

# Meta-analysis of Valve-in-Valve Transcatheter versus Redo Surgical Aortic Valve Replacement

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## Abstract

**Objective** The objective of this study was to determine whether valve-in-valve transcatheter aortic valve implantation (VIV-TAVI) is associated with better survival than redo surgical aortic valve replacement (SAVR) in patients with degenerated aortic valve bioprostheses, and we performed a meta-analysis of comparative studies.

**Methods** To identify all comparative studies of VIV-TAVI versus redo SAVR; MEDLINE, Embase, and the Cochrane Central Register of Controlled Trials were searched through October 2017. For each study, data regarding all-cause mortality in both the VIV-TAVI and redo SAVR groups were used to generate odds ratios (ORs). To assess selection bias, we generated ORs and (standardized) mean differences (MDs) for baseline characteristics. Study-specific estimates were combined in the random-effects model.

**Results** Of 446 potentially relevant articles screened initially, 6 reports of retrospective comparative studies enrolling a total of 498 patients were identified. Pooled analyses of baseline characteristics demonstrated no statistically significant differences in the proportion of women, patients with diabetes mellitus, patients with coronary artery disease, and patients with baseline New York Heart Association functional class of  $\geq$ III; baseline ejection fraction; and predicted mortality between the VIV-TAVI and redo SAVR groups. Patients in the VIV-TAVI group, however, were significantly older (MD, 4.20 years) and had undergone prior coronary artery bypass grafting more frequently (OR, 2.19) than those in the redo SAVR group. Main pooled analyses demonstrated no statistically significant differences in early (30 days or in-hospital) (OR, 0.91;  $p = 0.83$ ) and midterm (180 days–3 years) all-cause mortalities (OR, 1.42;  $p = 0.21$ ) between the VIV-TAVI and redo SAVR groups.

**Conclusion** In patients with degenerated aortic valve bioprostheses, especially elderly or high-risk patients, VIV-TAVI could be a safe, feasible alternative to redo SAVR. The lack of randomized data and differences in baseline characteristics in the present analysis emphasize the need for prospective randomized trials.

## Keywords

- ▶ degenerated aortic valve bioprostheses
- ▶ meta-analysis
- ▶ redo surgical aortic valve replacement
- ▶ valve-in-valve transcatheter aortic valve implantation

## Introduction

The use of valve-in-valve (VIV) transcatheter aortic valve implantation (TAVI) (VIV-TAVI) for the treatment of high-risk patients with degenerated aortic bioprostheses is associated with relatively low rates of mortality and major complica-

tions, improved hemodynamics and excellent improvement in functional and quality of life outcomes at 1 year,<sup>1</sup> whereas redo surgical aortic valve replacement (SAVR) is now performed with acceptable operative mortality of 4.6%.<sup>2</sup> Although mortality and morbidity are high compared with primary SAVR, the rates of stroke, vascular complications,

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and postoperative aortic regurgitation are low.<sup>2</sup> To our knowledge, however, there have been a few comparative studies of VIV-TAVI and redo SAVR to date. Because of its less invasiveness than redo SAVR, VIV-TAVI is expected to reduce mortality in patients with degenerated aortic valve bioprostheses who are at high surgical risk in the extreme. To determine whether VIV-TAVI is associated with better survival than redo SAVR, we herein performed a meta-analysis of comparative studies of VIV-TAVI versus redo SAVR.

## Materials and Methods

All comparative studies of VIV-TAVI versus redo SAVR enrolling patients with degenerated aortic valve bioprostheses were identified using a two-level search strategy. First, databases including MEDLINE, Embase, and the Cochrane Central Register of Controlled Trials were searched through October 2017 using Web-based search engines (PubMed and Ovid). Second, relevant studies were identified through a manual search of secondary sources including references of initially identified articles and a search of reviews and commentaries. All references were downloaded for consolidation, elimination of duplicates, and further analysis. Search terms included valve-in, TAVI-in, or TAV-in; redo, re-do, reoperation, re-operation, reoperative, re-operative, re-surgery, or re-surgical; and aortic valve.

Studies considered for inclusion met the following criteria: the design was a comparative study; the study population was patients with degenerated aortic valve bioprostheses; patients were assigned to VIV-TAVI versus redo SAVR; and main outcomes included all-cause mortality. Data regarding detailed inclusion criteria, device type, duration of follow-up, and all-cause mortality were abstracted (as available) from each individual study. We focused on mortality as an outcome of interest in the present meta-analysis. Data were extracted in duplicate by two investigators (H.T. and S.M.) and independently verified by a third investigator (T.A.). Disagreements were resolved by consensus.

