Bivalirudin plus a high-dose infusion versus heparin monotherapy in patients with ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention: a randomised trial

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Summary

Background Previous randomised trials of bivalirudin versus heparin in patients with ST-segment elevation myocardial infarction (STEMI) undergoing primary percutaneous coronary intervention (PCI) have reported conflicting results, in part because of treatment with different pharmacological regimens. We designed a large-scale trial examining bivalirudin with a post-PCI high-dose infusion compared with heparin alone, the regimens that previous studies have shown to have the best balance of safety and efficacy.

Methods BRIGHT-4 was an investigator-initiated, open-label, randomised controlled trial conducted at 87 clinical centres in 63 cities in China. Patients with STEMI undergoing primary PCI with radial artery access within 48 h of symptom onset who had not received previous fibrinolytic therapy, anticoagulants, or glycoprotein IIb/IIIa inhibitors were randomly assigned (1:1) to receive bivalirudin with a post-PCI high-dose infusion for 2–4 h or unfractionated heparin monotherapy. There was no masking. Glycoprotein IIb/IIIa inhibitor use was reserved for procedural thrombotic complications in both groups. The primary endpoint was a composite of all-cause mortality or Bleeding Academic Research Consortium (BARC) types 3–5 bleeding at 30 days. This trial is registered with ClinicalTrials.gov (NCT03822975), and is ongoing.

Findings Between Feb 14, 2019, and April 7, 2022, a total of 6016 patients with STEMI undergoing primary PCI were randomly assigned to receive either bivalirudin plus a high-dose infusion after PCI (n=3009) or unfractionated heparin monotherapy (n=3007). Radial artery access was used in 5593 (93·1%) of 6008 patients. Compared with heparin monotherapy, bivalirudin reduced the 30-day rate of the primary endpoint (132 events [4·39%] in the heparin group *vs* 92 events [3·06%] in the bivalirudin group; difference, 1·33%, 95% CI 0·38–2·29%; hazard ratio [HR] 0·69, 95% CI 0·53–0·91; p=0·0070). All-cause mortality within 30 days occurred in 118 (3·92%) heparin-assigned patients and in 89 (2·96%) bivalirudin-assigned patients (HR 0·75; 95% CI 0·57–0·99; p=0·0420), and BARC types 3–5 bleeding occurred in 24 (0·80%) heparin-assigned patients and five (0·17%) bivalirudin-assigned patients (HR 0·21; 95% CI 0·08–0·54; p=0·0014). There were no significant differences in the 30-day rates of reinfarction, stroke, or ischaemia-driven target vessel revascularisation between the groups. Within 30 days, stent thrombosis occurred in 11 (0·37%) of bivalirudin-assigned patients and 33 (1·10%) of heparin-assigned patients (p=0·0015).

Interpretation In patients with STEMI undergoing primary PCI predominantly with radial artery access, anticoagulation with bivalirudin plus a post-PCI high-dose infusion for 2–4 h significantly reduced the 30-day composite rate of all-cause mortality or BARC types 3–5 major bleeding compared with heparin monotherapy.

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Introduction

Primary percutaneous coronary intervention (PCI) is the standard-of-care in patients with ST-segment elevation myocardial infarction (STEMI).[1,2] Adjunctive anticoagulation and antiplatelet therapy are essential to prevent thrombotic complications during and after primary PCI, but might increase the risk of major bleeding, the occurrence of which has been associated with increased mortality.[3]

Unfractionated heparin and bivalirudin are the two most widely used procedural anticoagulants during primary PCI. Bivalirudin, a direct-acting thrombin inhibitor with a short half-life and predictable pharmacodynamics, was shown in early randomised

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Research in context

Evidence before this study

Primary percutaneous coronary intervention (PCI) is the standard of care for patients with ST-segment elevation myocardial infarction (STEMI). Selecting the optimal anticoagulation regimen during the PCI procedure is essential to reduce both ischaemic and haemorrhagic complications. We searched PubMed for articles published in English from Jan 1, 2008, to Aug 31, 2022, for relevant published clinical trials using the terms "bivalirudin", "heparin", "myocardial infarction", "percutaneous transluminal coronary angioplasty", and "randomised". There have been six previous major randomised trials of unfractionated heparin versus bivalirudin in STEMI. However, these studies used varying anticoagulation regimens, specifically heparin with or without the routine use of a glycoprotein IIb/IIIa inhibitor, and bivalirudin with or without a post-PCI infusion (and if so, of varying doses). Subgroup data from these trials have identified heparin without the routine use of a glycoprotein IIb/IIIa inhibitor and bivalirudin with a post-PCI high-dose infusion for 2–4 h as the two optimal anticoagulation regimens for use during primary PCI that are most likely to minimise ischaemic complications and haemorrhagic risks. However, these two regimens have never been directly compared in an adequately powered randomised trial, leading to confusion in guidelines and practice.

Added value of this study

The randomised BRIGHT-4 trial showed that among 6016 patients with STEMI undergoing primary PCI predominantly with radial artery access, bivalirudin with a median 3-h post-PCI high-dose infusion reduced the 30-day rates of the composite of all-cause mortality or BARC types 3–5 bleeding compared with heparin monotherapy. The reduction in major bleeding with bivalirudin was attributable to fewer large bleeds arising from non-access sites, whereas access-site-related major bleeding was infrequent. The secondary endpoint of all-cause mortality was also reduced with bivalirudin compared with heparin. Stent thrombosis rates were lower with the bivalirudin regimen, whereas the rates of reinfarction, ischaemia-driven target vessel revascularisation, and stroke were similar between the groups.

Implications of all the available evidence

Consistent with the results from previous smaller trials, the outcomes from this large-scale study confirm that anticoagulation with bivalirudin with a post-PCI high-dose infusion for 2–4 h reduces all-cause mortality and major bleeding compared with heparin monotherapy in patients with STEMI undergoing primary PCI.

trials to reduce bleeding and mortality compared with heparin. However, in these studies, the use of bivalirudin was restricted to the cardiac catheterisation laboratory, and its abrupt discontinuation was associated with an increased risk of stent thrombosis occurring within the first few hours after the procedure.[4–10] The use of bivalirudin plus a high-dose infusion (the same dose used in the catheterisation laboratory during the intervention) for 2–4 h after PCI might mitigate this risk without increasing bleeding.[6,8,11–13]

See Online for appendix

Conversely, much of the bleeding risk with heparin in these trials was attributed to the performance of PCI by femoral artery access and the routine use of glycoprotein IIb/IIIa inhibitors. PCI with radial artery access has been shown to reduce bleeding and mortality,[14] obviating the routine need for glycoprotein IIb/IIIa inhibition.[10,15,16] Thus, bivalirudin plus a high-dose infusion after PCI and heparin monotherapy (with glycoprotein IIb/IIIa inhibitor use reserved for procedural thrombotic complications in both groups) have emerged as the preferred anticoagulation regimens for patients with STEMI undergoing PCI. However, these regimens have never been directly compared in an adequately powered randomised controlled trial, resulting in uncertainty in the guidelines and clinical practice.[1,2]

We therefore conducted the Bivalirudin With Prolonged Full-Dose Infusion During Primary PCI Versus Heparin Trial (BRIGHT)-4 trial to examine whether a high-dose infusion of bivalirudin after PCI in patients with STEMI undergoing primary PCI with radial artery access is superior to heparin monotherapy in reducing mortality and major bleeding.

