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FASTTRACK CLINICAL RESEARCH
Interventional cardiology

Outcomes of transcatheter mitral valve replacement for degenerated bioprostheses, failed annuloplasty rings, and mitral annular calcification

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Aims We sought to evaluate the outcomes of transcatheter mitral valve replacement (TMVR) for patients with degenerated bioprostheses [valve-in-valve (ViV)], failed annuloplasty rings [valve-in-ring (ViR)], and severe mitral annular calcification [valve-in-mitral annular calcification (ViMAC)].

Methods and results From the TMVR multicentre registry, procedural and clinical outcomes of ViV, ViR, and ViMAC were compared according to Mitral Valve Academic Research Consortium (MVARC) criteria. A total of 521 patients with mean Society of Thoracic Surgeons score of 9.0 ± 7.0% underwent TMVR (322 patients with ViV, 141 with ViR, and 58 with ViMAC). Trans-septal access and the Sapien valves were used in 39.5% and 90.0%, respectively. Overall technical success was excellent at 87.1%. However, left ventricular outflow tract obstruction occurred more frequently after ViMAC compared with ViR and ViV (39.7% vs. 5.0% vs. 2.2%; $P < 0.001$), whereas second valve implantation was more frequent in ViR compared with ViMAC and ViV (12.1% vs. 5.2% vs. 2.5%; $P < 0.001$). Accordingly, technical success rate was higher after ViV compared with ViR and ViMAC (94.4% vs. 80.9% vs. 62.1%; $P < 0.001$). Compared with ViMAC and ViV groups, ViR group had more frequent post-procedural mitral regurgitation ≥moderate (18.4% vs. 13.8% vs. 5.6%; $P < 0.001$) and subsequent paravalvular leak closure (7.8% vs. 0.0% vs. 2.2%; $P = 0.006$). All-cause mortality was higher after ViMAC compared with ViR and ViV at 30 days (34.5% vs. 9.9% vs. 6.2%; log-rank $P < 0.001$) and 1 year (62.8% vs. 30.6% vs. 14.0%; log-rank $P < 0.001$). On multivariable analysis, patients with failed annuloplasty rings and severe MAC were at increased risk of mortality after TMVR [ViR vs. ViV, hazard ratio (HR) 1.99, 95% confidence interval (CI) 1.27–3.12; $P = 0.003$; ViMAC vs. ViV, HR 5.29, 95% CI 3.29–8.51; $P < 0.001$].

Conclusion The TMVR provided excellent outcomes for patients with degenerated bioprostheses despite high surgical risk. However, ViR and ViMAC were associated with higher rates of adverse events and mid-term mortality compared with ViV.

Keywords Mitral valve • Transcatheter valve implantation • Degenerated bioprostheses • Annuloplasty ring • Mitral annular calcification

Introduction

Mitral valve disease is the most common valvular disease in the developed countries and surgery is the gold standard treatment.[1,2] Due to a massive shift from mechanical to bioprosthetic valves with finite longevity, increasing numbers of patients are presenting with bioprosthetic mitral valve degeneration.[3] Recurrent mitral regurgitation (MR) is frequent after mitral valve repair, particularly in the setting of functional MR.[4] Mitral valve reoperation often entails high risk due to age, multiple comorbidities, and hostile anatomy. In addition, patients with severe mitral annular calcification (MAC) associated with mitral valve disease are considered as poor candidates for traditional surgery due to technical challenges and high perioperative mortality.[5]

Transcatheter mitral valve replacement (TMVR) is an emerging treatment for patients with severe mitral valve disease at high risk for conventional mitral valve surgery. Recent studies have demonstrated the efficacy and safety of TMVR for patients with degenerated bioprostheses, failed annuloplasty repair, and severe MAC.[6,7] Nevertheless, currently used devices were designed for the aortic position and TMVR requires invasive transapical or complex trans-septal approaches. Furthermore, the anatomical differences between mitral bioprosthetic valves, annuloplasty rings, and severely calcified mitral annulus lead to specific procedural challenges for each unique TMVR procedure. Identifying the predictors of adverse outcomes is essential as patients are selected and counselled regarding competing surgical and transcatheter options. In addition, the risk of bioprosthetic valve thrombosis is being increasingly recognized but limited data exists about thrombosis after TMVR. The lack of randomized trial data in this field highlights the importance of reporting outcomes from large-sample registries. Therefore, we created an international multicentre registry of TMVR to evaluate and compare TMVR associated procedural events and clinical outcomes.

Methods

Study design and patient population

The TMVR registry is an international, multicentre, observational study that enrolled consecutive patients undergoing TMVR for mitral degenerated bioprostheses [valve-in-valve (ViV)], failed annuloplasty rings [valve-

in-ring (ViR)], or severe MAC [valve-in-mitral annular calcification (ViMAC)]. The registry included 40 European and American centres and was initiated in November 2015. Patients were considered TMVR candidates if they had significant dysfunction (either stenosis, regurgitation, or both) of a bioprosthetic mitral valve, annuloplasty ring, or a calcified mitral annulus, with comorbid conditions that would preclude a conventional mitral valve surgery. The study was approved by the institutional review board of each institution when required; however, in some countries, for retrospective analysis of clinically acquired and anonymized data, the institutional review board waived the need for written patient informed consent.

