HEART LUNG and VESSELS

ORIGINAL ARTICLE

Heart, Lung and Vessels. 2014; 6(4): 232-243

Network meta-analysis on the comparative effectiveness and safety of transcatheter aortic valve implantation with CoreValve or Sapien devices versus surgical replacement

G. Biondi-Zoccai[1,2], M. Peruzzi[1], A. Abbate[2], Z.M. Gertz[2], U. Benedetto[3], E. Tonelli[4], F. D'Ascenzo[5], A. Giordano[6], P. Agostoni[7], G. Frati[1,8]

[1]Department of Medico-Surgical Sciences and Biotechnologies, Sapienza University of Rome, Latina, Italy; [2]VCU Pauley Heart Center, Virginia Commonwealth University, Richmond, VA, USA; [3]Department of Cardiac Surgery, Harefield Hospital, London, UK; [4]Department of Clinical and Molecular Medicine, Sapienza University of Rome, Rome, Italy; [5]Division of Cardiology, Department of Internal Medicine, University of Turin, Turin, Italy; [6]Unità Operativa di Interventistica Cardiovascolare, Presidio Ospedaliero Pineta Grande, Castel Volturno, and Unità Operativa di Emodinamica, Casa di Salute Santa Lucia, San Giuseppe Vesuviano, both in Italy; [7]Division of Cardiology, Utrecht University Medical Center, Utrecht, The Netherlands; [8]Department of AngioCardioNeurology, IRCCS Neuromed, Pozzilli, Italy

Heart, Lung and Vessels. 2014; 6(4): 232-243

ABSTRACT

Introduction: Surgical replacement for aortic stenosis is fraught with complications in high-risk patients. Transcatheter techniques may offer a minimally invasive solution, but their comparative effectiveness and safety is uncertain. We performed a network meta-analysis on this topic.
Methods: Randomized trials on transcatheter aortic valve replacement vs surgery were searched. The primary outcome was all cause death. Risk estimates were obtained with Bayesian network meta-analytic methods.
Results: Four trials with 1,805 patients were included. After a median of 8 months, risk of death and myocardial infarction was not different when comparing surgery versus transcatheter procedures, irrespective of device or access. Conversely, surgery was associated with higher rates of major bleeding (odds ratio vs CoreValve = 3.03 [95% credible interval: 2.23-4.17]; odds ratio vs transfemoral Sapien = 1.82 [1.21-2.70]; odds ratio vs transapical Sapien = 2.08 [1.20-3.70]), and acute kidney injury (odds ratio vs CoreValve = 2.08 [1.33-3.32]; odds ratio vs transapical Sapien = 2.78 [2.21-99.80]), but lower rates of pacemaker implantation (odds ratio vs CoreValve = 0.41 [0.28-0.59]), and moderate or severe aortic regurgitation (odds ratio vs CoreValve = 0.06 [0.02-0.27]; odds ratio vs Sapien = 0.17 [0.02-0.76]). Strokes were less frequent with CoreValve than with transfemoral Sapien (odds ratio = 0.32 [0.13-0.73]) or transapical Sapien (odds ratio = 0.33 [0.10-0.93]), whereas pacemaker implantation was more common with CoreValve (odds ratio vs surgery = 2.46 [1.69-3.61]; odds ratio vs transfemoral Sapien = 2.22 [1.27-3.85]).
Conclusions: Survival after transcatheter or surgical aortic valve replacement is similar, but there might be differences in the individual safety and effectiveness profile between the treatment strategies and the individual devices used in transcatheter aortic valve implantation.

Keywords: *aortic stenosis, mixed treatment comparison, network meta-analysis, TAVI, TAVR, transcatheter aortic valve implantation, transcatheter aortic valve replacement.*

Corresponding author:
Dr. Giuseppe Biondi-Zoccai
Department of Medico-Surgical Sciences and Biotechnologies
Sapienza University of Rome
Corso della Repubblica, 79 - 04100 Latina, Italy
e-mail: giuseppe.biondizoccai@uniroma1.it

INTRODUCTION

The burden of degenerative aortic stenosis continues to increase, and many patients with severe aortic stenosis are too sick or old to undergo surgery safely (1, 2). Accordingly, minimally invasive means to treat patients with aortic stenosis have been recently developed, including self-expandable or balloon-expandable aortic prostheses enabling transcatheter aortic valve implantation (TAVI) (3-5).

The evidence base on these novel technologies has accrued recently, thanks to the completion of several important randomized clinical trials (RCT) with careful adjudication of clinically relevant endpoints (4, 5). There is favorable data on the comparative risk-benefit balance of TAVI in comparison to medical therapy in patients with aortic stenosis but with prohibitive operative risk (4). However, comparative data on TAVI vs surgical aortic valve replacement (SAVR) in those with heightened but not prohibitive risk are less clear cut given differing impacts on meaningful outcomes (e.g. stroke risk being higher with TAVI vs bleeding risk being higher with (SAVR).

As systematic reviews exploiting network meta-analytic tools can provide more precise and robust as well as less optimistic effect estimates (6, 7), we aimed to conduct a comprehensive mixed treatment comparison of TAVI vs SAVR for severe aortic stenosis in patients at increased surgical risk.

METHODS

The present review was performed in keeping with the Cochrane Collaboration, Quality of Reporting of Meta-analyses (QUOROM) and Preferred Items for Reporting of Systematic Reviews and Meta-analyses (PRISMA) (8-10). All reviewing activities were independently performed by two reviewers, with divergences resolved after consensus.

MEDLINE/PubMed was searched for RCTs on TAVI in patients with severe aortic stenosis at high but not prohibitive surgical risk according to Biondi-Zoccai and colleagues on April 15, 2014 (11). Additional queries were conducted in the Cochrane Library, Google Scholar, and Scopus. No language restriction was enforced. Initially retrieved citations were screened first at the title and abstract level, and then appraised as full text. Studies were included if reporting was on a randomized trial of TAVI (using different TAVI devices or techniques) or TAVI vs SAVR in patients at high but not prohibitive surgical risk. Duplicate reports or studies focusing on patients at risk so high as to contraindicate SAVR were not included (12).

