TAVI AND THE CHALLENGES AHEAD

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TAVI AND THE CHALLENGES AHEAD

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EDITORIAL
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Editorial: TAVI and the Challenges Ahead

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Editorial on the Research Topic

TAVI and the Challenges Ahead

Transcatheter aortic valve implantation (TAVI) was introduced in 2002 and significant efforts in research and innovation have subsequently positioned this procedure as an important breakthrough in cardiovascular medicine (1). TAVI has become the preferred treatment strategy for symptomatic severe aortic stenosis (AS) among patients deemed to be at excessive- or high-risk for conventional surgical aortic valve replacement (SAVR) and is an alternative to surgery among intermediate- and low surgical-risk patients (2, 3).

Two decades of device iteration, refinement of procedural technique, growing operator experience, and enhanced patient selection, have significantly reduced peri-procedural complications and improved short and mid-term clinical outcomes. Central to these advances has been the concept of the Heart Team, a group of interdisciplinary healthcare professionals that each bring their experience to bear on the management of the individual patient with complex structural heart disease (1). Together the institutional Heart Team weight the anatomic, physiologic, and psychosocial aspects of each patient to develop an individualized treatment plan.

Despite the aforementioned success of TAVI, there remain important challenges to further streamline the procedure, reduce costs, and improve patient outcomes. In particular, extending TAVI to younger and lower risk patients in the aftermath of two key industry-sponsored low risk trials requires particular attention. Relevant topics for discussion include the relative merits/drawbacks of TAVI compared to SAVR, the impact and potential mitigation strategies for periprocedural stroke and permanent pacemaker implantation, the use of oral anticoagulation after TAVI, and the question of long-term transcatheter heart valve durability.

The present collection explores current and future challenges of TAVI, includes articles from a diagnostic and technical perspectives, and provides guidance on patient and vascular access selection, the importance and application of multimodal imaging, and outlines a pathway toward procedure simplification. The risk of cerebrovascular events and how to prevent them, the impact of concomitant mitral regurgitation and post-TAVI conduction abnormalities are explored and future directions in the TAVI space are discussed, including extension of the technology to younger patients, low-risk cohorts, and potentially, the role of the technology in patients with moderate aortic stenosis and heart failure.

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PRE-PROCEDURAL PLANNING AND TECHNIQUE

Advances in pre-procedural planning and refinement in procedural techniques have greatly improved clinical outcome. These developments are elegantly presented by Akodad and Lefèvre through a step-by-step approach starting with the indisputable need for a pre-TAVI multi-slice computed tomography (CT) for planning vascular access, valve type and size selection, and procedural execution. The authors describe their local experience of the benefits of fully percutaneous access, secondary radial access, conscious sedation rather than general anesthesia, rapid pacing over the left ventricular guide wire, implantation without pre-dilatation, and early discharge with limited use of the intensive care unit—restricted to patients with low-risk of post-procedural complications.

Biasco et al. dedicate a comprehensive review of vascular access sites for TAVI. The transfemoral approach is considered to be the first choice by guideline and consensus documents but alternative vascular access remains an important option in selected cases. Traditional alternate access routes include the transapical and transaortic approaches with novel and often fully percutaneous options including transaxillary, transcarotid, and transcaval accesses. The authors compare procedural success and clinical outcomes among alternate vascular access routes, underscoring that no prospective head-to-head comparisons exist.

Careful pre-procedural planning is crucial for successful TAVI. The role of MSCT imaging is particularly important in the setting of TAVI for the treatment of bicuspid aortic valve (BAV) disease. Das and Puri comprehensively summarize current data on imaging and interventional considerations in BAV. The authors highlight that asymmetric valve leaflets, the presence of a raphe, and heavy calcification among patients with BAV tend to yield more complex procedures. BAV patients undergoing TAVI may have a higher risk of valve malposition and frame underexpansion and hence increased rates of moderate to severe paravalvular regurgitation. Pre and post-dilatation can lead to aortic annular rupture if balloon sizing is excessive and the risk of ostial coronary artery occlusion and aortic dissection may be higher in patients with BAV undergoing TAVI. Recent device iteration and clinical evidence have documented improving procedural success and clinical outcomes among BAV patients, and prospective randomized controlled trials compared to surgery are called-for in this field.

O'Sullivan et al., in an original publication discuss pulmonary hypertension (PH) in patients undergoing TAVI. PH is a common finding in patients with severe symptomatic AS and has been associated with worse clinical outcomes. Among TAVI candidates, most PH is post-capillary in nature and thus associated with an increased left ventricular end-diastolic pressure. The gold standard assessment is with right heart catheterization however echocardiography provides indirect measurements of the pulmonary pressures. Pre-TAVI CT can also contain important clues that can be used to screen for PH. O'Sullivan et al. describe several potential markers, including a cut-off for the ratio between the pulmonary artery and the aortic artery diameters, which may help screening of patients undergoing TAVI.

CURRENT CHALLENGES

Armijo et al. have meticulously addressed the incidence, timing, relevance, and prevention of cerebrovascular events (CVE) after TAVI. In the original PARTNER tirals, CVE were thought to be higher after TAVI compared to SAVR (ascertainment bias), current suggests stroke may be more common after SAVR. In a meta-analysis including >72,000 patients, the 30-day post-TAVI stroke rate was 3.3% (4). Importantly, the majority of these events are disabling and profoundly impacting patient quality of life. Up to 95% of procedural CVEs are ischaemic and generally are related to an embolic source, including the aortic wall, calcified aortic valves, and thrombotic material. Sub-acute CVEs are usually local thrombotic events (valve-related) or caused by atrial arrhythmia. Antithrombotic strategies as well as cerebral embolic protection devices (CEPD) have the potential to reduce the frequency and impact of these events and several ongoing randomized trials in this space are discussed by the authors.

Along these lines, Demir et al. present a rigorous review of CEPD, which were introduced to mitigate the risk of CVE during the TAVI procedure. These devices capture or deflect embolic particles away from the supra-aortic vessels and have the potential to reduce CVEs. The authors summarize the available evidence for the Claret CEPD (Boston Scientific) and for the TriGuard (Keystone Heart, Venus MedTech) and describe a range of other devices in development. The Claret device is a dual filter deployed in the brachiocephalic and left common carotid arteries, but leaving the left vertebral artery unprotected. The largest trial with CEPD ($n = 363$) to date, failed to demonstrate a significant reduction in the total new lesion volume on diffusion weighted cerebral MRI in the protected territories compared to placebo (5). However, further randomized trials of this device with clinical stroke as a powered endpoint are ongoing. The TriGuard 3 CEP is a mesh filter that is positioned across the three cerebral vessels and has been recently awarded CE-mark approval. Initial data have shown reduction of new cerebral lesions as well as lower rates of clinical CVE.

Mitral regurgitation (MR) is a common echocardiographic finding in the elderly, and moderate or severe MR affects ∼20% of high-risk patients undergoing TAVI. Stähli et al. detail that moderate or severe MR is associated with worse clinical outcomes post-TAVI; however, it remains unsettled whether a direct cause-effect relationship exists. Importantly, in up to 60% of patients with MR undergoing TAVI, the severity of MR is improves at 30 days post TAVI, a finding that is hampered in patients with atrial fibrillation or severe PH. The authors describe transcatheter treatment options for residual post TAVI moderate to severe MR as well as important considerations for the timing of post-TAVI management of MR. The MitraClip (Abbott Vascular) has recently gained attention after the results of the COAPT trial which showed a significant reduction of mortality and

hospitalizations in heart failure patients with moderate to severe MR, when compared with medical therapy (6).

Conduction abnormalities remain a common complication after TAVI due to the anatomical vicinity of the conduction system and the landing zone of the bioprosthetic valve. Mangieri et al. discuss in-depth the frequency and impact of new-onset left bundle branch block (LBBB) and other conduction disturbance and the need for permanent pacemaker (PPM) implantation post-TAVI. The type of device utilized, the depth of implantation, and the need of pre- and post-dilation to reduce paravalvular regurgitation are major determinants. Acute TAVI-related injury to the conduction system may cause LBBB in ∼10–30% of patients and complete atrioventricular block (AVB) in ∼10–30%. Importantly, LBBB may resolve in up to 85% of patients while complete AVB may resolve in up to 50%. The decision to implant a PPM therefore, should be couple with sufficient in-hospital telemetry monitoring.

