Systematic review and meta-analysis of valve-in-valve transcatheter aortic valve replacement in patients with failed bioprosthetic aortic valves



Ahmed N. Mahmoud¹, MD; Mohamed M. Gad², MD; Islam Y. Elgendy³, MD; Ahmad A. Mahmoud⁴, MD; Yasmeen Taha⁴, MD; Akram Y. Elgendy⁵, MD; Keerat R. Ahuja², MD; Anas M. Saad², MD; Matheus Simonato⁶, MD; James M. McCabe¹, MD; Mark Reisman¹, MD; Samir R. Kapadia², MD; Danny Dvir¹*, MD

1. Division of Cardiology, University of Washington, Seattle, WA, USA; 2. Cleveland Clinic Heart and Vascular Institute, Cleveland, OH, USA; 3. Division of Cardiology, Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA; 4. Department of Medicine, University of Florida, Gainesville, FL, USA; 5. Division of Cardiology, University of Florida, Gainesville, FL, USA; 6. Escola Paulista de Medicina - Universidade Federal de São Paulo, São Paulo, Brazil

A.N. Mahmoud and M.M. Gad contributed equally to this article.

This paper also includes supplementary data published online at: https://eurointervention.pcronline.com/doi/10.4244/EIJ-D-19-00928

KEYWORDS

- aortic stenosis
- clinical research
- TAVI
- valve-in-valve

Abstract

Aims: The aim of this meta-analysis was to evaluate the evidence regarding the rates of procedural success and the incidence of adverse outcomes following valve-in-valve (VIV) transcatheter aortic valve replacement (TAVR) in patients with failed bioprosthetic aortic valves.

Methods and results: A systematic search of major electronic databases was conducted for studies relevant to patients with failed bioprosthetic aortic valves undergoing VIV-TAVR. The primary outcome was procedural success. A total of 5,553 patients from 24 studies were included. The mean Society of Thoracic Surgeons (STS) score was 7.84 \pm 5.14. The procedural success rate was high (97%, 95% confidence interval [CI]: 94-98%). At 30 days, all-cause mortality was 5% (95% CI: 3-6%), stroke 2% (95% CI: 1-2%), myo-cardial infarction 1% (95% CI: 1-2%), permanent pacemaker placement 6% (95% CI: 5-8%), and aortic regurgitation 7% (95% CI: 5-10%). At one year, the incidence of all-cause mortality was 12% (95% CI: 10-14%), stroke 3% (95% CI: 2-4%), myocardial infarction 1% (95% CI: 0-2%), and permanent pacemaker placement 7% (95% CI: 5-11%). At three years, the incidence of all-cause mortality was 29% (95% CI: 25-34%) and stroke 6% (95% CI: 5-9%).

Conclusions: VIV-TAVR appears to be associated with high procedural success rates and low adverse outcomes during the short-term and midterm follow-up period.

EuroIntervention 2020;16:539-548 published online

Jaa May 2020

*Corresponding author: Division of Cardiology, University of Washington, 1410 NE Campus Parkway, Seattle, WA 98195-6422, USA. E-mail: danny.dvir@gmail.com

Abbreviations

SAVR	surgical aortic valve replacement
TAVR	transcatheter aortic valve replacement
ViV	valve-in-valve

ViV-TAVR valve-in-valve transcatheter aortic valve replacement

Introduction

Bioprosthetic valves implanted with surgery or with the transcatheter approach have been shown to have a durability of up to 10 years post implantation¹. With the improved durability of newer generations of bioprosthetic valves and the accompanying lower bleeding and thromboembolic risks over mechanical valves, they are becoming an attractive alternative to treat severe aortic stenosis in younger patients <60 years old^{2,3}. As a direct consequence, the rates of redo aortic valve replacement procedures are expected to increase substantially in the near future, given the longer life expectancy of patients receiving aortic valve replacement⁴.

Transcatheter aortic valve replacement (TAVR) has emerged as an acceptable therapy for most of the spectrum of patients with severe aortic stenosis (i.e., from high-risk inoperable patients to low-risk patients)⁵⁻⁷. Redo surgical aortic valve replacement (SAVR) carries a higher risk of procedural complications and intraoperative mortality, and thus valve-in-valve (VIV) TAVR has emerged as an alternative to redo SAVR in patients with high operative mortality risk; however, the studies were mostly small and single-centred⁸.

Therefore, we aimed to conduct a systematic review and metaanalysis evaluating the available evidence regarding the short-term and midterm procedural outcomes of VIV-TAVR in patients with failed bioprosthetic aortic valves.

Editorial, see page 529

Methods

DATA SOURCES

The PubMed, Cochrane, and Embase electronic databases were searched from inception until January 2020 for observational cohort studies and randomised controlled trials reporting clinical outcomes in patients with VIV-TAVR. This meta-analysis was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and was prospectively registered on the PROSPERO international prospective register of systematic reviews: CRD42019136105.

The study screening and selection process (PRISMA diagram) is presented in **Supplementary Figure 1**. Details of the search strategy are shown in **Supplementary Table 1**.

INCLUSION AND EXCLUSION CRITERIA

A study was included if it satisfied the following criteria: i) a randomised trial, prospective cohort, or a retrospective cohort, ii) reporting outcomes of interest in patients undergoing VIV-TAVR. Studies that were published as conference abstracts, case reports, narrative reviews, studies with <20 patients, studies that were designed as case series or studies that included the same patient population were excluded from this analysis.

DATA EXTRACTION

Two authors (M.M. Gad and A.A. Mahmoud) independently screened the titles and abstracts of the searched studies, screened full-text studies, and extracted study and population characteristics and outcomes of interest.

DEFINITION OF OUTCOMES

The primary outcome was the procedural success as defined by the individual study **(Supplementary Table 2)**. The secondary outcomes were all-cause mortality, myocardial infarction, stroke, the incidence of aortic regurgitation, placement of a permanent pacemaker, and mean gradient across the valve at 30 days, one year, and three years.

ASSESSMENT OF STUDY QUALITY

The "Risk Of Bias In Non-randomised Studies - of Interventions" (ROBINS-I) scale was used to evaluate the risk of bias in the included studies⁹ (Supplementary Table 3).

STATISTICAL ANALYSIS

Single-arm proportion-weighted meta-analysis calculation was performed using the inverse variance method using the "meta" function of R statistical software¹⁰. Summary estimates were calculated using the DerSimonian and Laird random effects model¹¹. The I² statistic was used to assess the heterogeneity between the included studies. Continuity correction of 0.5 in studies with zero cell frequencies was utilised by the statistical package. Prespecified subgroup analyses were performed based on device type (balloon-expandable versus self-expanding), country (USAbased versus outside of the USA), study design (retrospective versus prospective), and procedure used in prior valve replacement (SAVR versus TAVR).

Results

DATA SYNTHESIS

Among 1,914 records initially screened by title and abstract, 24 studies satisfied our final inclusion and exclusion criteria, comprising a total of 5,553 patients with a bioprosthetic aortic valve undergoing VIV-TAVR¹²⁻³⁵. Six studies were not included, although they satisfied our inclusion criteria. One was excluded because a longer-term follow-up study was published using the same cohort³⁶. The remainder of excluded studies were subsets of larger cohorts of patients published in another study³⁷⁻⁴⁰. Ten studies were prospective^{12-14,16,20,26,29,32-34}, and the remainder of the studies were retrospective cohorts^{15,17-19,21-25,27,28,30,31,35} (Supplementary Table 4). The details of our systematic search are reported in the PRISMA figure (Supplementary Figure 1).

STUDY AND PATIENT CHARACTERISTICS

The weighted mean age of patients was 76.63 ± 8.78 years and 61.8% were male. The baseline pooled mean ejection fraction (EF) was $52.14\pm11.36\%$. The pooled mean Society of Thoracic Surgeons (STS) score was 7.84 ± 5.14 . Balloon-expandable

VIV-TAVR was performed exclusively in three studies^{20,31,34}, and six studies reported using self-expanding valves only^{13,15,19,21,26,28}. One study reported balloon-expandable and self-expanding valve outcomes separately²³. The duration of the follow-up ranged from 30 days to three years. Overall, most of the studies were deemed to be of high quality based on the ROBINS-I scale (**Supplementary Table 3**). The baseline characteristics of the studies are reported in **Supplementary Table 4**.

PROCEDURAL SUCCESS

A total of 22 studies reported procedural success of VIV-TAVR^{12,15-19,21-35}. VIV-TAVR had a high success rate: the weighted success rate was 97% (95% CI: 94-98%) (Figure 1). The outcome was characterised by a high degree of statistical heterogeneity (I²=91%). The trim-and-fill method was used to identify possible publication bias and to adjust for it (Supplementary Figure 2A). Sensitivity analysis was carried out excluding studies with possible overlap of the patient population (Supplementary Figure 2B). VIV-TAVR had a higher success rate when the previous valve was placed surgically (97%, 95% CI: 95-99%) compared to transcutaneous replacement (91%, 95% CI: 79-97%) (Supplementary Figure 2C). Meta-regression was used to create a model correlating procedural success with baseline STS score and age, with no statistically significant findings (Supplementary Figure 2D, Supplementary Figure 2E). Publication bias was evaluated, and the results are presented in Supplementary Figure 2F and Supplementary Figure 2G. A Bayes estimator for heterogeneity is presented in Supplementary Figure 2H. There was no evidence of subgroup differences in the success rates based on the valve type (p-interaction=0.28), study location (p-interaction=0.32), or study design (p-interaction=0.58) (Supplementary Figure 3).

SECONDARY OUTCOMES AT 30 DAYS

ALL-CAUSE MORTALITY AT 30 DAYS

A total of 22 studies reported 30-day all-cause mortality of VIV-TAVR^{12,14-19,21-35}. The 30-day mortality incidence was low (5%, 95% CI: 3-6%) (**Figure 2A**). The outcome was characterised by a high degree of statistical heterogeneity ($I^2=55\%$). There was no evidence of subgroup differences in the success rates based on the valve type (p-interaction=0.19), study location (p-interaction=0.29), or study design (p-interaction=0.49) (**Supplementary Figure 4**).

STROKE AT 30 DAYS

A total of 22 studies reported the incidence of stroke at 30 days of VIV-TAVR^{12,14-19,21-35}. The outcome was characterised by a low degree of heterogeneity (I²=0%). The overall weighted incidence of stroke at 30 days was low (2%, 95% CI: 1-2%) (Figure 2B).

Study	Events	Total		Proportion 95% Cl	Weight
Attinger-Toller 2019	37	37		1.00 [0.91; 1.00]	2.8%
Dauerman 2019	224	226	-+	0.99 [0.97; 1.00]	4.4%
Holzamer 2019	82	85		0.96 [0.90; 0.99]	4.6%
Landes 2019	30	30		1.00 [0.88; 1.00]	2.8%
Landes 2019	2,199	2,288	+	0.96 [0.95; 0.97]	5.3%
Miller 2019	61	66		0.92 [0.83; 0.97]	4.9%
Sedeek 2019	88	90		0.98 [0.92; 1.00]	4.4%
Tchétché 2019	201	202	-+	1.00 [0.97; 1.00]	3.7%
Choi 2018	40	40		1.00 [0.91; 1.00]	2.8%
Guimarães 2018	110	116		0.95 [0.89; 0.98]	5.0%
Ochiai 2018	35	37		0.95 [0.82; 0.99]	4.3%
Ochiai 2018	36	37		0.97 [0.86; 1.00]	3.7%
Tuzcu 2018	1,147	1,150	+	1.00 [0.99; 1.00]	4.7%
Wernly 2018	221	223	-+	0.99 [0.97; 1.00]	4.4%
Deeb 2017	225	227	-+	0.99 [0.97; 1.00]	4.4%
Grubitzsch 2017	24	27		0.89 [0.71; 0.98]	4.6%
Sang 2017	21	22		0.95 [0.77; 1.00]	3.7%
Sawaya 2017	48	68		0.71 [0.58; 0.81]	5.2%
Spaziano 2017	74	78		0.95 [0.87; 0.99]	4.8%
Puri 2016	25	25		1.00 [0.86; 1.00]	2.8%
Silaschi 2016	37	71		0.52 [0.40; 0.64]	5.2%
Wendt 2015	62	62		1.00 [0.94; 1.00]	2.8%
Ye 2015	40	42		0.95 [0.84; 0.99]	4.3%
Ihlberg 2013	43	45		0.96 [0.85; 0.99]	4.3%
Random effects model		5,294	<	0.97 [0.94; 0.98]	100.0%
Heterogeneity: I ² =91%, τ	² =2.2240, p	< 0.01	0.4 0.5 0.6 0.7 0.8 0.9 1.0		
			Success		

Figure 1. Forest plot showing valve-in-valve transcutaneous aortic valve repair procedural success.

