HEAT-PPCI

How Effective are Antithrombotic Therapies in Primary Percutaneous Coronary Intervention: A Randomised Controlled Trial Comparing Unfractionated Heparin and Bivalirudin

---

A Thesis submitted to National Heart and Lung Institute, Imperial College London for the degree of Doctor of Philosophy

2017

Dr Adeel Shahzad

Institute of Cardiovascular Sciences

School of Medicine, Imperial College, London

Main Abstract:

Aims:

Bivalirudin, with selective use of glycoprotein (GP) IIb/IIIa inhibitor agents, is an accepted standard of care in primary percutaneous coronary intervention (PPCI). We performed a trial to compare antithrombotic therapy with bivalirudin or unfractionated heparin (heparin) during PPCI. We also planned pre-specified secondary analyses comparing antiplatelet and antithrombotic effects of bivalirudin and heparin and the effects of P2Y12 inhibiting agents on platelet reactivity and clinical events.

Methods:

This was a single centre, open label, randomised controlled trial. We used a strategy of delayed consent and consecutive patients were included without initial discussion. Before angiography, patients were randomised to either heparin (70 units/kg) or bivalirudin (bolus 0·75 mg/kg; infusion 1·75 mg/kg/hour). Patients were followed for 28 days. The primary outcome measure was a composite of all-cause mortality, cerebrovascular accident (CVA), reinfarction or unplanned target lesion revascularization (TLR). The primary safety outcome was the rate of major bleeding - type 3-5 as per the Bleeding Academic Research Consortium (BARC) definitions. For patients recruited during working hours, we assessed ADP-induced platelet aggregation at the end of the index procedure and at 24 hours. The effects of P2Y12 inhibitors on the primary and safety outcomes were assessed in all patients.

Findings:

A total of 1829 patients were randomised (100% of eligible patients and 97% of all PPCI-related procedures). A PCI procedure was performed in 82% of cases. The rate of GP IIb/IIIa inhibitor use was: bivalirudin 13·5%, heparin 15·5%. The primary efficacy outcome measure was observed more frequently in patients treated with bivalirudin (8·7% v 5·7%, absolute risk difference = 3%; relative risk [RR] 1·52, 95% confidence interval [CI], 1·09 to 2·13; P=0·01). All elements of the composite favoured heparin but the difference was mainly related to an increased incidence of stent thrombosis with

bivalirudin (3·4% v 0·9%, RR 3·91, 95% CI 1·61 to 9·52; P=0·001), causing reinfarction events. There was no difference in major bleeding (3·5% bivalirudin v 3·1% heparin; RR 1·15, CI 0·70 to 1·89; P=0·59). There were no significant differences between patients who received heparin and bivalirudin in AA- and ADP-mediated platelet aggregation at the end of procedure (EOP) or at 24 hours. Multiple Electrode Aggregometry (MEA) data from 469 patients for antiplatelet therapy showed that prasugrel therapy resulted in significantly greater suppression of ADP-induced platelet aggregation at 40U (23, 78) when compared against ticagrelor 75U (41, 100.75) or clopidogrel 79U (56, 96); $p < 0.001$. After adjustment of baseline characteristics, there were no significant differences in the rates of MACE or major bleeding between the antiplatelet therapies.

Conclusions:

Use of heparin, rather than bivalirudin, is associated with a reduced rate of major adverse ischaemic events, with no increase in bleeding complications. More systematic use of heparin offers the potential for a substantial reduction in drug cost. There were no significant differences between heparin and bivalirudin with respect to AA- or ADP-mediated platelet aggregation. No significant differences were found between the antiplatelet therapies for clinical outcomes.

Acknowledgements:

I would like to express my sincere gratitude to:

- My supervisor and mentor, Prof. Rod Stables, for giving me this career and life-changing opportunity and for the invaluable guidance throughout this process. I owe it all to you.
- The rest of the HEAT-PPCI 'family' namely, Ian Kemp, Chris Mars, Keith Wilson, Claire Roome, Alexandra Thompson, Matthew Shaw and Ted Rose for their passionate participation and phenomenal input.
- My secondary supervisor, Prof. Jane Mitchell, for her continuous professional support.
- The clinical and research staff at Liverpool Heart and Chest Hospital for putting in the immense amount of efforts that were required for the success of a trial of this magnitude.
- My wife, Nadia, for providing me with unfailing moral and emotional support throughout these years. This accomplishment would not have been possible without you.
- My three wonderful children, Aleezeh, Shanzay and Ali who provided unending inspiration.

Dedication:

I dedicate this thesis to my parents.

Declaration:

No portion of this work referred to in the thesis has been submitted in support of an application for another degree or qualification of this or any other university or other institute of learning. The work in this thesis is my own and all else is appropriately referenced.

Copyright statement:

The copyright of this thesis rests with the author and is made available under a Creative Commons Attribution Non-Commercial No Derivatives licence. Researchers are free to copy, distribute or transmit the thesis on the condition that they attribute it, that they do not use it for commercial purposes and that they do not alter, transform or build upon it. For any reuse or redistribution, researchers must make clear to others the licence terms of this work.

Contents

Main Abstract: **2**
Aims: 2
Methods: 2
Findings: 2
Conclusions: 3
Acknowledgements: **4**
Dedication: **4**
Declaration: **5**
Copyright statement: **5**
Table of tables: **12**
Table of figures: **13**
Abbreviations: **14**
Chapter 1 – Main introduction and trial design: **17**
Background: **17**
Role of thrombin in atherogenesis: 17
Unfractionated Heparin (heparin)**:** 17
Direct Thrombin Inhibitors (DTI)**:** 18
Bivalirudin: 18
Rationale for the trial: **18**
Background: 18
Can Gp IIb/IIIa inhibitors be used in combination with bivalirudin? 20
Is 'heparin plus mandated, unselected Gp IIb/IIIa inhibitor therapy' an accepted, universal treatment strategy? 21
Do we have reason to believe bivalirudin is a more effective antithrombotic agent than heparin? 21
Are there any problems with bivalirudin therapy? 22
So what about monotherapy therapy with heparin? 23

The need for HEAT-PPCI trial: 23
Hypotheses: 24
Primary hypothesis: 24
Secondary hypotheses: 24
Aims: 24
Primary aim: 24
Secondary aims: 24
Methods: 25
Study design and population: 25
Ethical approval and delayed consent: 26
Study treatments and investigations: 26
Study design flow chart: 28
Outcome measures: 29
Study organisation: 33
Statistical methods and power calculation: 35
Microsoft Access Database Development: 37
Chapter 2 – Main study: 40
Abstract: 40
Background: 40
Methods 40
Findings: 40
Interpretation: 41
Patients: 41
Trial profile: 41
Baseline characteristics: 43
Procedural and treatment data: 44
Clinical outcomes: 45
Primary efficacy outcomes: 45
Primary safety outcomes: 45
Hierarchical outcomes: 48
Event curves: 48
Other secondary outcomes: 50
Subgroup analyses for Primary Composite Outcomes: 50

Discussion: **53**

Chapter 3 – Platelet function substudy - Comparison of the antiplatelet and antithrombotic effects of bivalirudin versus heparin **56**

Abstract: **56**

Background: 56

Methods: 56

Results: 56

Conclusions: 57

Introduction: **57**

Methods: **58**

Study Population and Design: 58

Blood sampling and Sample Analysis: 60

Statistical analysis: 62

Results: **63**

Antiplatelet effects of heparin versus bivalirudin: 65

Antithrombotic effects of heparin versus bivalirudin: 68

Clinical outcomes per group and HPR: 72

Discussion: **75**

Supplementary Discussion 79

Chapter 4 – Antiplatelet therapy substudy - Comparison of the effects of P2Y12 receptor antagonists on platelet function and clinical outcomes **81**

Abstract: **81**

Background: 81

Methods: 81

Results: 81

Conclusion: 82

Background: **82**

Methods: **83**

Study population and design: 83

Study medication: 83

Platelet function testing (PFT): 83

Statistics: 84

Ethical and regulatory approvals: 85

Results: **85**
Clinical outcomes: 85
ADP-induced platelet aggregation: 93
Discussion: **97**
Conclusion: **100**
Chapter 5 – Conduct of the trial and the ethics of delayed consent: **101**
Background: **101**
Essentials of informed consent: **101**
The concept of delayed consent: **102**
Consent is not informed in time-critical, life-threatening situations: **102**
Current regulations on delayed consent: **103**
Accessing a substitute decision maker: **104**
Delayed consent in HEAT-PPCI trial: **104**
Trial medication already established in clinical practice: **105**
The HEAT-PPCI experience with delayed consent: **106**
The option of declining participation: **106**
Alternatives to delayed consent: **107**
Delayed consent: The final word: **107**
Patient deaths before being approached for consent: **108**
Consequences of not including deaths without consent: 108
Misleading results: 108
Consequences of stopping the trial early: 108
Other important considerations specific to HEAT-PPCI: 109
Currently use of mortality data: 110
Provision from the declaration of Helsinki: 110
Provisions from Section 251 of the NHS act 2006: 111
Consequences of contacting next of kin or legal representative for consent in dead patients: 111
Unprecedented zone: 112
Conduct 1 - Recruitment of all eligible patients: **112**
Impact of selective recruitment: 112
Recruitment in HEAT-PPCI: 112
Steps taken to maximise recruitment rates: 113

Conduct 2 - Follow up: 114
Importance of comprehensive follow up: 114
Follow up in HEAT-PPCI: 114
Strategies implemented to minimise loss to follow up: 114
Hospital Episode Statistics (HES): 115
Conduct 3 - Open label study design: 116
Conduct 4 – Data Validation and Accuracy Checks: 117
Validation against Clinical Coding Department: 117
Validation against Clinical Audit Department: 117
Audit of case notes: 117
Data validation at the time of transcription: 118
Chapter 6 - Describing Activity in Primary Percutaneous Coronary Intervention: An Exploration of Denominators. From the HEAT Trial - A Systematic Evaluation of PPCI Activations in Liverpool, Explaining Denominators (*HEAT-SEALED*) 119
Abstract: 119
Background: 119
Objective: 119
Methods: 119
Results: 120
Conclusion: 120
Introduction: 120
Methods: 121
Results: 123
Discussion: 126
Data collection for PPCI patients: 126
Potential variation in PPCI reporting: 126
Evaluating the performance of a PPCI service: 127
Identifying Inappropriate Catheterisation Laboratory Activations (CLA): 127
Conclusion: 128
Chapter 7 – Substudy comparing hospital episode statistics (HES) and direct patient contact to identify outcomes 129
Abstract: 129

Background and objectives: 129
Study participants and design: 129
Main outcome measures: 129
Results: 130
Discussion: 130
Introduction: 130
Methods: 131
Patients and Study Design: 131
Comparing the methods of follow-up used to ascertain readmissions: 131
Method of assessing the diagnostic accuracy of HES data: 134
Results: 136
Patients excluded from readmissions analysis: 136
Readmissions Identified in the HES data: 138
Readmissions Identified by Direct Contact: 138
The diagnostic accuracy of HES data in identifying MACE and bleeding events during the index admission: 138
The diagnostic accuracy of HES data in identifying MACE and bleeding events during a readmission: 139
Discussion: 139
Current problems in trial follow-up: 139
HES advantages: 140
Highlights of HES: 140
Existing literature on HES: 141
HES limitations: 141
Study limitations: 143
Conclusion: 144
Final word: 145
Annexes: 146
Annexe 1 – ACT Data: 146
ACT monitoring: 146
Why is ACT monitoring required? 146
ACT monitoring systems: 146
ACT monitoring with heparin therapy: 147

ACT monitoring with bivalirudin therapy: 147
Trial medication dosing regime in HEAT-PPCI: 147
ACT monitoring system in HEAT-PPCI: 148
Accuracy of weight estimation: 149
Additional drug bolus administration data: 149
Limitations: 150
Conclusions: 150
Annexe 2 - Previous clinical evidence comparing heparin and bivalirdin: **150**
Bivalirudin Angioplasty Trial (BAT, 1995): 150
HERO-2 Trial (2001): 151
REPLACE-1 Trial (2004): 152
REPLACE-2 Trial (2003): 152
ACUITY Trial (2006): 153
HORIZONS-AMI trial (2008): 154
ISAR-REACT 3 trial (2008): 154
ISAR-REACT 3A study (2010): 155
ISAR-REACT 4 Trial (2013): 155
Annexe 3 - Follow up flowchart: 155
List of publications and presentations: 157
Papers: 157
Abstracts: 157
Presentations: 158
References: 159

Table of tables:

Table 1 Patient eligibility criteria 26
Table 2 Outcome measures 29
Table 3 Study Definition of Myocardial Infarction 31
Table 4 Study Definition of Cerebrovascular Accident 31

Table 5 Study definition of Major Bleeding 33
Table 6 Baseline characteristics, procedural data and medication 44
Table 7 Clinical outcomes at 28 days 47
Table 8 Hierarchical outcomes.....48
Table 9 Subgroup analyses for Primary Composite Outcome at 28 days.....52
Table 10 Summary of baseline characteristics, procedural data and drug use. 65
Table 11 Comparison of the agonist-mediated platelet aggregation.....67
Table 12 Clinical outcomes per study group and high platelet reactivity (HPR) 74
Table 13 Antiplatelet therapy substudy - Baseline characteristics for all patients 88
Table 14 Clinical outcomes in the entire study population 90
Table 15 Baseline characteristics for the platelet substudy cohort 95
Table 16 ICD-10 codes used to search the HES database and identify outcome events for stroke, myocardial infarction (MI) and bleeding events 135
Table 17 The readmissions confirmed by adjudication in the HEAT-PPCI trial are compared to the HES method and the direct contact method of identifying readmissions. 137
Table 18 ACT values 148
Table 19 Weight difference.....149

Table of figures:

Figure 1 Main study flow chart 28
Figure 2 Zone of equivalence and confidence interval boundaries.....36
Figure 3 An example of a table from Case Record Form B in HEAT-PPCI Access database.....37
Figure 4 Table relationships showing Case Record Form A layout in Microsoft Access database.....38
Figure 5 Table relationships showing Case Record Form B and Adverse Event Forms layout in Microsoft Access database 38
Figure 6 An example of a form in HEAT-PPCI Access database 39
Figure 7 Main trial patient flow diagram 42
Figure 8 Event curves for Primary Outcomes 49
Figure 9 Antithrombotic TEG substudy flowchart 59

Figure 10 Typical TEG trace 61
Figure 11 Comparison of Thrombelastography-derived indices 69
Figure 12 Comparison of Thrombelastography-derived indices between patients treated with unfractionated heparin and bivalirudin 71
Figure 13 Kaplan-Meier curves illustrating the cumulative incidence of the combined primary efficacy outcome measure for heparin 72
Figure 14 Kaplan-Meier curves illustrating the cumulative incidence of the combined primary efficacy outcome measure for bivalirudin 73
Figure 15 HEAT-PPCI antiplatelet therapy substudy flowchart 86
Figure 16 Odds ratio plot for clinical outcomes 92
Figure 17 Comparison of suppression of ADP-induced platelet aggregation 96
Figure 18 Evolution of P2Y12 inhibitor use over time 99
Figure 19 Results of validation audits against Clinical Coding Department records and case notes 117
Figure 20 HEAT-SEALED pathway results 124
Figure 21 Flow diagram outlining the follow up obtained by direct contact and HES methodology for identifying readmissions 133
Figure 22 Flow diagram outlining the clinical events identified in the HES data for the index admission. 134
Figure 23 HEAT-PPCI 28 day Follow up flowchart 156

Abbreviations:

AA	Arachidonic acid
ACT	Activated Clotting Time
ADP	Adenosine diphosphate
APC	Activated protein C
AST	Acute stent thrombosis
AUC	Area under the curve
AUC15	Area under the curve at 15 minutes
BARC	Bleeding Academic Research Consortium
BCIS	British Cardiovascular Intervention Society
CABG	Coronary artery bypass grafting
CAG	Confidentiality Advisory Group
CCAD	Central Cardiac Audit Database

CEC	Clinical events committee
CER	Comparative effectiveness research
CI	Confidence Interval
CK	Citrated kaolin
CKH	Citrated kaolin with heparinase
CKMB	Creatine kinase myocardial band
CLA	Catheterisation Laboratory Activation
CRF	Case record form
CVA	Cerebrovascular accident
CVD	Cardiovascular disease
DAPT	Dual antiplatelet therapy
DHHS	Department of Health and Human Services
DMSC	Data Monitoring and Safety Committee
DTI	Direct Thrombin Inhibitors
ECC	Ethics and Confidentiality Committee
EMS	Emergency Medical Services
EOP	End of procedure
ESC	European Society of Cardiology
FDA	Food and Drug Administration
GP	Glycoprotein
Heparin	Unfractionated heparin
HES	Hospital Episode Statistics
HPR	High platelet reactivity
IQR	Interquartile range
ITT	Intention-to-treat
LBBB	Left Bundle Branch Block
LD	Loading dose
LHCH	Liverpool Heart and Chest Hospital
LMWH	Low molecular weight heparin
LVEF	Left ventricular ejection fraction
MA	Maximum amplitude
MACE	Major adverse cardiac events
MEA	Multiple electrode aggregometry
MI	Myocardial Infarction

MINAP	Myocardial Infarction National Audit Programme
MLR	Multiple logistic regression
NIHR	National Institute of Health Research
NRES	National Research Ethics Service
OR	Odds ratio
PAR	Protease Activated Receptors
PAS	Patient administration system
PF	Platelet function
PFT	Platelet function test
PCI	Percutaneous coronary intervention
PPCI	Primary percutaneous coronary intervention
RCT	Randomised controlled trial
RR	Relative risk
SAE	Serious Adverse Event
ST	Stent thrombosis
s-TEG	Short thrombelastography
STEMI	ST segment elevation myocardial infarction
SURE	Service User Research Endeavour
TEG	Thrombelastography
TF	Tissue factor
TLR	Target Lesion Revascularisation
TMC	Thrombin-mediated clotting
URL	Upper Reference Limit

Chapter 1 – Main introduction and trial design:

Background:

Role of thrombin in atherogenesis:

Rupture of atherosclerotic plaque in a coronary artery exposes the lipid-rich core to blood stream and triggers the interaction between tissue factor and Factor VII initiating the coagulation cascade. Platelet activation results in expression of increased amounts of anionic phospholipids on their surface further promoting assembly of coagulation factor complexes. Coagulation pathway results in generation of thrombin (Factor IIa) from prothrombin which converts fibrinogen to fibrin[1]. Thrombin also directly binds to Protease Activated Receptors, PAR-1and PAR-4 on platelet surface resulting in further platelet activation [2 3]. Thrombin induced platelet activation can only be inhibited by thrombin inhibition as it is independent of prostaglandin and adenosine diphosphate pathways. Accepting the central role of thrombin in fibrin generation and platelet activation leading to arterial thrombogenesis, its inhibition is considered as mainstay in the treatment of acute coronary syndromes. Thrombin has as an active catalytic site as well as two exosites, exocite-1 and exocite-2[4]. Thrombin inhibition can be achieved by blocking these domains.

Unfractionated Heparin (heparin):

Heparin is a heterogeneous mucopolysaccharide constituting a mixture of glycosaminoglycan polymers with variable molecular weight (5–30 kD). It has an essential pentasaccharide sequence which has a special affinity to bind with antithrombin. The heparin-antithrombin complex inhibits thrombin with antithrombin binding at the active (catalytic) site and heparin binding at the exocite-2[4]. Binding of Heparin to antithrombin also accelerates the rate at which it inhibits Factor Xa. Heparin can also bind to various plasma proteins including fibronectin, vitronectin, histidine-rich glycoprotein, platelet Factor IV and von Willebrand factor[5 6] which can make its antithrombotic effect variable[7]. It is unable to inactivate clot-bound

thrombin. For the above reasons, heparin's antithrombotic activity requires monitoring.

Direct Thrombin Inhibitors (DTI):

Hirudin, the first DTI was originally derived from a medicinal leech, *Hirudo medicinalis* [8]. It is a 65-amino acid peptide that directly and irreversibly binds thrombin blocking its platelet aggregation activity and the coagulation cascade. It specifically binds to thrombin in a 1:1 stoichiometric complex with its carboxy-terminal domain interacting with thrombin exosite-1 and its globular amino-terminal domain getting attached to the active catalytic site[9]. Desirudin and lepirudin, called r-hirudins, are the recombinant forms of hirudin. Unlike heparin, DTIs inactivate clot bound thrombin and prevent thrombin induced platelet aggregation.

Bivalirudin:

Bivalirudin, a bivalent reversible DTI, is a synthetic derivative of hirudin. It is a 20-amino acid peptide. It is specific for thrombin, being active against both free and fibrin-bound types. It binds to thrombin in a 1:1 stoichiometric complex simultaneously at exosite 1 (substrate binding domain) and the active catalytic centre [10]. DTIs reflects their capacity to inactivate fibrin-bound thrombin. As thrombin binds to fibrin via exosite 1, the activity of agents that interact with the active site is not compromised when the enzyme binds to fibrin. Hirudin and bivalirudin bind to exosite 1, as well as the active site of thrombin. Consequently, they compete with fibrin for access to exosite 1. However, in the absence of heparin, thrombin has only weak affinity for fibrin so that these agents readily interact with fibrin-bound thrombin. Unlike heparin[11], DTIs do not bind to plasma proteins. As a result, they produce a more predictable anticoagulant response[12].

Rationale for the trial:

Background:

Primary Percutaneous Coronary Intervention (PPCI) has emerged as the optimum reperfusion strategy for patients presenting with ST-elevation myocardial infacrtion (STEMI)[13 14]. There is uncertainty about the optimum regime for adjunctive antithrombotic therapy in PPCI. Current treatment is based on the combined use of

both antiplatelet and antithrombotic agents. In the procedural phase and beyond, some form of dual-agent, oral antiplatelet therapy is currently the accepted standard[13] [14]. Additional antiplatelet effect can be obtained with the use of parenteral Glycoprotein (GP) IIb/IIIa receptor antagonists.

The two most commonly used antithrombotic agents are heparin and bivalirudin. Two contemporary trials have compared these agents in the PPCI setting. HORIZONS-AMI, compared bivalirudin to a combination of heparin plus mandated GP IIb/IIIa inhibitors[15]. In the more recent EUROMAX study[16], antithrombin treatment was started during transport. This latter trial compared bivalirudin against either heparin or low molecular weight (LMWH) heparin. The trial design enshrined asymmetrical use of GP IIb/IIIa inhibitors allowing routine or selective use with heparin (given in 69% of cases) and only 'bailout' use in the bivalirudin arm (11·5% of cases).

Interpretation of this evidence base is made more complex by the use of outcomes that combine both efficacy and safety measures. Bleeding rates, unsurprisingly, were higher with more widespread GP IIb/IIIa inhibitor administration. Stent thrombosis events were more common with bivalirudin therapy.

There is now general agreement that bleeding can be associated with less favourable outcomes, including increased rates of ischaemic events and, in the HORIZONS-AMI trial (examining the same therapies in the ST elevation setting) an impact on all-cause mortality[15]. The emergence of bivalirudin as an increasingly popular mainstream therapy in PCI has puzzled many observers. The drug is not new, and has been evaluated against heparin in a variety of clinical settings and indications for nearly 20 years. It is interesting to consider why bivalirudin has emerged as a popular, and apparently efficacious, clinical agent - so late in the natural history of its market availability.

In trying to decide the optimum adjunctive regime for antithrombotic therapy in PCI, we face a complex range of choices. We must select, not only individual agents, but consider the safety and efficacy implications of combination therapy. The number of options is substantial and potentially confusing. In an attempt to make sense of the situation we need to propose a more systematic approach to our reading of the current evidence base.

In the procedural phase and beyond, some form of dual, oral antiplatelet therapy is currently the accepted standard[17 18]. The next choice is in respect of our anti-thrombin agent. Here we face a mutually exclusive choice between three main agents: heparin, LMWH and bivalirudin. LMWH has a number of potential advantages over heparin and, in some studies in PCI, its routine application has secured clinical advantage over the more traditional agent[19 20]. There are however no substantial comparative studies between LMWH and bivalirudin. Beyond acknowledging the potential importance of LMWH, and that more studies are justified, we will not consider it further.

Finally, we have the option of using parenteral antiplatelet therapy with a Gp IIb/IIIa receptor antagonist. It is important to note that, in contrast to our initial treatment described above, the use of this drug class has never been considered 'mandatory' for universal application and, just as importantly, is potentially applicable with any other combination of agents.

A growing role for bivalirudin has been supported by trials, which like ISAR-REACT 4[21], randomised patients to treatment with bivalirudin or fixed combination therapy with heparin and a Gp IIb/IIIa inhibitor[15 22 23]. This design compromises one of the core principles of scientific experimentation. We generally seek to compare mutually exclusive options for a single factor - in our case one specific aspect of the treatment plan. We use intelligent study design and randomisation with the aim of creating study groups that are balanced in all respects, except for the subject under investigation. Let us consider some specific issues:

Can Gp IIb/IIIa inhibitors be used in combination with bivalirudin?

This combination is an accepted option. Bailout Gp IIb/IIIa inhibitor therapy in combination with bivalirudin has been an option in all studies and in HORIZONS-AMI was used in about 7% of patients randomised to bivalirudin[15]. In ACUITY, the combination was used as one of the three study groups created at randomisation[22]. Results in this group were very similar to those in patients receiving heparin plus a Gp IIb/IIIa inhibitor - both in terms of ischaemic outcomes and bleeding complications.

Is 'heparin plus mandated, unselected Gp IIb/IIIa inhibitor therapy' an accepted, universal treatment strategy?

The short answer is no. Unselected routine use never became established, even at the zenith of Gp IIb/IIIa inhibitor popularity. There has been more than 50% decrease in the use of these agents in the UK since 2005[24] and rest of the Europe is witnessing similar trends. The clinical utility of Gp IIb/IIIa inhibitors depends on the risk profile and specific features of the presentation or case[25-33]. Even in the setting of PPCI, their use is recommended in specific indications such as slow or no-reflow after PCI, the presence of large thrombus burden or inadequate antiplatelet loading during PPCI[13 14]. The potent anti-ischaemic efficacy of this drug class must be balanced against the risk of bleeding complications and a selective approach to administration is now the clinical norm.

The advent of more effective oral antiplatelet therapy with a more rapid onset of action, as well as early and high dose loading regimes may have reduced the potential for incremental anti-ischaemic protection with Gp IIb/IIIa inhibitors, whilst retaining the potential for bleeding complications.

Other practice changes over the years since their initial (and at the time, very welcome) introduction may also have had an impact. Thrombus aspiration is in widespread use and will, to some extent, impact the thrombotic burden. Improved practice patterns and public health measures mean that patients are receiving interventional management earlier in the clinical course when 'fresh thrombus' may be easier to treat than after propagation and organisation.

Do we have reason to believe bivalirudin is a more effective antithrombotic agent than heparin?

There are a number of aspects of the pharmacology of bivalirudin that hold out the promise of improved efficacy over the rather 'messy' chemistry of the heparins. However, bivalirudin has failed to establish any clear advantage in terms of anti-ischaemic efficacy[15 21-23 34-37].

Three major RCTs have performed a direct comparison between heparin and bivalirudin in an elective PCI setting. The first, HAS (Hirulog Angioplasty Study 1995),

concluded that there was no significant difference between the two trial medications for any of the efficacy end points[35]. This trial was re-analysed 6 years later and was presented as BAT (Bivalirudin Angioplasty Trial)[38]. Key features like the number of patients analysed, analysis time-points and primary outcome measures were changed making the results questionable.

REPLACE-1 in 2001 showed that a head-to-head comparison of bivalirudin and 'moderate dose' heparin (70 U/kg) in an elective PCI setting resulted in no differences in bleeding or ischaemic complications[37]. The investigators in REPLACE-2 added mandatory Gp IIb/IIIa inhibitor administration to the heparin arm and the results, not surprisingly, showed more bleeding complications in this arm as compared to bivalirudin monotherapy[23].

ISAR-REACT 3 (2008)[36] used a significantly higher dose of heparin (150 U/kg) than that in routine use or suggested by current international guidelines[18]. The results again showed no differences in ischaemic outcomes but more bleeding complications in the heparin arm. There is an established relationship between heparin dose and the incidence of bleeding complications. The investigators later conducted a further study, ISAR-REACT 3A, recruiting consecutive patients in a third arm receiving a lower dose of heparin (100 U/kg)[39]. They compared outcomes to the historical controls in the ISAR-REACT 3 trial. They concluded that there was no longer a significant difference in the bleeding outcomes between the patients that received bivalirudin in ISAR-REACT 3 when compared to the patients that received the lower dose of heparin (100 U/kg).

There is no real evidence base to suggest that bivalirudin confers superior anti-ischaemic protection over and above heparin alone. In studies designed to test the efficacy of anti-thrombin monotherapy against protocol-specified, combined use with Gp IIb/IIIa inhibitors, there would have been a strong case to include a 'heparin only limb' or to consider a factorial design. Most of the recent bivalirudin studies do not give us any insight into how heparin may have fared as a comparator agent.

Are there any problems with bivalirudin therapy?

There is the issue of cost. Bivalirudin costs about 400 times as much as heparin and a potential cost saving of 500 - 1000 Euros in each case must be attractive. Bivalirudin

must be reconstituted at the time of administration and, together with the need to maintain an intra-venous infusion, make its use a little more labour intensive and inconvenient. In the event of important acute bleeding there is no agent for immediate reversal, but the shorter half-life means that antithrombotic effect will be lost over the next few hours.

Both ACUITY[22] and HORIZONS-AMI[15] reported a significantly higher incidence of acute stent thrombosis in the patients that received bivalirudin in comparison to heparin. Following the data from the HORIZONS-SWITCH analysis[40] and a large analysis from the SCAAR registry[41], a growing school of thought is suggesting that administration of heparin along with bivalirudin may be required to reduce acute thrombotic events[42]. It is important to know if heparin alone could be sufficient to do the job.

So what about monotherapy therapy with heparin?

A report from the SCAAR registry, presented at the recent EuroPCR conference, analysed 41,537 patients that received heparin or bivalirudin during PCI. The study reported an adjusted odds ratio for 30-day mortality in favour of heparin (1.53 for complete case analysis)[43].

The need for HEAT-PPCI trial:

There is a need to assess the relative safety and efficacy of heparin and bivalirudin in a study design reflecting modern PPCI practice. The HEAT-PPCI trial was created with a pragmatic design. The use of GP IIb/IIIa inhibitor agents was reserved for selective, 'bail out' use in both arms as per the European Society of Cardiology (ESC) guidelines[13]. This approach sought to create a classic 'experiment' in which the two study groups, created at randomisation, are balanced – except for the mutually exclusive therapies under evaluation.

The study design also sought to address another common limitation of the randomised controlled trial (RCT) methodology. Many trials recruit only a modest proportion of the potential, eligible population. This selective inclusion can limit the generalisation of study findings in clinical practice. The mortality rate in HORIZONS-AMI was less than half of that declared by national registries and observed in individual centres[15]. Very sick patients, the elderly and the frail, patients with less-favourable socio-economic

status, females and those from ethnic minorities, are often not approached for study participation[44]. We obtained ethical approval for a policy of delayed consent and set ourselves the demanding goal to randomise all eligible patients entering the catheterisation laboratory in the setting of a PPCI activation - “Every Patient - Every Time”.

Hypotheses:

Primary hypothesis:

There is no significant difference between unfractionated heparin and bivalirudin in terms of safety and efficacy when used as adjunctive antithrombotic therapy in the treatment of patients with STEMI events managed by PPCI.

Secondary hypotheses:

- There is no significant difference between unfractionated heparin and bivalirudin in terms of ex-vivo inhibition of platelet aggregation in patients with STEMI managed by PPCI.
- Newer oral P2Y12 inhibitors, ticagrelor and prasugrel achieve higher suppression of ADP-induced platelet aggregation than clopidogrel in STEMI population undergoing PPCI
- Patients with the most favourable response to ADP antagonists have significantly lower MACE at 28 days than those with the least favourable response.
- Patients with the most favourable response to ADP antagonists have a significantly higher rate of type 3-5 BARC bleeding than those with the least favourable response.

Aims:

Primary aim:

To compare efficacy and safety of two antithrombotic agents, bivalirudin and heparin in STEMI patients undergoing PPCI.

Secondary aims:

1. To compare the antiplatelet effects of bivalirudin and heparin in patients

undergoing PPCI for STEMI.

2. To compare the effects of P2Y12 inhibitors on platelet reactivity and clinical outcomes in patients undergoing PPCI for STEMI.
3. To demonstrate that the adoption of 'delayed consent' methodology is safe and pragmatic in a trial recruiting patients in emergency STEMI setting.
4. To recruit all eligible patients presenting to the host institution to create a truly representative 'all-comer' real-world population.
5. To establish a system of denominator groupings, seeking to better describe the range of clinical activity resulting from an unselected series of PPCI activations.
6. To compare the efficacy of two methods of follow-up, direct patient contact and Hospital Episode Statistics (HES), in identifying patient readmissions.
7. To assess the diagnostic accuracy of HES data in identifying pre-specified clinical events, reported as outcome measures in the study.

Methods:

Study design and population:

This was a single centre, open-label RCT and all patients presenting to the PPCI service at the Liverpool Heart and Chest Hospital, UK (LHCH) during the recruitment period were assessed for trial eligibility. The exclusion criteria were limited to the following: age < 18 years of age; known intolerance, hypersensitivity or contraindication to any trial medication; active bleeding at presentation; artificial ventilation, reduced conscious level or other factors precluding the administration of oral antiplatelet therapy; physician refusal to administer antiplatelet loading (uncertain diagnosis/risk of bleeding) and previous enrolment in this trial.

Inclusion Criteria
All patients presenting with a suspected ST elevation myocardial infarction event with PPCI as the proposed index reperfusion strategy
Exclusion Criteria
1. ≤ 18 years of age 2. Known intolerance, hypersensitivity or contraindication to any trial medication 3. Active bleeding at presentation

4. Artificial ventilation, reduced conscious level or other factors precluding the administration of oral antiplatelet therapy
5. Physician refusal to administer antiplatelet loading (uncertain diagnosis/ risk of bleeding)
6. Previous enrolment in this trial

Table 1 Patient eligibility criteria

Ethical approval and delayed consent:

Full ethical approval was granted for the use of delayed consent. Patients were randomised and treated in an emergency setting and no attempt was made to discuss the trial or to seek consent during this phase. Surviving patients (or their appropriate representatives) were later approached for formal consent to continue as trial subjects, for the use of their data and to allow contact for the 28-day follow-up. STEMI has a high early hazard and a number of patients died after randomisation, but before consent could be obtained. Approval was sought and obtained from the national Confidentiality Advisory Group (CAG), to include the clinical data and outcome measures from these patients.

Study treatments and investigations:

All patients received dual antiplatelet therapy before PPCI as per routine practice at the host institution and its referring emergency departments. After entry to the catheter laboratory, and before the angiographic findings were known, patients received the trial medication as allocated at randomisation. Heparin was given as a bolus dose of 70 units/kg body weight pre-procedure. Additional doses were administered if activated clotting time (ACT) values 5-15 minutes after the bolus dose or at the end of the procedure were <200. Bivalirudin was given as a bolus of 0·75 mg/kg followed by infusion of 1·75 mg/kg per hour for the duration of the procedure. A re-bolus of 0·3 mg/kg was administered if ACT values 5-15 minutes after the bolus dose or at the end of the procedure were <225. ACT was monitored using Actalyke XL® MAX-ACT system. The GP IIb/IIIa inhibitor, abciximab, was allowed for selective use in both limbs as per the ESC guidelines (angiographic evidence of massive thrombus, slow or no-reflow or a thrombotic complication)[13]. The recommended dose was 0·25mg/kg intravenous bolus, followed by a continuous intravenous infusion of

0·125µg/kg/min (to a maximum of 10µg/min) for 12 hours. No other trial-related restrictions were imposed on the performance of angiography and PCI which were conducted in accordance with prevailing best local practice as determined by the attending interventional cardiologist. Blood sampling was performed 12-18 hours after the index procedure to assess CKMB release following index procedure in patients with suspected or proven diagnosis of myocardial infarction.

Study design flow chart:

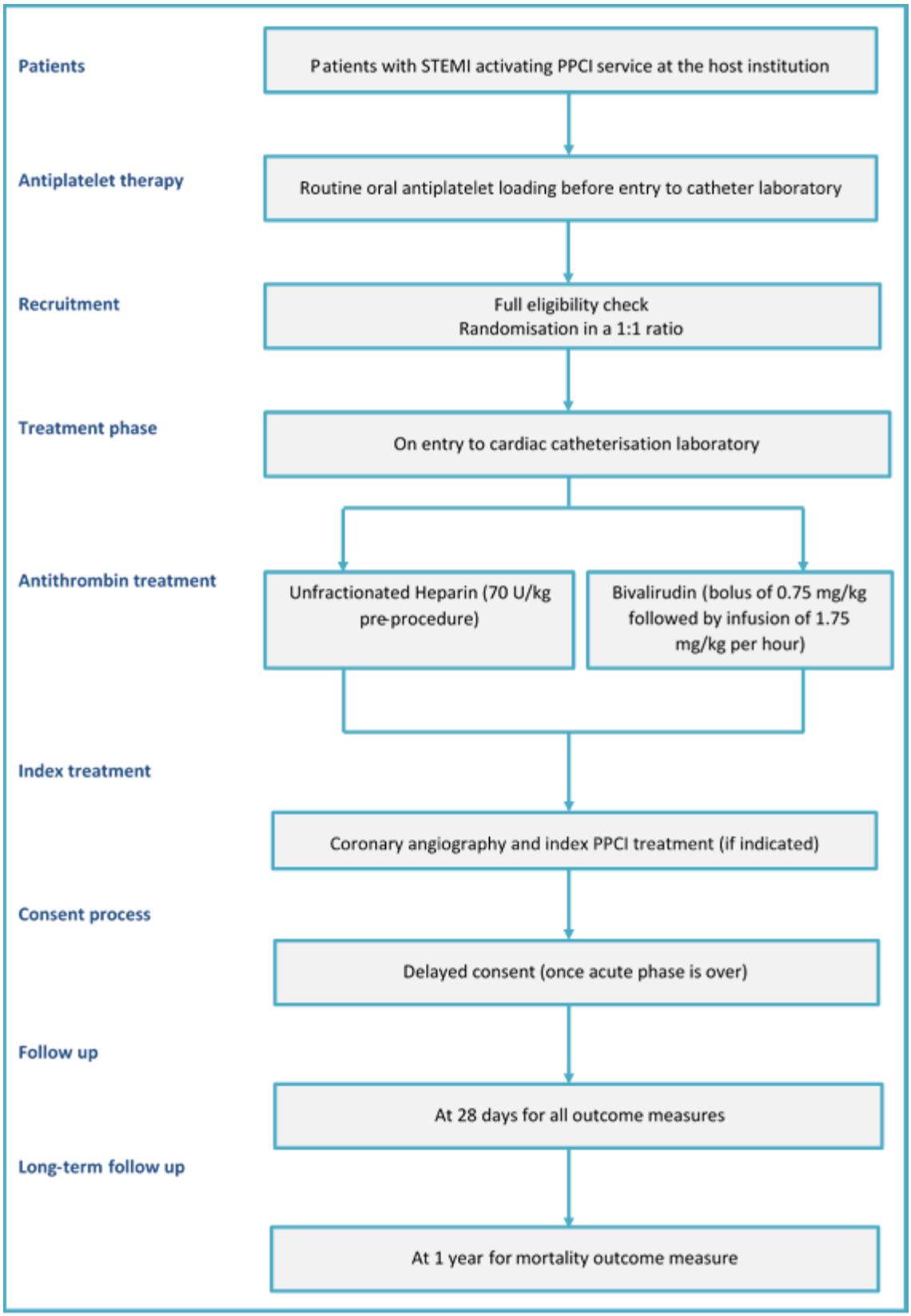


Figure 1 Main study flow chart

Outcome measures:

The primary efficacy outcome compared the rate of major adverse cardiac events (MACE) at 28 days. This is a composite of all-cause mortality, cerebrovascular accident (CVA), reinfarction or additional unplanned target lesion revascularisation (TLR). The primary safety outcome was the rate of major bleeding at 28 days, classified as type 3-5 according to the Bleeding Academic Research Consortium (BARC) definition. Key secondary outcome measures included stent thrombosis rates, cardiac enzyme release and minor bleeding (BARC type 2).

Primary Efficacy Outcome Measures
At 28 days – Major adverse cardiac events (MACE) in terms of the incidence of • All-cause mortality • CVA • Reinfarction or subsequent myocardial infarction • Additional unplanned target lesion revascularisation (TLR)
Primary Safety Outcome Measures
At 28 days – Type 3-5 bleeding according to Bleeding Academic Research Consortium (BARC) definition
Secondary Outcome Measures
• CKMB release following index procedure measured with a single estimation 12-18 hours after the procedure in patients with suspected or proven diagnosis of myocardial infarction • Minor bleeding: Type 2 bleeding according to BARC definition • Stent thrombosis rate (ARC definite or probable) [45] • For illustration, and to allow comparison with existing trials, the rate of Net Adverse Clinical Events (NACE), combining the primary safety and efficacy outcomes • Development of thrombocytopenia • Door-to-first device time

Table 2 Outcome measures

Pre-specified subgroup analyses involve assessment of the primary outcome according to the route of arterial vascular access, LV function, age, history of diabetes mellitus, type of P2Y12 inhibitor used and whether or not PCI was attempted. Definitions of the study outcomes are provided below.

Study definition of Death:

Deaths will be classified as cardiovascular or non-cardiovascular. Examples of cardiovascular causes of death include MI, cardiac failure, arrhythmia, CVA, bleeding, PE, dissection. All disease processes developing as a result of a sequence of events originating from the index event should also be considered cardiovascular including: sepsis, pneumonia etc. Only deaths due to a clear documented non-cardiovascular cause (e.g., cancer, road traffic accident) will be classified as non-cardiovascular.

Study Definition of Myocardial Infarction:

The diagnosis of reinfarction will be divided into two phases:

Phase 1: Reinfarction during hospitalisation for index infarct

This will comprise of either

- Chest pain: Recurrence of ischaemic type chest discomfort lasting ≥ 20 minutes

or

- New ECG changes: ST elevation ≥ 0.1 mV re-occurring in a patient having a lesser degree of ST elevation, new-onset T-wave changes, horizontal ST depression or new pathological Q waves (see table 1), in at least 2 consecutive leads. The changes should be distinct from the ECG changes secondary to the index event.

along with either

- Increase in cardiac enzyme activity: The rise of CKMB or Troponin has to be at least greater than 3 × 99th percentile Upper Reference Limit (URL) and re-elevation by at least 50% from previous baseline following a 25% decrease from the peak value (demonstrating a twin peak effect)

or

- Angiographic evidence of new thrombus, vessel occlusion or sub-total occlusion

Phase 2: Reinfarction after discharge for index infarct
Detection of rise of cardiac enzymes (Troponin or CKMB) with at least one value above the 99th percentile Upper Reference Limit (URL) together with at least one of the following: • Symptoms of ischaemia • ECG changes suggestive of new ischaemia (ST-T changes or new onset LBBB) • Development of new pathological Q waves*, in at least 2 consecutive leads Note: The following will also indicate re-infarction or subsequent myocardial infarction during both phases: Sudden, unexpected cardiac death, involving cardiac arrest, often with symptoms suggestive of myocardial ischaemia, and accompanied by presumably new ST elevation, or new LBBB, and/or evidence of fresh thrombus by coronary angiography and/or at autopsy, but death occurring before blood samples could be obtained, or at a time before the appearance of cardiac biomarkers in the blood.

Table 3 Study Definition of Myocardial Infarction

*New onset pathological Q waves as per the ESC/ACCF/AHA/WHF Task Force 2007 definition of prior myocardial infarction

Study Definition of Cerebrovascular Accident:

Acute event resulting in death or new neurological deficit lasting >24 hours classified by a physician as a stroke. This will be classified as:

Haemorrhagic CVA
• Intracerebral haemorrhage: Stroke with focal collections of intracerebral blood seen on a brain imaging (CT or MR) or at postmortem examination, not felt to represent haemorrhagic conversion. Subarachnoid haemorrhage is included in this category. • Subdural hematoma: High density fluid collection in subdural space on brain images or blood in the subdural space at autopsy.
Non-haemorrhagic CVA
• Cerebral infarction: Stroke without focal collection of intracerebral or extra cerebral blood on the brain image or at autopsy. • Infarction with haemorrhagic conversion: Cerebral infarction with blood seen on a brain image or at autopsy felt to represent haemorrhagic conversion and not a primary haemorrhage.

