European Review for Medical and Pharmacological Sciences 2019; 23: 5402-5412

Meta-analysis of the impact on early and late mortality of TAVI compared to surgical aortic valve replacement in high and low-intermediate surgical risk patients

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Abstract. – OBJECTIVE: We studied the impact of transcatheter aortic valve implantation (TAVI) compared to the surgical aortic valve replacement (SAVR) on 30-day and one-year mortality from randomized controlled trials (RCTs) in patients with severe aortic stenosis at high or low-intermediate surgical risk.

MATERIALS AND METHODS: All RCTs were retrieved through PubMed computerized database and the site https://www.clinicaltrials.gov from January 2010 until March 31st, 2019. The absolute risk reduction (RD) with the 95% confidence interval (CI) was used to assess the effectiveness of the intervention under comparison. We evaluated overall mortality rates at 30-day and one-year follow-up in the comparison between TAVI *vs.* SAVR. We also evaluated the role played by the site access for TAVI performed through the femoral or subclavian artery (TV-TAVI) *vs.* SAVR, or transapically (TA-TAVI) *vs.* SAVR.

RESULTS: In the "as-treated population" the overall 30-day mortality was significantly lower in TAVI (p=0.03) with respect to SAVR. However, the analysis for TAVI subgroups showed that 30-day mortality was (1) significantly lower in TV-TAVI *vs.* SAVR (p=0.006), (2) increased, not significantly, in TA-TAVI *vs.* SAVR (p=0.62). No significant differences were found between TAVI *vs.* SAVR at one-year follow-up.

CONCLUSIONS: The results of our meta-analysis suggest that TV-TAVI is a powerful tool in the treatment of severe aortic stenosis at high or low-intermediate surgical risk, with a significant lower mortality with respect to SAVR. On the contrary, SAVR seems to provide better results than TA-TAVI.

Key Words:
Aortic stenosis, SAVR, Transcatheter aortic-valve replacement, Transcatheter aortic valve implantation, TAVI, TAVR.

Introduction

Surgical aortic valve replacement (SAVR) in the past was the gold standard treatment for severe symptomatic native aortic valve stenosis (AS) at high or intermediate surgical risk[1]. Since the first intervention in 2002, transcatheter aortic valve implantation (TAVI) is recognized as an effective therapy for treatment of AS in high, intermediate, and even low-risk operable patients[2]. Recent randomized trials of TAVR showed that, in patients who were at intermediate or high risk for death with surgery, TAVR was either superior or non-inferior to standard therapies, including SAVR[3-13]. These results led to new of ESC and AHA/ACC guidelines, that recommend: (*1*) TAVI among high-risk patients with severe, symptomatic AS (stage D), after consideration by a heart valve team, Class I (LOE A); (*2*) TA-VI as a reasonable alternative to surgical AVR

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for patients with severe, symptomatic AS (stage D) and intermediate surgical risk, after consideration by a heart valve team (Class IIa, LOE B-R)[14,15]. However, in Europe 50% of TAVI are performed in patients at intermediate and 10% in low-surgical risk patients[16]. The site access route routinely used for TAVI is the transfemoral (TF) approach. However, transapical (TA), subclavian artery (TS), axillary artery (AX) and most recently direct aortic (DA) access have developed when TF is precluded because of small vessel caliber and peripheral vascular disease[17-19]. The TF-TAVI is reported to be associated to minor incidence of adverse events than TA-TAVI and SAVR. In adjunct SAVR performs better than TA-TAVI[20]. Moreover, there is insufficient evidence regarding the comparison of TAVI *vs.* SAVR in severe AS at low surgical risk[21,22]. In adjunct previous review and meta-analyses failed to formally rate either the quality of the evidence or the credibility of subgroup analyses or provide absolute risks[20,23,24]. This prompted us to update a meta-analysis of randomized controlled trials (RCTs) on the impact of TAVI compared to SVAR in high and low-intermediate surgical risk patients to assess: (1) mortality at 30-day and at one-year of follow-up and (2) the influence of the site access for TAVI.

Materials and Methods

This review and meta-analysis was performed in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement.

