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A systematic review on the safety of second-generation transcatheter aortic valves

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KEYWORDS

- paravalvular aortic regurgitation
- safety of transcatheter aortic valve implantation (TAVI)
- second-generation TAVI valves
- TAVI and pacemaker

Abstract

Aims: To review the outcomes of studies and the safety of newer transcatheter aortic valves (THV).

Methods and results: All studies reporting on second-generation THV were identified and pooled using the systematic review guidelines. Twenty-four reports on 1,708 patients and eight THV were included in the analysis. The pooled 30-day event rate for mortality after transcatheter aortic valve implantation (TAVI) was 5.7% (95% CI: 4.0-7.8), myocardial infarction (MI) was 1.7% (95% CI: 1.1-2.6), stage 3 acute kidney injury (AKI) was 3.4% (95% CI: 2.0-5.6), life-threatening bleeding was 5.1% (95% CI: 3.3-7.8), major vascular complications was 4.9% (95% CI: 3.5-6.6%), major bleeding was 10.5% (95% CI: 5.1-20.4), major stroke was 2.4% (95% CI: 1.7-3.4), permanent pacemaker utilisation was 13.5% (95% CI: 10.8-16.9), and coronary obstruction was 1.2% (95% CI: 0.6%-2.4%). Moderate or severe aortic insufficiency (AI) after TAVI was 4.2% (95% CI: 2.0-8.5). The pooled 30-day mean gradient and effective orifice area (EOA) were 11.63 mmHg (95% CI: 10.19-13.07) and 1.60 cm^2 (95% CI: 1.5-1.7), respectively. All estimates compare favourably to events reported for first-generation valves.

Conclusions: Our findings suggest that the new THV have a low risk of TAVI-related short-term complications.

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Abbreviations

CE	Conformité Européenne (European Conformity)
CI	confidence interval
DFM	Direct Flow Medical valve
DISCOVER	A registry to evaluate the Direct Flow Medical transcatheter aortic valve system
EHJ	European Heart Journal
EJCTS	European Journal of Cardio-Thoracic Surgery
FIM	first-in-man
GARY	German Aortic Valve Registry
ICI	innovations in cardiovascular interventions
IDE	investigational device evaluation
JACC	Journal of American College of Cardiology
JTCS	Journal of Thoracic and Cardiovascular Surgery
JUPITER	long-term safety and performance of the JenaValve trial
MC	multicentre
N	number of patients
NA	not available
PARTNER	Placement of AoRTic TraNscathetER Valves trial
Reg	registry
REPRISE	REpositionable Percutaneous Replacement of Stenotic Aortic Valve Through Implantation of Lotus™ Valve System study
SAVI	Symetis ACURATE TA™ valve implantation registry
TA	transapical
TCT	transcatheter cardiovascular therapeutics
TF	transfemoral
VARC	Valve Academic Research Consortium
UK	United Kingdom

Introduction

Transcatheter aortic valve implantation (TAVI) has seen an exponential utilisation in high surgical risk patients due to impressive results in randomised and non-randomised trials[1,2]. The wealth of this experience is shared by the Medtronic CoreValve® (Medtronic, Minneapolis, MN, USA) and the Edwards SAPIEN valve (Edwards Lifesciences, Irvine, CA, USA). However, despite their good results, both valves have significant limitations which restrict the expansion of TAVI to the intermediate- and low-risk population[1-6]. Neither device is truly repositionable or retrievable, making deployment a "single-shot" procedure and technically demanding. Malpositioning of the aortic prosthesis is therefore not uncommon and has been implicated in several TAVI-related complications which include paravalvular leak, coronary obstruction, valve embolisation, atrioventricular conduction block, heart failure and mortality. Major vascular complications with attendant risk of renal failure and mortality are also of concern with these early devices for TAVI. Newer, second-generation transcatheter aortic valves have been developed to overcome the limitations of the Medtronic CoreValve and Edwards SAPIEN valve to improve deliverability, prevent paravalvular leak and to reposition or retrieve when necessary. A number of devices with these desirable features are being investigated and have undergone successful clinical evaluation with promising results. Data on the safety and efficacy of these devices are, however, limited by the small number of patients enrolled in each study[7-15]. We therefore performed this systematic review on the safety and efficacy of newer, second-generation TAVI devices to obtain more conclusive results.

Methods

STUDY SELECTION

We conducted this systematic review on the published literature of outcomes after TAVI using second-generation valves. The review was conducted as per the QUOROM[16] (Quality of Reporting of Meta-Analysis) and MOOSE (Meta-Analysis of Observational Studies in Epidemiology) guidelines[17]. All valves (other than the Medtronic CoreValve/Edwards SAPIEN and SAPIEN XT or their precursors) which were designed to improve deliverability, sealing to prevent paravalvular leak and/or the ability to reposition or retrieve were considered to be second-generation valves. We reviewed the literature to identify all available valves, including the second-generation valves. A computerised search was then performed by two reviewers (G. Athappan and R.D. Gajulapalli) to identify all relevant studies using these second-generation valves published until January 2015 in the PubMed database or Major Conference proceedings. The following search terms were used: "TAVI", "TAVR", "Transcatheter Valve", "Transapical Valve", "ACURATE TA", "ACURATE TF", "ACURATE", "Engager", "JenaValve", "Portico", "Sadra Lotus" and "Direct Flow Medical Aortic Valve", "CENTERA", "CoreValve Evolut", "HLT valve" and "SAPIEN 3". Citations were screened at the title and abstract level and retrieved as a full report if they reported on safety outcomes with implantation of second-generation TAVI valves. Limiting the search parameters to the English language was subsequently applied. The full texts and bibliography of all potential articles were further reviewed in detail (G. Athappan) to seek additional relevant studies.

INCLUSION CRITERIA

Studies were included if the following criteria were satisfied: (a) TAVI was performed using second-generation valves, (b) the study included patients who had severe aortic stenosis of the native valve, and (c) a minimum of 10 patients were treated. When two similar studies were reported from the same institution or author, the most recent publication was included in the analysis.

EXCLUSION CRITERIA

Studies were excluded if any of the following criteria applied: (a) the outcome of interest was not clearly reported or was impossible to extract or calculate from the published results, or (b) the study involved valve-in-valve procedures.

DATA EXTRACTION

Relevant information was collected by G. Athappan/R.D. Gajulapalli and included, but was not limited to, first author, year and journal of publication, study design, inclusion/exclusion criteria, procedural outcomes, number of subjects included, subjects undergoing

successful TAVI, type of device and approach used, study population demographics, follow-up time period and safety and efficacy outcomes.

STUDY ENDPOINTS

Safety endpoints: 30-day mortality, major stroke, life-threatening bleeding, major vascular complications, major bleeding, stage 3 acute kidney injury (AKI), coronary obstruction, MI, moderate or severe paravalvular AI and permanent pacemaker implantation. Valve efficacy endpoint: mean gradient and effective orifice area (EOA) at 30 days.

STATISTICAL ANALYSIS

DerSimonian and Laird's random effects model was utilised to pool the estimates of 30-day safety and valve efficacy endpoints. Pooled event rates and 95% confidence intervals (95% CI) served as summary statistics. Reports with no reported events were excluded from the analysis. Statistical significance was set at $p<0.05$ (two-tailed). Heterogeneity was assessed by a Q-statistic and I^2 test. Significant heterogeneity was considered present for $I^2 \geq 50\%$. Subgroup analysis of studies reporting per VARC, core lab utilisation, transfemoral TAVI, transapical TAVI and post first-in-man (FIM) studies was also performed. The effect across subgroups (TF vs. TA) was compared using a Q-test for between-group heterogeneity. Data analysis was performed using Comprehensive Meta-Analysis Software Version 2 (BioStat, Englewood, NJ, USA)[18].

Results

Using the search keywords, 5,734 reports were identified, of which 175 relevant publications were identified at the abstract and title levels. By applying the inclusion and exclusion criteria, 24 reports **(Table 1)** on 21 unique trials were selected for the meta-analysis[7,11,13,14,19-38] **(Figure 1)**. The study characteristics are provided in **Online Table 1A & 1B** whilst the methodological characteristics of studies are given in **Online Table 2**. These 24 unique trials were on eight unique second-generation valves that included 1,708 patients. Eight of these unique reports were "first-in-man" (FIM) studies[7,13,14,19,20,22-26] on 236 patients (13.8%). In fifteen reports[7,13,14,19-21,27-29,33-38] the transfemoral access was used (six unique valves, 891 patients: 52.2%), while the transapical access[11,22-26,30-32,34] was used in nine (four unique valves, 817 patients: 47.8%). The ACURATE® valve (Symetis, Ecublens, Switzerland) and the SAPIEN 3 (Edwards Lifesciences) were available for both the transfemoral and the transapical approach.

The types of implanted device were Direct Flow Medical® transcatheter aortic valve system (Direct Flow Medical Inc., Santa Rosa, CA, USA), 410 (24.0%); Lotus™ valve system (Boston Scientific, Marlborough, MA, USA), 131 (7.7%); Portico™ valve (St. Jude Medical, St. Paul, MN, USA), 124 (7.3%); SAPIEN 3 valve (Edwards Lifesciences), 76 (10.3%); JenaValve (JenaValve Technology, Munich, Germany), 258 (15.1%); ACURATE TF (Symetis), 89 (5.2%), ACURATE TA (Symetis), 340 (19.9%), CENTERA valve (Edwards Lifesciences), 15 (0.9%); and the Medtronic Engager™ valve (Medtronic), in 165 (9.7%) patients.

Table 1. Selected studies of second-generation valves.