We conducted a meta-analysis of summary statistics from the individual studies because detailed patient-level data were not available for all studies. For each study, data regarding all-cause mortality in both the VIV-TAVI and redo SAVR groups were used to generate odds ratios (ORs) and 95% confidence intervals (CIs). To assess selection bias (differences in baseline characteristics of individuals in different intervention groups), we generated ORs for proportions (%) of women, patients with diabetes mellitus (DM), patients with coronary artery disease (CAD), patients undergoing prior coronary artery bypass grafting (CABG), and patients with baseline New York Heart Association (NYHA) functional class of  $\geq$ III; mean differences (MDs) for ages (year) and baseline left ventricular ejection fraction (LVEF [%]); and a standardized MD (SMD) for predicted mortality (%).

Study-specific estimates were combined using inverse variance-weighted averages of logarithmic ORs and MDs or SMDs in the random-effects model. Publication bias was assessed graphically using a funnel plot and mathematically using an adjusted rank-correlation test of Begg and Mazumdar<sup>3</sup> and a

linear regression test of Egger et al.<sup>4</sup> All analyses were conducted using Review Manager version 5.3 (available at: <http://community.cochrane.org/tools/review-production-tools/revman-5>) and Prometa 3 (available at: <https://idostatistics.com/prometa3/>).

## Results

As outlined in **►Supplementary Fig. S1** (available online only), of 446 potentially relevant articles screened initially, 6 reports<sup>5–10</sup> of comparative studies of VIV-TAVI versus redo SAVR enrolling a total of 498 (VIV-TAVI, 254; redo SAVR, 244) patients with degenerated aortic valve bioprostheses were identified and included (**►Table 1**). All were retrospective observational studies including two matched studies.<sup>5,10</sup> Patients were matched 1:1 on Society of Thoracic Surgeons Predicted Risk Of Mortality (STS-PROM) scores followed by sex, age, and year of procedure in a study,<sup>5</sup> and propensity scores among patients undergoing either VIV-TAVI or redo SAVR were matched to obtain matched pairs of patients in another study.<sup>10</sup> In the other four studies,<sup>6–9</sup> no adjustment was performed. Types of degenerated bioprostheses are summarized in **►Supplementary Table S1** (available online only). No concomitant procedure was performed in the redo SAVR group of four studies.<sup>5,6,8,9</sup> In a study,<sup>7</sup> concomitant CABG, mitral valve surgery, and others were performed in 20, 40, and 8.0% of patients, respectively. In another study,<sup>10</sup> concomitant CABG was performed in 26.9% of patients. Some end points except for mortality are summarized in **►Table 2**.

Pooled analyses of baseline characteristics (**►Table 3**) demonstrated no statistically significant differences in the proportion of women (44.9 vs. 39.3%;  $p = 0.37$ ; **►Supplementary Fig. S2**, available online only), patients with DM (21.1 vs. 15.1%;  $p = 0.05$ ; **►Supplementary Fig. S3**, available online only), patients with CAD (43.8 vs. 23.9%;  $p = 0.12$ ; **►Supplementary Fig. S4**, available online only), and patients with baseline NYHA functional class of  $\geq$ III (86.7 vs. 79.5%;  $p = 0.22$ ; **►Supplementary Fig. S5**, available online only); baseline LVEF (MD,  $-2.07\%$ ;  $p = 0.39$ ; **►Supplementary Fig. S6**, available online only); and predicted mortality (SMD,  $-0.03$ ;  $p = 0.91$ ; **►Supplementary Fig. S7**, available online only) between the VIV-TAVI and redo SAVR groups. Patients in the VIV-TAVI group, however, were significantly older than those in the redo SAVR group (MD, 4.20 years;  $p = 0.004$ ; **►Supplementary Fig. S8**, available online only). Furthermore, significantly more patients undergone prior CABG in the VIV-TAVI group than in the redo SAVR group (36.7 vs. 21.8%; OR, 2.19;  $p = 0.005$ ; **►Supplementary Fig. S9**, available online only).

