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Current results and remaining challenges of trans-catheter aortic valve replacement expansion in intermediate and low risk patients

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ABSTRACT

TAVR has become the standard treatment in patients at increased surgical risk (STS or EuroSCORE II ≥4% or logistic EuroSCORE *I* ≥ 10% or other risk factors not included in these scores such as frailty, porcelain aorta, sequelae of chest radiation) and it is increasingly being performed in patients at intermediate to low (STS or EuroSCORE II <4% or logistic EuroSCORE *I* < 10%) surgical risk. Although non-inferiority has been demonstrated in intermediate and low-risk patients, several challenges need to be addressed before expansion to younger patients. Current trends, trials results, and remaining challenges are summarized and discussed in this review.

1. Introduction

Transcatheter aortic valve replacement (TAVR) has become the therapeutic option of choice for patients with symptomatic, severe aortic valve stenosis (AS) who are at increased risk for surgical aortic valve replacement (SAVR) [1]. During the last decade, technological improvements in transcatheter heart valves (THVs) have led to a significant increase in TAVR safety and efficacy. The results from recent randomized controlled trials (RCTs) and large registries have expanded the indication for TAVR to lower risk patients as an alternative to SAVR [2–5]. Although the above-mentioned TAVR studies included patients with a lower surgical risk, the mean age of enrolled patients was not different compared to the early TAVR trials conducted in extreme or high risk patients. When considering further expansion of TAVR indications to encompass younger patients aged 75 years or less, there are still some challenges ahead. This review aims to summarize the evidence supporting the expansion of TAVR to lower-risk patients, and to discuss the potential advantages and challenges that this procedure will face in this subset of patients.

2. Procedural risk assessment

Which variables are considered to define a patient at low-intermediate operative risk? A multitude of relevant clinical and anatomical factors may influence operative complexity, complicating precise risk assessment in AS patients. Both, in clinical practice and in RCTs, the risk scores used to support an indication for TAVR have been inherited from cardiac surgery. All of the widely-used risk scores (STS-PROM, logistic EuroSCORE, EuroSCORE II) have important limitations in predicting operative mortality [6–7]. In the absence of a completely reliable risk model, the STS-PROM has mostly been applied, in clinical practice and clinical trials, for individual risk assessment. Historically, operative risk was classified as high (STS-PROM >8%), intermediate (STS-PROM of 4–8%), and low (STS-PROM <4%). However, while a surgical risk score accurately predicts SAVR outcomes [8–9], it overestimates TAVR mortality because of many confounders (i.e. general anaesthesia is not needed for TAVR, and most variables present in the surgical scores such as chronic pulmonary disease and renal insufficiency, have a lesser influence on TAVR outcomes). Furthermore, important additional factors such as active malignancy, frailty, porcelain aorta, chest wall radiation, liver cirrhosis, or neurological impairment, were not comprehensively integrated in these risk models. Accordingly, the guidelines acknowledge the imperfect nature of risk scores, and recommend that the decision to perform TAVR should be made on the basis of multidisciplinary Heart Team evaluation after a thoughtful clinical evaluation and the participation of patients and their families in the decision [1].

3. Current evidence from randomized trials and large registries

3.1. Randomized studies

Three RCTs and multiple international prospective registries have broadened the indications for TAVR to lower-risk patients.

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3.1.1. NOTION trial

The NOTION (Nordic Aortic Valve Intervention) trial randomized 280 AS patients aged >70 years (and no significant coronary artery disease) to TAVR ($n = 145$) with a first generation self-expanding THV (Medtronic CoreValve) or SAVR ($n = 135$) at three Scandinavian centres. Mean STS-PROM was 2.9 ± 1.6% in TAVR and 3.1 ± 1.7% in SAVR patients. The access route was trans-femoral (TF) in 96.5% of TAVR procedures [10].

Although the number of recruiting centres was relatively low and the sample size small, this study provided important information on selected low risk patients undergoing aortic valve replacement.

In the intention-to-treat population, no significant difference in the primary endpoint (composite rate of death from any cause, stroke, or myocardial infarction at 1 year) was found (13.1% vs. 16.3%; $p = 0.43$ for superiority). Even after stratifying patients into low- and intermediate-risk (i.e. STS <4% vs. ≥4%) there was no statistically significant difference in the composite end-point between the groups. TAVR patients suffered higher rates of permanent pacemaker (pPM) implantation and para-valvular leak (PVL), had a worse NYHA functional class, but less life-threatening bleeding, cardiogenic shock, new-onset atrial fibrillation, and acute kidney injury (AKI) [10]. Recent 5-year data confirmed non-inferiority of TAVR vs. SAVR regarding the composite end-point (TAVR 39.2% vs. SAVR 35.8%; $p = 0.78$) and the 5-year all-cause mortality of 27.7% was the lowest 5-year rate ever reported in a TAVR population [11].

