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Heart Valve Disease

Determinants and Outcomes of Acute Transcatheter Valve-in-Valve Therapy or Embolization

A Study of Multiple Valve Implants in the U.S. PARTNER Trial (Placement of AoRTic TraNscathetER Valve Trial Edwards SAPIEN Transcatheter Heart Valve)

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Objectives This study investigated the determinants and outcomes of acute insertion of a second transcatheter prosthetic valve (TV) within the first (TV-in-TV) or transcatheter valve embolization (TVE) after transcatheter aortic valve replacement (TAVR).

Background TAVR failure can occur with both TV-in-TV and TVE as a consequence of TAVR malpositioning. Only case reports and limited series pertaining to these complications have been reported to date.

Methods Patients undergoing TAVR in the PARTNER (Placement of AoRTic TraNscathetER Valve Trial Edwards SAPIEN Transcatheter Heart Valve) randomized trial (cohorts A and B) and accompanying registries were studied. Data were dichotomized for those with and without TV-in-TV or TVE, respectively.

Results From a total of 2,554 consecutive patients, 63 (2.47%) underwent TV-in-TV and 26 (1.01%) TVE. The indication for TV-in-TV was significant aortic regurgitation in most patients, often due not only to malpositioning but also to leaflet dysfunction. Despite similar aortic valve function on follow-up echoes, TV-in-TV was an independent predictor of 1-year cardiovascular mortality (hazard ratio [HR]: 1.86, 95% confidence interval [CI]: 1.03 to 3.38, $p = 0.041$), with a nonsignificant trend toward greater all-cause mortality (HR: 1.43, 95% CI: 0.88 to 2.33, $p = 0.15$). Technical and anatomical reasons accounted for most cases of TVE. A multivariable analysis found TVE to be an independent predictor of 1-year mortality (HR: 2.68, 95% CI: 1.34 to 5.36, $p = 0.0055$) but not cardiovascular mortality (HR: 1.30, 95% CI: 0.48 to 3.52, $p = 0.60$).

Conclusions Acute TV-in-TV and TVE are serious sequelae of TAVR, often resulting in multiple valve implants. They carry an excess of mortality and are caused by anatomic and technical factors, which may be avoidable with judicious procedural planning. (THE PARTNER TRIAL: Placement of AoRTic TraNscathetER Valve Trial; NCT00530894) (J Am Coll Cardiol 2013;62:418–30) © 2013 by the American College of Cardiology Foundation

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Transcatheter aortic valve replacement (TAVR) has shown both safety and efficacy (1) beyond 2 years (2,3). Malpositioning can result in transcatheter valve embolization (TVE) or valve failure. The latter can be treated conservatively, but poor clinical outcomes have been consistently observed with this approach (3,4). Transcatheter valve-in-valve (TV-in-TV) is an established technique to treat acute failure of TAVR (5,6) (it also has an important potential role in treating late TAVR failures, likely an issue in the future). Limited data exist for both TVE and TV-in-TV predictors and sequelae, with a notable absence of adjudicated and core laboratory assessments of clinical and hemodynamic outcome. Using core laboratory adjudicated data, this study sought to investigate the nature, determinants, and outcomes of 2 clinical scenarios in which multiple transcatheter valves may be implanted: TAVR failure with TV-in-TV and TVE.

Methods

Study design and procedure. In an as-treated (AT) analysis, patients undergoing TAVR in the PARTNER (Placement of AoRTic TraNscathetER Valve) Trial, including patients randomized in cohort A (those with high surgical risk), and B (those with inoperable conditions), and accompanying nonrandomized registries were studied. All patients underwent TAVR with the Edwards Sapien heart valve system (Edwards Lifesciences, LLC, Irvine, California). This valve was available in 2 sizes, 23 mm and 26 mm. The procedure was performed with guidance by transesophageal echocardiography (TEE) and fluoroscopy, as previously described (1).

Data were dichotomized for those with and without device embolization. Device embolization was defined as occurring when the "valve prosthesis moves during or after deployment such that it loses contact with the aortic annulus," as proposed by updated Valve Academic Research Consortium guidelines (7). In addition, TV-in-TV cases were compared to those that received a single TAVR in the annular position. A second valve was implanted at the discretion of the operator in a similar fashion to and within the first valve. The valve size used was the same as the first one in all cases.

Baseline demographic and core laboratory interpreted echocardiographic characteristics and clinical outcomes at 1 year were studied. Nonrandomized patients had the same data collection and core laboratory analysis as randomized patients. Additional information on indication, timing, severity, and mechanism of each respective complication and immediate outcomes was studied primarily by using a detailed review of procedure reports, with review of supplemental information from the intraprocedural TEE and angiograms for clarification, if required. A minority of patients had baseline cardiac computed tomography (CT) scans available that were systematically analyzed (8).

Outcomes. Clinical outcomes studied included acute procedural and 30-day outcomes and late outcomes up to 1 year. The principal end points compared were all-cause mortality, cardiovascular mortality, rehospitalization, stroke, and New York Heart Association (NYHA) functional class. Core laboratory echocardiographic data included valve areas, transvalvular gradients, left ventricular (LV) size and function, and valvular and paravalvular aortic regurgitation (AR), evaluated with baseline and follow-up transthoracic echocardiograms (TTEs).

Statistical analysis. Categorical variables were compared with the Fisher exact test. The Kolmogorov-Smirnov test was performed to test the normality for continuous variables and data expressed as mean ± SD or medians (interquartile range [IQR], compared by Student *t*-test or Wilcoxon rank sum test). Survival curves for time-to-event variables were

Abbreviations and Acronyms

AR = aortic regurgitation

AT = as-treated

BSA = body surface area

CABG = coronary artery bypass

CT = computed tomography

LV = left ventricular

TAVI = transcatheter aortic valve implantation

TAVR = transcatheter aortic valve replacement

TEE = transesophageal echocardiograms

THV = transcatheter heart valve

TIA = transient ischemic attack

TV = transcatheter prosthetic valve

TVE = transcatheter valve embolization

TV-in-TV = transcatheter prosthetic valve within a transcatheter prosthetic valve

V-in-V = transcatheter valve-in-surgical valve

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constructed on the basis of all available follow-up data with the use of Kaplan-Meier estimates and were compared using the log-rank test. For multivariable analyses, endpoints studied included death and cardiovascular death with candidate covariates for each outcome, those related to TV-in-TV or TVE to a significance level of ≤0.1. Cox regression models using stepwise selection was performed for a 1-year time point. To study changes in bioprosthetic gradients over time, longitudinal data analysis was performed using an SAS mixed model (SAS Institute, Cary, North Carolina) with repeated measurements. All statistical analyses were performed with the use of SAS version 9.2 software.

Results

Patients and baseline characteristics. A total of 2,554 patients consecutively treated with TAVR were studied. The cohort consisted of 519 randomized and 2,035 non-randomized patients. Of these, 63 (2.47%) patients underwent TV-in-TV and 26 (1.01%) experienced TVE.

TV-in-TV: nature, timing and underlying reasons. For TV-in-TV, 56 (88.9%) patients were immediate, 2 were early (just after surgical closure of the LV apex in transapical cases), and 5 were later (on post-operative days 1, 3, and 16 and months 2 and 4 post-procedure). Indications for TV-in-TV (Fig. 1) were significant post-TAVR AR in 61 cases (96.8%), 31 (50.8%) transvalvular cases (3 moderate, 1 moderate-severe, and 27 severe), 22 (36.1%) paravalvular cases (5 moderate, 2 moderate-severe, and 15 severe), and 8 (13.1%) mixed cases (1 moderate and 7 severe). Two additional cases were implanted primarily for unstable device position (1 very high, 1 very low).

In the 61 cases of AR (Fig. 1), 33 were due to leaflet malfunction and 25 were due to malpositioning; 3 were of unclear causes. For paravalvular AR, 20 of 22 (90.9%) cases were known to be associated with malpositioning (14 were implanted high, and 6 were implanted low) versus 2 of 31 (6.4%) cases with transvalvular AR (2 implanted low); for transvalvular AR, the predominant stipulated mechanism was leaflet malfunction in 29 of 31 (93.6%) cases. In the 33 overall cases of leaflet malfunction associated with either transvalvular or mixed AR, the putative causes by narrative and data review were not stated or were unclear in 31%, but in many cases there was an identified cause (Fig. 1). Causes included calcium impingement, leaflet overhang, post-dilation (disrupting the architecture of the bioprosthesis), hypotension starting prior to TAVR (with inadequate aortic pressure to close the leaflets of the deployed Sapien valve) and a tilted/canted valve.