Main pooled analyses demonstrated no statistically significant differences in early (30 days or in-hospital) (OR, 0.91;  $p = 0.83$ ) and midterm (180 days–3 years) all-cause mortalities (OR, 1.42;  $p = 0.21$ ) between the VIV-TAVI and redo SAVR groups (**►Table 4**; **►Fig. 1**).

To assess publication bias in the main meta-analyses, we generated a funnel plot of the OR versus the standard error

**Table 1** Included studies

Study	Adjustment	Transcatheter heart valve (%)									
		CoreValve	CoreValve Evolut	Lotus	Engager	JenaValve	Portico	Sapien	Sapien XT	Sapien 3	
Ejiofor et al (2016) <sup>5</sup>	Matched 1:1 on STS-PROM scores followed by sex, age, and year of procedure	22.7	0	0	0	0	0	45.5	31.8	0	
Erlebach et al (2015) <sup>6</sup>	None	34.0	0	0	0	2.0	0	0	60.0	4.0	
Grubitzsch et al (2017) <sup>7</sup>	None	CoreValve/CoreValve Evolut/Lotus, 44.4		0	0	0	0	Sapien/Sapien XT, 55.6		0	
Santarpino et al (2016) <sup>8</sup>	None	0	0	0	0	0	0	0	100	0	
Silaschi et al (2017) <sup>9</sup>	None	39.4	0	0	2.8	2.8	4.2	0	Sapien XT/Sapien 3, 50.7		
Spaziano et al (2017) <sup>10</sup>	Propensity-score matching	59.0	0	0	0	0	0	Sapien/Sapien XT/Sapien 3, 41.0			
Study	Surgical heart valve (%)										
	Stented bio-prosthesis	Stentless bioprosthesis		Sutureless bioprosthesis		Mechanical valve					
Ejiofor et al (2016) <sup>5</sup>	77.3	NR	NR								
Erlebach et al (2015) <sup>6</sup>	88.5	1.9	0								
Grubitzsch et al (2017) <sup>7</sup>	28.0	64.0	0								
Santarpino et al (2016) <sup>8</sup>	0	0	100								
Silaschi et al (2017) <sup>9</sup>	94.9	5.1	0								
Spaziano et al (2017) <sup>10</sup>	98.7	1.3	0								

Abbreviations: NR, not reported; STS-PROM, Society of Thoracic Surgeons Predicted Risk Of Mortality.

**Table 2** Clinical end points

Study	According to VARC-2 criteria	Myocardial infarction (%)		Stroke (%)		Bleeding complications (%)			Acute kidney injury (%)				
		VIV-TAVI	Redo SAVR	VIV-TAVI	Redo SAVR	VIV-TAVI	Redo SAVR	VIV-TAVI	Redo SAVR	VIV-TAVI	Redo SAVR		
Ejiofor et al (2016) <sup>5</sup>	NR	NR	9.1	0	9.1	NR	NR	9.1 <sup>a</sup>	4.5 <sup>a</sup>	9.1 <sup>a</sup>	4.5 <sup>a</sup>	0.546	
Eriebach et al (2015) <sup>6</sup>	Yes	2.0	1.9	4.0	1.9	NR	0.614	12.0 <sup>a</sup>	1.9 <sup>a</sup>	12.0 <sup>a</sup>	1.9 <sup>a</sup>	0.057	
Grubitzsch et al (2017) <sup>7</sup>	Yes	11.1	0	0	4.0	33.3	NR	14.8	24.0	14.8	32.0	NR	
Santarpino et al (2016) <sup>8</sup>	NR	16.7	0	0	0	0	NR	0 <sup>b</sup>	0	0 <sup>b</sup>	25.0 <sup>b</sup>	NR	
Silaschi et al (2017) <sup>9</sup>	Yes	1.4	1.7	0	3.4	9.9 <sup>e</sup>	NR	2.8 <sup>d</sup>	33.9 <sup>e</sup>	2.8 <sup>d</sup>	13.6 <sup>d</sup>	0.04	
Spaziano et al (2017) <sup>10</sup>	Yes	1.3	0	1.3	0	NR	1	3.8 <sup>e</sup>	NR	3.8 <sup>e</sup>	11.5 <sup>e</sup>	0.13	
Study	Vascular complications (%)	New PPMI (%)		ICU stay		Hospital stay (d)							
	VIV-TAVI	Redo SAVR	VIV-TAVI	Redo SAVR	VIV-TAVI	Redo SAVR	VIV-TAVI	Redo SAVR	VIV-TAVI	Redo SAVR	VIV-TAVI	Redo SAVR	p-Value
Ejiofor et al (2016) <sup>5</sup>	NR		4.5	4.5	0 (0-50) h <sup>f</sup>	68 (43-98) h <sup>f,g</sup>	5 (2-7) <sup>f</sup>	10.5 (8-18) <sup>f</sup>	0.001	10.5 (8-18) <sup>f</sup>	0.001	0.001	
Eriebach et al (2015) <sup>6</sup>	2.0	0	NR	21.2	8 ± 10 d	7.8 ± 13.7 d	13.7 ± 9.7	14.9 ± 13.8	0.928	13.7 ± 9.7	14.9 ± 13.8	0.633	
Grubitzsch et al (2017) <sup>7</sup>	7.4	0	NR	8.0	NR	NR	NR	NR	NR	NR	NR	NR	
Santarpino et al (2016) <sup>8</sup>	0	0	NR	12.5	2.3 ± 2 d	5.6 ± 5 d	10.8 ± 2.9	15 ± 8	NR	10.8 ± 2.9	15 ± 8	0.25	
Silaschi et al (2017) <sup>9</sup>	2.1	5.1	NR	27.1	2.0 ± 1.8 d	3.4 ± 2.9 d	<0.01	NR	<0.01	NR	NR	NR	
Spaziano et al (2017) <sup>10</sup>	NR		10.3	10.3	NR	NR	9 (7-13) <sup>f</sup>	12 (8-24) <sup>f</sup>	NR	9 (7-13) <sup>f</sup>	12 (8-24) <sup>f</sup>	0.001	

