A Systemic Review and Meta-Analysis of Sutureless Aortic Valve Replacement Versus Transcatheter Aortic Valve Implantation

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Background. **Sutureless aortic valve replacement (SU-AVR) and transcatheter aortic valve implantation (TAVI) are increasingly adopted methods to treat high-risk patients with severe aortic valve stenosis. We conducted a systematic review and meta-analysis to compare the clinical outcomes between these two recent methods to treat aortic valve disease.**

Methods. **We systematically searched multiple databases (January 2000 to October 2016) to identify original studies comparing clinical outcome between SU-AVR and TAVI. End points studied were early mortality, development of paravalvular leak, early stroke, bleeding events, and the need for pacemaker insertion. A random-effect inverse-variance weighted analysis was performed. Event rates were compared as odds ratio (OR) and 95% confidence interval (CI).**

Results. **The meta-analysis included seven observational studies comprising 617 SU-AVR and 621 TAVI patients. Early mortality was 2.5% and 5% in the SU-AVR and TAVI cohorts, respectively (OR, 0.52; 95% CI, 0.30 to 0.90; $p = 0.02$; $I^2 = 2\%$). Postprocedural significant paravalvular leak was much lower after SU-AVR (OR, 0.18l; 95% CI, 0.11 to 0.30; $p < 0.0001$). Postprocedural stroke (OR, 0.71; 95% CI, 0.24 to 2.08; $p = 0.53$) and the need for pacemaker insertion (OR, 0.884; 95% CI, 0.364 to 2.18; $p = 0.7$) were comparable between the two cohorts.**

Conclusions. **Our meta-analysis of observational studies demonstrates that early mortality is lower after SU-AVR than after TAVI in selected patients. The rates of stroke and pacemaker implant are comparable between procedures; however, the incidence of paravalvular leak is higher after TAVI.**

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Aortic valve stenosis is the most common valvular heart disease in the elderly. Although surgical aortic valve replacement (AVR) is the standard therapy for severe aortic stenosis, transcatheter aortic valve implantation (TAVI) has already emerged as an excellent alternative for high-risk candidates [1]. Furthermore, the indication of TAVI has recently been expanded to intermediate-risk or even low-risk patients [2, 3]. On one hand, despite considerably improved outcomes of TAVI compared with surgical AVR, paravalvular leak (PVL) and pacemaker implantation still remain concerns with TAVI [4]. On the other hand, sutureless AVR (SU-AVR) is increasingly an attractive option because it combines a direct surgical approach with reduced cardiopulmonary bypass time, and an added benefit is the ease of use with minimally invasive approaches [5]. We performed a systematic review to present current evidence comparing the clinical outcome of TAVI and SU-AVR.

Patients and Methods

A systematic review of English language peer reviewed articles (January 2000 to October 2016) was performed using MEDLINE, Web of Science, Scopus, and the Cochrane Database. Our inclusion criteria were (1) original studies comparing adult patients with severe aortic valve stenosis undergoing SU-AVR and TAVI, (2) study should report at least one clinical end point in our meta-analysis, (3) all studies must be written in English, and (4) studies should include at least 10 patients in each arm. Editorials, case reports, letters to the editor, and other review articles were excluded. To ensure completeness, we manually searched the references of prospective articles.

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Abbreviations and Acronyms

AVR = aortic valve replacement
CI = confidence interval
NS = not significant
OR = odds ratio
PVL = paravalvular leak
RE = random effect
SU-AVR = sutureless aortic valve replacement
TAVI = transcatheter aortic valve implantation

End Points Studied

The primary end point was early (30-day) mortality. Secondary end points were early stroke, major bleeding episodes, need for pacemaker insertion, and significant PVL.

Analysis

Statistical analysis was performed using R 3.2.2 software (The R Foundation for Statistical Computing, Vienna, Austria). An inverse variance weighted random effect model was used to pool the odds ratio (OR) for each study and obtained the pooled result. Survival data were obtained from the hazard ratios reported in the study. If count data were present, ORs and their 95% confidence intervals (CIs) were calculated in lieu of the hazard ratio. When numerical data were not available, Kaplan-Meier survival curves were analyzed to obtain the hazard ratio using a well-validated method [6, 7].

Heterogeneity was studied from the calculated Egger I^2 value. Conventionally accepted cutoffs of less than 25%, 25% to 75%, and more than 75% were implemented as low, moderate, or high heterogeneity, respectively [8]. Publication bias was not addressed due to the small sample size ($n < 10$). Results are presented at the 95% confidence level.