Table 4 Study Definition of Cerebrovascular Accident

Additional Unplanned Target Lesion Revascularisation (TLR):

TLR will be defined as any subsequent, unplanned revascularisation of any lesion treated at the index procedure within the original target segment or in the adjacent 5 mm of the distal or proximal vessel. In the case of surgical revascularisation, TLR will have occurred if there is the creation of a graft conduit to an epicardial vessel treated at the index procedure.

Study definition of Major Bleeding:

At 28 days – Type 3-5 bleeding according to BARC (Bleeding Academic Research Consortium) definition. These are as follows:

Type 3
Type 3a
Overt bleeding plus haemoglobin drop of 3 to <5*g/dL (provided haemoglobin drop is related to bleed)
Any transfusion with overt bleeding
Type 3b
Overt bleeding plus haemoglobin drop ≥ 5*g/dL (provided haemoglobin drop is related to bleed)
Cardiac tamponade
Bleeding requiring surgical intervention for control (excluding dental/nasal/skin/haemorrhoid)
Bleeding requiring intravenous vasoactive drugs
Type 3c
Intracranial haemorrhage (does not include microbleeds or haemorrhagic transformation; does include intraspinal)
Subcategories; confirmed by autopsy or imaging or LP
Intra-ocular bleed compromising vision
Type 4: CABG-related bleeding

Perioperative intracranial bleeding within 48 hrs
Reoperation following closure of sternotomy for the purpose of controlling bleeding
Transfusion of ≥ 5 units of whole blood or packed red blood cells within a 48 period
Chest tube output ≥ 2 L within a 24 h period
Note: If a CABG-related bleed is not adjudicated as at least a Type 3 severity event, it will be classified as 'not a bleeding event'
Type 5: Fatal bleeding
Type 5a: Probable fatal bleeding: no autopsy or imaging confirmation, but clinically suspicious
Type 5b: Definite fatal bleeding: overt bleeding or autopsy or imaging confirmation

Table 5 Study definition of Major Bleeding

Definition of thrombocytopenia:

Acquired thrombocytopenia will be defined as >25% reduction in platelet count in a patient with normal platelet count (150-400 $x10^9$/L) on admission and a measured level after randomisation of <150 $x10^9$/L. Acquired thrombocytopenia will be classified as mild (100-150 $x10^9$/L), moderate (50-100 $x10^9$/L), or severe (<50 $x10^9$/L).

Definition of door-to-first device time:

Door-to-first device time will be defined as time taken from ambulance arrival at a participating centre to the application of a therapeutic device to the culprit lesion (balloon, thrombus aspiration catheter – not guide wire).

Study organisation:

Computer Randomisation Application:

Randomisation tables were prepared, independent of clinicians performing PPCI. Randomisation was performed on a dedicated computer, running a bespoke randomisation application as its sole software function. The randomisation application had a secure 'front-end' interface and operators did not have access to the underlying application code or randomisation tables.

Backup Randomisation:

An emergency sealed envelope system for randomisation was also in place as a backup in case the computer system was unavailable for technical reasons. All envelopes were opaque and serial numbered to prevent allocation subversion. Envelope randomisation procedure was only used on 8 (0.43%) occasions during the trial recruitment.

Stratification and Block Randomisation:

To ensure that groups were similar for important prognostic features, stratification was applied using a) Age ≥ 75 years b) Presence of cardiogenic shock. Treatment allocation was controlled using a block system. For patients not in cardiogenic shock, block sizes were 2, 4 and 6 were used with random variation of block sizes to avoid the possibility of investigators being able to predict the next allocation on the basis of the historical pattern. For patients in cardiogenic shock and for all envelope randomisation allocations, the block sizes were 2 and 4.

Data collection and validation:

Patient case notes and electronic records were examined by the trial investigators, throughout the course of the index admission, to allow contemporaneous completion of the trial-specific case record forms (CRF). The CRF design prompted investigators to identify and record all potential clinical and outcome measure events.

All study primary and secondary end points were monitored against the host institutions' clinical coding department records. Quarterly audits were performed against the data collected by hospital clinical audit department to cross check the fate of all PPCI activations for the host institution. Regular 6 monthly medical practitioner led audits were undertaken to assess data collection accuracy and to validate it against the patient case records.

Clinical events review:

The clinical events committee (CEC) has been responsible for adjudicating all primary and key secondary outcome measures. These outcome measures were adjudicated by two independent adjudicators (internal and external) neither of whom was involved in the care of the patient. Each clinical event was summarised in detail by the

investigators who created a single modifiable PDF document containing all relevant anonymised information. This included a summary of the clinical events, all relevant discharge and procedural letters, results of blood tests and other investigations and autopsy results (where applicable). Adjudicators were blinded to the antithrombotic used. In case of a disagreement between the two adjudicators, a telephone conversation was organised between them to seek resolution by consensus. If the disagreement had persisted, then a third adjudicator would have been asked to give an opinion, but this was not required.

Interim safety analysis:

A Data Monitoring and Safety Committee (DMSC) was constituted and was afforded access to all aspects of the trial management structure, clinical data and administrative documentation. The DMSC performed a site visit after the enrolment of 900 patients. They reviewed trial progress, operational procedures and quality control audits. The DMSC performed a single, un-blinded analysis of the data for an interim safety analysis after the enrolment of 1200 patients, after which they recommended that recruitment should continue.

The study protocol was approved by the ethics committee and the trial was registered at www.clinicaltrials.gov (NCT01519518). The study was partially funded by unrestricted grants from The Medicines Company and AstraZeneca but these companies had no involvement in any aspect of trial design, conduct or reporting. The first author and the last author (who is also the principal investigator for the study) accept full responsibility for the accuracy and completeness of the data and all analyses. The full study protocol and statistical analysis plan are available at www.thelancet.com.

Statistical methods and power calculation:

In the HORIZONS-AMI trial, the 30 day MACE rate was 5·5%[15]. As our study would include all patients, including high risk presentations, we estimated a MACE event rate of 7·5%. Our statistical approach uses an established methodology[46]. This method considers the absolute difference in the observed event rates between the two treatment arms and uses two-sided testing to allow the rejection of the null hypothesis in favour of either therapy. Assuming an identical event rate at 7·5%, a sample size of

1800 patients would, within the upper boundary of a two-sided 95% confidence interval (CI), allow the exclusion of a 2·5% absolute difference in event rates. Equivalence would be assumed if the point estimate lay in the range ± 0·5% from the zero-difference point (figure 2).

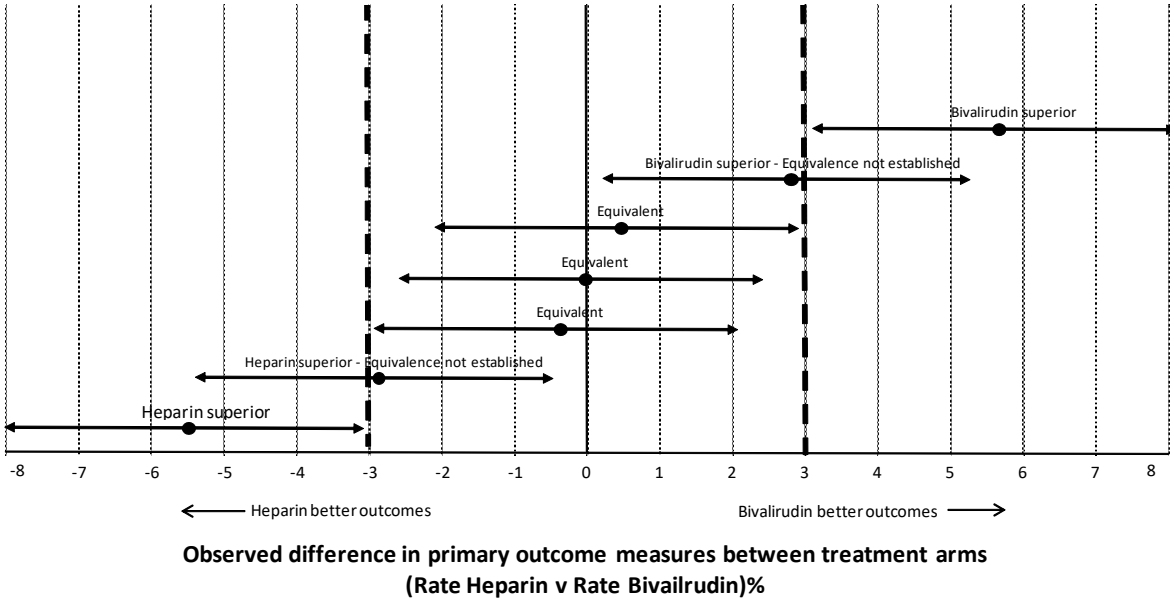


Figure 2 Zone of equivalence and confidence interval boundaries

All analyses have been performed according to the intention-to-treat (ITT) principle and patient data has been reported and analysed in the two trial groups as allocated at randomisation. Descriptive statistics are presented in terms of the numbers and proportions of patients or, for continuous variables, means or medians, range of observations, standard deviations and inter-quartile ranges. All proportions are presented in the form: numerator/denominator (%). All tests of significance are two-sided. Differences were considered significant with a maximal type I error risk of 5%. Categorical data has been compared with the use of a chi-square test (or Fisher's exact test when the absolute number of observed events in any group is five or less). Continuous data has been compared with the use of the t-test (or the Wilcoxon test in the case of non-normal data). Data analyses have been performed by independent statisticians. All statistical analyses have been performed with SAS software, version 9·3.

Microsoft Access Database Development:

A highly sophisticated database has been created by the HEAT-PPCI team. The database is written in Microsoft Access. We have created fields and tables in accordance with the data collected via the case record form (Figure 3). Relationships have been carefully defined between the tables to avoid redundancy of data and ensure easy extraction (figure 4 and 5). Patient specific data are kept in a separate table to ensure confidentiality. Tables containing adverse events data are organised in one-to-many relationships. This organised infrastructure is populated and used via a programmed interface, using data entry forms. The forms have an intuitive interface with clear presentation and easy navigation. The forms mirror the CRFs, field-to-field, page-to-page for easy transcription (Figure 6). An efficient system to raise, edit and resolve 'queries' has been established to tackle missing, ineligible or illogical data.

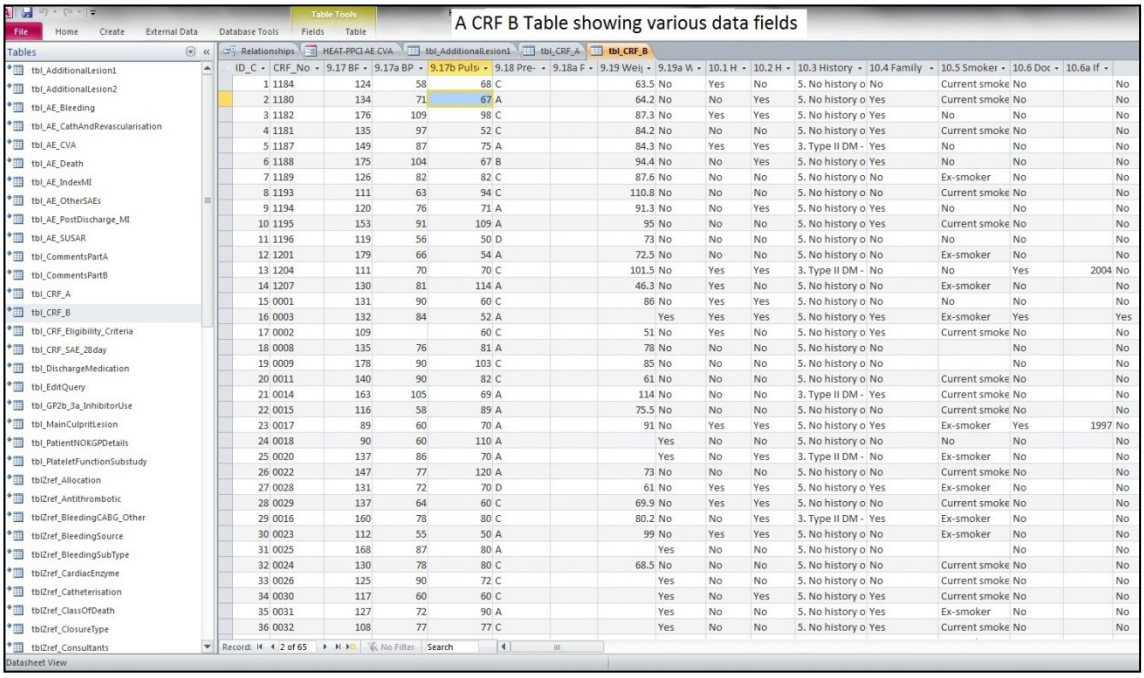


Figure 3 An example of a table from Case Record Form B in HEAT-PPCI Access database

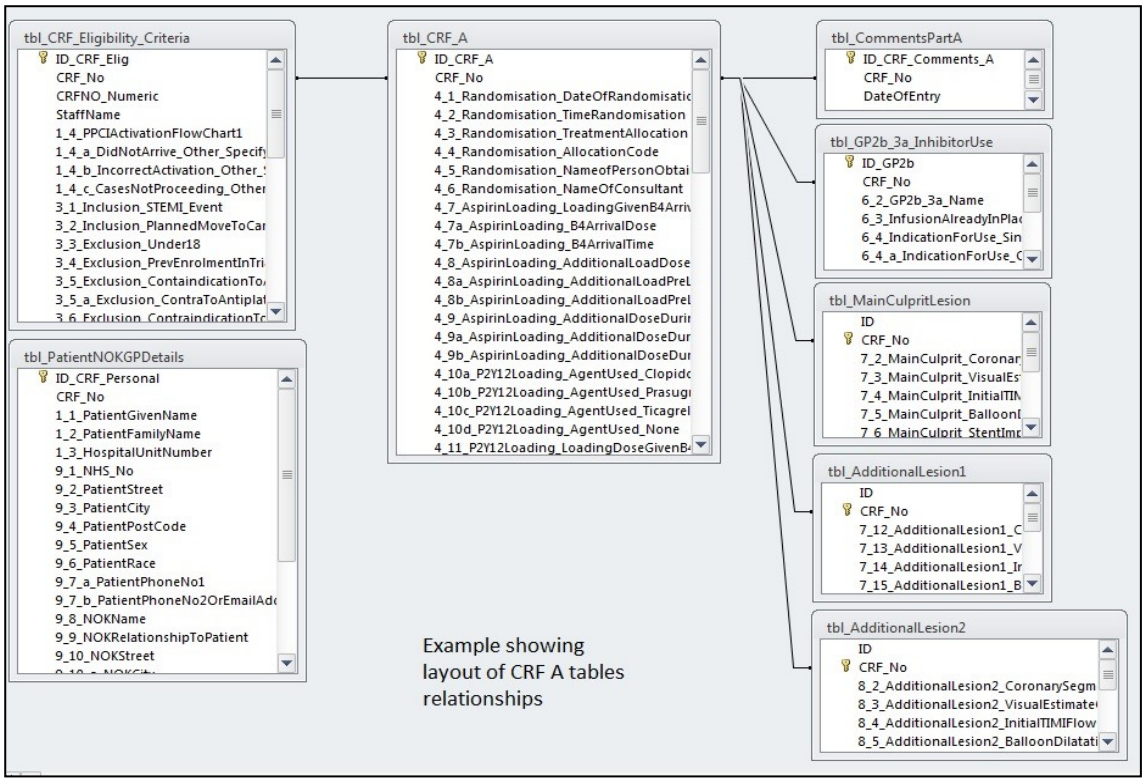


Figure 4 Table relationships showing Case Record Form A layout in Microsoft Access database

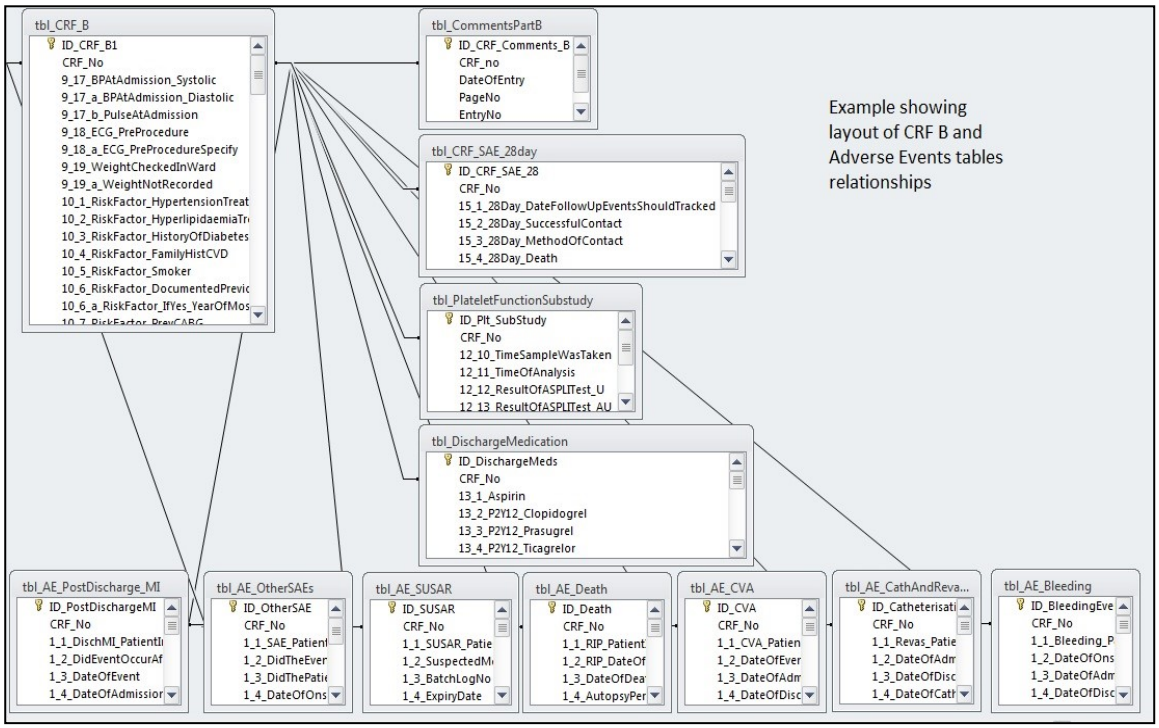


Figure 5 Table relationships showing Case Record Form B and Adverse Event Forms layout in Microsoft Access database

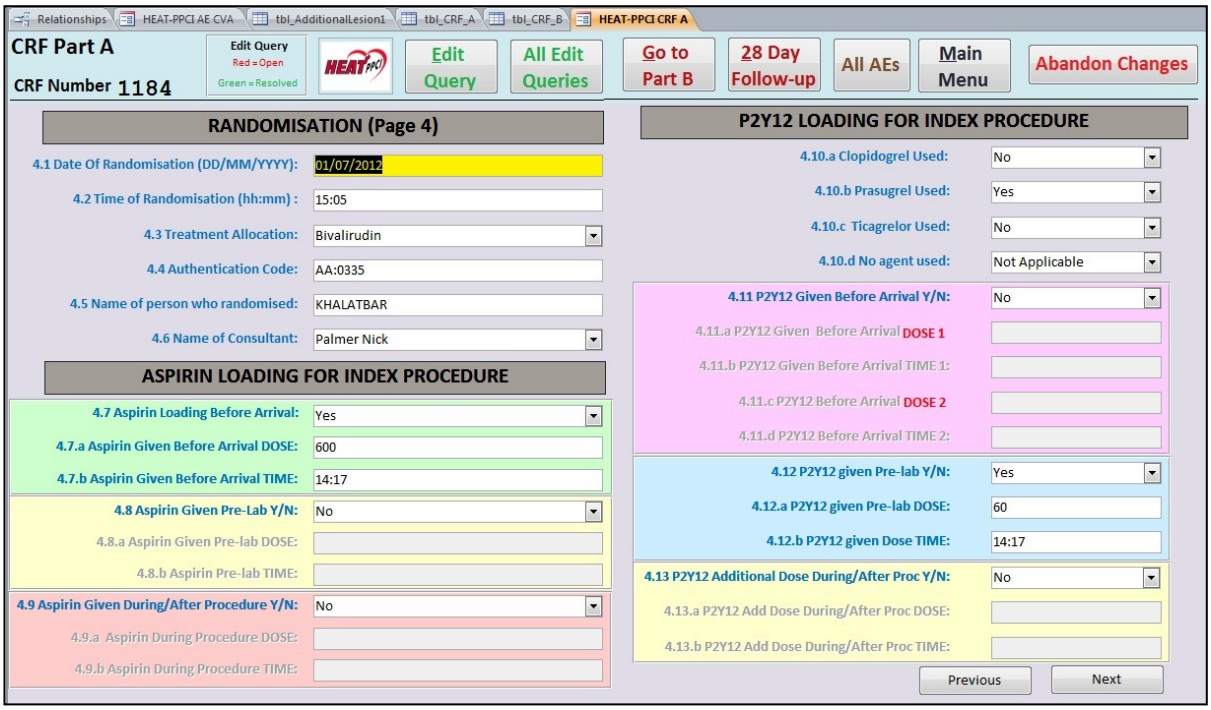


Figure 6 An example of a form in HEAT-PPCI Access database

Chapter 2 – Main study:

Abstract:

Background:

Bivalirudin, with selective use of glycoprotein (GP) IIb/IIIa inhibitor agents, is an accepted standard of care in primary percutaneous coronary intervention (PPCI). We performed a trial to compare antithrombotic therapy with bivalirudin or unfractionated heparin (heparin) during PPCI.

Methods

This was a single centre, open label, randomised controlled trial. We used a strategy of delayed consent and consecutive patients were included without initial discussion. Before angiography, patients were randomised to either heparin (70 units/kg) or bivalirudin (bolus 0·75 mg/kg; infusion 1·75 mg/kg/hour). Patients were followed for 28 days. The primary outcome measure was a composite of all-cause mortality, cerebrovascular accident (CVA), reinfarction or unplanned target lesion revascularization (TLR). The primary safety outcome was the rate of major bleeding - type 3-5 as per the Bleeding Academic Research Consortium (BARC) definitions.

Findings:

A total of 1829 patients were randomised (100% of eligible patients and 97% of all PPCI-related procedures). A PCI procedure was performed in 82% of cases. The rate of GP IIb/IIIa inhibitor use was: bivalirudin 13·5%, heparin 15·5%. The primary efficacy outcome measure was observed more frequently in patients treated with bivalirudin (8·7% v 5·7%, absolute risk difference = 3%; relative risk [RR] 1·52, 95% confidence interval [CI], 1·09 to 2·13; P=0·01). All elements of the composite favoured heparin but the difference was mainly related to an increased incidence of stent thrombosis with bivalirudin (3·4% v 0·9%, RR 3·91, 95% CI 1·61 to 9·52; P=0·001), causing reinfarction

events. There was no difference in major bleeding (3·5% bivalirudin v 3·1% heparin; RR 1·15, CI 0·70 to 1·89; P=0·59).

Interpretation:

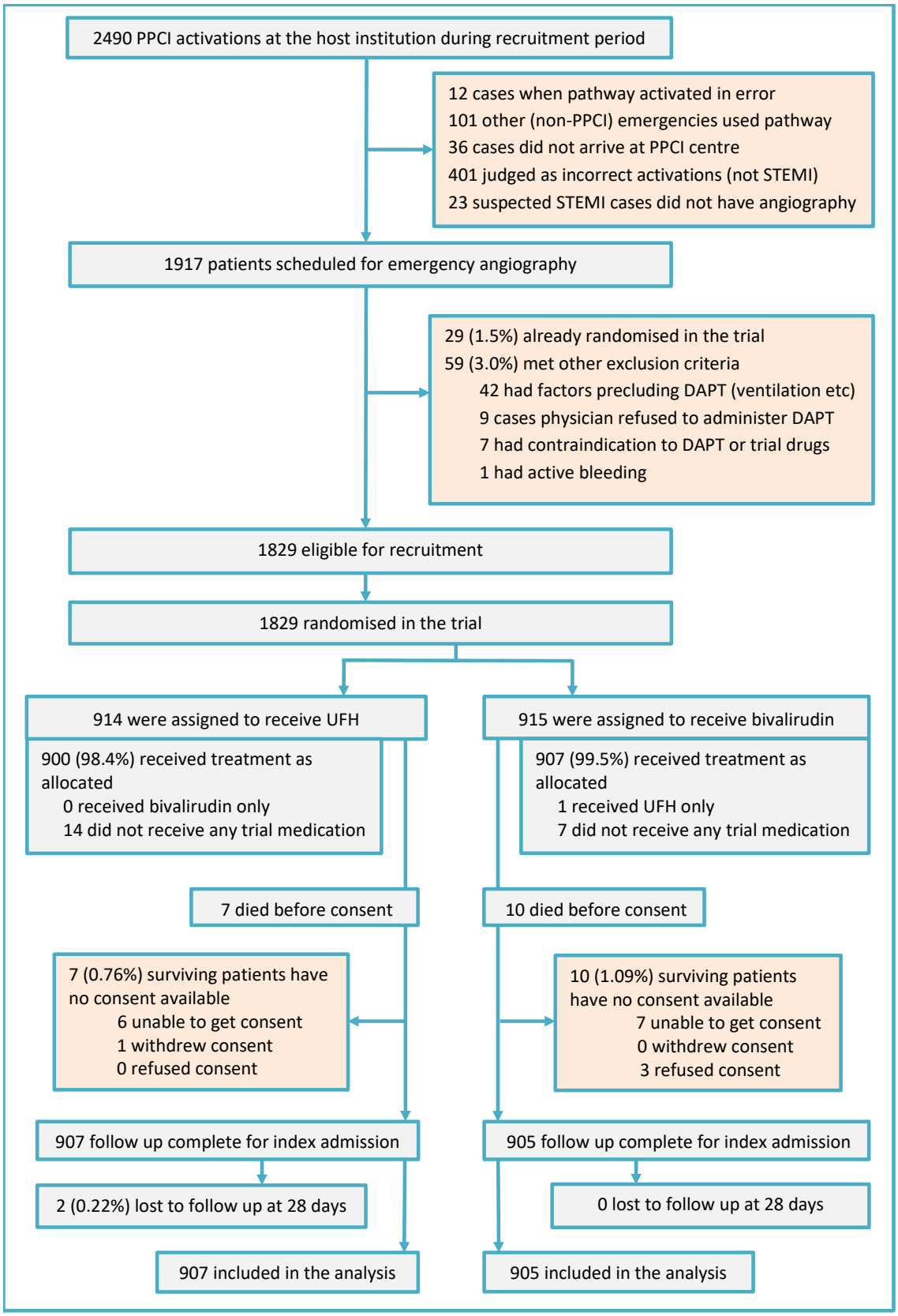
Use of heparin, rather than bivalirudin, is associated with a reduced rate of major adverse ischaemic events, with no increase in bleeding complications. More systematic use of heparin offers the potential for a substantial reduction in drug cost.

Patients:

Trial profile:

The trial profile is at Figure 7. From 7th February 2012 to 20th November 2013, the PPCI pathway system was activated at the host institution on 2490 occasions. Of this number, 1917 (76·98%) patients were scheduled for emergency angiography for a suspected STEMI event, and hence, considered for randomisation. Envelope randomisation was only used on eight (0·43%) occasions during the trial. Twenty-nine subjects were already enrolled in the trial and a further 59 (3·08%) met one or more of the limited exclusion criteria. Of the remaining 1829 eligible subjects, all were randomised in the trial. A total of 914 patients were assigned to the heparin arm, of which 14 (1·53%) did not receive any trial medication. Seven (0·76%) patients out of the 915 assigned to the bivalirudin arm did not receive any trial medication. There was only a single treatment cross-over during the study period with one patient randomised to the bivalirudin arm receiving heparin alone.

Seventeen (0·92%) patients died before the investigators were able to obtain consent (seven heparin arm, ten bivalirudin arm). Consent was not available for a further 17 surviving patients (13 contact lost before consent, one withdrawal and three refusals). These patients have been excluded from the analyses but we know, from national mortality tracking, that all were alive at 28 days after their randomisation. Two patients were tracked for the complete duration of their index admission but have no follow up after hospital discharge and to 28 days. These patients have been included in the analyses.



(PPCI denotes primary percutaneous coronary intervention, STEMI ST-elevation myocardial infarction and DAPT dual antiplatelet therapy)

Figure 7 Main trial patient flow diagram

Baseline characteristics:

The baseline characteristics of patients were well matched between the two groups included in the analyses (907 in the heparin arm and 905 in the bivalirudin arm) except higher rates of patient reported previous myocardial infarction and PCI in the bivalirudin group (Table 6).

Characteristic	**Bivalirudin (n=905)**	**Heparin (n=907)**
Age – yrs (median, IQR) [δ]	62.9 (53.7, 74.0)	63.6 (54.0, 73.8)
Female sex – no./total no. (%)	258/905 (28.5)	244/907 (26.9)
Caucasian race - no./total no. (%)	866/904 (95.8)	870/907 (95.9)
Weight – kg (median, IQR) [¶]	80 (67, 90)	80 (70, 90)
Comorbidities - no./total no. (%)		
Diabetes Mellitus	114/902 (12.6)	136/899 (15.1)
Hypertension	362/902 (40.1)	388/903 (43.0)
Hyperlipidaemia	327/893 (36.6)	342/899 (38.0)
Family history of CVD	388/891 (43.6)	401/894 (44.9)
Current smoker	371/888 (41.8)	379/888 (42.7)
Previous myocardial infarction	122/903 (13.5)	93/906 (10.3)
Previous PCI	76/903 (8.4)	54/904 (6.0)
Previous CABG	22/903 (2.4)	20/906 (2.2)
Symptom onset to randomisation interval – hrs (median, IQR) [§]	2.8 (1.7, 5.5)	2.7 (1.5, 5.3)
Blood tests on admission (median, IQR)		
Platelet count [#]	229 (186, 275)	223 (186, 266)
eGFR [†]	80 (64, 90)	80 (65, 90)
Haemoglobin [‡]	13.6 (12.4, 14.6)	13.7 (12.5, 14.7)
Aspirin use - no./total no. (%)	899/905 (99.3)	905/906 (99.8)
P_2Y_{12} inhibitor loading dose - no./total no. (%)		
Any agent	901/905 (99.6)	902/907 (99.5)
Clopidogrel	107/905 (11.8)	91/907 (10.0)
Prasugrel	247/905 (27.3)	250/907 (27.6)
Ticagrelor	554/905 (61.2)	569/907 (62.7)
GP IIb/IIIa inhibitor use - no./total no. (%)	122/905 (13.5)	140/906 (15.5)
Arterial access site- no./total no. (%)		
Femoral	171/905 (18.9)	161/907 (17.8)
Radial	727/905 (80.3)	744/907 (82.0)
Activated Clotting Time (ACT) – sec (median, IQR)		
5-15 min after bolus dose [Ŧ]	251 (229, 285)	224 (200, 256)
At the end of the procedure [Ψ]	246 (229, 270)	206 (188, 229)
Managed with PCI- no./total no. (%)	751/905 (83.0)	740/907 (81.6)

Thrombectomy	444/751 (59.1)	426/740 (57.6)
Single-vessel treated	700/751 (93.2)	668/740 (90.3)
Main culprit lesion treated with primary PCI		
Left main stem	7/751 (0.9)	7/740 (1.0)
Left anterior descending artery	304/751 (40.5)	298/740 (40.3)
Left circumflex coronary artery	99/751 (13.2)	109/740 (14.7)
Right coronary artery	333/751 (44.3)	324/740 (43.8)
Bypass graft	8/751 (1.1)	2/740 (0.3)
Balloon angioplasty only	51/751 (6.8)	42/740 (5.7)
Implantation of stent		
Any type	697/751 (92.8)	682/740 (92.2)
Drug eluting	599/751 (79.8)	591/740 (79.9)
TIMI III flow		
Before PCI	88/751 (11.7)	79/740 (10.7)
After PCI	701/751 (93.3)	686/740 (92.7)
Left Ventricular Function post index exent	832/903 (92.1)	835/906 (92.2)
Normal (EF ≥55%)	365/832 (43.9)	379/835 (45.4)
Mildly impaired (EF 45-54%)	218/832 (26.2)	210/835 (25.2)
Moderately impaired (EF 36-44%)	165/832 (19.8)	168/835 (20.1)
Severely impaired (EF ≤35%)	84/832 (10.1)	78/835 (9.3)
Medications at discharge- no./total no. (%)		
ACE inhibitor or ARB	707/842 (84.0)	725/844 (85.9)
Aspirin	788/842 (93.6)	799/844 (94.7)
Beta-blocker	728/842 (86.5)	731/844 (86.6)
P_2Y_{12} inhibitor	748/842 (88.8)	746/844 (88.4)
Statin	761/842 (90.4)	767/844 (90.9)

Table 6 Baseline characteristics, procedural data and medication

*IQR denotes interquartile range, CVD cardiovascular disease, PCI percutaneous coronary intervention, CABG coronary artery bypass grafting, eGFR estimated glomerular filtration rate, TIMI thrombolysis in myocardial infarction, ACE angiotensin-converting enzyme, and ARB angiotensin-receptor blocker. ᵟ No missing data; ¶ Total no. bivalirudin=818, heparin=813; § Total no. bivalirudin=896, heparin=891; # Total no. bivalirudin=886, heparin=889; † Total no. bivalirudin=836, heparin=850; ‡ Total no. bivalirudin=891, heparin=895; ᵀ Total no. bivalirudin=806, heparin=795; ᵠ Total no. bivalirudin=771, heparin=777.

Procedural and treatment data:

These are also summarised in table 7. Aspirin and P2Y12 inhibitor loading was achieved in >99·5% patients and was well matched in both groups. The procedure was completed with exclusive radial access in 81·2% cases (80·3% bivalirudin v 82·0% heparin). The rate of GP IIb/IIIa inhibitor use was similar in both arms (13·5%

bivalirudin v 15·5% heparin in ITT population; 15·9% bivalirudin v 18·7% heparin in PCI population). The main reasons for GP IIb/IIIa inhibitor use, reported by the operator were the presence of high intracoronary thrombus burden (69·32%), slow flow (15·34%), perceived failure of antiplatelet loading (e.g. with vomiting) (6·82%) and complex lesion/stent placement (3·98%). Post-procedure LV function assessment did not show any significant differences between the two groups (table 7).

PCI was attempted in a total of 1491 (82·28%) patients with similar procedural success rates in both arms (97·5% bivalirudin v 97·3% heparin). Of these, >90% patients had stent implanted. At least one drug eluting stent was implanted in 1190/1491 (80%) of cases managed with PCI. Thrombus aspiration rates were 59·1% in the bivalirudin arm and 57·6% in the heparin arm.

Clinical outcomes:

Primary efficacy outcomes:

The clinical outcome results are summarised in table 8. The MACE composite outcome occurred more frequently in patients treated with bivalirudin (8·7% v 5·7%, absolute risk difference = 3%; relative risk [RR] 1·52, 95% confidence interval [CI], 1·09 to 2·13; P=0·01). The advantage of heparin therapy was seen in all components of the primary efficacy outcome but there were no significant differences in the incidence of all-cause mortality (5·1% bivalirudin v 4·3% heparin) or CVA (1·6% bivalirudin v 1·2% heparin). The heparin advantage was primarily driven by a significant increase in the incidence of reinfarction in the bivalirudin arm (2·7% v 0·9%; RR 3·01%, 95% CI 1·36 to 6·66; P=0·004). The majority of these events were related to stent thrombosis events which were more frequent in the bivalirudin arm as compared to heparin arm (3·4% v 0·9%; RR 3·91, 95% CI 1·61 to 9·52; P=0·001). Stent thromboses were adjudicated as definite in 93·33% (28/30) cases, all of which resulted in an adjudicated reinfarction event and unplanned TLR.

Primary safety outcomes:

For the primary safety outcome, there was no significant difference in the incidence of major bleeding (BARC type 3-5) between the two groups (3·5% bivalirudin v 3·1% heparin; RR 1·15 CI 0·70 to 1·89; P=0·59). The rates of minor bleeding (BARC type 2)

were not significantly different between the two treatment arms (9·2% bivalirudin v 10·8% heparin). The combined rate of major or minor bleeding events did not show any significant difference (12·5% bivalirudin v 13·5% heparin).

Outcome	Bivalirudin (n=905)	Heparin (n=907)	Absolute Risk Difference (95% CI)	Relative Risk (95% CI)	P Value
Primary efficacy outcomes measures - no./total no. (%)	79/905 (8.7)	52/907 (5.7)	3.0 (0.6, 5.4)	1.52 (1.09, 2.13)	0.01
Death	46/905 (5.1)	39/907 (4.3)	0.8 (-1.2, 2.8)	1.18 (0.78, 1.79)	0.43
Cerebrovascular accident	15/905 (1.6)	11/907 (1.2)	0.4 (-0.7, 1.6)	1.37 (0.63, 2.96)	0.43
New myocardial infarction / re-infarction	24/905 (2.7)	8/907 (0.9)	1.8 (0.6, 3.1)	3.01 (1.36, 6.66)	0.004
Additional unplanned target lesion revascularisation	24/905 (2.7)	6/907 (0.7)	2.0 (0.8, 3.3)	4.01 (1.65, 9.76)	0.001
Bleeding outcomes - no./total no. (%)					
Major bleed (Primary safety outcome measure)†	32/905 (3.5)	28/907 (3.1)	0.4 (-1.2, 2.1)	1.15 (0.70, 1.89)	0.59
Minor bleed ‡	83/905 (9.2)	98/907 (10.8)	-1.6 (-4.4, 1.1)	0.85 (0.64, 1.12)	0.25
Any bleeding event	113/905 (12.5)	122/907 (13.5)	-1.0 (-4.1, 2.1)	0.93 (0.73, 1.18)	0.54
Other secondary outcome measures					
Stent thrombosis rate- no./total no. (%)	24/697 (3.4)	6/682 (0.9)	2.6 (1.0, 4.3)	3.91 (1.61, 9.52)	0.001
Definite	23/697 (3.3)	5/682 (0.7)	2.6 (1.1, 4.2)	4.50 (1.72, 11.77)	0.001
Probable	1/697 (0.1)	1/682 (0.1)	0.0 (-0.7, 0.7)	0.98 (0.06, 15.6)	>0.99
Acute (≤24hrs)	20/697 (2.9)	6/682 (0.9)	2.0 (0.6, 3.6)	3.26 (1.32, 8.07)	0.007
Subacute (>24hrs to 28 days) *	4/697 (0.6)	0/682 (0.0)	0.6 (-0.9, 1.5)	8.81 (0.48, 163.26)	0.12
Thrombocytopenia rate- no./total no. (%)	61/736 (8.3)	54/737 (7.3)	1.0 (-1.8, 3.7)	1.13 (0.80, 01.61)	0.49
Mild	55/736 (7.5)	48/737 (6.5)	1.0 (-1.7, 3.6)	1.15 (0.79, 1.67)	0.47
Moderate	3/736 (0.4)	5/737 (0.7)	-0.3 (-1.2, 0.6)	0.60 (0.14, 2.50)	0.73
Severe	3/736 (0.4)	1/737 (0.1)	0.3 (-0.4, 1.1)	3.00 (0.31, 28.81)	0.37
CKMB post-procedure - ng/ml ¶ (median, IQR)	97 (41.5, 199)	106 (42, 203)	-	-	0.55
Door to first device time (min) # (median, IQR)	29 (23, 36)	29 (23, 37)	-	-	0.33

Table 7 Clinical outcomes at 28 days

Hierarchical outcomes:

The contribution of the individual components to the primary efficacy outcome is shown in Table 8.

Outcome	Bivalirudin (n=905)		Heparin (n=907)	
	Hierarchy*	All events	Hierarchy*	All events
Primary efficacy outcomes – no. (%)				
Death	46 (5.1)	46 (5.1)	39 (4.3)	39 (4.3)
Cerebrovascular accident	11 (1.2)	15 (1.7)	6 (0.6)	11 (1.2)
New myocardial infarction / re-infarction	21 (2.3)	24 (2.7)	7 (0.8)	8 (0.9)
Additional unplanned target lesion revascularisation	1 (0.1)	24 (2.7)	0 (0.0)	6 (0.7)
Total events	79 (8.7)	109 (12.0)	52 (5.7)	64 (7.0)
Bleeding outcomes – no. (%)				
Major bleed	32 (3.5)	32 (3.5)	28 (3.1)	28 (3.1)
Minor bleed	81 (9.0)	83 (9.2)	94 (10.4)	98 (10.8)
Total events	113 (12.5)	115 (12.7)	122 (13.5)	126 (13.9)

**Censored by most severe event in the order specified*

Table 8 Hierarchical outcomes

Events have been censored by the most severe event in the observation period. Only a single event accrued from unplanned TLR, in the absence of another outcome event.

Event curves:

Figure 8 shows the event curves for the primary efficacy and safety outcome measures for both treatment groups. Figure 8a shows a landmark analysis for the primary outcomes from median day of discharge to 28 days.