Abbreviations: ICU, intensive care unit; NR, not reported; PPMI, permanent pacemaker implantation; SAVR, surgical aortic valve replacement; VARC, Valve Academic Research Consortium; VIV-TAVI, valve-in-valve transcatheter aortic valve implantation.

<sup>a</sup>New dialysis.  
<sup>b</sup>Renal failure requiring temporary dialysis.  
<sup>c</sup>Life-threatening or disabling bleeding.  
<sup>d</sup>Stage 2/3.  
<sup>e</sup>Renal failure requiring dialysis.  
<sup>f</sup>Median (interquartile range).  
<sup>g</sup>Only the 22.7% of patients required ICU stay.

**Table 3** Baseline characteristics

Study	Patient number		Age (y)		Women (%)		Diabetes mellitus (%)	
	VIV-TAVI	Redo SAVR	VIV-TAVI	Redo SAVR	VIV-TAVI	Redo SAVR	VIV-TAVI	Redo SAVR
Ejiofor et al (2016) <sup>5</sup>	22	22	75.0 ± 9.6	74.5 ± 10.4	36.4	40.9	45.5	22.7
Erlbach et al (2015) <sup>6</sup>	50	52	78.1 ± 6.7	66.2 ± 13.1	46.0	26.9	20.0	9.6
Grubitzsch et al (2017) <sup>7</sup>	27	25	75.3 ± 9.9	69.0 ± 8.6	76.9		NR	
Santaripino et al (2016) <sup>8</sup>	6	8	80.2 ± 2.3	78.8 ± 3	33.3	75.0	83.3	62.5
Silaschi et al (2017) <sup>9</sup>	71	59	78.6 ± 7.5	72.9 ± 6.6	42.3	39.0	11.3	10.2
Spaziano et al (2017) <sup>10</sup>	78	78	78.0 ± 8.0	77.4 ± 5.0	50.0	43.6	19.2	15.4
Total	254	244	MD, 4.20 (1.36, 7.04) <sup>a</sup>	0.004	OR, 1.24 (0.77, 2.00) <sup>a</sup>	0.37	OR, 1.67 (0.99, 2.80) <sup>a</sup>	0.05
Study	Coronary artery disease (%)		Prior CABG (%)		NYHA class ≥ III (%)			
	VIV-TAVI	Redo SAVR	VIV-TAVI	Redo SAVR	VIV-TAVI	Redo SAVR	VIV-TAVI	p-Value
Ejiofor et al (2016) <sup>5</sup>	NR		63.6	54.5	0.760	72.7	0.095	
Erlbach et al (2015) <sup>6</sup>	46.0	11.5	40.0	11.5	0.001	74.1	NR	
Grubitzsch et al (2017) <sup>7</sup>	50.0		25.0			90.4		
Santaripino et al (2016) <sup>8</sup>	NR		NR			NR		
Silaschi et al (2017) <sup>9</sup>	NR		32.4	16.9	NR	NR		
Spaziano et al (2017) <sup>10</sup>	42.3 <sup>b</sup>	32.1 <sup>b</sup>	0.25 <sup>b</sup>	23.1	0.37	80.8	83.3	NR
Total	OR, 3.02 (0.74, 12.26) <sup>a</sup>	0.12	OR, 2.19 (1.27, 3.76) <sup>a</sup>		0.005	OR, 2.37 (0.59, 9.46) <sup>a</sup>	0.22	
Study	Ejection fraction (%)		Predicted mortality (%)					
	VIV-TAVI	Redo SAVR	System	VIV-TAVI	Redo SAVR	p-Value		
