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Clinical Research

Bivalirudin vs Heparin in Patients Who Undergo Transcatheter Aortic Valve Implantation

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ABSTRACT

Background: We aimed to compare safety and efficacy of the direct thrombin inhibitor bivalirudin with unfractionated heparin (UFH) during transcatheter aortic valve implantation (TAVI).

Methods: In this retrospective analysis, 461 patients underwent TAVI between 2007 and 2012; 339 patients received bivalirudin, and 122 patients received UFH. In the bivalirudin group, the Sapien XT valve was implanted in 159 (46.9%) patients, and 180 (53.1%) received a Medtronic CoreValve. In the UFH group, only the Medtronic CoreValve was implanted. The primary outcome of interest was the incidence of any bleeding. Secondary outcomes of interest were all-cause mortality and cardiovascular mortality at 72 hours after the procedure and at 30 days.

Results: No significant difference between the groups was observed for life-threatening bleeding (2.4% for bivalirudin vs 3.3% for UFH; $P = 0.59$), major bleeding (8.3% vs 8.2%, respectively; $P = 0.98$) and minor bleeding (8.3% vs 7.4%, respectively; $P = 0.76$). At 72 hours after the procedure, all-cause mortality was 3.0% in the bivalirudin group and 3.3% for the UFH group ($P = 0.88$), whereas cardiovascular mortality was 3.0% in the bivalirudin group and 2.5% in the heparin group ($P = 0.77$). At 30 days, all-cause mortality was 5.3% vs 4.1% in

RÉSUMÉ

Introduction : Nous avions pour but de comparer l'innocuité et l'efficacité de la bivalirudine, un inhibiteur direct de la thrombine, à l'héparine non fractionnée (HNF) au cours de l'implantation valvulaire aortique par cathéter (IVAC).

Méthodes : Dans cette analyse rétrospective, 461 patients ont subi une IVAC entre 2007 et 2012; 339 patients ont reçu la bivalirudine et 122 patients ont reçu l'HNF. Dans le groupe recevant la bivalirudine, 159 (46,9 %) patients ont subi l'implantation de la valve Sapien XT et 180 (53,1 %) ont subi l'implantation d'une valve Medtronic CoreValve. Dans le groupe recevant la HNF, seule la valve Medtronic CoreValve a été implantée. Le critère d'intérêt principal était l'incidence de toute hémorragie. Les critères d'intérêt secondaires étaient la mortalité toutes causes confondues et la mortalité d'origine cardiovasculaire 72 heures après l'intervention et à 30 jours.

Résultats : Nous n'avons observé aucune différence significative entre les groupes en ce qui concerne l'hémorragie mettant la vie en danger (2,4 % pour la bivalirudine *vs* 3,3 % pour la HNF; $P = 0,59$), l'hémorragie grave (8,3 % *vs* 8,2 %, respectivement; $P = 0,98$) et l'hémorragie minime (8,3 % *vs* 7,4 %, respectivement; $P = 0,76$). Soixante-douze

In recent years, transcatheter aortic valve implantation (TAVI) has been established as a reliable treatment strategy for elderly patients with high-grade aortic stenosis and an increased surgical risk.[1,2] The transapical and transfemoral approaches for valve implantation are both well established. Besides the benefits of a less invasive treatment in an elderly and multimorbid patient population, transfemoral TAVI bears specific procedural risks, including bleeding complications[3] or vascular injuries,[4] because of the large sheath sizes. Moreover, thrombotic microemboli to the brain or elsewhere can occur.[4,5] Unfractionated heparin (UFH) is commonly used as an anticoagulant during TAVI to prevent thromboembolic events. The potentially increased periprocedural bleeding risk after UFH therapy might be reversed by protamine injection at the end of the procedure, as is the case for routine

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the bivalirudin and heparin groups ($P = 0.57$) and cardiovascular mortality was 4.4% vs 2.5% ($P = 0.33$). Device success (Valve Academic Research Consortium 2 composite end point) was 94.0% in the bivalirudin-treated and 92.6% in the UFH-treated patients ($P = 0.60$). The early safety at 30 days was 85.3% in the bivalirudin-treated group compared with 83.6% in the UFH-treated group ($P = 0.65$).

