Meta-Analysis of Effectiveness and Safety of Transcatheter Aortic Valve Implantation Versus Surgical Aortic Valve Replacement in Low-to-Intermediate Surgical Risk Cohort

Tomo Ando, MD[a,*], Said Ashraf, MD[a], Pedro Villablanca, MD, MSc[b], Toshiki Kuno, MD[c], Mohit Pahuja, MD[a], Mohamed Shokr, MD[a], Luis Afonso, MD[a], Cindy Grines, MD[d], Alexandros Briasoulis, MD, PhD[e], and Hisato Takagi, MD, PhD[f]

Transcatheter aortic valve implantation (TAVI) has been used to treat high surgical risk cohorts but has been expanded to treat low-to-intermediate risk cohort as well. We performed a systematic review and meta-analysis to compare the outcomes between TAVI and surgical aortic valve replacement (SAVR) in low-to-intermediate risk cohort. We queried PUBMED, EMBASE, and ClinicalTrial.gov for relevant articles. Randomized controlled trials that compared at least one of the outcomes of interest between TAVI and SAVR were included. Risk ratio (RR) and 95% confidence interval (CI) were pooled with a random-effects model to compare the risk of the primary outcome between the 2 procedures. The primary outcome was a composite of all-cause mortality or disabling/major stroke at 1 year. Seven studies with a total of 7,143 patients (3,665 TAVI) were included. All-cause mortality or disabling/major stroke at 30 days (6 studies, RR 0.71, 95% CI 0.49 to 1.03) was similar between TAVI and SAVR but was significantly lower in TAVI at 1 year (5 studies, RR 0.81, 95% CI 0.67 to 0.98). All-cause mortality was similar at both 30 days (7 studies, RR 0.90, 95% CI 0.67 to 1.21) and 1 year (6 studies, RR 0.89, 95% CI 0.76 to 1.04). Disabling/major stroke was similar between the 2 procedures (6 studies, RR 0.69, 95% CI 0.42 to 1.12) at 30 days but was significantly lower in TAVI at 1 year (5 studies RR 0.71, 95% CI 0.51 to 0.98). Age, gender, diabetes, and surgical risk score did not modulate the primary outcome. TAVI had a significantly lower composite of all-cause mortality or disabling/major stroke at 1 year compared with SAVR in low-to-intermediate surgical risk cohort. **(Am J Cardiol 2019;124:580−585)**

Transcatheter aortic valve implantation (TAVI) is a class IIa recommendation for intermediate surgical risk and there is no recommendation for low surgical risk patients. Surgical aortic valve replacement (SAVR) is a class I for low, intermediate, and high surgical risk patients.[1] Low-to-intermediate surgical risk patients comprised >90% of candidates for aortic valve replacement.[2] Therefore, it is important to compare the outcomes of TAVI and SAVR in this cohort. Recently, 2 trials have been published that compared outcomes between TAVI and SAVR in low-risk patients.[3,4] Our aim was to compare TAVI versus SAVR outcomes in low-to-intermediate surgical risk candidates that vast majority belong to with severe aortic stenosis requiring intervention. We hypothesized that TAVI confers similar clinical outcomes compared with SAVR.

Methods

A comprehensive online database search (PUBMED, EMBASE, and ClinicalTrial.gov) was performed from January 1, 2002 to March 20, 2019. The search term was (TAVI OR TAVR OR transcatheter aortic valve replacement OR TAVI OR percutaneous aortic valve replacement OR percutaneous aortic valve intervention OR aortic valve replacement OR aortic valve intervention) and (random OR randomized OR randomization OR randomized OR randomization). Two authors (TA and SA) independently searched the online database. Any disagreement was resolved through discussion. The third author (HT) was consulted when an agreement was not met between these 2 authors. We did not apply language restriction. First, the title of the manuscript was screened for potential eligibility to our study purpose and if considered relevant, an abstract was carefully read to assess for further consideration to evaluate the full manuscript. Full manuscripts were obtained after the final list of included studies was made. Reference list of finally included manuscripts was manually searched for further screening of relevant articles. No contact was made to the corresponding author when the study did not report outcomes of interest. This systematic