Ejiofor et al (2016) <sup>5</sup>	Median, 55.0 (IQR, 35–60)	Median, 55.0 (IQR, 50–60)	STS-PROM	7.54 ± 3.0	7.70 ± 3.4	0.360		
Erlbach et al (2015) <sup>6</sup>	49.8 ± 13.1	56.7 ± 15.8	EuroSCORE I	14.4 ± 10	27.4 ± 18.7	<0.001		
Grubitzsch et al (2017) <sup>7</sup>	52.0 ± 11.4		EuroSCORE II	13.0 ± 10.4	8.9 ± 6.5	0.054		
Santaripino et al (2016) <sup>8</sup>	53 ± 13	58 ± 20	EuroSCORE I	33.8 ± 13.8	36.4 ± 24.1	0.81		
Silaschi et al (2017) <sup>9</sup>	NR		EuroSCORE I	25.1 ± 18.9	16.8 ± 9.3	<0.01		
Spaziano et al (2017) <sup>10</sup>	50.7 ± 13.5	49.5 ± 13.4	EuroSCORE I	22.1 ± 16.0	22.1 ± 18.3	0.99		
Total	MD, -2.07 (-6.79, 2.64) <sup>a</sup>	0.39	SMD, -0.03 (-0.48, 0.43) <sup>a</sup>		0.91			

Abbreviations: CABG, coronary artery bypass grafting; EuroSCORE, European System for Cardiac Operative Risk Evaluation; IQR, interquartile range; MD, mean difference; NR, not reported; NYHA, New York Heart Association; OR, odds ratio; SAVR, surgical aortic valve replacement; SMD, standardized mean difference; STS-PROM, Society of Thoracic Surgeons Predicted Risk Of Mortality; VIV-TAVI, valve-in-valve transcatheter aortic valve implantation.

<sup>a</sup>95% confidence interval.

<sup>b</sup>Necessitating revascularization.

**Table 4** Early and midterm all-cause mortalities

Study	Early all-cause mortality (%)			Midterm all-cause mortality (%)		
	Follow-up	VIV-TAVI	Redo SAVR	Follow-up	VIV-TAVI	Redo SAVR
Ejiofor et al (2016) <sup>5</sup>	Operative	0	4.5	3 y	21.3 <sup>a</sup>	23.7 <sup>a</sup>
Erlebach et al (2015) <sup>6</sup>	30 d	4.0	0	1 y	4 <sup>a</sup>	17 <sup>a</sup>
Grubitzsch et al (2017) <sup>7</sup>	30 d	11.1	8.0	1 y	18.5	16.0
Santarpino et al (2016) <sup>8</sup>	In-hospital	0	0	21 ± 13 mo	0	0
Silaschi et al (2017) <sup>9</sup>	30 d	4.2	5.1	180 d	10.9	7.8
Spaziano et al (2017) <sup>10</sup>	30 d	3.8	6.4	1 y	11.5	12.8
Total	OR, 0.91 (0.39, 2.13) <sup>b</sup> ; <i>p</i> = 0.83			OR, 1.42 (0.82, 2.46) <sup>b</sup> ; <i>p</i> = 0.21		

Abbreviations: OR, odds ratio; SAVR, surgical aortic valve replacement; VIV-TAVI, valve-in-valve transcatheter aortic valve implantation.

<sup>a</sup>Kaplan–Meier's estimate.

<sup>b</sup>95% confidence interval.