Methods

Study design and participants

BRIGHT-4 was an investigator-initiated, open-label, randomised controlled trial conducted at 87 clinical centres in 63 cities in China (appendix pp 3–5). The study protocol was approved by the ethics committee of the General Hospital of Northern Theatre Command and at each participating centre (appendix pp 23–54). The study was performed in accordance with the principles of the Declaration of Helsinki. There were no major protocol amendments regarding the study population, sample size, or primary and secondary endpoints. However, because of the COVID-19 pandemic and reduction of funds, the longest clinical follow-up duration was shortened from 3 years to 1 year. There were no planned rules for early trial discontinuation. The final study protocol and statistical analysis plan are available in the appendix.

Patients of any age presenting with STEMI within 48 h of symptom onset undergoing primary PCI and who had not previously received heparin, bivalirudin, fibrinolytic therapy, or a glycoprotein IIb/IIIa inhibitor for the present admission to hospital were eligible for enrolment. Major inclusion and exclusion criteria are listed in the

appendix (p 6). Written informed consent was provided by all patients or their legal representatives before random assignment.

Randomisation and masking

Eligible patients were randomly assigned to receive bivalirudin or heparin in a 1:1 ratio using an interactive web response system with variable block sizes of 4 or 6. The allocation sequence was computer generated by an external programmer who was not involved in the trial and was accessed by approved study physicians or research coordinators through the web-based system. Patients were enrolled and treated by local approved study physicians. The study was open-label; the physicians, other health-care providers, and patients and their families were not masked to the treatment assignments.

Procedures

Study medications were administered before coronary angiography. Bivalirudin (Hansoh Pharmaceutical Group, Jiangsu, China) was given as a bolus of 0·75 mg/kg followed by an infusion of 1·75 mg/kg per h during the PCI procedure and for 2–4 h afterwards. An additional bolus of 0·3 mg/kg was given if the activated clotting time (Hemotec assay; Medtronic, Santa Rosa, CA, USA), measured 5 min after the initial bolus, was less than 225 s. The infusion dose was reduced to 1·0 mg/kg per h in patients with an estimated glomerular filtration rate of less than 30 mL/min, and to 0·25 mg/kg per h in patients on dialysis. Estimated glomerular filtration rate was calculated by the formula: $186 \times (\text{serum creatinine [mg/dL]})^{-1\cdot154} \times (\text{age})^{-0\cdot203} \times (0\cdot742 \text{ if female})$. In the heparin group, an initial bolus dose of 70 U/kg was administered. Additional heparin was administered if the 5-min post-bolus activated clotting time was less than 225 s. Provisional glycoprotein IIb/IIIa inhibition with tirofiban was allowed in both groups only for thrombotic complications during the PCI procedure. Dual antiplatelet therapy with aspirin and either clopidogrel or ticagrelor was administered to all patients. Other medications were given at physician discretion per current guidelines. The radial artery was the preferred route for vascular access. Primary PCI was otherwise performed per standard clinical practice. Follow-up was performed at 30 days, 6 months, and 12 months after random assignment, and was completed in all patients up to 30 days at the time of publication.

Outcomes

The primary endpoint was the composite of all-cause death or Bleeding Academic Research Consortium (BARC) types 3–5 bleeding occurring within 30 days after random assignment. Secondary endpoints were major adverse cardiac or cerebral events (the composite of all-cause death, recurrent myocardial infarction, ischaemia-driven target vessel revascularisation, or stroke) and its components; stent thrombosis according to Academic Research Consortium criteria;[17] BARC types 2–5 bleeding; the composite of all-cause death or BARC types 2–5 bleeding; acquired thrombocytopenia; and net adverse clinical events (the composite of major adverse cardiac or cerebral events or BARC types 3–5 bleeding).[18,19] The specific definitions for these outcomes are in the appendix (pp 7–12). All data were monitored at each hospital by an independent contract research organisation. All primary and secondary events were adjudicated by an independent clinical events committee masked to the therapy assignment. Post hoc analyses were performed to establish the site, treatment, and subsequent outcomes of major bleeding events, and the effect of tirofiban use on clinical outcomes. All other analyses were prespecified.

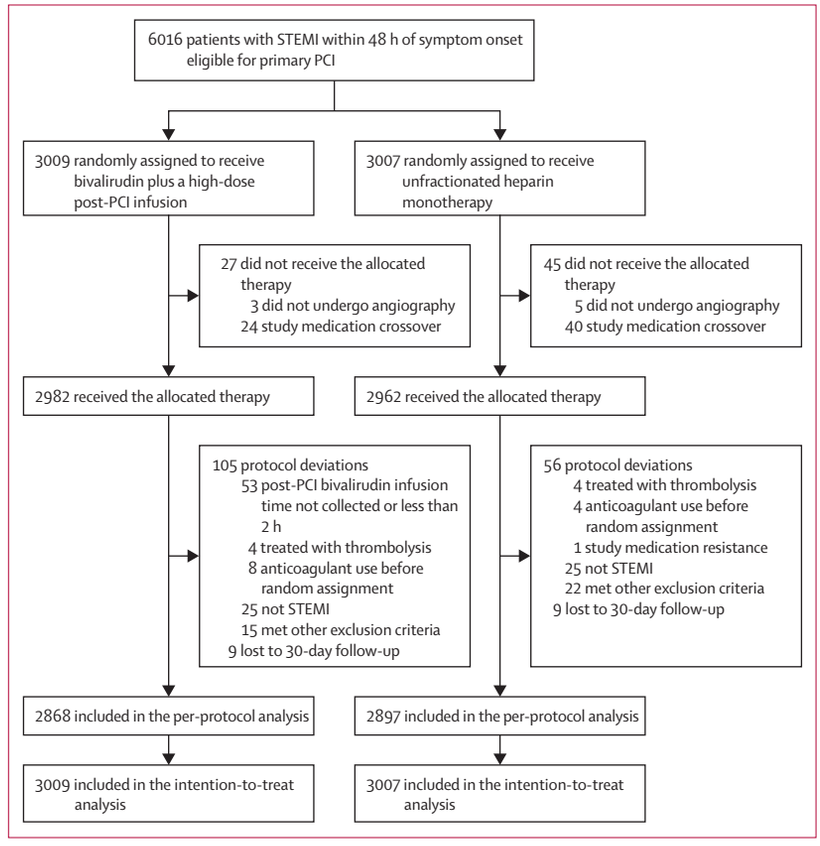


Figure 1: **Trial profile**
A screening log of the number of patients assessed and enrolled was not maintained given the emergency setting. STEMI=ST-segment elevation myocardial infarction. PCI=percutaneous coronary intervention.