Conclusions: Bivalirudin has a safety and efficacy profile similar to weight-adjusted UFH during the TAVI procedure.

heures après l'intervention, la mortalité toutes causes confondues a été de 3,0 % dans le groupe recevant la bivalirudine et de 3,3 % dans le groupe recevant la HNF ($P = 0,88$), tandis que la mortalité d'origine cardiovasculaire a été de 3,0 % dans le groupe recevant la bivalirudine et de 2,5 % dans le groupe recevant l'héparine ($P = 0,77$). À 30 jours, la mortalité toutes causes confondues a été de 5,3 % *vs* 4,1 % dans les groupes recevant la bivalirudine et l'héparine ($P = 0,57$) et la mortalité d'origine cardiovasculaire a été de 4,4 % *vs* 2,5 % ($P = 0,33$). Le taux de réussite des dispositifs (critère de jugement combiné du Valve Academic Research Consortium 2) a été de 94,0 % chez les patients traités par bivalirudine et de 92,6 % chez les patients traités par HNF ($P = 0,60$). L'innocuité à 30 jours a été de 85,3 % dans le groupe traité par bivalirudine comparativement à 83,6 % dans le groupe traité par HNF ($P = 0,65$).

Conclusions : La bivalirudine montre un profil d'innocuité et d'efficacité similaire à la HNF ajustée au poids durant l'IVAC.

open-heart surgery. In contrast, the direct thrombin inhibitor bivalirudin (Angiox; The Medicines Company, Parsipanny, NJ) offers a shorter half-life than heparin (25 minutes vs 1.5 hours, respectively) and therefore constitutes an attractive alternative for periprocedural anticoagulation.[6] However, no direct antagonist is available. Nevertheless, compared with heparin, bivalirudin has been demonstrated to reduce access site and nonaccess site bleeding complications in patients who undergo percutaneous coronary intervention (PCI) compared with heparin with glycoprotein IIb/IIIa inhibitors.[7,8] Moreover, bivalirudin has been shown to reduce major or life-threatening bleeding when used during balloon valvuloplasty of the aortic valve.[9] However, data regarding the performance of bivalirudin compared with weight-adjusted UFH peri-TAVI procedure are lacking.

Therefore, the aim of this retrospective analysis was to compare the safety and efficacy of peri-TAVI bivalirudin compared with weight-adjusted heparin 30 days after the procedure.

Methods

Patients

From November 2007 until October 2012, 461 consecutive patients (mean age 81.2 ± 6.7 years) underwent a TAVI because of symptomatic high-grade aortic stenosis at the Medizinische Klinik und Poliklinik I, University of Munich, Munich, Germany. Two different valve types were implanted: Medtronic CoreValve prosthesis (n = 302 patients) and Edwards Sapien XT prosthesis (n = 159). The decision about TAVI was made by the multidisciplinary heart board considering the patients' age, comorbidities, and feasibility of transfemoral access.

The TAVI procedure and concomitant therapy

TAVI procedures were performed in the catheterization laboratory using local anaesthesia and fluoroscopic guidance, with only mild analgesic and antiemetic medication without surveillance by an anaesthesiologist.[10] Detailed technical aspects of implantation of the Medtronic CoreValve or Edwards Sapien XT prosthesis have been previously reported.[2,10-12] Closure of vascular access at the end of procedure was obtained using a Prostar XL suture device (Abbott Vascular, Santa Clara, CA).

All patients were pretreated with aspirin (100 mg) and clopidogrel (600 mg) 1 day before the TAVI procedure. Peri-TAVI anticoagulation consisted of either weight-adjusted UFH at a target activated clotting time value between 250 and 300 seconds or bivalirudin (bolus and continuous infusion according to the manufacturer's recommendation), depending on the operator's choice. The TAVI program was initiated at our institution using only heparin as an anticoagulant in 2007. After the learning period, implantation was done either with heparin or bivalirudin depending on the operator's choice. Until 2010, only Corevalve prostheses were implanted. In 2010, the Edwards Sapien Valve was introduced at our centre. At this point, because of hypothetic beneficial effects in terms of bleeding complications, bivalirudin was exclusively used as the antithrombotic agent.

