EuroIntervention 2020;16:539-548 published online May 2020

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

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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±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%), myocardial 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.

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SUBMITTED ON 09/10/2019 - REVISION RECEIVED ON 1st 29/04/2020 / 2nd 12/05/2020 - ACCEPTED ON 15/05/2020

DOI: 10.4244/EIJ-D-19-00928

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 implantation[1]. 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 replacement[4].

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-centred[8].

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

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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 studies[9] **(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 software[10]. Summary estimates were calculated using the DerSimonian and Laird random effects model[11]. The I^2 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 (USA-based 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-TAVR[12-35]. 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 cohort[36]. The remainder of excluded studies were subsets of larger cohorts of patients published in another study[37-40]. 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±11.36%. 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 separately[23]. 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 (I^2=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 (I^2=0%). The overall weighted incidence of stroke at 30 days was low (2%, 95% CI: 1-2%) **(Figure 2B)**.

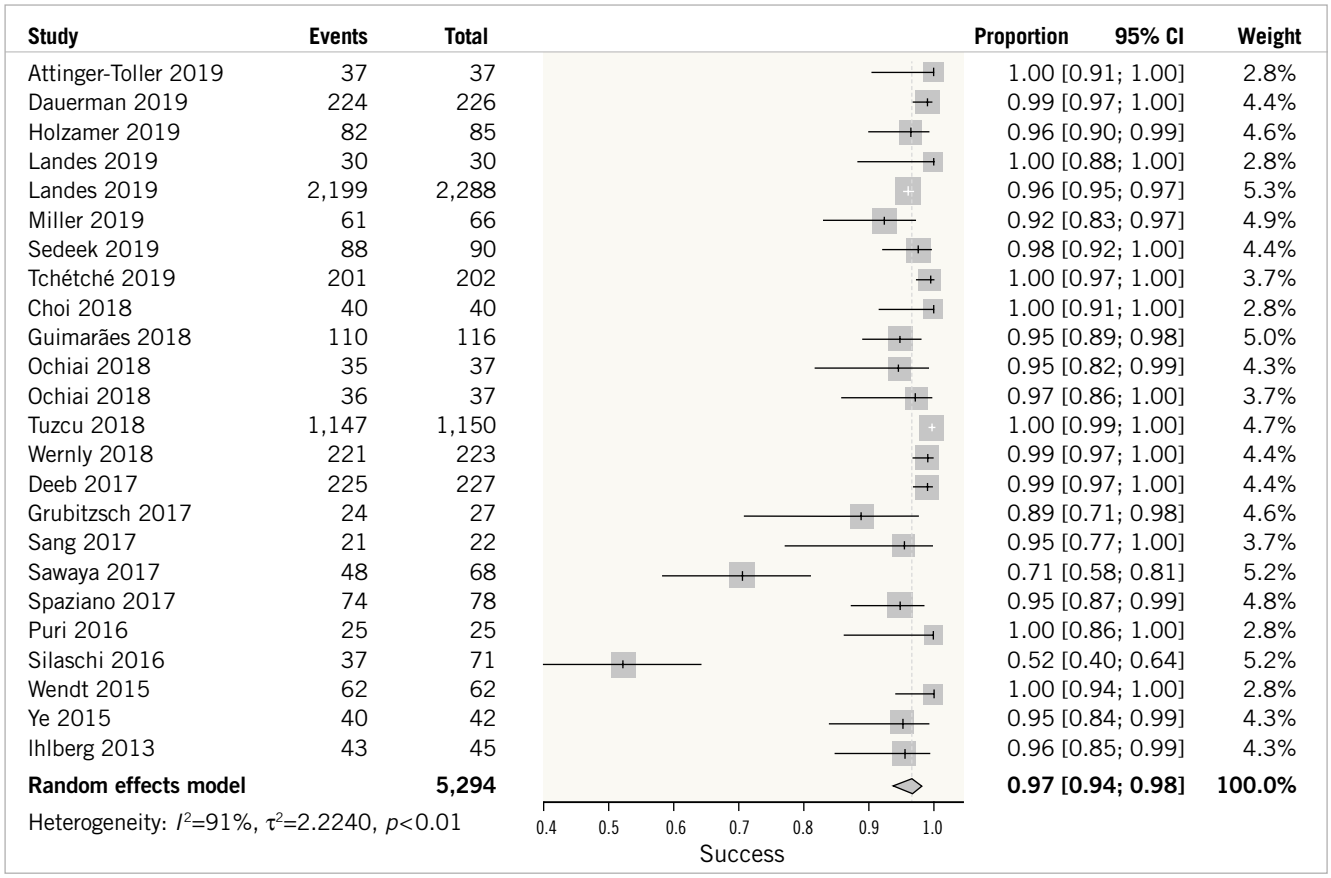


Figure 1. *Forest plot showing valve-in-valve transcutaneous aortic valve repair procedural success.*

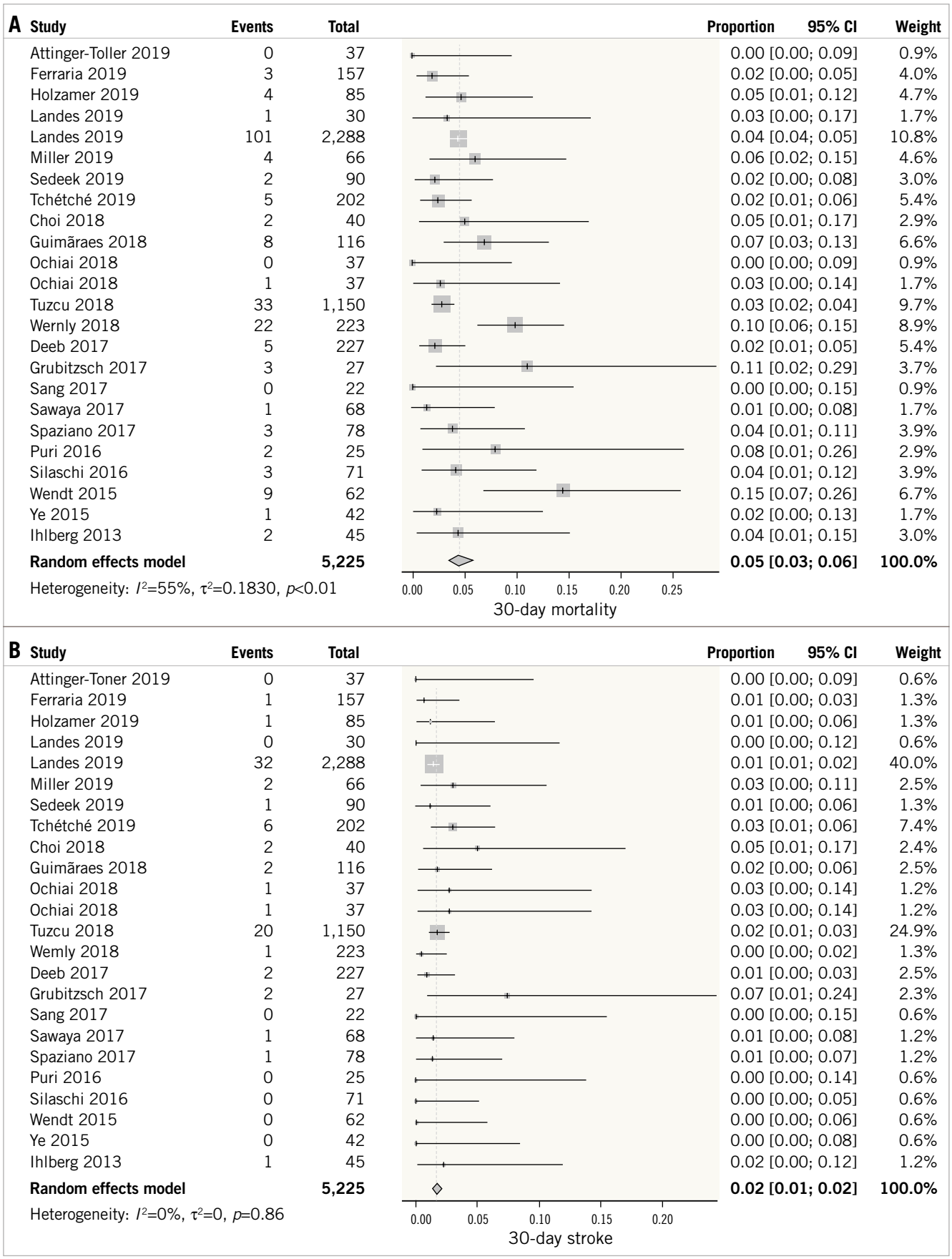


Figure 2. *Forest plot showing the incidence of 30-day all-cause mortality (A), stroke (B), myocardial infarction (C), and permanent pacemaker placement (D).*

