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Transcatheter versus surgical aortic valve replacement in severe, symptomatic aortic stenosis

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Abstract

Aortic stenosis (AS) is the most common type of valvular heart disease in the elderly. Surgical aortic valve replacement (SAVR) has been the standard practice for treating severe, symptomatic AS, but recently new treatment options have emerged. Transcatheter aortic valve replacement (TAVR) is now an established treatment option in patients at high surgical risk. In this review, we focus on recent developments and compare the two treatment methods in specific populations in terms of efficacy and safety (e.g., in patients with history of prior thoracic surgery, type of anesthesia employed, access site used or need for permanent pacing). The impact of comorbidities (pulmonary hypertension, arterial hypertension and obesity paradox), the cost-effectiveness of TAVR *vs.* SAVR and advances in transcatheter valve technology as well as issues that merit further investigation are further discussed. Moreover, outcomes and complications of TAVR in patients of different risk category (extremely high, high, intermediate and low risk) are analyzed. We strongly believe that during the following years, TAVR may evolve as the treatment of choice in a broader group of patients with symptomatic AS and beyond those with intermediate and high-risk features.

1   Introduction

One of the most common types of valvular heart disease in the elderly population is aortic stenosis (AS). As the ageing population increases, the prevalence of life-threatening, severe AS will rise.[1] In the US population over 75 year old, 12.4% suffer from AS. The current practice regarding severe symptomatic AS is surgical aortic valve replacement (SAVR), but the treatment options has evolved noticeably.[2,3] Transcatheter aortic valve replacement (TAVR) has emerged as a new alternative approach in patients at high surgical risk. Comparison of the two methods is essential for selecting the ideal therapy in each patient. In the current review, we provide all the most recent data regarding the efficacy and safety of TAVR over SAVR, as well as important issues regarding complications' pattern and incidence of the two techniques.[3]

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2   Historical background

The first transcatheter aortic stent valve in animals was described in 1992, by Andersen, *et al*.[4] presenting the results of the implantation in pigs. It is notable that the first transcatheter aortic stent valve was implanted in humans, in 2002, using the transeptal approach and femoral vein access due to the bulky characteristics of the first device.[5] In 2005, due to the technology progression, novel techniques and tools led to change the way we approach the patient from the femoral vein to the transfemoral artery position, making the technique easier for the doctor and the patient as well.[6] TAVR, in general, is indicated for high risk patients, using the appropriate risk scores, who suffered from severe symptomatic AS. Currently, FDA expanded the approval for the TAVR technique, for special device, for people with symptomatic AS who are considered to be not only high risk but intermediate as well. The two procedures are completely different since SAVR remains a well standardized technique for most of the patients, but TAVR tends to be the approach for most of them during the following years. The current commercially used valves and the most important characteristics of them are listed in Table 1.

Table 1. Current commercially used valves and the most important characteristics of them.

