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Worse survival after transcatheter aortic valve implantation than surgical aortic valve replacement: A meta-analysis of observational studies with a propensity-score analysis☆

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ABSTRACT

Objectives: To determine whether transcatheter aortic valve implantation (TAVI) improves (or impairs) follow-up overall survival compared with surgical aortic valve replacement (SAVR), we performed a meta-analysis of observational studies with a propensity-score analysis and another meta-analysis of randomized controlled trials (RCTs).

Methods: Databases including MEDLINE and EMBASE were searched through October 2015 using PubMed and OVID. Eligible studies were observational studies with a propensity-score analysis or RCTs of TAVI versus SAVR enrolling patients with severe aortic stenosis and reporting follow-up overall survival or all-cause mortality as an outcome. A hazard ratio (HR) with its 95% confidence interval (CI) of follow-up (including early) all-cause mortality for TAVI versus SAVR was abstracted from each individual study.

Results: Our search identified 19 observational studies with a propensity-score analysis enrolling a total of 6234 patients. The arithmetic means of 1-year and 3-year survival rates were 82.7% and 71.3% after TAVI and 84.8% and 77.9% after SAVR, respectively. A pooled analysis demonstrated a statistically significant 21% increase in the hazard of mortality with TAVI relative to SAVR (HR, 1.21; 95% CI, 1.05 to 1.39; $p = 0.010$). Another pooled analysis of 4 RCTs (enrolling a total of 1795 patients) demonstrated no statistically significant difference in mortality between TAVI and SAVR (HR, 0.92; 95% CI, 0.62 to 1.37; $p = 0.69$).

Conclusions: The arithmetic mean of 3-year survival rates was 71.3% after TAVI and 77.9% after SAVR. Compared with SAVR, TAVI appears to be associated with a significant increase in follow-up all-cause mortality.

1. Introduction

For patients with severe symptomatic inoperable (unsuitable for surgical aortic valve replacement [SAVR]) aortic stenosis (AS), transcatheter aortic valve implantation (TAVI) should be considered. For treatment of inoperable AS, the Placement of Aortic Transcatheter Valves (PARTNER) 1 trial [1] evidently demonstrated that TAVI was more beneficial to late clinical outcomes (survival and functional status) than standard treatment. For patients not inoperable but at moderate-to-high risk for SAVR; however, TAVI is probably unassociated with better early (30-day or in-hospital) all-cause mortality than SAVR [2–7]. Furthermore, in terms of follow-up overall survival (freedom from all-cause mortality), findings of TAVI versus SAVR have been still controversial. To our best knowledge with a systematic literature search, 4 randomized controlled trials (RCTs) [8–11] reported follow-up results. One RCT demonstrated significantly better follow-up overall survival in TAVI [10], another did significantly better survival in SAVR [9], and the other 2 did no significant difference in survival between TAVI and SAVR [8,11]. Although a lot of observational comparative studies have been conducted, results should be always interpreted with caution when they are included in meta-analyses because of greater potential biases for non-randomized studies compared with RCTs [12]. Particular concerns arise with respect to differences between patients in different intervention groups (selection bias). Unlike for RCTs, it would usually be appropriate to analyze adjusted (rather than unadjusted) effect estimates, i.e., analyses that attempt to control for confounding [12]. A

Abbreviations: AS, aortic stenosis; CABG, coronary artery bypass grafting; CI, confidence interval; EuroSCORE, European System for Cardiac Operative Risk Evaluation; HR, hazard ratio; LV, left ventricle; LVEF, LV ejection fraction; NOTION, Nordic Aortic Valve Intervention; OR, odds ratio; PAR, paravalvular aortic regurgitation; PARTNER, Placement of Aortic Transcatheter Valves; PMI, permanent pacemaker implantation; RCT, randomized controlled trial; RR, risk ratio; SAVR, surgical aortic valve replacement; STACCATO, prospective, randomized trial of transapical transcatheter aortic valve implantation vs. surgical aortic valve replacement in operable elderly patients with aortic stenosis; STS-PROM, Society of Thoracic Surgeons Predicted Risk of Mortality; TAVI, transcatheter aortic valve implantation.