Study devices and transcatheter mitral valve replacement procedures

Patients were selected for TMVR at the institutional level after discussions by the multidisciplinary heart team, and device type and access site were determined thereafter. Device size was selected based on a combination of the manufacture's reported diameter as well as multidetector row computed tomography and transoesophageal echocardiographic measurements.[8–10] The ViV software application was used to guide the proper device size selection (B.V. Valve in Valve Mitral app, http://www.ubqo.com/vivmitral). All TMVR procedures were conducted in accordance with local guidelines using standard techniques via trans-septal, transapical, or transatrial access. Balloon-expandable transcatheter valves [the Sapien, Sapien XT, Sapien 3 (Edwards Lifesciences, Irvine, CA, USA), and Melody (Medtronic, Minneapolis, MN)] or other transcatheter valves [Lotus (Boston Scientific, Natick, MA, USA) and Direct Flow (Direct Flow Medical Inc., Santa Rosa, CA, USA)] were implanted.[11–15] The sizes of transcatheter valves were categorized as previously described.[6]

Endpoints and definitions

The primary endpoints were all-cause mortality at 30 days and 1 year. Secondary endpoints were technical, device and procedural success, and other major clinical endpoints defined according to the Mitral Valve Academic Research Consortium (MVARC) criteria.[16] In the present study, we used modified criteria for significant mitral stenosis (MS) defined as a mean transmitral gradient ≥10 mmHg and/or an effective orifice area ≤1.0 cm^2 as previously described.[6] Bioprosthetic valve thrombosis was defined as valve dysfunction (mean transvalvular gradient ≥10 mmHg and/or restricted leaflet motion with echocardiography) secondary to thrombosis diagnosed on the basis of response to anticoagulation or surgical findings.

Data collection

Data collection included baseline clinical, echocardiographic and procedural characteristics, and clinical follow-up data, at pre-specified time points (1, 6, and 12 months and yearly thereafter). Follow-up was obtained by clinical visits and/or through telephone contacts. Referring cardiologists, general practitioners, and patients were contacted whenever necessary for further information. All data provided by each institution were anonymized and centrally collected, and all inconsistencies were resolved directly with local investigators.

Statistical analysis

Patients were stratified according to the type of TMVR procedures (ViV, ViR, or ViMAC). Dichotomous variables are presented as counts or percentages and compared using the χ^2 or Fisher exact test. Continuous variables are presented as mean with standard deviation. Comparisons of continuous variables among three groups were performed with the Analysis of Variance (ANOVA) or Kruskal–Wallis test as appropriate. Tukey test for multiple comparisons was used if statistical significance was achieved (see Supplementary material online, *Tables S1–S3*). Comparisons of continuous variables between two groups were performed using the Student's *t*-test or Mann–Whitney *U*-test. Cumulative rates of death, stroke, bleeding, major vascular complication, acute kidney injury, or valve thrombosis were calculated by using the Kaplan–Meier survival analysis, and the log-rank test was used for comparison across the groups. Univariable Cox regression models were used to evaluate potential predictors of all-cause mortality. Statistically significant variables with a *P*-value <0.10 by univariable analysis were included in the multivariable model. The final model was determined by backward elimination procedures with a threshold *P*-value <0.10. The proportional hazard assumption was confirmed by examination of log [-log (survival)] curves and by testing of partial (Schoenfeld) residuals, and no relevant violations were found. The estimated hazard ratio (HR) with 95% confidence interval (CI) was provided by the Cox model. All statistical analyses were performed using SPSS software (version 24.0, SPSS, Inc., Armonk, NY, USA). A two-sided *P*-value of <0.05 was considered to be statistically significant.

Results

Baseline characteristics

A total of 521 patients underwent TMVR across 40 participating centres between February 2009 and April 2018. Of the study population, 322 patients (61.8%) had TMVR for degenerated mitral bioprosthetic valves (ViV), 141 patients (27.1%) for failed annuloplasty rings (ViR), and 58 patients (11.1%) for degenerated mitral valve with severe MAC (ViMAC). The majority of patients were deemed at high risk for conventional surgery with a mean Society of Thoracic Surgeons (STS) score of 9.0% without significant difference across the three groups (ViV vs. ViR vs. ViMAC: 9.2 ± 7.2% vs. 8.1 ± 6.4% vs. 10.1 ± 6.9%; *P* = 0.12) (*Table 1*). However, baseline characteristics significantly differed across the three groups: The patients in ViMAC group were more likely to be female and have New York Heart Association functional Class IV heart failure symptoms and chronic pulmonary disease, whereas patients in ViR group were more likely to have prior coronary artery bypass graft surgery (CABG) and myocardial infarction with lower left ventricular ejection fraction (LVEF). The predominant mechanism of failure was MR in the ViR group but MS was the most frequent form of valve dysfunction in the ViMAC group.

Procedural data

Procedural details are summarized in *Table 2*. The majority of patients were treated via transapical access (59.5%) with the balloon-expandable Sapien valves (90.0%). The Sapien valves were more frequently used in the ViV group, whereas the large size device was more frequently used in the ViMAC group compared with ViV and ViR groups. Planned concomitant aortic valve replacement was performed in 20 patients (3.8%), more frequently with ViMAC compared with ViV and ViR (12.1% vs. 3.7% vs. 0.7%; *P* = 0.001). Balloon pre- and post-dilatation were more frequently performed in the ViMAC group compared with ViV and ViR groups. Contrast dose was the larger in the ViMAC group compared with the other two groups (64.8 ± 55.7 mL vs. 45.9 ± 66.5 mL vs. 36.5 ± 51.5 mL; *P* = 0.01), whereas fluoroscopic time was similar across the three groups.