A Study	Events	Total		Proportion 95% Cl	Weight
Attinger-Toller 2019	0	37	H	0.00 [0.00; 0.09]	0.9%
Ferraria 2019	3	157	_ <u></u>	0.02 [0.00; 0.05]	4.0%
Holzamer 2019	4	85		0.05 [0.01; 0.12]	4.7%
Landes 2019	1	30		0.03 [0.00; 0.17]	1.7%
Landes 2019	101	2,288	E1	0.04 [0.04; 0.05]	10.8%
Miller 2019	4	66		0.06 [0.02; 0.15]	4.6%
Sedeek 2019	2	90		0.02 [0.00; 0.08]	3.0%
Tchétché 2019	5	202		0.02 [0.01; 0.06]	5.4%
Choi 2018	2	40	<u>_</u>	0.05 [0.01; 0.17]	2.9%
Guimãraes 2018	8	116		0.07 [0.03; 0.13]	6.6%
Ochiai 2018	0	37	H	0.00 [0.00; 0.09]	0.9%
Ochiai 2018	1	37		0.03 [0.00; 0.14]	1.7%
Tuzcu 2018	33	1,150		0.03 [0.02; 0.04]	9.7%
Wernly 2018	22	223		0.10 [0.06; 0.15]	8.9%
Deeb 2017	5	227		0.02 [0.01; 0.05]	5.4%
Grubitzsch 2017	3	27	I	— 0.11 [0.02; 0.29]	3.7%
Sang 2017	0	22	H	0.00 [0.00; 0.15]	0.9%
Sawaya 2017	1	68		0.01 [0.00; 0.08]	1.7%
Spaziano 2017	3	78		0.04 [0.01; 0.11]	3.9%
Puri 2016	2	25	<u>n</u>	0.08 [0.01; 0.26]	2.9%
Silaschi 2016	3	71		0.04 [0.01; 0.12]	3.9%
Wendt 2015	9	62		0.15 [0.07; 0.26]	6.7%
Ye 2015	1	42		0.02 [0.00; 0.13]	1.7%
Ihlberg 2013	2	45		0.04 [0.01; 0.15]	3.0%
Random effects model		5,225	~	0.05 [0.03; 0.06]	100.0%
Heterogeneity: 12=55%, 1	r ² =0.1830, <i>p</i>	<0.01	0.00 0.05 0.10 0.15 0.20 0.25		
			30-day mortality		

30-day	mortal	ity
--------	--------	-----

B	Study	Events	Total		Proportion	95% CI	Weight
	Attinger-Toner 2019	0	37	+	0.00 [0.00	; 0.09]	0.6%
	Ferraria 2019	1	157		0.01 [0.00	; 0.03]	1.3%
	Holzamer 2019	1	85		0.01 [0.00	; 0.06]	1.3%
	Landes 2019	0	30	·	0.00 [0.00	; 0.12]	0.6%
	Landes 2019	32	2,288	+	0.01 [0.01	; 0.02]	40.0%
	Miller 2019	2	66		0.03 [0.00	; 0.11]	2.5%
	Sedeek 2019	1	90	-+	0.01 [0.00	; 0.06]	1.3%
	Tchétché 2019	6	202		0.03 [0.01	; 0.06]	7.4%
	Choi 2018	2	40		0.05 [0.01	; 0.17]	2.4%
	Guimãraes 2018	2	116		0.02 [0.00	; 0.06]	2.5%
	Ochiai 2018	1	37		0.03 [0.00	; 0.14]	1.2%
	Ochiai 2018	1	37		0.03 [0.00	; 0.14]	1.2%
	Tuzcu 2018	20	1,150	÷-	0.02 [0.01	; 0.03]	24.9%
	Wemly 2018	1	223	+	0.00 [0.00	; 0.02]	1.3%
	Deeb 2017	2	227		0.01 [0.00	; 0.03]	2.5%
	Grubitzsch 2017	2	27	-	— 0.07 [0.01	; 0.24]	2.3%
	Sang 2017	0	22	F	0.00 [0.00	; 0.15]	0.6%
	Sawaya 2017	1	68		0.01 [0.00	; 0.08]	1.2%
	Spaziano 2017	1	78		0.01 [0.00	; 0.07]	1.2%
	Puri 2016	0	25		0.00 [0.00	; 0.14]	0.6%
	Silaschi 2016	0	71	·	0.00 [0.00	; 0.05]	0.6%
	Wendt 2015	0	62		0.00 [0.00	; 0.06]	0.6%
	Ye 2015	0	42	•	0.00 [0.00	; 0.08]	0.6%
	Ihlberg 2013	1	45		0.02 [0.00	; 0.12]	1.2%
	Random effects model		5,225	\$	0.02 [0.01	; 0.02]	100.0%
	Heterogeneity: $I^2=0\%$, $\tau^2=0\%$	0, <i>p</i> =0.86		0.00 0.05 0.10 0.15 0.20			
				30-day stroke			

Figure 2. Forest plot showing the incidence of 30-day all-cause mortality (A), stroke (B), myocardial infarction (C), and permanent pacemaker placement (D).

C	Study	Events	Total	Р	roportion	95% CI	Weight
	Attinger-Toller 2019	0	37	B	0.00 [0.0	00; 0.09]	2.5%
	Ferraria 2019	2	157		0.01 [0.0	00; 0.05]	8.7%
	Landes 2019	0	30	B	0.00 [0.0	00; 0.12]	2.4%
	Miller 2019	2	66		0.03 [0.0	00; 0.11]	8.5%
	Tchétché 2019	1	202	<u> </u>	0.00 [0.0	00; 0.03]	4.7%
	Choi 2018	0	40	B	0.00 [0.0	00; 0.09]	2.5%
	Guimãraes 2018	4	116		0.03 [0.0	01; 0.09]	14.7%
	Tuzcu 2018	5	1,150	+	0.00 [0.0	00; 0.01]	17.6%
	Deeb 2017	2	227	*	0.01 [0.0	0; 0.03]	8.7%
	Grubitzsch 2017	1	27		0.04 [0.0	0; 0.19]	4.6%
	Sang 2017	0	22	B	0.00 [0.0	0; 0.15]	2.4%
	Sawaya 2017	0	68	B	0.00 [0.0	0; 0.05]	2.5%
	Spaziano 2017	1	78		0.01 [0.0	00; 0.07]	4.7%
	Silaschi 2016	1	71		0.01 [0.0	0.08]	4.7%
	Ye 2015	0	42	»	0.00 [0.0	0.08]	2.5%
	Ihlberg 2013	2	45		0.04 [0.0	01; 0.15]	8.4%
	Random effects model		2,378	\diamond	0.01 [0.0	01; 0.02]	100.0%
	Heterogeneity: $I^2=12\%$, $\tau^2=12\%$	=0.0941, <i>p</i> =	=0.32	0.00 0.05 0.10 0.15			
				30-day myocardial infarction			
D	Study	Events	Total	Р	roportion	95% CI	Weight
	Attinger-Toller 2019	1	37		0.03 [0.0	00; 0.14]	1.5%
	Ferraria 2019	5	157	- <u></u>	0.03 [0.0	01; 0.07]	4.7%
	Holzamer 2019	1	85		0.01 [0.0	00; 0.06]	1.6%
	Landes 2019	4	30		0.13 [0.0	04; 0.31]	3.9%
	Landes 2019	153	2,288		0.07 [0.0	06; 0.08]	9.6%
	Miller 2019	5	66		0.08 [0.0	03; 0.17]	4.6%
	Sedeek 2019	5	90		0.06 [0.0	02; 0.12]	4.7%
	Tchétché 2019	16	202		0.08 [0.0	05; 0.13]	7.3%
	Guimãraes 2018	6	116		0.05 [0.0	02; 0.11]	5.1%
	Ochiai 2018	4	37		0.11 [0.0	03; 0.25]	4.0%
	Ochiai 2018	2	37	I	0.05 [0.0	0.18]	2.6%
	Tuzcu 2018	34	1,150		0.03 [0.0	02; 0.04]	8.5%
	Wernly 2018	6	223		0.03 [0.0	01: 0.061	5.2%
	Deeb 2017	18	227		0.08 [0.0	05; 0.12]	7.5%
	Grubitzsch 2017	1	27		0.04 [0.0	0; 0.19]	1.5%
	Sang 2017	1	22		0.05 [0.0)0: 0.231	1.5%
	Sawava 2017	3	68		0.04 [0.0	01: 0.121	3.5%
	Spaziano 2017	9	78		0.12 [0.0	05: 0.211	5.9%
	Puri 2016	0	25	H	0.01 00.0	0.141	0.8%
	Silaschi 2016	7	71		0.10 [0.0	04: 0.191	5.4%
	Wendt 2015	11	62		0.18 [0.0	0.301	6.2%
	Ye 2015	0	42		0.00 [0.0	0.081	0.8%
	Ihlberg 2013	3	45	x	0.07 [0.0	01; 0.18]	3.4%
	Random effects model	-	5,185	\diamond	0.06 [0.0	05; 0.08]	100.0%
	Heterogeneity: I^2 =62%, τ^2 =	=0.1877, <i>p</i> ·	<0.01	0.00 0.05 0.10 0.15 0.20 0.25 0.30			
				30-day permanent pacemaker			

Figure 2 (contd). Forest plot showing the incidence of 30-day all-cause mortality (*A*), stroke (*B*), myocardial infarction (*C*), and permanent pacemaker placement (*D*).

MYOCARDIAL INFARCTION AT 30 DAYS

Sixteen studies evaluated the incidence of myocardial infarction at 30 days^{12,14,16,17,19,21,22,24,26-30,32,34,35}. The outcome had a low degree of heterogeneity between the studies (I²=12%). The overall weighted incidence of myocardial infarction was low (1%, 95% CI: 1-2%) (**Figure 2C**).

PERMANENT PACEMAKER PLACEMENT AT 30 DAYS

Twenty-one studies evaluated the outcome of permanent pacemaker placement at 30 days^{12,14-19,22-35}. The outcome was characterised by a high degree of heterogeneity between the studies (I²=62%). The overall incidence of pacemaker placement at 30 days was 6% (95% CI: 5-8%) (Figure 2D).

POST-PROCEDURE AORTIC REGURGITATION AND MEAN PRESSURE GRADIENT ACROSS THE VALVE AT 30 DAYS

Eighteen studies reported the outcome of post-procedure aortic regurgitation at 30 days^{12,16-19,21-29,31,32,34,35}. The outcome was characterised by a high degree of heterogeneity (I²=77%). The incidence of aortic regurgitation was 7% (95% CI: 5-10%) (**Supplementary Figure 5A**). The mean pressure gradient across the valve was reported by 17 studies^{12,14-19,22-24,26-28,30-32,35}. The outcome was characterised by a very high degree of heterogeneity across the included studies (I²=91%). The weighted mean pressure gradient across the valve was 16.16 mmHg (95% CI: 15.30-17.02 mmHg) (**Supplementary Figure 5B**).

