Statistics
Due to the skewed distributions of biological markers, differences within and between patient cohorts and serial changes over time were compared using non-parametric tests. The Mann Whitney U test was used to compare marker
expression between any two patient cohorts; the Kruskal–Wallis test was used to compare marker expression between all three patient groups; the Wilcoxon rank sum test was used to compare changes in platelet markers following intervention. Differences in categorical variables were compared using Chi square or Fisher's Exact tests.

6.5.6 Ethics
Ethical approval for platelet studies was granted by the North East London Regional Ethics Committee in March 2003 (reference number P/03/024).

6.6 RESULTS

6.6.1 Platelet activation following coronary angioplasty and stenting: stable versus ruptured / thrombotic plaque
Baseline differences in platelet activation between patient cohorts are demonstrated in table 6.2. The data shown represent all patients presenting with STEMI and CSA, including those who did not subsequently undergo a coronary angioplasty procedure. PMA levels were significantly elevated in patients with STEMI compared with chronic stable angina patients and controls. CD40L was significantly higher among both patient cohorts than in the control group. However, in contrast to PMA, CD40L expression was significantly lower in STEMI patients than the chronic stable angina cohort. There were no differences in plasma sCD40L, membrane P-selectin expression or plasma P-selectin release between cohorts at baseline sampling.
Table 6.2 Comparison of Platelet and Inflammatory markers at baseline sampling

<table>
<thead>
<tr>
<th>Cohort</th>
<th>PMA (%)</th>
<th>CD40L (%)</th>
<th>sCD40L (ng/ml)</th>
<th>Membrane P Selectin (%)</th>
<th>Plasma P Selectin (ng/ml)</th>
<th>IL-6 (pg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>STEMI n=25†</td>
<td>26.4 ± 4.4 (n=18)</td>
<td>12.4 ± 1.5 (n=21)</td>
<td>0.53 ± 0.13</td>
<td>3.9 ± 0.7 (n=21)</td>
<td>20.4 ± 2.9</td>
<td>4.8 ± 1.4</td>
</tr>
<tr>
<td>CSA n=23</td>
<td>16.2 ± 2.1</td>
<td>17.0 ± 1.3</td>
<td>0.77 ± 0.26</td>
<td>3.5 ± 0.5</td>
<td>18.9 ± 2.4</td>
<td>2.7 ± 0.43</td>
</tr>
<tr>
<td>CTL n=11</td>
<td>16.7 ± 1.5</td>
<td>3.7 ± 0.34</td>
<td>0.76 ± 0.21</td>
<td>1.9 ± 0.4</td>
<td>15.3 ± 4.3</td>
<td>0.6 ± 0.3</td>
</tr>
<tr>
<td>P values</td>
<td>0.042*</td>
<td>&lt;0.001*</td>
<td>All NS</td>
<td>All NS</td>
<td>All NS</td>
<td>0.003* NS**</td>
</tr>
<tr>
<td></td>
<td>0.029**</td>
<td>0.035**</td>
<td>0.002†</td>
<td>&lt;0.001 ††</td>
<td>&lt;0.001 ††</td>
<td></td>
</tr>
</tbody>
</table>

All data expressed as mean ± SEM.

* Kruskal Wallis comparison of STEMI vs. Chronic Stable Angina vs. Control Group
** Mann Whitney U test: STEMI vs. Chronic Stable Angina
† Mann Whitney U test: STEMI vs. Control Group
†† P value by Mann Whitney U: Chronic Stable Angina vs. Control Group

‡ n=25 except where otherwise stated

Effect of percutaneous intervention

Among STEMI patients undergoing primary angioplasty (ruptured plaque angioplasty), PMA levels and membrane P-selectin expression remained elevated 2 hours following balloon inflation, but fell significantly (by 49% in both cases) by 24 hours. Similarly plasma P-selectin levels fell by 30% at 24 hours (Figure 6.2a-c).

In contrast, PMA expression fell significantly (by 35%) 2 hours following balloon inflation among CSA patients undergoing elective angioplasty (stable plaque angioplasty), remaining unchanged by 24 hours, with similar final levels to those
following primary angioplasty. Membrane P-selectin levels also fell (by 38%) at 2 hours, and were unchanged at 24 hours, although this was not significant. Meanwhile, plasma P-selectin increased significantly by 32% (Figure 6.2a-c).

Platelet surface and soluble CD40L were unaffected by the angioplasty procedure in the setting of both primary angioplasty for STEMI and elective angioplasty for CSA (Figure 6.2d-e).

Interleukin 6 levels increased significantly at 2 and 24 hours following balloon inflation in both angioplasty cohorts (primary angioplasty 65% 0-2hrs, 239% 0-24 hrs; elective angioplasty 27% 0-2hrs, 137% 0-24hrs). IL6 appeared higher in STEMI patients than in stable patients at all time points but did not reach statistical significance (Figure 6.2f).
Figure 6.2  Comparison of platelet activation following primary angioplasty for STEMI (ruptured plaque angioplasty) and elective angioplasty for chronic stable angina (stable plaque angioplasty)

Data expressed as mean ± SEM

6.2a Platelet Monocyte Aggregate (PMA) Expression

PMA levels fall significantly by 2 hours following elective angioplasty (i.e. in the setting of stable plaque), but not following primary angioplasty (i.e. in the setting of plaque rupture). Levels fall significantly by 24 hours in both groups. (6.2a). Membrane P selectin expression demonstrates a similar pattern but does not reach statistical significance (6.2b). CD40L and sCD40L appear unaffected by the angioplasty process in both settings (6.2d and e). Angioplasty results in an increase in inflammation in both settings (6.2f).
6.2b Membrane P-selectin Expression (flow cytometry)

<table>
<thead>
<tr>
<th>%</th>
<th>T=0</th>
<th>T=2</th>
<th>T=24</th>
</tr>
</thead>
<tbody>
<tr>
<td>RUPTURED PLAQUE n=19</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>STABLE PLAQUE n=21</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
</tbody>
</table>

* p=0.002 (0-24 hours); p=NS (0-2 hours)
** p=0.05 (0-24 hours); p=NS (0-2 hours)

6.2c Plasma P Selectin (ELISA)

<table>
<thead>
<tr>
<th>ng/ml</th>
<th>T=0</th>
<th>T=2</th>
<th>T=24</th>
</tr>
</thead>
<tbody>
<tr>
<td>RUPTURED PLAQUE n=23</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>STABLE PLAQUE n=21</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
</tbody>
</table>

* p=0.027 (0-24 hours); p=0.012 (2-24 hours)
** p=0.05 (0-24 hours); p=0.005 (2-24 hours)
6.2d Platelet Surface CD40 Ligand (flow cytometry)

* All p=NS (0-2 hours, 0-24 hours, 2-24 hours)
** All p=NS (0-2 hours, 0-24 hours, 2-24 hours)

6.2e Plasma Soluble sCD40 Ligand (ELISA)

* All p=NS (0-2 hours, 0-24 hours, 2-24 hours)
** All p=NS (0-2 hours, 0-24 hours, 2-24 hours)
6.2f Inflammation – Plasma Interleukin 6 (ELISA)

* p=0.012 (0-2 hours); p=NS (0.065) (2-24 hours); p=0.002 (0-24 hours)
** p=0.017 (0-2 hours); p=0.02 (2-24 hours); p=0.003 (0-24 hours)

6.6.2 Influence of platelet activation on reperfusion and infarct size following primary angioplasty for STEMI

Platelet activation markers were not predictive of angiographic epicardial or microvascular flow pre-procedure. However, PMA expression below the median (20%) at presentation was associated with a significantly increased rate of TIMI grade 3 flow and myocardial blush grade (MBG) 3 post procedure among those patients undergoing primary angioplasty (Table 6.3a). There was no association with thrombus score or corrected TIMI frame count (cTFC). PMA formation below 20% was also associated with a significantly lower peak serum creatine kinase level (CK). There was no relation between the duration of ischaemia and PMA at presentation.
No significant association was found between CD40L expression and angiographic reperfusion (Table 6.3b). There was no association with sCD40L, and neither was related to CK release.

No association was detected between angiographic measures of reperfusion and either membrane P selectin expression or plasma P selectin release.

Platelet markers were not associated with the degree of ST segment resolution on the 12 lead ECG post procedure or at 24 hours.
Table 6.3 The Influence of baseline platelet marker expression on epicardial and microvascular reperfusion following primary angioplasty

**a. Platelet Monocyte Aggregate expression at baseline sampling (n=17): Above versus below median**

<table>
<thead>
<tr>
<th></th>
<th>PMA &lt; 20% n=9</th>
<th>PMA &gt; 20% n=8</th>
<th>( P (\chi^2) )</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pre Procedure</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TIMI 3</td>
<td>3</td>
<td>1</td>
<td>NS</td>
</tr>
<tr>
<td>MBG 3</td>
<td>4</td>
<td>2</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Post Procedure</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TIMI 3</td>
<td>9</td>
<td>4</td>
<td>0.015</td>
</tr>
<tr>
<td>MBG 3</td>
<td>7</td>
<td>2</td>
<td>0.03</td>
</tr>
<tr>
<td><strong>Peak CK median (IQR)</strong></td>
<td>500 (283-1015)</td>
<td>1462 (837-1945)</td>
<td>0.046*</td>
</tr>
</tbody>
</table>

* Mann Whitney U test

**b. Platelet surface CD40 Ligand expression at baseline sampling (n=19): Above versus below median**

<table>
<thead>
<tr>
<th></th>
<th>CD40L ≤ 13% n=10</th>
<th>CD40L &gt; 13% n=9</th>
<th>( P (\chi^2) )</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pre Procedure</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TIMI 3</td>
<td>1</td>
<td>3</td>
<td>NS</td>
</tr>
<tr>
<td>MBG 3</td>
<td>2</td>
<td>4</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Post Procedure</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TIMI 3</td>
<td>6</td>
<td>8</td>
<td>NS</td>
</tr>
<tr>
<td>MBG 3</td>
<td>3</td>
<td>6</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Peak CK median (IQR)</strong></td>
<td>1111 (559-2358)</td>
<td>727 (394-1294)</td>
<td>NS</td>
</tr>
</tbody>
</table>
6.6.3 Influence of early versus late anti-platelet therapy on platelet activation following primary angioplasty for STEMI

Table 6.4a compares baseline characteristics of patients treated with ‘early’ and ‘late’ anti-platelet therapy. Demographic and procedural details were matched. ET patients presented earlier relative to those treated with LT, such that the duration of symptoms at the time of blood sampling (t=0) and the total duration of ischaemia (pain to balloon time) were similar in both groups (Table 6.4b). ET was administered (median) 37 minutes earlier than LT. In keeping with data from a larger cohort of patients presented in the preceding chapter [see Chapter 5; 5.4.4 Angiographic reperfusion and ST segment resolution], TIMI 3 flow and MBG 3 were more frequent pre-procedure in the ET cohort compared with the LT group, although this did not reach significance in this platelet sub study. There was no difference in TIMI flow, MBG or ST resolution post procedure. Thrombus burden and cTFC did not differ significantly pre or post procedure (Table 6.4c).
Table 6.4 Comparison of patients undergoing primary angioplasty receiving early versus late anti-platelet therapy with clopidogrel and abciximab

Table 6.4a. Demographics and procedural characteristics

<table>
<thead>
<tr>
<th></th>
<th>Early Anti-platelet therapy N=15 (14 primary angioplasty)</th>
<th>Late Anti-platelet therapy N=10 (9 primary angioplasty)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>58 (11)</td>
<td>64 (13)</td>
<td>NS</td>
</tr>
<tr>
<td>Sex</td>
<td>9 male</td>
<td>8 male</td>
<td>NS</td>
</tr>
<tr>
<td>Smoker</td>
<td>14</td>
<td>7</td>
<td>NS</td>
</tr>
<tr>
<td>Diabetic</td>
<td>2</td>
<td>2</td>
<td>NS</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>5</td>
<td>2</td>
<td>NS</td>
</tr>
<tr>
<td>Prior MI</td>
<td>1</td>
<td>1</td>
<td>NS</td>
</tr>
<tr>
<td>Prior Revasc</td>
<td>0</td>
<td>0</td>
<td>NS</td>
</tr>
<tr>
<td>Procedure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Culprit Vessel</td>
<td>LAD 6</td>
<td>LAD 5</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cx 3</td>
<td>Cx 3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>RCA 5</td>
<td>RCA 2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Vein graft 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No Vessels</td>
<td>1.0 (0.4)</td>
<td>1.2 (0.6)</td>
<td>NS</td>
</tr>
<tr>
<td>Mean (sd)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No lesions</td>
<td>1.3 (0.7)</td>
<td>1.6 (1.0)</td>
<td>NS</td>
</tr>
<tr>
<td>Mean (sd)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No Stents</td>
<td>1.5 (0.85)</td>
<td>2.3 (1.2)</td>
<td>NS (0.07)</td>
</tr>
</tbody>
</table>
Table 6.4b. Symptom duration, time to reperfusion, and time to administration of anti-platelet therapy in patients treated with primary angioplasty: early versus late anti-platelet therapy with clopidogrel and abciximab.

<table>
<thead>
<tr>
<th></th>
<th>Early Anti-platelet therapy N=15 (14 primary angioplasty)</th>
<th>Late Anti-platelet therapy N=10 (9 primary angioplasty)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptoms at presentation med (IQR)</td>
<td>107 (43-175)</td>
<td>181 (142-541)</td>
<td>0.036</td>
</tr>
<tr>
<td>Symptoms at t=0 sampling median (IQR)</td>
<td>168 (104-243)</td>
<td>201 (142-541)</td>
<td>NS</td>
</tr>
<tr>
<td>Pain to balloon median (IQR)</td>
<td>247 (141-306)</td>
<td>248 (175-610)</td>
<td>NS</td>
</tr>
<tr>
<td>Abciximab to balloon median (IQR)</td>
<td>70 (63-90)</td>
<td>33 (20-43)</td>
<td>0.004</td>
</tr>
<tr>
<td>Peak CK median (IQR)</td>
<td>727 (382-1948)</td>
<td>1111 (382-1294)</td>
<td>NS</td>
</tr>
</tbody>
</table>
Table 6.4c Epicardial and microvascular reperfusion in patients undergoing primary angioplasty: Early versus late anti-platelet therapy

<table>
<thead>
<tr>
<th></th>
<th>Early Anti-platelet therapy</th>
<th>Late Anti-platelet therapy</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=15 (14 primary angioplasty)</td>
<td>N=10 (9 primary angioplasty)</td>
<td></td>
</tr>
<tr>
<td>Pre-angioplasty</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean TIMI flow (sd)</td>
<td>1.9 (1.3)</td>
<td>1.4 (1.1)</td>
<td>NS</td>
</tr>
<tr>
<td>TIMI grade 3 flow</td>
<td>7</td>
<td>1</td>
<td>NS</td>
</tr>
<tr>
<td>Mean MBG (sd)</td>
<td>1.8 (1.4)</td>
<td>0.6 (1.1)</td>
<td>0.054</td>
</tr>
<tr>
<td>MBG 3</td>
<td>8</td>
<td>1</td>
<td>0.027</td>
</tr>
<tr>
<td>Mean cTFC (sd)</td>
<td>51 (39)</td>
<td>63 (39)</td>
<td>NS</td>
</tr>
<tr>
<td>Mean Thrombus score (sd)</td>
<td>3.0 (1.7)</td>
<td>3.3 (1.0)</td>
<td>NS</td>
</tr>
<tr>
<td>Post-angioplasty</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean TIMI flow (sd)</td>
<td>2.9 (0.4)</td>
<td>2.4 (1.0)</td>
<td>NS</td>
</tr>
<tr>
<td>TIMI 3 flow</td>
<td>12</td>
<td>6</td>
<td>NS</td>
</tr>
<tr>
<td>Mean MBG (sd)</td>
<td>2.3 (1.1)</td>
<td>1.9 (1.3)</td>
<td>NS</td>
</tr>
<tr>
<td>MBG 3</td>
<td>9</td>
<td>4</td>
<td>NS</td>
</tr>
<tr>
<td>Mean cTFC (sd)</td>
<td>28 (26)</td>
<td>36 (31)</td>
<td>NS</td>
</tr>
<tr>
<td>Mean Thrombus score (sd)</td>
<td>0.3 (0.5)</td>
<td>0.2 (0.4)</td>
<td>NS</td>
</tr>
<tr>
<td>ST Resolution 60min % (sd)</td>
<td>71 (15)</td>
<td>66 (24)</td>
<td>NS</td>
</tr>
<tr>
<td>ST Resolution 24hr % (sd)</td>
<td>80 (12)</td>
<td>76 (20)</td>
<td>NS</td>
</tr>
</tbody>
</table>
PMA levels did not differ significantly between ET and LT cohorts at initial sampling. PMA expression fell significantly (by 34%) at 2 hours following balloon inflation in the ET group, but remained elevated in those receiving LT (figure 6.3a). Notably however, PMA expression at 2 hours was significantly lower among those patients achieving TIMI grade 3 flow post procedure (36% ± 9.5 vs. 16% ± 3.4, p=0.032), raising the possibility that arterial patency per se may have influenced the fall in PMAs rather than early anti-platelet therapy itself. Final TIMI flow post angioplasty was not associated with any of the other platelet markers, but was associated with lower peak CK (1685 IU [1182-2358] TIMI flow <3 vs. 578 IU [302-1243] TIMI 3, p=0.039) and IL-6 (9.8 pg/ml [6.6-40.6] vs. 4.1 pg/ml [2.7-8.9], p=0.037) at 24 hours.

Membrane P-selectin expression also fell (by 37%) at 2 hours following primary angioplasty in the ET group (though not reaching statistical significance, p=0.16), and increased significantly (by 118%, p=0.012) following LT (figure 6.3b). Plasma P-selectin followed an inverse pattern to that of Membrane P selectin and PMAs, remaining elevated at 2 hours in the ET cohort, and falling by 28% at 2 hours following therapy in the LT cohort, though this did not approach statistical significance (p=0.8, Figure 6.3c).