Procedural outcomes

Procedural and 30-day outcomes are summarized in *Table 3*. Procedural complications varied significantly between the three

Table 1 Baseline characteristics

	Overall (*n* = 521)	ViV (*n* = 322)	ViR (*n* = 141)	ViMAC (*n* = 58)	*P*-value
Age (years)	72.6 ± 11.9	72.6 ± 12.9	71.7 ± 9.7	74.7 ± 10.8	0.28
Female	282 (54.1)	189 (58.7)	52 (36.9)	41 (70.7)	<0.001[a,c]
NYHA functional Class III or IV	461 (88.5)	282 (87.6)	126 (89.4)	53 (91.4)	0.66
NYHA functional Class IV	167 (32.1)	104 (32.3)	36 (25.5)	27 (46.6)	0.015[b,c]
STS score (%)	9.0 ± 7.0	9.2 ± 7.2	8.1 ± 6.4	10.1 ± 6.9	0.12
Diabetes mellitus	124 (23.8)	75 (23.3)	30 (21.3)	19 (32.8)	0.21
Creatinine (mmol/L)	137 ± 114	130 ± 113	145 ± 104	158 ± 139	0.16
Hypertension	368 (70.6)	224 (69.6)	97 (68.8)	47 (81.0)	0.18
Peripheral vascular disease	59 (11.3)	37 (11.5)	15 (10.6)	7 (12.1)	0.95
Prior cerebrovascular accident	82 (15.7)	57 (17.7)	17 (12.1)	8 (13.8)	0.28
Chronic pulmonary disease	156 (29.9)	92 (28.6)	38 (27.0)	26 (44.8)	0.03[b,c]
Prior PCI	94 (18.0)	50 (15.5)	32 (22.7)	12 (20.7)	0.16
Prior CABG	173 (33.2)	93 (28.9)	69 (48.9)	11 (19.0)	<0.001[a,c]
Prior myocardial infarction	82 (15.7)	39 (12.1)	36 (25.5)	7 (12.1)	0.001[a,c]
Echocardiographic findings					
LVEF (%)	52.6 ± 13.7	55.3 ± 11.5	44.3 ± 15.7	57.7 ± 10.7	<0.001[a,c]
Mitral valve mean gradient (mmHg)	10.9 ± 5.9	12.1 ± 5.9	7.1 ± 4.8	11.8 ± 4.8	<0.001[a,c]
Mechanism of failure					
Regurgitation	238 (45.7)	118 (36.6)	109 (77.3)	11 (19.0)	<0.001[a,b,c]
Stenosis	173 (33.2)	131 (40.7)	9 (6.4)	33 (56.9)	
Combined	110 (21.1)	73 (22.7)	23 (16.3)	14 (24.1)	

CABG, coronary artery bypass graft surgery; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; STS, society of thoracic surgeons; ViMAC, valve in mitral annular calcification; ViR, valve in ring; ViV, valve in valve.
[a]$P < 0.05$ for ViV vs. ViR.
[b]$P < 0.05$ for ViV vs. ViMAC.
[c]$P < 0.05$ for ViR vs. ViMAC.

groups. Conversion to surgery and valve embolization were observed in 12 (2.3%) and nine patients overall (1.7%), more frequently after ViMAC compared with ViR and ViV. Left ventricular perforation was observed only after ViV (1.2%), whereas second valve implantation was more frequently performed in ViR group compared with ViMAC and ViV groups (12.1% vs. 5.2% vs. 2.5%; $P < 0.001$). Left ventricular outflow tract (LVOT) obstruction was observed in 37 patients (7.1%), with a significantly higher rate after ViMAC compared with ViR and ViV procedures (39.7% vs. 5.0% vs. 2.2%; $P < 0.001$). Technical success was achieved in 87.1% of the entire cohort, with a higher rate after ViV compared with ViR and ViMAC (94.4% vs. 80.9% vs. 62.1%; $P < 0.001$). Paravalvular leak closure was more frequently performed in the ViR group compared with ViV and ViMAC groups (7.8% vs. 2.2% vs. 0.0%; $P = 0.006$), whereas alcohol septal ablation was more frequently performed in the ViMAC group than ViV and ViR groups (12.1% vs. 0.6% vs. 0.7%; $P < 0.001$). There were no significant differences in atrial septal defect closure and surgical mitral valve replacement between the three groups.

Post-procedural LVEF remained lowest in the ViR group compared with ViV and ViMAC groups. Significant MS was only observed in seven patients (1.3%) of the entire cohort. Post-procedural MR ≥moderate was more frequently observed in the ViR group compared with ViMAC and ViV groups (18.4% vs. 13.8% vs. 5.6%; $P < 0.001$). Following the paravalvular leak closure, the rates of MR ≥moderate at 30 days remained higher in ViMAC and ViR groups than the ViV group (13.2% vs. 12.6% vs. 3.3%; $P < 0.001$) (see Supplementary material online, *Figure S1*). Device success was the highest in the ViV group followed by ViR and ViMAC groups (84.8% vs. 69.5% vs. 53.4%; $P < 0.001$).

