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Bivalirudin versus heparin in patients with or without bail-out GPI use: a pre-specified subgroup analysis from the BRIGHT-4 trial

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Abstract

Background Conflicting results comparing bivalirudin versus heparin anticoagulation in patients with ST-segment elevation myocardial infarction (STEMI) undergoing primary percutaneous coronary intervention (PCI), in part due to the confounding effect of glycoprotein IIb/IIIa inhibitors (GPI). The aim of the study was to compare the safety and effectiveness of bivalirudin plus a post-PCI high-dose infusion vs heparin with or without bail-out GPI use.

Methods We conducted a pre-specified subgroup analysis from the BRIGHT-4 trial that randomized 6016 STEMI patients who underwent primary PCI to receive either bivalirudin plus a post-PCI high-dose infusion for 2–4 h or heparin monotherapy. GPI use was only reserved as bail-out therapy for procedural thrombotic complications. The primary outcome was a composite of all-cause death or Bleeding Academic Research Consortium (BARC) types 3–5 bleeding at 30 days.

Results A total of 5250 (87.4%) patients received treatment without GPI while 758 (12.6%) received bail-out GPI. Bail-out GPI use was associated with an increased risk of the primary outcome compared to non-GPI use (5.28% vs. 3.41%; adjusted hazard ratio (aHR), 1.62; 95% confidence interval (CI), 1.13–2.33; $P=0.009$) and all-cause death (5.01% vs. 3.12%; aHR, 1.74; 95% CI, 1.20–2.52; $P=0.004$) but not in the risk of BARC types 3–5 bleeding (0.53% vs. 0.48%; aHR, 0.90; 95% CI, 0.31–2.66; $P=0.85$). Among patients without GPI use, bivalirudin was associated with lower rates of the primary outcome (2.63% vs. 4.21%; aHR, 0.55; 95% CI, 0.39–0.77; $P=0.0005$), all-cause death (2.52% vs. 3.74%; aHR, 0.58; 95% CI, 0.41–0.83; $P=0.003$), and BARC types 3–5 bleeding (0.15% vs. 0.81%; aHR, 0.19; 95% CI, 0.06–0.57; $P=0.003$) compared with heparin. However, among patients requiring bail-out GPI, there were no significant differences observed in the rates of the primary outcome (5.76% vs. 4.87%; aHR, 0.77; 95% CI, 0.36–1.66; $P=0.50$; $P_{interaction}=0.07$) or its individual components between bivalirudin and heparin groups.

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Conclusions Bivalirudin plus a post-PCI high-dose infusion was associated with significantly reduced 30-day composite rate of all-cause death or BARC types 3–5 bleeding compared with heparin monotherapy in STEMI patients undergoing primary PCI without GPI use. However, these benefits might be less pronounced in patients requiring bail-out GPI due to thrombotic complications during primary PCI.

Trial registration ClinicalTrials.gov NCT03822975.

Keywords BRIGHT-4, Glycoprotein IIb/IIIa inhibitors, Bivalirudin plus high-dose infusion, Heparin, Procedural thrombotic complications

Background

In patients with ST-segment elevation myocardial infarction (STEMI) undergoing primary percutaneous coronary intervention (PCI), optimal adjunctive anticoagulation and antiplatelet therapy are essential for maximizing clinical anti-ischaemic efficacy and minimizing the risk of bleeding complications [1–3]. Unfractionated heparin and bivalirudin are the two most commonly utilized procedural anticoagulants during primary PCI. However, conflicting results have emerged regarding the comparative safety and effectiveness of bivalirudin versus heparin, in part due to the confounding effect of the usage pattern of glycoprotein IIb/IIIa inhibitors (GPI) [4–11].

Despite the positive results of some large-scale randomized controlled trials (RCTs) demonstrating reduction of major bleeding events with the use of bivalirudin regardless of the administration of GPI in the heparin arm, other RCTs have demonstrated that bivalirudin may not decrease bleeding events when compared with heparin alone [6, 8–11]. Given the heterogeneity between trials, the results from meta-analyses also varied [12–17]. Therefore, with the widespread adoption of radial access and the introduction of potent platelet P2Y12 inhibitors, either planned or bail-out use of GPI has decreased, making this difference noteworthy [18–20]. Moreover, according to most recent guidelines, the use of GPI in STEMI is recommended only as bail-out therapy for angiographic evidence of refractory thrombus, slow- or no-reflow, and other thrombotic complications to improve coronary flow and reduce major adverse cardiac events [21–23]. However, the comparison between bivalirudin versus heparin has not been investigated in subgroup analyses or post hoc analyses of previous RCTs among patients with and without bail-out GPI use.

The Bivalirudin With Prolonged Full-Dose Infusion During Primary PCI Versus Heparin Trial (BRIGHT)-4 trial was designed to examine the efficacy and safety of bivalirudin with a 2–4 h post-PCI high-dose infusion compared with heparin alone during primary PCI, with GPI use was reserved only for procedural thrombotic complications in both arms. The present pre-specified subgroup analysis sought to compare the 30-day outcomes of bivalirudin plus a 2–4 h high-dose infusion vs heparin in STEMI patients with and without bail-out GPI use during primary PCI.

Methods

Study population

The BRIGHT-4 trial design has been previously published in detail [24]. In brief, BRIGHT-4 was an investigator-initiated, open-label, active drug-controlled randomized trial conducted at 87 clinical centers in 63 cities in China. Patients of any age presenting with STEMI within 48 h of symptom onset undergoing primary PCI were randomly assigned to receive bivalirudin with a prolonged high-dose infusion for 2–4 h after the procedure or unfractionated heparin alone in a 1:1 ratio using an interactive web response system [25]. The trial was approved by the institutional review board or ethics committee at each participating center, and all enrolled patients provided written consent before randomization.

Study treatments

Study medications were administered according to the assigned group before angiography in the catheterization laboratory. Bivalirudin was given as a bolus of 0.75 mg/kg followed by an infusion of 1.75 mg/kg per hour during the PCI procedure and for 2–4 h afterwards. In the heparin group, an initial bolus dose of 70 U/kg was administered. Monitoring of the activated clotting time (ACT) was conducted 5 min after the initial study drug administration. If the ACT was < 225 s, an additional bolus of 0.30 mg/kg of bivalirudin or an additional injection of 1000 U of heparin was given according to the study medication assignment. Repeated ACT testing was encouraged and further adjustments of study medications according to the ACT result were at physicians' discretion.

