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Bivalirudin Versus Heparin Anticoagulation in Transcatheter Aortic Valve Replacement

The Randomized BRAVO-3 Trial

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ABSTRACT

BACKGROUND Anticoagulation is required during transcatheter aortic valve replacement (TAVR) procedures. Although an optimal regimen has not been determined, heparin is mainly used. Direct thrombin inhibition with bivalirudin may be an effective alternative to heparin as the procedural anticoagulant agent in this setting.

OBJECTIVES The goal of this study was to determine whether bivalirudin offers an alternative to heparin as the procedural anticoagulant agent in patients undergoing TAVR.

METHODS A total of 802 patients with aortic stenosis were randomized to undergo transfemoral TAVR with bivalirudin versus unfractionated heparin during the procedure. The 2 primary endpoints were major bleeding within 48 h or before hospital discharge (whichever occurred first) and 30-day net adverse clinical events, defined as the combination of major adverse cardiovascular events (all-cause mortality, myocardial infarction, or stroke) and major bleeding.

RESULTS Anticoagulation with bivalirudin versus heparin did not meet superiority because it did not result in significantly lower rates of major bleeding at 48 h (6.9% vs. 9.0%; relative risk: 0.77; 95% confidence interval [CI]: 0.48 to 1.23; $p = 0.27$) or net adverse cardiovascular events at 30 days (14.4% vs. 16.1%; relative risk: 0.89; 95% CI: 0.64 to 1.24; risk difference: -1.72; 95% CI: -6.70 to 3.25; $p = 0.50$); regarding the latter, the prespecified noninferiority hypothesis was met ($p_{noninferiority} < 0.01$). Rates of major adverse cardiovascular events at 48 h were not significantly different (3.5% vs. 4.8%; relative risk: 0.73; 95% CI: 0.37 to 1.43; $p = 0.35$). At 48 h, the bivalirudin group had significantly fewer myocardial infarctions but more acute kidney injury events than the heparin group; at 30 days, these differences were no longer significant.

CONCLUSIONS In this randomized trial of TAVR procedural pharmacotherapy, bivalirudin did not reduce rates of major bleeding at 48 h or net adverse cardiovascular events within 30 days compared with heparin. Although superiority was not shown, the noninferiority hypothesis was met with respect to the latter factor. Given the lower cost, heparin should remain the standard of care, and bivalirudin can be an alternative anticoagulant option in patients unable to receive heparin in TAVR. (International, Multi-center, Open-label, Randomized Controlled Trial in Patients Undergoing TAVR to Determine the Treatment Effect [Both Safety and Efficacy] of Using Bivalirudin Instead of UFH [BRAVO-2/3]; NCT01651780) (J Am Coll Cardiol 2015;66:2860–8) © 2015 by the American College of Cardiology Foundation.

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Aortic stenosis affects 1% to 4% of the general population, with a higher incidence among elderly subjects (1). Although surgical aortic valve replacement has been the mainstay of treatment, transcatheter aortic valve replacement (TAVR) was introduced for patients deemed inoperable or at high surgical risk (2). TAVR has rates of major cardiovascular events comparable to open surgery and is superior to conservative treatment (3–6), but it still has significant complications. In randomized trials and daily practice, unfractionated heparin has been the standard empiric procedural anticoagulation regimen for TAVR. Although partial or complete reversal of heparin with protamine can be used, practice patterns vary, with guideline statements based on expert consensus rather than on evidence from randomized trials (2). The rapid expansion of TAVR procedures worldwide necessitates dedicated clinical investigation in the field of periprocedural pharmacology, with the goal of building a robust evidence base, deriving appropriate practice guidelines, and further improving clinical outcomes.

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Bivalirudin is a reversible direct thrombin inhibitor with a half-life of 25 min; it reduces major bleeding while providing stable effective anticoagulation in the setting of percutaneous coronary interventions compared with other regimens (7–12). The goal of the present prospective study was to examine whether bivalirudin offers an alternative to heparin as a procedural anticoagulant agent in patients undergoing TAVR as tested in retrospective studies (13,14).

METHODS

The BRAVO-3 (Effect of Bivalirudin on Aortic Valve Intervention Outcomes-3) trial was an open-label, randomized controlled trial comparing bivalirudin with unfractionated heparin in high-risk or inoperable patients undergoing TAVR, conducted in 31 European and North American sites (15). Clinical follow-up was performed on days 1 and 2, on the day of hospital discharge, and 30 days post-procedure.

The executive committee governed all aspects of the clinical trial. The Icahn School of Medicine at Mount Sinai clinical coordinating center was responsible for the study design; the identification, education, and training of participating sites, in close collaboration with the sponsor; study management; and organization and conduct of the study committees (Online Appendix). The study sponsor was responsible for funding; protocol development in collaboration with the executive committee and the clinical coordinating center; on-site monitoring and safety surveillance; statistical analyses; and data management. The institutional review board at each site approved the study protocol and activities. An independent clinical events committee reviewed and adjudicated all major clinical events. An independent data safety monitoring board was responsible for study oversight and the final sample size recommendation (adaptive study design).