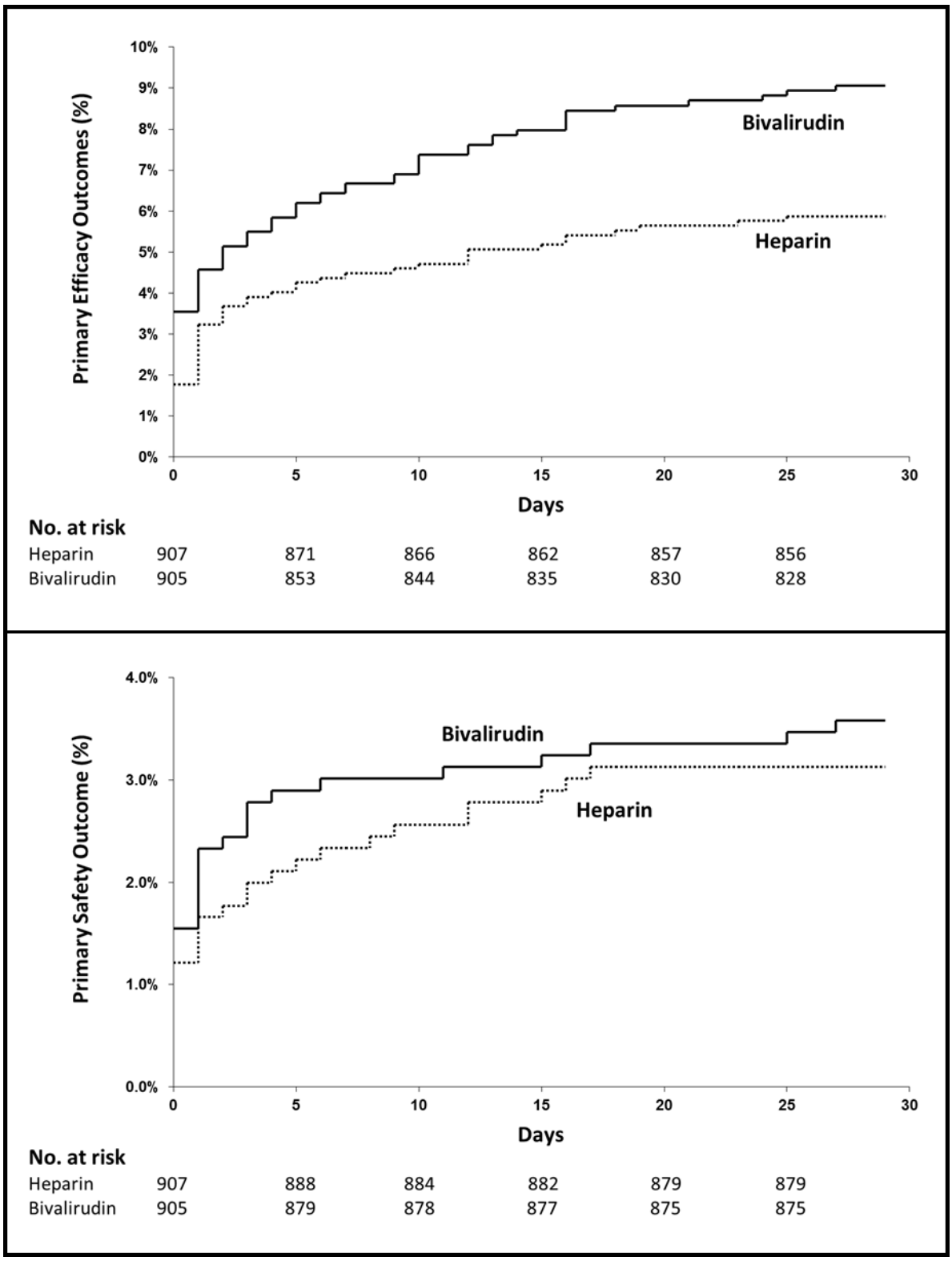


Figure 8 Event curves for Primary Outcomes

Graph A: Event curves for the composite primary outcome (MACE – combination of death, CVA, re-infarction and unplanned TLR) censored for the first event. **Graph B:** Event curves for primary safety outcome (major bleeding) censored for the first event

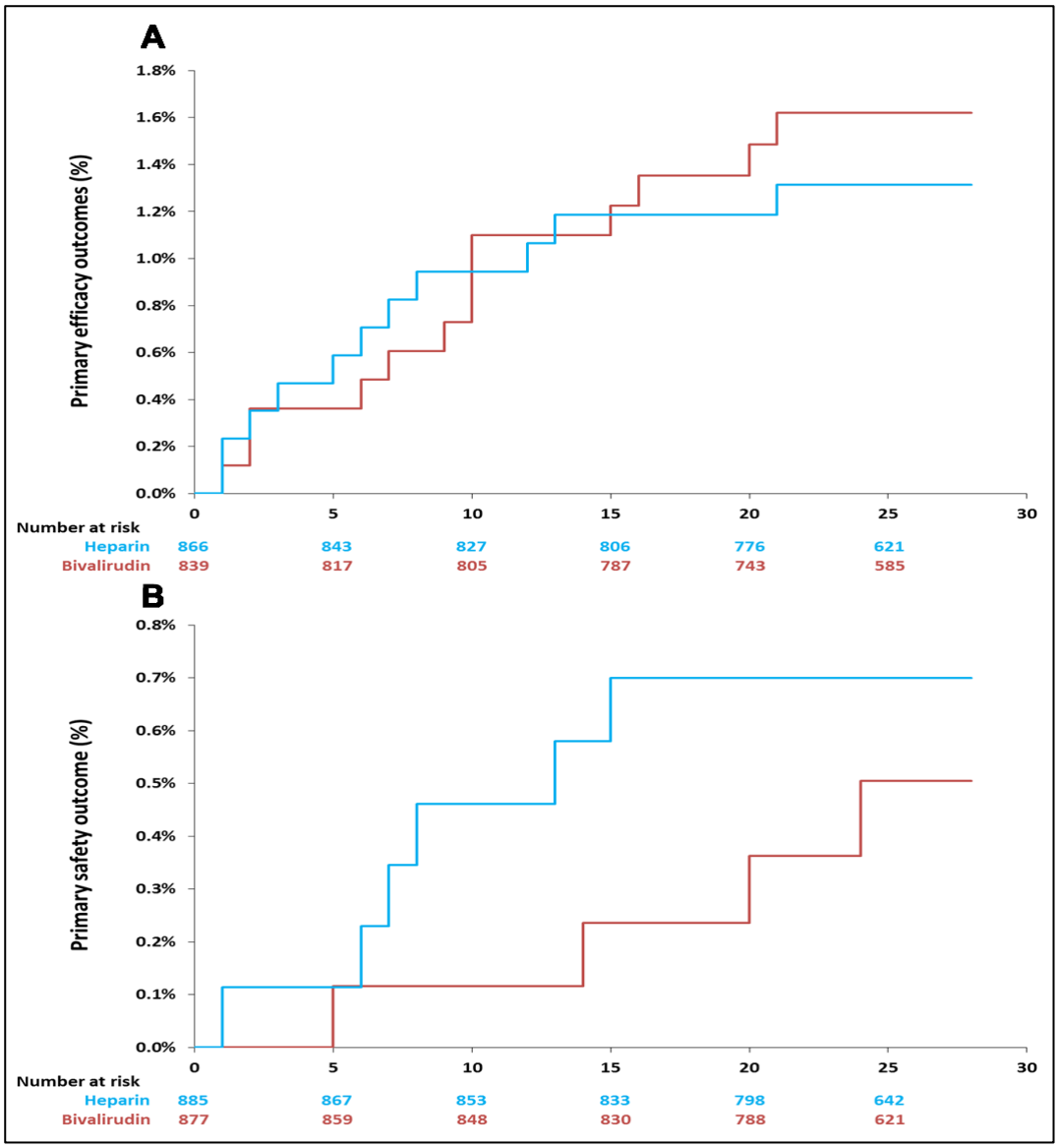


Figure 8a Landmark analysis for the primary outcomes from median day of discharge to 28 days

Other secondary outcomes:

There were no significant differences between the two arms in terms of rates of development of thrombocytopenia (8·3% bivalirudin v 7·3% heparin), median CKMB release post-procedure (97 ng/ml bivalirudin v 106ng/ml heparin) or median door to first device time (29min bivalirudin v 29min heparin).

Subgroup analyses for Primary Composite Outcomes:

Table 9 shows the analyses of the primary composite outcome of all the pre-specified subgroups. The results of subgroup analyses are consistent with those in the overall ITT analyses.

There is observed benefit of heparin in the diabetes subgroup. The number of patients in this cohort, and the subsequent number of events, are small. The could potentially be explored further in future in a larger cohort of patients. A recent meta-analysis specifically analysed the diabetic subgroup in trials comparing heparin and bivalirudin (including HEAT-PPCI)[47]. The results showed that the use of bivalirudin and heparin was associated with a similar risk of MACE, NACE, MI and mortality. Another meta-analysis, including HEAT-PPCI, published recently concluded that among patients with diabetes, there were similar rates of MACE, death, MI, and urgent revascularization at 30 days[48]. Bivalirudin caused less major and minor bleeding compared with heparin and GPI in this cohort. A secondary analysis suggests that the major bleeding benefit with bivalirudin may be driven by mandated use of GPI in heparin arm.

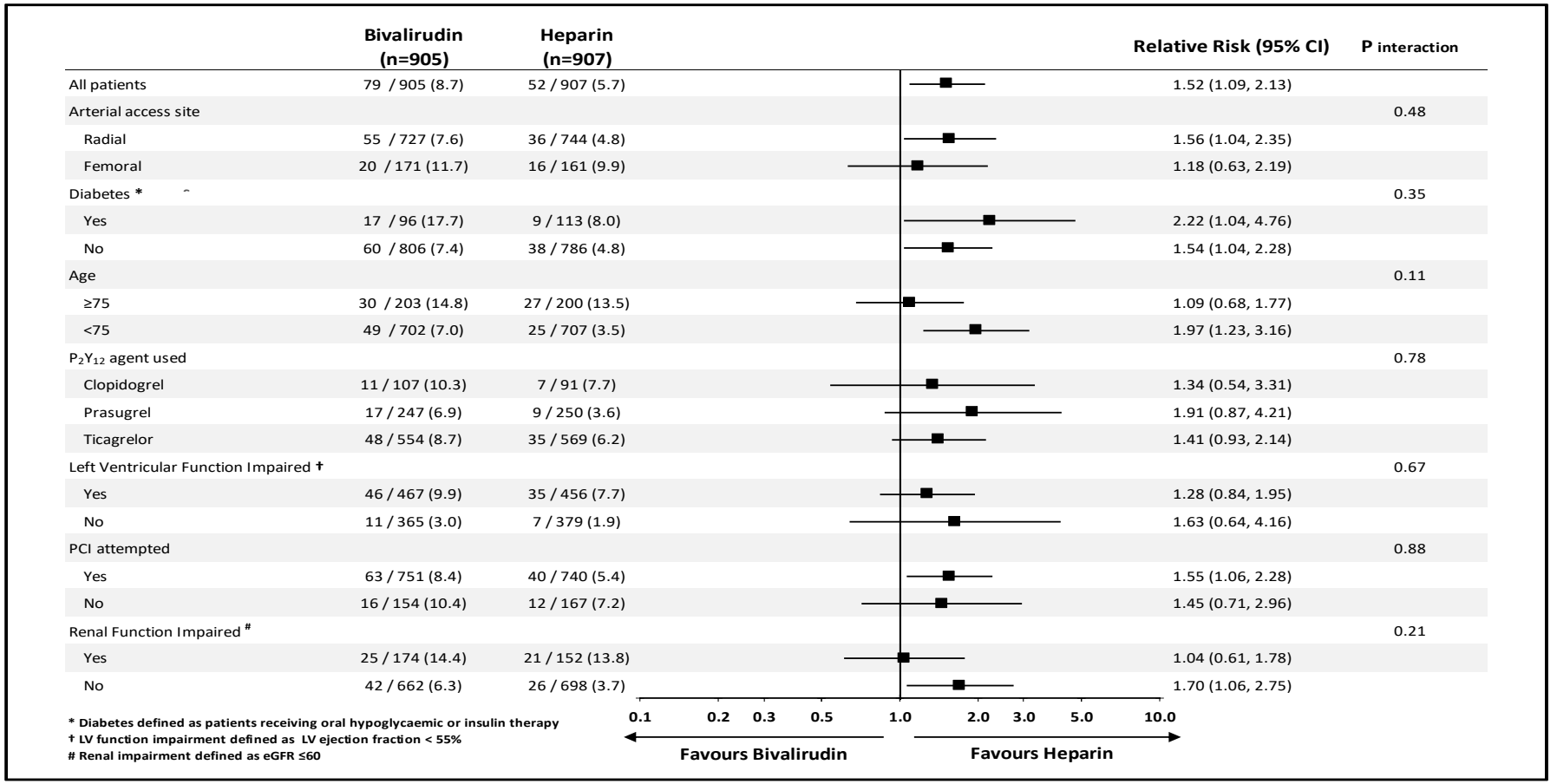


Table 9 Subgroup analyses for Primary Composite Outcome at 28 days

[δ]Access site indicates cases completed exclusively via radial access (radial group) v all other cases (femoral group) *Diabetes defined as patients receiving oral hypoglycaemic or insulin therapy; † Impaired LV function defined as Ejection Fraction < 55% in surviving patients after the index event.

Discussion:

We believe that HEAT-PPCI may be the only major trial to have achieved 100% recruitment of all eligible patients. More importantly, this represents about 97% of all cases managed with angiography at the study centre in the context of a PPCI presentation. Our approach has allowed us to recruit a true, unselected population reflecting the reality of clinical practice in a high-volume UK centre. Recruitment was completed in less than 22 months and this is testimony to the cohesion, dedication and discipline of the clinical teams at the Liverpool Heart and Chest Hospital. The strategy of delayed consent was well received by patients: refusal or withdrawal of consent was very rare (four cases).

Our study has strong internal validity but some limitations related to single-centre recruitment. Our patient population is almost exclusively Caucasian, but otherwise typical for UK practice. The near complete inclusion of a population selected by external referral (ambulance and emergency medical teams) is reassuring. The study examined the use of intra-vascular medication and used accepted, standardised approaches to dosing and administration. Procedures were performed under the care of 14 interventional cardiologists. Procedural detail and subsequent outcomes matched institutional and national norms and seem to reflect contemporary PPCI practice.

We used an open label design but the outcome measures were overt clinical events, supported by objective clinical observations - even in the case of reinfarction. All events were subject to blinded evaluation. An open label design was also used in the HORIZONS AMI and EUROMAX trials[15 16].

Heparin was administered at a dose of 70 units/kg of body weight. This avoids the increased bleeding complications associated with the use of higher doses[36], though some centres do use a more stringent regime at 50 units/kg. Bivalirudin dosing was in accordance with the licensed recommendations at trial initiation, which included cessation of the infusion at the end of the procedure.

The primary efficacy outcome measure suggests a significant advantage in favour of heparin over bivalirudin, mainly in terms of a reduced incidence of acute stent thrombosis and associated recurrent myocardial infarction. This finding is consistent with the demonstration of a significant increase in acute stent thrombosis, associated with bivalirudin therapy, in both HORIZONS-AMI (Bivalirudin 1·3% v heparin 0·3%, p<0·001) and EUROMAX (Bivalirudin 1·1% v heparin 0·2%, P=0·007). The absolute stent thrombosis rate reported with bivalirudin in HEAT-PPCI is higher and may be a reflection of a high-risk population (28 day mortality of 4·7% v 2·6% in HORIZONS-AMI). The magnitude of the difference may also be explained by the fact that bivalirudin patients were not 'protected' by additional administration of heparin - reported in 65% of HORIZONS-AMI patients randomised to bivalirudin[49]. Bivalirudin has been evaluated against heparin in a variety of clinical settings and indications over the last 20 years and has never established any clear advantage in terms of anti-ischaemic efficacy[16 21-23 35 36].

Both bivalirudin and heparin can be used in combination with GP IIb/IIIa inhibitor agents. In the ACUITY trial (examining PCI in the context of non-ST elevation acute coronary syndrome events), both antithrombotic agents were employed with mandated GP IIb/IIIa therapy and the outcomes in terms of anti-ischaemic efficacy and bleeding were near identical[22]. Reduced bleeding was seen in a third trial arm testing bivalirudin with selective use of the parenteral antiplatelet agent.

Most of the current evidence in PPCI has been obtained by comparing bivalirudin monotherapy with a combination of heparin plus GP IIb/IIIa inhibitors. In the acute phase, the reported advantages of bivalirudin are restricted to reduced bleeding complications which, in the HORIZONS-AMI trial, may have impacted medium term mortality[15]. Increased bleeding complications are likely to be related to the differential rates of GP IIb/IIIa inhibitors use. The universal, unselected use of GP IIb/IIIa inhibitors in PPCI is no longer routine therapy. The advent of more effective oral antiplatelet therapy, with early and high dose loading regimes may have reduced any incremental anti-ischaemic protection with GP IIb/IIIa inhibitors, whilst retaining the potential for bleeding complications. Public health and other measures mean that PPCI patients are treated earlier in the natural history of infarct evolution, when fresh thrombus may be easier to manage with interventional approaches. Technical advances, including a

possible impact from thrombus aspiration may also play a role[50 51]. The findings at angiography, the response to intervention and the perceived outcome of the PCI procedure may allow operators to identify patients who have most to gain from the addition of parenteral antiplatelet therapy. By the same token, bleeding risk can be avoided in patients with a good result or in those with risk factors from this complication. The optimum use pattern for GP IIb/IIa inhibitor agents is yet to be determined.

Bivalirudin with selective GP IIb/IIa inhibitor use has emerged as first-line therapy in the performance of PPCI. Our study builds on this evidence base and suggests that the use of heparin, rather than bivalirudin confers significant advantage in the avoidance of major adverse events – principally acute stent thrombosis and associated reinfarction events. There was no difference in major and minor bleeding rates. This may be an opportunity, rare in modern healthcare, to provide improved outcomes at much reduced cost. In our centre, routine use of heparin (rather than bivalirudin – costing approximately 400 times as much) would reduce immediate drug costs in our annual 1000 PPCI cases by £500,000.

Chapter 3 – Platelet function substudy - Comparison of the antiplatelet and antithrombotic effects of bivalirudin versus heparin

Abstract:

Background:

In randomised trials evaluating bivalirudin versus heparin, higher rates of acute stent thrombosis (AST) have been reported for bivalirudin, without mechanistic explanation. Furthermore, data are discrepant regards the effects of bivalirudin on platelet function. The aim of this prespecified HEAT-PPCI substudy was to compare antiplatelet and antithrombotic effects of bivalirudin and unfractionated heparin (heparin) using short thrombelastography (s-TEG).

Methods:

In a prespecified study, part of a larger HEAT PPCI Platelet Substudy, 185 (10.2%) patients underwent assessment using the *ex vivo* whole blood clotting assay, s-TEG, after excluding 86 patients who had received a Gp IIbIIIa inhibitor. Platelet function testing with s-TEG was performed (i) immediately at the end of procedure (EOP) and (ii) at 24 hours. Kaolin was used to stimulate thrombin-mediated clotting (TMC) in separate channels with (CKH) and without heparinase (CK). Adenosine diphosphate (ADP) & arachidonic acid (AA) agonists used in 2 other channels.

Results:

There were no significant differences between patients who received heparin and bivalirudin in AA- and ADP-mediated platelet aggregation at EOP or 24 hours. However, whilst heparin obliterated TMC, bivalirudin prolonged R time (19.9 min [15.9

- 30] vs. 8.4 min [7.5 - 10]; *P* < 0.0001), K time (2.5 min [1.9 - 3.5] vs. 2.2 min [1.8 - 2.7]; *P* = 0.005) and reduced the α-angle (58.6° [46.9 - 64.1] vs. 59.8° [54.5 - 65.4]; *P* = 0.05), but was associated with significantly greater maximum clot strength (MA 62.7 [58.6 - 67.4] vs. 58.6 [55 - 63]; *P* = 0.001) compared to control in response to kaolin.

Conclusions:

There were no differences between heparin and bivalirudin with respect to AA- or ADP-mediated platelet aggregation, and neither has significant antiplatelet properties. However, whilst heparin obliterated TMC, bivalirudin prolonged clot initiation and propagation delays clot initiation but also potentiated maximum clot strength. These data may offer an insight into the mechanism of AST in bivalirudin-treated patients.

Introduction:

In patients undergoing primary PPCI for STEMI, the risk of recurrent ischaemic events remains substantial despite effective inhibition of periprocedural platelet function with conventional dual antiplatelet therapy (DAPT), as platelets remain reactive to a multitude of other mediators, most notably thrombin, a potent platelet agonist and the final effector of the coagulation cascade. Furthermore, recently concerns have been raised in STEMI patients with respect to the delayed onset of action of new oral $P2Y_{12}$ inhibitors[52 53] previously reported to have a more reliable and superior antiplatelet effect compared to clopidogrel[54 55]. Adjunctive antithrombotic therapy therefore still remains critical for improving outcomes in patients undergoing PCI.

The optimal adjunctive antithrombotic regimen in PPCI presently remains to be elucidated. Historically, heparin has been the default anticoagulant administered during PCI. Unlike heparin, bivalirudin has the advantage that it doesn't bind plasma proteins, is not neutralised by platelet factor 4 antibodies, exerts its effector activity on thrombin directly without need for co-factors and can bind thrombin in the fluid phase as well as circulating clot-bound thrombin[56]. However, despite its favourable profile, net outcome benefits demonstrated in randomised controlled trials have been largely driven by reductions in bleeding complications rather than incremental benefits in reducing ischaemic events[57-61], and this generally when compared to heparin plus GP IIb/IIIa inhibitors.

Evolving trends in PPCI including use of potent $P2Y_{12}$ inhibitors, transradial access and selective 'bailout' use of GPI means that these trials no longer reflect contemporary practices. The HEAT-PPCI study performed a head-to-head comparison of heparin to bivalirudin with selective 'bailout' use of GP IIb/IIIa inhibitors in both arms in the setting of PPCI in a contemporary setting and demonstrated a significant reduction in major adverse cardiovascular events in favour of heparin without excessive bleeding complications[62]. This benefit was largely driven by a higher incidence of acute stent thrombosis (AST) in the bivalirudin arm, a finding that has also been reported in previous trials[59 61]. Presently, the mechanism of AST in bivalirudin-treated patients remains poorly understood. Furthermore, data on the antiplatelet effects of bivalirudin are discrepant.

The primary objective of this pre-specified HEAT-PPCI platelet substudy was to compare the antiplatelet and antithrombotic effects of bivalirudin and heparin in patients undergoing PPCI for STEMI.

Methods:

Study Population and Design:

All patients in this platelet substudy were part of the HEAT-PPCI trial. Patients who received a GPI were excluded from the present platelet substudy, which comprises 458 patients in whom evaluable platelet function data was available either at the end of the index PCI procedure (EOP) with either Multiple Electrode Aggregometry (MEA) or Thrombelastography (TEG). A flow chart of the study population showing all patients enrolled in the platelet substudy is illustrated in Figure 9.

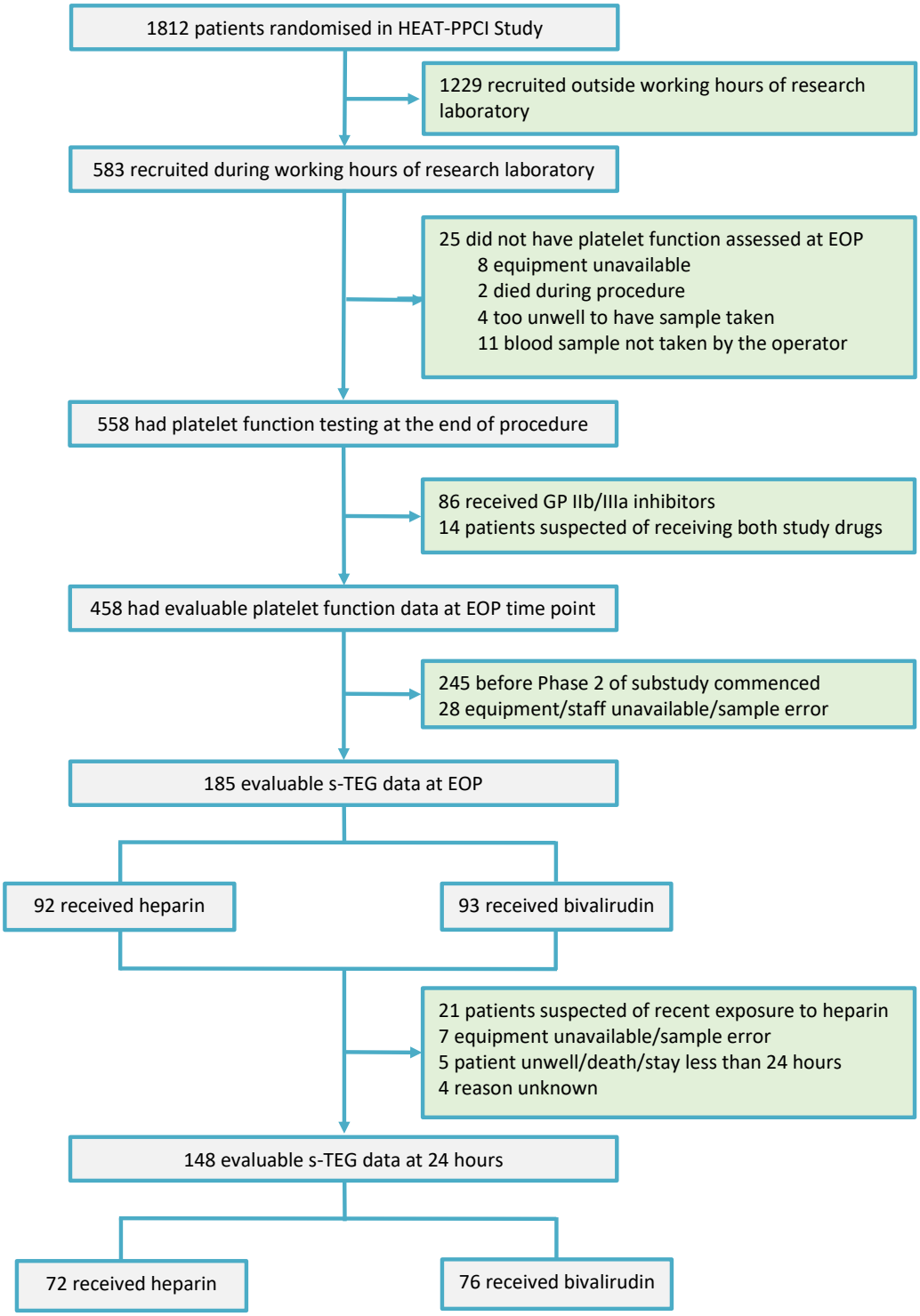


Figure 9 Antithrombotic TEG substudy flowchart

Due to logistic considerations patients were enrolled to this substudy only during the core operational hours of the cardiac catheterisation laboratory at Liverpool Heart and Chest Hospital. Furthermore, whilst MEA was available from the outset, the

Thromboelastography (TEG) assay wasn't available in the early course of the trial. Platelet function testing in this substudy was performed at EOP in the entire cohort, however we began collecting an additional sample at 24 hours for analysis following the introduction of TEG. Platelet function data at the 24-hour time point where possible was therefore only performed in a limited proportion of the substudy population.

Blood sampling and Sample Analysis:

Blood sampling:

Whole blood for platelet function testing was obtained via arterial sheath in the cardiac catheterisation lab at the EOP. In patients assigned to receive bivalirudin, the infusion was still running at the time of sampling. Blood sampling at the 24-hour time point was performed via venepuncture from the antecubital fossa. The first 10ml (2 ml during venesection) were discarded and then blood was drawn into one 6 ml lithium heparin Vacutainer®, and one 2 ml Vacutainer® of 3.2% sodium citrate for TEG platelet mapping, as well as one 3 ml vacuette containing hirudin as anticoagulant for Multiple Electrode Aggregometry (MEA). The tubes were filled to capacity and inverted gently a few times to ensure proper mixing with the anticoagulant *in situ*. According to manufacturer's instructions, blood samples were incubated at room temperature for at least 15 min for TEG platelet mapping and 30 min for MEA before platelet function testing was performed.

Multiple Electrode Aggregometry:

MEA, a whole blood assay based on measuring electrical impedance was performed with the Multiplate analyser (Roche diagnostics, Mannheim, Germany). Whole blood (300 µl) anticoagulated with hirudin was diluted 1:1 with 0.9% saline pre-warmed to 37°C before stirring for 3 minutes. Thereafter, platelet aggregation was initiated by addition of ADP (6.5 µM), AA (0.5 mM) and thrombin receptor activating peptide (32 µM) to the test cells. The change in impedance resulting from the adhesion and aggregation of platelets on the surface of two silver-coated highly conductive copper electrodes is analysed for each sensor unit for 6 minutes. This is transformed to arbitrary aggregation units and plotted against time, which is used to derive area under the aggregation curve (AUC) expressed in arbitrary aggregation units (U). All

material used including reagents were obtained from the manufacturer (Roche diagnostics, Mannheim, Germany).

TEG Platelet Mapping:

Briefly, the TEG technology is based on a stationary pin on a torsion wire being suspended into an oscillating cup containing a small volume of whole blood at 37°C. As clotting is stimulated with agonists, changes in its viscoelasticity are transmitted to the pin and the resulting torque generates an electrical signal producing a characteristic TEG® trace[63] (Figure 10).

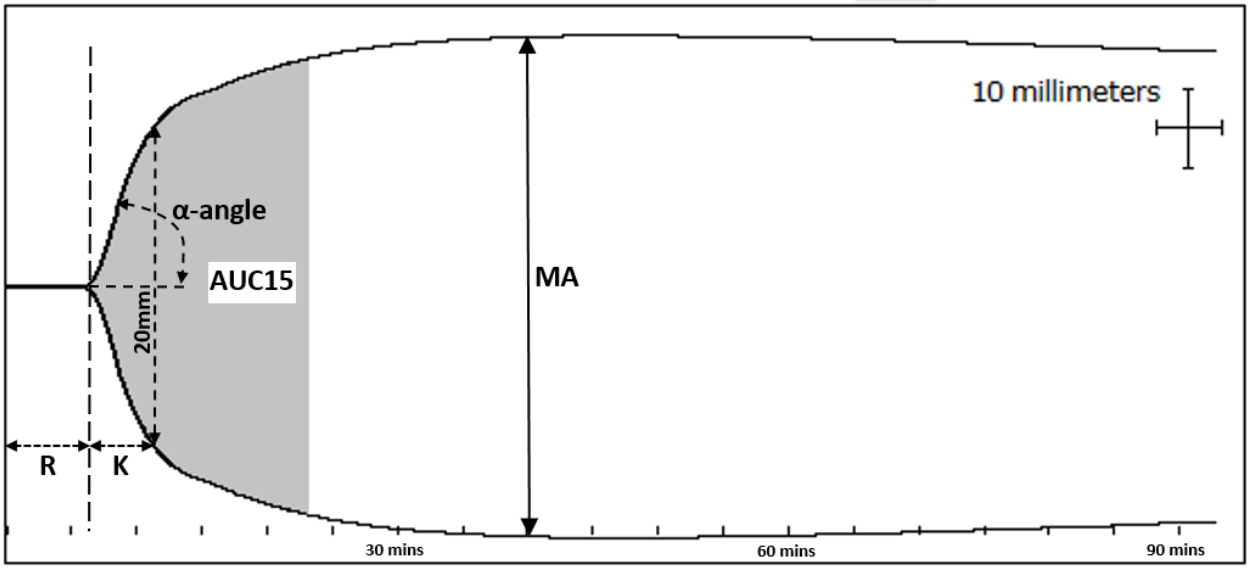


Figure 10 Typical TEG trace

Figure 10. A typical TEG trace illustrating the parameters R time (time to clot initiation), K time (time to reach amplitude of 20 mm), α-angle (gradient formed by angle of initial trace), maximum clot strength (MA), and Area under the curve at 15 minutes (AUC15) which reports on speed of clot formation as well as clot strength.

Samples were analysed using the modified TEG® platelet mapping system (Haemonetics Corp, MA, USA) as previously reported[63 64]. Platelet agonists employed in the standard channels include: (i) **Citrated blood activated by Kaolin (CK)**: kaolin stimulates clotting via the intrinsic coagulation pathway leading to thrombin generation and maximal platelet activation as thrombin is a potent platelet agonist, (ii) **Activator F™ (Act F)**: a mixture of reptilase and factor XIIIa, which generates fibrin clot without causing platelet activation (iii) **ADP**: a combination of Activator F™ and ADP (2µM), (iv) AA: a combination of Activator F™ and AA (1mM). In this platelet substudy

we used an additional fifth channel **(CKH)** in which citrated whole blood was stimulated by kaolin in a cup coated with heparinase to neutralise the effects of heparin. This channel provides a pure assessment of thrombin-mediated clotting (TMC) in the absence of heparin (endogenous or administered). It therefore served as a control channel for comparison of the antithrombotic effects of bivalirudin and heparin. Whole blood (340 µl of citrated blood for CK and CKH channel; 360 µl of heparinised blood for Act F, AA and ADP channels) was manually pipetted into the respective channels. In blood preserved with the calcium chelating agent, citrate (i.e. CK and CKH channel), clotting was initiated by recalcification using 0.2M calcium chloride.

The TEG haemostasis analyser (Haemonetics Corp., Massachusetts, USA) and automated analytical software were used to measure the physical properties of clot formation to produce a characteristic TEG trace. Observations were continued for at least 60 minutes. Individual TEG traces were used to derive parameters relating to clot dynamics including R time, K time, α-angle, maximum amplitude (MA) and the Short Thrombelastography (s-TEG) parameter Area under the curve at 15 minutes (AUC15), as illustrated in Figure 10.

Short Thrombelastography:

s-TEG is a novel modification of the TEG® platelet mapping assay, described and validated by the Southampton group[63 64], which is based upon the concept of "Area under the curve at 15 minutes" (AUC15). This incorporates both strength and speed of clot formation. AUC15 is calculated using bespoke software (Areafinder 2:1) developed using National Instrument Labview 7.0. AUC15 has been shown to correlate well with the conventional TEG® parameter maximum amplitude (MA) in assessment of responses to APT and is easily reproducible[64].

Statistical analysis:

As virtually all continuous data was not normally distributed, it is presented as median with interquartile range (IQR) and comparisons between groups was performed using the Mann-Whitney U test. Normality of data was confirmed using the Shapiro-Wilk test. Categorical variables are presented as frequencies (%) and were compared using the Chi-squared test. A P value <0.05 was considered to represent statistical

significance. Statistical analyses were performed using SPSS version 21 (IBM Corp., Armonk, NY, USA).

The interaction between the study arm and HPR on the hazard of the primary efficacy outcome measure was tested in a Cox proportional hazard model. Survival curves were constructed using the Kaplan-Meier method. For individual components of the primary efficacy outcome measure and AST, event-free survival amongst patients with HPR compared to those with no HPR were assessed per study group using the long-rank test.

Results:

Of the 1,812 patients randomised in the HEAT-PPCI trial 458 (25.3 %) had evaluable platelet function data. A significant proportion of patients enrolled to the trial did not have blood samples taken for platelet function testing (67.8%) as they presented outside the core operating times of the cardiac catheterisation laboratory. As outlined in the substudy flow chart (Fig. 9), 87 patients who received GPI were also excluded from the analysis.

Baseline characteristics in the substudy population (Table 10) were well matched between patients treated with bivalirudin (n = 228) and heparin (n = 230). The activated clotting time (ACT) values were significantly lower in the heparin -treated patients compared to the group receiving bivalirudin when measured at 5-15 minutes after bolus administration ($p < 0.00001$) and at EOP ($p < 0.00001$). Clinical follow-up at 30 days was completed (100%) for all 458 patients.

	Bivalirudin (n = 228)	**Heparin (n = 230)**	**p Value**
Age, years	65 [55 – 74.5]	65 [54 - 74]	0.33
Sex, female	72/228 (29.8%)	67/230 (29.1%)	0.87
Bodyweight, kg			
Data available	196 (86.0%)	203 (88.3%)	

Median [IQR]	77.5 [66.8 - 87.4]	78.5 [68.7 - 89]	0.49
Ethnicity, White	217/228 (96.9%)	218/226 (96.5%)	0.81
Comorbidities			
Hypertension	96/228 (42.1%)	99/229 (43.2%)	0.81
Hyperlipidaemia	86/224 (39.1%)	88/228 (38.6%)	0.81
Diabetes Mellitus	26/228 (11.4%)	30/229 (13.1%)	0.58
Family history of CVD	101/226 (44.7%)	101/226 (44.7%)	1.0
Current Smoker	83/227 (36.6%)	86/226 (38.1%)	0.74
Previous myocardial infarction	31/228 (13.6%)	25/230 (10.9%)	0.37
Previous PCI	16/239 (6.7%)	14/229 (6.1%)	0.80
Previous CABG	8/228 (3.5%)	5/230 (2.2%)	0.39
Platelet count			
Data available	224 (98.2%)	227 (98.7%)	
Median [IQR]	234.5 [190 – 288.5]	227 [190 - 264]	0.35
Estimated GFR			
Data available	225 (98.7%)	228 (99.1%)	
Median [IQR]	81 [63 - 90]	79 [64.5 - 90]	0.79
Haemoglobin			
Data available	226 (99.1%)	228 (99.1%)	
Median [IQR]	13.6 [12.3 - 14.6]	13.8 [12.7 -14.8]	0.17
$P2Y_{12}$ inhibitor			
Clopidogrel	26/228 (11.4%)	15/230 (6.5%)	0.07

Prasugrel	54/228 (23.7%)	71/230 (30.9%)	0.08
Ticagrelor	148/228 (64.9%)	141/230 (61.3%)	0.42
None	0	3/230 (1.3%)	0.08
Time between LD and EOP sampling (minutes)			
Aspirin			
Data available	229 (95.8%)	213 (92.6%)	
Median [IQR]	95 [76 - 113]	94 [78 - 110]	0.65
$P2Y_{12}$ inhibitor			
Data available	230 (96.2%)	213 (92.6%)	
Median [IQR]	68 [42 - 100]	60 [42 - 95]	0.44
ACT (5 - 15 minutes post-bolus)			
Data available	219 (96.1%)	216 (93.9%)	
Median [IQR]	253 [229 – 299.5]	224 [200 - 257]	< 0.00001
ACT at EOP			
Data available	200 (87.7%)	197 (85.7%)	
Median [IQR]	245 [230.5 – 266]	202 [182 - 223]	< 0.00001

CVD, cardiovascular disease; ACT, activated clotting time; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; GFR, glomerular filtration rate; IQR, interquartile range; LD, loading dose; EOP, end of PCI procedure

Table 10 Summary of baseline characteristics, procedural data and drug use.

Antiplatelet effects of heparin versus bivalirudin:

There were no significant differences in ADP-, AA- or TRAP-mediated platelet aggregation between the two groups at EOP or the 24-hour time (Table 11). Similarly,

there were no significant differences in $AUC15_{ADP}$ or $AUC15_{AA}$ between heparin and bivalirudin at EOP or the 24-hour time point (Table 11).

		End of Procedure				P value	24 hours				P value
		Heparin		Bivalirudin			Heparin		Bivalirudin		
		N	Median [IQR]	N	Median [IQR]		N	Median [IQR]	N	Median [IQR]	
MEA	**ASPItest**	229	24 [17 - 32]	228	22 [15- 30]	0.08	71	10 [5 - 18]	66	9.5 [4 - 15]	0.23
	ADPtest	229	71 [33 - 98]	228	63.5 [32 - 93]	0.29	72	20.5 [14.5 – 28]	67	17 [14.5 - 26]	0.31
	TRAPtest	224	119.5 [93.5 - 140.5]	223	120 [95.5 - 148]	0.39	70	79 [59 – 99]	68	74 [54 - 98]	0.38
s-TEG	**$AUC15_{AA}$**	91	457.3 [225.9 - 648.5]	93	378.6 [247.1 - 569.2]	0.55	68	150.1 [104.7 - 318.7]	74	227.1 [142.2 – 298.8]	0.07
	$AUC15_{ADP}$	91	460.8 [195.2 - 732.9]	93	536.9 [308.7 - 882.6]	0.09	70	140 [77.1 - 309.9]	75	187 [121 – 297.9]	0.09

s-TEG, Short Thrombelastography; MEA, Multiple electrode aggregometry; IQR, Interquartile range

Table 11
Comparison of the agonist-mediated platelet aggregation

Table 11. Comparison of the agonist-mediated platelet aggregation in patients treated with heparin to those treated with bivalirudin at the end of the PCI procedure and 24-hour time point.

Antithrombotic effects of heparin versus bivalirudin:

End of procedure:

In the control channel (i.e. CKH channel in patients treated with heparin where TMC was evaluated in the presence of heparinase), the median and IQR for R time was 8.4 min [7.5 - 10], K time was 2.2 min [1.8 - 2.7], α-angle was 59.8° [54.5 - 65.4], MA was 58.6 [55 - 63], and $AUC15_{CKH}$ was 965.7 [859.8 - 1090.4]. By contrast, in patients treated with heparin in the absence of heparinase (i.e. CK only), clotting in response to kaolin (i.e. TMC) at EOP was obliterated, at least for the duration of the observation period. Consequently, no further TEG parameters relating to time to clot initiation (R time), maximum clot strength (i.e. MA), K-time, α- angle or AUC15 (i.e. s-TEG) could be derived at this time point.

Compared to control (i.e. CKH channel in patients treated with heparin) (n=90), bivalirudin (n = 92) significantly prolonged R time (19.9 min [15.9 - 30] vs. 8.4 min [7.5 - 10]; $P < 0.0001$) and increased MA (62.7 [58.6 - 67.4] vs. 58.6 [55 - 63]; $P = 0.001$). It also significantly prolonged K-time (2.5 min [1.9 - 3.5] vs. 2.2 min [1.8 - 2.7]; $P = 0.005$) and decreased the α-angle (58.6° [46.9 - 64.1] vs. 59.8° [54.5 - 65.4]; $P = 0.05$). There were no significant differences in $AUC15_{CKH}$ at EOP (1010.2 [808.3 - 1161] vs. 965.7 [859.8 - 1090.4], $P = 0.82$) between patients treated with heparin and bivalirudin (Figure 11).

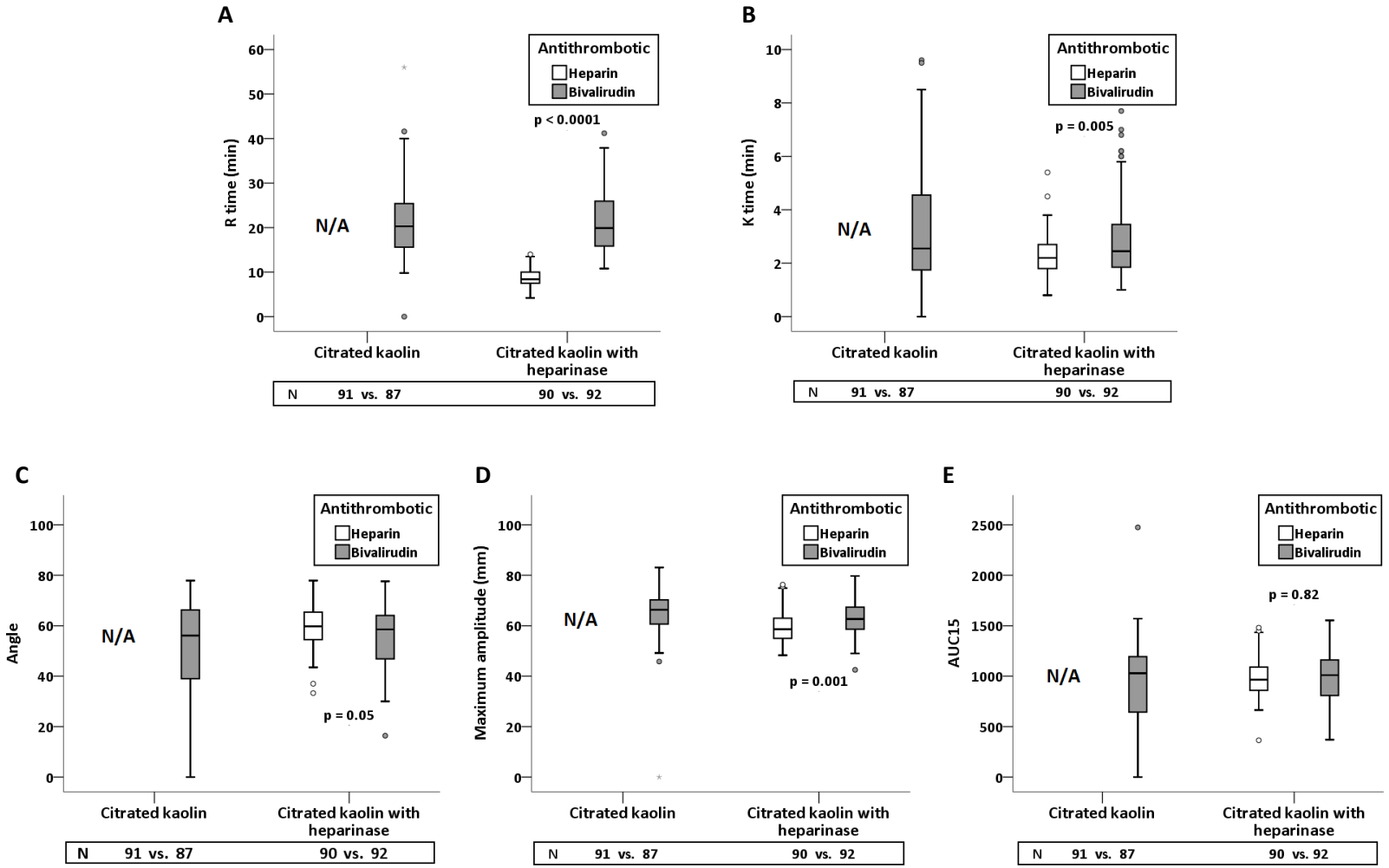


Figure 11 Comparison of Thrombelastography-derived indices

Figure 11. Comparison of Thrombelastography-derived indices between patients treated with heparin and bivalirudin at end of procedure when citrated whole blood was stimulated with kaolin (thrombin mediated clotting) in the presence (CKH channel) and absence of heparinase (CK channel): (A) R time; (B) area under the curve at 15 minutes (AUC15); (C) maximum amplitude; (D) K time; and (E) α-angle.

