GLOBAL CARDIOLOGY SCIENCE & PRACTICE
A Qatar Foundation Academic Journal

OPEN ACCESS

Lessons from the trials

TAVI: New trials and registries offer further welcome evidence – U.S. CoreValve, CHOICE, and GARY

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ABSTRACT

The introduction of transcatheter aortic valve implantation (TAVI) has resulted in a paradigm shift in the treatment of patients with severe aortic stenosis. Data from the recent U.S CoreValve Trial suggest, for the first time, that TAVI is associated with a significantly higher rate of survival at one year compared to surgical aortic valve replacement (SAVR) in the treatment of high-risk patients affected by severe aortic stenosis. The present review discusses this study and the current evidence about TAVI, for the treatment of severe aortic stenosis, from major trials and real world registries.

Keywords: U.S. CoreValve Trial, transcatheter aortic valve implantation, surgical aortic valve replacement, degenerative aortic valve stenosis

http://dx.doi.org/10.5339/gcsp.2014.12

Submitted: 23 April 2014
Accepted: 28 April 2014

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Cite this article as: Pighi M, Serdoz R, Kilic ID, Sherif SA, Lindsay A, Di Mario C. TAVI: New trials and registries offer further welcome evidence – U.S. CoreValve, CHOICE, and GARY, *Global Cardiology Science and Practice* **2014:12** http://dx.doi.org/10.5339/gcsp.2014.12

INTRODUCTION

The term 'pioneer' refers to one who ventures into the wilderness, preparing the way for others to follow. Just as for a climber who stares at the top of the mountain, thinking about a new way to conquer it, the same applies in science; there are people who try to put their efforts in finding new solutions to current unmet questions. In 2002, Alain Cribier reported the first-in-man case of percutaneous aortic-valve replacement,[1] showing a new perspective in the treatment of degenerative aortic valve stenosis. Just five years later, a committed group of investigators and an innovative company decided to take the risk of comparing a brand new technology, the transcatheter valve implantation/replacement (TAVI as we say in Europe, TAVR as they say in the United States), against the gold standard of treatment which had been around for 50 years, surgical excision of the old valve and reinsertion of a new biological or mechanical valve. The result of that brave and forward-looking decision was the PARTNER A trial.[2] They won their bet and almost ten years after the first experience, they proved the equivalency between these two therapeutic strategies, deserving the gold medal of being first. To be a follower, reaching the top of the mountain, after someone else has shown the way and how to find a safe foothold avoiding dangerous mistakes, does not have the same cachet. The perception about this second randomized trial with a self-expanding valve was that the study was going to deliver nothing more than a confirmation of the PARTNER cohort A results, mainly of interest for the company manufacturing this valve with no revolutionary messages for the cardiology community at large. Never have preconceptions on trials proved to be so wrong.

DESCRIPTION OF THE TRIAL

The U.S. CoreValve Trial[3] was first presented at the at the 63rd Annual American College of Cardiology Scientific Meeting in Washington DC, just after the national anthem and opening ceremony. It is a multicenter, randomized, non-inferiority trial, comparing transcatheter aortic-vave implantation (TAVI), by using a self-expanding transcatheter bioprosthesis, with surgical aortic valve replacement (SAVR) in patients with severe aortic stenosis and increased risk of death during surgery. Over a period of 20 months (February 2011 through September 2012) 45 hospitals across the United States enrolled a total of 795 patients (Figure 1) characterized by both severe