Routine use of procedural GPI was not permitted. Intravenous or intracoronary injection of the GPI tirofiban was allowed only for target vessel slow blood flow, no-reflow, refractory thrombus, or thrombotic complications occurring during PCI. If necessary, intravenous administration of tirofiban was administered either as a 10–25 μg/kg bolus injection (given over more than 5 min) followed by 0.15 μg/kg/min maintenance infusion

for up to 18 h, or (at operator discretion) as intracoronary administration at 500–750 μg per injection, with repeated injection intervals of 3–5 min and total dose no more than 1500–2250 μg, without a post-PCI infusion.

Dual antiplatelet therapy with aspirin and either clopidogrel or ticagrelor was administered to all patients. Other medications were given at physicians' discretion according to current guidelines. The radial artery was the preferred route for vascular access. Primary PCI was otherwise performed per standard clinical practice.

Study outcomes

The primary outcome was the composite of all-cause death or Bleeding Academic Research Consortium (BARC) types 3–5 bleeding occurring at 30 days. The secondary outcomes were major adverse cardiac or cerebral events (MACCE, defined as the composite of all-cause death, recurrent MI, ischemia-driven target vessel revascularization (TVR), or stroke) and its components; stent thrombosis (ST, as defined by Academic Research Consortium criteria) [26], BARC types 2–5 bleeding, the composite of all-cause death or BARC types 2–5 bleeding; acquired thrombocytopenia; and net adverse clinical events (NACE, defined as the composite of MACCE or BARC types 3–5 bleeding) [27, 28]. All primary and secondary events were adjudicated by an independent clinical events committee masked to the therapy assignment.

Statistical analysis

Categorical variables are presented as percentages and were compared using the $\chi 2$ test or Fisher's exact test. Continuous variables are presented as the mean ± standard deviation or median (interquartile ranges) and were compared using a Student's *t*-test or the Wilcoxon rank sum test. Time-to-first-event rates were estimated using Kaplan–Meier methodology and were compared by the log-rank test. To account for differences in baseline characteristics in this post-randomization subgroup analysis, multivariable Cox proportional-hazards regression was performed. The consistency of the treatment effect of bivalirudin versus heparin between patients with and without GPI use was evaluated with formal interaction testing. A p value of < 0.05 was considered statistically significant, and all p values are two sided. All statistical analyses were performed with SAS version 9.4.

Results

Baseline characteristics

Among 6016 patients enrolled in the BRIGHT-4 trial, 8 patients did not undergo angiography. A total of 6008 patients comprised the population for the present subgroup analysis, which were randomly assigned to receive either bivalirudin plus a 2–4-h high-dose infusion after PCI ($n=3006$) or heparin monotherapy ($n=3002$). A total of 5250 (87.4%) patients were treated without GPI (2659 in the bivalirudin group and 2591 in the heparin group) and 758 (12.6%) were treated with bail-out GPI. Bail-out GPI use was lower with bivalirudin compared with heparin (11.5% [347/3006] vs. 13.7% [441/3002], $P=0.01$). Compared with patients without GPI use, patients with bail-out GPI use were more likely to have anemia, lower rates of previous MI and stroke, and lower estimated glomerular filtration rate (eGFR) (Additional File 1: Table S1). As detailed in Table 1, while most baseline characteristics were well balanced between bivalirudin and heparin in patients with or without GPI use, the time from symptom onset-to-tertiary hospital arrival was significantly longer among those randomized to heparin vs. bivalirudin in those with GPI use.

Study medications and procedural characteristics

A similar percentage of patients in each group underwent intervention via radial artery access, 93.1% in total. Compared to patients without GPI use, patients treated with bail-out GPI more frequently received heparin and ticagrelor. Additional boluses of study medications, thrombus aspiration use, the presence of left main disease and pre-PCI or post-PCI TIMI flow of 0, longer procedural duration, more number and higher length of stents were all more common among patients with bail-out GPI use (Additional File 1: Table S2). As shown in Table 2, study medications and procedures were generally well matched between treatment arms. The median peak ACT was greater in patients administered bivalirudin regardless of bail-out GPI use, while additional boluses of study medications were more frequent in patients administered heparin. In patients with GPI use, the time from symptom onset-to-wire was significantly longer among those randomized to heparin vs. bivalirudin.

Clinical outcomes according to bail-out GPI use

Bail-out GPI use in the pooled bivalirudin and heparin group was associated with an increased risk of the primary outcome compared with patients not requiring bailout GPI use (5.28% vs. 3.41%; adjusted hazard ratio (aHR), 1.62; 95% confidence interval (CI), 1.13–2.33; $P=0.009$), as well as increased risks of all-cause death (5.01% vs. 3.21%; aHR, 1.74; 95% CI, 1.20–2.52; $P=0.004$), cardiovascular death (4.88% vs. 3.01%; aHR, 1.77; 95% CI, 1.21–2.58; $P=0.003$), MACCE (6.46% vs. 4.27%; aHR, 1.48; 95% CI, 1.07–2.05; $P=0.02$), and NACE (6.73% vs. 4.50%; aHR, 1.46; 95% CI, 1.06–2.00; $P=0.02$). The rates of BARC types 3–5 bleeding events (0.53% vs. 0.48%; aHR, 0.90; 95% CI, 0.31–2.66; $P=0.85$) were comparable in patients with and without bail-out

Table 1 Baseline characteristics according to GPI use and anticoagulation strategy