Statistical analysis

Assuming a 3·3% incidence of the primary endpoint in the heparin group and allowing for 1% loss to follow-up, 3000 patients per group (6000 total) would provide 80% power to detect a 1·2% absolute risk reduction with bivalirudin with a 2-sided α of 0·05.[6] Data were collected and analysed according to the predefined statistical analysis plan. All primary analyses were by intention to treat. Sensitivity analyses were performed in the

	Heparin (N=3007)	Bivalirudin (N=3009)
Age, years	60·6 (12·2)	60·5 (12·1)
≥65 years	1236 (41·1%)	1218 (40·5%)
<65 years	1771 (58·9%)	1791 (59·5%)
Sex		
Male	2372 (78·9%)	2350 (78·1%)
Female	635 (21·1%)	659 (21·9%)
BMI, kg/m^2	25·0 (3·8)	24·8 (3·6)
Medical history		
Hypertension	1518 (50·5%)	1564 (52·0%)
Diabetes	698 (23·2%)	667 (22·2%)
Smoking		
Active	1392 (46·3%)	1360 (45·2%)
Former	253 (8·4%)	237 (7·9%)
Never	1362 (45·3%)	1412 (46·9%)
Previous myocardial infarction	197 (6·6%)	188 (6·2%)
Previous percutaneous coronary intervention	186 (6·2%)	186 (6·2%)
Previous stroke	344 (11·4%)	353 (11·7%)
Killip class*		
I	1857 (61·8%)	1818 (60·4%)
II	828 (27·5%)	884 (29·4%)
III	227 (7·5%)	219 (7·3%)
IV	95 (3·2%)	88 (2·9%)
Haemoglobin, g/dL	14·0 (12·8–15·3)	14·0 (12·9–15·3)
Anaemia†	626 (20·8%)	599 (19·9%)
Platelet count, 10^9/L	220 (186–262)	221 (185–263)
Estimated glomerular filtration rate, mL/min per 1·73 m^2‡	102·6 (83·3–124·2)	102·0 (82·7–123·9)
<60 mL/min per 1·73 m^2	205 (6·8%)	211 (7·0%)
Symptom onset to first medical contact, h	2·2 (1·0–4·8)	2·1 (1·0–4·6)
Patients transferred from a non-tertiary hospital	1037/2965 (35·0%)	1081/2974 (36·3%)
Symptom onset to tertiary hospital arrival, h	3·3 (1·7–6·7)	3·3 (1·7–6·4)
≤12 h	2250/2563 (87·8%)	2279/2562 (89·0%)
>12 h	313/2563 (12·2%)	283/2562 (11·0%)

Data are shown as n (%), mean (SD), or median (IQR). *Defined as follows: class I, no clinical signs of heart failure; class II, rales or crackles in the lungs, a third heart sound, or an elevated jugular venous pressure; class III, pulmonary oedema; and class IV, cardiogenic shock or hypotension with evidence of peripheral vasoconstriction. †Defined as a haemoglobin concentration of less than 13 g/dL in men and less than 12 g/dL in women. ‡Calculated by the formula: 186 × (serum creatinine [mg/dL])$^{-1·154}$×(age)$^{-0·203}$×(0·742 if female).

Table 1: **Baseline characteristics of the study groups**

per-protocol population (defined as patients who received any dose of study medication and who met all inclusion criteria and no exclusion criteria) and among patients in whom PCI was performed. No imputation was used to infer missing values. Those with missing primary and secondary endpoint data were censored at the time of withdrawal of consent or loss to follow-up. Categorical variables were compared using the χ^2 test or Fisher's exact test. Continuous data were presented as the mean and standard deviation or median and IQR and were compared using a Student's t-test or the Wilcoxon rank-sum test. Time-to-first-event rates were estimated using the Kaplan-Meier method and were compared with the log-rank test. Hazard ratios (HR) and 95% CIs were established from a Cox model. The proportional hazards assumption for the primary outcome was confirmed graphically using log(–log) plots. The number of patients needed to treat with bivalirudin rather than heparin to prevent one primary endpoint event was calculated. Consistency of the treatment effect for the primary endpoint was examined in 19 prespecified subgroups. Detailed information of prespecified subgroups are listed in the appendix (pp 44–45). All statistical analyses were two-sided and were performed with SAS version 9.4. The trial is registered with ClinicalTrials.gov (NCT03822975).

Role of the funding sources

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Between Feb 14, 2019, and April 7, 2022, a total of 6016 patients with STEMI undergoing primary PCI were randomly assigned to receive either bivalirudin plus a high-dose infusion after PCI (n=3009) or unfractionated heparin monotherapy (n=3007; figure 1). Baseline characteristics are presented in table 1. Eight randomly assigned patients did not receive any study medication, including six who died during the transfer from the emergency room to the catheterisation laboratory and two judged by their physicians as unsuitable for coronary angiography. These patients were included in the intention-to-treat population.

Study medications and procedural details are shown in table 2. Coronary angiography was performed using radial artery access in 5593 (93·1%) of 6008 patients. PCI was performed in 5891 (97·9%) of 6016 patients, 5339 (90·6%) of whom were administered drug-eluting stents. Study medication compliance was high in both groups. The median peak activated clotting time was greater for patients administered bivalirudin (median, 321 s [IQR 278–365]) than those administered heparin (267 s [238–317]). Tirofiban was used in 347 (11·5%) patients in the bivalirudin group and 411 (13·7%) patients in the heparin group for procedural thrombotic complications (difference, 2·2%; 95% CI 0·5–3·8%; p=0·0122). In the bivalirudin group, the median duration of the post-PCI bivalirudin infusion was 3·0 h (IQR 2·2–4·0). Other medication use appears in the appendix (p 13).

Follow-up data at 30 days was available in 5998 (99·7%) randomised patients. The principal outcomes are shown

in table 3, figure 2, and the appendix (pp 19–22). The primary 30-day endpoint of all-cause mortality or BARC types 3–5 bleeding occurred in 132 (4·39%) patients in the heparin group and in 92 (3·06%) patients in the bivalirudin group (difference 1·33%; 95% CI 0·38–2·29%; HR 0·69; 95% CI 0·53–0·91; p=0·0070; number needed to treat: 76, 95% CI 44–264). All-cause mortality within 30 days occurred in 118 (3·92%) patients in the heparin group and in 89 (2·96%) patients in the bivalirudin group (HR 0·75; 95% CI 0·57–0·99; p=0·0420), and BARC types 3–5 bleeding occurred in 24 (0·80%) patients in the heparin group and in five (0·17%) patients in the bivalirudin group (HR 0·21; 95% CI 0·08–0·54; p=0·0014). In a post-hoc analysis, the reduction in major bleeding with bivalirudin compared with heparin was attributable to fewer large bleeds arising from non-access sites (mostly gastrointestinal), whereas access-site-related major bleeding was infrequent in both groups (table 3). Additional outcomes among patients in whom BARC types 3–5 bleeding occurred are shown in the appendix (p 14).