Several design, baseline, procedural, and outcome data were abstracted from short-listed studies. Outcomes of interest at the longest available follow-up up to 12 months were: all causes of death; stroke; acute myocardial infarction; acute kidney injury; major bleeding; permanent pacemaker requirement; moderate or severe aortic regurgitation. The valve Academic Research Consortium definitions were used throughout (12). In case of incomplete outcome data, effect estimates were computed imputing figures from Kaplan-Meier curves (13). The internal validity of included studies was appraised according to the Cochrane Collaboration approach, separately evaluating the risk of selection, performance, attrition and adjudication bias (8). Pairwise meta-analysis was first performed with a descriptive scope and to appraise statistical inconsistency and small study effects with RevMan (Cochrane Collaboration, Copenhagen, Denmark). Specifically, I-squared >50% was considered evidence of moderate or severe

inconsistency. Network meta-analysis was conducted, after appraisal of evidence geometry according to van Valkenhoef et al. (14), within a Bayesian framework and with Markov chain Monte Carlo (MCMC) resampling using WinBUGS (University of Cambridge, Cambridge, UK). A fixed-effect method was used throughout given the prevalent star-shaped network, computing point estimates (95% credibility intervals) for odds ratios (OR) as well as the probability of each treatment being the best one (Pbest). Indeed, star-shaped evidence networks are inefficiently analyzed with random effects as the random effect term of the model may lead to lack of convergence of chains or very large credible intervals (6). As the evidence network was prevalently star-shaped, we thus chose a priori to use a fixed effect model. In addition, the validity of this choice was confirmed also post hoc on deviance information criterion (DIC) estimates, always favoring the fixed effect model. Inferential estimates were based on 150,000 iterations after a burn-in phase of 50,000 iterations and graphical evidence of convergence of 3 independent MCMC chains. Consistency between direct and indirect estimates was appraised comparing consistency and inconsistency models (15).

Model fit was appraised by comparing values of DIC for fixed-effects and random-effects models. Results were also summarized graphically with boxplots (displaying 95% and 75% credible intervals, as well as median values). Specifically, boxplots were used as they are the default graphical representation provided by the WinBUGS package which also provides the quantitative statistical estimates, and thus any other graph (which should be obtained from a separate graphical package) would lack the real graphical precision provided by WinBUGS. Second, boxplots provide more precise and comprehensive information on the real posterior probability distribution which is used for statistical inference (as they provide median, 1st quartile, 3rd quartile, 2.5% quintile, and 97.5% quintile values).

RESULTS

A total of 3,678 citations were initially retrieved (76 from the Cochrane Library, 3,130 from Google Scholar, 204 from MEDLINE/PubMed, and 268 from Scopus). Four RCTs were finally included, with a total of 1,805 patients (*Table 1, Figure 1*). Specifically, the PARTNER Cohort A trial randomized 699 subjects after defining their eligibility to transapical vs transfemoral TAVI with the Sapien (Edwards Lifesciences, Irvine, CA, USA) device to Sapien vs SAVR (4). The Prospective, Randomized Trial of Transapical Transcatheter Aortic Valve Implantation vs Surgical Aortic Valve Replacement in Operable Elderly Patients with Aortic Stenosis (STACCATO) trial randomized patients to Sapien-TA vs SAVR, but was stopped prematurely after enrolment of 70 patients given an excess of adverse events in the Sapien-TA group (5). The US CoreValve trial randomized 795 patients to CoreValve (Medtronic, Minneapolis, MN, US) vs SAVR (14). In this trial the CoreValve could be implanted via the TF, transubclavian or direct aortic route, but most cases (323 out of 390 [82.8%]) were performed with a TF access. In this trial stroke was reported only with Kaplan-Meier estimates, and thus these were used to input effect estimates for the systematic review. Finally, the Randomized Comparison of Transcatheter Heart Valves in High Risk Patients With Severe Aortic Stenosis: Medtronic CoreValve Versus Edwards SAPIEN XT (CHOICE) trial compared Sapien vs CoreValve for TF access only (16).

Table 1 - *Design and patient features in the included studies.*

	CHOICE Trial	PARTNER Cohort A Trial	STACCATO Trial	US CoreValve Trial
Year of publication	2014	2011	2012	2014
Patients	241	699	70	795
Setting	Multicenter	Multicenter	Multicenter	Multicenter
Funding	Investigator-initiated	Sponsor-initiated	Investigator-initiated	Sponsor-initiated
Comparison	CoreValve-TF vs Sapien-TF	SAVR vs Sapien-TF vs Sapien-TA (randomization after decision of eligibility to TF vs TA)	SAVR vs Sapien-TA	SAVR vs CoreValve (TF, TS, or DA)
Follow-up	1 month	1 year	3 months	1 year
Bias in randomization or allocation	Low risk	Low risk	Low risk	Low risk
Selection bias	Low risk	Low risk	Low risk	Low risk
Performance bias	Low risk	Low risk	Low risk	Low risk
Attrition bias	Low risk	Low risk	Moderate risk (study prematurely terminated by DSMB for high event rate in TA arm)	Low risk
Adjudication bias	Low risk	Low risk	Low risk	Low risk
Age (years)	81	84	81	83
Female gender	64%	43%	70%	47%
Diabetes mellitus	29%	NA	6%	40%
LVEF	54%	53%	56%	NA
COPD	21%	43%	3%	9%
Renal failure	7%	9%	1%	12%
CAD	63%	75%	NA	75%
NYHA class III or IV	81%	94%	49%	86%
Logistic EuroSCORE	14%	29%	10%	18%
STS score	6%	12%	3%	8%
Aortic valve area (cm^2)	0.70	0.65	0.69	0.72

COPD = chronic obstructive pulmonary disease; DA = direct aortic access; DMSB = Data Safety and Monitoring Board; LVEF = left ventricular ejection fraction; NA = not available or applicable; NYHA = New York Heart Association; SAVR = surgical aortic valve replacement; STS = Society of Thoracic Surgery; TA = transapical; TF = transfemoral; TS = transubclavian.
STACCATO = Prospective, Randomized Trial of Transapical Transcatheter Aortic Valve Implantation vs. Surgical Aortic Valve Replacement in Operable Elderly Patients with Aortic Stenosis; CHOICE = Randomized Comparison of Transcatheter Heart Valves in High Risk Patients With Severe Aortic Stenosis: Medtronic CoreValve Versus Edwards SAPIEN XT; CAD = coronary artery disease; EuroSCORE = European System for Cardiac Operative Risk Evaluation.

