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ORIGINAL ARTICLE

Transcatheter versus surgical aortic valve replacement in low- and intermediate-risk patients: an updated systematic review and meta-analysis

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Abstract

Transcatheter aortic valve replacement (TAVR) has been recognized as a well-established alternative to surgical aortic valve replacement (SAVR) for symptomatic aortic stenosis with high surgical risk. With this updated systematic review and meta-analysis, we evaluated TAVR vs. SAVR in low- and intermediate-risk subjects. Studies comparing TAVR and SAVR in low-risk patients (defined as STS ≤ 8% or EuroSCORE ≤ 20%) were identified with electronic searches. The principal endpoint was all-cause mortality at short term (< 3 months), 1, and 2 years. Other outcomes of interest were cardiac mortality, neurological events, paravalvular leakage (PVL), myocardial infarction (MI), major bleeding, acute kidney injury (AKI), vascular complications, and new pacemaker (PM) implantation. Seventeen articles including 9805 (4956 TAVR and 4849 SAVR) patients were eligible. There was no significant difference in all-cause mortality at short term [odds ratio (OR) 0.83, 95% confidence interval (CI) 0.63–1.09], 1 year (OR 1.01, 95% CI 0.86–1.20) and 2 years (OR 0.86, 95% CI 0.64–1.16) between treatment groups. Subgroup analyses stratified by surgical risk score (low-risk subgroup: STS < 4% or EuroSCORE < 10%, intermediate-risk subgroup: the others) did not show interaction on primary endpoints. Compared to SAVR, TAVR had similar rates of neurological events, significantly lower risk of MI and AKI, but higher risk of vascular complications, new PM implantation and moderate/severe PVL. In low- and intermediate-risk patients, TAVR and SAVR have similar short- and mid-term all-cause mortality. Compared to SAVR, TAVR carries higher rates of vascular complications, PM implantation and moderate/severe PVL, but lower risk of MI and AKI.

Keywords Severe aortic stenosis · Transcatheter aortic valve replacement · Surgical aortic valve replacement · Low risk · Intermediate risk

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Introduction

Transcatheter aortic valve replacement (TAVR) has rapidly changed the paradigm of care for patients with symptomatic aortic stenosis (AS) that are deemed inoperable or at high surgical risk [1]. In fact, TAVR and surgical valve replacement (SAVR) now share the same guideline recommendation in high-risk AS patients [2]. Recently, encouraging results from randomized controlled trials (RCT) [3–5] and prospective registries [6, 7] have broadened the indications for TAVR as an alternative to SAVR for appropriately selected intermediate-risk patients (class IIa, level of evidence B) [8]. With constant improvements in operator experience and valve technology, TAVR is currently being performed in an ever-increasing number of low-risk patients [9]. Nevertheless, there is controversy in the literature whether available

data are robust enough to justify extending TAVR to low-risk subjects, given the unknown prosthesis, long-term durability and the non-negligible rates of TAVR complications such as paravalvular leakage (PVL), new pacemaker (PM) implantation and vascular complications. With this updated systematic review and meta-analysis, we aimed to comprehensively assess outcomes of low- and intermediate-risk patients with symptomatic severe AS undergoing TAVR vs. SAVR in randomized and observational studies.

Methods

This study was conducted according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) amendment to the Quality of Reporting of Meta-analyses statement [10] and the recommendations from the Cochrane Collaboration and Meta-analysis of Observational Studies in Epidemiology [11].

Search strategy and article selection

A systematic review was performed by a search of relevant studies from January 2002 to May 2017 conducted by 2 independent investigators (D.U. and G.D.) using MEDLINE, CENTRAL, Cochrane Controlled Trials Register, ProQuest, Google Scholar databases, conference proceedings for the Scientific Sessions of the American College of Cardiology, American Heart Association, European Society of Cardiology, Transcatheter Cardiovascular Therapeutics, and EuroPCR. Search details are available in Supplementary Appendix. We avoided using the keywords relevant to "intermediate risk" to include studies in which this subject was dealt as subgroup analysis. Both observational studies and RCT were considered for inclusion. Studies were included only if they compared TAVR and SAVR and if they fulfilled the following criteria: (1) the cohort included patients with symptomatic severe aortic stenosis; (2) the cohort consisted of low- or intermediate-risk patients, defined according to Society of Thoracic Surgeons (STS) score predicted risk of mortality ≤ 8%. Logistic EuroSCORE I ≤ 20% was used only if STS score was not available. Not only mean or median STS had to be ≤ 8% (or EuroSCORE ≤ 20%), but also the "mean + standard deviation" or "upper interquartile range" was required to be under the limit. Reference lists of selected articles were reviewed for other potentially relevant reports. We included all studies irrespective of type of TAVR device and route of vascular access. No language restrictions were applied. The most recent publication was included in case of possible overlapping (according to institution and inclusion period).