Valve	Study name	FIM/CE	N	Author/ presenter	Journal/ conference	Location	Centres	VARC2	Core lab	Access
Direct Flow	Treede[7]	FIM	21	Treede H	JTCS 2010	Germany	2	No	NA	TF
	DISCOVER[27]	CE	100	Schofer J	TCT 2013	Germany	10	NA	Yes	TF
	DFM registry[37]	Reg	105	Naber C	TCT 2014	Europe	8	Yes	NA	TF
	DISCOVER registry[36]	Reg	153	Davidson C	TCT 2014	Europe	MC	NA	NA	TF
	SALUS[35]	IDE	30	Tuzcu M	TCT 2014	USA	6	Yes	Yes	TF
Portico	Manoharan[19]	FIM	21	Manoharan G	TCT 2012	Canada/UK	2	NA	NA	TF
	Portico CE[28]	CE	103	Manoharan G	TCT 2014	Worldwide	MC	Yes	Yes	TF
Lotus	REPRISE I[20]	FIM	11	Chevalier B	ICI 2012	Australia	3	NA	Yes	TF
	REPRISE II[29]	CE	120	Meredith IT	TCT 2013	Australia/Europe	7	Yes	Yes	TF
SAPIEN 3	Dvir[33]	FIM	26	Dvir D	TCT 2013	Canada	2	NA	NA	TF
	Binder[14]			Binder R	JACC 2013					
	Webb[34]	IDE	150	Webb J	JACC 2014	Canada, Europe	16	Yes	Yes	TF/TA
ACURATE TF	CE mark[38]	CE	89	Mollmann H	TCT 2014	Brazil, Germany, Japan	6	Yes	NA	TF
ACURATE TA	Walther[22,23,30]	FIM	90	Walther T	TCT 2013	Germany	5	NA	NA	TA
	SAVI[30]	CE	250	Walther T	TCT 2013	Argentina/Germany	17	NA	No	TA
JenaValve	Mohr[24]	FIM	12	Mohr FW	Press release	Germany	1	NA	NA	TA
	CE mark[11]	CE	67	Treede H	EJCTS 2012	Germany	7	NA	NA	TA
	JUPITER[31]	CE	180	Treede H	TCT 2014	Europe	12	NA	NA	TA
Engager	Falk[25,26]	FIM	40	Falk V	EHJ 2010	Germany	3	No	NA	TA
	Treede[32]	CE	125	Treede H	TCT 2012	Europe	9	NA	Yes	TA
CENTERA	Binder[13]	FIM	15	Binder R	JACC Intv 2013	Canada/Germany	2	NA	No	TF

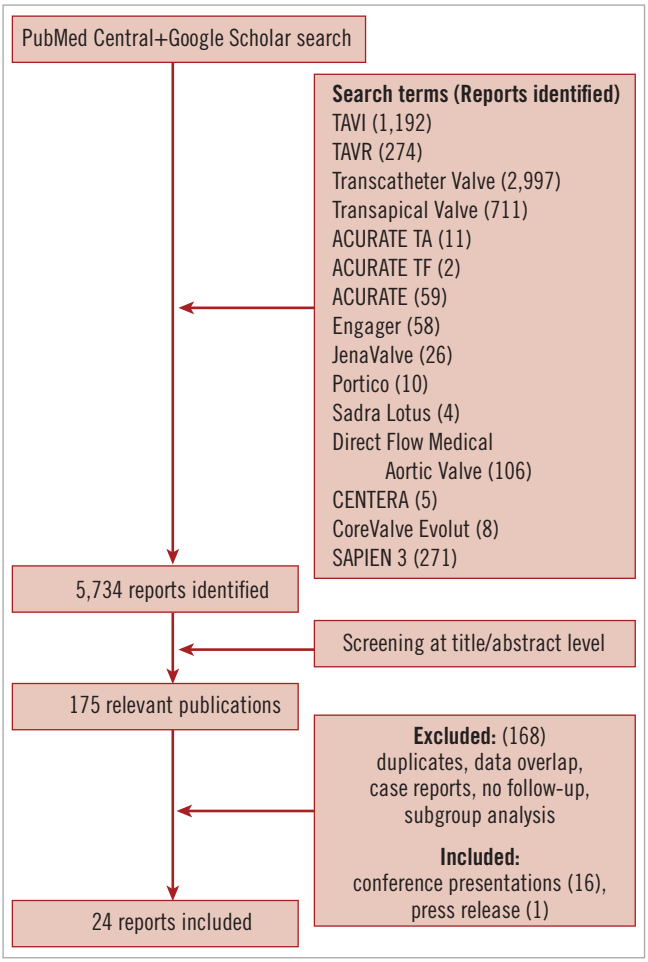

Figure 1. *Flow chart showing selection of studies.*

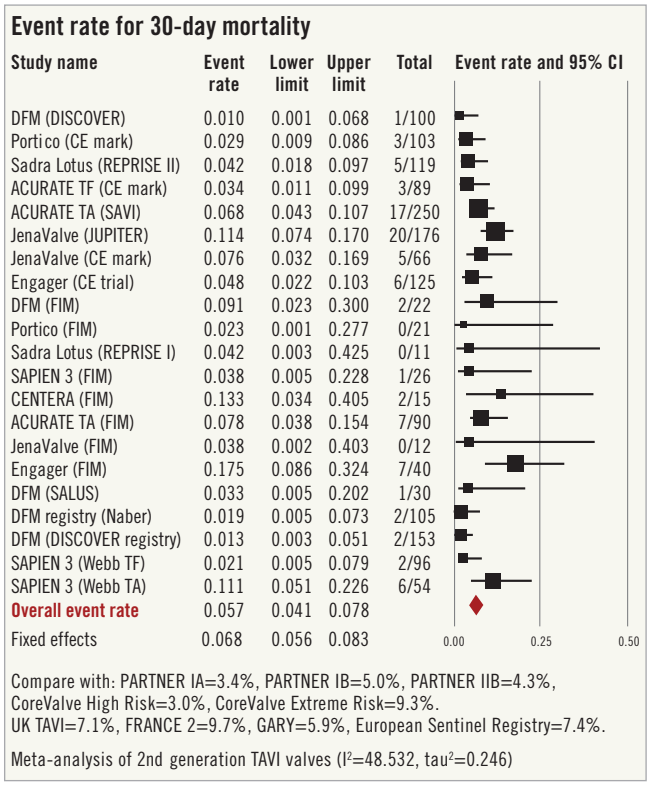

Figure 2. *Forest plot showing the individual and pooled event rates for mortality after TAVI from the included studies.*

Features of the individual valves are provided in **Online Table 3**. Reported device success ranged from 64.5% to 100%. The lowest device success was reported for the Direct Flow valve in the FIM study. Excluding FIM studies, the device's success was in the range of 89.5-100%. Twenty patients (1.1%) required more than one valve. Surgical conversion to valve replacement was needed in 24 patients (1.4%). Data on valve retrieval[7,27,29] and resheathing[9,13,19,28,29] were available in three and four reports, respectively. In the above reports, retrieval (24 attempts, 24 successful) and resheathing (57 attempts/57 successful) were successful in 100% of cases when attempted. Mean effective orifice area (EOA) and gradient at baseline were 0.67±0.18 cm^2 and 44.8±16.09 mmHg, respectively. Pooled post-TAVI mean EOA and gradient were 1.55 cm^2 (95% CI: 1.43-1.67) and 10.85 mmHg (95% CI: 9.59-12.11), respectively.

All-cause 30-day mortality rates were reported between 0% and 17.5%, with a pooled estimate rate of 5.7% (95% CI: 4.1%-7.8%, I^2=48.53) **(Figure 2)**. Myocardial infarction (MI) was reported as a complication of TAVR in 0% to 5.0% of studies, with a pooled estimate rate of 1.7% (95% CI: 1.1%-2.6%, I^2=0) **(Figure 3)**. Major strokes were reported from 0% to 9.1% and occurred at a pooled estimate rate of 2.4% (95% CI: 1.7%-3.4%, I^2=0) **(Figure 3)**.Coronary obstruction was seen in 1.2% (95% CI: 0.6%-2.4%, I^2=0.0) **(Figure 3)**. Acute kidney injury (AKI) stage 3 was seen in 0% to 16.7%, with a pooled estimate rate of 3.4% (95% CI: 2.0%-5.6%, I^2=36.47) **(Figure 3)**. Life-threatening bleeding **(Figure 4)** and major vascular complications **(Figure 4)** occurred at a pooled estimate rate of 5.1% (95% CI: 3.3%-7.8%, I^2=39.0) and 4.9% (95% CI: 3.5%-6.6%, I^2=0), respectively. Major bleeding was seen in 10.5% (95% CI: 5.1%-20.4%, I^2=77.56) of patients. The reported rates for a new permanent pacemaker implantation after TAVI ranged from 0% to 36.4%, with a pooled estimate rate of 13.5% (95% CI: 10.8%-16.9%, I^2=58.5) **(Figure 5)**. The occurrence of paravalvular AI of moderate or severe grade after TAVR was between 0% and 13.6%, with a pooled estimate rate of 3.2% (95% CI: 2.1%-5.0%, I^2=39.26) **(Figure 6)**. All the post-procedural complications are tabulated in **Online Table 4**.

In the transfemoral group **(Online Figure 1-Online Figure 9)** the event rate for all-cause 30-day mortality was 3.4% (95% CI: 2.3%-4.9%, I^2=0.0), for MI was 2.3% (95% CI: 1.4%-4.0%, I^2=0.0), for AKI stage 3 was 2.6% (95% CI: 1.5%-4.5%, I^2=0.0), and for life-threatening bleeding was 6.0% (95% CI: 3.7%-9.7%, I^2=41.59). The major vascular complications event rate was 4.2% (95% CI: 2.9%-6.1%, I^2=0.0), major stroke was seen in 2.5% (95% CI: 1.5%-3.9%, I^2=0.0), permanent pacemaker implantation event rate was 14.6% (95% CI: 9.9%-21.0%, I^2=69.17) and moderate or severe AI was 2.8% (95% CI: 1.8%-4.5%, I^2=0.0).

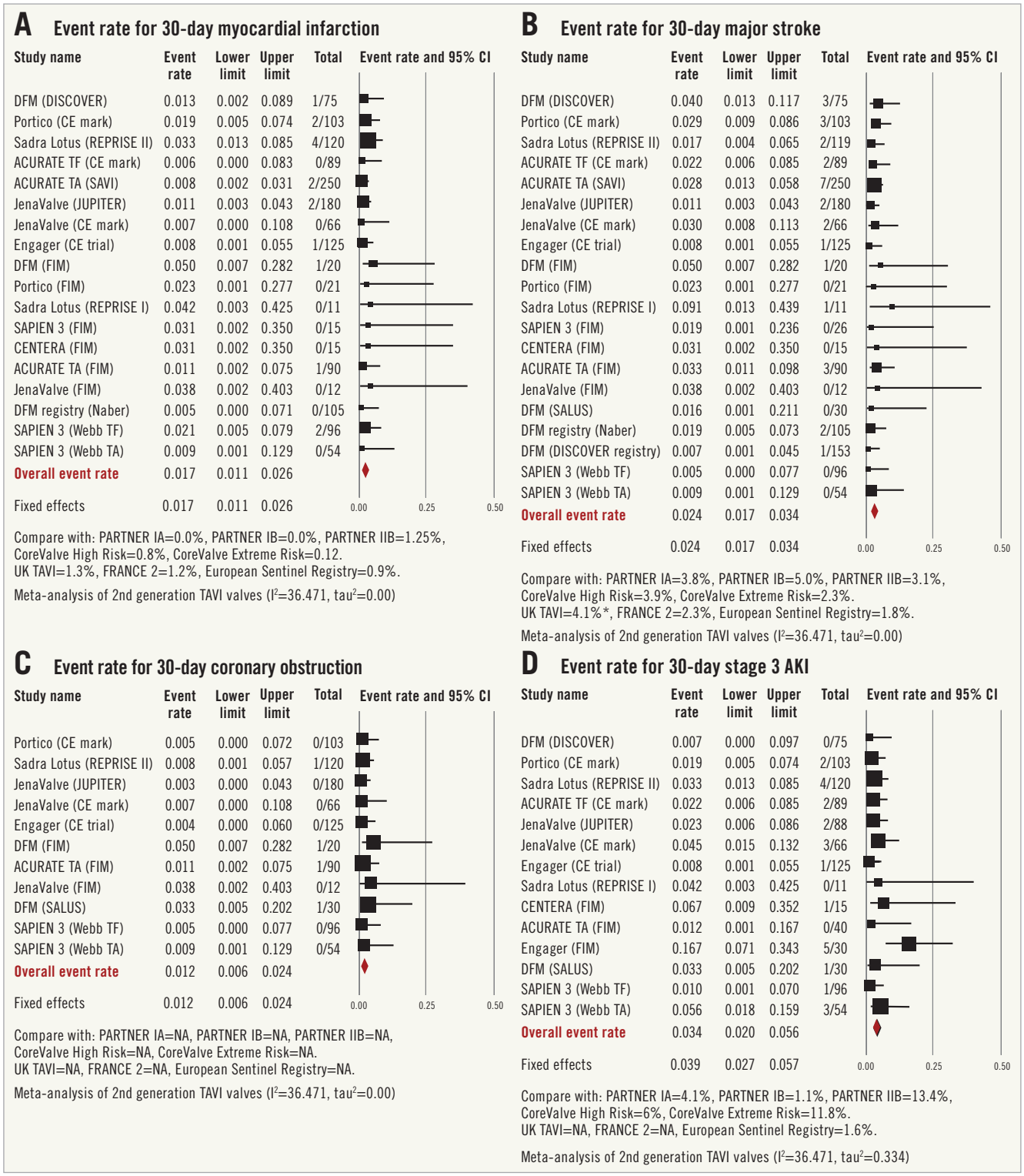

Figure 3. *Forest plot showing the individual and pooled event rates after TAVI from the included studies for: A) myocardial infarction, B) major stroke, C) coronary obstruction (CO) and D) acute kidney injury (AKI) stage 3.*