	Without GPI use (*N* = 5250)			With GPI use (*N* = 758)		
	Bivalirudin (*N* = 2659)	Heparin (*N* = 2591)	*P* value	Bivalirudin (*N* = 347)	Heparin (*N* = 411)	*P* value
Age, years	60.6 ± 12.1	60.6 ± 12.1	0.96	59.3 ± 12.4	60.3 ± 12.7	0.26
Male	2072 (77.9%)	2042 (78.8%)	0.44	277 (79.8%)	329 (80.1%)	0.94
Body mass index, kg/m^2	24.7 ± 3.5	25.0 ± 3.7	0.02	24.8 ± 3.9	24.9 ± 4.1	0.61
Hypertension	1395 (52.5%)	1314 (50.7%)	0.20	169 (48.7%)	201 (48.9%)	0.96
Diabetes mellitus	601 (22.6%)	603 (23.3%)	0.56	64 (18.4%)	93 (22.6%)	0.16
Smoking			0.45			0.23
Active	1199 (45.1%)	1211 (46.7%)		161 (46.4%)	180 (43.8%)	
Former	208 (7.8%)	204 (7.9%)		27 (7.8%)	47 (11.4%)	
Never	1252 (47.1%)	1176 (45.4%)		159 (45.8%)	184 (44.8%)	
Previous myocardial infarction	166 (6.2%)	182 (7.0%)	0.26	21 (6.1%)	15 (3.7%)	0.12
Previous percutaneous coronary intervention	162 (6.1%)	165 (6.4%)	0.68	23 (6.6%)	21 (5.1%)	0.37
Previous stroke	323 (12.2%)	312 (12.0%)	0.91	29 (8.4%)	30 (7.3%)	0.59
Killip class[a]			0.50			0.39
I	1612 (60.6%)	1597 (61.6%)		203 (58.5%)	259 (63.0%)	
II	784 (29.5%)	719 (27.8%)		100 (28.8%)	106 (25.8%)	
III	188 (7.1%)	200 (7.7%)		31 (8.9%)	27 (6.6%)	
IV	75 (2.8%)	75 (2.9%)		13 (3.8%)	19 (4.6%)	
Hemoglobin, g/dL	14.0 ± 1.8	14.1 ± 1.8	0.65	13.9 ± 1.7	13.9 ± 1.9	0.91
Anemia[b]	522 (19.6%)	521 (20.1%)	0.67	76 (21.9%)	103 (25.1%)	0.31
Platelet count, 10^9/L	230.0 ± 72.9	227.9 ± 65.6	0.27	223.9 ± 69.6	227.0 ± 67.9	0.53
Estimated glomerular filtration rate[c], ml/min/1.73 m^2	105.6 ± 34.0	106.0 ± 33.3	0.67	100.7 ± 33.3	101.5 ± 32.8	0.73
< 60 ml/min/1.73 m^2	176 (6.6%)	167 (6.5%)	0.80	34 (9.8%)	36 (8.8%)	0.62
Symptom onset-to-first medical contact, hours	2.1 (1.0–4.7)	2.2 (1.0–4.5)	0.96	2.0 (1.0–4.5)	2.2(1.0–6.0)	0.11
Patients transferred from a non-tertiary hospital	966 (36.8%)	874 (34.3%)	0.06	118 (34.2%)	161 (39.2%)	0.16
Symptom onset-to-tertiary hospital arrival, hours	3.3 (1.8–6.5)	3.3 (1.7–6.4)	0.29	2.8 (1.6–6.0)	3.6 (1.9–8.6)	0.001

Data are shown as *n* (%), mean (SD), or median (IQR)

[a] 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. [b]Defined as a haemoglobin concentration of less than 13 g/dL in men and less than 12 g/dL in women. [c]Calculated by the formula: 186 × (serum creatinine [mg/dL]) − 1.154 × (age) − 0.203 × (0.742 if female)

GPI use. The results remained consistent before and after multivariable analysis (Table 3).

Clinical outcomes according to anticoagulation strategies

Among patients without GPI use, bivalirudin plus a 2–4 h post-PCI high-dose infusion was associated with reduced risks of the primary outcome (2.63% vs. 4.21%; aHR, 0.55; 95% CI, 0.39–0.77; *P* = 0.0005), all-cause death (2.52% vs. 3.74%; aHR, 0.58; 95% CI, 0.41–0.83; *P* = 0.003), and BARC types 3–5 bleeding (0.15% vs. 0.81%; aHR, 0.19; 95% CI, 0.06–0.57; *P* = 0.003) compared with heparin monotherapy. The rates of cardiovascular death (2.44% vs. 3.59%; aHR, 0.58; 95% CI, 0.41–0.84; *P* = 0.003), ischemia-driven TVR (0.26%; vs. 0.58%; aHR, 0.39; 95% CI, 0.15–0.99; *P* = 0.047), ST (0.30% vs. 1.08%; aHR, 0.27; 95% CI, 0.12–0.62; *P* = 0.002), MACCE (3.57% vs. 4.98%; aHR, 0.64; 95% CI, 0.48–0.86; *P* = 0.003), and NACE (3.65%; vs. 5.36%; aHR, 0.61; 95% CI, 0.46–0.82; *P* = 0.0009) were also lower in patients treated with bivalirudin. No significant differences were observed in the rates of reinfarction, stroke, or BARC types 2–5 bleeding between the groups (Table 4). The unadjusted clinical outcomes at 30 days were shown in Additional File 1: Table S3.

Table 2 Procedure and treatment characteristics according to GPI use and anticoagulation type