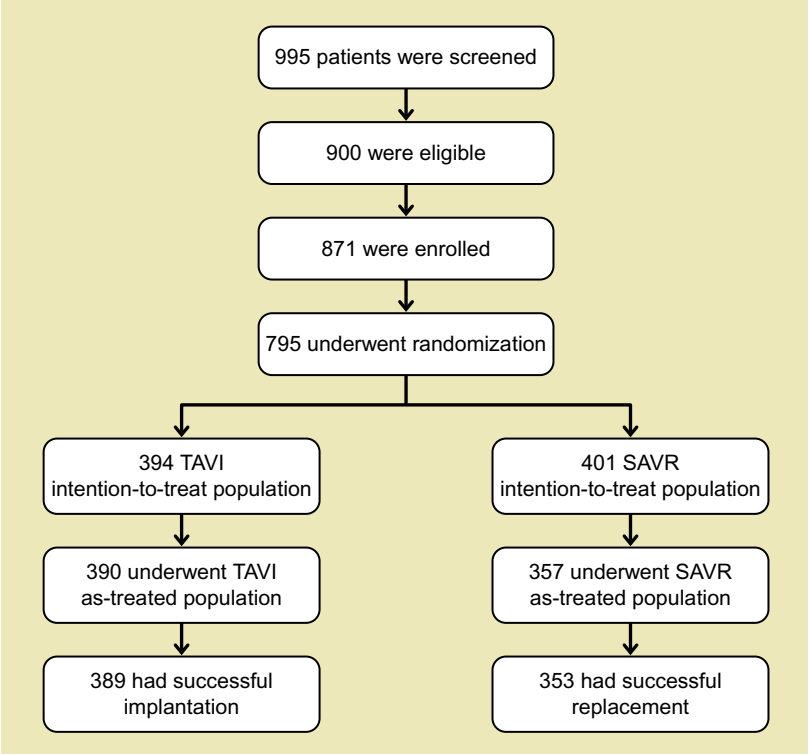

Figure 1. U.S CoreValve Trial Flow-chart (modified from Adams DH et al. N Engl J Med. 2014).

symptomatic aortic stenosis, and increased surgical risk (Table 1), as determined by the heart teams using Society of Thoracic Surgeons (STS) score and non-STS incremental risk factors (i.e. co-morbidity, disability and frailty scores). The primary hypothesis of the study was that the event rate at 1-year for death from any cause in the TAVI group would be non inferior to that in the surgical group. The secondary hypothesis was that the event rate at 30 days, or discharge for major adverse cardiovascular and cerebrovascular events in TAVI, would be superior to that in SAVR group.

The average duration of follow-up was 14.1 months in the TAVR group and 12.8 months in the SAVR group.

The analysis of the per protocol (as treated) population showed a rate of death from any cause at one year significantly lower in the TAVI group treated with the CoreValve prosthesis when compared to the surgical group (14.2% vs 19.1%; upper boundary of the 95 percent confidence interval, −0.4 percent; $p < 0.001$ for non-inferiority; $p = 0.04$ for superiority) (Figures 2 and 3). The survival benefit with TAVI was consistent across subgroup analyses, including by age (≤85 or >85), sex, diabetes, and STS risk score (greater or lower than the cut-off).

With regard to the secondary endpoint, the event rate at 30 days or discharge for major adverse cardiovascular and cerebrovascular events, the pre-specified combined endpoint, was not significantly lower in the TAVI group than in the surgical group) 8.2% v 10.9%, $p = 0.10$ for superiority). The main concern in the PARTNER cohort A trial was the higher incidence of stroke in the TAVI group while results were reversed in the US CoreValve trial, with a non-significantly lower risk for stroke at 30 days with TAVI than with surgery (4.9% vs. 6.2%, $p = 0.46$ for superiority).

Major vascular complications, the need of permanent pacemaker implantation and the rate of post-operative moderate or severe paravalvular regurgitation (Table 2) were significantly higher in the TAVI group than in the surgical group, both at 30 days and 1-year follow-up. On the contrary bleeding, acute kidney injury and new-onset or worsening atrial fibrillation were significantly more frequent in the SAVR patients.

The rate of major adverse cardiovascular and cerebrovascular events at 1 year was significantly lower in the TAVI group than in the surgical group (20.4% vs. 27.3%, $p = 0.03$). Of note, the rates of stroke in the TAVI and SAVR at 1 year (8.8% vs. 12.6%) maintained an insignificant difference in favour of TAVI ($p = 0.10$) (Figure 4).

Finally, the changes in NYHA functional class at the 1-year follow-up were non-inferior in the TAVI group, as compared with surgery ($p < 0.01$).

Table 1. Selected characteristics of the patients at baseline (As-treated population).