Data extraction

Three authors (D.U., G.D. and L.N.F.) independently assessed eligibility and quality of studies and extracted data. Discrepancies were resolved by consensus. Collected information included study design, quality indicators, baseline clinical characteristics, procedural details and clinical outcomes. Authors were contacted in case of incomplete or unclear data.

Outcomes of interest

The primary outcome assessed for the present study was all-cause mortality. Other outcomes of interest (with or without independent adjudication) were cardiac mortality, neurological events, moderate/severe PVL, myocardial infarction (MI), major bleeding, acute kidney injury (AKI), vascular complications, and new PM implantation. All endpoints were evaluated according to each study definition. Follow-up time points were defined as short term (< 3 months), 1 and 2 years.

Risk of bias assessment

Quality of studies was assessed using the Cochrane Collaboration's tool for assessing risk of bias [12] for randomized studies. For non-randomized studies, quality was evaluated using the RoBANS tool [13].

Validation of extracted articles

Our systematic review was not the first one on this topic; hence, we performed a separate systematic search of previously published meta-analyses. For each meta-analysis, we extracted and checked included studies. In this phase, we used a filter named Search Strategy Used to Create the Systematic Reviews Subset on PubMed [14] that was last modified in February 2017. Details of search code are available in Supplementary Appendix.

Statistical analysis

The outcomes were summarized computing odds ratios (OR) and 95% confidence intervals (CIs). Data across studies were combined using DerSimonian and Laird random effects models [15]. The results were also confirmed with a fixed effects model; however, the random effects model was prioritized in case of significant heterogeneity. The analysis was performed on an "intention-to-treat" basis, whenever possible. Subgroup analysis was performed according to surgical risk scores; studies with average STS score < 4 or

Logistic EuroSCORE < 10% were assigned to low-risk subgroup, while the others were assigned to intermediate-risk subgroup. Heterogeneity across studies was tested by the Cochran's Q statistic and Higgins' and Thompson's I^2 statistics. A threshold of $p < 0.10$ was used to define heterogeneity. I^2 was considered substantial when it was > 50% [16]. Funnel plots were used to visually assess potential publication bias. Sensitivity analyses were adopted for each outcome according to several pre-specified variables: definition of short term (excluding studies without analysis at 30 days), publication year (excluding studies published before 2015), risks of bias (excluding non-RCT with less than 4 items indicating a low risk of bias assessed by the RoBANS tool), sample size (excluding studies in which any comparator group contained fewer than 200 participants), information on patients' baseline characteristics (excluding studies in which the information of patients' characteristics was not shown), and rate of transfemoral approach (excluding studies with < 70% or unclear rate of transfemoral approach). The following covariates were assessed for their relationship with all-cause mortality, cardiac mortality and neurological events by meta-regression: age, gender, STS, EuroSCORE, percentage of self-expandable valves. Computations were performed with R (version 3.1.2 for Windows) packages meta and RcmdrPlugin. EZR.

Results

Systematic review

The study analysis PRISMA flow diagram is shown in Fig. 1. Seventeen studies involving 9805 patients (TAVR 4956, and SAVR 4849) met our inclusion criteria [3–7, 17–28], including 12 observational (8 propensity matched) and 5 randomized studies. A total of 9 meta-analyses were previously reported (listed in Supplementary appendix). Four studies included in our meta-analysis did not appear in any previous meta-analyses. Four studies included in other meta-analyses were excluded from our review: 3 included intermediate–high-risk patients, and one included SAVR patients already present in another study (Supplementary Table 1). The outline of extracted studies and the summary of patients' characteristics are shown in Tables 1, 2 (details in Supplementary Tables 2). Notably, mean age was ~ 80 years and over 93% of TAVR patients received first- and second-generation valves.