	Without GPI use (*N* = 5250)			With GPI use (*N* = 758)		
	Bivalirudin (*N* = 2659)	Heparin (*N* = 2591)	*P* value	Bivalirudin (*N* = 347)	Heparin (*N* = 411)	*P* value
Study medications						
Heparin	24 (0.9%)	2551 (98.5%)	-	0 (0.0%)	411 (100.0%)	-
Total dose during PCI, U	NA	5600 (4830–6810)	-	NA	5500 (4800–6500)	-
Bivalirudin	2635 (99.1%)	40 (1.54%)	-	347 (100.0%)	0 (0.0%)	-
Post-PCI infusion administered	2607/2607 (100.0%)	NA	-	346/346 (100.0%)	NA	-
Post-PCI infusion duration, hours	3.0 (2.10–4.0)	NA	-	3.0 (2.3–4.0)	NA	-
Additional bolus of study medications	90 (3.4%)	885 (34.2%)	< 0.0001	16 (4.6%)	169 (41.1%)	< 0.0001
Peak activated clotting time, sec	321.0 (278.0–365.0)	265.0 (238.0–313.0)	< 0.0001	319.0 (282.0–379.5)	278.5 (246.0–335.0)	< 0.0001
Dual antiplatelet therapy						
Aspirin	2639 (99.3%)	2577 (99.5%)	0.34	347 (100.0%)	408 (99.3%)	0.11
P2Y12 inhibitor			0.47			0.91
Clopidogrel	927 (34.9%)	928 (35.8%)		84(24.2%)	101 (24.6%)	
Ticagrelor	1732 (65.1%)	1663 (64.2%)		263 (75.8%)	310 (75.4%)	
Procedural data						
Arterial access			0.12			0.96
Transradial	2491 (93.7%)	2399 (92.6%)		322 (92.8%)	381 (92.7%)	
Transfemoral	168 (6.3%)	192 (7.4%)		25 (7.2%)	30 (7.3%)	
Invasive procedures						
Revascularization, any	2607 (98.0%)	2550 (98.4%)	0.31	346 (99.7%)	410 (99.8%)	0.90
Coronary arteries treated[a]						
Left main	20 (0.8%)	25 (1.0%)	0.41	6 (1.7%)	7 (1.7%)	0.98
Left anterior descending	1283 (49.2%)	1265 (49.6%)	0.78	174 (50.3%)	184 (44.9%)	0.14
Left circumflex	340 (13.0%)	332 (13.0%)	0.98	36 (10.4%)	39 (9.5%)	0.68
Right	1055 (40.5%)	1048 (41.1%)	0.65	145 (41.9%)	198 (48.3%)	0.08
Multivessel intervention	95 (3.6%)	124 (4.9%)	0.03	15 (4.3%)	18 (4.4%)	0.97
Percutaneous coronary intervention	2596 (97.6%)	2539 (98.0%)	0.37	346 (99.7%)	410 (99.8%)	0.90
Drug-eluting stent implantation	2352 (88.5%)	2297 (88.7%)	0.82	315 (90.8%)	375 (91.2%)	0.82
Number of stents	1.3 ± 0.5	1.3 ± 0.6	0.74	1.3 ± 0.6	1.4 ± 0.7	0.27
Total length of stents, mm	32.9 ± 16.0	32.7 ± 16.1	0.75	33.8 ± 15.8	35.9 ± 18.9	0.11
Balloon angioplasty only	244 (9.2%)	242 (9.3%)	0.84	31 (8.9%)	35 (8.5%)	0.84
Thrombus aspiration	454 (17.5%)	423 (16.7%)	0.43	79 (22.8%)	104 (25.4%)	0.42
PCI time intervals						
Symptom onset-to-wire time, hours	4.7 (3.0–7.9)	4.5 (3.0–7.9)	0.71	4.0 (2.8–7.1)	4.9 (2.9–10.7)	0.002
First medical contact-to-wire time, hours	1.7 (1.1–3.1)	1.7 (1.1–3.0)	0.78	1.5 (1.1–2.7)	1.8 (1.1–3.2)	0.12
Tertiary hospital door-to-wire time, hours	1.2 (0.9–1.6)	1.2 (0.9–1.7)	0.65	1.1 (0.8–1.5)	1.1 (0.8–1.7)	0.42
Procedure duration[b], min	28.0 (20.0–40.0)	29.0 (20.0–40.0)	0.25	34.0 (25.0–46.5)	33.0 (23.0–49.0)	0.57
PCI TIMI flow, site-assessed						
Pre-PCI			0.79			0.40
0	1930 (74.7%)	1901 (75.4%)		281 (81.2%)	342 (84.2%)	
1	180 (7.0%)	182 (7.2%)		12 (3.5%)	18 (4.4%)	
2	203 (7.9%)	181 (7.2%)		24 (6.9%)	22 (5.4%)	
3	271 (10.5%)	259 (10.3%)		29 (8.4%)	24 (5.9%)	
Post-PCI			0.048			0.78
0	8 (0.3%)	19 (0.8%)		3 (0.9%)	5 (1.2%)	
1	2 (0.1%)	4 (0.2%)		2 (0.6%)	1 (0.2%)	
2	19 (0.7%)	29 (1.2%)		10 (2.9%)	15 (3.7%)	

Table 2 (continued)

	Without GPI use (*N* = 5250)			With GPI use (*N* = 758)		
	Bivalirudin (*N* = 2659)	Heparin (*N* = 2591)	*P* value	Bivalirudin (*N* = 347)	Heparin (*N* = 411)	*P* value
3	2557 (98.9%)	2472 (97.9%)		330 (95.7%)	388 (94.9%)	
Staged PCI within 30 days	203 (7.6%)	202 (7.8%)	0.83	25 (7.2%)	33 (8.0%)	0.67
Coronary artery bypass graft surgery	11 (0.4%)	11 (0.4%)	0.95	0 (0.0%)	0 (0.0%)	-
Coronary angiography only	52 (2.0%)	41 (1.6%)	0.31	1 (0.3%)	1 (0.2%)	> 0.999

Data are shown as n (%), mean (SD), or median (IQR). *NA* not applicable, PCI percutaneous coronary intervention

[a] 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%

[b] Defined as the time from guiding catheter insertion to its withdrawal

Table 3 Clinical outcomes at 30 days in all patients (bivalirudin plus heparin pooled) with and without bail-out GPI use