CD40L and sCD40L remained unaffected by the timing of anti-platelet therapy (figure 6.3d,e). Baseline IL-6 was significantly higher at baseline sampling in patients receiving late anti-platelet therapy, and rose thereafter in both groups (although this was statistically significant only in the early therapy group) (figure 6.3f).
Figure 6.3 Influence of Early versus Late Anti-Platelet therapy with Clopidogrel and Abciximab on Platelet Activation following Primary Angioplasty for STEMI

6.3a Platelet Monocyte Aggregate (PMA) Expression

PMA levels fell significantly 2 hours following primary angioplasty in patients receiving early anti-platelet therapy, but remained elevated in those receiving late therapy, before falling to similar levels at 24 hours (6.3a). Membrane P-selectin increased 2 hours following intervention in patients receiving late therapy (6.3b). CD40L and sCD40L were unaffected by the timing of anti-platelet therapy (6.3d and e). Inflammation increased in both groups (6.3f).
6.3b Membrane P Selectin Expression (flow cytometry)

* p=NS early therapy (0-2 hours)
** p=0.012 late therapy (0-2 hours)

6.3c Plasma P-Selectin Expression (ELISA)

* p=NS early therapy (0-2 hours)
** p=NS late therapy (0-2 hours)
6.3d Platelet surface CD40 Ligand Expression (flow cytometry)

![Graph showing platelet surface CD40 Ligand expression at different time points.]

P=NS all time points

6.3e Plasma Soluble sCD40 Ligand (ELISA)

![Graph showing plasma soluble sCD40 Ligand at different time points.]

P=NS all time points
6.3f Inflammation – Plasma Interleukin 6 (ELISA)

* p=0.046 early therapy vs late therapy at T=0

** p=0.005 (0-2 hours); p=0.001 (0-24 hours); p=0.038 (2-24 hours)
6.6.4 Influence of abciximab therapy on platelet activation following elective coronary angioplasty for chronic stable angina

There were no significant differences in baseline platelet activation among CSA patients undergoing elective angioplasty treated with or without adjuvant abciximab. Furthermore abciximab did not appear to affect platelet activation following intervention in this cohort (Figure 6.4a-c). IL-6 was not significantly different between these groups, but increased significantly following angioplasty in both groups (figure 6.4d).

Figure 6.4 Influence of abciximab on platelet activation and inflammation following elective coronary angioplasty for chronic stable angina
Data expressed as mean ± SEM. All P=NS

6.4a Platelet Monocyte Aggregate Expression

![Bar Graph](image)

All P=NS
### 6.4b Membrane P selectin Expression (flow cytometry)

![Bar chart showing membrane P selectin expression](chart1)

All $P=NS$

### 6.4c Platelet surface CD40L expression (flow cytometry)

![Bar chart showing platelet surface CD40L expression](chart2)

All $P=NS$
**6.4d Inflammation: Plasma Interleukin-6 (ELISA)**

<table>
<thead>
<tr>
<th></th>
<th>ABCIXIMAB n=10</th>
<th>NO ABCIXIMAB n=11</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>T=0</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>T=2</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>T=24</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- *p=0.008 (0-24 hours); p=0.012 (2-24 hours), abciximab*
- **p=0.032 (0-2 hours), no abciximab**
6.7 DISCUSSION

This study highlights important differences in platelet responses to coronary angioplasty in two clinical and pathological settings, in addition to differences in expression of the separate platelet activation markers in each situation.

Platelet Monocyte Aggregates

*Ruptured vs. Stable Plaque*

The study demonstrated elevated PMA levels among patients with STEMI when compared with patients with stable coronary disease, and subjects with no history of ischaemic heart disease, a finding consistent with previous published data (31). In response to coronary angioplasty PIVIA levels fell significantly at 24 hours to similar levels in both the acute and stable settings. The fall was more rapid in patients with CSA, becoming apparent at 2 hours following the procedure. PMA levels remained elevated within the STEMI cohort at this time point. Furman et al have suggested that PMA elevation may be an early marker of subsequent myocardial infarction among patients presenting with ACS, potentially indicating the severity and thrombogenicity of plaque rupture (32). Thus while the angioplasty procedure did not appear to activate platelets, the persistence of PMA elevation in the STEMI group could imply continuing plaque disruption related to the underlying pathology that remains unaffected by the angioplasty procedure.

*Efficacy of Reperfusion*

Importantly, the PMA level at presentation also predicted the quality of reperfusion following primary angioplasty. Lower PMA levels were associated with improved epicardial and microvascular flow and smaller ultimate infarct size. This is also consistent with the theory that PMAs indicate plaque thrombogenicity. The fact that PMA levels were not associated with the degree of angiographic thrombus at presentation may imply that PMAs are a more sensitive indicator of the presence of thrombus than angiography. However this
may be over simplistic. It is more likely that PMA formation points to the severity of the ongoing pathological process within the plaque, or indeed may be directly mechanistic in mediating microvascular dysfunction. This could occur through a number of thrombotic and pro-inflammatory mechanisms. Sarma et al have demonstrated that monocyte binding to platelets occurs primarily through P-selectin and P-selectin glycoprotein ligand 1 (PGSL1) interaction, and that PMAs may be disaggregated using a monoclonal antibody to PGSL-1 (226). This mechanism has also independently been demonstrated to reduce myocardial reperfusion injury in cat model of ischaemia and reperfusion (227). In addition the process of P selectin binding itself promotes cytokine, tissue factor, and CD11b/CD18 expression by monocytes (228-230). These data lend support to the concept that there may be a therapeutic benefit to reducing PMA levels.

_Influence of Anti-platelet Therapy_

The primary angioplasty process in this study included a combination of aspirin, clopidogrel, and abciximab in all cases, in addition to the procedure itself. Therefore the effects of the procedure on platelet activation are inevitably the sum of all their effects. However, subgroup analysis of the STEMI cohort demonstrated that early administration of clopidogrel and abciximab therapy reduced platelet activation measured at 2 hours post balloon inflation, thereby altering the PMA response to resemble that of a stable plaque. That PMA remained elevated in those receiving later therapy is noteworthy as these patients had similar durations of ischaemia and still received therapy 33 minutes (median) prior to balloon inflation. Furman et al have established that PMA formation early after intervention can be reduced by administration of GPRA therapy among ACS patients undergoing coronary angioplasty, and independently of the effect of clopidogrel (87). The data presented here may suggest that in the presence of STEMI with a ruptured thrombotic plaque, the timing of therapy may be critical in order to achieve this result. Moreover, the reduction in PMA expression may provide a novel mechanism contributing to the benefit of early abciximab therapy for STEMI patients undergoing primary
angioplasty observed in clinical trials (83;126). It is possible to speculate that modification of PMA levels to resemble the response of a stable plaque could itself imply plaque stabilisation. However, it is also possible that the fall in PMA level was purely a reactive phenomenon. 2 hour PMA levels were also significantly lower among those achieving TIMI 3 flow post procedure, suggesting this may have been the effect of improved reperfusion rather than the therapy per se. Finally it must be recognised that subgroup analysis of the STEMI cohort was performed on small numbers of patients (particularly in the case of PMA analyses where there were 11 patients in the early anti-platelet therapy group and only 6 patients in the late anti-platelet therapy group). It is possible therefore that the absence of a fall in PMA formation at 2 hours in the late therapy group may have been a consequence of type II error.

P-selectin
Membrane P selectin expression behaved similarly to PMA formation following coronary intervention in the setting of STEMI, remaining unchanged at 2 hours and falling significantly by 24 hours. Plasma P selectin levels also fell 24 hours following primary angioplasty but increased significantly following intervention in CSA patients. However, P-selectin surface and plasma levels had no influence of epicardial or microvascular reperfusion pre or post procedure. Early anti-platelet therapy for STEMI resulted in a similar fall in P selectin expression 2 hours post procedure to that of PMAs, though not significant. Among patients receiving late therapy membrane P selectin levels increased.

The similarity in platelet responses between PMA and membrane P-selectin may be explained by the fact that PMA formation depends on a P-selectin dependent mechanism (220). This would also imply that P selectin expression and monocyte binding are in equilibrium. PMA levels appeared more sensitive than P selectin, in keeping with observations described by Michelson et al (31). This could explain the lack of correlation of P selectin expression with the efficacy of reperfusion. The differences in P selectin response to early and late
anti-platelet therapy lend further support to the notion that the benefit of early therapy may be mediated by beneficial effects on platelet activation.

**CD40 Ligand**

Baseline surface CD40L expression was elevated in both STEMI and CSA patients relative to controls. Interestingly CD40L was highest in stable patients and significantly lower in the setting of STEMI. There were no differences between cohorts in soluble sCD40L. In addition, primary and elective angioplasty had no significant measurable effect on either surface CD40L expression or sCD40L release. In contrast to PIVIA formation, CD40L expression did not appear to influence reperfusion following primary angioplasty for STEMI, and there was no demonstrable effect of early anti-platelet therapy.

The finding that CD40L expression was lower in STEMI patients than those with stable angina may be consistent with previous data from Garlichs et al that demonstrated platelet surface CD40L elevation among patients with unstable angina relative to those presenting with acute MI (40). In that study MI patients had an associated increase in sCD40L release, with the authors suggesting a continuum of surface CD40L up-regulation and sCD40L hydrolysis that might reflect the severity of the plaque rupture, with greater hydrolysis of surface sCD40L once CD40L is maximally expressed. However, this latter finding was not replicated in the present study. This may have been a consequence of the use of serum rather than plasma samples in that study. Serum assays have been demonstrated to overestimate sCD40L levels in unstable coronary patients (231;232), such that plasma assays are currently the preferred method of measuring platelet derived sCD40L (232). Indeed sCD40L levels in the study by Garlichs et al (40) were substantially higher than in either the cohort described here, or among ACS patients in other studies where citrated plasma was also used (87). Equally this disparity may be a result of differences in the study population. The present study included only acute STEMI patients, usually presenting early after symptom onset (median 2.5 hours), and commonly with
established thrombus. It is therefore possible that sCD40L and platelet CD40L were already sequestered in thrombus, and platelets may not have had the capability, or sufficient time to further up-regulate surface CD40L.

The apparent lack of CD40L response to angioplasty also merits consideration. It is possible that sampling at 2 hours following the procedure may have been too late to detect changes in sCD40L. A number of studies have demonstrated a significant increase in sCD40L as early as 10 minutes following peripheral or coronary angioplasty (233;234). On the other hand Furman et al also failed to demonstrate a change in sCD40L levels immediately after angioplasty or at 24 hours among acute coronary patients presenting without ST segment elevation in the absence of GPRA therapy, and when GPRA therapy was included sCD40L fell significantly at both time points (87).

It is also plausible that the lack of change in CD40L expression and sCD40L release among STEMI patients may have represented a balance between the dynamic processes of platelet activation by plaque rupture and injury, and stabilisation by combined anti-platelet therapy. A primary angioplasty control group treated without anti-platelet therapy could have addressed this issue, but was unethical given the established prognostic benefits of these therapies. However, the finding that CD40L and sCD40L also remained unchanged following elective angioplasty for CSA both in the presence and absence of abciximab militates against this argument.

Differences between CD40L and PMA
Unlike P selectin, CD40L expression appeared to behave differently to PMA levels in the experiments described here. Both PMA and CD40L have been suggested as markers of platelet activation, and as mediators of plaque instability, thrombosis and inflammation (34;185;220). Angioplasty in the setting of both stable and destabilised plaque was associated with increasing inflammation measured by IL-6 at each time point, consistent with previous
studies (235;236). However, PMA formation was modified by coronary intervention whereas CD40L was not. This may simply be a reflection of the sensitivity of PMA in this study. Larger sample sizes might have unmasked more subtle changes in CD40L yielding similar results. The only previous study of platelet activation following primary angioplasty was substantially smaller than the current study (29). Subsequent studies measuring PMA and CD40L expression in ACS patients using flow cytometry have recruited similar or slightly larger patient populations (30-200 patients) (31;32;40;87;237) However, studies assaying soluble CD40L have utilised stored samples from large randomised studies (88) resulting in statistically powerful results. While it is difficult to draw definitive conclusions, the results presented here may intimate that although CD40L is involved in the mechanism of plaque rupture and thrombus formation, circulating levels are not reflective of disease severity in the setting of established STEMI, and are not modified by coronary intervention. Moreover, if CD40L is a potential therapeutic target, alternative therapies may be necessary in addition to clopidogrel and GPRA therapy to improve outcomes in STEMI patients specifically.

Limitations
This study has important limitations. The prospective observational study design investigated platelet behaviour in the setting of established clinical and pharmacological practice, leading to a number of confounding factors that may have influenced the results. In addition logistic difficulties with patient recruitment resulted in small sample sizes which may have particular relevance to the results of subgroup analyses. The findings must therefore be viewed as hypothesis generating, and a stimulus for more specific hypothesis driven clinical and basic science research.

Specifically, it is not possible to separate the influence of the mechanical angioplasty process, and that of adjuvant anti-platelet therapy on platelet activation following angioplasty. It is possible that primary angioplasty may have
resulted in enhanced platelet activation in the absence of abciximab. As discussed earlier, it was deemed unethical to perform primary angioplasty without combined aspirin, clopidogrel, heparin and abciximab. The effects of simultaneous platelet suppression and activation could have canceled each other out, and may be relevant to the CD40L response in particular. In addition, as stated earlier, the CSA cohort was a heterogeneous group, almost half of which received abciximab therapy. Subgroup analysis in fact suggested that the abciximab did not influence the platelet response to elective angioplasty. However, it is possible that abciximab was administered in higher risk cases that might otherwise have demonstrated a heightened platelet response to angioplasty.

In comparing the influence of early and late anti-platelet therapy in the setting of primary angioplasty, the effects of abciximab and clopidogrel cannot be separated. The clopidogrel loading dose was administered a median of 62 minutes prior to intervention, suggesting that any effect is more likely to be the result of abciximab. This would be consistent with previous data in ACS patients suggesting that PMA formation in response to abciximab is independent of clopidogrel (87), and that suppression of surface expression of CD40L and P selectin following angioplasty in stable patients required early clopidogrel loading (236). Similarly, the influence of abciximab on platelet activation in the setting of CSA and STEMI cannot be directly compared due to the differences in the timing of administration of both this therapy and clopidogrel in each group.

It has already been discussed that the small sample sizes investigated may have had particular relevance to subgroup analysis of the STEMI cohort. Given that the majority of STEMI patients achieved arterial patency (TIMI grade 2 or 3 flow) post procedure, it is nonetheless impressive that PMA levels were predictive of improved epicardial and microvascular flow. However, it is possible that similar associations with other markers may have been missed. A larger study is therefore indicated before further conclusions can be drawn.
Moreover, the finding of an association between heightened PMA expression and impaired reperfusion does not imply causality. In addition it has already been discussed that the reduction in PMA formation at 2 hours following primary angioplasty in those receiving early anti-platelet therapy may have been a marker of successful reperfusion rather than a beneficial therapeutic effect.

Finally, the sampling time points (2 and 24 hours post balloon inflation) were chosen to detect the peak activation following angioplasty based on previous studies (31). As few studies have investigated these markers in this patient subgroup, it is possible that a delayed or biphasic activation platelet activation response may have been missed.

**Future Research**

The results of the platelet studies described here should now form the basis of larger studies to test hypotheses generated from this observational work.

In order to accurately compare platelet responses to coronary angioplasty in the setting of acute STEMI with stable coronary disease, an appropriately powered prospective study should now be performed. Subjects should be matched for age, sex, and coronary lesion location (e.g. proximal left anterior descending artery lesions), receiving standardised doses and timing of essential medical therapy (aspirin, clopidogrel, heparin) in order to control for confounding factors. STEMI patients should also be matched for symptom duration. The influence of abciximab therapy and timing of therapy could be further investigated through randomisation. Blood sampling should be performed at additional time points.

In addition basic science research should now be performed to investigate whether there is a causal link between the platelet activation markers studied here and microvascular dysfunction in vitro following ischaemia and reperfusion. Using the preliminary clinical data obtained from this study, a grant proposal has
been developed to study the influence of PMA formation and CD40 – CD40L interactions on microvascular flow in the mouse mesentery using intravital microscopy. The individual effects of anti-platelet therapies on these interactions may subsequently be investigated.

6.8 CONCLUSIONS

In this small prospective observational study primary angioplasty for ST segment elevation myocardial infarction did not increase platelet activation. Lower platelet monocyte aggregate levels at presentation predicted improved epicardial and microvascular flow following intervention, supporting the concept that PMA formation reflects the severity of plaque rupture, and may promote microvascular dysfunction. Administration of early anti-platelet therapy with abciximab and clopidogrel reduced platelet monocyte aggregate levels 2 hours following intervention. This mechanism may contribute to the benefit of early abciximab facilitation observed in clinical trials. A larger study is now indicated.
CHAPTER 7 Comparison of Primary Angioplasty and Thrombolytic Strategies for the treatment of ST segment Elevation Myocardial Infarction in North East London: Clinical outcome, resource utilisation and hospital stay
7.1 ABSTRACT

Thus far this thesis has described the development and delivery of a pilot primary angioplasty service in North East London. This chapter compares clinical outcomes and resource utilisation during the pilot programme with outcomes following the thrombolytic strategy.

Methods

Subjects
105 consecutive patients with confirmed STEMI delivered to a network heart attack centre (N-HAC) within a network of six hospitals with a view to primary angioplasty were compared with 192 STEMI patients presenting to one of the participating centres utilising the thrombolytic strategy; 105 admitted prior to and 87 following the instigation of the pilot primary angioplasty service. Data collection was prospective and non-randomised.

Outcomes

Clinical outcomes were assessed at median follow up of 19 (9-36) weeks. Analysis was by intention to treat. Major Adverse Cardiac Events (MACE) included death, non-fatal myocardial infarction (NFMI), stroke, and emergency revascularisation post discharge. Resource utilisation was measured by emergency readmission, the need for planned and unplanned cardiac catheterisation, and hospital stay during the index admission and subsequent cardiac hospitalisations.

Results

The primary angioplasty strategy significantly reduced mortality and MACE compared to thrombolysis (4% and 15% primary angioplasty vs. 11% and 25% thrombolysis, p=0.022 and 0.048 respectively). Stroke was reduced, though not significantly (1% primary angioplasty vs. 4% thrombolysis). The rate of NFMI was similar between groups (8% primary angioplasty vs. 7% thrombolysis,
p=NS). The need for unplanned cardiac catheterisation and emergency readmission was not reduced by the primary angioplasty strategy, with a similar number of readmissions occurring during follow up. Primary angioplasty reduced the length of inpatient hospital stay by a median 3 days (3 days (2-4) primary angioplasty vs. 6 days (4-9) thrombolysis, p<0.001). At the time of follow up the primary angioplasty strategy had saved 529 bed days per 100 patients treated when compared with thrombolysis, at the cost of 51 additional cardiac catheterisation procedures and 61 revascularisations.