Baseline clinical variables associated with TV-in-TV (Table 1) included male sex, higher body surface area (BSA), prior myocardial infarction (MI), prior coronary artery bypass graft (CABG), cardiomyopathy and major arrhythmia (predominantly driven by atrial fibrillation). Baseline echocardiographic variables associated with TV-in-TV included larger sinotubular junction diameter, lower aortic valve peak velocity, lower LV ejection fraction, larger LV end diastolic volume, and moderate or greater mitral regurgitation (Table 2). The independent predictors of TV-in-TV were male sex (odds ratio [OR]: 2.64, 95% CI: 1.31 to 5.30, p = 0.0063), prior CABG (OR: 2.08, 95% CI: 1.16 to 3.75, p = 0014), and lower baseline LV ejection fraction (per 10% reduction, OR: 1.03, 95% CI: 1.02 to 1.05, p = 0.0003).

Early and late outcomes of TV-in-TV. During the TAVR procedure for TV-in-TV cases, there was a greater need for hemodynamic support, higher volume of contrast used, higher radiation exposure, and longer procedure and fluoroscopy times (Table 3). There were higher levels of creatine kinase (CK) but not creatine kinase-myocardial band (CK-MB) or troponin with TV-in-TV (Table 3), suggesting greater non-cardiac muscle ischemia with TV-in-TV.

At 30 days, all-cause mortality (9.6% vs. 5.9%), cardiovascular mortality (8.0% vs. 4.2%), and rehospitalization (9.8% vs. 5.8%) were higher with TV-in-TV versus no TV-in-TV respectively, but these differences were not statistically significant (Table 3). Occurrence of stroke, renal failure, vascular complication or need for open aortic valve replacement was similar. There was, however, a greater need for a new pacemaker with TV-in-TV versus no TV-in-TV (at 30 days, the new pacemaker rate was 11.2% vs. 5.4%, p = 0.05). Of patients with electrocardiographic data, there was more abnormal conduction after TV-in-TV versus not and more left bundle branch block (LBBB); at discharge/7 days LBBB occurred in 48.5% with TV-in-TV versus 33.8% of those who did not require TV-in-TV, p = 0.08), despite no significant differences at baseline (Online Table 1).

There were no significant differences in aortic valve area or gradients acutely or at follow-up with TV-in-TV (Fig. 2). After TV-in-TV, mean aortic valve gradient on discharge TTE was 10.4 ± 4.5 mm Hg versus 10.7 ± 5.0 mm Hg with no TV-in-TV (p = 0.70). Only 1 case of TV-in-TV had a mean gradient ≥20 mm Hg (1.59%); that case had moderate paravalvular and mild central AR (severe total AR by core laboratory assessment) with two 26-mm Sapien prostheses implanted in an annulus measuring 24 mm by 2-dimensional (2D) TEE. Post-TAVR paravalvular, transvalvular, and total AR were similar (Online Table 2). Only 5 (7.9%) patients with TV-in-TV had residual total AR greater than mild (moderate or severe) on discharge or 7-day TTE; 1 had central AR, and 4 had paravalvular AR. Of the 4 with paravalvular AR, 3 were undersized on review of baseline cross-sectional annular area on computed tomography (CT) (annulus area > transcatheter heart valve (THV) area); 1 did not have baseline CT data, but a 23-mm SAPIEN valve was implanted in a borderline large annulus measuring 22 mm on 2D TEE.

At 1 year, TV-in-TV patients had higher all-cause mortality (33.3% vs. 21.0%, p = 0.02), cardiovascular mortality (24.4% vs. 9.1%, p = 0.0005), and a trend to more rehospitalization (25.5% vs. 17.7%, p = 0.12), but there were no significant differences in stroke rates (9.3% vs. 4.9%,

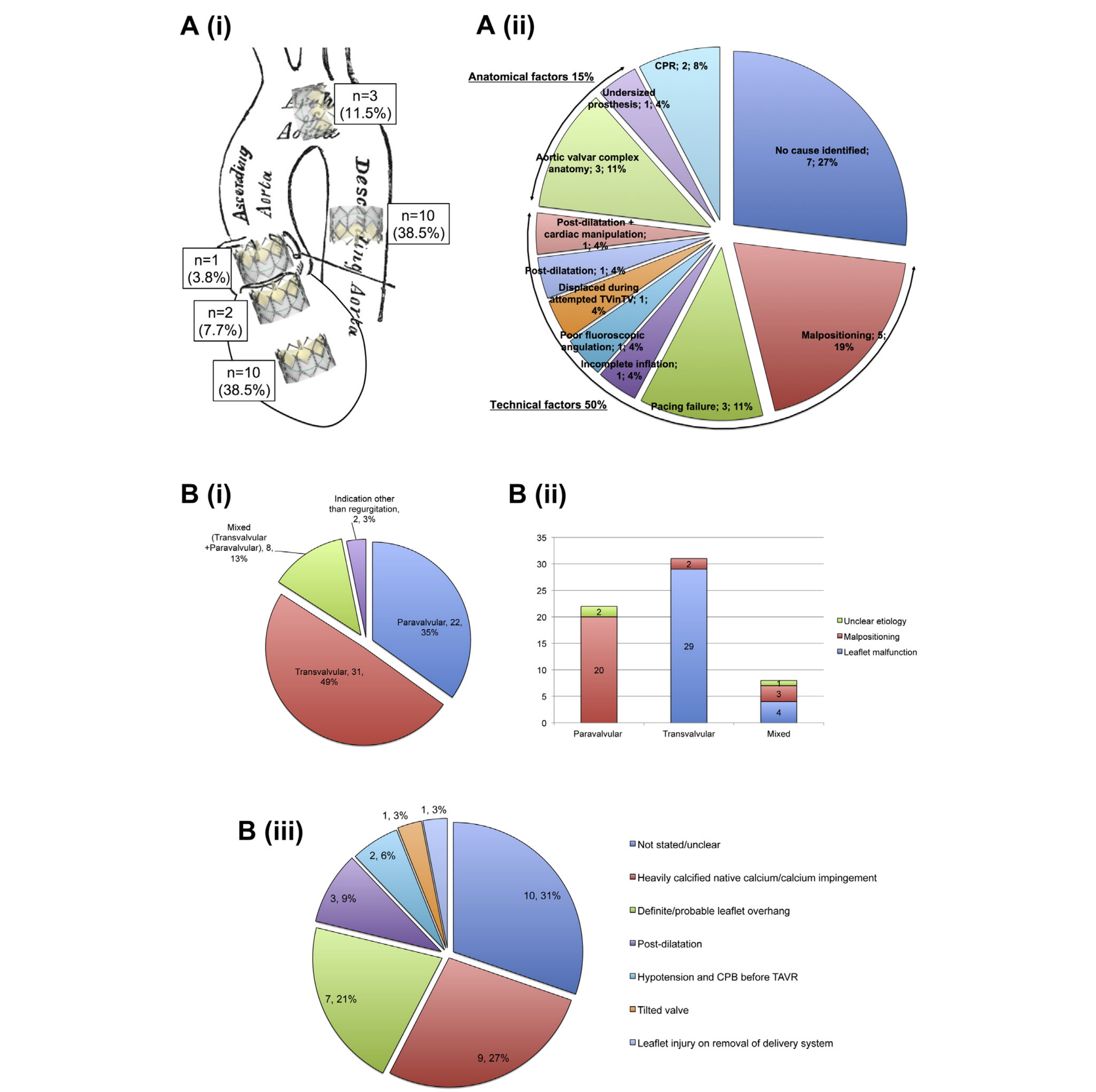

Figure 1 **Stratification of Underlying Causes of TVE and TV-in-TV**

(A) TVE. **(i)** Final location of embolization and **(ii)** operator-identified causes. **(B)** TV-in-TV. **(i)** Indications for TV-in-TV. **(ii)** Mechanisms of pre-TV-in-TV aortic regurgitation. **(iii)** Putative underlying causes are shown in cases where TV-in-TV was performed for leaflet malfunction.

p = 0.17) (Fig. 3). NYHA status at follow-up was similar (Online Fig. 2). TV-in-TV was an independent predictor of cardiovascular mortality (hazard ratio [HR]: 1.86, 95% confidence interval [CI]: 1.03 to 3.38, p = 0.041) but was not significantly associated with intermediate term all-cause mortality (HR: 1.43, 95% CI: 0.88 to 2.33, p = 0.15) (Online Table 3). A landmark analysis showed a more substantial difference in cardiovascular mortality between TV-in-TV and no TV-in-TV groups beyond 30 days than within the first 30 days postprocedure (Fig. 4).