	With GPI use (*N* = 758)	Without GPI use (*N* = 5250)	Unadjusted HR (95% CI)	*P* value	Adjusted HR[a] (95% CI)	*P* value
Primary endpoint: all-cause death or BARC types 3–5 bleeding	40 (5.28%)	179 (3.41%)	1.56 (1.11–2.20)	0.01	1.62 (1.13–2.33)	0.009
Death from any cause	38 (5.01%)	164 (3.12%)	1.62 (1.14–2.30)	0.008	1.74 (1.20–2.52)	0.004
From cardiovascular causes	37 (4.88%)	158 (3.01%)	1.64 (1.14–2.34)	0.007	1.77 (1.21–2.58)	0.003
BARC types 3–5 bleeding	4 (0.53%)	25 (0.48%)	1.11 (0.39–3.19)	0.85	0.90 (0.31–2.66)	0.85
Reinfarction	9 (1.19%)	33 (0.63%)	1.89 (0.91–3.96)	0.09	1.91 (0.90–4.08)	0.09
Ischemia-driven target vessel revascularization	5 (0.66%)	22 (0.42%)	1.58 (0.60–4.16)	0.36	1.39 (0.52–3.75)	0.51
Stroke	1 (0.13%)	28 (0.53%)	0.25 (0.03–1.82)	0.17	0.20 (0.03–1.55)	0.12
Stent thrombosis	8 (1.06%)	36 (0.69%)	1.54 (0.72–3.32)	0.27	1.34 (0.61–2.94)	0.46
Acute (< 24 h)	4 (0.53%)	14 (0.27%)	1.98 (0.65–6.01)	0.23	1.57 (0.49–5.08)	0.45
Subacute (1–30 days)	4 (0.53%)	22 (0.42%)	1.26 (0.44–3.67)	0.67	1.15 (0.39–3.40)	0.79
MACCE[b]	49 (6.46%)	224 (4.27%)	1.53 (1.13–2.09)	0.007	1.48 (1.07–2.05)	0.02
BARC types 2–5 bleeding	25 (3.30%)	115 (2.19%)	1.51 (0.98–2.33)	0.06	1.33 (0.86–2.08)	0.20
All-cause death or BARC types 2–5 bleeding	60 (7.92%)	265 (5.05%)	1.59 (1.20–2.10)	0.001	1.52 (1.13–2.03)	0.005
Acquired thrombocytopenia[c]	23 (3.04%)	197 (3.84%)	0.79 (0.51–1.22)	0.29	0.82 (0.53–1.28)	0.38
NACE[d]	51 (6.73%)	236 (4.50%)	1.51 (1.12–2.05)	0.007	1.46 (1.06–2.00)	0.02

Event rates are number of events (Kaplan–Meier estimated percentages). *BARC*, Bleeding Academic Research Consortium

[a] Model adjusted for age, sex, body mass index, hypertension, diabetes, smoking, previous myocardial infarction, previous percutaneous coronary intervention, previous stroke, Killip class, hemoglobin, platelet count, eGFR, medical therapy (procedural anticoagulants, aspirin, and P2Y12 inhibitors), arterial access, coronary arteries treated, multivessel intervention, thrombus aspiration, post-PCI TIMI flow and revascularization strategies. [b]Major adverse cardiac or cerebral events included all-cause death, myocardial infarction, ischemia-driven target vessel revascularization, or stroke. [c]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. [d]Net adverse clinical events included major adverse cardiac or cerebral events or BARC types 3–5 bleeding

Among patients with bail-out GPI use, there were no significant differences observed in the rates of the primary outcome (5.76% vs. 4.87%; aHR, 0.77; 95% CI, 0.36–1.66; $P = 0.50$; P for interaction = 0.07), all-cause death (5.76% vs. 4.38%; aHR, 0.91; 95% CI, 0.41–2.04; $P = 0.83$; P for interaction = 0.06) and BARC types 3–5 bleeding (0.29% vs. 0.73%; unadjusted HR, 0.39; 95% CI, 0.04–3.79; $P = 0.42$; P for interaction = 0.55) between patients assigned to the bivalirudin and heparin treatment respectively. Rates of other secondary outcomes including cardiovascular death, reinfarction, ischemia-driven TVR, stroke, ST, MACCE, and NACE were also comparable between the groups (Table 4). The pattern of GPI use (intravenous bolus plus a post-PCI infusion in 35.1% of patients and intracoronary boluses without a post-PCI infusion in 64.9% of patients) had no impact on clinical outcomes (Additional File 1: Table S4 and Fig. S1).

Time-to-event curves for the primary outcome, all-cause death, and BARC types 3–5 bleeding according to GPI use and anticoagulation strategy are shown in Fig. 1.

Table 4 Clinical outcomes at 30 days by bail-out GPI use and anticoagulation type

	Patients without bail-out GPI use ($N=5250$)				Patients with bail-out GPI use ($N=758$)				
	Bivalirudin ($N=2659$)	Heparin ($N=2591$)	Adjusted HR[a](95% CI)	*P* value	Bivalirudin ($N=347$)	Heparin ($N=411$)	Adjusted HR[a] (95% CI)	*P* value	$P_{interaction}$
Primary endpoint: all-cause death or BARC types 3–5 bleeding	70 (2.63%)	109 (4.21%)	0.55 (0.39–0.77)	0.0005	20 (5.76%)	20 (4.87%)	0.77 (0.36–1.66)	0.50	0.07
Death from any cause	67 (2.52%)	97 (3.74%)	0.58 (0.41–0.83)	0.003	20 (5.76%)	18 (4.38%)	0.91 (0.41–2.04)	0.83	0.06
From cardiovascular causes	65 (2.44%)	93 (3.59%)	0.58 (0.41–0.84)	0.003	20 (5.76%)	17 (4.14%)	0.92 (0.41–2.08)	0.84	0.048
BARC types 3–5 bleeding	4 (0.15%)	21 (0.81%)	0.19 (0.06–0.57)	0.003	1 (0.29%)	3 (0.73%)	0.39 (0.04–3.79)*	0.42	0.55
Reinfarction	13 (0.49%)	20 (0.77%)	0.63 (0.29–1.37)	0.24	4 (1.15%)	5 (1.22%)	0.64 (0.15–2.70)	0.54	0.60
Ischemia-driven target vessel revascularisation	7 (0.26%)	15 (0.58%)	0.39 (0.15–0.99)	0.047	2 (0.58%)	3 (0.73%)	0.40 (0.05–3.17)	0.39	0.59
Stroke	14 (0.53%)	14 (0.54%)	0.92 (0.41–2.04)	0.83	1 (0.29%)	0 (0.00%)	-	-	0.97
Stent thrombosis	8 (0.30%)	28 (1.08%)	0.27 (0.12–0.62)	0.002	3 (0.86%)	5 (1.22%)	0.54 (0.09–3.08)	0.49	0.26
Acute (< 24 h)	3 (0.11%)	11 (0.42%)	0.32 (0.08–1.25)	0.10	1 (0.29%)	3 (0.73%)	0.31 (0.02–3.99)	0.37	0.77
Subacute (1–30 days)	5 (0.19%)	17 (0.66%)	0.25 (0.09–0.69)	0.008	2 (0.58%)	2 (0.49%)	1.18 (0.17–8.38)*	0.87	0.21
MACCE[b]	95 (3.57%)	129 (4.98%)	0.64 (0.48–0.86)	0.003	26 (7.49%)	23 (5.60%)	0.94 (0.49–1.78)	0.84	0.044
BARC types 2–5 bleeding	55 (2.07%)	60 (2.32%)	0.94 (0.62–1.41)	0.76	8 (2.31%)	17 (4.14%)	0.41 (0.17–1.00)	0.049	0.30
All-cause death or BARC types 2–5 bleeding	119 (4.48%)	146 (5.63%)	0.75 (0.57–0.99)	0.04	26 (7.49%)	34 (8.27%)	0.62 (0.34–1.11)	0.11	0.65
Acquired thrombocytopenia[c]	90 (3.47%)	107 (4.21%)	0.91 (0.66–1.24)	0.55	7 (2.02%)	16 (3.90%)	0.64 (0.23–1.80)	0.40	0.33
NACE[d]	97 (3.65%)	139 (5.36%)	0.61 (0.46–0.82)	0.0009	26 (7.49%)	25 (6.08%)	0.83 (0.45–1.56)	0.57	0.050

