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Manuscript Draft

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Title: Twelve-month mortality from the How Effective are Antithrombotic Therapies in Primary Percutaneous Coronary Intervention (HEAT-PPCI) Trial

Article Type: Clinical Investigation

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Abstract:
Objectives
To report 12-month mortality from the HEAT-PPCI randomised trial.

Background:
There is ongoing uncertainty regarding the safety and efficacy of unfractionated heparin and bivalirudin when used for systemic anticoagulation in patients undergoing primary percutaneous coronary intervention (PPCI).

Methods:
In this open-label, randomised controlled trial (RCT) we enrolled consecutive adults with suspected ST-elevation myocardial infarction (STEMI). Patients were randomised to heparin (bolus 70U/kg) or bivalirudin (bolus 0.75mg/kg followed by an infusion 1.75mg/kg/h for the duration of the procedure). We report the pre-specified secondary outcome of all-cause mortality at 12 months.
Mortality was classified as cardiovascular or not, blinded to treatment allocation. Deaths in the first 28 days were classified by formal event adjudication and later events classified from death certificates.

Results:
Mortality status at 12 months was obtained for 1805/1812 = 99.6% of participants. Overall mortality was 160/1812 = 8.9%. There were more deaths in those randomised to bivalirudin (95/902=10.5% vs 65/903=7.2%; HR 1.48; 95% CI 1.08 to 2.03; p=0.015).
Most deaths were classified as cardiovascular (71/902=7.9% in the bivalirudin group and 53/904=5.9% in the heparin group). The difference between the rates of cardiovascular deaths in each treatment group did not reach statistical significance: HR 1.35; 95% CI 0.95 to 1.93; p =0.095.

Conclusions:
At 12 months, treatment with bivalirudin, rather than heparin, was associated with a higher rate of all-cause, but not cardiovascular

mortality. This is difficult to explain, raising the possibility that the mortality difference may have occurred by chance.

Research Data Related to this Submission

There are no linked research data sets for this submission. The following reason is given:
Data will be made available on request

Cover Letter

Dear Editor,

We ask that you consider our manuscript "*Unfractionated heparin versus bivalirudin in primary percutaneous coronary intervention: twelve-month mortality from the How Effective are Antithrombotic Therapies in Primary Percutaneous Coronary Intervention (HEAT-PPCI) Randomised Trial*" for publication in the American Heart Journal.

There remains uncertainty regarding the optimum antithrombotic for use during primary percutaneous coronary intervention. Randomised trials show conflicting results in relation to rates of major adverse cardiovascular events and bleeding, as well as short- or medium-term mortality. We believe this study is an interesting and important addition to the literature. HEAT-PPCI differs from other randomised trials in design and conduct. It recruited 97% of eligible patients over 24 months. A strategy of delayed consent allowed inclusion of patients even if they were unable to consent because of the severity of their condition ie cardiogenic shock. It also ensured that no trial medication was given to the participants prior to randomisation.

The HEAT-PPCI trial results were originally published in 2014 in the Lancet and showed that bivalirudin was associated with a higher rate of major adverse cardiovascular events at 28 days, driven predominantly by higher rates of acute stent thrombosis and recurrent infarction. The mortality rates at 28 days was similar between the groups.

This study examines the 12-month mortality rates between the two treatment groups to establish any differences in long term outcomes. The results show there were more deaths in those randomised to bivalirudin (95/902=10.5% vs 65/903=7.2%; RR 1.46; 95% CI 1.08 to 1.98; p=0.013). The rate of cardiovascular mortality at 12 months was also higher, but the difference did not reach conventional levels of statistical significance (71/902 = 7.9% versus 53/903=5.9%; RR 1.34; 95% CI 0.95 to 1.88; p=0.092). The rate of non-cardiovascular mortality at 12 months was significantly higher in the bivalirudin group (24/902=2.7% versus 12/903=1.3%; RR 2.00; 95% CI 1.02 to 3.93; p=0.043).

We investigated possible causes of the higher number of deaths in the bivalirudin group by comparing clinical markers of case complexity or adverse clinical course between the two groups. There were no significant differences. In addition, 23% of all deaths were attributable to a non-cardiovascular cause, with a significant difference in the number of non-cardiovascular deaths between the two groups. This is difficult to explain in terms of clinical plausibility and may, therefore, represent the play of chance.

This manuscript describes original work and is not under consideration by any other journal. The manuscript has been previously submitted to Eurointervention and reviewed by 3 reviewers. The editor decided not to publish the manuscript, however we have included the reviewers' comments and our responses in this submission. All authors have read and approved the manuscript and this submission. Dr Sarah Blake is the corresponding author. Prof. Stables reports grants from The Medicines Company and grants and personal fees from AstraZeneca during the conduct of the study. All other authors declare no conflicts of interest.

Thank you for receiving our manuscript and considering it for review.