Name	Size	Leaflets materials	Stent materials	Special characteristics	Sheaths required	Femoral artery minimum diameter
Edwards SAPIEN	23 mm & 26 mm	Initially Equine pericardial & later Bovine pericardial tissue	Stainless steel	Stent valve, balloon expandable	22 F & 24 F	7 mm & 8 mm
Edwards SAPIEN XT	20–23–26 & 29 mm	Bovine pericardial leaflets in a trifoliate configuration	Cobaltio-chromium stent	Stent valve, balloon expandable	18 F & 19 F	6 & 6.5 mm
Edwards Lifesciences SAPIEN 3		Bovine pericardial leaflets in a trifoliate configuration	Radiopaque, cobaltochromium frame	• Balloon expandable • Internal polyethylene terephthalate skirt		
Medtronic CoreValve	23–26–29–31 mm	Porcine pericardial leaflets in a trifoliate configuration	Self-expanding nitinol frame	Self-centering and partially retrievable valve	Initially 24 F & later 18 F [22F (OD)]	6 mm
CoreValve Evolute R	23–26–29 & 34 mm (only in the USA)	Porcine pericardial tissue in a trifoliate configuration	• Self-expanding nitinol frame radiopaque self-expanding nitinol support frame, supra-annular trileaflet porcine pericardial leaflets, and porcine pericardium fabric skirt • Radiopaque self-expanding nitinol support frame, supra annular • Porcine pericardium fabric skirt	• Fully recapture & reposition, extended Skirt • Indicated for small (18–20 mm) aortic annuli • Indicated for small aortic annuli (18–20 mm)	14 F [18F (OD)]	≥ 5 mm
Boston Scientific Lotus	23–27 mm and 25 mm is anticipated	Three bovine pericardial leaflets	• A braided nitinol frame	Can be subtly advanced or retracted or even completely retracted into the delivery sheath at any time prior to the final release	18 F	
Direct flow medical valve	25–27 mm	Tricuspid bovine peri-cardial valve attached to a polyester fabric cuff	• Nonmetallic percutaneous valve with an inflatable ring cuff frame	Fully repositionable and retrievable prior to final deployment through the introducer	18 F	
St. Jude Medical Portico	23–25 mm available and 27–29 mm (on evaluation in clinical trials)	Bovine pericardial trileaflets processed with the Linx anti-calcification technology	• Self-expanding Portico valve consists of a nitinol frame	A porcine pericardial sealing cuff		
Edwards Lifesciences Central	23–26 mm 29 mm (anticipated)	Three bovine pericardial tissue leaflets	• Self-expandable ultra-low profile valve • Nitinol frame	• Polyethylene terephthalate skirt Intended to minimize PV-AR. • The safety and performance study is currently ongoing	14 F	
10) Venus A Valve		A trileaflet bioprosthetic valve made of porcine pericardial leaflets	• Self-expanding nitinol stent frame	• The inclusion criteria were extended to bicuspid aortic valve disease • The first in-man Venus A-Valve trial is currently ongoing	18 F	
11) JenaValve	23–25–27 mm	A full porcine root valve	• A low-profile nitinol stent • Short stent design that Prevents coronary compromise by the native leaflets or stent struts, and that does not interfere with future coronary intervention	• Relies on an active clip fixation of the native aortic valve leaflets, thereby eliminating great radial forces on cardiac and aortic structures. • Aortic annuli ranging from 21–27 mm in diameter	Sheathless (transfemoral, transaxillary, transsubclavian approach, with a sheath (transaortic approach)	
12) Symetis ACURATE	• Small, medium, large • Annulus diameter ranging 20–27 mm	Biological tissue valve	• Self-expandable valve • Nitinol stent frame with well visible, under fluoroscopy, commissures with a circular radiopaque appearance	• Specifically transapical approach • Polyethylene terephthalate skirt is mounted at the proximal (intra-annular) part of the stent body	• 20 F • 15 F (the newer transfemoral version called ACURATE neo)	
13) Medtronic Engager	23–26 mm	Three leaflets cut from tissue-fixated bovine peri-cardium	• A self-expandable valve • Nitinol stent frame	• Annulus diameters from 21 to 27 mm	• 29 F (inner diameter) intro-ducer and a flexible delivery catheter with a 13 F shaft	

3   Major trials comparing TAVR versus SAVR

3.1   TAVR in high risk patients

The first large trial which compared the TAVR versus standard treatment in high-risk inoperable patients was the PARTNER 1B study.[7] The trial showed superior outcomes from TAVR versus conservative treatment for death from any cause and death from cardiovascular causes. This was a revolutionary step which changed the way physicians approached inoperable patients with severe symptomatic AS. The next step was the PARTNER 1A trial, where 699 high-risk patients with severe AS were randomly assigned to undergo either TAVR with a balloon-expandable bovine pericardial valve (both either transfemoral or the transapical approach) or SAVR.[8] The authors concluded that in high-risk patients with severe AS, the two procedures were associated with similar rates of death from any cause at 1 year. At 30 days, major vascular complications (11.0% *vs*. 3.2%, $P < 0.001$) and rates of stroke (8.3% *vs*. 4.3%, $P < 0.05$) were more frequent with TAVR over SAVR. The results were consistent even in the 2-year follow up with mortality rates 33.9% for TAVR *vs*. 35.0% for SAVR ($P = 0.78$). Importantly, TAVR was associated with an increased late mortality with a hazard ratio of 2.11 (95% CI: 1.43–3.1; $P < 0.001$) due to more mechanical complications of the valve such as paravalvular leak, which was more common in the TAVR group (6.9% for TAVR *vs*. 0.9% for SAVR, $P < 0.001$, at 2-year follow-up).[8]

A meta-analysis of five randomized trials and 31 observational studies including 16,638 patients showed no mortality difference of TAVR as compared with SAVR but potential benefit in low-to-intermediate risk patients undergoing transfemoral TAVR over SAVR (OR: 0.67; 95% CI: 0.42–1.07).[9] It was confirmed that the incidence of periprocedural myocardial infarction, major bleeding, acute kidney injury or new onset atrial fibrillation was lower with TAVR and the risk of pacemaker implantation, vascular complications, and paravalvular leak increased lower with SAVR.[9]