FUTURE DIRECTIONS

At the 2019 American College of Cardiology Annual Scientific Meeting, data from two large randomized controlled trials in low-risk cohorts were presented (2, 3). Balloon-expandable and self-expandable THV devices were non-inferior to SAVR for the pre-specified endpoints, and hence these trials will have far-reaching implications on current and future TAVI practice. The cohorts treated in these trials were almost 10 years younger than those included in high-risk cohorts. As De Backer and Søndergaard predicted in this section, the expansion to younger populations highlights the need for understanding the use of TAVI in patients with BAV: this morphology accounts for up to 50% of severe AS cases in patients <75 years of age. Long-term valve durability data is being collected, however, given that BAV has been largely excluded from RCTs, high quality registries or dedicated RCTs are required to further characterize the durability of TAVI prosthesis in BAV morphology. Furthermore, rates of complications may be distinctive in younger in BAV cohorts and merits careful investigation.

Voigtländer and Seiffert diligently explain this shift in focus from the early narrow high-risk TAVI cohort to the current broad all levels of surgical risk TAVI population. Patient has to date been classified according to the Society of Thoracic Surgeons Predicted Risk of Mortality (STS-PROM) at 30 days; being <4% low, 4 to 8% intermediate, and >8% high risk patients. However, this score does not include other important factors such as active malignancy, frailty, porcelain aorta, chest wall radiation, liver cirrhosis, or neurological impairment, which are important for the Heart Team decision-making. Other factors favoring TAVI include age >75, prior cardiac surgery, restricted mobility or anticipated prolonged rehabilitation, transfemoral access, severe chest deformation, or prosthesis-patient mismatch. The authors present highlights of data stemming from RCTs and registries that support the use of TAVI in intermediate-risk and data being gathered for low-risk cohorts.

Finally, Spitzer et al. open a new chapter for TAVI by providing the rationale for exploring this breakthrough therapy in patients with moderate AS in the presence of reduced left ventricular ejection fraction (LVEF). This new therapeutic target represents 0.8% of patients referred for echocardiographic assessment, and without intervention have been associated with a high rate of mortality and heart failure hospitalizations. The epidemiology, natural history, and patient characteristics are discussed, as well as the challenges in echocardiographic diagnosis of moderate AS in patient with reduced LVEF. An ongoing trial (NCT02661451) is testing the role of TAVI in this patient population. If proven successful, implementation of new clinical pathways to identify and derive these patients to a TAVI operator in a timely manner will be required, since currently patients with moderate AS are not considered a target of therapy.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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Challenges When Expanding Transcatheter Aortic Valve Implantation to Younger Patients

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The rapid expansion of transcatheter aortic valve implantation (TAVI) has been based upon robust clinical evidence derived from randomized controlled trials and large-scale international and national registries. Over the past decade, TAVI has evolved into a safe and effective procedure with predictable and reproducible outcomes. As a consequence, the TAVI technology is increasingly used to treat patients with a lower risk profile and the volume of TAVI now exceeds surgical aortic valve replacement (SAVR) in some countries. It may be anticipated that, in the near future, the majority of patients with severe symptomatic aortic valve stenosis will undergo TAVI as first line therapy, regardless of their age and risk profile. This article identifies some of the specific challenges that lie ahead when considering expansion of TAVI to younger patients.

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Keywords: aortic valve stenosis, transcatheter aortic valve implantation, young adults, bicuspid aortic valve, challenges

Transcatheter aortic valve implantation (TAVI) has become an established therapeutic option for patients with symptomatic, severe aortic valve stenosis (AS) who are at increased risk for conventional cardiac surgery (1–4). In recent years, the TAVI technology is also increasingly used to treat patients with a lower risk profile – this practice is supported by results from the NOTION, PARTNER-II and SURTAVI trials indicating that TAVI is a viable option for patients with a low to intermediate surgical risk profile (5–7).

Although TAVI, in many countries, has become the default therapy to treat AS patients aged 75 years or more, there is currently increasing discussion on how far to push the limits when considering treating younger patients. Although the above-mentioned lower-risk TAVI trials included patients with a lower surgical risk score, the mean age of enrolled patients was not different compared to the early TAVI trials conducted in extreme or high risk patients (**Figure 1**) (1–7). When considering further expansion of TAVI indications to encompass younger patients aged 75 years or less, there are still some challenges ahead.

Based on currently available data, it can be stated that TAVI is non-inferior to surgery in terms of mortality and stroke, and is likely to be superior if a transfemoral approach is possible. Surgical patients more frequently experience major bleedings, acute kidney injury, and new-onset atrial fibrillation, whereas TAVI is associated with a higher rate of major vascular complications, paravalvular regurgitation, and pacemaker implantations (3–7). When considering expansion of TAVI to younger patients < 75 years, it will be a must to obtain predictable and outstanding results, also for these latter procedural outcomes.

Over the past decade, the TAVI technology has matured; however, technological improvements have not come to a halt yet. New TAVI devices with lower-profile delivery systems have increased the proportion of patients who can be treated by transfemoral approach and have significantly reduced vascular complications (8). Newer generation TAVI devices also have an additional sealing skirt, which reduces the risk of paravalvular regurgitation, (9) and are often repositionable, which can result in higher implants thereby reducing the risk of conduction disorders (10).

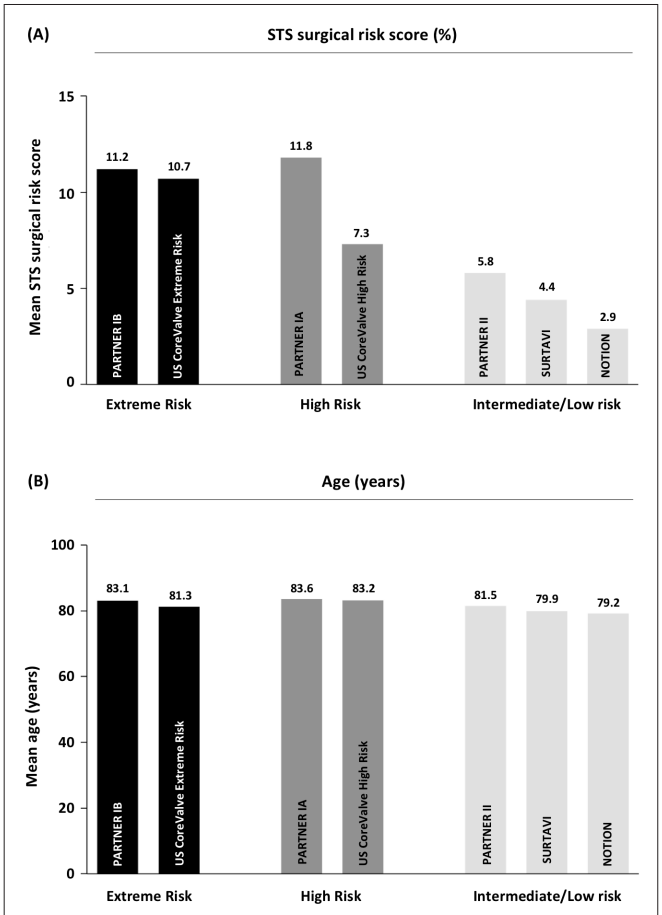

FIGURE 1 | Surgical risk and age profile in the different large randomized controlled TAVI trials, indicating the mean STS surgical risk score (in %) and mean age (in years) for the TAVI group in every respective study. STS, Society of Thoracic Surgeons; TAVI, transcatheter aortic valve implantation.

Furthermore, procedural outcomes have improved because of increased operator experience and developments in cardiac and vascular imaging, particularly using multidetector CT.

As TAVI would move into younger AS populations, one pitfall may be that treating bicuspid valves would become an increasing part of practice – with an estimate of 30–50% in those patients aged 75 years or less (11). Importantly, patients with bicuspid AS have typically been excluded from the large randomized controlled trials. Today, only limited data exist on outcomes of TAVI in bicuspid AS. In a recent meta-analysis of 13 observational studies, short-term outcome data indicated that TAVI for bicuspid AS is associated with high device success rates and a good safety profile. Mortality at 30 days was low and comparable to that achieved with the newest generation TAVI devices in tricuspid AS. However, there was a trend towards higher rates of significant paravalvular regurgitation (12%) and permanent pacemaker requirement (18%) in bicuspid AS cohorts undergoing TAVI (12). An important issue when considering TAVI in bicuspid AS is the assessments of these patients' anatomy and the modification of the TAVI technique, with specific attention to valve deployment and positioning. In order to overcome the limitations of the current generation TAVI devices with regards to paravalvular regurgitation and pacemaker requirement, the design of specific TAVI devices to treat bicuspid anatomy will become crucial.

Finally, extension of TAVI to younger patients with longer life-expectancy also raises the issue of durability. In 2016, some concern was raised about potential poor long-term durability of transcatheter heart valves – however, these results were based on less than 50 first generation valves and only echocardiographic findings were used to define valve degeneration (13) – which is in contrast with the "need for re-intervention" used as definition for surgical valve degeneration. Importantly, since then, robust 5 year follow-up data have come available demonstrating continued valve durability with low rates of hemodynamic valve dysfunction and/or re-intervention, and this for both balloon-expandable and self-expanding transcatheter heart valves (1–3, 14).