3.1.2. PARTNER 2A

The Placement of Aortic Transcatheter Valves (PARTNER) was an international trial involving 2032 intermediate-risk patients (mean age 81.5 years, mean STS-PROM score 5.8%), who were randomized either to TAVR with a second generation balloon-expandable (BE) THV (SAPIEN XT system, Edwards Lifesciences, Irvine, CA) or to SAVR [12]. TAVR in selected patients (subjects with concomitant severe coronary artery disease such as unprotected left main or syntax score >32, uni or bicuspid aortic valve, prior balloon aortic valvuloplasty, severe left ventricular dysfunction with left ventricular ejection fraction <20%, severe chronic kidney disease, were excluded) resulted non-inferior to SAVR with respect to the primary end-point (all-cause death or disabling stroke) at 2 years (19.3% in the TAVR group vs. 21.1% in the SAVR group; $p = 0.25$). Of note, the percentage of patients undergoing CABG in addition to SAVR was numerically higher compared to that underwent PCI in addition to TAVR (14.5% vs. 3.9%). Importantly, a subgroup analysis demonstrated superiority for the TF TAVR cohort compared to SAVR (16.3 vs. 20%, $p = 0.04$). Similar to the NOTION trial, TAVR resulted in lower rates of AKI, severe bleeding and new-onset atrial fibrillation, but was associated with higher rates of major vascular complications and significant PVL. Interestingly, rates of pPM implantations were not significantly different in both groups with a faster recovery and shorter hospitalization (in-hospital: 6 vs. 9 days, ICU: 2 vs. 4 days, $p < 0.001$) were observed after TAVR.

3.1.3. SURTAVI

In the Surgical Replacement and Transcatheter Aortic Valve Implantation (SURTAVI) trial [13], a total of 1746 intermediate-risk patients (mean age 79.8 years, mean STS score 4.5%) were randomized (recruitment period of almost 4 years) to TAVR with the use of a self-expandable (SE) prosthesis (CoreValve or Evolut R, Medtronic, Santa Rosa, CA) or SAVR. The primary endpoint (a composite of all-cause death and disabling stroke at 2 years) was similar in both treatment arms (12.6% [TAVR] vs. 14% [SAVR], posterior probability of non-inferiority >0.999). Again, higher rates of AKI, new onset atrial fibrillation, and transfusion requirements were observed after SAVR while hemodynamic measures were in favor of TAVR (trans-prosthetic gradients, effective orifice area), the incidence of PVL and the need for pPM implantation were lower after SAVR.

Furthermore, a sub-analysis of this randomized study explored the outcomes of TAVR vs. SAVR in patients with a STS-PROM score below 3% demonstrating a significantly lower rate of all-cause mortality or disabling stroke in TAVR vs. SAVR at 1-year follow-up (1.5% vs. 6.5% $p = 0.04$) [14].

These results are confirmed by different meta-analysis of RCTs comparing TAVR vs. SAVR in low to intermediate risk patients that consistently report no significant difference in mortality between the groups, increased risks of pPM implantation, major vascular complications and moderate-to-severe PVL associated with TAVR, though lower incidence of atrial fibrillation, severe bleeding, AKI and early stroke [15–19].

Although the data coming from PARTNER 2A, SURTAVI and meta-analysis of RCTs are consistent, longer-term follow-up (>2 years) are needed to better understand the performance of a THV vs. a surgical prosthesis over a long time period in lower risk patients.

3.1.4. PARTNER 3

The PARTNER 3 trial was a multicenter, RCT in which 1000 patients (mean age 73.5 years) were randomized to TAVR with TF placement of a third-generation BE THV (Sapien 3, Edwards Lifesciences, Irvine, CA; which has a lower sheath profile [14–16 vs. 16–18 French], a steerable commander delivery system and an outer sealing polyethylene terephthalate fabric skirt) vs. a standard SAVR in patients with severe AS and a low surgical risk (mean STS-PROM score 1.9%). The Kaplan–Meier estimate of the rate of the primary composite end point (death, stroke or re-hospitalization) at 1-year was significantly lower in the TAVR group than in the SAVR group (8.5% vs. 15.1%; absolute difference, −6.6 percentage points; 95% confidence interval [CI], −10.8 to −2.5; $p < 0.001$ for non-inferiority; hazard ratio, 0.54; 95% CI, 0.37 to 0.79; $p = 0.001$ for superiority). The requirements for both non-inferiority and superiority were met in favor of the percutaneous procedure. At 30 days, TAVR resulted in a lower rate of stroke than SAVR ($p = 0.02$), in lower rates of death or stroke ($p = 0.01$) and new-onset atrial fibrillation ($p < 0.001$). TAVR also resulted in a shorter index hospitalization than SAVR ($p < 0.001$). There were no significant between-group differences in major vascular complications, pPM insertions, or moderate/severe PVL [20]. Although this trial has several limitations, such as unblinded adjudication of the end-points (which could have resulted in bias in outcome assessment), selected population (excluded patients with poor TF access, bicuspid aortic valves or other anatomical or clinical factors that increased the risk of complications associated with either TAVR or SAVR) and limited follow-up (actually 1-year), the findings reported suggest that the value of TAVR (performed using a BE THV) as compared with SAVR may be independent of risk profiles in patients with severe symptomatic AS.

