

Supplementary material

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Table S1. Per-protocol analysis. Baseline and procedural characteristics of the study population along with endpoint rates

	Total (n = 91)	Protamine sulfate (n = 47, 52%)	Placebo (n = 44, 48%)	P- value
Demographics				
Female gender, n (%)	48 (53)	25 (53)	23 (52)	0.93
Age, years [IQR]	81.5 [76–85]	81.8 [77–85]	81 [75–86]	0.97
Baseline characteristics				
BMI, kg/m ² [IQR]	26.8 [23–28]	26 [23–29]	27 [23–28]	0.95
BSA, m ² [IQR]	1.79 [1.7–1.9]	1.79 [1.7–1.9]	1.78 [1.7–1.9]	0.99
logEuroSCORE, % [IQR]	10.3 [7.5–16.1]	10.5 [7.8–16.3]	10.3 [7–16]	0.87
Hypertension, n (%)	81 (89)	41 (87)	40 (91)	0.74
Diabetes, n (%)	38 (42)	24 (51)	14 (32)	0.09
GFR <30 ml/min, n (%)	9 (9)	4 (9)	4 (9)	1
History of bleeding, n (%)	10 (11)	6 (13)	4 (9)	0.74
Coronary artery disease, n (%)	68 (75)	37 (79)	31 (71)	0.47
Prior cardiac surgery, n (%)	11 (12)	7 (15)	4 (9)	0.53
History of stroke/TIA, n (%)	10 (11)	4 (9)	6 (14)	0.51
Atrial fibrillation, n (%)	38 (42)	20 (43)	18 (41)	1
COPD, n (%)	16 (18)	9 (19)	7 (16)	0.79

Prior pacemaker implantation, n (%)	21 (23)	8 (17)	13 (30)	0.2
Oral anticoagulation, n (%)	42 (46)	22 (47)	20 (46)	1
NYHA class 3–4, n (%)	31 (34)	16 (34)	15 (34)	1
LVEF, % [IQR]	59 [53–64]	60 [55–64]	58 [53–64]	0.77
LVEF <30%, n (%)	9 (10)	6 (13)	3 (7)	0.49
Mean AV pressure gradient, mm Hg [IQR]	42 [34–50]	42 [38–50]	42 [33–50]	0.93
Aortic valve area, cm ² /m ² [IQR]	0.4 [0.3–0.5]	0.7 [0.6–0.8]	0.43 [0.3–0.49]	0.16
Moderate or severe MR, n (%)	36 (40)	23 (49)	13 (30)	0.09
Serum creatinine, mg/dl [IQR]	1.19 [1–1.5]	1.22 [1.0–1.5]	1.14 [1–1.5]	0.8
Hemoglobin, g/dl [IQR]	12.5 [11.4–13.6]	12.6 [11–13.6]	12.4 [11.5–13.6]	0.84
Procedural and post-procedural data				
General anaesthesia, n (%)	5 (56)	3 (6)	2 (5)	1
Other than femoral access, n (%)	0 (0)	0 (0)	0 (0)	1
Self-expandable prosthesis, n (%)	85 (93)	42 (89)	43 (98)	0.21
Delivery system profile >16 French, n (%)	47 (52)	24 (51)	23 (52)	1
Predilation, n (%)	52 (57)	21 (45)	31 (71)	0.02
Postdilation, n (%)	32 (35)	12 (26)	20 (45)	0.052
Closure device, n (%)	100 (100)	47 (100)	44 (100)	1
Number of closure devices >2, n (%)	11 (12)	9 (19)	2 (5)	0.051
Successful closure, n (%)	86 (95)	43 (92)	43 (98)	0.36
ASARVI ≥3, n (%)	3 (6)	3 (6.4)	0 (0)	0.24

Need for peripheral angioplasty, n (%)	12 (13)	7 (15)	5 (11)	0.76
UFH, IU × 10 ³ [IQR]	7 [6-8]	7 [6-8]	7 [6-8]	0.55
UFH/kg, IU [IQR]	100 [86-111]	100 [87-117]	100 [86-109]	0.69
LVEF, % [IQR]	60 [55-65]	60 [55-65]	60 [52-65]	0.64
Mean AV pressure gradient, mmHg [IQR]	8 [6-10]	8.5 [5.8-11]	8 [6-10]	0.65
Aortic valve area, cm ² /m ² [IQR]	1.0 [1.0-1.02]	1.9 [1.7-2]	1.0 [1.0-1.0]	0.22
Serum creatinine, mg/dl [IQR]	1.26 [1-1.5]	1.27 [1-1.5]	1.2 [1-1.6]	0.95
Hemoglobin, g/dl [IQR]	9.8 [8.8-10.9]	9.8 [8.8-11.1]	9.8 [8.8-10.9]	0.76
Protamine sulfate				
Randomized to protamine, n (%)	47 (52)	–	–	–
Received protamine, n (%)	47 (52)	–	–	–
Protamine dose, mg [IQR]	–	35 [25-50]	–	–
Protamine dose per 100 IU of UFH, mg [IQR]	–	0.5 [0.4-0.6]	–	–
Endpoints				
30-day all-cause mortality, n (%)	4 (4)	3 (6)	1 (2)	0.62
Life threatening bleeding, n (%)	8 (9)	4 (9)	4 (9)	1
Major bleeding, n (%)	17 (19)	6 (13)	11 (25)	0.18
Minor bleeding, n (%)	6 (8)	4 (9)	2 (5)	0.68
Need for transfusion, n (%)	21 (23)	10 (21)	11 (25)	0.8
TIA, n (%)	2 (2)	0	2 (5)	0.23
Disabling stroke, n (%)	0 (0)	0 (0)	0 (0)	1
Need for permanent pacemaker, n (%)	22 (24)	11 (23)	11 (25)	1