3.2   TAVR in intermediate risk patients

An Italian observational, multicenter, "real-world" study, in a low-intermediate risk population, revealed comparable mortality, major adverse cardiac and cardiovascular events (MACCE) and rates of rehospitalization between SAVR and TAVR in a propensity-matched population of 1300 patient.[10]

In the PARTNER 2A randomized trial, TAVR was compared with SAVR in 2032 intermediate-risk patients. The primary endpoint of all-cause mortality or disabling stroke at two years was to be similar for both groups ($P_{noninferiority}=$ 0.001). TAVR resulted in higher rate of major vascular complications and more paravalvular regurgitation; while surgical replacement resulted in higher rates of acute kidney injury, severe bleeding and new-onset atrial fibrillation.[11]

The latest Surgical Replacement and Transcatheter Aortic Valve Implantation (SURTAVI) trial was a multinational, randomized, clinical trial which included 1746 patients at intermediate surgical risk, of whom 1660 underwent TAVR or surgical operation.[12] The incidence of primary endpoint, a composite of death from any cause or disabling stroke at 24 months was 12.6% and 14% in the two groups, respectively. Complications followed the same pattern shown in PARTNER 1A and 2A trials[8,11] and the aforementioned meta-analysis.[9] Based on the results of the SURTAVI trial and summarizing all the data regarding the intermediate risk patients, a new IIa indication was given for the TAVR procedure according to the 2017 AHA/ACC focused update of the 2014 AHA/ACC Guideline for the management of patients with valvular heart disease.[13]

4   TAVR *vs*. SAVR in low risk patients

Despite the already proven efficacy of TAVR, in high- and intermediate-risk patients, an expansion of the indication for TAVR in lower-risk patients is not justified. A recent analysis compared outcomes of TAVR *vs*. SAVR in patients with EuroSCORE II < 4%. The analysis demonstrated similar 30-day survival (97.4% after TAVR and 97.1% after SAVR, $P = 0.82$) after the two procedures. The survival at three years was 72.0% after TAVR and 83.4% after SAVR ($P = 0.0015$) with freedom from MACCE of 67.3% and 80.9% ($P < 0.001$), respectively. Moreover, incidence of cardiac tamponade (4.3% *vs*. 1.7%; $P = 0.049$), permanent pacemaker implantation (12.7% *vs*. 2.6%; $P < 0.001$), major vascular damage (7.6% *vs*. 0; $P < 0.001$), and moderate-to-severe paravalvular regurgitation (48.2% *vs*. 11.3%; $P < 0.001$) was more frequent after TAVR. On the contrary, the rate of cardiogenic shock, severe bleeding and acute kidney injury was higher after SAVR. The mean transvalvular gradient after TAVR was lower than after SAVR (10.6 *vs*. 14.4 mmHg; $P < 0.001$). The clear message was that in this low-risk group for surgery, SAVR appears more advantageous than TAVR. Further studies with new-generation valve prostheses are necessary before expanding indications of TAVR in lower-risk patients.[14]

5   TAVR in patients at extremely high risk of perioperative mortality

A single-center study, which included 319 patients who

underwent transapical or transaortic TAVR, compared patients with extremely high risk of perioperative mortality (EuroSCORE > 40%, *n* = 90) with those with a lower calculated risk (EuroSCORE < 40%, *n* = 229). There was not statistically significant difference between the two groups in 30-day mortality, stroke rate or the incidence of acute, stage III kidney injury. Statistically significant lower rates in the lower-risk group were observed regarding need for cardiopulmonary bypass (3.9% *vs.* 11.1%, *P* = 0.02) or sternotomy conversion (1.3% *vs.* 5.6%, *P* = 0.04), mean ventilation time and length of intensive care unit stay (2.9 *vs.* 6.8 days, *P* < 0.001). In conclusion, the safety of TAVR procedure is established even in patients with excessively high risk of perioperative mortality and MACCE.[15]

6   TAVR in nonagenarians

The nonagenarian are frequently an exclusion criterion when designing a randomized study. There is no enough data regarding this under-represented group of patients despite the dramatic increase of the average life expectancy. Meanwhile, the existing data and evidence has not yet confirmed the feasibility and safety of TAVR in this special group of patients. A recent study compared carefully selected patients > 90 years old, without many co-morbidities, versus younger patients who underwent TAVR. Major complications were similar, and all-cause mortality at 30 days and 1 year was not statistically different (2.9% and 12.5% in patients aged ≥ 90 *vs.* 2.8% and 12.3% in patients aged < 90, respectively). Only minor vascular complications (13.2% *vs.* 7.7%; *P* = 0.04) were more frequent among nonagenarians. Thus, clinicians should not deter, judiciously selected, nonagenarian patients with severe, symptomatic AS for TAVR.[16]

