Heart and Vessels (2019) 34:1984–1992
https://doi.org/10.1007/s00380-019-01442-w

ORIGINAL ARTICLE

# Network meta-analysis of new-generation valves for transcatheter aortic valve implantation

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Received: 8 March 2019 / Accepted: 24 May 2019 / Published online: 29 May 2019


## Abstract

To comprehensively compare and rank new-generation valves (NGVs) for transcatheter aortic valve implantation, we performed a network meta-analysis (NMA) of all eligible comparative studies. MEDLINE and EMBASE were searched through September 2018. We included all studies comparing 4 NGVs (ACURATE, Evolut R, Lotus, and SAPIEN 3) and an early generation valve (CoreValve) as the reference transcatheter heart valve (THV) each other and reporting at least one of postprocedural incidence of all-cause death, ≥ moderate aortic regurgitation (AR), and new permanent pacemaker implantation (PMI). To compare different THVs, a random-effects restricted-maximum-likelihood NMA based on a frequentist framework for indirect and mixed comparisons was used. Using surface under the cumulative ranking curve (SUCRA), the relative ranking probability of each THV was estimated and the hierarchy of competing THVs was obtained. We identified 29 eligible studies enrolling a total of 17,817 patients. In accordance with the estimated SUCRA probability, SAPIEN 3 was the best effective for a reduction in death (80.6%) and the second best for decreased ≥ moderate AR (74.4%) and PMI (74.1%) compared with the other THVs. Lotus was ranked the best for a reduction in ≥ moderate AR (94.5%;), whereas the worst for decreased PMI (1.2%) and the second worst for a reduction in mortality (38.6%). ACURATE was the best for decreased PMI (99.2%) and the second best for a reduction in mortality (77.9%). As a whole, SAPIEN 3 may be the best effective NGV among the 4 examined NGVs (ACURATE, Evolut R, Lotus, and SAPIEN 3).

**Keywords** Network meta-analysis · New-generation transcatheter heart valve · Transcatheter aortic valve implantation

## Introduction

Transcatheter aortic valve implantation (TAVI) using new-generation valves (NGVs) (NGV-TAVI) is suggested to be associated with lower postprocedural incidence of acute kidney injury, bleeding complications, and aortic regurgitation (AR) than TAVI using early-generation valves (EGVs) (EGV-TAVI), whereas incidence of new permanent pacemaker implantation (PMI), stroke, and all-cause death after NGV-TAVI may be similar to that after EGV-TAVI [1]. Several NGVs are currently used in clinical practice, and a number of studies have compared NGVs each other to date. Evidence drawn from direct comparisons, however, is limited to a few small-size studies. Because different comparators are used in existing studies, a conventional meta-analysis may not adequately assess comparative effectiveness of ≥ 3 different NGVs. Thus, to comprehensively compare and rank NGVs for TAVI focusing early postprocedural outcomes of interest (all-cause death, ≥ moderate AR, and PMI), we

**Electronic supplementary material** The online version of this article (https://doi.org/10.1007/s00380-019-01442-w) contains supplementary material, which is available to authorized users.

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performed a network meta-analysis (NMA) of all eligible comparative studies.

## Materials and methods

All studies comparing 7 NGVs (ACURATE, Direct Flow Medical, Engage, Evolut R, JenaValve, Lotus, and SAPIEN 3) for TAVI each other and reporting at least one of postprocedural incidence of all-cause death, ≥ moderate AR, and PMI were identified using a search of MEDLINE and EMBASE through September 2018. Search terms are described in Appendix. Majority of 21 comparisons included no or only one study (see Supplementary Tables S1–S3), thus we selected 4 NGVs (ACURATE, Evolut R, Lotus, and SAPIEN 3, for which ≥ 2 studies were included in each comparison) and a representative EGV (CoreValve) as the reference transcatheter heart valve (THV). Subsequently, all studies comparing ACURATE, CoreValve, Evolut R, Lotus, and SAPIEN 3 each other (including randomized controlled trials [RCTs] and observational comparative studies) were identified using search terms of *ACURATE* and *CoreValve*; *ACURATE* and *Evolut*; *ACURATE* and *Lotus*; *ACURAT E* and *SAPIEN 3*; *CoreValve* and *Evolut*; *CoreValve* and *Lotus*; *CoreValve* and *SAPIEN 3*; *Evolut* and *Lotus*; *Evolut* and *SAPIEN 3*; or *Lotus* and *SAPIEN 3*. Studies exclusively including TAVI for pure native AR and valve-in-valve TAVI were excluded.