In the transapical group **(Online Figure 1-Online Figure 9)** the event rate for all-cause 30-day mortality was 8.8% (95% CI: 6.6%-11.7%, I^2=27.23), for MI was 1.0% (95% CI: 0.5%-2.1%, I^2=0.0), for AKI stage 3 was 4.1% (95% CI: 1.7%-9.9%, I^2=62.03), and for life-threatening bleeding was 2.9% (95% CI: 1.3%-6.5%, I^2=11.23). The event rate for major vascular complications was 6.5% (95% CI: 3.1%-13.1%, I^2=32.03), major stroke was seen in 2.3% (95% CI: 1.4%-3.8%, I^2=0.0), permanent pacemaker implantation event rate was 12.1% (95% CI: 10%-14.5%, I^2=0.0) and moderate or severe AI was 3.7% (95% CI: 1.6%-8.5%, I^2=70.33).

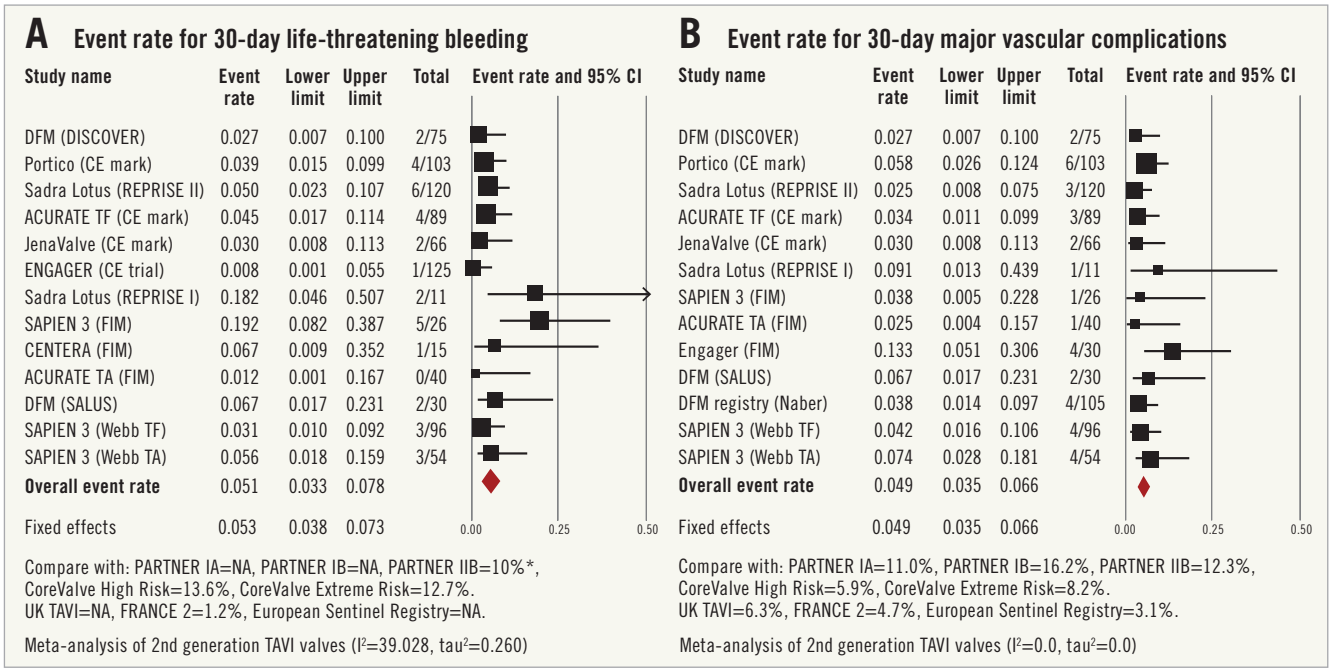

Figure 4. *Forest plot showing the individual and pooled event rates after TAVI from the included studies for: A) life-threatening bleeding and B) major vascular complications.*

Excluding FIM reports, the event rate for all-cause 30-day mortality was 4.7% (95% CI: 3.1%-6.9%, I^2=58.62), for MI was 1.5% (95% CI: 0.9%-2.4%, I^2=0.0), for AKI stage 3 was 2.8% (95% CI: 1.8%-4.3%, I^2=0.0), and for life-threatening bleeding was 4.0% (95% CI: 2.7%-5.8%, I^2=0.0). The event rate for major vascular complications was 4.3% (95% CI: 3.0%-6.1%, I^2=0.0), major

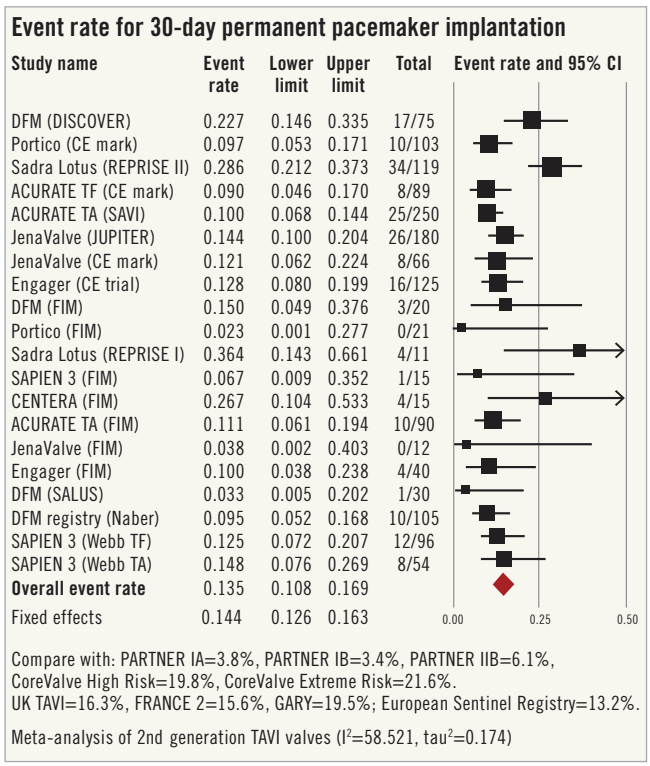

Figure 5. *Forest plot showing the individual and pooled event rates for permanent pacemaker implantation after TAVI from the included studies.*

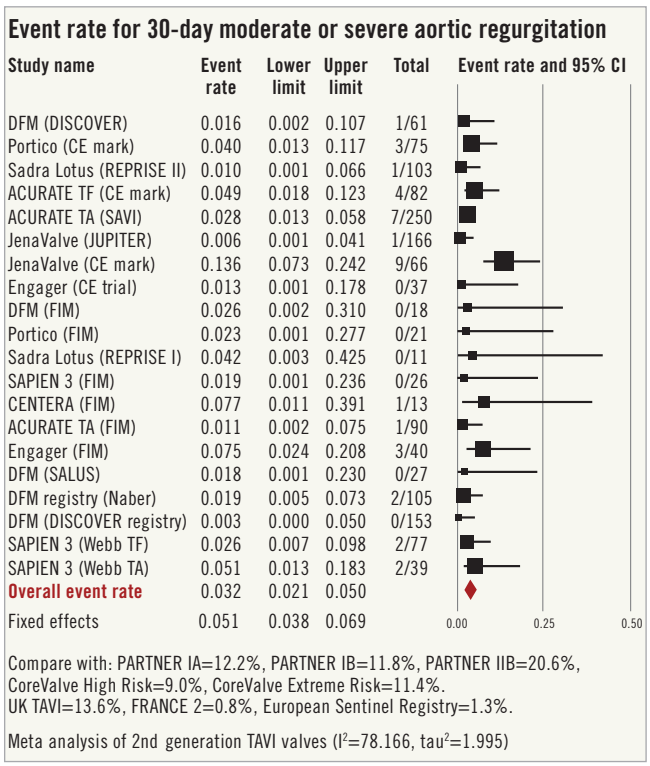

Figure 6. *Forest plot showing the individual and pooled event rates for moderate or severe aortic regurgitation after TAVI from the included studies.*

stroke was seen in 2.1% (95% CI: 1.5%-3.1%, I^2=0.0), permanent pacemaker implantation event rate was 13.4% (95% CI: 10.2%-17.3%, I^2=68.8) and moderate or severe AI was seen in 2.9% (95% CI: 1.6%-5.1%, I^2=56.13).

Pooled estimates of various outcomes according to studies reporting per VARC guidance and core lab utilisation, as well as balloon-expandable vs. self-expanding valves, are also provided in **Online Figure 10**, **Online Figure 11** and **Online Table 5**, respectively.

Discussion

The current analysis, which includes 1,708 patients from 24 studies on eight unique second-generation THV **(Figure 7)**, is the first pooled analysis reporting on the safety and efficacy of these new TAVI valves. The main results of the current analysis are as follows: 1) several new THV have entered the TAVI market with unique features and promising results, 2) these new THV have the potential to reduce several TAVI-related complications, 3) moderate to severe paravalvular AI after TAVI can be virtually eliminated with these new valves, 4) conduction abnormalities requiring permanent pacemaker implantation need to be addressed further in future designs, and 5) as a group, second-generation TAVI valves appear safe and effective in their initial experience; however, safety and efficacy at longer follow-up and of individual valves have yet to be determined.