STUDY POPULATION. Patients with aortic stenosis who were ≥18 years of age, at high surgical risk (defined as a European System for Cardiac Operative Risk Evaluation score of ≥18, or deemed inoperable), and scheduled for TAVR via transfemoral access were eligible for enrollment. The main exclusion criteria were planned surgical cutdown access; presence of a previous mechanical or mitral bioprosthetic valve; severe left ventricular dysfunction (ejection fraction <15%); minimal luminal diameter <6.5 mm for the common femoral artery; severe aortic or mitral regurgitation; concurrent percutaneous coronary intervention; recent bleeding or neurological event; and dialysis dependence. The full lists of inclusion and exclusion criteria are provided in the Online Appendix. All patients provided written informed consent.

ABBREVIATIONS AND ACRONYMS

BARC = Bleeding Academic Research Consortium

CI = confidence interval

TAVR = transcatheter aortic valve replacement

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STUDY MEDICATIONS. To achieve therapeutic levels of anticoagulation, bivalirudin (Angiomax/Angiox, The Medicines Company, Parsippany, New Jersey) was administered as an initial bolus of 0.75 mg/kg, followed by a continuous infusion at a rate of 1.75 mg/kg/h in patients with an estimated glomerular filtration rate ≥60 ml/min. The initial bolus was administered either through the valve delivery sheath or as an intravenous systemic administration. The intravenous infusion was initiated immediately after the bolus dose and stopped after successful valve implantation. The infusion rate was decreased to 1.4 mg/kg/h in patients with an estimated glomerular filtration rate of 30 to 59 ml/min and to 1 mg/kg/h in patients with a glomerular filtration rate <30 ml/min. Heparin dosing and administration included a recommended target activated clotting time of >250 s; the decision for reversal with protamine at the end of the procedure was subject to standard local institution practice. Patients underwent TAVR according to the standard practices at each site, including the use of pre-procedural medications and the selection of a commercially available valve system. After the procedure, study recommendations were for patients to receive aspirin at a dosage of 75 to 100 mg/day for at least 1 year and clopidogrel at 75 mg/day for a period defined by institutional standard practices.

STUDY OUTCOMES. The first co-primary outcome was major bleeding (defined as BARC [Bleeding Academic Research Consortium] ≥3b [16]; detailed in the Online Appendix) within 48 h or before hospital discharge, whichever occurred first. The second co-primary outcome was the rate of net adverse cardiovascular events within 30 days, defined as the composite of major adverse cardiovascular events (all-cause mortality, myocardial infarction, or stroke) and major bleeding. Other secondary endpoints included bleeding defined according to additional bleeding scales (from the VARC [Valve Academic Research Consortium], TIMI [Thrombolysis In Myocardial Infarction], GUSTO [Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries], ACUITY/HORIZONS [Acute Catheterization and Urgent Intervention Triage Strategy/Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction], and other BARC types [Online Appendix]) and the composite of major adverse cardiovascular events, as well as its individual components. Other outcomes of interest included acute kidney injury, transient ischemic attacks, major vascular complications, acquired thrombocytopenia, and new post-procedural atrial fibrillation/flutter. All secondary endpoints were assessed at 48 h or hospital discharge, whichever occurred first, and at 30 days.

STATISTICAL ANALYSIS. The original sample size assumed an estimated rate of major bleeding of 19% in the control group and a relative risk reduction of 47% in the experimental group; thus, a sample size of 522 patients (261 per arm) would be needed for an 80% power to detect a significant bleeding reduction at an alpha level <0.05. The study was also powered to show noninferiority for 30-day net adverse cardiovascular events with a margin of 8.0% difference in event rates. BRAVO-3 had an adaptive sample size design that included a prospectively planned opportunity for an increase in the sample size based on analysis of interim bleeding data after two-thirds of patients completed 30-day follow-up. After reviewing the summary report produced by the independent statistician, the data safety monitoring board issued a recommendation to continue the trial unmodified until the predefined maximum of 800 patients were enrolled, according to the interim statistical analysis plan (Online Appendix).