24-hour time point:

At 24 hours, there were no significant differences in any TEG parameters (R time, K time, α angle, MA or AUC15) between patients treated with heparin and bivalirudin, regardless of whether heparinase was present (i.e. CKH) or not (i.e. CK only

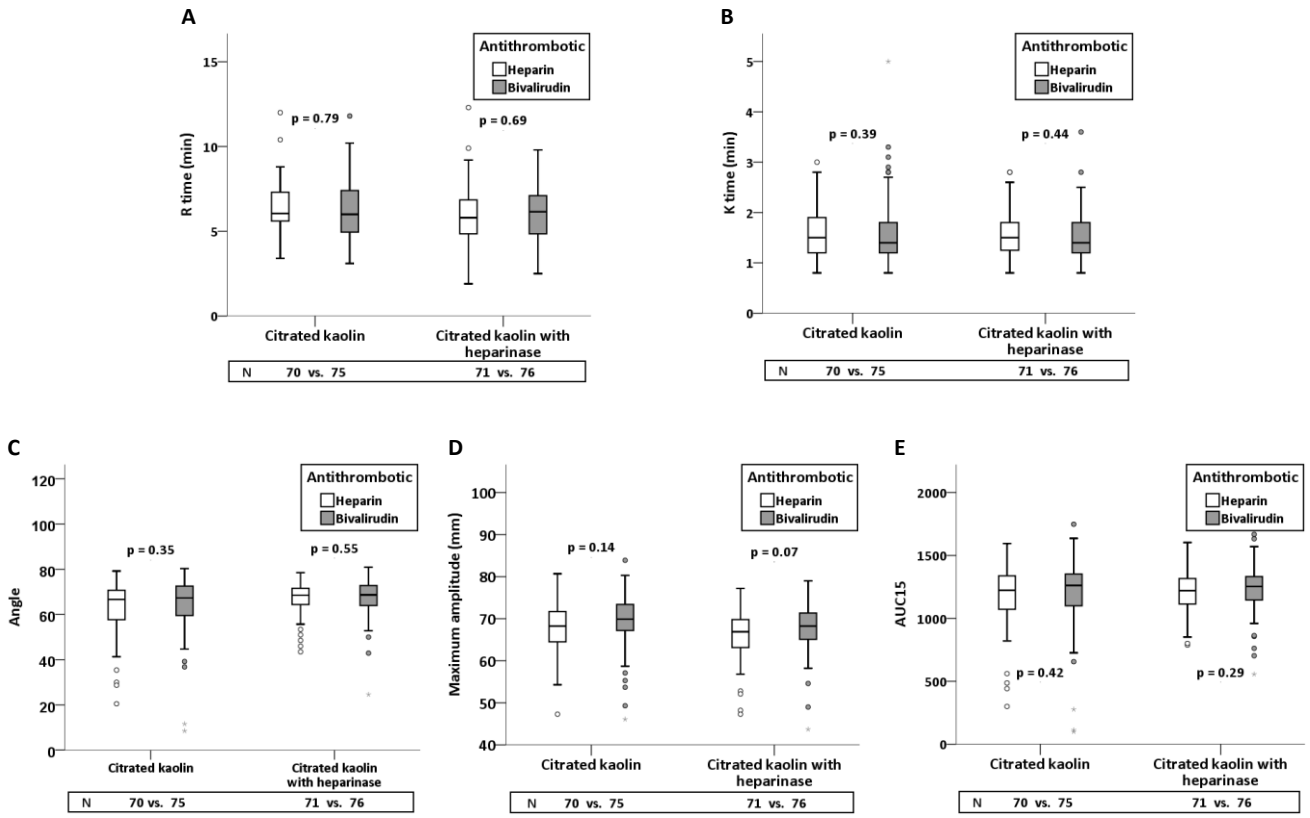


Figure 12 Comparison of Thrombelastography-derived indices between patients treated with unfractionated heparin and bivalirudin

Figure 12. Comparison of Thrombelastography-derived indices between patients treated with unfractionated heparin and bivalirudin at 24 hours when citrated whole blood was stimulated with kaolin (thrombin mediated clotting) in the presence (CKH channel) and absence of heparinase (CK channel): (A) R time; (B) area under the curve at 15 minutes (AUC15); (C) maximum amplitude (MA); (D) K time; and (E) α-angle.

Clinical outcomes per group and HPR:

In patients tested with MEA at the EOP time point (n = 457) and the incidence of the primary efficacy endpoint was numerically higher in patients with HPR (n = 299/457, 65.4%) versus no-HPR (n = 158/457, 34.6%) patients, though this did not reach levels of statistical significance (7.4% vs. 3.8%; OR 2.0; 95% CI: 0.8 to 4.9; *P* = 0.14). In patients treated with heparin, the incidence of the combined primary efficacy endpoint was similar in HPR versus no-HPR patients (2% vs. 1.3%; OR 1.5; 95% CI: 0.2 to 14.5; p = 0.72) (Figure 13). In patients treated with bivalirudin, the incidence of the combined primary efficacy endpoint was numerically higher in HPR patients compared to those with no-HPR (13.3% vs. 6%; OR 2.2; 95% CI: 0.8 to 5.8; *P* = 0.12) though this did not meet criteria for statistical significance either (Figure 14).

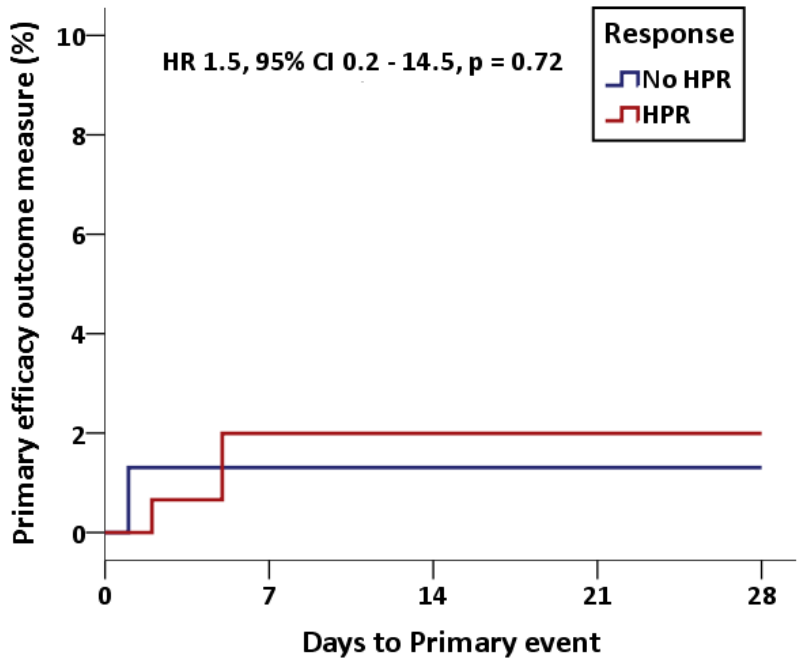


Figure 13 Kaplan-Meier curves illustrating the cumulative incidence of the combined primary efficacy outcome measure for heparin

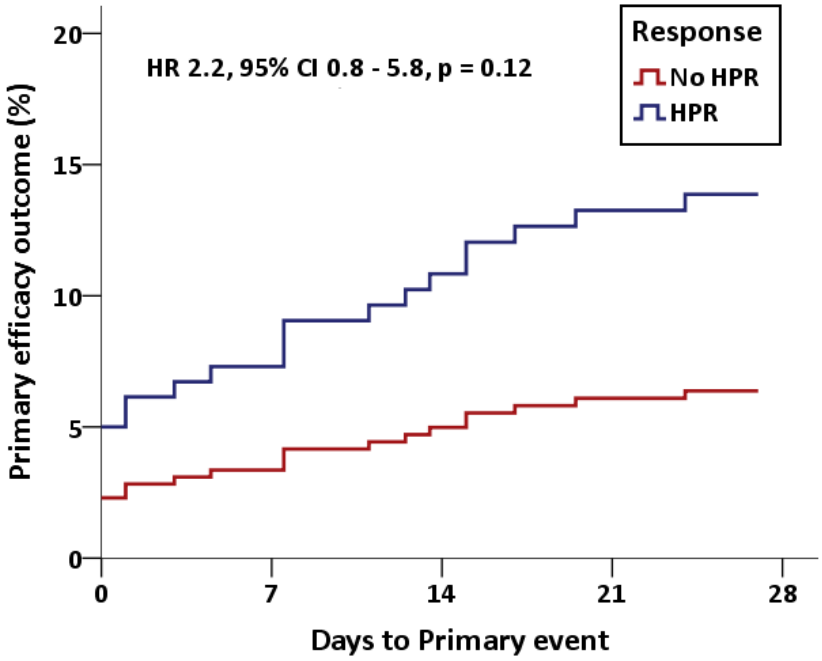


Figure 14 Kaplan-Meier curves illustrating the cumulative incidence of the combined primary efficacy outcome measure for bivalirudin

Figure 13 and 14. Kaplan-Meier curves illustrating the cumulative incidence of the combined primary efficacy outcome measure (a composite of death, cerebrovascular accident, reinfarction, urgent target lesion revascularisation) in 28 days following primary percutaneous coronary intervention, based on the presence of high platelet reactivity (HPR) to ADP at the end of procedure using multiple electrode aggregometry: (Fig 13) patients treated with unfractionated heparin (n = 229); (Fig 14) patients treated with bivalirudin (n = 239).

The individual components of the combined primary efficacy endpoint as well as the incidence of AST, were evaluated according to the randomly allocated intervention and the presence or absence of HPR (Table 12). Nevertheless, none of these showed significant differences between HPR and no-HPR patients regardless of whether they received heparin or bivalirudin during the PCI procedure.

Outcome	Total	Heparin (n = 229)			Bivalirudin (n = 228)		
		HPR (n = 152)	no HPR (n = 77)	p Value	HPR (n = 147)	no HPR (n = 81)	p Value
Primary efficacy outcome measures	28	3 (2%)	1 (1.3%)	0.72	19 (13.3%)	5 (6.0%)	0.12
Death	15	1 (0.7%)	1 (1.3%)	0.63	9 (6.1%)	4 (4.9%)	0.71
Cerebrovascular accident	4	1 (0.7%)	1 (1.3%)	0.62	2 (1.4%)	0	0.29
New MI or reinfarction	11	1 (0.7%)	0	0.48	9 (6.1%)	1 (1.2%)	0.09
Unplanned TLR	10	0	0	N/A	9 (6.1%)	1 (1.2%)	0.09
Definite AST	9	0	0	N/A	8 (5.4%)	1 (1.2%)	0.12

AST, acute stent thrombosis; TLR, target lesion revascularisation; HPR, high platelet reactivity; MI, myocardial infarction; Heparin, unfractionated heparin

Table 12 Clinical outcomes per study group and high platelet reactivity (HPR)

As a significant proportion of primary efficacy events occurred within the first 24 hours (i.e. 9 AST), and MEA data at 24 hours was only available in a limited proportion of individuals it was not possible to perform meaningful analysis of clinical outcomes at this time point. Furthermore, as the TEG assay was not available in the early course of the trial and therefore only performed in a proportion of the substudy population, there was no value in evaluating clinical outcomes with this assay, particularly given the low overall event rate (i.e. 28/458, 6.1%).

Discussion:

There are two principal findings reported in this platelet substudy of the HEAT-PPCI trial. Firstly, based on MEA there were no significant differences in ADP-, AA- and TRAP-mediated platelet aggregation between heparin and bivalirudin at either time point (i.e. EOP or 24 hours), a result that was confirmed with s-TEG (ADP and AA only). Secondly, based on viscoelastic measures of clotting with s-TEG, heparin obliterated TMC. By contrast, bivalirudin prolonged time to clot initiation (R time) and propagation (K time and α-angle), although recovery of thrombin activity upon decay of bivalirudin was associated with significantly greater maximum clot strength (i.e. MA) compared to control. This may provide a mechanistic explanation for the higher incidence of AST using bivalirudin reported in HEAT-PPCI[62] and other studies evaluating bivalirudin as an adjunctive antithrombotic in PPCI[59 65].

Using flow cytometry, previous studies have compared the effects of bivalirudin and heparin on platelet agonist-mediated platelet activation, both *ex vivo*[66 67] and *in vitro*[68-70] with mixed results (see supplement below for detailed discussion). In the present platelet substudy there were no significant differences in ADP-, AA-, and TRAP-mediated platelet aggregation between heparin and bivalirudin with MEA at either time point (i.e. EOP or 24 hours). It is reassuring that platelet function testing with s-TEG also found no significant differences between groups with respect to ADP- and AA-mediated platelet aggregation. Our findings are also in accordance with the DEACON

study which found no significant differences between heparin and bivalirudin in ADP-induced aggregation with LTA in patients undergoing PCI, regardless of whether they had been treated with GPI[71].

Whilst conventional assays for monitoring heparin-related blood clotting (e.g. ACT and activated partial thromboplastin time) terminate early after fibrin gel formation occurs in response to trace amounts of thrombin (< 5%), TEG continues profiling several aspects of clot dynamics on a temporal basis beyond the initiation phase (i.e. clot propagation) which is typically characterised by a burst of thrombin generation (> 95%). TEG is therefore ideally suited for comprehensive characterisation of the effects of thrombin inhibitors on the viscoelastic properties of clot formation. Indeed, several studies have already systematically evaluated a range of thrombin inhibitors with TEG, based on *in vitro* testing in healthy volunteers[72-76]. In accordance with our findings, these studies have shown that all thrombin inhibitors, including heparin and bivalirudin, prolong time to clot initiation (i.e. R time) and clot propagation (i.e. K time and α-angle) in a dose-dependent manner. However, the effects of direct thrombin inhibitors (DTIs) in prolonging clot initiation and propagation are modest in comparison to those of heparin, which has the steepest concentration-response curve, which is consistent with our findings. In the present study, heparin obliterated TMC at EOP, at least for the duration of the observation period. These findings are also consistent with previous reports demonstrating that heparin not only inhibits clot initiation and propagation, but also significantly attenuates clot strength and rigidity in a concentration-dependent manner[72 75 76].

To our knowledge, the present study is the first to demonstrate that bivalirudin augments maximum clot strength, a finding that could have important implications in the context of AST. By contrast, the existing evidence is discrepant with respect to the reported effects of bivalirudin on the tensile strength of a (MA). Specifically, Young *et al* showed that clot rigidity and elasticity were relatively preserved even at high doses of bivalirudin, once kaolin-activated clotting finally commenced following a prolonged lag period[72]. By contrast, Taketomi *et al* showed that at therapeutic concentrations (similar to those employed in PCI) bivalirudin resulted in modest increases in MA in response to direct stimulation with thrombin, when compared to control, though this was not statistically significant in their study[74]. It is noteworthy that we evaluated the

pharmacodynamic effects of these anticoagulants *ex vivo* in a large real-world population of STEMI patients undergoing PPCI which likely represents a more prothrombotic state than that prevalent in blood from healthy volunteers tested *in vitro*.

The differences between heparin and bivalirudin reported in this study are consistent with their known pharmacological properties. Specifically, heparin-mediated binding of antithrombin leads to the formation of a tenary complex and irreversible conformational changes to the active site of thrombin. By contrast, bivalirudin, comprises a peptide directed against the thrombin active site linked via a tetraglycine spacer to a synthetic dodecapeptide analogue of the C-terminus of hirudin[77] that binds to exosite 1 on thrombin (i.e. the binding site for fibrinogen and thrombomodulin). Once bound in a bivalent fashion (i.e. to the active site and exosite 1), thrombin is rendered inactive only transiently. Circulating proteases including thrombin itself cleave bivalirudin close to the N-terminus liberating the amino-terminal moiety from the active site, thereby allowing resumption of thrombin's catalytic activities[78]. Its relatively short plasma half-life (~ 25 minutes) has been cited as a plausible explanation for the higher incidence of AST associated with bivalirudin. Undoubtedly, this mechanistic explanation has greater biological relevance given that there is now also convincing evidence for a delayed onset of action of $P2Y_{12}$ inhibitors in STEMI[52 79]. Consequently, this has prompted analyses of prolonged post-PCI infusions of bivalirudin as a strategy to mitigate the higher incidence of AST, which has shown encouraging results[80 81].

Nevertheless, numerous studies have also reported that at low concentrations, bivalirudin[75 76 82] and other DTIs[83 84], produce a paradoxical increase in tissue factor (TF)-triggered thrombin generation (TG) *in vitro*. Furthermore, studies have also shown that TF-stimulation results in a paradoxical rise in markers of TG (e.g. prothrombin fragment 1+2, thrombin-antithrombin complex) in blood samples treated with bivalirudin[76 85] or other DTIs[84]. However, no increases in TG have been reported in patients treated with Factor (F) Xa inhibitors or heparin which also has intrinsic antithrombin-mediated activity against various clotting factors including FXa[75 76]. This exaggerated TG at low concentrations of DTIs has been attributed to the suppression of the thrombin-thrombomodulin (TM)-induced negative-feedback inhibition of

protein C activation. Activated protein C (APC) naturally exerts a potent anticoagulant effect via proteolysis of factor (F) Va and FVIIIa, thereby attenuating TG. Linder *et al* have demonstrated that a variety of direct (e.g. hirudin and melagatran) and indirect thrombin inhibitors (e.g. heparin) inhibit APC generation to a similar extent[86]. A critical role for APC and TM in exaggerated TG associated with DTIs at low concentrations is suggested by the following observations from previous studies: (i) enhanced TG was not observed in the absence of protein C in both rat models[87] and human plasma[83 84]; (ii) the extent of enhancement of TG in human plasma was greater in the presence of TM compared to in its absence[83 84]; and (iii) APC reversed enhancement of TG in a dose-dependent manner[83].

Following proteolytic cleavage, the carboxyl-terminal remnant of bivalirudin transforms into a competitive inhibitor of exosite 1 substrates including fibrinogen and TM[78], thus potentially exerting an ongoing inhibitory effect on thrombin-TM mediated activation of protein C. We can therefore speculate that a mechanism of rebound clotting activation could potentially explain the increase in clot strength at EOP and excess of AST observed in patients treated with bivalirudin. Nevertheless, further studies to elucidate the mechanism and clinical significance of this phenomenon are necessary.

Limitations: This substudy has several limitations that merit consideration. Firstly, we have assumed that baseline platelet reactivity prior to drug administration was similar in both treatment groups, though this was not formally confirmed. There was absence of a true control group i.e. an assessment of TEG data pre-drug administration. In patients treated with heparin, there may still be a heparin effect present despite the presence of heparinase in the cup. We were also unable to compare the effects of these antithrombotic regimens at therapeutic doses on TG as this was neither measured directly nor via assayed via surrogate markers. Heparinase inactivates not only therapeutically administered heparin, but also naturally occurring heparins, which could explain restoration of coagulation with CKH channel, but not the CK channel. Finally, we have not examined the validity of using the CKH channel in patients treated with heparin as a control group for comparison against patients treated with bivalirudin.

In conclusion, whilst there were no significant differences between heparin and bivalirudin with respect to their effects on platelet aggregation in response to ADP, AA and TRAP, we did observe important differences in the viscoelastic properties of clot formation in response to thrombin stimulation. Whilst heparin obliterated TMC bivalirudin prolonged clot initiation and propagation, but was also associated with a significant increase in maximum clot strength. These findings may provide some insight into the mechanism of the elevated risk of AST observed in bivalirudin patients observed in HEAT-PPCI and other trials, which may be related to loss of negative feedback inhibition of TG via APC. Further mechanistic and clinical studies are required to determine the optimal antithrombotic strategy in the setting of PPCI for STEMI.

Supplementary Discussion

Antiplatelet effects of Bivalirudin versus heparin

Using a flow cytometry, studies have previously compared the effects of bivalirudin and heparin on agonist-mediated platelet activation, both *ex vivo*[66 67] and *in vitro*[68-70]. Bivalirudin has been shown to have modest inhibitory effects on platelet activation though some authors have reported that it potentiates P-Selectin surface expression[88]. By contrast, heparin has mostly been shown to potentiate platelet activation by initiating outside-in signalling via direct binding to $\alpha_{IIb}\beta_3$ integrin[89], though again there are some conflicting reports[90]. However, the overall significance of differential surface expression of platelet activation markers with these antithrombotic agents on agonist-mediated clotting and clinical outcome measures remains poorly understood.

A study by Gallandat Huet *et al* in cardiac surgical patients demonstrated that both bivalirudin and heparin significantly attenuated ADP-mediated platelet aggregation when used to preserve blood, however the effects of bivalirudin were more pronounced[85]. By contrast, using MEA and light transmittance aggregometry (LTA), Sibbing *et al* demonstrated that in PCI patients preloaded with clopidogrel, whilst heparin had no significant effects, bivalirudin resulted in significant incremental inhibition of ADP-mediated aggregation[91]. Such anti-aggregatory effects, albeit modest in magnitude, are significant and therefore at least in theory might be expected to mitigate the early hazard of peri-procedural ischaemic events including

AST. However, thus far there is no consistent randomised data supporting a superiority for bivalirudin over heparin with respect to ischaemic end points. On the contrary, bivalirudin has been consistently associated with an elevated risk of AST[59 62 65], at least in the absence of a prolonged post-PCI infusion[81], a finding which has led to the downgrading of recommendations for bivalirudin to a class IIa level of evidence in the recent European guidelines[92]. In the present platelet substudy there were no significant differences in ADP-, AA-, and TRAP-mediated platelet aggregation between heparin and bivalirudin with MEA at either time point (i.e. EOP or 24 hours).

Clinical outcomes per group and HPR:

Agonist-induced platelet aggregation was significantly higher at EOP compared to 24 hours with both assays. Consequently, despite early administration of DAPT and widespread use of potent $P2Y_{12}$ inhibitors in the substudy (> 90%) a significantly higher proportion of the cohort exhibited HPR to ADP with MEA at EOP compared to the 24 hour time point (65.4% vs. 6.0%). These results are consistent with previous reports which showed a delayed onset of the pharmacodynamic effects of prasugrel and ticagrelor in the setting of PPCI for STEMI, thereby suggesting a possible role for a rapidly acting intravenous $P2Y_{12}$ inhibitor such as cangrelor in this population. Moreover, these results also confirm that neither antithrombotic agent (i.e. heparin or bivalirudin) has potent inhibitory effects on agonist-mediated platelet aggregation. The incidence of the efficacy endpoint in this substudy was numerically higher in HPR versus no-HPR patients (13.3% vs. 6.0%) treated with bivalirudin, though not statistically significant (p = 0.12). However, a platelet substudy of ISAR-REACT 4 trial by Sibbing *et al* did report significantly higher incidence of death, MI and urgent TLR in patients with HPR treated with bivalirudin in the context of PCI for non-ST elevation MI[93]. These apparent discrepancies with our data are likely explained by a disproportionately higher incidence of HPR at EOP combined with a low overall event rate in this substudy population. It is also noteworthy that all 9 AST events in this substudy occurred in patients treated with bivalirudin. This is unlikely to represent a chance finding as an excess of AST in STEMI patients treated with bivalirudin has been previously reported.[59 62 65]. An important limitation if this substudy was that the pharmacodynamic effects of $P2Y_{12}$ blockade had not reached steady state by the time platelet function testing was performed at the EOP. This substudy was therefore not

sufficiently powered to confidently exclude an interaction between the study intervention received and clinical impact of HPR to ADP though trends from our data and results from previous studies suggest such an interaction may exist.

Chapter 4 – Antiplatelet therapy substudy - Comparison of the effects of P2Y12 receptor antagonists on platelet function and clinical outcomes

Abstract:

Background:

We report pre-specified, secondary analyses comparing effects of P2Y12 inhibiting agents on platelet reactivity and clinical events.

Methods:

All patients received pre-procedural oral anti-platelet therapy. During the early stages of the trial, the P2Y12 inhibitor of choice was prasugrel with some use of clopidogrel. Later, routine therapy switched to ticagrelor. During working hours, Multiple Electrode Aggregometry (MEA) was used to assess ADP-induced platelet aggregation at the end of the index procedure. The effect of P2Y12 inhibitors on the primary efficacy (major adverse cardiac events - MACE) and safety (major bleeding) outcomes was assessed in all patients. Multiple logistic regression (MLR) was used to adjust for differences in baseline characteristics.

Results:

With MEA data from 469 patients, prasugrel therapy resulted in significantly greater suppression of ADP-induced platelet aggregation at 40U (23, 78) when compared

against ticagrelor 75U (41, 100.75) or clopidogrel 79U (56, 96); p < 0.001. In the entire study population (n = 1803), prasugrel therapy was associated with significantly fewer MACE events (26/497; 5.2%) in comparison to ticagrelor (83/1123; 7.4%) or clopidogrel (18/183; 9.8%); p value 0.045. For major bleeding, there were no significant differences between the three groups - clopidogrel (3/183; 1.6%), prasugrel (13/497; 2.6%) and ticagrelor (43/1123; 3.8%). Patients treated with clopidogrel had more high-risk features and use of clopidogrel was more common in the early phase of the trial. After adjustment, there were no significant differences in the rates of MACE or major bleeding.

Conclusion:

In HEAT PPCI, patients who received prasugrel (rather than clopidogrel or ticagrelor) had significantly greater suppression of ADP-induced platelet aggregation at the end of the procedure. In the entire study population, prasugrel therapy was associated with a reduced MACE rate. After adjusting for baseline characteristics, the results were not statistically significant. For bleeding outcomes, there were no significant differences between the antiplatelet therapies.

Background:

In the management of STEMI, current guidelines recommend administration of dual antiplatelet therapy as early as possible after diagnosis[14 94]. Newer agents, ticagrelor and prasugrel, have been shown to have a faster, more potent and more consistent antiplatelet action in comparison to clopidogrel. In clinical trials recruiting mixed acute coronary syndrome populations, the newer agents have demonstrated superior efficacy to clopidogrel and are now the preferred agents[95 96], although advantage in primary PCI subgroups is more difficult to establish.

Studies have shown that the therapeutic response to P2Y12 inhibitors may be slower in STEMI patients than in other populations[97-100]. Specifically, in a substantial proportion of patients, even the newer P2Y12 inhibitors may fail to achieve adequate suppression of ADP-induced platelet aggregation at 2 hours following a loading dose (LD) [101 102]. Previous randomised trials comparing measures of platelet inhibition with prasugrel and ticagrelor in STEMI population have shown comparable results [101-103].

We report pre-specified, secondary analyses from the HEAT-PPCI trial comparing the effects of P2Y12 inhibitors on platelet reactivity and clinical outcomes.

Methods:

Study population and design:

This substudy reports results from two distinct denominator groups: a) Clinical outcomes were assessed on all patients recruited in the HEAT-PPCI trial. b) Tests to assess suppression of ADP-induced platelet aggregation were performed on patients recruited during the normal working hours of the research laboratory for sample analysis (0900-1700 hrs, Monday-Friday).

Study medication:

All patients received pre-procedural dual anti-platelet therapy with aspirin and a P2Y12 inhibitor. During the early stages of the trial, the P2Y12 inhibitor of choice was prasugrel. Use of clopidogrel was also allowed depending on the operator preference but was generally reserved for patients > 75 years of age, having a bodyweight < 60 kg or a previous history of CVA. The clinical guidelines at the host institution changed during the course of the trial and ticagrelor became the default P2Y12 inhibitor. The recommended loading doses (LD) were 60mg for prasugrel, 600mg for clopidogrel and 180mg for ticagrelor. For inter-hospital transfers, the antiplatelet LD was administered at the referring hospital prior to transfer. For direct ambulance admissions, the P2Y12 inhibitor loading was performed on arrival at the host institution.

Platelet function testing (PFT):

MEA was performed using the Multiplate analyser (Roche diagnostics, Mannheim, Germany). This is a whole blood assay based on measures of electrical impedance. ADP-induced platelet aggregation is initiated by addition of ADP (6.5 µM) to the test cells. The change in impedance resulting from the adhesion and aggregation of platelets on the surface of two silver-coated highly conductive copper electrodes is analysed for each sensor unit for 6 minutes[104]. These values are transformed to units and plotted against time. From this, one can measure the area under the curve expressed as arbitrary aggregation units (U). All materials including reagents were obtained from the manufacturer (Roche diagnostics, Mannheim, Germany).

Whole blood for platelet function testing was obtained via the arterial sheath in the cardiac catheterisation lab at the end of the index procedure (EOP). In patients assigned to receive bivalirudin, the infusion was still running at the time of sampling. The first 10ml were discarded and then blood was drawn into a 3 ml blood collection tube. The tubes were filled to capacity and inverted gently a few times to ensure proper mixing with the anticoagulant in situ.

We also pre-specified the assessment for the presence of high platelet reactivity (HPR) to ADP. This was defined as MEA ADPtest > 46 U based on previous studies and the latest consensus document of the Working Group for On-Treatment Platelet Reactivity[105].

Statistics:

Categorical variables were presented as numerator / denominator (percentage). Comparisons were made using chi-squared or Fisher's exact tests as appropriate. Non-normally distributed continuous data (normality assessed by means of the Kolmogorov–Smirnov test) were presented as median with inter-quartile ranges (IQR) and were compared with two-sided Wilcoxon test and Wilcoxon matched-pairs signed-ranks test as appropriate.

Multivariable logistic regression using backwards elimination was used to adjust for differences in baseline characteristics. The following baseline parameters were offered to the model: age, gender, weight, antithrombotic therapy, diabetes, cardiogenic shock, hypertension, hyperlipidaemia, smoking status, previous MI, P2Y12 inhibitor treatment, GP IIb/IIIa inhibitor use, femoral arterial access, mildly impaired EF, moderately impaired EF and severely impaired EF.

MACE was subsequently adjusted for moderate and severe LVEF impairment, diabetes, female sex and antithrombotic therapy. Bleeding outcomes were adjusted for cardiogenic shock, femoral access site and severe LV EF impairment.

In order to generate odds ratios specific to each of the three P2Y12 agents and to take into account potential differences in casemix for these three groups, crude and

casemix adjusted logistic regression models were produced for MACE and bleeding outcomes.

In all cases a p-value ≤ 0.05 was considered statistically significant. All statistical analyses have been performed with SAS software, version 9.3 (SAS Institute, Cary, NC).

Ethical and regulatory approvals:

The main study protocol including the platelet substudy was approved by the National Research Ethics Service (NRES, North West) and the UK Medicines and Healthcare Products Regulatory Agency. The main trial was registered at www.clinicaltrials.gov (NCT01519518). The study was partially funded by unrestricted grants from The Medicines Company and AstraZeneca but these companies had no involvement in any aspect of trial design, conduct or reporting. The first author and the last author (who is also the principal investigator for the main study) accept full responsibility for the accuracy and completeness of the data and all analyses.

Results:

Clinical outcomes:

Of the 1812 patients recruited in HEAT-PPCI, 1803 received loading dose of P2Y12 inhibitors (clopidogrel 183, prasugrel 497 and ticagrelor 1123). This is illustrated in

figure 15.

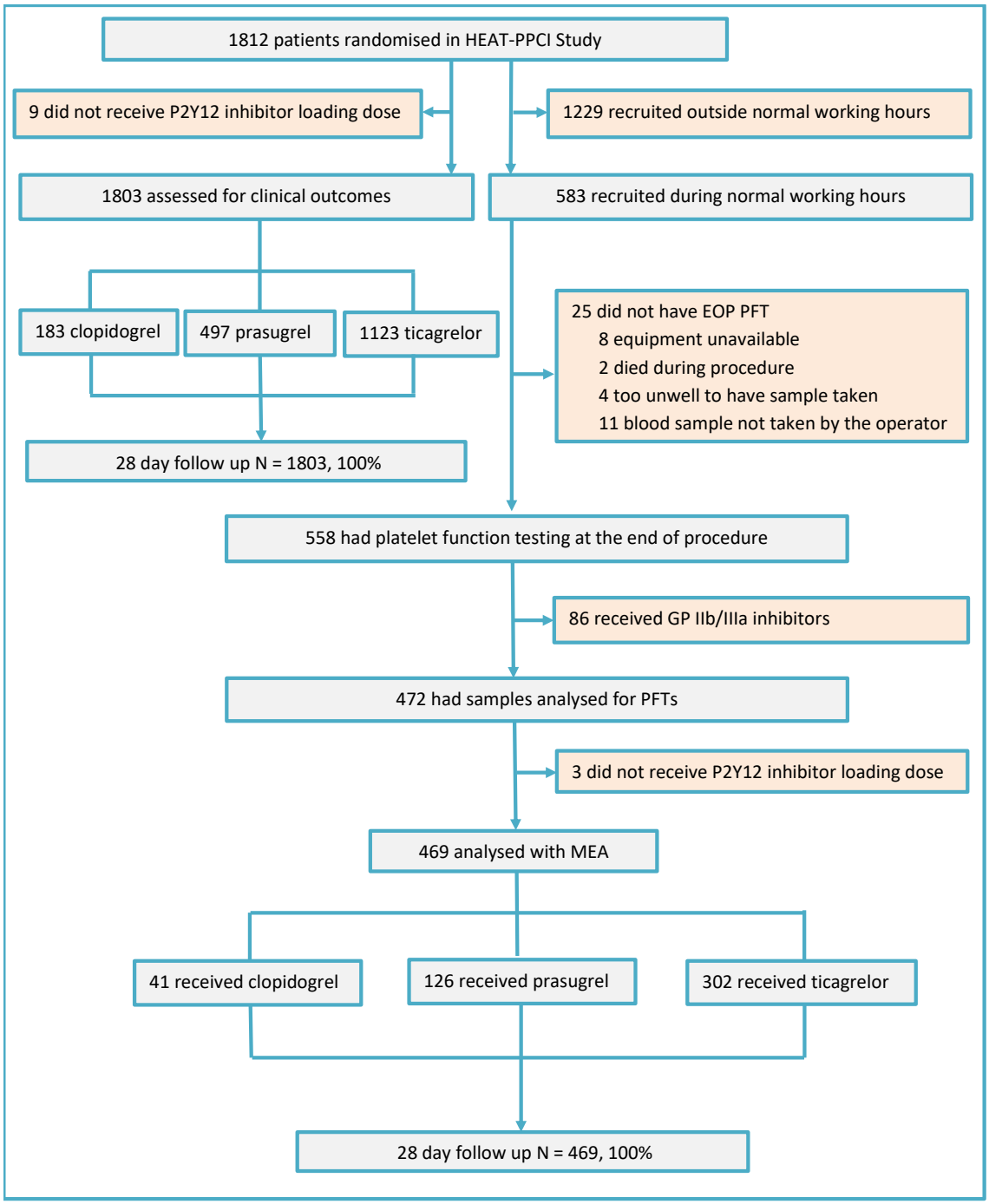


Figure 15 HEAT-PPCI antiplatelet therapy substudy flowchart

Follow-up at 28 days was complete in 100% patients. Baseline characteristics of the population in the three groups are demonstrated in Table 13.

	Clopidogrel (n = 183)	Prasugrel (n = 497)	Ticagrelor (n = 1123)	p value for Clopidogrel vs. Others
Age (years)	66 (55, 78)	62 (53, 72)	62 (53, 73)	0.001
Female sex	70 / 183 (38.3)	124 / 497 (25.0)	305 / 1123 (27.2)	0.001
Race - White British	178 / 182 (97.8)	476 / 497 (95.8)	1074 / 1123 (95.6)	0.17
Weight (kg)	76 (66, 86)	80 (70, 92)	80 (70, 90)	0.029
Comorbidities				
Diabetes	37 / 183 (20.2)	62 / 495 (12.5)	151 / 1116 (13.5)	0.010
Hypertension	98 / 183 (53.6)	201 / 495 (40.6)	447 / 1120 (39.9)	0.001
Hyperlipidaemia	85 / 182 (46.7)	191 / 491 (38.9)	390 / 1111 (35.1)	0.006
Family history of CVD	76 / 181 (41.9)	211 / 495 (42.6)	500 / 1100 (45.5)	0.51
Current smoker	63 / 181 (34.8)	197 / 491 (40.1)	489 / 1099 (44.5)	0.031
Previous myocardial infarction	35 / 183 (19.1)	53 / 496 (10.7)	125 / 1122 (11.1)	0.001
Previous PCI	19 / 183 (10.4)	29 / 496 (5.9)	81 / 1121 (7.2)	0.07
Previous coronary artery bypass grafting	4 / 183 (2.2)	11 / 496 (2.2)	27 / 1122 (2.4)	>0.99
Cardiogenic shock	2 / 183 (1.1)	4 / 497 (0.8)	19 / 1123 (1.7)	>0.99
Antithrombotic drug				
Heparin	83 / 183 (45.4)	250 / 497 (50.3)	569 / 1123 (50.7)	0.18
Bivalirudin	100 / 183 (54.6)	247 / 497 (49.7)	554 / 1123 (49.3)	
Additional P2Y12 inhibitor				
Clopidogrel	-	12 / 497 (2.4)	3 / 1123 (0.3)	-
Glycoprotein IIb/IIIa inhibitor use	20 / 183 (10.9)	57 / 497 (11.5)	182 / 1123 (16.2)	0.16
Arterial access site				
Femoral	40 / 183 (21.9)	85 / 497 (17.1)	204 / 1123 (18.2)	0.18
Radial	141 / 183 (77.1)	411 / 497 (82.7)	914 / 1123 (81.4)	0.12
Managed with PCI	129 / 183 (70.5)	412 / 497 (82.9)	944 / 1123 (84.1)	<0.001
Symptom onset to randomisation time (hr)	3.5 (1.9, 8.8)	3.0 (1.8, 5.8)	2.5 (1.5, 4.8)	<0.001
Door to Balloon time (mins)	28 (23, 36)	28 (22, 35)	29 (23, 37)	0.75
Left ventricular function after index event	166 / 183 (90.7)	459 / 497 (92.4)	1036 / 1123 (92.3)	0.45
Normal (ejection fraction ≥55%)	77 / 166 (46.4)	215 / 459 (46.8)	452 / 1036 (43.6)	0.66

Mildly impaired (ejection fraction 45–54%)	33 / 166 (19.9)	129 / 459 (28.1)	264 / 1036 (25.5)	0.07
Moderately impaired (ejection fraction 36–44%)	37 / 166 (22.3)	80 / 459 (17.4)	215 / 1036 (20.8)	0.43
Severely impaired (ejection fraction ≤35%)	19 / 166 (11.5)	35 / 459 (7.6)	105 / 1036 (10.1)	0.39

Table 13 Antiplatelet therapy substudy - Baseline characteristics for all patients

Patients that received clopidogrel appear to have a significantly higher risk profile especially for older age, lower body weight, history of diabetes, previous myocardial infarction and previous PCI. The prasugrel group has a more favourable risk factor profile than the other two cohorts.

Median duration from the time of administration of P2Y12 inhibitor LD to EOP was 65 min (IQR 42 – 98). This was significantly higher for clopidogrel (95 min; IQR 60-120) in comparison to prasugrel (70 min; IQR 45-98) or ticagrelor (60 min; IQR 40-92); p 0.001. The median duration from time sample was obtained to the analysis was 50 min (IQR 20-70).

Table 14 shows clinical outcomes in the entire study population.

Table: Clinical outcomes at 28 days

	Outcome freq (%)	Crude Analysis		Adjusted Analysis	
		OR (95%CI)	P value	OR (95%CI)	P value
MACE					
Clopidogrel (n = 183)	18 (9.8)	1.46 (0.87, 2.47)	0.15	1.57 (0.86, 2.87)	0.14
Prasugrel (n = 497)	26 (5.2)	0.64 (0.41, 0.99)	0.045	0.70 (0.41, 1.21)	0.20
Ticagrelor (n = 1123)	83 (7.4)	1.07 (0.73, 1.54)	0.74	1.01 (0.65, 1.59)	0.96
Major Bleeding		**OR (95%CI)**	**P value**	**OR (95%CI)**	**P value**
Clopidogrel (n = 183)	3 (1.6)	0.46 (0.14, 1.48)	0.19	0.50 (0.15, 1.66)	0.26
Prasugrel (n = 497)	13 (2.6)	0.73 (0.39, 1.35)	0.31	0.80 (0.41, 1.60)	0.53
Ticagrelor (n = 1123)	43 (3.8)	1.57 (0.89, 2.78)	0.12	1.46 (0.79, 2.70)	0.23

Table 14 Clinical outcomes in the entire study population

Prasugrel therapy was associated with significantly fewer MACE events (26/497; 5.2%) in comparison to ticagrelor (83/123; 7.4%) or clopidogrel (18/183; 9.8%); p value 0.045. For major bleeding, there were no significant differences between the three groups - clopidogrel (3/183; 1.6%), prasugrel (13/497; 2.6%) and ticagrelor (43/1123; 3.8%). After adjustment of the baseline characteristics using MLR, there were no significant differences in the rates of either MACE or major bleeding (Table 14).

Figure 16 illustrate the differences between the three groups for MACE and bleeding outcomes before and after the adjustment.

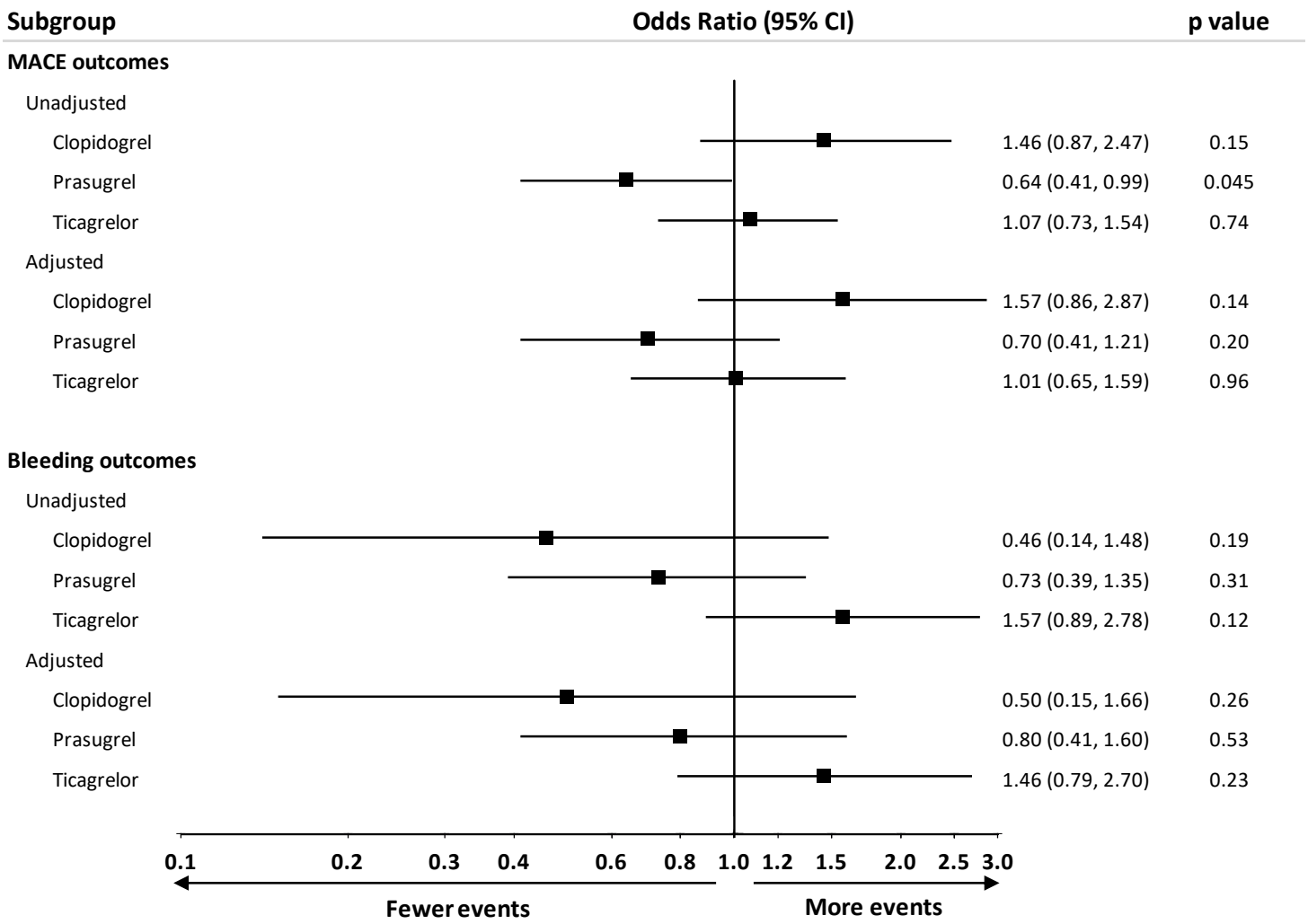


Figure 16 Odds ratio plot for clinical outcomes

ADP-induced platelet aggregation:

Figure 15 outlines the flow of patients included in the platelet function substudy. Of the 1812 patients randomised in the HEAT-PPCI trial, 584 (32.2%) were recruited during the normal working hours. Patients that received Glycoprotein IIb/IIIa inhibitors (15.4%) were excluded from the analysis. The baseline characteristics from the final cohort of 469 patients that underwent analysis are shown in table 15.

The risk factor profiles appear more matched in this cohort. Figure 17 illustrates the results. Prasugrel therapy resulted in significantly greater suppression of ADP-induced platelet aggregation at 40U (23, 78) when compared against ticagrelor 75U (41, 100.75) or clopidogrel 79U (56, 96); $p < 0.001$.