Risk of bias assessment

The summary of risk bias assessment is shown in Supplementary Table 3 and Supplementary Fig. 1. It was impossible to blind the approach to treatment; hence, the effect of treatment approach on medical staff was inevitable. On the other hand, even though patients knew the selected approach, the influence of such knowledge on outcome was limited.

Endpoints

The pooled analysis of primary and single outcomes is summarized in Figs. 2, 3 (details in Supplementary Fig. 3a–c). No significant difference in all-cause mortality was present between TAVR and SAVR at short term (OR 0.83, 95% CI 0.63–1.09; $p = 0.17$), 1 year (OR 1.01, 95% CI 0.86–1.20; $p = 0.86$), and 2 years (OR 0.86, 95% CI 0.64–1.16; $p = 0.32$). Subgroup analyses stratified by surgical risk score did not show an interaction with interventional strategy on all-cause mortality within 1 year (short term: p for interaction = 0.93, 1 year: p for interaction = 0.97); no studies reported 2-year outcome was assigned to low-risk subgroup. With regard to short-term 1-year pacemaker implantation, the interaction approached significance (Supplementary Fig. 3a, b). There was no publication bias for these analyses

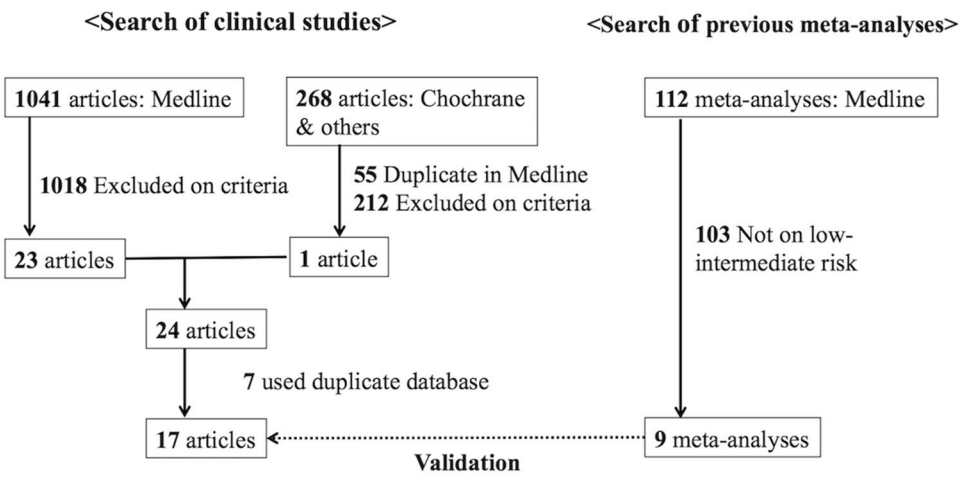

Fig. 1 Flowchart of article extraction and validation process

Table 1 Characteristics of included studies

	Year	Design	Sample size		Surgical risk score	Surgical risk score		Definition of short term	Self-expanding (%)	Transfemoral approach (%)
			TAVR (*n*)	SAVR (*n*)		TAVR	SAVR			
Tully [20]	2015	Obs	80	66	LES	13 (9, 19)	10.5 (7, 15.5)	30 days	0	92.1
Macon [21]	2015	Obs	35	37	STS	4.24 ± 2.3	4.84 ± 2.2	In hospital	NA	NA
Abdul-Jawad Altisent [22]	2016	Obs	46	37	STS	4.4 ± 1.7	4.7 ± 1.7	30 days	0	71.7
Tokarek [23]	2016	Obs	39	40	LES	9.5 (7, 14)	4.5 (2.3, 6.6)	30 days	20.5	100
Latib [24]	2012	PSM	111	111	STS	4.57 ± 2.28	4.60 ± 2.63	30 days	36.9	100
Osnabrugge [25]	2012	PSM	42	42	LES	12.9 ± 6.8	12.5 ± 6.4	In hospital	100	100
OBSERVANT [6]	2015	PSM	650	650	LES	9.5 ± 7.1	10.2 ± 9.2	30 day	60.4	81.8
Schymik [26]	2015	PSM	216	216	LES	8.7 ± 2.7	8.8 ± 2.8	30 days	19.8	58.7
Bestehorn [27]	2015	PSM	470	470	LES	13.2 ± 2.8	13.0 ± 2.4	In hospital	NA	100
Castrodeza [28]	2016	PSM	70	70	STS	4.6 ± 2.1	4.3 ± 2.4	NA	97.1	93
NY cardiac surgery [29]	2016	PSM	136	136	NYS	<3%	<3%	NA	NA	TF recommended
German Federal Council [7]	2017	PSM	805	805	LES	6.8 ± 1.7	4.2 ± 1.4	In hospital	NA	100
STACCATO [30]	2012	RCT	34	36	STS	3.1 ± 1.5	3.4 ± 1.2	3 months	0	100
CoreValve US Pivotal [31]	2015	RCT	202	181	STS	≤7%	≤7%	NA	100	TF recommended
NOTION [3]	2015	RCT	145	135	STS	2.9 ± 1.6	3.1 ± 1.7	30 days	100	96.5
PARTNER 2 [4]	2016	RCT	1011	1021	STS	5.8 ± 2.1	5.8 ± 1.9	30 days	0	76.3
SURTAVI [5]	2017	RCT	864	796	STS	4.4 ± 1.5	4.5 ± 1.6	30 days	100	94

Surgical risk scores are shown as "mean ± standard deviation" or "median (interquartile range)"

TAVR transcatheter aortic valve replacement, *SAVR* surgical aortic valve replacement, *Obs* observational study, *PSM* propensity score matching, *RCT* randomized control trial, *LES* Logistic European System for Cardiac Operative Risk Evaluation, *STS* Society of Thoracic Surgery score, *NYS* New York State score, *TF* transfemoral approach, *NA* not available