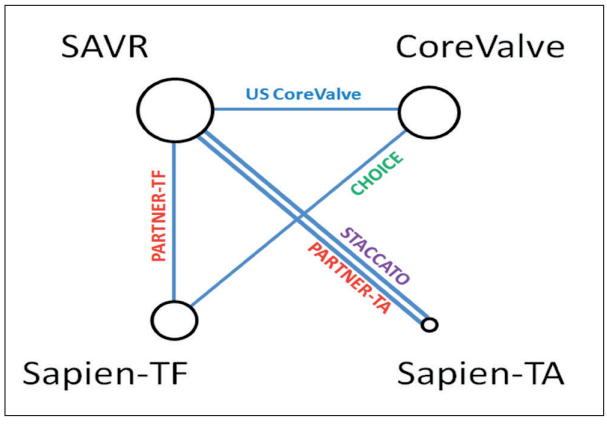

Figure 1 - *Evidence network, showing the four alternative treatments and individual studies with different colors.*
SAVR = surgical aortic valve replacement; TA = transapical; TF = transfemoral; STACCATO = Prospective, Randomized Trial of Transapical Transcatheter Aortic Valve Implantation vs Surgical Aortic Valve Replacement in Operable Elderly Patients with Aortic Stenosis; CHOICE = Randomized Comparison of Transcatheter Heart Valves in High Risk Patients With Severe Aortic Stenosis: Medtronic CoreValve Versus Edwards SAPIEN X.

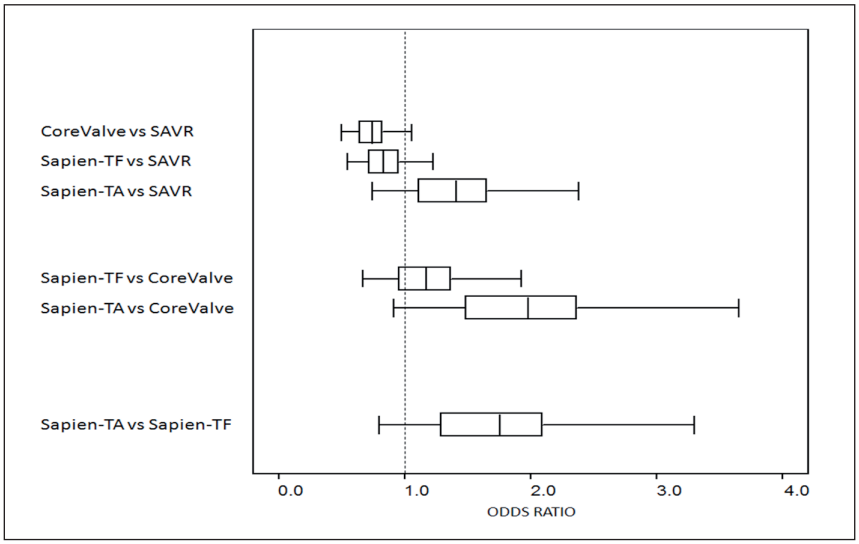

Figure 2 - *Risk of death, reported as boxplots for odds ratios (with values < 1 favoring the first treatment, and values > 1 favoring the second treatment).*
SAVR = surgical aortic valve replacement; TA = transapical; TF = transfemoral.

Table 2 - *Network effect estimates for clinical outcomes at up to 1 year of follow-up.*

