Meta-analysis Comparing Outcomes of Self-Expanding Versus Balloon-Expandable Valves for Transcatheter Aortic Valve Implantation

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There are two commercially available transcatheter heart valve systems: balloon expandable valves (BEV) and self-expanding valves (SEV). However, there is a paucity of randomized trials comparing both systems. Electronic databases (Medline, the Cochrane Library, Web of Science, and clinicaltrials.gov) and major conference proceedings were searched for randomized trials of patients with symptomatic severe aortic stenosis and received transcatheter aortic valve implantation (TAVI) with a SEV or BEV or surgical aortic valve replacement. The main efficacy outcomes were all-cause mortality and stroke at the longest available follow-up. The main analysis was performed using a random-effects network meta-analysis complemented by several subgroup and sensitivity analyses. Ten trials with 9,439 patients (mostly undergoing transfemoral TAVI) were included. At a median of 27 months, there was no difference between BEV and SEV valves in terms of all-cause mortality (odds ratio [OR] 1.05, 95% confidence interval [CI] 0.79 to 1.42). The incidence of any stroke was higher with BEV (OR 1.51, 95% CI 1.01 to 2.26), but there was no difference in the incidence of disabling stroke. At 30-days, BEV valves were associated with lower incidence of new permanent pacemaker placement (OR 0.50, 95% CI 0.32 to 0.79) and moderate/severe paravalvular regurgitation (OR 0.39, 95% CI 0.22 to 0.68). In conclusion, in patients with severe symptomatic aortic stenosis undergoing transfemoral TAVI, SEV and BEV were associated with similar all-cause mortality. BEV were associated with a higher incidence of any stroke driven by nondisabling strokes, but lower incidence of new permanent pacemaker placement and moderate/severe paravalvular regurgitation compared with SEV. **(Am J Cardiol 2020;128:202−209)**

Transcatheter aortic valve implantation (TAVI) has revolutionized the management of patients with symptomatic severe aortic stenosis. Recently, the role of TAVI has expanded from high to low surgical risk patients.[1-4] There are two commercially available transcatheter heart valve systems: self-expanding and balloon-expandable valves. In the pivotal trials comparing TAVI with surgical aortic valve replacement (SAVR), only one system was utilized in the individual trials.[1,2,5-8] Studies providing a direct comparison between both devices are scarce.[9,10] Randomized trials comparing both systems were underpowered to determine the differences on the individual clinical end-points.[11-13] By providing indirect evidence, network meta-analyses could provide insights regarding the comparative effectiveness and safety of interventions when the number of head to head trials are limited. The objective of this systematic review and network meta-analysis was to pool data from randomized trials to provide an indirect comparison of the effectiveness and safety of self-expanding versus balloon-expandable valves.

Methods

An electronic search of MEDLINE, Web of Science, the Cochrane database (CENTRAL), and clinicaltrials.gov along with major conference proceedings was conducted from inception through February 2020 with no language restriction using the search algorithm in Supplemental Table 1. The bibliography of the retrieved studies was reviewed. This meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension statement for network meta-analyses.[14] The protocol for this meta-analysis was prospectively registered at the PROSPERO international prospective register of systematic reviews (CRD42020148903). Randomized trials which met any of the following inclusion criteria were included: i) head to head comparing self-expanding versus balloon-expandable valves; or ii) comparing TAVI versus SAVR for symptomatic severe aortic stenosis. Trials comparing TAVI versus

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medical therapy alone were excluded. Observational studies were excluded for inherent risk of bias.

Two independent authors (I.Y.E. and M.M.G.) extracted the data on the study design (design, clinical setting, period of recruitment, duration of follow-up, number of patients randomized), patient characteristics (age, sex, relevant comorbidities, and baseline surgical risk), and interventional strategies (type of transcatheter heart valve systems, or SAVR), and clinical outcome data. Any discrepancies were resolved by consensus. The number of events that occurred in each arm of the trial was tabulated. The quality assessment of each trial was assessed using the Cochrane risk of bias tool.