TVE: nature, timing, and underlying reasons. TVE occurred in 20 patients (76.9%) immediately after valve deployment, in 5 (19.2%) early (within an hour of implantation but not immediate) and in 1 (3.8%) late (7 hours postprocedure and related to cardiopulmonary resuscitation). Although the majority of TVE cases (16 of 26 [61.5%])

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Table 1 Baseline Clinical Variables Associated With TV-in-TV and TVE

	All Patients (n = 2,554)	TV-in-TV (n = 63)	No TV-in-TV (n = 2,491)	p Value	TVE (n = 26)	No TVE (n = 2,528)	p Value
Age, yrs	84.46 ± 7.17 (2,536)	83.24 ± 6.30 (63)	84.49 ± 7.19 (2,473)	0.058	81.32 ± 8.21 (26)	84.49 ± 7.16 (2,510)	0.04
Male	52.4% (1,337/2,552)	81.0% (51/63)	51.6% (1,285/2,489)	<0.0001	76.9% (20/26)	52.1% (1,317/2,526)	0.53
BSA	1.80 ± 0.25 (2,543)	1.89 ± 0.26 (63)	1.80 ± 0.25 (2,480)	0.01	1.92 ± 0.22 (26)	1.80 ± 0.25 (2,517)	0.006
STS score	11.49 ± 4.28 (2,545)	11.43 ± 4.54 (63)	11.49 ± 4.27 (2,482)	0.38	10.32 ± 3.49 (26)	11.50 ± 4.28 (2,519)	0.20
Logistic EuroScore	26.49 ± 16.21 (2,470)	30.19 ± 20.54 (59)	26.40 ± 16.09 (2,411)	0.35	26.66 ± 15.16 (26)	26.49 ± 16.23 (2,444)	0.85
CAD	77.8% (1,984/2,551)	85.7% (54/63)	77.5% (1,929/2,488)	0.12	76.9% (20/26)	77.8% (1,964/2,525)	0.92
Prior MI	26.0% (661/2,538)	44.4% (28/63)	25.5% (632/2,475)	0.0007	38.5% (10/26)	25.9% (651/2,512)	0.15
Prior PCI	39.8% (1,015/2,548)	39.7% (25/63)	39.8% (989/2,485)	0.99	50.0% (13/26)	39.7% (1,002/2,522)	0.29
Prior CABG	42.7% (1,089/2,551)	66.7% (42/63)	42.0% (1,046/2,488)	<0.0001	57.7% (15/26)	42.5% (1,074/2,525)	0.12
Cerebrovascular disease	26.3% (657/2,501)	37.1% (23/62)	26.0% (634/2,439)	0.05	20.0% (5/25)	26.3% (652/2,476)	0.47
Peripheral vascular disease	42.8% (1,079/2,522)	52.4% (33/63)	42.5% (1,046/2,459)	0.12	50.0% (13/26)	42.7% (1,066/2,496)	0.45
Porcelain aorta	4.0% (102/2,533)	3.2% (2/63)	4.0% (100/2,470)	1.00	4.0% (1/25)	4.0% (101/2,508)	1.00
Prior BAV	23.4% (594/2,540)	30.2% (19/63)	23.2% (574/2,477)	0.20	26.9% (7/26)	23.3% (587/2,514)	0.67
Pulmonary hypertension	39.0% (943/2,421)	42.9% (27/63)	38.9% (917/2,358)	0.52	33.3% (8/24)	39.0% (935/2,397)	0.57
Permanent pacemaker	21.4% (547/2,551)	27.4% (17/62)	21.3% (530/2,489)	0.25	26.9% (7/26)	21.4% (540/2,525)	0.49
Renal disease (CR ≥2)	16.6% (423/2,550)	12.7% (8/63)	16.7% (415/2,487)	0.40	7.7% (2/26)	16.7% (421/2,524)	0.29
COPD	43.4% (1,108/2,554)	39.7% (25/63)	43.5% (1,084/2,491)	0.54	53.8% (14/26)	43.3% (1,094/2,528)	0.28
Chest wall radiation	2.6% (67/2,533)	1.6% (1/63)	2.7% (66/2,470)	1.00	8.0% (2/25)	2.6% (65/2,508)	0.14
Chest wall deformities	1.9% (49/2,533)	1.6% (1/63)	1.9% (48/2,470)	1.00	4.0% (1/25)	1.9% (48/2,508)	0.39
Frailty	12.4% (299/2,419)	11.1% (7/63)	12.4% (292/2,356)	0.76	0.0% (0/24)	12.5% (299/2,395)	

Values are mean ± SD (N) or % (n/N).

BAV = balloon aortic valvuloplasty; BSA = body surface area; CABG = coronary artery bypass graft; CAD = coronary artery disease; COPD = chronic obstructive pulmonary disease; MI = myocardial infarction; PCI = percutaneous coronary intervention; STS = Society of Thoracic Surgeons; TVE = transcatheter valve embolization; TV-in-TV = transcatheter prosthetic valve within a transcatheter prosthetic valve.

Table 2 Baseline Echocardiographic Variables Associated With TV-in-TV and TVE

	All (n = 2,554)	TV-in-TV (n = 63)	No TV-in-TV (n = 2,491)	p Value	TVE (n = 26)	No TVE (n = 2,528)	p Value
TTE AV annulus diameter (cm)	1.91 ± 0.27 (1,939)	2.01 ± 0.33 (44)	1.91 ± 0.27 (1,895)	0.10	2.07 ± 0.19 (18)	1.91 ± 0.27 (1,921)	0.004
TTE AV annulus diameter/valve size deployed (mm)	0.78 ± 0.10 (1,902)	0.80 ± 0.14 (44)	0.78 ± 0.10 (1,858)	0.30	0.083 ± 0.009 (18)	0.078 ± 0.011 (1,884)	0.06
TEE AV annulus diameter (cm)	21.44 ± 1.87 (2,548)	21.94 ± 1.79 (63)	21.43 ± 1.87 (2,485)	0.03	21.96 ± 1.84 (26)	21.44 ± 1.87 (2,522)	0.10
TEE AV annulus diameter (mm)/valve size deployed (mm)	0.88 ± 0.06 (2,500)	0.89 ± 0.06 (63)	0.88 ± 0.06 (2,437)	0.04	0.88 ± 0.06 (26)	0.88 ± 0.06 (2,474)	0.42
Sinotubular junction diameter (cm)	2.35 ± 0.38 (1,669)	2.51 ± 0.41 (42)	2.35 ± 0.38 (1,627)	0.007	2.62 ± 0.28 (14)	2.35 ± 0.38 (1,655)	0.003
Aortic root diameter (cm)	3.12 ± 0.41 (2,143)	3.38 ± 0.46 (51)	3.11 ± 0.40 (2,092)	<0.0001	3.34 ± 0.22 (18)	3.12 ± 0.41 (2,125)	0.003
AV peak velocity (cm/s)	416.15 ± 64.64 (2,408)	395.30 ± 73.93 (59)	416.67 ± 64.32 (2,349)	0.01	397.14 ± 52.22 (24)	416.29 ± 64.70 (2,384)	0.11
AV mean gradient (mm Hg)	43.83 ± 14.31 (2,424)	40.26 ± 16.08 (59)	43.92 ± 14.26 (2,365)	0.02	39.40 ± 10.22 (24)	43.86 ± 14.33 (2,400)	0.11
AV area (EOA) (cm^2)	0.65 ± 0.19 (2,384)	0.67 ± 0.24 (57)	0.65 ± 0.19 (2,327)	0.80	0.72 ± 0.18 (21)	0.65 ± 0.19 (2,363)	0.08
LVED volume (ml)	132.56 ± 49.82 (1,181)	176.39 ± 59.36 (28)	131.49 ± 49.11 (1,153)	<0.0001	152.60 ± 92.08 (10)	132.38 ± 49.34 (1,171)	0.77
LVES volume (ml)	66.89 ± 41.06 (1,181)	105.85 ± 53.06 (28)	65.95 ± 40.29 (1,153)	<0.0001	86.96 ± 83.39 (10)	66.72 ± 40.54 (1,171)	0.66
LV ejection fraction	52.50 ± 12.94 (2,444)	44.34 ± 14.02 (60)	52.70 ± 12.85 (2,384)	<0.0001	51.14 ± 13.25 (24)	52.50 ± 12.94 (2,420)	0.48
% of patients with mitral regurgitation				0.72			0.49
None (n)	3.2% (78/2,427)	3.3% (2/60)	3.2% (76/2,367)		0.0% (0/24)	3.2% (78/2,403)	
Trace	24.5% (594/2,427)	20.0% (12/60)	24.6% (582/2,367)		25.0% (6/24)	24.5% (588/2,403)	
Mild	50.4% (1,223/2,427)	45.0% (27/60)	50.5% (1,196/2,367)		41.7% (10/24)	50.5% (1,213/2,403)	
Moderate	18.9% (458/2,427)	30.0% (18/60)	18.6% (440/2,367)		33.3% (8/24)	18.7% (450/2,403)	
Severe	3.0% (74/2,427)	1.7% (1/60)	3.1% (73/2,367)		0.0% (0/24)	3.1% (74/2,403)	
Moderate or severe	21.9% (532/2,427)	31.7% (19/60)	21.7% (513/2,367)	0.06	33.3% (8/24)	21.8% (524/2,403)	0.17
% of patients with transvalvular aortic regurgitation				0.91			0.05
None	10.6% (264/2,493)	13.1% (8/61)	10.5% (256/2,432)		20.0% (5/25)	10.5% (258/2,468)	
Trace	31.7% (790/2,493)	32.8% (20/61)	31.7% (770/2,432)		12.0% (3/25)	31.9% (787/2,468)	
Mild	44.8% (1,118/2,493)	45.9% (28/61)	44.8% (1,090/2,432)		44.0% (11/25)	44.9% (1,108/2,468)	
Moderate	9.5% (236/2,493)	6.6% (4/61)	9.5% (232/2,432)		20.0% (5/25)	9.4% (231/2,468)	
Severe	0.9% (23/2,493)	0.0% (0/61)	0.9% (23/2,432)		0.0% (0/25)	0.9% (23/2,468)	
Moderate or severe	10.7% (259/2,431)	6.7% (4/60)	10.8% (255/2,371)	0.31	20.8% (5/24)	10.6% (254/2,407)	0.17