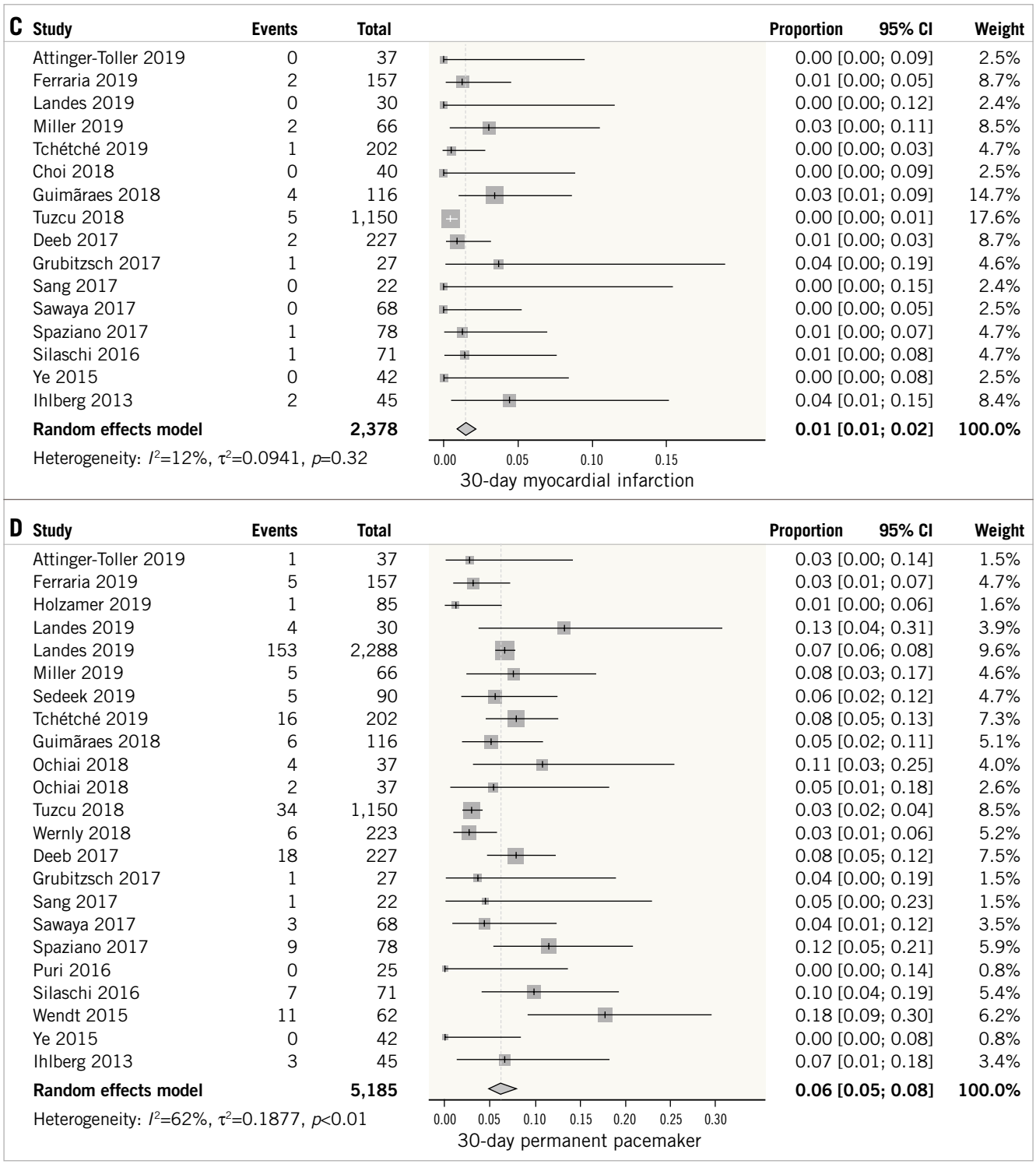


Figure 2 (contd). *Forest plot showing the incidence of 30-day all-cause mortality (A), stroke (B), myocardial infarction (C), and permanent pacemaker placement (D).*

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 (I^2=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 (I^2=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 (I^2=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 (I^2=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 (I^2=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 volume[41]. 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 valves[42-45].

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 trial[6].

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 random-effects 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.

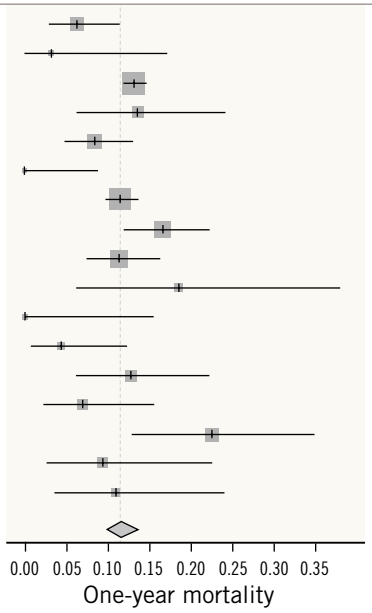
Impact on daily practice

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**	**0.12**	**[0.10; 0.14]**	**100.0%**

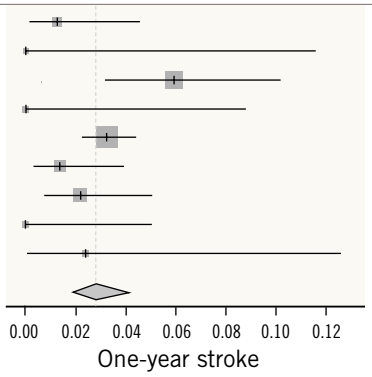
Heterogeneity: I^2=51%, τ^2=0.0494, p<0.01



B

Study	Events	Total	Proportion	95% CI	Weight
Ferraria 2019	2	157	0.01	[0.00; 0.05]	7.3%
Landes 2019	0	30	0.00	[0.00; 0.12]	2.1%
Tchétché 2019	12	202	0.06	[0.03; 0.10]	23.4%
Chol 2018	0	40	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	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**	**0.03**	**[0.02; 0.04]**	**100.0%**

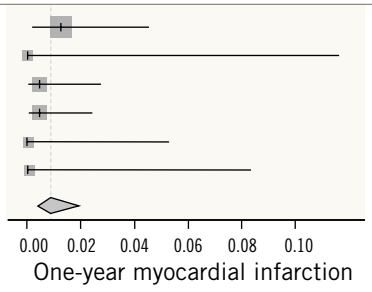
Heterogeneity: I^2=31%, τ^2=0.1006, p=0.17



C

Study	Events	Total	Proportion	95% CI	Weight
Ferraria 2019	2	157	0.01	[0.00; 0.05]	36.2%
Landes 2019	0	30	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	0.00	[0.00; 0.05]	9.1%
Ye 2015	0	42	0.00	[0.00; 0.08]	9.1%
Random effects model		**726**	**0.01**	**[0.00; 0.02]**	**100.0%**

Heterogeneity: I^2=0%, τ^2=0, p=0.93



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	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%, τ^2=0.0971, p=0.15

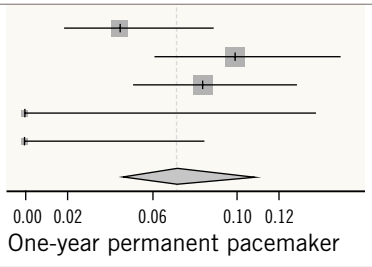


Figure 3. *Forest plot showing the incidence of one-year all-cause mortality (A), stroke (B), myocardial infarction (C), and permanent pacemaker placement (D).*

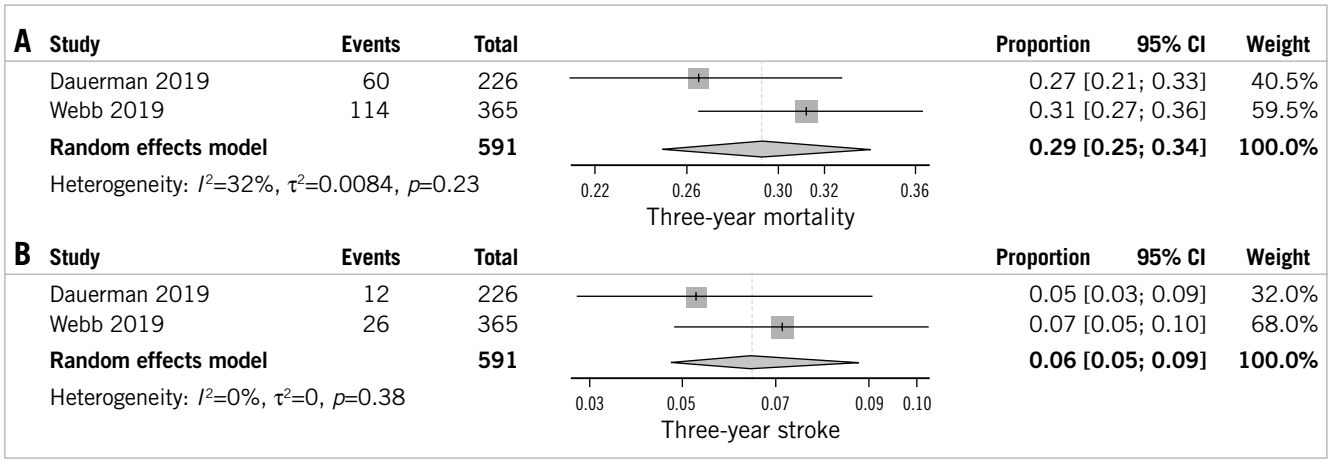


Figure 4. *Forest plot showing the incidence of three-year all-cause mortality (A), and stroke (B).*

Conflict of interest statement

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

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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.

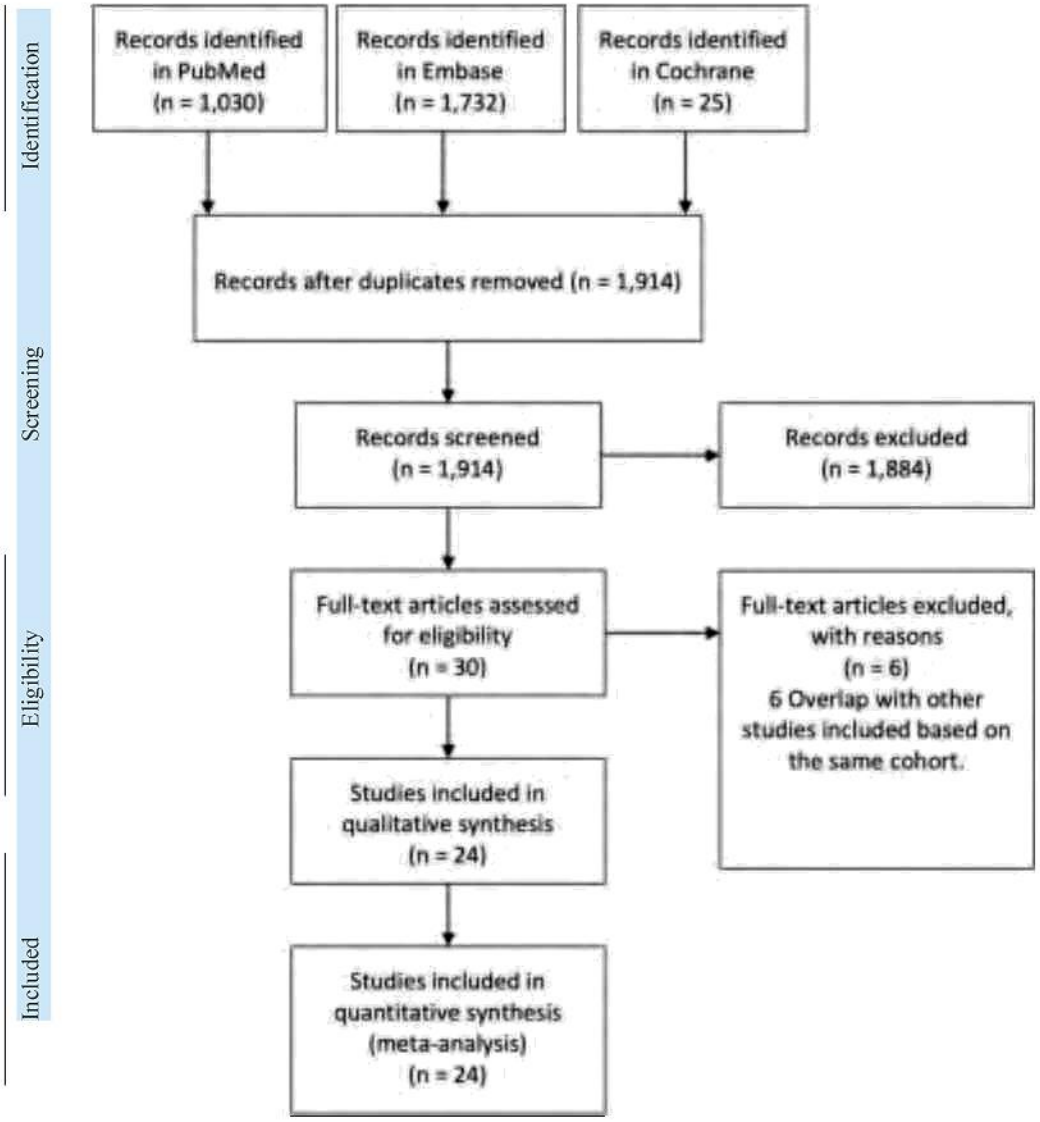
Supplementary Table 2. Definition of procedural success in the included studies.