7   Low ejection fraction and TAVR

Severe reduced left ventricular ejection fraction (LVEF) is associated with worse outcomes in SAVR, especially when there is no contractile reserve. In a study including low-flow/low-gradient AS patients without contractile reserve undergoing TAVR, perioperative mortality was 22% and the main cause was cardiogenic shock (83.4%).[17] In the German TAVI Registry, 1432 patients who underwent TAVR were separated into two groups (A: LVEF ≤ 30%, *n* = 169, mean age 79.9 ± 6.7 years, logistic EUROSCORE 34.2% ± 17.8%; B: LVEF > 30%, *n* = 1263, age 82.0 ± 6.1 years, logistic EUROSCORE 18.9% ± 12.0%). High procedural success rates [95.9% (A) and 97.6% (B)] and excellent outcomes in survival and NYHA classification at 30

days were observed in both groups. Moreover, the quality of life improvement, according to the self-assessment in health condition (scale 0-100) was significant, with a larger benefit for patients of group A (28 *vs.* 19 patients, *P* < 0.0001). However, group A was associated with higher rates of mortality at 30 days (14.3% *vs.* 7.2%) and 1 year (33.7% *vs.* 18.1%, *P* < 0.001), low cardiac output syndrome (*P* < 0.01) and need for resuscitation (*P* < 0.05).[18]

8   TAVR in patients with or without previous coronary artery by-pass graft

The perioperative risk in patients with history of previous coronary artery by-pass graft (CABG) is increased in SAVR. A recent study, based on data from the FRANCE-2 registry, compared the outcome and the overall survival in patients who underwent TAVR with and without history of CABG in 683 patients. On multivariate analysis, CABG was not associated with greater 1-year post-TAVR mortality. Finally, this study concluded that previous CABG not only does not adversely affect outcome in patients who underwent TAVR, but also it could be an alternative procedure to surgery, especially in high-risk patients with history of CABG.[19]

A meta-analysis based on data from five cohort studies evaluated the relative perioperative and long-term survival of patients with previous CABG who underwent TAVR *vs.* those who underwent SAVR. It was demonstrated that both procedures were equally safe and effective with 1-year all-cause-mortality of 17.2% *vs.* 16.4%, thereby making TAVR an alternative therapy to SAVR in CABG patients.[20]

9   TAVR and previous chest radiation

The patients with severe AS undergoing SAVR and history of mediastinal radiation therapy (XRT) have significantly worse longer-term survival versus a matched cohort group of patients (mortality rate 48% in XRT group *vs.* 7% in the comparison group at a 6 ± 3 years follow-up), as shown in a recent study.[21] In another study, the authors compared the outcomes in post chest radiation patients with matched control patients undergoing TAVR and tried to identify predictive factors of survival. It was demonstrated that 30-day survival was 92% in both groups, but patients in the radiation group displayed lower, albeit not statistically significant survival rates compared to the controls at 5-year follow-up (33% ± 10% *vs.* 42% ± 11%; *P* = NS). Moreover, the main cause of death in the radiation group was respiratory failure. Nevertheless, in this population, it was shown a sustained post-procedural improvement in functional results after TAVR.[22]

10   Redo SAVR or valve-in-valve with TAVR

During the last years, there is an increased rate of bio-prosthetic aortic valves implantations compared with mechanical valves, resulting in an increased need of a future reoperation in case of bioprosthetic valve malfunction. Given the frailty of this sub-group population and their co-morbidities, the pending dilemma is redo aortic valve surgery (SAV-in-SAV) or transcatheter valve-in-valve (TAV-in-SAV) implantation. A recent single-centre study with 102 patients showed similar, good early clinical outcomes of both SAV-in-SAV and TAV-in-SAV procedures. In particular, thirty-day mortality was not significantly different between the two groups [TAV-in-SAV *vs.* SAV-in-SAV: 2 (4%) *vs.* 0, $P = 0.238$]. However, 1-year survival was statistically significant lower in the TAV-in-SAV than in the SAV-in-SAV group (83% *vs.* 96%, $P < 0.001$). It is notable that the patients in the TAV-in-SAV group were significantly older, had a higher mean logistic EuroSCORE and exhibited a lower mean LVEF than patients in the SAV-in-SAV group. Nonetheless, redo surgery still remains the standard of care in cases of failing of surgical bioprosthetic valves.[23]