Yours sincerely,

Dr S R Blake

Highlights:

- This study shows that use of bivalirudin in PPCI was associated with a significantly higher risk of all-cause mortality at 12 months.
- Cardiovascular causes of death at 12 months were not significantly different between the treatment groups.
- There was a statistically significant difference in non-cardiovascular deaths which raises the possibility that the overall mortality difference may have occurred by chance.

Twelve-month mortality from the *How Effective are Antithrombotic Therapies in Primary Percutaneous Coronary Intervention* (HEAT-PPCI) Trial

Abbreviated title: HEAT-PPCI 12-month mortality

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Role of the funding source

The HEAT-PPCI trial 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.

Declarations of interest

RHS reports grants from The Medicines Company and grants and personal fees from AstraZeneca during the conduct of the study. All other authors declare no competing interests.

Author contributions

SRB reviewed the data, designed and performed the final analysis, and drafted the manuscript. AS was principle investigator for HEAT-PPCI trial. IK designed the HEAT database. CR, AS, IK, CM and KW were active in clinical conduct and follow-up of patients in the HEAT-PPCI trial. KW acted as the patient representative for trial conduct. RHS was the senior investigator for HEAT-PPCI. AS, IK, CM, KW and RHS reviewed the manuscript.

Submission declaration
This manuscript describes original work and is not under consideration by any other journal.

Ethical approval

The HEAT-PCI trial received full ethical approval and is registered on clinicaltrials.gov (see link below). This study used data obtained as part of the HEAT-PPCI study. No patients were contacted or affected by the study.

Data Sharing Statement

Participants gave informed consent for data sharing when recruited into the HEAT-PPCI trial. The presented data are anonymised, and no identifiable data has been included in the manuscript.

HEAT PPCI Trial registration: ClinicalTrials.gov number NCT01519518

Abstract

Objectives

To report 12-month mortality from the HEAT-PPCI randomised trial.

Background:

There is ongoing uncertainty regarding the safety and efficacy of unfractionated heparin and bivalirudin when used for systemic anticoagulation in patients undergoing primary percutaneous coronary intervention (PPCI).

Methods:

In this open-label, randomised controlled trial (RCT) we enrolled consecutive adults with suspected ST-elevation myocardial infarction (STEMI). Patients were randomised to heparin (bolus 70U/kg) or bivalirudin (bolus 0.75mg/kg followed by an infusion 1.75mg/kg/h for the duration of the procedure). We report the pre-specified secondary outcome of all-cause mortality at 12 months.

Mortality was classified as cardiovascular or not, blinded to treatment allocation. Deaths in the first 28 days were classified by formal event adjudication and later events classified from death certificates.

Results:

Mortality status at 12 months was obtained for 1805/1812 = 99.6% of participants. Overall mortality was 160/1812 = 8.9%. There were more deaths in those randomised to bivalirudin (95/902=10.5% vs 65/903=7.2%; HR 1.48; 95% CI 1.08 to 2.03; p=0.015).

Most deaths were classified as cardiovascular (71/902=7.9% in the bivalirudin group and 53/904=5.9% in the heparin group). The difference between the rates of cardiovascular deaths in each treatment group did not reach statistical significance: HR 1.35; 95% CI 0.95 to 1.93; p =0.095.

Conclusions:

At 12 months, treatment with bivalirudin, rather than heparin, was associated with a higher rate of all-cause, but not cardiovascular mortality. This is difficult to explain, raising the possibility that the mortality difference may have occurred by chance.

Keywords: heparin, bivalirudin, primary percutaneous coronary intervention, ST-elevation myocardial infarction

Conclusions: Treatment with bivalirudin was associated with a higher rate of all-cause, not cardiovascular mortality, raising the possibility that the difference occurred by chance.

Introduction

There is continuing debate about the relative safety and efficacy of unfractionated heparin and bivalirudin when used as the peri-procedural systemic anticoagulant at the time of emergency percutaneous coronary intervention for the acute reperfusion of myocardial infarction. Several clinical trials and meta-analyses have addressed this issue (1-9). There is general agreement that the use of bivalirudin is associated with an increased rate of subsequent stent thrombosis but may induce less bleeding when compared to higher dose heparin regimes or the combined use of heparin and glycoprotein IIbIIIa receptor antagonist (GPI) agents (1-3,7). Trials report conflicting results regarding potential advantages of either agent in terms of short- or medium-term mortality, although it is difficult to compare results because of differential use of GPIs between the treatment groups. The aim of this study was to report the 12-month mortality in the trial: How Effective are Antithrombotic Therapies in Primary Percutaneous Coronary Intervention (HEAT-PPCI).