Supplementary Table 3. Quality assessment of included studies.

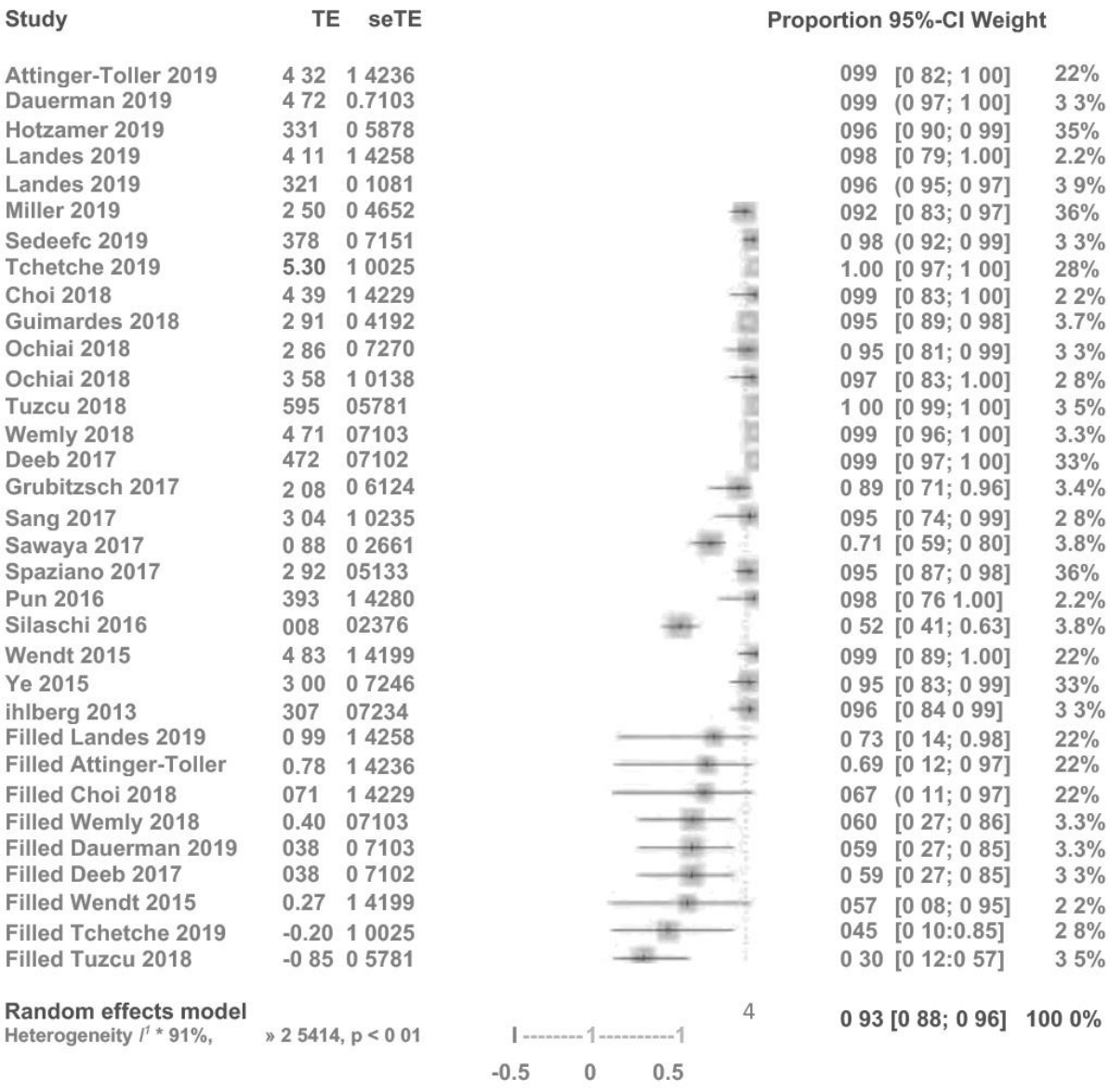
Supplementary Table 4. Characteristics of included studies and patient population.

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

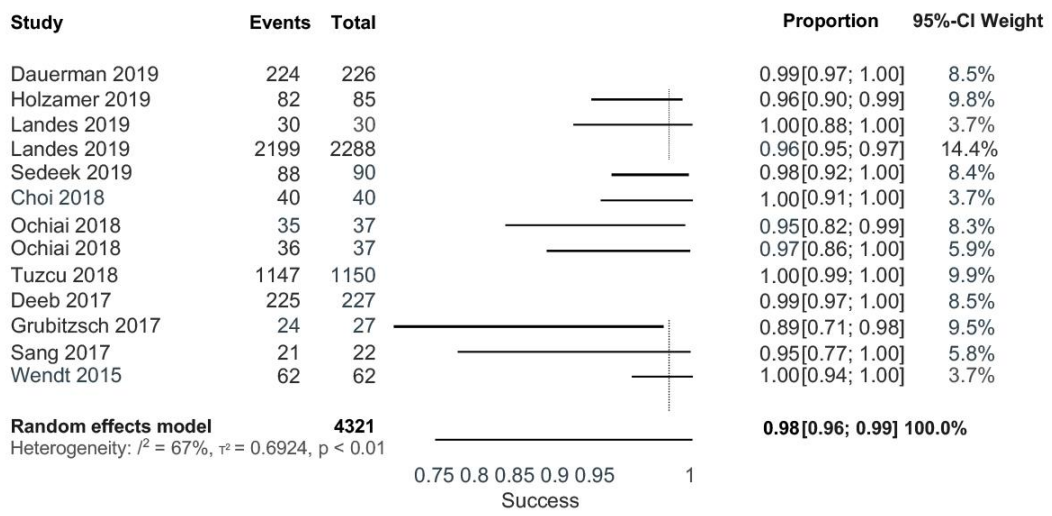
Supplementary data



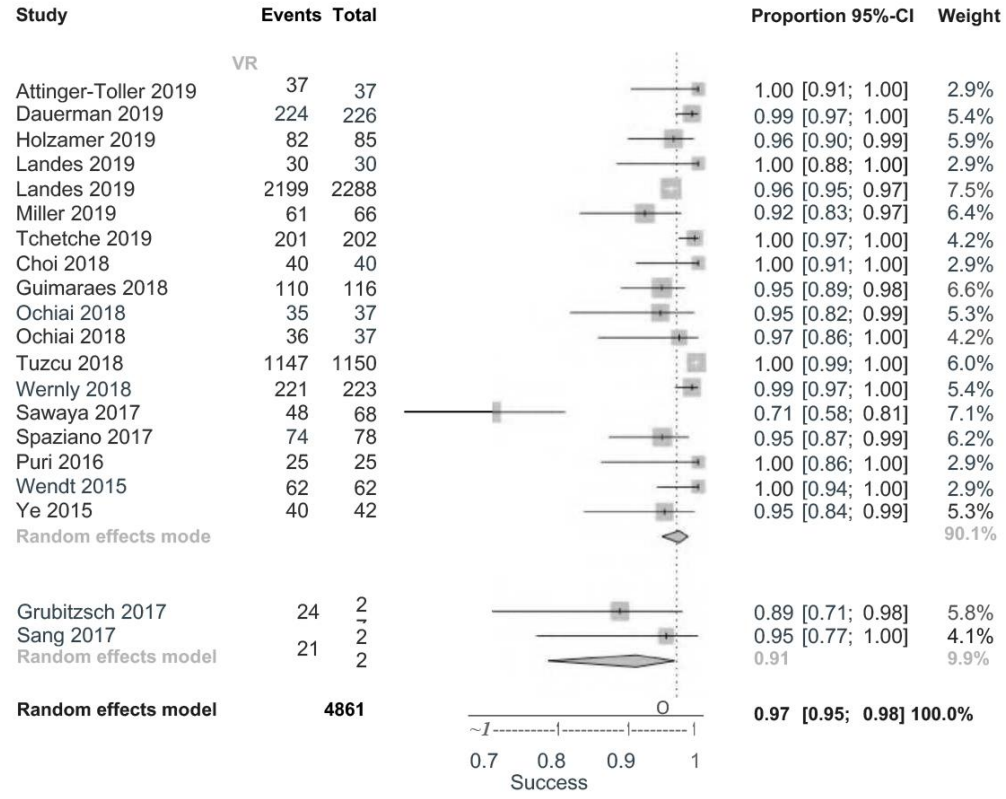
Supplementary Figure 1. Search strategy according to PRISMA guidelines.



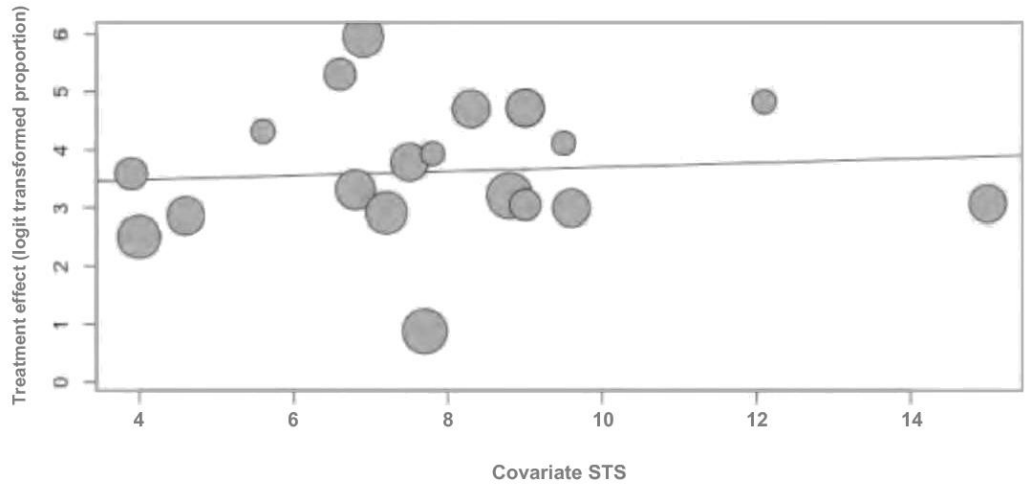
Supplementary Figure 2A. Forest plot showing procedural success using the trim-and-fill method to account for heterogeneity.