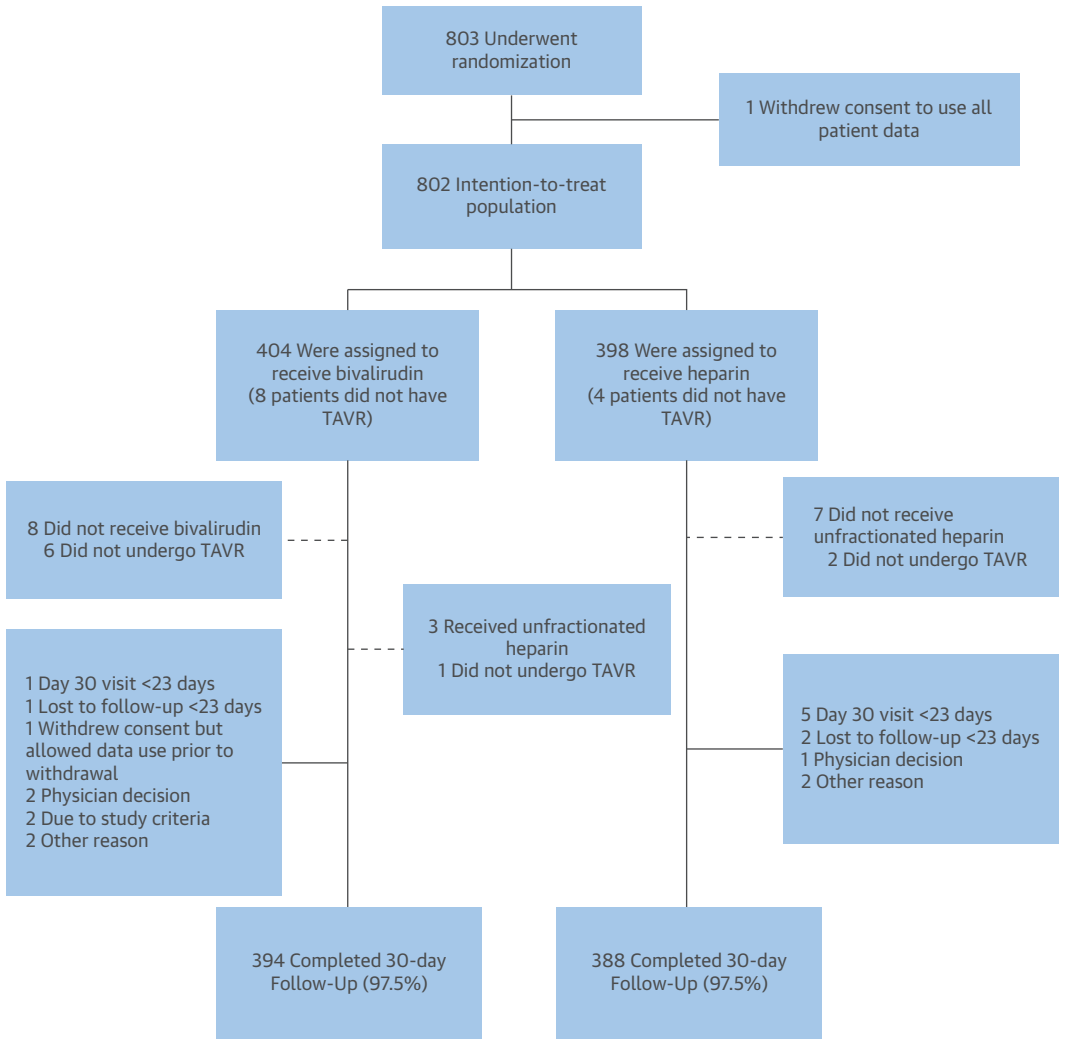
Continuous variables are reported as mean ± SD or median (interquartile range) and were tested by using the Student *t* test. Categorical variables are reported as frequencies and percentages and were tested by using the chi-square test. The primary data analysis was performed according to the intention-to-treat principle. Tabulated event rates were tested by using the chi-square test. The Kaplan-Meier method was used for the time-to-event analysis based on all available follow-up data, and the log-rank test was used for the comparison. Statistical analyses were performed by using SAS version 9.2 (SAS Institute, Inc., Cary, North Carolina).

RESULTS

Between October 2012 and May 2015, a total of 802 patients with severe, symptomatic aortic stenosis were enrolled at 31 sites in 7 countries and randomized to receive bivalirudin (n = 404) versus unfractionated heparin (n = 398) during TAVR. Eighteen patients did not undergo the assigned treatment (11 in the bivalirudin group and 7 in the heparin group) for the reasons detailed in **Figure 1**. The 30-day follow-up data were available for 394 (97.5%) patients in the bivalirudin group and 388 (97.5%) patients in the heparin group.

The baseline characteristics of the patients were well matched between groups (**Table 1**). The population was elderly (mean age 82.3 ± 6.5 years) with a mean European System for Cardiac Operative Risk

FIGURE 1 Randomization, Management, and Follow-Up at 48 h and 30 Days



TAVR = transcatheter aortic valve replacement.

Evaluation score of 17.0 ± 10.3%. Overall, 29.8% (239 of 802) had diabetes mellitus, 19.3% (155 of 802) had chronic obstructive pulmonary disease, and 10.4% (83 of 800) had experienced prior cerebrovascular events. Procedure and treatment data are shown in **Table 2**. An initial heparin bolus of 72.6 ± 26.8 IU/kg (median 69.4 IU/kg; interquartile range 53.0 to 87.5 IU/kg) was used in the control group.