	Clopidogrel (n = 41)	Prasugrel (n = 126)	Ticagrelor (n = 302)	p value for Clopidogrel vs. Others	p value for Prasugrel vs. Others
Age (years)	67 (54, 79)	61 (52, 72)	65 (55, 74)	0.25	0.023
Female sex	11 / 41 (26.8)	34 / 126 (27.0)	95 / 302 (31.5)	0.66	0.41
Race - White British	40 / 40 (100)	123 / 126 (97.6)	288 / 302 (95.4)	0.38	0.58
Weight (kg)	82 (67, 86)	80 (70, 92)	76 (67, 86)	0.76	0.047
Comorbidities					
Diabetes	5 / 41 (12.2)	14 / 126 (11.1)	38 / 302 (12.6)	>0.99	0.68
Hypertension	23 / 41 (56.1)	55 / 126 (43.7)	125 / 302 (41.4)	0.08	0.92
Hyperlipidaemia	22 / 40 (55.0)	46 / 125 (36.8)	111 / 298 (37.3)	0.026	0.62
Family history of CVD	23 / 41 (56.1)	54 / 126 (42.9)	131 / 297 (44.1)	0.13	0.60
Current smoker	11 / 41 (26.8)	49 / 126 (38.9)	116 / 298 (38.9)	0.13	0.78
Previous myocardial infarction	7 / 41 (17.1)	13 / 126 (10.3)	36 / 302 (11.9)	0.31	0.51
Previous PCI	4 / 41 (9.8)	7 / 126 (5.6)	20 / 301 (6.6)	0.34	0.57
Previous coronary artery bypass grafting	1 / 41 (2.4)	4 / 126 (3.2)	8 / 302 (2.7)	>0.99	0.75
Cardiogenic shock	0 / 41 (0)	1 / 126 (0.8)	5 / 302 (1.7)	>0.99	>0.99
Antithrombotic drug					
Heparin	15 / 41 (36.6)	71 / 126 (56.3)	141 / 302 (46.7)	0.11	0.037
Bivalirudin	26 / 41 (63.4)	55 / 126 (43.7)	161 / 302 (53.3)		
Additional P2Y12 inhibitor					
Clopidogrel	-	5 / 126 (4.0)	0 / 302 (0)	-	0.010
Glycoprotein IIb/IIIa inhibitor use	0 / 41 (0)	0 / 126 (0)	0 / 302 (0)	-	-
Arterial access site					
Femoral	7 / 41 (17.1)	29 / 126 (23.0)	49 / 302 (16.2)	0.86	0.10
Radial	34 / 41 (82.9)	97 / 126 (77.0)	252 / 302 (83.4)	0.83	0.11
Managed with PCI	27 / 41 (65.9)	105 / 126 (83.3)	232 / 302 (76.8)	0.059	0.07
Symptom onset to randomisation time (hr)	3.8 (1.3, 9.9)	2.9 (1.6, 5.5)	2.5 (1.5, 4.7)	0.034	0.26
Door to Balloon time (mins)	28 (22, 41)	27 (22, 34)	28 (22, 35)	0.82	0.51

Delay from P2Y12 to proc sample (mins)	95 (60, 120)	70 (45, 98)	60 (40, 92)	<0.001	0.32
Left ventricular function after index event	39 / 41 (95.1)	120 / 126 (95.2)	278 / 302 (92.1)	>0.99	0.28
Normal (ejection fraction ≥55%)	15 / 39 (38.5)	64 / 120 (53.3)	133 / 278 (47.8)	0.19	0.21
Mildly impaired (ejection fraction 45–54%)	12 / 39 (30.8)	26 / 120 (21.7)	69 / 278 (24.8)	0.34	0.40
Moderately impaired (ejection fraction 36–44%)	10 / 39 (25.6)	25 / 120 (20.8)	52 / 278 (18.7)	0.35	0.77
Severely impaired (ejection fraction ≤35%)	2 / 39 (5.1)	5 / 120 (4.2)	24 / 278 (8.6)	>0.99	0.14

Table 15 Baseline characteristics for the platelet substudy cohort

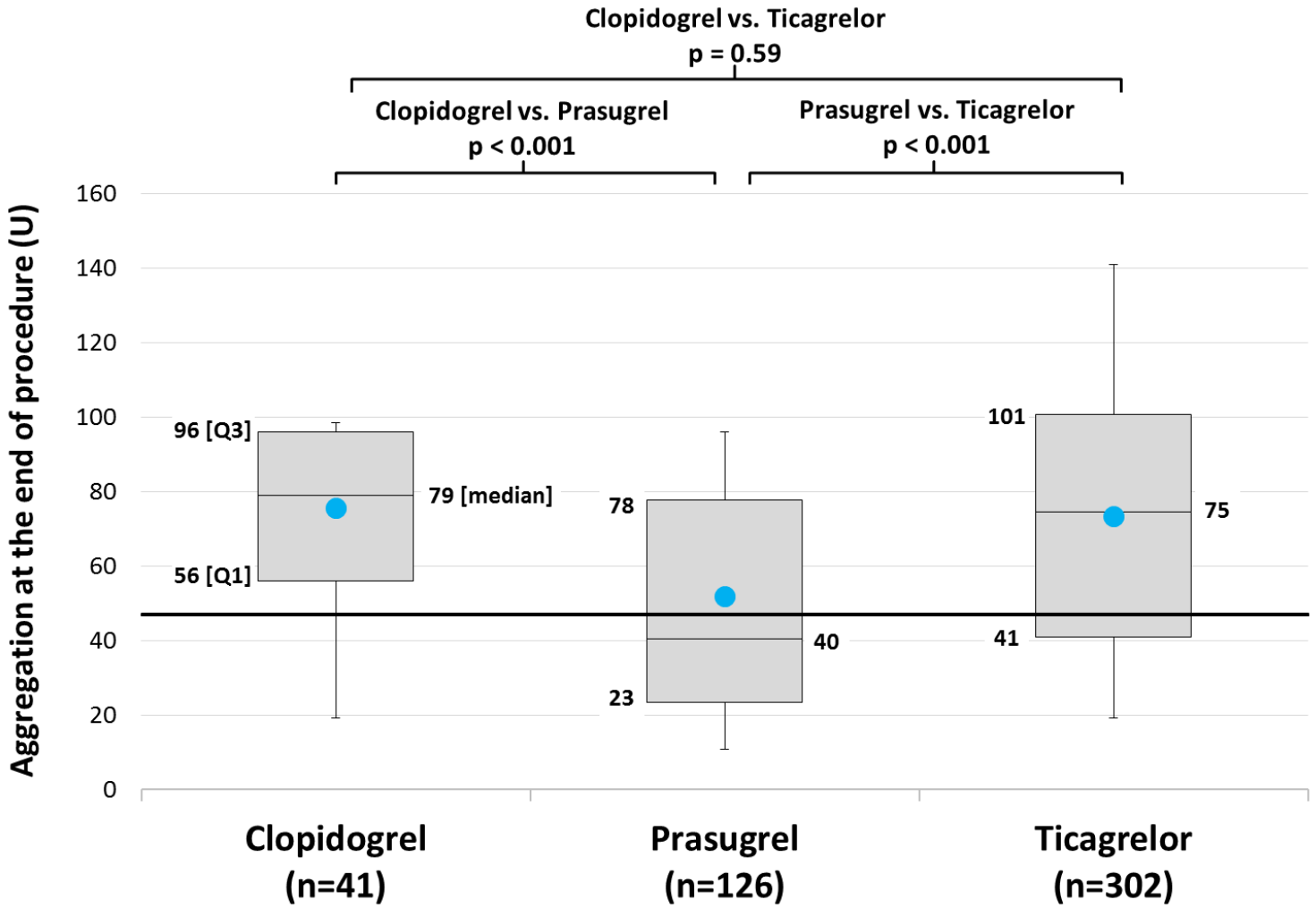


Figure 17 Comparison of suppression of ADP-induced platelet aggregation

Assessing the HPR values, a significantly higher number of patients achieved adequate suppression of ADP-induced platelet aggregation of < 46 U at the end of the procedure in the prasugrel group (70 / 126; 55.6%) in comparison to the clopidogrel (7 / 41; 17.1%) or ticagrelor (84 / 302; 27.8%); $p < 0.001$.

Discussion:

The results show a significantly higher level of suppression of ADP-induced aggregation with prasugrel in the acute phase compared to ticagrelor or clopidogrel. Previous trials have suggested that both ticagrelor and prasugrel induce higher levels of platelet inhibition as compared to clopidogrel and decrease the proportion of patients with HPR[98 106 107]. Comparing prasugrel and ticagrelor against each other in STEMI setting, RAPID 1 study showed that 60mg prasugrel LD was non-inferior to 180mg ticagrelor LD in reducing the primary end point of the study of HPR 2 hours after drug administration[101]. In RAPID 2 study, there was no significant difference in platelet inhibition 1 hour after administration between an increased oral ticagrelor LD of 360mg when compared with the standard prasugrel LD (P2Y12 reaction units of 248 v 236 respectively; $p = 0.89$) [103]. Alexopoulos et al found no differences between the two agents in STEMI and both drugs exhibited an initial delay in the onset of their antiplatelet action[102]. After 6-12 hrs, ticagrelor has been shown to achieve significantly better suppression of ADP-induced aggregation when compared to prasugrel[108 109].

Despite the observed higher degree of suppression of ADP-induced aggregation in the prasugrel group compared to clopidogrel or ticagrelor, after adjustment for baseline characteristics by MLR, this did not translate into significantly different rates of MACE or bleeding events. The recently published randomised controlled trial, PRAGUE-18, comparing prasugrel and ticagrelor in STEMI population was prematurely terminated for futility[110]. No significant differences were found for primary (death, re-infarction, urgent TLR, CVA or major bleeding) [4.0% vs 4.1% respectively; $p = 0.98$] or key secondary end points (cardiovascular death, nonfatal MI, or CVA) [2.7% vs 2.5%; $p = 0.86$] at 30 days. The post hoc analyses of the PLATO and TRITON studies looking specifically at STEMI populations provide similar indications [111 112]. In PLATO-STEMI

subgroup analysis, the primary end point (myocardial infarction, stroke, or cardiovascular death) with ticagrelor was 9.4% at 12 months[112]. In TRITON-STEMI, the primary endpoint (cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke) with prasugrel was achieved in 10.0% patients at 15 months[111]. However, it is not possible to compare the two cohorts directly due to differences in study designs and patient populations.

Due to the emergency nature of the STEMI setting, effective inhibition of ADP-induced platelet aggregation remains a concern as there is insufficient time in the initial phase for antiplatelet agents to work [97-100]. This overall inadequate level of ADP suppression achieved by antiplatelet agents in the acute phase could explain why prasugrel, even with relatively higher rate of ADP suppression, failed to impact the clinical outcomes in the adjusted population. Previously, it has been observed that even the newer agents require at least 4 hours to reach an optimal biological efficacy following the LD in STEMI patients[101 102]. With the apparently most efficacious agent prasugrel, only just over half of the patients exhibited adequate ADP suppression at the end of the procedure. The predefined definitions of "adequate" response of antiplatelet agents to ADP-induced aggregation are not biologically relevant[105]. This could also account for the failure of these agents to effect clinical outcomes in the acute phase when being compared against each other.

Our study demonstrated no significant differences for bleeding outcomes when comparing prasugrel and ticagrelor. PRAGUE-18 study[110] and recent data from 12 European registries[113] have shown similar findings.

This study has several limitations. Data are observational and not randomised. Hence, we should exercise caution in interpretation of the results. There is a significant mismatch between the baseline characteristics of the three groups. Figure 18 shows

the trend of administration of P2Y12 inhibitors over the course of the trial.

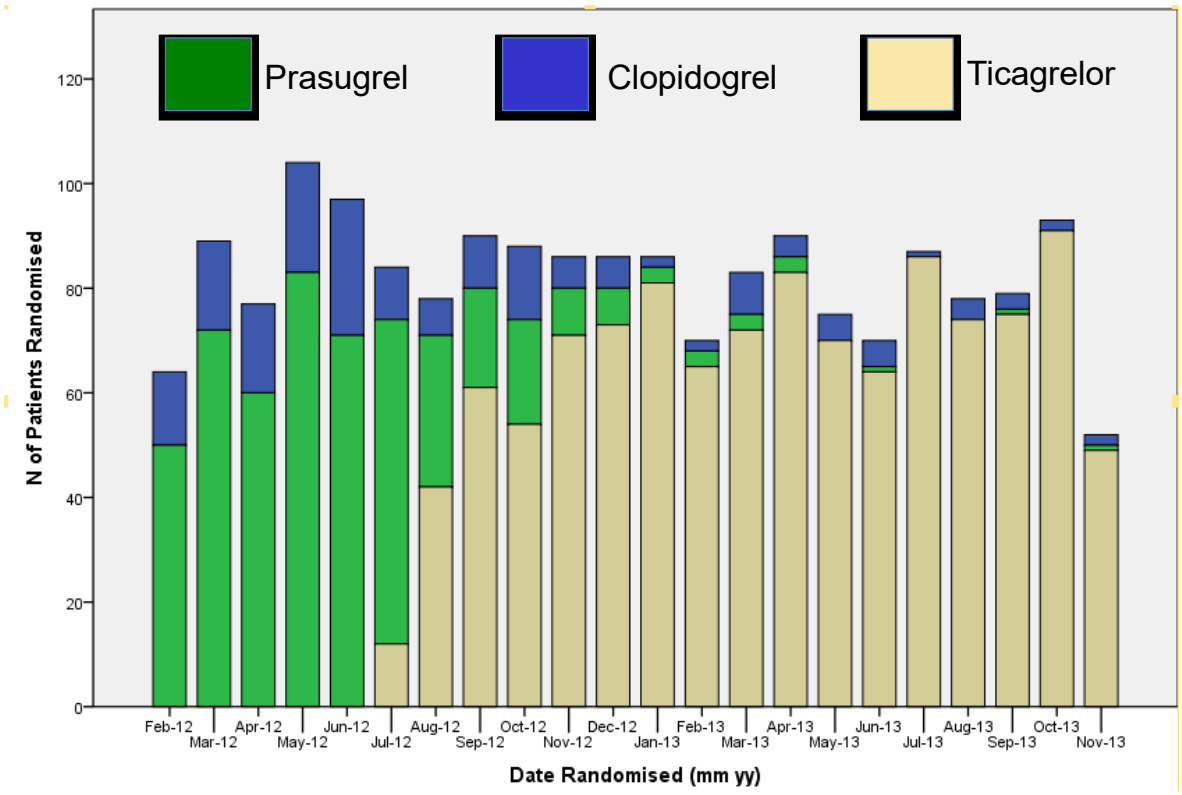


Figure 18 Evolution of P2Y12 inhibitor use over time

During the initial phase of the trial, prasugrel was the antiplatelet agent of choice. Administration of clopidogrel was at operator's discretion at some peripheral centres but was mainly given to the patients older than 75 years, body weight < 60 kg or a previous history of CVA. This diverted a higher risk population towards receiving clopidogrel rather than prasugrel. Some use of clopidogrel continued in the later phase when ticagrelor became the predominant P2Y12 inhibiting agent. The reasons include guideline recommendation at one peripheral hospital and occasionally operator's discretion for patients that were already on long term clopidogrel therapy or were presumed to have a higher bleeding risk.

There is also a significant mismatch between the median duration from time of P2Y12 inhibitor administration to EOP. The above mentioned peripheral hospital is located farthest from the host institution which may explain the longer duration of LD administration to EOP for the clopidogrel group.

When comparing against prasugrel, the ticagrelor cohort had shorter duration between drug administration to the time a sample was taken for PFTs. This could have influenced the level of platelet inhibition achieved and should be considered when evaluating the prasugrel advantage in this regard. Another limitation of the study is the lack of data regarding administration of morphine. Morphine administration has shown to influence absorption of the antiplatelet agents and consequently, the level of platelet inhibition achieved[101 103]. The shorter duration of symptom onset to randomisation time for ticagrelor cohort could have affected the platelet reactivity levels following morphine administration for symptom relief. A MLR model was used to adjust for the differences in baseline characteristics. Statistical significance for MACE was lost after adjustment for the baseline risk profile adjustment.

Future considerations include an adequately powered randomised controlled trial comparing prasugrel and ticagrelor in STEMI setting comparing clinical outcomes and assessing platelet function. ISAR-REACT 5 trial is currently recruiting patients in this regard[114].

Conclusion:

In HEAT PPCI antiplatelet therapy observational substudy, patients who received prasugrel (rather than clopidogrel or ticagrelor) had significantly greater suppression of ADP-induced platelet aggregation at the end of the procedure. However, this did not translate into reduction in ischaemic events in comparison to ticagrelor or clopidogrel after adjusting the population for baseline characteristics. For bleeding outcomes, there were no significant differences between the antiplatelet therapies.

Chapter 5 – Conduct of the trial and the ethics of delayed consent:

Background:

HEAT-PPCI trial adopted the approach of delayed consent. Patients were randomised and treated in the acute phase without mention of the trial. The surviving subjects were later approached for full informed consent for use of their data and to approve future follow-up contact. We discuss the rationale and ethics of the delayed consent methodology.

Essentials of informed consent:

The provision of informed consent before recruitment into a clinical trial is a requirement for the ethical conduct of clinical research. For a consent to be valid and informed, three essential elements need to be fulfilled. These are information disclosure, voluntary participation and decision-making capacity[115-118]. For valid consent, information provided to a research subject should include the nature of the health condition for which the research is proposed; the purpose of the study; details of the study treatment or intervention; probable risks and benefits associated with research participation; availability, risks and benefits of alternative treatments; right to withdraw at any time without any negative consequences and any other information deemed necessary[118-120]. The potential participant should be given adequate time to weigh the risks and benefits to process all the information to reach a decision. The capacity of an individual to reach a decision depends on his or her cognitive abilities. Decisional capacity comprises four elements: (a) understanding the information; (b) appreciation of the situation; (c) rational manipulation of the information; (d) making and communicating a choice (decision)[118 121].

The concept of delayed consent:

Delayed consent involves the enrolment of patients into a clinical trial in the acute phase before obtaining consent. Written informed consent to continue participation and for use of study-related data is obtained subsequently from the patients at an appropriate point in the clinical course. Delayed consent has been used in large clinical trials that have included critically ill participants[122-124].

Consent is not informed in time-critical, life-threatening situations:

The HEAT-PPCI trial compared the use of antithrombotic agents in the acute phase management of ST elevation myocardial infarction (STEMI)[125]. STEMI is a time-critical, emergency setting. Early reperfusion is the key treatment aim and research has established that each additional minute of treatment delay is associated with less favourable outcomes [126 127]. To speed up and hence improve the efficacy of treatment, the host institution (and many other UK centres) does not seek written or fully informed verbal consent for the PPCI procedure itself.

Even in the absence of time constraint, informed consent before potential emergency or life-saving treatment may not always be possible especially in critically ill patients. The nature of the presenting condition itself together with any first-line treatments administered are likely to present a real challenge to rational decision making. AMI patients usually are faced with an unheralded emergency situation. Distress, anxiety and emotional shock are commonplace. Most are in pain and may have received opiate or other analgesia with sedative effect. This set of circumstances, in any other given scenario, would be considered to have compromised the ability of a patients to provide informed consent.

Multiple studies have suggested that patients with acute myocardial infarction have difficulty processing information necessary to give informed consent for acute care research [128-132]. The majority of the patients suffering from an AMI are not regarded as being capable of reaching more than a limited level of understanding in this situation[133]. A substudy of the HERO-2 trial, which was performed in an AMI setting, concluded that overall, the patients' comprehension of the consent information was poor and they were not competent to give autonomous consent [129]. The consent

process of the ISIS-4 trial was studied which showed that only 31% of patients perceived that they had full comprehension of the trial, while 50% claimed they had partial understanding and 19% had no understanding at all [131]. Consent validity was also assessed in the DANAMI-2 trial. It showed that 28% of participants were unable to read the consent form [130]. A large-scale physicians' survey gave the same impression [133]. Eighty six percent of the physicians in the survey felt that patients were unable to understand all the information given to them, and were unable to give fully informed consent.

Studies have shown that seriously ill patients rarely demonstrate an adequate understanding of consent forms[134 135] and often do not even understand the meaning or implications of randomisation[136]. A survey assessing the attitude of the community towards consent for research in critically ill patients who lacked decision-making capacity found that most were comfortable with waiving and deferring their consent for a hypothetical low-risk scenario[137]. Another survey involving former ICU patients demonstrated that most were agreeable or neutral about potential enrolment in hypothetical research using delayed consent[138].

Current regulations on delayed consent:

In this emergency setting, it would be reasonable to say that consent, if taken, is of doubtful value. Informed consent from AMI patients cannot be seen as a contract between equal and autonomous parties. Evidence suggests that any prolongation of this process is likely to do more harm by delaying treatment and increasing the risk of mortality and morbidity in these patients. Some may question the ethical stance of burdening a patient in the throes of an AMI with the requirement for a snap consideration of an inevitably complex decision process. They will not be afforded adequate time or resources but are expected to reach a considered conclusion and respond accordingly.

For the above reasons, options of waiver of consent and delayed consent have been allowed by regulatory bodies. The Food and Drug Administration's (FDA) 'Final Rule' permits an exception from informed consent requirements for emergency research in life-threatening situations [139 140]. This has been adopted by the Department of Health and Human Services (DHHS)[141]. At the end of 2006, the UK issued an amendment to

the clinical trials directive to permit randomisation without consent in emergency situations with ethical committee approval [142]. The 2008 update of Declaration of Helsinki also permits waiver of consent and deferred consent for research in life-threatening conditions[120]. With delayed consent, patients are included in the trial without initial discussion. At a later stage, consent is requested from the patient or their representatives. Delayed consent has been accepted as a reasonable alternative in emergency situations and is preferred over a complete waiver of consent [143-145].

Under the Common Rule in the Code of Federal Regulations, institutional review boards can waive or alter the requirement for obtaining informed consent when the following criteria are met: "(1) the research involves no more than minimal risk to the subjects; (2) the waiver or alteration will not adversely affect the rights and welfare of the subjects; (3) the research could not practicably be carried out without the waiver or alteration; and (4) whenever appropriate, the subjects will be provided with additional pertinent information after participation."

Accessing a substitute decision maker:

The need for immediate treatment could make it difficult to access the next of kin or a substitute decision maker in time to enrol the patient into a clinical trial[146 147]. When available, patients' next of kin, relatives or other substitute decision makers can be emotionally overwhelmed from the circumstances of the patient's presenting condition. They have been reported to experience anxiety, depression, and fatigue[148-150] such that they are unable to consider participation of the patient in research[151].

Delayed consent in HEAT-PPCI trial:

In HEAT-PPCI, we adopted the process of delayed consent. The study fulfilled all four requirements of the Common Rule criteria for waiver of consent. Performed in the STEMI setting, the priority was to provide emergency treatment to the patients without any delay. The median door to first device time for the trial patients was 29 minutes. This is in line with normal standard of care in this setting[152]. The median delay from arrival to randomisation was only 5 minutes highlighting the time-critical nature of care delivery.

HEAT-PPCI study is a true representation of modern CER trials where genuine clinical equipoise exists. Both treatments compared in the trial were used in their licenced clinical indication and had a Class I recommendation in this clinical setting at the time of trial initiation [18 153]. Both treatments were in routine use at the host institution and most parts of the developed world prior to the trial commencement. During the trial, both agents were administered only during the index procedure. There was no long term or on-going therapy. Apart from the selection of the anti-thrombotic agent by randomisation, no other aspect of clinical care was affected. Patients were unlikely to have a preference of one medication over the other. It was also unlikely that the process of obtaining specific consent would have served the patient in any meaningful way.

The study received full approval from the National Research Ethics Service (NRES), UK. The strategy was also reviewed and approved by two other independent national bodies, the Confidentiality Advisory Group (CAG) and the Medicines and Healthcare products Regulatory Agency (MHRA). Furthermore, the process was approved by the patients' research representative group at the host institution called the Service Users Research Endeavour (SURE) group. A data safety monitoring committee was also in place to detect any possible excessive harm caused by either of the study treatments.

Trial medication already established in clinical practice:

It has been argued that consent might not be necessary in some pragmatic comparative effectiveness research trials (CER) [154] if the study has no apparent effects on the risks or burdens that patients otherwise face in clinical care and the interventions do not differ on matters of importance to patients. A pre-requisite for this would be a mature health care system with ethically robust oversight policies and practices. The obligation to seek specific consent for research should depend on the risk–benefit ratios of the intervention and the alternatives [155]. We should consider the odds for a patient to have a rational preference between two well-matched treatments already widely used in clinical practice in the same setting. Patients with STEMI following the PPCI treatment pathway have almost no control on the treatment options provided to them including the choice of the hospital or the medical team.

Procedural preferences like route of arterial access, use of adjunctive therapies, stent selection depend on the habits of the operators.

The HEAT-PPCI experience with delayed consent:

The strategy of delayed consent was subject to a rigorous clinical evaluation in a contemporary clinical setting with a favourable response from clinicians and colleagues. During the recruitment phase of the trial, the research team were supported by a full-time patient representative whose task was to assess and review trial conduct as a patient advocate. The most powerful endorsement of the method is to be found in the response of the near 1800 patients who engaged in the delayed consent process. All but three gave full, informed and written consent. This favourable opinion was further confirmed, even after a period of further reflection, with near-complete engagement in the process of data collection at 28 days. This overwhelming positive response to the adoption of delayed consent has also been seen previously in NICE-SUGAR trial[122]. A survey examining the opinions of actual participants in NICE-SUGAR trial regarding the process of delayed consent showed that 95.6% of respondents would have consented to participate in the study if asked before enrolment[156].

The option of declining participation:

The refusal rate in HEAT-PPCI is much lower than other randomised trials in STEMI. Where studied, these rates have been found to be in the range of 10-15%[51 157 158]. A patient may decline participation in a study even in an emergency setting. This may be due to the need for seeking simplicity in that situation or refusal to make a choice due to lack of information and time available to them. If for any reason, a patient has a formed belief that he or she does not want to be a part of a research venture, then we deny them the right to decline, at least in the acute phase. Failure to mention the research process upfront takes away that right of refusal from the patient. This is a limitation of the process of delayed consent. Arguments have also been raised that not mentioning the research upfront may reduce the perception of transparency and may reduce the trust of patients and public in provision of medical care [159]. Looking specifically at HEAT-PPCI, the clinical course of the patients in the acute phase had not

been disadvantaged by being a part of the trial and they had the option to opt out at the consent phase.

Alternatives to delayed consent:

Other modified versions of informed consent have also been used in emergency research. The EUROMAX trial in the setting of STEMI, used 'abridged consent'[16]. All patients initially provided a brief written or oral consent in an ambulance or a non-PCI hospital before administration of the trial related medication. This consent was subsequently confirmed by a more formal final written informed consent. The TASTE trial adopted a similar strategy with initial oral consent which was confirmed with a more detailed written version within 24 hours of randomisation[51]. IMMEDIATE trial, performed in the same setting utilised a quick assent with a paramedic reading an information card to the patient prior to randomization. Full written consent was obtained once the patient was stabilized at the hospital[157]. Other strategies like informed refusal or 'opting-out' have also been described. Following a brief verbal description of the trial, the patients are given the option to opt out or refuse participation[159].

Delayed consent: The final word:

The approach in HEAT PPCI should not be seen as a general endorsement of a delayed consent methodology. We decided it was the most appropriate option in the special circumstances of this trial. Arguments have been put forward that it would have been unethical to have done the study differently[160] and that attempting to get consent from patients would have increased the risk of harm.

We do not advocate the method of delayed consent as a tool to assist with rapid recruitment or a method of convenience. However, if used in an appropriate setting, it could have additional benefits of faster enrolment of a more 'real-world' population. It would make the research process more simple and efficient encouraging more trials to be undertaken in the critical care setting.

Patient deaths before being approached for consent:

Despite recent advances in the treatment of STEMI, this condition remains one of the leading causes of in-hospital death[161]. The 30 day mortality rate for STEMI patients having PPCI as the primary management strategy is 5%[162]. The hazard is at its greatest during the in-hospital stay and most of the deaths occur during the acute phase[163]. At Liverpool Heart and Chest Hospital, the in-hospital (0-5 day) mortality for PPCI cases is 4% - a figure that is typical for UK centres. We have observed similar figures for the patients recruited for HEAT-PPCI. Out of the 800 patients recruited so far, we have encountered 30 deaths. 18 (60%) of these died during the acute phase before we were able to approach the patient for consent.

Consequences of not including deaths without consent:

As an all-comers trial, we are anticipating the 28-day event rate for the composite primary outcome to be approximately 7.5%. Death is the most important component of the primary outcome measure (MACE – Major Adverse Cardiac Events) and is expected to constitute two thirds of all events. If we are unable to include 60% of deaths, we will lose approximately 40% of MACE. This will reduce statistical power and render the results flawed and invalid[143] particularly if there was a time-dependant effect of one agent over another with excess of deaths in one arm.

Misleading results:

It has been shown that exclusion of data of patients who die before deferred consent jeopardises the study results[164]. This problem is not new and has been faced in many research studies in the acute setting [164].

Consequences of stopping the trial early:

If we are not allowed to include the patients who die before consent, the trial will lose its integrity. To avoid publishing potentially inaccurate and misleading results, the trial will have to be stopped on ethical grounds.

HEAT-PPCI is the first ever trial studying a head to head comparison of bivalirudin and heparin in the PPCI setting. The results of this trial could potentially change national

and international guidelines for the management of STEMI. If we stop the trial early, this important clinical information would not be available for future clinical use.

There are more significant ethical issues associated with termination of incomplete studies[165]. It leads to waste of time and efforts put in by the already recruited and by the investigators. It would be ethically unfair to the patients already recruited if the trial is stopped early and this could lead to frustration and concern. Jeopardizing studies by not using data is likely to reduce patients' participation in the future.

Other important considerations specific to HEAT-PPCI:

No experimental therapy:

Both treatments being compared in this study are established and are in routine use throughout the developed world. Both agents are included in the national[166] and international guidelines[153 167] for STEMI management. Moreover, both have been in routine use at the host institution. The patients would receive one of the two medications anyways even if they are not part of the trial.

Single administration of trial medication

Randomisation controls the choice of antithrombotic therapy used during the index procedure. This is a single administration complete within minutes of randomisation. The participants do not receive any other trial related intervention.

The purpose of 'Delayed Consent':

Participation in the trial does not affect the participants' medical or nursing management at all. By the time the patients have their ethically approved delayed consent, all trial related interventions are over. The delayed consent serves three important purposes: (a) providing the participants with study information (b) taking permission for the data to be used (c) taking permission for 28-day follow up contact. If the participant dies during the acute phase, the 28-day follow up becomes not applicable. Using data will not harm the patient or relatives, provided that appropriate confidentiality and privacy measures have been applied.

Currently use of mortality data:

Use of early death in CONSORT reporting:

CONSORT (Consolidated Standards of Reporting Trials) statement is considered as the most prominent guideline for reporting of RCTs[168]. Clinical studies are required to present the 'CONSORT' trial profile flow diagram as part of their report. The reporting of patient deaths before being randomised or consented is an integral part of this flow diagram. We have provided a few examples in Annexe A at the end of this report.

Publishing mortality data online:

Liverpool Heart and Chest Hospital (and many other PCI centres) publishes named operator PPCI mortality figures online as part of routine clinical governance activity. This data is also used for several internal reviews and audits.

Use of data by BCIS and CCAD:

Mortality statistics and data about angioplasty patients are freely available via British Cardiovascular Intervention Society (BCIS)[24 169]. It is a legal requirement for all deaths in the UK to be registered to the NHS Central Register[170]. All UK PCI centres are bound to provide angioplasty mortality information to the BCIS Central Cardiac Audit Database (CCAD). The PPCI outcomes especially mortality are subject of monthly reviews. This information added to the national database is tagged with the patients' NHS number which is patient specific identifiable information[169]. BCIS and the NHS Information Centre encourage this data to be used in audits and for research purposes[170].

Even if we exclude the data for the patients that die before consent in the context of HEAT-PPCI, this data will be submitted to the BCIS CCAD. Once included in CCAD, this data will be used in the future for audits and may be used for other research purposes.

Provision from the declaration of Helsinki:

The Declaration of Helsinki does not require discarding data if deferred consent was not obtainable because the patient died[171]. If it is not possible to obtain consent, the Declaration of Helsinki allows research to proceed if the condition that prevents obtaining the consent is a necessary characteristic of the research population[171] .

Provisions from Section 251 of the NHS act 2006:

Section 251 of the NHS Act 2006 (previously section 60 of the Health and Social Care Act 2001) permits the common law duty of confidentiality to be set aside so that information which identifies patients can be used without their consent[172]. The Ethics and Confidentiality Committee (ECC) advises the Secretary of State for Health on whether applications for support under section 251 of the NHS Act 2006 should be approved. The following criteria have to be satisfied to obtain section 251 support: (a) The reason for using the information has to be for the purpose of improving patient care or in the public interest; and (b) It has to be for a medical purpose; and (c) The purpose cannot be achieved using de-identified data; and (d) Seeking consent for the use of identifiable data is not practicable. The ECC has already provided support to a variety of research projects[173 174]. We fulfil the criteria to apply for section 251 support. If the need arises, we could request the assistance of the Regional Ethics Committee (REC) in the application to ECC.

Consequences of contacting next of kin or legal representative for consent in dead patients:

In response to our application for a protocol clarification regarding mortality data, the REC has advised us to contact the relatives or legal representatives. If not possible, then the patients' data should be excluded from the trial.

STEMI is a sudden, dramatic and an unexpected life-threatening emergency. The relatives of these patients are not prepared for the potential death of their loved ones. In the event of the patient's death, it would be both inappropriate and insensitive to approach the distressed and grieving families. Confronting bereaved relatives represents additional burden[175], which healthcare providers have the duty to relieve or prevent[176].

We have consulted the patients' representative group at the host institution called the Service User Research Endeavour (SURE) group. SURE group comprises of previous and current patients at Liverpool Heart Chest Hospital and reviews the research projects from the patients' perspective. The group also has acknowledged the potential problems faced by the grieving relatives. They have advised us to refrain from this practice as it is likely to bring more harm than good.

Unprecedented zone:

HEAT-PPCI is the first ever randomised controlled trial to adopt the method of delayed consent in the setting of an acute myocardial infarction. We have successfully applied this approach and have received very encouraging results. On the basis of rationale discussed above, we feel that we should be allowed to include the data for patents that die early before being approached for consent. We apologise that this intention was not more overtly stated in the original protocol submitted to REC. If we are to maintain the validity of our study, we believe that this is the right approach.

Conduct 1 - Recruitment of all eligible patients:

Impact of selective recruitment:

A well-designed RCT mirrors the scientific rigour of classic experimentation and is considered the 'gold standard' design in clinical research[177]. A valid criticism of most contemporary RCTs is that the patients recruited are not truly representative of the general population[44]. Current cardiology studies[16 178-183] may recruit as few as 2 - 10% of the general patient population, presenting with the diagnosis of interest. Sick, frail, the elderly, patients with lower socio-economic status or patients from ethnic minorities are less likely to be recruited in trials[184]. Investigators are also reluctant to include patients that are homeless, have cognitive or mental health issues or if there is a language barrier. This may simply be because the researcher cannot be sure that the patient will adhere to a treatment plan and respond to follow up. This selective accrual undermines the inferences we deduce from the study results[185 186]. There is now widespread agreement that problems with the applicability of published results to routine clinical practice (often called generalisation) is one of the most substantial limitations of evidence-based practice derived from modern randomised trials.

Recruitment in HEAT-PPCI:

Recruitment of a truly representative 'all-comer' population would present a considerable challenge. The exclusion criteria in HEAT-PPCI were kept to the minimum possible. As a result, 97% of patients that entered the cardiac catheter laboratories during the recruitment period for a procedure were found to be eligible for recruitment. All patients eligible for recruitment were randomised in the trial. HEAT-PPCI may be the first ever major clinical trial to include 100% of the eligible population.

Steps taken to maximise recruitment rates:

The recruitment in HEAT-PPCI was performed 24 hours a day, seven days a week, by staff providing complex interventional care in a high risk and emergency setting. This required meticulous planning, motivation, training and education.

1. Prior to the commencement of the trial, study specific lectures were delivered to the clinicians, nursing staff and co-ordinators. Educational posters were designed and displayed in key locations. These location-specific posters covered information regarding the process of randomisation, eligibility criteria and answers to the 'frequently asked questions'.
2. We used various methods and tools to increase awareness of the study before and during the recruitment phase. These included designing a project logo, distribution of trial specific merchandise to staff and study promotional posters.
3. The randomisation process was quick and simplistic and all relevant staff was provided with multiple training sessions. The CRF had a two part design. Only the first part was completed by the on-call team and captured only minimal acute-phase information. It had user-friendly design and easy-to-follow instructions.
4. The research team developed a good working relationship with all relevant members of staff. This resulted in a greater level of motivation and engagement in trial related activities across the host institution.
5. Ongoing support was provided in the form of regular email updates and newsletters. Training sessions were organised throughout the recruitment phase for newly employed staff.

The process of delayed consent can also allow more comprehensive recruitment to studies in the emergency setting. Investigators may find it difficult to approach patients with significant pain or haemodynamic instability. This may introduce selection bias, favouring the inclusion of patients at lower risk. This may explain the observation that the mortality rates reported by contemporary AMI trials are lower than institutional and national norms declared by key registries[15 16].

Conduct 2 - Follow up:

Importance of comprehensive follow up:

Even an otherwise robust RCT can suffer with substantial loss to follow up. Incomplete follow up can bias the results of a trial if patients who drop out are different from those who complete follow up or if there are differential dropout rates between study groups. There are no universally agreed criteria for acceptable follow up rates. Some researchers suggest that more than 5% loss starts to introduce problems, whereas a loss greater than 20% potentially poses serious threats to the internal validity of the trial[187].

Follow up in HEAT-PPCI:

Successful recruitment of an unselected 'real world' population has the potential to make the processes of study treatment compliance and subsequent follow up much more challenging. Investigators and patients are denied the opportunity to decline participation on this basis. Generally, in RCTs, a higher proportion of patients would be cooperative, compliant, motivated and effective communicators. These patients are more likely to respond to follow up contacts. In a true all-comers trial, with no initial consideration of the nature and demands of the research, achieving comprehensive follow up is more demanding. In HEAT-PPCI, we included patients with ages ranging from 27-102 years, subjects with home addresses in four continents or with no fixed abode, patients that had mental health issues, dementia or other special needs. The collection of comprehensive follow-up in this population proved a substantial and unique challenge.

Strategies implemented to minimise loss to follow up:

We adopted several specific measures to minimize loss to follow-up:

1. The trial design was simplified. Patients were not required to undergo or attend for any trial-specific procedures after the index intervention.
2. From the time of first contact, usually during the informed consent process, the research team sought to build a positive relationship with the patient. This required good interpersonal skills. An adequate, clear and concise explanation

was provided so that the participants could identify with and understand the importance of the trial.

3. Patients were given trial-specific, credit card sized 'passports' that would fit in their wallets. These passports contained basic study information and prompted patients and their physicians to record relevant information in the event of hospital admission during the follow up phase.
4. Prior to all direct contact methods, a patient mortality check utilising the PAS (patient administration system) was performed to ensure that deceased patients were identified before direct contact was attempted.
5. Patients were contacted primarily by post, telephone email or text, taking into account personal preference. The postal contact letters included a stamped addressed reply envelope. If the above methods failed, the investigators attempted to contact the patient by recorded delivery letter.
6. We established telephone contact using several attempts at different times and on different days. Patients or alternate contacts were also phoned during evenings and weekends if necessary.
7. Should the above methods failed, patients were contacted during a future admission or attendance to an outpatient clinic (if applicable).
8. For non-responders, their GP was contacted to provide any available information.

We used assertive tracking and the non-respondents were approached on multiple occasions until a response was achieved.

Hospital Episode Statistics (HES):

HES scheme is a government record based system that tracks all admissions, outpatient and emergency attendances within the NHS in England[188]. At the end of the follow up period in HEAT-PPCI, a hospital episode statistic check was run on all patients included in the analysis. It identified all recorded episodes of care provided to a patient in the 28 days following their randomisation. All patient reports were cross checked against HES.

With rigorous and relentless application of these approaches, we have achieved exceptionally high rates of follow-up (>99.5%) and have set a benchmark for future emergency true 'all-comers' trials.

Conduct 3 - Open label study design:

HEAT-PPCI adopted the open label study design. A blinded study in this emergency setting would have been associated with many practical difficulties and substantial additional expense.

- Bivalirudin is reconstituted from a powder form and requires a continuing infusion. Heparin is supplied as a liquid and given as a bolus. Blinding could have only been maintained if all patients were treated with both administration strategies (one the active and the other the placebo).
- Each subject would have required a patient-specific drug pack containing the treatment reflecting that allocated at randomisation, and a bail-out option providing the alternative agent. The packs would have also needed paired provision of additional agents for additional 'top-up' administration - based on Activated Clotting Time (ACT) evaluation.
- Resulting ACT values are different for the two agents and ACT measurement would demand blinded assessment by specific staff who would then control additional dosing.
- Drug doses for both heparin and bivalirudin are weight adjusted. Packaging of drugs to maintain blinding and administrating regimens are even more complicated if weight adjustment for doses is required.
- All of these measures would have to be applied by routine clinical staff in an emergency treatment setting, in which treatment delay is known to be associated with less favourable outcomes.

Despite an open label design, we do not think that the study has been compromised by systematic bias. We did not observe any differences, between the two trial groups, in the use of oral or systemic anti-platelet therapy, in the conduct of PCI revascularisation or in the provision of secondary prevention medication. Almost all key outcome measure events were overt clinical events with clear diagnoses based on acute imaging and other clinical findings. All primary outcome events were adjudicated by individuals

blinded to the treatment allocation. It is important to note that other key trials in the same setting also had open label design[15 16].

Conduct 4 – Data Validation and Accuracy Checks:

Validation against Clinical Coding Department:

A quarterly audit was performed to assess data collection accuracy and validate it against the records of the Clinical Coding Department. The Clinical Coding Department at the host institution has a very comprehensive and reliable database. The audits validated all trial outcome measures and Serious Adverse Events (SAE) against this database. The results showed are shown in table 16. Anomalies were investigated and HEAT-PPCI CRFs were modified as required.

	Audit 1 (Feb-Apr 12)	**Audit 2** (Aug-Oct 12)	**Audit 3** (Feb-Apr 13)	**Audit 4** (Aug-Oct 13)
Clinical coding data versus study data (% accuracy)				
All outcome measures	100	99	100	100
SAEs	98	97	99	100
Case notes review versus study data (% accuracy)				
All data	96	98	97	97
All outcome measures	100	99	100	100
SAEs	100	99	98	100

Figure 19 Results of validation audits against Clinical Coding Department records and case notes

Validation against Clinical Audit Department:

A quarterly audit was performed against the data collected by the Clinical Audit department. This mainly comprises of cross checking the fate of all PPCI activations for the host institution.

Audit of case notes:

6 monthly SHO led audits of the patient case notes to cross check the accuracy of all types of data collection have also been programmed into the schedule.

Data validation at the time of transcription:

At the point of data input into the Access database (section 10.5), we integrated various checks into the system to minimise typing errors and entry of out-of-range data. One example of this is setting logical ranges for blood tests, dates and times of events.

Chapter 6 - Describing Activity in Primary Percutaneous Coronary Intervention: An Exploration of Denominators. From the **HEAT** Trial - A **S**ystematic **E**valuation of PPCI **A**ctivations in **L**iverpool, **E**xplaining **D**enominators (***HEAT-SEALED***)

Abstract:

Background:

The provision of PPCI in the emergency management of STEMI is expensive and resource intensive. Accurate data collection is essential not only for outcomes analysis but also to characterise activity and performance for regions, centres and operators. Inconsistency in the use of denominators currently creates problems in data interpretation.

Objective:

To establish a system of denominator groupings, seeking to better describe the range of clinical activity resulting from an unselected series of PPCI activations.

Methods:

The HEAT-SEALED pathway designates a key denominator group (n1-n9) to each phase of PPCI activity and identifies a final 'destination category' for each patient leaving the pathway. HEAT-PPCI is a true 'all-comers' trial and provides an ideal platform to collect data for prospective validation of the pathway. We report data from all PPCI activation events for the HEAT-PPCI trial.