3.1.5. Evolut TAVR in low risk patients

In this RCT a total of 1468 patients with severe symptomatic AS underwent randomization to TAVR using a SE supra-annular THV (CoreValve or Evolut R or Evolut Pro) or SAVR. The patients' mean age was 74 years while mean STS-PROM score was 1.9%. The 24-month estimated incidence of death or disabling stroke (primary end-point) was 5.3% in the TAVR vs. 6.7% in the SAVR group demonstrating non-inferiority of the percutaneous vs. the surgical procedure (difference, −1.4 percentage points; 95% Bayesian credible interval for difference, −4.9 to 2.1; posterior probability of non-inferiority >0.999). The pre-specified criterion for superiority was not met. At 30 days, patients who had undergone TAVR, as compared with SAVR, had a lower incidence of disabling stroke (0.5% vs. 1.7%), bleeding complications (2.4% vs. 7.5%), AKI (0.9% vs. 2.8%), and atrial fibrillation (7.7% vs. 35.4%) and a higher incidence of moderate or severe aortic regurgitation (3.5% vs. 0.5%) and pPM implantation (17.4% vs. 6.1%) [21]. The most important limitations of this study are the incomplete 24-month follow-up of the entire cohort and the unblinded end-point adjudication for all end-points, which may have resulted in bias in end-point assessment. Furthermore, the latest-generation Evolut PRO THV was used in only 22.3% of the patients who received TAVR and this may have influenced the higher incidence of moderate or severe aortic regurgitation in the

TAVR group. However, also these randomized data as well as those coming from the PARTNER 3 RCT open to another less invasive therapeutic option for the treatment of patients with tricuspid, stenotic aortic valve.

3.1.6. Comparison analyses (not randomized)

A pre-specified propensity match analysis comparing the 1-year clinical outcomes of 963 intermediate-risk patients included in the SAPIEN 3 observational study (*S3i*) vs. 747 patients of the *PARTNER 2A* surgical cohort (mean age 81.9 years, mean STS-PROM score 5.2%) showed that TF TAVR was superior to SAVR for the composite endpoint of mortality, stroke, and moderate/severe PVL. As opposed to PARTNER 2A, TAVR patients involved in this analysis received the new generation SAPIEN 3 THV. Probably due to the lower sheath profile of this new generation BE THV system the incidence of 30-day major vascular complications was similar between the TAVR vs. the SAVR group (6.1% vs. 5.4%) [22].

The German Aortic Valve Registry (GARY) recently reported real-world data comparing 1-year clinical outcomes of 7613 patients at intermediate surgical risk (STS-PROM score 4%–8%) underwent isolated TAVR ($n = 6469$) vs. SAVR. Patients treated by TAVR were significantly older and had higher risk scores. Unadjusted in-hospital mortality rates were equal for TAVR and SAVR (3.6% vs. 3.6%, $p = 0.9$), whereas unadjusted 1-year mortality was significantly higher in patients after TAVR (17.5% vs. 10.8%, $p < 0.001$). After propensity score matching, the difference in 1-year mortality between patients with TAVR (performed through a trans-vascular access) and SAVR was no longer significant (17.1% versus 15.7%, $p = 0.59$) [23]. In accordance with the results from RCTs, this large registry analysis suggests that both TAVR (performed through a trans-vascular access) and SAVR are reasonable treatment options in a real-world population with AS and intermediate surgical risk.

The *Low Risk TAVR* (Feasibility of Transcatheter Aortic Valve Replacement in Low-Risk Patients With Symptomatic, Severe Aortic Stenosis) trial is a prospective, single-arm multicenter trial involving 200 low risk patients (STS-PROM score below 3% and absence of comorbidity that would increase surgical risk, including, but not limited to frailty, porcelain aorta, severe pulmonary hypertension, and advanced liver disease) underwent TAVR (most performed under moderate sedation with a BE THV) compared vs. 719 patients who underwent isolated SAVR in the same participating centres.