The main efficacy outcomes for this analysis were all-cause mortality, and any stroke at the longest available follow-up. The secondary efficacy outcomes included: cardiovascular mortality, and disabling stroke. The main safety outcomes were new pacemaker placement implantation, moderate to severe paravalvular leak at 30-days. The secondary safety outcomes included disabling or life-threatening bleeding, and major vascular complications at 30-days. The definition of the outcomes was in accordance to the Valve Academic Research Consortium or the more recent Valve Academic Research Consortium-2 end point definitions, whenever reported.

Outcomes were analyzed by an intention-to-treat analysis. The network meta-analysis was performed using a random effects model to account for the heterogeneity between the trials. Inconsistency was examined by comparing the deviance residuals and deviance information criterion statistics in fitted consistency and inconsistency models from the entire network on each node. Summary estimates were reported as odds ratios (OR) and corresponding 95% confidence intervals (CI). Statistical heterogeneity was calculated across the trials using I^2 statistics. Values <25%, 25-50%, >50% corresponding to low, moderate, and high degree of heterogeneity, respectively. Publication bias was assessed using Egger's test.

The following prespecified subgroup analyses were conducted for the main efficacy and safety outcomes: i) according to the baseline surgical risk (i.e., high, intermediate, low-risk); ii) comparing the different valve types. If a trial utilized more than one iteration of valves in an arm, we categorized this arm according to the predominant valve used (i.e., >70%); iii) according to the time of follow-up (30 days, 1-year, and 5-years) for the main efficacy outcomes. A sensitivity analysis for the outcome of moderate/severe paravalvular leak excluding the older trials as the assessment and sizing of moderate/severe paravalvular leak was suboptimal. All analyses were conducted using the Rstudio software and netmeta package (2015; Integrated Development for R. and RStudio, Inc, Boston, MA).

Results

The final number of records included in this meta-analysis was 10 trials (from 19 reports) (Figure 1).[1,2,5-8,11-13,15-24] One trial compared a self-expanding valve versus commercially available valves (including any self-expanding and balloon-expandable valves) without reporting the outcomes