CLINICAL OUTCOMES. The trial outcomes are summarized in **Table 3** and shown in the **Central Illustration**, Online Tables 1 to 5, and Online Figure 1. After 48 h of the TAVR procedure, major bleeding (BARC ≥3b) occurred in 6.9% of the bivalirudin-treated patients compared with 9.0% of the heparin-treated patients (relative risk: 0.77; 95% confidence interval [CI]: 0.48 to 1.23; p = 0.27); the superiority hypothesis was not met. After 30 days, net adverse cardiovascular events occurred in 14.4% of the bivalirudin-treated patients and in 16.1% of heparin-treated patients (risk difference: -1.72; 95% CI: -6.70 to 3.25; relative risk: 0.89; 95% CI: 0.64 to 1.24; p = 0.50); the pre-specified noninferiority hypothesis was met ($p_{noninferiority}$ <0.01). When noninferiority was tested in the "per-treatment" population, the results for 30-day net adverse cardiovascular events were qualitatively similar: 14.8% for bivalirudin versus 15.9% for heparin (relative risk: 0.93; 95% CI: 0.67 to 1.29; $p_{superiority}$ = 0.66; risk difference: -1.14; 95% CI: -6.20 to 3.92; $p_{noninferiority}$ ≤0.01).

TABLE 1 Baseline Characteristics of the Study Population

	Bivalirudin (n = 404)	Heparin (n = 398)
Age, yrs	82.3 ± 6.5	82.3 ± 6.5
Women	195 (48.3)	196 (49.2)
Logistic EuroSCORE, %*	17.2 ± 10.7	16.9 ± 9.9
Median (interquartile range)	15.2 (9-22)	15.4 (9-23)
Diabetes mellitus	125 (30.9)	114 (28.6)
Oral treatment	41 (10.1)	42 (10.6)
Insulin treatment	47 (11.6)	40 (10.1)
Chronic kidney disease		
Glomerular filtration rate <30 ml/min	18 (4.5)	22 (5.5)
Glomerular filtration rate 30–59 ml/min	205 (50.7)	193 (48.5)
Peripheral artery disease	60 (14.9)	59/397 (14.9)
Prior stroke/transient ischemic attack	45/403 (11.2)	38/397 (9.6)
Stroke	31/403 (7.7)	26/397 (6.5)
Transient ischemic attack	14/403 (3.5)	12/397 (3.0)
Chronic obstructive pulmonary disease	68 (16.8)	87 (21.9)
Heart disease		
Coronary artery disease	209 (51.7)	196/397 (49.4)
Prior myocardial infarction	63/400 (15.8)	53/394 (13.5)
Prior atrial fibrillation	158/403 (39.2)	139/397 (35.0)
Prior ventricular tachycardia	11/391 (2.8)	9/381 (2.4)
Previous coronary bypass graft surgery	61 (15.1)	56 (14.1)
Previous balloon aortic valvuloplasty	29 (7.2)	31/397 (7.8)
Left ventricular ejection fraction, %	53.9 ± 12.8	53.4 ± 12.9
Hemoglobin, g/dl	12.5 ± 1.7	12.7 ± 1.6
Platelet count, × 10^9/l	217.7 ± 73.9	217.2 ± 71.4
Antiplatelet medications as prior maintenance therapy		
Aspirin	276/402 (68.7)	272/397 (68.5)
≤160 mg	266/402 (66.2)	266/397 (67.0)
$P2Y_{12}$ inhibitor	135/402 (33.6)	115/397 (29.0)
Aspirin plus $P2Y_{12}$ inhibitor	113/402 (28.1)	101/397 (25.4)

Values are mean ± SD, n (%), or n/N (%). There were no significant ($p < 0.05$) between-group differences. *The logistic European System for Cardiac Operative Risk Evaluation (EuroSCORE) is calculated by means of a logistic-regression equation; online and downloadable versions of the EuroSCORE calculator are available on the EuroSCORE Web site.

In terms of the secondary outcomes at 48 h, the rate of net adverse cardiovascular events was 8.9% with bivalirudin and 12.6% with heparin (relative risk: 0.71; 95% CI: 0.47 to 1.06; p = 0.09). Rates of major adverse cardiovascular events were 3.5% with bivalirudin and 4.8% with heparin (relative risk: 0.73; 95% CI: 0.37 to 1.43; p = 0.35). Rates of stroke or death did not differ between study treatments. Myocardial infarction was more frequent with heparin (0% vs. 1.3%; p = 0.03), whereas acute kidney injury was more frequent with bivalirudin (10.9% vs. 6.5%; p = 0.03), driven mainly by an increase in stage 1 injury.