Results

After duplicates were excluded, 48 relevant abstracts were identified from 92 initial search results for secondary review. Finally, seven observational comparative studies [4, 9–14] fulfilled our inclusion criteria (Fig 1). However, five studies [4, 9, 10, 13, 14] did provide propensity-matched data. In the SU-AVR cohort, the Perceval valve (Sorin Biomedica Cardio Srl, Sallugia, Italy) was used in five studies [4, 10, 11, 13, 14], and the Enable sutureless bioprosthesis (Medtronic Inc, Minneapolis, MN, USA) was used in two studies [9, 12]. For TAVI, four studies [10, 12–14] implemented the Sapien or Sapien XT (Edwards Lifesciences, Inc, Irvine, CA), and one study [11] used the CoreValve (Medtronic, Minneapolis, MN).

Patients in one study [10] were operated on through a right anterior minithoracotomy, and the other studies [4, 9, 11–14] used partial or complete sternotomy or right thoracotomy approaches among the SU-AVR patients. The transapical approach was used for the entire TAVI cohort in two studies [12, 14], and the transfemoral approach was used for the entire TAVI cohort in one study [11]. One study reported 1.3% of patients underwent TAVI through an alternative route [4]. Table 1 summarizes the preoperative demographics for the patients included in our review.

Early Mortality

Early mortality was reported in all of the included studies (Fig 2) [4, 9–14]. Early mortality was significantly lower in the SU-AVR patients compared with TAVI patients (OR, 0.52; 95% CI, 0.30 to 0.90; $p = 0.02$). The result also demonstrated lack of heterogeneity ($I^2 = 2\%$).

Postprocedural Stroke

Stroke rates were reported in all of the included studies [4, 9–14]. The stroke rates of SU-AVR and TAVI were 1.1% and 1.7%, respectively (OR, 0.71; 95% CI, 0.24 to 2.08; $p = 0.53$). The result again did not demonstrate any significant heterogeneity ($I^2 = 0\%$).

Significant PVL

This outcome was reported in all the included studies (Fig 3) [4, 9–14]. SU-AVR was associated with a significantly lower chance of PVL (OR, 0.18; 95% CI, 0.11 to 0.30; $p < 0.0001$). The pooled results did not demonstrate any heterogeneity ($I^2 = 0\%$; $p = 0.17$). Leave-one-out analysis demonstrated that three studies (Biancari and colleagues [4], Santarpino and colleagues [13], and D'Onofrio and colleagues [14]) were most influential in determining pooled results. The incidence of significant PVL was 11% in the TAVI and 1.5% in the SU-AVR cohort.

Pacemaker Implant

Conduction disturbances needing pacemaker implantation were reported in all of the included studies [4, 9–14]. The risk of a pacemaker implantation was comparable between the two cohorts (OR, 0.884, 95% CI, 0.364 to 2.18; $p = 0.7$). The result demonstrates moderate heterogeneity ($I^2 = 63\%$; $p = 0.01$). As demonstrated in the Galbraith plot (Fig 4), heterogeneity is predominantly due to two studies (Muneretto and colleagues [11] and D'Onofrio and colleagues [14]).

Table 2 reports the clinical outcome comparing SU-AVR with TAVI by the device used. In another study regarding outcomes by different devices (Enable vs Sapien, CoreValve) [9], PVL was also significantly high in TAVI groups. One study [13] compared procedural costs between SU-AVR with the Perceval valve and TAVI and reported that when cost of device and diagnostic testing were included, SU-AVR was more cost-effective than transcatheter-based therapy.

Comment

AVR has been considered to be the gold standard therapy for patients with severe aortic valve stenosis [15]. During the past few years, the outcomes of TAVI in