SECONDARY OUTCOMES AT ONE YEAR

ALL-CAUSE MORTALITY AT ONE YEAR

Sixteen studies reported the outcome of all-cause mortality at one year^{14,16,17,19,21,24-30,32-35}. The outcome was characterised by a moderate degree of heterogeneity ($I^2=51\%$). The overall incidence of mortality at one year following VIV-TAVR was 12% (95% CI: 10-14%) (Figure 3A).

STROKE AT ONE YEAR

The outcome of stroke was reported by nine studies^{14,16,19,21,24-26,32,34}. The outcome was characterised by a low degree of heterogeneity ($I^2=31\%$). The overall weighted incidence of stroke at one year remained low (3%, 95% CI: 2-4%) (Figure 3B).

MYOCARDIAL INFARCTION AT ONE YEAR

Six studies reported the outcome of myocardial infarction at one year following VIV-TAVR^{14,16,19,26,29,34}. The outcome was characterised by a low degree of heterogeneity (I²=0%). The overall weighted incidence of myocardial infarction remained low (1%, 95% CI: 0-2%) (Figure 3C).

PERMANENT PACEMAKER PLACEMENT AT ONE YEAR

The outcome of permanent pacemaker placement was reported by five studies^{14,19,26,31,34}. The outcome was characterised by a moderate degree of heterogeneity ($I^2=40\%$). The incidence of permanent pacemaker placement at one year was 7% (95% CI: 5-11%) (**Figure 3D**).

OUTCOMES AT THREE YEARS

Two studies reported the outcomes of VIV-TAVR patients beyond one year^{13,20}. At three years, the incidence of all-cause mortality was 29% (95% CI: 25-34%) and the incidence of stroke was 6% (95% CI: 5-9%) (**Figure 4**).

Discussion

This meta-analysis of 24 studies, including 5,553 patients undergoing VIV-TAVR, demonstrated that VIV-TAVR is associated with favourable short-term and midterm outcomes. The use of VIV-TAVR was associated with high procedural success rates. The incidence of 30-day mortality was 5%, at one year 12%, and at three years 29%. The incidence of stroke and that of myocardial infarction were low at 30 days following the procedure and remained low at one year. The indicators of valve stability, such as clinically significant aortic regurgitation and mean pressure gradient across the valve, remained low at 30 days.

The procedural success rates varied significantly among the included studies with evidence of a high degree of heterogeneity in the outcome rates. One possible explanation for such a discrepancy could be the variation in the procedural volume from one study to another. The correlation between TAVR volume and improved outcomes was recently explored in a large study by Vemulapalli et al, showing improved outcomes in centres with high TAVR volume compared to those with low volume⁴¹. It is also expected that the procedural success rates would increase over time, given the continuing advances in TAVR technology with the development of newer-generation valves with better deliverability, lower profile and improved designs to lower the rates of paravalvular leak and mean gradient across the valves⁴²⁻⁴⁵.

Although we included a cohort of patients with high surgical morbidity and mortality risk (mean STS score 7.84), the incidences of mortality and stroke reported in our meta-analysis were not exceedingly high (around 5% for 30-day mortality and 2% for stroke). In some subgroups the incidence of mortality was similar to that reported in trials of *de novo* TAVR in intermediate-risk patients (~3%)⁶. The incidences of these outcomes remained low even after one year, with incidences similar to the lower risk cohort of the PARTNER 2 trial⁶.

Limitations

Although the current meta-analysis represents the largest study to date exploring the outcomes of VIV-TAVR, it is not free from limitations. Some of the limitations of the current meta-analysis include a high degree of heterogeneity in many of the outcomes explored. We attempted to mitigate such an effect by analysing the randomeffects incidences, using the trim-and-fill method, and by conducting various subgroup analyses to explore the reasons for the heterogeneity. The lack of patient-level data hindered the exploration of the impact of the STS preoperative risk score on various outcomes of interest. Despite these limitations, our study addresses a relevant knowledge gap for operators and for counselling patients regarding the rates of procedure success and outcomes with VIV-TAVR.

Conclusions

VIV-TAVR appears to be associated with high procedural success rates and favourable short-term to midterm outcomes in patients with failed bioprosthetic valves, with an acceptable rate of adverse events compared with TAVR in intermediate- to high-risk patients. Future studies are encouraged to confirm the durability of the VIV procedure in the long term.

Impact on daily practice

This meta-analysis demonstrates that valve-in-valve transaortic valve replacement performed by experienced operators has a high success rate and is associated with a low risk of adverse events in the short and mid term.

A	Study	Events	Total		Proportion 95% CI	Weight
	Ferraria 2019	10	157		0.06 [0.03; 0.11]	5.7%
	Landes 2019	1	30		0.03 [0.00; 0.17]	0.8%
	Landes 2019	304	2,288	+	0.13 [0.12; 0.15]	16.9%
	Miller 2019	9	66		0.14 [0.06; 0.24]	5.0%
	Tchétché 2019	17	202		0.08 [0.05; 0.13]	7.9%
	Choi 2018	0	40	▶	0.00 [0.00; 0.09]	0.4%
	Tuzcu 2018	134	1,150	-	0.12 [0.10; 0.14]	15.5%
	Wemly 2018	37	223		0.17 [0.12; 0.22]	11.0%
	Deeb 2017	26	227		0.11 [0.08; 0.16]	9.7%
	Grubilzsch 2017	5	27		0.19 [0.06; 0.38]	3.0%
	Sang 2017	0	22		0.00 [0.00; 0.15]	0.4%
	Sawaya 2017	3	68		0.04 [0.01; 0.12]	2.3%
	Spaziano 2017	10	78		0.13 [0.06; 0.22]	5.5%
	Silaschi 2016	5	71		0.07 [0.02; 0.16]	3.4%
	Wendt 2015	14	62		0.23 [0.13; 0.35]	6.3%
	Ye 2015	4	42		0.10 [0.03; 0.23]	2.8%
	Ihlberg 2013	5	45		0.11 [0.04; 0.24]	3.3%
	Random effects model		4.798	\diamond	0.12 [0.10: 0.14]	100.0%
	Heterogeneity, /2-51%	$r^2 = 0.0494$ p	-0.01			
	Theterogeneity: 7 – 51 %,	ι =0.0494, ρ	.0.01	One-year mortality		
В	Study	Events	Total		Proportion 95% CI	Weight
	Ferraria 2019	2	157		0.01 [0.00; 0.05]	7.3%
	Landes 2019	0	30	b	0.00 [0.00; 0.12]	2.1%
	Tchétché 2019	12	202		0.06 [0.03; 0.10]	23.4%
	Chol 2018	0	40	a	0.00 [0.00; 0.09]	2.1%
	Tuzcu 2018	37	1,150		0.03 [0.02; 0.04]	34.5%
	Wemly 2018	3	223		0.01 [0.00; 0.04]	10.1%
	Deeb 2017	5	227		0.02 [0.01; 0.05]	14.5%
	Silaschi 2016	0	71	H	0.00 [0.00; 0.05]	2.1%
	Ye 2015	1	42	+	0.02 [0.00; 0.13]	3.9%
	Random effects model		2.142	\diamond	0.03 [0.02: 0.04]	100.0%
	Heterogeneity, /2=31%	$r^2 = 0.1006 \ p$	-0.17		,	
		ι =0.1000, <i>p</i> -	-0.17	One-year stroke		
C	Study	Events	Total		Proportion 95% CI	Weight
	Ferraria 2019	2	157		0.01 [0.00; 0.05]	36.2%
	Landes 2019	0	30	H	0.00 [0.00; 0.12]	9.0%
	Tchétché 2019	1	202		0.00 [0.00; 0.03]	18.3%
	Deeb 2017	1	227	-	0.00 [0.00; 0.02]	18.3%
	Sawaya 2017	0	68	H	0.00 [0.00; 0.05]	9.1%
	Ye 2015	0	42	B	0.00 [0.00; 0.08]	9.1%
	Random effects model		726	\diamond	0.01 [0.00; 0.02]	100.0%
	Heterogeneity: $I^2=0\%$, τ^2	=0, <i>p</i> =0.93		0.00 0.02 0.04 0.06 0.08 0.10 One-year myocardial infarction		
D	Study	Events	Total		Proportion 95% CI	Weight
	Ferraria 2019	7	157		0.04 [0.02; 0.09]	22.5%
	Tchétché 2019	20	202		0.10 [0.06; 0.15]	36.4%
	Deeb 2017	19	227		0.08 [0.05; 0.13]	35.9%
	Puri 2016	0	25	H	0.00 [0.00; 0.14]	2.6%
	Ye 2015	0	42	+	0.00 [0.00; 0.08]	2.6%
	Random effects model		653		0.07 [0.05: 0.11]	100.0%
	Heterogeneity: $I^2=40\%$.	t ² =0.0971, <i>p</i> =	=0.15	0.00 0.02 0.06 0.10 0.12		
	_ , ,			One-year permanent pacemaker		

Figure 3. Forest plot showing the incidence of one-year all-cause mortality (*A*), stroke (*B*), myocardial infarction (*C*), and permanent pacemaker placement (*D*).

A	Study	Events	Total					Proportion	95% CI	Weight
	Dauerman 2019	60	226		1			0.27 [0.	21; 0.33]	40.5%
	Webb 2019	114	365					0.31 [0.	27; 0.36]	59.5%
	Random effects model		591				>	0.29 [0.	25; 0.34]	100.0%
	Heterogeneity: $I^2=32\%$, $\tau^2=0$	0.0084, <i>p</i> =0	.23	0.22	0.26	0.30 0.32	0.36			
					Three-ye	ar mortalit	у			
В	Study	Events	Total					Proportion	95% CI	Weight
	Dauerman 2019	12	226		1			0.05 [0.	03; 0.09]	32.0%
	Webb 2019	26	365			1		0.07 [0.	05; 0.10]	68.0%
	Random effects model		591				_	0.06 [0.	05; 0.09]	100.0%
	Heterogeneity: $I^2=0\%$, $\tau^2=0$,	<i>p</i> =0.38		0.03	0.05 Three-y	0.07 vear stroke	0.09 0.10			

Figure 4. Forest plot showing the incidence of three-year all-cause mortality (A), and stroke (B).

Conflict of interest statement

D. Dvir is a consultant to Edwards Lifesciences and Medtronic. The other authors have no conflicts of interest to declare.

References

1. Blackman DJ, Saraf S, MacCarthy PA, Myat A, Anderson SG, Malkin CJ, Cunnington MS, Somers K, Brennan P, Manoharan G, Parker J, Aldalati O, Brecker SJ, Dowling C, Hoole SP, Dorman S, Mullen M, Kennon S, Jerrum M, Chandrala P, Roberts DH, Tay J, Doshi SN, Ludman PF, Fairbairn TA, Crowe J, Levy RD, Banning AP, Ruparelia N, Spence MS, Hildick-Smith D. Long-Term Durability of Transcatheter Aortic Valve Prostheses. *J Am Coll Cardiol.* 2019; 73:537-45.

2. Johnston DR, Soltesz EG, Vakil N, Rajeswaran J, Roselli EE, Sabik JF 3rd, Smedira NG, Svensson LG, Lytle BW, Blackstone EH. Long-term durability of bioprosthetic aortic valves: implications from 12,569 implants. *Ann Thorac Surg.* 2015;99:1239-47.

3. Elgendy IY, Mahmoud AN, Gad MM, Elbadawi A, Rivero F, Alfonso F. Transcatheter or Surgical Aortic Valve Replacement for Low Surgical Risk Patients: Meta-Analysis of Randomized Trials. *JACC Cardiovasc Interv.* 2019; 12:1399-401.

4. van Geldorp MW, Jamieson WRE, Kappetein AP, Ye J, Fradet GJ, Eijkemans MJ, Grunkemeier GL, Bogers AJ, Takkenberg JJ. Patient outcome after aortic valve replacement with a mechanical or biological prosthesis: weighing lifetime anticoagulant-related event risk against reoperation risk. *J Thorac Cardiovasc Surg.* 2009;137:881-6, 886e1-5.