Methods

HEAT-PPCI was an open-label, randomised controlled trial and enrolled consecutive adults investigated with angiography in the context of a primary PCI presentation at Liverpool Heart and Chest Hospital (Liverpool, UK). Patients were randomised to heparin (bolus 70U/kg) or bivalirudin (bolus 0.75mg/kg followed by an infusion 1.75mg/kg/h for the duration of the procedure). Participants were tracked during their index admission for clinical outcome events and then followed up for 28 days following randomisation. The design and 28-day results of the HEAT-PPCI trial have been published previously (10). The protocol for HEAT-PPCI specified an extended follow-up period for analysis of mortality at 12 months. This study reports the results of the prespecified analysis and a post-hoc analysis for cardiovascular and non-cardiovascular cause of death.

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

To investigate possible associations between 12-month mortality and events that occurred during the index admission, we examined the association between patients who had sustained at least one non-fatal major adverse cardiac or cerebrovascular event (MACE) at 28 days and subsequent mortality. We also compared the procedural characteristics and hospital admission duration of the two randomised treatment groups.

Statistical analysis

All analyses were performed according to intention to treat. Data are presented as (n/d = p%) for categorical variables and as means (standard deviations) or medians (interquartile ranges) for continuous variables after testing for normality. We compared categorical data with the chi-squared test (or Fisher's

exact test when the absolute number of observed events in any group was five or less). We compared continuous data with the t test (or the Wilcoxon test in the case of non-normal data). We used time-to-event curves to show the mortality data (patients were censored at the time of last follow-up). The protocol pre-specified comparison with the Cox proportional hazards model, unadjusted for other covariates, to calculate hazard ratios (HRs) and 95% confidence intervals. A p value of < 0.05 (2 sided) was considered statistically significant. SPSS version 24 (SPSS Inc., Chicago, IL, USA) was used for analyses.

Results

Between 7th February 2012 to 20th November 2013, 1829 patients were enrolled into the HEAT-PPCI trial. It was not possible to obtain consent in 13 cases, and in 4 cases participants refused to give, or withdrew consent (Figure 1). Therefore, 1812 patients were included in the initial analysis. Vital status at 12 months was obtained in 1805/1812, representing 99.6% of consented participants. Overall mortality at 12 months was 160/1805 = 8.9%. It was not possible to obtain death certificates for 3 subjects and in a single additional case it was not possible to determine the cause of death from the information presented. For the purpose of this analysis, these cases were assumed to be cardiovascular deaths.

Figure 1 (single column fitting image, does not need to be in color):