	SAVR	CoreValve	Sapien-TF	Sapien-TA
Death	Pbest = 0.8 % OR vs CoreValve = 1.39 (0.95-1.99) OR vs Sapien-TF = 1.22 (0.81-1.82) OR vs Sapien-TA = 0.74 (0.42-1.35)	Pbest = 65.8 % OR vs SAVR = 0.72 (0.50-1.05) OR vs Sapien-TF = 0.93 (0.54-1.99) OR vs Sapien-TA = 0.54 (0.27-1.10)	Pbest = 30.7 % OR vs SAVR = 0.82 (0.55-1.23) OR vs CoreValve = 1.08 (0.64-1.84) OR vs Sapien-TA = 0.61 (0.30-1.26)	Pbest = 2.7 % OR vs SAVR = 1.35 (0.74-2.38) OR vs CoreValve = 1.87 (0.91-3.65) OR vs Sapien-TF = 1.65 (0.80-3.30)
Stroke	Pbest = 4.5 % OR vs CoreValve = 1.43 (0.94-2.27) OR vs Sapien-TF = 0.46 (0.19-1.05) OR vs Sapien-TA = 0.47 (0.16-1.24)	Pbest = 93.8 % OR vs SAVR = 0.70 (0.44-1.06) OR vs Sapien-TF = 0.32 (0.13-0.73) OR vs Sapien-TA = 0.33 (0.10-0.93)	Pbest = 0.1 % OR vs SAVR = 2.20 (0.95-5.34) OR vs CoreValve = 3.12 (1.37-7.84) OR vs Sapien-TA = 1.04 (0.26-3.70)	Pbest = 1.6 % OR vs SAVR = 2.12 (0.80-6.08) OR vs CoreValve = 3.06 (1.08-9.75) OR vs Sapien-TF = 0.96 (0.27-3.91)
Acute myocardial infarction	Pbest = 16.6 % OR vs CoreValve = 0.79 (0.23-2.56) OR vs Sapien-TF = 0.40 (0.01-5.03) OR vs Sapien-TA = 1.54 (0.24-11.10)	Pbest = 13.7 % OR vs SAVR = 1.27 (0.39-4.33) OR vs Sapien-TF = 0.52 (0.01-7.14) OR vs Sapien-TA = 2.01 (0.22-19.61)	Pbest = 13.0 % OR vs SAVR = 2.50 (0.20-67.41) OR vs CoreValve = 1.93 (0.14-67.28) OR vs Sapien-TA = 3.85 (0.19-90.92)	Pbest = 56.6 % OR vs SAVR = 0.65 (0.09-4.17) OR vs CoreValve = 0.50 (0.05-4.61) OR vs Sapien-TF = 0.26 (0.01-5.15)
Major bleeding	Pbest = 0 % OR vs CoreValve = 3.03 (2.23-4.17) OR vs Sapien-TF = 1.82 (1.21-2.70) OR vs Sapien-TA = 2.08 (1.20-3.70)	Pbest = 85.8 % OR vs SAVR = 0.33 (0.24-0.45) OR vs Sapien-TF = 0.60 (0.38-0.94) OR vs Sapien-TA = 0.70 (0.36-1.32)	Pbest = 1.0 % OR vs SAVR = 0.55 (0.37-0.83) OR vs CoreValve = 1.68 (1.07-2.65) OR vs Sapien-TA = 1.16 (0.58-2.38)	Pbest = 13.2 % OR vs SAVR = 0.48 (0.27-0.83) OR vs CoreValve = 1.44 (0.76-2.76) OR vs Sapien-TF = 0.86 (0.42-1.72)
Acute kidney injury	Pbest = 0 % OR vs CoreValve = 2.08 (1.33-3.32) OR vs Sapien-TF = 1.39 (0.66-2.86) OR vs Sapien-TA = 2.78 (2.21-99.80)	Pbest = 36.9 % OR vs SAVR = 0.48 (0.30-0.75) OR vs Sapien-TF = 0.66 (0.31-1.37) OR vs Sapien-TA = 1.30 (0.10-33.32)	Pbest = 5.4 % OR vs SAVR = 0.72 (0.35-1.52) OR vs CoreValve = 1.51 (0.73-3.22) OR vs Sapien-TA = 1.96 (0.15-47.61)	Pbest = 57.7 % OR vs SAVR = 0.36 (0.01-4.52) OR vs CoreValve = 0.77 (0.03-9.62) OR vs Sapien-TF = 0.51 (0.02-6.47)
Pacemaker implantation	Pbest = 34.4 % OR vs CoreValve = 0.41 (0.28-0.59) OR vs Sapien-TF = 0.91 (0.49-1.61) OR vs Sapien-TA = 0.95 (0.34-2.78)	Pbest = 0 % OR vs SAVR = 2.46 (1.69-3.61) OR vs Sapien-TF = 2.22 (1.27-3.85) OR vs Sapien-TA = 2.33 (0.81-6.67)	Pbest = 23.8 % OR vs SAVR = 1.11 (0.62-2.04) OR vs CoreValve = 0.45 (0.26-0.79) OR vs Sapien-TA = 1.06 (0.33-3.57)	Pbest = 41.8 % OR vs SAVR = 1.05 (0.36-2.95) OR vs CoreValve = 0.43 (0.15-1.24) OR vs Sapien-TF = 0.94 (0.28-3.06)
Moderate or severe aortic regurgitation	Pbest = 98.8 % OR vs CoreValve = 0.06 (0.01-0.27) OR vs Sapien = 0.17 (0.02-0.76)	Pbest = 0 % OR vs SAVR = 15.91 (3.76-123.10) OR vs Sapien = 2.56 (0.76-11.12)	Pbest = 1.2 %* OR vs SAVR = 5.91 (1.31-57.38)* OR vs CoreValve = 0.39 (0.09-1.31)*	

*only cumulative data for both Sapien-TF and Sapien-TA are available in the literature, and thus network meta-analysis could only be computed for the combination of Sapien-TF and Sapien-TA. OR = odds ratio; Pbest = probability of being the best treatment; SAVR = surgical aortic valve replacement; TA = transapical; TF = transfemoral.

Pairwise meta-analyses are reported only as hypothesis-generating data in the *online only supplement*. Network meta-analysis comparing the effectiveness and safety of SAVR, CoreValve, Sapien-TF and Sapien-TA after a median of 8 months showed that the risk of death was similar irrespective of treatment (*Table 2, Figure 2*). The risk of stroke was lower with CoreValve than with Sapien (*Figure 3*). Acute myocardial infarction was similar irrespective of treatment (*Figure 4*). Acute kidney injury was less likely with CoreValve than with SAVR (*Figure 5*). Major bleeding was less common with any TAVI device or access in comparison to SAVR, with CoreValve superior to Sapien-TF, and possibly also superior to Sapien-TA (*Figure 6*). Permanent pacemaker implantation was required in more instances after CoreValve implantation than after SAVR or Sapien implantation (*Figure 7*). The analysis for moderate or severe aortic regurgitation, which was limited by the fact that the PARTNER trial has not reported detailed data on both Sapien-TF and Sapien-TA, but only cumulative data, suggested that SAVR was better than both CoreValve and