5. Mack MJ, Leon MB, Thourani VH, Makkar R, Kodali SK, Russo M, Kapadia SR, Malaisrie SC, Cohen DJ, Pibarot P, Leipsic J, Hahn RT, Blanke P, Williams MR, McCabe JM, Brown DL, Babaliaros V, Goldman S, Szeto WY, Genereux P, Pershad A, Pocock SJ, Alu MC, Webb JG, Smith CR; PARTNER 3 Investigators. Transcatheter Aortic-Valve Replacement with a Balloon-Expandable Valve in Low-Risk Patients. *N Engl J Med.* 2019;380:1695-705.

6. Leon MB, Smith CR, Mack MJ, Makkar RR, Svensson LG, Kodali SK, Thourani VH, Tuzcu EM, Miller DC, Herrmann HC, Doshi D, Cohen DJ, Pichard AD, Kapadia S, Dewey T, Babaliaros V, Szeto WY, Williams MR, Kereiakes D, Zajarias A, Greason KL, Whisenant BK, Hodson RW, Moses JW, Trento A, Brown DL, Fearon WF, Pibarot P, Hahn RT, Jaber WA, Anderson WN, Alu MC, Webb JG; PARTNER 2 Investigators. Transcatheter or Surgical Aortic-Valve Replacement in Intermediate-Risk Patients. *N Engl J Med.* 2016; 374:1609-20.

7. Gad MM, Ahuja KR, Bazarbashi N, Karrthik AK, Kaur M, Mick SL, Reed GW, Tuzcu EM, Krishnaswamy A, Kapadia SR. The Impact of Hospital

Characteristics on the Outcomes of Interventional Cardiac Procedures. JACC Cardiovasc Interv. 2019;12:1872-4.

8. Yamashita K, Fukushima S, Shimahara Y, Hamatani Y, Kanzaki H, Fukuda T, Izumi C, Yasuda S, Kobayashi J, Fujita T. Early outcomes of transcatheter aortic valve implantation for degenerated aortic bioprostheses in Japanese patients: insights from the AORTIC VIV study. *Gen Thorac Cardiovasc Surg.* 2019;67: 1038-47.

9. Sterne JA, Hernán MA, Reeves BC, Savović J, Berkman ND, Viswanathan M, Henry D, Altman DG, Ansari MT, Boutron I, Carpenter JR, Chan AW, Churchill R, Deeks JJ, Hróbjartsson A, Kirkham J, Jüni P, Loke YK, Pigott TD, Ramsay CR, Regidor D, Rothstein HR, Sandhu L, Santaguida PL, Schünemann HJ, Shea B, Shrier I, Tugwell P, Turner L, Valentine JC, Waddington H, Waters E, Wells GA, Whiting PF, Higgins JP. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *BMJ*. 2016;355:i4919.

10. Schwarzer G. meta: an R package for meta-analysis. 2007. https://cran.r-project.org/web/packages/meta/meta.pdf

11. DerSimonian R, Kacker R. Random-effects model for meta-analysis of clinical trials: an update. *Contemp Clin Trials*. 2007;28:105-14.

12. Attinger-Toller A, Htun NM, Murdoch D, Perlman GY, Alenezi A, Sathananthan J, Blanke P, Leipsic J, Thompson C, Ye J, Cheung A, Wood D, Webb JG. Transcatheter aortic valve-in-valve implantation for failed surgical bioprosthetic valves. A minimalist approach without contrast aortography or echocardiographic guidance. *Catheter Cardiovasc Interv.* 2020;95:45-53.

13. Dauerman HL, Deeb GM, O'Hair DP, Waksman R, Yakubov SJ, Kleiman NS, Chetcuti SJ, Hermiller JB Jr, Bajwa T, Khabbaz K, de Marchena E, Salerno T, Dries-Devlin JL, Li S, Popma JJ, Reardon MJ. Durability and Clinical Outcomes of Transcatheter Aortic Valve Replacement for Failed Surgical Bioprostheses. *Circ Cardiovasc Interv.* 2019;12:e008155.

14. Ferrari E, Stortecky S, Heg D, Muller O, Nietlispach F, Tueller D, Toggweiler S, Noble S, Maisano F, Roffi M, Jeger R, Grünenfelder J, Huber C, Windecker S, Wenaweser P. The hospital results and 1-year outcomes of transcatheter aortic valve-in-valve procedures and transcatheter aortic valve implantations in the native valves: the results from the Swiss-TAVI Registry. *Eur J Cardiothorac Surg.* 2019;56:55-63.

15. Holzamer A, Kim WK, Rück A, Sathananthan J, Keller L, Cosma J, Bauer T, Nef H, Amat-Santos IJ, Brinkert M, Husser O, Pellegrini C, Schofer J, Nerla R, Montorfano M, Giannini F, Stella P, Kuwata S, Hilker M, Castriota F, Ussia GP, Webb JG, Nietlispach F, Toggweiler S. Valve-in-Valve Implantation Using the ACURATE Neo in Degenerated Aortic Bioprostheses: An International Multicenter Analysis. *JACC Cardiovasc Interv.* 2019;12:2309-16.

16. Landes U, Dvir D, Schoels W, Tron C, Ensminger S, Simonato M, Schäfer U, Bunc M, Aldea GS, Cerillo A, Windecker S, Marzocchi A, Andreas M, Amabile N, Webb J, Kornowski R. Transcatheter aortic valve-invalve implantation in degenerative rapid deployment bioprostheses. *EuroIntervention.* 2019;15:37-43.

17. Miller M, Snyder M, Horne BD, Harkness JR, Doty JR, Miner EC, Jones KW, O'Neal KR, Reid BB, Caine WT, Clayson SE, Lindley E, Gardner B, Connors RC, Bowles BJ, Whisenant BK. Transcatheter Aortic Valve-in-Valve Replacement for Degenerated Stentless Bioprosthetic Aortic Valves: Results of a Multicenter Retrospective Analysis. *JACC Cardiovasc Interv.* 2019;12:1217-26.

18. Sedeek AF, Greason KL, Sandhu GS, Joseph DA, Holmes DR Jr, Schaff HV. Transcatheter Valve-in-Valve Vs Surgical Replacement of Failing Stented Aortic Biological Valves. *Ann Thorac Surg.* 2019;108:424-30.

19. Tchétché D, Chevalier B, Holzhey D, Harnath A, Schäfer U, Teiger E, Manigold T, Modine T, Souteyrand G, Champagnac D, Oh JK, Li S, Verhoye JP, Kornowski R; VIVA Investigators. TAVR for Failed Surgical Aortic Bioprostheses Using a Self-Expanding Device: 1-Year Results From the Prospective VIVA Postmarket Study. *JACC Cardiovasc Interv.* 2019;12:923-32.

20. Webb JG, Murdoch DJ, Alu MC, Cheung A, Crowley A, Dvir D, Herrmann HC, Kodali SK, Leipsic J, Miller DC, Pibarot P, Suri RM, Wood D, Leon MB, Mack MJ. 3-Year Outcomes After Valve-in-Valve Transcatheter Aortic Valve Replacement for Degenerated Bioprostheses: The PARTNER 2 Registry. *J Am Coll Cardiol.* 2019;73:2647-55.

21. Choi CH, Cheng V, Malaver D, Kon N, Kincaid EH, Gandhi SK, Applegate RJ, Zhao DXM. A comparison of valve-in-valve transcatheter aortic valve replacement in failed stentless versus stented surgical bioprosthetic aortic valves. *Catheter Cardiovasc Interv.* 2019;93:1106-15.

22. de Freitas Campos Guimaraes L, Urena M, Wijeysundera HC, Munoz-Garcia A, Serra V, Benitez LM, Auffret V, Cheema AN, Amat-Santos IJ, Fisher Q, Himbert D, Garcia Del Blanco B, Dager A, Le Breton H, Paradis JM, Dumont E, Pibarot P, Rodés-Cabau J. Long-Term Outcomes After Transcatheter Aortic Valve-in-Valve Replacement. *Circ Cardiovasc Interv.* 2018;11:e007038.

23. Ochiai T, Yoon SH, Sharma R, Miyasaka M, Nomura T, Rami T, Maeno Y, Chakravarty T, Nakamura M, Cheng W, Makkar R. Outcomes of Self-Expanding vs. Balloon-Expandable Transcatheter Heart Valves for the Treatment of Degenerated Aortic Surgical Bioprostheses - A Propensity Score-Matched Comparison. *Circ J.* 2018;82:2655-62.

24. Tuzcu EM, Kapadia SR, Vemulapalli S, Carroll JD, Holmes DR Jr, Mack MJ, Thourani VH, Grover FL, Brennan JM, Suri RM, Dai D, Svensson LG. Transcatheter Aortic Valve Replacement of Failed Surgically Implanted Bioprostheses: The STS/ACC Registry. *J Am Coll Cardiol.* 2018;72: 370-82.

25. Wernly B, Zappe AK, Unbehaun A, Sinning JM, Jung C, Kim WK, Fichtlscherer S, Lichtenauer M, Hoppe UC, Alushi B, Beckhoff F, Wewetzer C, Franz M, Kretzschmar D, Navarese E, Landmesser U, Falk V, Lauten A. Transcatheter valve-in-valve implantation (VinV-TAVR) for failed surgical aortic bioprosthetic valves. *Clin Res Cardiol.* 2019;108:83-92.

26. Deeb GM, Chetcuti SJ, Reardon MJ, Patel HJ, Grossman PM, Schreiber T, Forrest JK, Bajwa TK, O'Hair DP, Petrossian G, Robinson N, Katz S, Hartman A, Dauerman HL, Schmoker J, Khabbaz K, Watson DR, Yakubov SJ, Oh JK, Li S, Kleiman NS, Adams DH, Popma JJ. 1-Year Results in Patients Undergoing Transcatheter Aortic Valve Replacement With Failed Surgical Bioprostheses. *JACC Cardiovasc Interv.* 2017;10:1034-44.

27. Grubitzsch H, Zobel S, Christ T, Holinski S, Stangl K, Treskatsch S, Falk V, Laule M. Redo procedures for degenerated stentless aortic xenografts and the role of valve-in-valve transcatheter techniques. *Eur J Cardiothorac Surg.* 2017; 51:653-9.

28. Sang SLW, Beute T, Heiser J, Berkompas D, Fanning J, Merhi W. Early Outcomes for Valve-in-valve Transcatheter Aortic Valve Replacement in Degenerative Freestyle Bioprostheses. *Semin Thorac Cardiovasc Surg.* 2018; 30:262-8.

29. Sawaya FJ, Deutsch MA, Seiffert M, Yoon SH, Codner P, Wickramarachchi U, Latib A, Petronio AS, Rodés-Cabau J, Taramasso M, Spaziano M, Bosmans J, Biasco L, Mylotte D, Savontaus M, Gheeraert P, Chan J, Jorgensen TH, Sievert H, Mocetti M, Lefèvre T, Maisano F, Mangieri A, Hildick-Smith D, Kornowski R, Makkar R, Bleiziffer S, Sondergaard L, De Backer O. Safety and Efficacy of Transcatheter Aortic Valve Replacement in the Treatment of Pure Aortic Regurgitation in Native Valves and Failing Surgical Bioprostheses: Results From an International Registry Study. *JACC Cardiovasc Interv.* 2017;10:1048-56.

30. Spaziano M, Mylotte D, Theriault-Lauzier P, De Backer O, Sondergaard L, Bosmans J, Debry N, Modine T, Barbanti M, Tamburino C, Sinning JM, Grube E, Nickenig G, Mellert F, Bleiziffer S, Lange R, de Varennes B, Lachapelle K, Martucci G, Piazza N. Transcatheter aortic valve implantation versus redo surgery for failing surgical aortic bioprostheses: a multicentre propensity score analysis. *EuroIntervention*. 2017;13:1149-56.