11   Effectiveness and safety of different TAVR devices versus SAVR

A network meta-analysis which included four trials (CHOICE trial, PARTNER Cohort A trial, STACCATO trial, US CoreValve trial) evaluated the all-cause mortality in patients underwent TAVR (either transapical Sapien, transfemoral Sapien, CoreValve) *vs.* SAVR. Both procedures appeared similar regarding safety and efficacy and each procedure followed the same pattern of complications, as previously described. Within the same study, a comparison between the transcatheter devices demonstrated less strokes with CoreValve, than with transfemoral or transpical Sapien, whereas pacemaker implantation was more common with the Core-Valve.[24]

12   Peri-procedural bleeding after TAVR versus SAVR

According to a recent paper from Genereux, *et al.*,[25] bleeding complications after SAVR is about 22.7%. The authors concluded that high-risk patients with AS who enrolled in the PARTNER I randomized trial, bleeding complications occurred more frequently after SAVR than after TAVR and were also related with a worse long-term prognosis (1-year mortality). The implication of bleeding com-

plications on one year clinical outcomes were confirmed in another study with 129 patients who underwent TAVR.[26] The serious bleeding events according to the Valve Academic Research Consortium 2 (VARC-2) criteria were 19.4%, of which 7% were life-threatening/disabling and 12.4% were major bleedings. Even if TAVR seems to be a safer procedure in comparison to SAVR regarding bleeding complications, the latter remain a frequent event and is associated with decreased short and mid-term survival (4.0% *vs.* 20.0%, $P = 0.02$) and 1-year mortality (11.1% *vs.* 40.0%, $P < 0.002$). Moreover, according to the study results, diabetes mellitus (OR: 2.93, 95% CI: 1.08–7.93; $P = 0.03$) and trans-subclavian access (OR: 4.38, 95% CI: 2.13–14.29; $P = 0.01$) are independent risk factors for serious bleeding events.

13   Antithrombotic therapy following TAVR and SAVR

The administration of antiplatelet treatment after TAVR is not well established and is based on expert opinion (level of evidence C). According to the recently published American Heart Association (AHA) guidelines, clopidogrel 75 mg daily for the first 6 months and life-long aspirin 75–100 mg daily are recommended.[13]

In a pooled analysis of individual patient data from 672 participants who underwent TAVR, single antiplatelet treatment was compared to dual antiplatelet therapy (DAPT). No difference was observed between the two groups in the primary endpoint that was a composite of net adverse clinical and cerebral events (NACE) including MACCE and major bleeding at 30-days. In the aspirin-only group, a NACE rate of 13% was observed *vs.* 15% in the DAPT group (OR: 0.83, 95% CI: 0.48–1.43; $P = 0.50$). Additionally, there was not statistically significant difference between the two groups in all-cause mortality, ACS, or stroke, with a tendency of less life-threatening and major bleeding events in the aspirin-only group ($P = 0.09$). Further investigation is recommended by the authors for the value of clopidogrel administration when added to aspirin after TAVR.[27]

In contrast, life-long anticoagulation is not required in patients with aortic bioprostheses. Nevertheless, the risk of ischemic stroke early postoperatively, especially in the first 90 to 180 days after a bioprosthetic AV replacement (AVR), is increased. In a large observational Danish registry, a lower risk of stroke and death with vitamin K antagonists (VKA) therapy extending up to six months was observed, without significantly increase in bleeding events. Thus, the recent AHA/ACC guidelines recommend that anticoagulation with VKA may be reasonable for at least 3 months and

perhaps for as long as 6 months after bioprosthetic AVR in patients at low bleeding risk.[28]

Oral anticoagulation with VKA is universally indicated in patients with mechanic aortic valves life-long. In a nationwide population-based study that aimed to demonstrate rates of stroke/thromboembolism and major bleeding in specific age categories and identify risk factors for adverse events in patients with mechanic aortic prostheses, the observation was that the rate of first major bleeding was 2.6 per 100 patient-years with AVR ($P < 0.001$). Additionally, increasing age and history of major bleeding were identified as independent risk factors for major bleeding incidents.[29]