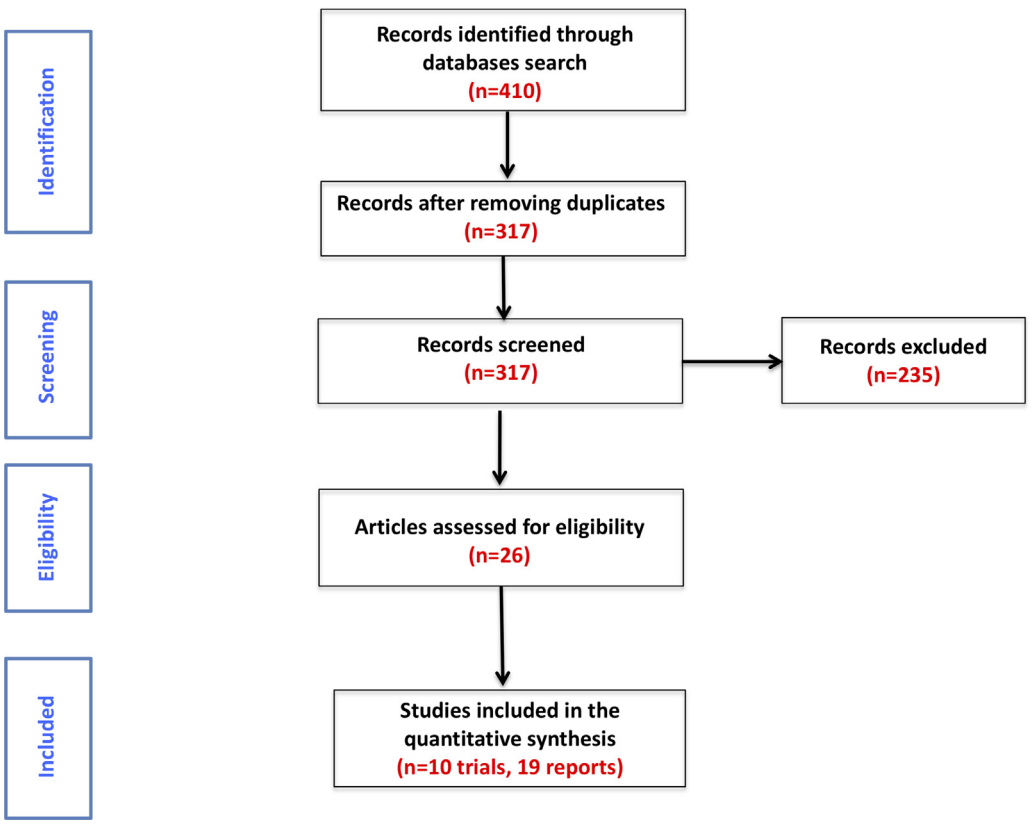

Figure 1. Flow diagram of the study search. Summary of how the systematic search was conducted and eligible studies were identified.

Table 1
Characteristics, longest follow-up duration, and the interventional strategies of the included trials

Trial (ref #)	Year	SEV	BEV	SAVR	Type of TAVR valve	Transfemoral TAVR, n	Target population	STS-PROM, mean*	Longest follow-up, months
SOLVE TAVI[12]	2020	225	222	NA	SEV: Evolut R BEV: Sapien 3	447 (100%)	Intermediate risk	7.7/7.6	1
SCOPE 1[13]	2019	372	367	NA	SEV: Accurate Neo BEV: Sapien 3	739 (100%)	High risk	3.7/3.4‡	1
Evolute low risk[1]	2019	734	NA	734	CoreValve (4%), Evolut R (74%), Evolut Pro (22%)	727 (99%)†	Low risk	1.9/1.9	24
PARTNER 3[2]	2019	NA	503	497	Sapien 3	503 (100%)	Low risk	1.9/1.9	12
SURTAVI[5]	2017	879	NA	867	CoreValve (84%), Evolut R (16%)	864 (100%)	Intermediate risk	4.4/ 4.5	24
PARTNER 2A[6,18]	2017, 2019	NA	1,011	1,021	Sapien XT	775 (77%)†	Intermediate risk	5.8/5.8	60
NOTION[15-17]	2015, 2016, 2018	145	NA	135	CoreValve	145 (100%)	Low risk	2.9/3.1	60
CHOICE[11,19]	2014, 2015	120	121	NA	SEV: CoreValve BEV: Sapien XT	241 (100%)	High risk	5.6/6.2	12
US CoreValve high risk[7,20-22]	2014, 2015, 2016, 2018	394	NA	401	CoreValve	394 (100%)	High risk	7.3/7.5	60
PARNTER 1A[8,23,24]	2011, 2012, 2015	NA	348	351	Sapien	244 (70%)‡	High risk	11.8/ 11.7	60

* Results are presented as TAVR/SAVR, as SEV/BEV for SOLVE TAVI, SCOPE 1, and CHOICE
† The remainder underwent a transthoracic approach, except Evolute low risk 0.6% underwent a subclavian approach
‡ Median reported. BEV= balloon-expandable valve; NA= not applicable; SAVR= surgical aortic valve replacement; SEV= self-expanding valve

separately for each valve type in the control arm, so this trial was excluded from this analysis.[25] Another trial comparing mechanically-expanded versus self-expanding valves (both are self-expanding valve) was also excluded.[26] The network meta-analysis included 10 trials with 9,439 patients (2,864 in the self-expanding valve group, 2,569 in the balloon-expandable group, and 4,006 in the SAVR group). Transfemoral TAVI was utilized in most cases. The characteristics of the network are presented in Supplemental Figure 1. The duration of follow-up ranged from 1 to 60 months (weighted median follow-up 27 months). Table 1 summarizes the patient and trial characteristics, follow-up duration, and the target population per the individual trials, and Supplemental Table 2 reports the pertinent patient baseline demographics. Performance bias was unclear in all the trials, otherwise the trials were deemed to be of high quality (Supplemental Table 3).