Values are mean ± SD (N) or % (n/N). p values are based on the chi-square test or Fisher exact test, as appropriate, for categorical variables and on Wilcoxon rank sum test for medians for continuous variables.

AV = aortic valve; EOA = effective orifice area; LV = left ventricular; LVED = left ventricular end-diastolic; LVES = left ventricular end-systolic; TEE = transesophageal echocardiography; TTE = transthoracic echocardiography; other abbreviations as in Table 1.

Table 3 Periprocedural and 30-Day Outcomes Associated With TV-in-TV and TVE

	All (n = 2,554)	TV-in-TV (n = 63)	No TV-in-TV (n = 2,491)	p Value	TVE (n = 26)	No TVE (n = 2,528)	p Value
Periprocedural variables							
Prior TAVR procedures performed in treating center	75.26 ± 57.73	81.94 ± 57.72	75.09 ± 57.81	0.35	56.8 ± 45.8	75.4 ± 57.8	0.10
Access approach							0.05
Transfemoral	57.7% (1,474/2,554)	52.4% (33/63)	57.8% (1,441/2,491)	0.39	76.9% (20/26)	57.6% (1,455/2,528)	
Transapical	42.3% (1,080/2,554)	47.6% (30/63)	42.2% (1,050/2,491)	0.39	23.1% (6/26)	42.4% (1,073/2,528)	
% of patients with valve size shown (mm)							
23 mm	52.1% (1,305/2,504)	41.3% (26/63)	52.4% (1,279/2,441)	0.08	34.6% (9/26)	52.3% (1,295/2,478)	0.07
26 mm	47.8% (1,198/2,504)	58.7% (37/63)	47.6% (1,161/2,441)	0.08	65.4% (17/26)	47.7% (1,182/2,478)	0.07
Hemodynamic support (CPB or IABP)	8.0% (203/2,543)	28.6% (18/63)	7.5% (185/2,480)	<0.0001	50.0% (13/26)	7.6% (191/2,517)	<0.0001
Cardiopulmonary bypass	5.2% (133/2,543)	25.4% (16/63)	4.7% (117/2,480)	<0.0001	38.5% (10/26)	4.9% (124/2,517)	<0.0001
IABP during procedure	4.2% (108/2,543)	11.1% (7/63)	4.1% (101/2,480)	0.02	19.2% (5/26)	4.1% (104/2,517)	<0.0001
Conversion to open heart surgery	1.4% (36/2,542)	1.6% (1/63)	1.4% (35/2,479)	0.60	30.8% (8/26)	1.2% (29/2,516)	<0.0001
Volume of contrast media (n with available data)	123.89 ± 121.21 (2,455)	201.92 ± 382.60 (60)	121.93 ± 106.28 (2,395)	0.0006	222.39 ± 131.66 (23)	122.88 ± 120.72 (2,431)	<0.0001
Time in catheter lab or OR (min), (n with available data)	222.00 [191.00–260.00] (2,545)	267.50 [226.00–338.00] (62)	221.00 [190.00–259.00] (2,483)	<0.0001	343.00 [239.00–418.00] (26)	222.00 [190.00–259.00] (2,519)	<0.0001
Total procedure time (skin-to-skin) (min)	106.00 [82.00–144.00] (2,531)	143.00 [107.00–210.00] (63)	105.00 [81.00–143.00] (2,468)	<0.0001	196.00 [152.00–313.50] (24)	105.00 [81.00–143.00] (2,506)	<0.0001
Fluoroscopy total time	18.00 [12.00–26.00] (2,426)	25.00 [18.00–36.00] (61)	17.00 [12.00–25.00] (2,365)	<0.0001	35.50 [27.00–63.00] (22)	17.00 [12.00–25.00] (2,403)	<0.0001
Radiation exposure (n with available data)	4,650.03 ± 11,104.52 (1,715)	7,751.15 ± 16,154.78 (47)	4,562.65 ± 10,922.76 (1,668)	0.005	6,411.33 ± 12,475.21 (15)	4,637.22 ± 11,097.25 (1,699)	0.27
Days in hospital post-procedure, (n with available data)	6.00 [5.00–8.00] (1,593)	7.00 [4.00–9.00] (31)	6.00 [5.00–8.00] (1,562)	0.39	6.00 [4.00–8.00] (10)	6.00 [5.00–8.00] (1,582)	0.87
24 h post-procedure							
CK (U/l)	155.00 [68.00–352.00] (1,218)	212.00 [115.00–438.00] (33)	154.00 [68.00–348.00] (1,185)	0.02	353.00 [183.50–1,137.00] (8)	155.00 [68.00–349.00] (1,210)	0.02
Change from ≤1 × ULN at baseline	71.00 [6.00–278.50] (968)	206.00 [26.00–408.00] (25)	69.00 [6.00–275.00] (943)	0.03	248.00 [80.00–1,401.00] (6)	70.50 [6.00–277.00] (962)	0.05
CK-MB (U/l)	7.00 [3.60–17.00] (1,377)	7.00 [3.70–17.40] (31)	7.00 [3.60–17.00] (1,346)	0.55	11.50 [5.40–19.90] (6)	7.00 [3.60–17.00] (1,371)	0.58
Troponin I (ng/ml)	1.32 [0.45–5.44] (1,276)	1.14 [0.52–7.94] (30)	1.33 [0.45–5.39] (1,246)	0.57	2.02 [0.99–6.74] (10)	1.31 [0.45–5.40] (1,265)	0.25
30-day outcomes (KM estimates)							
Mortality							
All cause	6.0% (154)	9.6% (6)	5.9% (148)	0.27	26.9% (7)	5.8% (147)	<0.0001
Cardiovascular	4.3% (109)	8.0% (5)	4.2% (104)	0.16	23.4% (6)	4.1% (103)	<0.0001
Repeat hospitalization	5.9% (145)	9.8% (6)	5.8% (139)	0.19	5.0% (1)	5.9% (144)	0.88
Stroke or TIA	3.8% (96)	4.8% (3)	3.8% (93)	0.68	13.2% (3)	3.7% (93)	0.02
Stroke	3.3% (84)	4.8% (3)	3.3% (81)	0.51	9.0% (2)	3.3% (82)	0.15
Death from any cause or major stroke	8.2% (209)	12.8% (8)	8.1% (201)	0.21	26.9% (7)	8.0% (202)	0.0001
Myocardial infarction	0.8% (20)	0.0% (0)	0.8% (20)	0.47	3.8% (1)	0.8% (19)	0.057
Open aortic valve replacement	0.5% (14)	0.0% (0)	0.6% (14)	0.55	26.9% (7)	0.3% (8)	<0.0001
Vascular complications	13.1% (333)	9.6% (6)	13.2% (327)	0.39	43.2% (11)	12.8% (322)	<0.0001
Bradyarrhythmic event	6.7% (167)	12.8% (8)	6.5% (159)	0.05	4.2% (1)	6.7% (166)	0.69
Permanent pacemaker	5.6% (140)	11.2% (7)	5.4% (133)	0.05	4.2% (1)	5.6% (139)	0.82
Renal failure (dialysis required)	2.9% (72)	3.2% (2)	2.9% (70)	0.89	17.4% (4)	2.8% (68)	<0.0001
Dialysis lasting >30 days	0.6% (15)	0.0% (0)	0.6% (15)	0.53	0.0% (0)	0.6% (15)	0.72