[a]Wayne State University/Detroit Medical Center, Detroit, Michigan; [b]Henry Ford Hospital, Detroit, Michigan; [c]Mount Sinai Beth Israel, New York, New York; [d]North Shore University Hospital, Hofstra Northwell School of Medicine, Manhasset, New York; [e]University of Iowa Hospitals and Clinics, Iowa, Iowa; and [f]Shizuoka Medical Center, Shizuoka, Japan.
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*Corresponding author: Tel: 313-745-2620; fax: 313-745-8643.
E-mail address: andotomo@hotmail.co.jp (T. Ando).

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review and meta-analysis was performed in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guideline.[5]

Inclusion criteria were as follows: (1) study design was a randomized controlled trial; (2) the primary outcome or at least one of the secondary outcomes were compared between TAVI and SAVR; (3) patients were at low or intermediate surgical risk assessed by mean or median perioperative risk of death <8% in both TAVI and SAVR. Exclusion criteria were as follows: (1) nonrandomized study design, review articles, or case reports; (2) outcome of interest was not reported; (3) a substudy of a randomized controlled trial; (4) abstracts presented at conferences not published yet in peer-reviewed journals.

The primary outcome was a composite of all-cause mortality or disabling/major stroke at 1 year. Secondary outcomes were all-cause mortality or disabling/major stroke at 30 days, all-cause mortality at 30 days and 1 year and disabling/major stroke at 30 days and at 1 year. The quality of included studies was evaluated by 2 authors (TA and SA) independently with the Cochrane risk of bias tool.

The Review Manager (RevMan) Version 5.3 (Nordic Cochrane Centre, the Cochrane Collaboration, 2012, Copenhagen, Denmark) software was used to calculate the pooled effect size with risk ratio (RR) and 95% confidence intervals (CI) by Mantel-Haenszel method. Event numbers were extracted from the studies and calculated from the percentages if not provided. Cohort number and data were extracted from the planned type of analysis in each trial (intention to treat or as-treated analysis). For example, when the study was planned to examine the outcomes in intention to treat analysis, the cohort and event numbers were abstracted from that cohort. Random-effects model was used to pool the RR and estimate 95% CI in every outcome regardless of the heterogeneity among studies as it allows more conservative assessment of the pooled effect size. A fixed-effect model was also checked for every outcome as a sensitivity analysis. Significant heterogeneity was considered to be present when the I^2 index was over 50% or p for heterogeneity was <0.05. A sensitivity analysis was performed with pooling data extracted from only the as-treated population for every outcome. For the primary outcome, a subgroup analysis was performed based on the valve type (balloon expandable vs self-expandable) and surgical risk score (mean surgical risk score above or below 4). A meta-regression analysis was performed to assess whether age, male gender, diabetes, atrial fibrillation, or surgical risk score modulated the primary outcome. The funnel plot was visually speculated for asymmetry and "trim and fill" method was used to calculate the RR and 95% CI to account for funnel plot asymmetry. Comprehensive Meta-Analysis version 2 (Biostat, Englewood, New Jersey) was used to perform the "trim and fill" method. A p value of <0.05 was considered significant.

Results

Figure 1 shows the study selection flow chart. Seven randomized controlled trials were identified.[3,4,6–10] The STACCATO trial randomized patients to transapical TAVI or SAVR. The US CoreValve study was intended to recruit high surgical risk patients but the mean Society of Thoracic Surgeons score was <8 in both groups and therefore was included in our analysis. The NOTION trial randomized all-comers regardless of the patients' perioperative risk score but was included because the perioperative risk was low in both arms, approximately 3.0. The PARTNER 2 and the SURTAVI trials both randomized patients at intermediate surgical risk into TAVI or SAVR. The PARTNER 3 and the Evolut Low-Risk trials both randomized patients considered at low surgical risk. Patient characteristics of the included studies are summarized in Table 1. Two studies[6,7] used the Valve Academic Research Consortium[11] and 5 studies[3,4,8–10] used the Valve Academic Research Consortium 2 criteria[12] to define major and disabling stroke, respectively.