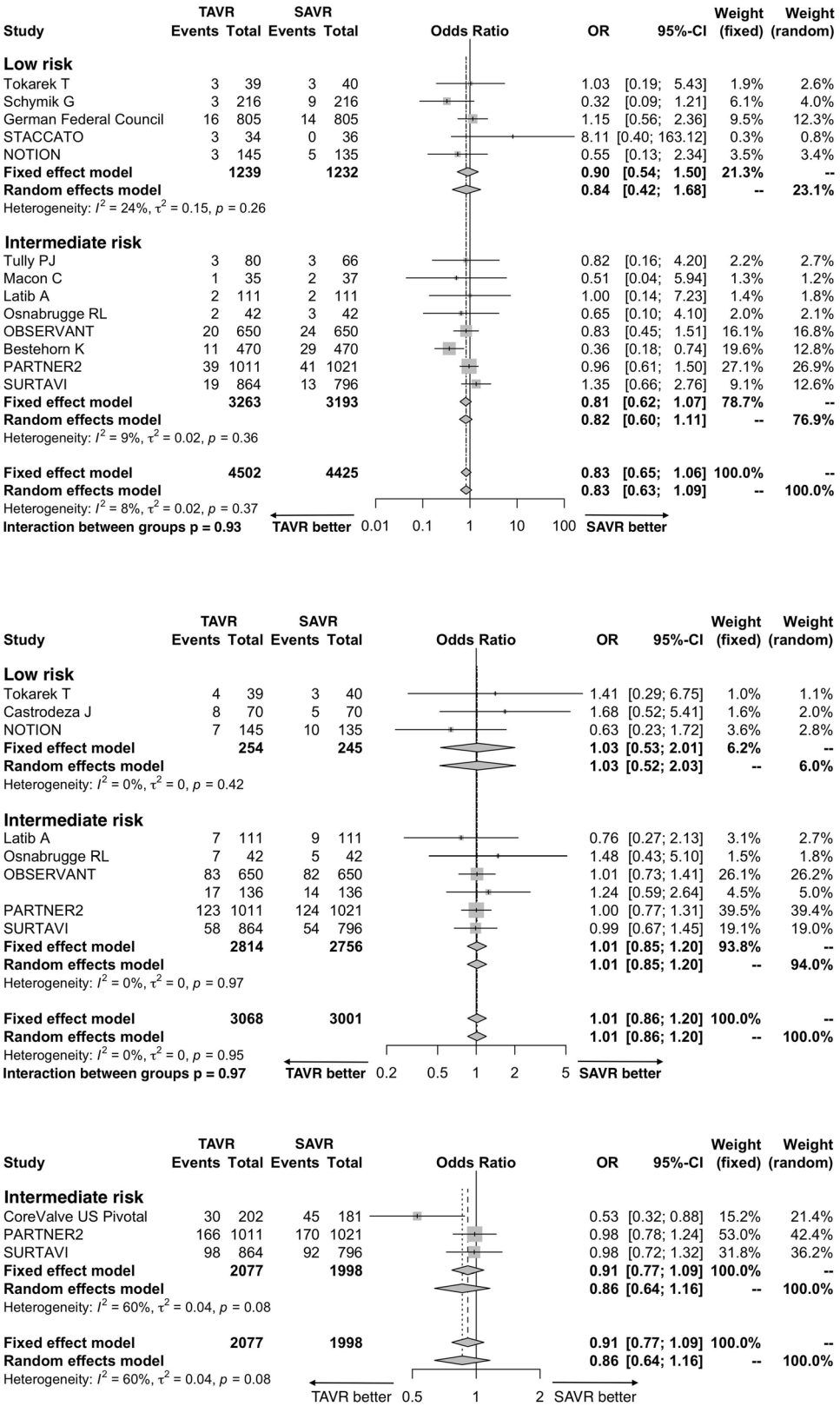

Fig. 2 Fixed and random effects meta-analyses of transcatheter aortic valve replacement vs. surgical aortic valve replacement stratified by surgical risk score for the primary outcome of all-cause mortality at short term, 1 and 2 years. **a** Short term (< 3 months) ($p = 0.17$). **b** 1 year ($p = 0.86$). **c** 2 year ($p = 0.32$). Studies with average STS score < 4 or Logistic EuroSCORE < 10% were assigned to low-risk subgroup, while the others were assigned to intermediate-risk subgroup. *OR* odds ratio, *CI* confidence interval, *TAVR* transcatheter aortic valve replacement, *SAVR* surgical aortic valve replacement, *W* weight, *Obs* observational study, *PSM* propensity score matching, *RCT* randomized control trial

of all-cause mortality (Supplementary Fig. 2), but substantial heterogeneity was observed for 2-year outcome comparison (Fig. 2c).