There was no difference between balloon-expandable and self-expanding valves in regards to all-cause mortality (OR 1.06, 95% CI 0.79 to 1.42). Compared with self-expanding valves, SAVR was associated with similar all-cause mortality (OR 0.88, 95% CI 0.71 to 1.10). Similarly, balloon-expandable valves were associated with similar all-cause mortality compared with SAVR (OR 0.83, 95% CI 0.66 to 1.05). (Figure 2). This outcome was characterized by a moderate degree of statistical heterogeneity (I^2=30%). Balloon-expandable valves were associated with a higher incidence of any stroke compared with self-expanding valves (OR 1.51, 95% CI 1.01 to 2.26). The incidence of any stroke was similar between SAVR and self-expanding valves (OR 1.25, 95% CI 0.93 to 1.67). Similarly, there was no difference in the incidence of any stroke between balloon-expandable valves and SAVR (OR 0.83, 95% CI 0.59 to 1.15) (Figure 2). This outcome was also characterized by a moderate degree of statistical heterogeneity (I^2=32%).

Regarding the secondary efficacy outcomes, there was no difference between balloon-expandable and self-expanding valves in terms of cardiovascular mortality (OR 1.12, 95% CI 0.78 to 1.59) (Supplemental Figure 2A). The outcome of disabling stroke was reported by eight trials; three of these trials used a definition of "major stroke".[7,8,11] There was no difference between balloon-expandable and self-expanding valves in the incidence of disabling stroke (OR 1.77, 95% CI 0.92 to 3.41 (Supplemental Figure 2B). There was no evidence of publication bias for any of the efficacy outcomes using Egger's test (all p values>0.05). The summary estimates were consistent for the efficacy outcomes on fixed effects analysis (Supplemental Table 4).

Balloon-expandable valves were associated with a lower incidence of new pacemaker placement implantation compared with self-expanding valves (OR 0.50, 95% CI 0.32 to 0.79). SAVR was associated with lower incidence of new pacemaker placement implantation, compared with self-expanding valves (OR 0.26, 95% CI 0.17 to 0.40). SAVR was also associated with a lower incidence of new pacemaker placement implantation compared with balloon-expandable valves (OR 0.53, 95% CI 0.33 to 0.83) (Figure 3). This outcome was characterized by a high degree of statistical heterogeneity (I^2=74%). Compared with self-expanding valves, balloon-expandable valves were associated with a lower incidence of moderate/severe paravalvular leak (OR 0.39, 95% CI 0.22 to 0.68). SAVR was associated with a lower incidence of moderate/severe paravalvular leak, compared with self-expanding valves (OR 0.26, 95% CI 0.17 to 0.40). SAVR was also associated with a lower incidence of moderate/severe paravalvular