At 30-day follow-up, rates of composite major adverse cardiovascular events were similar between the randomized treatments, whereas the differences in myocardial infarction and acute kidney injury noted at 48 h were no longer significant. BARC ≥3b bleeding occurred in 78 (9.7%) patients overall and was associated with a mortality rate of 20.5%, whereas BARC 1 or 2 bleeding (n = 214 [26.7%]) had a mortality rate of 2.3% (Online Table 2). BARC ≥3 bleeding occurred in 216 (26.9%) patients and was associated with a mortality rate of 10.6%. There were no significant differences between treatment groups regarding these bleeding results.

In subgroup analyses, rates of major bleeding with self-expanding TAVR (5.7% with bivalirudin vs. 10.6% with heparin; relative risk: 0.54; p = 0.14) or balloon-expandable TAVR (7.6% with bivalirudin vs. 8.0% with heparin; relative risk: 0.94; p = 0.85) were similar. Neither valve type nor sheath size (≥18-F vs. <18-F) seemed to affect the rate of major bleeding (Online Figure 1).

Major vascular complications at 30 days, with or without major bleeding, did not differ between the 2 groups (Online Table 3). Most differences in acute kidney injury were mild (stage 1) (**Table 3**) and occurred in the subgroup with baseline estimated glomerular filtration rate <30 ml/min (Online Table 4); no other significant outcome differences were observed in this subgroup (Online Table 5).

DISCUSSION

In patients undergoing transfemoral TAVR, procedural anticoagulation with bivalirudin did not significantly reduce the primary outcomes of major bleeding at 48 h or net adverse cardiovascular events at 30 days compared with heparin. Analysis of secondary outcomes also did not demonstrate any important differences between study treatments, indicating that bivalirudin may be used as an alternative to heparin during TAVR without any superiority claim and taking into account the much higher cost associated with its current use.

The primary hypothesis of BRAVO-3 was that bivalirudin would reduce major bleeding compared with heparin in TAVR procedures to an extent similar to that observed in coronary intervention trials (9,10,17,18). Although a statistically significant difference in the primary endpoint of BARC ≥3b bleeding was not observed, numerically lower major bleeding rates were noted with bivalirudin that were also consistent with the TIMI major bleeding definition. These results likely reflect the substantial differences that exist between the coronary and TAVR patient populations and the respective procedures because considerably larger arterial sheath/catheter sizes are used in TAVR. The lack of statistically significant differences in overall bleeding rates between treatment groups in the present study may also be due to sample size limitation (despite the attempt to overcome this factor by using an adaptive trial design).

Major bleeding is an important concern in complex procedures such as TAVR, in which large arterial sheaths are used in high-risk patients. The higher mortality in patients with BARC ≥3b bleeding within 30 days (20.5%) compared with that in patients with BARC 1 or 2 (2.3%) bleeding illustrates the significance of bleeding complications after TAVR in relation to mortality. In the present study, there was no significant difference in bleeding or mortality between the groups despite numerically more failures in access site device closure in the bivalirudin arm. Among patients who did not have a BARC bleeding event, mortality was very low (overall: 3.3%; bivalirudin: 2.5%; heparin: 4.2%).

The co-primary endpoint of net adverse cardiovascular events at 30 days did not differ between the groups. The data observed regarding risk differences (upper limit of 95% CI of 3.25%) would also be significant for an absolute noninferiority margin of 4% (i.e., smaller margin than the prespecified 8%). This combined endpoint of bleeding and ischemic events includes the counterbalance of anticoagulation benefits in the prevention of ischemic events with bleeding risks. In this first randomized trial of TAVR pharmacology, the dosage experience of coronary interventions was largely utilized; in this context, our findings suggest correct dosing for bivalirudin (i.e., no obvious underdose or overdose of study drug), which was sufficient to prevent ischemic events without increasing the risk of bleeding compared with heparin despite the unavailability of a bivalirudin antidote. A similar dosage was also used in 2 nonrandomized, smaller cohort studies with bivalirudin in valvuloplasty and TAVR (13,14).

The composite of major adverse cardiovascular events is an important endpoint for all cardiac interventions, especially high-risk procedures such as TAVR. Although the rates of death (1.5% for bivalirudin vs. 1.8% for heparin) and stroke (2.0% for both) at 48 h were low overall and similar between the groups, no myocardial infarctions occurred in the bivalirudin arm compared with 5 in the heparin arm (1.3%, p = 0.03). At 30 days, there were no significant differences in the rates of death, myocardial infarction, or stroke. Pathology data have indicated the presence of tissue factor in the leaflets of stenotic aortic valves (19,20). Exposure of tissue factor to the circulation during TAVR may create a highly thrombogenic local substrate. Whether more effective suppression of this process with direct thrombin inhibition may be the basis of the aforementioned findings in relation to myocardial infarction rates remains to be tested in future trials. Alternatively, the difference observed in rates of early myocardial infarction may be due to chance (21).