Conclusions
Primary angioplasty utilising a network heart attack centre model significantly improves clinical outcomes compared with thrombolysis, and radically reduces hospital stay. However, strategies are still required to reduce emergency non cardiac readmissions and unplanned catheterisation procedure. Delivery of a 24 hour seven day service should now be considered.
7.2 INTRODUCTION

The preceding chapters of this thesis have described the development of a network primary angioplasty pilot service in North East London. A central hypothesis of the thesis was that primary angioplasty can be delivered safely and effectively in a United Kingdom population, with improved efficiency and clinical outcomes compared with thrombolysis. Effective delivery of therapy has been established utilising two complementary access strategies [chapter 5]. This chapter now compares clinical outcomes and resource utilisation during the pilot programme with outcomes following the thrombolytic strategy.

7.3 METHODS

7.3.1 Subjects

Primary Angioplasty
105 patients with confirmed STEMI were admitted to a network heart attack centre (N-HAC) either directly via ambulance or transferred from one of 5 participating A&E departments [chapter 5]. 103 underwent primary angioplasty (PA), one patient was referred for bypass surgery, and the other was treated medically. The service operated during working hours (0800-1700 on weekdays).

Thrombolysis
Outcomes were compared separately with two cohorts of patients with confirmed STEMI presenting to one of the participating network centres (centre E) [see chapter 2; Figure 2.1] utilising the thrombolytic strategy (TL). 87 patients were admitted between April 2003 and April 2004 presenting outside the operating hours the daytime pilot primary angioplasty service ('TL pilot'). In order to control for the potential selection bias caused by the differential hours of operation of each strategy, a historical cohort of 105 consecutive patients with confirmed STEMI admitted over a 24 hour seven day period between October 2001 and October 2002 prior to the instigation of the pilot primary angioplasty
service was also investigated ('TL pre pilot'). Baseline characteristics of the study cohorts are demonstrated in table 7.1.

7.3.2 Outcomes
Follow up data were available in 94% of cases for a median of 19 weeks (9-36) (table 7.1). Analysis was by intention to treat. Major Adverse Cardiac Events (MACE) included death, non-fatal myocardial infarction (NFMI), stroke, and emergency revascularisation post discharge as defined in chapter 2 [2.6 Clinical Outcomes]. Emergency cardiac readmissions, planned (elective) and unplanned (emergency) cardiac catheterisation procedures and revascularisations were also recorded.

Hospital stay during the index admission was compared, both inclusive and exclusive of hospitalisation following transfer to the cardiac centre where appropriate. Patients were discharged according to physician preference following thrombolysis. Following primary angioplasty early hospital discharge was permitted for uncomplicated patients at 48 hours [chapter 4; Table 4.4], with the remainder discharged according to physician preference. The duration of hospital stay following subsequent readmissions was also recorded for patients in the primary angioplasty and TL pilot cohort.

7.3.3 Statistics
Comparison of continuous variables between cohorts was assessed using non parametric tests due to the skewed distribution of data (Mann Whitney U and Kruskal - Wallis tests). Chi square and Fisher's exact test were used to compare categorical variables.
## Table 7.1 Baseline characteristics of study cohorts

<table>
<thead>
<tr>
<th></th>
<th>Primary Angioplasty (n=105)</th>
<th>TL pilot (n=87)</th>
<th>TL pre pilot (n=105)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean age (sd)</strong></td>
<td>59.4 (12.6)</td>
<td>61 (14)</td>
<td>61 (13)</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Male sex (%)</strong></td>
<td>76</td>
<td>82</td>
<td>81</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Smoker (%)</strong></td>
<td>70</td>
<td>68</td>
<td>-</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Diabetes (%)</strong></td>
<td>18</td>
<td>31</td>
<td>-</td>
<td>0.17</td>
</tr>
<tr>
<td><strong>Hypertension (%)</strong></td>
<td>41</td>
<td>44</td>
<td>-</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Ethnicity</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Caulasian</td>
<td>71</td>
<td>49</td>
<td>54</td>
</tr>
<tr>
<td></td>
<td>- Asian</td>
<td>26</td>
<td>37</td>
<td>40</td>
</tr>
<tr>
<td></td>
<td>- Black</td>
<td>2</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>- Other</td>
<td>1</td>
<td>8</td>
<td>2</td>
</tr>
<tr>
<td><strong>Prior MI</strong></td>
<td>5 (12.2%)</td>
<td>11 (14.5%)</td>
<td>-</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Prior Revascularisation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>- PCI</td>
<td>1</td>
<td>1 (1.3%)</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>- CABG</td>
<td>0</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td><strong>Symptom duration at presentation med (IQR)</strong></td>
<td>110 (60-200)</td>
<td>174 (80-337)</td>
<td>-</td>
<td>0.004</td>
</tr>
<tr>
<td><strong>Symptom onset within 12 hours</strong></td>
<td>82%</td>
<td>84%</td>
<td>-</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Treatment received</strong></td>
<td>PA 98%</td>
<td>TL 80%</td>
<td>93%</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Anterior STEMI</strong></td>
<td>44%</td>
<td>32%</td>
<td>39%</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Cardiogenic Shock</strong></td>
<td>3%</td>
<td>2%</td>
<td>3%</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Peak CK med (IQR)</strong></td>
<td>787 (427-1728)</td>
<td>680 (140-1228)</td>
<td>-</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Follow up weeks med (IQR)</strong></td>
<td>16 (9-28)</td>
<td>17 (8-28)</td>
<td>28 (12-51)</td>
<td>0.004</td>
</tr>
<tr>
<td><strong>Follow up available</strong></td>
<td>103 (98%)</td>
<td>77 (89%)</td>
<td>98 (93%)</td>
<td>NS</td>
</tr>
</tbody>
</table>

- Data not recorded
7.4 RESULTS

7.4.1 Baseline Characteristics

There were baseline differences between study cohorts. Firstly the duration of follow up was similar for the primary angioplasty and 'TL pilot' cohorts, but longer in the 'TL pre pilot' group (Table 7.1). Nevertheless, the timing of MACE was similar between the three groups (median [IQR] 2 weeks [0-6] PA; 3 weeks [1-8] TL pilot; 3 weeks [2-12] TL pre pilot). Secondly the proportion of patients of Asian origin was higher in both the thrombolytic groups reflecting the catchment population of the admitting centre rather than that of the North East sector. This may also explain the higher proportion of diabetic subjects, although this was non significant. Finally symptom duration at presentation was shorter in the primary angioplasty cohort, although the proportion of patients presenting within 12 hours was similar.

7.4.2 Major Adverse Cardiac events

7.4.2.1 Primary angioplasty versus thrombolysis

Figure 7.1 demonstrates clinical endpoints for each cohort. MACE was significantly lower in the primary angioplasty cohort than in the pilot thrombolysis group, driven predominantly by a significant mortality reduction. MACE following primary angioplasty was also lower than the historical thrombolysis cohort, but did not reach significance. Stroke was lower in the PA group. However, non fatal MI was similar in all groups. Event rates were lower (though not significantly) in the historical thrombolytic cohort (TL pre pilot) than those admitted outside working hours after commencement of the pilot (TL pilot).
Figure 7.1 Major Adverse Cardiac Events at median follow up 19 weeks

*\( p=0.013 \) PA vs. TL pilot

**\( p=0.035 \) PA vs. TL pilot

**Key**

<table>
<thead>
<tr>
<th>PA</th>
<th>Pilot Primary Angioplasty</th>
</tr>
</thead>
<tbody>
<tr>
<td>TL pilot</td>
<td>Thrombolysis Strategy during the pilot service (outside working hours)</td>
</tr>
<tr>
<td>TL pre pilot</td>
<td>Thrombolysis Strategy prior to commencement of the pilot</td>
</tr>
</tbody>
</table>
7.4.2.2 Influence of multi-vessel coronary disease among patients assigned to primary angioplasty

Of 103 patients undergoing primary angioplasty, 47 (46%) had multivessel coronary disease (more than one vessel with greater than 70% luminal stenosis). Of these, 33 (70%) underwent intervention to the culprit vessel only, with the remaining 14 (30%) undergoing immediate multi-vessel coronary angioplasty. There was no detectable difference in event rates between patients with multivessel and single vessel disease (Figure 7.2). There was a higher rate of non fatal MI among patients with single vessel disease compared with multivessel disease, although this did not approach significance.

Among the subgroup of primary angioplasty patients with multi-vessel coronary disease, there was a higher rate of non fatal MI, unplanned revascularisation, and in turn MACE, in those patients undergoing culprit vessel revascularisation only during the index admission, although this did not approach significance in this small subgroup (Figure 7.3). Equally, among those patients undergoing single vessel angioplasty, there were no significant differences in outcome between patients with multi-vessel disease compared single vessel disease (Figure 7.4).
Figure 7.2 Major adverse events among 101* STEMI patients presenting to the Network Heart Attack Centre (N-HAC) undergoing primary angioplasty: Influence of multi-vessel coronary disease

All comparisons not statistically significant.

* 2 patients lost to follow up
Figure 7.3  Major Adverse Events among patients with multivessel coronary disease undergoing primary angioplasty (n=46): Influence of culprit versus multi-vessel coronary angioplasty

All comparisons not statistically significant
Figure 7.4 Major Adverse Events among patients undergoing single vessel primary angioplasty (n=87): Influence of single vessel versus multi-vessel coronary disease

- **Death**: Single vessel disease (n=54) - 2, Multi-vessel PCI (n=33) - 18
- **NFMI**: Single vessel disease (n=54) - 3, Multi-vessel PCI (n=33) - 6
- **CVA**: Single vessel disease (n=54) - 0, Multi-vessel PCI (n=33) - 7
- **Emergency revasc**: Single vessel disease (n=54) - 2, Multi-vessel PCI (n=33) - 12
- **MACE**: Single vessel disease (n=54) - 18, Multi-vessel PCI (n=33) - 18

Legend: ■ Single vessel disease (n=54) □ Multi-vessel PCI (n=33)
7.4.3 Resource Utilisation

Contrary to expectation, the number of emergency cardiac readmissions was not reduced by the primary angioplasty strategy (Figure 7.5). In addition the number of unplanned cardiac catheterisation procedures and emergency revascularisations were similar in all cohorts.

The proportion of emergency readmissions with either troponin positive ACS or recurrent STEMI were similar in all cohorts (Table 7.2). However, a higher proportion of patients re-presented with a troponin negative chest pain syndrome from within the primary angioplasty cohort compared to those treated with thrombolysis, although this was not significant.

The rate of inpatient transfer for cardiac catheterisation and subsequent revascularisation during the index admission and post discharge were similar in both thrombolytic cohorts (Table 7.3 and Table 7.4). By the end of follow up the primary angioplasty strategy had resulted in 51 additional cardiac catheterisations and 61 additional revascularisations per 100 patients treated compared to thrombolysis, when all planned and unplanned procedures were included. (Additional revascularisations were calculated using the combined average from the thrombolytic cohorts).
Figure 7.5 Emergency readmissions and unplanned cardiac catheterisation procedures at a median of 19 weeks follow up

<table>
<thead>
<tr>
<th></th>
<th>PA n=103</th>
<th>TL pilot n=77</th>
<th>TL pre pilot n=98</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emergency readmission</td>
<td>21</td>
<td>18</td>
<td>14</td>
</tr>
<tr>
<td>Unplanned Catheter</td>
<td>14</td>
<td>13</td>
<td>8</td>
</tr>
<tr>
<td>Unplanned revasc</td>
<td>8</td>
<td>8</td>
<td>8</td>
</tr>
</tbody>
</table>
Table 7.2 Diagnosis following Emergency Readmission

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>PA n=22 (21%)</th>
<th>TL pilot n=20 (26%)</th>
<th>TL pre pilot n=18 (18%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chest pain syndrome</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Troponin negative</td>
<td>13 (59%)</td>
<td>8 (40%)</td>
<td>8 (44%)</td>
</tr>
<tr>
<td>NSTE-ACS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Troponin positive</td>
<td>5 (23%)</td>
<td>6 (30%)</td>
<td>4 (22%)</td>
</tr>
<tr>
<td>Recurrent STEMI</td>
<td>3 (14%)</td>
<td>3 (15%)</td>
<td>2 (11%)</td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• LVF</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>• Arrhythmia</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>• CVA</td>
<td>0</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>• Non Cardiac death</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>
Table 7.3 Cardiac catheter procedures performed during the index admission and during follow up

<table>
<thead>
<tr>
<th></th>
<th>PA</th>
<th>TL pilot</th>
<th>TL pre pilot</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=105</td>
<td>N=87</td>
<td>N=105</td>
</tr>
<tr>
<td>INPATIENT PROCEDURES</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All Catheterisation</td>
<td>100%</td>
<td>44 (51%)</td>
<td>59 (56%)</td>
</tr>
<tr>
<td>Indication</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischaemia driven</td>
<td>1 (1%)</td>
<td>17 (20%)</td>
<td>24 (23%)</td>
</tr>
<tr>
<td>Protocol driven</td>
<td>-</td>
<td>27 (31%)</td>
<td>35 (33%)</td>
</tr>
<tr>
<td>PROCEDURES DURING FOLLOW UP</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All outpatient</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Catheterisation</td>
<td>22 (21%)*</td>
<td>15 (18%)</td>
<td>17 (17%)</td>
</tr>
<tr>
<td>Unplanned</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Catheterisation</td>
<td>14 (14%)</td>
<td>10 (13%)</td>
<td>8 (8%)</td>
</tr>
<tr>
<td>TOTAL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No Catheter studies per 100 patients treated</td>
<td>121</td>
<td>68</td>
<td>72</td>
</tr>
</tbody>
</table>

* Includes 6 cardiac catheter studies immediately prior to planned 'staged' non culprit PCI, 1 patient undergoing routine coronary angiography following a primary angioplasty to the left main stem, and 1 patient with recurrent stable angina.
Table 7.4 Revascularisation procedures performed during the index admission and during follow up

<table>
<thead>
<tr>
<th></th>
<th>PA N=105</th>
<th>TL pilot N=87</th>
<th>TL pre pilot N=105</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>INPATIENT PROCEDURES</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Revascularisation</td>
<td>103 (98%)</td>
<td>32 (37%)</td>
<td>41 (40%)</td>
</tr>
<tr>
<td>· PCI</td>
<td>103</td>
<td>27</td>
<td>37</td>
</tr>
<tr>
<td>· CABG</td>
<td>0</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td><strong>PROCEDURES DURING FOLLOW UP</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All Revascularisation</td>
<td>13 (13%)</td>
<td>10 (12%)</td>
<td>12 (12%)</td>
</tr>
<tr>
<td>· PCI</td>
<td>13</td>
<td>5</td>
<td>9</td>
</tr>
<tr>
<td>· CABG</td>
<td>0</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>Emergency Revascularisation</td>
<td>8 (8%)</td>
<td>6 (8%)</td>
<td>6 (6%)</td>
</tr>
<tr>
<td>· PCI</td>
<td>2</td>
<td></td>
<td>5</td>
</tr>
<tr>
<td>· CABG</td>
<td>4</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Revascularisations per 100 patients treated</td>
<td>111 (All PCI)</td>
<td>48 (11 CABG)</td>
<td>51 (7 CABG)</td>
</tr>
</tbody>
</table>
7.4.4 Hospital Stay

Inpatient hospital stay was significantly reduced by the primary angioplasty strategy by a median of 2 days compared to the historical cohort, and 3 days compared to thrombolysis during the pilot period (Table 7.5).

Early hospital discharge was associated with a similar event rate post discharge to those discharged later (Table 7.6). A significantly higher proportion of those patients allowed home early required a subsequent unplanned cardiac catheterisation procedure, though this did not lead to an increase in repeat revascularisations.

Although the number of cardiac readmissions was similar in both the PA and the 'TL pilot' cohorts, the median duration of hospital stay for readmission following PA was substantially shorter (Table 7.5). The primary angioplasty strategy saved 529 bed days per 100 patients treated, when all index and subsequent hospitalisations were included.
Table 7.5 Analyses of hospital stay during index admission and following readmission

<table>
<thead>
<tr>
<th></th>
<th>PA N=105</th>
<th>TL pilot N=87</th>
<th>TL pre pilot N=105</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>INDEX ADMISSION</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospital stay</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Excluding cardiac centre</td>
<td>NA</td>
<td>5 (4-9.25)</td>
<td>4 (1.5-6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Days: median (IQR)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospital stay including cardiac centre</td>
<td>3 (2-4)</td>
<td>6 (5-12)</td>
<td>5 (4-9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Days: median (IQR)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>FOLLOW UP</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALL READMISSIONS</td>
<td>27 (26%)</td>
<td>23 (30%)</td>
<td>-</td>
<td>NS</td>
</tr>
<tr>
<td>Hospital Stay</td>
<td>2 (1-7)</td>
<td>7 (2-16)</td>
<td>-</td>
<td>0.049</td>
</tr>
<tr>
<td>Days: median (IQR)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EMERGENCY READMISSIONS</td>
<td>22 (21%)</td>
<td>20 (26%)</td>
<td>17 (17%)</td>
<td>NS</td>
</tr>
<tr>
<td>Hospital Stay</td>
<td>3 (1-7)</td>
<td>6 (1-15)</td>
<td>-</td>
<td>NS</td>
</tr>
<tr>
<td>Days: median (IQR)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospital Stay</td>
<td>3 (2-5)</td>
<td>7 (5-17)</td>
<td>-</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Days: median (IQR)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospital Days per 100 patients treated</td>
<td>613</td>
<td>1142</td>
<td>-</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

- Data not recorded
Table 7.6 Effect of early discharge on event rate among patients allocated to primary angioplasty

<table>
<thead>
<tr>
<th></th>
<th>48 hr Discharge N=36</th>
<th>&gt; 48 hr Discharge N=66</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Event Rate post discharge</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Composite MACE</td>
<td>4 (11%)</td>
<td>8 (12%)</td>
<td>NS</td>
</tr>
<tr>
<td>• Death</td>
<td>0</td>
<td>1 (2%)</td>
<td>NS</td>
</tr>
<tr>
<td>• NFMI</td>
<td>3 (8%)</td>
<td>5 (8%)</td>
<td>NS</td>
</tr>
<tr>
<td>• Stroke</td>
<td>0</td>
<td>0</td>
<td>NS</td>
</tr>
<tr>
<td>• Emergency Revasc</td>
<td>3 (8%)</td>
<td>5 (8%)</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Resource Utilisation</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Emergency readmission</td>
<td>9 (25%)</td>
<td>13 (20%)</td>
<td>NS</td>
</tr>
<tr>
<td>Unplanned Catheter</td>
<td>8 (22%)</td>
<td>6 (9%)</td>
<td>0.049</td>
</tr>
</tbody>
</table>
7.5 DISCUSSION

7.5.1 Clinical Outcome

These data demonstrate that the pilot primary angioplasty service was associated with a significant reduction in mortality and overall MACE when compared to contemporaneous and historical patient cohorts allocated to thrombolysis. Importantly, mortality, and stroke rates were comparable to those observed in randomised controlled trials to date, with a slightly elevated rate of non fatal MI (127). However, the non-randomised and time dependent nature of this study necessitates some caution in interpretation. Trials comparing these reperfusion strategies have demonstrated only modest reductions in mortality with the major benefit emanating from a reduction in non fatal MI (127; 132). In the present study this situation was reversed, with a sizeable mortality reduction but a similar incidence of non fatal MI in all cohorts.