Some of the new THV have been engineered to improve the efficacy and safety of TAVI. Common features of these particular THV are retrievability and repositionability (resheathing) features which allow the operator to implant one valve, assess its size, position, haemodynamics and function *in vivo*, reposition it or remove it as needed, and implant a new valve when the valve is misplaced or is malfunctioning. Paravalvular AI is widely regarded as the "Achilles heel" of TAVI[3]. The ability to assess paravalvular leak early in the deployment process along with the ability to retrieve and reposition these newer valves has the potential to reduce paravalvular leak. Furthermore, each of these newer TAVI valves has unique features that improve positioning and sealing and which reduce paravalvular leak after TAVI.

In our pooled analysis of all reported studies using these aforementioned second-generation THV the risk of moderate or severe AI was 4.2% (95% CI: 2.0%-8.5%). The incidence of moderate or severe paravalvular AI after TAVI using first-generation THV was 11.7% (95% CI: 9.6%-14.1%) in a pooled analysis of 45 reports[5]. In the Placement of AoRTic TraNscathetER Valves (PARTNER) II trial[39], moderate or severe AI was seen in 11.8% of patients implanted with the Edwards SAPIEN valve. In the Placement of AoRTic TraNscathetER Valves (PARTNER) II trial[40] moderate or severe AI was seen in 24.2% of patients implanted with the Edwards SAPIEN XT valve and in 16.9% of patients implanted with the Edwards SAPIEN valve (p=0.12). Similarly, in the CHOICE trial[41] moderate or severe AI was seen in 11.2% of patients (18.3% with the self-expanding and 4.1% with the balloon-expandable valve). In the CoreValve US pivotal trial[42] paravalvular leak of moderate or severe intensity was observed in 11.5% of patients at 30 days. The inequality in incidence of post-TAVI AI among the aforementioned studies may be related in part to the variability in assessment. In the randomised PARTNER (Placement of Aortic Transcatheter Valve) trials and CoreValve US pivotal trial assessment of AI was performed by an independent echocardiographic core laboratory. In the CHOICE trial, assessment of AI was performed using an angiographic core lab. Assessment of post-TAVI AI with second-generation THV was performed by individual sites with or without core lab oversight. However, despite the differences in assessment, reduction in post-TAVI moderate or severe AI appears pronounced with second-generation THV.

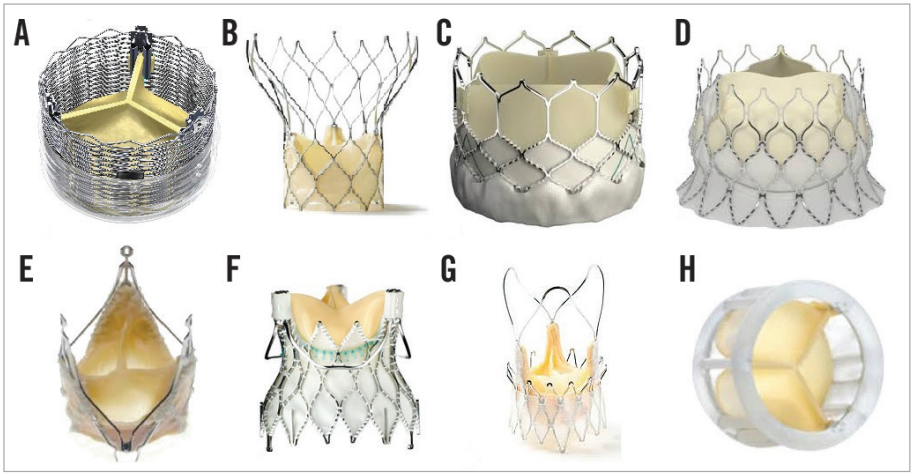

Figure 7. *Second-generation transcatheter aortic valves. A) Sadra™ Lotus Medical valve (Boston Scientific SciMed Inc, Maple Grove, MN, USA); B) Portico® valve (St. Jude Medical); C) Edwards SAPIEN 3 valve (Edwards Lifesciences); D) Edwards CENTERA valve (Edwards Lifesciences); E) JenaValve (JenaValve Technology); F) Engager™ valve (Medtronic Inc.); G) Symetis ACURATE™ valve (Symetis SA); H) Direct Flow Medical® valve (Direct Flow Medical).*

Short-term survival was comparable to previously reported data from first-generation THV. Overall, the rate of other periprocedural complications including major vascular complications, major bleeding, myocardial infarction and AKI stage 2/3 were also low, despite the learning curve. There is a theoretical concern that repositioning and retrieving of the newer valves can lead to aortic injury and atheroembolism resulting in stroke. However, this was not borne out in our analysis. The risk of stroke in our pooled analysis was 2.4% (95% CI: 1.7%-3.4%). The risk of stroke with first-generation valves is in the order of 3.2% (95% CI: 2.1%-4.8%)[3]. The ultra-low profile of the second-generation delivery catheters is expected to reduce the risk of stroke from trafficking in the aortic arch, while the more controlled delivery of the newer devices is likely to reduce stroke during the deployment stage. Most second-generation TAVI valves do not require rapid pacing, which may be linked to functional cardiac arrest and possibly strokes in the watershed areas of the brain.

The incidence of new onset conduction system disease requiring permanent pacemaker implantation was 13.5% (95% CI: 10.8%-16.9%) in our pooled analysis of second-generation THV. In a weighted meta-analysis of first-generation TAVI valves the risk of pacemaker implantation was 13.9% (95% CI: 10.6%-18.9%)[3]. The risk of pacemaker implantation was more frequent with use of the Lotus valve (29.2%) and Edwards CENTERA valve (26.6%). Low rates of pacemaker implantation were reported by the other valves: Direct Flow valve (13.4%), JenaValve (13.1%), SAPIEN 3 (12.7%), Engager valve (12.1%), ACURATE TA/TF valve (10%) and Portico valve (8%). Similar findings of a low pacemaker implantation with the JenaValve were reported by Seiffert et al in their experience with second-generation THV[43]. However, unlike their experience, the Engager valve was not associated with higher rates of pacemaker implantation in our analysis. The higher rate of pacemaker implantation was attributed to the skirt of the Engager valve protruding into the left ventricular outflow tract. Whether the particular design increases conduction system disease needs further investigation. In line with the design of the Portico valve (lack of flared inflow) pacemaker implantation rates were the lowest (8.0%).

We acknowledge heterogeneity in our analysis. The I^2 value for 30-day mortality, MI, major stroke, coronary obstruction, AKI, life-threatening bleeding, major vascular complications was less than 50%, suggesting low to moderate heterogeneity, but was >50% for the 30-day event rate for AI and PPM implantation **(Figure 2-Figure 6)**. We investigated the cause of heterogeneity by conducting subgroup analyses and by exploring differences in the baseline clinical characteristics of the enrolled patients. However, substudy analysis (fixed vs. random effects) comparing the approach (TA vs. TF) did not show any significant difference. Subgroup analysis of core lab-reported AI was also similar to the overall pooled analysis **(Online Figure 1-Online Figure 9)**. In addition, the pooled event rates for TAVI-related complications when comparing the balloon-expandable (BE) and self-expanding (SE) valves do not show significant variation. Clinical characteristics of the enrolled population in the individual studies were not dissimilar **(Online Table 1A, Online Table 1B)**.

Limitations

There are several major limitations in this analysis. The second-generation TAVI valves are not homogeneous. Each second-generation THV has a unique design and concept which influences the safety and efficacy profile of the individual valves. We disregarded these differences in our analysis and pooled all valves assuming sameness. The experience with these devices was limited in number and also to a few experienced centres worldwide. Real-world outcomes may not be similar. Incomplete reporting was frequent. We also only pooled data that were available and clearly reported. This may have influenced our results for certain outcomes. Individual patient data analysis, though ideal, was not performed.

Conclusions

Several new second-generation TAVI valves have been designed to make TAVI simple and safe. The early results with these valves are promising with significant reduction in TAVI-related adverse outcomes. While none of them has been directly compared to first-generation TAVI devices, the results suggest improvement compared to first-generation valves. Nevertheless, safety and efficacy at longer follow-up and of individual valves have yet to be determined.

Impact on daily practice

The new THV which are entering the TAVI market have unique and useful features, appear to be safe, and have the potential to reduce several TAVI-related complications while maintaining valve efficacy. Moderate to severe paravalvular AI after TAVI can be virtually eliminated.

Conflict of interest statement

The authors have no conflicts of interest to declare.

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Supplementary data

Online Table 1A. Baseline characteristics of the included studies.

Online Table 1B. Baseline clinical characteristics of subjects in the included studies (values in %).

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Online Table 5. Pooled event rates for TAVI-related complications using the balloon-expandable (BE) and self-expanding (SE) valves.

Online Figure 1. Forest plot showing the individual and pooled event rates for mortality after TAVI stratified by access site.

Online Figure 2. Forest plot showing the individual and pooled event rates for myocardial infarction after TAVI stratified by access site.

Online Figure 3. Forest plot showing the individual and pooled event rates for major stroke after TAVI stratified by access site.

Online Figure 4. Forest plot showing the individual and pooled event rates for stage 3 acute kidney injury after TAVI stratified by access site.

Online Figure 5. Forest plot showing the individual and pooled event rates for life-threatening bleeding after TAVI stratified by access site.

Online Figure 6. Forest plot showing the individual and pooled event rates for major vascular complications after TAVI stratified by access site.

Online Figure 7. Forest plot showing the individual and pooled event rates for major bleeding after TAVI stratified by access site.

Online Figure 8. Forest plot showing the individual and pooled event rates for permanent pacemaker implantation after TAVI stratified by access site.

Online Figure 9. Forest plot showing the individual and pooled event rates for moderate or severe aortic regurgitation after TAVI stratified by access site.

Online Figure 10. Forest plot showing the pooled event rates from studies reporting on VARC defined endpoints.

Online Figure 11. Forest plot showing the individual and pooled event rates for aortic regurgitation after TAVI assessed by a core lab.

The supplementary data are published online at: http://www.pcronline.com/eurointervention/92nd_issue/211

Supplementary data

Online Table 1A. Baseline characteristics of the included studies.