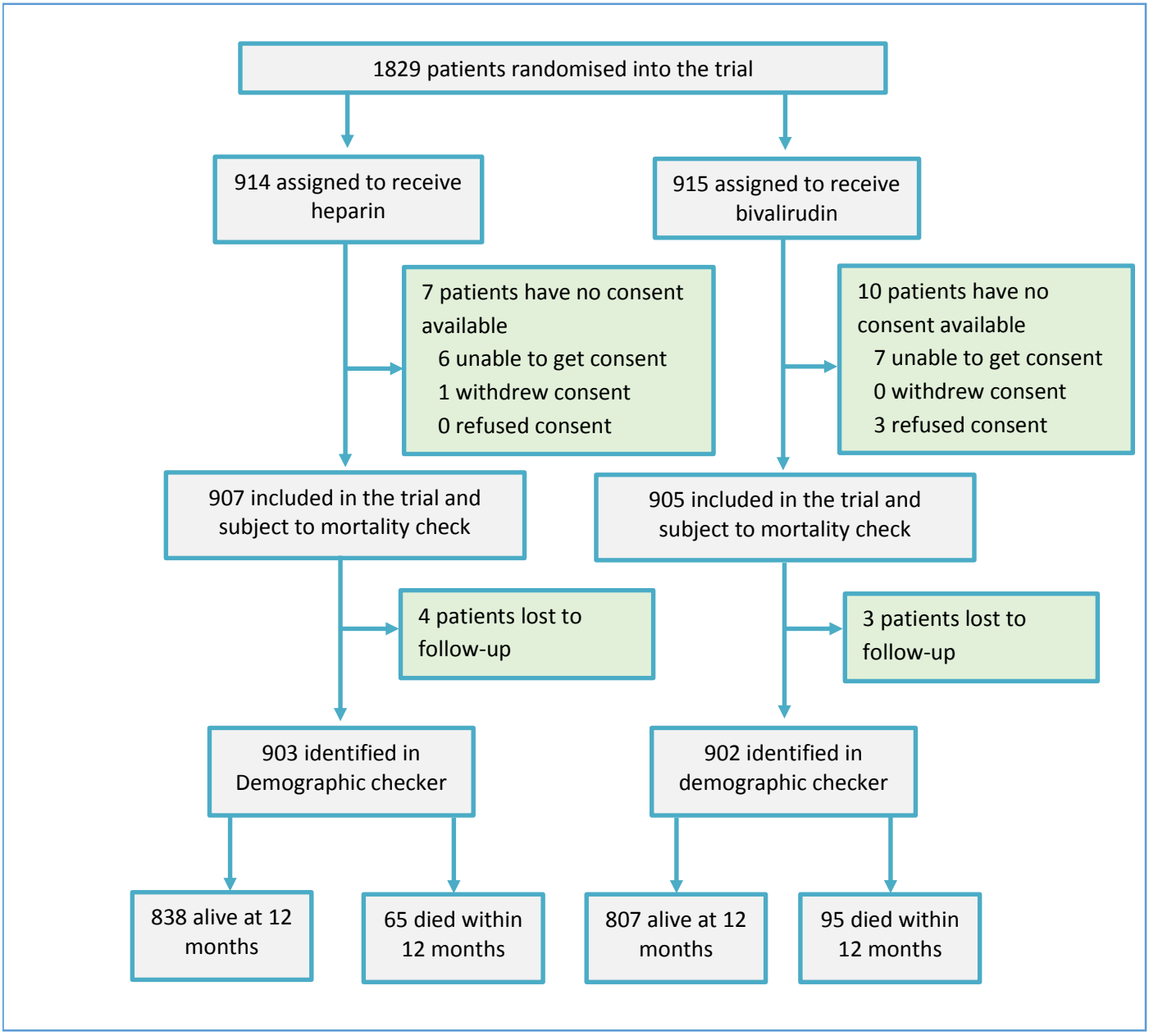

Figure 1 caption: *Flow diagram showing mortality rates at 12 months for participants in HEAT-PPCI*

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

Table I:
Title: All-cause and cardiovascular mortality rates at 12 months.

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

*95% confidence interval

Table I caption: The absolute risk and relative risk are displayed, excluding patients lost to follow-up at 12 months.

Figure 2 shows the event curves and hazard ratios for all-cause mortality and cardiovascular mortality for both treatment groups. The hazard for patients was highest during or immediately after the acute event, with 18/160=11.3% of all deaths over 12 months occurring on the day of randomisation (with an equal distribution between the treatment groups).

Figure 2: (single column fitting image, does need to be in color):

