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TITLE: Transcatheter Aortic Valve Implantation for Severe Aortic Stenosis in the Australian Regional Population

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TITLE

Transcatheter Aortic Valve Implantation for Severe Aortic Stenosis in the Australian Regional Population

ABSTRACT

Objective: To compare clinical and functional outcomes of regional and urban patients after transcatheter aortic valve implantation (TAVI) for severe aortic stenosis (AS).

Methods: Data was collected at patient follow up post TAVI at 30 days and 12 months. Patients were stratified by residential postcodes into remoteness areas using the Australian Statistical Geography Standard (ASGS).

Design: Retrospective cohort study.

Setting: Single-centre tertiary referral hospital.

Participants: Patients undergoing TAVI (n=142) from 2009 to 2018 were analysed, with 77 patients (54.2%) residing in regional Victoria and New South Wales.

Main outcome measures: Procedural success, adverse event rates, readmission rates, mortality rates, loss to follow-up and functional improvement.

Results: Patients residing in regional areas had a lower mean age (81.8 vs 83.7 years; P=0.034) and proportion of stage 4/5 chronic kidney disease (1.3% vs 9.2%; P=0.030)

compared to urban patients. Procedural characteristics and immediate post-procedural outcomes were similar between both groups. There was no statistically significant difference in mortality, readmission rates or loss to follow-up between the two cohorts. Regional patients demonstrated poorer rates of functional improvement at 30 days (50.7% vs 67.7%; P=0.040), however this difference was not sustained at 12 months (79.2% vs 71.0%; P=0.489). Frailty (adjusted OR= 0.174; P=0.033) was demonstrated to be an independent predictor of poor 30-day functional improvement.

Conclusion: Regional patients treated with TAVI for severe AS have non-inferior 30-day and 12-months outcomes when compared to urban patients. Frailty is a predictor of poor functional improvement post TAVI.

KEYWORDS

Cardiovascular medicine; therapeutics; rural population health; health systems; models of regional service delivery;

What is already known on this subject:

- Historically patients in regional Australia have poorer cardiovascular outcomes compared to those in urban areas.
- Transcatheter aortic valve implantation is the gold-standard intervention for severe aortic stenosis in symptomatic high-risk and inoperable patients.
- The current literature examines clinical and functional outcome data in primarily urban patients.

What this study adds:

- This study demonstrates that regional patients have similar complication rates and mortality to their urban counterparts, thus filling a gap in the literature about whether patients from non-urban areas are compromised by the reduced access to complex cardiovascular services, primarily delivered in a tertiary setting.

- This study identifies frailty as an independent predictor of poorer short-term functional outcomes.

Introduction

Australians living in regional and remote areas have inferior health outcomes compared to their urban counterparts[1]. Australian regional and rural health services have limited access to invasive therapies for acute coronary syndromes[2,3], and patients require lengthy transfers to tertiary referral centres, which may delay definitive treatment[2-5]. Non-urban patients are also less likely to have a regular general practitioner affecting referral patterns, specialist access and continuity of care[6].

Severe aortic stenosis (AS) is the most common type of valvular heart disease in the developed world and has a rising prevalence due to an increasingly elderly population[7]. Early referral for aortic valve intervention is recommended once symptoms of heart failure, syncope and chest pain occur as morbidity and mortality rates are high without treatment.

Transcatheter aortic valve implantation (TAVI) is a minimally invasive endovascular procedure that is superior to surgical aortic valve replacement (SAVR) for the treatment of severe AS for inoperable and high-risk patients[8-10]. TAVI involves delivery of a bioprosthetic aortic valve into the aortic annulus via a retrograde approach from the aorta (Figure 1). The majority of cases are performed via the femoral artery, however subclavian, direct aortic and transapical approaches can be used. Patients do not require cardiopulmonary bypass or a sternotomy, and can be discharged as early as day one post procedure[11].

In 2017, the use of TAVI was approved by the Australian Government for the treatment of severe AS, with the number of procedures expected to rise up to 10 times in the future[11]. TAVI is non-inferior to SAVR in individuals with intermediate-risk severe AS[12].

Risk factors and predictors of mortality have been well-established in the literature, however there is no Australian data that identifies if a disparity exists between regional and remote patients compared to urban patients in the treatment of severe AS.

