A meta-analysis of adjusted observational studies for mortality in transapical versus transfemoral aortic valve implantation

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ARTICLE INFO

Article history:
Received 28 February 2014
Accepted 29 March 2014
Available online 8 April 2014

Keywords:
Aortic stenosis
Meta-analysis
Transapical transcatheter aortic valve implantation
Transcatheter aortic valve implantation
Transfemoral transcatheter aortic valve implantation

Transcatheter aortic valve implantation (TAVI) for severe aortic stenosis (AS) can be performed using several approaches including a retrograde transfemoral (TF), transsubclavian, transaortic, or antegrade transapical (TA). The most-used approach for TAVI is the TF retrograde route because it is minimally invasive and it is feasible under conscious sedation in a totally percutaneous fashion [1]. TA-TAVI becomes the procedure of choice in instances where patients have excessive atherosclerotic disease of the iliofemoral vessels and aorta, and peripheral access is not feasible [2]. To the best of our knowledge and belief, despite the increasing number of studies comparing mortality in TA- versus TF-TAVI, all of them are observational studies, neither randomized controlled trials nor propensity score matched studies. Further, most studies compared unadjusted mortality and reported inconclusive results. A number of studies, however, used a multivariable regression analysis to identify independent predictors of mortality. To determine which procedure achieves better survival, TA- or TF-TAVI for AS, we perform a meta-analysis of "adjusted" observational studies using a multivariable regression analysis.

To identify all adjusted observational studies of TA- versus TF-TAVI enrolling patients with AS, MEDLINE and EMBASE were searched through October 2013 using PubMed and OVID. Search terms included *aortic*, *valve*, *transfemoral*, and *transapical*. Eligible studies were observational studies of TA- vs TF-TAVI enrolling patients with AS and using a multivariable logistic and/or Cox proportional regression analysis to identify independent predictors of perioperative (30-day or in-hospital) and midterm (≥6-month) all-cause mortality. An adjusted odds and/or hazard ratio (OR/HR) for perioperative and/or midterm mortality was abstracted from each individual study. To combine more data, when an adjusted OR/HR in a multivariable regression model was unavailable because of statistical non-significance, we abstracted a statistically non-significant OR/HR in a univariable model. Study-specific estimates were combined using inverse variance-weighted averages of logarithmic ORs/HRs in both fixed- and random-effects models. 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 OR/HR estimates for the remaining studies. Publication bias was assessed graphically using a funnel plot and mathematically using a linear regression test. Mixed-effects (unrestricted maximum likelihood) meta-regression analyses were performed to determine whether the effects of TA-TAVI on midterm mortality were modulated by the pre-specified factors: i.e. mean age (years), logistic European System for Cardiac Operative Risk Evaluation (EuroSCORE) (%), and follow-up duration (month); and proportion (%) of men and patients with peripheral vascular disease (PVD). All analyses were conducted using Review Manager version 5.2 (Nordic Cochrane Centre, Copenhagen, Denmark) and Comprehensive Meta-Analysis version 2 (Biostat, Englewood, NJ).

Our search identified 19 reports [3–21] of 18 eligible studies enrolling a total of 6606 patients with AS. The study characteristics, patient profiles, and risk estimates of mortality are summarized in Table 1. A pooled analysis of 9 studies demonstrated a statistically significant 61% increase in perioperative (30-day) all-cause mortality with TA- relative to TF-TAVI in the fixed-effects model (OR, 1.61; 95% confidence interval [CI], 1.21–2.13; $P = 0.0009$; Fig. 1A). A pooled analysis of 12 studies demonstrated a statistically significant 25% increase in midterm (6–-42 months) all-cause mortality with TA- relative to TF-TAVI in the fixed-effects model (HR, 1.25; 95% CI, 1.09–1.44; $P = 0.002$; Fig. 1B). There was minimal trial heterogeneity and accordingly little difference in the pooled results from random-effects modeling. Exclusion of any single study from the analysis did not substantively alter the overall results of our analysis (Fig. 2A and B). To assess publication bias we generated a funnel plot of the logarithm of effect size vs the precision (reciprocal of standard error) for each study (Fig. 3A and B). There was no evidence of significant publication bias ($P = 0.90/0.09$ for perioperative/midterm mortality, respectively). The meta-regression coefficient was not statistically significant for mean age ($P = 0.27$), logistic EuroSCORE ($P = 0.22$) and follow-up duration ($P = 0.11$); and proportion of patients with PVD ($P = 0.24$). That for proportion of men, however, was significantly positive (0.04111; 95% CI, 0.00175–0.08047; $P = 0.04$; Fig. 4).