At 30 days, there were zero all-cause mortality and in-hospital stroke in the TAVR group versus 1.7% and 0.6% in the SAVR group. Permanent PM rates were similar between TAVR and SAVR (5.0% vs. 4.5%) while the rates of new-onset atrial fibrillation (3.0%) and length of stay (2.0 ± 1.1 days) were low in the TAVR group. Of note, 14% of TAVR patients had evidence of subclinical leaflet thrombosis at 30 days. This data demonstrate that TAVR is safe in low-risk AS patients even if more studies are needed to better understand mechanisms, predictors and long-term prognostic implications of subclinical THV leaflet thrombosis [24].

Low-risk patients (STS-PROM score < 4) underwent isolated TAVR ($n = 6062$) or SAVR ($n = 14,867$) enrolled in the German Aortic Valve Registry (GARY) [25] were compared by a weighted propensity score model in order to assess in-hospital, 30-day, and 1-year mortality between groups. TAVR patients showed a significantly higher in-hospital (TAVR vs. SAVR: 98.5% vs. 97.3%; $p = 0.003$) and 30-day (TAVR vs. SAVR: 98.1% vs. 97.1%; $p = 0.014$) survival than SAVR patients. At 1-year, survival rates did not differ significantly (TAVR vs. SAVR: 90.0% vs. 91.2%; p 0.158) (Tables 1 and 2).

3.1.7. Minimally invasive surgical aortic valve replacement vs. TAVR

In recent years, minimally invasive (through a right antero-lateral mini-thoracotomy or mini-sternotomy) SAVR has been increasingly adopted with the goal to reduce the invasiveness of the surgical procedure (reducing the intra-operative trauma and bleeding and accelerating the post-operative recovery) but to offer the same quality, safety and results as the standard conventional procedure.

Data coming from a meta-analysis of propensity match studies demonstrated a benefit of this approach over the standard one, in terms of a lower incidence of cardiac output syndrome and atrial fibrillation at the price of a longer aortic cross-clamp and cardiopulmonary bypass times [26].

Theoretically, the mini-invasive approach could be an appealing option (compared to conventional SAVR) for high risk AS patient requiring valve replacement. Data coming from a single centre propensity match analysis comparing SAVR using a sutureless bioprosthetic valve ($n = 37$) vs. a BE first generation THV ($n = 37$) in high risk patients (median logistic Euroscore I: 14%) of whom 51.6% treated through the TF route, reported a not significant in-hospital mortality (TAVR 8.1% vs. SAVR 0%, $p = 0.2$) and stroke (TAVR 5.4% vs. SAVR 0%, $p = 0.3$) rates between the groups whereas mild-to-moderate PVL occurrence was significantly higher in the TAVR group [27].

Furthermore, a recent meta-analysis of six propensity score matching studies comparing sutureless SAVR vs. TAVR in high or intermediate risk patients reported lower 30-day, 1- and 2-year mortality in the SAVR group as well as lower incidences of post-operative stroke, moderate-to-severe PVL and major vascular complications whereas the incidence of bleedings requiring transfusions was higher in the SAVR compared to TAVR group [28]. Although of interest, these data deserve a careful interpretation due to the relatively low number of patients not enrolled in RCTs. Trials aiming to compare TF TAVR vs. SAVR through a mini-invasive approach using a sutureless valve are required to better understand the potential benefit of the less invasive surgical strategy in the management of high-to-intermediate risk patients.

Table 1
Longest-available results from main studies comparing TAVR vs. SAVR in low-intermediate risk patients.

Study name	Time to end-point	Mean overall age (years)	Mean overall STS-PROM (%)	All-cause mortality (%)		Disabling stroke (%)		PM implantation (%)		Moderate/severe PVL (%)		Major vascular complications (%)		New onset atrial fibrillation (%)	
				TAVR	SAVR	TAVR	SAVR	TAVR	SAVR	TAVR	SAVR	TAVR	SAVR	TAVR	SAVR
NOTION	2 years	79.1 ± 4.8	2.9 ± 1.6	8.0	9.8	3.6	5.4	41.3	4.2	15.4	0.9	5.6	1.5	22.7	60
PARTNER 2	2 years	81.6 ± 6.7	5.8 ± 2.0	16.7	18	6.2	6.4	11.8	10.3	5.5	0.6	7.9	5.0	11.3	27.3
SURTAVI	2 years	79.8 ± 6.2	4.5 ± 1.5	11.4	11.6	2.6	4.5	25.9*	6.6*	4.9	0	6.0*	1.1*	12.9	43.4
SURTAVI Low-risk	1 year	75.2 ± 6.0	2.4 ± 0.6	1.5	5.7	0	1.7	24.6	3.4	3.6	0	3.1	0	15.4	47.3
LRT	30-days	71.8 ± 7.2	1.7 ± 0.5	0	1.7	0	0.6	5**	4.5**	NA	NA	NA	NA	3	4.8
GARY Low-risk	1 year	70.84 ± 10.88	2.3 ± 0.8	10	8.8	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
PARTNER 3	1 year	73.4 ± 5.9	1.9 ± 0.7	1.0	2.5	1.2	3.1	7.3	5.4	0.6	0.5	2.8	1.5	7.0	40.9
Evolut Low Risk TAVR	2 years	73.9 ± 5.9	1.9 ± 0.7	4.5	4.5	1.1	3.5	19.4°°	6.7°°	3.5°°	0.5°°	3.8°°	3.5°°	9.8°°	38.3°°