Search Strategy and Data Sources

A systematic literature search for "TAVI" or "TAVR" was performed through PubMed computerized database and through the site https://www.clinicaltrials.gov from January 2010 until March 31st, 2019. Additional manual search was performed consulting relevant systematic reviews to check the included trials. All RCTs designed for a direct comparison of TAVI *vs.* SVAR in patients with severe, symptomatic AS were included. The access site for TAVI was also collected. TF-TAVI together to TS-TAVI and AX-TAVI were named transvascular TAVI (TV-TAVI). Two investigators independently selected and examined the trial design (superiority or non-inferiority), site access and the method employed to analyze the results. Discrepancy in data extraction was resolved in discussion with a third author, until consensus was achieved. The search was restricted to English-language journals. Exclusion criteria were all studies performed without the random design allocation of patients to TAVI or SAVR treatments, observational studies, conference abstract and proceedings.

Data Analysis

The analysis was performed with the Review Manager [Computer program] Version 5.3. Copenhagen: The Nordic Cochrane Centre, the Cochrane Collaborations, 2014. The absolute risk reduction (RD) with the 95% confidence interval (CI) was used to assess the effectiveness of the intervention under study.

The Forest plots were examined to detect homogeneity/heterogeneity among studies. Homogeneity/heterogeneity were quantified with the Cochran's Q test and I^2 statistics. The Mantel-Haenszel fixed effect model was adopted instead of the random effect model in the absence of heterogeneity[25]. The primary endpoints were a composite of death from any cause at 30-day and at one-year of follow-up. Overall mortality rates at 30-day and one-year follow-up was assessed in the comparison between TAVI *vs.* SAVR. We also evaluated the influence by the site access for TAVI performed through the femoral or subclavian artery (TV-TAVI) *vs.* SAVR, or transapically (TA-TAVI) *vs.* SAVR. We performed intention to treat (ITT) and "as treated" analysis in the comparison between TAVI *vs.* SAVR. We choose "as treated analysis" in the comparisons of subgroups TV-TAVI *vs.* SAVR and TA-TAVI *vs.* SAVR, as suggested by the regulatory agencies, because the data are derived mainly from non-inferiority trial design (www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm). Bidirectional α error <0.05 was considered as statistically significant.

Results

Of 6,089 studies identified for screening, after detailed review, 8 RCTs and 14 related articles meet the inclusion criteria and were selected[4,5,7,12,13,26-34]. The selected RCTs included 8,090 patients initially randomized to TAVI or SAVR. PRISMA flow diagram for the study selection process is reported in the Figure 1. Out of 8 RCTs, 6 were designed to compare the non-inferiority of TAVI *vs.* SAVR and includes 7,740