It is possible that the mortality differences observed may have been exaggerated by patient selection rather than treatment per se. Whereas thrombolysis patients were investigated from one centre within the network, primary angioplasty patients were recruited from centres across North East London. Failure to transfer high risk patients from other participating Accident and Emergency departments for primary angioplasty cannot therefore be excluded. In addition the daytime operation of the primary angioplasty service may have further skewed the outcome in favour of this strategy. The Zwolle group have demonstrated improved outcomes following primary angioplasty during routine duty hours (209). Nevertheless, any bias favouring selection of low risk patients for primary angioplasty should have been reduced by the 'accept all' protocol whereby patients were delivered to the N-HAC by A&E physicians or LAS crews without referral to medics or cardiologists [chapter 4].

Delivery of thrombolysis may also be less effective out of hours. Indeed, the rate of prescription of thrombolysis was lower in the contemporaneous 'out of hours'
thrombolytic group compared with the historical cohort. In addition there was a lower MACE rate among the historical cohort despite longer follow up. Thus a low risk primary angioplasty cohort may have been compared with high risk thrombolytic groups, which will have been only partially redressed by inclusion of the historical thrombolytic group. Even so, the proportion of patients presenting with cardiogenic shock was similarly low in all three cohorts.

The lack of a reduction in non fatal MI following primary angioplasty also warrants consideration. There have been wide variations in the reported rates of NFIVII following reperfusion therapy, depending on the regimen used and the definition of the endpoint (between 2 and 9% at 30 days) (238). In this study any elevation of troponin above the local reference value was included in the NFVI endpoint, in accordance with the joint European Society of Cardiology (ESC) / American College of Cardiology (ACC) guidelines (44). It is likely that defining NFVI using peak CK elevation (of 1.5 or 2 times the upper limit of the reference range) would have reduced the rate of NFMI (239), although whether this would have been lower following primary angioplasty relative to thrombolysis remains uncertain. These data are not available as the centres investigated no longer use CK routinely for all cardiac admissions, and there is no standard cut off for troponin elevation, especially where troponin I assays are used (as is the case in the North East London Network).

It is also likely however, that the rate of NFMI among thrombolysis patients was lower than may be expected from a ‘real world’ STEMI cohort. This may have been a reflection of the fact that over half of the patients allocated to thrombolysis underwent cardiac catheterisation during the index admission, of whom above 70% were revascularised, thereby reducing the risk of subsequent re-infarction.

It is also possible that the revascularisation strategy may have had an impact on the rate of non fatal MI in the primary angioplasty cohort. These patients
predominantly underwent culprit vessel revascularisation only. In those patients with multi-vessel disease this was associated with a higher rate of non fatal MI, and unplanned revascularisation compared with those undergoing complete revascularisation, though this was not statistically significant. Angiographic (17), angioscopic (18), and intravascular ultrasound (IVUS) (19) studies have previously established that multiple complex plaques coexist throughout the coronary tree in patients presenting with STEMI, though there is debate as to their prognostic importance (17;19;20). However, no definite conclusions can be drawn from this small subgroup of patients. A definitive answer to the question of multi-vessel versus culprit vessel angioplasty in STEMI patients with multi-vessel disease can only be appropriately addressed in the context of a randomised controlled trial.

Finally the rate of non fatal MI could have been spuriously low in the thrombolytic cohorts. It is possible that some events may not have been captured. Whereas primary angioplasty readmissions were tracked at all centres across the network, thrombolysis patients were predominantly tracked through the referring centre only. Notably some primary angioplasty patients were readmitted to a network centre other than the centre of origin for the index admission. In addition follow up data were available for a higher proportion of primary angioplasty patients.

7.5.2 Resource utilisation
Contrary to expectation, the primary angioplasty strategy did not result in a reduction in emergency cardiac readmission, unplanned cardiac catheterisation, or unplanned revascularisation. The rate of readmission was however consistent with recent international registry data (43). Again the lack of difference between primary angioplasty and thrombolytic cohorts may have been a consequence of inpatient revascularisation in the thrombolytic groups resulting in fewer episodes of recurrent ischaemia following thrombolysis. However, a higher proportion of patients were readmitted with troponin negative chest pain from among the
primary angioplasty cohort, raising the possibility that many of these admissions may not have been ischaemic. The lack of an associated increase in revascularisation and shorter hospital stay following readmission among primary angioplasty patients supports this notion. However, the reason for a higher rate of non ischaemic chest pain readmissions following primary angioplasty remains unclear.

The primary angioplasty strategy radically reduced the duration of hospital stay compared to thrombolysis. This difference in hospitalisation increased further when cardiac readmissions were taken into account. Furthermore, the saving of 529 days per 100 patients treated with primary angioplasty was calculated in comparison with thrombolysis at the centre with the shortest STEMI hospitalisation within the network [see chapter 3 Table 3.2]. This suggests that the potential bed day savings compared to current practice across the sector would be considerably higher.

The reduction in hospital stay was a consequence of the early discharge policy for uncomplicated patients following primary angioplasty combined with the prolongation of hospital stay caused by transfer to the cardiac centre for invasive investigation following thrombolysis [see chapter 3; 3.4 RESULTS]. The early discharge policy appeared safe, in that there was no difference in MACE compared to those discharged later. However, there was a significantly higher rate of subsequent unplanned cardiac catheterisation in the early discharge group, though not resulting in a commensurate increase in revascularisation. All patients allocated to early discharge were reviewed by the cardiac rehabilitation team prior to discharge, and invited to a follow up visit at the N-HAC within 10 days for physician and cardiac rehabilitation review, in order to ensure patient education and dose titration of secondary preventive therapy. It may therefore be surprising that this ‘low risk’ group required additional invasive investigations. It is possible that despite these measures, early discharge did not allow sufficient patient confidence or education, resulting in more frequent re-
presentations with non cardiac pain. In the context of an evolving pilot programme, and the associated early discharge protocol, there may have also been a desire among clinicians to perform early coronary angiography in such cases rather than leave uncertainty while arranging non invasive investigation. These data may suggest that selection of patients for early discharge may require criteria specific to the individual in addition to clinical criteria.

As stated in chapter 5, the data presented here represent outcomes from an evolving rather than established service. Thus far the primary angioplasty service has demonstrated improved clinical outcomes compared with thrombolysis, with a major reduction in hospital stay. However, strategies are required to further reduce both ischaemic and non ischaemic readmissions following discharge. In addition favourable outcomes must be proven with expansion of the protocol outside working hours.

7.6 CONCLUSIONS

Primary angioplasty in North East London significantly reduced mortality and major adverse cardiac events among patients with STEMI relative to thrombolysis. However, strategies are still required to reduce emergency non cardiac readmissions and unplanned catheterisation procedures. Primary angioplasty saved 529 hospital bed days per 100 patients treated compared with thrombolysis, at the cost of 51 additional cardiac catheterisation procedures and, and 61 revascularisations. Delivery of a 24 hour seven day service should now be considered.
CHAPTER 8 General Discussion and Conclusions
8.1 SUMMARY OF FINDINGS

This thesis has described the development, instigation and expansion of a pilot primary angioplasty service within a metropolitan population in North East London. The impact of protocol design on clinical outcomes and service delivery has been investigated, and resource utilisation compared with the thrombolytic strategy within a section of this population. In addition the influence of platelet activation as a possible biological mechanism determining the efficacy of reperfusion has been explored, and in turn the impact of service design, specifically the use of pharmacological facilitation, on platelet activation has been studied.

The stimulus to redesign delivery of reperfusion therapy for patients presenting with ST segment elevation myocardial infarction (STEMI) was initially based on the increasing body of evidence that primary angioplasty was superior to thrombolysis in terms of clinical outcome (127), and has been discussed in detail in chapter 1 [1.6 Mechanical Reperfusion Therapy for ST segment Elevation Myocardial Infarction - Primary Angioplasty]. However, chapter 3 demonstrated that existing delivery of reperfusion therapy in North East London using the thrombolytic strategy was associated with a significant burden of invasive investigation and revascularisation, resulting in substantial prolongation of hospital stay across the network. This was in spite of effective delivery of the therapy itself, and highlights the limitations of NSF targets focussed on prescription of therapy rather than clinical outcome. Moreover, chapter 3 also demonstrated inequities in both referral practice and access to tertiary cardiac services across the network. These findings suggested that there was an existing need to reassess the provision of reperfusion therapy within North East London, with the aim of improving access to cardiac catheterisation and revascularisation and reducing resource utilisation. This provided an additional rationale for development of a pilot primary angioplasty service locally.
The process of service design, instigation and expansion described in chapter 4 was itself dynamic. An existing tertiary cardiac centre was selected to function as the network heart attack centre (N-HAC) for the period of the pilot. Partnership with the London Ambulance Service (LAS) was an essential feature of the process from the outset, and allowed the development an optimal pathway for rapid access to reperfusion therapy, using independent pre hospital diagnosis by LAS crews without the need for formal referral. However the impact and importance of an additional access strategy from A&E departments within the network became apparent only once the pilot commenced. The latter protocol led to over 50% of all recruitment, and resulted in the development of a dedicated patient transfer system (‘SCATS’) by LAS [chapter 4]. In addition it afforded the opportunity to investigate the use of upstream anti-platelet therapy prior to transfer in the protocol.

These two access strategies were compared in chapter 5. As expected, pre hospital diagnosis with direct ambulance catheter lab access significantly reduced the time to reperfusion in those undergoing a primary angioplasty procedure, when compared with A&E transfer. However, the 'accept all' no referral policy was associated with lower diagnostic accuracy for STEMI among patients delivered by LAS crews relative to their counterparts in A&E. The fact that many of those LAS patients without STEMI had a high risk NSTE-ACS suggests that this issue was a result of unfamiliarity with the protocol rather than an inability to recognise ACS patients with ST elevation. This finding demonstrates the necessity of continuing education for all stakeholders, and may imply that referral mechanisms such as ECG telemetry should be investigated to avoid unnecessary mobilisation of the N-HAC team in future, particularly when expansion to a 24 hour protocol is considered.

The most recent European and North American guidelines governing the management of ST segment elevation myocardial infarction recommends that in patients treated with primary angioplasty the door to balloon (DTB) time should
not exceed 90 minutes (136; 240). The direct access strategy achieved this target in 94% of cases. However this target does not refer specifically to patients transferred from distant centres. In this situation a European taskforce has recommended a target of 120 minutes (212), which was achieved in 65% of A&E transfer patients. In the North American guidelines transfer is not recommended if the delay to the primary angioplasty strategy (DTB-DTN) exceeds 60 minutes (136), at which point the mortality benefit may be lost (135). A&E transfer patients had a median delay of 69 minutes. Although this falls outside this window, it is well within the 93 minutes necessary to derive a benefit in MACE (135). While this may be acceptable, chapter 5 also highlighted that there may be opportunities to further streamline the patient pathway through participating A&E departments.

Despite the delay incurred by the transfer strategy, clinical outcomes and myocardial infarct size were similar to those in the direct access group. This is interesting as 79% of A&E transfer patients presented within 3 hours of symptom onset, when the outcome of reperfusion therapy is likely to be most time dependent (137). This is therefore likely to have been the consequence of pre transfer anti-platelet therapy with clopidogrel and abciximab, which was associated with a significantly higher frequency (more than double) of TIMI grade 3 flow in the infarct related artery at angiography prior to coronary intervention. The implication of this finding is that early reperfusion following pre transfer therapy compensated for transfer delay. The benefit of pre transfer therapy may also translate to the direct access cohort, such that the optimal future strategy may be the administration of therapy in the pre-hospital setting. It is important to recognise however that in terms of service delivery these strategies remain complementary. The development of the two protocols was borne of necessity. At inception direct access was preferred, offering the most rapid access to reperfusion. However, A&E transfer remains essential to ensure access to therapy for self presenters, patients developing ST elevation in the department, and as a safety net for LAS crews where the diagnosis is uncertain.
Chapter 6 of this thesis investigated potential biological mechanisms that may determine outcome following primary angioplasty. Platelet behaviour was studied in a subgroup of 25 patients from the primary angioplasty cohort in order to investigate the influence of platelet activation on reperfusion following primary angioplasty, and the effect of early anti-platelet therapy on the platelet response to the primary angioplasty process. The markers studied included platelet monocyte aggregates (PMA) and CD40 ligand (CD40L), both of which themselves possess pro-inflammatory and pro-thrombotic properties, and have previously been implicated as promoters of plaque instability and thrombogenicity (185; 220). PMA formation at presentation but not CD40L expression determined the efficacy of both epicardial and microvascular reperfusion in addition to infarct size following primary angioplasty. Furthermore, early anti-platelet therapy resulted in a more rapid reduction of PMA post intervention, modifying the platelet response to resemble that observed following coronary angioplasty in the setting of stable coronary disease. These data support the concept that PMA reflect plaque thrombogenicity and may implicate them as direct mediators of microvascular dysfunction in the setting of STEMI. In addition, reduction of PMA may provide a novel plaque stabilising mechanism explaining the benefit of early abciximab therapy prior to primary angioplasty observed in clinical trials (83; 126). These results could help explain why unlike abciximab, thrombolytic agents have been associated with adverse clinical outcomes when used to facilitate primary angioplasty (217). Thrombolysis also improves patency prior to intervention, but has been demonstrated to enhance other markers of platelet activation. Thus the assertion that the mechanism of benefit from pre transfer anti-platelet therapy was the result of early coronary reperfusion may be over simplistic. Further studies investigating PMA in the setting of thrombolysis could be considered to test this hypothesis.

The central hypothesis of this thesis was that primary angioplasty could be delivered safely and effectively in a United Kingdom population, improving both
service efficiency and clinical outcomes compared with thrombolysis. The
previous chapter compared clinical outcomes and resource utilisation during the
pilot programme with outcomes following the thrombolytic strategy at one of the
participating centres. Although this comparison was non randomised and
involved relatively small sample sizes, primary angioplasty was associated with
significant reductions in mortality and overall MACE. Interestingly however, there
was no reduction in non fatal myocardial infarction, which has driven the MACE
reduction in a number of clinical trials (127). The rate of non fatal MI was similar
to that observed in previous primary angioplasty studies, but lower than might be
expected among patients treated with thrombolysis. This may have been a
consequence of 39% of thrombolysis patients undergoing revascularisation
during the index admission, although this proportion was still lower than
evidence would predict [chapter 2].

Disappointingly the pilot primary angioplasty service did not result in a reduction
in emergency readmission, unplanned cardiac catheterisation, or emergency
revascularisation. However, readmissions from among the primary angioplasty
cohort were predominantly with troponin negative chest pain, and although
many of these patients underwent invasive investigation, few required
revascularisation. Notably, there were more readmissions among uncomplicated
patients discharged early (at 48 hours). It is possible that 48 hour discharge may
not have allowed sufficient education or confidence among some patients,
leading to brief non ischaemic readmissions in the early post discharge period.
The fact that nearly all of these subjects underwent angiography but not
revascularisation is likely to reflect a clinical tendency to early invasive
investigation of possible complications during the evolution of the pilot service.

The major advantage of the primary angioplasty strategy in terms of resource
utilisation was the radical reduction in hospital stay. This result was a
combination of earlier discharge following primary angioplasty (even when 48
hour discharge was excluded) and prolonged stay following thrombolysis, as
discussed in chapter 2. Furthermore, the reduction in hospital stay increased when emergency readmissions were included. The prolongation of repeat hospitalisation following thrombolysis is more difficult to explain but may indicate a greater degree of severity of MACE events including stroke and non-fatal MI. Hospital stay was reduced by 529 days per 100 patients treated when compared to the centre with the shortest hospital stay within the network. The potential impact of hospital stay reduction across the North East London Cardiac Network is therefore considerable, particularly if translated to a 24 hour service.

8.2 FUTURE DIRECTIONS

8.2.1 Service Development

The data from this thesis have demonstrated that within the confines of a daytime service during working hours primary angioplasty can be delivered in North East London safely and effectively, achieving published international guidelines, improving clinical outcomes, and radically reducing hospital stay compared to the thrombolytic strategy. These results provide convincing evidence that the service should now be adopted as the preferred reperfusion strategy for the North East London Cardiac Network on a 24 hour seven day basis.

Temporal expansion of the protocol will provide important challenges. This initiative would make the North East London programme the largest primary angioplasty service in the UK, and the only one serving an entire hospital network with a population of nearly two million inhabitants. The pilot service has demonstrated areas where service delivery can be improved. These include the speed of transit through participating A&E departments, increasing the proportion of patients recruited directly via LAS, and increasing diagnostic specificity by these crews. These issues can be addressed rapidly through sustained education programmes for all stakeholders. ECG telemetry could be
investigated as a means of improving diagnostic accuracy further, and could form the basis of a pilot sub-study for selected LAS crews.

In addition the move to a 24 hour service will also present new hurdles that have not yet been addressed. Outcomes will need to be maintained out of hours, when the cardiac catheter lab is not fully staffed, and where there is greater potential for reperfusion delay. Additional staffing will be required at the N-HAC, an already problematic issue for fledgling district labs without on-call requirements. Changes in working practice will be required by medical all staff in order to deliver the service while meeting European working time directives.

In addition to resolving working practices within the N-HAC, 24 hour working will also affect LAS and A&E personnel across the network. The expanded use of the ‘SCATS’ protocol will result in more frequent movement of LAS crews out of their usual operational area, potentially compromising local response times for non cardiac emergencies. Meanwhile, although all participating A&E departments already function on a 24 hour basis, on site cover by senior A&E staff (registrars and consultants) may be reduced outside daytime hours. This might lead to a reduction in the diagnostic accuracy and appropriateness of inter-hospital transfers, and difficulties releasing staff trained in advanced life support to escort these patients with the ambulance crew. Finally the high turnover of junior medical staff across the six participating A&E departments will necessitate an ongoing programme of continued education to maintain familiarity with the protocol.