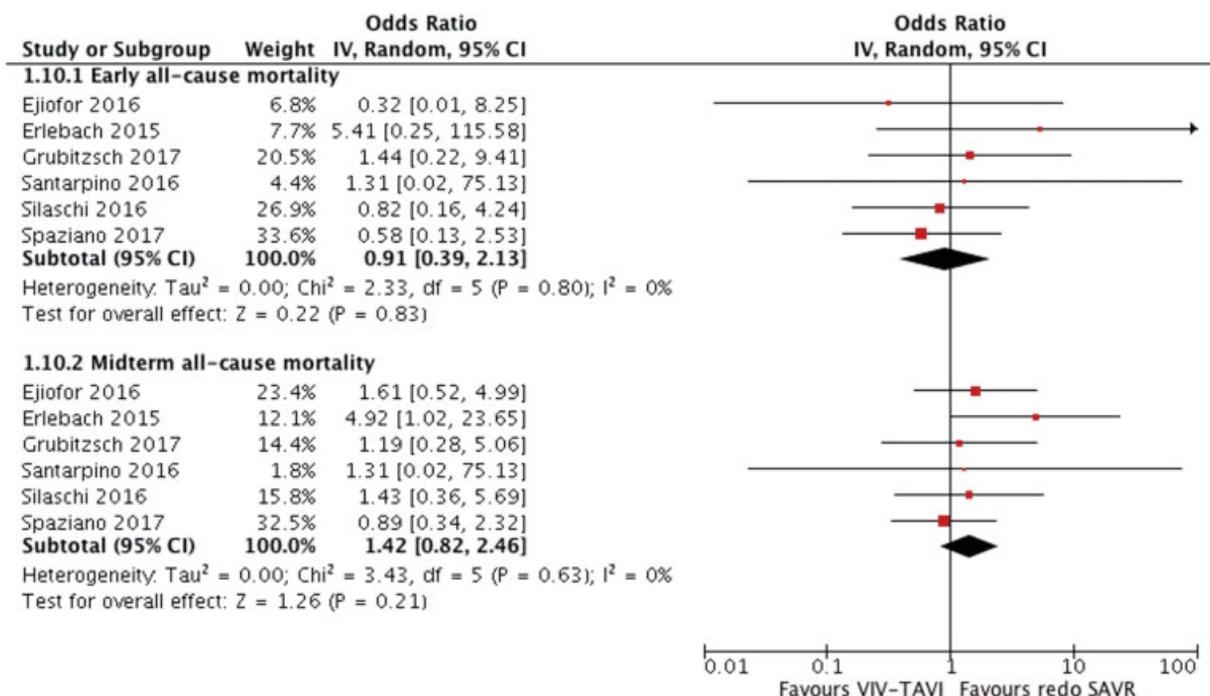
for each study (► **Supplementary Figs. S10** and **S11**, available online only). There was no evidence of significant publication bias: *p* for early all-cause mortality = 0.348 and 0.494 (► **Supplementary Fig. S10**, available online only) and *p* for midterm all-cause mortality = 0.573 and 0.493 (► **Supplementary Fig. S11**, available online only) by the tests of Begg and Mazumdar<sup>3</sup> and Egger et al,<sup>4</sup> respectively.

## Discussion

The results of the present meta-analysis suggest no difference in survival between VIV-TAVI and redo SAVR in patients with degenerated aortic valve bioprostheses. Although the proportion of women, patients with DM, patients with base-

line NYHA functional class of ≥III, baseline LVEF, and predicted mortality were similar between the VIV-TAVI and redo SAVR groups, patients in the VIV-TAVI group were older than those in the redo SAVR group.

Adding that older patients underwent VIV-TAVI, the following findings could explain similar survival between VIV-TAVI and redo SAVR despite less invasiveness of VIV-TAVI than redo SAVR. In the study by Ejiofor et al,<sup>5</sup> 22.7% of VIV-TAVI patients had mild paravalvular leaks compared with none in the SAVR group (*p* = 0.048). Erlebach et al<sup>6</sup> showed that the rate of postprocedural new dialysis (12.0 vs. 1.9%; *p* = 0.057), paravalvular leak (18.0 vs. 0%), and mean aortic valve gradient (18.8 ± 8.7 vs. 13.8 ± 5.4 mm Hg; *p* = 0.008) were higher in the VIV-TAVI group compared with the redo



**Fig. 1** Early and midterm all-cause mortalities. CI, confidence interval; IV, inverse variance; SAVR, surgical aortic valve replacement; VIV-TAVI, valve-in-valve transcatheter aortic valve implantation.