An observational study that included 890 patients from two registries (RESOLVE and SAVORY) demonstrated data for the prevalence of subclinical leaflet thrombosis in bioprosthetic valves as depicted in 4D computer tomography (CT) imaging after TAVR and SAVR. Additionally, the effect of novel oral anticoagulants (NOACs) on the subclinical leaflet thrombosis was analyzed. Higher rates of subclinical leaflet thrombosis were observed in TAVR than in SAVR group (13% *vs.* 4%) and in patients on DAPT than in patients on oral anticoagulants (15% *vs.* 4%); NOACS and warfarin were equally effective. Moreover, subclinical leaflet thrombosis resolved in 100% of patients treated with oral anticoagulants (NOACs or warfarin), but it remained or even progressed in 91% of patients that did not receive anticoagulants ($P < 0.0001$). The comments from the authors according to these results were that it seems more reasonable to prescribe oral anticoagulation especially for the younger patients.[30]

14　Impact of anesthesia type on outcomes

There is still no wide-ranging consensus concerning the use of general instead of local anesthesia with sedation throughout the TAVR procedure. Data from the multicenter ADVANCE study showed clearly that both types are equally safe without significant differences between them, regarding all-cause mortality (25.4% *vs.* 23.9%, $P = 0.78$), cardiovascular mortality or stroke through 2-year follow-up. As expected, major vascular complications were more likely to happened, in the local anesthesia group, due to inappropriate movements of the patient. Moreover, the total hospital stay was comparable between the two types of anesthesia, concluding that the final decision has to be individualized.[31]

The results of another recent retrospective study confirmed the above data. The authors concluded that there was no significant difference between the two types of anesthesia regarding the mid-term survival.[32] Importantly, considering the access route for TAVR (transapical or transfemoral), no significant difference could be found in the mid-term survival.[32]

15　Transfemoral TAVR *vs.* Transapical TAVR

An important issue regarding high risk patients who are unable to proceed with SAVR, is safety and efficacy between the transfemoral transcatheter aortic valve replacement (TF-TAVR) as compared with the transapical transcatheter aortic valve replacement (TA-TAVR). There are controversial results in the recent literature. In the observational study of effectiveness of avR-TAVI procedures for severeaortic stenosistreatment study (OBSERVANT study), patients who underwent TF-TAVR and TA-TAVR were evaluated on the immediate and intermediate outcome with propensity score matching. The 30-days frequencies after TA-TAVR over TF-TAVR in the 199 matched pairs were as follows: 8.0% and 4.0% for mortality ($P = 0.102$), postoperative stroke 2.0% and 1.0% ($P = 0.414$), cardiac tamponade 4.1% and 1.5% ($P = 0.131$), pacemaker implantation 8.7% and 13.3%, $P = 0.414$) and infections 6.7% and 3.6% ($P = 0.180$). Furthermore, TA-TAVR was associated with significant more red blood cell transfusion ($P = 0.0002$) and acute kidney injury ($P < 0.0001$) compared with TF-TAVR. Three-year survival rate was 69.1% after TF-TAVR and 57.0% after TA-TAVR ($P = 0.006$), whereas freedom from MACCEs was 61.9% after TF-TAVR and 50.4% after TA-TAVR ($P = 0.011$). Therefore, the transfemoral approach whenever feasible, should be considered the preferable access route for TAVR.[33]

A confirming retrospective review from Mayo Clinic showed that the access did not influence treatment-related mortality rates. The transapical access was chosen in patients with more comorbidities [higher Society of Thoracic Surgeons score (STS), more peripheral vascular disease, older patients, more previous CABG]. Despite differences in baseline patients' risk, statistically significant difference was only shown in the rate of paravalvular regurgitation grade (transapical, 2.9%; transfemoral, 10.4%; $P = 0.001$). The conclusion was in line with the previous demonstrated results, confirming that access does not have impact on treatment-related mortality rates.[34]

A meta-analysis of 14 published studies showed that the 30-day mortality was 7.5% versus 11.6% respectively with similarly higher rates for stroke and MACCE favoring the transfemoral access.[35]

16   TF-TAVR *vs*. TA-TAVR in sub-groups without difference in Logistic Euroscore

Given the imbalance of the logistic EuroSCOREs between TA and TF patients, a recent Chinese meta-analysis assessed the rates in mortality and other complications among patients undergoing either TF-TAVR (n = 666) or TA-TAVR (n = 457) without significant between-group differences regarding the logistic EuroSCORE. This analysis revealed that TF-TAVR has a higher risk of vascular complication (14.7% *vs*. 7.1%, P = 0.01) and postoperative heart block (13.4% *vs*. 4.6%, P = 0.03), but a similar incidence of stroke (4.7% *vs*. 2.6%, P = 0.21) and mortality at 30 days (9.2% *vs*. 11.4%; P = 0.14) as well as beyond one year. According to these results, TA approach is an alternative and feasible choice for patients with severe AS.[36]