At short term, TAVR was associated with a significant reduction in MI and AKI, but had significantly higher risk of vascular complications, moderate/severe PVL and PM

Table 2 Baseline patients' characteristics

	TAVR	SAVR	*P*
Age, years (mean ± SD)	79.7 ± 6.0	79.5 ± 6.2	0.12
Body mass index, kg/m^2 (mean ± SD)	27.6 ± 5.6	27.6 ± 5.6	0.94
Male (%)	49.1	48.4	0.52
Diabetes (%)	29.8	29.2	0.55
Hypertension (%)	86.3	85.0	0.36
Coronary disease (%)	51.9	51	0.48
Previous MI (%)	11.0	10.8	0.83
Previous CABG (%)	20.1	21.9	0.18
Previous cerebral vascular disease (%)	16.0	15.6	0.68
Peripheral vascular disease (%)	19.7	20.8	0.24
COPD or chronic lung disease (%)	20.0	18.2	0.06
Atrial fibrillation or flutter (%)	24.4	24.2	0.88
New-generation THV (%)	6.3	–	–

TAVR transcatheter aortic valve replacement, *SAVR* surgical aortic valve replacement, *MI* myocardial infarction, *CABG* coronary artery bypass graft, *COPD* chronic obstructive pulmonary disease, *THV* transcatheter heart valve, *SD* standard deviation