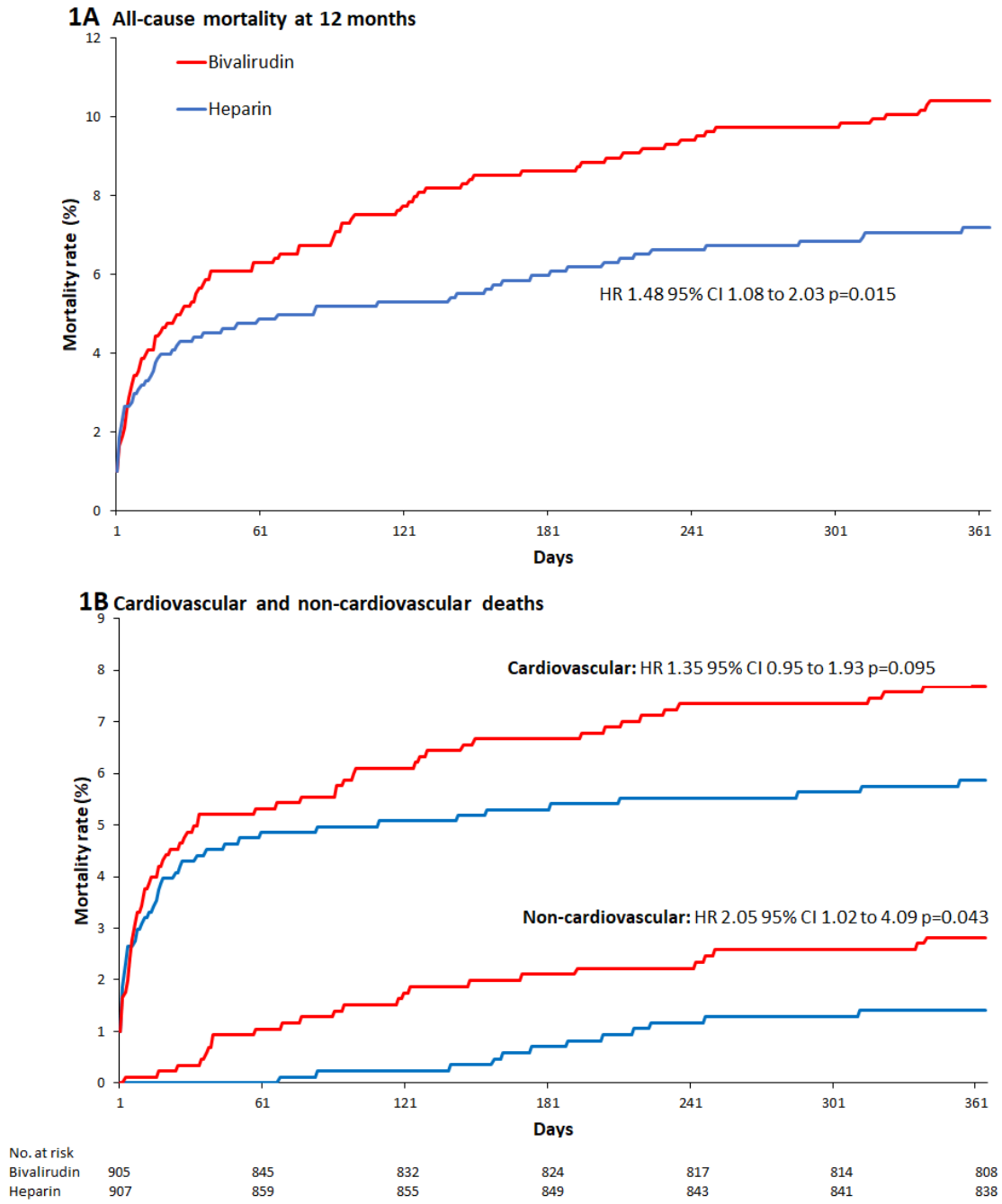

Figure 2 caption: (1A) All-cause mortality (1B) Cardiovascular and non-cardiovascular mortality. (HR denotes hazard ratio, 95% CI; 95% confidence interval)

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

Table II:

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

*major adverse cardiovascular event; [†]cerebrovascular accident; [‡]myocardial infarction; [§]unplanned target lesion revascularisation

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

As a surrogate for complexity of the clinical course during index management we compared the rates of use of intra-aortic balloon pumps, inotropes, temporary pacing wires and endo-tracheal intubation There were no significant differences between the two randomised groups. When comparing the length of overall hospital admission or the time spent in high-dependency areas such as the intensive care unit and the coronary care unit, there was no significant difference between the two groups (Table 3).

Table III:

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

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

[†]intensive care unit; [‡]coronary care unit

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

Discussion

Main findings

In this single-centre, randomised trial, bivalirudin was compared to heparin in patients undergoing primary PCI (PPCI). The rate of all-cause mortality at 12 months was significantly higher in the bivalirudin group. These results differ from other trials comparing heparin and bivalirudin in PPCI (5, 8, 11).

What is known

The HORIZONS-AMI randomised trial compared bivalirudin monotherapy versus heparin plus a GPI (8, 12). The 3-year follow-up showed a lower rate of all-cause and cardiovascular mortality in the bivalirudin group (all-cause mortality: 5.9% vs. 7.7%; HR 0.75; 95% CI 0.58 to 0.97; p=0.03, cardiovascular mortality: 2.9% vs 5.1%; HR 0.56; 95% CI 0.40-0.80; p=0.001) (8). This trial reported lower rates of major bleeding in the bivalirudin group (6.9% vs 10.5%; HR 0.64; 95% CI 0.51-0.80; p=0.0001). Bleeding is an accepted risk factor for subsequent mortality so any increased bleeding rates may have an impact on mortality (13).

The MATRIX trial, a large multi-centre RCT comparing bivalirudin monotherapy versus heparin plus discretional GPIs in STEMI and high-risk NSTEMI, also showed lower bleeding rates and lower mortality in the bivalirudin group (9). (Bleeding events: 2.2% vs 3.3%; RR 0.68; 95% CI 0.51 - 0.91, all-cause mortality: 3.6% vs 4.6%; RR 0.79; 95% CI 0.63 to 0.99, cardiovascular mortality: 2.2% vs 3.0%; RR 0.74; 95% CI 0.55-0.99. P values were not reported.) Both HORIZONS-AMI and MATRIX involved differential use of GPIs between the treatment groups created at randomisation. This may have influenced outcomes, including bleeding and subsequent mortality, and makes it difficult to compare the independent effects of the antithrombotic agents under evaluation.

The BRIGHT randomised trial compared bivalirudin monotherapy with heparin monotherapy and with heparin plus GPIs in a three-arm design. This showed that 30-day bleeding rates was lowest in the bivalirudin arm and highest in the heparin plus GPI arm (4.1% vs 7.5% vs 12.3% p=<0.001) but there was no significant difference in mortality rates between the 3 arms at 1-year follow-up. Similarly, the EUROMAX randomised trial, comparing bivalirudin with heparin, with routine or optional use of GPI in the heparin arm, showed a lower rate of major bleeding at 30 days in the bivalirudin group (2.6% vs 6.0%; RR 0.43; 95% CI 0.28 to 0.66; p=<0.001). This may be related to the differential use of GPIs between the groups (7% GPI use in bivalirudin cases vs 69.1% in heparin cases) but there was no significant difference in all-cause or cardiovascular mortality at 1 year (all cause: 2.7% in each group; RR 1.02; 95% CI 0.72 to 1.45; p=0.92, cardiovascular: 4.0% vs 4.3%; RR0.93; 95% CI 0.63 to 1.39; p=0.74) (11).