The rates of reinfarction, ischaemia-driven target vessel revascularisation, and stroke were similar between the groups (all non-significant, p>0·05; table 3). The incidence of stent thrombosis was reduced in the bivalirudin group compared with the heparin group (11 events [0·37%] *vs* 33 events [1·10%]; HR 0·33, 95% CI 0·17–0·66; p=0·0015), occurring less frequently after bivalirudin both within the first 24 h post-PCI and between 1 and 30 days. Composite net adverse clinical events occurred in 125 (4·15%) patients in the bivalirudin group and in 167 (5·55%) patients in the heparin group (HR 0·74; 95% CI 0·59–0·94; p=0·0124). The rates of BARC type 2 (minor) bleeding were similar between the groups (p=0·77). The composite outcome of all-cause mortality or BARC types 2–5 bleeding was reduced in patients treated with bivalirudin (HR 0·80; 95% CI 0·65–0·99; p=0·0449). Outcomes in patients treated with tirofiban for procedural thrombotic complications are shown in the appendix (pp 15–16).

The principal results were similar in the per-protocol population (n=5765) and among patients in whom PCI was performed (n=5891; appendix pp 17–18). The benefits of bivalirudin in reducing all-cause death or BARC types 3–5 bleeding compared with heparin were consistent in most of the 19 prespecified subgroups examined, including age, sex, P2Y12 inhibitor use, and initial activated clotting time, except that patients presenting with pulmonary oedema or cardiogenic shock (Killip class III–IV), a BMI greater than or equal to the median (25 kg/m^2), and a high Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes with Early Implementation of the ACC/AHA Guidelines (CRUSADE) bleeding score might have had less clinical benefit in terms of all-cause death or BARC types 3–5 bleeding with bivalirudin than heparin

	Heparin (N=3007)	Bivalirudin (N=3009)	p value
Study medications			
Heparin	2962/3002 (98·7%)	24/3006 (0·8%)	..
Total dose during PCI, U	5570 (4800–6775)	NA	..
Bivalirudin	40/3002 (1·3%)	2982/3006 (99·2%)	..
Post-PCI infusion administered	NA	2953/2953 (100·0%)	..
Post-PCI infusion duration, h	NA	3·0 (2·2–4·0)	..
Additional bolus of study medications	1054 (35·1%)	106 (3·5%)	..
None	5 (0·2%)	3 (0·1%)	..
Tirofiban for procedural thrombotic complications	411 (13·7%)	347 (11·5%)	0·0122
Intracoronary	269 (8·9%)	223 (7·4%)	..
Intravenous	142 (4·7%)	124 (4·1%)	..
Peak activated clotting time, s*	267 (238–317)	321 (278–365)	<0·0001
Dual antiplatelet therapy	2990 (99·4%)	2989 (99·3%)	0·62
Aspirin	2990 (99·4%)	2989 (99·3%)	0·62
P2Y12 inhibitor	3007 (100·0%)	3009 (100·0%)	0·59
Clopidogrel	1033 (34·4%)	1014 (33·7%)	..
Ticagrelor	1974 (65·6%)	1995 (66·3%)	..
Invasive procedures			
Arterial access†			
Transradial	2780/3002 (92·6%)	2813/3006 (93·6%)	0·14
Transfemoral	222/3002 (7·4%)	193/3006 (6·4%)	..
Revascularisation, any	2960 (98·4%)	2953 (98·1%)	0·37
Coronary arteries treated‡			
Left main	32/2960 (1·1%)	26/2953 (0·9%)	0·43
Left anterior descending	1449/2960 (49·0%)	1457/2953 (49·3%)	0·77
Left circumflex	371/2960 (12·5%)	376/2953 (12·7%)	0·82
Right	1246/2960 (42·1%)	1200/2953 (40·6%)	0·26
Multivessel intervention	142/2960 (4·8%)	110/2953 (3·7%)	0·0413
PCI	2949 (98·1%)	2942 (97·8%)	0·42
Drug-eluting stent implantation	2672/2949 (90·6%)	2667/2942 (90·7%)	0·95
Number of stents	1·3 (0·6)	1·3 (0·5)	0·39
Total length of stents, mm	33·1 (16·6)	33·0 (16·0)	0·68
Balloon angioplasty only	277/2949 (9·4%)	275/2942 (9·3%)	0·95
Non-drug-coated	257/2949 (8·7%)	266/2942 (9·0%)	0·66
Drug-coated	20/2949 (0·7%)	9/2942 (0·3%)	0·0412
Thrombus aspiration	527/2949 (17·9%)	533/2942 (18·1%)	0·81
PCI time intervals			
Symptom-onset-to-wire time, h	4·5 (3·0–8·2)	4·6 (2·9–7·8)	0·57
First-medical-contact-to-wire time, h	1·7 (1·1–3·0)	1·7 (1·1–3·0)	0·77
Tertiary-hospital-door-to-wire time, h	1·1 (0·9–1·7)	1·1 (0·9–1·6)	0·51
Procedure duration, min§	30 (20–41)	29 (20–42)	0·30
PCI thrombolysis in myocardial infarction flow, site-assessed			
Pre-PCI	N=2929	N=2930	0·53
0	2243 (76·6%)	2211 (75·5%)	..
1	200 (6·8%)	192 (6·6%)	..
2	203 (6·9%)	227 (7·7%)	..
3	283 (9·7%)	300 (10·2%)	..

(Table 2 continues on next page)

	Heparin (N=3007)	Bivalirudin (N=3009)	p value
(Continued from previous page)			
Post-PCI	N=2933	N=2931	0·0430
0	24 (0·8%)	11 (0·4%)	..
1	5 (0·2%)	4 (0·1%)	..
2	44 (1·5%)	29 (1·0%)	..
3	2860 (97·5%)	2887 (98·5%)	..
Staged PCI within 30 days	235/3002 (7·8%)	228/3006 (7·6%)	0·72
Coronary artery bypass graft surgery	11 (0·4%)	11 (0·4%)	0·99
Coronary angiography only	42 (1·4%)	53 (1·8%)	0·26
None	5 (0·2%)	3 (0·1%)	0·51

Data are shown as n (%), mean (SD), or median (IQR). NA=not applicable. PCI=percutaneous coronary intervention. *Activated clotting time was measured in 2685 patients in the heparin group and 2776 patients in the bivalirudin group. †Angiography was not performed in three patients in the bivalirudin group and five in the heparin group. ‡Per patient; some patients had more than one epicardial coronary artery treated during the index percutaneous coronary intervention or bypass graft procedure, so the total is more than 100%. §Defined as the time from guiding catheter insertion to its withdrawal.

Table 2: **Medications and procedural results**

compared with all other groups in which the composite 30-day rate of death or BARC types 3–5 bleeding was consistently reduced with bivalirudin (figure 3).

Discussion

The practice of primary PCI in STEMI has evolved greatly over the last several decades. Before the present study, six large-scale trials had been performed in which more than 15 000 patients with STEMI undergoing primary PCI with either femoral or radial artery access were randomly assigned to procedural anticoagulation with bivalirudin (with or without a post-PCI infusion) or heparin (with or without routine glycoprotein IIb/IIIa inhibition).[4–6,10,15,16] Based on these studies, bivalirudin with a post-PCI high-dose infusion and heparin monotherapy have emerged as the favoured anticoagulation regimens during primary PCI to minimise both ischaemic events and haemorrhagic complications, with PCI preferentially performed using radial artery access to further reduce bleeding and mortality. However, these two specific anticoagulation regimens have never been directly compared in a study adequately powered to show meaningful differences in all-cause death, major bleeding, or other important outcomes. To address this evidence gap we performed the present trial, in which 6016 patients presenting with STEMI undergoing PCI predominantly with radial artery access were randomly assigned to bivalirudin with a post-PCI high-dose infusion for 2–4 h versus unfractionated heparin monotherapy, with glycoprotein IIb/IIIa inhibitor use in both groups reserved for procedural thrombotic complications.