Recently, ESC, EAPCI and EACTS have published a consensus on standard definitions of structural valve deterioration (SVD) and bioprosthetic valve failure (BVF) in order to assess long-term durability of transcatheter and surgical aortic bioprosthesis (15). There should be clear distinction between SVD (the principal etiology) and BVF (the clinical correlate). SVD includes permanent (irreversible) intrinsic changes of the valve (i.e., leaflet tear, calcification, pannus deposition, flail, or fibrotic leaflet) leading to degeneration and/or dysfunction, which in turn may result in stenosis or intra-prosthetic regurgitation. The term BVF integrates severe SVD (i.e., the etiology) with its clinical consequences – thereby avoiding over-interpretation of valve-related outcomes in asymptomatic patients with no clinical impact – and is recommended to be used as the main outcome of interest in studies assessing the long-term performance of TAVI 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 non-structural valve dysfunction. 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 TAVI, paravalvular leak closure or SAVR); and (3) severe hemodynamic SVD.

These definitions have been applied to the NOTION trial (7) – including 80% low risk patients – showing that, after five years, the rate of SVD was lower in transcatheter heart valves as compared to surgical aortic bioprosthesis (3.9% vs. 26.1%, respectively; $p < 0.001$), whereas the rate of BVF was similar in both groups (8.9% vs. 9.5%, respectively; $p = 0.89$) – as presented at EuroPCR 2017.

As a large portion of the younger AS patients has a bicuspid valve, data on transcatheter heart valve durability and long-term outcomes in this specific cohort will also become essential. Given the anatomical characteristics of a stenotic bicuspid aortic valve, a concern may be that the implanted transcatheter heart valve may not fully expand or not become fully circular with asymmetric leaflets as a result. Although this should not necessarily lead to immediate valvular dysfunction, it has recently been reported that asymmetrical leaflet expansion may be associated with an increased risk of subclinical leaflet thrombosis (16). In

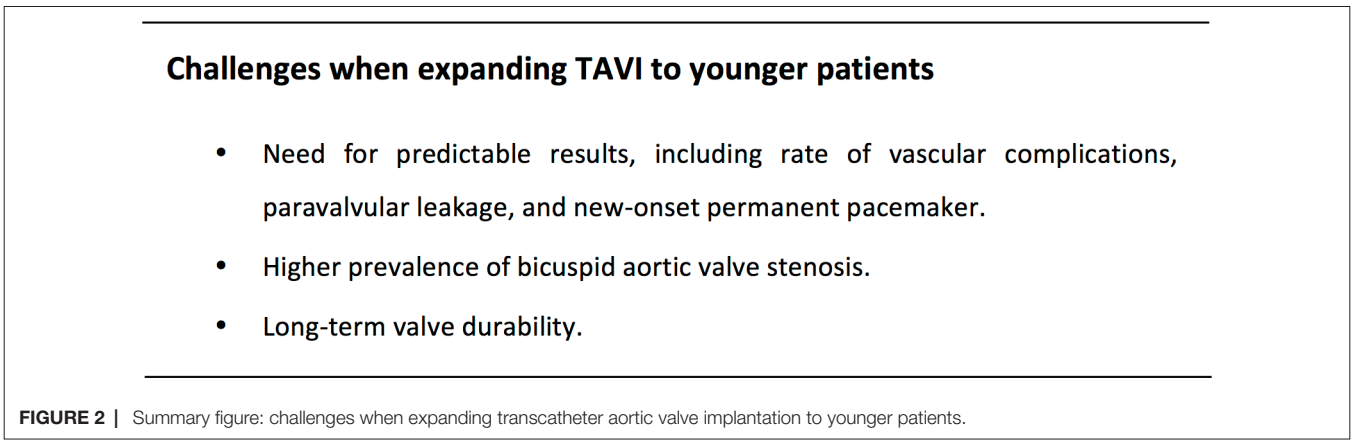

FIGURE 2 | Summary figure: challenges when expanding transcatheter aortic valve implantation to younger patients.

addition, leaflet asymmetry may also have an impact on long-term valve durability. This is still important missing information when one considers treating a younger bicuspid AS patient with TAVI.

In conclusion, the rapid expansion of TAVI has been based upon robust clinical evidence derived from randomized controlled trials and large-scale international and national registries. Over the past decade, TAVI has evolved into a safe and effective procedure with predictable and reproducible outcomes. As a consequence, the volume of TAVI now exceeds SAVR in some countries (17). It may be anticipated that, in the near future, the majority of patients with severe symptomatic AS will undergo TAVI as first line therapy, regardless of their age and risk profile. This article identifies some of the specific challenges that lie ahead when considering expansion of TAVI to younger patients (**Figure 2**). With ongoing developments of the TAVI technology, it can be expected that most of these obstacles will be overcome within the next decade. Still, it will be essential to provide the necessary clinical evidence – within the framework of a randomized trial – comparing TAVI with SAVR. Although large TAVI trials have been initiated by Edwards Lifesciences (USA) and Medtronic (USA) in low-risk AS cohorts, this is not a guarantee that young patients will be enrolled. In additon, patients with bicuspid AS are excluded from these trials. Currently, the only large randomized controlled trial comparing TAVI with SAVR in low-risk, younger patients ≤ 75 years of age, not excluding bicuspid valves, is the NOTION-2 trial (ClinTrials.Gov: NCT02825134). This randomized trial should provide the needed clinical evidence to evaluate the use of TAVI in young, low-risk AS patients.

AUTHOR CONTRIBUTIONS

ODB and LS both contributed to the concept, writing process and revision of this manuscript.

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Screening For Pulmonary Hypertension With Multidetector Computed Tomography Among Patients With Severe Aortic Stenosis Undergoing Transcatheter Aortic Valve Implantation

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Aim: To assess the accuracy of multi-detector computed tomography (MDCT) derived pulmonary vessel measurements in predicting pulmonary hypertension (PH) among patients with severe symptomatic aortic stenosis (AS) undergoing transcatheter aortic valve implantation (TAVI).

Background: PH is common among patients with severe AS undergoing TAVI and is associated with adverse outcomes. MDCT is the imaging modality of choice to assess anatomical dimensions among patients selected for TAVI.

Methods: One hundred and thirty-nine patients with severe AS undergoing TAVI with both CT scans and right heart catheterizations (RHC) were included. CT diameters of the main pulmonary artery (MPA), right (RPA) and left (LPA), and ascending aorta (AA) were measured. The relationship between CT measurements and PA pressures assessing using RHC was tested with linear regression.

Results: The CT derived ratio of the diameter of the MPA to the diameter of the AA (PA/AA_{ratio}) correlated best with mean PA pressure ($R^2 = 0.48$) and PA systolic pressure ($R^2 = 0.50$). Receiver operating characteristic curve analysis showed that the PA/AA_{ratio} is a moderate predictor of PH (AUC 0.74, 95% CI 0.65–0.83, $p < 0.0001$) and that the optimal cut off point is 0.80 (sensitivity 56%, specificity 88%, positive predictive value 95.5%, negative predictive value 30.6% for PH).

Conclusions: Elderly patients with severe AS and PA/AA_{ratio} values ≥ 0.80 on MDCT are more likely to have PH but PH cannot be reliably excluded among such patients with lower PA/AA_{ratio} values.

Keywords: aortic stenosis, pulmonary hypertension, computed tomography, right heart catheterization, hemodynamics, transcatheter aortic valve implantation

INTRODUCTION

Transcatheter aortic valve implantation (TAVI) is a less invasive alternative treatment option to surgical aortic valve replacement (SAVR) among patients with symptomatic severe aortic stenosis (AS) (1). Patients selected for TAVI tend to be inoperable or high risk for conventional SAVR and typically have a high prevalence of co-morbidities including coronary artery disease, atrial fibrillation, concomitant valvular heart disease, and chronic renal failure (2). In addition, pulmonary hypertension (PH) is common among patients with severe AS undergoing TAVI and is associated with worse clinical outcomes as compared with patients without PH (3). The identification of PH prior to TAVI is therefore important for appropriate risk stratification and may help in determining which patients should be selected for TAVI vs. SAVR. Right heart catheterization is the gold standard method for diagnosing PH, which is defined as a mean pulmonary artery pressure ≥25 mmHg (4). However, right heart catheterization is an invasive procedure and is not routinely performed prior to TAVI. Transthoracic echocardiography can provide an estimate of the pulmonary artery systolic pressure but cannot reliably detect whether PH is present or not (5). Multi-detector computed tomography (MDCT) is recommended as the imaging modality of choice prior to TAVI to determine annular and aortic root dimensions as well as iliofemoral anatomy prior to TAVI (6). Whether or not MDCT measurements of the pulmonary vasculature provide a reliable estimate of the presence of PH among patients with severe AS selected for TAVI is unknown. Therefore, the aim of this study was to assess the accuracy of MDCT derived pulmonary vessel measurements in predicting the presence of PH among patients with severe symptomatic AS undergoing TAVI.