The VALIDATE-SWEDEHEART trial is the largest and most recent trial evaluating bivalirudin versus heparin in PCI (4). This multi-centre randomised registry-based study compared bivalirudin monotherapy with heparin monotherapy, excluding any patient treated with GPI in either group. The results of 180-day follow-up showed no difference in rates of major bleeding, all-cause mortality or cardiovascular mortality (major bleeding: 8.6% in each group; HR 1.00; 95% CI 0.84 to 1.19; p=0.98, all-cause mortality: 2.9% vs 2.8%; HR 1.05; 95% CI 0.78 to 1.41; p=0.76, cardiovascular mortality: 2.4% vs 2.3%; HR 1.04; 95% CI 0.75 to 1.45; p=0.80). However only 47% of eligible patients were enrolled in the trial and those not enrolled tended to be higher risk than those selected for inclusion. The NAPLES III trial randomised patients undergoing PCI to bivalirudin monotherapy or heparin monotherapy and compared rates of in-hospital major bleeding showing no significant difference between the two groups (OR 0.78 95%CI 0.35 to 1.72 p=0.54) (14). Several meta-analyses have been performed comparing heparin and bivalirudin in PCI (1-3, 6). The most recent, by Nührenberg et al, evaluates 12 RCTs comparing bivalirudin and heparin including VALIDATE-SWEDEHEART (6). This analysis showed that there was no difference in mortality between the groups and the bleeding rates were similar with balanced use of GPI (OR 0.88; 95% CI 0.67–1.16; p = 0.35; p for heterogeneity < 0.01).

What this study adds

HEAT-PPCI remains the only trial of antithrombotic therapy in PPCI to achieve near 100% recruitment of all eligible patients. Exclusion criteria was minimal and all adult patients with suspected STEMI who had not previously been enrolled in the trial were included. The study was more representative of typical practice and mortality rates were comparable to those reported by US and UK registries (15, 16). HEAT-PPCI compared bivalirudin with heparin with use of GPI as bailout only in both groups, resulting in 13% use in the bivalirudin group and 15% in the heparin group. The relative safety and efficacy of bivalirudin and heparin can only be reliably tested if the use of GPIs is similar in both groups.

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

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

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

Limitations

The main limitations of HEAT-PPCI trial have been previously described (10). There are some limitations of this study which should be mentioned. The trial was not powered for 12-month mortality. Therefore, there is poor precision in estimates of hazard ratio for 12-month mortality. Deaths that occurred between 28 days and 12 months following randomisation were determined as cardiovascular or not based on information from the death certificate alone. Medical notes were not available for these patients which may have affected the accuracy of the classification.

Conclusion

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

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The response to Reviewers' comments:

Reviewer #1: This is a report of 12-month mortality from the HEAT-PPCI trial in which 1,829 patients scheduled for primary PCI were randomly allocated to either bivalirudin or heparin. After 28 days, the use of bivalirudin as compared to heparin was associated with higher risk of acute ST and re-infarction. In the present study, patients assigned to bivalirudin as compared to those assigned to heparin displayed a higher (all-cause) mortality risk after 12 months. The authors found no interaction with those adverse events occurring within 28 days and the subsequent risk of mortality within 1 year. Some remarks:

Comment 1. The main results of HEAT-PPCI trial have been posted online on 4th July 2014. The investigators should explain why they waited such a long time to present data contained in this manuscript and which is the additive scientific value of such analysis in light of the lack of power for the endpoint mortality.

Response to Comment 1:

The delay in obtaining the mortality data was due to difficulties in accessing the Office of National Statistics records. Our initial approach was to obtain data by a request to NHS Digital. The HEAT-PPCI trial obtained an agreement under Section 251 to allow collection of data from patients who had died. This was not accepted by NHS Digital because the consent form did not specify the use of NHS Digital and electronic databases as a method of follow-up. Instead we were able to access information from the death certificates which are freely available on application from the UK registry office. This process took considerable time and delayed the completion of the study.

We reported the 12-month mortality as part of the pre-specified analysis of the HEAT-PPCI trial. Although the trial was not powered for mortality, we are obliged to report this outcome. This approach mirrors all similar trials comparing the use of heparin and bivalirudin. The results are valuable in this context and have been made available for a forthcoming meta-analysis of studies in this area.

Comment 2. Patients were included in the HEAT-PPCI trial from 7th February 2012 to 20th November 2013: Although the analysis of 12-month mortality was prespecified, a follow-up longer than 12 months should be available to the investigators.

Response to Comment 2:

Our research team has access to the Demographics Batch Service which provides information about the vital status of all patients in the NHS. We could, therefore, have chosen a longer follow-up period. However, the ethics approval for HEAT-PPCI covered the pre-specified 12 month mortality follow-up so this is the data we have reported. We would also observe that – as time progresses – there is the potential for a reduction in 'signal to noise ratio'. One might expect that the effects related to a single administration of a drug might be best observed in the short and medium term.