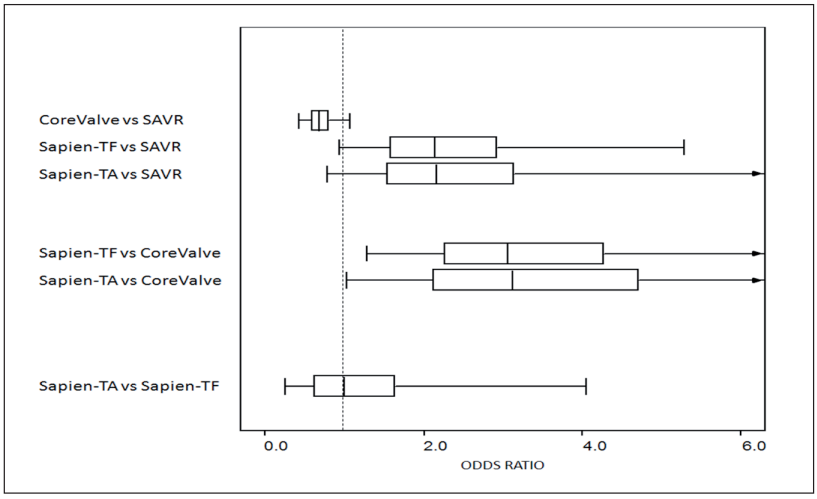

Figure 3 - *Comparative risk of stroke, reported as boxplots for odds ratios (with values < 1 favoring the first treatment, and values > 1 favoring the second treatment).*
SAVR = surgical aortic valve replacement; TA = transapical; TF = transfemoral.

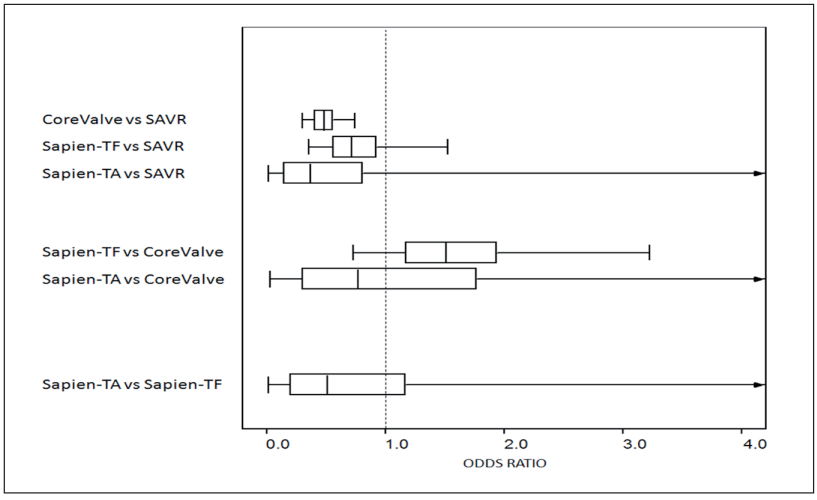

Figure 4 - *Comparative risk of acute myocardial infarction, reported as boxplots for odds ratios (with values < 1 favoring the first treatment, and values > 1 favoring the second treatment).*
SAVR = surgical aortic valve replacement; TA = transapical; TF = transfemoral.

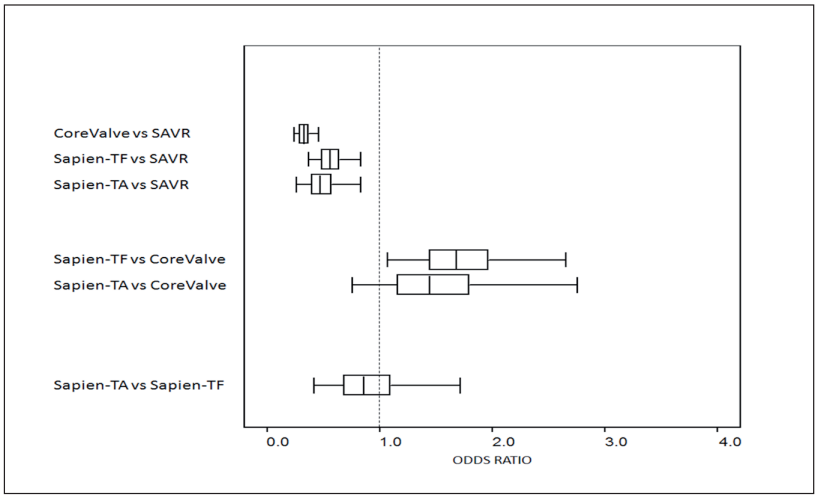

Figure 5 - *Comparative risk of acute kidney injury, reported as boxplots for odds ratios (with values < 1 favoring the first treatment, and values > 1 favoring the second treatment). SAVR = surgical aortic valve replacement; TA = transapical; TF = transfemoral.*

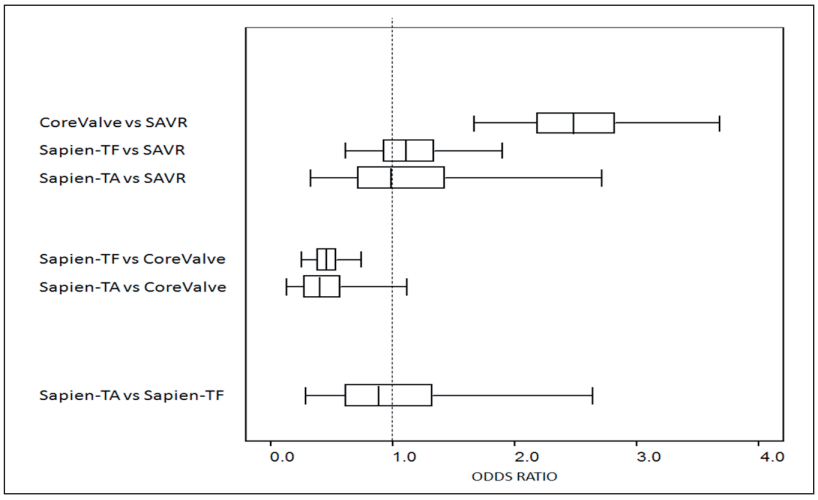

Figure 6 - *Comparative risk of major bleeding, reported as boxplots for odds ratios (with values < 1 favoring the first treatment, and values > 1 favoring the second treatment). SAVR = surgical aortic valve replacement; TA = transapical; TF = transfemoral.*