Antiplatelet therapy after TAVI consisted of clopidogrel 75 mg daily for either 1 month (after the Edwards Sapien XT prosthesis implantation) or 3 months (after the Medtronic CoreValve prosthesis implantation) and 100 mg daily of aspirin indefinitely. Patients in need of chronic oral anticoagulation with phenprocoumon were treated with anticoagulation alone.

Definitions and outcomes of interest

The primary outcome of interest was the occurrence of any bleeding according to the Valve Academic Research Consortium (VARC) 2 criteria (life-threatening bleeding, major bleeding, or minor bleeding; definitions described in detail previously[13]). Secondary outcomes of interest were (1) all-cause mortality and cardiovascular mortality 72 hours after the TAVI procedure; (2) all-cause mortality and cardiovascular mortality at the 30-day follow-up; and (3) early safety defined as freedom from all-cause death, stroke, life-threatening bleeding, acute kidney injury requiring hemodialysis, coronary artery obstruction, major vascular complications, and valve-related dysfunction.

Cardiovascular mortality was defined according to the VARC 2 criteria. Stroke was defined as an acute episode of focal or global neurological dysfunction caused by hemorrhage

Table 1. Baseline characteristics

	Total (n = 461)	Bivalirudin (n = 339)	Heparin (n = 122)	*P*
Age	81.16 ± 6.67	81.42 ± 6.35	80.44 ± 7.49	0.165
Male sex	201 (43.6%)	149 (44.0%)	70 (57.4%)	0.799
Logistic EuroScore, %	22.20 ± 12.38	21.73 ± 11.97	23.50 ± 13.42	0.176
Coronary artery disease	239 (51.8%)	178 (52.5%)	61 (50.0%)	0.685
1-vessel disease	59 (12.9%)	42 (12.5%)	17 (13.9%)	0.477
2-vessel disease	51 (11.1%)	42 (12.4%)	9 (7.4%)	0.130
3-vessel disease	116 (25.2%)	85 (25.1%)	31 (25.4%)	0.954
PCI in the past 30 days	116 (25.2%)	79 (23.3%)	37 (30.3%)	**0.125**
PCI more than 30 days previously	111 (24.1%)	67 (19.8%)	44 (36.1%)	**< 0.001**
Previous CABG	51 (11.1%)	35 (10.3%)	16 (13.1%)	0.399
Previous MI	45 (9.8%)	33 (9.7%)	12 (10.0%)	0.933
Atrial fibrillation	147 (32.1%)	109 (32.2%)	38 (31.7%)	0.907
Peripheral artery disease Fontaine ≥ II	47 (10.2%)	30 (8.8%)	17 (13.9%)	0.111
GFR < 30 mL/h	51 (11.8%)	41 (12.7%)	10 (9.0%)	0.553
GFR 30-60 mL/h	249 (57.4%)	182 (56.3%)	67 (60.4%)	
GFR > 60 mL/h	133 (30.6%)	99 (30.6%)	34 (30.6%)	

P values in bold font highlighting significant differences.

CABG, coronary artery bypass grafting; GFR, glomerular filtration rate; MI, myocardial infarction; PCI, percutaneous coronary intervention.

or infarction, whereas a transient ischemic attack was defined as a transient episode of focal neurological dysfunction caused by ischemia, without acute infarction. Myocardial infarction was defined as the occurrence of new ischemic symptoms (eg, chest pain) or new ischemic signs (eg, new ST segment changes) and increased levels of cardiac biomarkers. Vascular complications, bleeding, and kidney injury, device success, and 30-day combined safety were defined in accordance with the VARC 2 criteria.[13]

Aortic annulus diameter, calcification pattern of the aortic valve leaflets, and distance of the coronary arteries from the aortic annulus were determined using dual source computed tomography scans (Definition Flash, Siemens Medical Solutions, Forchheim, Germany).