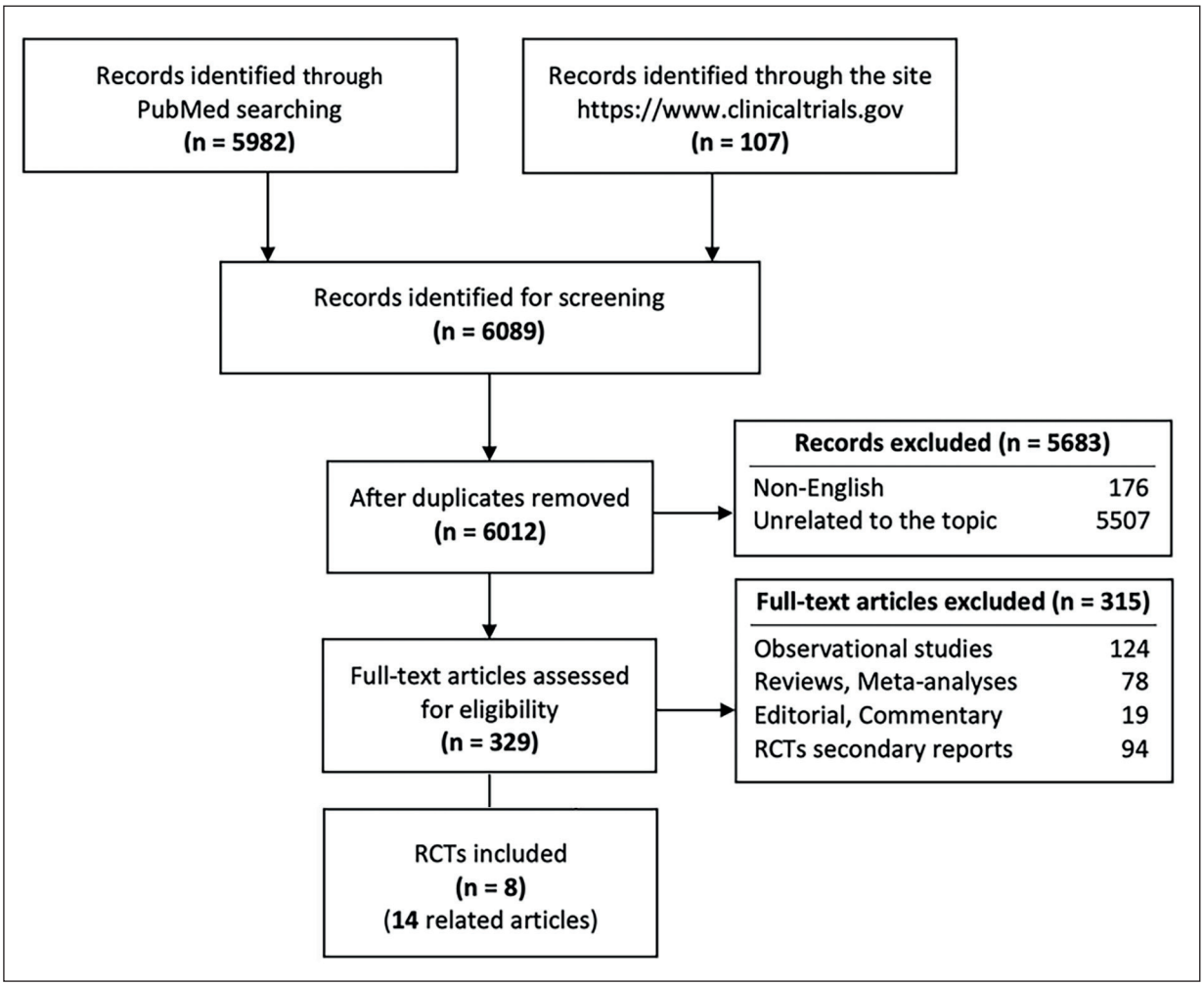

Figure 1. Flowchart of the study selection process. RCTs: Randomized controlled trials.

randomized patients, 2 were designed to compare the superiority of TAVI *vs.* SAVR in 350 patients randomized to treatments (Table I). The characteristics of the RCTs included are reported in Table I-II. ITT or "as treated" analysis was not performed in all the comparisons due to missing data (Table II). Indeed PARTNER 3[34], report only results for "as treated" patients while, for SURTAVI trial[12], only modified ITT data were available. We found no significant difference on 30-day mortality between TAVI *vs.* SAVR in ITT analysis (RD: -0.00; 95% CI from -0.01 to 0.00; p=0.45). In "as treated" population 30-day mortality was significantly lower for TAVI compared to SAVR (RD: -0.01, 95% CI from -0.02 to -0.00, p=0.03) (Figure 2). When we analyzed TAVI subgroups, a significant reduction in 30-day mortality was observed in TV-TAVI *vs.* SAVR (RD: -0.01; 95% CI from -0.02 to -0.00; p=0.006). Increased, not significantly, 30-day mortality was observed in TA-TAVI compared to SAVR, (RD: 0.02; 95% CI from -0.04 to 0.08; p=0.62) (Figure 3). The trials included had homogeneous data into each subgroup (I^2=6% in TV-TAVI and I^2=0% in TA-TAVI) (Figure 3). The results at one-year follow-up showed that in the comparison between TAVI *vs.* SAVR, there was a non-significant 2% absolute risk reduction (RD: -0.02; 95% CI from -0.04 to 0.00; p=0.06). No significant differences were also found in the comparison between TAVI subgroups *vs.* SAVR (Figure 4).

Discussion

TAVI is considered equal or even superior to SAVR regarding early mortality when TF access is used[35]. TF-TAVI seems to be associated

Table I. Selected trials.