We assessed the study quality by means of the RoBANS [Risk of Bias Assessment Tool for Nonrandomized Studies] [Appendix reference A20] for observational comparative studies and by use of the Cochrane Collaboration's tool for assessing risk of bias [Appendix reference A21] for RCTs. From each study, we extracted the following baseline patient characteristics: age; proportion of men and patients with diabetes mellitus, coronary artery disease, prior percutaneous coronary intervention, prior coronary artery bypass grafting, prior PMI, ≥ moderate AR, cerebrovascular disease, chronic obstructive pulmonary disease, and peripheral vascular disease; and Society of Thoracic Surgeons Predicted Risk Of Mortality. Outcomes of interest were early postprocedural (defined as in-hospital or 30-day) incidence of the following: all-cause death, ≥ moderate (as authors of each study defined) AR (including both central and paravalvular regurgitation), and new permanent PMI. For each study, odds ratios (ORs) (preferentially adjusted estimates if possible) of the outcomes were extracted. Two researchers (HT, TK) extracted data in duplicate, a third investigator (TA) independently ascertained them, and discordance was solved by consensus. To compare different THVs, a random-effects restricted-maximum-likelihood NMA based on a frequentist framework for indirect and mixed comparisons was used. Using surface under the cumulative ranking curve, the relative ranking probability of each THV was estimated and the hierarchy of competing THVs was obtained. The side-splitting approach, which assesses the difference between direct and indirect estimates for a specific comparison, was used to check for the presence of inconsistency. The global inconsistency test was also used to check the assumption of consistency in the entire network. Publication bias was appraised with visual estimation of funnel plot. All analyses were conducted with STATA version 13.1 (StataCorp LLC, College Station, TX) using the "network" commend.

## Results

### Search results

We identified 29 eligible studies [2-30] comparing the 4 NGVs (ACURATE, Evolut R, Lotus, and SAPIEN 3) and the reference EGV (CoreValve) for TAVI each other and enrolling a total of 17,817 patients (see Supplementary Table S4). There were only one RCT [3] of Lotus vs CoreValve plus Evolut R and 8 matched observational studies [5, 6, 9, 10, 14, 15, 17, 26] (including 6 propensity-score matched studies [6, 10, 14, 15, 17, 26]). Risk of bias of the studies is summarized in Supplementary Fig. S1. Baseline patient characteristics are summarized in Table 1 and Supplementary Table S5: age, 81.3 (SAPIEN 3) to 82.2 years (Lotus); men, 33.6 (ACURATE) to 50.2% (Lotus); diabetes mellitus, 25.7 (Lotus) to 34.8% (Evolut R); coronary artery disease, 57.8 (Lotus) to 63.9% (CoreValve); prior percutaneous coronary intervention, 32.8 (Lotus) to 35.6% (ACURAT E); prior coronary artery bypass grafting, 11.9 (ACURAT E) to 21.1% (Lotus); prior PMI, 8.3 (ACURATE) to 16.8% (Evolut R); ≥ moderate AR, 10.2 (ACURATE) to 19.4% (Evolut R); cerebrovascular disease, 11.2 (Lotus) to 12.8% (ACURATE); chronic obstructive pulmonary disease, 14.4 (ACURATE) to 28.0% (Lotus); peripheral vascular disease, 11.7 (Lotus) to 26.5% (CoreValve); and Society of Thoracic Surgeons Predicted Risk Of Mortality, 5.8 (SAPIEN 3) to 8.1% (CoreValve).

### Incidence of outcomes

Early postprocedural incidence of all-cause death was reported in 23 studies including a total of 15,751 patients (ACURATE, 2.2%; CoreValve, 5.1%; Evolut R, 3.3%; Lotus, 3.5%; SAPIEN 3, 2.2%; see Fig. 1, Supplementary Table S6), ≥ moderate AR in 24 studies enrolling a total of 12,627 patients (ACURATE, 4.7%; CoreValve, 8.7%; Evolut R, 6.4%; Lotus, 0.5%; SAPIEN 3, 1.8%; see Fig. 2, Supplementary Table S7), and PMI in 27 studies including a total of 14,133 patients (ACURATE, 10.1%; CoreValve, 9.6%;