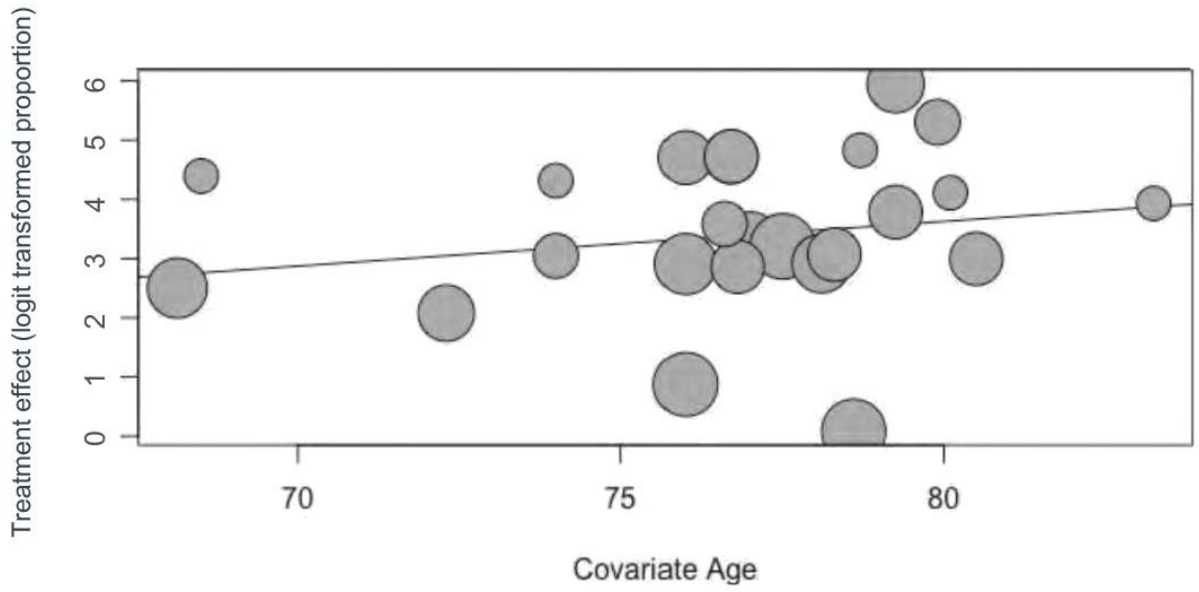
Supplementary Figure 2B. Sensitivity analysis excluding studies with potential but not confirmed study overlap.



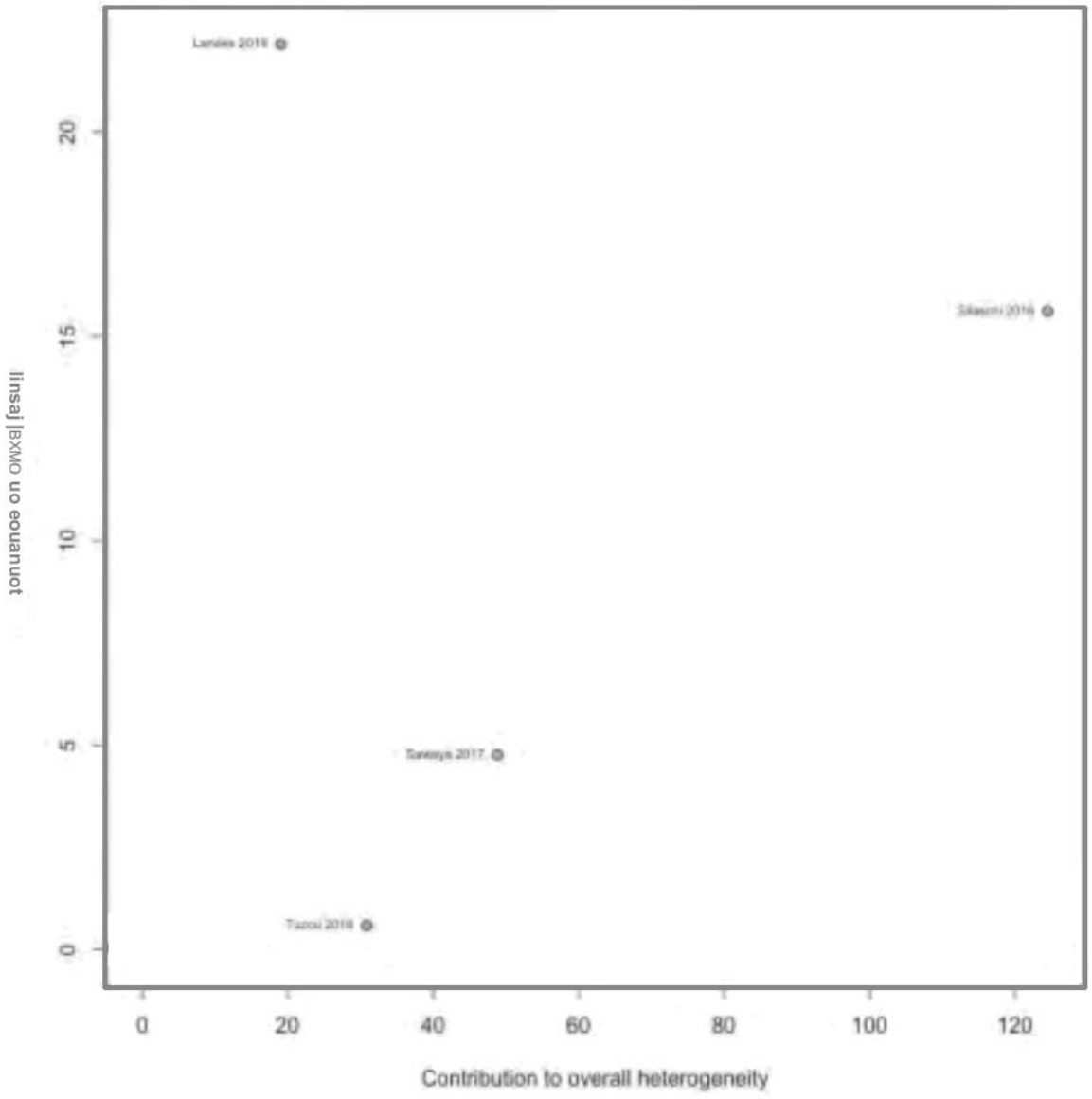
Supplementary Figure 2C. Subgroup analysis based on procedure used to implant failed bioprosthetic valve.



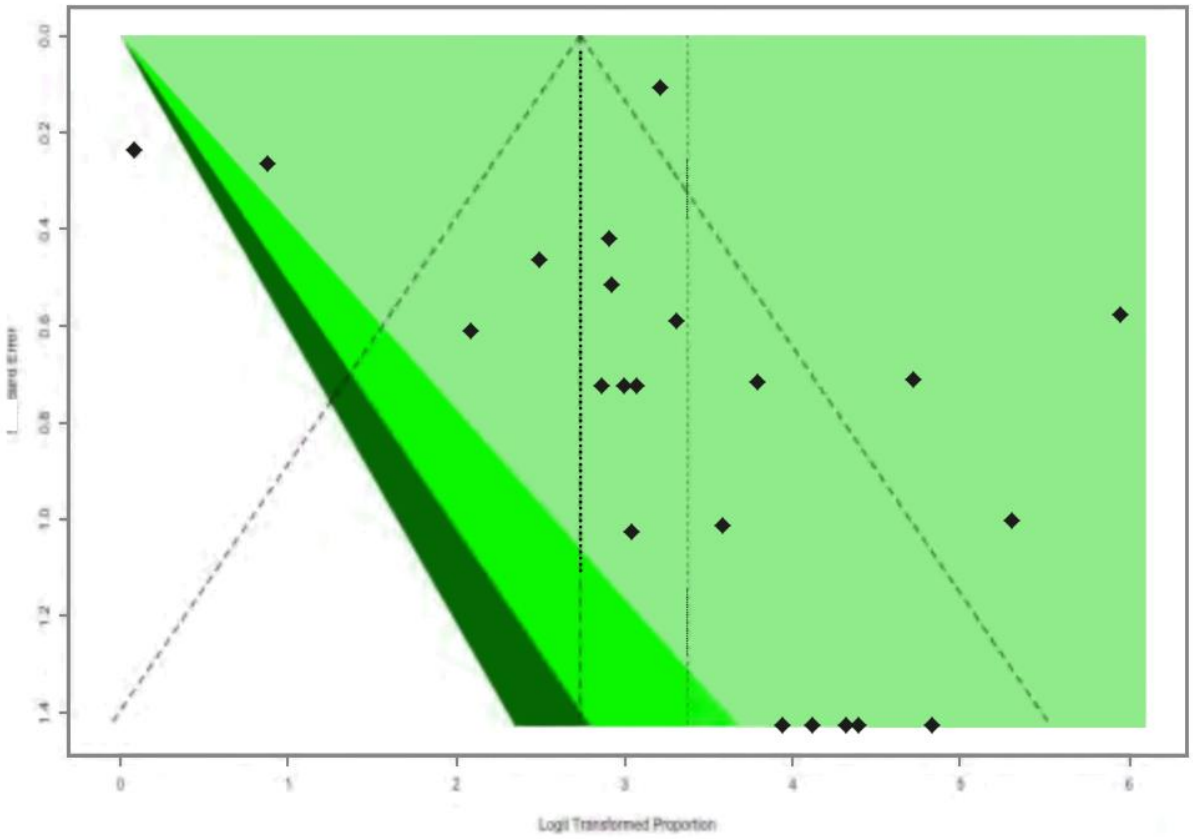
Supplementary Figure 2D. Meta-regression of procedural success and STS score.