Event rates are number of events (Kaplan–Meier estimated percentages). *BARC*, Bleeding Academic Research Consortium

[a] Model adjusted for age, sex, body mass index, hypertension, diabetes, smoking, previous myocardial infarction,previous percutaneous coronary intervention, previous stroke, killip class, hemoglobin, platelet count, eGFR, medical therapy (aspirin, and P2Y12 inhibitors), arterial access, coronary arteries treated, post-PCI TIMI flow and additional bolus of study medications. [b]Major adverse cardiac or cerebral events included all-cause death, myocardial infarction, ischemia-driven target vessel revascularization, or stroke. [c]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. [d]Net adverse clinical events included major adverse cardiac or cerebral events or BARC types 3–5 bleeding. *An unadjusted HR (95% CI) was reported because the number of events is too small to be adjusted

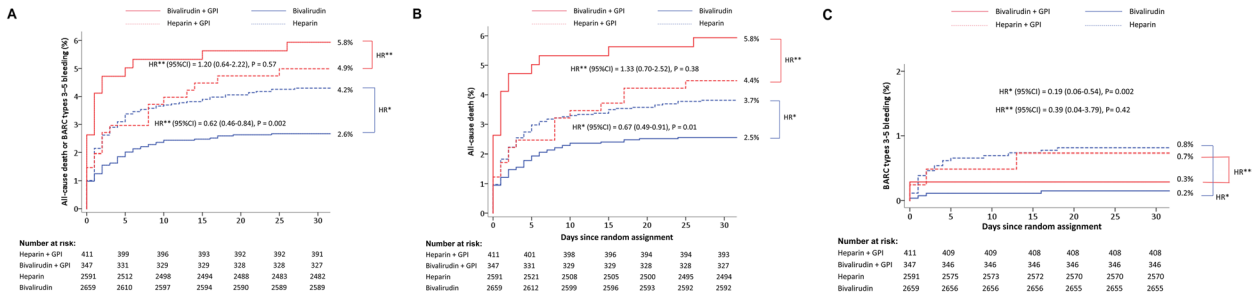
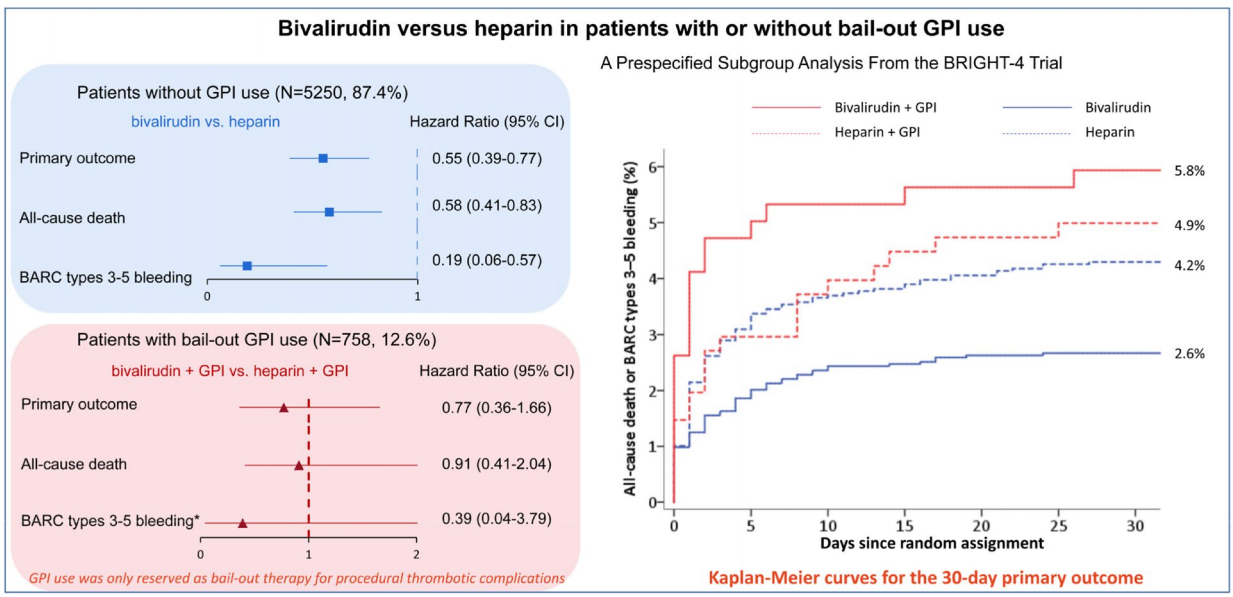


Fig. 1 Kaplan–Meier curves for the 30-day primary endpoint of all-cause death or BARC types 3–5 bleeding. Cumulative incidences during follow-up in patients treated with bivalirudin plus a post-PCI high-dose infusion vs heparin, each with or without bail-out GPI use, for (**A**) the primary outcome (the composite of all-cause death or BARC types 3–5 bleeding); **B** all-cause death; and (**C**) BARC types 3–5 bleeding. * Unadjusted HR for bivalirudin without GPI versus heparin without GPI. ** Unadjusted HR for bivalirudin with GPI versus heparin with GPI. BARC, Bleeding Academic Research Consortium; GPI, glycoprotein IIb/IIIa inhibitors; HR, hazard ratio; CI, confidence interval

Discussion

As summarized in the Central Illustration, in this prespecified subgroup analysis from the BRIGHT-4 trial, the principal findings are that (1) compared with patients treated without GPI, patients who received bail-out GPI for procedural thrombotic complications during primary PCI experienced a higher risk of all-cause death but not major bleeding. (2) In patients without GPI use, bivalirudin plus a 2–4-h high-dose infusion post-PCI was associated with a reduction in the 30-day composite rate of all-cause death or BARC types 3–5 major bleeding compared with heparin monotherapy. (3) In contrast, in patients who received bail-out GPI, both ischemic and bleeding outcomes were not significantly different between patients treated with bivalirudin and heparin.