8.2.2 Clinical Research

The role of facilitation of primary angioplasty with anti-platelet therapy has been investigated in this thesis within the confines of a non randomised prospective observational study. As discussed in chapter 1 the role of facilitation remains a matter for debate [1.6.4 Pharmacological facilitation of Primary
Angioplasty. Provision of a 24 hour service will allow the opportunity to investigate the nature and timing of facilitation in the setting of a randomised controlled trial. At present the weight of evidence is moving away from thrombolysis prior to primary angioplasty, favouring the use of upstream abciximab (126;217). Recently however, anti-thrombin agents including bivalirudin have been proposed as an alternative to glycoprotein IIb/IIIa antagonists in the setting of coronary intervention (241). A randomised trial is currently being planned to operate in the North East London network comparing the use of upstream abciximab (with heparin in the catheter lab), with bivalirudin for STEMI either prior to transfer or in the catheter lab. In addition, the logistics of a sub study investigating pre-hospital administration of therapy by ambulance crews are being investigated.

Although 48 hour discharge for uncomplicated patients was not associated with an increase in MACE, the safety of this protocol has not yet been established. A retrospective qualitative study of the patient experience following early discharge is planned in the first instance to investigate further the issue of frequent non ischaemic readmissions. Thereafter a randomised trial comparing early versus later discharge is required to prove equivalence of these strategies.

8.2.3 Platelet Research

As a consequence of the logistics of performing flow cytometry within six hours of venesection at multiple time points, the platelet studies presented in the thesis were limited by sample size. The results of the platelet studies described should now form the basis of larger studies to test hypotheses generated from this observational work. Firstly, a larger prospective study controlled for demographic, clinical and therapeutic characteristics is required to confirm the results of the studies presented in this thesis. Thereafter, the influence of PMA on microvascular dysfunction following reperfusion may be investigated further using a small animal model of ischaemia and reperfusion. A grant proposal has already been developed, investigating the influence of both PMA and CD40 -
CD40L interactions on microvascular flow in the mouse mesentery using interracial microscopy.

Secondly, the finding that early anti-platelet therapy may modify the platelet response to balloon and stent insertion to resemble that of a stable plaque may suggest a plaque stabilising mechanism. In order to investigate the relationship between plaque morphology and platelet activation in STEMI, a protocol is currently being developed to correlate platelet marker expression at presentation with plaque morphology in vivo determined using advanced intravascular ultrasound technology (virtual histology, Volcano therapeutics, Rancho Cordova, CA).

Finally, the use of an alternative anti-thrombotic regime prior to intervention suggests that a platelet sub study should be planned in conjunction with the bivalirudin randomised trial proposed above. Also, as has been suggested earlier, the impact of thrombolytic therapy on these markers could provide valuable information that may further elucidate the mechanism of benefit of abciximab over thrombolysis for facilitation of primary angioplasty observed in clinical trials. However, due to the success of the pilot service, the opportunity to recruit patients receiving thrombolysis no longer exists within North East London during working hours, and would therefore need to be performed elsewhere.

8.3 CONCLUSIONS
Despite effective delivery of thrombolytic therapy, this reperfusion strategy necessitates frequent early revascularisation, leading to prolonged hospital stay in North East London. Primary angioplasty can be delivered safely and effectively to this population using a regional heart attack centre model. Direct ambulance access to the catheter lab significantly reduces the time to reperfusion. Where this cannot be performed, upstream anti-platelet therapy with abciximab and clopidogrel prior to transfer from an Accident and
Emergency department may compensate for inter hospital transfer delays. The efficacy of reperfusion following primary angioplasty can be determined by the degree of platelet activation at presentation, and in turn platelet activation may be modified by early anti-platelet therapy. Within the limitations of a daytime service primary angioplasty improves clinical outcome compared to thrombolysis, and is associated with a radical reduction in hospital stay. Delivery of a 24 hour seven day service should now be addressed.
REFERENCES


4. Reimer KA, Jennings RB. The "wavefront phenomenon" of myocardial ischemic cell death. II. Transmural progression of necrosis within the framework of ischemic bed size (myocardium at risk) and collateral flow. Lab Invest 1979;40(6):633-44.


43. Goldberg RJ, Currie K, White K, Brieger D, Steg PG, Goodman SG et al. Six-month outcomes in a multinational registry of patients hospitalized...


54. Yusuf S, Wittes J, Friedman L. Overview of results of randomized clinical trials in heart disease. II. Unstable angina, heart failure, primary


113. Ellis SG, Da Silva ER, Spaulding CM, Nobuyoshi M, Weiner B, Talley JD. Review of immediate angioplasty after fibrinolytic therapy for acute


170. Engler RL, Dahlgren MD, Peterson MA, Dobbs A, Schmid-Schonbein GW. Accumulation of polymorphonuclear leukocytes during 3-h


190. Scharf RE, Tomer A, Marzec UM, Teirstein PS, Ruggeri ZM, Harker LA. Activation of platelets in blood perfusing angioplasty-damaged coronary


APPENDIX 1a

Direct Access to London Chest Hospital for Patients presenting to London Ambulance Service with ST segment elevation MI

Pilot for Service
Discussion Document

Dr Elliot J Smith, Research Registrar
Cardiac Research Office
London Chest Hospital
Bonner Road
London E2 9JX
Tel: 020 8983 2213
Fax: 020 8983 2262
Email: elliot.smith@bartsandthelondon.nhs.uk

Prof Martin T Rothman
Professor of Interventional Cardiology
Director of Cardiac Research & Development
Barts & The London NHS Trust
The London Chest Hospital
Tel: 44 208 983 2216
Fax: 44 208 983 2381
PA Laura Roberts
PA email: laura.roberts@bartsandthelondon.nhs.uk
Direct angioplasty Proposal

Patients presenting with acute ST segment elevation MI (STEMI) via the London Ambulance Service (LAS) will have direct access to the London Chest Hospital for immediate angiography with a view to primary angioplasty where appropriate.

Background

The current strategy for treating patients presenting with acute (ST segment elevation) myocardial infarction (STEMI) at Barts and the London NHS trust is the administration of intravenous thrombolysis, to dissolve clot and reopen the occluded blood vessel (infarct related artery). The drug is most effective when given early, and thus reduction of the ‘door to needle time’ remains a National Service Framework directive.

However, even with rapid effective administration of the newest combinations of thrombolytic and anti platelet therapies the percentage of patients presenting with ST elevation MI achieving good (TIMI-3) flow in the infarct related artery is no more than 60-70% [1,2]. In those who do achieve reperfusion, the rate of re-occlusion is also unacceptably high (6 –13% early, and up to 30% at 30 days) [3,4]. Despite this thrombolysis remains the predominant reperfusion strategy in the United Kingdom.

Primary (or direct) angioplasty can provide TIMI-3 flow in 90-95% of cases, and is a superior reperfusion strategy where skilled operators are readily available [5,6,7], with improved outcomes for patients treated with stents and adjunctive glycoprotein GpIbIIa receptor antagonists [8]. Mechanisms of providing access to this therapy locally and nationally have not yet been investigated.

Aims

The aim is to examine our local provision of reperfusion therapy, and assess strategies to improve both delivery of treatment and patient outcomes. Therefore in addition to a pilot primary angioplasty service, this process will involve:

- Audit of current practice, to provide a context for prospective analysis (salient data presented in this document)
- Prospective audit of STEMI treatment with thrombolysis (at the Royal London and Newham General Hospitals)
- Implementation and audit of guidelines on the treatment of failure to reperfuse following standard thrombolytic therapy
We will compare reperfusion strategies collecting data prospectively, looking specifically at the following areas

- **Clinical**
  Delivery of treatment, with follow up of patient outcomes

- **Logistic**
  Address the practical issues related to service provision

- **Financial**
  Calculate the actual costs of each strategy (medications, consumables etc.)
  Calculate the financial impact on length of hospital stay, transfer time, and readmission rates for the Trust and for purchasers (early intervention may free beds in RLH and therefore decrease costs vs increased early costs of intervention)

The data collected over the pilot period will inform recommendations on the style of service we should plan in the future. These options could include:

- Continuation of thrombolysis as primary treatment for STEMI, with no plan for primary angioplasty

- Continuation of thrombolysis as primary treatment for STEMI with an explicit rapid invasive response to failure to reperfuse

- A *selective* primary angioplasty service targeting those shown to be at high risk, or who benefit most (e.g. patients with anterior ST elevation)

- Consideration of an expanded primary angioplasty service
Mechanism of pilot implementation

Patient Selection
- Chest pain onset < 6 hours
- ST elevation (identified by trained ambulance personnel)
- LBBB excluded
- No age limit

Patient Population
- 6 participating ambulance stations serving Tower Hamlets
- Royal London Hospital catchment area only

Hours of operation
- Blue Calls taken 0800 – 1600 Monday to Friday
- Not on Bank Holidays
- Not on audit days outside London Chest

Logistics
- Blue call from LAS via designated phone in each lab – arrival time 6-15 minutes
- Catheter lab space identified (if >60 mins delay then thrombolysis to be given (responsibility of designated Registrar)
- Patient admission directly to the catheter lab holding area (not CCU)
- Inpatient stay at London Chest
- Translation issues pertaining to the large non-english speaking local population will be addressed by the on site trained interpreter(s)
- It is accepted that there may rarely be instances of incorrect diagnosis, or significant co-morbidity. These patients will need to relocate to A+E without cardiac intervention (urgent transfer policy agreed with LAS). In the intervening period we will be medically responsible for the patient.

Start Date
- March 2003
- LAS currently ready
- Minor building work to be completed in catheter lab (shelving and drug cupboard in clinical area)
**Current Activity at Barts and the London NHS trust**

*Data from 1st Oct 2001 - 1st Oct 2002 Royal London Hospital*
Analysis of 1 year's data from RLH of patients who would fit the entry criteria for the proposed pilot study at LCH

105 patients (age 21-91 mean 61, 85 male) presented with **chest pain and ST elevation** on ECG (entry diagnosis definite or probable MI)
82.5% presented via LAS (either directly or via GP)
17.5% walk-in

98 (93%) received thrombolysis
2 failure of administration, 5 contraindicated
98% of those eligible received therapy

Agents used
- 34 SK (streptokinase)
- 47 TnK (Tenectoplasce)
- 17 tPA (alteplase)

Door to needle time
- 53% <20mins
- 74% <30mins*
- 83.5% <40mins

*Data from the MINAP report Jan- June 2002 show the Royal London Hospital reaches government targets on door to needle time (75% <30mins) (*Royal College of Physicians, November 19th 2002)*

1 primary angioplasty

8/105 (7.8%) died in hospital (9 by 30days, 10 at 3months)
1 death occurred in those not receiving lysis
STEMI Inpatient Transfers for Cardiac Catheterisation

58/105 (55%) transferred as inpatients for angiography with a view to inpatient revascularisation
5/7 who did not receive thrombolysis were transferred as inpatients, but only 1 was transferred immediately

(4 dead within 24 hours, prior to opportunity for PCI as a consequence of AMI)

20/58 (34%) transferred day 0 or day 1
11/20 were transferred as a consequence of failure to reperfuse following thrombolysis

(NB. Of the 47/105 who were not transferred for inpatient angiography, a further 6 patients were identified with failed thrombolysis)

Reason for transfer

36 ‘symptoms’ including 11 failed thrombolysis, 4 re-infarct, and post infarct angina

22 ‘protocol’ pain free with high risk features

(+10 booked for outpatient angiography)

In total of 65% of all STEMI pts were referred for angiography

3/10 of those patients referred for outpatient angiography were readmitted with an acute coronary syndrome before their booked angiogram date (2 within 30 days). All 3 were listed for inpatient angiography and underwent angioplasty that admission.
The diagram shows 23/105 (22%) patients remained free of death, failure to reperfuse, reinfarction, recurrent ischaemia or invasive investigation/revascularisation at 3 months.
Impact on Transfer time and Length of Hospital Stay

<table>
<thead>
<tr>
<th>Transfer time n=58</th>
<th>Range</th>
<th>Mean</th>
<th>Median</th>
<th>Mode</th>
</tr>
</thead>
<tbody>
<tr>
<td>Days</td>
<td>0-20</td>
<td>3.6</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Days*</td>
<td>2-20*</td>
<td>5.3*</td>
<td>5*</td>
<td>6*</td>
</tr>
</tbody>
</table>

*Excluding patients transferred on day 0 or 1

<table>
<thead>
<tr>
<th>Hospital stay</th>
<th>Range</th>
<th>Mean</th>
<th>Median</th>
<th>Mode</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inpatient Cardiac Catheter n=58</td>
<td>1-36</td>
<td>8.1</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>Inpatient Cardiac Catheter* n=38</td>
<td>3-36*</td>
<td>9.8*</td>
<td>7*</td>
<td>5*</td>
</tr>
<tr>
<td>No Inpatient Cardiac Catheter n=37/47</td>
<td>0 - 24</td>
<td>5.43</td>
<td>5</td>
<td>4</td>
</tr>
</tbody>
</table>

*Excluding patients transferred on day 0 or 1

Conclusion

- Even with effective delivery of thrombolysis reaching NSF targets, over half those patients admitted with STEMI were transferred for inpatient cardiac catheterisation.

- Over one third necessitated very early transfer for failed reperfusion, re-infarction or recurrent symptoms.

- The current strategy incurs actual transfer costs (i.e. additional ambulance and escort personnel) and bed day wastage driven by delays till transfer and ensuing prolonged inpatient stay.
Projected Workload for Pilot

1.10.01 – 1.10.02
AMI patients arriving RLH between 0800 – 1700 56/105 (53%)

82.5% arrived via London Ambulance service

Projected STEMI admissions 5/7 days per week, over 1 year 40
Projected STEMI admissions 5/7 via LAS over 1 year 33

Expect mean 2.75 patients per calendar month

Currently we perform inpatient catheter/PCI on 55% of these patients

Current work predicts 1.5 patients per calendar month are already being treated invasively Mon-Fri 0800 - 1700

Additional workload will be 1.25 patients per calendar month

This would not be expected to have a major impact on current workload, or compromise treatment of patients waiting for inpatient catheterisation with non-ST segment elevation acute coronary syndromes.
References


7. Weaver WD, Simes RJ, Betriu A et al. Comparison of primary coronary angioplasty and intravenous thrombolytic therapy for acute myocardial infarction: a quantitative review. JAMA 1997 Dec 17;278(23):2093-8

APPENDIX Ib

Protocol for Daytime Access to Immediate Angiography for Patients Presenting to the Royal London Hospital Accident and Emergency Department

Discussion Document

Dr Elliot J Smith  
Research Registrar, The London Chest Hospital

Mr Mark Whitbread  
Cardiac Care Manager, London Ambulance Service

Dr. Anthony Mathur  
Senior Lecturer and Honorary Consultant, Barts and the London NHS Trust

Prof Adam D Timmis  
Professor of Clinical Cardiology, Barts and the London NHS Trust

Prof Martin T Rothman  
Professor of Interventional Cardiology, Barts and the London NHS Trust
Background

As you may be aware, The London Chest Hospital (LCH) opened its Direct Access pilot primary angioplasty service to blue calls from London Ambulance Service (LAS) in April 2003. The service offers daytime access for patients presenting with ST segment elevation Myocardial Infarction (STEMI) to immediate angiography with a view to immediate culprit vessel angioplasty.

Based on Audit data from patients presenting to the Royal London Hospital (RLH) A&E with chest pain and ST elevation from October 2001-2002, we expected that 2-4 patients to present via LAS per calendar month during the hours of operation of Monday – Friday 0800-1600 hours (see the attached Acute MI discussion document 25.11.2). Thus far we have in fact received fewer patients than expected, though it is still early days. In addition there is a desire to meet the needs of those patients who self-present to A&E or develop ST elevation in A&E during these hours. This has stimulated the development of a protocol for early transfer and angiography for this patient group.

There is a large body of evidence supporting primary angioplasty as the preferred reperfusion strategy for STEMI patients when compared with thrombolysis (23 randomised controlled trials to date) (1). There is further strong evidence that it is also safe and effective to transfer STEMI patients from a non-invasive centre to an intervention centre with a view to primary angioplasty(2,3). In these studies no thrombolytic therapy was administered prior to transfer. Furthermore patients with transfer times of up to 3 hours still had reduced event rates when compared to patients treated with on site thrombolysis. There is also emerging data to support a ‘facilitated’ angioplasty approach where pharmacological therapy (including either reduced dose thrombolysis, glycoprotein IIbIIIa receptor blockade, or a combination) is administered initially to increase the likelihood of arterial patency, followed by immediate angiography and angioplasty (4,5). We await the data from ongoing trials to elucidate the optimal combination. However, although there is some data to support a strategy of full dose thrombolysis, followed by ‘rescue’ angioplasty for patients who do not achieve acceptable ST segment resolution (6), this is associated with an elevated bleeding risk.

Our interpretation of this data is that patients self-presenting to RLH A&E would be best served by being transferred as early as possible from RLH to LCH without antecedent thrombolysis. All patients meeting inclusion/exclusion criteria would be offered immediate transfer to LCH for angiography with a view to PCI where appropriate. This would be performed with a call to LAS via the existing emergency transfer telephone. The ambulance service can provide crews rapidly via this mechanism, in order to deliver the patient directly to the cardiac catheter lab table in no more than 30 minutes following arrival in A&E. The protocol has the advantage of including patients with contraindications to thrombolysis.
The following document contains a draft protocol to facilitate transfer of these patients. This has been designed to integrate with the existing DIRECT AMI protocol (a copy of which is enclosed), and the current RLH guidelines for management of ST segment Elevation MI. They represent a framework for discussion that may be adapted to meet the needs of the patients, and the A&E and Cardiology departments.

1. INCLUSION / EXCLUSION CRITERIA
The following criteria mirror the DIRECT AMI LAS criteria.

**Hours of operation:**
*Monday to Friday 0800hrs – 1600hrs*
Patients arriving after 0730 can be included as they would be expected to receive catheterisation by 0800. Patients arriving after 1600 precisely should not be offered immediate transfer, and should therefore receive usual therapy (i.e. thrombolysis where indicated)

**INCLUSION CRITERIA:**
- Patients with Chest Pain suggestive of ACS
- Most recent sustained pain (>20 minutes) within 6 hours
- ECG showing ST Elevation in TWO or more contiguous leads
  - AT LEAST 2 mm ANTERIOR LEADS
  - AT LEAST 1mm non-anterior LEADS
- Orientated and Conscious

**EXCLUSION CRITERIA:**
- Left Bundle Branch Block – LBBB on 12 Lead ECG
- Unconscious Patients
- Cardiogenic Shock (BP < 85mmHg)
- Confused
- Previous CVA with dense hemiplegia / other severe disability
- Patients in Cardiac Arrest
- Intubated patients

*NB. While Cardiac Arrest and Cardiogenic Shock are exclusion criteria for this immediate transfer protocol, they may of course be discussed on an individual case basis with the on call Cardiology SpR.*

2. DIAGNOSIS
The diagnosis of definite or probable STEMI will be made in the usual manner, based on symptoms and ECG.

*However this ECG must be corroborated by a second senior physician (SpR or Consultant in Accident and Emergency or Medicine)*
3. BLOOD SAMPLING
The usual samples should be taken before thrombolysis, but with the addition of a group and save sample.