Values are mean ± SD, % (n/N), mean ± SD (N), median (interquartile range) (N), or % (n). p values are based on the chi-square or Fisher exact test, as appropriate, for categorical variables and on the Wilcoxon rank sum test for medians for continuous variables. For KM estimates, p values are from the log rank test.

CPB = cardiopulmonary bypass; CK = creatine kinase; CKMB = creatine kinase-myocardial band; IABP = intra-aortic balloon pump; IQR = interquartile range; KM = Kaplan-Meier; OR = operating room; TIA = transient ischemic attack; ULN = upper limit of normal; other abbreviations are shown in Table 1.

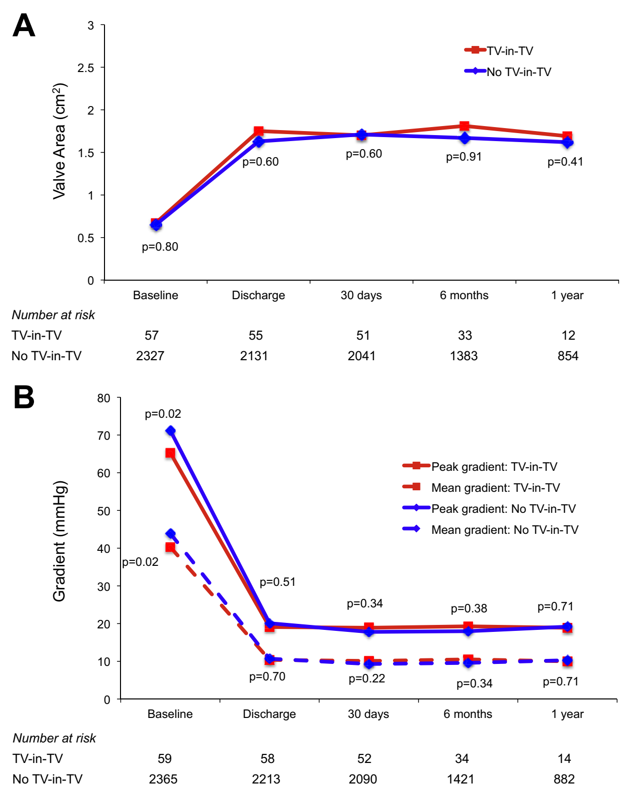

Figure 2 **TV-in-TV and Bioprosthetic Hemodynamics by Echocardiography**

(A) Aortic valve areas at multiple time points stratified by TV-in-TV (p = 0.15 in the longitudinal mixed model for the slope of TV-in-TV vs. no TV-in-TV). **(B)** Peak (p = 0.23 in the longitudinal mixed model for the slope of TV-in-TV vs. no TV-in-TV) and mean (p = 0.24 in the longitudinal mixed model for the slope of TV-in-TV vs. no TV-in-TV) gradients at multiple time points stratified by TV-in-TV.

did have multiple transcatheter valve implants (Online Fig. 1), surgical aortic valve replacement was performed in 8 patients, and in 2 needed no further intervention. There was some overlap in the populations studied in those 2 cases of TVE rectified by TV-in-TV: 1 patient had the first TAVR positioned in the left ventricular outflow tract (LVOT), and a second was implanted in an overlapping fashion at the annular level, and in the other case, the first TAVR was positioned low, a second high, and a third between the 2 at the annular level, overlapping with and stabilizing the 2 previous devices. In one case of TVE, movement into the left ventricle was caused by an attempt at TV-in-TV for initial TAVR failure.

Initial direction of embolization was aortic (above the aortic annulus) in 13 patients (50%) and ventricular (below the aortic annulus) in 13 patients (50%); in 1 patient, although the initial direction of embolization was ventricular, the operators were able to pull the valve to an aortic location by inflating a balloon within it (Online Fig. 1, Online Table 4). Of the 26 cases of embolization, 14 (53.8%) were managed percutaneously, and 12 (46.2%) required conversion to open heart surgery. There were more valve embolizations in procedures performed by the transfemoral (TF) approach: 20 of 1,455 (1.37%) TF cases and 6 of 1,073 (0.58%) transapical (TA) cases resulting in embolization (p = 0.05). Despite this, a smaller proportion of TF cases had a final ventricular position, with 7 of 20 (35.0%) of the embolizations ventricular in those treated by the TF approach versus 5 of 6 (83.3%) by the TA approach (p = 0.065).

Patients with valve embolization had a higher BSA and were more likely to be males (Table 1). Patients with valve embolization also had on average larger aortic annuli by 2D TTE and a trend toward lower mean aortic valve gradients at baseline (Table 2).

A cause for embolization was defined in post-procedural operator reports in 73% of cases (Fig. 1). The most commonly stated causes were malpositioning (19%), annulus/aortic valvular complex anatomy (15%, an undersized prosthesis, an angulated aorta, sinus/commissural asymmetry and heavily calcified and bulky leaflets), and pacing failure (11%). A valve was considered malpositioned when an operator stated in the procedural report that the initial positioning of the prosthesis prior to deployment was either too high or too low. Other stated causes of embolization included post-cardiopulmonary resuscitation, postdilation, cardiac manipulation, displacement during attempted transcatheter valve-in-valve, poor fluoroscopic angle for implantation, and incomplete/delayed device balloon inflation (Fig. 1). There was a trend to fewer prior TAVR procedures performed in the treating center for patients with embolized valves, 56.8 ± 45.8 in patients with embolized valves versus 75.4 ± 57.8 in patients without embolized valves, indicating there was a tendency for TVE to diminish with a center's increasing experience. An analysis of the relative contribution of the first 20 cases of a center's experience to embolization by approach revealed that 5 of 20 cases of embolization (25%) occurred with the TF approach during centers' first 20 cases, whereas 5 of 6 cases (83%) of embolization occurred with the TA approach during centers' first 20 cases.

A large proportion of cases had no stated cause of embolization (7 of 26, 27%). A retrospective review of available baseline contrast-enhanced CT scans or procedural fluoroscopy or TEE data revealed important technical/anatomical contributory causes of TVE in the form of incorrect crimping of the TAVR device on the delivery system, device undersizing, a small sinotubular junction with ventricular embolization, and marked paucity of aortic valve calcification (Online Appendix).