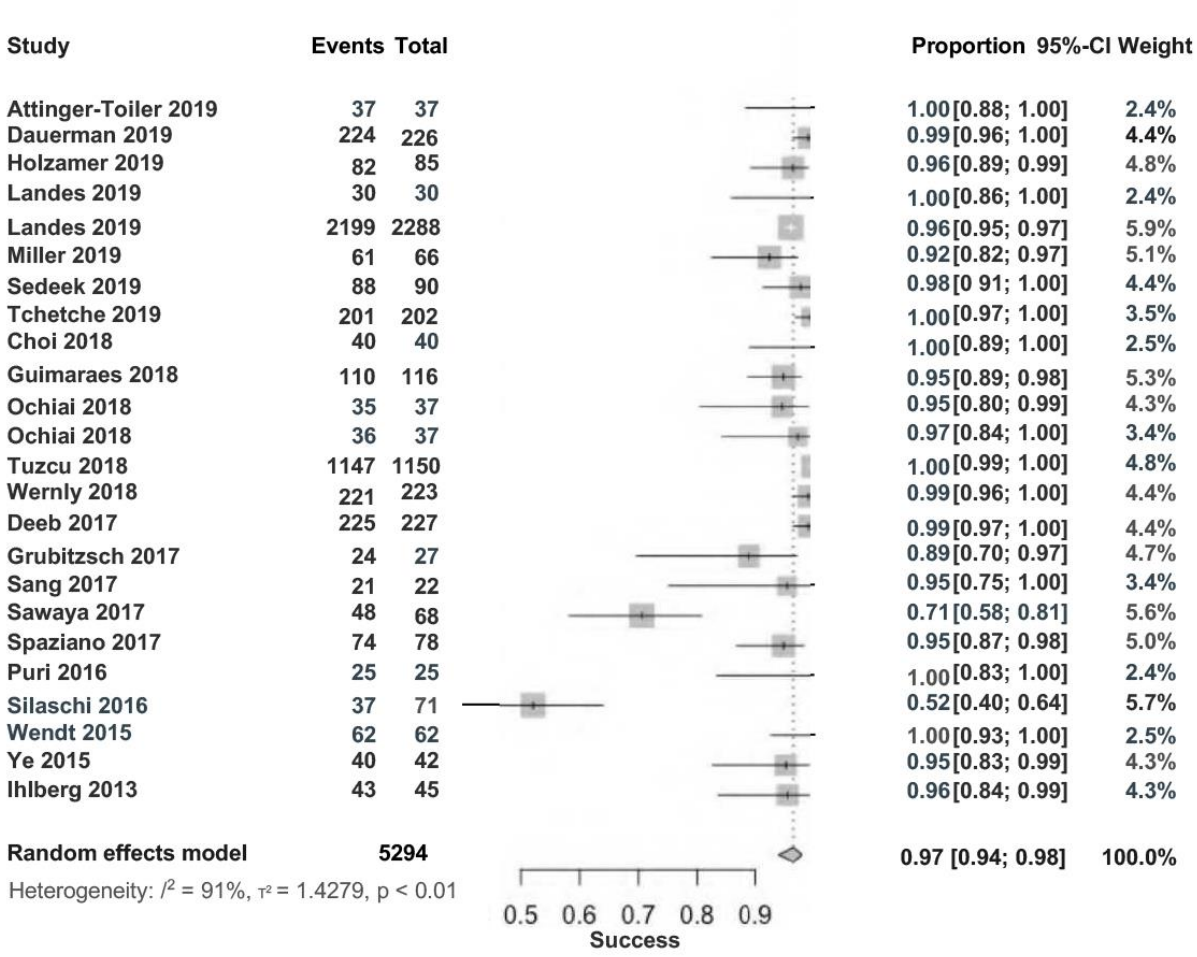
Supplementary Figure 2E. Meta-regression of procedural success and age.



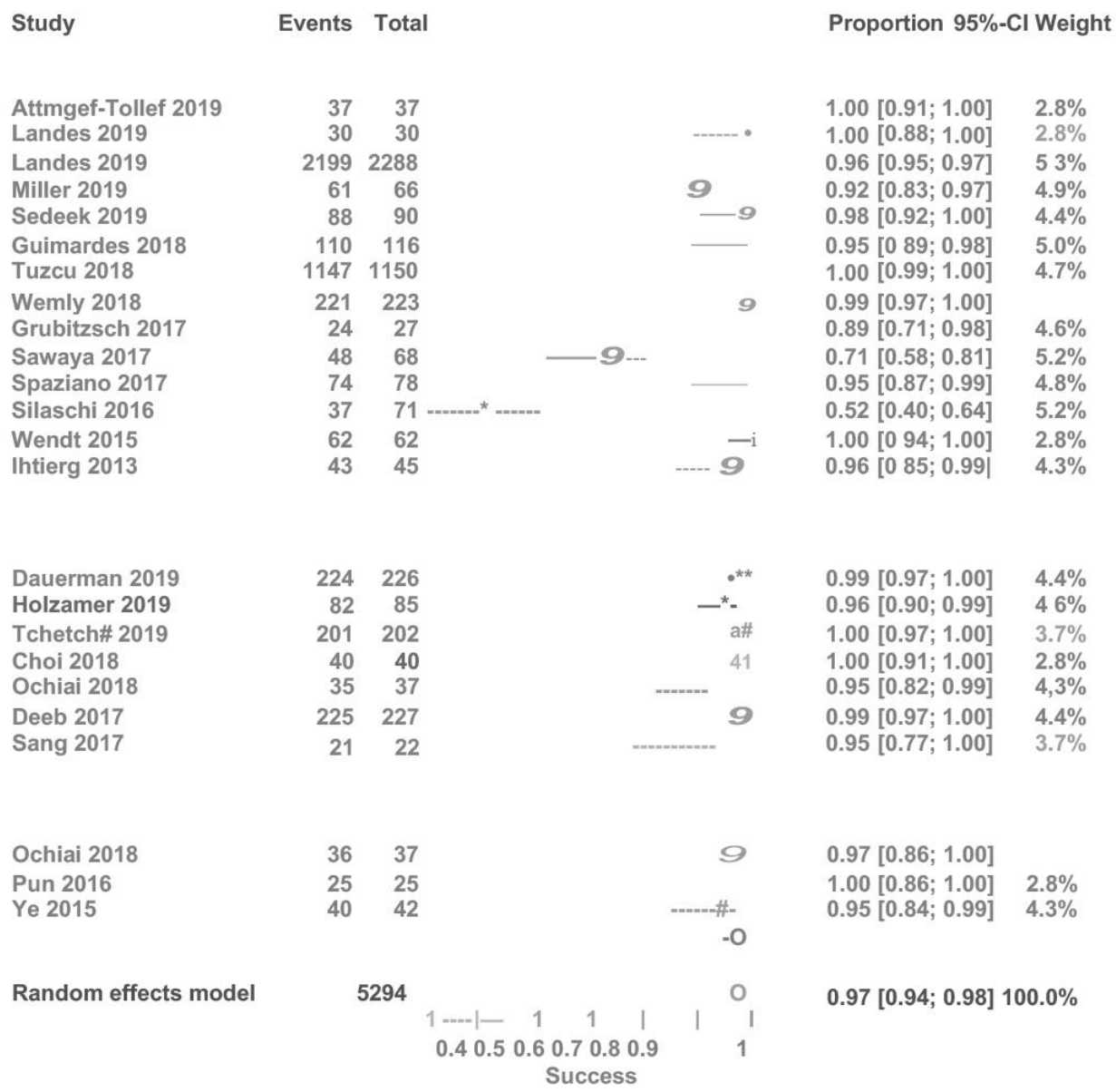
Supplementary Figure 2F. Baujat plot for publication bias.



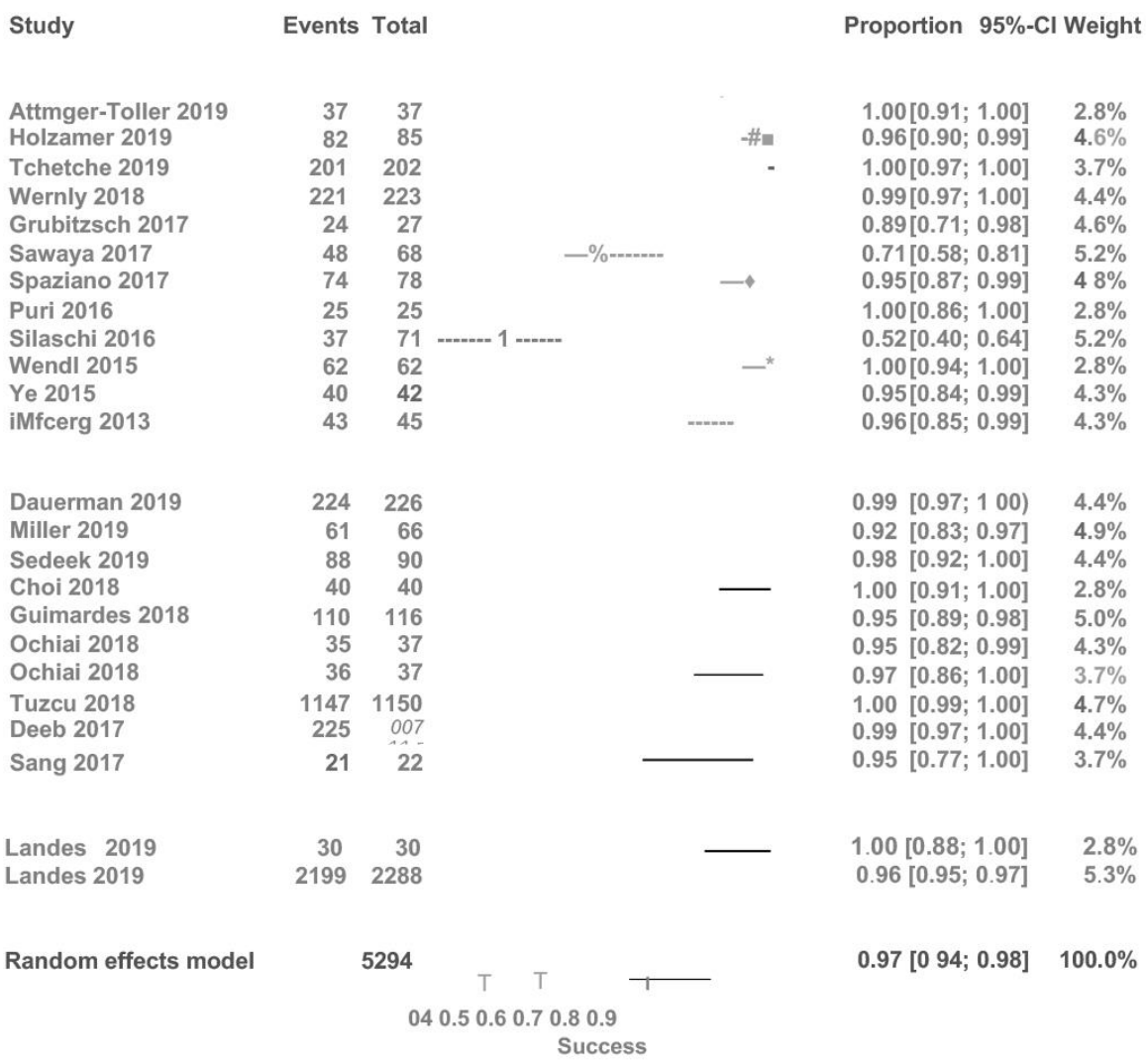
Supplementary Figure 2G. Funnel plot.