Valve	Study name	STS score	EuroSCORE	Age (yrs)	Female	MG (mmHg)	AVA (cm²)	NYHA III/IV
Direct Flow	Treede[7]	23±9	28±7	82±4	52	49±14	0.54±0.16	71
	DISCOVER[27]	9.7±8.7	22.5±11.3	83	50	45.9	0.7	55
	DFM registry[37]	NA	NA	NA	NA	NA	NA	NA
	DISCOVER registry[36]	10.47	NA	NA	NA	NA	NA	NA
	SALUS[35]	8±3.7	6±3.5	83±7.5	67	44.5	0.67	93
Portico	Manoharan[19]	7.1±2.8	18.9±9.6	84.3±4.4	100	43.4±15.2	0.66±0.17	71.5
	Portico CE[28]	6.1±3.4	16.3±7.9	83.8±4.9	96.3	45.5±13.1	0.6±0.2	77.8
Lotus	REPRISE I[20]	NA	NA	NA	NA	53.9±20.9	0.7±0.2	45.5
	REPRISE II[29]	7.1±4.6	6.9±5.8	84.4±5.3	56.7	46.4±15	0.7±0.2	75.8
SAPIEN 3	Dvir[33]	6.1±3.6	NA	79.2±9.3	11.5	39.6±15.7	0.67±0.16	NA
	Binder[14]							
	Webb[34]	7.4±4.5	6.2±5.5	83.6±5	54	45.2±14.5	0.6±0.2	86.7
ACURATE TF	CE mark[38]	7.5±8.2	26.6±7.7	83.7±4.4	65.2	43.6±17.1	0.7±0.2	94.4
ACURATE TA	Walther[22,23,30]	8.4±6.4	20.4±8.7	83.5±9.1	69	50.7±14.5	NA	100
	SAVI[30]	8±5.9	22.3±12.7	80.9±6.3	49.2	43.3±17.4	0.7±0.2	92.7
JenaValve	Mohr[24]	NA	22.4	86.3	100	NA	NA	100
	CE mark[11]	NA	NA	NA	NA	NA	NA	NA
	JUPITER[31]	7.3±6.9	22.3±14	80.4±5.9	NA	39.4±13.7	0.8±0.2	83.4
Engager	Falk[25,26]	NA	23.4±11.9	83.4±3.8	83	52.1±14.1	NA	90
	Treede[32]	5.6±2.9	18.4±9	82±4.7	62.4	NA	NA	82.4
CENTERA	Binder[13]	7.3±4	NA	80.2±7.4	67	36.3±14.2	0.7±0.1	94

Values provided as mean±standard deviation where available. AVA: aortic valve area; DFM: Direct Flow Medical; DISCOVER: a registry to evaluate the Direct Flow Medical transcatheter aortic valve system; JUPITER: long-term safety and performance of the JenaValve trial; MG: mean gradient; NYHA: New York Heart Association; REPRISE: REpositionable Percutaneous Replacement of Stenotic Aortic Valve Through Implantation of Lotus™ Valve System study; SAVI: Symetis ACURATE TA™ Valve Implantation registry; STS: Society of Thoracic Surgeons; TA: transapical; TF: transfemoral

Online Table 1B. Baseline clinical characteristics of subjects in the included studies (values in %).

Valve	Study name	MI	CVA	PCI	CABG	CAD	PVD	LVEF	COPD	PHTN
Direct Flow	Treede[7]	10	13	26	10	52	26	NA	19	NA
	DISCOVER[27]	NA	NA	NA	15	50	NA	62±6	NA	NA
	DFM registry[37]	NA	NA	NA	NA	NA	NA	NA	NA	NA
	DISCOVER registry[36]	NA	NA	NA	NA	NA	NA	NA	NA	NA
	SALUS[35]	13	NA	NA	13	73	NA	NA	NA	NA
Portico	Manoharan[19]	NA	NA	NA	10	NA	NA	57±14	20	NA
	Portico CE[28]	11	10	17	5	48	6	NA	NA	26
Lotus	REPRISE I[20]	NA	18	18	NA	46	9	62±8	NA	NA
	REPRISE II[29]	NA	4	23	21	54	14	NA	17	NA
SAPIEN 3	Dvir[33]	NA	18	NA	40	85	NA	55±10	33	NA
	Binder[14]									
	Webb[34]	17	7	35	15	59	17	NA	26	NA
ACURATE TF	CE mark[38]	NA	NA	NA	NA	NA	NA	NA	NA	NA
ACURATE TA	Walther[22,23,30]	NA	13	NA	NA	NA	13	56±13	23	NA
	SAVI[30]	NA	NA	NA	NA	NA	NA	NA	NA	NA
JenaValve	Mohr[24]	NA	0	NA	NA	42	NA	NA	25	NA
	CE mark[11]	NA	21	NA	16	54	45	54±11	36	34
	JUPITER[31]	NA	NA	NA	NA	NA	NA	NA	NA	NA
Engager	Falk[25,26]	NA	10	NA	3	47	47	NA	17	3
	Treede[32]	11	NA	21	15	55	39	57±11	15	15
CENTERA	Binder[13]	33	NA	NA	27	NA	NA	56±11	27	NA

Values provided as mean±standard deviation where available. CABG: coronary artery bypass grafting; CAD: coronary artery disease; COPD: chronic obstructive pulmonary disease; CVA: cerebrovascular accident; DFM: Direct Flow Medical; DISCOVER: a registry to evaluate the Direct Flow Medical transcatheter aortic valve system; JUPITER: long-term safety and performance of the JenaValve trial; LVEF: left ventricular ejection fraction; MI: myocardial infarction; PVD: peripheral vascular disease; PCI: percutaneous coronary intervention; PHTN: pulmonary hypertension; REPRISE: REpositionable Percutaneous Replacement of Stenotic Aortic Valve Through Implantation of Lotus™ Valve System study; SAVI: Symetis ACURATE TA™ Valve Implantation registry; TA: transapical; TF: transfemoral

Online Table 2. Methodological characteristics of included studies.

Valve	Study name	Recruitment	Adjudication	ITT	Funding	MACE
Direct Flow	Treede[7]	Non-randomised	Clinical events committee	Yes	DFM	NA
	DISCOVER[27]	Non-randomised	Clinical events committee	NA	DFM	NA
	DFM registry[37]	Non-randomised	NA	NA	DFM	NA
	DISCOVER registry[36]	Non-randomised	NA	NA	DFM	NA
	SALUS[35]	Non-randomised	Clinical events committee	NA	DFM	NA
Portico	Manoharan[19]	Non-randomised	NA	NA	NA	NA
	Portico CE[28]	Non-randomised	Safety committee	NA	NA	NA
Lotus	REPRISE I[20]	Non-randomised	Clinical events committee	Yes	BSC	Death, MI, CVA, TVR
	REPRISE II[29]	Non-randomised	Clinical events committee	Yes	BSC	NA
SAPIEN 3	Dvir[33]	Non-randomised	NA	NA	NA	NA
	Binder[14]					
	Webb[34]	Non-randomised	NA	NA	NA	NA
ACURATE TF	CE mark[38]	Non-randomised	NA	NA	NA	NA
ACURATE TA	Walther[22,23,30]	Non-randomised	NA	NA	Symetis	Death, MI, CVA, TVR
	SAVI[30]	Non-randomised	Independent committee	NA	NA	Death, MI, CVA, TVR
JenaValve	Mohr[24]	Non-randomised	NA	NA	NA	NA
	CE mark[11]	Non-randomised	Independent medical reviewer	NA	JenaValve	NA
	JUPITER[31]	Non-randomised	Independent medical reviewer	Yes	NA	NA
Engager	Falk[25,26]	Non-randomised	NA	NA	Medtronic	NA
	Treede[32]	Non-randomised	Clinical events committee	NA	Medtronic	NA
CENTERA	Binder[13]	Non-randomised	NA	NA	NA	NA

BSC: Boston Scientific Company; CVA: cerebrovascular accident; DFM: Direct Flow Medical; ITT: intention-to-treat analysis; MACE: major adverse cardiac events; MI: myocardial infarction; NA: not available; TA: transapical; TF: transfemoral; TVR: target vessel revascularisation

Online Table 3. Features of individual valves.

Valve	Access	Unique features	Sheath	Size	Reposi-tionable	Frame	Retriev-able	Leaflet	Deployment
Direct Flow Medical	TF	Durable seal, no rapid pacing	18 Fr 19 Fr	25,27	Yes	Non-metallic	Yes	Bovine pericardial	Self-expanding
St. Jude Medical Portico	TF, TA	Fully resheathable, no need for pacing	18 Fr	23,25 27,29	Yes	Nitinol	Yes	Bovine pericardial	Self-expanding
Boston Scientific Lotus	TF	Adaptive seal, centre marker, axially compressible	18 Fr	NA	Yes	Nitinol	Yes	Bovine pericardial	Self-expanding
Edwards SAPIEN 3	TF, TA	Ultra-low delivery, increased frame height with cuffed skirt to decrease leak	14 Fr 16 Fr	23,26,29	No	Cobalt	No	Bovine pericardial	Balloon-expandable
Symetis ACURATE	TF, TA	Supra-annular anchoring, tactile feedback	NA	23,25,27	Yes	Nitinol	Yes	Porcine	Self-expanding
JenaValve	TF, TA	Tactile feelers, no pacing, active fixation against valve leaflets, low frame profile, no need for pacing	18 Fr	23,25,27	Yes	Nitinol	Yes	Porcine	Self-expanding
Medtronic Engager	TA	Tactile feelers, enlarged proximal skirt	NA	23,26	Yes	Nitinol	Yes	Bovine pericardial	Self-expanding
Edwards CENTERA	TF	Motorised deployment, single operator use	14,16,18 Fr	23,26,29	Yes	Nitinol	No	Bovine pericardial	Self-expanding

Online Table 4. Post-procedural complications.