Paravalvular leak and grade of aortic regurgitation were evaluated angiographically using the method described by Sellers et al.[14] In cases when aortic regurgitation was judged to be more than trace, hemodynamic measurements were used to further evaluate aortic regurgitation.

Statistical analysis

We divided the population into 2 groups according to the type of peri-TAVI anticoagulation used: bivalirudin or UFH. Statistical analyses were performed using the SPSS software package (version 22.0; SPSS Inc, Chicago, IL). The continuous variables are expressed as the mean ± SD and compared using the Student *t* test. The categorical data are expressed as numbers and percentages and compared using Pearson χ^2 test or Fisher exact test as appropriate. To assess whether the data followed a normal distribution, we performed the Kolmogrov-Smirnov test. In cases of nonparametric distribution, the Mann-Whitney *U* test was applied for continuous variables. A 2-tailed $P < 0.05$ was considered significant. The odds ratios are expressed along with lower and upper 95% confidence interval. Survival curves were constructed using Kaplan-Meier estimates based on all available data and compared using the log-rank test.

Results

Of the 461 patients included in this retrospective analysis, 339 patients (73.5%) received bivalirudin, and 122 patients (26.5%) received UFH peri-TAVI. No differences were observed between the 2 groups regarding baseline characteristics except for a lower incidence of PCI > 30 days before TAVI in the bivalirudin group (19.8% vs 36.1% in the UFH group; $P < 0.001$; Table 1). The most frequently implanted prosthesis was the Medtronic CoreValve in 53.1% of patients in the bivalirudin group and 100% in the UFH group. Differences were observed in the procedural data, and reached statistical significance for sheath size and radiation parameters (Table 2).

The peri-procedural and 30-day outcomes are shown in Table 3. The overall device success was 93.6% with no

Table 2. Procedural data

	Total	Bivalirudin	Heparin	*P*
Sheath size				
16 F	38 (8.2%)	38 (11.2%)	0 (0%)	**< 0.001**
18 F	404 (87.6%)	282 (83.2%)	122 (100%)	
20 F	18 (3.9%)	18 (5.3%)	0 (0%)	
Surgical closure	17 (3.7%)	13 (3.8%)	4 (3.3%)	0.780
X-ray exposure, minutes	17.2 ± 10.9	16.7 ± 8.72	18.79 ± 15.6	0.081
cGY × cm^2	7936 ± 4901	7353 ± 4521	9485 ± 5541	**< 0.001**
Contrast agent, mL	171.1 ± 101.3	166.4 ± 58.6	183.8 ± 170.83	0.105
Contrast agent, mL/kg	2.44 ± 1.60	2.38 ± 0.98	2.67 ± 2.64	0.151
Transfusion	31 (6.7%)	21 (6.2%)	10 (8.2%)	0.449

P values in bold font highlighting significant differences.

F, French.

Table 3. Clinical outcome according to VARC 2

	Total	Bivalirudin	Heparin	*P*
All-cause immediate procedural mortality < 72 hours	14 (3.1%)	10 (3.0%)	4 (3.3%)	0.880
Cardiovascular immediate procedural mortality < 72 hours	13 (2.8%)	10 (3.0%)	3 (2.5%)	0.766
All-cause 30-day mortality	23 (5.0%)	18 (5.3%)	5 (4.1%)	0.574
Cardiovascular 30-day mortality	18 (3.9%)	15 (4.4%)	3 (2.5%)	0.328
Bleeding	87 (18.9%)	64 (18.9%)	23 (18.9%)	0.995
Life-threatening	12 (2.6%)	8 (2.4%)	4 (3.3%)	0.585
Major	38 (8.2%)	28 (8.3%)	10 (8.2%)	0.983
Minor	37 (8.0%)	28 (8.3%)	9 (7.4%)	0.758
Vascular complication	87 (18.9%)	63 (18.6%)	24 (19.7%)	0.792
Major	48 (10.5%)	34 (10.2%)	14 (11.5%)	0.690
Minor	39 (8.6%)	29 (8.7%)	10 (8.2%)	0.870
Myocardial infarction	9 (2.0%)	5 (1.5%)	4 (3.3%)	0.217
Ischemic stroke	6 (1.3%)	6 (1.8%)	0 (0%)	0.139
Hemorrhagic stroke	3 (0.7%)	2 (0.6%)	1 (0.8%)	0.787
Acute kidney injury	179 (38.8%)	133 (39.2%)	46 (37.7%)	0.766
Stage 1	41 (8.9%)	29 (8.6%)	12 (9.8%)	0.670
Stage 2	135 (29.3%)	102 (30.1%)	33 (27.0%)	0.527
Stage 3	3 (0.7%)	2 (0.6%)	1 (0.8%)	0.787
Device Success	93.6%	94.0%	92.6%	0.596
Early Safety at 30 days	84.9%	85.3%	83.6%	0.650