TABLE 2 Procedural Information

	Bivalirudin (n = 404)	Heparin (n = 398)
Procedural success*	393 (97.3)	388 (97.5)
Valve type		
Balloon expandable	251/395 (63.5)	249/392 (63.5)
Self-expanding	140/395 (35.4)	142/392 (36.2)
Nonballoon active expansion	4/395 (1.0)	1/392 (0.3)
Duration of procedure, min	35.0 (24–50)	36.0 (24–49)
Sheath size of valve system		
<18-F	128/393 (32.6)	127/390 (32.6)
18-F	216/393 (55.0)	208/390 (53.3)
>18-F	49/393 (12.5)	55/390 (14.1)
Valvuloplasty performed	325/401 (81.0)	313/395 (79.2)
Additional TAVR device used	16/395 (4.1)	12/393 (3.1)
Embolic protection device used	7/397 (1.8)	4/393 (1.0)
Closure technique used for valve implantation access site		
Not attempted	4/396 (1.0)	3/393 (0.8)
Successful deployment	359/396 (90.7)	367/393 (93.4)
Attempted but failed	33/396 (8.3)	23/393 (5.9)
Antiplatelet therapies		
Prior loading with clopidogrel†	152/402 (37.8)	142/397 (35.8)
Post-procedural		
Aspirin	343/401 (85.5)	348/397 (87.7)
$P2Y_{12}$ inhibitor‡	299/401 (74.6)	296/397 (74.6)
Aspirin plus $P2Y_{12}$ inhibitor	264/401 (65.8)	262/397 (66.0)
Post-procedural oral anticoagulant therapy	111/400 (27.8)	119/397 (30.0)
≤48 h§	31/400 (7.8)	39/397 (9.8)
>48 h to <30 days	90/400 (22.5)	91/397 (22.9)

Values are n (%), n/N (%), or median (interquartile range). There were no significant ($p < 0.05$) between-group differences. *Valve implantation without intraprocedural major adverse cardiovascular events or conversion to thoracotomy. †Neither prasugrel nor ticagrelor was used. ‡Clopidogrel (575 of 798 [72.1%]), prasugrel (1 of 798 [0.1%]), or ticagrelor (3 of 798 [0.4%]). §Vitamin K antagonist (50 of 797 [6.2%]), dabigatran (6 of 797 [0.8%]), rivaroxaban (4 of 797 [0.1%]), or fondaparinux (10 of 797 [1.2%]).

The overall procedural success rate in the present study was >97%, indicating that high-quality centers with experienced operators participated in this trial. We observed complication rates somewhat lower than those reported in earlier TAVR device trials (6,22); although not directly comparable, these findings may reflect advances in device technology and increased operator experience. However, the occurrence of these events reinforces the importance of implementing an optimal periprocedural anticoagulation regimen.

Co-existing conditions are common among elderly subjects. Our study patients had a mean age of 82 years, and approximately 30% were diabetic, 20% had lung disease, and 5% had advanced chronic kidney disease (stage 4 or 5). Rates of major vascular complications with or without related bleeding were not significantly different between the study groups. The overall rate of acute kidney injury was significantly higher in the bivalirudin group at 48 h (mostly stage 1), and only a trend remained at 30 days. This