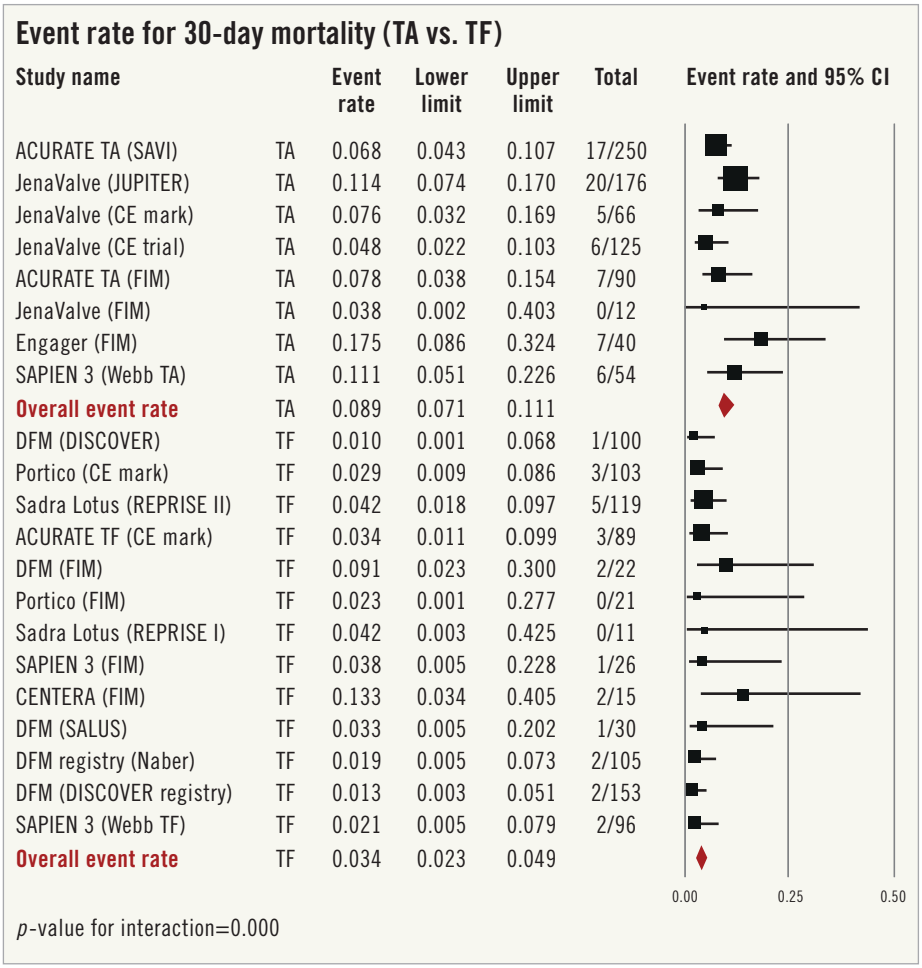
Valve	Study name	N	Mortality	Major stroke	Life-threat-ening bleeding	Major bleeding	MI	AKI > stage 3	Major vascular complications	AR > moderate	PPM	CO
Direct Flow	Treede[7]	22	2	1	NA	NA	1	NA	NA	0/18	3	1
	DISCOVER[27]	100	1	3/75	2/75	NA	1/75	0/75	2/75	1/61	17/75	NA
	DFM registry[37]	105	2	2	NA	NA	0	NA	4	2	10	NA
	DISCOVER registry[36]	153	2	1	NA	NA	NA	NA	NA	0	NA	NA
	SALUS[35]	30	1	0	2	NA	NA	1	2	0	1	1
Portico	Manoharan[19]	21	0	0	NA	NA	0	NA	NA	0	0	NA
	Portico CE[28]	103	3	3	4	9	2	2	6	3/75	10	0
Lotus	REPRISE I[20]	11	0	1	2	NA	0	0	1	0	4	NA
	REPRISE II[29]	120	5	2	6	NA	4	4	3	1/103	34	1
SAPIEN 3	Dvir[33]	26	1	0	5	NA	0/15	NA	1	0/26	1/15	NA
	Binder[14]											
	Webb[34]	150	8	0	6	30	2	4	8	4	20	0
ACURATE TF	CE mark[38]	89	3	2	4	NA	0	2	3	4/82	8	NA
ACURATE TA	Walther[22,23,30]	90	7	3	0	NA	1	0	1	1	10	1
	SAVI[30]	250	17	7	NA	NA	2	NA	NA	7	25	NA
JenaValve	Mohr[24]	12	0	NA	NA	NA	0	NA	2	NA	0	0
	CE mark[11]	66	5	2	2	NA	0	3	2	9	8	0
	JUPITER[31]	180	20	2	NA	NA	2	2/88	NA	1/166	26	0
Engager	Falk[25,26]	40	7	NA	NA	NA	NA	5/30	4/30	3	4	NA
	Treede[32]	125	6	1	1	3	1	1	NA	0/37	16	0
CENTERA	Binder[13]	15	2	0	1	1	0	1	NA	1	4	NA

AKI: acute kidney injury; AR: aortic regurgitation; CO: coronary obstruction; DFM: Direct Flow Medical, DISCOVER: a registry to evaluate the Direct Flow Medical transcatheter aortic valve system; JUPITER: long-term safety and performance of the JenaValve trial; MI: myocardial infarction; N: number of patients followed up; NA: not available; PPM: permanent pacemaker; REPRISE: REpositionable Percutaneous Replacement of Stenotic Aortic Valve Through Implantation of Lotus™ Valve System study; SAVI: Symetis ACURATE TA™ Valve Implantation registry; TA: transapical, TF: transfemoral

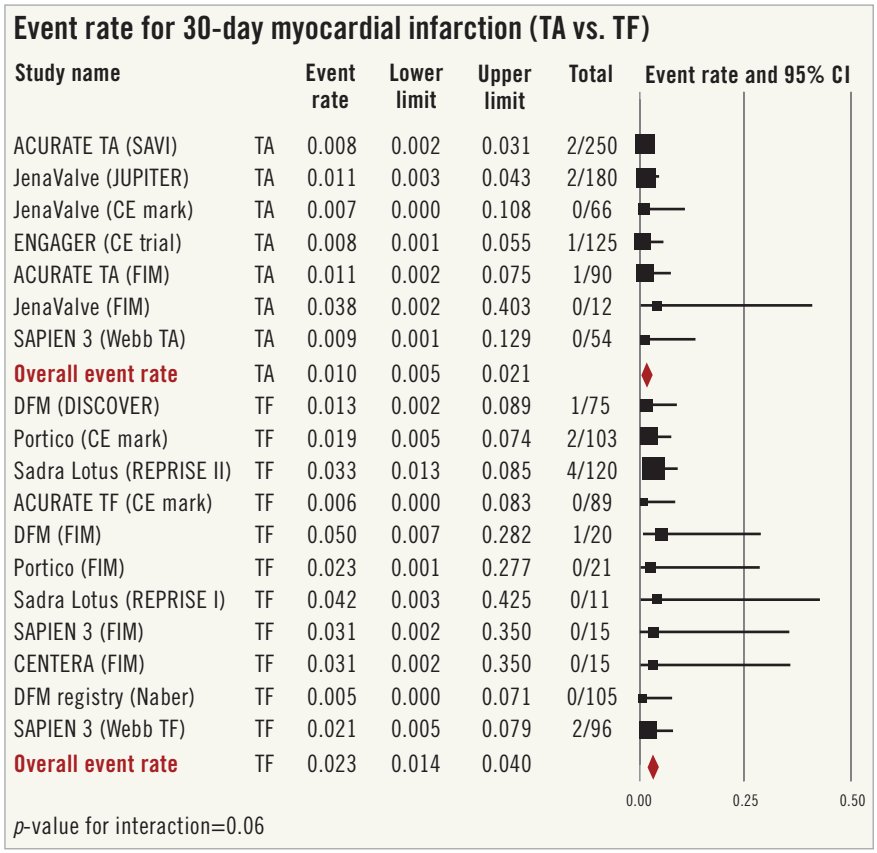
Online Table 5. Pooled event rates for TAVI-related complications using the balloon-expandable (BE) and self-expanding (SE) valves.

Outcome	Included studies (n) BE/SE	Event rate (%), 95% CI balloon-expandable valves	Event rate (%), 95% CI self-expanding valves	*p*-value for interaction
Mortality	3/18	5.1% (1.6-15.5)	5.7% (4.0-8.0)	0.955
Myocardial infarction	3/15	1.9% (0.6-5.8)	1.7% (1.1-2.7)	0.823
Major stroke	3/17	1.0% (0.2-4.6)	2.5% (1.8-3.5)	0.240
AKI 3	2/12	2.9% (0.6-13.5)	3.4% (1.9-5.9)	0.882
Life-threatening bleeding	3/10	7.3% (2.3-21.1)	4.4% (2.9-6.5)	0.092
Major vascular complications	3/10	5.3% (2.8-9.9)	4.7% (3.3-6.8)	0.751
Coronary obstruction	2/9	0.7% (0.1-4.7)	1.3% (0.6-2.8)	0.546
AI ≥moderate	3/17	3.4% (1.3-8.2)	3.1% (1.8-5.2)	0.671
PPM	3/17	12.9% (8.6-19.0)	13.6% (10.5-17.6)	0.579

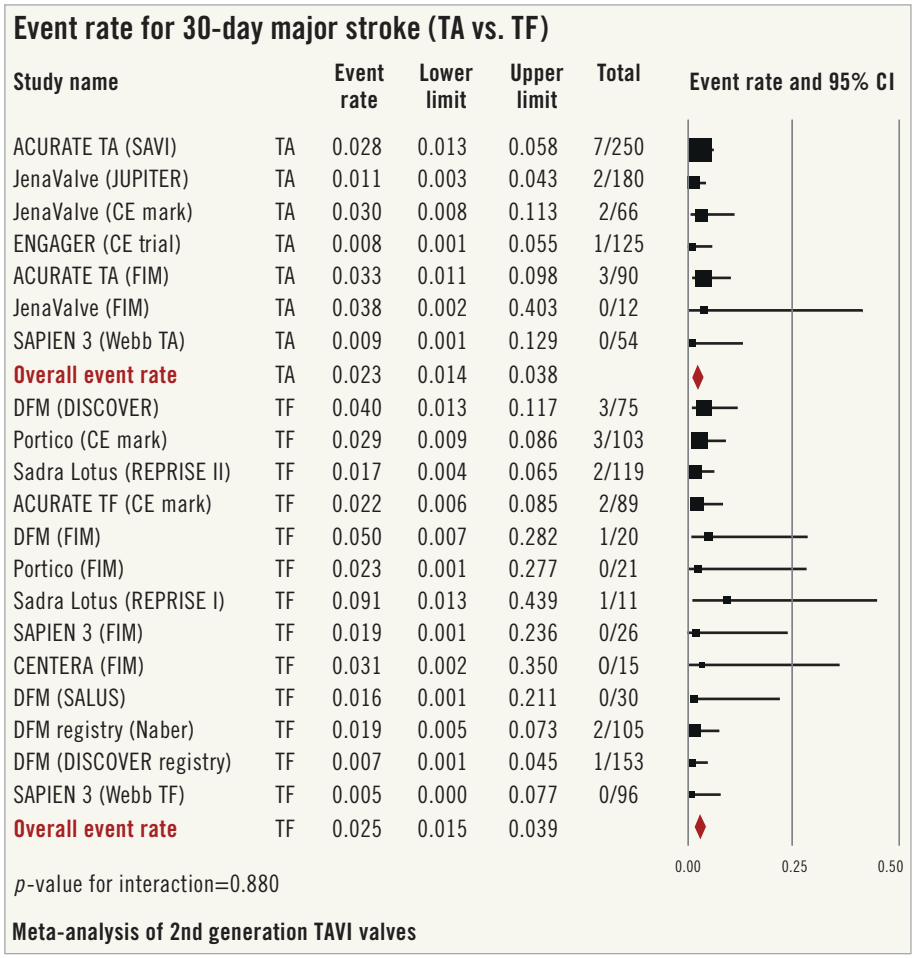
AI: aortic incompetence; AKI 3: acute kidney injury stage 3; BE: balloon-expandable valve; CI: confidence interval; n: number; PPM: permanent pacemaker; SE: self-expanding valve