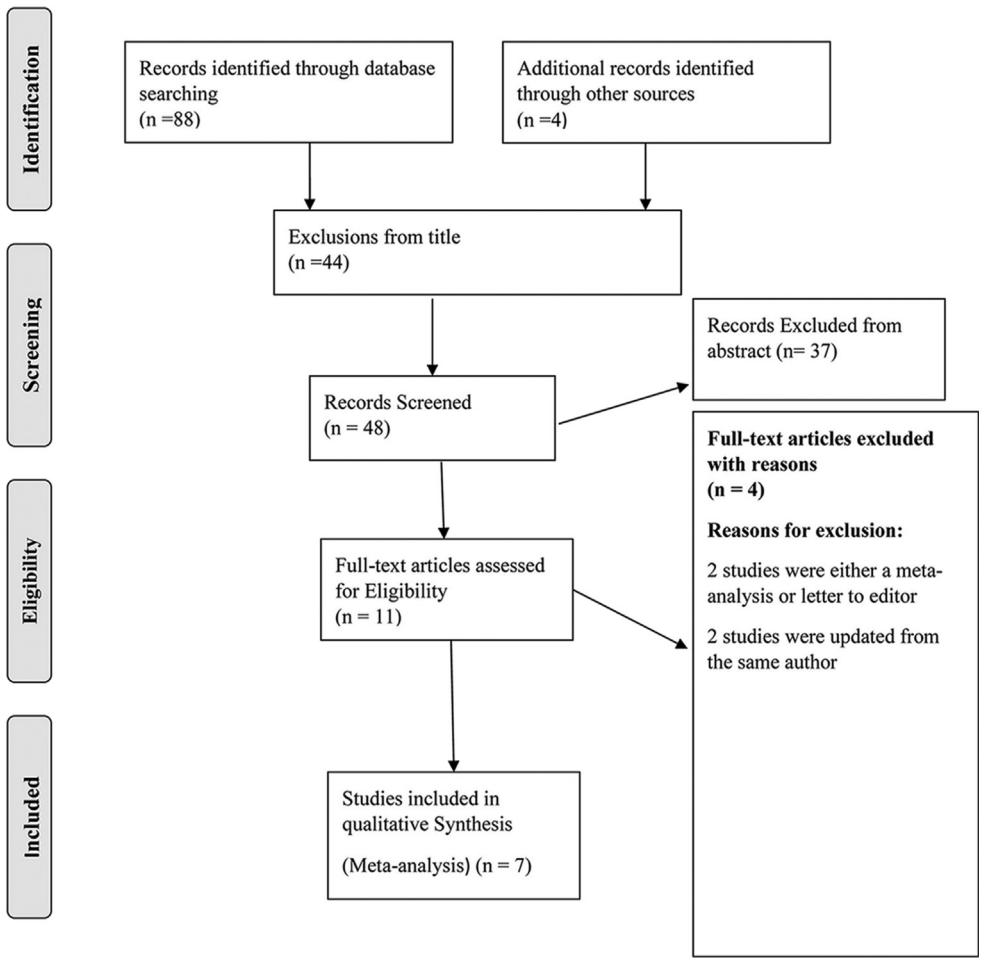

Fig 1. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses diagram demonstrates the selection process adopted in our study.

high-risk or inoperable patients have been widely reported in the literature, with a 30-day mortality of between 6% and 12% and a 1-year survival of approximately 80% [16]. On one hand, TAVI has some benefit with regards to early survival and functional status compared with surgical AVR [17] but still has drawbacks such as PVL and higher rate of pacemaker insertion [11]. On the other hand, SU-AVR offers the combination of valve excision and replacement with a short cardiopulmonary bypass time [18].

A prior meta-analysis demonstrated reduced mortality after SU-AVR rather than after TAVI [19]. Their conclusions are supported by our updated review. Because our data are based on observational retrospective analyses, one reason could likely be that very high-risk patients underwent TAVI rather than SU-AVR. Our meta-analysis included only retrospective observational studies; however, in the absence of randomized controlled trials, a propensity-matched study could be a robust alternative in this subject.

Our results also demonstrated that the rate of pacemaker insertion was comparable between the two groups (OR, 0.884; 95% CI, 0.364 to 2.18; $p = 0.7$). In general, the self-expandable nature of the sutureless bioprosthesis such as CoreValve leads to persistent compression of the conduction system and therefore results in the negative effect of conduction system such as left bundle branch block [14]. However, a balloon-expandable device, such as Sapien, does not expand after deployment and therefore has a little effect on damaging membranous septum or the conduction system of the heart [14]. In the TAVI cohort, Muneretto and colleagues [11], who implemented self-expandable valves in their study, reported the highest incidence of pacemaker implant in our pooled studies. Recent data support the increased need for pacemaker implant after self-expandable TAVI valves [20].

Significant PVL has always remained a concern after TAVI. Recent studies demonstrate that any degree of leak leads to poorer long-term survival [13]. Surgery decalcifies the annulus and hence naturally leads to a reduced risk for PVL [10], as shown in our results. Although the incidence of PVL has reduced with improvement in device technology, large real-world data confirming these results are still lacking. TAVI devices are also limited in their ability to be used for patients with a bicuspid aortic valve. SU-AVR therapy can be used for all patients with aortic stenosis.