Early and late outcomes of TVE. Patients with embolized valves were much more likely to require hemodynamic support (Table 3). There was a significantly higher rate of conversion to open heart surgery and use of contrast and fluoroscopy, and procedure times were significantly increased by embolization. TVE had a greater 30-day mortality when it occurred with the TA versus the TF approach and when the final TAVR position was ventricular versus aortic (p = NS

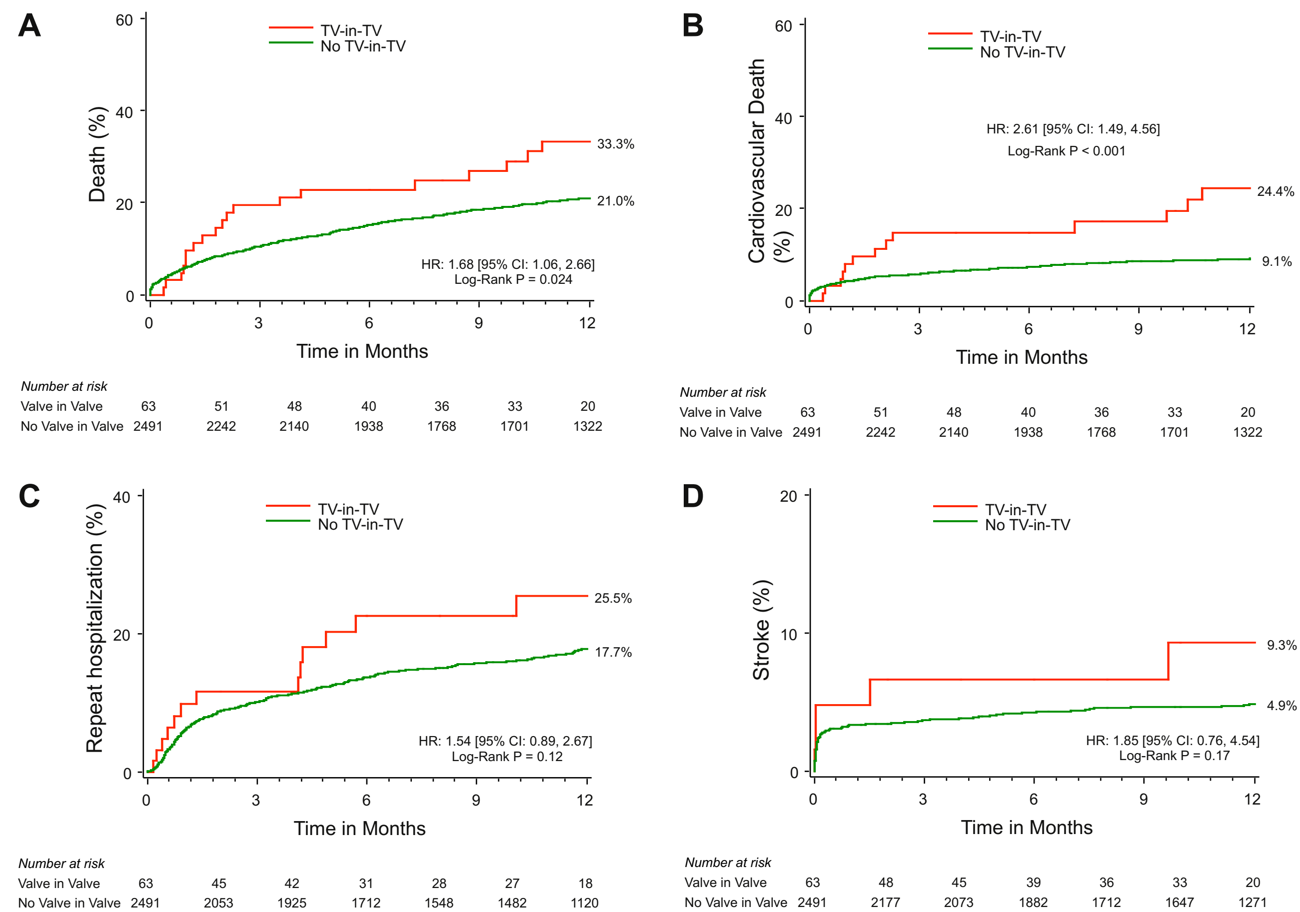

Figure 3 **Late Outcomes With TV-in-TV**

Outcomes stratified by TV-in-TV including **(A)** all-cause mortality; **(B)** cardiovascular mortality; **(C)** rehospitalization; and **(D)** stroke.

for both) (Online Fig. 3). Similarly, conversion to surgery carried a 30-day mortality of 33.3% (4 of 12 patients) compared to 14.3% (2 of 14 patients) in those managed percutaneously (1 of whom did not receive a transcatheter valve and died 6 days post-procedure); (p = 0.36).

At 30 days, death, cardiac death, and stroke were significantly greater with embolization. Major bleeding, major vascular complications, and requirement for open aortic valve replacement were also substantially increased. There was a greater frequency of neurological events (stroke and/or transient ischemic attack [TIA]) with TVE at 30 days (13.2% vs. 3.7%, p = 0.02) but the differences were driven by only 3 cases of stroke/TIA: 1 major and 1 minor stroke and 1 case of TIA. TVE was not a significant predictor of stroke (HR: 2.67, 95% CI: 0.66 to 10.85, p = 0.15).

Although predominantly driven by early event rates, late adverse outcomes remained significantly higher with embolization (Table 4, Fig. 5). At 1 year, embolization remained a significant independent predictor of mortality (HR: 2.68, 95% CI: 1.34 to 5.36, p = 0.0055) (Online Table 3). In a landmark analysis, patients with embolization seemed to carry an incremental risk of late all-cause mortality but not cardiovascular mortality (Fig. 4).

Discussion

The most important findings from this study are that both TV-in-TV and TVE carry a heavy burden of complications and that all cases had probable underlying causes, either stated by the operator or apparent from a retrospective review of the data; these causes were either anatomical or technical, and many could be considered preventable through appropriate procedural planning.

TV-in-TV was performed in 2.47% of cases, mostly as a "rescue" for moderate or more valvular or paravalvular AR. TV-in-TV avoided emergency surgery for failed TAVR in 98.4% (62 of 63) of cases. Rescue TV-in-TV was associated with longer procedure times, more frequent requirement for hemodynamic support, increased radiation exposure and contrast use, larger total CK enzyme leakage, and longer