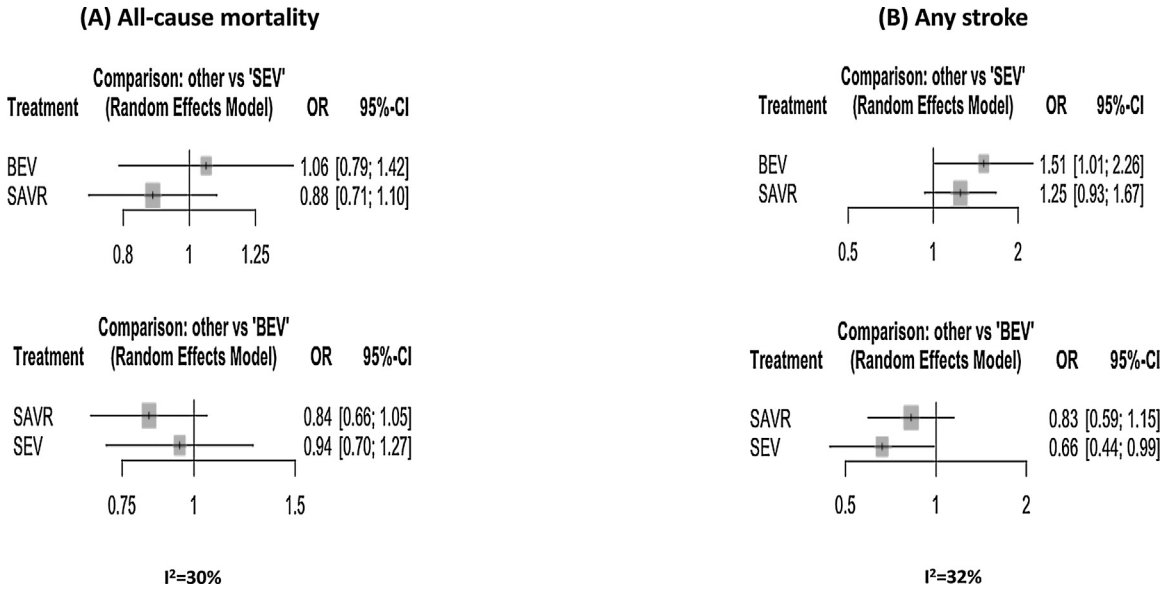

Figure 2. (*A*) Network random effects analysis for all-cause mortality; (*B*) any stroke; Forest plots for the comparisons among treatments included in the network. BEV= balloon-expandable valves; CI= confidence interval; OR= odds ratio; SEV= self-expanding valves; SAVR= surgical aortic valve replacement

leak, compared with balloon-expandable valves (OR 0.17, 95% CI 0.08 to 0.34) (Figure 3). This outcome was characterized by no statistical heterogeneity (I^2=0%).

As regards to the secondary safety outcomes, there was no difference between balloon-expandable and self-expanding valves in the incidence of disabling or life-threatening bleeding (OR 0.49, 95% CI 0.21 to 1.12), and major vascular complications (OR 0.74, 95% CI 0.41 to 1.34). (Supplemental Figure 3). The direct and indirect comparisons were consistent for the safety outcomes. There was no evidence of publication bias for any of the safety outcomes using Egger's test (all p values>0.05). The findings of the fixed effects analysis for the safety outcomes were consistent with the random effects model (Supplemental Table 4).

Subgroup analysis according to baseline surgical risk showed that there were no significant differences between self-expanding and balloon-expandable valves on any of the main efficacy and safety outcomes (Supplemental Table 5). Subgroup analysis based on the individual valve showed that Sapien XT ranked for the highest incidence of any stroke, whereas CoreValve ranked worst for new permanent pacemaker implantation, and Acurate Neo followed ranked