The principal findings from our study are that: (1) bivalirudin with a post-PCI high-dose infusion for a median of 3 h resulted in a 31% (HR 0·69) relative reduction and 1·33% absolute reduction in the primary 30-day composite endpoint of all-cause mortality or BARC types 3–5 bleeding (number needed to treat, 76 patients to prevent 1 event), compared with heparin monotherapy; (2) in addition to major bleeding being reduced, all-cause mortality at 30 days was significantly lower in patients treated with bivalirudin than those treated with heparin; (3) stent thrombosis rates within 30 days were lower with bivalirudin compared with heparin, whereas the rates of reinfarction, ischaemia-driven target vessel revascularisation, and stroke were similar with the two regimens; and (4) the relative reductions in the primary endpoint with bivalirudin were consistent in the per-protocol population and in patients in whom PCI was performed, as well as across most prespecified subgroups, except those presenting with pulmonary oedema or cardiogenic shock, a high BMI (≥25 kg/m²), or a high CRUSADE bleeding risk score.

In the randomised HORIZONS-AMI[4] and EUROMAX[5] trials, anticoagulation with bivalirudin during primary PCI in patients with STEMI reduced major bleeding and cardiac death compared with heparin plus glycoprotein IIb/IIIa inhibition in most patients, albeit with an increase in acute (<24 h) stent thrombosis and reinfarction. Subsequently, the hypothesis was introduced that the routine glycoprotein IIb/IIIa inhibitor use with heparin was causing excess bleeding and was unnecessary in the contemporary era, in which PCI is performed predominately with radial artery access.

In the single-centre HEAT-PPCI trial,[10] heparin monotherapy and bivalirudin resulted in similar 28-day rates of mortality and major bleeding, and rates of stent thrombosis and reinfarction were increased with bivalirudin. Investigators then posited that the excess stent thrombosis hazard in the early post-procedure period observed in these trials was attributable to the shorter half-life of bivalirudin (25 min) compared with heparin (60–90 min), and that continuing the bivalirudin infusion at the PCI dose for 2–4 h post-procedure might mitigate this risk. In the multicentre BRIGHT trial,[6] bivalirudin plus a post-PCI high-dose infusion for a median 3-h duration resulted in lower rates of major bleeding and similar rates of stent thrombosis and reinfarction compared with heparin with or without glycoprotein IIb/IIIa inhibition; however, this study was not large enough to elicit differences in mortality. The subsequent large-scale MATRIX[15] and VALIDATE-SWEDEHEART[16] trials failed to show differences in survival between the agents (and the reductions in bleeding with bivalirudin were inconsistent), although these studies were confounded by the enrolment of patients with and without STEMI, allowing bivalirudin to be used either without a post-PCI infusion or with a low-dose or high-dose infusion, permitting the co-administration of heparin in patients assigned to receive bivalirudin, and allowing routine glycoprotein IIb/IIIa inhibitor use in some patients assigned to receive heparin. Previous meta-analyses of bivalirudin versus heparin have also reported variable findings,[20–24] which is