In addition, blood should be taken for research purposes into the bottles provided as for all ACS patients. Patients can be consented formally following venesection by a member of the cardiac research team (as per ethics committee approval). These samples are particularly relevant in this patient group.

4. PRE-TRANSFER THERAPY
- **Aspirin 300mg** should be administered if it has not already been given in the ambulance.
- **Clopidogrel 300mg** should be administered.
- **Abciximab (Reopro)** should be given if readily available, but must not delay patient transfer.
- Analgesia can be administered as per usual protocols

5. MECHANISM OF REFERRAL
Once the patient has been identified as a transfer candidate, the plan to transfer for immediate angiography should be discussed with the patient, and the possibility of angioplasty. The patient does not need to be formally consented at this stage (this will be performed by a SpR at LCH). However on rare occasions where patients strongly object to invasive therapy, they can be excluded without proceeding further.

- The ECG and PATIENT MUST BE REVIEWED BY the A&E SpR or consultant before referral takes place. The patient does not need to be discussed with the on call medical team.

- A call should be made to LAS via the existing emergency transfer phone in A&E. The attending ambulance will then inform LCH of the transfer via Ambulance Control using the existing BLUE PHONE and giving the usual CASMEET information (see Direct AMI protocols book). This will occur as the ambulance leaves for LCH giving a 10 minute warning.

- Provided the patient fulfils inclusion/exclusion criteria in the opinion of the A&E SHO and SpR (or consultant), the patient does not need to be discussed with the on call Cardiology SpR.

- All other patients NOT MEETING THE ABOVE CRITERIA who are felt to be potential early transfer candidates **MUST BE DISCUSSED IN THE USUAL MANNER WITH THE ON CALL SPR AND MUST NOT BE SENT TO LCH DIRECTLY. THIS PROTOCOL IS DESIGNED FOR STEMI ONLY.**
Under rare circumstances where on arrival the patient is not felt to warrant angiography, a cardiology SpR will inform A&E immediately. The patient will usually be transferred back to A&E.

6. TRANSFER
The patient will be transferred with a physician in attendance. Where necessary an English speaking relative should be allowed to accompany the patient.

7. ARRIVAL AT LCH
On arrival at LCH the patient will be transferred directly to catheter lab recovery, and treated as per the DIRECT AMI protocol.

The patient’s existing notes and ECGs should be attached to the DIRECT AMI ICP, which should be used for all other clinical entries. The patient will remain an inpatient at LCH.
8. FLOW CHART

DIAGNOSIS OF ST SEGMENT ELEVATION ACUTE MI

FULFILLS INCLUSION/EXCLUSION

YES

INFORM PATIENT OF TRANSFER OPTION

AGREE

Take Blood. Then Administer:
- Aspirin 300mg (if not already)
- Clopidogrel 300mg
- Abciximab (Repopro) when available

CALL LAS

TRANSFER PATIENT to LCH with physician

NO

USUAL A&E TREATMENT

DISAGREE
References


APPENDIX Ic

Direct Access to London Chest Hospital for Patients presenting to London Ambulance Service with ST segment elevation MI

Pilot for Service

EXPANSION TO NEWHAM GENERAL HOSPITAL
Discussion Document

Dr EJ Smith  Research Registrar, London Chest Hospital
Mr M Whitbread  Cardiac Lead, London Ambulance Service
Dr. K Ranjandaylan  Consultant Cardiologist, Newham General Hospital
Prof MT Rothman  Professor of Interventional Cardiology, London Chest Hospital
Prof AD Timmis  Professor of Clinical Cardiology Barts and the London NHS Trust, and Consultant Cardiologist Newham General Hospital
The Current Direct Angioplasty Pilot Service at London Chest Hospital

Patients presenting with acute ST segment elevation MI (STEMI) via the London Ambulance Service (LAS) currently have direct access to the London Chest Hospital for immediate angiography with a view to primary angioplasty where appropriate. This pilot service is open to emergency ‘blue’ calls 0800-1600 hours weekdays, bringing patients who would normally be taken to the Royal London A&E.

Background

Rationale for Primary Angioplasty
The current UK strategy for treating patients presenting with acute (ST segment elevation) myocardial infarction (STEMI) is the administration of intravenous thrombolysis. The drug is most effective when given early, and thus reduction of the ‘door to needle time’ remains a National Service Framework directive.

However, even with rapid effective administration of the newest combinations of thrombolytic and anti-platelet therapies the percentage of patients presenting with ST elevation MI achieving optimal (TIMI-3) flow in the infarct related artery is no more than 60-70% (1,2). In those who do achieve reperfusion, the rate of re-oclusion is also unacceptably high (up to 30% at 30 three months)(3). Despite this thrombolysis remains the predominant reperfusion strategy in the United Kingdom.

Primary (or direct) angioplasty can provide TIMI-3 flow in 90-95% of cases, and has been demonstrated to be a superior reperfusion strategy when compared with thrombolysis (4), with improved outcomes for patients treated with stents and adjunctive glycoprotein GpIIbIIa receptor antagonists (5-7). Mechanisms of providing access to this therapy locally and nationally have not yet been investigated.

Rationale for Expansion
The Pilot service opened to ‘Blue Calls’ from LAS in April 2003. Based on audit data from patients presenting to the Royal London Hospital (RLH) A&E with chest pain and ST elevation from October 2001-2002, we expected that 2-4 patients to present via LAS per calendar month during the hours of operation (Monday – Friday 0800-1600 hours).

Thus far we have in fact received fewer patients than expected, though it is still early days. In addition there is a desire to meet the needs of local patients presenting via LAS from within neighbouring A&E catchment areas. This has stimulated discussion regarding the expansion of the pilot service to Newham Hospital Catchment area. Our aim is to expand the number of
patients treated to that originally expected. Newham is in close proximity to LCH, and also served by LAS crews trained in 12 lead ECG recognition.

Safety of transfer from Newham Catchment area to LCH
Recently published data have demonstrated that it is safe to transfer STEMI patients from a non-invasive centre to an intervention centre with a view to primary angioplasty (without administration of antecedent thrombolysis at the referring centre), and that this strategy is more effective than on site thrombolysis (8-10). In these studies transfer times of up to 2 hours were permissible, with a mean of 30 minutes. This excludes the time spent in a district hospital before transfer. Transfer times from the NGH catchment would reliably be expected to be below 30 minutes. Furthermore, with a strategy of pre-hospital diagnosis and patient delivery directly to LCH catheter lab, there would be no delay through NGH A&E. Thus we feel that it is safe to transfer patients diagnosed with STEMI directly to LCH, even if they are within closer reach of NGH A&E at the point of diagnosis.

Aims
The aim of the pilot is to examine our local provision of reperfusion therapy, and assess strategies to improve both delivery of treatment and patient outcomes. Therefore in addition to the pilot primary angioplasty service, this process involves ongoing audit of current practice, and prospective comparison of patient outcomes following treatment with usual therapy outside the hours of operation.

We are already collecting data prospectively using for the MINAP database. In addition we intend to collect data looking specifically at the following areas

- **Clinical**
  Delivery of treatment, with follow up of patient outcomes, including ECG evidence of reperfusion

- **Logistic**
  Addressing the practical issues related to service provision

- **Financial**
  Calculation of the actual costs of each strategy (medications, consumables etc)
  Calculation of the financial impact on length of hospital stay, transfer time, and readmission rates for the Trust and for purchasers (early intervention may free beds in RLH and therefore decrease costs vs. increased early costs of intervention)
The data collected over the pilot period will inform recommendations on the style of service we should plan in the future. These options could include:

- Continuation of thrombolysis as primary treatment for STEMI, with no plan for primary angioplasty
- Continuation of thrombolysis as primary treatment for STEMI with an explicit rapid invasive response to failure to reperfuse
- A *selective* primary angioplasty service targeting those shown to be at high risk, or who benefit most (e.g. patients with anterior ST elevation)
- Consideration of an expanded primary angioplasty service
Current Mechanism of Pilot implementation

Patient Selection

Inclusion Criteria
- Chest pain onset < 6 hours
- ST elevation (identified by trained ambulance personnel)
- Conscious
- No age limit

Exclusion Criteria
- Unconscious
- Cardiogenic Shock despite filling (BP < 85mmHg)
- Confused
- Previous CVA with dense hemiplegia / other severe disability
- Patients in established Cardiac Arrest
- Intubated patients

Ambulance Crews
- 6 participating ambulance stations serving Tower Hamlets and Newham
- Currently only Royal London Hospital catchment area. At present if the patient is nearer to NGH they go there.

Hours of operation
- Blue Calls taken 0800 – 1600 Monday to Friday (in order to ensure the last patient would be on the table before 1700)
- Not on Bank Holidays
- Not on audit days outside London Chest

Logistics
- Blue call from LAS via designated phone in the cath lab – arrival time 6-15 minutes
- Catheter lab space identified (if >60 mins delay then thrombolysis to be given - responsibility of designated Registrar)
- Patient admission directly to the catheter lab holding area (not CCU)
- Inpatient stay at London Chest
- Translation issues pertaining to the large non-english speaking local population will be addressed by the on site trained interpreter(s)
- It is accepted that there may rarely be instances of incorrect diagnosis, or significant co-morbidity. These patients will need to relocate to A+E without cardiac intervention (urgent transfer policy agreed with LAS). In the intervening period we will be medically responsible for the patient.

Start Date
- Opened April 2003
Projected Workload contributed by Newham

Background Audit Data

(Data from 1st Oct 2001 - 1st Oct 2002 Newham General Hospital)

104 patients (age 34-97 mean 63; 74 male) presented with chest pain and ST elevation (entry diagnosis probable or definite MI) – LBBB excluded

90 (86.5%) admitted via LAS

84 (81%) received thrombolysis
8% too late, 7% risk haemorrhage

DTN (mean 73, median 30 mins)
39% < 30mins
42% < 40mins

Cardiac Catheterisation
22 (20%) transferred for inpatient cardiac catheter
31 (30%) listed before discharge for outpatient cardiac catheter
Total 50% referred for invasive investigation

6/104 died (5%) in hospital

Workload
43% (45) presented within the period 0800-1600
Actual number admitted via LAS and within pilot time window 38/104 (36.5%)
Project 27 patients within this time window – 5/7 days a week

2.3 patients p.c.m

Application of exclusion criteria, and account for audit days, bank holidays and unforeseen closures will further reduce this number.

Thus we would expect to supplement recruitment by a maximum of 2 patients per month
Comparison with Barts and the London NHS trust
Audit Data for the same period

(Data from 1st Oct 2001 - 1st Oct 2002 Royal London Hospital)

105 patients (age 21-91 mean 61, 85 male) presented with chest pain and
ST elevation on ECG (entry diagnosis definite or probable MI)
82.5% presented via LAS

98 (93%) received thrombolysis
2 failure of administration, 5 contraindicated

Door to needle time
74% <30mins*
83.5% <40mins

Cardiac Catheterisation
58 (55%) referred for inpatient cardiac catheter
10 (9.5%) listed prior to discharge for outpatient angiography
65% of all STEMI pts were referred for angiography

8/105 (7.8%) died in hospital

Projected Workload
AMI patients arriving RLH between 0800 – 1700 56/105 (53%)
82.5% arrived via London Ambulance service
Projected STEMI admissions 5/7 days per week, over 1 year 40
Projected STEMI admissions 5/7 via LAS over 1 year 33

Expect mean 2.75 patients per calendar month
References


APPENDIX Id

DRAFT PROPOSAL

NORTH EAST LONDON SECTOR CARDIAC NETWORK
AND BLT CARDIAC DEPARTMENT

Direct Access To BLT For Patients Presenting To London Ambulance Service And A&E Departments With ST Segment Elevation Myocardial Infarction (STEMI)

Business Case Proposal for a 24-hour Seven-day Service Serving Northeast London

Dr. Elliot J. Smith, Barts and the London NHS Trust
Prof. Martin T. Rothman, BLT
Dr. Anthony W. Nathan, BLT
Mr. Steve Hart, BLT
Ms. Fiona Halstead, BLT
Ms. Clare Parker, BLT
Ms. Suzanne Marsello, BLT
Mr. Mark Whitbread, London Ambulance Service

Date: January 2004
1. INTRODUCTION
The purpose of this paper is to

- Introduce the concept of Primary Angioplasty for acute myocardial infarction (AMI)
- Document progress with regard to the 'pilot' London Chest direct transfer initiative for patients presenting with ST elevation to the London Ambulance Service from the Royal London catchment population
- Review audited outcomes of this pilot
- Propose developments in working practice which would be necessary to introduce a 24 hour 7 day service

2. CLINICAL RATIONALE FOR PRIMARY ANGIOPLASTY

Introduction
Thrombolytic therapy remains the predominant reperfusion strategy for ST segment elevation myocardial infarction (STEMI) in the United Kingdom with government policy directed towards optimising thrombolytic delivery. The drug is most effective when given early, and thus reduction of the 'door to needle time' remains a National Service Framework directive.

However the superiority of primary angioplasty over thrombolysis has now been demonstrated in multiple randomised trials dating back to the early 1990s (1). With the data currently available from 'real world' trials employing contemporary interventional techniques it is necessary for health providers to address the logistics of delivering primary angioplasty to the majority of their STEMI patients.

Problems With Thrombolysis
While the large multi-centre randomised controlled trials of the 1980s and early 1990s demonstrated that thrombolysis saves lives, this was only when compared to aspirin alone (2-6). Newer bolus preparations such as tenecteplase and reteplase have greater clot specificity, and are easier to administer. However, their efficacy is similar to standard preparations, and prognostic benefits have remained much the same (7-9). With optimal therapy only 50-70% of patients achieve complete effective patency (TIMI-3 flow) in the infarct related artery (7,8,10), and even where thrombolysis is effective the rate of early reocclusion remains unacceptably high (6-13% early, and up to 30% by 30 days) (11;12).

Furthermore, a significant proportion of patients are ineligible for treatment, and perhaps more importantly, a significant number who are eligible are denied treatment. The MIR and MITRA registries (21,092 patients) demonstrated that 48% of STEMI patients did not receive reperfusion therapy – 29% being ineligible, and 19% with no obvious contraindication (13).
Primary angioplasty can achieve TIMI-3 flow in 90-95% of cases, and treats both the occlusive thrombus and the ruptured plaque. Meta analysis of the short-term results of 10 randomised controlled trials conducted prior to 1997 demonstrated a mortality of 4.4% with angioplasty versus 6.5% using thrombolysis (p=0.02), with the composite endpoint of death or non fatal MI of 7.2% vs. 11.9% respectively (p<0.001) (14). Stroke was also significantly reduced. Long-term follow up data from Zwolle group (15) demonstrated an absolute mortality reduction of 11% (13% angioplasty vs. 24% streptokinase) after a mean of 5 years. Patients presenting with cardiogenic shock fare better following primary angioplasty (16), and it is the only reperfusion strategy available to those ineligible for thrombolysis.

Since the publication of these studies percutaneous coronary intervention (PCI) has evolved. Stenting following primary angioplasty reduces six month major adverse cardiac events (MACE) when compared with balloon angioplasty alone (POBA) (17), with further improvements in outcome with the addition of Glycoprotein receptor antagonist therapy (18). As yet it is not clear whether there may also be a role for pre-procedural thrombolysis (either alone or in combination with GPRA therapy) to ‘facilitate’ primary angioplasty. Results of ongoing trials such as FINESSE and ASSENT IV will address this issue in due course. What is clear is that contemporary primary angioplasty necessitates a combined mechanical and pharmacological approach.

Transfer for Primary Angioplasty
Until recently the problem with primary angioplasty has been the requirement that patients have immediate access to on-site cardiac catheter lab facilities and experienced operators. It has therefore been perceived to be impossible to offer such therapy to all infarct patients. This has been challenged with the advent of landmark trials demonstrating the safety and efficacy of acute inter-hospital transfer for primary angioplasty from district general hospitals (DGHs) without such facilities to a regional cardiac centre.

DANAMI-2 (19) randomised regional centre and DGH patients to on-site thrombolysis with tPA or primary angioplasty with stenting in most cases (93%). This was a high-risk group of patients with >4mm ST elevation and with symptoms for up to 12 hours. The composite endpoint of death / reinfarction / stroke was significantly reduced in the PCI group (13.7% versus 8.0% p=0.0003). Remarkably, this outcome was observed allowing transfer times (time from first presentation to arrival at the cardiac centre) of up to 3 hours. The results are all the more striking as primary angioplasty was not available in 2 of 5 participating centres prior to the study, and operators were trained during a pilot period.

PRAGUE-2 (20) has provided further support for a primary PCI transfer strategy. It randomised DGH patients to on-site thrombolysis with streptokinase or transfer for PCI. Although the mortality reduction (10% thrombolysis (TL) vs. 6.8% PCI) did not reach significance across all patients, it became significant in patients who presented greater than 3 hours following onset of symptoms (15.3% TL versus 6% PCI P<0.02). This is in keeping with the exponential deterioration in efficacy of thrombolysis with increasing
symptom duration that we might expect, which appears significantly attenuated with PCI (21).

A recent meta-analysis of 23 trials comparing primary angioplasty and thrombolysis (22) included all these transfer studies, and other trials employing current interventional techniques (12 using stents and 8 using GPRA therapy). Mortality following PCI was significantly reduced (whether or not cardiogenic shock patients were included), as was stroke and non-fatal MI (figure 1). This is contemporary primary angioplasty in a wider group of patients than previously described.

Summary
Clinical evidence clearly demonstrates that primary (or direct) angioplasty is a superior reperfusion strategy when compared with thrombolysis, yet this service is not routinely available in England.