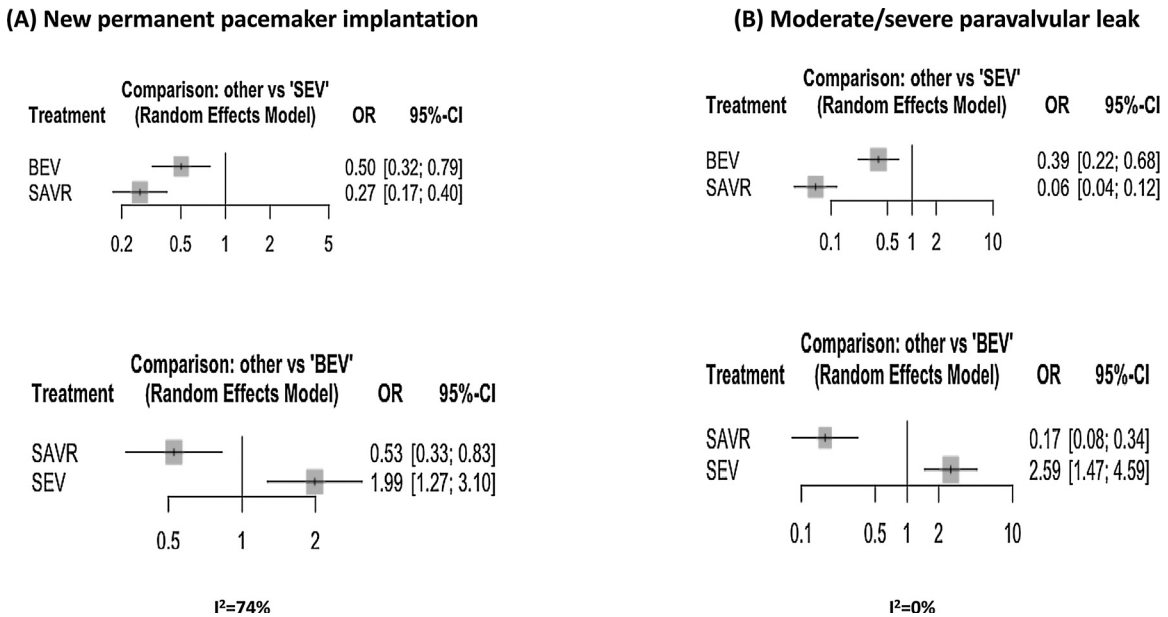

Figure 3. (*A*) Network random effects analysis for new permanent pacemaker implantation; (*B*) moderate/severe paravalvular leak; Forest plots for the comparisons among treatments included in the network. BEV= balloon-expandable valves; CI= confidence interval; OR= odds ratio; SEV= self-expanding valves; SAVR= surgical aortic valve replacement

worst for moderate/severe paravalvular leak (Supplemental Figures 4, 5). The subgroup analysis based on the follow-up duration showed no difference in all-cause mortality and any stroke between self-expanding valves, balloon-expandable valves, and SAVR at 30-days, 1-year, and 5-years (Supplemental Table 6). The sensitivity analysis excluding the older trials with suboptimal assessment and sizing of moderate/severe paravalvular leak (i.e., PARTNER 1A, US CoreValve high risk, and CHOICE),[7,8,11] showed consistent findings for the outcome of moderate/severe paravalvular leak (Supplemental Figure 6).

Discussion

In this network meta-analysis of 10 randomized trials with 9,439 patients with severe symptomatic aortic stenosis, we demonstrated that there was no difference between balloon-expandable and self-expanding valves in regards to all-cause mortality at a median of 27 months. Balloon-expandable valves were associated with a higher incidence of any stroke, but no difference in the incidence of disabling stroke, compared with self-expanding valves. Self-expanding valves were associated with a higher incidence of new permanent pacemaker implantation and moderate/severe paravalvular leak compared with balloon-expandable valves at 30-days. There was no difference between both devices in terms of cardiovascular mortality, disabling or life-threatening bleeding, and major vascular complications (Figure 4). Although we observed no difference in the main efficacy and safety outcomes between self-expanding valves and balloon-expandable valves based on the baseline surgical risk and the follow-up duration, these subgroup analyses were characterized by a wide 95% CIs, and a chance of Type II error due to the small number of trials included in these subgroup analyses.

In this meta-analysis, we observed that balloon-expandable valves were associated with a higher incidence of any stroke compared with self-expanding valves. In the SOLVE TAVI trial, the rate of any stroke was significantly higher with balloon-expandable valves.[12] In addition, the rates of any stroke were numerically higher with balloon-expandable valves in the other two head to head trials,[11,13] albeit these trials were not powered for this outcome. Contrary to these findings, a large observational study showed that balloon-expandable valves were associated with lower rates of stroke at 30-days, which was driven by higher stroke rates