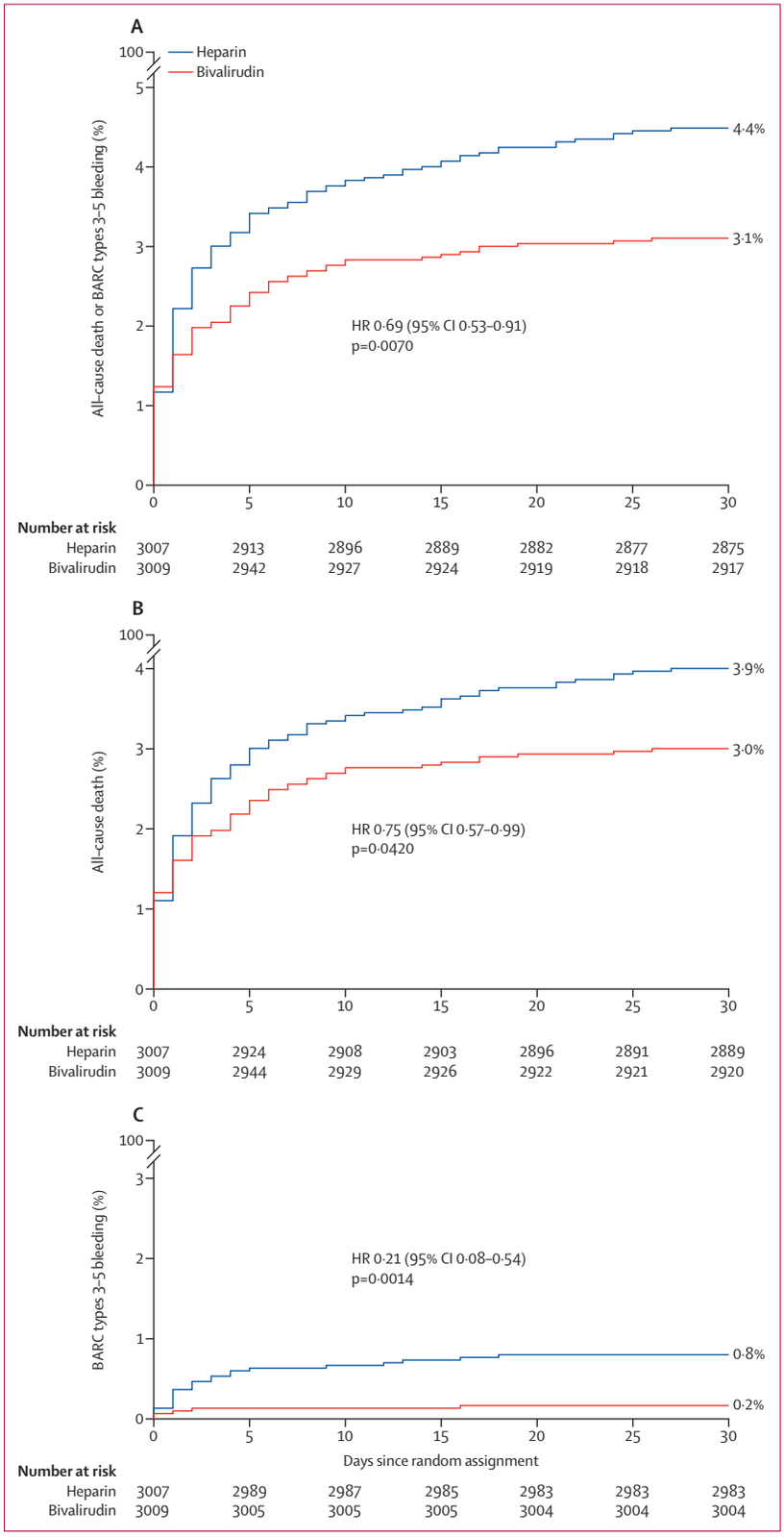
	Heparin (N=3007)	Bivalirudin (N=3009)	Absolute difference (95% CI)	Hazard ratio (95% CI)	p value
Primary endpoint: all-cause death or BARC types 3–5 bleeding	132 (4·39%)	92 (3·06%)	1·33% (0·38% to 2·29%)	0·69 (0·53 to 0·91)	0·0070
Death from any cause	118 (3·92%)	89 (2·96%)	0·97% (0·05% to 1·89%)	0·75 (0·57 to 0·99)	0·0420
From cardiovascular causes	113 (3·76%)	87 (2·89%)	0·87% (–0·04% to 1·77%)	0·77 (0·58 to 1·01)	0·063
BARC types 3–5 bleeding	24 (0·80%)	5 (0·17%)	0·63% (0·28% to 0·98%)	0·21 (0·08 to 0·54)	0·0014
Access-site-related	1 (0·03%)	0	..	..	..
Non-access-site-related	23 (0·76%)	5 (0·17%)	0·60% (0·25% to 0·94%)	0·22 (0·08 to 0·57)	0·0019
Gastrointestinal	17 (0·57%)	4 (0·13%)	0·43% (0·13% to 0·73%)	0·23 (0·08 to 0·70)	0·0091
Other	6 (0·20%)	1 (0·03%)	0·17% (–0·01% to 0·34%)	0·17 (0·02 to 1·38)	0·10
Reinfarction	25 (0·83%)	17 (0·56%)	0·27% (–0·15% to 0·69%)	0·68 (0·37 to 1·26)	0·22
Ischaemia-driven target vessel revascularisation	18 (0·60%)	9 (0·30%)	0·30% (–0·04% to 0·64%)	0·50 (0·22 to 1·11)	0·089
Stroke	14 (0·47%)	15 (0·50%)	–0·03% (–0·38% to 0·32%)	1·07 (0·52 to 2·22)	0·85
Stent thrombosis, definite or probable	33 (1·10%)	11 (0·37%)	0·73% (0·03% to 1·16%)	0·33 (0·17 to 0·66)	0·0015
Acute (<24 h)	14 (0·47%)	4 (0·13%)	0·33% (0·06% to 0·61%)	0·29 (0·09 to 0·87)	0·0268
Subacute (1–30 days)	19 (0·63%)	7 (0·23%)	0·40% (0·07% to 0·73%)	0·37 (0·15 to 0·87)	0·0231
Major adverse cardiac or cerebral events*	155 (5·15%)	123 (4·09%)	1·07% (0·01% to 2·13%)	0·79 (0·62 to 1·00)	0·051
BARC bleeding, types 2–5	77 (2·56%)	63 (2·09%)	0·47% (–0·29% to 1·23%)	0·82 (0·59 to 1·14)	0·24
Type 2	55 (1·83%)	58 (1·93%)	–0·10% (–0·78% to 0·59%)	1·06 (0·73 to 1·53)	0·77
Type 3	21 (0·70%)	4 (0·13%)	0·57% (0·24% to 0·89%)	0·19 (0·07 to 0·55)	0·0023
Type 4	0	0	..	..	..
Type 5	3 (0·10%)	1 (0·03%)	0·07% (–0·06% to 0·20%)	0·33 (0·03 to 3·20)	0·34
All-cause death or BARC types 2–5 bleeding	183 (6·09%)	147 (4·89%)	1·20% (0·05% to 2·35%)	0·80 (0·65 to 0·99)	0·0449
Acquired thrombocytopenia†	123/2949 (4·17%)	97/2942 (3·30%)	0·87% (–0·09% to 1·84%)	0·79 (0·60 to 1·03)	0·081
Net adverse clinical events‡	167 (5·55%)	125 (4·15%)	1·40% (0·31% to 2·49%)	0·74 (0·59 to 0·94)	0·0124

Event rates are number of events (Kaplan-Meier estimated percentages). BARC=Bleeding Academic Research Consortium. *Major adverse cardiac or cerebral events included all-cause death, myocardial infarction, ischaemia-driven target vessel revascularisation, or stroke. †Defined as nadir platelet count of less than 150×10^9/L after the index procedure in patients in whom the baseline platelet count was more than 150×10^9/L. ‡Net adverse clinical events included major adverse cardiac or cerebral events or BARC types 3–5 bleeding.

Table 3: **Clinical outcomes at 30 days after random assignment**

unsurprising because study-level analyses cannot account for heterogeneity in patients or treatments nor assess outcomes in subgroups.

The BRIGHT-4 trial was thus designed to examine the outcomes of procedural anticoagulation with the two regimens most likely to minimise both ischaemic and bleeding complications in a large, relatively unrestricted population of patients with STEMI undergoing primary PCI with radial artery access. In this trial, bivalirudin with a post-PCI high-dose infusion for a median of 3 h reduced the 30-day composite incidence of all-cause death or BARC types 3–5 major bleeding compared with heparin monotherapy. With radial artery use in 93·1% of patients, major access-site-related bleeding was infrequent with both regimens, occurring in only one patient. However, bivalirudin decreased major bleeding arising from non-access sites compared with heparin, the occurrence of which has been more strongly related to subsequent mortality than access-site-related major bleeding.[25,26] The lower rate of major bleeding with bivalirudin plus a median 3-h post-PCI high-dose infusion compared with heparin alone might be attributed to its more consistent pharmacokinetics and pharmacodynamics, less non-specific protein binding, and freedom from heparin-induced thrombocytopenia. Bivalirudin with a post-PCI high-dose infusion was also effective in suppressing ischaemic complications, resulting in similar rates of reinfarction and lower rates of stent thrombosis within 30 days compared with heparin monotherapy, which was consistent with that seen in patients with STEMI at 30 days from the VALIDATE-SWEDEHEART trial.[16] Provisional glycoprotein IIb/IIIa inhibitor use for procedural thrombotic complications was also required less frequently in BRIGHT-4 after bivalirudin than after heparin monotherapy, reflecting the facts that heparin (but not bivalirudin) activates platelets, and that bivalirudin (but not heparin) inhibits fibrin-bound and fluid-phase thrombin.[27,28] The net effect is that bivalirudin plus a median 3-h post-PCI high-dose infusion reduced



30-day mortality in patients with STEMI undergoing primary PCI predominantly with radial artery access compared with heparin monotherapy.

Of note, the 30-day rates of BARC types 3–5 bleeding were lower in both treatment groups in the present study than in other multicentre trials such as MATRIX.[15] The reasons for this difference might relate to the use, in this study, of a lower initial dose of heparin, a higher use of radial artery access (essentially eliminating access-site-related major bleeding), or a more judicious use of glycoprotein IIb/IIIa inhibitors in the heparin group, or a combination of these factors. We cannot, however, exclude differences in ascertainment between studies, although BARC types 3–5 bleeding events are major adverse outcomes that are difficult to miss, and all patient charts were independently monitored. Nonetheless, given the substantial reduction in bleeding with bivalirudin compared with heparin in the present and most previous trials, and the strong association between non-access-site-related bleeding and subsequent death,[25,26] had major bleeding been even more frequent the survival advantage of bivalirudin might have been greater.