17   Implantation of permanent pacemaker in patients after TAVR

Atrioventricular conduction disturbances needing permanent pacemaker implantation (PPMI) in patients after TAVR, is one of the most common complications of this procedure.[37] On the other hand, the need for PPMI subsequently to SAVR is uncommon. In a recent meta analysis, the overall prevalence of PPMI after SAVR is in the order of 5.0% [SAVR alone, 4.8%; SAVR + CABG, 4.6%; SAVR + MVR (mitral valve replacement), 7.7%; SAVR + MVR: 10%].[38] The incidence of PPMI depends on the design and the ability of precise delivery of the prosthesis. According to the FRANCE-2 registry, the developments of delivery devices of the CoreValve system failed to translate into a significant decrease in the incidence of PPMI after TAVR, with PPMI occurring in about 28%–30% of the patients and all-cause mortality being similar between the groups that received or not received PPM (16.3 *vs*. 16.9%, P = 0.82). Moreover, PPMI does not necessarily imply long-term pacing dependence, thereby supporting the view of the need for new valve and delivery system technologies in order to reduce PPMI rates.[39] In the aforementioned SURTAVI trial, the need of PPMI was 25.9% after TAVR, with similar rates among patients who received either CoreValve (25.5%) or EvolutR valve (26.7%).[12] In a multicenter study that aimed to evaluate whether TAVR with SAPIEN-3 is a viable alternative to SAVR in intermediate or high risk patients, the rate of new pacemaker implantation was 13.3% at 30 days, a rate lower than that referred with self-expanding valves.[40]

18   Pulmonary hypertension in patients undergoing TAVR

Pulmonary hypertension (PH) is a very strong predictive

risk factor of perioperative mortality in patients undergoing TAVR and is included both in the STS and EuroSCORE logistic calculation. A recent study assessed the impact of PH on prognosis. A pre-procedural right-heart catheterization determined pre-capillary or post-capillary PH categories and demonstrated that pre-capillary PH did not improve after TAVR (49.0 ± 12.6 *vs*. 51.6 ± 14.3 mmHg; P = 0.36), while post-capillary PH improved (57.8 ± 14.1 *vs*. 50.4 ± 17.3 mmHg; P = 0.015). Nevertheless, both PH groups had by two to three-fold higher 1-year mortality rate, when compared with patients without preexistent PH.[41]

19   Obesity paradox and TAVR

It is common knowledge that elevated body mass index (BMI) is a predictor of mortality after surgery.[42] An Italian meta-analysis with 10,196 patients found that greater BMI is associated with significantly less in-hospital and 30-day early (P = 0.001) less mid-term as well as long-term post-TAVR mortality (P = 0.04). The authors concluded that obviously there is an obesity paradox in TAVR procedures.[43]

20   Arterial hypertension after TAVR

It is accepted that morbidity and mortality after SAVR increase when arterial hypertension (HT) coexists. The same applies in patients with uncontrolled HT (blood pressure ≥ 140/90 mmHg) undergoing TAVR. In one study, all-cause (6.5% *vs*. 16%; P = 0.04) and cardiovascular (3.7% *vs*. 11.6%, P = 0.035) mortality was significantly higher among hypertensive as compared with normotensive patients. The uncontrolled HT at the time of discharge may also contribute to delayed, post-procedural symptomatic improvement as assessed either with New York Heart Association (NYHA) functional class (class increase of: 1.4 ± 0.8 *vs*. 0.8 ± 1.0; P = 0.002), or with the six-minute walk test (6-MWT) (distance increase: 100 ± 71 *vs*. 30 ± 64 m; P < 0.001).[44]

21   Minimally invasive strategy versus conventional strategy

A retrospective study assessed the safety and efficacy of a minimally invasive strategy (MIS) versus conventional strategy (CS) during transfemoral TAVR cases. MIS is based mostly on local anesthesia and conscious sedation, performed in the cath laboratory without transesophageal echocardiography guidance. They used all commercially available valves. Even though the baseline characteristics

were similar and procedural success was comparable (99.1% in MIS and 98.9% in CS, *P* = NS), Minimally invasive strategy was associated with notable cost-saving, thanks to shorter postprocedural hospital stay [median, 3.0 (2.0–5.0) days for MIS *vs*. 6.0 (3.5–8.0) days for CS] and lower cost. Moreover, both procedures showed similar survival rates at a median follow-up of 230 days.[45]