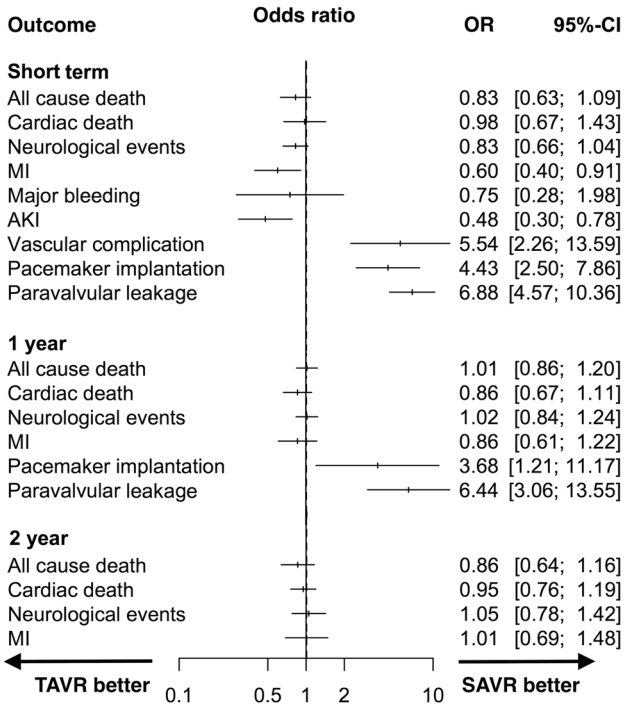

Fig. 3 Pooled odds ratio by random effects model of clinical outcomes at short term, 1 and 2 years. *OR* odds ratio, *CI* confidence interval, *TAVR* transcatheter aortic valve replacement, *SAVR* surgical aortic valve replacement, *MI* myocardial infarction, *AKI* acute kidney injury

implantation. Moreover, TAVR was associated with a non-significant reduction in major bleeding and neurological events, compared to SAVR. At 1 and 2 years, no difference emerged between TAVR and SAVR in terms of cardiac mortality, neurological events and MI. However, TAVR continued to be associated with a significant higher risk of PM implantation and moderate/severe PVL at 1 year (Fig. 3). Publication bias was absent for these analyses, but substantial heterogeneity was observed for some comparisons (Supplementary Fig. 3a-c).

Type of approach

Figure 4 presents results of stratified meta-analysis according to access route (transfemoral or transapical). When compared to SAVR, there was a trend towards survival benefit for patients undergoing TAVR through the transfemoral but not the transapical access (OR 0.70, 95% CI 0.48–1.02 vs. OR 1.91, 95% CI 0.87–4.17; $p = 0.02$). The other individual endpoints are reported in Supplementary Fig. 4, showing that the transapical approach was not superior to SAVR.

Meta-regression analysis

As shown in Supplementary Table 4, meta-regression analysis did not show any significant interaction between age, gender, STS, EuroSCORE, or proportion of self-expandable valves, and outcome. This analysis was not performed for the 2-year time point because of the low number of studies reporting it.

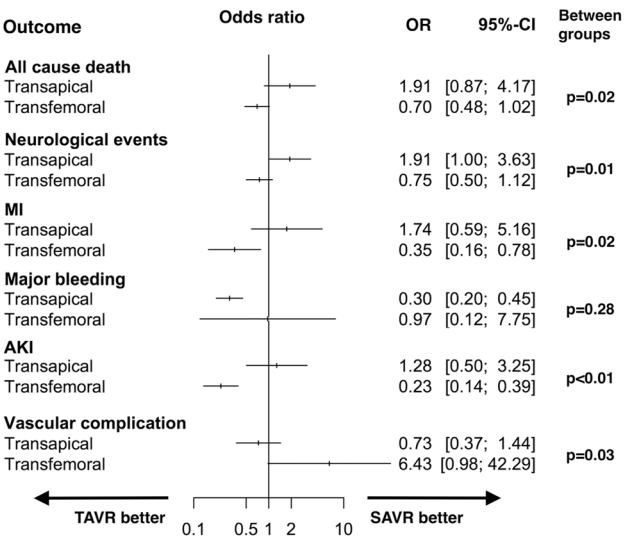

Fig. 4 Subgroup analysis on short-term outcome between transapical and transfemoral approaches. *OR* odds ratio, *CI* confidence interval, *TAVR* transcatheter aortic valve replacement, *SAVR* surgical aortic valve replacement, *MI* myocardial infarction, *AKI* acute kidney injury

Sensitivity analysis

Sensitivity analyses of each outcome according to definition of short term, publication year, risks of bias, sample size and the rate of transfemoral approach confirm the results of the main analyses (Supplementary Table 5). Heterogeneity of all-cause death at 2 years was not present when the access for TAVR was mainly transfemoral and when we excluded studies not reporting baseline characteristics of the patients (Supplementary Table 6).