Baseline characteristics	TAVI group ($n = 390$)	SAVR group ($n = 357$)
Age – yr	83.1 ± 7.1	83.2 ± 6.4
Female – no. (%)	183 (46.9)	170 (47.6)
NHYA class – no. (%)*		
Class II	56 (14.4)	47 (13.2)
Class III	255 (65.4)	248 (69.5)
Class IV	79 (20.3)	62 (17.4)
STS PROM estimate – %†	7.3 ± 3.0	7.5 ± 3.4
Logistic Euroscore – %∫	17.7 ± 13.1	18.6 ± 13.0
Diabetes mellitus – no. (%)	136 (34.9)	162 (45.4)
Chronic kidnay disease (stage 4 or 5) – no./total no. (%)	47/386 (12.2)	45/352 (12.8)
Hystory of hypertension – no. (%)	371 (95.1)	343 (96.1)
Peripheral vascular disease – no./total no. (%)	159/387 (41.1)	148/355 (41.7)
Prior stroke – no./total no. (%)	49/390 (12.60	50/356 (14.0)
Coronary artery disease – no./total no. (%)	294/390 (75.4)	111/357 (31.1)
Prior CABG – no./total no. (%)	115/390 (29.5)	111/357 (31.1)
Prior PCI – no./total no. (%)	133/390 (34.1)	134/357 (37.5)
Preexisting pacemaker or defibrillator – no./total no. (%)	91/390 (23.3)	76/357 (21.3)
Prior myocardial infarction – no./total no. (%)	99/390 (25.4)	90/357 (25.2)
Congestive heart failure – no./total no. (%)	372/390 (95.4)	345/357 (96.6)
Prior atrial fibrillation/flutter – no./total no. (%)	159/389 (40.9)	164/357 (45.9)

No significant between-group differences in baseline characteristics (with exception of diabetes mellitus, $p = 0.003$).
*New York heart Association; Society of Thoraci Surgeon Predictor Risk of Mortality (STS PROM); ∫ The Logistic European System of Cardiac Operative Risk Evaluation (EuroSCORE); (modified from Adams DH et al. N Engl J Med. 2014).

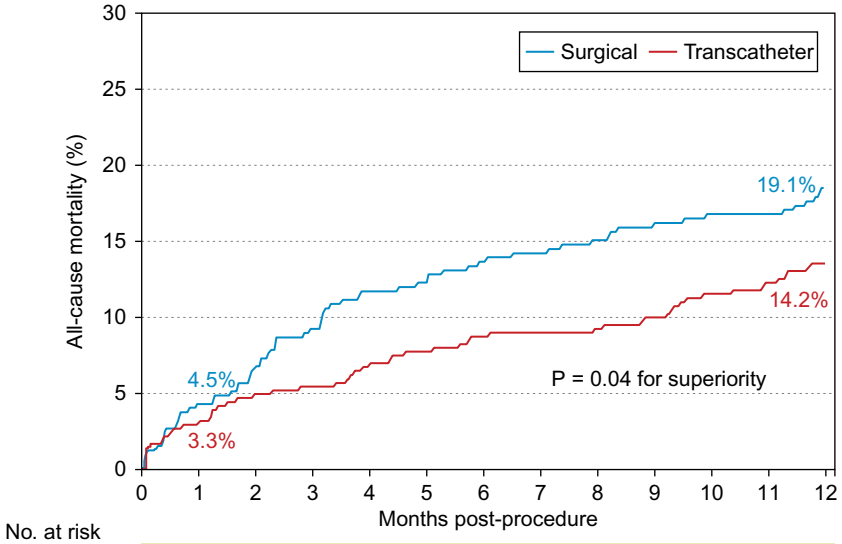

Figure 2. Kaplan–Meier Cumulative Frequency of Death from Any Cause – 12 months post-procedure. The rate of death from any cause in the TAVR group was noninferior to that in the surgical group ($p < 0.001$). A subsequent test for superiority at 1 year showed that TAVR was superior to surgical replacement ($p = 0.04$); (modified from Adams DH et al. N Engl J Med. 2014).