METHODS

Patient Population

This is a retrospective analysis of prospectively collected data within a database that includes all patients with severe AS, who underwent TAVI at our institution between August 2011 and September 2015 ($n = 184$). All patients were deemed inoperable or at high risk for surgery by a multidisciplinary team consisting of invasive cardiologists and surgeons. Included in the present analysis were all patients with symptomatic severe AS, a full preprocedural right and left heart catheterization and a pre-procedural multidetector computed tomography (MDCT). Data collection was facilitated by using the nation-side prospective TAVI registry (SWISS TAVI Registry) into which all patients from our institution are prospectively enrolled. The cohort study complies with the Declaration of Helsinki, was approved by the local Ethics Committee, and all patients provided informed written consent.

Cardiac Catheterization

All included patients underwent coronary angiography and right and left heart catheterization for haemodynamic assessment prior to TAVI. Intracardiac pressures were recorded with fluid filled catheters connected to pressure transducers as previously described (7).

Right Heart Pressures

(PH) was defined as a mean pulmonary artery pressure ≥ 25 mmHg and was subdivide into pre-capillary PH (left-ventricular end-diastolic pressure ≤ 15 mmHg) and post-capillary PH (LVEDP >15 mmHg). Furthermore, post-capillary PH was further subdivided into isolated post-capillary PH (diastolic pulmonary gradient ≤ 7 mmHg) and combined post- and pre-capillary PH (diastolic pulmonary gradient > 7 mmHg).

Transcatheter Aortic Valve Implantation

TAVI was performed as previously described (7). Vascular access was transfemoral using the Edwards Sapien Valve XT/S3 (ESV, Edwards Lifesciences, Irvine, CA, USA), the Medtronic CoreValve Revalveing System, the Medtronic Evolut R (MCRS; Medtronic Inc., Minneapolis, MN, USA), and the Lotus Valve (Boston Scientific) and transapical for the ESV.

MDCT Protocol and Measurements for PH Assessment

All included patients underwent CT for preinterventional assessment of aortic annulus size and evaluation of vascular access using a second-generation, multidetector 128-slice dual source CT (Somatom Definition Flash, Siements Healthcare, Forchheim, Germany). Images were reviewed on a stationary workstation by an investigator who had no knowledge of any clinical information or the RHC results. Calipers were set for measuring the widest short-axis diameter of the main pulmonary artery within 3 cm of the bifurcation, the right pulmonary artery and left pulmonary artery and the ascending aorta, respectively on axial sections. The diameter of the AA was measured at the level of the MPA.

Statistics

Continuous data are presented as means ± standard deviations (SD), and categorical variables are depicted as percentages and numbers. Categorical variables were compared by means of the χ^2 test (or Fisher's test for two group comparisons), and continuous variables were compared using the unpaired *t*-test for two groups or ANOVA for 3 or more groups. ROC analysis were performed to assess the AUC and to compare sensitivity and specificity for different cut-off values using the Youden Index. Sensitivity, specificity, negative predictive value (NPV), and positive predictive value (PPV) were calculated and shown in percentages. Time-to-event data are presented using Kaplan-Meier curves, with incidence rates calculated from life-tables at 2-year follow-up. Log-rank test was used to declare significance. A p-value < 0.05 were considered statistically significant. All analyses were performed with SPSS 22, Release 22.0.0.1 or STATA (version 12, StataCorp, College Station, TX, USA).

TABLE 1 | Baseline characteristics.

	All patients *N* = 139	No PH *N* = 25	PH *N* = 114	*P*-value
DEMOGRAPHICS				
Age (years)	83.58 ± 4.98	81.70 ± 3.97	84.0 ± 5.10	0.04
Female gender, n (%)	59 (42.4)	13 (52.0)	46 (40.4)	0.20
PHYSICAL DIMENSIONS				
Height (cm)	165.58 ± 7.81	167.06 ± 8.16	165.06 ± 7.67	0.09
Weight (kg)	71.24 ± 15.76	67.40 ± 15.01	72.09 ± 15.85	0.18
Body mass index (kg/m²)	25.93 ± 5.33	23.81 ± 4.72	26.39 ± 5.37	0.03
BSA (m²)	1.81 ± 0.23	1.77 ± 0.23	1.82 ± 0.23	0.30
CARDIAC RISK FACTORS				
Diabetes mellitus, n (%)	27 (19.4)	4 (16.0)	23 (20.2)	0.44
Hypercholesterolemia, n (%)	30 (21.6)	8 (32.0)	22 (19.3)	0.13
Hypertension, n (%)	92 (66.2)	15 (60.0)	77 (67.5)	0.31
PAST MEDICAL HISTORY				
Coronary artery disease, n (%)	64 (46.0)	12 (48)	52 (45.6)	0.50
Previous myocardial infarction, n (%)	11 (7.9)	3 (12.0)	8 (7.0)	0.31
Previous coronary artery bypass graft, n (%)	12 (8.6)	1 (4.0)	11 (9.6)	0.32
Previous percutaneous coronary intervention, n (%)	23 (16.5)	4 (16.0)	19 (16.7)	0.60
Previous cerebrovascular event, n (%)	19 (13.7)	6 (24)	13 (11.4)	0.10
Peripheral vascular disease, n (%)	32 (23.0)	5 (20.0)	27 (23.7)	0.46
Chronic obstructive pulmonary disease, n (%)	15 (10.8)	3 (12.0)	12 (10.5)	0.53
Previous pacemaker, n (%)	16 (11.5)	2 (8.0)	14 (12.3)	0.42
Renal failure (GFR < 60 ml/min/1.73 m^2)	99 (71.2)	17 (68.0)	82 (71.9)	0.43
HEART RHYTHM				
Atrial fibrillation, n (%)	34 (24.5)	4 (16.0)	30 (26.3)	0.26
SYMPTOMS				
Syncope, n (%)	15 (10.9)	4 (16.0)	11 (9.7)	0.28
New york heart association (NYHA) functional class				
NYHA III/IV, n (%)	114 (82.0)	18 (72.0)	96 (84.2)	0.13
Canadian cardiovascular society (CCS) angina status				
CCS III/IV, n (%)	9 (6.5)	2 (8.0)	7 (6.1)	0.51
RISK ASSESSMENT				
Logistic EuroScore (%)	20.71 ± 13.25	14.20 ± 10.73	22.16 ± 13.36	0.01
STS Score (%)	4.95 ± 2.84	3.94 ± 2.13	5.17 ± 2.93	0.05
LABORATORY VALUES				
HS Troponin T (ng/ml)	30.72 ± 25.00	22.17 ± 21.52	32.59 ± 25.41	0.06
NT-Pro Brain Natriurtic Peptide (pg/mL)	3,338 ± 3,831	1,554 ± 1,774	3,749 ± 4,058	<0.0001

RESULTS

Patient Characteristics

Baseline characteristics are given in **Table 1**. A total of 139 patients with symptomatic severe AS undergoing TAVI had complete MDCT and RHC data and were included in the present analysis. Eighty-Two percentage ($n = 114$) patients had PH defined as a mean PA pressure $\geq$ 25 mmHg. PH patients comprised 12 patients with precapillary PH, 86 patients with isolated post-capillary PH and 16 patients with combined precapillary and post-capillary PH (**Figure 1**). Patients with PH were significantly older, had a higher body mass index and had significantly higher surgical risk scores at baseline. In addition, NT-pro-BNP values at baseline were significantly higher among PH patients as compared with no PH patients (**Table 1**) ($p < 0.0001$).

Echocardiographic and Invasive Haemodynamic Characteristics

Baseline echocardiographic and invasive haemodynamic characteristics are shown in **Tables 2**, **3**, respectively. As compared with no PH, patients with PH had significantly larger left ventricular end-diastolic diameters ($p = 0.026$), higher non-invasive right ventricular/right atrial gradients ($p = 0.026$), higher left ventricular end-diastolic pressures ($p = 0.005$), higher pulmonary and right ventricular pressures ($p < 0.0001$) and lower pulmonary artery saturation measurements ($p = 0.026$).

Procedural Characteristics

Procedural characteristics are shown in **Table 4**. The majority of patients underwent TAVI via the transfemoral route (78%) under general anesthesia (91%) with the Edwards SAPIEN 3 valve (35%). Balloon predilatation was performed in most cases (86%) and only a minority of patients underwent concomitant revascularization.