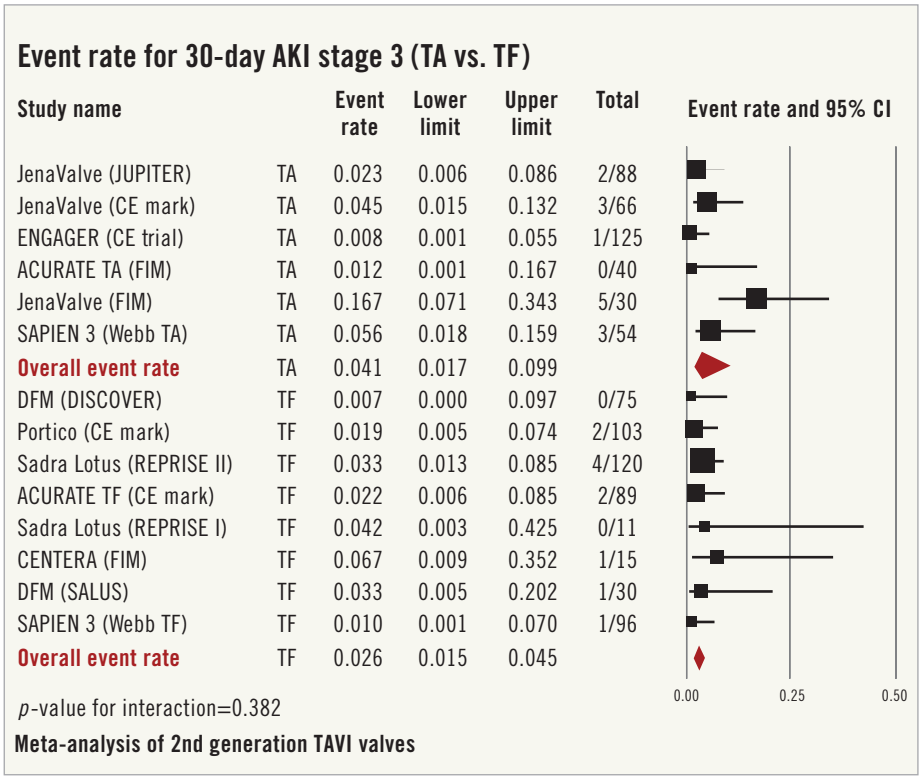
Online Figure 1. *Forest plot showing the individual and pooled event rates for mortality after TAVI stratified by access site. CE: Conformité Européenne (European Conformity); DFM: Direct Flow Medical valve; DISCOVER: a registry to evaluate the Direct Flow Medical transcatheter aortic valve system; JUPITER: long-term safety and performance of the JenaValve trial; PARTNER: Placement of AoRTic TraNscatheter Valves trial; REPRISE: REpositionable Percutaneous Replacement of Stenotic Aortic Valve Through Implantation of Lotus™ Valve System study; SAVI: Symetis ACURATE TA™ Valve Implantation registry; TA: transapical; TF: transfemoral*



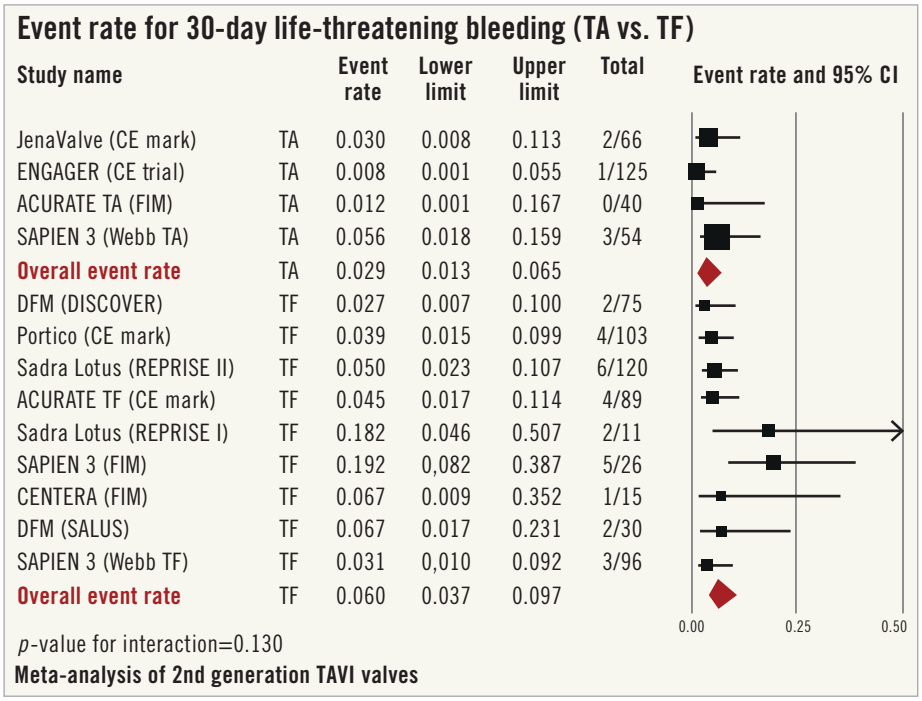
Online Figure 2. *Forest plot showing the individual and pooled event rates for myocardial infarction after TAVI stratified by access site. CE: Conformité Européenne (European Conformity); DFM: Direct Flow Medical valve; DISCOVER: a registry to evaluate the Direct Flow Medical transcatheter aortic valve system; JUPITER: long-term safety and performance of the JenaValve trial; PARTNER: Placement of AoRTic TraNscatheter Valves trial; REPRISE: REpositionable Percutaneous Replacement of Stenotic Aortic Valve Through Implantation of Lotus™ Valve System study; SAVI: Symetis ACURATE TA™ Valve Implantation registry; TA: transapical; TF: transfemoral*



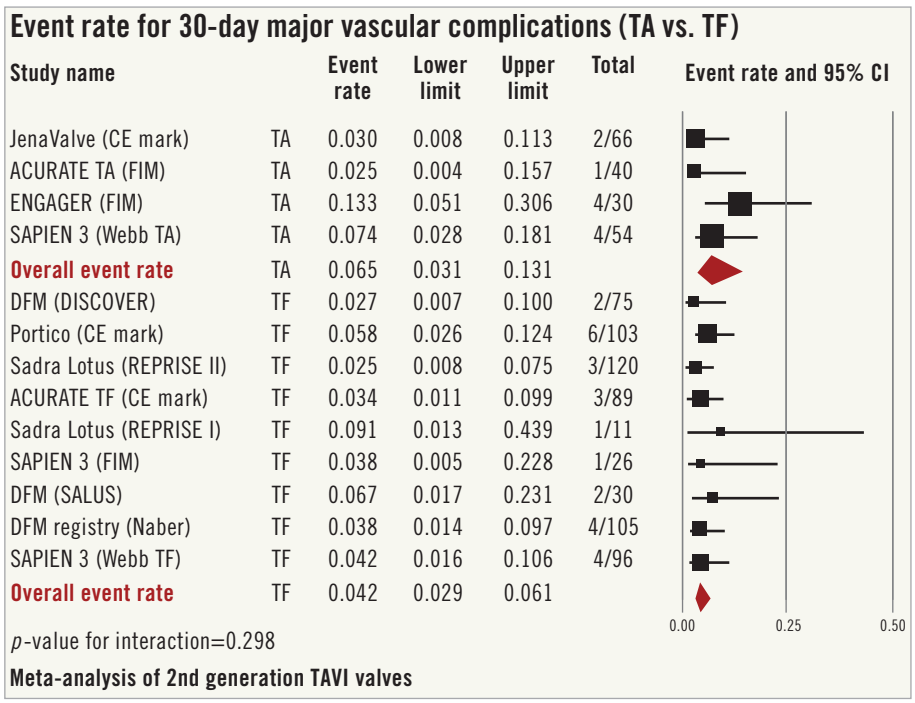
Online Figure 3. *Forest plot showing the individual and pooled event rates for major stroke after TAVI stratified by access site. CE: Conformité Européenne (European Conformity); DFM: Direct Flow Medical valve; DISCOVER: a registry to evaluate the Direct Flow Medical transcatheter aortic valve system; JUPITER: long-term safety and performance of the JenaValve trial; PARTNER: Placement of AoRTic TraNscatheter Valves trial; REPRISE: REpositionable Percutaneous Replacement of Stenotic Aortic Valve Through Implantation of Lotus™ Valve System study; SAVI: Symetis ACURATE TA™ Valve Implantation registry; TA: transapical; TF: transfemoral*



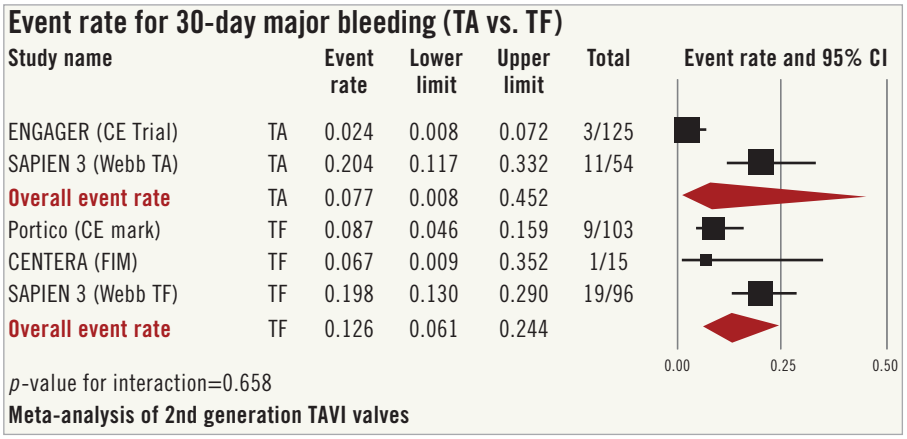
Online Figure 4. *Forest plot showing the individual and pooled event rates for stage 3 acute kidney injury after TAVI stratified by access site. CE: Conformité Européenne (European Conformity); DFM: Direct Flow Medical valve; DISCOVER: a registry to evaluate the Direct Flow Medical transcatheter aortic valve system; JUPITER: long-term safety and performance of the JenaValve trial; PARTNER: Placement of AoRTic TraNscatheter Valves trial; REPRISE: REpositionable Percutaneous Replacement of Stenotic Aortic Valve Through Implantation of Lotus™ Valve System study; SAVI: Symetis ACURATE TA™ Valve Implantation registry; TA: transapical; TF: transfemoral*