VARC, Valve Academic Research Consortium.

difference between the 2 groups. Furthermore, no differences were observed in the primary and secondary outcomes of interest.

No significant difference was observed with regard to life-threatening bleeding (2.4% in the bivalirudin group vs 3.3% in the heparin group; $P = 0.585$), major bleeding (8.3% vs 8.2%; $P = 0.983$), and minor bleeding (8.3% vs 7.4%; $P = 0.758$) according to VARC 2 (Table 3). Periprocedural all-cause and cardiovascular mortality were 3.0% and 3.0% in the bivalirudin group and 3.3% and 2.5% in the UFH group. At the 30-day follow-up, all-cause mortality was 5.3% in the bivalirudin group and 4.1% in the heparin group ($P = 0.57$), similar to cardiovascular mortality (4.4% for bivalirudin vs 2.5% for heparin; $P = 0.33$; Fig. 1). The early safety end point at day 30 was achieved in 84.9% of all cases, 85.3% in the bivalirudin group, and 83.6% in the UFH group ($P = 0.65$).

No significant difference was observed with regard to thrombotic complications or severity of kidney injury according to the VARC 2 definition (Table 3).

Subgroup analysis revealed no clear difference between the 2 anticoagulation approaches (Fig. 2).

Discussion

In this analysis of a large number of patients who underwent TAVI and received either bivalirudin or UFH, there was no difference regarding life-threatening, or major or minor bleeding complications using the VARC 2 bleeding definitions. We found no difference between bivalirudin and heparin with respect to 72-hour and 30-day mortality (cardiovascular and all cause) or early 30-day safety.

The study extends previous findings with bivalirudin used as an anticoagulant in patients who underwent balloon valvuloplasty.[9] In this procedure, smaller sheaths are used than during the TAVI procedure. Notably, at the 2 centres in which the Valvuloplastie study[9] was conducted arterial sheaths were inserted in both groins, as is routine in the TAVI procedure. Still, the overall incidence of bleeding (9.8% vs 16.7%, bivalirudin vs heparin) was lower than in our TAVI study (18.9% vs 18.9%). Consistently, Bleeding Academic Research Consortium (BARC) bleeding ≥ 3 (4.9%) reached only half the level found for bivalirudin in our TAVI study (10.7%), although this advantage was not found for the heparin group (13.2%) compared with our TAVI heparin group (11.5%). However, a smaller-access sheath size and shorter procedure length and a more acute patient condition might all account for differences between both analyses. Another possible reason for less bleeding with valvuloplasty vs TAVI is that there are fewer sheath manipulations at the puncture site, because for TAVIs, several dilators are used sequentially before the final sheath is introduced.

With a moderately sized access puncture and preclosure, bivalirudin might be capable of avoiding BARC bleeding ≥ 3. However, when larger sheaths are used (up to 20-French in our study), this advantage might be less visible.

A preclosure, which helped to reduce bleeding after balloon valvuloplasty in the **B**lockade of the glycoprotein IIb/IIIa **R**eceptor to **A**void **V**ascular **O**cclusion (BRAVO) balloon valvuloplasty study,[15-17] was inserted in all cases of our cohort.