Results:

Our findings demonstrate important differences between the sizes of key PPCI denominator groups and hence the potential for variation in reported outcomes depending on the denominator category selected. The main figures are: All activations (n1 = 2490); all suspected MI cases (n4 = 1940, 77.91%); patients in whom angiography was performed (n5 = 1904, 76.46%); cases in which diagnosis was confirmed with a probable culprit lesion (n6 = 1657, 66.54%) and cases with complete PCI success (n9 = 1441, 57.87%).

Conclusion:

The HEAT-SEALED pathway offers a practical and comprehensive solution to the problem of describing denominators in STEMI and PPCI. Routine application would facilitate a more consistent and precise description of activity and outcome.

Introduction:

PPCI is now considered the gold standard treatment for STEMI[13 14]. PPCI activity is expanding as this becomes the dominant treatment modality for emergency reperfusion. In the 12 months between April 2011 and March 2012, 32,439 patients in UK were recorded as having a STEMI event[189]. Reperfusion treatment was delivered to 70% of these patients and of these, 95% had PPCI as their index therapy[189] (approx. 330-380 PPCI procedures/million[190]). In the US, according to the CathPCI registry, the number of STEMI patients receiving PPCI is exceeding 100,000 per year[191-195] (estimated 300-350 PPCI procedures/million[14 193 196]).

The provision of a high quality PPCI service is a complex and demanding task. This involves public health education and a number of different aspects of emergency care provision – with several, otherwise disparate, agencies and teams involved in delivery. Public health education seeks to encourage an earlier 'call for help' to reduce the time interval between the onset of symptoms and presentation. Improvements in the response of Emergency Medical Services (EMS) and the receiving medical teams should help reduce the delays associated with the move to an appropriate facility and the provision of reperfusion therapy[190]. There appears to be a relationship between the quality of service and more favourable outcomes[14 189 197-201]. This has prompted

great interest in improving systems and performance with audits and analysis, often co-ordinated at national level[152 189 202].

There is a self-evident need to record accurate data to facilitate clear reporting of patient risk profiles, presentation characteristics, procedural data and outcomes. There is also a need for consistency in reporting the performance and activity levels of different regions, PPCI centres and individual operators.

Currently, there is no consistent and agreed system to describe denominators for STEMI. For instance, of all those suffering STEMI, a proportion will die of cardiac arrest and never reach hospital. Those who do reach hospital may be unsuitable for reperfusion therapy, and those who are suitable may be taken to the cardiac catheter laboratory, but may not require PPCI for clinically appropriate reasons. It is therefore difficult to analyse PPCI activity and outcomes as authors may choose to use different denominators for reported figures. To demonstrate high volume activity, one might choose to quote the total number of PPCI activations at a centre. To reflect more favourable mortality figures, one might restrict the patient population to those with successful reperfusion. These 'floating denominators' can make it difficult to interpret and compare reports of PPCI activity and outcome.

Methods:

The HEAT-SEALED (HEAT Trial – Structured Evaluation of Activations in Liverpool, Explaining Denominators) pathway was initially designed in Nov 2010, from first principles, on the basis of accumulated clinical experience. It became a part of the documentation of the integrated care pathway for PPCI patients at Liverpool Heart and Chest Hospital (LHCH) in 2011. In the HEAT-SEALED pathway, the first column of the flowchart designates a key denominator group (n1-n9) to each phase of the PPCI pathway. The second column describes the flow of clinical activity associated with each step. The last column identifies a possible final destination category for each patient leaving the pathway and operators must choose the option that best characterises their patient.

HEAT-PPCI is a true 'all-comers' trial and all PPCI pathway activations are assessed for eligibility and documented by trained research staff. The trial therefore provides an

ideal platform to collect data for this prospective study. For HEAT-PPCI, patients were recruited from 7th February 2012 to 20th November 2013. We report data from all activation events of the LHCH PPCI pathway during this period (n1 = 2490).

The PPCI service was activated at the host institution either directly by ambulance services or by local referring hospitals. This regional hospital referral network comprised 11 hospitals located in the Merseyside and North Wales serving a catchment area of 2.5 million people. In the peripheral centres, doctors working in the emergency department were responsible for the diagnosis of STEMI and activation of the PPCI pathway. For direct ambulance admissions, paramedics were responsible for this process. Both services were independent in decision making and did not require input from the on-call team at the host institution.

The diagnoses of inappropriate CLAs (non-cardiac diagnosis, non-ischaemic cardiac diagnosis and ACS suspected but not ST elevation) were made by the attending cardiologists at the host institution. This was based on the patients' clinical history, examination and the findings of ECGs and echocardiography. STEMI was defined as ongoing cardiac sounding chest pain along with the following ECG changes: ST-segment elevation measured at the J point, found in two contiguous leads and be ≥2mm in precordial leads or ≥ 1mm in limb leads. Posterior STEMI was defined as new onset ST-segment depression in leads V1–V3 along with positive R wave in leads V1-V3 (or concomitant ST-segment elevation ≥1 mm recorded in leads V7–V9). New onset persistent Left Bundle Branch Block (LBBB) was also considered as one of the criteria to activate the PPCI pathway. Pericarditis was defined as a combination of two or more of the following: a) Retrosternal or left precordial chest pain (may be radiating to the trapezius ridge, pleuritic in nature and/or varying with posture); b) Presence of pericardial rub on auscultation; c) ECG showing concavely shaped ST-segment elevation (+/- PR segment depression); d) Evidence of pericardial effusion on echocardiography.

HEAT-PPCI study records have been compared against the data collected by the hospital clinical quality and audit department. The audit team is responsible for the submission of data to the UK national registries for PCI and acute myocardial infarction. We have carefully scrutinised all data for any mismatches between HEAT-

PPCI case record form and hospital audit system records. In the event of such a mismatch between the two datasets, or if the data were not available in the audit department records, the data were validated against the patient's case notes.

Results:

Figure 20 shows the HEAT-SEALED pathway along with a summary of the results. Of all PPCI activations, 2377 (95.46%) were considered 'genuine' (n2) – representing confirmed activations for the planned provision of index, emergency reperfusion in cases of suspected STEMI. The cases that were not classified as genuine mainly comprised non-PPCI emergencies (e.g. rescue PCI) using the PPCI activation system. The total number of cases arriving at the PPCI centre (n3) was 2341 (94.01%). 'Dropouts' before arrival resulted mainly from a change in patients' clinical status or from a change in the suspected initial diagnosis, resulting in cancellation of the activation call.

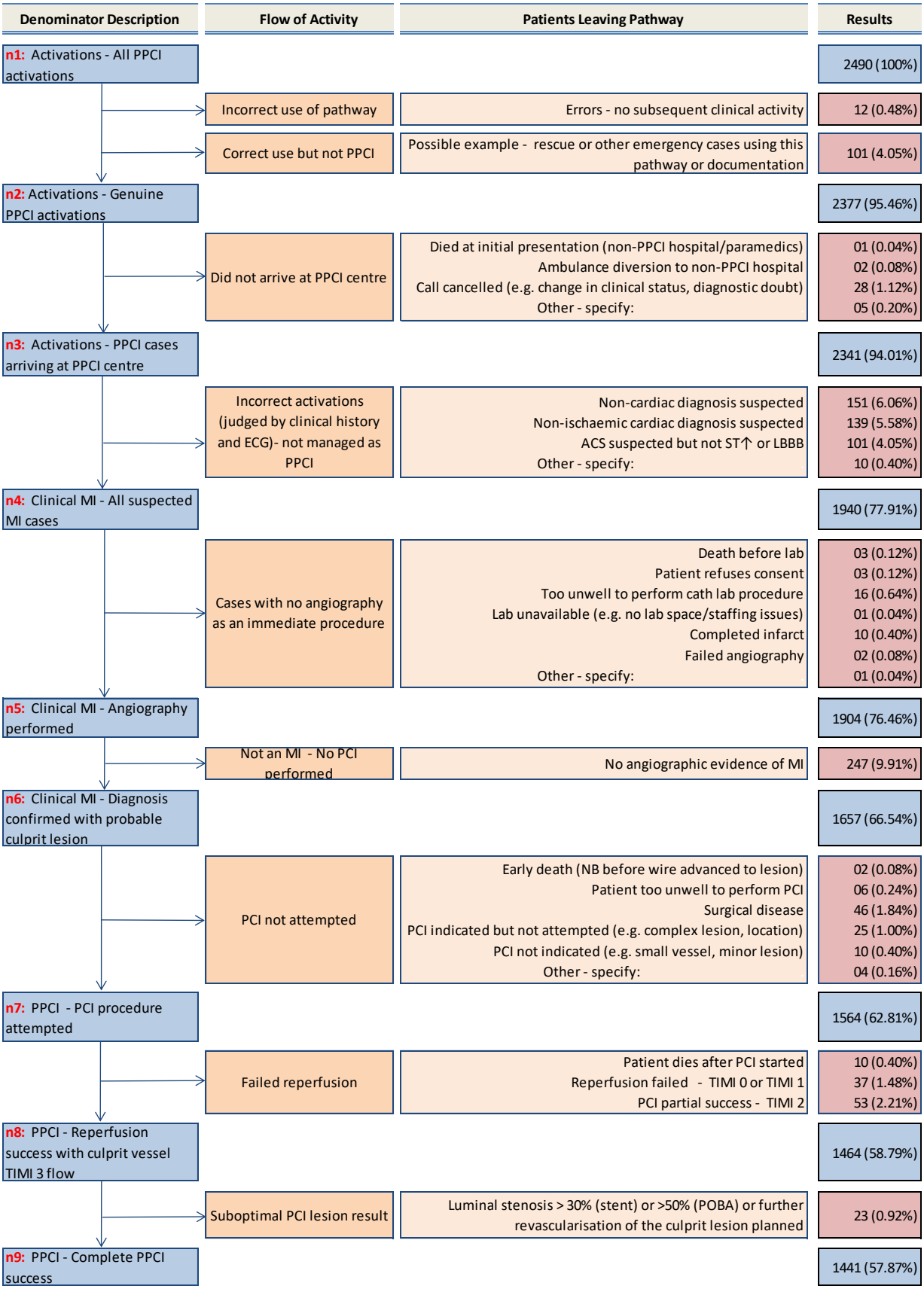


Figure 20 HEAT-SEALED pathway results

The number of patients that reached the PPCI centre, but were considered as incorrect activations on clinical grounds was 401 (16.1%). The breakdown for these cases comprised non-cardiac diagnoses (e.g. pulmonary embolism, chest infection, musculoskeletal chest pain and GI related problems), non-ischaemic cardiac diagnoses (mainly pericarditis) and cases in which an acute coronary syndrome (ACS) was suspected but the ECGs did not fulfil the criteria for STEMI.

The total number of cases that were deemed appropriate to proceed to the catheter laboratory was 1940 (77.91%) (n4) and coronary angiography was performed in 1904 (76.46%) cases (n5). The reasons for patients not being able to proceed to angiography were mainly clinical (3 patients died before entering the lab, 16 were too unwell to have angiography, 10 had already completed the infarct and 2 had failed access to coronaries). The breakdown for the 16 patients that were considered to be 'too unwell' to have angiography is as follows: 11 had acute left ventricular failure, 2 had acute respiratory system pathology and 3 were deemed very frail for the procedure. The diagnoses and final decisions were made by the attending cardiologists.

Of the patients that had angiography, 247 (9.91%) did not have any angiographic evidence of acute myocardial infarction. Thus, the diagnosis of myocardial infarction was supported by an angiogram with identification of a probable culprit lesion in 66.54% (1657) of total activations (n6). PCI was attempted in 1564 (62.81%) cases (n7). The main reasons for not having PCI were the presence of surgical disease or PCI being judged impractical. The total number of patients who had reperfusion success with TIMI III flow in the culprit vessel was 1464 (58.79%) (n8). Despite achieving TIMI III flow, 23 (0.92%) cases were deemed to have suboptimal PCI result. The reasons for this include presence of residual stenosis of 30% or more following stent implantation or 50% or more following balloon angioplasty (POBA), or if further revascularisation of the culprit lesion was planned. Complete PCI success (n9) was achieved in 57.87% cases.

Discussion:

Data collection for PPCI patients:

There has been considerable and rapid growth in PPCI activity over the last decade. Developing standards has been difficult as, until recently, only limited data have been available. Currently, there are two national systems collecting data for STEMI patients in UK. These are British Cardiovascular Interventional Society Central Cardiac Audit Database (BCIS-CCAD) and Myocardial Infarction National Audit Programme (MINAP). For BCIS-CCAD, data are collected mainly for the patients that undergo a coronary intervention[169] whereas MINAP is responsible for collecting data for all acute coronary syndrome events, including STEMI patients[189]. There are variations between the two systems in the way data are collected and analysed. Currently, neither system includes any robust mechanism for identifying the outcome of all PPCI pathway activations. To the best of our knowledge, other large registries in EU and US also lack a comprehensive structure to interpret and demonstrate the outcomes of all PPCI activations[192 203-206].

Potential variation in PPCI reporting:

The results of this study show a considerable absolute difference between various PPCI denominators. Patient numbers are eroded at each step. The number of successful PCI cases (n9) is only 57.87% of the total number of activations (n1). The potential for the presentation of misleading or inconsistent data is obvious.

Using the results of our study, one could potentially report on PPCI performance using n8/n7 (achieving TIMI III flow in all patients in which PCI was attempted), which would give a 'success rate' of 93.6% (1464/1564 x 100). However, if n9/n7 (achieving complete success in all patients in which PCI was attempted) was used, the 'success rate' would be 92.1%, and this would fall further to 86.9% if n9/n6 (achieving complete success in all patients in which a culprit lesion was confirmed) is used. This problem of selective rate reporting can only be solved by using the correct and appropriate denominator.

Evaluating the performance of a PPCI service:

The HEAT-SEALED pathway has given us an efficient mechanism to evaluate the performance of PPCI service provision. Every individual denominator will help us evaluate different parts of the system. The case numbers at n2 (all genuine activations) will provide the denominator for the overall assessment of the service. Any consideration that integrates outcomes associated with the emergency diversion of some patients, with a non-cardiac diagnosis, to a cardiac unit will use this figure.

We can calculate the dropout rate at each step to identify the discrepancies in practice between operators and institutions. The ratio n4/n2 will inform discussions about the diagnostic performance of the EMS and will be affected by local protocols and thresholds to initiate a PPCI activation.

A consideration of n5/n4 may provide information about the threshold of an institution or an individual operator to perform angiography in this emergency, demanding and often high risk setting (perhaps suggesting some cardiologists being too bold or too cautious). Review of n6/n5 may illuminate differences in the use of angiography as a means of 'ruling out' infarction in cases with diagnostic uncertainty.

The ratio n7/n4 may provide some indication of the willingness of the operators to attempt PCI reperfusion and n9/n7 or n8/n7 will, to some extent, be a reflection of technical skills and other factors related to the performance of PCI.

More detailed information is of course available at all stages of the pathway. For example, the breakdown of dropout between n5/n4 could help to identify deficiencies in the provision and administrative performance of services (e.g. how many patients failed to have a procedure due to unavailability of lab space or staffing issues).

Identifying Inappropriate Catheterisation Laboratory Activations (CLA):

A number of other authors have noted a 'false positive' or inappropriate CLA rate of 10-36%[207-209]. The dropout rate between PPCI pathway activation and patient receiving angiography can be reduced to much lower levels (<1%) if there is communication with the PPCI centre prior to activation of the pathway[207 208 210 211]. In contrast, rates are higher if there is no prior contact with the PPCI centre[209 212]. In the UK, the guidelines

suggest that the PPCI pathway should be activated in the periphery without involvement of the cardiac centre and Liverpool has adopted this approach[190].

Inappropriate CLAs represent a significant challenge for a PPCI system. Higher rates can lead to misuse of scarce and expensive resources and (in the absence of dedicated staff, working a full shift system) may result in the on-call personnel becoming tired and demoralised. In theory, a patient with a genuine myocardial infarction event may have their reperfusion delayed if the PPCI facility and team are engaged in a procedure being performed mainly to confirm a suspected false activation.

ST segment elevation on the presenting ECG can be difficult to interpret and can be associated with conditions other than myocardial infarction[213-220]. Correct ECG analysis can reduce the inappropriate CLA rate by 45%[208]. In our study, 78% (401/514) of all inappropriate CLAs were due to incorrect initial ECG interpretation.

It is important to note however that an attempt to minimise CLA events may result in more 'false negative' assessments by referring staff - with genuine STEMI cases being denied optimum reperfusion. The problem of inappropriate CLAs and the extent of its impact on the system are yet to be quantified with precision. Currently there is no robust system in place to record and analyse the inappropriate CLAs. Use of the HEAT-SEALED pathway could help to address these issues.

Conclusion:

This prospective validation exercise demonstrates that the HEAT-SEALED pathway offers a practical and comprehensive solution to the problem of describing denominators in STEMI and PPCI. More universal application of this system would help us improve the description, analysis and interpretation of service provision, to compare different services and facilitate better practice and improved outcomes.

Chapter 7 – Substudy comparing hospital episode statistics (HES) and direct patient contact to identify outcomes

Abstract:

Background and objectives:

The examination of electronic databases describing hospital episode events could provide an effective and cost-efficient alternative to traditional trial follow-up. The accuracy of hospital episode statistics (HES) data in identifying hospitalisation and individual clinical events is unclear. The aim of this study is to compare HES data with information obtained from direct patient contact in the determinisation of any hospitalisation and in the identification of individual outcome events.

Study participants and design:

Follow-up to 28 days was reported based on information from both direct patient contact and examination of Hospital Episode Statistics (HES). Seventy-three patients died during the index admission and 39 patients remained inpatients at 28 days and were excluded from the analysis. We compared HES and traditional methods for the identification of re-hospitalisation after the index admission and for the identification of key outcome measure events both during the index phase and during subsequent follow-up.

Main outcome measures:

A comparison of readmission rates and clinical events rates at 28 days, as determined by the different methods of follow-up.

Results:

Sensitivity and specificity of the HES method in ascertaining readmissions was 91.6% (95%CI 86.4 to 94.9) and 100% (95% CI 99.7 to 100) which compared favourably to the direct contact method. The sensitivity and specificity of the direct contact method in ascertaining readmissions was 86.8% (95%CI 80.9 to 91.1) and 95.5% (95% CI 94.3 to 96.4). HES identified 75% (6/8) of confirmed readmission MACE with 24 false positives when using physician adjudicated events as the criterion standard.

Discussion:

HES performs better in the ascertainment of a readmission event and provides an effective and cost-efficient method of initial follow-up. When matched to study protocol definitions HES performs less well in the determination of the occurrence of specific clinical events. However, HES does provide an indication of the fate of the patient as perceived by the health care system and thus the health costs borne by the system.

Introduction:

Almost all clinical research demands the tracking of clinical events over time. Loss to follow-up and incomplete or erroneous reporting can compromise the external and internal validity of a trial. Ensuring complete follow-up can present numerous difficulties for study investigators. Traditional methods are often expensive and time-consuming, involving direct contact with each study participant sometimes on multiple occasions over a prolonged follow-up period.

National hospital episode statistics (HES) report information for all patient care delivered in the UK home nation NHS facilities. The data is primarily collected to allow health care providers to be paid according to levels of clinical activity. Each episode of care is identified from the patients' hospital notes and recorded as codes in a centralised database.

To maximise completeness of data, HEAT-PPCI used both traditional methods and hospital episode statistics (HES) data to follow up participants. The objective of this

study is to use the data from the HEAT-PPCI trial to compare the two methods of follow-up used to identify readmissions.

A second objective is to assess the diagnostic accuracy of the HES data in identifying pre-specified clinical events, reported as outcome measures in the study. HES data includes diagnostic and procedure codes as well as dates of admissions and can, therefore, be used to identify specific clinical events. We have compared HES-derived event rates with those reported as meeting the protocol specified definitions following formal and blinded adjudication of the clinical record by two independent clinicians.

Methods:

Patients and Study Design:

HEAT-PPCI trial patients were tracked during their index admission for clinical events, by careful review of case notes, and followed up for 28 days following randomisation.

Comparing the methods of follow-up used to ascertain readmissions:

The primary objective of follow-up in HEAT-PPCI was to establish vital status and the occurrence of any pre-specified outcome measures. This involved identifying all additional overnight admissions during the follow-up period and was achieved by directly contacting each participant to ask if they had been readmitted to hospital. In addition, HES data was requested for each patient and used to identify readmissions. Those who died during the index event or remained inpatients at 28 days following randomisation were excluded from analysis (see Figure 22). Participants randomised into the HEAT-PPCI trial who had both HES follow-up and who also responded to direct contact follow-up were included. Each method of follow-up was compared to a 'gold standard' reflecting the total number of readmissions identified from any source and subsequent confirmation by review of the medical notes.

In HEAT-PPCI, each readmission, identified by either direct contact or HES was confirmed or refuted by reviewing the medical notes. Key clinical information from each confirmed readmission was reviewed by a physician adjudication panel, blinded to treatment allocation and index procedure angiographic results, who would then

establish if outcome events had occurred in terms of specific event definitions declared in the trial protocol.

Follow-up by direct contact was attempted for all participants in the HEAT-PPCI trial. Patients or their relevant care-providers were contacted at four to six weeks following randomisation and were asked if the patient had been admitted overnight to any hospital in the 28 days since their discharge from the index period. Methods of direct contact used included post, telephone or email. Should this method fail on three occurrences, investigators attempted contact by a recorded delivery letter. In case of unsuccessful contact, patients were seen during a future admission or attendance to outpatient clinic, or their general practitioner (GP) was contacted to provide information. The eventual method of contact used was recorded for all patients (Figure 21).

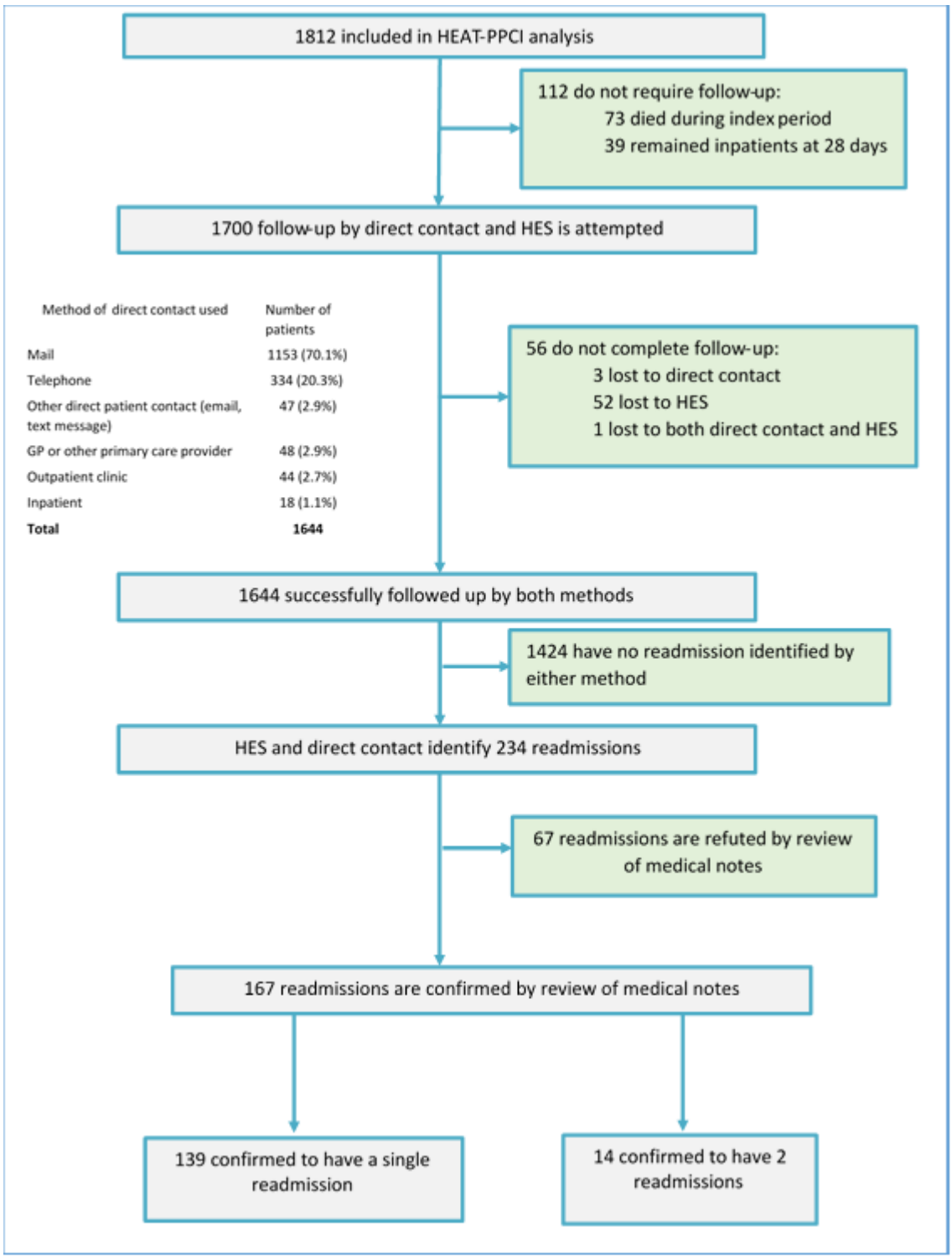


Figure 21 Flow diagram outlining the follow up obtained by direct contact and HES methodology for identifying readmissions

Method of assessing the diagnostic accuracy of HES data:

A patient mortality check utilising the patient administration system was performed to identify deceased patients before follow-up was attempted, so this outcome was not included in this study.

This analysis included all patients who were randomised in the HEAT-PPCI trial and for whom a HES return was obtained (Figure 22).

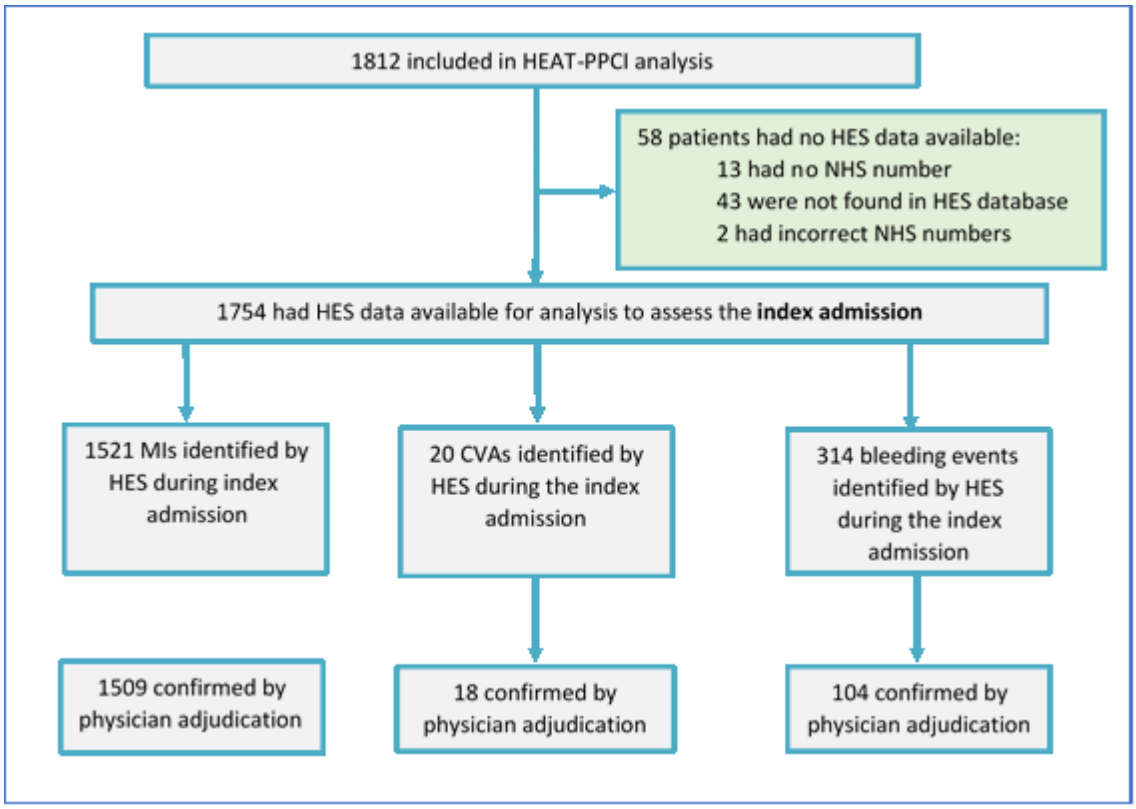


Figure 22 Flow diagram outlining the clinical events identified in the HES data for the index admission.

The HES data was examined to identify clinical codes that indicated the occurrence of both the index MI, any MACE and any bleeding event, during the index admission and the subsequent follow-up period.

To identify all the index MIs and reinfarctions, the relevant ICD-10 codes were used to search the HES database (Table 16).

ICD-10 codes used to identify MIs	**Decoded diagnosis**
I210	ACUTE TRANSMURAL MYOCARDIAL INFARCTION OF ANTERIOR WALL

I211	ACUTE TRANSMURAL MYOCARDIAL INFARCTION OF INFERIOR WALL
I212	ACUTE TRANSMURAL MYOCARDIAL INFARCTION OF OTHER SITES
I213	ACUTE TRANSMURAL MYOCARDIAL INFARCTION, UNSPECIFIED
I214	ACUTE SUBENDOCARDIAL MYOCARDIAL INFARCTION
I219	ACUTE MYOCARDIAL INFARCTION, UNSPECIFIED
I220	SUBSEQUENT MYOCARDIAL INFARCTION OF ANTERIOR WALL
I221	SUBSEQUENT MYOCARDIAL INFARCTION OF INFERIOR WALL
I228	SUBSEQUENT MYOCARDIAL INFARCTION OF OTHER SITES
I229	SUBSEQUENT MYOCARDIAL INFARCTION OF UNSPECIFIED SITE

ICD-10 codes used to identify strokes	**Decoded diagnosis**
I606	SUBARACHNOID HAEMORRHAGE FROM OTHER INTRACRANIAL ARTERIES
I609	SUBARACHNOID HAEMORRHAGE, UNSPECIFIED
I611	INTRACEREBRAL HAEMORRHAGE IN HEMISPHERE, CORTICAL
I618	OTHER INTRACEREBRAL HAEMORRHAGE
I629	INTRACRANIAL HAEMORRHAGE (NONTRAUMATIC), UNSPECIFIED
I630	CEREBRAL INFARCTION DUE TO THROMBOSIS OF PRECEREBRAL ARTERIES
I633	CEREBRAL INFARCTION DUE TO THROMBOSIS OF CEREBRAL ARTERIES
I634	CEREBRAL INFARCTION DUE TO EMBOLISM OF CEREBRAL ARTERIES
I638	OTHER CEREBRAL INFARCTION
I639	CEREBRAL INFARCTION, UNSPECIFIED
I64X	STROKE, NOT SPECIFIED AS HAEMORRHAGE OR INFARCTION

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

Table 16 ICD-10 codes used to search the HES database and identify outcome events for stroke, myocardial infarction (MI) and bleeding events

This included searching the fields containing all diagnostic codes used as the primary diagnosis, secondary diagnosis, through to the tenth diagnostic code for a given

admission. All additional unplanned target lesion revascularisation events in the HEAT-PPCI trial occurred during the index admission. This analysis therefore excluded unplanned target lesion revascularisation from the codes used to search HES.

To identify all CVAs, the ICD-10 codes that identified CVAs were used to search the HES data (Table 16). Bleeding events were identified using ICD-10 codes that suggested haemorrhage or blood loss (Table 16). No reliable method was found to stratify the bleeding events into degrees of severity from the HES data, so all bleeds identified were included in the analysis and compared to all bleeds (both major and minor) confirmed by physician adjudication. To assess diagnostic accuracy of HES, the outcomes identified using this method were compared with the outcomes confirmed by physician adjudication.

Results:

Patients excluded from readmissions analysis:

Of the 1812 patients recruited into the HEAT-PPCI trial, 73 patients died during the index period and 39 remained inpatients at 28 days following randomisation. Therefore 1700 had the potential to be re-admitted and were subject to follow-up after their index admission (Figure 21). Of these, 96.7% (1644/1700) were successfully followed by both direct contact and HES. 3% (53/1700) patients were lost to HES follow-up and 0.2% (4/1700) lost to direct contact follow-up. 1 patient was lost to both HES follow-up and direct contact. In this trial 13 patients did not have NHS numbers submitted to HES and therefore no HES data was found. 11 of the 13 patients did not live in England, which is the most likely explanation for the omission of an NHS number in the trial database (Table 17). 2 patients had incorrect NHS numbers recorded in the trial database and 43 patients did not return HES data despite an assigned NHS number.

Table 17 The readmissions confirmed by adjudication in the HEAT-PPCI trial are compared to the HES method and the direct contact method of identifying readmissions.

	Outcome from Physician Adjudication		**Sensitivity (CI)**	**Specificity (CI)**	**PPV (CI)**	**NPV (CI)**
	Readmission	No Readmission				
HES detects Readmission	**153**	**0**				
HES does not detect Readmission	**13**	**1492**	92.2 (87.1 to 95.4)	100 (99.7 to 100)	100 (97.6 to 100)	99.1 (98.5 to 99.5)
	Readmission	No Readmission				
DC detects Readmission	**145**	**67**				
DC does not detect Readmission	**22**	**1424**	86.8 (80.9 to 91.1)	95.5 (94.3 to 96.4)	68.4 (61.9 to 74.3)	98.5 (97.7 to 98.9)
	Readmission MACE	No Readmission MACE				
HES detects Readmission MACE	**6**	**24**				
HES does not detect Readmission MACE	**2**	**1612**	75.0 (40.9 to 92.9)	98.5 (97.8 to 99.0)	20.0 (9.5 to 37.3)	99.9 (99.5 to 99.9)
	Index MI	No Index MI				
HES detects Index MI	**1509**	**12**				
HES does not detect Index MI	**24**	**209**	98.4 (97.7 to 98.9)	94.6 (91.0 to 96.9)	99.2 (98.6 to 99.5)	89.7 (85.1 to 93.0)
	Readmission MI	No Readmission MI				
HES detects Readmission MI	**2**	**25**				
HES does not detect Readmission MI	**1**	**1614**	66.7 (20.8 to 93.9)	98.5 (97.6 to 98.9)	7.4 (2.1 to 23.4)	99.9 (99.7 to 100)
	CVA before Discharge	No CVA before Discharge				
HES detects CVA before discharge	**18**	**2**				
HES does not detect CVA before discharge	**3**	**1731**	85.7 (65.4 to 95.0)	99.9 (99.6 to 100)	90.0 (69.9 to 97.2)	99.8 (99.5 to 99.9)
	Readmission CVA	No Readmission CVA				
HES detects CVA on Readmission	**4**	**0**				
HES does not detect Readmission CVA	**1**	**1639**	80.0 (37.6 to 96.4)	100 (99.8 to 100)	100 (51.0 to 100)	99.9 (99.7 to 100)
	Bleed before Discharge	No Bleed before Discharge				
HES detects Bleeding Event before Discharge	**104**	**210**				
HES does not detect Bleeding Event before Discharge	**32**	**1408**	76.4 (68.7 to 82.8)	87.0 (85.3 to 88.6)	33.1 (28.1 to 38.5)	97.8 (96.9 to 98.4)
	Readmission Bleed	No Readmission Bleed				
HES detects Readmission Bleeding Event	**14**	**5**				
HES does not detect Readmission Bleeding Event	**11**	**1614**	56.0 (37.1 to 73.3)	99.7 (99.3 to 99.9)	73.7 (51.2 to 88.2)	99.3 (98.8 to 99.6)

Readmissions Identified in the HES data:

153 readmissions were identified in the HES data, in 1644 patients (Table 17). All 153 readmission events were subsequently confirmed by notes review, giving a PPV of 100% (CI 97.6 to 100). No false positive results were identified. Of the 1505 cases with no identified readmissions, 13 events were found to be false negatives giving a NPV of 99.1% (CI 98.4 to 99.4). 14 patients had 2 readmissions in the follow-up period, 100% of these readmissions were identified in the HES database.

Readmissions Identified by Direct Contact:

The direct contact method identified 212 readmissions in 207 patients (Table 3). Of these 212 readmissions,145 readmissions were confirmed by notes review. 67 were found to be false positives, giving a PPV of 68.4% (61.9 to 74.3). This high rate of false positives is most likely due to patients reporting hospital attendances that did not include an overnight stay and therefore did not fit the trial definition of a readmission.

Of the 1437 cases identified as having no readmissions, 22 events in 13 patients were found to be false negatives, giving a NPV of 98.5% (CI 97.7 to 98.9). Of the 14 patients readmitted twice in the follow-up period, direct contact identified 16 of the 28 readmissions, identifying only 1 readmission in 6/14 and no readmissions in 3/14 patients.

The diagnostic accuracy of HES data in identifying MACE and bleeding events during the index admission:

Of the 1812 patients included in the trial, 58 did not return any HES data, 1754 were therefore included in the analysis to ascertain the diagnostic accuracy of HES data in identifying MACE during the index admission (Figure 22). The full results are presented in Table 17. 98.5% (1509/1533) of the index MIs were identified in the HES data, with 12 false positive events, giving a NPV of 87.9% (CI 85.1 to 93.0). HES identifies 60% (18/30) CVAs during the index admission, with 2 false positives, giving a NPV of 99.8% (CI 99.5 to 99.9). HES identifies 76.5% (104/136) of the confirmed bleeding events that occurred during the index admission and 210 false positives, giving a NPV of 97.8 (CI 96.9 to 98.4).

The diagnostic accuracy of HES data in identifying MACE and bleeding events during a readmission:

The same 1644 patients that were included in the analysis to identify readmission by both methods were used to ascertain the diagnostic accuracy of the HES data in identifying clinical events during readmissions (Figure 21). Detailed data on the clinical events identified during readmissions are displayed in Table 3. The key finding is that when using physician-adjudicated events as the criterion standard, HES identified 75% (6/8) of confirmed readmission MACE, with 24 false positives, giving a NPV of 99.9% (CI 99.5 to 99.9). HES identified 56% (14/25) bleeding events during readmissions, with 5 false positives, giving a NPV of 99.3% (CI 98.8 to 99.6).

Discussion:

Current problems in trial follow-up:

Obtaining follow-up in clinical trials traditionally involves direct patient contact by the study team. This method can result in inaccurate follow-up data for several reasons:

Trial patients need to understand and co-operate with the follow-up process which requires an understanding of specific trial definitions, such as, the trial definition of a readmission event in the HEAT-PPCI trial. These details may not be easily understood by patients with little knowledge of clinical research, resulting in inadvertent reporting of inaccurate information to the research team.

Patients who do not wish to engage with the research team for personal reasons, such as embarrassment related to a medical problem, may not report events for fear of being questioned in more detail. Some patients may also know that reporting events creates additional work in the trial and choose not to report events because they do not want to burden the research team.

Relying on the recollection of each individual trial patient may lead to errors. During a stressful health period, patients may struggle to recollect all hospital admissions, particularly if multiple readmissions are experienced in a short time-period. They may perceive outpatient appointments as readmissions, or readmissions to a different specialty to be irrelevant and therefore not mention them to the research team.

Our study showed that HES follow-up identified 4.9% more confirmed readmissions than direct contact. Direct contact missed 42.9% (12/28) of the readmissions in patients who experienced multiple readmissions in the follow-up period. This is likely to be due to the multiple issues faced when using the direct contact method of follow-up. HES identified 100% (28/28) of the readmissions in this group of patients.

HES advantages:

Using HES data for follow-up removes the need to directly contact any trial patient therefore reducing errors associated with this method. In addition, using HES data is likely to reduce the workload of trial and subsequently the overall cost.

When a patient reports a clinical event or readmission, this is thoroughly investigated by the research team, who must review the medical notes to confirm or refute the claim. Reducing the number of false positive results in follow-up reduces the workload and cost of the trial. Our study found that HES data did not identify any readmissions events that were found to be false positives. In comparison, 31.6% of the readmissions identified by direct contact were found to be false positives. If HES data is used, the reduction in workload may incentivise centres to increase trial recruitment.

When faced with a smaller cost of follow-up, smaller centres may be encouraged to set up new trials. It is likely that recruitment for trials would be higher if follow up can be achieved without the active participation of patients.

Highlights of HES:

HES captures all events and diagnoses as perceived by the health service. It records what the system says has occurred during a hospital admission and is the determinant of cost. This information may better reflect the true societal impact, both clinically and financially, of an intervention under examination. Traditional trial follow-up pre-specifies the definitions of a clinical event using thresholds for confirming a diagnosis that may not accurately reflect the patient experience or cost to the health service. A recent paper looked at the non-fatal/non-MACE adverse events in a trial comparing PCI to CABG in patients with 2 or 3-vessel coronary artery disease[221]. The results showed that CABG caused a greater number of non-MACE events despite the original trial publication reporting favourably for CABG because of the lower number of MACE

adverse events[178]. MACE are commonly used as the primary outcome measures in trials of cardiovascular interventions. This can give a misleading impression of patient experience and healthcare cost of trial because admissions for non-fatal/non-MACE adverse events are excluded from analysis. These events may be numerous and are likely to affect the patient as well as incur costs to hospitals. Because HES identifies any ED attendance or hospital admission, this data could be used in trials wishing to examine the broader physical and psychological impact of a treatment. Each diagnostic code in HES is associated with a tariff that determines how much the hospital is paid per admission. HES therefore identifies the healthcare costs of an admission and could be used in trial aiming to analyse the economic impact of treatments. A recent trial in patients with prostate cancer validated use of HES data as a way of costing patient admissions[222] with no significant difference found when compared to cost of admission calculated by notes review.

Existing literature on HES:

An increasing number of studies are using HES data to evaluate outcome measures[223]. A recent systematic review looked at studies of the accuracy of HES data when compared to clinical registries and case notes. Although there is no consensus for an acceptable threshold of diagnostic accuracy, the median accuracy of the HES diagnostic codes was 80.3% when compared to notes review or clinical registry data[224]. This review also found that there has been an improvement in the diagnostic accuracy of HES data over time. The studies included were all observational studies using HES data to evaluate clinical outcomes[223]. So far, no studies have investigated the accuracy of HES data in identifying outcomes in randomised controlled trials which is what this study aimed to address.

HES limitations:

Although there are advantages of using HES data in clinical trials, there are several limitations. Each hospital has a team of coders who assign the ICD-10 codes to each patient admission. There is likely to be variability between trusts and even between individual coders which may affect the quality of HES data. In 2013-14 an audit was performed of the clinical coding at 50 acute trusts assessing the accuracy of the ICD-10 codes allocated to each admission. The average error rate, defined as a change to the

codes that would results in a change in the payment received by each trust, was 7%[225]. The lowest percentage error for a given trust was 1.1% and the highest 45.8%, demonstrating considerable variability in the accuracy of clinical coding across trusts. This variability will impact accuracy of clinical outcomes identified if HES is used as a method of identifying readmissions or outcomes in a clinical trial. Physician involvement has been suggested as a method of improving clinical coding date, with one study showing improved accuracy of data using this approach[224]. Improvements in clinical coding would enable HES to be used for research purposes, as well as accurately calculating health care costs within a hospital trust.

The HES database uses the NHS number as the sole unique identifier of each patient. This is useful in trials with lengthy follow-up because the NHS number remains the same even if a patient moves or changes their name or phone number. However, patients without an NHS number will be missed. In this study, 3% of patients did not return any data in the HES database. 22.4% (13/58) patients who returned no HES data did not have an NHS number so the HES database would not be able to identify the patient. 3.4% (2/58) were found to have an error in their NHS numbers so did not return data. This error could be reduced by using a simple check digit code to ensure all NHS numbers are correct. Using more meticulous methods of checking and rechecking the NHS number by the study team would also reduce errors.

74% (43/58) of the missing data was patients whose NHS numbers were entered into the HES database correctly but did not return any data. This suggests that there may be missing data within the HES database itself. Although NHS Digital does do data quality checks, they could not provide statistics on missing data in the HES database however the issue of missing data within HES has been frequently reported in other studies[224]. We investigated this missing data by contacting NHS England and asking for them to recheck the missing patients for any data corresponding to the index admission which we knew had taken place. 93.0% (40/43) had HES data available for the index admission. It is unclear why the original HES data extract was missing data for these patients but the introduction of a new process for requesting HES data through DARS (Data Access Request Service) should reduce these errors.