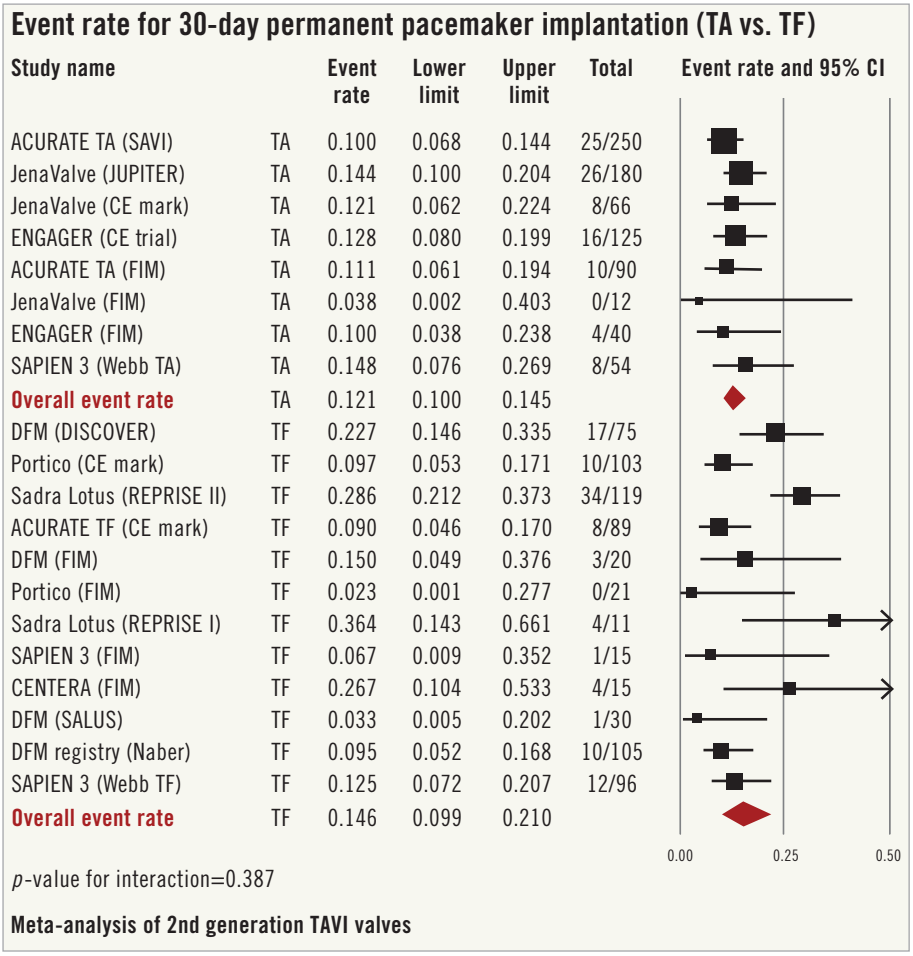
Online Figure 5. *Forest plot showing the individual and pooled event rates for life-threatening bleeding after TAVI stratified by access site. CE: Conformité Européenne (European Conformity); DFM: Direct Flow Medical valve; DISCOVER: a registry to evaluate the Direct Flow Medical transcatheter aortic valve system; JUPITER: long-term safety and performance of the JenaValve trial; PARTNER: Placement of AoRTic TraNscatheter Valves trial; REPRISE: REpositionable Percutaneous Replacement of Stenotic Aortic Valve Through Implantation of Lotus™ Valve System study; SAVI: Symetis ACURATE TA™ Valve Implantation registry; TA: transapical; TF: transfemoral*



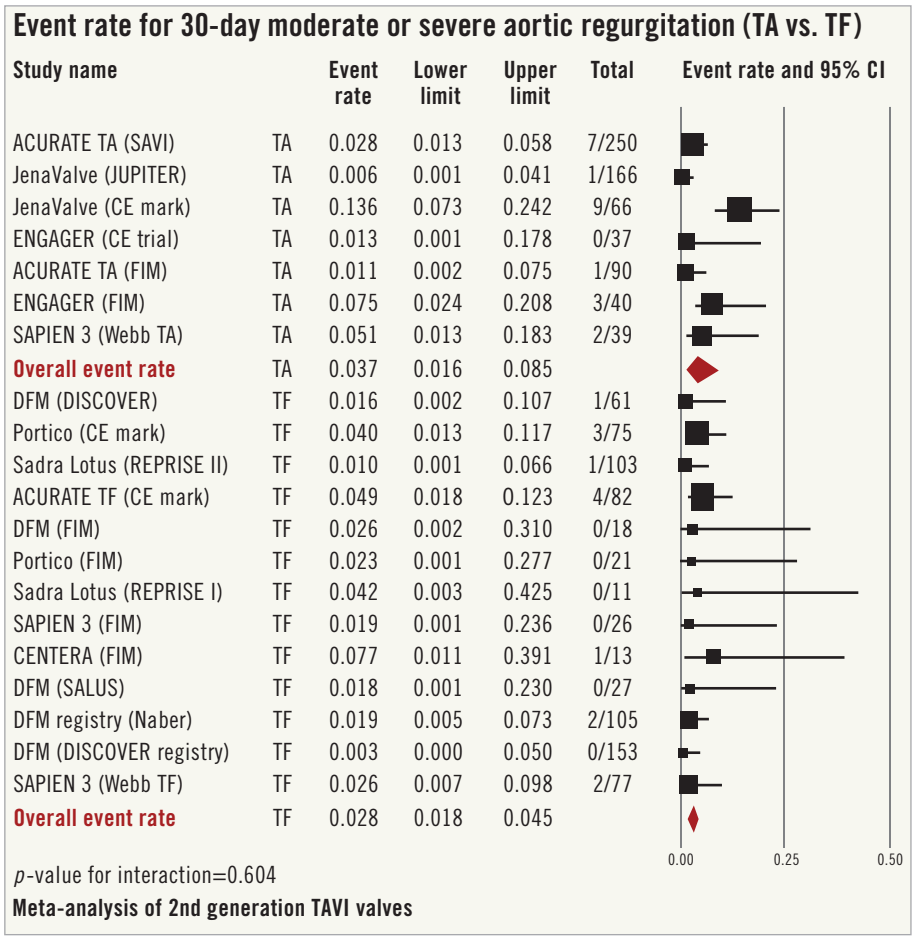
Online Figure 6. *Forest plot showing the individual and pooled event rates for major vascular complications after TAVI stratified by access site. CE: Conformité Européenne (European Conformity); DFM: Direct Flow Medical valve; DISCOVER: a registry to evaluate the Direct Flow Medical transcatheter aortic valve system; JUPITER: long-term safety and performance of the JenaValve trial; PARTNER: Placement of AoRTic TraNscatheter Valves trial; REPRISE: REpositionable Percutaneous Replacement of Stenotic Aortic Valve Through Implantation of Lotus™ Valve System study; SAVI: Symetis ACURATE TA™ Valve Implantation registry; TA: transapical; TF: transfemoral*



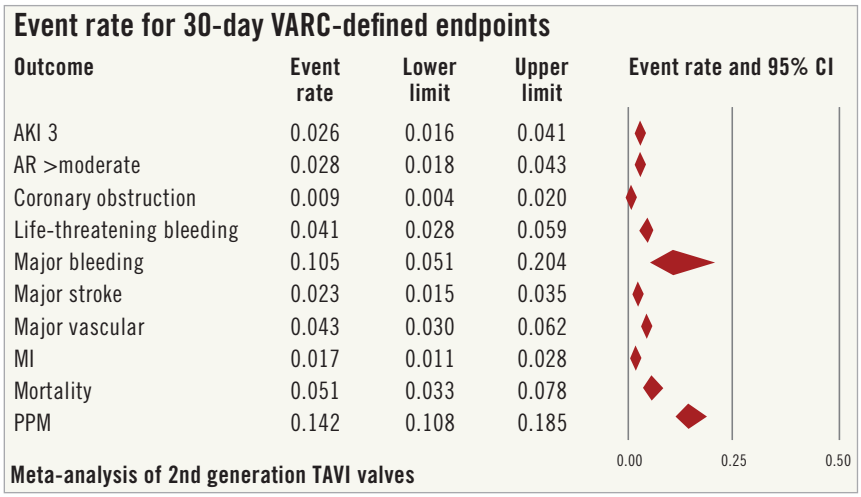
Online Figure 7. *Forest plot showing the individual and pooled event rates for major bleeding after TAVI stratified by access site. CE: Conformité Européenne (European Conformity); DFM: Direct Flow Medical valve; DISCOVER: a registry to evaluate the Direct Flow Medical transcatheter aortic valve system; JUPITER: long-term safety and performance of the JenaValve trial; PARTNER: Placement of AoRTic TraNscatheter Valves trial; REPRISE: REpositionable Percutaneous Replacement of Stenotic Aortic Valve Through Implantation of Lotus™ Valve System study; SAVI: Symetis ACURATE TA™ Valve Implantation registry; TA: transapical; TF: transfemoral*



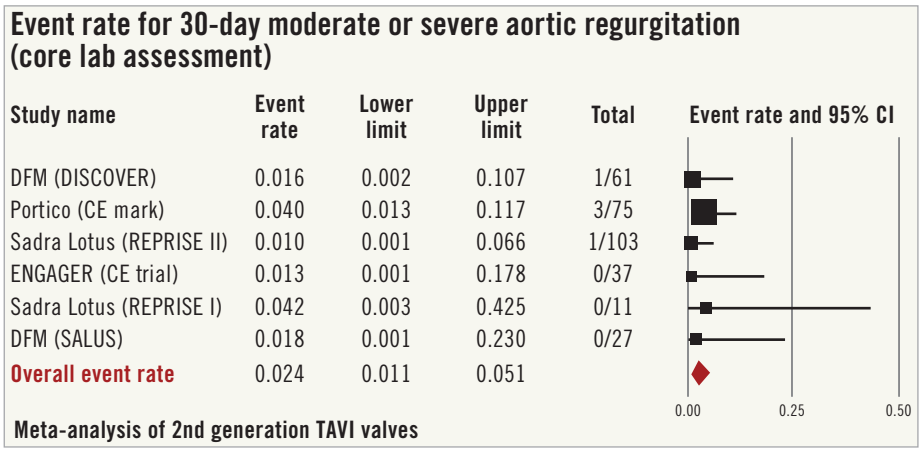
Online Figure 8. *Forest plot showing the individual and pooled event rates for permanent pacemaker implantation after TAVI stratified by access site. CE: Conformité Européenne (European Conformity); DFM: Direct Flow Medical valve; DISCOVER: a registry to evaluate the Direct Flow Medical transcatheter aortic valve system; JUPITER: long-term safety and performance of the JenaValve trial; PARTNER: Placement of AoRTic TraNscatheter Valves trial; REPRISE: REpositionable Percutaneous Replacement of Stenotic Aortic Valve Through Implantation of Lotus™ Valve System study; SAVI: Symetis ACURATE TA™ Valve Implantation registry; TA: transapical; TF: transfemoral*



Online Figure 9. *Forest plot showing the individual and pooled event rates for moderate or severe aortic regurgitation after TAVI stratified by access site. CE: Conformité Européenne (European Conformity); DFM: Direct Flow Medical valve; DISCOVER: a registry to evaluate the Direct Flow Medical transcatheter aortic valve system; JUPITER: long-term safety and performance of the JenaValve trial; PARTNER: Placement of AoRTic TraNscatheter Valves trial; REPRISE: REpositionable Percutaneous Replacement of Stenotic Aortic Valve Through Implantation of Lotus™ Valve System study; SAVI: Symetis ACURATE TA™ Valve Implantation registry; TA: transapical; TF: transfemoral*



Online Figure 10. *Forest plot showing the pooled event rates from studies reporting on VARC-defined endpoints. AKI: acute kidney injury; AR: aortic regurgitation; MI: myocardial infarction; PPM: permanent pacemaker implantation*



Online Figure 11. *Forest plot showing the individual and pooled event rates for aortic regurgitation after TAVI assessed by a core lab. CE: Conformité Européenne (European Conformity); DFM: Direct Flow Medical valve; DISCOVER: a registry to evaluate the Direct Flow Medical transcatheter aortic valve system; JUPITER: long-term safety and performance of the JenaValve trial; PARTNER: Placement of AoRTic TraNscatheter Valves trial; REPRISE: REpositionable Percutaneous Replacement of Stenotic Aortic Valve Through Implantation of Lotus™ Valve System study; SAVI: Symetis ACURATE TA™ Valve Implantation registry; TA: transapical; TF: transfemoral*