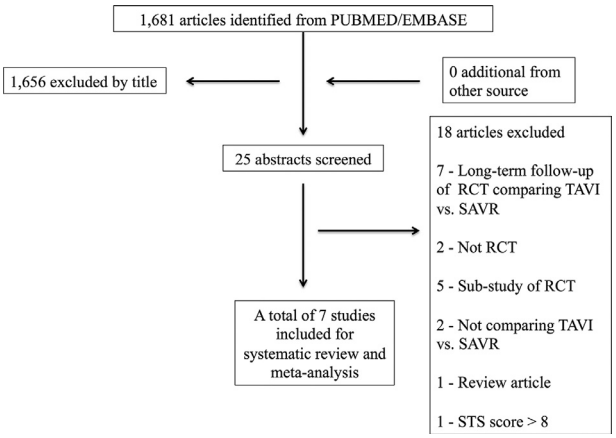

Figure 1. Study selection flow chart.

TAVI had significantly lower all-cause mortality or disabling/major stroke at 1 year (5 studies, 8.7% vs 10.7%, RR 0.81, 95% CI 0.67 to 0.98, p = 0.03, $I^2 = 29\%$; Figure 2). Subgroup analysis with the self-expandable valves showed consistent results (3 studies, 7.8% vs 9.8%, RR 0.79, 95% CI 0.64 to 0.96, p = 0.02, $I^2 = 0\%$), whereas there was no significant difference when studies that used only the balloon-expandable valves were analyzed (2 studies, 10.0% vs 11.7%, RR 0.65, 95% CI 0.26 to 1.60, p = 0.35, $I^2 = 69\%$). When studies with mean perioperative risk score between 4 and 8 were pooled, there was a trend toward benefit in TAVI compared with SAVR (3 studies, 12.3% vs 14.2%, RR 0.87, 95% CI 0.75 to 1.01, p = 0.06, $I^2 = 0\%$). When only studies with perioperative risk score <4 were pooled, TAVI had a significantly lower risk for the primary outcome compared with SAVR (2 studies, 2.1% vs 3.9%, RR 0.56, 95% CI 0.34 to 0.90, p = 0.02, $I^2 = 0\%$). A meta-regression analysis showed that age, gender, perioperative risk score, diabetes, and atrial fibrillation did not significantly modulate the primary outcome (Table 2).

There was a trend toward favorable outcome with TAVI for all-cause or disabling/major stroke at 30 days (6 studies, 3.5% vs 4.8%, RR 0.71, 95% CI 0.49 to 1.03, p = 0.07, $I^2 = 41\%$). There were no differences in all-cause mortality at 30 days (7 studies, 2.3% vs 2.6%, RR 0.90, 95% CI 0.67 to 1.21, p = 0.49, $I^2 = 0\%$) and at 1 year (6 studies, 7.3% vs 8.3%, RR 0.89, 95% CI 0.76 to 1.04, p = 0.16, $I^2 = 0\%$). The risk of disabling/major stroke at 30 days was

Table 1
Summary of included studies

Study	Cohort		Age		Male		Surgical risk score	
	TAVI	SAVR	TAVI	SAVR	TAVI	SAVR	TAVI	SAVR
STACCATO	34	36	80 ± 3.6	82 ± 4.4	26.5%	33.3%	3.1 ± 1.5%	3.4 ± 1.2%
CoreValve US study	390	357	83.1 ± 7.1	83.2 ± 6.4	53.1%	52.4%	7.3 ± 3.0%	7.5 ± 3.4%
NOTION	145	135	79.2 ± 4.9	79.0 ± 4.7	53.8%	52.6%	2.9 ± 1.6%	3.1 ± 1.7%
PARTNER 2	1,011	1,022	81.5 ± 6.7	81.7 ± 6.7	54.2%	54.8%	5.8 ± 2.1%	5.8 ± 1.9%
SURTAVI	864	796	79.9 ± 6.2	79.7 ± 6.1	57.6%	55.0%	4.4 ± 1.5%	4.5 ± 1.6%
Evolut low-risk	725	678	74.1 ± 5.8	73.6 ± 5.9	64.0%	66.2%	1.9 ± 0.7%	1.9 ± 0.7%
PARTNER 3	496	454	73.3 ± 5.8	73.6 ± 6.1	67.5%	71.1%	1.9 ± 0.7%	1.9 ± 0.6%