Clinical outcomes

All-cause 30-day mortality was the highest in the ViMAC group followed by the ViR and ViV groups (34.5% vs. 9.9% vs. 6.2%; $P < 0.001$). There were no significant differences in stroke and major or extensive bleeding between the three groups. Life-threatening or fatal bleeding tended to be more frequent in the ViR group, whereas major vascular complication and Stage 2 or 3 acute kidney injury occurred more frequently in the ViMAC group. Procedural success was highest in the ViV group followed by the ViR and ViMAC groups (73.6% vs. 57.4% vs. 41.4%; $P < 0.001$). In general, there were no significant differences in procedural complications between trans-septal and transapical approaches with the exceptions of higher rates of atrial septal defect closure and alcohol septal ablation and lower rate of life-threatening or fatal bleeding with trans-septal access (see Supplementary material online, *Table S4*). Patients were divided into early experience and late experience groups according to the median number of TMVR procedures at each institution. Compared with the early experience group, the late experience group had lower rates of conversion to surgery, 30-day mortality, life-threatening or fatal

Table 2 Procedural data

	Overall ($n = 521$)	ViV ($n = 322$)	ViR ($n = 141$)	ViMAC ($n = 58$)	*P*-value
Access site					
Trans-septal access	206 (39.5)	125 (38.8)	50 (35.5)	31 (53.4)	0.09
Transapical access	310 (59.5)	193 (59.9)	91 (64.5)	26 (44.8)	
Transatrial access	5 (1.0)	4 (1.2)	0 (0.0)	1 (1.7)	
Device type					
Sapien valves	469 (90.0)	302 (93.8)	120 (85.1)	47 (81.0)	<0.001[a,b]
Sapien	27 (5.8)	20 (6.6)	7 (5.8)	0 (0.0)	0.004[b,c]
Sapien XT	154 (32.8)	108 (35.8)	40 (33.3)	6 (12.8)	
Sapien 3	288 (61.4)	174 (57.6)	73 (60.8)	41 (87.2)	
Lotus	30 (5.8)	12 (3.7)	9 (6.4)	9 (15.5)	<0.001[a,b]
Direct flow	18 (3.5)	4 (1.2)	12 (8.5)	2 (3.4)	
Melody	4 (0.8)	4 (1.2)	0 (0.0)	0 (0.0)	
Device size					
Small	48 (9.2)	28 (8.7)	18 (12.8)	2 (3.4)	0.03[a,c]
Medium	196 (37.6)	115 (35.7)	62 (44.0)	19 (32.8)	
Large	277 (53.2)	179 (55.6)	61 (43.3)	37 (63.8)	
Planned concomitant aortic valve replacement	20 (3.8)	12 (3.7)	1 (0.7)	7 (12.1)	0.001[b,c]
TAVR	16 (3.1)	8 (2.5)	1 (0.7)	7 (12.1)	0.001[b,c]
Surgery	4 (0.8)	4 (1.2)	0 (0.0)	0 (0.0)	0.58
Apical rail	20 (3.8)	10 (3.1)	7 (5.0)	3 (5.2)	0.54
Balloon pre-dilatation	49 (9.4)	35 (10.9)	5 (3.5)	9 (15.5)	0.01[a,c]
Balloon post-dilatation	45 (8.6)	12 (3.7)	22 (15.6)	11 (19.0)	<0.001[a,b]
Contrast dose (mL)	42.7 ± 57.2	36.5 ± 51.5	45.9 ± 66.5	64.8 ± 55.7	0.01[b]
Fluoroscopic time (min)	25.7 ± 24.1	24.0 ± 26.2	28.1 ± 20.1	29.0 ± 20.2	0.30

TAVR, transcatheter aortic valve replacement; ViMAC, valve in mitral annular calcification; ViR, valve in ring; ViV, valve in valve.
[a]$P < 0.05$ for ViV vs. ViR.
[b]$P < 0.05$ for ViV vs. ViMAC.
[c]$P < 0.05$ for ViR vs. ViMAC.

bleeding, and Stage 2 or 3 acute kidney injury, mainly driven by the improved outcomes of ViV with increased experience (see Supplementary material online, *Table S5* and *Figure S2A–C*).

Mid-term mortality

Over a median follow-up period of 160 days (interquartile range 60–420 days), a total of 117 patients died in the overall cohort (53 patients in the ViV group, 34 patients in the ViR group, and 30 patients in the ViMAC group). The 1-year all-cause and cardiovascular mortality were 23.5% and 20.2% in the entire cohort, respectively (*Figure 1*). The 1-year all-cause mortality rate was highest in the ViMAC group followed by ViR and ViV groups (62.8% vs. 30.6% vs. 14.0%; ViR vs. ViV; adjusted HR 1.99, 95% CI 1.27–3.12; $P = 0.003$; ViMAC vs. ViV; adjusted HR 5.29, 95% CI 3.29–8.51; $P < 0.001$) (*Figure 2A* and Supplementary material online, *Figure S3*). Landmark analysis showed higher late mortality (30–360 days) in the ViMAC group (43.2%) compared with the ViR (23.0%) and ViV groups (8.4%) (*Figure 2B*). Patients with post-procedural MR ≥moderate had significantly higher 1-year all-cause mortality compared with those with MR ≤mild (41.5% vs. 21.4%; log rank $P = 0.01$) (*Figure 3*). However, there was no significant difference in 1-year all-cause mortality between trans-septal and transapical approaches (see Supplementary material online, *Figure S4*). After adjustment with multivariable analysis, STS score, chronic pulmonary disease, pre-procedural status of mitral valve (ViV vs. ViR vs. ViMAC), and post-procedural MR ≥moderate were independently associated with all-cause mortality in the entire cohort (*Table 4*). For each TMVR procedure, factors associated with increased mortality were STS score and LVEF for ViV group, post-procedural MR ≥moderate for ViR group, STS score and prior CABG for ViMAC group (see Supplementary material online, *Tables S6–S8*).