31. Puri R, Byrne J, Muller R, Baumbach H, Eltchaninoff H, Redwood S, Cheema A, Dubois C, Ihlberg L, Wijeysundera HC, Cerillo A, Götberg M, Klaaborg KE, Pelletier M, Blanco-Mata R, Edwards R, Gandolfo C, Muir D, Meucci F, Sinning JM, Stella P, Veulemans V, Virtanen M, Regueiro A, Thoenes M, Pibarot P, Pelletier-Beaumont E, Rodés-Cabau J. Transcatheter aortic valve implantation in patients with small aortic annuli using a 20 mm balloon-expanding valve. *Heart.* 2017;103:148-53.

32. Silaschi M, Wendler O, Seiffert M, Castro L, Lubos E, Schirmer J, Blankenberg S, Reichenspurner H, Schäfer U, Treede H, MacCarthy P, Conradi L. Transcatheter valve-in-valve implantation versus redo surgical aortic valve replacement in patients with failed aortic bioprostheses. *Interact Cardiovasc Thorac Surg.* 2017;24:63-70.

33. Wendt D, Al-Rashid F, Kahlert P, El-Chilali K, Demircioglu E, Neuhauser M, Liakopoulos O, Dohle DS, Erbel R, Jakob H, Thielmann M. Conventional aortic valve replacement or transcatheter aortic valve implantation in patients with previous cardiac surgery. *J Cardiol.* 2015;66:292-7.

34. Ye J, Cheung A, Yamashita M, Wood D, Peng D, Gao M, Thompson CR, Munt B, Moss RR, Blanke P, Leipsic J, Dvir D, Webb JG. Transcatheter Aortic and Mitral Valve-in-Valve Implantation for Failed Surgical Bioprosthetic Valves: An 8-Year Single-Center Experience. *JACC Cardiovasc Interv.* 2015;8: 1735-44.

35. Ihlberg L, Nissen H, Nielsen NE, Rück A, Busund R, Klaarborg KE, Soendergaard L, Harnek J, Miettinen H, Eskola M, Wahba A, Laine M. Early clinical outcome of aortic transcatheter valve-in-valve implantation in the Nordic countries. *J Thorac Cardiovasc Surg.* 2013;146:1047-54.

36. Dvir D, Webb J, Brecker S, Bleiziffer S, Hildick-Smith D, Colombo A, Descoutures F, Hengstenberg C, Moat NE, Bekeredjian R, Napodano M, Testa L, Lefevre T, Guetta V, Nissen H, Hernandez JM, Roy D, Teles RC, Segev A, Dumonteil N, Fiorina C, Gotzmann M, Tchetche D, Abdel-Wahab M, De Marco F, Baumbach A, Laborde JC, Kornowski R. Transcatheter aortic valve replacement for degenerative bioprosthetic surgical valves: results from the global valve-in-valve registry. *Circulation*. 2012;126: 2335-44.

37. Eggebrecht H, Schäfer U, Treede H, Boekstegers P, Babin-Ebell J, Ferrari M, Möllmann H, Baumgartner H, Carrel T, Kahlert P, Lange P, Walther T, Erbel R, Mehta RH, Thielmann M. Valve-in-valve transcatheter aortic valve implantation for degenerated bioprosthetic heart valves. *JACC Cardiovasc Interv.* 2011;4:1218-27.

38. Erlebach M, Wottke M, Deutsch MA, Krane M, Piazza N, Lange R, Bleiziffer S. Redo aortic valve surgery versus transcatheter valve-in-valve implantation for failing surgical bioprosthetic valves: consecutive patients in a single-center setting. *J Thorac Dis.* 2015;7:1494-500.

39. Conradi L, Silaschi M, Seiffert M, Lubos E, Blankenberg S, Reichenspurner H, Schaefer U, Treede H. Transcatheter valve-in-valve therapy using 6 different devices in 4 anatomic positions: clinical outcomes and technical considerations. *J Thorac Cardiovasc Surg.* 2015;150:1557-65.

40. Dvir D, Webb JG, Bleiziffer S, Pasic M, Waksman R, Kodali S, Barbanti M, Latib A, Schaefer U, Rodés-Cabau J, Treede H, Piazza N, Hildick-Smith D, Himbert D, Walther T, Hengstenberg C, Nissen H, Bekeredjian R, Presbitero P, Ferrari E, Segev A, de Weger A, Windecker S, Moat NE, Napodano M, Wilbring M, Cerillo AG, Brecker S, Tchetche D, Lefèvre T, De Marco F, Fiorina C, Petronio AS, Teles RC, Testa L, Laborde JC, Leon MB, Kornowski R; Valve-in-Valve International Data Registry Investigators. Transcatheter aortic valve implantation in failed bioprosthetic surgical valves. *JAMA*. 2014;312:162-70.

41. Vemulapalli S, Carroll JD, Mack MJ, Li Z, Dai D, Kosinski AS, Kumbhani DJ, Ruiz CE, Thourani VH, Hanzel G, Gleason TG, Herrmann HC, Brindis RG, Bavaria JE. Procedural Volume and Outcomes for Transcatheter Aortic-Valve Replacement. *N Engl J Med.* 2019;380:2541-50.

42. Ahuja KR, Gad MM, Bazarbashi N, Karrthik AK, Raheja H, Goel S, Reed G, Puri R, Krishnaswamy A, Kapadia SR. Impact of Hospital Transcatheter Aortic Valve Replacement Volume on Incidence and Outcomes of Cardiac Tamponade. *JACC Cardiovasc Interv.* 2019;12:2232-4.

43. Bazarbashi N, Ahuja K, Gad MM, Sammour YM, Kaur M, Karrthik A, Saad AM, Khubber S, Dhaliwal K, Mick SL, Navia JL, Puri R, Reed GW, Krishnaswamy A, Kapadia SR. The utilization of single versus double Perclose devices for transfemoral aortic valve replacement access site closure: Insights from Cleveland Clinic Aortic Valve Center. *Catheter Cardiovasc Interv.* 2020; 96:442-7.

44. Chahine J, Kadri AN, Gajulapalli RD, Krishnaswamy A, Mick S, Perez O, Lak H, Nair RM, Montane B, Tak J, Tuzcu EM, Griffin B, Svensson LG, Harb SC, Kapadia SR. Outcomes of Transcatheter Aortic Valve Replacement in Mixed Aortic Valve Disease. *JACC Cardiovasc Interv.* 2019;12:2299-306.

45. Giustino G, Sorrentino S, Mehran R, Faggioni M, Dangas G. Cerebral Embolic Protection During TAVR: A Clinical Event Meta-Analysis. *J Am Coll Cardiol.* 2017;69:465-6.

Supplementary data

Supplementary Figure 1. Search strategy according to PRISMA guidelines.

Supplementary Figure 2A. Forest plot showing procedural success using the trim-and-fill method to account for heterogeneity.

Supplementary Figure 2B. Sensitivity analysis excluding studies with potential but not confirmed study overlap.

Supplementary Figure 2C. Subgroup analysis based on procedure used to implant failed bioprosthetic valve.

Supplementary Figure 2D. Meta-regression of procedural success and STS score.

Supplementary Figure 2E. Meta-regression of procedural success and age.

Supplementary Figure 2F. Baujat plot for publication bias.

Supplementary Figure 2G. Funnnel plot.

Supplementary Figure 2H. Forest plot with Bayesian analyses with informative prior distributions for the residual between-study variance.

Supplementary Figure 3A. Forest plot showing subgroup analysis of procedural success by type of valve used.

Supplementary Figure 3B. Forest plot showing subgroup analysis of procedural success by location of study.

Supplementary Figure 3C. Forest plot showing subgroup analysis of procedural success by study design.

Supplementary Figure 4A. Forest plot showing subgroup analysis of 30-day all-cause mortality.

Supplementary Figure 4B. Forest plot showing subgroup analysis of 30-day all-cause mortality by location of study.

Supplementary Figure 4C. Forest plot showing subgroup analysis of 30-day all-cause mortality by study design.

Supplementary Figure 5A. Forest plot showing incidence of aortic regurgitation.

Supplementary Figure 5B. Forest plot showing mean gradient across implanted valve.

Supplementary Table 1. Search strategy.

Supplementary Table 2. Definition of procedural success in the included studies.

Supplementary Table 3. Quality assessment of included studies.

Supplementary Table 4. Characteristics of included studies and patient population.

The supplementary data are published online at: https://eurointervention.pcronline.com/ doi/10.4244/EIJ-D-19-00928



Supplementary data



Supplementary Figure 1. Search strategy according to PRISMA guidelines.

Study	TE seTE	Pro	portion 95%-CI Weig	lht
Attinger Teller 2010	1 22 1 1226		000 002.4001	22%
Dauerman 2019	4 72 0 7103		099 [0 82, 1 00]	3 3%
Hotzamer 2019	331 0 5878			35%
Landes 2019	4 11 1 4258		098 [0 79; 1.00]	2.2%
Landes 2019	321 0 1081		096 (0 95: 0 97]	3 9%
Miller 2019	2 50 0 4652		092 [0 83; 0 97]	36%
Sedeefc 2019	378 07151	-	0 98 (0 92; 0 99]	3 3%
Tchetche 2019	5.30 1 0025	2	1.00 [0 97; 1 00]	28%
Choi 2018	4 39 1 4229		099 [0 83; 1 00]	2 2%
Guimardes 2018	2 91 0 4192		095 [0 89; 0 98]	3.7%
Ochiai 2018	2 86 0 7270		0 95 [0 81; 0 99]	3 3%
Ochiai 2018	3 58 1 0138	-8	097 [0 83; 1.00]	28%
Tuzcu 2018	595 05781	10	1 00 [0 99; 1 00]	3 5%
Wemly 2018	4 71 07103	1	099 [0 96; 1 00]	3.3%
Deeb 2017	472 07102		099 [0 97; 1 00]	33%
Grubitzsch 2017	2 08 0 6124		0 89 [0 71; 0.96]	3.4%
Sang 2017	3 04 1 0235		095 [0 74; 0 99]	28%
Sawaya 2017	0 88 0 2661	· · · · · · · · · · · · · · · · · · ·	0.71 [0 59; 0 80]	3.8%
Spaziano 2017	2 92 05133		095 [0 87; 0 98]	36%
Pun 2016	393 1 4280		098 [0 76 1.00]	2.2%
Silaschi 2016	008 02376		0 52 [0 41; 0.63]	3.8%
Wendt 2015	4 83 1 4199	2	099 [0 89; 1.00]	22%
Ye 2015	3 00 0 7246		0 95 [0 83; 0 99]	33%
ihlberg 2013	307 07234		096 [0 84 0 99]	3 3%
Filled Landes 2019	0 99 1 4258		0 73 [0 14; 0.98]	22%
Filled Attinger-Toller	0.78 1 4236		0.09 [0 12, 0 97]	2270
Filled Momby 2018	0/1 14229		067 (011; 097]	22%
Filled Dauerman 2010	0.40 07103		050 [0 27, 0 85]	2.3%
Filled Deeb 2017	038 07103	100	0.59 [0.27, 0.85]	3.3%
Filled Wendt 2015	0 27 1 4199		0 55 [0 27, 0 05]	2 20/
Filled Tchetche 2010	_0.20 1.0025		045 [0 10:0 85]	2 8%
Filled Tuzcu 2018	-0.85 0.5781		0.30 [0.12:0.57]	3 5%
11100 10200 2010	0000000		0.00 [0.17.0.01]	0 0 /0
Random effects model		4	0 93 [0 88: 0 96]	100 0%
Heterogeneity <i>I</i> ¹ * 91%,	» 2 5414, p < 0 01	1		
		-0.5 0 0.5		

Supplementary Figure 2A. Forest plot showing procedural success using the trim-and-fill

method to account for heterogeneity.