☆ All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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propensity-score analysis including matching, stratification, and covariate adjustment is a powerful tool to strengthen causal inferences drawn from observational studies [13]. Especially, propensity-score matching is superior at reducing bias compared with stratification and covariate adjustment [14]. To determine whether TAVI improves (or impairs) follow-up overall survival compared with SAVR, we performed a meta-analysis of observational studies with a propensity-score analysis and another meta-analysis of RCTs. Furthermore, discrepancy (if it exists) between the results of the former and the latter would be discussed.

2. Methods

All observational studies with a propensity-score analysis and RCTs, which compared follow-up overall survival after TAVI versus SAVR for severe AS, were identified using a two-level search strategy. First, databases including MEDLINE and EMBASE were searched through October 2015 using Web-based search engines (PubMed and OVID). Search terms for observational studies with a propensity-score analysis included *percutaneous*, *transcatheter*, *transluminal*, *transarterial*, *transapical*, *transaortic*, *transcarotid*, *transaxillary*, *transsubclavian*, *transiliac*, *transfemoral*, or *transiliofemoral*; *aortic valve*; and *propensity*. Second, relevant studies were identified through a manual search of secondary sources including references of initially identified articles and a search of reviews and commentaries. All references were downloaded for consolidation, elimination of duplicates, and further analysis. Studies considered for inclusion met the following criteria: the design was an observational comparative study with a propensity-score analysis; the study population was patients with severe AS; patients were assigned to TAVI versus SAVR; and outcomes included follow-up (≥6-month) overall survival or all-cause mortality.

A hazard ratio (HR) with its 95% confidence interval (CI) of follow-up (including early) all-cause mortality for TAVI versus SAVR was abstracted from each individual study. For studies that did not report an HR with corresponding variance, this was calculated from Kaplan–Meier curve data or summary data (observed numbers of events on each arm and a log-rank, Mantel Haenszel, or even Cox regression p value) using a HR calculations spreadsheet provided by Tierney et al. [15] based on statistical methods reported by Parmar et al. [16] and Williamson et al. [17]. A result from propensity-score matching was preferentially extracted rather than that from propensity-score adjustment or stratification. Study-specific estimates were combined using inverse variance-weighted averages of logarithmic HRs in the random-effects model.

Sensitivity analyses were performed to assess the contribution of each study to the pooled estimate by excluding individual studies one at a time and recalculating the pooled HR estimates for the remaining studies. Publication bias was assessed graphically using a funnel plot and mathematically using an adjusted rank correlation test of Begg and Mazumdar [18] and a linear regression test of Egger and colleagues [19]. A maximum likelihood random-effects meta-regression analysis was performed to determine whether the effect of TAVI was modulated by the pre-specified factors, i.e., the mean logistic European System for Cardiac Operative Risk Evaluation (EuroSCORE) (%), Society of Thoracic Surgeons Predicted Risk of Mortality (STS-PROM) (%), and follow-up duration (year). A meta-regression graph depicts the effect of TAVI on the outcome (plotted as a logarithmic HR on the *y*-axis) as a function of a given factor (plotted as a mean of that factor on the *x*-axis). A meta-regression coefficient (slope of the meta-regression line) shows the estimated increase in logarithmic HR per unit increase in the covariate. Since logarithmic HR >0 corresponds to HR >1 and logarithmic HR <0 corresponds to HR <1, a negative coefficient would indicate that as a given factor increases, the HR decreases, i.e., TAVI is more beneficial in reducing the outcome of interest.

Search terms for RCTs included *percutaneous*, *transcatheter*, *transluminal*, *transarterial*, *transapical*, *transaortic*, *transcarotid*, *transaxillary*, *transsubclavian*, *transiliac*, *transfemoral*, or *transiliofemoral*; *aortic valve*; and *randomized*, *randomly*, or *randomization*. Eligible studies were RCTs of TAVI versus SAVR enrolling patients with severe AS and reporting follow-up (≥3-month) overall survival or all-cause mortality as an outcome.