Moderate or severe PVL, n (%)	14 (15)	6 (13)	8 (18)	0.57
Length of stay, days [IQR]	8 [6–14]	7 [6–15]	9 [6–14]	0.26
Any bleeding, n (%)	31 (34)	14 (30)	17 (39)	0.39
Major + life threatening bleeding, n (%)	25 (28)	10 (21)	15 (34)	0.24
Major + minor bleeding, n (%)	23 (25)	10 (21)	13 (30)	0.47

Abbreviations: AR, aortic regurgitation; ASARVI, access-site or access-related vascular injury; AV, aortic valve; BMI, body mass index; BSA, body surface area; COPD, chronic obstructive pulmonary disease; GFR, glomerular filtration rate; IQR, interquartile range; LVEF, left ventricle ejection fraction; MR, mitral regurgitation; NYHA, New York Heart Association; PS, protamine sulfate; TIA, transient ischemic attack; UFH, unfractionated heparin

Table S2. Per-protocol analysis. Univariable logistic regression analysis of the composite of VARC-defined major and life-threatening bleeding occurrence

	Univariate		
	OR	CI	P-value
Demographics			
Female gender	1.9	0.73–4.9	0.19
Age per 1 year	0.99	0.93–1.1	0.86
Baseline characteristics			
BMI per kg/m ²	0.99	0.88–1.1	0.88
Hypertension	0.87	0.21–3.7	0.85
Diabetes	0.57	0.21–1.5	0.25
GFR <30 ml/min	2.9	0.68– 12.86	0.15
History of bleeding	0.63	0.12–3.2	0.58
History of stroke / TIA	1.15	0.27–4.8	0.9
Oral anticoagulation	1.1	0.44–2.8	0.83
Serum creatinine per 1 mg/dl	1.95	0.61–6.2	0.26
Hemoglobin per 1 g/dl	1.13	0.87– 1.46	0.37
Procedural data			
General anaesthesia	3.3	0.28– 40.2	0.34
Delivery system profile >16 French	0.82	0.33–2.1	0.67
Number of closure devices >2	1.61	0.43–6	0.48
Successful closure	0.23	0.36–1.5	0.12
ASARVI ≥3	5.6	0.49–65	0.17
Need for peripheral angioplasty	0.86	0.2–3.5	0.84
UFH/kg per 1 IU	0.99	0.97–1	0.44

Randomized to protamine	0.52	0.2–1.3	0.17
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Abbreviations: AR, aortic regurgitation; ASARVI, access-site or access-related vascular injury; AV, aortic valve; BMI, body mass index; BSA, body surface area; CI, confidence intervals; COPD, chronic obstructive pulmonary disease; GFR, glomerular filtration rate; LVEF, left ventricle ejection fraction; MR, mitral regurgitation; NYHA, New York Heart Association; OR, odds ratio; PS, protamine sulfate; TIA, transient ischemic attack; UFH, unfractionated heparin

Table S3. Per-protocol analysis. Impact of protamine sulfate administration on study endpoints occurrence

	OR	CI	P-value
30-day all-cause mortality, n (%)	2.9	0.29–29	0.36
Life threatening bleeding, n (%)	0.93	0.22–3.9	0.9
Major bleeding, n (%)	0.44	0.15–1.3	0.14
Minor bleeding, n (%)	1.95	0.34–11	0.45
Need for transfusion, n (%)	0.81	0.3–2.2	0.67
TIA, n (%)	–	–	–
Disabling stroke, n (%)	–	–	–
Any bleeding, n (%)	0.67	0.28–1.6	0.37
Major + life threatening bleeding, n (%)	0.52	0.2–1.3	0.17
Major + minor bleeding, n (%)	0.64	0.25–1.67	0.37

*at 48 hours

Abbreviations: CI, confidence interval; OR, odds ratio; TIA, transient ischemic attack