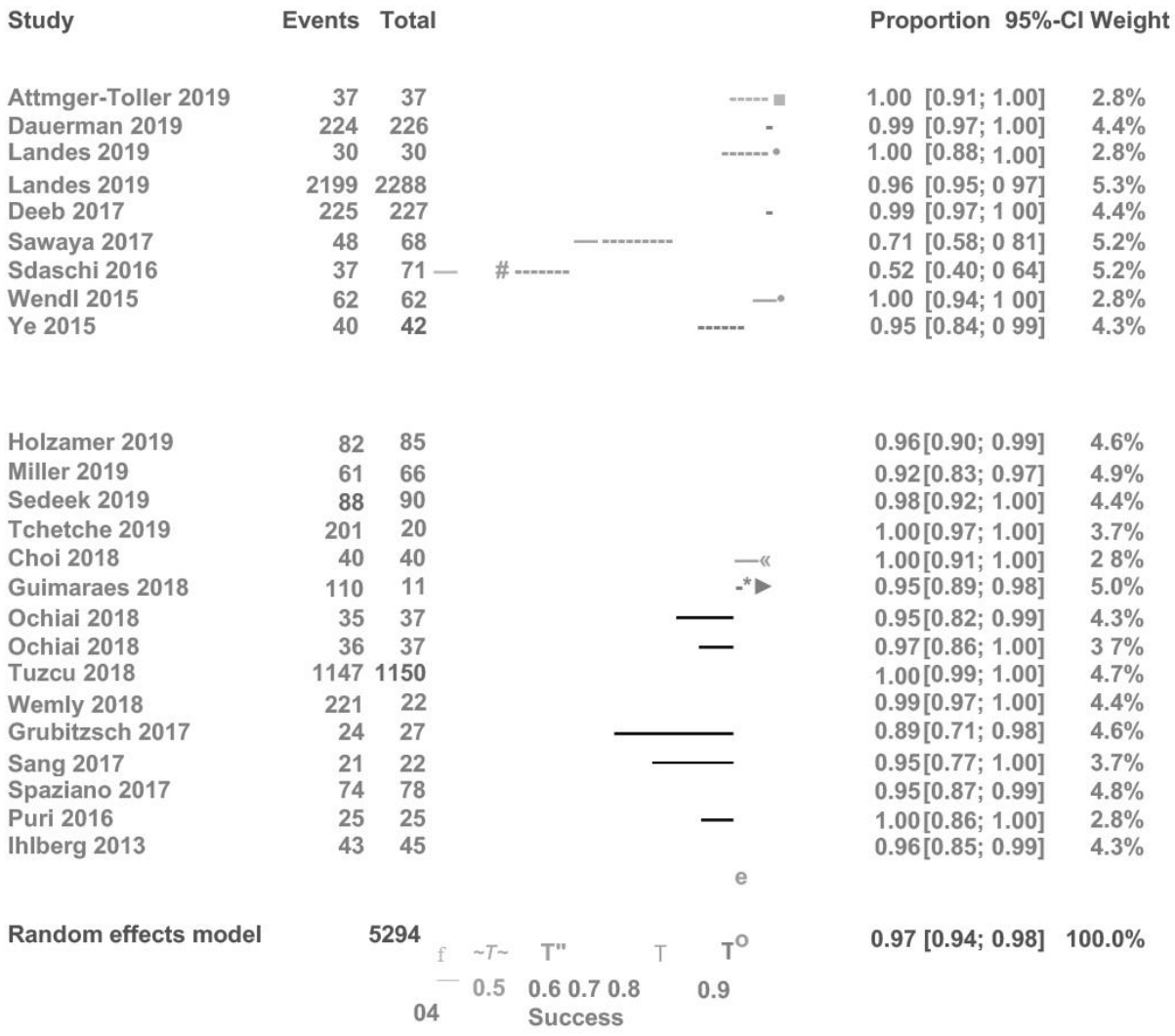
Supplementary Figure 2H. Forest plot with Bayesian analyses with informative prior distributions for the residual between study variance.



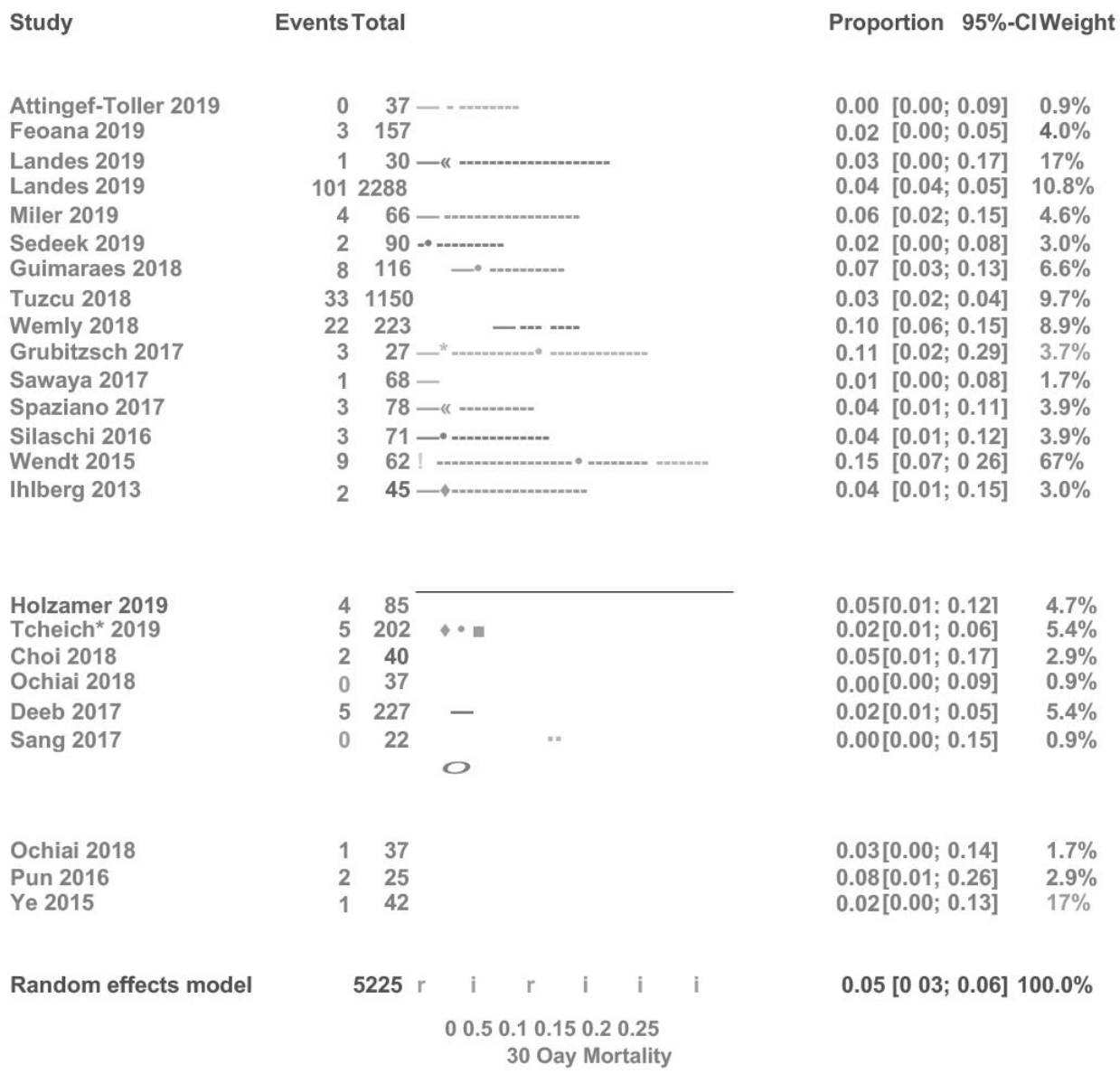
Supplementary Figure 3A. Forest plot showing subgroup analysis of procedural success by type of valve used.