Table 1. Preoperative Demographic Data for the Patients Included in Our Meta-Analysis

Study, Year	Country	Patients, No.		Age, Years		Male, %		Diabetes, %		Hypertension, %		Predicted Risk of Mortality	
		SU-AVR	TAVI	SU-AVR	TAVI	SU-AVR	TAVI	SU-AVR	TAVI	SU-AVR	TAVI	SU-AVR	TAVI
Biancari [4], 2016	Finland	144	144	79.4 ± 5.4	79.0 ± 6.0	38.9	37.5	4.2	3.5	NA	NA	4.1 ± 3.2[a]	3.6 ± 2.6[a]
Miceli [10], 2016	Italy	37	37	79 ± 4.5	78.8 ± 7.4	35.1	40.5	27	18.9	86.5	83.8	16.1 ± 11[b]	15.7 ± 8.5[b]
D'Onofrio [14], 2016	Italy	214	214	77.4 ± 5.4	77.7 ± 7.9	35.5	35.0	27.6	27.1	88.8	74.8	10.5 ± 6.2[b]	12.4 ± 9.1[b]
Muneretto [11], 2015	Italy	53	55	79 ± 4	81 ± 6	30.2	43.6	20.8	27.3	88.7	65.5	16 ± 11.7[b]	20.4 ± 12.7[b]
Kamperidis [9], 2015	Nether-land	40	40	79 ± 4.5	79 ± 5.9	100	100	NA	NA	NA	NA	15.9 ± 10.6[b]	15.5 ± 8.4[b]
Santarpino [13], 2015	Germany	102	102	80 ± 4	79 ± 7	41	43	39	36	86	92	17 ± 14[b]	18 ± 11[b]
Doss [12], 2012	Germany	27	29	78 ± 4	84.7 ± 6	40.7	27.6	40.7	37.9	NA	NA	13.7 ± 6.3[b]	35.3 ± 4.2[b]

[a] Logistic European System for Cardiac Operative Risk Evaluation 2011 revision. [b] Logistic European System for Cardiac Operative Risk Evaluation.

NA = not available; SU-AVR = sutureless aortic valve replacement; TAVI = transcatheter aortic valve implantation.

Fig 2. The forest plot demonstrates that the pooled early mortality after sutureless aortic valve replacement is lower than after transcatheter aortic valve implantation (odds ratio [OR], 0.52; 95% confidence interval [CI] 0.30 to 0.90; p = 0.02). The horizontal lines represent the 95% CI. The solid squares indicate the mean difference and are proportional to the weights used in the meta-analysis. The diamond indicates the weighted mean difference, and the lateral tips of the diamond indicating the associated CI. (RE = random effect.)

Fig 3. The incidence of severe paravalvular leak aftertranscatheter aortic valve implantation is much higher than after sutureless aortic valve replacement. The horizontal lines represent the 95% confidence interval (CI). The solid squares indicate the mean difference and are proportional to the weights used in the meta-analysis. The diamond indicates the weighted mean difference, and the lateral tips of the diamond indicate the associated CI. (OR = odds ratio; RE = random effect.)