Thrombosis and anticoagulation

Information regarding antithrombotic prophylaxis and valve thrombosis was available in 411 patients (78.9%). Among them, 295 patients (71.8%) received anticoagulation therapy and the remaining 116 (28.2%) patients received antiplatelet therapy after TMVR (see Supplementary material online, *Figure S5A*). During the entire follow-up, clinical thrombosis was observed in 10 patients after ViV (nine patients with stented porcine valves and one patient with a pericardial valve) and one patient after ViR but none after ViMAC. The timing of thrombosis varied significantly from within 24 h to 2 years after the index TMVR procedure (see Supplementary material online, *Figure S5B*). At 1-year follow-up, the cumulative incidence of thrombosis was significantly higher in patients without anticoagulation compared with those with anticoagulation (6.6% vs. 1.6%; log-rank $P = 0.019$) (*Figure 4*).

Table 3 Procedural and 30-day outcomes

	Overall ($n = 521$)	ViV ($n = 322$)	ViR ($n = 141$)	ViMAC ($n = 58$)	*P*-value
Procedural outcomes					
Conversion to surgery	12 (2.3)	3 (0.9)	4 (2.8)	5 (8.6)	0.004[d]
Valve embolization	9 (1.7)	3 (0.9)	2 (1.4)	4 (6.9)	0.01[d]
Left ventricular perforation	4 (0.8)	4 (1.2)	0 (0.0)	0 (0.0)	0.58
Need for second valve implantation	28 (5.4)	8 (2.5)	17 (12.1)	3 (5.2)	<0.001[c]
LVOT obstruction	37 (7.1)	7 (2.2)	7 (5.0)	23 (39.7)	<0.001[d,e]
Technical success	454 (87.1)	304 (94.4)	114 (80.9)	36 (62.1)	<0.001[c,d,e]
Re-intervention	73 (14.0)	35 (10.9)	25 (17.7)	13 (22.4)	0.02[c,d]
Paravalvular leak closure	18 (3.5)	7 (2.2)	11 (7.8)	0 (0.0)	0.006[c,e]
Atrial septal defect closure	36 (6.9)	23 (7.1)	7 (5.0)	6 (10.3)	0.38
Alcohol septal ablation	10 (1.9)	2 (0.6)	1 (0.7)	7 (12.1)	<0.001[d,e]
Mitral valve replacement	10 (1.9)	6 (1.9)	3 (2.1)	1 (1.7)	0.98
Surgery	8 (1.5)	4 (1.2)	3 (2.1)	1 (1.7)	0.77
TMVR	2 (0.4)	2 (0.6)	0 (0.0)	0 (0.0)	>0.99
Device success	402 (77.2)	273 (84.8)	98 (69.5)	31 (53.4)	<0.001[c,d,e]
Post-procedural echocardiographic findings					
LVEF (%)	51.4 ± 13.7	53.3 ± 12.5	44.4 ± 14.7	58.0 ± 11.5	<0.001[c,e]
Mean gradient (mmHg)	6.1 ± 2.9	5.9 ± 2.8	6.7 ± 3.1	5.4 ± 3.1	0.019[c,e]
Mean gradient ≥10 mmHg	43 (8.3)	23 (7.1)	16 (11.3)	4 (6.9)	0.29
Mitral valve area (cm^2)	2.2 ± 1.0	2.2 ± 1.2	2.0 ± 0.6	2.6 ± 1.1	0.10
Mitral stenosis[a]	7 (1.3)	3 (0.9)	4 (2.8)	0 (0.0)	0.24
Mitral regurgitation moderate or higher after procedure	52 (10.0)	18 (5.6)	26 (18.4)	8 (13.8)	<0.001[c,d]
Mitral regurgitation moderate or higher at 30 days[b]	31 (6.6)	10 (3.3)	16 (12.6)	5 (13.2)	<0.001[c,d]
30-Day outcomes					
All-cause mortality	54 (10.4)	20 (6.2)	14 (9.9)	20 (34.5)	<0.001[d,e]
Stroke	9 (1.9)	7 (2.3)	0 (0.0)	2 (3.9)	0.10
Bleeding					
Major or extensive	20 (4.2)	14 (4.6)	5 (3.9)	1 (1.8)	0.81
Life-threatening or fatal	18 (3.7)	7 (2.3)	9 (6.7)	2 (4.5)	0.07
Major vascular complication	14 (2.8)	5 (1.6)	5 (3.8)	4 (8.0)	0.019[d]
Acute kidney injury (Stage 2 or 3)	34 (7.0)	14 (4.6)	13 (9.7)	7 (15.3)	0.006[c,d]
Procedural success	343 (65.8)	237 (73.6)	81 (57.4)	24 (41.4)	<0.001[c,d,e]

LVOT, left ventricular outflow tract; TMVR, transcatheter mitral valve replacement; ViMAC, valve in mitral annular calcification; ViR, valve in ring; ViV, valve in valve.
[a]Defined as mean gradient ≥10 mmHg and mitral valve area ≤1.0 cm^2.
[b]Four hundred and sixty-seven patients survived at 30 days were included.
[c]$P < 0.05$ for ViV vs. ViR.
[d]$P < 0.05$ for ViV vs. ViMAC.
[e]$P < 0.05$ for ViR vs. ViMAC.

Discussion

The major findings of the present study are as follows: (i) TMVR provided excellent outcomes for patients with degenerated bioprosthetic valves but TMVR for failed annuloplasty rings and MAC were associated with frequent procedural complications; (ii) patients with failed annuloplasty rings and severe MAC were at increased risk of mortality after TMVR; and (iii) valve thrombosis was more frequently observed after TMVR in patients without anticoagulation compared with those with anticoagulation.