DISCUSSION

Four years ago, the landscape of the therapeutic options for valvular heart disease changed dramatically after the publication of the PARTNER trial,[4] which represented the most important breakthrough in the field of percutaneous treatment of aortic valve stenosis since the introduction of the first artificial aortic valves in the late 1950s. The PARTNER cohort A trial[2] showed for the first time that in high-risk patients, affected by severe aortic stenosis, both surgical and transcatheter procedures for aortic-valve replacement were associated with similar rates of survival at 1 year, expanding the indications coming from the Cohort B of the trial showing superiority of TAVI on medical treatment for inoperable aortic valve stenosis. These conclusions immediately translated into new guidelines issued by the European Society of Cardiology and ACC/AHA/SCAI. The most important finding of the U.S.

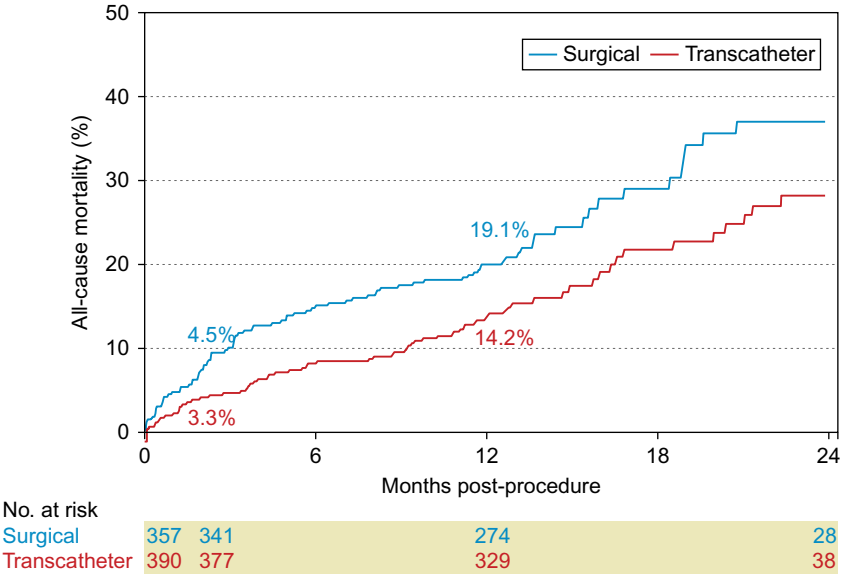

Figure 3. Kaplan–Meier Cumulative Frequency of Death from Any Cause – 24 months post-procedure.

Table 2. Selected Procedural Outcomes at 30 days and 1 Year (As-treated population).

	30 Days			1 Year		
Outcome – no. (%)*	**TAVI group ($n = 390$)**	**SAVR group ($n = 357$)**	***p* value**	**TAVI group ($n = 390$)**	**SAVR group ($n = 357$)**	***p* value**
Major vascular complication	23 (5.9)	6 (1.7)	0.003	24 (6.2)	7 (2.0)	0.004
Bleeding event						
Life-threatening	53 (13.6)	125 (35.0)	<0.001	64 (16.6)	136 (38.4)	<0.001
Major bleeding	109 (28.1)	123 (34.5)	0.05	114 (29.5)	130 (36.7)	0.03
Acute kidney injury	23 (6.0)	54 (15.1)	<0.001	23 (6.0)	54 (15.1)	<0.001
Cardiogenic shock	9 (2.3)	11 (3.1)	0.51	9 (2.3)	11 (3.1)	0.51
Cardiac perforation	5 (1.3)	0	0.03	5 (1.3)	0	0.03
Permanent pacemaker implantation	76 (19.8)	25 (7.1)	<0.001	85 (22.3)	38 (11.3)	<0.001
New-onset or worsening atrial fibrillation	45 (11.7)	108 (30.5)	<0.001	60 (15.9)	115 (32.7)	<0.001
	30 Days			**1 Year**		
Outcome – no. (%)	**TAVI group ($n = 365$)**	**SAVR group ($n = 317$)**	***p* value**	**TAVI group ($n = 299$)**	**SAVR group ($n = 228$)**	***p* value**
Total aortic regurgitation†	36 (10.0)	4 (1.3)	<0.001	21 (7.0)	3 (1.3)	<0.01
Paravalvular regirgitation†	32 (9.0)	3 (1.0)	<0.001	18 (6.1)	1 (0.5)	<0.001

* All data are reported as Kaplan-Meier estimates at the specific time point.; † Moderate or severe; (modified from Adams DH et al. N Engl J Med. 2014).