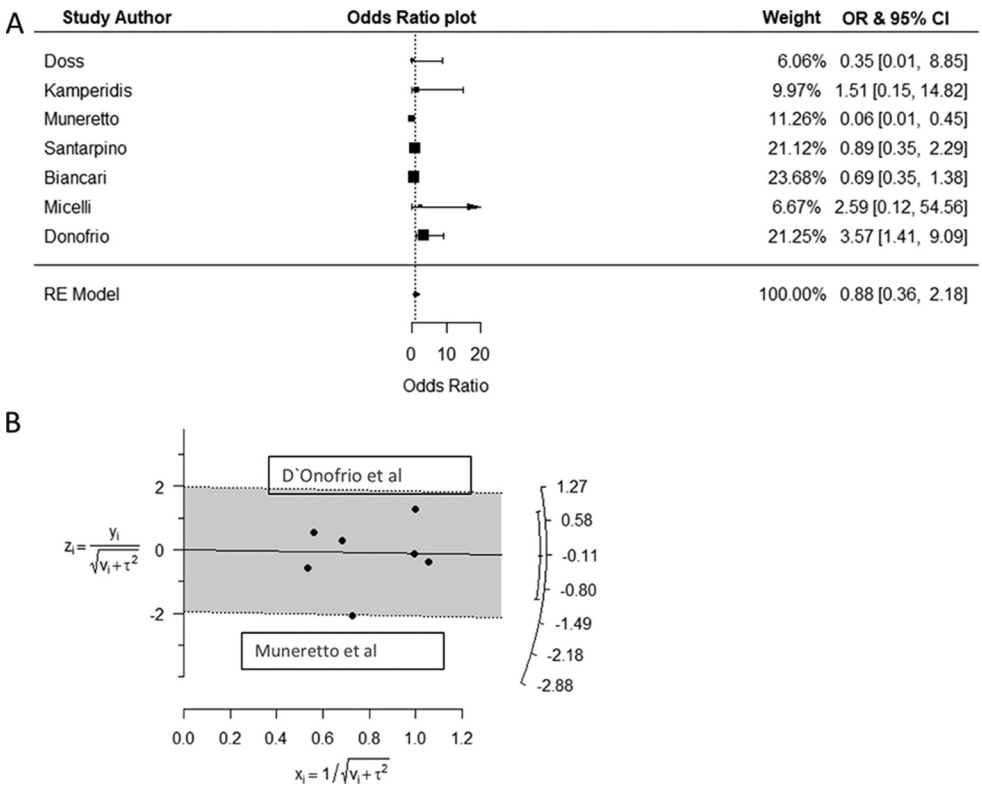

Fig 4. (A) The forest plot demonstrates that the pooled incidence of pacemaker implantation is comparable between cohorts (odds ratio [OR], 0.88; 95% confidence interval [CI], 0.36 to 2.18), but this end point demonstrates moderate heterogeneity ($I^2 = 63\%$). The horizontal lines represent the 95% CI. The solid squares indicate the mean difference and are proportional to the weights used in the meta-analysis. The diamond indicates the weighted mean difference, and the lateral tips of the diamond indicate the associated CI. (RE = random effect.) (B) The Galbraith plot demonstrates that two studies (Muneretto and colleagues [11] and D'Onofrio and colleagues [14]) are outliers contributing significantly to this reported heterogeneity.

Table 2. Outcome Comparison Between Sutureless Aortic Valve Replacement and Transcatheter Aortic Valve Implantation by the Device Used and Transfemoral Versus Transapical Approach in Transcatheter Aortic Valve Implantation

Variable	Perceval[a] (%)	Sapien[b] (%)	*p* Value
Matched patients (Perceval, n = 214; Sapien, n = 214) not related with the route of approach [14]			
Device success	98.6	88.8	<0.001
PVL	2.8	35.3	<0.001
Severe PVL	0.5	5.1	<0.001
Pacemaker insertion	9.4	2.8	0.004
Matched Perceval (n = 105) vs transapical Sapien (n = 105) [14]			
Device success	98.1	94.3	NS
Mild PVL	2.9	36.1	<0.001
Severe PVL	1.0	1.0	NS
Pacemaker insertion	9.5	3.8	0.09
Matched Perceval (n = 206) vs transfemoral Sapien (n = 206) [14]			
Device success	98.1	85.9	<0.001
PVL	3.4	33.5	<0.001
Severe PVL	0.5	6.3	0.001
Pacemaker insertion	9.2	5.8	0.19
	Perceval [11]	CoreValve[c] [11]	
Pacemaker insertion	2	25.5	<0.001
Peripheral vascular complication	0	14.5	<0.001
Hospital mortality	0	1.8	NS

[a] Sorin Biomedica Cardio Srl, Sallugia, Italy. [b] Edwards Lifescience, Inc, Irvine, California. [c] Medtronic, Minneapolis, Minnesota.

NS = not significant; PVL = paravalvular leak.

We also presented how different the outcomes between two procedures are based on the type of device and the route of approach in TAVI, even though we did not have statistical analysis. Although the outcomes are variable according to the route of approach in TAVI, the study by D'Onofrio and colleagues [14] is definitely valuable because we can easily compare outcomes in SU-AVR with those in TAVI according to the method of approach (Table 2). In general, the transapical approach is more invasive than the transfemoral approach. However, the transapical approach has better outcome as long as surgical experiences are accumulated. Notably, we need to keep in mind that a new generation of the devices for TAVI is rapidly emerging. A recent report suggests that the new Sapien-3 valve significantly reduces PVL compared with the second-generation of Sapien-XT [21].

Data on cost comparison between these two procedures are very limited. Importantly, when considering overall cost, we should include the additional risk and expenditure associated with the need for reintervention. Although present follow-up is very limited, increased PVL may lead to increased need for reintervention in patients undergoing TAVI.

We accept that present data are very limited and do not allow us to present robust conclusions. However, as the scope of TAVI increases to moderate-risk and even lower-risk patients with aortic stenosis, our responsibility as clinicians is to provide the best and most durable procedure. Increased overall experience with both procedures will over time provide clearer guidelines for selecting from the vast array of options available.

Conclusion

Sutureless and transcatheter AVR are both good alternatives for high-risk patients with severe aortic stenosis. Sutureless AVR has a lower incidence of PVL and early mortality. The rates of pacemaker implant and stroke are comparable with both techniques. Future studies with longer follow-up are needed to determine superiority and guidelines for selecting either method.

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