**Table 1** Summary baseline patient characteristics

| Variables | ACURATE | CoreValve | Evolut R | Lotus | SAPIEN 3 |
|---|---|---|---|---|---|
| Patient number | 452 | 8272 | 5032 | 1285 | 2776 |
| Age (years) | 81.5 | 82.0 | 81.4 | 82.2 | 81.3 |
| Men (%) | 33.6 | 37.5 | 37.8 | 50.2 | 40.5 |
| Diabetes mellitus (%) | 33.3 | 33.9 | 34.8 | 25.7 | 33.2 |
| Coronary artery disease (%) | 59.2 | 63.9 | 62.6 | 57.8 | 62.6 |
| Prior percutaneous coronary intervention (%) | 35.6 | 34.8 | 33.8 | 32.8 | 34.4 |
| Prior coronary artery bypass grafting (%) | 11.9 | 18.2 | 13.3 | 21.1 | 15.8 |
| Prior permanent pacemaker implantation (%) | 8.3 | 16.3 | 16.8 | 15.2 | 15.5 |
| ≥ Moderate aortic regurgitation (%) | 10.2 | 19.1 | 19.4 | 12.0 | 19.1 |
| Cerebrovascular disease (%) | 12.8 | 12.7 | 12.4 | 11.2 | 12.4 |
| Chronic obstructive pulmonary disease (%) | 14.4 | 16.9 | 14.5 | 28.0 | 17.0 |
| Peripheral vascular disease (%) | 11.9 | 26.5 | 24.0 | 11.7 | 23.5 |
| STS-PROM (%) | 6.1 | 8.1 | 7.6 | 6.4 | 5.8 |

*STS-PROM* Society of thoracic surgeons predicted risk of mortality

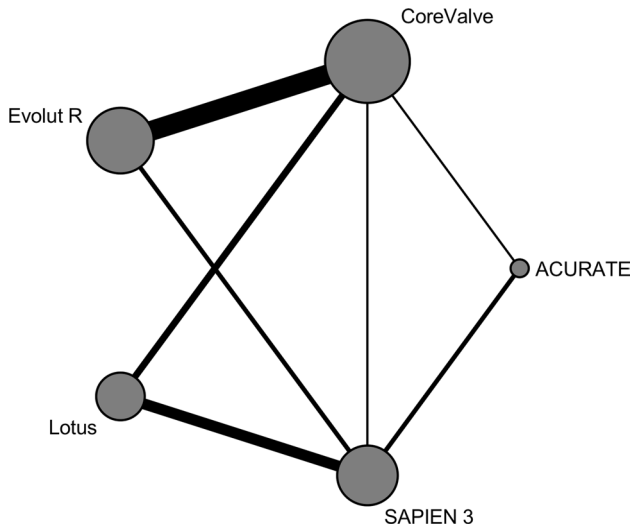


**Fig. 1** Network of available valve comparisons for postprocedural all-cause mortality. The size of nodes is proportional to the number of individuals assigned to each valve and the thickness of lines to the number of direct comparisons in studies

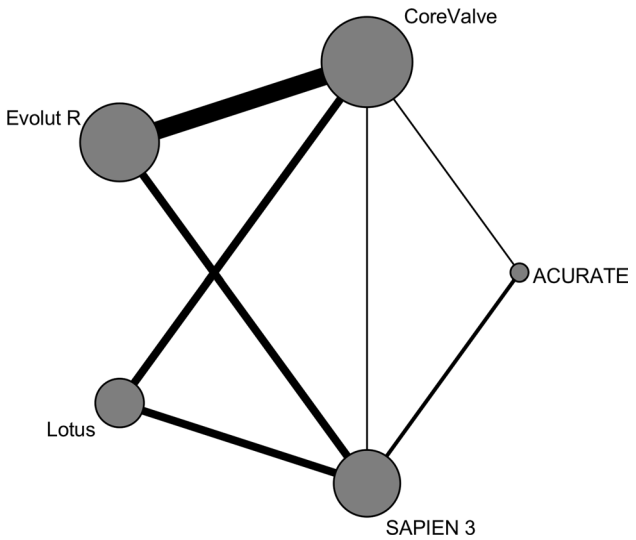


**Fig. 2** Network of available valve comparisons for postprocedural incidence of ≥ moderate aortic regurgitation. The size of nodes is proportional to the number of individuals assigned to each valve and the thickness of lines to the number of direct comparisons in studies

Evolut R, 6.2%; Lotus, 35.7%; SAPIEN 3, 15.6%; see Fig. 3, Supplementary Table S8).

## Relative ranking probability

In accordance with the estimated surface under the cumulative ranking curve probability, SAPIEN 3 was the best effective THV for a reduction in all-cause mortality (80.6%; see Fig. 4, Supplementary Fig. S2) and the second best for decreased incidence of ≥ moderate AR (74.4% see Fig. 5, Supplementary Fig. S3) and PMI (74.1%; see Fig. 6, Supplementary Fig. S4) compared with the other THVs (see Table 2). Lotus was ranked the best for a reduction in incidence of ≥ moderate AR (94.5%; see Fig. 5, Supplementary Fig. S3), whereas the worst for decreased incidence of PMI (1.2%; see Fig. 6, Supplementary Fig. S4) and the second worst for a reduction in all-cause mortality (38.6%; see Fig. 4, Supplementary Fig. S2). ACURATE was the best for decreased incidence of PMI (99.2%; see Fig. 6, Supplementary Fig. S4) and the second best for a reduction in all-cause mortality (77.9%; see Fig. 4, Supplementary Fig. S2).