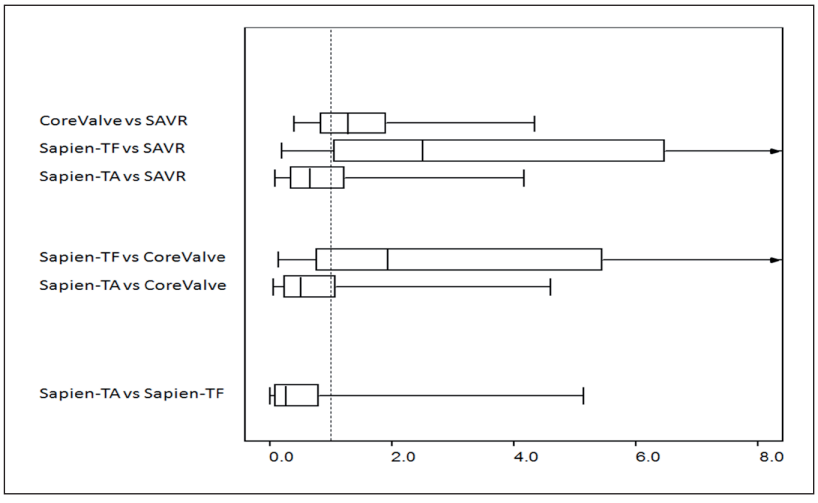

Figure 7 - *Comparative risk of permanent pacemaker implantation, reported as boxplots for odds ratios (with values < 1 favoring the first treatment, and values > 1 favoring the second treatment). SAVR = surgical aortic valve replacement; TA = transapical; TF = transfemoral.*

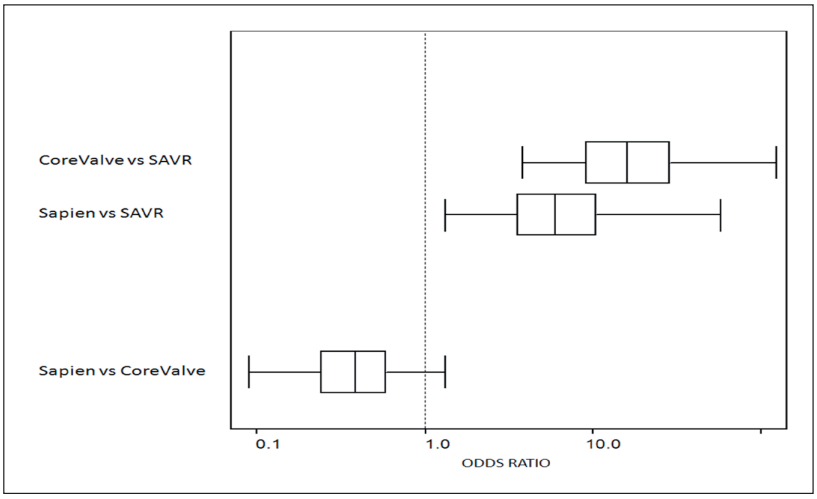

Figure 8 - *Comparative risk of moderate or severe aortic regurgitation, reported as boxplots for odds ratios (with values < 1 favoring the first treatment, and values > 1 favoring the second treatment). SAVR = surgical aortic valve replacement.*

Sapien, but Sapien was nonetheless better than CoreValve (*Figure 8*).
As an additional sensitivity analysis, we computed effect estimates for stroke excluding data imputed graphically (i.e. stroke data from the US CoreValve trial) (14), obtaining results similar in magnitude and direction to the overall analysis.

DISCUSSION

To the best of our knowledge this is the first meta-analysis comparing different treatment for patients with severe aortic stenosis in terms of survival and peri-procedural complications. When compared with SAVR, TAVI appeared to be associated with a lower risk of periprocedural complications but an increased risk of moderate-to-severe aortic regurgitation, and a neutral effect on long-term survival. The burden of degenerative aortic stenosis continues to increase due to increased life expectancy, yet many patients who would be candidates for SAVR are considered to be at too high a risk to safely undergo SAVR and therefore die of untreated severe aortic stenosis (17).

From a pathophysiologic point of view the hemodynamic overload generated by severe aortic stenosis imposes mechanical and neurohormonal challenges on cardiac walls, initially triggering compensatory left ventricular hypertrophy, but eventually activating complex biological responses evolving into maladaptive remodelling with relevant differences between genders (18). As a result, this multifaceted mechanism culminates in tissue remodelling, leading to a progressive loss of regional and global cardiac function that after a long latency phase evolves rapidly to progress finally into a high rate of death. For decades surgical replacement of the aortic valve has been the sole suitable therapeutic option in patients with severe aortic stenosis even in the presence of significant co-morbidity. To date, large improvements in minimally invasive technology such as TAVI have been recently developed and have increased dramatically in the last decade. After the first-in-man implantations, TAVI has become an established procedure in patients with aortic stenosis and high surgical risk. Before adding to the complexity of data analysis by including second and third generation TAVI devices,

we performed a comprehensive network meta-analysis to best characterize the pros and cons of the different strategies and possibly fill any remaining gaps concerning the effectiveness and safety of this procedure. All the procedures, from CoreValve to Sapien-TF or TA and SAVR, showed the same protective effect on prognosis, with a significant improvement in survival compared with non-intervention. In-hospital operative complications (e.g. bleeding) were reduced by TAVI when compared to SAVR, apart from pacemaker implantation, while TAVI increased the risk of aortic regurgitation after the procedure. Rates of stroke did not differ among surgical and transcatheter interventions, while CoreValve proved superior to both TA and TF. Differently from other procedures like percutaneous coronary interventions vs coronary artery bypass graft, clinically relevant strokes did not differ between the more invasive surgical approach and the percutaneous one as previously reported in another pairwise systematic review, when including both observational and randomized controlled studies (19, 20).

This may be related to the different profile of patients, who are older with a larger burden of comorbidities and to the different interventions with a higher risk of embolization especially during the manipulation of aortic arch. Our findings of reduced rates of stroke for CoreValve may relate to the size of the delivery system, the need for rapid ventricular pacing with Sapien, or its self-expanding mechanism.