Study	Events	Total		Proportion	95%-CI Weight
Dauerman 2019	224	226		0.99[0.97; 1.00]	8.5%
Holzamer 2019	82	85		0.96[0.90; 0.99]	9.8%
Landes 2019	30	30		1.00[0.88; 1.00]	3.7%
Landes 2019	2199	2288		0.96[0.95; 0.97]	14.4%
Sedeek 2019	88	90		0.98[0.92; 1.00]	8.4%
Choi 2018	40	40		1.00[0.91; 1.00]	3.7%
Ochiai 2018	35	37		0.95[0.82; 0.99]	8.3%
Ochiai 2018	36	37		0.97[0.86; 1.00]	5.9%
Tuzcu 2018	1147	1150		1.00[0.99; 1.00]	9.9%
Deeb 2017	225	227		0.99[0.97; 1.00]	8.5%
Grubitzsch 2017	24	27		0.89[0.71; 0.98]	9.5%
Sang 2017	21	22		0.95[0.77; 1.00]	5.8%
Wendt 2015	62	62		1.00[0.94; 1.00]	3.7%
Random effects model Heterogeneity: $l^2 = 67\%$, $\tau^2 =$	= 0.6924,	4321 p < 0.01	0.75 0.8 0.85 0.9 0.95 1 Success	0.98[0.96; 0.99]	100.0%

Supplementary Figure 2B. Sensitivity analysis excluding studies with potential but not

confirmed study overlap.

Study	Events	Total	Proportion 95%-CI	Weight
Study Attinger-Toller 2019 Dauerman 2019 Holzamer 2019 Landes 2019 Landes 2019 Miller 2019 Tchetche 2019 Choi 2018 Guimaraes 2018 Ochiai 2018 Ochiai 2018 Tuzcu 2018	Events VR 37 224 82 30 2199 61 201 40 110 35 36 1147	Total 37 226 85 30 2288 66 202 40 116 37 37 1150	Proportion 95%-Cl 1.00 [0.91; 1.00] 0.99 [0.97; 1.00] 0.96 [0.90; 0.99] 1.00 [0.88; 1.00] 0.96 [0.95; 0.97] 0.92 [0.83; 0.97] 1.00 [0.97; 1.00] 1.00 [0.91; 1.00] 0.95 [0.89; 0.98] 0.97 [0.86; 1.00] 1.00 [0.99: 1.00]	Weight 2.9% 5.4% 5.9% 2.9% 6.4% 4.2% 6.6% 5.3% 4.2% 6.0%
Wernly 2018 Sawaya 2017 Spaziano 2017 Puri 2016	221 48 74 25	223 68 78 25	 0.99 [0.97; 1.00] 0.71 [0.58; 0.81] 0.95 [0.87; 0.99] 1.00 [0.86; 1.00]	5.4% 7.1% 6.2% 2.9%
Wendt 2015 Ye 2015 Random effects mode	62 40	62 42	 1.00 [0.94; 1.00] 0.95 [0.84; 0.99]	2.9% 5.3% 90.1%
Grubitzsch 2017 Sang 2017 Random effects model	24 21	2 2 2	 0.89 [0.71; 0.98] 0.95 [0.77; 1.00] 0.91	5.8% 4.1% 9.9%
Random effects model		4861	 0.97 [0.95; 0.98] 10	00.0%

Supplementary Figure 2C. Subgroup analysis based on procedure used to implant failed

bioprosthetic valve.



Supplementary Figure 2D. Meta-regression of procedural success and STS score.



Supplementary Figure 2E. Meta-regression of procedural success and age.



Supplementary Figure 2F. Baujat plot for publication bias.



Supplementary Figure 2G. Funnel plot.

Study	Events	Total				Proportion 95%	CI Weight
Attinger-Toiler 2019 Dauerman 2019 Holzamer 2019	37 224 82	37 226 85			-	1.00[0.88; 1.00] 0.99[0.96; 1.00] 0.96[0.89: 0.99]	2.4% 4.4% 4.8%
Landes 2019	30	30				1 00[0.86: 1.00]	2.4%
Landes 2019 Miller 2019 Sedeck 2010	2199 61	2288 66		-		0.96[0.95; 0.97] 0.92[0.82; 0.97]	5.9% 5.1%
Tchetche 2019 Choi 2018	201 40	202 40				1.00[0.97; 1.00] 1.00[0.89; 1.00]	3.5% 2.5%
Guimaraes 2018 Ochiai 2018 Ochiai 2018	110 35 36	116 37 37		_		0.95[0.89; 0.98] 0.95[0.80; 0.99] 0.97[0.84: 1.00]	5.3% 4.3% 3.4%
Tuzcu 2018 Wernly 2018	1147 221	1150 223				1.00[0.99; 1.00] 0.99[0.96; 1.00]	4.8% 4.4%
Deeb 2017 Grubitzsch 2017 Sang 2017	225 24 21	227 27 22			-	0.99[0.97; 1.00] 0.89[0.70; 0.97] 0.95[0.75; 1.00]	4.4% 4.7% 3.4%
Sawaya 2017 Spaziano 2017	48 74	68 78	_		-	0.71[0.58; 0.81] 0.95[0.87; 0.98]	5.6% 5.0%
Puri 2016 Silaschi 2016	25 37	25 71 -		-		1.00[0.83; 1.00] 0.52[0.40; 0.64]	2.4% 5.7%
Ye 2015	62	62			100	1.00[0.93; 1.00]	2.5%
Ihlberg 2013	43	45		-		0.96[0.84; 0.99]	4.3%
Random effects model	5	294			\$	0.97 [0.94; 0.98]	100.0%
Heterogeneity: $/^2 = 91\%$, τ^2	= 1.4279, p	< 0.01	0.5 0.6 Si	0.7 0.8 Iccess	0.9		

Supplementary Figure 2H. Forest plot with Bayesian analyses with informative prior

distributions for the residual between study variance.

Study	Events	Total		Proportion 95%-	CI Weight
Attmgef-Tollef 2019	37	37		1.00 [0.91; 1.00]	2.8%
Landes 2019	30	30		1.00 [0.88; 1.00]	2.8%
Landes 2019	2199	2288		0.96 [0.95; 0.97]	5 3%
Miller 2019	61	66	9	0.92 [0.83; 0.97]	4.9%
Sedeek 2019	88	90	—9	0.98 [0.92; 1.00]	4.4%
Guimardes 2018	110	116		0.95 [0 89; 0.98]	5.0%
Tuzcu 2018	1147	1150		1.00 [0.99; 1.00]	4.7%
Wemly 2018	221	223	9	0.99 [0.97; 1.00]	
Grubitzsch 2017	24	27		0.89 [0.71; 0.98]	4.6%
Sawaya 2017	48	68	—— 9	0.71 [0.58; 0.81]	5.2%
Spaziano 2017	74	78		0.95 [0.87; 0.99]	4.8%
Silaschi 2016	37	71 -	*******	0.52 [0.40; 0.64]	5.2%
Wendt 2015	62	62	—-i	1.00 [0 94; 1.00]	2.8%
Ihtierg 2013	43	45	9	0.96 [0 85; 0.99	4.3%
Dauerman 2019	224	226	**	0.99 [0.97; 1.00]	4.4%
Holzamer 2019	82	85	*-	0.96 [0.90; 0.99]	4 6%
Tchetch# 2019	201	202	a#	1.00 [0.97; 1.00]	3.7%
Choi 2018	40	40	41	1.00 [0.91; 1.00]	2.8%
Ochiai 2018	35	37		0.95 [0.82; 0.99]	4,3%
Deeb 2017	225	227	9	0.99 [0.97; 1.00]	4.4%
Sang 2017	21	22	NO. 00-00-00-00-00-00-00-00-00-00-00-00-00-	0.95 [0.77; 1.00]	3.7%
Ochiai 2018	36	37	9	0.97 [0.86; 1.00]	
Pun 2016	25	25		1.00 [0.86; 1.00]	2.8%
Ye 2015	40	42	#-	0.95 [0.84; 0.99]	4.3%
			-0		
Random effects model		5294	0	0.97 [0.94: 0.98] 1	00.0%
			I	[
			0.4 0.5 0.6 0.7 0.8 0.9 1		
			Success		

Supplementary Figure 3A. Forest plot showing subgroup analysis of procedural success by

type of valve used.

Study	Events	Total		Proportion	95%-CI	Weight
Attmger-Toller 2019	37	37		1.00[0.91;	1.00]	2.8%
Holzamer 2019	82	85	-##	0.96[0.90;	0.99]	4.6%
Tchetche 2019	201	202		- 1.00[0.97;	1.00]	3.7%
Wernly 2018	221	223		0.99[0.97;	1.00]	4.4%
Grubitzsch 2017	24	27		0.89[0.71;	0.98]	4.6%
Sawaya 2017	48	68		0.71[0.58;	0.81]	5.2%
Spaziano 2017	74	78	+	0.95[0.87;	0.99]	48%
Puri 2016	25	25		1.00[0.86;	1.00]	2.8%
Silaschi 2016	37	71	1	0.52[0.40;	0.64]	5.2%
Wendl 2015	62	62		* 1.00[0.94;	1.00]	2.8%
Ye 2015	40	42		0.95[0.84;	0.99]	4.3%
iMfcerg 2013	43	45		0.96[0.85;	0.99]	4.3%
Dauarman 2010	224	226		0.00 10.07	1.00)	A A0/
Millor 2019	61	220		0.00 [0.07,	0.071	4.4/0
Sodook 2010	88	00		0.92 [0.03,	1 001	4.3 /0
Choi 2018	40	40		4 00 [0.52,	1.00]	2 90/
Guimardes 2018	110	116		0.05 [0.91;	0.001	Z.0 /0
Ochiai 2018	35	37		0.95 [0.89,	0.90]	J.0 %
Ochiai 2018	36	37		0.95 [0.02,	1 001	2 70/
Tuzou 2019	1147	1150		1 00 10 00.	1.00]	J.1 /0
Deeb 2017	225	007		1.00 [0.99;	1.00]	4.170
Sepa 2017	24			0.95 [0.97,	1.00]	3 7%
Sang 2017	21	22		0.55 [0.77,	1.00]	3.1 /0
Landes 2019	30	30	·	1.00 [0.88;	1.00]	2.8%
Landes 2019	2199	2288		0.96 [0.95;	0.97]	5.3%
Random effects model		5294		0.97 [0 94:	0.981	100.0%
	,	0.001	тт —		1001	
		04	0.5 0.6 0.7 0.8 0.9			
			Success			

Supplementary Figure 3B. Forest plot showing subgroup analysis of procedural success by

location of study.

Study	Events	Total			Proportion 95%	Cl Weight
Attmger-Toller 2019	37	37			1.00 [0.91: 1.00]	2.8%
Dauerman 2019	224	226		-	0.99 [0.97: 1.00]	4.4%
Landes 2019	30	30		0	1.00 [0.88; 1.00]	2.8%
Landes 2019	2199	2288			0.96 [0.95; 0 97]	5.3%
Deeb 2017	225	227		-	0.99 [0.97; 1 00]	4.4%
Sawaya 2017	48	68			0.71 [0.58; 0 81]	5.2%
Sdaschi 2016	37	71 —			0.52 [0.40; 0 64]	5.2%
Wendl 2015	62	62			1.00 [0.94; 1 00]	2.8%
Ye 2015	40	42		100 00 00 00 00 00	0.95 [0.84; 0 99]	4.3%
Holzamer 2019	82	85			0.96[0.90; 0.99]	4.6%
Miller 2019	61	66			0.92[0.83: 0.97]	4.9%
Sedeek 2019	88	90			0.98[0.92; 1.00]	4.4%
Tchetche 2019	201	20			1.00[0.97; 1.00]	3.7%
Choi 2018	40	40		—«	1.00[0.91; 1.00]	28%
Guimaraes 2018	110	11		-*►	0.95[0.89; 0.98]	5.0%
Ochiai 2018	35	37	·-		0.95[0.82; 0.99]	4.3%
Ochiai 2018	36	37			0.97[0.86; 1.00]	37%
Tuzcu 2018	1147	1150			1.00[0.99; 1.00]	4.7%
Wemly 2018	221	22			0.99[0.97; 1.00]	4.4%
Grubitzsch 2017	24	27	55 20		0.89[0.71; 0.98]	4.6%
Sang 2017	21	22			0.95[0.77; 1.00]	3.7%
Spaziano 2017	74	78			0.95[0.87; 0.99]	4.8%
Puri 2016	25	25		_	1.00[0.86; 1.00]	2.8%
Ihlberg 2013	43	45			0.96[0.85; 0.99]	4.3%
				e		
Random effects model		5294		-0	0.97 [0.94: 0.98]	100.0%
		f ~	- <i>T</i> ~ T " T	T		
		- (0.5 0.6 0.7 0.8	0.9		
		04	Success			

Supplementary Figure 3C. Forest plot showing subgroup analysis of procedural success by

study design.