Discussion

The main findings of our study, the largest comprehensive meta-analysis on TAVR vs. SAVR in low- and intermediate-risk patients, are as follows: (1) All-cause death, cardiac mortality and neurological event rates were similar between TAVR and SAVR throughout the follow-up period; moreover, the ORs were similar between low- and intermediate- risk score subgroups; (2) transfemoral TAVR trended towards better short-term survival compared to SAVR; (3) at short term, TAVR resulted in lower incidence of MI and AKI, but was associated with higher rates of vascular complications, moderate/severe PVL and new PM implantation.

Since the pioneering experience of Alain Cribier in 2002 [29], TAVR has progressively climbed down the risk-spectrum ladder. After being proven superior to standard medical therapy in inoperable patients [30], it achieved the same guideline recommendation as SAVR in high-surgical risk subjects [2]. Recently, the PARTNER 2 [4] and SURTAVI [5] trials showed favorable outcomes also in the intermediate-risk category. Accordingly, it is debated whether the available body of evidence is sufficient to broaden the indication of TAVR to low- than high-risk patients. Despite this uncertainty, 50% of European TAVR centers are already offering TAVR to intermediate-risk patients and 10% are even treating low-risk subjects [9].

In our updated meta-analysis, we found that transcatheter and surgical treatment of symptomatic severe AS with lower surgical risk score had similar all-cause and cardiac mortality throughout the follow-up period, with a trend towards better outcome for TAVR performed by the transfemoral, but not via the transapical approach. Notably, pooled analysis did not show significant heterogeneity, publication bias, or differences in study design in the short-term and 1-year outcome. The heterogeneity at 2 years became smaller after sensitivity analysis incorporating information on patients' baseline characteristics, and rate of transfemoral approach. Limited data (only 3 studies were available for this analysis) preclude more definitive conclusions. Our encouraging results extend the favorable TAVR findings of high-risk patients to low-risk categories, and confirm previous reports suggesting that, particularly when performed transfemorally, TAVR might be comparable to surgical treatment also in terms of survival as far as within mid-term period [4, 31]. In fact, transfemoral (but not transapical) TAVR trended to be superior to SAVR in terms of all-cause and cardiac mortality and of most of individual endpoints. Notably, with the advent of new-generation devices, the transfemoral approach is now feasible in more than 90% of cases [32] and it is associated with less complications, shorter length of hospital stay, better quality of life [33] and reduced costs [34]. In most of the remaining patients, other arterial access (subclavian or transcaval) obviates the need for thoracic procedures. Nevertheless, we should be careful to extrapolate these results to younger patients. In fact, "low-risk" does not necessarily mean "younger", since the mean age of patients in our meta-analysis was still around 80 years of age. With the unknown transcatheter valve durability, TAVR should not be offered to low-risk young subjects until long-term follow-up data are available. Neurological events, although rare, are associated with a marked increase in morbidity and mortality after both SAVR and TAVR [35, 36], and this is of particular concern as TAVR is offered to low-risk and younger patients. The similar outcome with respect to neurological events of SAVR and TAVR observed by our analysis is particularly reassuring, also considering the fact that most TAVR patients included in our study were treated with older devices (mainly Edwards Sapien XT™ and Medtronic CoreValve™). In fact, new-generation devices have shown an impressive reduction (down to 1%) in 30-day disabling stroke rates [5, 31], made possible by the reduced delivery sheaths' profile and the adoption of steerable delivery catheters. As expected, in our meta-analysis moderate/severe PVL was more common with TAVR than SAVR. Notably, in high-risk patients, this has been associated with worse long-term outcome [37]. Again, the gap between TAVR and SAVR is expected to diminish with new-generation devices [38], due to the addition of external cuffs to fill the prosthesis–annulus interface and the ability to reposition some of the new devices [31, 39–41]. The same is true for vascular complications, which were also higher with TAVR than SAVR. In fact, downsizing of delivery sheaths profile (from 18–24 F to 14–16 F) not only increased the percentage of AS patients amenable to transfemoral approach, but also dramatically reduced the rate of access site complications [31]. In our low-risk population, conduction disturbances leading to new PM implantation were more common after TAVR than SAVR, confirming findings in higher risk categories [42]. In general, the risk of atrioventricular block is independent of surgical risk and—as for PVL—is mostly influenced by anatomical features (such as left ventricular outflow tract calcifications) and valve characteristics (degree of oversizing, prosthesis design, etc.). Interestingly, PM implantation rates have not changed with new-generation valves, probably