Figure 1. Keeley et al. Meta analysis of 23 randomised trials of Primary Angioplasty versus Thrombolysis
Adapted from Keeley EC, Boura JA, Grines CL. The Lancet 2003;361:13-20
3. PILOT PROJECT
NORTH EAST LONDON
PRIMARY ANGIOPLASTY DAYTIME – WEEKDAY ONLY SERVICE
APRIL 2003 – JANUARY 2004

BACKGROUND
The key to providing the earliest possible reperfusion is pre-hospital diagnosis and delivery of patients directly to a dedicated team in the catheter lab, bypassing delays in Accident and Emergency. In DANAMI-2 the door to balloon times for transfer patients were comparable to and in some cases shorter than those presenting to a cardiac centre. While this seems a positive result demonstrating rapid patient transfer, it also suggests significant delays in regional centre A&E departments.

Many NE London ambulances have ECG capabilities, with crews trained in 12-lead ECG recognition. We propose a ‘direct access’ strategy where crews can deliver suitable patients diagnosed in the field directly to the catheter lab. However, where patients present themselves directly to hospital, there will also be a mechanism to rapidly transfer these patients in addition. This latter group will have anti-platelet therapy administered in the A&E pre-transfer.

This model has been the basis of a pilot primary angioplasty programme that is currently operating on the London Chest Hospital site. It opened to London Ambulance Service (LAS) calls in April 2003, offering a daytime weekday only service to three East London hospital catchments. Data collected and experience to date are included in this proposal, informing the development of the 24-hour seven-day service.

Taking this proposal forward require changes in working practice. It will also necessitate investment. This business case sets out the alterations in working practice, projected workload and costs.

Initial ‘pilot’

- Patients presenting with STEMI via the London Ambulance Service (LAS) from the catchment population of Tower Hamlets would have direct access to the London Chest Hospital for immediate angiography with a view to primary angioplasty.

- This was based on pre-hospital diagnosis of STEMI by trained participating LAS crews with on board 12 lead ECG capabilities.

The service was initially open to patients presenting via LAS, between 0800-1600 weekdays, and only within the Royal London Hospital (RLH) catchment area.

Based on audit data previously presented it was expected that we would treat 2.75 patients pcm, and a maximum of one patient per week.
Our actual experience was that LAS delivered only 4 patients in the first four months, 2 of whom were confirmed as STEMI on arrival. This was a result of a combination of factors including frequent closure (bank holidays, audit days, British Cardiac Society, Euro PCR live case day), and missed direct presentations to A&E.

Extended ‘pilot’
Two additional initiatives were adopted to increase patient numbers to the previously expected level (average one patient per week).

- An immediate transfer protocol from RLH A&E for STEMI patients (opened August 18th)
- Expansion to include patients picked up by LAS in the Newham and Homerton hospital catchment (opened August 14th)
- We will expand to accept A&E transfers from Newham and Homerton in early 2004.

These initiatives were adopted in collaboration with LAS and RLH A&E, and with consultation of Newham Hospital Cardiology and A&E departments, Newham PCT, and the North East London Cardiac Network board. In addition there has been a commitment from the LCH cardiologists and cath lab staff to avoid any weekday closures unless essential.

Service Delivery and Patient Experience Outcomes of Pilot
Figures 2 and 3 demonstrate the 19 admissions to LCH thus far.
FIGURE 2: SOURCE OF PRESENTATION

19 PATIENTS TRANSFERRED

- 2 non ACS
- 12 via LAS
  - 7 Definite STEMI
  - 3 NSTE-ACS
  - 5 Definite ACS
- 7 A&E Transfer
  - 7 ME Transfer
  - 112 via LAS

FIGURE 3: OUTCOME ACCORDING TO ECG / CLINICAL DIAGNOSIS MADE ON ARRIVAL AT LONDON CHEST

TOTAL 19 PATIENTS

- 12 Definite STEMI (63.2%)
- 5 NSTE-ACS (3T+ve)
  - 3 'prob STE'
  - 2 Not STE (26.3%)
- 2 non ACS (10.5%)
- 11 PRIMARY PCI

- 4 Cardiac Catheter
- 2 PCI
- 1 Admitted ON
  - 1 back to RLH A&E
- 11 PRIMARY PCI

No Cardiac Catheter
12/19 patients were diagnosed as definite ST elevation events. The table below demonstrates the rapid instigation of treatment on arrival. Patients are rapidly assessed by a cardiologist, and transferred to the catheter lab table, where angiography is performed with angioplasty as necessary.

<table>
<thead>
<tr>
<th>EFFICACY OF DELIVERY</th>
<th>Mean (mins)</th>
<th>Median</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arrival to table N=12</td>
<td>16.4</td>
<td>15</td>
<td>10-30</td>
</tr>
<tr>
<td>Door (LCH) to balloon N=11</td>
<td>42.6</td>
<td>38</td>
<td>19-104</td>
</tr>
</tbody>
</table>

All procedures were successful. There was one (femoral) in-hospital complication necessitating prolonged hospital stay, but no additional therapy.

**Evaluation of pilot**

While the number of patients treated is small, it has been demonstrated that primary angioplasty can be delivered effectively at the London Chest Hospital with favourable door-to-balloon times, in-hospital outcomes, and early discharge. This has been achieved with the development of explicit protocols for direct access and A&E transfer respectively. There is also an infrastructure for interdisciplinary collaboration (between LAS, Cardiology and A&E), and ongoing support from the Cardiac Network, with frequent feedback to PCTs involved. To date no major logistical problems (such as bed occupancy, or cath lab availability) have been experienced.

At present the pilot service recruits patients during daytime hours (0800-1600) on weekdays as follows:

1. Direct access of LAS crews from Royal London (RLH), Newham (NGH) and Homerton (HOM) catchments.

2. STEMI transfers from the RLH A&E.

This will expand to accept A&E transfers from Newham and Homerton in early 2004.

The protocol used for the pilot phase sets out clear and specific inclusion and exclusion criteria, and transfer mechanisms. It lends itself to being adopted by a wider catchment on a 24-hour basis and to include other hospital A&Es, with adaptations outside normal working hours.

Since opening to direct access admissions for RLH catchment in April 2003, the programme has gradually expanded to receive RLH A&E transfers and subsequently direct admissions from Newham and Homerton.
4.24-HOUR, SEVEN DAY SERVICE PROPOSAL

BACKGROUND
Based on the success of the pilot project it is proposed that this extended into a 24 hour 7 day service in a two phased approach:

PHASE 1
The proposal is an adaptation of the existing pilot protocol, with changes to cater for out of hours staffing and working practice.

The first phase would involve a modified protocol for receiving patients out of hours (5pm-8am) for the existing participating hospitals, Royal London, Newham and Homerton.

1. Recruitment and transfer
The method of recruitment will remain as per the existing protocol. The service will continue to accept all patients that fulfill inclusion and exclusion without formal referral.

1. Transfer from home
- Paramedic ambulance crews make the diagnosis using on board 12 lead ECG equipment, and transfer directly to the London Chest Hospital
- This will continue for the 3 hospitals in East Central LAS sector (RLH, NGH, HOM)

2. Rapid critical transfer from A&E Departments
a. This will occur in the East Central LAS Sector when:
   - Paramedic crews are not available to make diagnosis
   - Paramedic crews are uncertain regarding suitability of the patient
   - Patients self present to A&E
   - Patients develop new ST segment elevation in A&E

A&E transfers – Pre transfer therapy
The existing protocol for pre transfer therapy with a glycoprotein IIb/IIIa receptor antagonist bolus (abciximab – ReoPro TM), and clopidogrel will be administered to patients form RLH, HOM, NGH. These patients would usually be expected to undergo cardiac catheterisation within 60 minutes.

Out of Hours Transfer Protocol
Calls received between 0800-1600 on weekdays will be received according to the current Pilot Primary Angioplasty Protocol.

Calls received after 1600 will be dealt with as follows:
- The call will be diverted to CCU automatically and received by a nominated senior nurse bleep holder.
- The AMI bleep will be activated as usual. This will alert the out-of-hospital cardiac team.
The patient will be received onto CCU, NOT INTO THE LAB, and assessed by a resident SHO and subsequently the non-resident specialist registrar (SpR) on call, pending arrival of the on call catheter lab team. Maximum call to arrival time must not exceed 1 hour, as per trust guidelines.

All procedural aspects will be performed as per the existing protocol.

**Proposed Starting Date**

Subject to being able to recruit to the additional posts required to cover the on-call component of the service, it would be possible to begin from the 1.4.04.

**PHASE 2**

Expansion of recruitment to three further hospital catchments: King George Hospital (Ilford), Oldchurch and Whipps Cross.

Rapid "critical" transfer from A&E Departments as described above will be the ONLY transfer method from the further hospitals (KGH, OCH, WX). These patients will receive anti-platelet pharmacotherapy starting in A&E before transfer, to give them a better than 75% chance of having TIMI3 flow on arrival.

**A&E transfers – Pre transfer therapy**

½ dose TPA (or TNK or Reteplase) is proposed for patients from OCH, WX, KGH. These patients may less reliably undergo catheterisation within 60 minutes.

**Implications for LAS sectors**

The initially proposed hospitals lie in the Central LAS sector (NGH, HOM, RLH), the others in the northeast sector. Moving vehicles between sectors may lead to a shortage of local emergency vehicles. The LAS is committed to the pilot and to addressing this problem, but this is not felt to be achievable in the timescale proposed for the implementation of Phase 1, hence the proposal of Phase 2 involving the other 3 hospitals. There is a commitment from LAS to provide the critical transfer service to this patient group as soon as is feasible.

Patients from further other catchment areas including North central London and Essex sectors would be accepted as part of the service, subject to the appropriate ambulance service being able to commit to the extended geographical transfer times arising through redirecting transfers to the London Chest Hospital.

**Proposed starting date:**

This would be dictated according to the progress of discussions with the A&E Departments in other hospitals and the LAS in relation to the impact of the service development on their ability to meet their own performance targets.
Patient Numbers
The projected workload is based on audit data from the six participating hospitals (Table 1). This information is now 2 years old and more recent information is being gathered.

**TABLE 1**

<table>
<thead>
<tr>
<th></th>
<th>Admissions with definite or Probable STEMI October 2001-2002</th>
<th>Inpatient angiogram No. (%)</th>
<th>Outpatient Angiogram Planned No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>KGH</td>
<td>114</td>
<td>51 (45)</td>
<td>30</td>
</tr>
<tr>
<td>NGH</td>
<td>104</td>
<td>22 (21)</td>
<td>31</td>
</tr>
<tr>
<td>RLH</td>
<td>105</td>
<td>59 (56)</td>
<td>12</td>
</tr>
<tr>
<td>OCH (est)*</td>
<td>130</td>
<td>70 (54)</td>
<td>-</td>
</tr>
<tr>
<td>HOM (est)*</td>
<td>70</td>
<td>50 (71)</td>
<td>-</td>
</tr>
<tr>
<td>WX (est)*</td>
<td>100</td>
<td>55 (55)</td>
<td>-</td>
</tr>
<tr>
<td>TOTAL</td>
<td>523</td>
<td>309 (59)</td>
<td></td>
</tr>
</tbody>
</table>

* Est = Estimations pending full data collection

Thus we would initially predict receiving 1.4 patients per day (10 patients per week).

However, based on initial experience from the pilot programme we will also expect to receive some Non-ST elevation Acute Coronary Syndrome (NSTE-ACS) patients.

Figures 2 and 3 represent recruitment from April 2003 – January 2004. These data demonstrate that we must cater to receive up to 25% more patients than these figures predict.

This would result in 654 patients per year (1.8 patients per day, 12.6 patients per week)

Calculation of costs is therefore based on receiving an average of 2 patients per day.

It should however be made clear that a minimum of 50% of these ‘additional’ procedures are already being performed at BLT during daytime hours as ‘query proceed’ cases. The majority from these particular hospitals are performed on the London Chest site. This means that there is the existing catheter lab capacity to commence the proposed service with immediate effect.
5. NON FINANCIAL BENEFITS ARISING THROUGH PROJECT

Hospital bed day savings
At present evidence suggests patients who remain uncomplicated following STEMI should be eligible for discharge after 4 days. However in practice patients are kept in much longer. In a recent study Kaiser Permanente, a non-profit health maintenance organisation in California, reported an average hospital stay for acute myocardial infarction in the year 2000 of 4 days compared with 5 days for US Medicare patients and 9 days for NHS patients (23).

Previous Royal London Hospital Experience
Our own experience based on audit data (October 2002-3) is displayed below (table 2). The overall mean stay was 7.9 days.

Notably, the 56% of patients requiring inpatient cardiac catheterisation had a prolonged stay, driven by delays in inter hospital transfer. The mean stay increased to 9.6 days when transfers for early (<48 hours) ischaemic complications were excluded.

<table>
<thead>
<tr>
<th>Referred for Inpatient Angiography</th>
<th>N</th>
<th>Mean</th>
<th>Median</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>59</td>
<td>8.1</td>
<td>6</td>
<td>1-36</td>
</tr>
<tr>
<td>40/59 urgent transfers excluded</td>
<td>9.6</td>
<td>7</td>
<td>3-36</td>
<td></td>
</tr>
<tr>
<td>Data for 31/39 Deaths excluded</td>
<td>6.4</td>
<td>5</td>
<td>2-24</td>
<td></td>
</tr>
</tbody>
</table>

Hospital Discharge – Advantages of Primary Angioplasty
Uncomplicated patients following primary angioplasty may be discharged on the third day of admission (24). Our own pilot primary angioplasty protocol allows for discharge of uncomplicated patients at 48 hours. This is based on the fact that all risk stratification (with angiography and echocardiography) is performed within this period, and evidence that the vast majority of major complications occur within this time period, with further problems occurring at a relatively constant rate out to 30 days (25).

In addition, recent evidence demonstrates that the rate of re-admission with non-fatal myocardial infarction following primary angioplasty is significantly reduced relative to thrombolysis (26).
Hospital Discharge – Experience from London Chest Pilot Primary Angioplasty Programme

Since opening to calls from LAS 19 patients have been delivered to LCH with a view to primary angioplasty. 12 were diagnosed with definite ST elevation, 11 of whom underwent primary angioplasty.

Mean hospital stay was 2.9 days (one patient stayed nine days following a femoral complication (table 2).

In addition 5 patients with non-ST elevation syndromes were admitted, 4 of whom underwent angiography, 3 undergoing PCI. The mean hospital stay for these patients was 1.2 days. If they had presented via A&E, these patients would normally have been listed for later routine inpatient transfer and angiography.

Table 2 PILOT PRIMARY ANGIOPLASTY: duration of hospital stay

<table>
<thead>
<tr>
<th>PATIENTS</th>
<th>MEAN STAY</th>
<th>MEDIAN STAY</th>
<th>RANGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>STEMI n=12</td>
<td>2.9</td>
<td>2</td>
<td>1-9</td>
</tr>
<tr>
<td>NSTE-ACS n=5</td>
<td>1.2</td>
<td>1</td>
<td>1-2</td>
</tr>
<tr>
<td>Non Cardiac n=2</td>
<td>NA</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

If we extrapolate these data to our projected 1-year (six-hospital) population we would expect major savings in terms of hospital stay.

654 patients @ mean 2.9 Days 1896 hospital days

654 patients @ mean 7.9 Days 5166 hospital days

Days saved

3270

Days Saved per 100 patients

500

This is a conservative estimate based on the Royal London Hospital mean hospital stay, and assuming all 654 primary angioplasty patients would incur a ‘STEMI’ stay.

Benefits To Local Hospitals

- Savings on the cost of thrombolitics in the local hospitals (data is currently being collected).
- Reduction in the number of patients presenting to local A&E Departments, thus reducing the pressure around meeting targets.
- Improved efficiency of bed usage will be delivered in beds on each of the provider trusts within NE London sector. Transfer data are currently being examined from an audit relating to this.
• A small proportion of patients (25-30% of local transfers) have an ACS without ST elevation but have continuing pain. These patients could be transferred immediately and be investigated/treated immediately using the same team. This would give the on-call teams a more realistic workload and would drastically reduce transfer times.

6. SUMMARY
We have demonstrated that we currently deliver a working daytime 'Regional Heart Attack Centre' model for primary angioplasty in East London which benefits both patients and Trusts in terms of speed of care and length of hospital stay. The existing protocol requires minimal change in order to offer a 24-hour 7 day service to a wider population. We have addressed the mechanisms for delivering this service to ensure we are able to deliver an evidence-based and cost-effective service.

In addition to the direct benefits of this reperfusion strategy to patients, the programme will reduce Accident and Emergency waiting times, hospital stay, and readmission rates. These potential benefits will be prospectively audited during the first year of the service.

The proposal has been developed in partnership with the LAS, NEL Cardiac Network and the relevant acute hospital Trusts, and if approved would be an excellent example of successful working across a network area to the benefit of the patient.

Next Steps
The proposal will be taken to the North East London Cardiac Network to obtain the support of key stakeholders.

Directors of A&E Departments in the local hospitals will be consulted in relation to the impact of the proposal on their existing working practice.

Due to the benefits of the proposal to all parties it is not anticipated that there will be any irresolvable concerns.
7. COSTS: PHASE 1

1. CATHETER LAB CAPACITY / CONSUMEABLES

It is expected that we will perform approximately 550-560 DIRECT AMI procedures per year.
(Pilot data (Figure 2+3) predict catheter studies on 85% of transfers, PCI for 70% of transfers). This work will be spread throughout the 24-hour seven-day period. However it will be offset by a reduction in STEMI inpatient transfers undergoing daytime catheter/query proceed studies (which currently make up 20-25% of all inter-hospital transfers). As seen in table 1 above, this should account for at least half of the total number, which means that the catheter lab capacity is readily available.

**ESTIMATED ADDITIONAL WORKLOAD 300 procedures maximum**
50-65% of these will be performed out of hours. Therefore we would not expect to need additional daytime lab capacity.

2. BEDS / ASSOCIATED WARD STAFF

There must be sufficient capacity to accept 2 patients per day, with an average hospital stay of 2.5 days.

We recommend 3 additional dedicated AMI transfer beds.

**CAPITAL EXPENDITURE – 3 additional fully equipped beds**

<table>
<thead>
<tr>
<th>WORKS</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monitors, Oximetry</td>
<td>£45,000</td>
</tr>
<tr>
<td>Oxygen Supply, Suction</td>
<td></td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td>£45,000</td>
</tr>
</tbody>
</table>

**REVENUE**
These beds will require 1:3 nursing, necessitating 5.8 additional nurses.

3. EMERGENCY STAFF

**Catheter Lab**

While existing on call arrangements can be preserved, there will be a significantly increased workload. Staff may be expected to be called on 50-75% of evenings. In such cases they will not be expected to work the following day (morning) in line with EWTD. This will necessitate recruitment of staff.

The staffing proposed will enable cover for out of hours activity on a daily basis.

a. **Nursing**

2 additional catheter lab nurses are required
**b. Radiographers**  
Radiographers already perform a 24 hour on site service. There is therefore no additional cost.