## Inconsistency

No inconsistency between evidence drawn from direct and indirect comparisons was noted for all the 3 outcomes

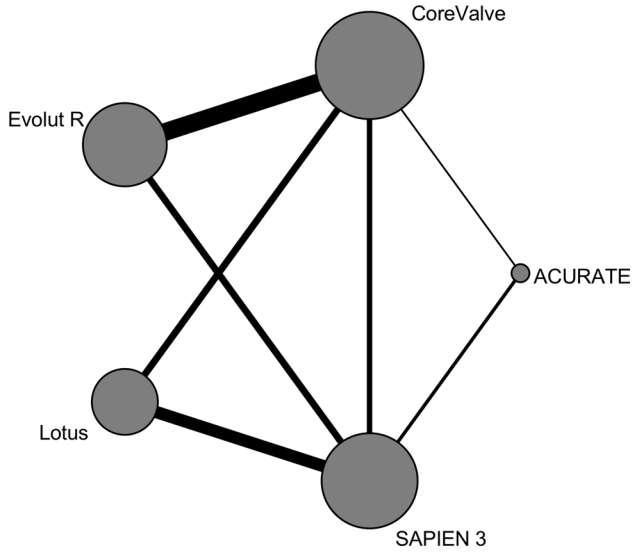


**Fig. 3** Network of available valve comparisons for postprocedural incidence of new permanent pacemaker implantation. The size of nodes is proportional to the number of individuals assigned to each valve and the thickness of lines to the number of direct comparisons in studies

(see Supplementary Tables S9–S11). The absence of funnel-plot asymmetry suggesting publication bias was visually shown in the comparison-adjusted funnel plot (extension of the common funnel plot in cases of multiple treatment comparisons [31]) (see Figs. 7, 8, 9).

## Discussion

The present NMA corresponding to the most comprehensive data for currently available NGVs for TAVI suggests that (1) patients undergoing TAVI with SAPIEN 3 are at the lowest risk of early postprocedural all-cause death and the second lowest risk of ≥ moderate AR and PMI; (2) despite the lowest risk of ≥ moderate AR, those using Lotus are at the highest risk of PMI and the second highest risk of all-cause death; and (3) those using ACURATE are at the lowest risk of PMI and the second lowest risk of all-cause death. As a whole, SAPIEN 3 may be the best effective NGV for TAVI among the 4 examined NGVs (ACURATE, Evolut R, Lotus, and SAPIEN 3). Although an NMA can analyse studies with multiple interventions and integrate studies comparing different interventions, it depends on a strong assumption that studies with different comparisons are similar in every respect in addition to the compared interventions [32]. The involved indirect comparisons may incur the bias of observational studies, e.g. owing to confounding, because of not randomized comparisons [32].

A previous (published in 2016) one-group meta-analysis (by Athappan et al. [33]) of 24 studies for NGVs (ACURAT E, CENTERA, Direct Flow Medical, Engager, JenaValve, Lotus, Portico, and SAPIEN 3) enrolling a total of 1708 patients showed favorable 30-day outcomes (all-cause death, 5.7%; ≥ moderate AR, 4.2%; PMI, 13.5%). Another (published in 2017) one-group meta-analysis (by Barbanti et al. [34]) of 37 studies for NGVs (ACURATE, Evolut R, JenaValve, Lotus, Portico, and SAPIEN 3) including a total of 10,822 patients found very low 30-day all-cause mortality