22 Access-related vascular complications

The ideal method of access for transfemoral TAVR is not yet well documented. One study compared the surgical cut-down approach, with the complete percutaneous access. Surgical cut-down technique provided less access and bleeding complications (20.6% *vs*. 8.1%, *P* = 0.04 and 18.1% *vs*. 4.4%, *P* = 0.03, respectively), but did not differ with the percutaneous approach regarding major complications (*P* = NS). It appears that both techniques are complementary and necessary for an individualized arterial access depending on patient's characteristics and anatomy, expertise of the interventional cardiologists and the availability of vascular surgeons.[46]

23 First versus second generation self-expandable transcatheter heart valves

A case-matched comparison of new type, nitinol-based second generation (SymetisAcurate Neo TF™) heart valves and first generation, self-expandable valves (CoreValve™), showed superiority regarding the post-interventional pressure gradients (7.0 ± 2.8 *vs*. 8.8 ± 4.0 mmHg, *P* = 0.006), the effective orifice area (EOA) (1.9 ± 0.3 *vs*. 1.8 ± 0.2 cm^2, *P* = 0.015), the severity of residual paravalvular leakage (PVL, 2.9% *vs*. 15.94%, *P* = 0.013) and the rate of PPM implantation (8.7% *vs*. 44.9%, *P* < 0.001). However, there was not shown statistically significant differences in the all-cause 30-day mortality rate (5.8% *vs*. 10.14%, *P* = 0.36) and in the disabling stroke (2.9% *vs*. 5.8%, *P* = 0.41), respectively. Thus, further clinical evaluation through larger patient cohorts is needed, but the results were really promising.[47]

24 Cost-effectiveness of TAVR *vs*. SAVR

TAVR as compared with SAVR is a similarly safe, effective and efficacious alternative treatment option for high risk patients with severe, symptomatic AS. A number of studies have addressed the cost-effectiveness of the procedure. A more detailed analysis on this issue can be found in the paper of Kourkoveli, *et al*.[48] in this issue of the Journal

Geriatric of Cardiology. In-hospital cost, length of stay and outcomes between TAVR and SAVR were studied in a trial which compared 595 TAVR patients matched with 1785 SAVR patients in a 1: 3 ratio. The results showed no difference in mean ($181,912 *vs*. $196,298) or median ($152,993 *vs*. $155,974) hospital cost between TAVR and SAVR (*P* = 0.60), while the TAVR patients had significant shorter duration of hospital stay (mean 9.76 *vs*. 12.01 days, *P* < 0.001, respectively). Post procedural in-hospital death or stroke did not show any significant difference. The authors concluded that TAVR is an equal alternative to SAVR regarding financial data and leads in an approximately 2-day shorter duration of hospitalization.[49]

25 Future considerations

Because pharmacological therapy is not effective in severe, symptomatic AS and sometimes could be harmful, the only effective treatment is TAVR. TAVR is now approved mostly for those patients who are not surgical candidates due to advanced age and comorbid conditions. Following the increasing experience in the real life and given the fact that the logistics are becoming less prohibitive in favor of the less invasive approach, TAVR came here to stay as a treatment of choice in inoperable, high-risk and intermediate risk patients. This is an important modification of the way the medical community has faced so far a severe and frequent medical situation such as severe AS. The expansion of the indications for TAVR in intermediate-risk patients is viewed as an evolutionary therapy to the TAVR revolution. The expansion of the indication for the TAVR is based on positive clinical data from the Nordic Aortic Valve Intervention (NOTION) trial, from a subset analysis from the CoreValve U.S. High Risk Pivotal trial and more recently incorporating the results of the SURTAVI trial. The results revealed that similar clinical outcomes to SAVR can be accomplished by using the TAVR technique in patients who are mostly surgical candidates, including low rates of all-cause mortality and major stroke, low incidences of procedural complications and excellent blood flow with the newer TAVR technique, mostly with the CoreValve Evolut R bioprosthesis valve.

26 Conclusions

TAVR revolutionized the landscape of structural heart disease by halving mortality over medically-treated patients and showing at least the same good results as SAVR both in high-risk and intermediate-risk patients with severe symptomatic aortic stenosis. Future technical developments and

randomized tials will probably broaden the spectrum of indications for TAVR toward lower-risk patients with severe AS.

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