Comment 3. It is unclear to this reviewer whether the causes of death were adjudicated by the clinical event committee originally involved in the primary endpoint analysis.

Response to Comment 3: The later outcomes in this study (after 28 days) were not adjudicated by the original clinical events committee. The events were adjudicated by a new committee drawn from

the current research team at the Liverpool Heart and Chest Hospital. This has been clarified in the manuscript:

during this period was then ascertained by obtaining death certificates from the national or local registry offices. The cause of death was classified as cardiovascular or non-cardiovascular by an adjudication panel, blinded to treatment allocation. The panel used to review the events was different from the panel used to adjudicate events at 28 days. Cardiovascular causes of death included: myocardial infarction, cardiac failure, arrhythmia, cerebrovascular accident,

– 4. There is no landmark analysis (time point 28 days) exploring a possible time-dependence of mortality risk.

Response to Comment 4:

We are grateful to the reviewers for their suggestion of performing a landmark analysis. After careful consideration we do not think a landmark analysis is appropriate for this study. Bivalirudin and heparin were given on day 1 of randomisation. Therefore, any difference in mortality is likely to appear early following the acute event. Indeed, the majority of deaths (18/1812=11%) occur on day 1 of randomisation. By ignoring these events we are likely to miss the differences between the two treatments. Performing a landmark analysis at 28 days would highlight the difference in mortality in patients who survived to 28 days. However, this does not add any information regarding the reasons for this difference and we cannot explain it. No other heparin and bivalirudin trial (for example, HORIZONS-AMI and EUROMAX) looking at the mortality at medium-term follow-up uses a landmark analysis.

Comment 5. "Trials report conflicting results regarding potential advantages of either agent in terms of short- or medium-term mortality". This sentence is not correct: indeed, the advantage attributable to bivalirudin was mainly due to the concomitant use of glycoprotein IIb/IIa inhibitors in those patients receiving heparin. In this regard, the study-design of the HEAT-PPCI trial was disruptive, since glycoprotein IIb/IIa inhibitors were administered only as bail-out in both study arms.

Response to Comment 5:

We agree that the differential use of GPIs between the treatment arms in most trials makes comparison difficult. We have amended the manuscript to reflect this uncertainty, as suggested by the reviewer:

Introduction

There is continuing debate about the relative safety and efficacy of unfractionated heparin and bivalirudin when used as the peri-procedural systemic anticoagulant at the time of emergency percutaneous coronary intervention (PCI) for the acute reperfusion of myocardial infarction. Several clinical trials and meta-analyses have addressed this issue (1-9). There is general agreement that the use of bivalirudin is associated with an increased rate of subsequent stent thrombosis but may induce less bleeding when compared to higher dose heparin regimes or the combined use of heparin and glycoprotein IIbIIIa receptor antagonist (GPI) agents (1-3,7). Trials report conflicting results regarding potential advantages of either agent in terms of short- or medium-term mortality, although it is difficult to compare results because of differential use of GPIs between the treatment groups. The aim of this study was to report the

Reviewer #2: In the present study Blake et al. report the pre-specified secondary outcome of all-cause mortality at 12 months from the HEAT-PPCI randomised trial. In this open-label, randomised controlled trial the Authors enrolled consecutive adults with suspected ST-elevation myocardial infarction (STEMI). Patients were randomised to heparin (70U/kg) or bivalirudin (bolus 0.75mg/kg; infusion 1.75mg/kg/h). Mortality was classified as cardiovascular or not, blinded to treatment allocation. Deaths in the first 28 days were classified by formal event adjudication and later events classified from death certificates. Mortality status was obtained for 1805/1812 = 99.6% of participants. Overall mortality was 160/1805 = 8.9%. There were more deaths in those randomised to bivalirudin (95/902=10.5% vs 65/903=7.2%; HR 1.48; 95% CI 1.08 to 2.03; p=0.015). Most deaths were classified as cardiovascular (71/902=7.9% in the bivalirudin group and 53/904=5.9% in the heparin group). The
difference between the rates of cardiovascular deaths in each treatment group did not reach statistical significance: HR 1.37; 95% CI 0.96 to 1.96; p =0.081. The Authors conclude that at 12 months, treatment with bivalirudin, rather than heparin, was associated with a higher rate of all-cause, but not cardiovascular mortality. This is difficult to explain, raising the possibility that the mortality difference may have occurred by chance.

1) In the study design reported at the clinicaltrial.gov the Secondary Outcome Measures include "All cause mortality at 1-year". No difference has been reported between cardiovascular vs non cardiovascular death. Therefore this seems to be a non-prespecified post-hoc analysis.