The results of our analysis suggest that TA-TAVI may be associated with worse perioperative and midterm all-cause mortality than TF-TAVI, which was robust in sensitivity analyses without publication bias. One of meta-regression analyses would indicate that as proportion of men increases, TF-TAVI is more beneficial in reducing midterm mortality. Results of the following adjusted observational studies [22–25] and meta-analysis [26] could explain the survival benefit for TF- over TA-TAVI demonstrated in the present meta-analysis. TA-TAVI was the only independent predictor of a higher rise in creatine kinase-MB and one of the independent predictors of a higher rise in cardiac troponin T (cTnT) following the procedure, and the degree of increase in cTnT was identified as the independent predictor of cardiac mortality at 9 ± 10 months of follow-up [22]. TA access was also identified as one of independent predictors of peri-procedural life-threatening or disabling (LT/D) bleeding [23] and those for development of serious (either LT/D or major) bleeding [24], and occurrence of LT/D event independently predicted all-cause mortality during the first year following TAVI [24]. Further, the only independent predictor of acute kidney injury (AKI) was TA access, and one of the independent predictors of 1-year death was post-

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

Table 1
Study characteristics, patient profiles and risk estimates for mortality.

Study	Patient (n)		Prosthesis		Age (year)		Men (%)		PVD (%)	
	TA	TF	TA	TF	TA	TF	TA	TF	TA	TF
Amabile [3]	29	97	SAPIEN	SAPIEN, 85.6%; CoreValve, 14.4%	83.2 ± 6.3		41		32	
Dworakowski [4]	84	67	SAPIEN		82.2 ± 0.8	83 ± 0.8	46.4	64.2	35.7	10.4
FRANCE [5]	71	161	SAPIEN	SAPIEN, 59.0%; CoreValve, 41.0%	82.1 ± 7.3	SAPIEN, 83.2 ± 7.3; CoreValve, 82.5 ± 5.9	64.3	53.4	11.3[b]	4.3[b]
FRANCE 2 [6]	567	2361	SAPIEN XT	SAPIEN XT, 65.2%; CoreValve, 34.8%	81.5 ± 7.4	83.0 ± 7.2	58.6	47.4	48.1	12.5
Godino [7]	15	107	SAPIEN	SAPIEN, 57.0%; CoreValve, 43.0%	78.8 ± 6.5	79.7 ± 7	33.3	52.3	66.7	24.3
Gurvitch [8]	101	169	N/A		81 ± 7	83 ± 12	37	59	66	16
Hayashida [9]	83	169	Edwards[c]	Edwards[c], 81.7%: CoreValve 18.3%	83.1 ± 6.3[d]		34.1	46.7	33.5[d]	
Hemmann [10]	152	274	SAPIEN	SAPIEN, 32%; CoreValve, 68%	81 ± 7	80 ± 8	46	48	59	41
Himbert [11]	24	51	SAPIEN		82 ± 10	82 ± 7	66.7	49.0	29.2	7.8
Mok [12]	194[e]	125	SAPIEN, 57.4%; SAPIEN XT, 38.9%; SAPIEN 3, 2.5%; PORTICO, 1.3%		80 ± 8		46.1		34.8	
Rodés-Cabau [13] Rodés-Cabau [14]	177	162	Cribier, SAPIEN, SAPIEN XT		80 ± 8	83 ± 8	34.5	56.1	50.3	19.1
Schymik [15]	126	174	SAPIEN	SAPIEN, 75.3%; CoreValve, 24.7%	81 ± 6	82 ± 5	38.9	36.2	28.6	12.3
Seiffert [16]	177	149	SAPIEN, SAPIEN XT	SAPIEN/SAPIEN XT, 69.8%; CoreValve, 30.2%	Mean, 80.5 (95% CI, 79.5–81.5)	SAPIEN/SAPIEN XT, mean, 81.6 (95% CI, 79.983.3); CoreValve, mean, 78.2 (95% CI, 75.9–80.5)	43.5	45.6	52.5[g]	22.1[g]
Spargias [17]	32	59	SAPIEN	SAPIEN, 59.3%; SAPIEN XT, 13.6%; CoreValve, 27.1%	81 ± 7	82 ± 5	38	31	37	27
Watanabe [18]	114	249	Edwards	CoreValve	83.1 ± 6.4[h]		50.3[h]		33 1[h]	
Webb [19]	55	113	Cribier, SAPIEN, SAPIEN XT		Median, 83 (IQR, 76–87)	Median, 85 (IQR, 79–88)	40.0	57.5	76.4	15.9
Wenaweser [20]	43	27	SAPIEN		78.1 ± 9.6	83.9 ± 4.0	55.8	40.7	39.5	11.1
Zhao [21]	20	28	SAPIEN, 20.8%; SAPIEN XT,		82.3 ± 5.0	83.4 ± 7.9	64.0	46.4	40.0	25.0

CI, confidence interval; EuroSCORE, European System for Cardiac Operative Risk Evaluation; HR, hazard ratio; IQR, interquartile range; LLCI, lower limit of 95% CI; N/A, not available; OR, odds ratio; PE, point estimate; PVD, peripheral vascular disease; RE, risk estimate; STS-PROM, Society of Thoracic Surgeons Predicted Risk of Mortality; TA, transapical; TF,, ULCI, upper limit of 95% CI.

[a] HR for cardiovascular death.
[b] Previous peripheral artery disease surgery.
[c] Previous peripheral artery disease surgery.
[d] Including 8 transsubclavian (TS) patients.
[e] Including transapical (TAo) patients.
[f] Updating Rodés-Cabau et al. [131] with longer follow-up.
[g] Extracardiac arteropathy.
[h] Including TS (n = 9) and TAo (n = 81) patients.