Study	Events Total		Proportion	95%-CIWeight
Attingef-Toller 2019	0 37		0.00 [0.00;	0.09] 0.9%
Feoana 2019	3 157		0.02 [0.00;	0.05] 4.0%
Landes 2019	1 30		0.03 [0.00;	0.17] 17%
Landes 2019	101 2288		0.04 [0.04;	0.05] 10.8%
Miler 2019	4 66		0.06 [0.02;	0.15] 4.6%
Sedeek 2019	2 90	-•	0.02 [0.00;	0.08] 3.0%
Guimaraes 2018	8 116	0	0.07 [0.03;	0.13] 6.6%
Tuzcu 2018	33 1150		0.03 [0.02;	0.04] 9.7%
Wemly 2018	22 223		0.10 [0.06;	0.15] 8.9%
Grubitzsch 2017	3 27	[*]	0.11 [0.02;	0.29] 3.7%
Sawaya 2017	1 68		0.01 [0.00;	0.08] 1.7%
Spaziano 2017	3 78		0.04 [0.01;	0.11] 3.9%
Silaschi 2016	3 71	0	0.04 [0.01;	0.12] 3.9%
Wendt 2015	9 62		0.15 [0.07;	0 26] 67%
Ihlberg 2013	2 45		0.04 [0.01;	0.15] 3.0%
Holzamer 2019	4 85		0.0510.01.0	121 / 7%
Tcheich* 2019	5 202	+ * =	0.02[0.01: (0.061 5.4%
Choi 2018	2 40		0.05[0.01: 0	0.171 2.9%
Ochiai 2018	0 37		0.00[0.00; 0	0.09 0.9%
Deeb 2017	5 227	2	0.02[0.01; 0	0.05] 5.4%
Sang 2017	0 22		0.00100.0	0.15 0.9%
		0		-
Ochiai 2018	1 37		0.03[0.00; 0	0.14] 1.7%
Pun 2016	2 25		0.08[0.01; 0	0.26] 2.9%
Ye 2015	1 42		0.02[0.00; 0	0.13] 17%
Random effects model	5225	ririii	0.05 [0 03;	0.06] 100.0%
		0.0 5.0 1.0 15.0 2.0 25		
		0 0.5 0.1 0.15 0.2 0.25		
		SU Day Mortanty		

Supplementary Figure 4A. Forest plot showing subgroup analysis of 30-day all-cause mortality

by type of valve used.

Study	Events Total	Proportion 95%-CI Weight
Attinger-Toller 2019	0	0.00[0.00; 0.09] 0.9%
Ferrana 2019	3 7-	0.02[0.00; 0.05] 4 0%
Holzamer 2019	4 157	0.05[0.01: 0.12] 4.7%
Tchetche 2019	5 85	0.02[0.01; 0.06] 5.4%
Wemly 2018	202	0.10[0.06; 0.15] 8.9%
Grubitzsch 2017	22 223	0.11[0.02; 0.29] 3 7%
Sawaya 2017	1 68	0.01[0.00; 0.08] 1.7%
Spaziano 2017	3 78	0.04[0.01; 0.11] 3.9%
Puri 2016	2 25	0.08[0.01; 0.26] 2.9%
Silaschi 2016	3 71	0.04[0.01; 0.12] 3.9%
Wendt 2015	9 62	0.15[0.07; 0.26] 6.7%
Ye 2015	1 42	0.02[0.00; 0.13] 17%
Ihlberg 2013	2 45	- 0.04[0.01; 0.15] 3 0%
Landes 2019 Landes 2019	1 30 101 2288	0.03 [0.00; 0.17] 17% 0.04 [0.04; 0.05]
Miller 2019	4 66 1 *	0.06[0.02; 0.15] 4,6%
Sedeek 2019 Choi 2019	2 90	
Cuimaraaa 2019	2 40 *	
Guimaraes 2018	8 110 —••	
Ochiai 2018	0 37 » . 4 37	
Tuzou 2019	22 1150	0.03[0.00; 0.04] 0.7%
Doob 2017	5 227	0.02[0.02, 0.04] 5.7%
Sang 2017	0 22 >= *=	0.00[0.00; 0.15] 0.0%
Sally 2017	0 22 " = =	0.00[0.00, 0.15] 0.3%
Random effects model	5225 0	0.05 [0 03; 0.06]100.0%
	0 05 0 1 0.15 30 Day	0.2 0.25 Mortality

Supplementary Figure 4B. Forest plot showing subgroup analysis of 30-day all-cause mortality

by location of study.

Study	Events	Total	Proportion 95%	%*CI Weight
Attinger-Toller 2019	0	37—	0.00 [0.00; 0.09]	0.9%
Ferrana 2019	3	157	0.02 [0.00; 0.05]	4.0%
Landes 2019	1	30 —	0.03 [0.00; 0.17]	17%
Landes 2019	101	2288	0.04 [0.04; 0.05]	10.8%
Deeb 2017	5	227 — -	0.02 [0.01; 0.05]	5.4%
Sawaya 2017	1	68	0.01 [0.00; 0.08]	1.7%
Silascbi 2016	3	71*	0.04 [0.01; 0.12]	3.9%
Wendt 2015	9	62 *	0.15 [0.07; 0.26]	6.7%
Ye 2015	1	42 —	0.02 [0.00; 0.13]	17%
Holzamer 2019	4	85	0.05 [0.01; 0.12]	4.7%
Miller 2019	4	66	0.06 [0.02; 0.15]	4.6%
Sedeek 2019	2	90	0.02 [0.00; 0.08]	3.0%
Tchetche 2019	5	20	0.02 [0.01; 0.06]	5.4%
Choi 2018	2	40	0.05 [0.01; 0.17]	2.9%
Guimaraes 2018	8	11	0.07 [0.03; 0.13]	6.6%
Ochiai 2018	0	37	0.00 [0.00; 0.09]	0.9%
Ochiai 2018	1	37	0.03 [0 00; 0.14]	1.7%
Tuzcu 2018	33	1150	0.03 [0 02; 0.04]	97%
Wemly 2018	22	22	0.10 [0.06; 0.15]	8.9%
Grubitzsch 2017	3	27	0.11 [0.02; 0.29]	3.7%
Sang 2017	0	22	0.00 (0.00; 0.15]	0.9%
Spaziano 2017	3	78	0.04 [0.01; 0.11]	3.9%
Puri 2016	2	25	0.08 [0.01; 0.26]	2.9%
Ihlberg 2013	2	45	0.04 [0.01; 0.15]	3.0%
Random effects model	5	225	0.05 [0.03: 0.06]	100.0%
		0 0.05 0.1 0.15 0.2 0.25		
		30 Day Mortality		

Supplementary Figure 4C. Forest plot showing subgroup analysis of 30-day all-cause mortality

by study design.

Study	Events	Total		Proport	ion 9	5%-CI	Weight
Attinger-Toller 2019	0	37*		0.00	[0.00: (0.091	1.4%
Landes 2019	1	30		0.03	[0.00; (0.17]	2.3%
Landes 2019	107	2288		0.05	[0.04: 0	0.061	8.4%
Miller 2019	1	66	-•	0.02	[0.00; 0	0.08	2.4%
Sedeek 2019	1	90	*	0.01	[0.00; 0	0.06	2.4%
Tchetche 2019	6	202		0.03	[0.01; 0	0.06	6.0%
Choi 2018	3	40	B	0.08	[0.02; (0.20]	4.4%
Guimaraes 2018	5	116	-1	0.04	[0.01; 0	0.10]	5.6%
Ochiai 2018	8	37		0.22	[0.10; 0	0.38]	6.1%
Ochiai 2018	4	37		0.11	[0.03; (0.25]	5.0%
Tuzcu 2018	38	1150	B :	0.03	[0.02; 0	0.05]	8.1%
Wernly 2018	23	223		0.10	[0.07; 0	0.15]	7.7%
Deeb 2017	8	227		0.04	[0.02; 0	0.07]	6.4%
Grubitzsch 2017	5	27	»	0.19	[0.06; 0	0.38]	5.3%
Sang 2017	0	22	* :	0.00	[0.00; 0	0.15]	1.4%
Sawaya 2017	4	68	*	0.06	[0.02; (0.14]	5.1%
Puri 2016	4	25	#	0.16	[0.05; 0	0.36]	4.8%
Silaschi 2016	7	71	*	0.10	[0.04; 0	0.19]	6.1%
Ye 2015	4	42		0.10	[0.03; (0.23]	5.0%
Ihlberg 2013	9	45	1	0.20	[0.10; (0.35]	6.3%
Random effects model	2	4843	0	0.0	7 [0.05;	0.10]	100.0%
Heterogeneity: $I^2 = 77\%$, 1	r² = 0.3804.	o < 0.0	1 ¹ 1 1 1 1 A				
	0 0.05 0.1 0.1	5 0.2 0.2	25 0.3 0.35				
3	80-Day Aor	tic Reg	jurgitation				

Supplementary Figure 5A. Forest plot showing incidence of aortic regurgitation.

Study	Me	ean	MRAW	95%-CI	Weight
Attinger-Toller 2019 Ferraria 2019		-:	i3.oo 14.14	[10.97; 15.03] [12.90; 15.38]	5.0% 6.0%
Holzamer 2019 Landes 2019		_	- 16.00 14.60	[14.30; 17.70] [11.63; 17.57]	5.4% 3.8%
Landes 2019 Miller 2019			16.20 13.25	[15.84; 16.56] [12.62; 13.88]	6.8% 6.7%
Sedeek 2019 Tchetche 2019		_	19.00 17.50	[16.73; 21.27] [16.31; 18.69]	4.6% 6.1%
Guimaraes 2018 Ochiai 2018		*	18.50 — : 12.10	[16.59; 20.41] [10.13; 14.07]	5.1% 5.1%
Ochiai 2018 Tuzcu 2018			19.00 16.00	[16.65; 21.35] [15.65; 16.35]	4.5% 6.8%
Deeb 2017 Grubitzsch 2017		-j#sr	17.00 14.00	[15.86; 18.14] [11.44; 16.56]	6.1% 4.3%
Sang 2017 Spaziano 2017			11.00 18.10	[8.91; 13.09] [16.46; 19.74]	4.9% 5.5%
Puri 2016 Silaschi 2016		,	24.00 19.70	[20.86; 27.14] [17.91; 21.49]	3.6% 5.3%
Iniberg 2013			16.40	[13.86; 18.94]	4.3%
Random effects model Heterogeneity: $I^2 = 91\%$, $T^2 =$	2.^702 , <i>b</i> < 0.0	0 1 i 1 10.20	<u>16.16 ri</u>	5.30; 17.021	100.0%
	Mean Gra	adient			

Supplementary Figure 5B. Forest plot showing mean gradient across implanted valve.