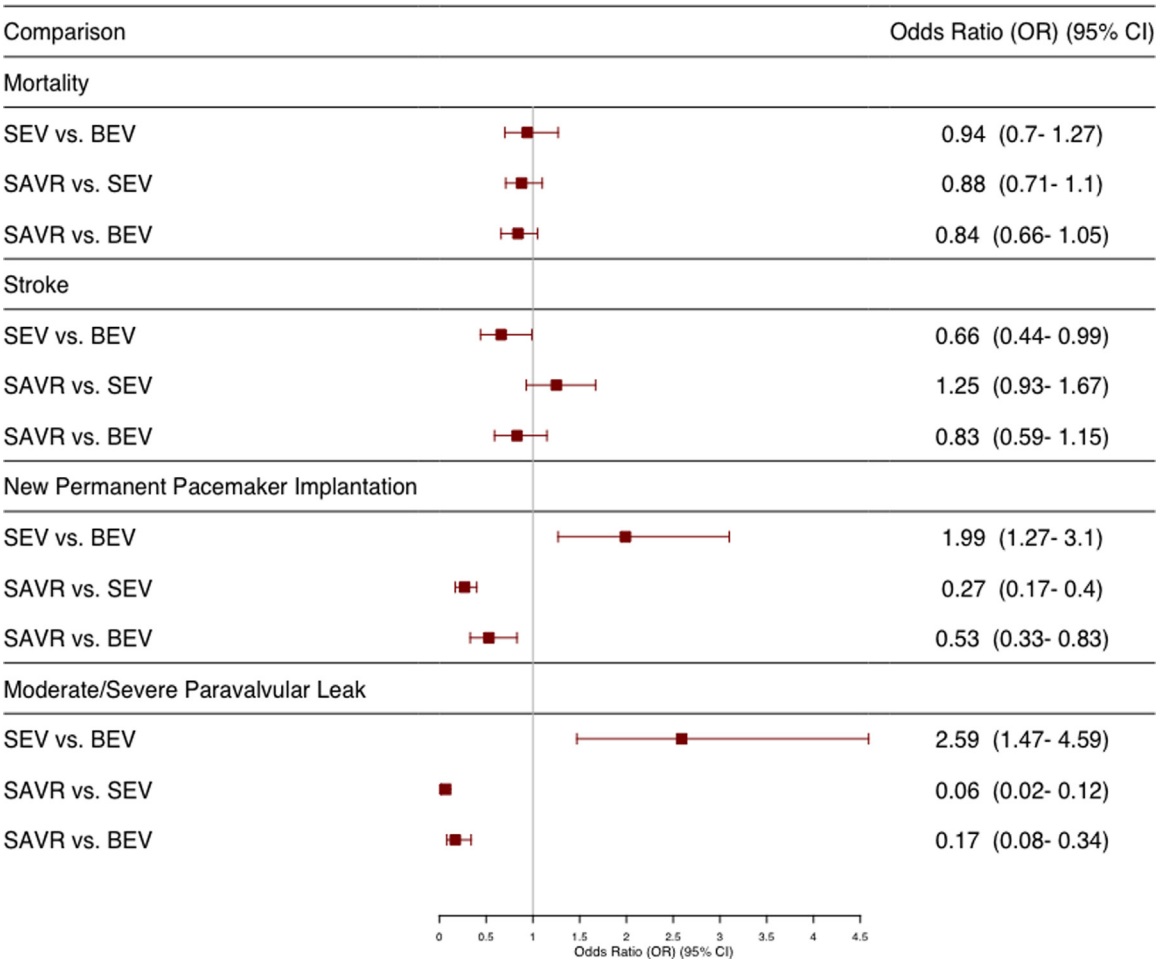

Figure 4. Forest plots for the main efficacy and safety outcomes in this meta-analysis. For each comparison, boxes and horizontal lines correspond to the respective point estimate and accompanying 95% confidence interval. BEV= balloon-expandable valves; CI= confidence interval; SAVR= surgical aortic valve replacement; SEV= self-expanding valves

with the newer generation self-expanding valves.[9] In one study of 100 patients who underwent transfemoral TAVI with a double filter embolic protection device, the largest debris was retrieved in those treated with balloon-expandable devices (SAPIEN 3) as compared with other devices (Evolut R and Lotus).[27] Notably, the difference in stroke in this meta-analysis appears to be driven by nondisabling stroke since there was no difference in the incidence of disabling stroke between both devices.