Trial NCT* registry number	Recruitment period	Country	Centre (n)	Surgical risk	Hypothesis	Transcatheter heart valve	RCT Design
PARTNER Cohort A[4,7,26] NCT00530894	2007-2009	Canada, USA, Germany	25	High	Non-inferiority	Edwards Sapien	Includes two parallel, multicenter, randomized trials individually powered for: 1) **Cohort A**: high-risk surgical pts (non-inferiority trial: TF and TA-TAVI *vs.* SAVR; n = 699 pts); 2) **Cohort B:** inoperable pts (superiority trial: TF-TAVI *vs.* Standard atherapy, n = 358 pts).
STACCATO[27] Not available	2008-2011	Europe (Denmark)	2	Operable elderly pts	Superiority	Edwards Sapien	Superiority trial designed to compare TA-TAVI *vs.* SAVR in operable elderly pts (age > 75 yrs) with severe AS.
CoreValve US Pivotal[13,28-30] NCT01240902	2011-2012	USA	45	High	Non-inferiority	Medtronic CoreValve	Enrolls pts whit symptomatic severe AS into two separate cohorts: 1) **Extreme surgical risk,** a non-randomized study of inoperable pts treated with TAVI; 2) **High-risk cohort:** a multicenter non-inferiority trial including pts at high risk randomly assigned to TAVI (IF and non-IF access) and SAVR. Initially 390 and 357 pts were reported respectively in TAVI and SAVR groups. After the publication of the initial report, 2 additional pts were included in ITT and 3 in "as treated" populations.
NOTION[31,32] NCT01057173	2009-2013	Europe (Denmark, Sweden)	3	Low (82%), intermediate	Superiority	Medtronic CoreValve	A randomized, multicenter trial to compare TAVI with SAVR in unselected pts (all-comers population) ≥ 70 years with severe degenerative AS, eligible for surgery. The site access was TF (96.5%) and TS (3.5%) for TAVI. The results did not take the subgroups into account.
PARTNER 2[5] NCT01314313	2011-2013	Canada, USA	57	Intermediate	Non-inferiority	Edwards SAPIEN XT	The trial investigated the non-inferiority of TAVI *vs.* SAVR in intermediate risk pts with severe AS. Out of 2032 pts randomized, 1021 were assigned to SAVR and 1011 to TAVI.
SURTAVI[12] NCT01586910	2012-2016	Canada, Europe, USA	87	Intermediate	Non-inferiority	- Medtronic CoreValve (84%), - Medtronic Evolut R (16%)	The trial assessed the non-inferiority of TAVI *vs.* SAVR in pts with symptomatic, severe AS at intermediate surgical risk. TAVI was compared with SAVR according to the modified-ITT population principles, regardless the access route.
Evolut Low Risk[33] NCT02701283	2016-2018	Australia , Canada Europe, Japan, New Zealand, USA	86	Low	Non-inferiority	- Medtronic CoreValve (3.6%), - Medtronic Evolut R (74.1%), - Medtronic Evolut PRO (22.3%)	Designed to demonstrate that the safety and effectiveness of the Medtronic TAVI system was non-inferior to SAVR in the treatment of severe AS at low surgical risk. The estimated sample involved the recruitment of 1200 pts. However, 1468 pts were enrolled to allow the completion of a randomized sub-study.
PARTNER 3[34] NCT02675114	2016-2017	USA, Australia, Canada, Japan, New Zealand	71	Low	Non-inferiority	Edwards Sapien 3	A multicenter randomized trial comparing TAVI with SVA in pts with severe AS at low surgical risk.

*NCT: National Clinical Trial (https://www.clinicaltrials.gov). AS: aortic stenosis; ITT: intention to treat; IF: iliofemoral; pts: patients; RCT: randomized clinical trial; SAVR: surgical aortic valve replacement; TAVI: transcatheter aortic valve replacement; TA: transapical; TF: transfemoral; TS: transsubclavian.

Table II. TAVI access site, number of pts allocated into the two arms for ITT and "as treated population". Longest follow-up.