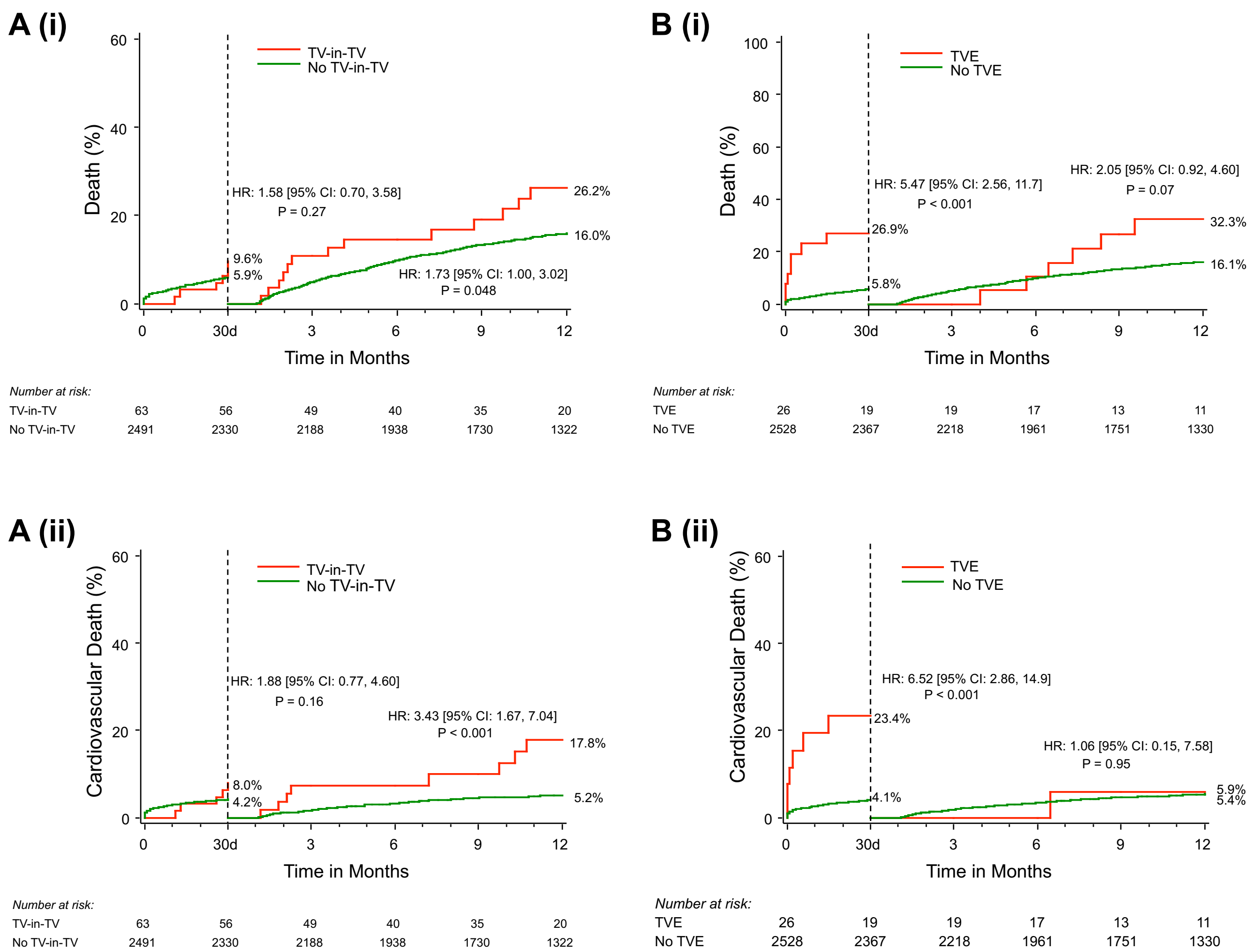

Figure 4 **Landmark Analysis of the Effect of TV-in-TV and TVE on Mortality**

Kaplan-Meier plot is shown with the start date for analysis reset at 30 days. **(A)** Effect of TV-in-TV in mortality; **(B)** effect of TVE on mortality. **(i)** All-cause mortality. **(ii)** Cardiovascular mortality.

hospital stays. TV-in-TV was also associated with a higher incidence of cardiac conduction abnormalities and permanent pacemaker implantation.

TVE occurred in 1.01% of patients and in most cases was immediate and managed percutaneously with a further TAVR positioned at the aortic annulus. TVE resulted in significantly higher rates of hemodynamic support and conversion to open heart surgery and use of contrast and fluoroscopy, and procedure times were also significantly increased. There appeared to be trends toward worse outcomes with TVE occurring in TF versus TA procedures and in ventricular versus aortic TVE. In multivariable analyses, TVE and TV-in-TV were independent predictors of 1-year all-cause and cardiovascular mortality, respectively.

TV-in-TV in context. After TV-in-TV, only 5 of 63 (7.9%) patients had significant postprocedural AR, similar to that in the larger TAVR population without TV-in-TV. In contrast to prior series of balloon-expandable (5) and self-expanding TV-in-TV (6), in whom malpositioning-related paravalvular AR was the predominant cause of post-TAVR AR, we saw a high frequency of transvalvular regurgitation (49.2%). Online Table 5 summarizes the findings of the three studies evaluating TV-in-TV.

The differences are probably due to the structure of the valves used. The prior balloon-expandable series used the SAPIEN XT valve (5), whose leaflets are in a partially closed configuration even when open. Our series used exclusively an earlier device iteration, the Edwards-SAPIEN valve, whose leaflets have a default open configuration. This is thought to have a greater likelihood of the native leaflets outside the deployed TAVR frame overhanging the prosthesis and making contact with the new prosthetic leaflets, causing them to "freeze" or "stick" (5). This hypothesis is supported by the recently reported data from the PARTNER 2B trial (9),

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Table 4 Kaplan-Meier Outcomes for TV-in-TV and TVE at 1 Year

Outcome	All (n = 2,554)	TV-in-TV (n = 63)	No TV-in-TV (n = 2,491)	p Value	TVE (n = 26)	No TVE (n = 2,528)	p Value
Death from any cause	21.3% (514)	33.3% (19)	21.0% (495)	0.02	50.5% (13)	21.0% (502)	<0.0001
Death from cardiovascular cause	9.5% (224)	24.4% (13)	9.1% (211)	0.0005	27.9% (7)	9.3% (217)	0.0002
Repeat hospitalization*	17.9% (396)	25.5% (13)	17.7% (383)	0.12	21.2% (4)	17.9% (393)	0.62
Death from any cause or repeat hospitalization	32.5% (792)	48.9% (29)	32.1% (763)	0.004	54.2% (14)	32.3% (779)	0.002
Stroke or TIA	6.2% (144)	9.3% (5)	6.1% (139)	0.37	13.2% (3)	6.1% (141)	0.10
TIA	1.2% (27)	0.0% (0)	1.2% (27)	0.43	4.2% (1)	1.2% (26)	0.10
Stroke	5.0% (117)	9.3% (5)	4.9% (112)	0.17	9.0% (2)	4.9% (115)	0.33
Minor	4.1% (96)	7.7% (4)	4.0% (92)	0.25	4.2% (1)	4.1% (95)	0.87
Major	0.9% (21)	1.6% (1)	0.9% (20)	0.47	4.8% (1)	0.9% (20)	0.057
Death from any cause or major stroke	23.0% (559)	34.6% (20)	22.8% (539)	0.03	50.5% (13)	22.8% (547)	0.0002
Myocardial infarction	1.5% (34)	1.8% (1)	1.5% (33)	0.82	3.8% (1)	1.4% (33)	0.19

Values are % (n). *Due to aortic stenosis or complications of the valve procedure.
Abbreviations are shown in Tables 1 and 3.

where TV-in-TV occurred in 3.7% of SAPIEN cases compared to 1.1% cases with SAPIEN XT implants ($p = 0.05$). (Similarly, the self-expanding CoreValve [Medtronic, Inc., Minneapolis, Minnesota] device consists of a long stent frame that covers the native leaflets completely, preventing the possibility of leaflet overhang, which may account for the absence of transvalvular AR in the study by Ussia et al. [6]).