As expected, rates of complications like bleedings and acute kidney injury were reduced by TAVI. According to various definitions, they interest at least 25% of patients undergoing TAVI sharing similar risk factors such as reduced renal function and diabetes mellitus with an ominous impact on prognosis, both in-hospital and at follow up (21-26).

Similarly, as largely described, the very superficial location of the left bundle branch in the uppermost part of the leftward ventricular septum and its close proximity to the aortic valve complex probably represents the most important reason to explain atrio-ventricular blocks and consequently pacemaker implantation after TAVI (27). In this setting, Corevalve, when compared to Sapien, has been related to a higher incidence of atrio-ventricular block because of the deeper implantation of the lower one third of the prosthesis stent frames, which are characterized by high radial forces for secure anchoring of the stent (28). Although it increased costs, this complication was not shown to have a negative impact on prognosis. Further analyses will be required to compare intensive care unit stay, total hospital stay, need for prolonged intubation or hemodialysis.

Finally, aortic regurgitation was shown more frequent in patients with TAVI than with aortic surgery, without differences between TAVI approaches. Our analysis confirmed the similar results of TAVI (both TF and TA) for aortic regurgitation, although all performed inferiorly to surgery. Despite being challenging to correctly evaluate, degree of aortic regurgitation has been shown to negatively affect prognosis, and therefore the reduction in in-hospital complications with TAVI vs SAVR may be offset by late events related to the presence of moderate-to-severe aortic regurgitation.

Moreover, while this finding may be questionable for high risk patients without alternatives as it may show a different impact on patients with a low or intermediate risk consequently with a longer life expectancy due to the lower burden of comorbidities (29). Future research should be focused on this complication, both to correctly address patients without risk fac-

tors for aortic regurgitation and to the development of new valves with a lower risk of regurgitation.

Limitations of this work include those typical of all systematic reviews, pairwise meta-analyses, and mixed treatment comparisons (6). In addition, the prevalently star-shaped evidence base implies that most inference is based on indirect comparisons, which require of course future confirmation or disproval in head-to-head randomized trials.

Finally, the assumption underlying a sizable portion of our analyses that patients undergoing TF and TA TAVI are reasonably similar in risk, notwithstanding peripheral artery disease burden, may not be shared by all clinicians and researchers.

CONCLUSION

The long-term outlook after TAVI is promising in comparison to SAVR, but there might be differences in the individual safety and effectiveness profile between the competing treatment strategies and the individual devices used in transcatheter aortic valve implantation.

REFERENCES

1. Wenaweser P, Stortecky S, Heg D, Tueller D, Nietlispach F, Falk V, et al. Short-term clinical outcomes among patients undergoing transcatheter aortic valve implantation in Switzerland: the Swiss TAVI registry. EuroIntervention 2014. Epub ahead of print. PMID: 24694729.
2. D'Ascenzo F, Ballocca F, Moretti C, Barbanti M, Gasparetto V, Mennuni M, et al. Inaccuracy of available surgical risk scores to predict outcomes after transcatheter aortic valve replacement. J Cardiovasc Med (Hagerstown) 2013; 14: 894-8.
3. Colombo A, Bianconi L, Montorfano M, Michev I, Biondi-Zoccai GG, Airoldi F, et al.Severe aortic stenosis successfully treated with percutaneous aortic valve implantation. Ital Heart J Suppl 2005; 6: 291-6.
4. Smith CR, Leon MB, Mack MJ, Miller DC, Moses JW, Svensson LG, et al. Transcatheter versus surgical aortic-valve replacement in high-risk patients. N Engl J Med 2011; 364: 2187-98.
5. Nielsen HH, Klaaborg KE, Nissen H, Terp K, Mortensen PE, Kjeldsen BJ, et al. A prospective, randomised trial of transapical transcatheter aortic valve implantation vs. surgical aortic valve replacement in operable elderly patients with aortic stenosis: the STACCATO trial. EuroIntervention 2012; 8: 383-9.
6. Biondi-Zoccai G, editor. Network Meta-Analysis: Evidence Synthesis with Mixed Treatment Comparison. Hauppauge, NY: Nova Science Publishers; 2014.
7. Ioannidis JP. Why most published research findings are false. PLoS Med 2005; 2: 124.
8. Higgins JPT, Green S, editors. Cochrane handbook for systematic reviews of interventions. New York: Wiley; 2009.
9. Biondi-Zoccai GG, Lotrionte M, Abbate A, Testa L, Remigi E, Burzotta F, et al. Compliance with QUOROM and quality of reporting of overlapping meta-analyses on the role of acetylcysteine in the prevention of contrast associated nephropathy: case study. BMJ 2006; 332: 202-9.
10. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. BMJ. 2009; 339: b2700.
11. Biondi-Zoccai GG, Agostoni P, Abbate A, Testa L, Burzotta F. A simple hint to improve Robinson and Dickersin's highly sensitive PubMed search strategy for controlled clinical trials. Int J Epidemiol 2005; 34: 224-5.
12. Leon MB, Smith CR, Mack M, Miller DC, Moses JW, Svensson LG, et al. PARTNER Trial Investigators Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. N Engl J Med 2010; 363: 1597-607.
13. Adams DH, Popma JJ, Reardon MJ, Yakubov SJ, Coselli JS, Deeb GM, et al. Transcatheter Aortic-Valve Replacement with a Self-Expanding Prosthesis. N Engl J Med 2014; 370: 1790-8.
14. van Valkenhoef G, Tervonen T, Zhao J, de Brock B, Hillege HL, Postmus D. Algorithmic parameterization of mixed treatment comparisons. Stat Comput 2012; 22: 1009-111.
15. Greco T, Landoni G, Biondi-Zoccai G, D'Ascenzo F, Zangrillo A. A Bayesian network meta-analysis for binary outcome: how to do it. Stat Methods Med Res 2013. Epub ahead of print. PMID: 23970014.
16. Abdel-Wahab M, Mehilli J, Frerker C, Neumann FJ, Kurz T, Tölg R, et al. Comparison of Balloon-Expandable vs Self-expandable Valves in Patients Undergoing Transcatheter Aortic Valve Replacement: The CHOICE Randomized Clinical Trial. JAMA 2014; 311: 1503-14.
17. Green P, Woglom AE, Genereux P, Daneault B, Paradis JM, Schnell S, et al. The impact of frailty status on survival after transcatheter aortic valve replacement in older adults with severe aortic stenosis: a single-center experience. JACC Cardiovasc Interv 2012; 5: 974-81.
18. D'Ascenzo F, Gonella A, Moretti C, Omedè P, Salizzoni S, La Torre M, et al. Gender differences in patients undergoing TAVI: a multicentre study. EuroIntervention 2013; 9: 367-72.
19. Palmerini T, Biondi-Zoccai G, Reggiani LB, Sangiorgi D, Alessi L, De Servi S, et al. Risk of stroke with coronary artery bypass graft surgery compared with percutaneous coronary intervention. J Am Coll Cardiol 2012; 60: 798-805.
20. D'Ascenzo F, Barbero U, Moretti C, Palmerini T, Della Riva D, Mariani A, et al. Percutaneous coronary intervention versus coronary artery bypass graft for stable angina: Meta-regression of randomized trials. Contemp Clin Trials 2014; 38: 51-58.
21. Panchal HB, Ladia V, Desai S, Shah T, Ramu V. A meta-analysis of mortality and major adverse cardiovascular and cerebrovascular events following transcatheter aor-