The present study is the largest TMVR registry published to date demonstrating procedural challenges and prognosis across different population. TMVR provided excellent outcomes for patients with degenerated bioprosthetic valves despite high surgical risk. Procedural complications were observed in less than 3% of procedures, consistent with the previous reports.[17] The 30-day mortality after mitral ViV in the present study (6.2%) was acceptable considering the higher in-hospital and 30-day mortality after redo mitral valve surgeries (9.2–12.6%) in previously published studies.[18–20] As the present large study is consistent with recent reports with comparable early and mid-term mortality, TMVR is an attractive option for patients with degenerated bioprosthetic mitral valves.

Transcatheter mitral valve replacement for patients with failed annuloplasty repair and severe MAC poses unique and serious procedural challenges, namely LVOT obstruction and post-procedural MR. Previous studies showed that LVOT obstruction occurred more frequently after ViMAC (7.4% to 17%) and ViR (13.3% to 20%) compared with ViV and was associated with increased 1-year

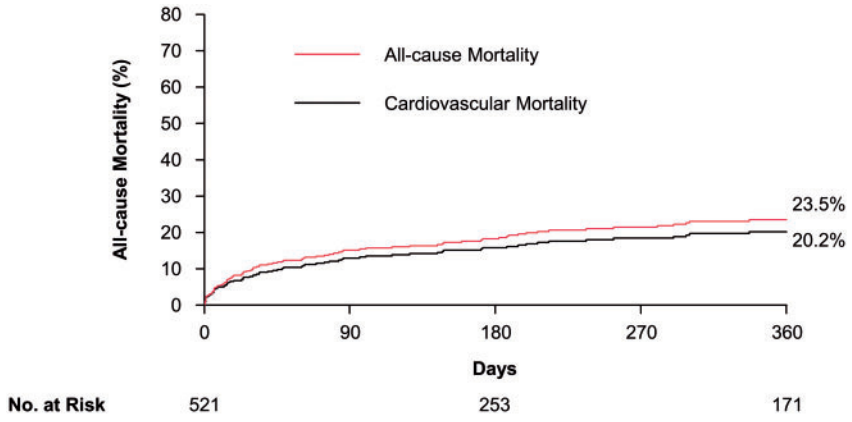

Figure 1 Cumulative incidences of all-cause and cardiovascular mortality in overall cohort. The cumulative incidences of all-cause (red line) and cardiovascular mortality (black line) of the overall cohort are shown.

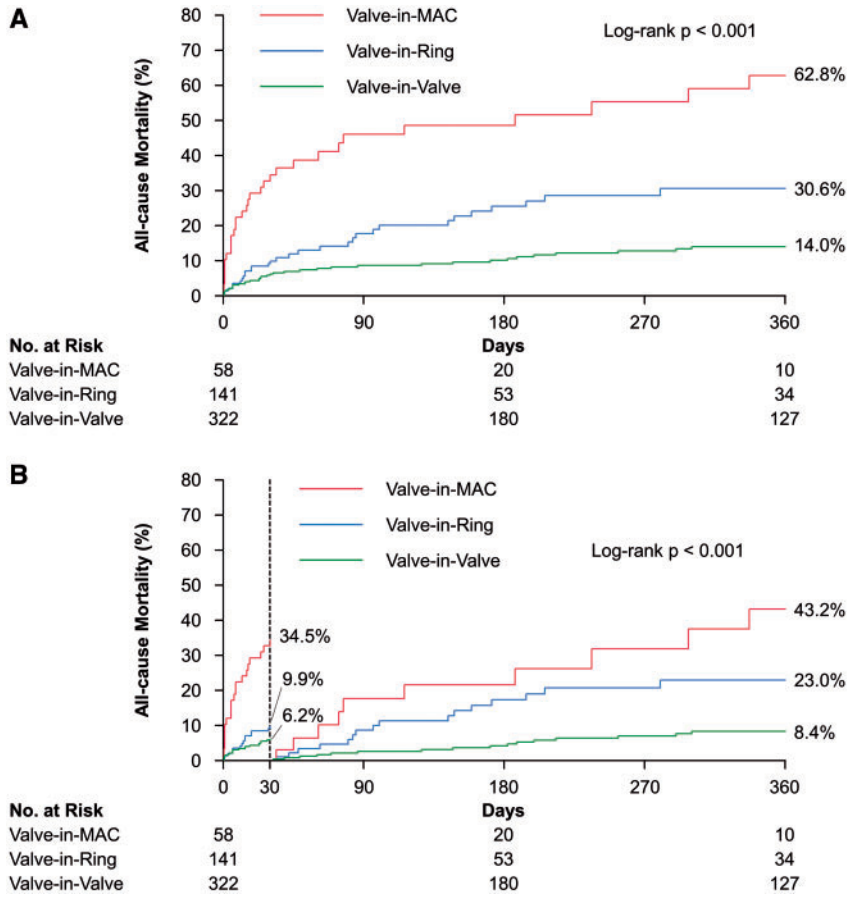

Figure 2 All-cause mortality according to transcatheter mitral valve replacement procedure. (*A*) The cumulative all-cause mortality rates of patients undergoing mitral valve-in-valve (green line), valve-in-ring (blue line), and valve-in-MAC (red line) are shown. (*B*) The cumulative all-cause mortality rates with landmark analyses (0–30 days and 30–360 days) showed increased early mortality (0–30 days) but also late mortality (30–360 days) after valve-in-MAC compared with valve-in-ring and valve-in-valve. MAC, mitral annular calcification.