In this meta-analysis, self-expanding valves were associated with a higher incidence of new permanent pacemaker implantation, as compared with balloon-expandable valves. The radial force exerted on the left ventricular outflow as well as the depth of implantation of self-expanding valves are contributing factors to the difference in the incidence of new permanent pacemaker implantation. On treatment ranking, we observed that the CoreValve (first-generation self-expanding valve) was associated with the highest incidence of new permanent pacemaker implantation. A recent study suggested that using a patient-specific approach to minimize the depth according to the membranous septum was associated with a reduction in the need for new permanent pacemaker implantation with self-expanding valves.[28]

Moderate/severe paravalvular leak after TAVI has been a major concern as it is associated with long-term mortality. This complication was seen more frequently in the early TAVI experience with older generation devices, consistent with our subgroup analysis based on the valve type. With the maturation of TAVI experience, there have been more careful attempts to assess the aortic annulus to minimize this risk. Even in the sensitivity analysis excluding the older trials, we still observed a higher incidence of moderate/severe paravalvular leak with self-expanding valves. On treatment ranking, we noted that the first-generation devices were associated with the highest incidence of moderate/severe paravalvular leak. The newer generation self-expanding valve with an external pericardial wrap (Evolut PRO) which was only implanted in <25% in one trial in this meta-analysis[1] has been associated with minimal paravalvular leak.[29]

The choice of self-expanding versus balloon-expandable valves is mostly based on the operator and institution's experience, some anatomical considerations oftentimes support the use of self-expanding valves such as small annuli and/or annular calcification. This network meta-analysis provides a comprehensive analysis inclusive only of randomized trials comparing the efficacy and safety of self-expanding versus balloon-expandable valves. By including the TAVI arm from the pivotal trials comparing TAVI versus SAVR, we increased the power of this meta-analysis to provide an indirect comparison between self-expanding versus balloon-expandable valves. In an updated conventional meta-analysis of randomized trials, TAVI was associated with lower all-cause mortality compared with SAVR at years.[3] Since we categorized the corresponding TAVI arm from these pivotal trials to one of the arms of the network, our network meta-analysis did not show a difference in all-cause mortality between the 3 arms. A previous network meta-analysis showed no difference in all-cause mortality between both devices.[30] This updated analysis included 2 additional head to head trials comparing both devices, and was complemented by several subgroup and sensitivity analyses. By increasing the sample size, our analysis provided more refined estimates. However, the findings from this meta-analysis should be interpreted in the context of certain limitations. First, the included trials enrolled patients with different risk profile and utilized several iterations of devices. Hence, we performed subgroup analyses based on the baseline surgical risk and according to the device. Second, we noted a high degree of statistical heterogeneity for the secondary safety outcomes. We attempted to mitigate this risk by using a random effects analysis as the main model, and by performing several subgroup and sensitivity analyses to explore the heterogeneity. Third, the newer generation self-expanding valve (i.e., Evolut Pro) was not represented in this meta-analysis. Finally, the lack of patient-level data precluded a full evaluation for differences in patient-level covariates across comparisons.

In patients with severe symptomatic aortic stenosis undergoing mostly transfemoral TAVI, self-expanding and balloon-expandable were associated with similar all-cause mortality. Balloon-expandable valves were associated with a higher incidence of any stroke driven by nondisabling strokes, but a lower new permanent pacemaker placement and moderate/severe paravalvular regurgitation compared with self-expanding valves.

Author Contributions

IE: data collection, data interpretation, drafting manuscript, final critical revision of the manuscript and final approval. MG: data analysis, data collection, data interpretation, final critical revision of the manuscript and final approval. AM: data interpretation, final critical revision of the manuscript and final approval. DD: final critical revision of the manuscript and final approval. SK: final critical revision of the manuscript and final approval. FA: final critical revision of the manuscript and final approval. DC: final critical revision of the manuscript and final approval.

Disclosures

The authors declare that they have no known competing financial interests or personal relations that could have appeared to influence the work reported in this study.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2020.05.007.

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