Whether there are differences in safety and effectiveness between bivalirudin and heparin anticoagulation in patients undergoing primary PCI for STEMI remains a matter of debate. This comparison has been complicated in prior studies by the confounding effect of the usage pattern of GPI. Previous RCTs have shown that bivalirudin reduces major bleeding and mortality compared with heparin; however, GPI were routinely administered to patients who were randomized to receive heparin in many of these trials [4, 5]. In a pooled patient-level analysis of the HORIZONS-AMI and EUROMAX trials, 84.8% of patients administered heparin received GPI, while only



Central illustration. Thirty-day outcomes of bivalirudin plus a post-PCI high-dose infusion for 2-4 hours compared with heparin in patients with and without bail-out GPI use.

The primary outcome was a composite of all-cause death or BARC types 3-5 bleeding at 30 days. *All HR (95% CI) were adjusted for potential confounding factors, except for BARC types 3-5 bleeding in patients with bail-out GPI use, which could not be adjusted due to the low number of events. BARC, Bleeding Academic Research Consortium; GPI, glycoprotein IIb/IIIa inhibitors; CI, confidence interval.

8.8% of patients administered bivalirudin were treated with GPI [29]. A meta-analysis reporting that a bivalirudin-based regimen decreases the risk of bleeding compared with a heparin-based regimen found that the magnitude of the reduction depended on concomitant GPI use [12]. Therefore, when comparing the outcomes of anticoagulants during PCI, the impact of GPI must be considered.

In the BRIGHT-4 trial in which GPI were used provisionally, 12.6% of patients experienced procedural thrombotic complications that required bail-out GPI use during primary PCI. This occurrence, while uncommon, was slightly greater than some previous RCTs [30], with a 4.6% GPI bail-out rate reported from the BRAVE-4 study of patients with STEMI and a 2.6% GPI bail-out rate reported from the VALIDATE-SWEDEHEART trial of patients with STEMI and NSTEMI [10, 31]. The somewhat higher incidence of bail-out GPI utilization observed in our study can be attributed to several factors, including the inclusion of only STEMI patients, a real-world setting with fewer exclusion criteria, enrollment of patients within 48 h of symptom onset, and the absence of anticoagulant therapy prior to catheterization laboratory admission. Our results indicated an elevated risk of ischemic events among patients requiring bail-out GPI without an increased risk of major bleeding. The higher mortality may be in part attributable to the fact that patients who received bail-out GPI were more likely to have other risk factors, such as anemia, Killip class ≥ III, eGFR ≤ 60 ml/min, and pre-PCI or post-PCI TIMI flow of 0. Moreover, they also underwent more complex PCI procedures as indicated by extended procedural duration, increased number and longer total length of stents, greater need for thrombus aspiration, and a higher frequency of target left main disease. The lack of increased risk of major bleeding associated with bail-out GPI use in this study may be attributed to the fact that the majority of GPI was used through the intracoronary route (64.9%) and a post-procedure maintenance intravenous infusion was not utilized.

To examine the potential influence of GPI use in both arms, we conducted separate comparisons between bivalirudin and heparin for populations that received GPI and those that did not. The findings indicated that differences in the benefits of bivalirudin compared with heparin according to required GPI use may exist. Among patients treated without GPI in whom refractory thrombotic complications with either agent did not occur, bivalirudin plus a post-PCI high-dose infusion improved 30-day clinical outcomes, with significant reductions in all-cause death and major bleeding compared with heparin monotherapy. In contrast, among patients who required bail-out GPI use for refractory thrombotic complications, outcomes were comparable between the two arms. Although significant differences favoring bivalirudin may not have been observed because of the smaller sample size of the GPI cohorts, the interaction *P*-value for the primary endpoint according to randomization and GPI use was borderline ($P=0.07$), suggesting a difference may indeed exist. Specifically, the bleeding benefit of bivalirudin compared with heparin was evident whether GPI was used. However, the mortality benefit of bivalirudin was seen only in patients without GPI use. Additional studies are required to confirm this observation and explore its potential mechanism.

The 70 U/kg initial heparin dosage use in the BRIGHT-4 trial was consistent with recommended guidelines in STEMI patients undergoing primary PCI and was similar to the doses used in prior investigations [1–3]. The VALIDATE-SWEDEHEART study reported an initial heparin dose of 76.9 U/kg for the STEMI subgroup, and the MATRIX study documented an average heparin dose of 78.1 U/kg [8, 11]. In addition, ACT was monitored 5 min after heparin administration, and those with ACT < 225 s were supplemented until they reached the goal, avoiding the possible risks caused by insufficient heparin dosage. Thus, the mean heparin dose after additional boluses was 83.3 U/kg in our study. Higher ACT values were achieved in the bivalirudin group compared with heparin, and second boluses were rarely required. In contrast to heparin which in most patients was discontinued post-PCI, therapeutic levels of bivalirudin were also achieved for 2–4 h given the routine use of a post-PCI high-dose infusion. Nonetheless, lower rates of bleeding with bivalirudin occurred compared with heparin, regardless of whether GPI use was required. Of note, previous studies have also demonstrated that higher peak ACT levels with bivalirudin are not associated with additional bleeding risk, since the correlation between bivalirudin plasma concentration and activity are not accurately reflected by the ACT value [32–34].

The route of bail-out GPI use (intravenous with a post-PCI infusion vs. intracoronary without a post-PCI infusion) had no apparent impact on clinical outcomes. Previous studies have reported that an intravenous GPI bolus followed by a post-procedure maintenance infusion provides a stable and sustained antithrombotic effect [35]. Bolus intracoronary GPI delivered in the infarct artery may result in higher local concentrations of drug and reduce infarct size [36, 37]. The use of bolus-only intracoronary GPI in selected patients has also demonstrated utility and safety in a contemporary real-world population of STEMI patients undergoing primary PCI [38]. The optimal delivery route and regimen for GPI administration require further study.