With respect to bleeding, bivalirudin was successfully used to reduce bleeding in patients who underwent PCI for ST-elevation myocardial infarction.[18,19] Of note, our bivalirudin cohort displayed higher rates of major bleeding (8.3%) compared with PCI patients (major: 3.0% in Stone et al.[18] and 5.1% in Stone et al.[19]), because of a difference in the procedure and larger sheaths used. Notably, a CoreValve requires an 18-French sheath (total n = 302; 53.1% of the bivalirudin group vs 100% of the heparin group; $P < 0.001$). A Sapien XT was implanted in 159 patients, all treated with bivalirudin. These valves require various sheath sizes, with size 16-French sheaths used for the 23-mm Sapien XT (total n = 38; 11.2% of the bivalirudin patients), 18-French sheaths are used for the 26-mm Sapien XT (total n = 103; 30.4% of the bivalirudin patients) and 20-French sheaths used for the 29-mm Sapien XT (total n = 18; 5.3% of the bivalirudin patients).

Apart from the bleeding and thrombosis reflected in the rates of stroke or vascular complications is a possible complication of the TAVI procedure. Although not being

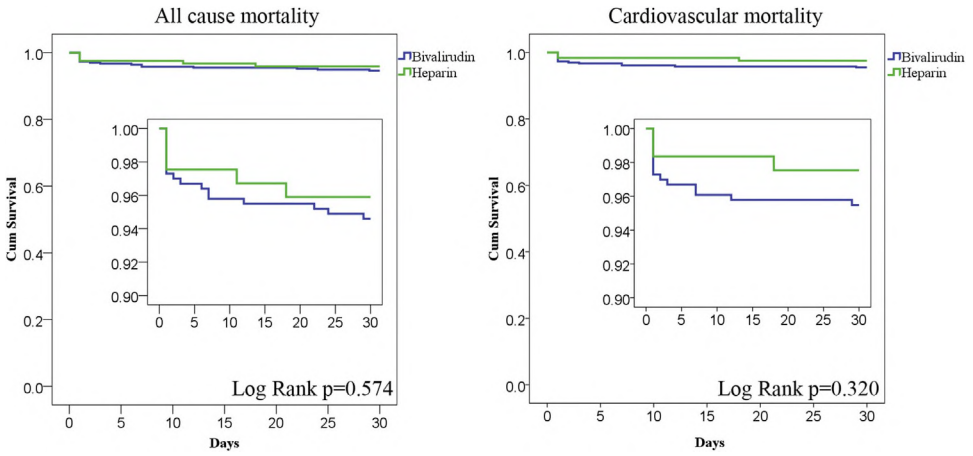

Figure 1. Kaplan-Meier analysis showing all cause and cardiovascular mortality at 30 days. Cum, cumulative.