Trial NCT* registry number	Access route	ITT population							"As Treated" population							
		TAVI					SAVR	Total	TAVI					SAVR	Total	Follow-up
		TF	TS	TA	DA	Overall			TF	TS	TA	DA	Overall			
PARTNER Cohort A[4,7,26] NCT00530894	TF, TA	244	–	104	–	348	351 *vs.* - TF 248 - TA 103	699	240	–	104	–	344	313 *vs.* - TF 221 - TA 92	657	5 yrs
STACCATO[27] Not available	TA	–	–	34	–	34	36	70	–	–	34	–	34	35	69	3 months
CoreValve US Pivotal[13,28-30] NCT01240902	TF, TS, DA	330	DM	–	DM	394**	401** *vs.* - IF 333 - Non-IF 68	795	324	13	–	54	391**	359**	750	5 yrs
NOTION[31,32] NCT01057173	TF, TS	DM	DM	–	–	145	135	280	137	5	–	–	142	134	276	6 yrs
PARTNER 2[5] NCT01314313	TF, TA, DA	775	–	174	62	1011	1021** *vs.* - TF 775 - TA/DA 246	2032	DM	–	DM	DM	994	944	1938	2 yrs
SURTAVI[12] NCT01586910	TF, TS, DA	DM	DM	–	DM	879 (modified ITT 864)	867 (modified ITT 796)	1746 (modified ITT 1660)	DM	DM	–	DM	863	794	1657	2 yrs
Evolut Low Risk[33] NCT02701283	TF, TS, DA	DM	DM	–	DM	734	734	1468	718	4	–	3	725	678	1403	2 yrs
PARTNER 3[34] NCT02675114	TF	503	–	–	–	503	497	1000	496	–	–	–	496	454	950	1 yrs

*NCT: National Clinical Trial (https://www.clinicaltrials.gov). **Data from ITT population are derived from Adams et al[29]; for "as treated" population from Conte et al[30]. DA: direct aortic; IF: ili ofemoral; ITT: intention to treat; SAVR: surgical aortic valve replacement; TAVI: transcatheter aortic valve replacement; TA: transapical; TF: transfemoral; TS: transsubclavian.