SAVR group. At follow-up ( $21 \pm 13$  months) echocardiographic evaluation in the study by Santarpino et al,<sup>8</sup> 87.5% of patients had no patient–prosthesis mismatch (PPM) and only 12.5% had mild/moderate PPM in the redo SAVR group, whereas only 16.7% had no PPM, 50.0% had mild/moderate PPM, and 33.3% had severe PPM in the VIV-TAVI group. The mean indexed effective orifice area (EOA) was  $0.96 \pm 0.08$  versus  $0.71 \pm 0.15$  cm<sup>2</sup>/m<sup>2</sup> in the redo SAVR versus VIV-TAVI group, respectively ( $p = 0.001$ ).<sup>8</sup> Silaschi et al<sup>9</sup> showed that a mean gradient of  $\geq 20$  mm Hg was present in 46.5% after VIV-TAVI versus 5.1% after SAVR ( $p < 0.01$ ) and the proportion of severe PPM (defined by indexed EOA  $\leq 0.65$  cm<sup>2</sup>/m<sup>2</sup>) tended to be higher compared with that of redo SAVR (14.1 vs. 3.4%;  $p = 0.06$ ). Decrease in transprosthetic gradients was stronger ( $p = 0.01$ ) after redo SAVR (25.0 mm Hg) than after VIV-TAVI (13.3 mm Hg).<sup>9</sup> At 30 days in the study by Spaziano et al,<sup>10</sup> redo SAVR was associated with a lower mean gradient compared with VIV-TAVI ( $14.3 \pm 6.2$  vs.  $18.1 \pm 7.4$  mm Hg; coefficient, 3.78 mm Hg; 95% CI, 0.95–6.60 mm Hg;  $p = 0.01$ ) and moderately elevated postprocedural mean gradients  $>20$  mm Hg were more frequently reported after VIV-TAVI than after redo SAVR (36 vs. 17%; OR, 3.74; 95% CI, 1.48–9.41;  $p = 0.04$ ). The above-mentioned findings unfavorable for VIV-TAVI may offset its less invasiveness than redo SAVR and affect early and midterm survival.

Although baseline CAD may affect follow-up mortality after VIV-TAVI and/or redo SAVR, there was no difference in the proportion of patients with CAD between the VIV-TAVI and redo SAVR groups (**► Supplementary Fig. S4**, available online only). More patients, however, had undergone prior CABG in the VIV-TAVI group than in the redo SAVR group (**► Supplementary Fig. S9**, available online only). Only Grubitzsch et al<sup>7</sup> (in the six studies included in the present meta-analysis) reported data on a patent internal mammary artery (IMA) graft, and VIV-TAVI patients presented more frequently with a patent IMA graft than redo SAVR (33.3 vs. 8.0%;  $p = 0.040$ ). Patients undergoing SAVR after CABG in the presence of a patent bypass graft (especially left IMA to left anterior descending artery graft) are at high risk of graft injury; therefore, surgeons should specifically consider to prevent graft injury.<sup>11</sup> Injury of a patent left IMA graft during dissection can have serious consequences, and the rate of injury has been reported to be 5 to 40%, with perioperative mortality to be 9 to 50%.<sup>12–14</sup> Therefore, surgeons may avoid redo SAVR in patients with prior CABG, in whom VIV-TAVI can be selected.

In the PARTNER 2 Valve-in-Valve Registry,<sup>1</sup> a multivariate Cox's proportional hazard regression model was used to assess the adjusted association between mortality and risk factors: STS-PROM, labeled valve size, transcatheter heart valve (THV) size, mean gradient  $\geq 20$  mm Hg, and severe PPM. Although there were no significant differences in mortality comparing previous surgical valve sizes (15.5% for 21 mm vs 11.4% for  $>21$  mm; hazard ratio [HR], 1.39; 95% CI, 0.73–2.63;  $p = 0.3156$ ), mortality was significantly greater at 1 year with a larger postprocedural mean gradient (16.7% for  $\geq 20$  mm Hg vs. 7.7% for  $<20$  mm Hg; HR, 2.27; 95% CI, 1.16–4.46;  $p = 0.0140$ ).<sup>1</sup> Trends toward increased mortality in patients with PPM (10.3% for severe PPM vs. 9.7% for