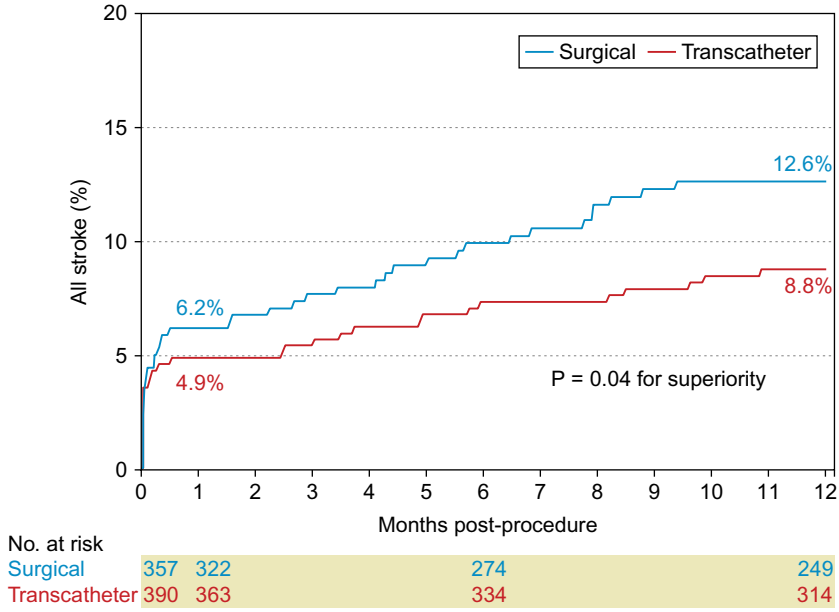

Figure 4. All stroke.

CoreValve trial was the proof of a superiority of percutaneous approach in respect of surgery, with an absolute 1-year survival advantage of nearly 5%, in high-risk patients affected by severe aortic stenosis. Although, the first thought would be to use these results as an evidence of superiority of CoreValve in respect of the balloon-expandable Edwards SAPIEN valve used in PARTNER, it is important to urge caution in comparing the performance and outcome between trials using different device access and patient characteristics. The absolute figures of death for any cause between the U.S. CoreValve (TAVI 13.9%, SAVR 18.7%) and the PARTNER A trial (TAVI 24.2%,SAVR, 26.8%) reflect those differences. At the ACC meeting the investigators explained this difference with the high expertise of the cardiac surgeons involved in the trial but it is hard to believe that an 8% difference in survival after surgery between the two trials, could be explained by surgical progress in the absence of major changes in technique. More likely the higher survival rate in the CoreValve surgical group is explained by the lower baseline surgical risk of the patients enrolled in the study, as shown by the STS score presented by both surgical and transcatheter groups in the CoreValve study (7.4% in the CoreValve US v 11.8% in PARTNER A), (Table 3). In the latter, indeed, the investigators used as a guideline an STS score of at least 10%, to identify high operative risk. On the contrary, in the CoreValve trial the risk of death from aortic-valve surgery was determined on the basis of assessments that combined both traditional surgical risk score (STS PROM) and other risk factors, such as levels of disability and frailty. The lower STS risk of the US CoreValve population gives us a first opportunity to assess results in intermediate-risk patients now investigated in trials such as PARTNER 2A and SURTAVI.[5]

In both the PARTNER and CoreValve prospective randomised trials, patients were highly selected and surgical risks were estimated based on the opinion of a cardiologist and cardiac surgeon reviewed by a panel appointed by the trial coordinators. Therefore the results may not represent the “real world” transcatheter and surgical aortic valve replacement experience, in particular in Europe. The recently published German Aortic Valve Registry (GARY)[6] represented the first registry not limited only to patients undergoing TAVI, but also including patients receiving SAVR, with and without coronary artery bypass grafting. This offered not only the opportunity to analyse the in-hospital outcome after TAVI using various devices, but also to understand how TAVI and SAVR are used, and how outcomes compare in real life. Since the publication the, higher mortality in the TAVI arm of the registry (7.7%), especially when compared with isolated (without concomitant CABG) SAVR (2.1%), has been presented as an example of undue uncontrolled application of a new technique against evidence-based medicine, driven by commercial rather than scientific motivation.[7] The U.S CoreValve study replies to these criticisms, confirming that the excess mortality in the TAVI arm was only caused by the enormous disparity in baseline characteristics of the two groups. Indeed, in the GARY registry, TAVI patients were

Table 3. Selected Characteristics of the U.S. CoreValve and PARTNER Cohort A studies.