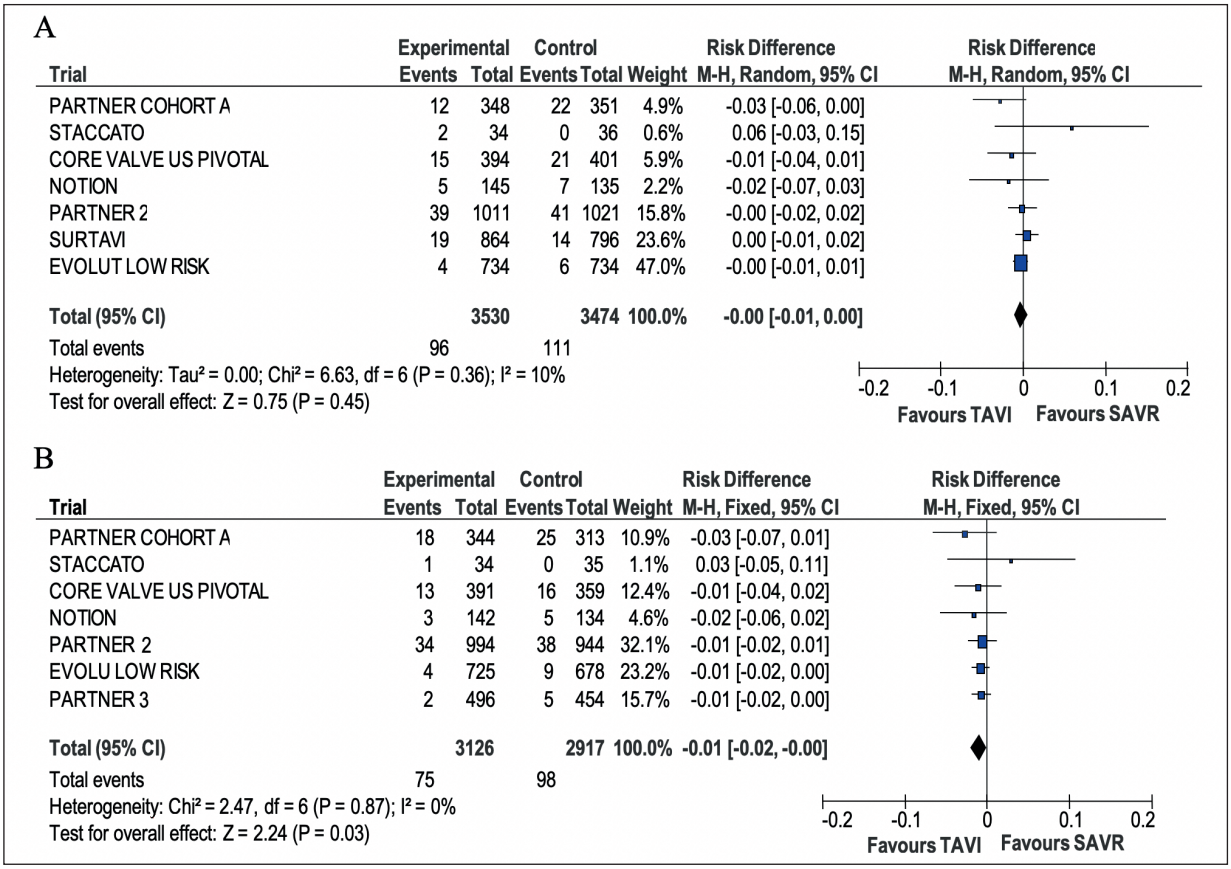

Figure 2. 30-day mortality in overall TAVI population of patients. ***A***, ITT; ***B***, "as treated". ITT: intention to treat.

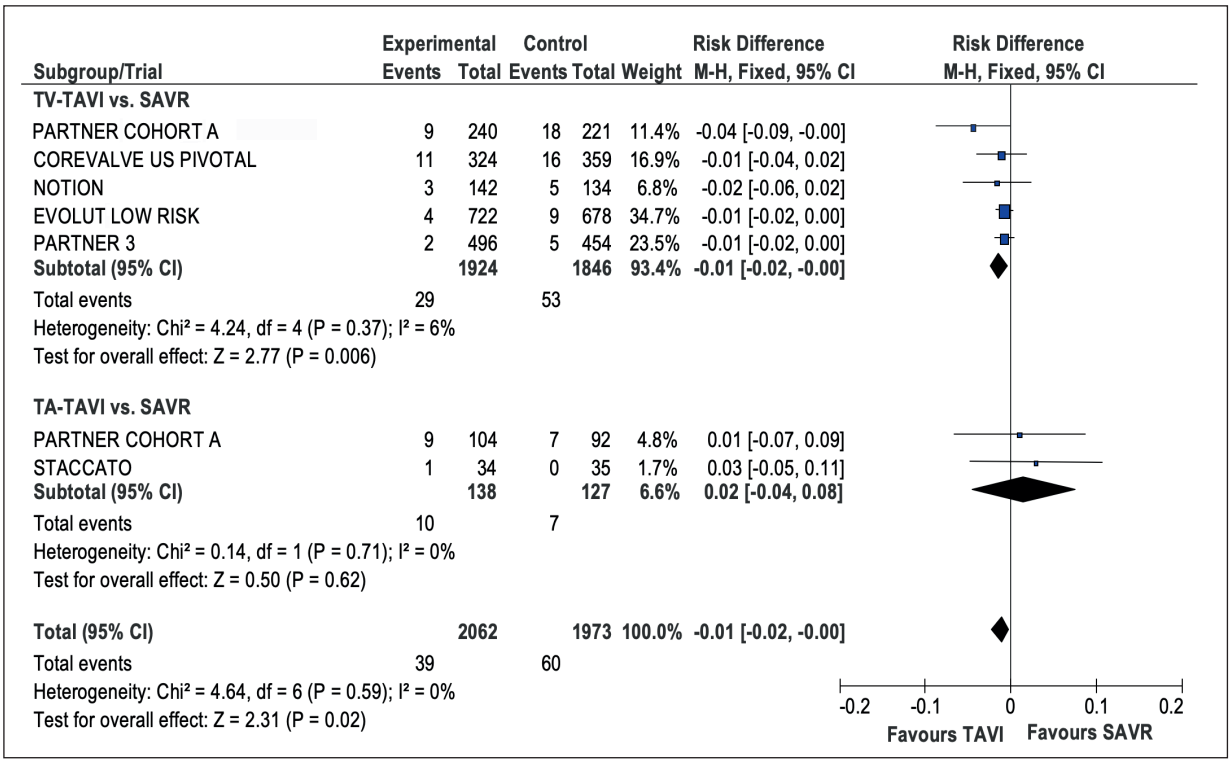

Figure 3. 30-day mortality in TAVI "as treated" subgroups population.