HES data only reports admissions that occur in hospitals in England. 2 of the 14 false negative readmission events in HES occurred outside this area. This limits the usefulness of HES data in tracking patients who move outside of England, or those who live abroad but are admitted to an English hospital for the index event. One solution would be to limit study inclusion to those with NHS numbers who are resident in England. However, this limits the inclusiveness of the trial and does not solve the issue of patients who are admitted to hospitals abroad or who live on the border of England. There is an equivalent of HES data for Wales and Scotland, which also use ICD-10 codes and should be used in addition to the English HES database. No system exists for Northern Ireland or the Republic of Ireland at present.

Because of the ICD-10 codes used in the HES database, it is not possible to apply the usual range of trial qualifiers to the outcome of unplanned target lesion revascularisation. For example, the ICD-10 codes do not distinguish between target lesion and target vessel or planned and unplanned revascularisation. This is a key limitation in using HES data in identifying clinical outcomes in trials of cardiovascular intervention. One solution would be to ensure future treatment intentions are recorded on the clinical record form of each patient following the index event. This information could then be used with the HES database to establish if further intervention was planned or unplanned.

Study limitations:

This study reported very small numbers of readmission MACE following the index event. For example, only 4 strokes occurred after the index admission. It is therefore impossible to draw conclusions on key diagnoses like strokes from such small numbers.

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

Because the HES data is made up of ICD-10 codes taken from the medical notes, the frequency of clinical events is likely to be overestimated when compared to the pre-defined trial definitions used to establish outcome events in the HEAT-PPCI trial. When compared to physician adjudicated outcome measures, 80% of readmission MACE detected by HES were false positives. HES data did not identify 25% readmission MACE. The highly specific trial definitions of MACE were not developed to be comparable to ICD-10 codes used in HES. The accuracy of outcome identification using HES could be improved by tailoring the definitions of pre-specified outcome measures to ICD-10 diagnostic codes.

Conclusion:

A combination of HES and direct contact provides a comprehensive method of follow-up superior to either method alone. HES is superior to direct contact in ascertaining readmission events and may reduce the resource burden and cost of follow-up in clinical studies. A HES-based approach may also provide information about the general patient experience and total healthcare costs of a trial. Using HES may support patient recruitment and the completeness of follow-up by reducing the workload for both investigators and patients.

Final word:

Following the publication of the results of the HEAT-PPCI trial, two further studies BRAVE-4 and MATRIX, comparing heparin and bivalirudin in the STEMI setting, showed similar results. BRAVE-4[226] study was unable to demonstrate significant differences in ischaemic, safety or net clinical outcomes between prasugrel plus bivalirudin and clopidogrel plus heparin. MATRIX[227] trial again showed no significant differences in the rates of MACE and net adverse clinical events between bivalirudin and heparin. The results of the BRIGHT[228] trial were discordant and showed significant reduction in net adverse clinical events and bleeding complications with bivalirudin when compared to both heparin alone and heparin plus tirofiban. Six meta-analyses[229-234] have been published since and have incorporated the data from HEAT-PPCI, BRIGHT, BRAVE-4 as well as previous trials comparing the two antithrombotic agents. Two consistent messages across the results of these meta-analyses in the STEMI setting are: a) Use of bivalirudin is associated with significantly higher rates of acute stent thrombosis. b) Two independent predictors for bleeding complications in the heparin arm are the rate of use of GP IIbIIIa inhibitors and the dose of heparin used. The most recent VALIDATE-SWEDEHEART[235] trial with more than 3000 patients with STEMI has once again shown that the rate of MACE or major bleeding was not lower with bivalirudin in comparison to heparin monotherapy. The results were consistent across major patient subgroups, regardless of baseline clinical and angiographic characteristics. The rates of stent thrombosis were similar. This could be explained by the facts that more than 90% of patients in the bivalirudin received a bolus of heparin before or during the procedure and that two thirds of patients received a prolonged infusion of high-dose bivalirudin.

The results from the HEAT-PPCI trial proved to be a catalyst that has resulted in change of clinical practice globally as well as change in International STEMI guidelines. There has been a significant decline in the use of bivalirudin in STEMI setting[236]. The 2014 ESC guidelines on myocardial revascularisation downgraded the use of bivalirudin in STEMI patients undergoing PPCI from class I[13] to class IIa[94].

Annexes:

Annexe 1 – ACT Data:

ACT monitoring:

Activated clotting time (ACT) is a point of care test used to monitor coagulation. It measures the time in seconds needed for a blood sample to clot when exposed to an activator of the intrinsic pathway of the coagulation cascade[237]. The type of activator used affects the reported value for the ACT. Kaolin and celite are the mostly commonly used activators. Other activators that have been used in clinical practice are glass beads, silica and thromboplastin.

Why is ACT monitoring required?

It is normal practice to perform PCI procedures using systemic anticoagulation. Inadequate anticoagulation may result in thrombotic complications while over-dosing may be associated with more prevalent bleeding complications. ACT is the most commonly used method in clinical practice to monitor anticoagulation during invasive procedures. Measurement of ACT helps to confirm the following:

- That an antithrombotic drug has been administered
- That the drug has reached the circulation
- That an appropriate dose was given.
- That an anticoagulation effect is maintained (with repeat testing over time).

Common procedures where ACT monitoring is performed include cardiopulmonary bypass, cardiac catheterisation, vascular surgery and hemodialysis[238].

ACT monitoring systems:

A number of different systems for ACT estimation are in routine use. The most common ones are Hemochron (401, 801, Response), Medtronic (HMS, HemoTec ACTII, ACTplus) and i-STAT. These systems use a single activator (kaolin or celite) during processing. Each analyser has a different detection system to measure clot formation.

Each system yields different ACT results. There is no easy or accurate method of correlation between the systems. The reference and therapeutic target ranges depend on the method used. ACT results obtained by different methods cannot be used interchangeably[239 240]. Lack of consistency and variability between the readings of various kits is an important limitation of ACT monitoring.

ACT monitoring with heparin therapy:

ACT is the most commonly used method for monitoring and guiding heparin therapy during invasive intravascular procedures. Various studies have demonstrated a linear heparin/dose response curve for the ACT[241 242].

ACT monitoring with bivalirudin therapy:

Several studies have identified potential problems with the use of ACT estimation with bivalirudin therapy[243-246]. ACT readings have been reported to be insufficiently sensitive to higher levels of bivalirudin and the relationship is not linear. For this reason, routine ACT monitoring during PCI is not recommended for bivalirudin therapy. The manufacturer does not recommend routine ACT monitoring for bivalirudin except in patients with renal failure. Checking the ACT value 5 minutes post bolus dose may have some value as confirmation of drug administration.

Trial medication dosing regime in HEAT-PPCI:

In HEAT-PPCI, we used standard doses of the trial medication. Weighing patients in this emergency setting was not possible. Weights declared by patients or estimated by the clinical team were used to calculate dosing of both trial medications. Heparin was given as a bolus dose of 70 units/kg body weight pre-procedure. An additional, 'top-up', dose was administered if ACT values 5-15 minutes after the initial dose, or at the end of the procedure were <200. Bivalirudin dosing was administered (as per the manufacturer's recommendations) as a bolus of 0·75 mg/kg followed by infusion of 1·75 mg/kg per hour for the duration of the procedure. An additional bolus of 0·3 mg/kg was administered if ACT values 5-15 minutes after initial dosing, or at the end of the procedure were <225. The additional bolus regime was again in accordance with the manufacturer's recommendations.

ACT monitoring system in HEAT-PPCI:

In HEAT-PPCI, ACT was monitored using Actalyke XL® MAX-ACT system[247]. This modified technology uses three activators (celite, kaolin and glass beads). This results in a greater proportion of Factor XII being converted to Factor XIIa - producing shorter clotting times.

When compared to the traditional machines that employ single agent (kaolin or celite) activators, MAX-ACT consistently produces lower ACT readings. For heparin, its readings were found to be 30-60 seconds lower[248-251]. For bivalirudin therapy, mean values using the MAX-ACT system have been reported as being 94 seconds less than the kaolin-based assays[252].

ACT measurement results: ACT readings for HEAT-PPCI patients are provided in the table below:

	Heparin			**Bivalirudin**		
	n	Median	IQR	n	Median	IQR
ACT 5-15 min	795	224	200-256	806	251	229-285
ACT end	777	206	188-229	771	246	229-270

Table 18 ACT values

ACT= Activated Clotting Time (seconds); IQR= Inter-quartile range; SD= Standard deviation

Accuracy of weight estimation:

In HEAT-PPCI patients were weighed during their index admission. This allowed us to compare the estimated weight (used, in the emergency phase, for drug administration) and the true body weight. Weights were accurate to ± 2kg in half of the patients and to ± 5kg in about 80% of the population. There was no systematic bias with comparable rates of both under- and over-estimation of weight.

Percentile	**5**	**10**	**25**	**50**	**75**	**90**	**95**
Weight Difference (kg)	-8.5	-5.5	-2.0	0.0	2.1	5.0	8.1

Table 19 Weight difference

The weight difference is calculated as the weight used for dosing minus the subsequent true body weight. A positive value implies the potential for overdosing of antithrombotic and vice versa.

Additional drug bolus administration data:

We recorded the rate of additional bolus administration in patients receiving the trial medication. Additional, supplemental bolus doses were administered in 35.2% (315/895) of patients in the heparin arm and 12.7% (114/898) in the bivalirudin arm. Supplemental bolus rates may appear high due to the following factors: a) The trial protocol enforced ACT estimations at two different time points with a requirement for additional bolus administration if indicated. More frequent ACT estimation will result in more frequent detection of sub therapeutic results. b) Use of the MAX-ACT system means that a greater proportion of cases will demonstrate values below the additional bolus threshold. The manufacturer's recommendations in the bivalirudin summary of product characteristics do not address the potential variability of ACT results obtained from different systems. The HEAT-PPCI trial protocol followed currently available guidelines. Education, instruction and support were provided to clinical teams by the The Medicines Company before and during the initial phase of the trial and our strategies related to drug administration and ACT monitoring were approved. Total

dose of heparin (including additional boluses) used in the study per actual body weight was 102.4 units/kg. We plan to explore this data further to gather more information in this regard.

Limitations:

Our data have some limitations. We did not record the timing of additional bolus dosing, or, specifically whether it was given during or at the end of the procedure. We also did not mandate a repeat ACT after an 'end of procedure additional bolus dose' to explore the subsequent antithrombotic effect.

Conclusions:

In HEAT-PPCI the dose and administration schedule for trial medication was in accordance with the trial protocol, international guidelines and licenced recommendations. Fastidious ACT monitoring was performed at two time-points during the index procedure. The routine use of the MAX-ACT system may have resulted in an increased rate of administration of additional bolus doses. Despite this, the ACT values in HEAT-PPCI appear similar to those reported in HORIZONS-AMI[15] (after adjustment of the reported numerical values returned by the different measurement systems). The ACT data has not been reported for the EUROMAX trial.

Annexe 2 - Previous clinical evidence comparing heparin and bivalirdin:

Bivalirudin Angioplasty Trial (BAT, 1995):

Earlier known as Hirulog Angioplasty Study (HAS), it reported on 4098 patients with unstable angina and planned PCI and compared heparin (IV bolus 175 U/kg bodyweight followed by infusion of 15 U/kg/h) with bivalirudin (bolus of 1.0 mg/kg bodyweight followed by infusion of 2.5 mg/kg/h for 4 h and 0.2 mg/kg/h for 14 to 20 h) [35]. Bivalirudin was found to be at least as effective as high-dose heparin in preventing ischaemic complications and was associated with some reduction in bleeding complications. The sponsor concluded that the results of the study provided insufficient evidence of an advantage over heparin to warrant the cost of further development of the drug and it was decided to terminate further clinical studies on bivalirudin [253].

After establishing backing of a new sponsor, The Medicines Company, the HAS trial was reanalysed and presented as Bivalirudin Angioplasty Trial (BAT) in 2001[38]. The reanalysis included 4312 patients (including 214 that did not receive treatment) and used fixed time points of 7, 90 and 180 days after randomization for analysis rather than hospital discharge. The primary end point goal posts were slightly modified as well. Instead of death, clinical MI, abrupt vessel closure, or rapid clinical deterioration of cardiac origin requiring bypass surgery, intra-aortic balloon pumping, or repeat coronary angioplasty, they used death, any revascularization, and either clinical or enzymatic evidence of MI. The results showed statistically significant reduction in the new combined primary end point by 22% (p=0.039) and significant bleeding complications were lowered by 63% (3.5% vs 9.3%; p<0.001) in favour of bivalirudin.

Apart from the caveats associated with re-analyses of trials, there are certain points to consider about this reanalysis. The investigators acknowledged that they would not have published the results if those were not in favour of bivalirudin leading to republication bias[253]. The new primary end point included any revascularization and not target vessel or urgent revascularization which clouded any specific effects of the study drugs on the original vessel. In the study design, a much higher heparin dose was used (bolus of 175 U/kg followed by 18-24 hour infusion of 15 U/kg/hour). This is more than twice the dose currently in practice in USA and Europe and, thus, predisposed the heparin group to higher risk of bleeding complications. Above all, this trial does not represent modern clinical practice as it antedates the routine use of stents and thienopyridines.

HERO-2 Trial (2001):

The Hirulog and Early Reperfusion or Occlusion (HERO)-2 trial randomised 17,073 patients to receive either bivalirudin or heparin on top of streptokinase in STEMI patients [254]. It will be interesting to point out that the bivalirudin arm actually had higher incidence of bleeding complications in comparison to the heparin arm. This difference was statistically significant across the whole spectrum [major bleeding (0.7% vs 0.5%, P = 0.07), moderate bleeding (1.4% vs 1.1%, P = 0.05) and minor bleeding (12.8% vs 9.0%, p < 0.0001)].

REPLACE-1 Trial (2004):

The Randomized Evaluation of PCI Linking Angiomax to Reduced Clinical Events (REPLACE) -1 trial randomized 1,056 patients who underwent elective or urgent revascularizion receiving either heparin (70 U/kg initial bolus) or bivalirudin (0.75 mg/kg bolus, 1.75 mg/kg/hour infusion during the procedure)[37]. Glycoprotein (GP) IIb/IIIa blockade was at the physician's discretion and was given to 72% of patients. Primary outcome data (a combination of death, MI, and urgent TLR within 48 h) did not differ between study groups (5.6% vs 6.9%, *P* = 0.40) and were independent of the use or non-use of Gp IIb/IIIa inhibitors. Major bleeding occurred in 2.1% of those assigned to bivalirudin versus 2.7% of those assigned to heparin and hence, there was no statistically significant difference (*P* = 0.52).

The reduction in bleeding events was limited to patients who did not receive GP IIb/IIIa inhibitors, suggesting that the benefits of bivalirudin with respect to bleeding were negated by routine GP IIb/IIIa inhibitor use. Overall, the trial underpinned the fact that a head-to-head comparison of bivalirudin and 'normal practice dose' heparin in a PCI setting had no difference in bleeding or ischaemic complications in the absence of Gp IIb/IIIa inhibitor influence.

REPLACE-2 Trial (2003):

The REPLACE-2 study included 6,010 lower risk patients undergoing PCI randomized to receive either intravenous bivalirudin (0.75-mg/kg bolus plus 1.75 mg/kg per hour for the duration of PCI), with provisional use of Gp IIb/IIIa inhibitors or heparin (65-U/kg bolus) with planned use of Gp IIb/IIIa inhibitors (abciximab or eptifibatide) [23]. The study concluded that bivalirudin was statistically non-inferior to heparin plus Gp IIb/IIIa inhibitor group in terms of composite primary end point (9.2% vs 10.0% , P = 0.32). However, this was mainly driven by 41% relative reduction in major bleeding which was included in the composite primary end point. The reduction in major bleeding with bivalirudin was significant when trial defined bleeding criteria was used (2.4% vs 4.1%, P < 0.001). But when TIMI major bleeding criteria was used, there was no significant between the two groups (0.6% vs. 0.9%, respectively, P = 0.30).

ACUITY Trial (2006):

In the ACUITY trial 13,819 patients with moderate or high-risk acute coronary syndromes who were undergoing an early invasive strategy were assigned to one of three antithrombotic regimens: Heparin plus a Gp IIb/IIIa inhibitor, bivalirudin plus a Gp IIb/IIIa inhibitor, or bivalirudin alone [22]. The study found no significant differences between the bivalirudin plus Gp IIb/IIIa inhibitor vs heparin plus Gp IIb/IIIa inhibitor groups in terms of composite ischemia end point (7.7% and 7.3%, respectively), major bleeding (5.3% and 5.7%), and the net clinical outcome end point (11.8% and 11.7%). In terms of the primary, composite ischemic endpoint, bivalirudin alone was statistically non-inferior to heparin plus Gp IIb/IIIa inhibitor group (7.8% vs. 7.3%, P = 0.39) and significantly reduced rates of major bleeding (3.0% vs. 5.7%, P < 0.001) and the net clinical outcome end point (10.1% vs. 11.7%; P = 0.02).

In the trial design, major bleeding was defined very broadly and included haematoma ≥5 cm as one of its parameters [255]. This has generally been kept as part of 'minor bleeding criteria' in various other antithrombotic trials. Bivalirudin significantly reduced this end point (32 in the bivalirudin monotherapy group vs 102 in the heparin plus Gp IIb/IIIa group, P < 0.001) and it had an overall impact in the final results from bleeding complications. One of the main disagreements over ACUITY (and later HORIZONS-AMI) trial design has been the use of the term 'net clinical outcome end point' which is a combination of composite ischemia end point and major bleeding [255]. By combining the two different entities, a haematoma ≥5 cm as well as MI or death were allocated equal values in determining the primary end point. In the trial, a third of the patients did not receive pre-procedural thienopyridine. Bivalirudin was found to be inferior to heparin plus Gp IIb/IIIa inhibitor in this group (ischaemic event rate 9.1% vs 7.1%) [256]. This has been one of the findings that lead to the recommendation that patients going for bivalirudin monotherapy must receive thienopyridine pre-treatment before the angiogram or PCI. One year results of ACUITY continued to show the non-inferiority of bivalirudin to heparin plus Gp IIb/IIIa inhibitors combination but the significant reduction in major bleeding present at 30 days was lost [257]. This may be partially because the trial was not statistically powered to show mortality or bleeding difference at 1 year. There is no data in the trial results detailing the arterial access site comparisons. Radial approach has rapidly gained popularity especially in Europe

and is associated with significantly less bleeding complications [258 259]. In the current European settings of trans-radial dominance, the difference in bleeding complications between the two groups is very likely to lose its significance.

HORIZONS-AMI trial (2008):

The Harmonizing Outcomes with RevascularIZatiON and Stents in Acute Myocardial Infarction (HORIZONS-AMI) trial randomized 3,602 patients undergoing Primary PCI to either heparin plus a Gp IIb/IIIa inhibitor or bivalirudin monotherapy [15]. The results showed reduction in 30-day rate of net adverse clinical events (9.2% vs. 12.1%, P=0.005), owing to a lower rate of major bleeding (4.9% vs. 8.3%, P < 0.001). There was an increased incidence of acute stent thrombosis within 24 hours in the bivalirudin group which diluted out at 30 days. Bivalirudin monotherapy arm showed significantly lower 30-day rates of death from cardiac causes (1.8% vs. 2.9%, P = 0.03) and death from all causes (2.1% vs. 3.1%, P = 0.047).

Two thirds of patients in the bivalirudin group received heparin before randomization and were later 'switched' to the bivalirudin monotherapy. Only 615 patients truly received bivalirudin monotherapy. It has been shown that the patients who received pre-randomization heparin had significant reduction in acute stent thrombosis (0.9% vs 2.6%, P = 0.006) [260]. The fact that majority of the bivalirudin monotherapy group patients received heparin beforehand calls for cautious interpretation of the final results. Blurring the boundaries between treatment groups even further is that fact that 7.2% patients in bivalirudin group received bail-out Gp IIb/IIIa inhibitors [15]. These were given for valid and important indications such as sustained absence of reflow after PCI, presence of giant thrombus or large thrombus burden. These categories are unlikely to receive bivalirudin monotherapy in 'real life' acute settings and will require Gp IIb/IIIa inhibitors for treatment.

ISAR-REACT 3 trial (2008):

ISAR REACT-3 trial compared bivalirudin and heparin in 4,570 biomarker negative patients undergoing PCI > 2 hours after pre-treatment with 600 mg of clopidogrel[36]. It revealed less bleeding complications with bivalirudin compared with heparin (3.1% vs 4.6%, p = 0.008). Overall, there was no difference in 30-day or 1 year net clinical benefit between the two regimens. The obvious problem with the trial was the

significantly higher heparin dose of 140 U/kg. This is more than twice the dose currently in practice in USA and Europe and that makes it very difficult to interpret and accept the findings of the trial.

ISAR-REACT 3A study (2010):

The ISAR-REACT 3A study tried to overcome the issue of high dose of heparin. In this trial, a total of 2,505 eligible patients were consecutively included and received a reduced single bolus dose of 100 U/kg heparin [39]. The trial compared the lower dose heparin with historical controls of the ISAR-REACT 3 trial. Interestingly, the statistical significance of the results in terms of fewer bleeding complications was lost when bivalirudin was compared to the lower heparin dose of 100 U/kg.

ISAR-REACT 4 Trial (2013):

In this issue of the journal, Schulz and colleagues present new data describing one-year outcomes from the ISAR-REACT 4 trial[21]. This study recruited patients undergoing PCI in the setting of a non-ST elevation, acute coronary syndrome presentation. Subjects were randomised to two different peri-procedural antithrombotic regimes: bivalirudin or combination therapy with heparin and abciximab. The reported rates of death, non-fatal myocardial infarction and target vessel revascularisation are near identical. It is interesting to note that an increased risk of bleeding, observed at 30 days, in patients receiving abciximab therapy, did not result in differences in key outcome measures at one year.

Annexe 3 - Follow up flowchart:

We carefully designed a 28-day follow-up flowchart (figure 23) indicating various timelines and methods required for patient follow up.

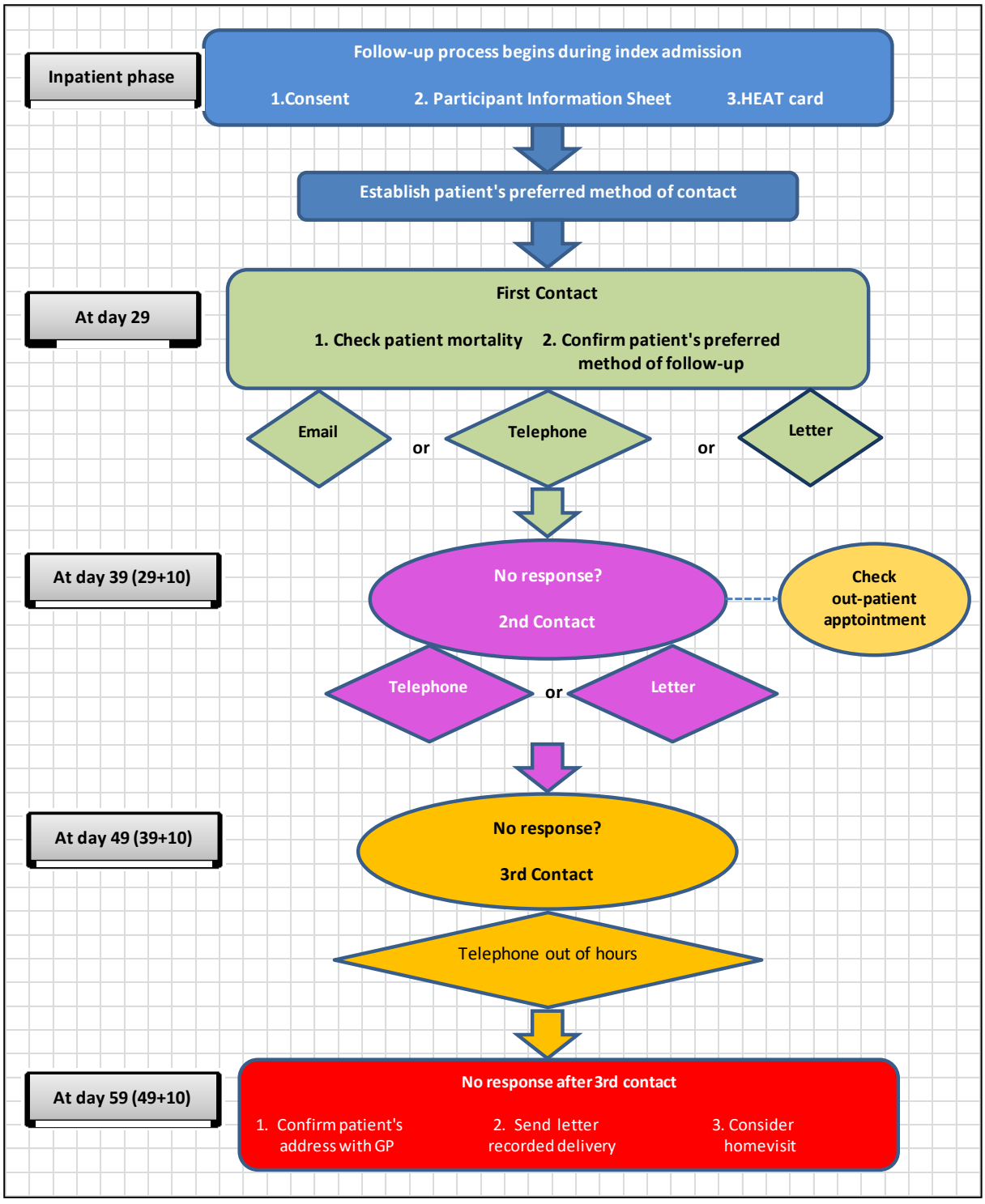


Figure 23 HEAT-PPCI 28 day Follow up flowchart

List of publications and presentations:

Papers:

- Unfractionated heparin versus bivalirudin in primary percutaneous coronary intervention (HEAT-PPCI): an open-label, single centre, randomised controlled trial. A Shahzad, I Kemp, C Mars, C Roome, K Wilson, R Cooper, M Andron, C Appleby, M Fisher, A Khand, B Kunadian, J D Mills, J L Morris, W L Morrison, S Munir, N D Palmer, R A Perry, D R Ramsdale and R H Stables, for the HEAT-PPCI trial investigators. Lancet 2014; 384: 1849–58.

- Describing Activity in Primary Percutaneous Coronary Intervention: An Exploration of Denominators. From the HEAT Trial - A Systematic Evaluation of PPCI Activations in Liverpool, Explaining Denominators (HEAT-SEALED). A Shahzad, C Mars, I Kemp, R Cooper, P Arnold, J McLenachan, H Gray, J Morris, R H Stables. Journal of Invasive Cardiology. 2016;28(6):247-252.

- Comparison of the antiplatelet and antithrombotic effects of bivalirudin versus unfractionated heparin in patients undergoing primary percutaneous coronary intervention: results from the HEAT-PPCI Platelet Substudy. A Shahzad, V Khanna, C Mars, I Kemp, Kala Thayalasamy, R Cooper, Scott Harris, R Stables, N Curzen. Thrombosis and Haemostasis; doi.org/10.1016/j.thromres.2018.09.062

- Comparison of the effects of P2Y12 receptor antagonists on platelet function and clinical outcomes in patients undergoing Primary PCI: A substudy of the HEAT-PPCI trial. A Shahzad, V Khanna, C Mars, I Kemp, R Cooper, N Curzen, R H Stables. EuroIntervention. 2018 Mar 20;13(16):1931-1938. doi: 10.4244/EIJ-D-17-00408.

- Antithrombotic therapy in PCI: Why not Heparin? A Shahzad, R Cooper, R H Stables. EuroIntervention 2013; 9:423-426.

- Bivalirudin versus heparin use for patients undergoing PPCI - Authors' reply. A Shahzad, R H Stables. Lancet Volume 385, Issue 9982, 23 May 2015, Pages 2045-2046.

Abstracts:

- HEAT-PPCI antiplatelet therapy substudy: Comparison of the effect of P2Y12 receptor antagonists on platelet function and clinical outcomes in patients undergoing Primary PCI. A Shahzad, V Khanna, C Mars, I Kemp, R Cooper, N Curzen, R H Stables. Heart Suppl. Issue 2016.

- Comparison of the antiplatelet and antithrombotic effects of bivalirudin versus unfractionated heparin in patients undergoing primary percutaneous coronary intervention: results from the HEAT-PPCI Platelet Substudy. A Shahzad, V Khanna, C Mars, I Kemp, Kala Thayalasamy, R Cooper, Scott Harris, R Stables, N Curzen. EuroPCR annual conference 2015.

- Unfractionated heparin versus bivalirudin in primary percutaneous coronary intervention (HEAT-PPCI): an open-label, single centre, randomised controlled trial. A Shahzad, I Kemp, C Mars, C Roome, K Wilson, R Cooper, M Andron, C Appleby, M Fisher, A Khand, B Kunadian, J D Mills, J L Morris, W L Morrison, S Munir, N D Palmer, R A Perry, D R Ramsdale and R H Stables. Heart suppl. Issue; BCIS ACI annual conference 2015.

- Results from the HEAT-PPCI trial: Unfractionated heparin versus bivalirudin in primary percutaneous coronary intervention. A Shahzad, I Kemp, C Mars, C Roome, K Wilson, R Cooper, M Andron, C Appleby, M Fisher, A Khand, B Kunadian, J D Mills J L Morris, W L Morrison, S Munir, N D Palmer, R A Perry, D R Ramsdale and R H Stables. Eurothrombosis annual conference 2014.

- Radial versus femoral access in HEAT-PPCI study: MACE and bleeding outcomes – Exploring the limitations of observational research. A Kumar, S Aggarwal, S Imran, A Shahzad, R H Stables. Heart Suppl. Issue 2016.

Presentations:

International:

2014	HEAT-PPCI trial results	Eurothrombosis, Paris
2014	Debate: DAPT therapy – 6 months are enough – For	Eurothrombosis, Paris
2014	Mechanical thrombectomy – Current evidence	Eurothrombosis, Paris
2014	HEAT-PPCI trial	Ticagrelor Science Conference, Barcelona
2014	HEAT-PPCI trial results in a Late-Breaking Clinical Trials (LBCT) session	ACC Annual Conference, Washington DC
2007	Evaluation of the success of DC Cardioversion and its Follow up in patients with Atrial Fibrillation	ESC, Lisbon

National:

2016	Results from HEAT-PPCI antiplatelet therapy substudy	Advisory Board Daiichi Sankyo, London
2016	HEAT-PPCI antiplatelet therapy substudy	BCIS ACI, London
2015	Antiplatelet and antithrombotic therapies	International Cardiology Symposium, Manchester

2015	Young Investigator Award poster presentation	BCIS ACI, London
2014	HEAT-PPCI trial results	Scientific year in review, London
2014	HEAT-PPCI trial at RCP	ICMS Annual symposium, London
2014	Results from the HEAT-PPCI	Aggrastat review board, Glasgow
2013	HEAT-PPCI trial at RCP	ICMS Annual symposium, London
2012	Rationale and design of HEAT-PPCI trial	Coronary Artery Disease group meeting, Imperial College, London
2012	Rationale and design of HEAT-PPCI trial	ICMS Inaugural Research day, London

References:

1. Weitz JI, Hudoba M, Massel D, et al. Clot-bound thrombin is protected from inhibition by heparin-antithrombin III but is susceptible to inactivation by antithrombin III-independent inhibitors. Journal of Clinical Investigation 1990;**86**(2):385-91.

2. Henrik A, Daniel LG, Kazuo F, et al. Protease-Activated Receptor 1 Is the Primary Mediator of Thrombin-Stimulated Platelet Procoagulant Activity. Proceedings of the National Academy of Sciences of the United States of America 1999;**96**(20):11189-93.

3. De Candia E, Hall SW, Rutella S, et al. Binding of Thrombin to Glycoprotein Ib Accelerates the Hydrolysis of Par-1 on Intact Platelets. Journal of Biological Chemistry 2001;**276**(7):4692-98.

4. Tulinsky A. Molecular Interactions of Thrombin. Seminars in thrombosis and hemostasis 1996;**22**(2):117-24.

5. Lane DA, Denton J, Flynn AM, et al. Anticoagulant activities of heparin oligosaccharides and their neutralization by platelet factor 4. Biochemical Journal 1984;**218**(3):725-32.

6. de Romeuf C, Mazurier C. Heparin binding assay of von Willebrand factor (vWF) in plasma milieu--evidence of the importance of the multimerization degree of vWF. Thromb Haemost 1993;**69**(5):436-40.

7. Young E, Prins M, Levine MN, et al. Heparin binding to plasma proteins, an important mechanism for heparin resistance. Thromb Haemost 1992;**67**(6):639-43.

8. Becker RC. Hirudin-based anticoagulant strategies for patients with suspected heparin-induced thrombocytopenia undergoing percutaneous coronary interventions and bypass grafting. Journal of Thrombosis and Thrombolysis 2000;**10**(SUPPL. 1):S59-S68.

9. Rydel TJ, Ravichandran KG, Tulinsky A, et al. The Structure of a Complex of Recombinant Hirudin and Human α-Thrombin. Science 1990;**249**(4966):277-80.

10. Maraganore JM, Bourdon P, Jablonski J, et al. Design and characterization of hirulogs: A novel class of bivalent peptide inhibitors of thrombin. Biochemistry 1990;**29**(30):7095-101.

11. Kaminski M, McDonagh J. Inhibited thrombins. Interactions with fibrinogen and fibrin. Biochemical Journal 1987;**242**(3):881-87.

12. Marbet GA, Verstraete M, Kienast J, et al. Clinical pharmacology of intravenously administered recombinant desulfatohirudin (CGP 39393) in healthy volunteers. Journal of cardiovascular pharmacology 1993;**22**(3):364.

13. Steg PG, James SK, Atar D, et al. ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. European Heart Journal 2012;**33**(20):2569-619.

14. 2013 ACCF/AHA Guideline for the Management of ST-Elevation Myocardial Infarction: Executive Summary: A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Catheterization and Cardiovascular Interventions 2013;**82**(1):E1-E27.

15. Stone GW, Witzenbichler B, Guagliumi G, et al. Bivalirudin during primary PCI in acute myocardial infarction. N Engl J Med 2008;**358**(21):2218-30.

16. Steg PG, van 't Hof A, Hamm CW, et al. Bivalirudin Started during Emergency Transport for Primary PCI. The New England journal of medicine 2013;**369**(23):2207-17.

17. Anderson JL, Adams CD, Antman EM, et al. 2012 ACCF/AHA focused update incorporated into the ACCF/AHA 2007 guidelines for the management of patients with unstable angina/non-ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation 2013;**127**(23):e663.

18. Wijns W, Kolh P, Danchin N, et al. Guidelines on myocardial revascularization. European Heart Journal 2010;**31**(20):2501-55.

19. Montalescot G, Zeymer U, Silvain J, et al. Intravenous enoxaparin or unfractionated heparin in primary percutaneous coronary intervention for ST-elevation myocardial infarction: the international randomised open-label ATOLL trial. The Lancet 2011;**378**(9792):693-703.

20. Silvain J, Beygui F, Barthélémy O, et al. Efficacy and safety of enoxaparin versus unfractionated heparin during percutaneous coronary intervention: systematic review and meta-analysis. BMJ 2012;**344**.

21. Kastrati A, Neumann F-J, Schulz S, et al. Abciximab and Heparin versus Bivalirudin for Non–ST-Elevation Myocardial Infarction. The New England journal of medicine 2011;**365**(21):1980-89.

22. Stone GW, McLaurin BT, Cox DA, et al. Bivalirudin for patients with acute coronary syndromes. N Engl J Med 2006;**355**(21):2203-16.

23. Lincoff AM, Bittl JA, Harrington RA, et al. Bivalirudin and Provisional Glycoprotein IIb/IIIa Blockade Compared with Heparin and Planned Glycoprotein IIb/IIIa Blockade during Percutaneous Coronary intervention: REPLACE-2 Randomized Trial. Journal of the American Medical Association 2003;**289**(7):853-63.

24. British Cardiovascular Intervention Society. http://www.bcis.org.uk/pages/page_box_contents.asp?pageid=697&navcatid=11. Central Cardiac Audit Database 2011.

25. De Luca G, Navarese E, Marino P. Risk profile and benefits from Gp IIb-IIIa inhibitors among patients with ST-segment elevation myocardial infarction treated with primary angioplasty: A meta-regression analysis of randomized trials. European Heart Journal 2009;**30**(22):2705-13.

26. Kastrati A, Mehilli J, Sch++hlen H, et al. A Clinical Trial of Abciximab in Elective Percutaneous Coronary Intervention after Pretreatment with Clopidogrel. New England Journal of Medicine 2004;**350**(3):232-38.

27. Kastrati A, Mehilli J, Neumann FJ, et al. Abciximab in patients with acute coronary syndromes undergoing percutaneous coronary intervention after clopidogrel pretreatment: The ISAR-REACT 2 randomized trial. Journal of the American Medical Association 2006;**295**(13):1531-38.

28. Hamm CW, Heeschen C, Goldmann B, et al. Benefit of Abciximab in Patients with Refractory Unstable Angina in Relation to Serum Troponin T Levels. The New England journal of medicine 1999;**340**(21):1623-29.

29. Heeschen C, Hamm CW, Goldmann B, et al. Troponin concentrations for stratification of patients with acute coronary syndromes in relation to therapeutic efficacy of tirofiban. The Lancet 1999;**354**(9192):1757-62.

30. Stone GW, Bertrand ME, Moses JW, et al. Routine upstream initiation vs deferred selective use of glycoprotein IIb/IIIa inhibitors in acute coronary syndromes: the ACUITY Timing trial. JAMA 2007;**297**(6):591.

31. Subherwal S, Bach RG, Chen AY, et al. Baseline risk of major bleeding in non-ST-segment-elevation myocardial infarction: the CRUSADE (Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the ACC/AHA Guidelines) Bleeding Score. Circulation 2009;**119**(14):1873.

32. Giugliano RP, White JA, Bode C, et al. Early versus Delayed, Provisional Eptifibatide in Acute Coronary Syndromes. The New England journal of medicine 2009;**360**(21):2176-90.

33. Boersma E, Harrington RA, Moliterno DJ, et al. Platelet glycoprotein IIb/IIIa inhibitors in acute coronary syndromes: a meta-analysis of all major randomised clinical trials. The Lancet 2002;**359**(9302):189-98.

34. Lincoff AM, Kleiman NS, Kereiakes DJ, et al. Long-term efficacy of bivalirudin and provisional glycoprotein IIb/IIIa blockade vs heparin and planned glycoprotein IIb/IIIa blockade during percutaneous coronary revascularization: REPLACE-2 randomized trial. JAMA 2004;**292**(6):696-703.

35. Bittl JA. Comparative safety profiles of hirulog and heparin in patients undergoing coronary angioplasty. American Heart Journal 1995;**130**(3 II):658-65.

36. Kastrati A, Neumann FJ, Mehilli J, et al. Bivalirudin versus unfractionated heparin during percutaneous coronary intervention. New England Journal of Medicine 2008;**359**(7):688-96.

37. Lincoff AM, Bittl JA, Kleiman NS, et al. Comparison of bivalirudin versus heparin during percutaneous coronary intervention (the Randomized Evaluation of PCI Linking Angiomax to Reduced Clinical Events [REPLACE]-1 trial). American Journal of Cardiology 2004;**93**(9):1092-96.

38. Bittl JA, Chaitman BR, Feit F, et al. Bivalirudin versus heparin during coronary angioplasty for unstable or postinfarction angina: Final report reanalysis of the Bivalirudin Angioplasty Study. American Heart Journal 2001;**142**(6):952-59.

39. Schulz S, Mehilli J, Neumann FJ, et al. ISAR-REACT 3A: a study of reduced dose of unfractionated heparin in biomarker negative patients undergoing percutaneous coronary intervention. Eur Heart J 2010;**31**(20):2482-91.

40. Dangas GD, Mehran R, Nikolsky E, et al. Effect of switching antithrombin agents for primary angioplasty in acute myocardial infarction: The HORIZONS-SWITCH analysis. Journal of the American College of Cardiology 2011;**57**(23):2309-16.

41. Koutouzis M, Lagerqvist B, James S, et al. Unfractionated heparin administration in patients treated with bivalirudin during primary percutaneous coronary intervention is associated lower mortality and target lesion thrombosis: A report from the Swedish coronary angiography and angioplasty registry (SCAAR). Heart 2011.

42. Langrish JP, Fox KAA. Optimal antithrombotic treatment during primary percutaneous coronary intervention? Heart 2011;**97**(18):1459.

43. Angeras O. SCAAR: Could cheap heparin replace pricy bivalirudin in PCI for non-STE-ACS? http://www.theheart.org/article/1541851.do. 2013. 2013.

44. Kaptchuk TJ. The double-blind, randomized, placebo-controlled trial: Gold standard or golden calf? Journal of Clinical Epidemiology 2001;**54**(6):541-49.

45. Cutlip DE, Windecker S, Mehran R, et al. Clinical end points in coronary stent trials: A case for standardized definitions. Circulation 2007;**115**(17):2344-51.

46. Jones B, Jarvis P, Lewis JA, et al. Trials to assess equivalence: The importance of rigorous methods. British Medical Journal 1996;**313**(7048):36-39.

47. Zhang J, Yang X. Efficacy and safety of bivalirudin versus heparin in patients with diabetes mellitus undergoing percutaneous coronary intervention: A meta-analysis of randomized controlled trials. Medicine 2017;**96**(29):e7204.

48. Nairooz R, Sardar P, Amin H, et al. Short- and long-term outcomes in diabetes patients undergoing percutaneous coronary intervention with bivalirudin compared with heparin and glycoprotein IIb/IIIA inhibitors: A meta-analysis of randomized trials. Catheterization and Cardiovascular Interventions 2015;**86**(3):364-75.

49. Dangas GD, Mehran R, Nikolsky E, et al. Effect of Switching Antithrombin Agents for Primary Angioplasty in Acute Myocardial Infarction The HORIZONS-SWITCH Analysis. J Am Coll Cardiol 2011;**57**(23):2309-16.

50. Svilaas T, Vlaar PJ, van der Horst IC, et al. Thrombus Aspiration during Primary Percutaneous Coronary Intervention. The New England journal of medicine 2008;**358**(6):557-67.

51. Fröbert O, Lagerqvist B, Olivecrona GK, et al. Thrombus Aspiration during ST-Segment Elevation Myocardial Infarction. The New England journal of medicine 2013;**369**(17):1587-97.

52. Parodi G, Valenti R, Bellandi B, et al. Comparison of prasugrel and ticagrelor loading doses in ST-segment elevation myocardial infarction patients: RAPID (Rapid Activity of Platelet Inhibitor Drugs) primary PCI study. J Am Coll Cardiol 2013;**61**(15):1601-6.

53. Alexopoulos D, Xanthopoulou I, Gkizas V, et al. Randomized assessment of ticagrelor versus prasugrel antiplatelet effects in patients with ST-segment-elevation myocardial infarction. Circ Cardiovasc Interv 2012;**5**(6):797-804.

54. Wiviott SD, Braunwald E, McCabe CH, et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes. N Engl J Med 2007;**357**(20):2001-15.

55. Wallentin L, Becker RC, Budaj A, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. N Engl J Med 2009;**361**(11):1045-57.

56. Capodanno D, De Caterina R. Bivalirudin for acute coronary syndromes: premises, promises and doubts. Thromb Haemost 2014;**113**(3).

57. Stone GW, McLaurin BT, Cox DA, et al. Bivalirudin for patients with acute coronary syndromes. N Engl J Med 2006;**355**(21):2203-16.

58. Kastrati A, Neumann FJ, Mehilli J, et al. Bivalirudin versus unfractionated heparin during percutaneous coronary intervention. N Engl J Med 2008;**359**(7):688-96.

59. Stone GW, Witzenbichler B, Guagliumi G, et al. Bivalirudin during primary PCI in acute myocardial infarction. N Engl J Med 2008;**358**(21):2218-30.

60. Kastrati A, Neumann FJ, Schulz S, et al. Abciximab and heparin versus bivalirudin for non-ST-elevation myocardial infarction. N Engl J Med 2011;**365**(21):1980-9.

61. Zeymer U, van 't Hof A, Adgey J, et al. Bivalirudin is superior to heparins alone with bailout GP IIb/IIIa inhibitors in patients with ST-segment elevation myocardial infarction transported emergently for primary percutaneous coronary intervention: a pre-specified analysis from the EUROMAX trial. Eur Heart J 2014;**35**(36):2460-7.