TAVR: transcatheter aortic valve replacement; SAVR: surgical aortic valve replacement; PM: pacemaker; PVL: paravalvular leak; LRT: low risk TAVR Trial.
*: 30-day results; **: in-hospital results; NA: not available; °°: at 1-year follow-up.

Table 2
Currently ongoing randomized trials comparing TAVR vs. SAVR in low-risk and in specific sub-set of patients with aortic stenosis.

	NOTION 2	DEDICATE	Bicuspid low risk	TAVR Unload	Early TAVR
Active since	2016	2017	Not recruiting	2016	2017
Estimated completion date	2024	2024	NA	2022	2031
Risk profile/subset	STS-PROM < 3% and Age < 75 years	STS-PROM 2–6%	Predictive operative mortality risk < 3% Bicuspid aortic valves	LVEF < 50% Moderate AS	Asymptomatic severe AS
Sample size (patients, $n=$)	992	1600	150	600	1109
THV used	Each CE marked	Each CE marked	Evolut Pro or Evolut R	Sapien 3	Sapien 3
Route for TAVR	TF only	TF/TA/Tax/TAo	TF/TAx	TF	TF
Primary end-point	All-cause mortality, myocardial infarction or stroke	Overall survival	All-cause mortality or disabling stroke	All-cause mortality Disabling stroke Hospitalizations related to HF Change in KCCQ	All-cause death, all stroke, and unplanned cardiovascular hospitalization
Design	Non-inferiority RCT	Non-inferiority RCT	Non-inferiority RCT	Superiority vs. medical therapy	
Time-to-primary end-point	1-year	5-years	30-days	1-year	2-years
Maximum follow-up interval	1 year	5 years	10 years	2 years	10 years
Reference ClinicalTrial.gov	NCT02825134	NCT03112980	NCT03635424	NCT02661451	NCT03042104

THV: transcatheter heart valve; RCT: randomized controlled trial; TF: transfemoral; TAx: transaxillary/transsubclavian; TA: transapical; Tao: transaortic; NA: not available.
TAVR: trans-catheter aortic valve replacement; LVEF: left ventricular ejection fraction; AS: aortic stenosis; HF: heart failure; KCCQ: Change in Kansas City Cardiomyopathy Questionnaire.

4. Remaining challenges

Over the past decade, THV technology has significantly improved. New THV devices with lower-profile delivery systems have increased the proportion of patients who can be treated by the TF route and have significantly reduced vascular complications [29]. Newer generation THV also have an additional sealing skirt, which reduces the risk of PVL [30], and are often repositionable, which can result in higher implants thereby reducing the risk of conduction disorders [31]. As TAVR moves into younger AS populations, additional challenges need to be addressed.

4.1. Stenotic bicuspid aortic valves

As TAVR is performed in younger patients, the prevalence of bicuspid AS will considerably increase with an estimate of 30–50% in those patients aged 75 years or less [32]. Importantly, patients with bicuspid AS have typically been excluded from the large RCTs. Therefore, we do not have definitive data on how THVs perform against SAVR in the presence of bicuspid valves. Therefore SAVR is actually considered the gold-standard treatment for bicuspid AS in case of acceptable surgical risk.

An important issue when considering TAVR in bicuspid AS is the assessments of these patients' anatomy (i.e. frequent aortic root aneurysm and low coronary take-off). Appropriate valve sizing (probably best at supra-annular or intra-leaflet level vs. the traditional annular level [33]) and the modification of the implantation technique, with specific attention to valve deployment and positioning (higher risk of aortic injury because of associated aortopathy even in absence of dilatation) are fundamentals according to a careful pre-procedural CT-scan evaluation. Percutaneous treatment of bicuspid AS has been associated with increased procedural risk (more frequent occurrence of aortic root injury) and suboptimal short-term result (higher rates of PVL and pPM implantation). As a large proportion of the younger AS patients has a bicuspid valve, data on THV durability and long-term outcomes in this specific cohort will be of paramount importance. Given the anatomical features of a stenotic bicuspid aortic valve, THV implanted may not fully expand or not become fully circular with asymmetric leaflets as a result. Although this should not necessarily lead to immediate structural valve deterioration (SVD), it has recently been reported that asymmetrical leaflet expansion may be associated with an increased risk of subclinical leaflet thrombosis [34]. Even if recent data coming from studies of TAVR in bicuspid vs. tricuspid valves demonstrated a similar prognosis [35–36], the design of specific THV devices to treat bicuspid anatomy will become crucial to reduce the risk of PVL and pPM requirement in younger patients.