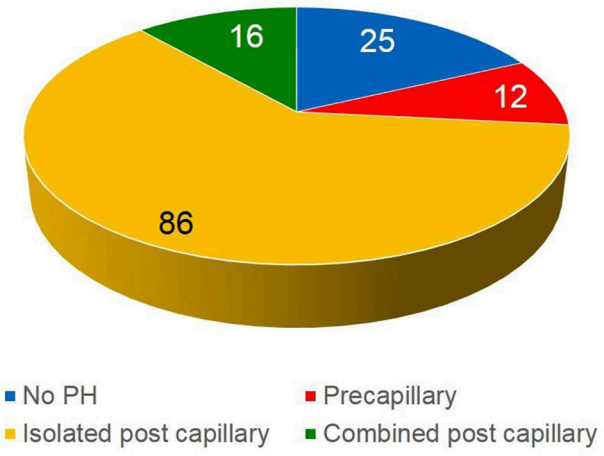

FIGURE 1 | Classification of the patient population ($n = 139$).

MDCT Measurements Referring to PH

MDCT measurements of the pulmonary and aortic vasculature are shown in **Tables 5**, **6**. As compared with no PH, patients with PH had significantly larger diameters of MPA ($p = 0.001$), RPA ($p = 0.004$), LPA ($p = 0.029$), and PA/AA_{ratio} ($p < 0.0001$). No significant differences in ascending aorta or aortic annular measurements were observed between groups. As compared with no PH, patients with combined post-capillary PH had significantly larger MPA ($p = 0.006$), RPA ($p = 0.011$) diameters and PA/AA_{ratio} ($p < 0.0001$) (Supplementary Table 1). In addition, patients with precapillary PH had significantly larger LPA and RPA diameters as compared with patients without PH (supplementary Table 1).

The PA/AA_{ratio} exhibited the best correlation with PA pressures (**Figure 2**) (r^2 0.48 for mean PA, $p < 0.0001$; r^2 0.50 for PA systolic pressure, $p < 0.0001$; r^2 0.41 for diastolic PA pressure,

TABLE 2 | Baseline echocardiography characteristics.

	All patients $N = 139$	No PH $N = 25$	PH $N = 114$	*P*-value
AORTIC STENOSIS SEVERITY				
Aortic valve area (cm^2)	0.71 ± 0.20	0.75 ± 0.22	0.70 ± 0.19	0.43
Aortic maximal velocity, cm/s	4.3 ± 0.69	4.0 ± 0.4	4.3 ± 0.7	0.16
Mean gradient (mmHg)	46.6 ± 14.0	47.3 ± 12.5	46.5 ± 14.4	0.83
Peak gradient (mmHg)	72.0 ± 21.1	70.1 ± 17.4	72.2 ± 21.9	0.75
LV GEOMETRY AND 2D MEASUREMENTS				
LV end-systolic diameter, mm	32.5 ± 11.1	26.3 ± 12.3	34.0 ± 10.5	0.06
LV end-diastolic diameter, mm	45.3 ± 10.4	40.0 ± 12.4	46.6 ± 9.4	0.026
LV mass index, g/m^2	131.69 ± 33.0	121.7 ± 52.1	133.7 ± 27.7	0.49
LV SYSTOLIC FUNCTION				
LV ejection fraction, %	56.1 ± 12.9	58.8 ± 10.0	55.4 ± 13.5	0.35
ASSOCIATED VALVULAR ABNORMALITY				
Aortic regurgitation				0.74
None	58 (41.7)	11 (44.4)	47 (41.2)	
Mild	58 (41.7)	8 (32.0)	50 (43.9)	
Moderate	5 (3.6)	1 (4.0)	4 (3.5)	
Severe	3 (2.2)	1 (4.0)	2 (1.8)	
Mitral regurgitation				0.30
None	33 (23.7)	7 (28.0)	26 (22.8)	
Mild	62 (44.6)	14 (56.0)	48 (42.1)	
Moderate	32 (23.0)	2 (8.0)	30 (26.3)	
Severe	3 (2.2)	0 (0)	3 (2.6)	
Tricuspid regurgitation				
None	48 (34.5)	9 (36.0)	39 (34.2)	0.86
Mild	63 (45.3)	10 (40.0)	53 (46.5)	
Moderate	15 (10.8)	3 (12.0)	12 (10.5)	
Severe	2 (1.4)	0 (0)	2 (1.8)	
RIGHT SIDED HEMODYNAMICS				
RV-RA gradient, mmHg	38.2 ± 13.5	28.0 ± 6.4	40.4 ± 13.7	0.026

TABLE 3 | Invasive haemodynamic characteristics.

	All patients $N = 139$	No PH $N = 25$	PH $N = 114$	*P*-value
AORTIC STENOSIS SEVERITY				
Aortic valve area (cm^2)	0.64 ± 0.30	0.72 ± 0.36	0.63 ± 0.29	0.19
Peak-to-peak gradient (mmHg)	54.95 ± 26.03	50.48 ± 23.96	55.88 ± 36.45	0.37
Mean gradient (mmHg)	44.74 ± 18.24	41.42 ± 17.25	45.44 ± 18.44	0.34
SYSTEMIC VASCULAR LOAD				
Systolic arterial pressure (mmHg)	138.34 ± 28.65	132.32 ± 26.04	139.66 ± 29.14	0.25
Diastolic arterial pressure (mmHg)	66.10 ± 14.39	66.04 ± 11.71	66.11 ± 14.96	0.98
Mean arterial pressure	95.09 ± 17.31	92.88 ± 14.11	95.58 ± 17.95	0.48
Systemic vascular resistance ($mmHg.min.L^{-1}$)	1,839 ± 761	1,729 ± 578	1,861 ± 792	0.47
LV SYSTOLIC FUNCTION				
Ejection fraction (%)	53.80 ± 14.30	56.87 ± 13.21	53.15 ± 14.50	0.26
LV systolic pressure (mmHg)	197.10 ± 38.37	186.87 ± 37.30	199.22 ± 38.41	0.16
LV end diastolic pressure (mmHg)	26.13 ± 9.57	21.13 ± 7.23	27.17 ± 9.69	0.005
Stroke volume (ml)	57.36 ± 23.61	63.43 ± 21.25	56.17 ± 23.96	0.20
Stroke volume index (ml/m^2)	32.01 ± 12.16	35.51 ± 10.82	31.32 ± 12.33	0.15
Cardiac output (L/min)	4.12 ± 1.35	4.47 ± 1.25	4.05 ± 1.36	0.19
Cardiac index ($l/(min*m^2)$	2.30 ± 0.68	2.50 ± 0.59	2.26 ± 0.69	0.14
Heart rate (beats/min)	75.82 ± 16.97	71.08 ± 14.71	76.86 ± 17.31	0.12
RIGHT SIDED HEMODYNAMICS				
PA systolic pressure (mmHg)	53.38 ± 16.72	33.72 ± 5.09	57.69 ± 15.22	<0.0001
PA diastolic pressure (mmHg)	22.37 ± 8.53	12.72 ± 3.42	24.49 ± 7.83	<0.0001
Mean PA pressure (mmHg)	35.76 ± 11.57	21.28 ± 2.59	38.94 ± 10.27	<0.0001
RV systolic pressure, mmHg	53.82 ± 15.19	36.64 ± 6.67	57.62 ± 13.86	<0.0001
RA mean pressure (mmHg)	9.38 ± 4.89	5.68 ± 2.72	10.17 ± 4.90	<0.0001
Diastolic pressure gradient ≥ 7 mmHg, n (%)	26 (18.8)	1 (0.7)	25 (21.9)	0.031
COMPONENTS OF FICK EQUATION				
Aortic saturation (%)	92.72 ± 3.88	94.01 ± 3.18	92.45 ± 3.97	0.07
Pulmonary artery saturation (%)	60.62 ± 11.08	65.18 ± 6.81	59.66 ± 11.58	0.026
Hemoglobin (g/dl)	12.43 ± 1.49	12.75 ± 1.34	12.36 ± 1.53	0.51

$p < 0.0001$). Using Receiver Operating Characteristic Curves, the PA/AA_{ratio} correlated best with PH (AUC 0.74), whereas MPA (AUC 0.65), RPA (AUC 0.67), and LPA (AUC 0.64) exhibited lower sensitivity and specificity (**Figure 3**). The optimal cut-off point of the PA/AA_{ratio} in predicting the presence of PH defined as an invasive mean PA pressure is 0.80 with a sensitivity of 56%, specificity of 88%, negative predictive value of 30.6%, and positive predictive value of 95.5% (**Figure 4**).