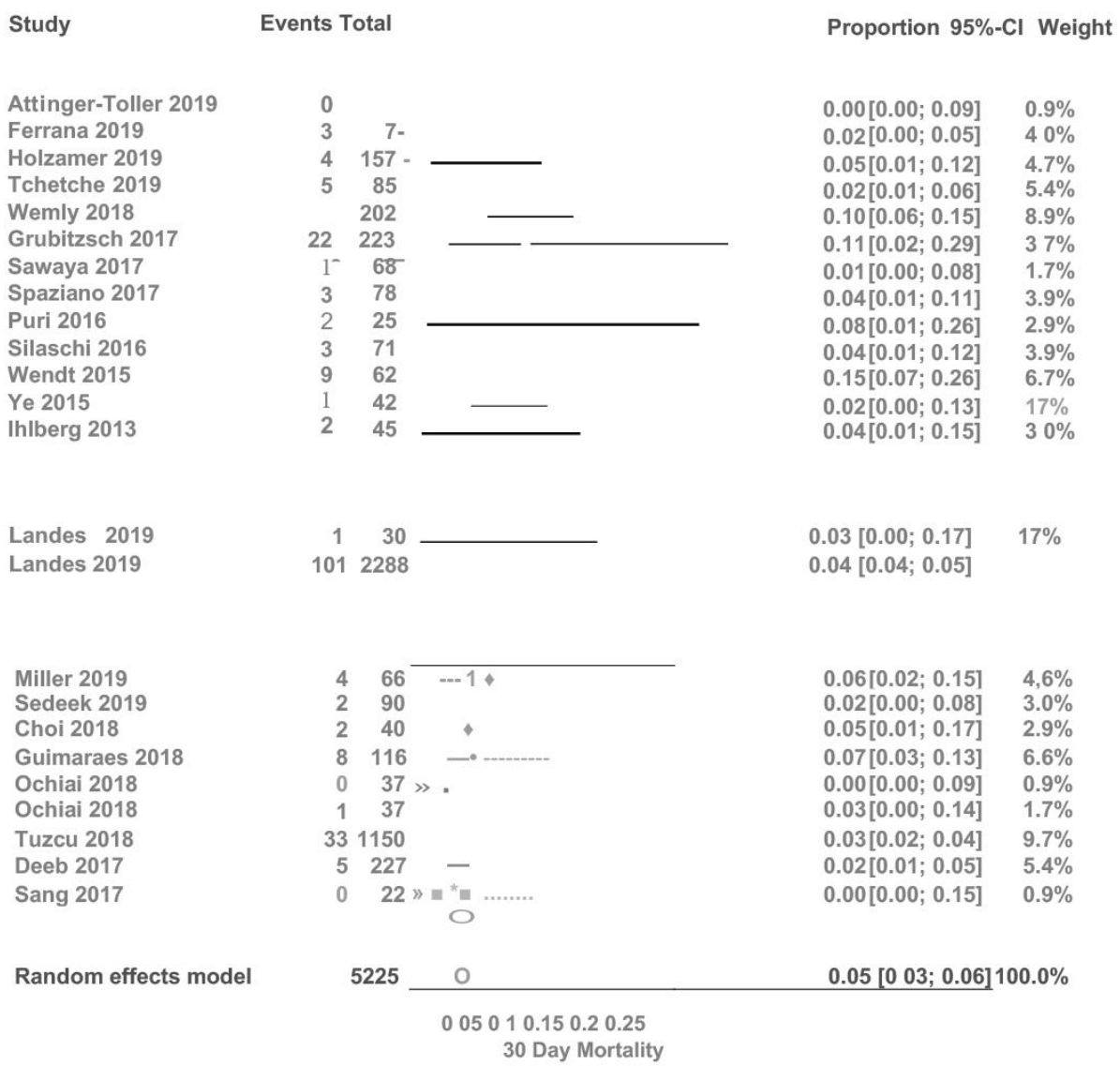
Supplementary Figure 3B. Forest plot showing subgroup analysis of procedural success by location of study.



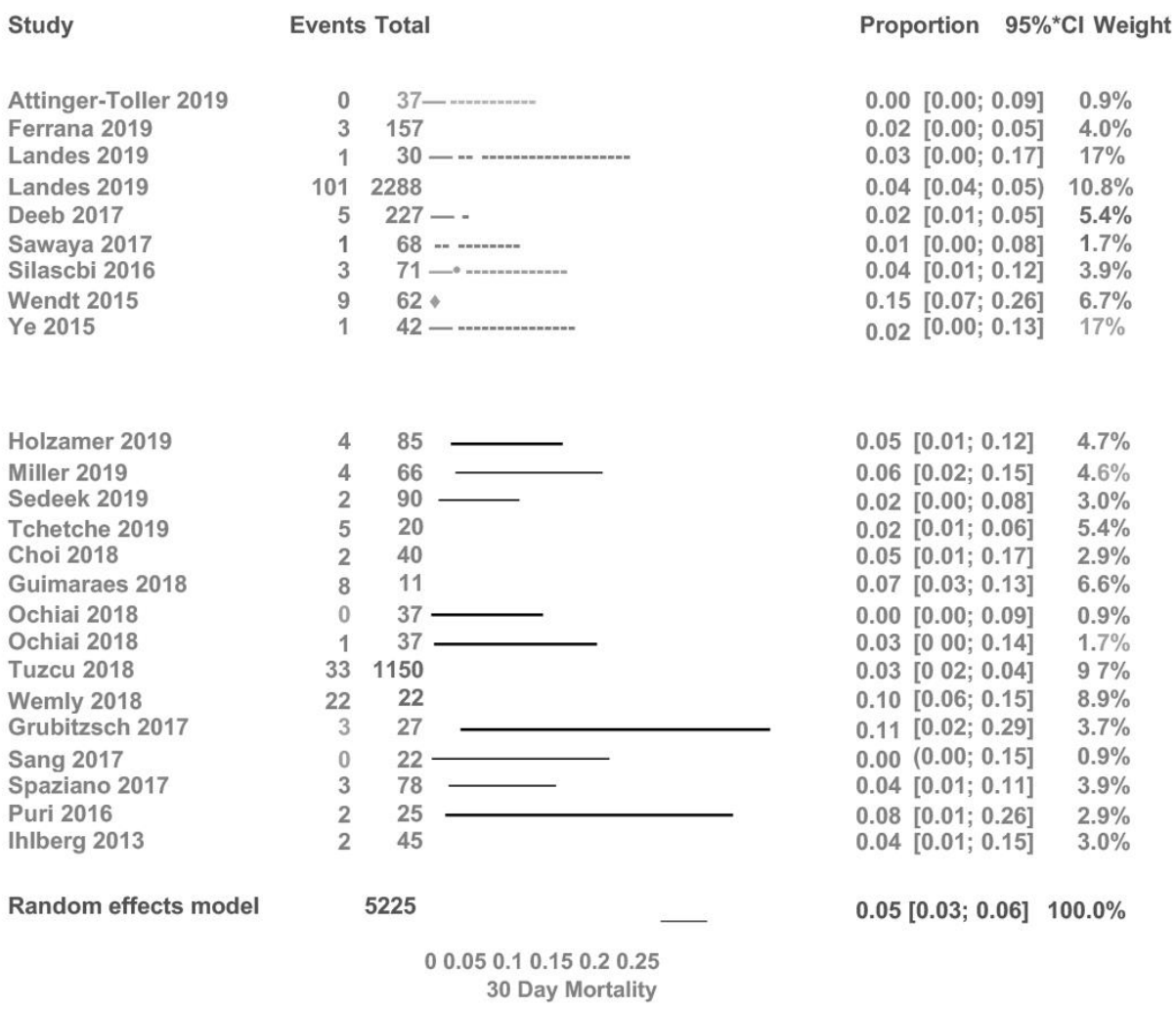
Supplementary Figure 3C. Forest plot showing subgroup analysis of procedural success by study design.



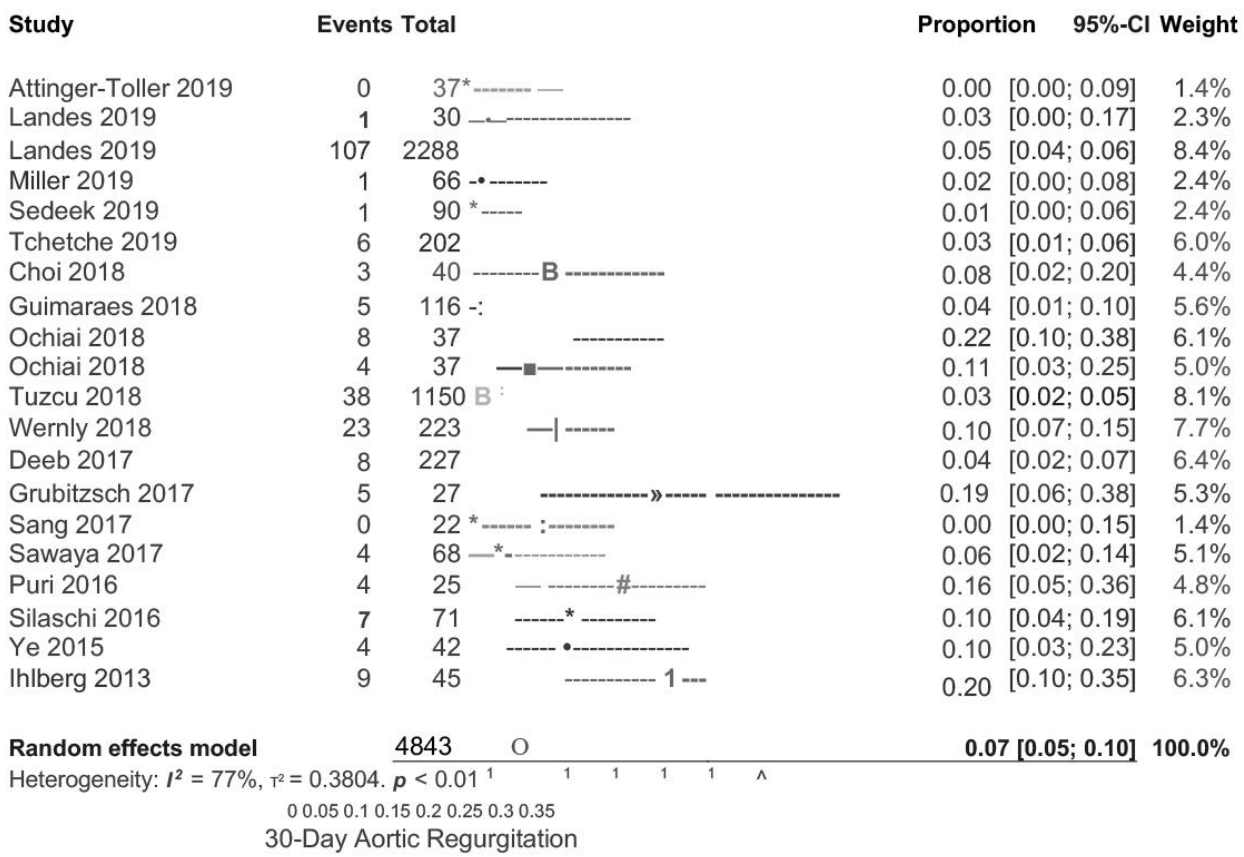
Supplementary Figure 4A. Forest plot showing subgroup analysis of 30-day all-cause mortality by type of valve used.