Study	Prior stroke		Diabetes		Atrial fibrillation		Renal insufficiency	
	TAVI	SAVR	TAVI	SAVR	TAVI	SAVR	TAVI	SAVR
STACCATO	NR	NR	2.9%	8.3%	NR	NR	*2.9%	*0%
CoreValve US study	12.6%	14.0%	34.9%	45.4%	40.9%	45.9%	**12.2%	**12.8%
NOTION	NR	NR	17.9%	20.7%	27.8%	25.6%	*1.4%	*0.7%
PARTNER 2	NR	NR	37.7%	34.2%	31.0%	35.2%	*5.0%	*5.2%
SURTAVI	6.6%	7.2%	34.1%	34.8%	28.1%	26.5%	*1.6%	*2.1%
Evolut low-risk	NR	NR	31.4%	30.5%	15.4%	14.5%	*0.4%	*0.1%
PARTNER 3	3.4%	5.1%	31.2%	30.2%	15.7%	18.8%	*0.2%	*0.2%

NOTION = Nordic Aortic Valve Intervention; NR = not reported; PARTNER = Placement of Aortic Transcatheter Valve; SAVR = surgical aortic valve replacement; STACCATO = Transapical Transcatheter Aortic Valve Implantation versus Surgical Aortic Valve Replacement in Operable Elderly Patients with Aortic Stenosis; SURTAVI = Surgical Replacement and Transcatheter Aortic Valve Implantation; TAVI = transcatheter aortic valve implantation.

* Creatinine level >2.0 mg/dl.

** Estimated glomerular filtration rate of <29 ml/min.

comparable between TAVI and SAVR (6 studies, 1.8% vs 2.7%, RR 0.69, 95% CI 0.42 to 1.12, p = 0.13, $I^2 = 38\%$) but 1-year disabling/major stroke was significantly reduced in TAVI (5 studies, 2.8% vs 3.9%, RR 0.71, 95% CI 0.51 to 0.98, p = 0.04, $I^2 = 24\%$; Supplementary Figure 1A to E). When STACCATO trial was removed, all-cause mortality or disabling/major stroke (RR 0.70, 95% CI 0.52 to 0.94, p = 0.02, $I^2 = 21\%$) at 30 days was significantly lower in TAVI but disabling/major stroke (RR 0.65, 95% CI 0.41 to 0.1.04, p = 0.07, $I^2 = 36\%$) and all-cause mortality (RR 0.90, 95% CI 0.67 to 1.21, p = 0.49, $I^2 = 0\%$) at 30 days remained consistent.

Overall, the included studies were low risk for biases. The results are summarized in Supplementary Table 1. Funnel plots were visually assessed for every outcome (Supplementary Figure 2A to F). It raised suspicion for asymmetry in 1-year all-cause mortality or disabling/major stroke, 30-day all-cause mortality, 1-year all-cause mortality, and 1-year disabling/major stroke. The RR and 95% CI after trim and fill method were as follows: all-cause mortality or disabling/major stroke (2 studies trimmed, RR 0.86, 95% CI 0.70 to 1.06), 1-year all-cause mortality (3 studies trimmed, RR 0.97, 95% CI 0.80 to 1.18), and 1-year disabling/major stroke (2 studies trimmed, RR 0.79, 95% CI 0.54 to 1.16). The 30-day all-cause mortality was unchanged.

When only the as-treated population and events were pooled, results were consistent except that 30-day all-cause mortality or disabling/major strokes were significantly lower in TAVI (6 studies, 3.3% vs 4.7%, RR 0.69, 95% CI 0.49 to 0.97, p = 0.03, $I^2 = 33\%$; Supplementary Figure 3A to E). The all-cause mortality or disabling/major stroke at 1-year remained lower in TAVI (5 studies, 8.6% vs 10.8%, RR 0.80, 95% CI 0.68 to 0.94, p = 0.006, $I^2 = 14\%$; Figure 3).