62. Shahzad A, Kemp I, Mars C, et al. Unfractionated heparin versus bivalirudin in primary percutaneous coronary intervention (HEAT-PPCI): an open-label, single centre, randomised controlled trial. Lancet 2014;**384**(9957):1849-58.

63. Hobson AR, Petley GW, Dawkins KD, et al. A novel fifteen minute test for assessment of individual time-dependent clotting responses to aspirin and clopidogrel using modified thrombelastography. Platelets 2007;**18**(7):497-505.

64. Sambu N, Hobson A, Curzen N. "Short" thrombelastography as a test of platelet reactivity in response to antiplatelet therapy: validation and reproducibility. Platelets 2011;**22**(3):210-6.

65. Steg PG, van 't Hof A, Hamm CW, et al. Bivalirudin started during emergency transport for primary PCI. N Engl J Med 2013;**369**(23):2207-17.

66. Pepke W, Eisenreich A, Jaster M, et al. Bivalirudin inhibits periprocedural platelet function and tissue factor expression of human smooth muscle cells. Cardiovasc Ther 2013;**31**(2):115-23.

67. Busch G, Steppich B, Sibbing D, et al. Bivalirudin reduces platelet and monocyte activation after elective percutaneous coronary intervention. Thromb Haemost 2009;**101**(2):340-44.

68. Schneider DJ, Keating F, Sobel BE. Greater inhibitory effects of bivalirudin compared with unfractionated heparin plus eptifibitide on thrombin-induced platelet activation. Coron Artery Dis 2006;**17**(5):471-76.

69. Schneider DJ, Sobel BE. Streamlining the design of promising clinical trials: in-vitro testing of antithrombotic regimens and multiple agonists of platelet activation. Coron Artery Dis 2009;**20**(2):175-78.

70. Aggarwal A, Sobel BE, Schneider DJ. Decreased platelet reactivity in blood anticoagulated with bivalirudin or enoxaparin compared with unfractionated heparin: implications for coronary intervention. J Thromb Thrombolysis 2002;**13**(3):161-65.

71. Saucedo JF, Aude W, Pacheco R, et al. Inhibition of platelet aggregation with eptifibatide, bivalirudin, and heparin in patients undergoing percutaneous coronary intervention receiving clopidogrel pretreatment (The PharmacoDynamic Evaluation of Angiomax, Clopidogrel with or without INtegrilin [DEACON] study). The American journal of cardiology 2005;**95**(12):1453-56.

72. Young G, Yonekawa KE, Nakagawa PA, et al. Differential effects of direct thrombin inhibitors and antithrombin-dependent anticoagulants on the dynamics of clot formation. Blood Coagul Fibrinolysis 2007;**18**(2):97-103.

73. Nielsen VG, Steenwyk BL, Gurley WQ, et al. Argatroban, bivalirudin, and lepirudin do not decrease clot propagation and strength as effectively as heparin-activated antithrombin in vitro. The Journal of heart and lung transplantation 2006;**25**(6):653-63.

74. Taketomi T, Szlam F, Vinten-Johansen J, et al. Thrombin-activated thrombelastography for evaluation of thrombin interaction with thrombin inhibitors. Blood Coagul Fibrinolysis 2007;**18**(8):761-67.

75. Xu Y, Wu W, Wang L, et al. Differential profiles of thrombin inhibitors (heparin, hirudin, bivalirudin, and dabigatran) in the thrombin generation assay and thromboelastography in vitro. Blood Coagul Fibrinolysis 2013;**24**(3):332-38.

76. Tanaka KA, Szlam F, Sun HY, et al. Thrombin generation assay and viscoelastic coagulation monitors demonstrate differences in the mode of thrombin inhibition between unfractionated heparin and bivalirudin. Anesth Analg 2007;**105**(4):933-39.

77. White HD. Pharmacological and clinical profile of bivalirudin in the treatment of patients with acute coronary syndrome. Expert Opin Drug Metab Toxicol 2009;**5**(5):529-38.

78. Warkentin TE, Koster A. Bivalirudin: a review. Expert Opin Pharmacother 2005;**6**(8):1349-71.

79. Alexopoulos D, Galati A, Xanthopoulou I, et al. Ticagrelor versus prasugrel in acute coronary syndrome patients with high on-clopidogrel platelet reactivity following percutaneous coronary intervention: a pharmacodynamic study. J Am Coll Cardiol 2012;**60**(3):193-9.

80. Clemmensen P, Wiberg S, van't Hof A, et al. Acute stent thrombosis after primary percutaneous coronary intervention: insights from the EUROMAX trial (European Ambulance Acute Coronary Syndrome Angiography). JACC Cardiovasc Interv 2015;**8**(1_PB):214-20.

81. Han Y, Guo J, Zheng Y, et al. Bivalirudin vs heparin with or without tirofiban during primary percutaneous coronary intervention in acute myocardial infarction: the BRIGHT randomized clinical trial. JAMA 2015;**313**(13):1336-46.

82. Orfeo T, Brummel-Ziedins KE, Mann KG. Influence of bivalirudin on tissue factor-triggered coagulation. Blood Coagul Fibrinolysis 2007;**18**(5):407-14.

83. Furugohri T, Sugiyama N, Morishima Y, et al. Antithrombin-independent thrombin inhibitors, but not direct factor Xa inhibitors, enhance thrombin generation in plasma through inhibition of thrombin-thrombomodulin-protein C system. Thromb Haemost 2011;**106**(6):1076-83.

84. Perzborn E, Heitmeier S, Buetehorn U, et al. Direct thrombin inhibitors, but not the direct factor Xa inhibitor rivaroxaban, increase tissue factor-induced hypercoagulability in vitro and in vivo. J Thromb Haemost 2014;**12**(7):1054-65.

85. Huet RCG, Cernak V, de Vries AJ, et al. Bivalirudin is inferior to heparin in preservation of intraoperative autologous blood. Thromb Res 2012;**130**(2):163-65.

86. Linder R, Frebelius S, Grip L, et al. The influence of direct and antithrombin-dependent thrombin inhibitors on the procoagulant and anticoagulant effects of thrombin. Thromb Res 2003;**110**(4):221-26.

87. Furugohri T, Shiozaki Y, Muramatsu S, et al. Different antithrombotic properties of factor Xa inhibitor and thrombin inhibitor in rat thrombosis models. Eur J Pharmacol 2005;**514**(1):35-42.

88. Holinstat M, Colowick NE, Hudson WJ, et al. Dichotomous effects of exposure to bivalirudin in patients undergoing percutaneous coronary intervention on protease-activated receptor-mediated platelet activation. J Thromb Thrombolysis 2013;**35**(2):209-22.

89. Gao C, Boylan B, Fang J, et al. Heparin promotes platelet responsiveness by potentiating αIIbβ3-mediated outside-in signaling. Blood 2011;**117**(18):4946-52.

90. Eslam RB, Reiter N, Kaider A, et al. Regulation of PAR-1 in patients undergoing percutaneous coronary intervention: effects of unfractionated heparin and bivalirudin. Eur Heart J 2009;**30**(15):1831-36.

91. Sibbing D, Busch G, Braun S, et al. Impact of bivalirudin or unfractionated heparin on platelet aggregation in patients pretreated with 600 mg clopidogrel undergoing elective percutaneous coronary intervention. Eur Heart J 2008;**29**(12):1504-9.

92. Kolh P, Windecker S, Alfonso F, et al. 2014 ESC/EACTS Guidelines on myocardial revascularization: the Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). Developed with the special contribution of the European Association of Percutaneous Cardiovascular Interventions (EAPCI). Eur J Cardiothorac Surg 2014;**46**(4):517-92.

93. Sibbing D, Bernlochner I, Schulz S, et al. Prognostic Value of a High On-Clopidogrel Treatment Platelet Reactivity in Bivalirudin Versus Abciximab Treated Non–ST-Segment Elevation Myocardial Infarction Patients: ISAR-REACT 4 (Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment-4) Platelet Substudy. J Am Coll Cardiol 2012;**60**(5):369-77.

94. StephanWindecker, Kolh P, Alfonso F, et al. 2014 ESC/EACTS Guidelines on Myocardial Revascularization. Revista Española de Cardiología (English Edition) 2015;**68**(2):144.

95. Wallentin L, Becker RC, Budaj A, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. New England Journal of Medicine 2009;**361**(11):1045-57.

96. Wiviott SD, Braunwald E, McCabe CH, et al. Prasugrel versus Clopidogrel in Patients with Acute Coronary Syndromes. New England Journal of Medicine 2007;**357**(20):2001-15.

97. Heestermans AACM, van Werkum JW, Taubert D, et al. Impaired bioavailability of clopidogrel in patients with a ST-segment elevation myocardial infarction. Thrombosis Research 2008;**122**(6):776-81.

98. Alexopoulos D, Theodoropoulos KC, Stavrou EF, et al. Prasugrel Versus High Dose Clopidogrel to Overcome Early High on Clopidogrel Platelet Reactivity in Patients with ST Elevation Myocardial Infarction. Cardiovascular Drugs and Therapy 2012;**26**(5):393-400.

99. Biscaglia S, Tebaldi M, Vranckx P, et al. Effects of pre-hospital clopidogrel administration on early and late residual platelet reactivity in ST-segment elevation myocardial infarction patients undergoing primary intervention. Journal of Thrombosis and Haemostasis 2013;**11**(1):192-94.

100. Valgimigli M, Tebaldi M, Campo G, et al. Prasugrel Versus Tirofiban Bolus With or Without Short Post-Bolus Infusion With or Without Concomitant Prasugrel Administration in Patients With Myocardial Infarction Undergoing Coronary Stenting: The FABOLUS PRO (Facilitation through Aggrastat By drOpping or shortening Infusion Line in patients with

ST-segment elevation myocardial infarction compared to or on top of PRasugrel given at loading dOse) Trial. JACC: Cardiovascular Interventions 2012;**5**(3):268-77.

101. Parodi G, Valenti R, Bellandi B, et al. Comparison of Prasugrel and Ticagrelor Loading Doses in ST-Segment Elevation Myocardial Infarction Patients: RAPID (Rapid Activity of Platelet Inhibitor Drugs) Primary PCI Study. Journal of the American College of Cardiology 2013;**61**(15):1601-06.

102. Alexopoulos D, Xanthopoulou I, Gkizas V, et al. Randomized Assessment of Ticagrelor Versus Prasugrel Antiplatelet Effects in Patients with ST-Segment–Elevation Myocardial Infarction. Circulation: Cardiovascular Interventions 2012;**5**(6):797-804.

103. Parodi G, Bellandi B, Valenti R, et al. Comparison of double (360 mg) ticagrelor loading dose with standard (60 mg) prasugrel loading dose in ST-elevation myocardial infarction patients: The Rapid Activity of Platelet Inhibitor Drugs (RAPID) primary PCI 2 study. American Heart Journal 2014;**167**(6):909-14.

104. Tóth O, Calatzis A, Penz S, et al. Multiple electrode aggregometry: a new device to measure platelet aggregation in whole blood. Thrombosis and haemostasis 2006;**96**(6):781.

105. Tantry US, Bonello L, Aradi D, et al. Consensus and Update on the Definition of On-Treatment Platelet Reactivity to Adenosine Diphosphate Associated With Ischemia and Bleeding. Journal of the American College of Cardiology 2013;**62**(24):2261-73.

106. Zeymer U, Mochmann H-C, Mark B, et al. Double-Blind, Randomized, Prospective Comparison of Loading Doses of 600 mg Clopidogrel Versus 60 mg Prasugrel in Patients With Acute ST-Segment Elevation Myocardial Infarction Scheduled for Primary Percutaneous Intervention: The ETAMI Trial (Early Thienopyridine treatment to improve primary PCI in Patients with Acute Myocardial Infarction). JACC: Cardiovascular Interventions 2015;**8**(1, Part B):147-54.

107. Gurbel PA, Bliden KP, Butler K, et al. Randomized Double-Blind Assessment of the ONSET and OFFSET of the Antiplatelet Effects of Ticagrelor Versus Clopidogrel in Patients With Stable Coronary Artery Disease: The ONSET/OFFSET Study. Circulation 2009;**120**(25):2577-85.

108. Laine M, Gaubert M, Frère C, et al. COMparison of Platelet reactivity following prAsugrel and ticagrelor loading dose in ST-Segment elevation myocardial infarctION patients: The COMPASSION study. Platelets 2015;**26**(6):570-72.

109. Perl L, Zemer-Wassercug N, Rechavia E, et al. Comparison of platelet inhibition by prasugrel versus ticagrelor over time in patients with acute myocardial infarction. Journal of Thrombosis and Thrombolysis 2015;**39**(1):1-7.

110. Motovska Z, Hlinomaz O, Miklik R, et al. Prasugrel Versus Ticagrelor in Patients With Acute Myocardial Infarction Treated With Primary Percutaneous Coronary Intervention: Multicenter Randomized PRAGUE-18 Study. Circulation 2016;**134**(21):1603.

111. Montalescot G, Wiviott SD, Braunwald E, et al. Prasugrel compared with clopidogrel in patients undergoing percutaneous coronary intervention for ST-elevation myocardial infarction (TRITON-TIMI 38): double-blind, randomised controlled trial. The Lancet;**373**(9665):723-31.

112. Steg PG, James S, Harrington RA, et al. Ticagrelor Versus Clopidogrel in Patients With ST-Elevation Acute Coronary Syndromes Intended for Reperfusion With Primary Percutaneous Coronary Intervention: A Platelet Inhibition and Patient Outcomes (PLATO) Trial Subgroup Analysis. Circulation 2010;**122**(21):2131-41.

113. Danchin N, Lettino M, Zeymer U, et al. Use, patient selection and outcomes of P2Y12 receptor inhibitor treatment in patients with STEMI based on contemporary European registries. European Heart Journal - Cardiovascular Pharmacotherapy 2016.

114. Schulz S, Angiolillo D, Antoniucci D, et al. Randomized Comparison of Ticagrelor versus Prasugrel in Patients with Acute Coronary Syndrome and Planned Invasive Strategy—Design and Rationale of the Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment (ISAR-REACT) 5 Trial. J of Cardiovasc Trans Res 2014;**7**(1):91-100.

115. Sprung CL, Winick BJ. Informed consent in theory and practice: legal and medical perspectives on the informed consent doctrine and a proposed reconceptualization. Crit Care Med 1989;**17**(12):1346-54.

116. Meisel A, Roth LH, Lidz CW. Toward a model of the legal doctrine of informed consent. The American journal of psychiatry 1977;**134**(3):285-9.

117. Frohock FM. A History and Theory of Informed Consent. By Ruth R. Faden and Tom L. Beauchamp (with Nancy M. P. King) (New York: Oxford University Press, 1986. xv, 392p. $29.95). American Political Science Review 1988;**82**(01):271-73.

118. Gupta UC. Informed consent in clinical research: Revisiting few concepts and areas. Perspectives in Clinical Research 2013;**4**(1):26-32.

119. ICH harmonized tripartite guideline: Guideline for Good Clinical Practice. Journal of postgraduate medicine 2001;**47**(1):45-50.

120. WMA Declaration of Helsinki - 2008 update. Ethical Principles for Medical Research Involving Human Subjects 2008.

121. Appelbaum PS, Grisso T. Assessing patients' capacities to consent to treatment. The New England journal of medicine 1988;**319**(25):1635-8.

122. Intensive versus Conventional Glucose Control in Critically Ill Patients. New England Journal of Medicine 2009;**360**(13):1283-97.

123. Intensity of Continuous Renal-Replacement Therapy in Critically Ill Patients. New England Journal of Medicine 2009;**361**(17):1627-38.

124. A Comparison of Albumin and Saline for Fluid Resuscitation in the Intensive Care Unit. New England Journal of Medicine 2004;**350**(22):2247-56.

125. Shahzad A, Kemp I, Mars C, et al. Unfractionated heparin versus bivalirudin in primary percutaneous coronary intervention (HEAT-PPCI): an open-label, single centre, randomised controlled trial. The Lancet;**384**(9957):1849-58.

126. Cannon CP, Gibson CM, Lambrew CT, et al. Relationship of symptom-onset-to-balloon time and door-to-balloon time with mortality in patients undergoing angioplasty for acute myocardial infarction. Journal of the American Medical Association 2000;**283**(22):2941-47.

127. De Luca G, Suryapranata H, Ottervanger JP, et al. Time Delay to Treatment and Mortality in Primary Angioplasty for Acute Myocardial Infarction: Every Minute of Delay Counts. Circulation 2004;**109**(10):1223-25.

128. Smithline HA, Mader TJ, Crenshaw BJ. Do patients with acute medical conditions have the capacity to give informed consent for emergency medicine research? Academic Emergency Medicine 1999;**6**(8):776-80.

129. Williams BF, French JK, White HD. Informed consent during the clinical emergency of acute myocardial infarction (HERO-2 consent substudy): A prospective observational study. Lancet 2003;**361**(9361):918-22.

130. Gammelgaard A, Mortensen OS, Rossel P. Patients' perceptions of informed consent in acute myocardial infarction research: A questionnaire based survey of the consent process in the DANAMI-2 trial. Heart 2004;**90**(10):1124-28.

131. Yuval R, Halon DA, Merdler A, et al. Patient comprehension and reaction to participating in a double-blind randomized clinical trial (ISIS-4) in acute myocardial infarction. Archives of Internal Medicine 2000;**160**(8):1142-46.

132. Ockene IS, Miner J, Shannon TA, et al. The consent process in the Thrombolysis in Myocardial Infarction (TIMI--phase I) trial. Clinical Research 1991;**39**(1):13-17.

133. Agard A, Herlitz J, Hermeren G. Obtaining informed consent from patients in the early phase of acute myocardial infarction: Physicians' experiences and attitudes. Heart 2004;**90**(2):208-10.

134. Jubelirer SJ. Level of reading difficulty in educational pamphlets and informed consent documents for cancer patients. The West Virginia medical journal 1991;**87**(12):554-7.

135. Lavelle-Jones C, Byrne DJ, Rice P, et al. Factors affecting quality of informed consent. BMJ 1993;**306**(6882):885-90.

136. Snowdon C, Garcia J, Elbourne D. Making sense of randomization; responses of parents of critically ill babies to random allocation of treatment in a clinical trial. Social Science & Medicine 1997;**45**(9):1337-55.

137. Burns KE, Magyarody NM, Duffett M, et al. Attitudes of the general public toward alternative consent models. American journal of critical care : an official publication, American Association of Critical-Care Nurses 2011;**20**(1):75-83.

138. Scales DC, Smith OM, Pinto R, et al. Patients' preferences for enrolment into critical-care trials. Intensive care medicine 2009;**35**(10):1703-12.

139. Protection of human subjects; informed consent--FDA. Final rule. Federal register 1996;**61**(192):51498-533.

140. Regulations and Guidance on the Protection of Human Subjects: Clinical Investigator, IRB, and Sponsor Responsibilities: exception from informed consent requirements for emergency research. U.S. Department of Health and Human Services, Food and Drug Administration , Philadelphia, pp. Clinical Research Resources, LLC 2006:63-73.

141. U.S. Department of Health and Human Services, Food and Drug Administration (March 2000). Guidance for institutional review boards, clinical investigators, and sponsors: Exception from informed consent requirements for emergency research (21 CFR 50.24). Available at: http://www.fda.gov/ora/ compliance-ref/bimoJ emrfinal.pdf. Fed Regist 2000.

142. Medicines for Human Use (Clinical Trials) Amendment (No.2) Regulations 2006. Statutory Instrument 2006 No 2984 2006.

143. Jansen TC, Kompanje EJO, Bakker J. Deferred proxy consent in emergency critical care research: Ethically valid and practically feasible. Critical Care Medicine 2009;**37**(SUPPL. 1):S65-S68.

144. Lemaire F. Waiving consent for emergency research. European Journal of Clinical Investigation 2005;**35**(5):287-89.

145. Abramson NS, Safar P. Deferred consent: Use in clinical resuscitation research. Annals of Emergency Medicine 1990;**19**(7):781-84.

146. Annane D, Outin H, Fisch C, et al. The effect of waiving consent on enrollment in a sepsis trial. Intensive care medicine 2004;**30**(2):321-4.

147. Cooke CR, Erickson SE, Watkins TR, et al. Age-, sex-, and race-based differences among patients enrolled versus not enrolled in acute lung injury clinical trials. Crit Care Med 2010;**38**(6):1450-7.

148. McAdam JL, Dracup KA, White DB, et al. Symptom experiences of family members of intensive care unit patients at high risk for dying. Crit Care Med 2010;**38**(4):1078-85.

149. Pochard F, Azoulay E, Chevret S, et al. Symptoms of anxiety and depression in family members of intensive care unit patients: ethical hypothesis regarding decision-making capacity. Crit Care Med 2001;**29**(10):1893-7.

150. Pochard F, Darmon M, Fassier T, et al. Symptoms of anxiety and depression in family members of intensive care unit patients before discharge or death. A prospective multicenter study. Journal of critical care 2005;**20**(1):90-6.

151. Mehta S, Quittnat Pelletier F, Brown M, et al. Why substitute decision makers provide or decline consent for ICU research studies: a questionnaire study. Intensive care medicine 2012;**38**(1):47-54.

152. British Cardiovascular Intervention Society. http://www.bcis.org.uk/pages/page_box_contents.asp?pageid=697&navcatid=11. Central Cardiac Audit Database 2011. 2011.

153. Kushner FG, Hand M, Smith J, et al. 2009 Focused Updates: ACC/AHA Guidelines for the Management of Patients With ST-Elevation Myocardial Infarction (Updating the 2004 Guideline and 2007 Focused Update) and ACC/AHA/SCAI Guidelines on Percutaneous Coronary Intervention (Updating the 2005 Guideline and 2007 Focused Update). Journal of the American College of Cardiology 2009;**54**(23):2205-41.

154. Faden RR, Beauchamp TL, Kass NE. Informed Consent, Comparative Effectiveness, and Learning Health Care. New England Journal of Medicine 2014;**370**(8):766-68.

155. Is Informed Consent Always Necessary for Randomized, Controlled Trials? New England Journal of Medicine 1999;**341**(6):448-50.

156. Potter JE, McKinley S, Delaney A. Research participants' opinions of delayed consent for a randomised controlled trial of glucose control in intensive care. Intensive care medicine 2013;**39**(3):472-80.

157. Selker HP, Beshansky JR, Sheehan PR, et al. Out-of-hospital administration of intravenous glucose-insulin-potassium in patients with suspected acute coronary syndromes: the IMMEDIATE randomized controlled trial. JAMA 2012;**307**(18):1925.

158. Thiele H, Zeymer U, Neumann F-J, et al. Intraaortic Balloon Support for Myocardial Infarction with Cardiogenic Shock. The New England journal of medicine 2012;**367**(14):1287-96.

159. Dickert NW, Miller FG. Involving patients in enrolment decisions for acute myocardial infarction trials. BMJ : British Medical Journal 2015;**351**.

160. Shaw D. HEAT-PPCI sheds light on consent in pragmatic trials. The Lancet;**384**(9957):1826-27.

161. Rosamond W, Flegal K, Furie K, et al. Heart disease and stroke statistics--2008 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Circulation 2008;**117**(4):e25.

162. West RM, Cattle BA, Bouyssie M, et al. Impact of hospital proportion and volume on primary percutaneous coronary intervention performance in England and Wales. European Heart Journal 2011;**32**(6):706-11.

163. Antman EM, Anbe DT, Armstrong PW, et al. ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction--executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 1999 Guidelines for the Management of Patients With Acute Myocardial Infarction). Circulation 2004;**110**(5):588.

164. Jansen T, Bakker J, Kompanje E. Inability to obtain deferred consent due to early death in emergency research: effect on validity of clinical trial results. Intensive care medicine 2010;**36**(11):1962-65.

165. Treweek S, Pitkethly M, Cook J, et al. Strategies to improve recruitment to randomised controlled trials. The Cochrane database of systematic reviews 2010(4):MR000013.

166. Bivalirudin for the treatment of ST-segment-elevation myocardial infarction. https://www.nice.org.uk/guidance/ta230/resources/bivalirudin-for-the-treatment-of-stsegmentelevation-myocardial-infarction-82600363875013. 2011.

167. Van De Werf F, Bax J, Betriu A, et al. Management of acute myocardial infarction in patients presenting with persistent ST-segment elevation. European Heart Journal 2008;**29**(23):2909-45.

168. Moher D, Schulz KF, Altman D. The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomized trials. JAMA 2001;**285**(15):1987.

169. Ludman PF. British Cardiovascular Intervention Society Registry for audit and quality assessment of percutaneous coronary interventions in the United Kingdom. Heart 2011;**97**(16):1293.

170. The NHS Information Centre. http://www.ic.nhs.uk/. NHS IC 2012. 2012.

171. Helsinki WMADo. Ethical Principles for Medical Research Involving Human Subjects Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and Last Amended by the 52nd WMA General Assembly, Edinburgh,Scotland, October 2000. 2000.

172. Section 251 of the NHS Act 2006 (previously Health and Social Care Act 2001); http://www.nigb.nhs.uk/s251/abouts251. accessed April 2009. 2006.

173. Knowles RL, Bull C, Wren C, et al. Ethics, governance and consent in the UK: implications for research into the longer-term outcomes of congenital heart defects. Archives of Disease in Childhood 2011;**96**(1):14.

174. Register of approved section 251 applications, http://www.nigb.nhs.uk/s251/registerapp. (last updated 23 November 2012). 2006.

175. Radecki CM, Jaccard J. Psychological Aspects of Organ Donation: A Critical Review and Synthesis of Individual and Next-of-Kin Donation Decisions. Health Psychology 1997;**16**(2):183-95.

176. Kämäräinen A, Silfvast T, Saarinen S, et al. Conduct of emergency research in patients unable to give consent—Experiences and perceptions of patients, their consent providing next of kin, and treating physicians following a prehospital resuscitation trial. Resuscitation 2011;**83**(1):81-85.

177. Valentinuzzi ME. Friedman L M, Furberg C D, DeMets D L: Fundamentals of Clinical Trials 3rd edition. BioMedical Engineering OnLine 2004;**3**(1):1-2.

178. Stables RH. Coronary artery bypass surgery versus percutaneous coronary intervention with stent implantation in patients with multivessel coronary artery disease (the Stent or Surgery trial): A randomised controlled trial. Lancet 2002;**360**(9338):965-70.

179. Laarman GJ, Suttorp MJ, Dirksen MT, et al. Paclitaxel-eluting versus uncoated stents in primary percutaneous coronary intervention. New England Journal of Medicine 2006;**355**(11):1105-13.

180. Grines CL, Cox DA, Stone GW, et al. Coronary angioplasty with or without stent implantation for acute myocardial infarction. New England Journal of Medicine 1999;**341**(26):1949-56.

181. Stone GW, Grines CL, Cox DA, et al. Comparison of angioplasty with stenting, with or without abciximab, in acute myocardial infarction. New England Journal of Medicine 2002;**346**(13):957-66.

182. Brener SJ, Barr LA, Burchenal JEB, et al. Randomized, placebo-controlled trial of platelet glycoprotein IIb/IIIa blockade with primary angioplasty for acute myocardial infarction. Circulation 1998;**98**(8):734-41.

183. Andersen HR, Nielsen TT, Vesterlund T, et al. Danish multicenter randomized study on fibrinolytic therapy versus acute coronary angioplasty in acute myocardial infarction: Rationale and design of the DANish trial in Acute Myocardial Infarction-2 (DANAMI-2). American Heart Journal 2003;**146**(2):234-41.

184. White E, Armstrong BK, Saracci R. *Principles of exposure measurement in epidemiology : collecting, evaluating, and improving measures of disease risk factors*. Oxford [etc.]: Oxford University Press, 2008.

185. Joseph G, Dohan D. Diversity of participants in clinical trials in an academic medical center. Cancer 2009;**115**(3):608-15.

186. Ruffin MT, Baron J. Recruiting subjects in cancer prevention and control studies. Journal of Cellular Biochemistry 2000;**77**(S34):80-83.

187. *Evidence-based medicine : how to practice and teach EBM*. 2nd ed. Edinburgh: Churchill Livingstone, 2000.

188. Hospital Episode Statistics. Health and social care infromation centre. http://www.hscic.gov.uk/hes. 2014.

189. Gavalova L WC. The Myocardial Ischaemia National Audit Project (MINAP): Annual Public Report April 2011 - March 2012. www ucl ac uk/nicor 2012. 2012.

190. Myocardial infarction with ST-segment-elevation (STEMI) 2013 NICE guidelines: full version. https://www.nice.org.uk/guidance/cg167/documents/myocardial-infarction-with-stsegmentelevation-stemi-nice-version2. 2013.

191. Masoudi FA, Ponirakis A, Yeh RW, et al. Cardiovascular Care Facts: A Report From the National Cardiovascular Data Registry: 2011: A Report From the National Cardiovascular Data Registry: 2011. Journal of the American College of Cardiology 2013;**62**(21):1931-47.

192. Moussa I, Hermann A, Messenger JC, et al. The NCDR CathPCI Registry: a US national perspective on care and outcomes for percutaneous coronary intervention. Heart 2013;**99**(5):297.

193. Brennan JM, Curtis JP, Dai D, et al. Enhanced Mortality Risk Prediction With a Focus on High-Risk Percutaneous Coronary Intervention: Results From 1,208,137 Procedures in the NCDR (National Cardiovascular Data Registry): Results From 1,208,137 Procedures in the NCDR (National Cardiovascular Data Registry). JACC: Cardiovascular Interventions 2013;**6**(8):790-99.

194. Baklanov DV, Kaltenbach LA, Marso SP, et al. The Prevalence and Outcomes of Transradial Percutaneous Coronary Intervention for ST-Segment Elevation Myocardial Infarction:

Analysis From the National Cardiovascular Data Registry (2007 to 2011): Analysis From the National Cardiovascular Data Registry (2007 to 2011). Journal of the American College of Cardiology 2013;**61**(4):420-26.

195. McManus DD, Gore J, Yarzebski J, et al. Recent Trends in the Incidence, Treatment, and Outcomes of Patients with STEMI and NSTEMI. The American Journal of Medicine 2011;**124**(1):40-47.

196. Jacobs AK, Antman EM, Faxon DP, et al. Development of systems of care for ST-elevation myocardial infarction patients: executive summary. Circulation 2007;**116**(2):217.

197. Birkhead JS, Weston C, Lowe D. Impact of specialty of admitting physician and type of hospital on care and outcome for myocardial infarction in England and Wales during 2004-5: observational study. BMJ 2006;**332**(7553):1306.

198. Krumholz HM, Bradley EH, Nallamothu BK, et al. A Campaign to Improve the Timeliness of Primary Percutaneous Coronary Intervention: Door-to-Balloon: An Alliance for Quality. JACC: Cardiovascular Interventions 2008;**1**(1):97-104.

199. Terkelsen CJ, Sørensen JT, Maeng M, et al. System delay and mortality among patients with STEMI treated with primary percutaneous coronary intervention. JAMA 2010;**304**(7):763.

200. Jernberg T, Johanson P, Held C, et al. Association between adoption of evidence-based treatment and survival for patients with ST-elevation myocardial infarction. JAMA 2011;**305**(16):1677.

201. Benedek I, Gyongyosi M, Benedek T. A prospective regional registry of ST-elevation myocardial infarction in Central Romania: Impact of the Stent for Life Initiative recommendations on patient outcomes. American Heart Journal 2013;**166**(3):457-65.

202. CathPCI Registry: For diagnostic cardiac catheterizations and percutaneous coronary interventions. https://www.ncdr.com/webncdr/cathpci/. 2013.

203. Harnek J, Nilsson J, Friberg O, et al. The 2011 outcome from the Swedish Health Care Registry on Heart Disease (SWEDEHEART). Scandinavian cardiovascular journal : SCJ 2013;**47 Suppl 62**:1.

204. Abildstrøm SZ, Madsen M. The Danish Heart Register. Scandinavian Journal of Public Health 2011;**39**(7 suppl):46-49.

205. Hanssen M, Cottin Y, Khalife K, et al. French Registry on Acute ST-elevation and non ST-elevation Myocardial Infarction 2010. FAST-MI 2010. Heart 2012;**98**(9):699.

206. Fox KAA, Goodman SG, Anderson FA, et al. From guidelines to clinical practice: the impact of hospital and geographical characteristics on temporal trends in the management of acute coronary syndromes. The Global Registry of Acute Coronary Events (GRACE). European heart journal 2003;**24**(15):1414.

207. Kaluski E, Maher J, Gerula C, et al. Optimizing primary PCI beyond "door to intervention time"—are we there yet? Cardiovascular Revascularization Medicine 2010;**11**(2):84-90.

208. Prasad SB, Richards DAB, Sadick N, et al. Clinical and Electrocardiographic Correlates of Normal Coronary Angiography in Patients Referred for Primary Percutaneous Coronary Intervention. The American Journal of Cardiology 2008;**102**(2):155-59.

209. McCabe JM, Armstrong EJ, Kulkarni A, et al. Prevalence and factors associated with false-positive ST-segment elevation myocardial infarction diagnoses at primary percutaneous coronary intervention–capable centers: a report from the Activate-SF registry. Archives of internal medicine 2012;**172**(11):864.

210. Larson DM, Menssen KM, Sharkey SW, et al. "False-positive" cardiac catheterization laboratory activation among patients with suspected ST-segment elevation myocardial infarction. JAMA 2007;**298**(23):2754.

211. Cantor WJ, Hoogeveen P, Robert A, et al. Prehospital diagnosis and triage of ST-elevation myocardial infarction by paramedics without advanced care training. American Heart Journal 2012;**164**(2):201-06.

212. Kontos MC, Kurz MC, Roberts CS, et al. An Evaluation of the Accuracy of Emergency Physician Activation of the Cardiac Catheterization Laboratory for Patients With Suspected ST-Segment Elevation Myocardial Infarction. Annals of Emergency Medicine 2009;**55**(5):423-30.

213. Hiss RG, Lamb LE, Allen MF. Electrocardiographic findings in 67,375 asymptomatic subjects: X. Normal values ∗. The American Journal of Cardiology 1960;**6**(1):200-31.

214. Surawicz B, Parikh SR. Prevalence of male and female patterns of early ventricular repolarization in the normal ECG of males and females from childhood to old age. Journal of the American College of Cardiology 2002;**40**(10):1870-76.

215. Kambara H, Phillips J. Long-term evaluation of early repolarization syndrome (normal variant RS-T segment elevation). The American journal of cardiology 1976;**38**(2):157.

216. Wang K, Asinger RW, Marriott HJL. ST-Segment Elevation in Conditions Other Than Acute Myocardial Infarction. The New England journal of medicine 2003;**349**(22):2128-35.

217. Sgarbossa EB, Pinski SL, Barbagelata A, et al. Electrocardiographic Diagnosis of Evolving Acute Myocardial Infarction in the Presence of Left Bundle-Branch Block. The New England journal of medicine 1996;**334**(8):481-87.

218. Madias JE, Sinha A, Agarwal H, et al. ST-segment elevation in leads V1-V3 in patients with LBBB. Journal of electrocardiology 2001;**34**(1):87.

219. Acute Pericarditis. The New England journal of medicine 2005;**352**(11):1163-63.

220. Spodick DH, Greene TO, Saperia G. Images in cardiovascular medicine. Acute myocarditis masquerading as acute myocardial infarction. Circulation 1995;**91**(6):1886.

221. Roberts EB, Perry R, Booth J, et al. Adverse events following percutaneous and surgical coronary revascularisation: Analysis of non-MACE outcomes in the Stent or Surgery (SoS) Trial. International Journal of Cardiology 2016;**202**:7-12.

222. Thorn JC, Turner EL, Hounsome L, et al. Validating the use of Hospital Episode Statistics data and comparison of costing methodologies for economic evaluation: an end-of-life case study from the Cluster randomised triAl of PSA testing for Prostate cancer (CAP). BMJ Open 2016;**6**(4).

223. Sinha S, Peach G, Poloniecki JD, et al. Studies using English administrative data (Hospital Episode Statistics) to assess health-care outcomes—systematic review and recommendations for reporting. The European Journal of Public Health 2013;**23**(1):86-92.

224. Burns EM, Rigby E, Mamidanna R, et al. Systematic review of discharge coding accuracy. Journal of Public Health 2012;**34**(1):138-48.

225. The Quality of Clinical Coding in the NHS. www.chkscouk/userfiles/files/The_quality_of_clinical_coding_in_the_NHSpdf. 2014.

226. Schulz S, Richardt G, Laugwitz KL, et al. Prasugrel plus bivalirudin vs. clopidogrel plus heparin in patients with ST-segment elevation myocardial infarction. Eur Heart J 2014;**35**(34):2285-94.

227. Valgimigli M, Frigoli E, Leonardi S, et al. Bivalirudin or Unfractionated Heparin in Acute Coronary Syndromes. New England Journal of Medicine 2015;**373**(11):997-1009.

228. Han Y, Guo J, Zheng Y, et al. Bivalirudin vs heparin with or without tirofiban during primary percutaneous coronary intervention in acute myocardial infarction: The bright randomized clinical trial. JAMA 2015;**313**(13):1336-46.

229. Bangalore S, Toklu B, Kotwal A, et al. Anticoagulant therapy during primary percutaneous coronary intervention for acute myocardial infarction: a meta-analysis of randomized trials in the era of stents and P2Y 12 inhibitors. BMJ : British Medical Journal 2014;**349**(nov11 4).

230. Lipinski MJ, Lhermusier T, Escarcega RO, et al. Bivalirudin versus heparin for percutaneous coronary intervention: an updated meta-analysis of randomized controlled trials. Cardiovascular Revascularization Medicine 2014;**15**(6-7):315-22.

231. Cavender MA, Sabatine MS. Bivalirudin versus heparin in patients planned for percutaneous coronary intervention: a meta-analysis of randomised controlled trials. The Lancet 2014;**384**(9943):599-606.

232. Cassese S, Byrne R, Schunkert H, et al. TCT-460 Bivalirudin versus heparin during percutaneous coronary intervention: a meta-analysis of randomized trials, 2014:B135-B35.

233. Farag M, Gorog DA, Prasad A, et al. Bivalirudin versus unfractionated heparin: a meta-analysis of patients receiving percutaneous coronary intervention for acute coronary syndromes: BMJ Publishing Group, 2017.

234. Verdoia M, Schaffer A, Barbieri L, et al. Bivalirudin as compared to unfractionated heparin in patients undergoing percutaneous coronary revascularization: A meta-analysis of 22 randomized trials. Thrombosis Research 2015;**135**(5):902-15.

235. Erlinge D, Omerovic E, Fröbert O, et al. Bivalirudin versus Heparin Monotherapy in Myocardial Infarction. New England Journal of Medicine 2017;**377**(12):1132-42.

236. Secemsky EA, Kirtane A, Bangalore S, et al. Use and Effectiveness of Bivalirudin Versus Unfractionated Heparin for Percutaneous Coronary Intervention Among Patients With ST-Segment Elevation Myocardial Infarction in the United States. JACC: Cardiovascular Interventions 2016;**9**(23):2376-86.

237. Hattersley PG. Activated coagulation time of whole blood. Jama 1966;**196**(5):436-40.

238. College of American Pathologists. Surveys 2010 CT1-A, Participant Survey. 2010.

239. Van Cott EM. Coagulation point-of-care testing. Clinics in laboratory medicine 2001;**21**(2):337-50.

240. Bowers J, Ferguson JJ. Use of the activated clotting time in anticoagulation monitoring of intravascular procedures. Texas Heart Institute journal / from the Texas Heart Institute of St Luke's Episcopal Hospital, Texas Children's Hospital 1993;**20**(4):258.

241. Schriever HG, Epstein SE, Mintz MD. Statistical correlation and heparin sensitivity of activated partial thromboplastin time, whole blood coagulation time, and an automated coagulation time. American journal of clinical pathology 1973;**60**(3):323.

242. Congdon JE, Kardinal CG, Wallin JD. Monitoring heparin therapy in hemodialysis. A report on the activated whole blood coagulation time tests. Jama 1973;**226**(13):1529-33.

243. Measday MA, Zucker ML, Pan C-M, et al. Optimizing management of hirudin anticoagulation. The journal of extra-corporeal technology 2005;**37**(1):66.

244. Koster A, Chew D, Gründel M, et al. Bivalirudin monitored with the ecarin clotting time for anticoagulation during cardiopulmonary bypass. Anesthesia and analgesia 2003;**96**(2):383.

245. Cho L, Kottke-Marchant K, Lincoff AM, et al. Correlation of Point-of-Care ecarin clotting time versus activated clotting time with bivalirudin concentrations. The American Journal of Cardiology 2003;**91**(9):1110-13.

246. Casserly IP, Kereiakes DJ, Gray WA, et al. Point-of-care ecarin clotting time versus activated clotting time in correlation with bivalirudin concentration. Thrombosis Research 2004;**113**(2):115-21.

247. Goto K, Lansky AJ, Fahy M, et al. Predictors of outcomes in medically treated patients with acute coronary syndromes after angiographic triage: an Acute Catheterization And Urgent Intervention Triage Strategy (ACUITY) substudy. Circulation 2010;**121**(7):853-62.

248. Leyvi G, Shore-Lesserson L, Harrington D, et al. An investigation of a new activated clotting time "MAX-ACT" in patients undergoing extracorporeal circulation. Anesthesia and analgesia 2001;**92**(3):578.

249. Machin D, Devine P. The effect of temperature and aprotinin during cardiopulmonary bypass on three different methods of activated clotting time measurement. The journal of extra-corporeal technology 2005;**37**(3):265.

250. Prisco D, Paniccia R. Point-of-Care Testing of Hemostasis in Cardiac Surgery. Thrombosis Journal 2003;**1**:1-1.

251. Welsby I, McDonnell E, El-Moalem H, et al. Activated Clotting Time Systems Vary In Precision And Bias And Are Not Interchangeable When Following Heparin Management Protocols During Cardiopulmonary Bypass. Journal of Clinical Monitoring and Computing 2002;**17**(5):287-92.

252. Jones PM, Bainbridge D, Dobkowski W, et al. Comparison of MAX-ACT and K-ACT Values When Using Bivalirudin Anticoagulation During Minimally Invasive Hybrid Off-Pump Coronary Artery Bypass Graft Surgery. Journal of Cardiothoracic and Vascular Anesthesia 2011;**25**(3):415-18.

253. Antman EM, Braunwald E. A second look at bivalirudin. American Heart Journal 2001;**142**(6):929-31.

254. White H, White HD, Simes RJ, et al. Thrombin-specific anticoagulation with bivalirudin versus heparin in patients receiving fibrinolytic therapy for acute myocardial infarction: The HERO-2 randomised trial. Lancet 2001;**358**(9296):1855-63.

255. Stone GW, Bertrand M, Colombo A, et al. Acute Catheterization and Urgent Intervention Triage strategY (ACUITY) trial: study design and rationale. American Heart Journal 2004;**148**(5):764-75.

256. Saucedo JF. Balancing the benefits and risks of antiplatelet agents in patients with non-ST-segment elevated acute coronary syndromes and undergoing percutaneous coronary intervention. Journal of Thrombosis and Thrombolysis 2010;**30**(2):200-09.

257. White HD, Ohman EM, Lincoff AM, et al. Safety and Efficacy of Bivalirudin With and Without Glycoprotein IIb/IIIa Inhibitors in Patients With Acute Coronary Syndromes Undergoing Percutaneous Coronary Intervention. 1-Year Results From the ACUITY (Acute Catheterization and Urgent Intervention Triage strategY) Trial. Journal of the American College of Cardiology 2008;**52**(10):807-14.

258. Sciahbasi A, Pristipino C, Ambrosio G, et al. Arterial Access-Site-Related Outcomes of Patients Undergoing Invasive Coronary Procedures for Acute Coronary Syndromes

(from the ComPaRison of Early Invasive and Conservative Treatment in Patients With Non-ST-ElevatiOn Acute Coronary Syndromes [PRESTO-ACS] Vascular Substudy). American Journal of Cardiology 2009;**103**(6):796-800.

259. Agostoni P, Biondi-Zoccai GGL, De Benedictis ML, et al. Journal of the American College of Cardiology 2004;**44**(2):349-56.

260. Dangas GD, Caixeta A, Mehran R, et al. Frequency and predictors of stent thrombosis after percutaneous coronary intervention in acute myocardial infarction. Circulation 2011;**123**(16):1745-56.