moderate PPM vs. 6.9% for no PPM) were not significant ( $p = 0.8617$ ).<sup>1</sup> Also, in the studies<sup>6,9</sup> included in the present meta-analysis, postprocedural gradients were higher after VIV-TAVI than redo SAVR ( $18.8 \pm 8.7$  vs.  $13.8 \pm 5.4$  mm Hg [ $p = 0.008$ ],<sup>6</sup> 19.7 vs. 12.2 mm Hg [ $p = 0.01$ ]).<sup>9</sup> Careful patient selection, preoperative image assessment, and accurate valve deployment during the procedure may be required to reduce postprocedure gradients after VIV-TAVI.<sup>5</sup> Redo SAVR rather than VIV-TAVI may be preferred in younger patients with degenerated aortic valve bioprostheses. Indeed, patients undergoing redo SAVR were younger than those undergoing VIV-TAVI in three<sup>6,7,9</sup> of the six studies included in the present study (**► Table 2**), which was confirmed in our meta-analytic evaluation (**► Supplementary Fig. S8**, available online only).

In the Global Valve-in-Valve Registry<sup>15</sup> including 202 patients with degenerated bioprostheses, there were no significant differences between the CoreValve and Edwards SAPIEN groups in mortality, major vascular complication, or stroke at 30 days and 1 year survival. Implantation of Edwards SAPIEN versus CoreValve, however, was an independent predictor for high postprocedural gradients ( $p = 0.02$ ). The difference is probably secondary to the fundamental dissimilarity between the devices (intra-annular and supra-annular functioning part of Edwards SAPIEN and CoreValve, respectively), which suggests that CoreValve depends much less on surgical bioprosthesis dimensions and its functioning part may have larger potential orifice area.<sup>15</sup> High implantation inside failed bioprostheses is also a strong independent correlate of lower postprocedural gradients in both self-expandable and balloon-expandable THVs.<sup>16</sup> In the Valve-in-Valve International Data registry<sup>16</sup> evaluating 292 consecutive patients, the strongest independent correlate for lower gradients after VIV-TAVI was high device position ( $p = 0.001$ ) in addition to CoreValve Evolut (vs. SAPIEN XT) use ( $p = 0.02$ ), which suggests that it would be possible to obtain better hemodynamic results in VIV-TAVI if the THV functions above the surgical valve stent.<sup>17</sup>

Patients undergoing VIV-TAVI are particularly at risk for PPM because the TAVI prosthesis is implanted within the frame of the previous surgical bioprosthetic valve, thereby reducing the maximum EOA achieved with the new valve.<sup>18</sup> There have recently been a few publications on the concept of fracturing the surgical bioprosthetic valve ring with a high-pressure balloon inflation to dilate the surgical valve and permit further expansion of the THV.<sup>18–20</sup> For the combined cohort, the mean gradient was reduced from 41 mm Hg preprocedure to 11 mm Hg after bioprosthetic valve fracture and VIV-TAVI, which corresponds to an improvement in EOA from 0.75 to 1.7 cm<sup>2</sup>.<sup>18–20</sup> The benefit of bioprosthetic valve fracture to improve the procedural results of VIV-TAVI is evident, whereas these patients would have been left with a suboptimal EOA and gradient with VIV-TAVI alone.<sup>18</sup>

## Limitations

Our analysis must be viewed in the context of its limitations. First, we used only data from retrospective observational

comparative studies, not randomized controlled trials. Although the proportion of women, patients with DM, patients with baseline NYHA functional class of  $\geq$ III, baseline LVEF, and predicted mortality were similar between the VIV-TAVI and redo SAVR groups, patients in the VIV-TAVI group were older than those in the redo SAVR group. In studies included in the present meta-analysis, patients were pre-selected by a heart team, and therefore, the groups are biased. Second, our results may be influenced by publication bias. This risk was minimized through an exhaustive search of the available literature. Although the statistical tests did not indicate publication bias, there is clearly limited power to detect such bias, given the small number of studies examined.

## Conclusion

In patients with degenerated aortic valve bioprostheses, especially elderly or high-risk patients, VIV-TAVI could be a safe and feasible alternative to redo SAVR. The lack of randomized data and differences in baseline characteristics in the present analysis emphasize the need for prospective randomized trials.

### Conflict of Interest

None declared.

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