The TAVI recruitment service for regional Australians at St. Vincent's Hospital consists of outreach clinics performed in regional centres by St Vincent's cardiologists visiting a designated area. The main sites include Sale, Echuca, Wodonga, Shepparton, Bairnsdale, Swan Hill and Mallacoota. This is complemented by telehealth consultations with patients, general practitioner education on the natural history and new treatment methods for aortic stenosis. These sessions emphasize the importance of early referral particularly in elderly and frail patients.

The aim of this study was to compare post procedural and clinical outcomes for regional versus urban patients undergoing TAVI for severe AS.

Methods

Patient population and study design

This single-centre retrospective, observational study analysed 142 consecutive patients with severe symptomatic AS undergoing TAVI between 2009 and 2018.

Patient selection

After presenting with symptoms of dyspnoea, syncope or chest pain, patients are referred by general practitioners to cardiologists affiliated to the tertiary hospital. This was either via private outreach clinics in regional centres of population 10,000 persons or greater within Victoria and New South Wales, or directly as an inter-hospital transfer.

Upon diagnosis of aortic stenosis, the decision for conservative, endovascular or surgical intervention is made in consultation with the multidisciplinary Heart team, consisting of interventional and non-interventional cardiologists, cardiac surgeons, nurses, allied health staff and cardiology imaging specialists. Patients received a TAVI if they were diagnosed with severe symptomatic AS (mean aortic valve gradient ≥ 40mmHg or aortic valve area <1.0cm^2) and were precluded from SAVR due to intermediate, high or inoperable perioperative risk as determined by the Heart Team.

Definitions and data collection

Patients were then stratified by residential postcodes into remoteness areas using the Australian Statistical Geography Standard (ASGS), a measure used by the Australian Bureau of Statistics to geographically classify Australians by their access to services. A total of 65 patients resided in a geographic location identified as within the remoteness area 'Major Cities of Australia' (Urban), 59 patients within 'Inner Regional Australia' and 18 patients within 'Outer Regional Australia'. All of the patients enrolled lived in Victoria or New South Wales, with 2 patients residing greater than 500km away in an outer regional area. There were no patients enrolled from remoteness areas corresponding to 'Remote Australia' or 'Very Remote Australia'. 'Regional' hereafter refers to the cohort of Australians living within Inner Regional and Outer Regional Australia remoteness areas.

Primary outcome measures included procedural success, major adverse events, mortality, functional improvement, readmission rates and loss to follow-up. Major adverse events were defined as any peri-procedural myocardial infarction, stroke or major vascular complication. Functional improvement refers to a reduction in New York Heart Association (NYHA) Functional Classification Class post-procedurally. Frailty is defined using the Rockwood Clinical Frailty Scale[13], with a score of greater than or equal to 5 identifying patients who were 'frail'.

Patients were followed up 30 days and 12 months post-operatively, to assess clinical and echocardiographic improvement in aortic stenosis, and to monitor for any post-operative

complications. The study protocol was approved by the local human research ethics committee (Ethics ID: QA 061/17A).

Statistical analysis

Descriptive statistics of regional and urban patients were tabulated by demographic, comorbidities, and pre-operative and post-operative biochemical, echocardiographic and functional parameters. Categorical outcomes were compared using $\chi 2$ analysis, and continuous outcomes by Student's t-test or the nonparametric Wilcoxon rank-sum test. A p-value < 0.05 was considered statistically significant. Odds ratios were initially calculated using logistic regression to examine the relationship between remoteness area and clinical outcomes, and then adjusted for demographics and other clinically relevant variables. All statistical analyses were performed using the STATA/SE 14.1 software (StataCorp LP, College Station, Texas, USA).

Results

Baseline characteristics

A total of 142 patients underwent TAVI. Routes of access included transfemoral (n=127), transapical (n=7), trans-subclavian (n=5), and direct aortic (n=2) alternative approach. The mean age was 82.7 ± 0.9 years, with 54.2% being female. Risk prediction scores used in cardiac surgery were calculated including the EuroSCORE II (mean 8.0% ± 1.4%), and the Society of Thoracic Surgeons (STS) score (mean = 3.4%). Comorbidities amongst the patient population included ischaemic heart disease (58.4%), atrial fibrillation (27.7%), peripheral vascular disease (20.6%), diabetes mellitus (27.5%), and hypertension (83.1%). Baseline characteristics are shown in Table 1.