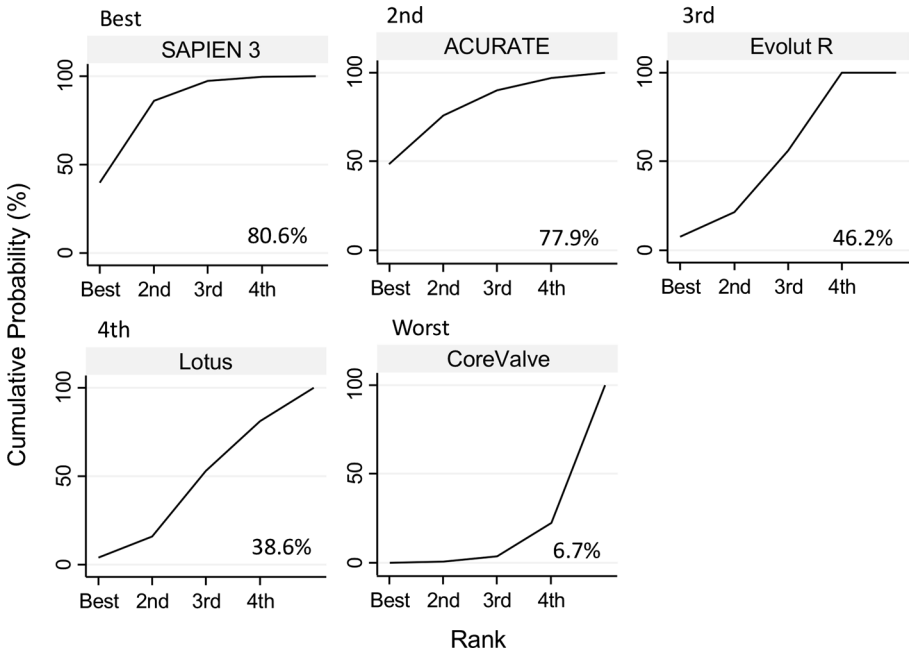


**Fig. 4** Surface under the cumulative ranking curve of available valves for postprocedural all-cause mortality

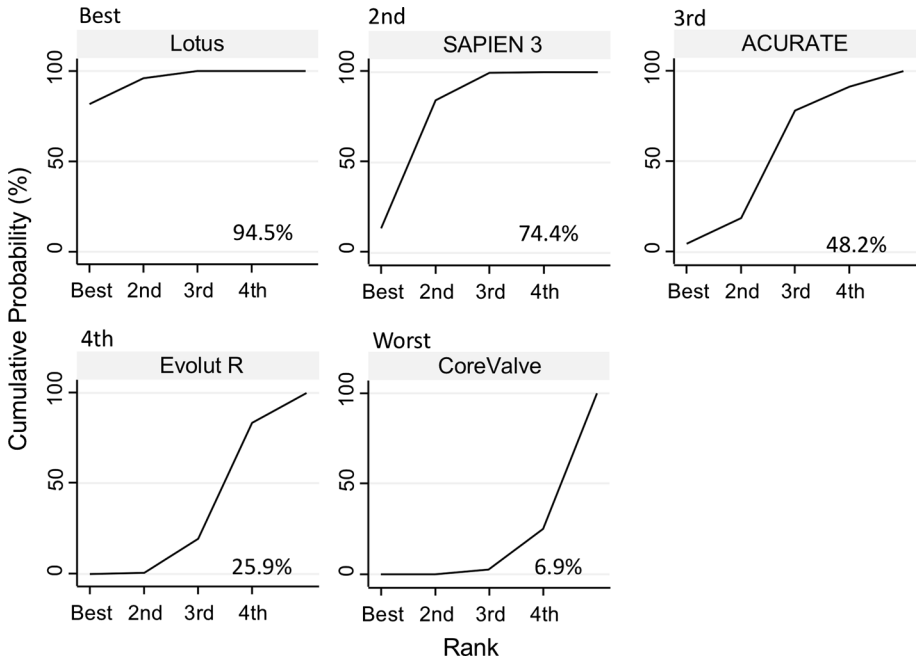


**Fig. 5** Surface under the cumulative ranking curve of available valves for postprocedural incidence of ≥ moderate aortic regurgitation