4.2. Permanent pacemaker implantation

Conduction disturbances requiring pPM implantation occur more frequently after TAVR vs. SAVR [37]. Factors independent from surgical risk such as THV design and anatomical aspects (aortic valve and left ventricular outflow tract) mostly influence pPM implantation rates which are similar between high and lower-risk patients (particularly when a SE THV is implanted). As for mild PVL, it is unknown how frequently pPM implantation and ventricular asynchrony will negatively impact mortality or physical performance on long-term follow-up in younger patients. On the other hand, it is clear that young patients are exposed to the risk of pPM-related complications (i.e. lead infection, endocarditis and for secondary tricuspid regurgitation) for a longer period of time.

Also for this reason, the design of newer generation THV should take into account this important point which could be very important to favor a broadened use of TAVR in young patients.

4.3. THV durability

Extension of TAVR to younger AS patients with longer life-expectancy (>15–20 years) is actually limited because very little is known on long-term (≥10 years) THV durability. A recently published consensus document by EAPCI/ESC/EACTS standardized the definitions of SVD and bioprosthetic valve failure (BVF) to assess long-term durability of transcatheter and surgical aortic bioprostheses [38]. SVD includes irreversible intrinsic changes of the valve (i.e. calcification, flail, leaflet tear, pannus deposition, or fibrotic leaflet) leading to degeneration and/or dysfunction, potentially resulting in stenosis or regurgitation. The precise mechanism of SVD are not known but likely include tissue disruption or thickening over time because of mechanical stress in conjunction with abnormal flow shear stress at the surface of valve leaflets, collagen fiber disruption, and tissue calcification [39].

The term BVF integrates severe SVD (the etiology) with its clinical consequences and is recommended to be used as the main outcome of interest in studies assessing the long-term performance of TAVR and SAVR. Importantly, BVF may occur in the setting of SVD but also as the consequence of pathophysiological processes unrelated to SVD, such as thrombosis, endocarditis or nonstructural valve dysfunction. In particular, a broad spectrum of THV thrombosis presentation has been described, from incidental findings to severe obstructive valve thrombosis with clinical heart failure, occurring at variable time after TAVR [40–41].

The diagnostic criteria include a hemodynamic deterioration (i.e., increase of mean transprosthetic gradient or significant new/worsening intraprosthetic regurgitation), increased thickness or reduced

leaflet motion. Notably, a recent computed tomography–based study reported a higher rate of reduced leaflet motion in TAVR patients than surgically implanted aortic valve patients (13% versus 4% respectively; $p = 0.001$) [42]. Regression of reduced leaflet motion or hypo-attenuated leaflet thickening has been reported both after introduction of anticoagulation or without any adjustment of the antithrombotic regimen [34,43].

BVF includes any of the following: (1) bioprosthetic valve dysfunction at autopsy, very likely related to the cause of death, or "valve-related death"; (2) aortic valve re-intervention (i.e. valve-in-valve TAVR, PVL closure or SAVR); and (3) severe hemodynamic SVD. Long-term follow-up (7 years) data from a real world German experience (in 300 high-risk and inoperable patients) using first generation THVs demonstrated a 14.9% crude incidence of SVD (CoreValve 11.8% vs. Sapien 22.6%; $p = 0.01$) according to the EAPCI/ESC/EACTS definitions [44]. The same, have been also applied to the NOTION trial showing a lower 6-year rate of SVD in THV as compared to surgical aortic bio-prosthesis (4.8% vs. 24%; $p < 0.001$) in low-risk patients, whereas there were no differences in non-structural valve deterioration or endocarditis rates and BVF between the groups [45]. Recently, the 5-year echocardiographic follow-up on 459 high risk patients underwent TAVR demonstrated good durability for both first generation types of THV with 2.5% severe SVD in cumulative incidence function. In addition, the presence of severe SVD was not associated with excess mortality [46]. Table 3 summarizes long-term durability data after THV implantation.

However, obtaining longer-term (>5 years) follow-up results from low-risk patients enrolled in RCTs is mandatory to provide definite data on valve durability post-TAVR.