Patients residing in urban areas had a greater mean age and a higher prevalence of chronic kidney disease compared to regional patients. This translated to urban patients having higher Society of Thoracic Surgeons (STS) risk prediction score (4.3% to 2.8%; P=0.001). Regional patients had numerically higher rates of diabetes however this was not statistically significant. Urban patients had a greater proportion of peripheral arterial

disease, advanced heart failure symptoms NYHA III-IV, and prior balloon aortic valvuloplasty for symptom relief.

Early outcomes

Immediate post-procedural outcomes are listed in Table 1. Procedural success was observed in 141 patients, with only one operative morality due to acute severe aortic regurgitation. Overall there was no difference in major vascular complications, stroke, acute kidney injury, decompensated heart failure and permanent pacemaker insertion between both groups. A comparison of outcomes at 30-day and 12-month follow-up between urban and regional patients is shown in Table 2. Interestingly, multivariate analysis at 30-days demonstrated that higher a EuroSCORE operative risk calculation and frailty were predictors of patients who would not demonstrate functional improvement post-TAVI (Table 3).

Late outcomes

A greater, though non-significant, proportion of urban patients were lost to follow-up at 12 months. Urban patients demonstrated an improvement in NYHA Functional Class 30 days post-procedurally compared to Regional patients, however there was no statistically significant difference in functional improvement at 12 months. Additionally, there was no difference in haemodynamics on transthoracic echocardiography (including aortic valve area increase, and reduction in mean aortic valve gradient) post procedure between both groups.

Discussion

No previous literature has examined the outcomes of Australian regional patients undergoing TAVI for severe AS. This study demonstrates no difference in procedural success, 30-day or 12-month mortality rates between regional and urban patients. The 30-day (3.9%) and 12-month (5.2%) all-cause mortality rate is consistent with the current literature[9], reflecting best practice in terms of patient selection and procedural success.

The difference in prevalence of advanced chronic kidney disease between urban and regional patients may partially be explained by the older patient population, although possible preference for palliative therapy rather than renal replacement therapy for regional patients with end-stage kidney disease is a possible contributing factor[14].

Whilst regional patients had poorer functional improvement at 30 days on bivariate analysis, this was non-significant after controlling for demographics and outcome parameters. This suggests that increased surgical risk and frailty were the major variables to explain the disparity in improvement, rather than remoteness.

One interesting observation of this study is the higher rate of patient follow up in the regional group compared to the urban patients, despite data suggesting non-urban patients are less likely to have a general practitioner than urban counterparts[6].

Previous international work has demonstrated significant heterogeneity in the treatment of aortic stenosis amongst different regions[15]. For example, one United States analysis found regional patients with severe AS were less likely to be offered aortic valve intervention and had higher rates of hospitalisation for heart failure attributable to the disease[16]. Dedicated and focused regional systems of care in aortic valve intervention has demonstrated improvements in outcomes and shorter length of stay[17]. The greatest strength of this outreach service is the identification of regional patients who would benefit from therapy at an early stage to allow for a favorable outcome equal to that of urban patients. Our study highlights the importance that regional Australian patients are not denied aortic valve intervention on the basis of geographical restriction[11]. It also highlights the framework required to run a successful TAVI program and service regional areas of need.

Continuity of care in the primary care setting is essential to ensure that patients have their post-procedural recovery carefully monitored, and adverse events identified in a timely manner in order to prevent complications that require hospital readmission. Our data demonstrates that regional status is not associated with poorer post-operative

complication and readmission rates. Well fostered patient-clinician relationships and prompt follow-up post-procedure is a potential reason for the findings, as every patient that underwent TAVI had a regular general practitioner.

Frailty is an increasingly studied geriatric syndrome common in cardiovascular disease populations, characterised by vulnerability due to age related decreases in physiological reserve[18]. This study found that frailty was associated with a poor short-term functional improvement post TAVI when using the Rockwood Clinical Frailty Scale. Previous literature has used frailty measures such as the Duke Activity Status Index[19] to assess functional improvement after aortic valve intervention. The Rockwood Clinical Frailty Scale is a tool that has been explored in combined risk models to predict late mortality[20-22], however this is the first study demonstrate the utility to predict changes in functional status in patients post-TAVI. Furthermore, the role of the primary care physician in highlighting and advocating the importance of cardiac rehabilitation after TAVI in frail patients is crucial, as this has been shown to improve functional capacity and quality of life[22]. In addition, optimisation of diet and exercise pre-operatively may be of benefit, improve resilience of the individual against physiologic stressors[23], thereby improving recovery time after surgery.