Clinical Outcomes at 30-Days and 2-Years

Clinical outcomes at 30-days and 2-years are shown in **Table 7**. As compared with no PH, no significant differences in all-cause mortality (Hazard Ratio 0.80, 95% confidence interval 0.18–3.60, $p = 0.77$) or cardiovascular mortality (HR 4.29, 95% CI 0.60–30.45, $p = 0.11$) were observed at 2 years among patients with PH (**Figure 5**). In addition, no significant differences in other VARC-2 endpoints (cerebrovascular accidents, major bleeding, vascular complications, acute renal failure, and permanent pacemaker implantation) were observed between groups at 30-days or 2 years (**Table 7**).

DISCUSSION

In the present study we sought to assess the reliability of screening for PH using MDCT derived measurements of the pulmonary arteries as compared with gold standard pulmonary artery pressure measurements derived from right heart catheterization among patients with severe AS undergoing TAVI. The key finding was that PA/AA_{ratio} was the most useful parameter to use to screen for PH among patients with severe AS undergoing TAVI with moderate to high specificity but relatively low sensitivity. We found that the best PA/AA_{ratio} cutoff for screening for PH is 0.80. Therefore, patients with a larger PA/AA_{ratio} on CT are more likely to have PH (high positive predictive value) but PH cannot be reliably ruled out among patients with smaller PA/AA_{ratio} values (low negative predictive value). PH is common among patients with severe AS selected for TAVI and is associated with worse clinical outcomes as compared with patients without PH (3, 8–10). Right heart catheterization is the gold standard method for diagnosing PH but is not routinely performed prior to TAVI. Conversely, MDCT is almost always performed

prior to TAVI in order to assess aortic annular and vascular dimensions for procedural planning (6). Consequently, MDCT may serve as a useful screening tool for the presence of PH among patients selected to undergo TAVI and help with risk stratification.

CT Derived Anatomical Indicators of PH

Truong et al. determined the age and sex specific distribution and normal reference values for main pulmonary artery diameter and the PA/AA_{ratio} by CT in an asymptomatic community-based population ($n = 3,171$, mean age 51 ± 10 years) (11). The investigators observed the 90th percentile cutoff value for PA/AA_{ratio} was 0.90 for both males and females but that the PA/AA_{ratio} was inversely proportional to age (11). The authors observed that that the PA/AA_{ratio} was smaller in older participants owing to progressive aortic enlargement with increasing age (11). In the present study, the mean age of the study sample was 84 ± 5 years and this may account for the fact that we observed a smaller PA/AA_{ratio} of 0.80 to be the optimal predictor of PH. Prior studies in younger patients with more heterogeneous diseases have suggested that a $PA/AA_{ratio} \geq 1.0$ is the optimal cutoff point to diagnose PH on CT. A small retrospective study ($n = 50$, median age 47.5 years) found that a $PA/AA_{ratio} > 1.0$ was the best predictor of chronic pulmonary arterial hypertension with a sensitivity, specificity and positive and negative predictive values for PH of 70, 92, 96, and 52% (12). Similary, Sanal et al. observed in a retrospective study among patients with pulmonary embolism (mean age 59 ± 15 years) that a $PA/AA_{ratio} \geq 1.0$ had a 59% sensitivity, 82% specificity, a 55% positive predictive value, and a 84% negative predictive value for diagnosing moderate to severe PH defined as a pulmonary

TABLE 4 | Procedural characteristics.

	All patients N = 139	No PH N = 25	PH N = 114	*P*-value
Access route				0.42
Femoral, n (%)	109 (78.4)	22 (88.0)	87 (76.3)	
Apical, n (%)	29 (20.9)	3 (12.0)	26 (22.8)	
Direct aortic, n (%)	1 (0.7)	0 (0)	1 (0.9)	
Valve type				0.83
Edwards Sapien 3, n (%)	49 (35.3)	8 (32.0)	41 (36.0)	
Edwards Sapien valve XT, n (%)	31 (22.3)	5 (20.0)	26 (22.8)	
Medtronic CoreValve, n (%)	42 (30.2)	9 (36.0)	33 (28.9)	
Medtronic Evolut R, n (%)	10 (7.2)	1 (4.0)	9 (7.9)	
Boston Scientific Lotus, n (%)	7 (5.0)	2 (8.0)	5 (4.4)	
Anesthesia				0.15
General, n (%)	127 (91.4)	21 (84.0)	106 (93.0)	
Local, n (%)	12 (8.6)	4 (16.0)	8 (7.0)	
Balloon predilation				0.76
Balloon predilation	119 (85.6)	21 (84.0)	98 (86.0)	
Revascularisation				0.37
Revascularisation, n (%)	5 (3.6)	0 (0)	5 (4.4)	
Procedural Specifications				0.74
Post-preocedure moderate-severe AR, n (%)	17 (12.2)	2 (8.0)	15 (13.2)	

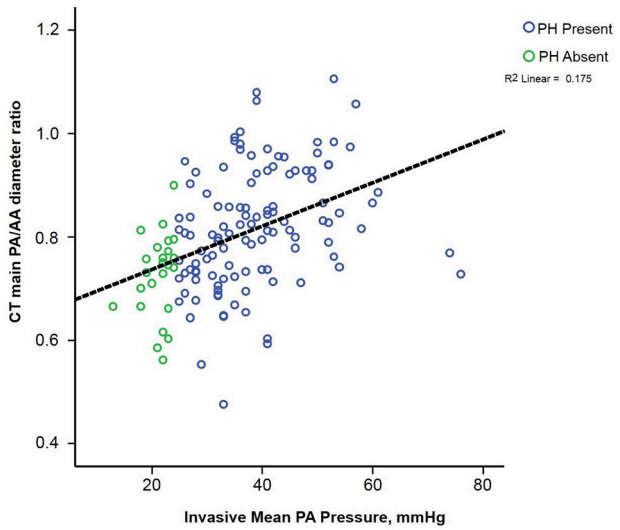

FIGURE 2 | Scatterplot illustrating the correlation between the CT derived pulmonary artery/ascending aorta ratio.

TABLE 5 | Computer Tomography characteristics.

	All patients N = 139	No PH N = 25	PH N = 114	*P*-Value
PULMONARY VASCULAR DIAMETERS				
Main pulmonary artery, mm	28.01 ± 4.33	26.03 ± 2.92	28.44 ± 4.48	0.001
Right pulmonary artery, mm	27.25 ± 4.08	25.13 ± 4.47	27.71 ± 3.86	0.004
Left pulmonary artery, mm	25.70 ± 3.07	24.49 ± 3.24	25.96 ± 2.98	0.029
Main pulmonary artery/ascending aorta ratio	0.80 ± 0.12	0.73 ± 0.08	0.82 ± 0.12	<0.0001
AORTIC ANNULUS MEASUREMENTS				
Ascending aorta, mm	35.11 ± 4.21	36.06 ± 4.17	34.91 ± 4.21	0.21
Annulus perimeter, mm	89.22 ± 14.81	91.03 ± 14.87	88.82 ± 14.90	0.63
Annulus area, mm^3	483 ± 115	529 ± 138	472 ± 107	0.11

artery systolic pressure ≥ 50 mmHg on Doppler Echo (13). Mohamed Hoesein et al. (14) assessed the accuracy of CT PA diameter and PA/AA_{ratio} for PH in end-stage COPD among 92 patients (mean age 55 years) and found that a PA/AAratio >1 had a negative predictive value of 77.9% and a positive predictive value of 63.1%. However, the results of the present study would suggest that in an elderly patient population, such as those selected to undergo TAVI, a $PA/AA_{ratio} \geq 1.0$ would not be sensitive enough as we observed a sensitivity of just 4.4% when $PA/AA_{ratio} \geq 1.0$ was used to predict the presence of PH. Therefore, the key observation of this study is that a lower PA/AA_{ratio} value is required to screen for PH among TAVI patients. To date only one other study assessed the value of CT pulmonary vascular measurements as a predictor of PH and mortality in symptomatic severe AS (15). In contrast to the present study, the authors did not observe that PA/AA_{ratio} was any better at predicting PH as compared with MPA. The reasons for this are unclear but may relate to the fact that the pulmonary artery measurements may have been made during end-systole rather than end-diastole. The investigators also did not find any significant differences between MPA diameters of patients with combined post-and pre-capillary PH and no PH, whereas we observed significant differences between these groups (15).

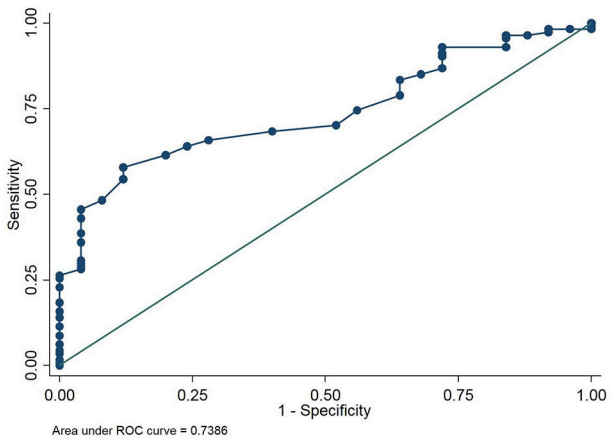

FIGURE 3 | Receiver operating characteristic curve testing the ability of the CT derived pulmonary artery/ascending aorta ratio to detect PH defined as a mean pulmonary artery pressure ≥ 25 mmHg.