Characteristics	U.S. CoreValve	PARTNER Cohort A
N of patients (TAVR/SAVR)†	795 (394/401)	699 (348/351)
Enrolment period (interval, n months)	Feb 2011-Sept 2012 20 months	May 2007-Aug 2009, 28 months
Aortic-valve stenosis	Aortic-valve area ≤0.8 cm^2 or*Aortic-valve index ≤0.5 cm^2/m^2 and Mean aortic-valve gradient >40 mmHg or Peak aortic-jet velocity of more than 4.0 m/s	
Surgical high risk definition	Risk of death within 30 days after surgery >15%	Risk of death within 30 days after surgery >15% and/or STS score ≥10%
Mean STS score (%)	TAVI (7.4 ± 3.0) SAVR (7.5 ± 3.2)	TAVI (11.8 ± 3.3) SAVR (11.7 ± 3.5)
Mean Logistic EUROscore (%)	TAVI (17.6 ± 13.0) SAVR (18.4 ± 12.8)	TAVI (29.3 ± 16.5) SAVR (29.2 ± 15.6)
Aortic prosthesis	Medtronic CoreValve	Edwards-Sapien heart-valve system
Heart team	2 cariac surgeons, 1 interventional cardiologist	Surgeon
Dual antiplatelet therapy	Aspirin ≥81 mg o.d. plus Clopidogrel 75 mg o.d at least for 3 months after the procedure	Asprin plus Clopidogrel for 6 months after the procedure
Study design	Non-inferiority (predefined non-inferiority margin of 7.5 percentage points for the difference in risk between the two treatments)	
Primary endpoint	Rate of death from any cause at 1-year in the intention to treat population	Rate of death from any cause at 1-year in the as-treated population

† intention-to-treat population; * U.S CoreValve trial only;

older (mean age 83.3 ± 6.1 vs 68.3 ± 11.3 years, comparable to the mean age reported in the transcatheter cohort of the US CoreValve trial, 83.2 ± 7.1 years), and presented with more co-morbidities, proving that German cardiologists and surgeons were motivated by the genuine belief that TAVI lowers complications and shortens hospital stay in elderly patients with severe aortic stenosis who are at high risk for conventional surgery.

Speculations on the differences in performance and results of the CoreValve and Sapien in US CoreValve and PARTNER Cohort A are also invalidated by these baseline characteristics, with the addition than in PATNER Cohort A almost half of the patients received a transapical approach, a minimally-invasive surgical route that is applied in patients with peripheral vascular disease and/or small femorals. High-risk by definition, but may also carry an additional risk by itself, and has been largely replaced by a transaortic or transubclavian approach, now also using CoreValve.[8,9] The CoreValve System has been approved by the U.S. Food and Drug Administration (FDA) only in January 2014 and procedures have now been halted by judiciary decisions. CoreValve received CE (Conformité Européenne) Mark in 2007, so that thousands of patients have been treated in Europe with these two devices. So far, comparative data for the efficacy and safety of balloon-expandable and self-expandable valves have been derived from different retrospective registries.[10–13] In these studies, 30-day outcomes ranged from 5.0% to 9.6% for mortality, 1.5% to 4.3% for stroke, 0.3% to 1.2% for myocardial infarction, 6.7% to 21.5% for moderate paravalvular regurgitation (PVR), and 6% to 24.2% for post-TAVI permanent pacemaker placement. Although, all these registries have provided important information highlighting the strengths and weaknesses of the 2 devices in a real-world scenario, nevertheless, due to enrolment of large numbers of patients from multiple centers, which represents the strength of such data, the differences in patient populations, the difficulties in achieving rigorous data collection standards, and the lack of a core laboratory oversight represent common, important limitations of these studies. The challenge of comparing, in a randomized fashion, the performances of these two devices, has been faced by the recently published CHOICE trial.[14] In this German, investigator-initiated, multicenter, open-label, randomized trial, 241 patients with severe aortic stenosis, and at least intermediate surgical risk, underwent transcatheter aortic valve replacement with an Edwards Sapien XT or Medtronic CoreValve. The primary endpoint was device success, a procedural composite endpoint described by the Valve Academic Research Consortium[15] including:

(1) successful vascular access, delivery, and deployment of the device and successful retrieval of the delivery system;
(2) correct position of the device in the proper anatomical location;
(3) intended performance of the prosthetic heart valve (AVA >1.2 cm2, mean aortic valve gradient <20 mm Hg, or peak velocity <3 m/s, without moderate or severe prosthetic valve aortic regurgitation); and
(4) only one valve implanted in the proper anatomical location.

The study, which represented the first head-to-head randomized comparison in patients undergoing transcatheter aortic valve replacement, showed higher success rate with the balloon-expandable than with the SE device (96% vs. 76%; $p < 0.001$), primarily because of less-frequent moderate or severe aortic regurgitation (4% vs. 18%; $p < 0.001$) and need for a second valve (0.8% vs. 5.8%; $p = 0.03$). However, no significant between-group differences were observed in procedural or 30-day mortality or in symptom improvement. The rate of new permanent pacemaker implantation was higher with the self-expandable device (38% vs. 17%; $p = 0.001$), and the stroke rate was non-significantly higher with the balloon-expandable system (5.8% vs. 2.6%; $p = 0.33$). Although the primary endpoint of device success favored the Edwards Sapien device, the lack of significant between-group differences in mortality, symptom improvement, or stroke at short-term follow-up undermines the clinical relevance of the conclusion. A higher rate of pacemaker implantation or the need of a second valve may increase procedural cost but are not necessarily proof of inferior efficacy of the CoreValve. Aortic regurgitation is also more frequent with the CoreValve and has been shown to be associated with greater late mortality but it is unclear whether this applies to mild or only moderate and severe regurgitation and the estimation of the degree of regurgitation is extraordinary subjective, with no possibility to reliably quantify it also with off-line Core Laboratory analysis. Persistent aortic regurgitation probably identifies patients with massive valve calcifications with a higher a priori risk, a difference difficult to correct in retrospective multivariate analyses. This is the only explanation of the paradox shown in the largest TAVI registry, the EORP Pilot Sentinel transcatheter valve registry, showing no differences in in-hospital

and 1 year mortality with Edwards Sapien XT and CoreValve despite a significantly greater incidence of aortic valve regurgitation.[10] Similarly, other minor differences between CoreValve US and PARTNER such as the higher stroke rate in the latter trial using a balloon expandable valve are not worth mentioning because both the devices used in these trials have seen or will see soon major changes. In particular between the original SAPIEN requiring a 24 Fr sheath for insertion and the new SAPIEN 3 going through 14 and 16 Fr sheaths and with an extreme flexibility to follow the aortic arch without scratching it there are so profound differences to make impossible the application of data from old trials.

WHAT HAVE WE LEARNED?

For the first time, in a randomized setting, TAVI with a self-expandable prosthesis has been proved to be associated with a significantly higher rate of survival at 1 year than SAVR in the treatment of high-risk patients affected by severe aortic stenosis. However, we doubt that TAVI (which in the 2012 guidelines on valvular heart diseases endorsed by the European Society of Cardiology received a class IIa recommendation) will jump to Class I with SAVR sinking to Class III for the patients meeting the inclusion criteria of the U.S. CoreValve trial. A critical aspect, which cannot be fully investigated and clarified because of the limited follow-up available, even for the first patients implanted, is the durability of the valvular prosthesis. Modern biological valves in adults have durability in excess of 15–20 years. The valves implanted transcatheter undergo the same preservation and decalcification processes, but the impact of crimping or stretching on longer than 5–10 years follow-up is speculative. With all these caveats, there is no doubt that US CoreValve will translate into a more liberal recommendation to TAVI, with score far below 10 STS and 20 EuroScore if other indices of frailty suggest better suitability of the patient for a less invasive treatment which certainly improves periprocedural morbidity, and now also impacts on late mortality.

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