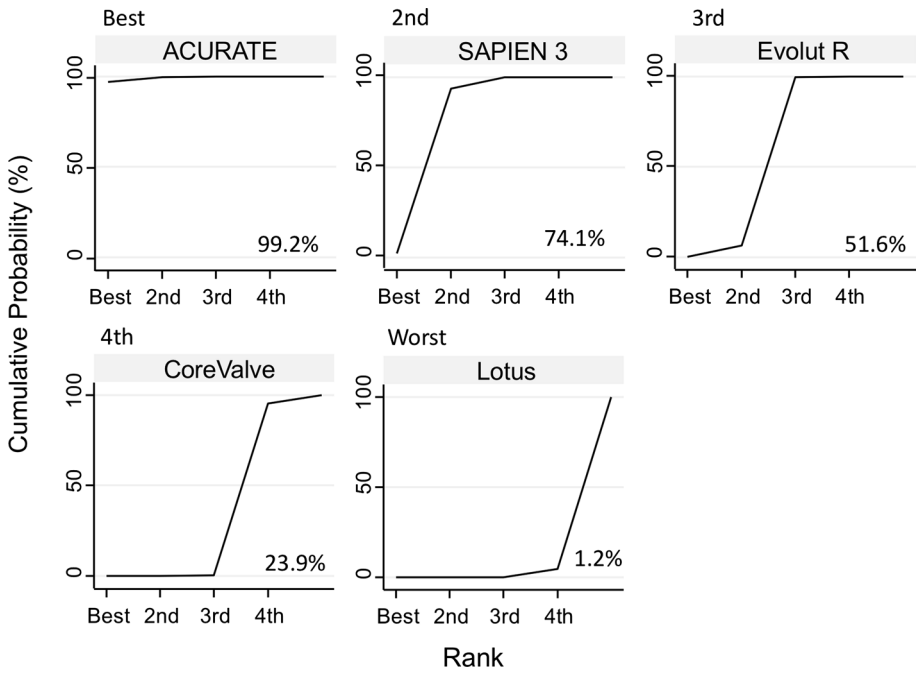


**Fig. 6** Surface under the cumulative ranking curve of available valves for postprocedural incidence of new permanent pacemaker implantation

rates (2.2%), improved performance with 1.6% of ≥ moderate AR rates, and the unresolved issue for PMI rates (16.2%). Recently (published in 2018), Ando et al. [1] (our colleagues) performed conventional (2-group) meta-analysis of 6 matched observational studies enrolling a total of 585 and 647 patients respectively undergoing TAVI with NGVs (ACURATE, Direct Flow Medical, Evolut R, Lotus, and SAPIEN 3) and EGVs (CoreValve, SAPIEN, and SAPIEN XT) and reported lower rate of early ≥ moderate AR (5.3% versus 14.4%; OR, 0.35; $p=0.001$) but remained similar all-cause mortality (3.5% versus 5.0%; OR, 0.77; $p=0.43$) and PMI rates (11.0% versus 14.6% OR, 0.76; $p=0.52$). The findings by Ando et al. [1], however, were gross effects of NGVs compared with EGVs.

More recent (published in 2018) systematic review (by van Rosendael et al. [35]) of 40 studies for PMI including 17,139 patients may be greatly suggestive to the present findings for PMI. Incidence rates of PMI after NGV-TAVI

**Table 2** League table: odds ratios of the effect of valves for outcomes

| All-cause death | | Control | | | | |
|---|---|---|---|---|---|---|
| | | SAPIEN 3 | ACURATE | Evolut R | Lotus | CoreValve |
| Experimental | SAPIEN 3 | ***80.6*** | 1.01 [0.46, 2.24] | 0.65 [0.29, 1.46] | 0.64 [0.34, 1.21] | 0.44 [0.20, 0.98]* |
| | ACURATE | | ***77.9*** | 0.64 [0.23, 1.75] | 0.63 [0.23, 1.70] | 0.43 [0.16, 1.17] |
| | Evolut R | | | ***46.2*** | 0.98 [0.40, 2.41] | 0.68 [0.56, 0.82]* |
| | Lotus | | | | ***38.6*** | 0.69 [0.29, 1.66] |
| | CoreValve | | | | | ***6.7*** |
| ≥ Moderate aortic regurgitation | | Control | | | | |
| | | Lotus | SAPIEN 3 | ACURATE | Evolut R | CoreValve |
| Experimental | Lotus | ***94.5*** | 0.52 [0.14, 1.83] | 0.26 [0.04, 1.51] | 0.13 [0.03, 0.52]* | 0.09 [0.03, 0.32]* |
| | SAPIEN 3 | | ***74.4*** | 0.50 [0.13, 1.98] | 0.26 [0.09, 0.78]* | 0.18 [0.06, 0.56]* |
| | ACURATE | | | ***48.2*** | 0.52 [0.10, 2.57] | 0.36 [0.08, 1.74] |
| | Evolut R | | | | ***25.9*** | 0.70 [0.33, 1.49] |
| | CoreValve | | | | | ***6.9*** |
| New permanent pacemaker implantation | | Control | | | | |
| | | ACURATE | SAPIEN 3 | Evolut R | CoreValve | Lotus |
| Experimental | ACURATE | ***99.2*** | 0.59 [0.34, 1.03] | 0.43 [0.22, 0.83]* | 0.29 [0.15, 0.55]* | 0.20 [0.11, 0.37]* |
| | SAPIEN 3 | | ***74.1*** | 0.72 [0.47, 1.10] | 0.49 [0.33, 0.72]* | 0.34 [0.25, 0.46]* |
| | Evolut R | | | ***51.6*** | 0.68 [0.51, 0.90]* | 0.47 [0.29, 0.75]* |
| | CoreValve | | | | ***23.9*** | 0.69 [0.45, 1.06] |
| | Lotus | | | | | ***1.2*** |