Our study had a number of important limitations to be noted. Prompt referral for further evaluation of aortic stenosis in a tertiary centre requires access to primary care, thus regional patients may have demonstrated noninferior outcomes due to selection bias. Another caveat of our study is the small patient population, which may have obscured differences in functional improvement and adverse events conferred by remoteness area.

Regional patients had a slightly lower risk prediction STS score, which may have improved post-procedural outcomes and obscured any significant difference in outcome conferred by remoteness area. Cardiac rehabilitation data was not included as part of our study. Participation rates in these programs may provide an explanation for the equality of functional outcomes in these two groups long term. Finally, there were no patients from remote or very remote Australia in our study, mainly due to the majority of referrals

from Victoria a state with relatively high population density which has a small remote population. This does limit the generalisation of these results to a remote Australian population, although this could be a foundation for future analysis.

In conclusion, despite previous literature demonstrating inferior cardiovascular outcomes for non-urban patients, this analysis demonstrates regional patients have non-inferior 30-day and 12-month outcomes post TAVI for the treatment of severe symptomatic AS, when compared to urban patients. Frailty is a predictor of poor functional improvement post TAVI, regardless of geographical location.

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Figure 1 Legend

Figure 1 - Successful Transfemoral TAVI Insertion: A - Pigtail catheter for contrast aortography in the ascending aorta, B - Balloon Expandable TAVI bioprosthesis well seated in the aortic annulus, C - Temporary pacing wire used for valve deployment and if bradyarrhythmia is experienced post procedure, D - Left ventricle

Table 1: Demographic, clinical, echocardiographic, procedural characteristics and post-procedural outcomes according to remoteness area of patients.

		Total (n=142)	Urban (n=65)	Rural (n=77)
Demographics				
	Age, years	82.7 ± 5.4	83.7 ± 5.7	81.8 ± 5.1
	Female, n	77 (54.2)	32 (49.2)	45 (58.4)
Clinical characteristics				
	BMI, kg/m²	27.8 ± 5.0	27.7 ± 5.1	27.8 ± 4.9
	CFS ≥ 5, n	65/113 (57.5)	31/54 (57.4)	34/59 (57.6)
	EuroSCORE II, %	5.3 [2.3-10.9]	5.6 [2.8-12.6]	4.8 [2.0-9.0]
	STS score, %	3.4 [2.6-5.3]	4.3 [2.9-6.6]	2.8 [2.2-5.1]
	Hypertension, n	118 (83.1)	55 (84.6)	63 (81.8)
	Diabetes, n	39 (27.5)	13 (20.0)	26 (33.8)
	Ischaemic heart disease, n	83 (58.4)	38 (58.5)	45 (58.4)
	Peripheral arterial disease, n	26 (20.6)	14 (23.3)	12 (18.2)
	Previous stroke, n	10 (7.8)	4 (6.6)	6 (8.8)
	Atrial fibrillation, n	39 (27.7)	18 (28.1)	21 (27.3)
	CKD Stage 4 or 5, n	7 (4.9)	6 (9.2)	1 (1.3)
	NYHA Functional Class III or IV, n	53 (39.3)	29 (45.3)	24 (33.8)
	PPM, n	22 (15.5)	13 (20.0)	9 (11.7)
	Previous balloon aortic valvuloplasty, n	30 (21.1)	18 (27.7)	12 (15.6)
Echocardiographic parameters				
	AV area, cm²	0.65 [0.51-0.80]	0.62 [0.55-0.81]	0.70 [0.50-0.79]
	Mean AV gradient, mmHg	48 [41-60]	47 [41-59]	49 [43-60]
	Peak AV gradient, mmHg	79 [67-99]	75.5 [65.5-95]	80 [68.9-96]
	LVEF, %	60 [55-65]	60 [55-65]	61 [55-65]
	RVSP, %	41 [34-50]	43 [36-50]	39 [34-51]
Procedural characteristics				
	Transfemoral, n	127 (90.0)	59 (90.8)	68 (89.4)
	Transapical, n	7 (5.0)	4 (6.2)	3 (4.0)
	Subclavian, n	5 (3.6)	1 (1.5)	4 (5.3)
	Transaortic, n	2 (1.4)	1 (1.5)	1 (1.3)
	Balloon-expanding valves, n	74 (54.4)	36 (57.1)	38 (52.1)
	Self-expanding valves, n	62 (45.6)	27 (42.9)	35 (48.0)
	Valve size ≥ 29mm, n	53 (37.3)	20 (30.8)	33 (42.9)
Immediate post-procedural outcomes				
	Procedural success, n	141 (99.3)	65 (100)	76 (98.7)
	Moderate-severe AR grade, n	16 (11.3)	8 (12.3)	8 (10.4)
	Bleeding complications, n	41 (29.7)	17 (27.0)	24 (32.0)
	Major vascular complications, n	10 (7.1)	4 (6.2)	6 (8.0)
	Cardiac tamponade, n	3 (2.2)	1 (1.6)	2 (2.7)
	Stroke, n	4 (2.9)	1 (1.6)	3 (4.0)
	ADHF, n	17 (12.5)	7 (11.2)	10 (13.5)
	AKI, n	27 (19.0)	11 (16.9)	16 (20.8)
	LBBB, n	22 (15.7)	9 (13.9)	13 (17.3)
	PPM insertion, n	12 (17.6)	13 (20.0)	12 (15.6)
	Hospital length of stay, days	7 [5-11]	8 [5-11]	7 [5-11]
	ICU length of stay ≥ 2 days, n	7 (5.4)	4 (6.6)	3 (4.4)