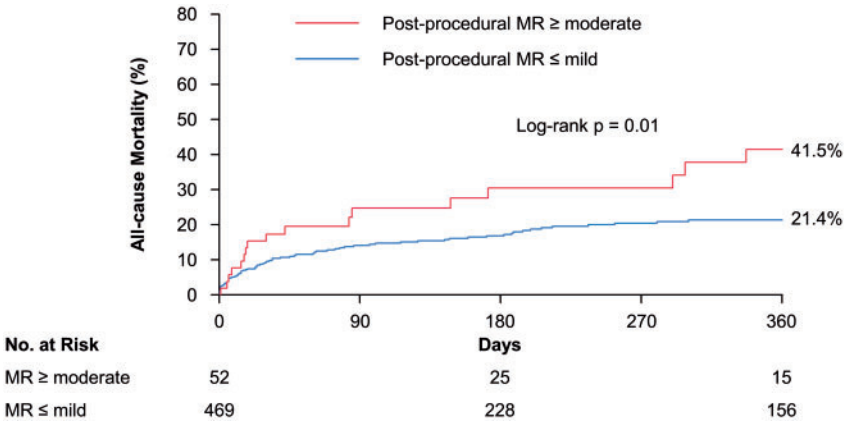

Figure 3 All-cause mortality according to post-procedural mitral regurgitation. The cumulative all-cause mortality rates in patients with moderate or greater post-procedural mitral regurgitation (red line) and those with none or mild post-procedural mitral regurgitation (blue line) are shown. MR, mitral regurgitation.

Table 4 Predictors of all-cause mortality

	Univariate model		Multivariate model	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Age	1.02 (1.00–1.04)	0.015		
Female	1.09 (0.75–1.58)	0.65		
NYHA functional Class IV	1.29 (0.63–2.67)	0.48		
STS score	1.04 (1.02–1.06)	0.001	1.02 (1.01–1.06)	0.006
Peripheral vascular disease	1.39 (0.83–2.32)	0.21		
Previous cerebrovascular accident	1.07 (0.66–1.76)	0.78		
Chronic pulmonary disease	1.80 (1.25–2.61)	0.002	1.54 (1.06–2.24)	0.025
Predominant mitral regurgitation at baseline	1.26 (0.88–1.81)	0.22		
LVEF per increase of 10%	0.92 (0.80–1.05)	0.21		
Prior CABG	0.99 (0.67–1.45)	0.95		
Prior myocardial infarction	1.02 (0.62–1.69)	0.93		
Transseptal access	1.12 (0.76–1.65)	0.58		
Pre-procedural mitral valve status				
Failed annuloplasty rings vs. degenerated bioprostheses	1.96 (1.27–3.02)	0.003	1.99 (1.27–3.12)	0.003
Severe MAC vs. degenerated bioprostheses	5.85 (3.68–9.29)	<0.001	5.29 (3.29–8.51)	<0.001
Need for second valve implantation	1.21 (0.56–2.59)	0.63		
LVOT obstruction	2.87 (1.66–4.96)	<0.001		
Post-procedural mitral regurgitation moderate or greater	2.00 (1.25–3.21)	0.004	1.72 (1.06–2.81)	0.029
Mean gradient 10 mmHg or more at post-procedure	1.30 (0.71–2.35)	0.40		

CABG, coronary artery bypass graft surgery; CI, confidence interval; HR, hazard ratio; LVEF, left ventricular ejection fraction; LVOT, left ventricular outflow tract; MAC, mitral annular calcification; NYHA, New York Heart Association; STS, society of thoracic surgeons.

mortality.[7,21,22] Therefore, identifying patients at high risk for LVOT obstruction is essential for successful ViMAC and ViR procedures. The incidence of LVOT obstruction was surprisingly high in the present study (39.7%), which may be attributable to the following: (i) inconsistent assessment of risk for LVOT obstruction with imaging modalities, particularly in the early experiences and (ii) variable definitions of LVOT obstruction between the studies. Left ventricular outflow tract obstruction was defined according to MVARC (increment in mean gradient ≥10 mmHg from baseline) in the present study but defined as LVOT obstruction with hemodynamic compromise in recently reported studies.[7,22] A comprehensive analysis of mitral valve and left ventricular anatomy to predict LVOT

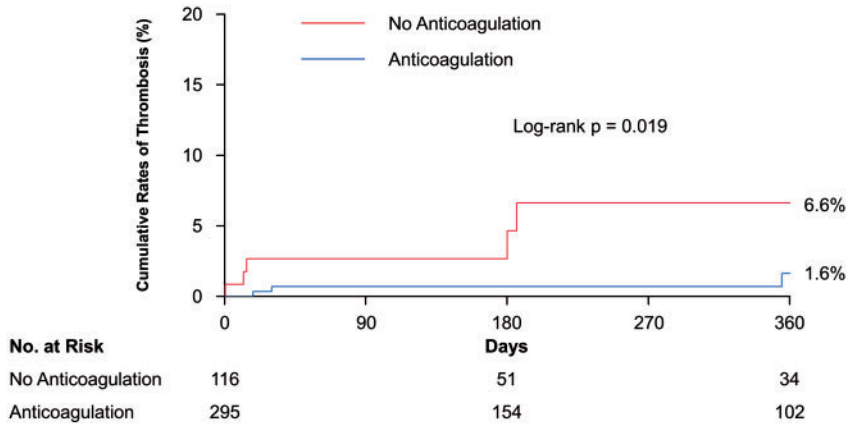

Figure 4 Incidences of valve thrombosis. The cumulative rates of valve thrombosis in patients with or without anticoagulation (blue and red lines, respectively) are shown.