because of the additional external skirt incorporated by most devices to minimize paravalvular leakage. Nevertheless, the impact on outcome of new PM implantation has not been yet definitely assessed [43, 44], at least in part because conduction disturbances can revert after TAVR, thus reducing ventricular pacing time. Granted that, we cannot exclude that long-term right ventricular pacing could impair outcome of low-risk and more active patients, in addition to requiring repeated battery and device exchanges.

There are currently three RCTs (PARTNER 3, Evolut R Low Risk and NOTION 2) randomizing low-risk patients with symptomatic severe AS to SAVR or TAVR with new-generation devices. The results of these studies will not be available before the end of next year, and we will have to wait much longer for definitive data on long-term prosthesis durability.

Limitations

As with all meta-analyses, its accuracy is determined by the quality of the included studies. Given the lack of individual patient-level data, we were unable to perform all subgroup analyses. Moreover, we did not include only RCTs, but also observational studies. Accordingly, we cannot exclude patient selection bias that may have influenced our results. For the definition of surgical risk, we adopted STS and Euroscore. It is known that these scores accurately predict SAVR outcomes [45, 46], but largely overestimate TAVR 30-day mortality in TAVR patients. Nevertheless, no other TAVR risk score is routinely used in clinical practice, mostly because of their complexity and poor accuracy [47, 48]. It was impossible to perform a network meta-analysis to indirectly compare transfemoral and transapical approach because of the low number of studies comparing SAVR to transapical TAVR ($n=2$). Furthermore, baseline characteristics of patients undergoing transfemoral and transapical approach are known to be different. A significant heterogeneity in outcomes was present at 2 years, but not after excluding CoreValve US Pivotal. The limited number of studies with follow-up longer than 2 years and the differences in endpoint definitions (such as for bleeding events) and indication for intervention (for PM implantation) does not permit further inferences. Another limitation of the present analysis is that most patients included in our study underwent TAVR with previous generation devices, which are not used in current clinical practice anymore. Finally, the most important limitation of the present study is perhaps the limited follow-up period. In fact, as we move into low-risk categories, the issue of transcatheter valve durability will become of paramount importance. With these missing data, TAVR is unlikely to replace surgery in younger patients even if the ongoing RCTs in low-risk categories will show non-inferiority to SAVR. Importantly, our studies did not include emerging data on valve deterioration and thrombosis, which are gradually accumulating in SAVORY (NCT02426307) and RESOLVE (NCT02318342) registries. Of note, ours is not the first meta-analysis on this topic, but is the one including the highest number of studies and, consequently, the largest low-risk population (Supplementary Table 1). We were very strict on risk definition, excluding reports in which mean ± standard deviation or upper interquartile range was > 8% for STS and > 20% for EuroSCORE.

Conclusions

Compared with SAVR, TAVR is associated with similar all-cause mortality, cardiac mortality and neurological events in low- and intermediate-risk patients throughout 2 years of follow-up. Rates of vascular complications, new PM implantation and moderate/severe PVL are higher with TAVR, while SAVR carries an increased risk of AKI and MI. Patients undergoing transfemoral, but not transapical TAVR, tend to have better short-term survival compared to SAVR.

Compliance with ethical standards

Conflict of interest G Tarantini received lecture fees from Edwards Lifesciences, Medtronic and Boston Scientifics. The other authors have no relevant conflict of interest to disclose.

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