Values are n (%), median [interquartile range], or mean ± SD.
BMI= Body Mass Index; CFS= Clinical Frailty Scale; STS score= Society of Thoracic Surgeons score; CKD= Chronic Kidney Disease; NYHA= New York Heart Association; PPM= Permanent Pacemaker; AV= Aortic Valve; LVEF= Left Ventricular Ejection Fraction; RVSP= Right Ventricular Systolic Pressure; CVA= Cerebrovascular Accident; ADHF= Acute Decompensated Heart Failure; AKI= Acute Kidney Injury; LBBB= Left Bundle Branch Block.

Table 2: Follow-up outcomes at 30 days and 12 months

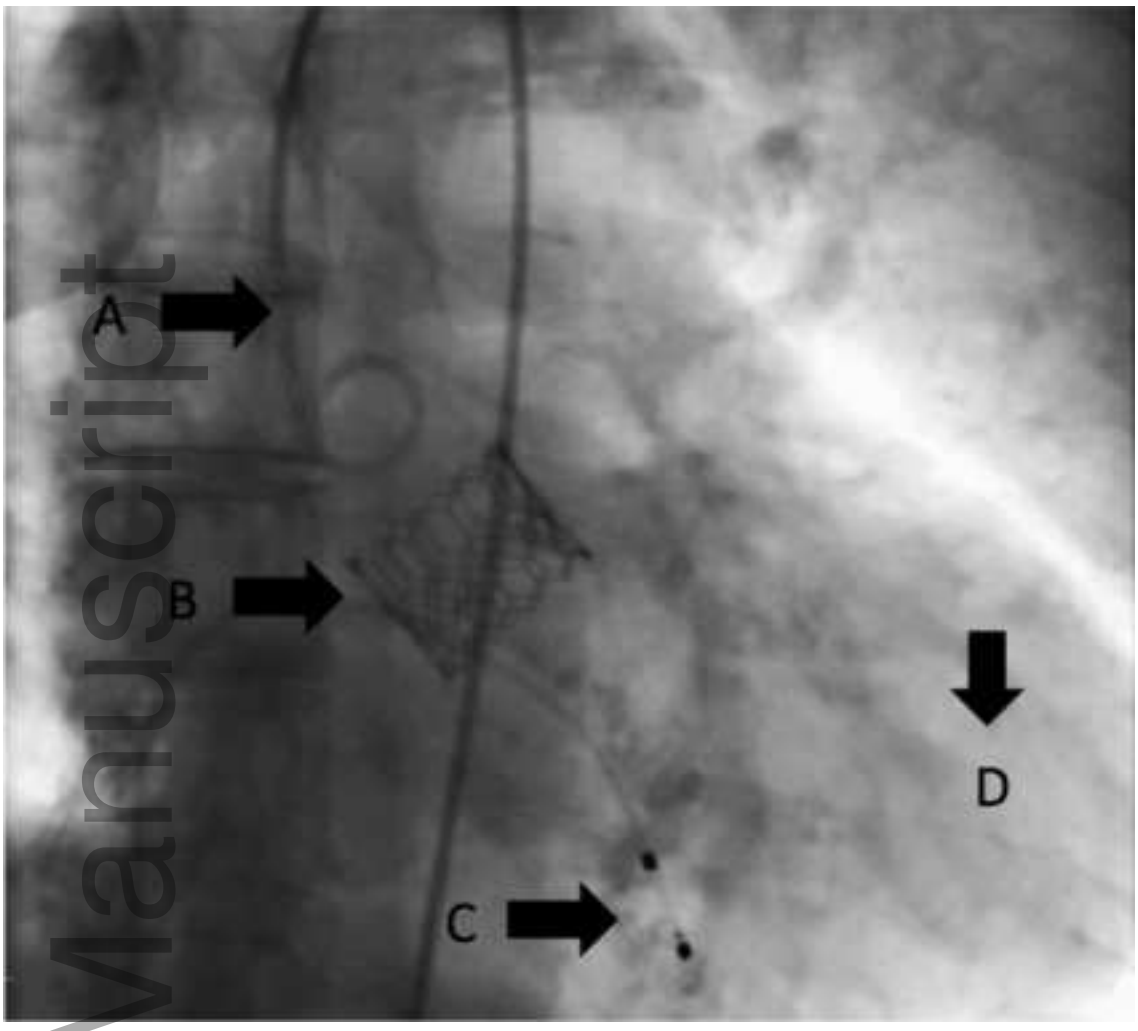
		All (n=142)	Urban (n=65)	Rural (n=77)	p-value
30 day follow-up					
	Functional improvement †, %	58.5	67.7	50.7	**0.040**
	AV area improvement, cm^2	0.8 [0.5-1.0]	0.7 [0.47-1.0]	0.83 [0.6-0.97]	0.639
	Mean AV gradient improvement, mmHg	35 [30-48]	34 [29-48]	38 [30-47]	0.502
	Adverse event ††, %		15.9	13.7	0.721
	Readmission, %	15.3	17.0	13.7	0.651
	Mortality, %	2.1	0	3.9	0.108
	Lost to follow-up, %	0.7	0	1.4	0.354
12 month follow-up					
	Functional improvement, %	74.6	71.0	79.2	0.489
	AV area improvement, cm^2	0.74 [0.54-0.9]	0.7 [0.6-0.88]	0.9 [0.48-1]	0.736
	Mean AV gradient improvement, mmHg	37 [27.7-50]	33 [27-45]	38.6 [34-54]	0.073
	Adverse event, %		15.8	20	0.651
	Readmission, %	43.5	45.2	40.7	0.713
	Mortality, %	7.0	9.2	5.2	0.349
	Lost to follow up, %	9.3	11.3	7.3	0.468