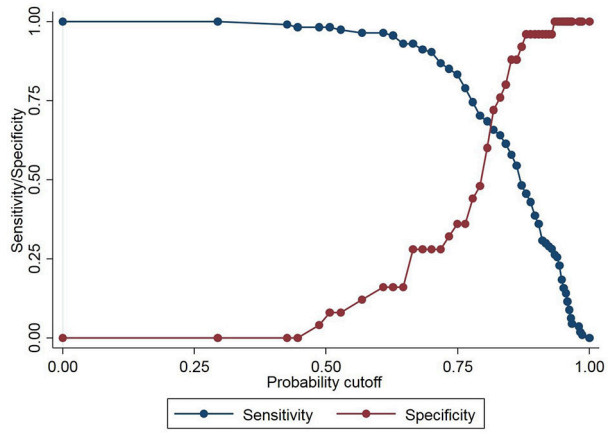

FIGURE 4 | Graph illustrating the best cut-off point for the CT derived pulmonary artery/ascending aorta ratio to detect PH. The best cutoff derived from the Youden index was 0.80.

TABLE 6 | Diagnostic accuracy of computed tomography for detecting pulmonary hypertension.

	Sensitivity (%)	Specificity (%)	NPV (%)	PPV (%)
MPA ≥ 29 mm	39.5	84.0	23.3	91.8
MPA ≥ 30 mm	28.9	84.0	20.6	89.2
MPA ≥ 31 mm	24.6	100.0	22.5	100.0
MPA ≥ 32 mm	19.3	100.0	21.4	100.0
MPA ≥ 29 mm (only men)	47.8	76.9	29.4	88.0
MPA ≥ 31 mm (only men)	30.4	100.0	28.9	100.0
MPA ≥ 27 mm (only females)	52.9	83.3	23.8	94.7
MPA ≥ 29 mm (only females)	33.8	91.7	19.6	95.8
MPA ≥ 31 mm (only females)	20.6	100.0	18.2	100.0
PA/AA ratio ≥ 0.75	69.3	56.0	28.6	87.8
PA/AA ratio ≥ 0.80	56.1	88.0	30.6	95.5
PA/AA ratio ≥ 0.85	36.8	96.0	25.0	97.7
PA/AA ratio ≥ 0.90	28.1	100.0	23.4	100.0
PA/AA ratio ≥ 0.95	14.9	100.0	20.5	100.0
PA/AA ratio ≥ 0.1.0	4.4	100.0	18.7	100.0

AA, ascending aorta; MPA, main pulmonary artery.

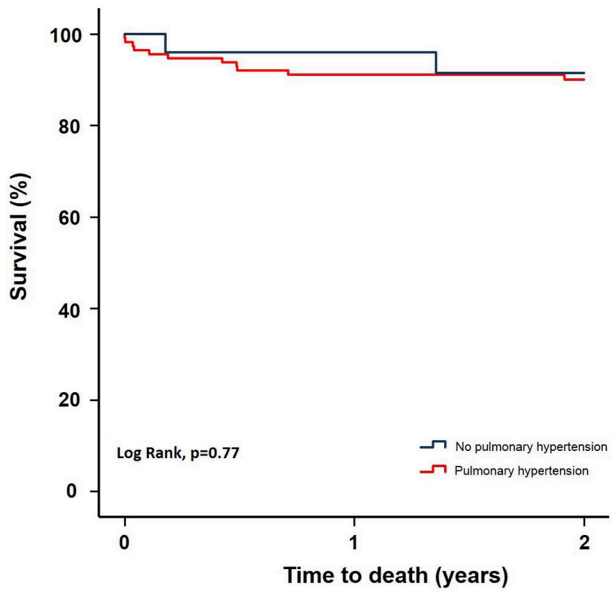

FIGURE 5 | Kaplan-Meier survival curve for patients with and without PH.

TABLE 7 | Clinical outcomes.

	No PH $N = 25$	PH $N = 114$	*P*-value
30 DAYS FOLLOW-UP			
All cause death, n (%)	0 (0)	4 (3.5)	0.45
Cardiovascular death, n (%)	0 (0)	0 (0)	
Cerebrovascular events	1 (4.0)	0 (0)	0.18
Major stroke, n (%)	0 (0)	0 (0)	
Minor stroke, n (%)	0 (0)	0 (0)	
Transient ischemic attack, n (%)	1 (4.0)	0 (0)	0.18
Bleeding	4 (16.0)	19 (16.7)	0.60
Life-threatening, n (%)	1 (4.0)	3 (2.6)	0.55
Major, n (%)	1 (4.0)	7 (6.1)	0.56
Acute renal failure, n (%)	0 (0)	1 (0.9)	0.82
Access site complications	3 (12.0)	9 (7.9)	0.37
Major, n (%)	1 (4.0)	4 (3.5)	0.64
Minor, n (%)	2 (8.0)	5 (4.4)	0.37
New permanent pacemaker, n (%)	4 (16.0)	15 (13.2)	0.46
2 YEAR FOLLOW-UP			
All cause death, n (%)	2 (8.0)	11 (9.6)	0.58
Cardiovascular death, n (%)	2 (8.0)	2 (1.8)	0.15
Cerebrovascular events	1 (4.0)	4 (3.5)	0.64
Major stroke, n (%)	0 (0)	2 (1.8)	0.67
Minor stroke, n (%)	0 (0)	1 (0.9)	0.82
Transient ischemic attack, n (%)	1 (4.0)	1 (0.9)	0.33
All cause death or major stroke, n (%)	2 (8.0)	13 (11.4)	0.47

Limitations

The present study is a single center retrospective study with several limitations. Although we observed no significant differences in adverse clinical outcomes between patients with and without PH no definitive conclusions on the effect of PH on mortality can be drawn from this study as too few events occured. However, the main aim of this study was not to compare clinical outcomes between patients with and without PH, but rather to assess the accuracy of CT measurements of the pulmonary vessels in predicting the presence of PH. The presented conclusions are preliminary and only hypothesis generating and that further research is needed. Further studies should test whether we are able to diagnose different severities of PH, since the implications of severe PH are completely different from mild.

CONCLUSIONS

In the present study we found that PA/AA_{ratio} demonstrates the strongest correlation with mean PA and PA systolic pressures and that the optimal cutoff is 0.80 in predicting the presence of PH with high specificity but moderate to low sensitivity.

AUTHOR CONTRIBUTIONS

CO, MM, RZ, DK, and FE: conception and design of the study. CO and MM: analysis and interpretation of data. CO: drafting of the manuscript. All authors revising the manuscript critically for important intellectual content and final approval of the manuscript submitted.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2018.00063/full#supplementary-material

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REVIEW
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Transcatheter Aortic Valve Replacement and Concomitant Mitral Regurgitation

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Mitral regurgitation frequently coexists in patients with severe aortic stenosis. Patients with moderate to severe mitral regurgitation at the time of transcatheter aortic valve replacement are at increased risk of future adverse events. Whether concomitant mitral regurgitation is independently associated with worse outcomes after TAVR remains a matter of debate. The optimal therapeutic strategy in these patients—TAVR with evidence-based heart failure therapy, combined TAVR and transcatheter mitral valve intervention, or staged transcatheter therapies—is ill-defined, and guideline-based recommendations in patients at increased risk for open heart surgery are lacking. Hence, a thorough evaluation of the aortic and mitral valve anatomy and function, along with an in-depth assessment of the patients' baseline risk profile, provides the basis for an individualized treatment approach. The aim of this review is therefore to give an overview of the current literature on mitral regurgitation in TAVR, focusing on different diagnostic and therapeutic strategies and optimal clinical decision making.

Keywords: transcatheter aortic vave replacement, mitral valve insufficiency, mitral valve repair, aortic stenosis, aortic valve, mitral valve

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INTRODUCTION

Concomitant mitral regurgitation is frequently observed in patients with severe aortic stenosis (1–3). About 20% of patients undergoing transcatheter (TAVR) or surgical (SAVR) aortic valve replacement for severe aortic stenosis have concomitant more than mild mitral regurgitation (1–3). Whether concomitant mitral regurgitation is independently associated with worse outcomes after aortic valve replacement is uncertain (4). A thorough evaluation of the aortic and mitral valve anatomy and function is important in these patients and mainly based on transthoracic and transesophageal echocardiography. An in-depth understanding of the underlying pathophysiological mechanism provides the basis for an individualized treatment approach and optimal procedural planning. Emerging minimally invasive surgical and transcatheter treatment strategies offer novel, less-invasive therapeutic options for combined, staged or hybrid procedures when severe aortic stenosis and mitral regurgitation do coexist, particularly in elderly patients, obviating the need for open heart surgery (5). The treatment of first choice in these patients, however, remains a matter of debate, and guideline-based recommendations are lacking.