Supplementary Table 1. Search strategy.

#1

Valve in valve OR Valve-in-Valve OR ViV [Title/Abstract]))

#2

(((((TAVR[Title/Abstract]) OR TAVI[Title/Abstract]) OR Percutaneous aortic valve replacement[Title/Abstract]) OR Transcatheter aortic valve replacement[Title/Abstract]) OR transcatheter aortic valve implantation[Title/Abstract])

#3

#1 AND #2

Study	Year	Procedural success assessment
Attinger-Toller et al	2019	- According to the Valve Academic Research Consortium-2 consensus document (VARC-2)
Dauerman et al	2019	- According to VARC-2
Ferraria et al	2019	- According to VARC-2
Holzamer et al	2019	- According to VARC-2
Landes et al	2019	- According to VARC-2
Miller et al	2019	- Correct positioning of prosthetic heart valve and the
		absence of periprocedural death, myocardial infarction (MI)
		or stroke.
		- According to VARC-2
Sedeek et al	2019	- According to VARC-2
		- Severe patient to prosthesis mismatch was defined as an
		indexed effective orifice valve area $\leq 0.65 \text{ cm}^2/\text{m}^2$
Tchetche et al	2019	- According to VARC-2
Webb et al	2019	- According to VARC-2
Choi et al	2018	- According to VARC-2
Guimaraes et al	2018	- Procedural success: correct positioning of the prosthetic heart valve
		Without incidence of major adverse cardiac and
		cerebrovascular
		events during the in-hospital period.
		- Device success was defined according to VARC-2
Ochiai et al	2018	- Post-procedural aortic valve (AV) mean gradient
		- Other endpoints according to VARC-2
Tuzcu et al	2018	- According to VARC-1-2
Wernly et al	2018	- According to VARC-2
Deeb et al	2017	- Device success and absence of in-hospital MACCE

Supplementary Table 2. Definition of procedural success in the included studies.

		- According to VARC-2
Grubitzsch et al	2017	- According to VARC-2
Sang et al	2017	- According to VARC-2
Sawaya et al	2017	- According to VARC-2
Spaziano et al	2017	- According to VARC-2
Puri et al	2016	- According to VARC-2
		- Severe patient to prosthesis mismatch was defined as an
		indexed effective orifice value area $\leq 0.65 \text{ cm}^2/\text{m}^2$
Silaschi et al	2016	- According to VARC-2
		- Transoesophageal echocardiography was used to EOA
		transcatheter heart valves (THV)
Wendt et al	2015	- According to VARC-2
Ye et al	2015	- According to VARC-2
Ihlberg et al	2013	- Technical success
		- According to VARC-2

		Pre-in	tervention	At	Post intervention				
				interventi					
				on					
Study	Ve	Confoun	Selecti	Interventi	Deviatio	Missin	Measure	Selecti	Overal
Study	ar	ing	on	on	ns from	o data	ment of	on of	l bias
	ui	1115	on	classificat	intended	5 uutu	outcomes	the	1 0145
				ion	intervent		outcomes	renorte	
				ion	ion			d	
					1011			u results	
Attinger	201	Low	Moder	Low	Moderat	Low	Low	Low	Moder
-Toller		LUW	ate	LOW		LOW	LOW	LUW	ate
et al			ate		C				aic
Dauerm	201	Low	Low	Low	Low	Low	Low	Low	Low
an et al	201 Q	LOW		LOW	LOW	LOW	LOW	LOW	LOw
Eerraria	201	Low	Moder	Low	Low	Low	Low	Moder	Moder
et al	201 Q	LOW	ate	LOW	LOW	LOW	LOW	ate	ate
Holzam	201	Low	Low	Low	Low	Low	Low	Low	Low
er et al	9			LOW	LOW	LOW	LOW		
Landes	201	Low	Moder	Low	Moderat	Low	Low	Low	Moder
et al	9		ate		e	2011	2011		ate
Miller	201	Low	Moder	Low	Low	Low	Low	Low	Moder
et al	9		ate		Low	2011	Low	Low	ate
Sedeek	201	Low	low	low	low	low	low	Low	Low
et al	9								
Tchetch	201	Low	Low	Low	Low	Low	Low	Low	Low
e et al	9								
Webb et	201	Low	Low	Low	Low	Low	Low	Moder	Moder
al	9							ate	ate
Choi et	201	Low	Low	Low	Low	Low	Low	Low	Low
al	8								
Guimar	201	Low	Low	Low	Low	Low	Low	Low	Low
aes et al	8								
Ochiai	201	low	Low	Low	Low	Moder	Low	Low	Moder
et al	8					ate			ate
Tuzcu	201	Low	Low	Low	Low	Low	Low	Low	Low
et al	8								
Wernly	201	Low	Low	Low	Low	Low	Low	Low	Low
et al	8								
Deeb et	201	Low	Low	Low	Low	Low	Low	Low	Low
al	7								
Grubitz	201	Low	Moder	Low	Low	Low	Low	Low	Moder
sch et al	7	_	ate		_				ate
Sang et	201	Low	Moder	Low	Low	Low	Low	Low	Moder
al	7		ate						ate
Sawaya	201	Moderat	Moder	Low	Low	Low	Low	Low	Moder
et al	7		ate						ate

Supplementary Table 3. Quality assessment of included studies.

Spazian	201 Low	Low	Low	Low	Low	Low	Low	Low
Puri et al	201Low	Moder ate	Low	Low	Low	Low	Low	Moder ate
Silaschi et al	201 Low 6	Moder ate	Low	Low	Low	Low	Low	Moder ate
Wendt et al	201 Low 5	Low	Low	Low	Low	Low	Low	Low
Ye et al	201Low 5	Moder ate	Low	Low	Low	Low	Low	Moder ate
Ihlberg et al	201Low 3	Low	Low	Low	Low	Low	Low	Low

N	Autho r	Y ea r	Valve ^T yp ^e	Stud y Desi g n	Sa mp le Siz e	Ag e, m e an (S D)	M a les , %	S T S, m ea n (S D	B M I, m ea n (S D)	Ejec tion Frac tion mea (SD)	Hyper t ension , %	Dia bete s Mel litus , %	Cor onar y Arte ^r y Dise ase, %	Sm o kin g , %	Hi st o ry of M yo ca rd i	His tor y of Str oke , %
1	Attinger Toller et al	20 19	Both	Pros pe ctive	37	74 (1 0	78	5. 6 (2 4)	N R	53 (14)	65	32	NR	NR	NR	NR
2	Dauerm a n et al	20 19	Self- expanda b le	Pros pe ctive	226	76 7 (1	63 3	9 (6 7)	N R	NR	92	39.8	72.6	NR	72. 6	72. 6
3	Ferraria et al	20 19	Both	Pros pe ctive	157	78 62 (9. 11	60 5	6. 4 2 (5 0	2 6 .6 3 (4	54.5 7 (13. 07)	76. 4	20.4	54.5	NR	12. 7	14. 6
4	Holza mer et al	20 19	Self- expanda b	Retr os pecti	85	77 (8)	54	6. 8 (6	N R	54 (11)	87	29	51	NR	11	NR
5	Landes et al	20 19	Both	Pros pe ctive	228 8	77 5 (1	58 7	8. 8 (8	2 7 (5	52 (13)	NR	23.3 0	NR	NR	NR	16
	Landes et al	20 19	Both	Pros pe ctive	30	80 .(7.	17 2	9. 5 (7	2 7 .1 (5	56 (8)	NR	25.1	NR	NR	NR	30. 8
6	Miller et al	20 19	Both	Retr os pecti v	66	68 13	80 3	$\begin{array}{c c} 4 \\ (1 \\ \dot{0} \\ 8 \end{array}$	N R	NR	NR	NR	NR	NR	NR	NR
7	Sedeek et al	20 19	Both	Retr os pecti v e	90	79 25 (2.	81	7. 5 (1	2 8 (2	56 (4.8 9)	88	28	64	NR	NR	33
8	Tchetc he et al	20 19	Self- expanda b le	Retr os pecti v	202	79 (7.	47 5	6. 6 (5	N R	NR	83. 5	26.2	NR	NR	10. 9	7.5
9	Webb et al	20 19	Balloo n expanda b	Pros pe ctive	365	78 9 (1	64 1	9. 1 (4 ·7)	N R	NR	NR	31.2	57.3	NR	NR	12. 1

10	Choi et al	20 18	Self- expanda b le	Retros pectiv e	40	68. 5 (14)	75. 00	N R	29 .4 4 (6 .03	53.9 (10. 6)	65.3	24. 6	53. 1	40. 6 3	NR	NR	
1 1	Guima rae s et al	20 18	Both	Retros pectiv e	116	76 (11)	64. 70	N R	26 .9 (5	55 (13. 4)	73.3	31. 9	63. 8	26. 7	NR	22. 7	
1 2	Ochiai et al	20 18	Self- expandi ng	Retros pectiv e	37	76. 8 (12 .8)	67. 60	$4. \\ 6 \\ (1 \\ 2)$	N R	50.9 (17)	86.5	8.1	NR	NR	NR	10. 8	
	Ochiai et al	20 18	Balloo n- expanda b le	Retros pectiv e	37	76. 6 (12 .3)	70. 30	3. 9 (1 6	N R	50 (12. 8)	83.8	10. 8	NR	NR	NR	NR	
1 3	Tuzcu et al	20 18	Both	Retros pectiv e	115 0	79. 25 (3. 19)	60. 80	6. 9 (1 8 3	N R	55 (4.6 1)	90.5	32. 1	58. 6)	NR	NR	NR	
1 4	wernly et al	20 18	Both	Retros pectiv e	223	76 (11)	58. 00	8. 3 (1 0. 1)	36 (4 8)	51 (18)	85	28	61	NR	8	12	
1 5	Deeb et al	20 17	Self- expanda b le	Prosp e ctiv	227	76. 7 (10 .8)	63. 00	9 (6 7)	N R	NR	92.1	91	72. 7	64. 7	19. 8	23. 7	
1 6	Grubitzs c h et al	20 17	Both	Retros pectiv e	27	72. 3 (9. 7)	77. 00	N R	26 .9 (4	52 (11. 4)	NR	NR	50	NR	6	23	
1 7	Sang et al	20 17	Self- expanda b	Retros pectiv e	22	74 (9)	64. 00	9 (7	N R	53 (12)	NR	NR	NR	NR	NR	NR	
1 8	Sawaya et al	20 17	Both	Prosp e ctiv	68	76 (12)	66. 00	7.7 (6)	25 (5)	51.7 (13)	84	25	NR	NR	15	15	
1 9	Spazian o et al	20 17	Both	Retros pectiv e	78	78. 1 (8)	51. 00	7. 2 (4	N R	50.7 (13)	72	20	43	NR	NR	7	
2 0	Puri et al	20 16	Balloo n expanda b le	Retros pectiv e	25	83. 25 (1. 46)	12. 00	7. 8 (2 2 3	25 .9 (4 .8)	60 (9.9)	NR	20	52	NR	NR	26	
2 1	Silasc hi	20 16	Both	Prosp e	71	78. 6	57. 70	N R	N R	NR	NR	11. 3	NR	NR	NR	14. 1	_

						(7. 6)										
2	Wendt	20	Both	Prosp	62	78	69.	1	2	48.1	91.9	38.7	NR	NR	NR	Ν
2	et	15		e			40	2	7	(13)						R
	al			ctiv		7 (5.		.1	.1 (4							
2	Ye et	20	Balloo	Prosp	42	80	67.	9.	Ν	57.5	NR	23.8	69	NR	NR	16
3	al	15	n expanda b	e ctiv e		5 (9.	70	6 (1 4	R	0						7
2	Ihlberg	20	Both	Retros	45	78	58.	1	N	46.3	NR	18	NR	NR	13	18
4	et al	13		pectiv e		3 (8	00	5 (1	R	(12. 8)					_	
						64		8)								