Response to Comment 1:

As the reviewer correctly notes, the pre-specified analysis states “All-cause mortality at 1-year”. We

Methods

HEAT-PPCI was an open-label, randomised controlled trial and enrolled consecutive adults investigated with angiography in the context of a primary PCI presentation at Liverpool Heart and Chest Hospital (Liverpool, UK). Participants were tracked during their index admission for clinical outcome events and then followed up for 28 days following randomisation. The design and 28-day results of the HEAT-PPCI trial have been published previously (10). The protocol for HEAT-PPCI specified an extended follow-up period for analysis of mortality at 12 months. This study reports the results of the prespecified analysis and a post-hoc analysis for cardiovascular and non-cardiovascular cause of death.

have therefore amended the manuscript to reflect that the reported differences in cardiovascular and non-cardiovascular mortality is a post-hoc analysis:

2) It would be interesting to perform Landmark analysis in order to show difference in mortality from 0 to 28 days (primary endpoint) and from 29 to 360 days (secondary endpoint). This would clarify any significant difference between the 2 antithrombotic regimens in the early and late period.

Response to Comment 2:

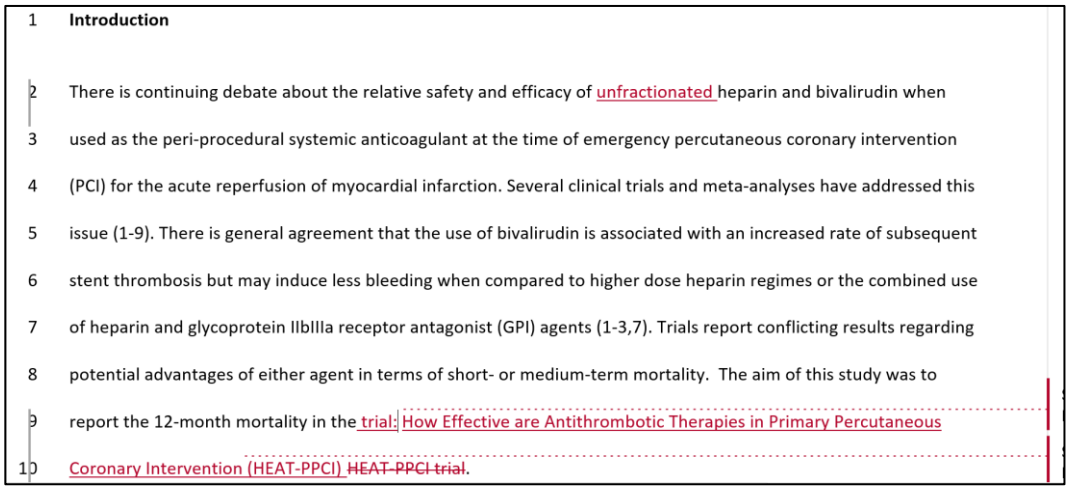
Please refer to the response to comment 4 by reviewer 1.

3) Minor comments

a. Introduction:
i. First line: should be "unfractionat ed heparin"
ii. spell out HEAT-PPCI trial

Response to Comment 3:

The manuscript has been amended to include the minor comments suggested by the reviewer:



Introduction

There is continuing debate about the relative safety and efficacy of unfractionated heparin and bivalirudin when used as the peri-procedural systemic anticoagulant at the time of emergency percutaneous coronary intervention (PCI) for the acute reperfusion of myocardial infarction. Several clinical trials and meta-analyses have addressed this issue (1-9). There is general agreement that the use of bivalirudin is associated with an increased rate of subsequent stent thrombosis but may induce less bleeding when compared to higher dose heparin regimes or the combined use of heparin and glycoprotein IIbIIIa receptor antagonist (GPI) agents (1-3,7). Trials report conflicting results regarding potential advantages of either agent in terms of short- or medium-term mortality. The aim of this study was to report the 12-month mortality in the trial: How Effective are Antithrombotic Therapies in Primary Percutaneous Coronary Intervention (HEAT-PPCI) ~~HEAT-PPCI trial~~.

Reviewer #3: The HEAT-PPCI study is a well conducted important study. They now present 12 months mortality data.
They see a significantly higher mortality rate for bivalirudin. This is surprising compared to other studies. It is also surprising that the difference is developed rather late, after 1-2 months when the comparators are about 1 hour infusions. The author do not find any explanation for this.
They should explain that bivalirudin was administered without any additional heparin and no post-PCI infusion was done. These are important differences compared to other trials.

Response to reviewer 3:

The manuscript has been amended to include the information suggested by the reviewer:

Methods and results:

In this open-label, randomised controlled trial (RCT) we enrolled consecutive adults with suspected ST-elevation myocardial infarction (STEMI). Patients were randomised to heparin (bolus 70U/kg) or bivalirudin (bolus 0.75mg/kg followed by an~~;~~ infusion 1.75mg/kg/h for the duration of the procedure). We report the pre-specified secondary outcome of all-cause mortality at 12 months.