In this regard, the PARTNER 3 and Evolut R Low Risk RCTs will provide 10-year echocardiographic data assessing the incidence of SVD and/or BVF in low-risk young patients that underwent TAVR.

4.4. TAVR-in-TAVR

Considering the probable extension of TAVR to younger patients with longer life expectancy, treatment of SVD with a TAVR-in-TAVR will probably increase. Recent data demonstrated that "redo TAVR" for the treatment of THV failure is feasible, safe, and associated with favorable haemodynamic results [47]. However, an open challenge following TAVR-in-TAVR approach is coronary cannulation, which will be required more frequently as we treat young patients that may need future coronary intervention. In this regard, special attention should be payed to the choice of the first implanted THV type, in order to minimize the potential obstruction in getting future access to the coronary ostia given by the THV tissue/frames. In this regard the best THV device to perform a TAVR-in-TAVR procedure is actually unknown.

4.5. Stroke

Disabling stroke is a rare but potentially devastating complication following TAVR or SAVR, particularly when occurring in younger patients [48]. Early reports showed a higher stroke rate associated with TAVR when treating high-risk patients [3]. Successive improvements in THV technology (i.e. reduction in the profile of delivery catheters facilitating prosthesis positioning with less need for manipulation within the native valve) and peri-procedural anaesthesiologic management with a larger use of conscious sedation (potentially associated to a higher degree of intra-procedural haemodynamic stability) versus general anaesthesia led to a reduction in early stroke rate [13,22,49].

Indeed, more recent data have demonstrated a lower incidence of disabling stroke after TAVR vs. SAVR in low-risk patients [14,20,21,24]. Although rare, every effort should be made to avoid cerebral embolic events in low-risk patients. In this regard, the use of embolic protection devices (EPD) could be a helpful choice to prevent as well as the use of neuroimaging guided endovascular approaches to solve, an acute brain injury. Two randomized trials of TAVR protected by EPD reported no benefits in terms of disabling stroke reduction but showed a significantly lower frequency of clinically silent ischaemic cerebral lesions detected by magnetic resonance imaging [50]. Importantly, the impact of the silent ischaemic lesions on long-term neurological function is unknown and this issue may be particularly relevant in case of TAVR in lower-risk and younger patients.

Besides the risk of peri-procedural stroke, mid- and long-term thrombo-embolism is increased by new-onset atrial fibrillation and subclinical leaflet thrombosis. The first has consistently been more frequently observed with SAVR while the second with TAVR [12,13,42,51–53]. Interestingly, adjunctive pharmacotherapy after TAVR is not standardized, even if anticoagulation with novel oral anticoagulants or warfarin (but not dual antiplatelet therapy) is effective

Table 3
Main (comparative and single-arm) studies on transcatheter heart valve durability.

Author (year)	Population	Study type	Patient's surgical risk profile	Valve type	Follow-up (years)	SVD definition used	SVD rate (%)	SVD requiring re-intervention (%)
Toggweiler S et al. (2013) [54]	TAVR only ($n = 111$)	Registry	High	CE or ESV	5	VARC 1	3.4 (moderate degeneration)	0
Barbanti M et al. (2015) [55]	TAVR only ($n = 353$)	Registry	High	MCV	5	VARC 1	1.4 (prosthesis failure) 2.8 (mild degeneration)	0.5% (VIV)
Mack MJ et al. (2015) [56]	TAVR ($n = 348$) vs. SAVR ($n = 351$)	Randomized	High	ESV vs. BSV	5	SVD requiring SAVR	0	0
Dvir D et al. (2016) [57]	TAVR only ($n = 378$)	Registry	High	CE, ESV, SXT	6–10	Mean gradient ≥ 20 mmHg and/or moderate central AR	50	NR
Gerckens U et al. (2017) [58]	TAVR only ($n = 860$)	Registry	High	MCV	5	VARC 2	2.6	1.2
Didier R et al. (2018) [59]	TAVR only ($n = 4201$)	Registry	High	MCV, ESV, SXT	5	EAPCI/ESC/EACTS	2.5 (severe) 13.3 (moderate-severe)	NR
Aldalati O et al. (2018) [59]	TAVR ($n = 269$) vs. SAVR ($n = 174$)	Registry	High	ESV, SXT, S3, Lotus vs. BSV	6.5	VARC 2	61 vs. 69 ($p = NS$)	0.4
Deusch MA et al. (2018) [44]	TAVR only ($n = 300$)	Registry	High	MCV vs. ESV	7	EAPCI/ESC/EACTS	11.8 vs. 22.6 ($p < 0.001$)	1.1 (VIV)
Sondegaard L et al. (2019) [45]	TAVR ($n = 139$) vs. SAVR ($n = 135$)	Randomized	Low	MCV vs. BSV	6	EAPCI/ESC/EACTS	4.8 vs. 24 ($p < 0.001$)	2.2 vs. 0.7 ($p = 0.6$)
Blackman DL et al. (2019) [60]	TAVR only ($n = 241$)	Registry	High	ESV, SXT, MCV	5–10	EAPCI/ESC/EACTS	9	NR