In the context of current practice with radial artery access and potent P2Y12 inhibitor use, the present study provides additional evidence to previous studies that demonstrate that bivalirudin improves 30-day clinical outcomes compared with heparin monotherapy in patients without GPI use [4, 5, 7]. Given that all GPI use

in the present study was unplanned and given to treat thrombotic complications, it is notable that the necessity for bail-out GPI use (reflecting fewer procedural thrombotic complications) was less with bivalirudin compared with heparin, likely attributable to bivalirudin's more consistent thrombin inhibition which can bind and inhibit the activity of not only soluble thrombin but also thrombin bound to fibrin [39]. Greater platelet passivation may also underlie why bivalirudin has been shown to reduce microvascular obstruction compared with heparin [39, 40]. Furthermore, major or minor bleeding events were less with bivalirudin, even in patients who required bail-out GPI use due to thrombotic complications. Therefore, for patients with STEMI undergoing primary PCI, bivalirudin plus a post-PCI high-dose infusion for 2–4 h should be considered the preferred anticoagulation regimen, irrespective of the need for bail-out GPI use. Although bivalirudin is now generic in most countries and thus inexpensive, the cost-effectiveness of bivalirudin plus a post-PCI high-dose infusion compared with heparin and provisional GPI use needs to be further evaluated.

Limitations

Certain limitations of this study should be noted. First, although this was a pre-specified subgroup analysis from the BRIGHT-4 trial, the use of GPI was reserved for procedural thrombotic complications; as such, the GPI and non-GPI groups were not stratified nor randomized. While we presented the outcomes of multivariable analysis adjusted for numerous possible confounding covariates, an effect of unmeasured confounders cannot be excluded. Consequently, the current observations should be regarded as hypothesis generating. Second, the relatively small sample size of patients requiring bail-out GPI may increase the risk of a type 2 error (false negative findings). The comparison of bivalirudin and heparin within this subset was not sufficiently powered to yield definite conclusions. Limitations of the parent trial also apply to the current analysis. This includes the lack of power to detect the safety and efficacy of bivalirudin versus heparin in STEMI patients with late presentation, given that approximately 88% of patients in BRIGHT-4 presented within 12 h of symptom onset. The applicability of the findings also do not extend to patients using the potent oral P2Y12 inhibitor prasugrel, which is not available in China.

Conclusions

In the present pre-specified subgroup analysis from the BRIGHT-4 trial, the use of bail-out GPI for refractory procedural thrombotic complications was required less frequently during primary PCI with bivalirudin compared with heparin, but was associated with a poor prognosis regardless of the procedural anticoagulant used. Compared with heparin monotherapy, bivalirudin plus a post-PCI high-dose infusion for 2–4 h reduced the 30-day composite rate of all-cause death or BARC types 3–5 bleeding in patients with STEMI undergoing primary PCI in whom the use of GPI was not required. However, these benefits might be less pronounced for patients who require bail-out GPI use due to thrombotic complications during primary PCI. These exploratory findings are hypothesis-generating and further evaluation of these strategies in prospective and adequately powered trials is warranted.

Abbreviations

STEMI	ST-segment elevation myocardial infarction
PCI	Percutaneous coronary intervention
GPI	Glycoprotein IIb/IIIa inhibitors
RCTs	Randomized controlled trials
BARC	Bleeding Academic Research Consortium
ACT	Activated clotting time
MACCE	Major adverse cardiac or cerebral events
TVR	Target vessel revascularization
ST	Stent thrombosis
NACE	Net adverse clinical events
HR	Hazard ratio
CI	Confidence interval

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12916-024-03579-6.

Additional file 1: Table S1. Baseline characteristics in all patients (heparin and bivalirudin pooled) by bail-out GPI use. Table S2. Procedures and treatments characteristics in all patients (heparin and bivalirudin pooled) by bail-out GPI use. Table S3. The unadjusted clinical outcomes at 30 days by bail-out GPI use and anticoagulation type. Table S4. Primary and secondary outcomes according to the anticoagulation strategies and the route of bail-out GPI use. Fig. S1. Interaction between treatment and the route of bail-out GPI use on 30-day outcomes.

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Authors' contributions

YH and GWS designed this study. JL, MQ, XF, KC, DZ, YZ, XZ, GZ, NT, ZZ, XP, QY, ZL,YL and YH participated in the enrolment of patients and clinical follow-up. YL, ZL, and YH were responsible for clinical trial operations. YL, ZL, MQ, and YH had full access to and verified all the study data. JL, YL, MQ and YH analyzed the data and wrote the manuscript. YH and GWS made crucial revisions to the manuscript. All other authors reviewed the manuscript and provided critical comments for revision. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
The trial was approved by the ethics committee at the General Hospital of Northern Theater Command (Shengyang, China) (NO. k-2018–3). The study was performed in accordance with the principles of the Declaration of Helsinki. Written informed consent was provided by all patients or their legal representatives before random assignment.

Consent for publication
Not applicable.

Competing interests
Dr. Stone has received speaker honoraria from Medtronic, Pulnovo, Abiomed, Amgen, Boehringer Ingelheim; has served as a consultant to Abbott, Daiichi Sankyo, Ablative Solutions, CorFlow, Cardiomech, Robocath, Miracor, Vectorious, Apollo Therapeutics, Elucid Bio, Cardiac Success, Valfix, TherOx, HeartFlow, Neovasc, Ancora, Occlutech, Impulse Dynamics, Adona Medical, Millennia Biopharma, Oxitope, HighLife, Elixir, Remote Cardiac Enablement, Aria; and has equity/options from Cardiac Success, Ancora, Cagent, Applied Therapeutics, Biostar family of funds, SpectraWave, Orchestra Biomed, Aria, Valfix, Xenter. Dr. Stone's employer, Mount Sinai Hospital, receives research grants from Shockwave, Abbott, Abiomed, Bioventrix, Cardiovascular Systems Inc, Phillips, Biosense-Webster, Vascular Dynamics, Pulnovo, V-wave and PCORI (via Weill Cornell Medical Center). The other authors declare that they have no potential competing interests.

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