Ranges in parentheses are 95% confidence intervals. Odds ratios < 1 show that the valve listed in the left column is more beneficial than the one in the top row. Valves are ordered according to efficacy ranking. Surface under the cumulative ranking curve values (%) are given in the diagonal (bold Italic). The larger the surface under the cumulative ranking curve value, the better the valve

*Statistically significant ($p < 0.05$)

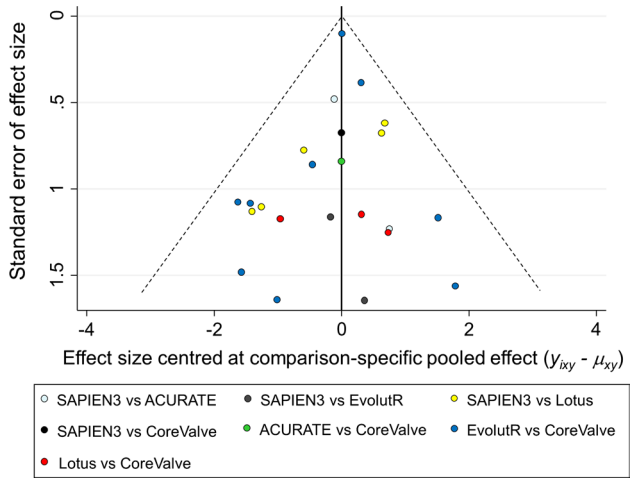


**Fig. 7** Comparison-adjusted funnel plot for postprocedural all-cause mortality. The bold vertical line represents the null hypothesis that the study-specific effect sizes do not differ from the respective comparison-specific pooled effect estimates. The 2 dashed oblique lines represent a 95% confidence interval for the difference between study-specific effect sizes and comparison-specific summary estimates. $Y_{ixy}$ is the noted effect size in study $i$ that compares $x$ with $y$. $\mu_{xy}$ is the comparison-specific summary estimate for $x$ versus $y$

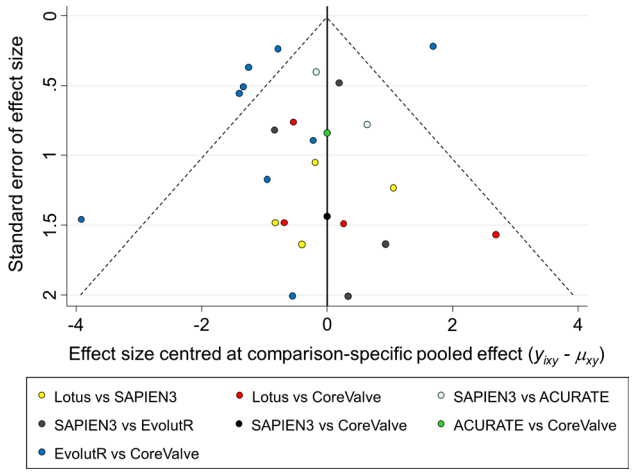


**Fig. 8** Comparison-adjusted funnel plot for postprocedural incidence of ≥ moderate aortic regurgitation. The bold vertical line represents the null hypothesis that the study-specific effect sizes do not differ from the respective comparison-specific pooled effect estimates. The 2 dashed oblique lines represent a 95% confidence interval for the difference between study-specific effect sizes and comparison-specific summary estimates. $Y_{ixy}$ is the noted effect size in study $i$ that compares $x$ with $y$. $\mu_{xy}$ is the comparison-specific summary estimate for $x$ versus y

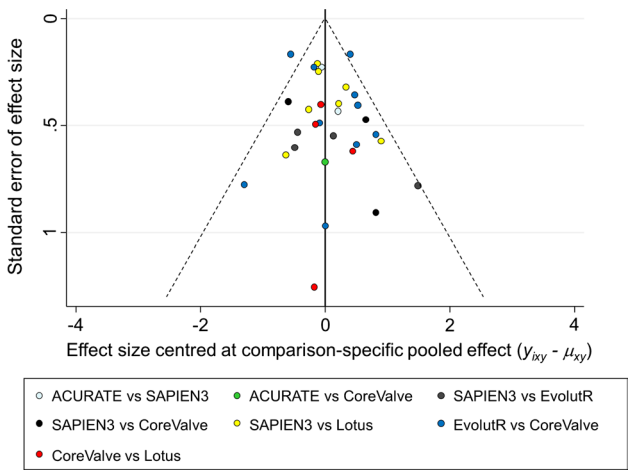


**Fig. 9** Comparison-adjusted funnel plot for postprocedural incidence of new permanent pacemaker implantation. The bold vertical line represents the null hypothesis that the study-specific effect sizes do not differ from the respective comparison-specific pooled effect estimates. The 2 dashed oblique lines represent a 95% confidence interval for the difference between study-specific effect sizes and comparison-specific summary estimates. $Y_{ixy}$ is the noted effect size in study $i$ that compares $x$ with $y$. $\mu_{xy}$ is the comparison-specific summary estimate for $x$ versus $y$