SVD: structural valve deterioration; TAVR: trans-catheter aortic valve replacement; CE: Cribier Edwards; ESV: Edwards Sapien Valve; MCV: Medtronic Core Valve; VIV: Valve-in-Valve; SAVR: surgical aortic valve replacement; SXT: Sapien XT; NR: not reported; BSV: bio-prosthetic surgical valve; EAPCI: European Association Percutaneous Coronary Intervention; ESC: European Society of Cardiology; EACTS: European Association, Cardiac and Thoracic Surgery.

in prevention and resolution of leaflet thrombosis and subsequent impaired leaflet motion.

4.6. Paravalvular leak

Technological advances in THVs design in association with improvements in procedural planning contributed to the decrease in the incidence of moderate/severe PVL compared to early TAVR experiences [48]. In the two recent low-risk RCTs the incidence of moderate-to-severe PVL was relatively low ranging from 0.6% (using a new generation BE THV) to 3.5% (using a SE THV) [14,24]. Despite the low rates, TAVR remained inferior to SAVR with regard to this end-point even in low-risk patients when treated with a SE THV. On the other hand, no differences were reported between TAVR performed using a third generation BE THV vs. SAVR. This aspect is relevant and should be taken into account during the decision making process in lower risk patients. Furthermore, factors that are independent of age, surgical risk, and THV design, such as the presence of annular and/or left ventricular outflow tract calcifications, eccentric annulus and bicuspid AS, will continue to affect TAVR performance on PVL [48].

5. A new heart team era?

Over recent years, increasing operator experience with TAVR has meant that the procedure can now be planned in details and safely performed under local anaesthesia, in a catheterization laboratory [61] through a TF approach (>90% of TAVR cases) [62] by a minimalist heart team (MHT) led by the local "cardiovascular physicians" that have the higher endovascular experience and catheter skills (usually interventional cardiologists). Data coming from a German Registry show that absence of an on-site surgeon and surgical team from the procedure did not increase TAVR mortality or morbidity [63]. There is also a growing debate as to whether having the entire surgical team present in TAVR is economically sustainable or necessary [64], particularly giving the low rate of complications (i.e. annular rupture, coronary occlusion, ventricular perforation) requiring surgical conversion [65]. Although the (wrong) feeling of some cardiac surgeons is that they could be excluded from TAVR procedure [62] it is widely believed that the role of the modern Heart Team (composed by a cardiac surgeon, an interventional cardiologist, a clinical cardiologist and a cardiovascular anaesthesiologist appropriately trained and proficient in the active management of valvular heart disease) remains, today more than in the past, definitely central. With widening knowledge and expertise, the Heart Team plays a key role in every decision-making process [66]. The ESC/EACTS guidelines advocate centralized care, with a Class I recommendation that TAVR is performed in a heart valve centre with on-site surgery and within an environment that provides comprehensive diagnostic and treatment options (even choosing the best context where to perform the procedure favoring HR over cath-lab in case of planned surgical accesses or high-risk of intra-procedural complications due to specific anatomical features). These heart valve centres, where a multidisciplinary team works together on a regular basis with established communication structures, seem to be ideally placed to become high-volume centres of excellence for the treatment of heart valve disease. An interdisciplinary heart team approach with sufficient training is, in our opinion, the most important strategy to further improve clinical outcomes after both, surgical or percutaneous AVR.

6. Conclusions

TAVR has become the first line therapy in patients who are not suitable for SAVR and it is favored over SAVR in patients suitable for TF access at increased/intermediate surgical risk (STS or EuroSCORE II ≥4% or logistic EuroSCORE *I* ≥ 10% or other risk factors not included in these scores such as frailty, porcelain aorta, sequelae of chest radiation).

Recent data coming from RCTs comparing TAVR vs. SAVR in low-risk patients (STS-PROM<4%) demonstrated that TAVR performed by experienced operators through the TF route is associated with lower rates of major clinical events compared to SAVR at 1- and 2-year follow-up, respectively [20–21].

Whatever the decision (TAVR or SAVR), interventional cardiologists and cardiac surgeons need to cooperate and work together (in a cath-lab or in a HR deciding case-by-case in line with some specific pre-assessed procedural aspects or theoretical risks) according to their skills and needs with the aim to offer the best treatment for each patient with severe AS.

Conflict of interest

The authors report no relationships that could be construed as a conflict of interest.

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