Strengths of BRIGHT-4 include its large size, few exclusion criteria, and use of radial artery access in most patients. Excluding patients with pre-random-assignment use of heparin or bivalirudin and restricting tirofiban use for patients with procedural thrombotic complications allowed the specific effects of bivalirudin with a post-PCI high-dose infusion and heparin monotherapy to emerge. However, our study has limitations. First, as with all previous randomised controlled trials of anticoagulation in STEMI, the present study was open-label, introducing potential bias. However, all outcomes were adjudicated by an independent clinical events committee that was masked to the therapy assignment on the basis of prespecified criteria after a review of the source documents, in part lessening this concern. Second, the analyses of secondary endpoints and subgroups were not adjusted for multiple comparisons, increasing the risk of a type 1 error (false positive finding); these results should therefore not be used to infer definitive treatment effects. The benefit of bivalirudin in reducing the primary composite endpoint was consistent in most prespecified subgroups, other than possibly in the approximately 10% of patients who presented with pulmonary oedema or cardiogenic shock and in those with a high BMI or a high CRUSADE bleeding risk score. Because bivalirudin is degraded by endogenous peptidases that might be affected by congestive low output states,[8] the neutral

Figure 2: **Kaplan-Meier curves for the 30-day primary endpoint and its components in the intention-to-treat population.**
(A) The composite of all-cause mortality or BARC types 3–5 bleeding. (B) All-cause mortality. (C). BARC types 3–5 bleeding. BARC=Bleeding Academic Research Consortium. HR=hazard ratio.

	All-cause death or BARC types 3–5 bleeding, events/total (%)		Hazard ratio (95%CI)	p value for interaction
	Bivalirudin	Heparin		
Age ≥65 years				0·83
Yes	70/1218 (5·7%)	99/1236 (8·0%)	0·71 (0·52–0·97)	
No	22/1791 (1·2%)	33/1771 (1·9%)	0·66 (0·38–1·13)	
Sex				0·059
Male	45/2350 (1·9%)	83/2372 (3·5%)	0·54 (0·38–0·78)	
Female	47/659 (7·1%)	49/635 (7·7%)	0·92 (0·62–1·38)	
BMI ≥25 kg/m²				0·0384
Yes	39/1337 (2·9%)	41/1395 (2·9%)	0·99 (0·64–1·54)	
No	53/1672 (3·2%)	91/1612 (5·6%)	0·56 (0·40–0·78)	
Killip class				0·0002
I	18/1818 (1·0%)	52/1857 (2·8%)	0·35 (0·21–0·60)	
II	12/884 (1·4%)	22/828 (2·7%)	0·51 (0·25–1·03)	
III	44/219 (20·1%)	42/227 (18·5%)	1·10 (0·72–1·68)	
IV	18/88 (20·5%)	16/95 (16·8%)	1·25 (0·64–2·45)	
Diabetes				0·29
Yes	23/667 (3·4%)	43/698 (6·2%)	0·56 (0·34–0·93)	
No	69/2342 (2·9%)	89/2309 (3·9%)	0·76 (0·56–1·04)	
eGFR <60 mL/min/1·73m²				0·58
Yes	21/211 (10·0%)	25/205 (12·2%)	0·82 (0·46–1·47)	
No	71/2798 (2·5%)	107/2802 (3·8%)	0·66 (0·49–0·89)	
Anaemia				0·82
Yes	25/599 (4·2%)	39/626 (6·2%)	0·67 (0·40–1·10)	
No	67/2410 (2·8%)	93/2381 (3·9%)	0·71 (0·52–0·97)	
P2Y12 inhibitor given at admission				0·16
Ticagrelor	50/1995 (2·5%)	83/1974 (4·2%)	0·59 (0·42–0·84)	
Clopidogrel	42/1014 (4·1%)	49/1033 (4·7%)	0·87 (0·58–1·32)	
Any other anticoagulant treatment after procedure				0·62
Yes	36/1799 (2·0%)	57/2000 (2·9%)	0·70 (0·46–1·06)	
No	54/1207 (4·5%)	72/1002 (7·2%)	0·62 (0·43–0·88)	
GRACE score				0·29
<140	6/1322 (0·5%)	15/1361 (1·1%)	0·41 (0·16–1·06)	
≥140	86/1687 (5·1%)	117/1646 (7·1%)	0·71 (0·54–0·94)	
CRUSADE score				0·0433
<30	33/2281 (1·4%)	67/2300 (2·9%)	0·49 (0·32–0·75)	
≥30	59/728 (8·1%)	65/707 (9·2%)	0·88 (0·62–1·26)	
First medical contact to PCI time				0·61
≤90 mins	20/1103 (1·8%)	33/1112 (3·0%)	0·61 (0·35–1·06)	
>90 mins	36/1125 (3·2%)	49/1127 (4·3%)	0·73 (0·48–1·13)	
Access site				0·72
Femoral	18/193 (9·3%)	26/222 (11·7%)	0·79 (0·43–1·43)	
Radial	72/2813 (2·6%)	103/2780 (3·7%)	0·69 (0·51–0·93)	
Multivessel intervention				0·75
Yes	7/110 (6·4%)	11/142 (7·7%)	0·82 (0·32–2·13)	
No	77/2843 (2·7%)	115/2818 (4·1%)	0·69 (0·52–0·92)	
GPI during procedure				0·066
Yes	20/347 (5·8%)	20/411 (4·9%)	1·20 (0·64–2·22)	
No	70/2659 (2·6%)	109/2591 (4·2%)	0·62 (0·46–0·84)	
Left main or proximal LAD intervention				0·98
Yes	29/842 (3·4%)	41/789 (5·2%)	0·66 (0·41–1·06)	
No	55/2111 (2·6%)	85/2171 (3·9%)	0·66 (0·47–0·93)	
Circulation assist device				0·87
Yes	8/78 (10·3%)	14/93 (15·1%)	0·67 (0·28–1·60)	
No	82/2928 (2·8%)	115/2909 (4·0%)	0·71 (0·53–0·94)	
No or slow reflow				0·39
Yes	7/44 (15·9%)	11/73 (15·1%)	1·06 (0·41–2·73)	
No	76/2887 (2·6%)	112/2860 (3·9%)	0·67 (0·50–0·90)	
ACT after first bolus injection				0·31
<225 s	6/123 (4·9%)	35/848 (4·1%)	1·18 (0·50–2·81)	
≥225 s	77/2653 (2·9%)	72/1837 (3·9%)	0·74 (0·54–1·02)	