All analyses were conducted using Review Manager version 5.3 (available from http://tech.cochrane.org/revman) and Comprehensive Meta-Analysis version 3 (Biostat, Englewood, NJ).

3. Results

As outlined in Supplemental Fig. S1, our search identified 19 observational studies with a propensity-score analysis [20–38] enrolling a total of 6234 patients (Tables 1 and 2). Of them, merely 3 studies [26,32,34] used propensity-score covariate adjustment, and the other 16 did propensity-score matching. We were able to abstract a HR with its 95% CI directly from 5 studies [28,30,32,35,36] and calculated it from the Kaplan–Meier curve or summary data in the other 14 studies. All studies were at high risk of detection bias (blinding of outcome assessment) because of their non-randomized and observational nature.

Three [28,31,37] of the 19 studies demonstrated a statistically significant benefit of SAVR over TAVI for follow-up all-cause mortality. The arithmetic means of 1-year and 3-year survival rates were 82.7% and 71.3% after TAVI and 84.8% and 77.9% after SAVR, respectively (Table 2). A pooled analysis of all the 19 studies demonstrated a statistically significant 21% increase in mortality with TAVI relative to SAVR (HR, 1.21; 95% CI, 1.05 to 1.39; $p = 0.010$; Fig. 1). To assess the impact of qualitative heterogeneity in study design and patient selection on the pooled effect estimate, we performed several sensitivity analyses. First, excluding merely one study [24] that exclusively enrolled dialysis patients and combining the remaining 18 studies demonstrated still a statistically significant benefit for SAVR (HR, 1.24; 95% CI, 1.06 to 1.44; $p = 0.006$; Fig. 2). Second, eliminating 3 studies [23,27,31] that compared TAVI with sutureless AVR and pooling the remaining 16 studies generated an attenuated but still statistically significant result favoring SAVR (HR, 1.16; 95% CI, 1.01 to 1.33; $p = 0.031$; Supplemental Fig. S2). Third, excluding 4 studies [29,32,37,38] that enrolled exclusively patients with previous cardiac surgery and combining the remaining 15 studies demonstrated an attenuated but still statistically significant result favoring SAVR (HR, 1.17; 95% CI, 1.01 to 1.35; $p = 0.037$; Supplemental Fig. S3). Fourth, eliminating 3 studies [26,32,34] that used propensity-score covariate adjustment and pooling the remaining 16 studies that applied propensity-score matching generated still a statistically significant benefit for SAVR (HR, 1.23; 95% CI, 1.05 to 1.46; $p = 0.013$; Supplemental Fig. S4). Fifth, excluding 2 studies [12,30] with <1-year follow-up and combining the remaining 17 studies with mid- to long-term (≥1-year) follow-up demonstrated still a statistically significant benefit for SAVR (HR, 1.22; 95% CI, 1.04 to 1.44; $p = 0.013$; Supplemental Fig. S5). Sixth, exclusion of any single study from the meta-analysis did not substantively alter the overall result favoring SAVR (Fig. 2). In a study by Wendt et al. [37], we calculated a statistically significant HR of 2.12 (95% CI, 1.16 to 3.85) for TAVI versus SAVR from survival curves (illustrating "p < 0.001" in a figure) of the propensity-score matched groups using the spreadsheet of Tierney et al. [15] and then inputted it into the meta-analysis.However, the authors of the original article [37] reported in the text a statistically non-significant HR of 0.651 (95% CI, 0.257 to 1.651; $p = 0.36$) for SAVR versus TAVI (corresponding to a HR of 1.535 [95% CI 0.606 to 3.891] for TAVI versus SAVR) using the Cox's proportional hazards regression model adjusted for the propensity score. Finally, inputting the non-significant HR of 1.535 (instead of the significant HR of 2.12) into the meta-analysis generated an attenuated but still statistically significant result favoring SAVR (HR, 1.17; 95% CI, 1.02 to 1.33; $p = 0.03$).

To assess publication bias, we generated a funnel plot of the logarithm of effect size (HR) versus the precision (reciprocal of standard error) for each study (Fig. 3). There was no evidence of significant