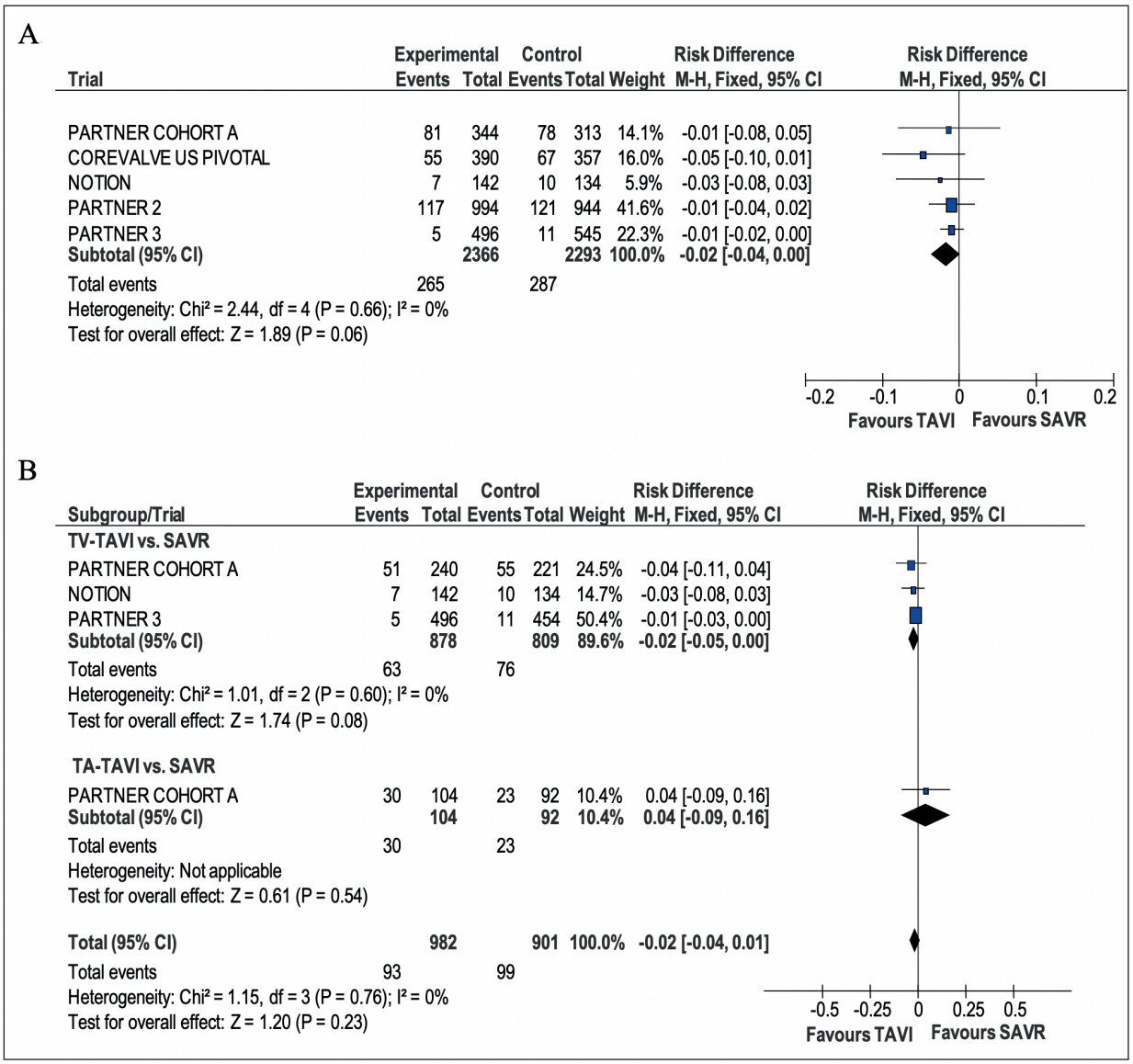

Figure 4. One-year mortality in TAVI "as treated" population. ***A***, Overall population. ***B***, Subgroups of patients.