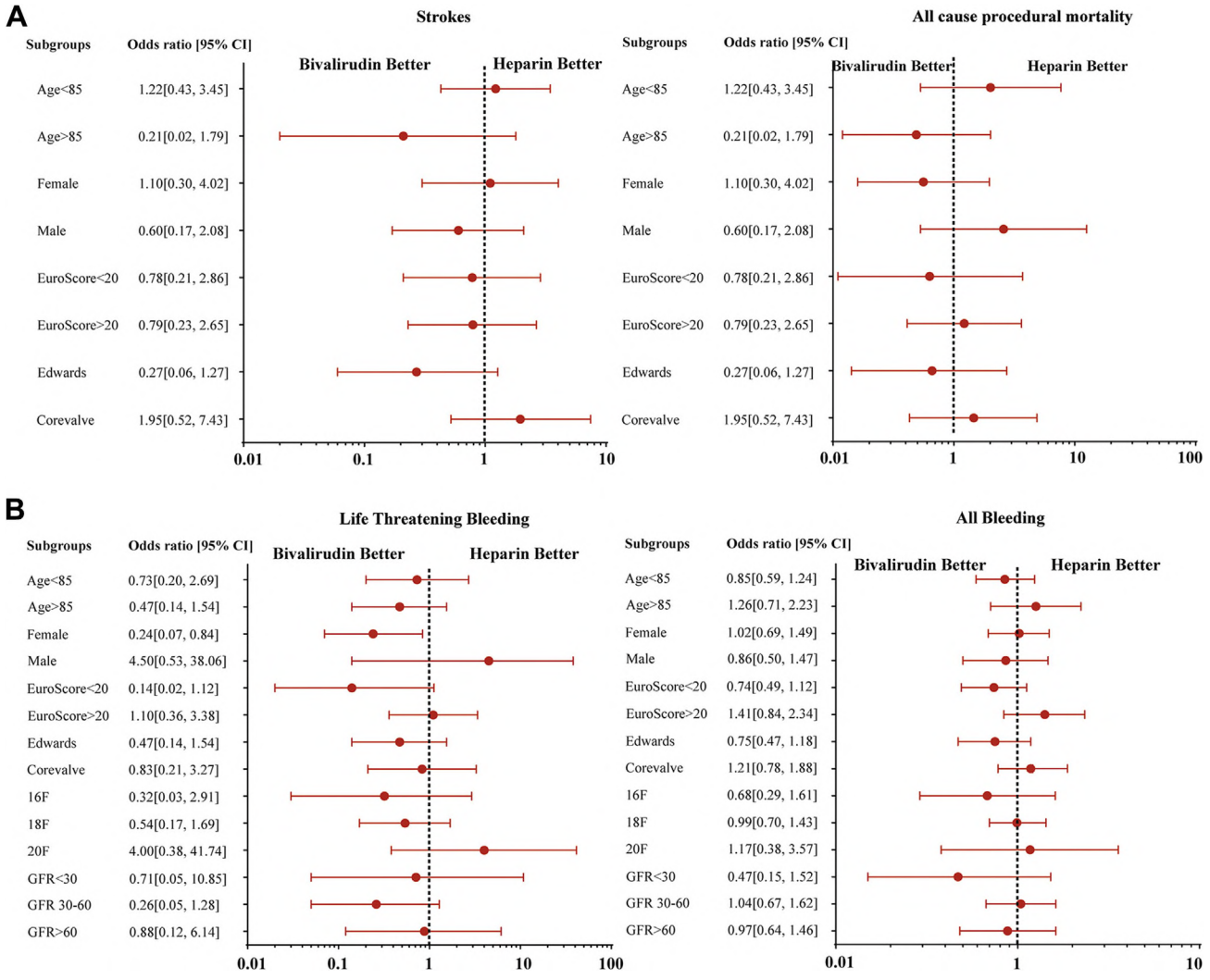

Figure 2. (**A**) Subgroup stratification for stroke and all-cause procedural mortality. (**B**) Subgroup stratification for life-threatening bleeding and total bleeding complications.

significant, in our population, there was a trend toward more ischemic stroke in the bivalirudin group (1.8% vs 0.0%; $P = 0.139$). In contrast, this trend was reversed in the study conducted by Kini et al.[9] Therefore, results from the upcoming BRAVO 2/3 trial are needed to clarify this issue.

The limitation of this project is its retrospective nature and the lack of randomization in a single-centre patient cohort. These shortcomings are expected to be overcome with a prospective controlled multicentre randomized trial (BRAVO 2/3).

In summary, bivalirudin appears to be a good alternative to weight-adjusted UFH as peri-TAVI anticoagulation with a robust safety and efficacy profile. Still, because of bivalirudin's higher cost and lack of significant advantage, at the moment, bivalirudin as a peri-TAVI anticoagulant should be reserved for cases in which heparin is contraindicated (Supplementary Material).

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Philipp Lange, Martin Greif, and Dario Bongiovanni contributed equally to this work.

Disclosures

The authors have no conflicts of interest to disclose.

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Supplementary Material

To access the supplementary material accompanying this article, visit the online version of the *Canadian Journal of Cardiology* at www.onlinecjc.ca and at http://dx.doi.org/10.1016/j.cjca.2015.02.029.