tic valve implantation versus surgical aortic valve replacement for severe aortic stenosis. Am J Cardiol 2013; 112: 850-60.
22. Moretti C, D'Amico M, D'Ascenzo F, Colaci C, Salizzoni S, Tamburino C, et al. Impact on Prognosis of Periprocedural Bleeding after TAVI: Mid-Term Follow-Up of a Multicenter Prospective Study. J Interv Cardiol 2014; 27: 293-9.
23. Bernelli C, Chieffo A, Montorfano M, Maisano F, Giustino G, Buchanan GL, et al. Usefulness of baseline activated clotting time-guided heparin administration in reducing bleeding events during transfemoral transcatheter aortic valve implantation. JACC Cardiovasc Interv 2014; 7: 140-51.
24. D'Ascenzo F, Moretti C, Salizzoni S, Bollati M, D'Amico M, Ballocca F, et al. 30 days and midterm outcomes of patients undergoing percutaneous replacement of aortic valve according to their renal function: a multicenter study. Int J Cardiol 2013; 167: 1514-8.
25. Sinning JM, Adenauer V, Scheer AC, Lema Cachiguango SJ, Ghanem A, Hammerstingl C, et al. Doppler-based renal resistance index for the detection of acute kidney injury and the non-invasive evaluation of paravalvular aortic regurgitation after transcatheter aortic valve implantation. EuroIntervention 2014; 9: 1309-16.
26. Conrotto F, D'Ascenzo F, Giordana F, Salizzoni S, Tamburino C, Tarantini G,et al. Impact of diabetes mellitus on early and midterm outcomes after transcatheter aortic valve implantation (from a multicenter registry). Am J Cardiol 2014; 113: 529-34.
27. Bleiziffer S, Ruge H, Hörer J, Hutter A, Geisbüsch S, Brockmann G, et al. Predictors for new-onset complete heart block after transcatheter aortic valve implantation. JACC Cardiovasc Interv 2010; 3: 524-30.
28. Khawaja MZ, Rajani R, Cook A, Khavandi A, Moynagh A, Chowdhary S, et al. Permanent pacemaker insertion after CoreValve transcatheter aortic valve implantation: incidence and contributing factors (the UK CoreValve Collaborative). Circulation 2011; 123: 951-60.
29. Abdel-Wahab M, Comberg T, Büttner HJ, El-Mawardy M, Chatani K, Gick M, Geist V, et al. Aortic regurgitation after transcatheter aortic valve implantation with balloon- and self-expandable prostheses: a pooled analysis from a 2-center experience. JACC Cardiovasc Interv 2014; 7: 284-92.

Cite this article as: Biondi-Zoccai G, Peruzzi M, Abbate A, Gertz ZM, Benedetto U, Tonelli E, D'Ascenzo F, Giordano A, Agostoni P, Frati G. Network meta-analysis on the comparative effectiveness and safety of transcatheter aortic valve implantation with CoreValve or Sapien devices versus surgical replacement. Heart, Lung and Vessels. 2014. 2014; 6(4): 234-243.

Source of Support: Nil. **Disclosures:** Dr. Biondi-Zoccai has consulted for DirectFlow Medical.

Acknowledgments: Dr. Biondi-Zoccai was, at the time of the preparation of this manuscript, the Congdon Visiting Scholar at the VCU Pauley Heart Center, Virginia Commonwealth University, Richmond, VA, USA.

Appendix

MEDLINE/PubMed was searched with the following string: transcatheter AND aortic AND valve AND (implantation OR replacement) AND (corevalve OR sapien) AND stenosis AND (randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized controlled trials[mh] OR random allocation[mh] OR double-blind method[mh] OR single-blind method[mh] OR clinical trial[pt] OR clinical trials[mh] OR (clinical trial[tw] OR ((singl*[tw] OR doubl*[tw] OR trebl*[tw] OR tripl*[tw]) AND (mask*[tw] OR blind[tw])) OR (latin square[tw]) OR placebos[mh] OR placebo*[tw] OR random*[tw] OR research design[mh:noexp] OR follow-up studies[mh] OR prospective studies[mh] OR cross-over studies[mh] OR control*[tw] OR prospectiv*[tw] OR volunteer*[tw]) NOT (animal[mh] NOT human[mh]) NOT (comment[pt] OR editorial[pt] OR meta-analysis[pt] OR practice-guideline[pt] OR review[pt])).