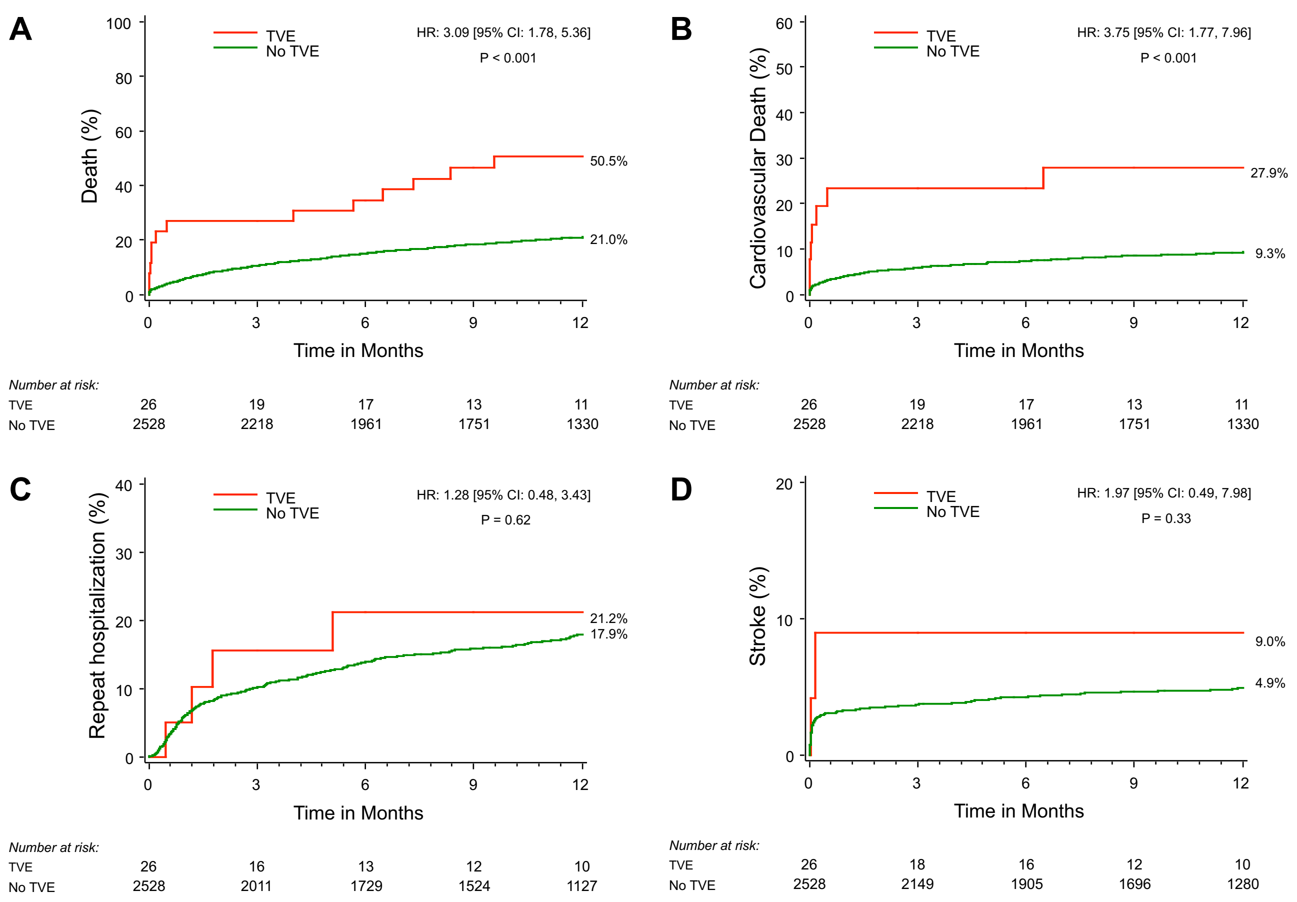

Figure 5 Impact of Transcatheter Valve Embolization on Outcome

(A) All cause mortality. **(B)** Cardiovascular mortality. **(C)** Stroke. **(D)** Rehospitalization.

We saw male sex to be the most important independent predictor of TV-in-TV. Device undersizing by echocardiography did not appear to account for this, with no difference in the annular dimension:valve size ratio (Table 2). There were limited baseline CT data available, and it is known that relative undersizing by cross-sectional measures is relatively more substantial in males than in females (10).

The number of prior TAVR procedures performed in the treating center, a measure of each center's clinical experience in TAVR, did not differ for TV-in-TV cases (Table 2), suggesting that the learning curve for the TAVR procedure did not contribute to this complication. There may be a lower threshold for TV-in-TV with greater operator experience that counteracts any reduction in the need for the maneuver.

Valvular function and implications for late TV-in-TV. The former study of balloon-expandable TV-in-TV showed no statistically significant differences in TAVR valve gradients acutely (5). In contrast, the investigators found a later statistically significant but clinically insignificant difference in gradients at 1 year (15 $\pm$ 4 mm Hg vs. 11 $\pm$ 4 mm Hg, $p = 0.02$) that we did not. The Italian registry reported no difference in gradients at follow-up after TV-in-TV with the CoreValve self-expanding TAVR (6).

All TV-in-TV studies (Online Table 5) concur on the similarities in gradients after TV-in-TV, which appear lower than that seen after transcatheter valve-in-surgical valve (V-in-V) for degenerated bioprostheses, where mean gradients $\geq$20 mm Hg have been seen in 40% of cases with balloon-expandable TAVR (11). We saw a mean gradient of $\geq$20 mm Hg in only 1 patient (1.6%). This may be because, in contrast to V-in-V, performed in surgical (mostly stented) bioprostheses, the landing zone in TV-in-TV is a more compliant metal frame; in view of this, forceful expansion of a second transcatheter valve is conceivably strong enough to achieve potentially similar intraluminal dimensions. This may also have relevance to the changes seen in cardiac conduction.

Impact of TV-in-TV on survival and cardiac conduction. Prior TV-in-TV studies (5,6) were underpowered for definitive conclusions on outcomes. Despite the absence of differences in intermediate term valvular function, we found TV-in-TV to be an independent predictor of cardiovascular mortality. Although the underlying mechanisms for this remain unclear, the excess of abnormal conduction and permanent pacemaker implantation could be important. Induced LBBB remains an area of controversy. Although Urena et al. (12) found that new-onset LBBB in 30.2% of 202 patients after balloon-expandable TAVR was not associated with increased 1-year mortality, a larger multidevice registry of Houthuizen et al. (13) showed an excess mortality regardless of device deployed. Putative risk mechanisms associated with LBBB are progression to high-degree atrioventricular conduction disorders and a dyssynchrony-related reduction in cardiac function.

Of 63 cases of TV-in-TV in the present study, the first valve was malpositioned in 28 cases and implanted low (toward the ventricle) in 10 of these. Low malpositioning is relatively rare with the balloon-expandable valve but has been shown to be related to the increased incidence of LBBB but not permanent pacemaker implantation (12).

Observations from this study have implications for the future, if late degeneration is observed in TAVR prostheses and late elective TV-in-TV is considered. Similar gradients and valvular functions at early and midterm follow-up suggest that elective TV-in-TV is likely to offer favorable hemodynamic results. The increased cardiovascular mortality we observed from emergent, acute TV-in-TV cannot be extrapolated to the late, elective setting. Nevertheless, until this is better understood, TV-in-TV procedures, whether performed early or late, demand close cardiological follow-up.

TVE in context. There has been a considerable variability among series in the reported incidence of TVE. The SAPIEN Aortic Bioprosthesis European Outcome (SOURCE) registry reported an incidence of 0.3% (14) whereas the incidence was 10% in an early pre-US PARTNER experience of the TA approach (15). We saw a tendency for TVE to diminish with a center's increasing experience. This phenomenon appeared more marked with the TA approach, with 83% of cases of embolization occurring with the TA approach during centers' first 20 cases. Interestingly, there were no TVEs in more than 500 TF implants in the recently presented PARTNER 2B trial; in all likelihood this was attributable to increased operator and site experience (9).

There are several important points related to the interaction between access approach (TF or TA) and final location of the embolized valve (aortic or ventricular) (Online Table 6). Although there was a trend toward more embolizations by the TF approach, the TA approach was associated with more ventricular embolization and a higher consequent rate of mortality. Indeed, aortic embolization in TF cases appeared less dangerous in that the only patient that died did not receive a TAVR. Accordingly, whether it is after or before dealing with the embolized valve, TAVR should be completed. Despite relatively more ventricular embolizations with the TA approach, the outcome of ventricular embolization appeared better with this approach; this may be related to the procedural setup and the ability to convert to emergent open surgery efficiently.

Although TVE was mostly immediate, several cases occurred some time later, up to 1-h postimplantation. We saw only 1 case of late embolization at 7 hours post-procedure in the context of cardiopulmonary resuscitation. Spontaneous late ventricular embolization has been reported up to 2 days post-procedure, in a case of TV-in-TV (16); such a phenomenon is likely attributable to device undersizing.

Although TVE is often related to technical factors such as timing of balloon inflation and suboptimal rapid pacing, anatomic factors emerged as an equally important cause of TVE. We saw larger annuli in cases with embolization (2.04 cm [IQR 1.94 to 2.23 cm] vs. 1.92 cm [IQR 1.73 to

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2.06 cm], p = 0.004) (Table 2). Despite being identified by the operator in only 1 case, undersizing was present in at least 7 of 26 (26.9%) of cases. Similarly, Tay et al. (17) described several cases of undersizing by 2D TEE measurements in their 7 patient series. We also saw device oversizing to contribute to TVE, with ventricular embolization in a case with a disproportionately small sinotubular junction.

Misplacement can clearly contribute to both TVE and TV-in-TV. In this regard, accurate determination of the annulus location with a coplanar fluoroscopic projection is essential.

Study limitations. This was a retrospective analysis of 2 relatively rare complications. As such, information was based mainly on a review of procedural notes, with a reliance on the accuracy of center-led reporting. There were limited CT data available at baseline, restricting comprehensive interpretation. Our findings were based on the first generation of the balloon-expandable Sapien prosthesis, which may limit its applicability to the more recent Sapien XT prosthesis.

Conclusions

Acute transcatheter valve failure and TVE can often be rectified through the implantation of multiple valves, facilitating a successful immediate outcome. Despite this, both TV-in-TV and TVE predicted adverse outcomes at 1 year. Considerable effort should therefore be invested in their avoidance, particularly because they are often caused by anatomic and technical pitfalls that may be preventable with judicious procedural planning.

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Key Words: embolization ▪ outcomes ▪ TAVI ▪ TAVR ▪ transcatheter valve ▪ TVE ▪ valve-in-valve.

APPENDIX

For an expanded results section and the supplemental tables and figures, please see the online version of this article.