Values are medians [interquartile range], or %.
† Functional improvement is defined as a decrease in NYHA Class post-procedurally.
†† Adverse event is defined as any myocardial infarct, stroke, new-onset atrial fibrillation, left bundle branch block, pulmonary embolus or gastrointestinal bleeding that occurred in the post-operative period on discharge.

Table 3: Bivariate and stepwise multivariate logistic regression model for predictors of functional improvement at 1 month follow-up.

	Bivariate analysis		Multivariate analysis	
	Unadjusted OR (95% CI)	**P-value**	**Adjusted† OR (95% CI)**	**P-value**
Age, years	0.992 (0.933-1.055)	0.805	0.976 (0.897-1.062)	0.573
Female	0.819 (0.420-1.595)	0.557	0.859 (0.290-2.540)	0.783
Rural patients	0.490 (0.247-0.972)	0.041	0.418 (0.157-1.112)	0.081
EuroSCORE II	0.978 (0.938-1.020)	0.305	0.802 (0.667-0.965)	0.019
Frailty	0.566 (0.250-1.279)	0.171	0.174 (0.035-0.869)	0.033††
eGFR, mL/min	0.991 (0.973-1.010)	0.338	0.980 (0.953-1.008)	0.159
Valve size ≥29mm	0.407 (0.203-0.814)	0.011	0.453 (0.164-1.250)	0.127
Major or life-threatening bleeding complications	0.455 (0.137-1.513)	0.199	1.351 (0.175-10.427)	0.773
Vascular complications	1.151 (0.547-2.421)	0.710	2.302 (0.757-7.001)	0.142

† Each variable has been adjusted for the effects of all others in the table.
†† Single interaction variable involving EuroSCORE II and Frailty (defined as Clinical Frailty Scale ≥ 5) was presented in the model, and corrected for (P=0.037).
CI= confidence interval; eGFR= estimated glomerular filtration rate.



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