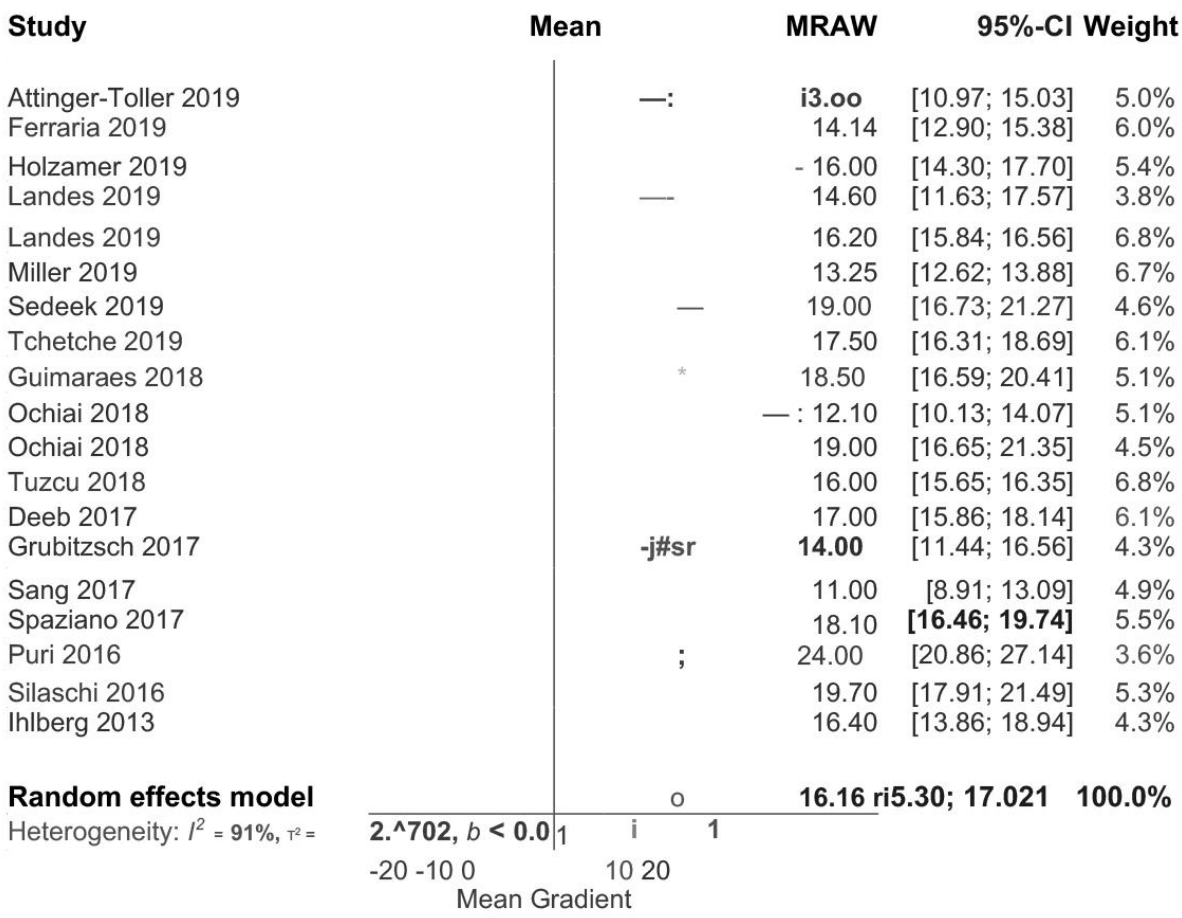
Supplementary Figure 4B. Forest plot showing subgroup analysis of 30-day all-cause mortality by location of study.



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.

#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

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

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 ≤ 0.65 cm^2/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

		- 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 valve area ≤ 0.65 cm^2/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

Supplementary Table 3. Quality assessment of included studies.

		Pre-intervention		At intervention	Post intervention				
Study	Year	Confounding	Selection	Intervention classification	Deviations from intended intervention	Missing data	Measurement of outcomes	Selection of the reported results	Overall bias
Attinger-Toller et al	2019	Low	Moderate	Low	Moderate	Low	Low	Low	Moderate
Dauerman et al	2019	Low	Low	Low	Low	Low	Low	Low	Low
Ferraria et al	2019	Low	Moderate	Low	Low	Low	Low	Moderate	Moderate
Holzamer et al	2019	Low	Low	Low	Low	Low	Low	Low	Low
Landes et al	2019	Low	Moderate	Low	Moderate	Low	Low	Low	Moderate
Miller et al	2019	Low	Moderate	Low	Low	Low	Low	Low	Moderate
Sedeek et al	2019	Low	low	low	low	low	low	Low	Low
Tchetche et al	2019	Low	Low	Low	Low	Low	Low	Low	Low
Webb et al	2019	Low	Low	Low	Low	Low	Low	Moderate	Moderate
Choi et al	2018	Low	Low	Low	Low	Low	Low	Low	Low
Guimaraes et al	2018	Low	Low	Low	Low	Low	Low	Low	Low
Ochiai et al	2018	low	Low	Low	Low	Moderate	Low	Low	Moderate
Tuzcu et al	2018	Low	Low	Low	Low	Low	Low	Low	Low
Wernly et al	2018	Low	Low	Low	Low	Low	Low	Low	Low
Deeb et al	2017	Low	Low	Low	Low	Low	Low	Low	Low
Grubitzsch et al	2017	Low	Moderate	Low	Low	Low	Low	Low	Moderate
Sang et al	2017	Low	Moderate	Low	Low	Low	Low	Low	Moderate
Sawaya et al	2017	Moderat	Moderate	Low	Low	Low	Low	Low	Moderate

Spaziano et al	2017	Low	Low	Low	Low	Low	Low	Low	Low
Puri et al	2016	Low	Moderate	Low	Low	Low	Low	Low	Moderate
Silaschi et al	2016	Low	Moderate	Low	Low	Low	Low	Low	Moderate
Wendt et al	2015	Low	Low	Low	Low	Low	Low	Low	Low
Ye et al	2015	Low	Moderate	Low	Low	Low	Low	Low	Moderate
Ihlberg et al	2013	Low	Low	Low	Low	Low	Low	Low	Low

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

N	Author	Year	Valve Type	Study Design	Sample Size	Age, mean (SD)	Males, %	STS, mean (SD)	BMI, mean (SD)	Ejection Fraction mean (SD)	Hypertension, %	Diabetes Mellitus, %	Coronary Artery Disease, %	Smoking, %	History of Myocardi	History of Stroke, %
1	Attinger-Toller et al	2019	Both	Prospective	37	74 (10)	78	5.6 (2.4)	NR	53 (14)	65	32	NR	NR	NR	NR
2	Daueman et al	2019	Self-expandable	Prospective	226	76.7 (10)	63.3	9 (6.7)	NR	NR	92	39.8	72.6	NR	72.6	72.6
3	Ferraria et al	2019	Both	Prospective	157	78.62 (9.11)	60.5	6.42 (5.03)	26.63 (4	54.57 (13.07)	76.4	20.4	54.5	NR	12.7	14.6
4	Holzamer et al	2019	Self-expandable	Retrospecti	85	77 (8)	54	6.8 (6)	NR	54 (11)	87	29	51	NR	11	NR
5	Landes et al	2019	Both	Prospective	2288	77.5 (1	58.7	8.8 (8.1)	27 (5	52 (13)	NR	23.30	NR	NR	NR	16
	Landes et al	2019	Both	Prospective	30	80.1 (7.8)	17.2	9.5 (7)	27.1 (5	56 (8)	NR	25.1	NR	NR	NR	30.8
6	Miller et al	2019	Both	Retrospectiv	66	68.13 (6	80.3	4 (1.08	NR	NR	NR	NR	NR	NR	NR	NR
7	Sedeek et al	2019	Both	Retrospective	90	79.25 (2.84	81	7.5 (1.6	28 (2.2)	56 (4.89)	88	28	64	NR	NR	33
8	Tchetche et al	2019	Self-expandable	Retrospectiv	202	79.9 (7.8)	47.5	6.6 (5.1)	NR	NR	83.5	26.2	NR	NR	10.9	7.5
9	Webb et al	2019	Balloon expandable	Prospective	365	78.9 (10	64.1	9.1 (4.7)	NR	NR	NR	31.2	57.3	NR	NR	12.1

10	Choi et al	2018	Self-expandable	Retrospective	40	68.5 (14)	75.00	NR	29.44 (6.03)	53.9 (10.6)	65.3	24.6	53.1	40.63	NR	NR
11	Guimaraes et al	2018	Both	Retrospective	116	76 (11)	64.70	NR	26.9 (5	55 (13.4)	73.3	31.9	63.8	26.7	NR	22.7
12	Ochiai et al	2018	Self-expanding	Retrospective	37	76.8 (12.8)	67.60	4.6 (1.2)	NR	50.9 (17)	86.5	8.1	NR	NR	NR	10.8
	Ochiai et al	2018	Balloon-expandable	Retrospective	37	76.6 (12.3)	70.30	3.9 (1.6	NR	50 (12.8)	83.8	10.8	NR	NR	NR	NR
13	Tuzcu et al	2018	Both	Retrospective	1150	79.25 (3.19)	**60.80**	6.9 (1.83	NR	55 (4.61)	**90.5**	**32.1**	**58.6**)	NR	NR	NR
14	Wernly et al	2018	Both	Retrospective	223	76 (11)	58.00	8.3 (10.1)	36 (4.8)	51 (18)	85	28	61	NR	8	12
15	Deeb et al	2017	Self-expandable	Prospective	227	76.7 (10.8)	63.00	9 (6.7)	NR	NR	92.1	91	72.7	64.7	19.8	23.7
16	Grubitzsch et al	2017	Both	Retrospective	27	72.3 (9.7)	77.00	NR	26.9 (4	52 (11.4)	NR	NR	50	NR	6	23
17	Sang et al	2017	Self-expandable	Retrospective	22	74 (9)	64.00	9 (7.	NR	53 (12)	NR	NR	NR	NR	NR	NR
18	Sawaya et al	2017	Both	Prospective	68	76 (12)	66.00	7.7 (6.2)	25 (5)	51.7 (13)	84	25	NR	NR	15	15
19	Spaziano et al	2017	Both	Retrospective	78	78.1 (8)	51.00	7.2 (4.9)	NR	50.7 (13)	72	20	43	NR	NR	7
20	Puri et al	2016	Balloon expandable	Retrospective	25	83.25 (1.46)	12.00	7.8 (2.23	25.9 (4.8)	60 (9.9)	NR	20	52	NR	NR	26
21	Silaschi	2016	Both	Prospe	71	78.6	57.70	NR	NR	NR	NR	11.3	NR	NR	NR	14.1

						(7.6)											
22	Wendt et al	2015	Both	Prospe ctive	62	78.7 (5.	69.40	12.1 (1	27.1 (4	48.1 (13)	91.9	38.7	NR	NR	NR	NR	
23	Ye et al	2015	Balloon expandable	Prospe ctive	42	80.5 (9.8)	67.70	9.6 (1.4	NR	57.5 ()	NR	23.8	69	NR	NR	16.7	
24	Ihlberg et al	2013	Both	Retrospective	45	78.3 (8.64	58.00	15 (10.8)	NR	46.3 (12.8)	NR	18	NR	NR	13	18	