**c. Technicians**  
2 additional catheter lab technicians are required

**Physicians**

**a. Senior House Officers** – the current SHO rota will be preserved. There are no additional cost implications. The SHO will be the first medical contact for the patient. This will be of additional training value to the respiratory SHOs who participate in this rota. At times where multiple inpatients require immediate attention, help may be sought from on call anaesthetic staff.

**b. Specialist Registrar** – The current SpR rota will also be preserved, remaining non-resident.

**c. Consultants** – There will be a dedicated AMI intervention on call rota comprising all DGH interventionists serving the participating hospitals, and local interventionists serving RLH. This will be based on the London Chest site, operating independently of which centre is on call for non-STEMI emergencies.

(As experience with this system progresses, it is expected that senior interventional fellows will gain sufficient experience to operate independently without on site consultant supervision, subject to achievement of an agreed competency level)

**Surgical Cover** will be agreed across both sites (LCH and St. Bartholomew’s), as STEMI patients very rarely require immediate surgical intervention. Therefore there will be no impact on the surgical rota.

4. **FOLLOW UP**  
A dedicated clinic will follow all patients at 6 weeks. Subsequent follow up will revert to local hospitals.

**CLINIC COST (estimated for 10 patients per week)**  
Cardiac rehabilitation and diabetic care will be handed back to the local hospital.

5. **AUDIT**  
The whole patient population will be subject to regular and continuous audit and as such will require dedicated audit/data collection staff support. This is mandatory, and will require IT support.
A dedicated fellow (Senior SpR grade) will continue to oversee and implement the project, with responsibility for continued data analysis, and quarterly reports to the participating hospitals, BLT trust and the Cardiac Network Board. In addition, it is proposed that a coordinator for the project is appointed.

COSTS: PHASE 2
It is not possible to accurately detail the costs involved in Phase 2 until the full implications of the area expansion for LAS have been determined. However, additional costs will include:

- LAS costs
- An additional 2 beds and nursing staff
- The cost/availability of staff from transferring hospitals to accompany patients being transferred from A&E. Over 70% of these would usually transfer to BLY anyway but the change to an acute rather than planned transfer may have a cost implication
- It will not be necessary to further increase the on-call staffing for the catheter labs from Phase 1
## Costings for direct AMI paper

<table>
<thead>
<tr>
<th>Area</th>
<th>WTE</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CTU</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nurse grade F</td>
<td>2</td>
<td>81,650</td>
</tr>
<tr>
<td>Nurse grade E</td>
<td>2</td>
<td>72,910</td>
</tr>
<tr>
<td>Nurse grade D</td>
<td>2</td>
<td>68,310</td>
</tr>
<tr>
<td></td>
<td></td>
<td>222,870</td>
</tr>
<tr>
<td><strong>Labs</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Additional posts</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nurses (grade E)</td>
<td>2</td>
<td>70,150</td>
</tr>
<tr>
<td>Technician (MTO4)</td>
<td>2</td>
<td>83,260</td>
</tr>
<tr>
<td>SpR?</td>
<td>1</td>
<td>70,929</td>
</tr>
<tr>
<td></td>
<td></td>
<td>224,339</td>
</tr>
<tr>
<td>On call payments (above those currently paid)</td>
<td>Assumes 3 hrs per night</td>
<td></td>
</tr>
<tr>
<td>Nurse</td>
<td></td>
<td>19,391</td>
</tr>
<tr>
<td>Technician</td>
<td></td>
<td>16,920</td>
</tr>
<tr>
<td></td>
<td></td>
<td>36,311</td>
</tr>
<tr>
<td><strong>Other pay costs</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Outpatients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Standard cost for 1 outpatient clinic per week</td>
<td></td>
<td>10,000</td>
</tr>
<tr>
<td>Project coordinator</td>
<td>1</td>
<td>31,740</td>
</tr>
<tr>
<td>Research Fellow (no on call duties)</td>
<td>1</td>
<td>52,836</td>
</tr>
<tr>
<td><strong>Total revenue costs</strong></td>
<td></td>
<td>578,096</td>
</tr>
</tbody>
</table>

| **Capital costs** |   |       |
| Monitoring for 3 beds | | 45,000|
Reference List


APPENDIX le

DIRECT AMI UPDATE October 2004

The Primary Angioplasty Pilot Service at Barts
and the London NHS Trust

Progress Report and Proposed Expansion to serve the North
East London Cardiac Network

Elliot J Smith and Martin T Rothman on behalf of the Primary Angioplasty Working Group
1. Introduction

At present the pilot primary angioplasty service treats patients diagnosed with **ST segment Elevation Myocardial Infarction (STEMI)** diagnosed within 'East Central London' within working hours. In practice this means any patient diagnosed with STEMI within the catchments of the Royal London Hospital, Homerton University Hospital and Newham University Hospital between 0800 and 1600 Monday to Friday. This represents the pilot phase (phase 1) of the project, which was designed to demonstrate the feasibility, efficiency, safety and efficacy of a Regional Heart Attack Centre (RHAC) model of infarct management in our metropolitan UK population.

Patients are identified either by specially **trained London Ambulance Service (LAS) crews** in the community or by **any of the three participating A&E departments** and taken immediately to the cardiac catheter lab at the London Chest Hospital without referral, where the occluded coronary artery can be reopened mechanically by **angioplasty**, rather than receiving standard thrombolytic therapy.

The success of the pilot has led to the desire to offer this service to all STEMI patients within the North East London Cardiac Network. In practice this would mean accepting STEMI patients from within the catchments of Whipps Cross Hospital, Oldchurch Hospital and King George Hospital in addition to the existing areas (Figure 2).

**Phase 2** of the process will expand the service geographically, but will continue to operate during working hours only. This will ensure there is a smooth learning curve similar to that experienced by the existing LAS crews and A&E departments.

**Phase 3** will allow transition to a 24 hour seven day service. This will be the first coordinated RHAC Network service in the United Kingdom.
2. Objectives of the Scheme

The objectives of the scheme are to:

1. Provide equity of access to state of the art evidence based care (primary angioplasty) for all heart attack patients in Northeast London, irrespective of postcode.

2. Deliver immediate coronary intervention wherever necessary with speed, efficiency, and equity of access.

3. Provide an integrated patient journey through the network, from pre-hospital diagnosis, through the RHAC, and with a network wide rehabilitation and education process coordinated between the RHAC and local DGH. This will ensure a patient centred approach well beyond the initial intervention.

3. The Primary Angioplasty Pilot at Barts and the London NHS Trust

Phase 1 – The Pilot

The pilot primary angioplasty service opened in April 2003, initially serving only the local population (the Royal London Hospital), operating during working hours only (weekdays 0800-1700). We sought to provide data as to the safety and feasibility of a RHAC model for all STEMI patients in Northeast London (and Essex). The pilot has since expanded and currently treats patients presenting not only to BLT, but also STEMI patients diagnosed within the catchments of Homerton and Newham hospitals during working hours. The pilot has proven successful in terms of service delivery, safety, and patient outcomes, with key benefits including a radical reduction in hospital stay. Patients are received directly into the cardiac catheter lab, and the culprit artery opened rapidly where necessary. Data are summarised below:
A. EXPERIENCE TO DATE

Total Number of patients delivered to LCH for consideration of Primary Angioplasty, with discharge diagnosis, and treatment received.

B. EFFICIENT DELIVERY OF THERAPY

TABLE 1: Patients are rapidly assessed, moved to the catheter lab table, and angioplasty performed.

<table>
<thead>
<tr>
<th>N=41 STEMI</th>
<th>Mean (sd)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arrival at LCH to Cath Lab table</td>
<td>16 mins (7)</td>
</tr>
<tr>
<td>Arrival LCH to Balloon inflation</td>
<td>39 mins (11)</td>
</tr>
</tbody>
</table>
C. IMPROVED OUTCOMES FOLLOWING PRIMARY ANGIOPLASTY

The black columns represent patients presenting to the RHAC during the pilot service diagnosed with definite ST segment Elevation Myocardial Infarction. The Grey columns represent STEMI patients assigned to thrombolysis during the pilot period (i.e. performed out of hours). The third column shows all patients with STEMI treated in a 12 month period prior to the instigation of primary angioplasty. Follow up was for a mean of 21 weeks.
D. IMPACT ON HOSPITAL STAY

Uncomplicated patients are discharged at 48 hours. 80% of all patients admitted are discharged by day 3.

The table demonstrates that hospital stay is radically reduced following primary angioplasty. 57% of thrombolysis patients were transferred for inpatient coronary angiography, which further prolonged hospital stay.

<table>
<thead>
<tr>
<th>Hospital Stay (days)</th>
<th>Primary Angioplasty n=41</th>
<th>Thrombolysis (during pilot) n=76</th>
<th>Thrombolysis (pre pilot) n=96</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALL Patients</td>
<td>3.1 (1.4)</td>
<td>8.5 (6)</td>
<td>7.3 (5)</td>
</tr>
<tr>
<td>Mean (sd)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NOT Transferred for inpatient angiography</td>
<td>NA</td>
<td>7.2 (5)</td>
<td>5.6 (4)</td>
</tr>
<tr>
<td>Mean (sd)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transferred for inpatient angiography</td>
<td>NA</td>
<td>9.2 (6.8)</td>
<td>8.2 (6.6)</td>
</tr>
<tr>
<td>Mean (sd)</td>
<td>n=41 (54%)</td>
<td></td>
<td>n=57 (59%)</td>
</tr>
</tbody>
</table>

Awards for the Pilot Service (Phase 1)

These achievements have been recognised by the Department of Health, with the service receiving the regional award for outstanding achievement in Emergency care at the Health and Social Care Awards 2004. In addition our team is one of three nominees for the Cardiology award at the Hospital Doctor Awards 2004, and one of four finalists for the Health Services Journal Awards 2004 in the category 'Improving Patient Access.'

Geographical and Temporal Expansion (Phases 2 and 3)

We now propose to expand the service to provide firstly geographical (Phase 2), and secondly temporal equity (Phase 3) for STEMI patients diagnosed anywhere within the North East London Cardiac Network. The service aims to treat all patients presenting with suspected STEMI via the RHAC model, within the catchments of the existing participating hospitals (Royal London, Homerton, and Newham Hospitals), in addition to those of King George (Ilford), Oldchurch Hospital, and Whipps Cross Hospitals.
Phase 2
The London Ambulance Service with Barts and the London NHS Trust will offer this service to the three additional catchments and their respective A&E departments from Jan 4th 2005. The service will continue to operate on weekdays (excluding bank holidays) receiving STEMI patients diagnosed at the centre of origin between 0800 and 1600. It is anticipated that Phase 3 (a 24-hour seven-day service) will commence later in 2005.

4. Implications to Participating District Hospitals and respective Accident and Emergency Departments

Key Benefits
All patients presenting with chest pain and ST segment Elevation will be treated initially at Barts and the London NHS Trust. In addition all outpatient follow up will be performed at the RHAC. This will have the following key advantages:

1. Reduction in district hospital admissions with ACS by 25-30%
2. Reduction in waiting time for inter-hospital transfer of high risk Non-ST-elevation ACS (as 30% of patients listed for transfer are admitted with STEMI)
3. Reduction in A&E presentations with STEMI by 50%. (Based on experience within the current network, 50% of patients are admitted to the RHAC directly via LAS from the community).
4. A guarantee that those STEMI patients that still present to A&E will never incur prolonged waits in A&E (as they will be transferred immediately without referral).

Cost and Projected Workload

1. Pre transfer therapy:
Patients admitted to A&E will require one dose of clopidogrel orally, and a bolus dose of abciximab. They will not require thrombolysis. The net cost is c. £100 per patient compared with aspirin and thrombolysis.

However, this cost will be incurred in only half the current total number of patients receiving thrombolysis (as explained above). Furthermore, less than 25% of these patients will require an inpatient stay at the district hospital (following transfer back to the DGH after primary angioplasty. The majority are sent home from the RHAC).
2. Procedures

Audit data from Barts and the London NHS Trust demonstrate:
(Follow up of 105 patients admitted with chest pain and ST elevation October 2001-2000)².

68% of patients ultimately undergo angiography following presentation with STEMI
48% of patients undergo revascularisation (90% undergoing angioplasty).

Recent data from the primary angioplasty pilot:
90% of patients presenting to the RHAC undergo immediate angiography
80% of patients presenting to the RHAC undergo immediate revascularisation (all angioplasty)

Projected Workload
Across the Network over 24 hours, a maximum of 700 patients would be expected to present to the RHAC per annum. Based on the data above:

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Expected Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>90% undergo immediate angiography:</td>
<td>630</td>
</tr>
<tr>
<td>vs. 68%</td>
<td>476</td>
</tr>
<tr>
<td>Additional angiographic procedures (6 Trusts)</td>
<td>154</td>
</tr>
<tr>
<td>Additional angiographic procedures per Network Trust per year</td>
<td>26</td>
</tr>
<tr>
<td>80% undergo revascularisation (all coronary angioplasty):</td>
<td>560</td>
</tr>
<tr>
<td>48% undergo revascularisation (all coronary angioplasty):</td>
<td>336</td>
</tr>
<tr>
<td>Additional angioplasty procedures (6 Trusts)</td>
<td>224</td>
</tr>
<tr>
<td>Additional angioplasty procedures per Network Trust per year</td>
<td>37</td>
</tr>
</tbody>
</table>

Thus the absolute increase in invasive investigation and revascularisation as a proportion of all revascularisation is small.
5. Service Model

The Phase 2 service model is outlined below. This is a geographical extension of the existing service. A sample A&E Transfer form is included (Appendix A).

A. PRE-HOSPITAL

1. All Patients diagnosed with possible STEMI fulfilling entry criteria (Table 3) within the Northeast London Cardiac Network will have immediate and direct access to a Regional Heart Attack Centre (RHAC) for primary angioplasty.

2. Patients will be selected by trained LAS crews making a pre hospital diagnosis using on-board 12 lead ECG equipment, and without referral. LAS crews will have clearance to bypass the nearest ME in favour of the RHAC.

3. STEMI patients presenting to any A&E department within the network will also have access to the RHAC via immediate LAS transfer - also without referral. These will be performed as ‘critical transfers’ giving them a 999 priority. These patients will have the opportunity to receive pre-transfer therapy where possible, facilitating rapid treatment at the RHAC.
   a. Patients presenting first to an Accident and Emergency department will receive oral clopidogrel and intravenous abciximab (a glycoprotein IIb/IIIa receptor antagonist) prior to transfer, in addition to the usual aspirin.

4. The RHAC will be based on the London Chest Site

5. First notification of an incoming STEMI patient will be performed by the incoming LAS crew, irrespective of their origin (i.e. from the community or a participating A&E department). The call will be received via a designated telephone line in the catheter lab (0800-1600). On receipt of the call, a 'DIRECT AMI' bleep will be sent to the receiving team (SpR, SHO, Cardiac physiologist, cath lab nurse, radiographer, porter, security, and bed manager).

B. ON ARRIVAL AT THE RHAC

6. The patient will always be received into the catheter lab, and assessed by the resident SpR, and a decision taken as to suitability

7. Unless contraindicated, all patients will receive aspirin, clopidogrel, and abciximab (reopro) prior to angiography (unless already administered).

8. Angiography will be performed according to the usual primary angioplasty protocol. Culprit vessel angioplasty and stenting will be performed where appropriate, with other vessels treated at the operator’s discretion.
C. INPATIENT STAY

9. Patients will remain monitored on CCU for 24 hours
10. Uncomplicated patients (age<75, successful angioplasty, moderate or better LV function, free from arrhythmia) will be discharged home at 48 hours
11. Patients expected to stay more than 48 hours will be transferred back to their local hospital under the care of the local cardiology team
12. Patients will receive all prognostic therapy prior to discharge unless contraindicated

D. FOLLOWING DISCHARGE

13. All patients will be reviewed within one week of discharge by the local cardiac rehabilitation service. Data will be sent electronically from the BLT rehabilitation team. Clinical problems can be assessed by the local cardiology team, but will always be communicated via the local rehabilitation team to the BLT rehabilitation team and thereby to the coordinating 'Direct AMI' SpR. This will ensure rigorous data flow.
14. All patients will be reviewed once at BLT 8 weeks following discharge in a nurse led doctor supervised clinic (coordinated through the cardiac rehabilitation team). This will be the only formal outpatient follow up.
15. Data will also be collected at 6 months and 1 year via telephone questionnaire.
16. This will provide the only network wide coordinated rehab programme for STEMI.
17. Data will be entered onto a designated server, with regular downloading to the CCAD / MINAP database.

Table 3: Inclusion and Exclusion Criteria

<table>
<thead>
<tr>
<th>INCLUSION CRITERIA</th>
<th>EXCLUSION CRITERIA*</th>
</tr>
</thead>
<tbody>
<tr>
<td>· Chest pain; Sustained cardiac pain</td>
<td>· Left Bundle Branch Block</td>
</tr>
<tr>
<td>within the preceding 12 hours</td>
<td></td>
</tr>
<tr>
<td>· ST segment Elevation on ECG</td>
<td>· Cardiogenic Shock</td>
</tr>
<tr>
<td>· Orientated, conscious</td>
<td>· Intubated / ventilated</td>
</tr>
<tr>
<td>· Age ≥ 18 years</td>
<td>· Established Cardiac Arrest</td>
</tr>
<tr>
<td></td>
<td>· Confused / reduced conscious level</td>
</tr>
<tr>
<td></td>
<td>· Previous Stroke with dense hemiplegia</td>
</tr>
</tbody>
</table>
6. Conclusion
The pilot primary angioplasty service has already proven safety, efficiency and clinical effectiveness operating during daytime hours and serving a network of three feeding hospital catchments, and has been recognised by the Department of Health for its achievements in improving emergency care. The service has the support of the North East London Cardiac Network Board, Barts and the London NHS Trust Chief executive, the London Ambulance Service and all currently participating A&E departments.

We now propose expansion of the existing protocol geographically during working hours on weekdays. This will offer significant benefits not only to the patients but also the participating Trusts, in reducing inpatient hospital stay, and interhospital transfer delays, with a negligible increase in procedural activity. We look forward to offering this daytime service from Tuesday 4th January. A 24-hour service is ultimate goal of this initiative, and will represent the final phase in the development of this service.

The map demonstrates the phase 1 (current) catchment and the proposed phase 2 catchment. The participating Hospitals are shown, with the expected number of STEMI patients seen per year highlighted.
Reference List

1. NHS. Health and Social Care Awards.  
   Ref Type: Internet Communication

   Ref Type: Abstract