obstruction is essential for optimal TMVR patient selection. Furthermore, prophylactic alcohol septal ablation and laceration of mitral anterior leaflet have recently emerges as option to prevent TMVR associated LVOT obstruction and promise to mitigate this important complications.[23,24]

The impact of significant residual MR on increased mortality and late adverse events has been widely recognized in patients undergoing surgical or transcatheter mitral valve repair.[25,26] The present study identified significant post-procedural MR as an independent predictor of increased mortality after TMVR. The rates of MR ≥moderate after ViR (18.4%) and ViMAC (13.8%) were suboptimal although post-procedural MR ≥Grade 3 (moderate to severe) was modest (4.2% and 1.7%, respectively). The present study demonstrated improved major clinical outcomes with increased experience, but no significant improvements in LVOT obstruction and post-procedural MR were observed in the late experience group. Further clinical experience, better patient selection and advancement in device technology promise to improve TMVR outcomes.

Increased mid-term mortality after ViR in the present study may be affected by frequent procedural complications as well as underlying mitral valve disease. Patients treated with ViR had more frequent prior CABG and myocardial infarction with lower LVEF, suggesting higher proportion of functional MR as the underlying aetiology of mitral valve disease. Since recurrence of MR after mitral valve repair was associated with increased long-term mortality, the potential benefit of ViR for severe MR may be confounded by advanced age, cardiac and non-cardiac comorbidities.[25,27] The 30-day mortality in the present study (9.9%) was comparable to those after ViR from reported studies (6.7–11.4%),[22,28] as well as those after redo mitral valve repair (9.0% and 9.2%).[19,29] Nevertheless, relatively high rates of 1-year mortality after ViR in the present study (30.6%) should be cautiously interpreted. Recent study reported that the 1-year mortality rate after mitral valve reoperation of 23.1%, mainly related to high in-hospital mortality (12.6%).[20] Although direct comparison is difficult, landmark analysis in the present study showed higher late mortality after ViR (23.0%), suggesting the adverse impact of post-procedural MR in this population.

Patients with MAC associated with mitral valve disease experienced surprisingly higher early and mid-term mortality after TMVR (34.5% and 62.8%, respectively). Notably, these mortality rates were comparable to those reported recently by Guerrero *et al.*[7] (25.0% and 53.7%). As LVOT obstruction and post-procedural MR contribute to the increased mortality, every effort should be made to predict and prevent these serious complications with dedicated imaging analysis. Given high late mortality (43.2%) shown by landmark analysis in patients with MAC, appropriate patient selection is essential to avoid futile TMVR procedures.

Bioprosthetic valve thrombosis is a multifactorial phenomenon affected by anatomic, procedural, and pharmacological factors.[30] The risk of valve thrombosis is higher in the mitral position than the aortic position, highest in the first few months after implantation, and may continue thereafter. In the present study, the majority of thrombosis (90.9%) was observed after mitral ViV. Interestingly, the valve thrombosis was more frequently observed in previous porcine valves (nine patients) compared with pericardial valves (one patient), consistent with previous surgical aortic valve replacement and aortic valve-in-valve publications.[31,32] The lower rate of thrombosis in patients with anticoagulation compared with those without anticoagulation suggests that anticoagulant thromboprophylaxis may be beneficial, particularly for the first few months after TMVR procedures. Considering the wide-ranged timeframe of thrombosis after TMVR, serial echocardiographic follow-up, while balancing individual thromboembolic and haemorrhage risks may guide decisions regarding the extension of anticoagulation until future studies clarify the optimal thromboprophylaxis after TMVR.

Study limitations

This study had the inherent limitations of an observational study without centre-independent adjudication of adverse events. Our findings are subject to potential selection bias and confounding factors including differences in baseline characteristics across the groups. Despite adjustment with available covariates, the residual confounding factors might account for biased outcomes. Several variables that are known to affect the outcomes such as anaemia

or frailty were not available in the present study. The cumulative rates of cardiovascular mortality and nonfatal outcomes might be overestimated by competing risk of non-cardiovascular and all-cause mortality, respectively. Finally, selections of device type and access site were determined at each institution and may have affected the observed outcomes.

Conclusions

The TMVR provided excellent outcomes for patients with degenerated bioprostheses despite high surgical risk. However, ViR and ViMAC were associated with higher rates of adverse events and mid-term mortality compared with ViV.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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A.U. and J.K. have served as proctors for Abbott, Boston Scientific, Edwards Lifesciences, and Medtronic. G.H.L.T. has served as a proctor for Edwards Lifesciences. C.M.B. is on the Advisory Board of Medtronic and Boston Scientific and on the Speakers' Bureau of Abbott Vascular. J.E.D. has served as a consultant for Edwards and the Medtronic advisory board. A.L. has received a consulting fees from P&F. L.N.-F. has served as a proctor for Abbott Vascular and has received speaking fees from Edwards Lifesciences. J.-B.M. has served as a consultant for Edwards Lifesciences. F.D. has served as a proctor and consultant for Edwards Lifesciences and Neovasc and received a travel grant from Abbott, Boston Scientific, Edwards Lifesciences, and Neovasc, and participated in clinical trials (TIARA II CE Mark trial and TENDYNE CE Mark trial). H.C.W. has received research grants from Edwards Lifesciences and Medtronic. 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