ranged 2.3–36.1%. For balloon-expandable THVs, PMI rates after EGV (SAPIEN)-TAVI remained low (2.3–28.2%) compared with those after NGV (SAPIEN 3)-TAVI (4.0–24.0%). For self-expandable THVs, PMI rates after NGV (Evolut R)-TAVI (14.7–26.7%) were lower (but remained relatively high) than those after EGV (CoreValve)-TAVI (16.3–37.7%) [35].

ACURATE was the best effective for a reduction in incidence of PMI and the second best effective for decreased all-cause mortality. The reduction in PMI incidence could be explained by a supra-annular design of ACURATE, which may less likely interfere with the conduction system [10]. Furthermore, ACURATE less protrudes to the left ventricular outflow tract than mechanistically similar (self-expandable) THVs (e.g. CoreValve) [12], and the radial force of its X-shaped stent design is merely medium as compared with SAPIEN 3 [15]. Despite the best effectiveness for a reduction in incidence of ≥ moderate AR, Lotus was the worst effective for decreased incidence of PMI and the second worst effective for a reduction in all-cause mortality. An adaptive seal enclosing the lower frame of Lotus complies with irregular surfaces of the native annulus, which possibly decreases incidence of ≥ moderate AR [36]. Whereas an additional sealing skirt of the device to evade AR increases the width of the frame at the device inflow level, which may lead to greater compression on the underlying conduction system [22]. A very high radial strength and a high metal density of the device frame also may transiently disturb the left bundle branch [11]. SAPIEN 3 was the second best effective for decreased incidence of ≥ moderate AR and PMI and the best effective for a reduction in all-cause mortality. The present finding of decreased all-cause mortality after TAVI using SAPIEN 3, however, should be interpreted with caution, because mean predicted mortality rates in the SAPIEN 3 group was the lowest (5.8%) among the other THVs (ACURATE, 6.1%; Lotus, 6.4%; Evolut R, 7.6%; CoreValve, 8.1%; see Supplementary Table S5). Meanwhile, a propensity-score matched study [17] reported non-significantly lower all-cause mortality rate (1.1% versus 5.4%; $p = 0.10$) in the SAPIEN 3 than Lotus group despite similar predicted mortality rates ($8.7 \pm 8.0\%$ versus $9.0 \pm 5.2\%$).

The present results should be interpreted with caution because of their limitations. First, only one RCT and a few matched observational studies were included, accordingly baseline patient characteristics were non-negligibly dissimilar among compared THVs (see Supplementary Table S5). Under the exiting circumstances of lacking RCTs, however, our findings based on the NMA are not the best but must be better evidence than the results of each small-size observational study included. Second, although publication bias may militate against the present findings, exhaustively searching available literature minimized the risk and the comparison-adjusted funnel plot did not detect funnel-plot asymmetry suggesting publication bias. Third, we focused limited outcomes (i.e. early postoperative incidence of all-cause death, ≥ moderate AR, and PMI) and NGVs (i.e. ACURATE, Evolut R, Lotus, and SAPIEN 3). A future NMA including more studies (especially RCTs) and investigating other outcomes (e.g. early postoperative incidence of myocardial infarction and stroke, longer-term mortality and morbidity, etc.) and NGVs (e.g. Direct Flow Medical, Engage, JenaValve, etc.) would be required.

In conclusion, SAPIEN 3 was the best effective for a reduction in early postprocedural all-cause mortality and the second best effective for decreased ≥ moderate AR and PMI, Lotus was ranked the worst for a reduction in PMI and the second worst for decreased all-cause mortality despite the best rank for a reduction in ≥ moderate AR, and ACURATE was the best for decreased PMI and the second best for a reduction in all-cause mortality. As a whole, SAPIEN 3 may be the most effective NGV for TAVI among the 4 examined NGVs (ACURATE, Evolut R, Lotus, and SAPIEN 3).

## Compliance with ethical standards

**Conflict of interest** None of the authors declare any potential conflict of interest.

**Research involving human participants and/or animals** The present study is a meta-analysis of published articles, and neither a human nor animal study that should be approved by the appropriate ethics

committee and performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

**Informed consent** The present study is a meta-analysis of published articles, and accordingly, there are no persons who gave their informed consent prior to their inclusion in the study.

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