Discussion

Our finding of lower all-cause mortality or disabling/major stroke rate in TAVI suggests that TAVI may be the

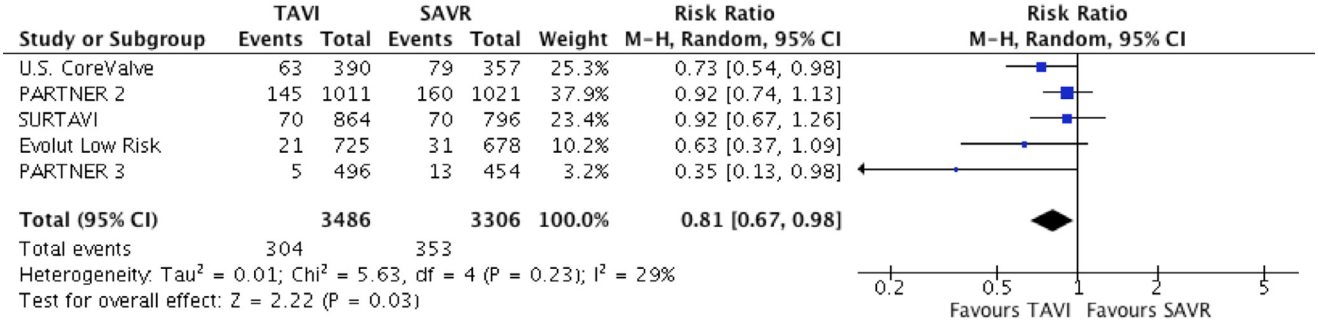

Figure 2. Forest plot of all-cause mortality or disabling/major stroke according to each study's primary analysis.

Table 2
Meta-regression analysis of the primary outcome

Variable	Number of studies	Slope	Lower limit	Upper limit	p value
Age	5	0.032	−0.025	0.090	0.27
Male	5	−0.028	−0.069	0.012	0.17
Diabetes	5	0.0048	−0.053	0.062	0.87
Perioperative risk score	5	0.028	−0.067	0.12	0.56
Atrial fibrillation	5	0.0032	−0.016	0.022	0.74

preferred approach in low-to-intermediate surgical risk patients. Several concerns although remain in TAVI before this shift in treatment. One of the issues is the valve durability but 2 studies have recently shed light on this issue. Blackman et al[13] reported a long-term structural valve degeneration post-TAVI (median 5.8 years, range 5 to 10 years) from the United Kingdom registry that showed 8.7% of moderate and 0.4% of severe valve degeneration. Søndergaard et al[14] reported that structural valve deterioration was significantly higher in SAVR (24.0% vs 4.8%) at 6 years. From these studies, the concern of valve durability in low-to-intermediate risk cohort is less for now. Another concern is the subclinical leaflet thrombosis that has been reported to be higher in TAVI than SAVR and possibly associated with worse outcomes.[15,16] Subclinical leaflet thrombosis has also been reported in 14% of the low-risk patients.[17] Although oral anticoagulations were effective in many cases, recent GALILEO trial, which randomized patients without atrial fibrillation into rivaroxaban or aspirin monotherapy after 3 months of dual therapy (rivaroxaban plus aspirin) or dual-antiplatelet (clopidogrel plus aspirin), was halted early due to higher adverse events in the rivaroxaban arm.[18] It still remains unclear whether routine surveillance of subclinical leaflet thrombosis is required and further study is warranted to determine the best antithrombotic and anticoagulation regimen post-TAVI.