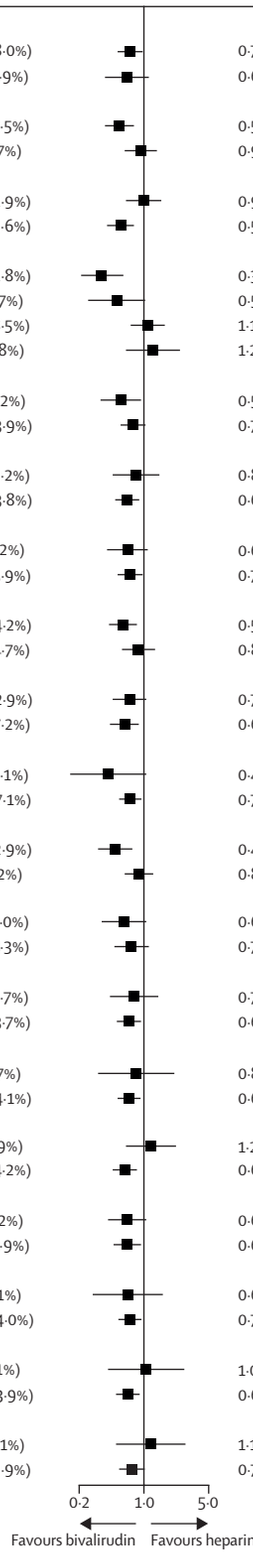


Figure 3: **Prespecified subgroup analyses in the intention-to-treat population for the 30-day primary composite endpoint.**
The Forest plot displays the interactions between 19 prespecified subgroups and randomised treatment for the primary composite outcome of all-cause mortality or BARC types 3–5 bleeding at 30 days. A 20th prespecified subgroup, the Optimal antiPlatelet Therapy in Chinese patients with Coronary Artery Disease score, was not calculated because the left ventricular ejection fraction, an important component of this score, was not routinely assessed per protocol. ACT=activated clotting time. BARC=Bleeding Academic Research Consortium. CRUSADE=Can Rapid risk stratification of Unstable angina patients Suppress Adverse outcomes with Early implementation of the ACC/AHA Guidelines. eGFR=estimated glomerular filtration rate. GPI=glycoprotein IIb/IIIa inhibitor. GRACE=the Global Registry of Acute Coronary Events. LAD=left anterior descending. PCI=percutaneous coronary intervention.

outcome in patients with Killip class III and IV is plausible but requires confirmation from additional studies. The interaction with BMI has not, to our knowledge, been reported from previous studies and thus warrants cautious interpretation. The marginal interaction between the CRUSADE score and treatment is also uncertain because nearly all previous studies have shown a greater effect of bivalirudin compared with heparin in patients at a high risk of bleeding. In this regard, the beneficial effects of bivalirudin were not mitigated in patients who were older (≥65 years) and in those with anaemia, two of the strongest risk factors for bleeding. The modest number of patients at a high risk of bleeding (high CRUSADE score) and absence of correction for multiple comparisons might thus have resulted in a spurious finding.

Third, in the present study, we enrolled patients with STEMI undergoing primary PCI as late as 48 h after symptom onset. Although primary PCI is most effective if performed within 12 h, based on current evidence, the most recent societal guidelines published in 2018 provide a confirmative recommendation for primary PCI after 12 h if symptoms are ongoing, and a recommendation that PCI is probably beneficial for all patients presenting within 12–48 h after symptom onset.[2] Regardless, approximately 88% of patients in BRIGHT-4 presented within 12 h of symptom onset; further study is warranted to examine the safety and efficacy of bivalirudin versus heparin in patients with STEMI and late presentation. Additional data is also required on the two agents in other subgroups of patients that were either excluded from enrolment or were poorly represented in the trial, such as patients with cardiogenic shock and those treated with heparin or fibrinolysis before PCI.

Fourth, the potent oral P2Y12 inhibitor prasugrel was not available in China and was therefore not used in the present study. Ticagrelor was used in approximately two-thirds of patients in BRIGHT-4, and clopidogrel in the other third. In the ISAR REACT-5 trial,[29] there were no significant differences in the rates of death or BARC types 3–5 bleeding in patients with STEMI undergoing primary PCI who were randomly assigned to prasugrel or ticagrelor,[29] and in the present trial the relative treatment effects of bivalirudin compared with heparin were consistent in patients treated with ticagrelor and clopidogrel. We therefore believe that the present results would also be consistent in patients treated with prasugrel.

Fifth, follow-up is currently complete up to 30 days. Although 1 month is the appropriate timepoint to assess the acute effects of varying anticoagulation regimens during primary PCI, 1-year follow-up from this study is required to establish whether the magnitude of the safety and efficacy benefits of bivalirudin observed at 30 days are decreased over time as events inevitably accrue in both treatment groups. Finally, a screening log was not maintained, given the emergency setting of the patients enrolled. Nonetheless, the broad enrolment criteria and characteristics of the included patients suggest the results are generalisable. In this regard, although east Asian patients have differences in genetic polymorphisms affecting their response to antiplatelet agents compared with populations from the USA, UK, and Europe,[30] we are not aware of genetic, social, or other differences between populations that should affect the relative outcomes of anticoagulant agents. In addition, the results of the previous BRIGHT trial (also enrolled in China) were in general consistent with other randomised trials of heparin versus bivalirudin, and the present results are consistent with those from the European MATRIX trial, in which 30-day mortality occurred in 2·4% of patients treated with heparin monotherapy (n=2816) and in 0·8% of patients treated with bivalirudin with a post-PCI high-dose infusion (n=618), with BARC types 3–5 bleeding occurring in 2·3% of patients treated with heparin and 0·3% of of patients treated with bivalirudin.[15]

Among patients with STEMI undergoing primary PCI predominantly with radial artery access, bivalirudin with a median 3-hour post-PCI high-dose infusion reduced the 30-day composite rate of all-cause mortality or BARC types 3–5 major bleeding compared with heparin monotherapy.

Contributors

YH and GWS designed this study. All authors except GWS participated in the enrolment of patients and clinical follow-up. YiLi, ZL, and YH were responsible for clinical trial operations. YiLi, ZL, MQ, and YH had full access to and verified all the study data. YiLi, ZL, MQ, YH, and GWS analysed the data and wrote the manuscript. All other authors reviewed the manuscript and provided critical comments for revision. All authors approved the final version of the manuscript and had final responsibility for the decision to submit for publication.

Declaration of interests

GWS has received speaker honoraria from Abiomed, Infraredx, Medtronic, and Pulnovo; has served as a consultant to Abiomed, Ablative Solutions, Adona Medical, Amgen, Ancora, Apollo Therapeutics, Cardiomech, CorFlow, Elucid Bio, Gore, HeartFlow, Impulse Dynamics, Millennia Biopharma, Miracor, Neovasc, Occlutech, Robocath, TherOx, Valfix, and Vectorious; and has equity and options from Ancora, Applied Therapeutics, Aria, Biostar family of funds, Cagent, Cardiac Success, Orchestra Biomed, SpectraWave, Valfix, and Xenter. GWS's daughter is an employee at IQVIA. Institutional disclosure: GWS's employer, Mount Sinai Hospital, receives research support from Abbott, Abiomed, Biosense-Webster, Bioventrix, Cardiovascular Systems, Phillips, Pulnovo, Shockwave, Vascular Dynamics, and V-wave. All other authors declare no competing interests.

Data sharing

The authors are willing to share deidentified individual data with researchers who provide a methodologically sound proposal. Interested parties should contact the corresponding author of this article via email.

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