TABLE 3 Clinical Outcomes of the Intention-to-Treat Population

	Bivalirudin (n = 404)	Heparin (n = 398)	Relative Risk (95% CI)	p Value
Co-primary endpoints				
Major bleeding (BARC ≥3b) at 48 h or before discharge*	28 (6.9)	36 (9.0)	0.77 (0.48–1.23)	0.27
Net adverse cardiovascular events at 30 days	58 (14.4)	64 (16.1)	0.89 (0.64–1.24)	0.50
Secondary endpoint at 48 h or before hospital discharge*				
Net adverse cardiovascular events	36 (8.9)	50 (12.6)	0.71 (0.47–1.06)	0.09
Major adverse cardiovascular events	14 (3.5)	19 (4.8)	0.73 (0.37–1.43)	0.35
Death	6 (1.5)	7 (1.8)	0.84 (0.29–2.49)	0.76
Myocardial infarction	0	5 (1.3)	NA	0.03
Stroke	8 (2.0)	8 (2.0)	0.99 (0.37–2.60)	0.98
VARC (life-threatening or major)	88 (21.8)	78 (19.6)	1.11 (0.85–1.46)	0.45
TIMI (major)	16 (4.0)	26 (6.5)	0.61 (0.33–1.11)	0.10
GUSTO (severe/life-threatening)	15 (3.7)	13 (3.3)	1.14 (0.55–2.36)	0.73
ACUITY/HORIZONS (major)	105 (26.0)	97 (24.4)	1.07 (0.84–1.35)	0.60
BARC 3a	63 (15.6)	53 (13.3)	1.17 (0.84–1.64)	0.36
BARC 1 and 2	84 (20.8)	84 (21.1)	0.99 (0.75–1.29)	0.91
TIMI minor	67 (16.6)	57 (14.3)	1.16 (0.84–1.60)	0.38
Transient ischemic attack	0	0	NA	NA
Acute kidney injury	44 (10.9)	26 (6.5)	1.67 (1.05–2.65)	0.03
Stage 1	33 (8.2)	22 (5.5)	1.48 (0.88–2.49)	0.14
Stage 2	6 (1.5)	2 (0.5)	2.96 (0.60–14.56)	0.29
Stage 3	5 (1.2)	2 (0.5)	2.46 (0.48–12.62)	0.45
Major vascular complications	35 (8.7)	36 (9.0)	0.96 (0.61–1.49)	0.85
New onset atrial fibrillation/flutter	13 (3.2)	10 (2.5)	1.28 (0.57–2.89)	0.55
Thrombocytopenia	67 (16.6)	69 (17.3)	0.96 (0.70–1.30)	0.78
Secondary endpoint at 30 days				
Major bleeding (BARC ≥3b)	36 (8.9)	42 (10.6)	0.84 (0.55–1.29)	0.43
Major adverse cardiovascular events	31 (7.7)	32 (8.0)	0.95 (0.59–1.53)	0.85
Death	19 (4.7)	19 (4.8)	0.99 (0.53–1.83)	0.96
Myocardial infarction	2 (0.5)	7 (1.8)	0.28 (0.06–1.35)	0.11
Stroke	14 (3.5)	11 (2.8)	1.25 (0.58–2.73)	0.57
Transient ischemic attack	0	0	NA	NA
Acute kidney injury	76 (18.8)	55 (13.8)	1.36 (0.99–1.87)	0.06
Stage 1	60 (14.9)	46 (11.6)	1.28 (0.90–1.84)	0.17
Stage 2	10 (2.5)	5 (1.3)	1.97 (0.68–5.71)	0.20
Stage 3	6 (1.5)	5 (1.3)	1.18 (0.36–3.84)	0.78
Major vascular complications	37 (9.2)	38 (9.5)	0.96 (0.62–1.48)	0.85
New onset atrial fibrillation/flutter	22 (5.4)	16 (4.0)	1.35 (0.72–2.54)	0.34
Thrombocytopenia	97 (24.0)	92 (23.1)	1.04 (0.81–1.33)	0.77

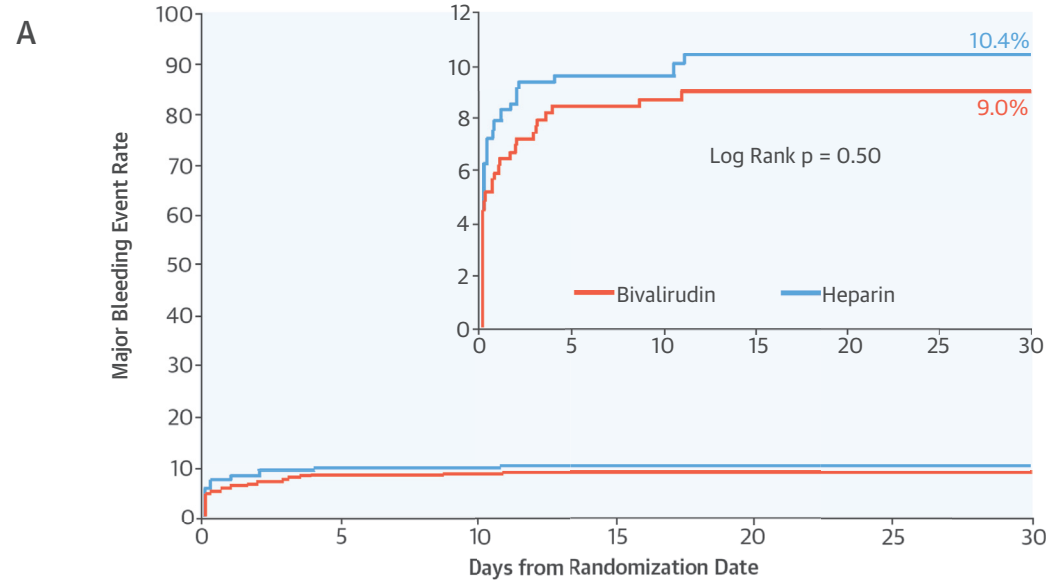
Values are n (%), unless otherwise specified. *Whichever occurred first.

ACUITY/HORIZONS = Acute Catheterization and Urgent Intervention Triage Strategy/Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction; BARC = Bleeding Academic Research Consortium; CI = confidence interval; GUSTO = Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries; NA = not applicable; TIMI = Thrombolysis In Myocardial Infarction; VARC = Valve Academic Research Consortium.

unexpected finding has not been reported before (7–12), and no plausible biological mechanism exists. Although acute kidney injury was more frequent in the bivalirudin group at 30 days, this finding did not seem to affect mortality compared with the heparin arm, even in patients with advanced kidney disease at baseline. Finally, patients were stratified during randomization according to balloon-expandable (63.5%) or self-expanding (35.8%) valves; the main study outcomes were not affected by the valve type.