Stroke remains to be a major perioperative issue with both TAVI and SAVR. The main mechanism of stroke in TAVI is considered to be debris embolization related to the procedure and therefore iteration of the valve itself has a limited role in decreasing the incident of perioperative strokes in TAVI. Perioperative stroke significantly increases the risk of mortality, compromise quality of life in survivors, and adds tremendous healthcare cost.[19–21] Given all the negative consequences of perioperative strokes mentioned, our findings suggest that TAVI could be the preferred strategy in low-to-intermediate risk patients. A recent analysis showed a reduced risk of periprocedural stroke with the use of the embolic protection device[22] and efforts should be made to use it especially in a high-risk group such as higher age, renal disease, porcelain aorta, peripheral artery disease, and previous stroke.[23] It is interesting that the difference was not detected at 30 days but was observed at 1 year, suggesting that the risk of disabling/major strokes was probably lower in TAVI during 30 days to 1 year. New-onset atrial fibrillation has been higher in SAVR in many studies[7–10] and the difference in antithrombotic regimens between post-TAVI and SAVR may account for lower stroke risk in TAVI.

There are several limitations to our meta-analysis. First, this was a meta-analysis of only the randomized controlled trials with strict inclusion and exclusion criteria. Therefore, our results may not be reproducible in patients excluded from the trials. However, a meta-analysis of randomized controlled trials could minimize biases and results could provide robust evidence. Second, the embolic protection device was used in the Evolut Low-Risk trial and could have affected our results. However, the proportion of its use was very low (1.2% in TAVI) and its impact on our outcomes could be minimal. Third, the NOTION trial was not included for the assessment of the primary outcome as it did not report 1-year all-cause mortality or disabling/major stroke. Fourth, the definition of disabling/major stroke was different between studies but it was either the Valve Academic Research Consortium or the Valve Academic Research Consortium 2 definitions. Fifth, the latest transcatheter devices could have positively affected the outcomes in the 2 low-risk trials. Lastly, the trim and fill method suggested that the primary outcome and 1-year disabling/major stroke could be similar between TAVI and SAVR. The asymmetry of funnel plot could be caused by reasons other than publication bias such as heterogeneity of the studies, reporting biases, artifact, and chances.[24] In

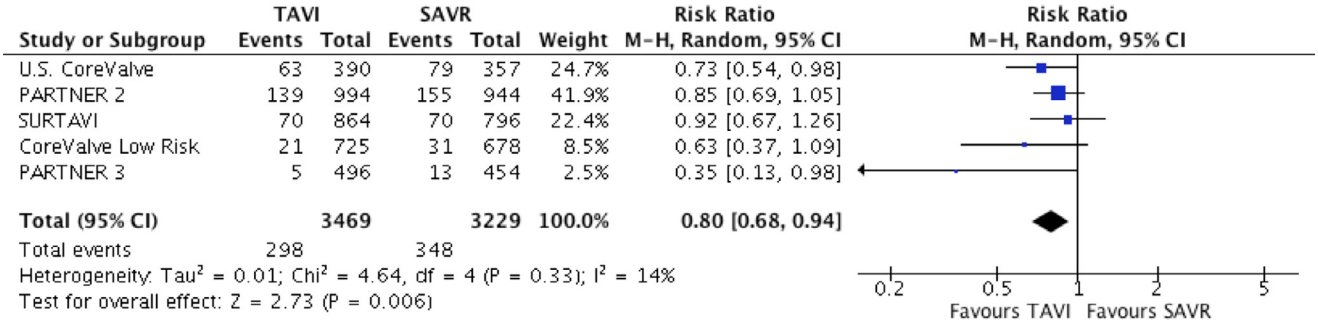

Figure 3. Forest plot of all-cause mortality or disabling/major stroke from as-treated population.

addition, the trim and fill method does not take into account the underlying reason for funnel plot asymmetry and is based on the strong assumption that the funnel plot should be symmetrical. Moreover, the calculated pooled estimate includes data with imputed intervention effect and results are often extremely difficult to interpret.[24]

In conclusion, TAVI had significantly lower all-cause mortality or disabling/major stroke and disabling/major stroke compared with SAVR in low-to-intermediate surgical risk patients at 1 year. Long-term comparative outcomes (>5 years) between TAVI and SAVR are warranted.

Disclosures

Tomo Ando holds stock of Edwards Lifesciences. Other authors have no conflicts of interest to disclose.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.amjcard.2019.05.017.

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