with significantly higher early and intermediate survival compared with TA-TAVR[36]. TA-TAVI, widely used in the past, is nowadays considered inferior to TF-TAVI[37-40] and its role is at a turning point. The PARTNER trial investigators demonstrated the negative impact of TA-TAVI on two-year all-cause mortality in patients with and without left ventricular dysfunction[41]. The PARTNER 3 trial investigators reported that in patients with severe aortic stenosis who were at low-surgical risk, the rate of the composite of death, stroke, or re-hospitalization at 1 year was significantly lower with TAVI than with SAVR[34]. Indeed the EVOLUT LOW RISK trial investigators showed that in patients with severe AS who were at low surgical risk, TAVI with a self-expanding supra-annular bioprosthesis was non-inferior to SAVR with respect to the composite end point of death or disabling stroke at 24 months[33]. However, recent registries have shown conflicting results on post-operative mortality when the access sites for TAVI entered the analysis[41]. Furthermore, a recent contemporary large study on utilization and outcomes of TF *vs.* TA-TAVI in real-world patient populations, showed that TF approach should be preferred over a TA approach for TAVI whenever possible[42,43]. In adjunct the analysis of data from UK TAVI registry showed that TA and DA-TAVI were associated with similar survival, both significantly worse than with the TF route[38,44].

Moreover, TS access for TAVI provide result similar to TF-TAVI and may represent the safest non femoral access route[37,38]. However, data from observational studies could overestimate the treatments effect due to the lack of randomization[45,46]. On the contrary, RCTs are considered a key tool for comparative effectiveness research, because, through randomization: (*1*) patients are assigned to experimental or control group by chance in order to reduce errors or bias and (*2*) only the real differences due to the treatment are remarked[47,48]. Based on these observations, we have chosen to perform a meta-analysis on the available RCTs in order to examine the impact of TAVI and SAVR on death from any cause at 30-day and at one-year of follow-up in patients with AS at high and low-intermediate surgical risk (Figure 2, 4). In the meta-analysis we also assessed the role played by the site access for TAVI (Figure 3, 4). As confirmation of the actuality of the TV approach for TAVI, the majority of the patients included in the meta-analysis (93.4%) belonged to the TV-TAVI subgroup and a lower number (6.6%) to the TA-TAVI subgroup (Figure 3). We did not found significant differences between TAVI *vs.* SAVR at 30-day (ITT population) and one-year mortality (Figure 2, 4). The estimate is the result of two opposite trends: a significant reduction in mortality in TV-TAVI compared to SAVR (p=0.006) and an increased mortality, although not significant, in TA-TAVI compared to SAVR (p=0.62) (Figure 3). The results demonstrate that the analysis performed without outlining the importance of take into account the arterial access site for TAVI can be confusing and lead to biased results[49]. Again, our findings are in agreement with those of the STACCATO trial[27], which, designed to investigate the superiority of TA-TAVI compared to SAVR, showed a negative effect of TA-TAVI with respect to SAVR. In fact, the trial, designed to enroll 200 patients, was interrupted prematurely after enrolling only 70 patients, due to an excess of adverse events in the TA-TAVI group. Finally the significant beneficial impact on the 30-day mortality of TV-TAVI can be attributable to its non-invasive nature, with respect to TA-TAVI and SAVR[41], that are full-fledged surgical procedures and as such imply a different postoperative course[43]. The choice to include in the meta-analysis only the RCTs to avoid bias, does not exclude the limitation of the insufficient number of patients enrolled. In addition, we could not perform the analysis of data with both ITT and "as treated" approach due to the lack of details related to the TAVI subgroups (Table II). Indeed, in SURTAVI[12] only the analysis for ITT patient population and in PARTNER 3[34] only "as treated" analysis were performed.

Conclusions

Our meta-analysis show the lack of significant differences on the incidence of 30-day and one-year mortality of TAVI *vs.* SAVR in the overall data analysis. However, the analysis can lead to misleading results when the comparisons are performed without taking into account the subgroups selected on the basis of the arterial access site for TAVI. Indeed, in the analysis of TAVI subgroups, our data suggest the significant superiority of TV-TAVI *vs.* SAVR in terms of 30-day mortality reduction, irrespective of surgical risk category. Finally, TA-TAVI was affected by higher, not significant, occurrence of 30-day mortality compared to SAVR.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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