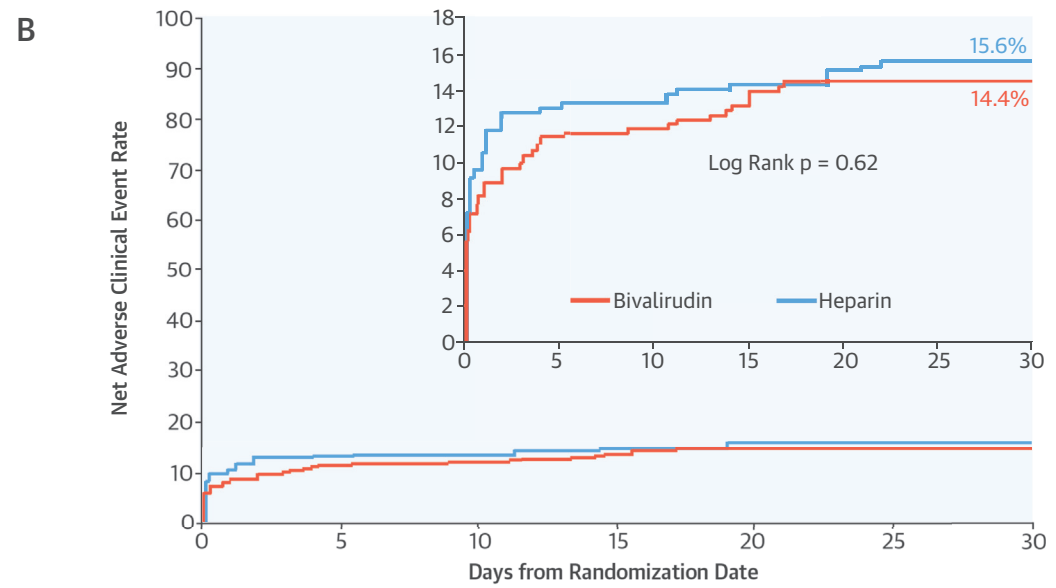
STUDY LIMITATIONS. BRAVO-3 was an open-label trial and may be subject to treatment bias, and data on standard of care were not available from all sites. The procedure (including heparin dosing and administration, and the decision on whether to use protamine reversal) and the use of antithrombotic therapies post-procedure were performed according to standard local institution practices. Although this approach may lead to inconsistency in the comparator groups, it is also representative of everyday clinical practice. Finally, the lack of data on protamine use

CENTRAL ILLUSTRATION **Time-to-Event Curves Through 30 Days**



Patients at Risk

Bivalirudin	404	364	357	353	348	340	278
Heparin	398	353	351	347	344	332	269



Patients at Risk

Bivalirudin	404	354	349	342	337	329	270
Heparin	398	344	341	336	332	319	261

Dangas, G.D. et al. J Am Coll Cardiol. 2015; 66(25):2860–8.

(A) Major bleeding (Bleeding Academic Research Consortium ≥3b). The 48-h Kaplan-Meier rates were 7.2% for bivalirudin and 9.1% for heparin. **(B)** Net adverse clinical events. The 48-h Kaplan-Meier rates were 9.7% for bivalirudin and 12.6% for heparin.

prevented us from performing subgroup analyses in patients who did or did not undergo heparin reversal.

CONCLUSIONS

Procedural administration of bivalirudin, compared with unfractionated heparin, did not meet superiority because it did not reduce the co-primary outcomes of BARC ≥3b major bleeding at 48 h or net adverse cardiovascular events at 30 days in high-risk or inoperable patients with severe, symptomatic aortic stenosis undergoing TAVR. In addition, given heparin's lower cost, this agent should remain the standard of care, and bivalirudin may be an alternative anticoagulant for the minority of patients who cannot receive heparin in TAVR procedures (e.g., because of heparin-induced thrombocytopenia or allergy).

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Among patients with severe aortic stenosis undergoing TAVR, intraprocedural anticoagulation with the direct thrombin inhibitor bivalirudin was noninferior but not superior to unfractionated heparin with respect to major bleeding at 48 h or adverse events at 30 days after the procedure.

TRANSLATIONAL OUTLOOK: Further research is needed to define the optimum antithrombotic strategies during and after TAVR.

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KEY WORDS anticoagulation, bivalirudin, major bleeding, transcatheter aortic valve replacement

APPENDIX For a complete list of the BRAVO-3 investigators (Valve Pharmacology Consortium), as well as a full description of the Methods and additional Results, please see the online version of this article.