The aim of this review is therefore to give an overview of the current literature on mitral regurgitation in TAVR, with particular focus on the different diagnostic and therapeutic strategies available and on the clinical decision-making process in patients at increased surgical risk.

ASSESSMENT OF MITRAL REGURGITATION IN PATIENTS WITH SEVERE AORTIC STENOSIS

In mitral regurgitation, besides the grading of the regurgitation severity, identification of the underlying etiology, particularly the distinction between primary and secondary mitral regurgitation, is of great importance to guide therapeutic management. The assessment of the mitral valve apparatus and the type of dysfunction is mainly based on transthoracic and/or transesophageal echocardiography with multimodality imaging used in specific situations (6, 7). Although transthoracic echocardiography is diagnostic in most cases, transesophageal echocardiography complements the assessment when transthoracic image quality is suboptimal and further diagnostic refinement is required (6, 7). Transesophageal echocardiography not only provides additional important information on the etiology of the disease, but also helps to determine the feasibility of dedicated transcatheter mitral valve procedures. Three-dimensional (3D) echocardiography facilitates anatomic and functional interpretation, particularly in patients with complex valvular pathologies (6, 8, 9).

Mitral regurgitation may either be primary/degenerative due to abnormalities of the valvular apparatus itself such as mitral valve prolapse, flail leaflets, and chordal rupture, or secondary/functional due to restricted leaflets, mostly caused by left ventricular dilatation and dysfunction in ischemic cardiomyopathy and chronic pressure overload related to aortic stenosis (10). Annular dilatation and left atrial enlargement causing insufficient leaflet closure, e. g., in patients with long-standing atrial fibrillation, may also be an underlying cause. Mixed forms exist when both pathologies overlap. As the mitral valvular apparatus is often calcified in patients with degenerative aortic stenosis, pure secondary mitral regurgitation is unlikely in this context (4).

An integrated approach using qualitative, semi-quantitative, and quantitative echocardiographic parameters allows for a comprehensive assessment of mitral regurgitation (9, 11, 12). Color flow imaging is the most common way to detect mitral regurgitation, with quantification based on the integration of further measures such as vena contracta width, PISA radius, regurgitation volume and effective regurgitant orifice area (EROA) (6). The evaluation of mitral regurgitation in aortic stenosis may, however, be challenging as jet velocity may be increased due to high left ventricular pressures (4). On the other hand, concomitant mitral regurgitation impacts on transvalvular gradient and flow in severe aortic stenosis, which may hamper echocardiographic assessment (13).

A thorough echocardiographic evaluation of the mitral valve apparatus is needed to determine the feasibility of transcatheter mitral valve interventions (14–16). Unfavorable echocardiographic criteria for percutaneous edge-to-edge mitral valve repair include severe leaflet calcifications in the grasping area, rheumatic leaflet thickening, perforated leaflets or clefts, and a mobile length of the posterior mitral valve leaflet of <7 mm, along with insufficient mechanical coaptation in functional (coaptation depth >11 mm, coaptation length <2 mm) and excessive flail gap in degenerative disease (fail gap >10 mm and flail width >15 mm, **Table 1**) (15–17). A pre-procedural mitral valve area of >4 cm^2 is recommended in order to reduce the risk of post-procedural mitral valve stenosis (17). Advanced imaging modalities such as multidetector computed tomography (MDCT) complement the assessment of these patients. Besides the evaluation of the aorto-iliacal axis in TAVR patients, MDCT provides important information on the mitral valve apparatus, particularly on annular dimensions, the extent and localization of calcifications, and the spacial relationship to adjacent structures (16, 18, 19).

TABLE 1 | Favorable echocardiographic criteria for transcatheter edge-to-edge mitral valve repair with the MitraClip® system.

Favorable echocardiographic criteria	Unfavorable echocardiographic criteria
Regurgitation located in the midportion of the valve	Rheumatic valve disease
Absence of leaflet calcifications in the grasping area	Leaflet perforation or clefts
Mitral valve area >4 cm2	Mitral stenosis
Posterior leaflet length ≥10 mm	Posterior leaflet length <7 mm
Flail gap <10 mm and flail width <15 mm	
Coaptation depth <11mm and coaptation length >2 mm	

Adapted from Wunderlich and Siegel (17).

IMPACT OF MITRAL REGURGITATION ON OUTCOMES IN PATIENTS WITH SEVERE AORTIC STENOSIS

Patients with aortic stenosis and coexisting moderate to severe mitral regurgitation are known to have a worse clinical risk profile as compared to those without, which is also reflected by higher surgical risk scores (20, 21). They are older, have a higher prevalence of atrial fibrillation and prior myocardial infarction, and poorer left ventricular systolic function (LVEF) (20–22). Whether concomitant mitral regurgitation independently affects outcomes in patients undergoing AVR remains an ongoing matter of debate, particularly whether secondary mitral regurgitation is related with outcomes irrespective of left ventricular dysfunction. While some studies did not observe any association between the presence of mitral regurgitation and adverse events after SAVR (23, 24), others demonstrated an increased risk of mortality, heart failure, and need for future mitral valve repair/replacement when mitral regurgitation

was treated medically (2, 25, 26). While in some studies, mitral regurgitation did not emerge as independent predictor of mortality after TAVR (2, 20, 27), the majority of studies clearly pointed toward an increased risk of mortality when coexistent moderate to severe mitral regurgitation was present at the time of TAVR (28–34). In a meta-analysis including 4,839 TAVR patients, all-cause mortality was significantly higher in patients with moderate to severe mitral regurgitation (29). Similarly, in a multicenter registry including 1,007 patients undergoing TAVR with the CoreValve Revalving System, 1-year mortality was significantly higher in patients with moderate or severe mitral regurgitation as compared to those without (31). Differences in the grading methodology of mitral regurgitation which was based on qualitative echocardiographic measures in most studies, along with varying inclusion criteria, mainly regarding the etiology and severity of mitral regurgitation, may hamper comparisons among studies. Most interestingly, in the PARTNER (Placement of AoRTic TraNscathetER Valve) trial, patients with moderate to severe mitral regurgitation seemed to experience an even greater benefit from TAVR than those without, as reflected in a smaller number needed to treat to prevent a fatality (35).

TREATMENT STRATEGIES IN PATIENTS WITH SEVERE AORTIC STENOSIS AND MITRAL REGURGITATION

As double valve surgery is associated with an increased mortality as compared to SAVR or combined SAVR and coronary artery bypass grafting (36), transcatheter therapeutic options represent promising less-invasive treatment alternatives to open heart surgery in high-risk patients. Despite the high prevalence of concomitant mitral regurgitation in patients with severe aortic stenosis and the associated substantial morbidity and mortality, randomized trials investigating different therapeutic strategies are lacking. Whether concomitant mitral regurgitation should be treated medically or addressed in combined or staged procedures is ill-defined, and optimal patient selection and timing of interventions need to be determined. The evidence in this field is mostly stemming from observational data and case series, which precludes firm conclusions. Given the lack of guideline-based recommendations, personalized treatment strategies based on associated symptoms, the individual valvular pathology, the comorbid burden, and the estimated procedural risk are advocated (10). Irrespective of attempted surgical or transcatheter approaches to mitral regurgitation, guideline-based heart failure management is essential in these patients before evaluating the regurgitation severity.

The Guideline-Based Heart Team Approach

All patients with severe symptomatic aortic stenosis and concomitant mitral regurgitation, who are at increased surgical risk, are evaluated by a multidisciplinary Heart Team to ensure comprehensive risk stratification and optimal patient selection. Besides technical aspects, associated symptoms, the burden of comorbidities, patient's life expectancy, patient's frailty, and the quality of life need to be taken into account to deliver best quality of care (10). Thereby, a balanced decision on the optimal treatment strategy is taken for each individual patient.

Guideline-based indications for mitral valve procedures are summarized in **Table 2**. The distinction between primary and secondary mitral regurgitation is emphasized in this context. Although mitral valve repair/replacement is considered the gold standard in patients with symptomatic severe mitral regurgitation (10), benefits in those with secondary forms are less clear as lack of survival benefit and an increased risk of recurrence have been reported (37), finally resulting in lower levels of evidence for treatment recommendations in this patient subgroup. According to current guidelines of the European Society of Cardiology (ESC) (10), intervention for severe chronic primary mitral regurgitation is indicated in symptomatic patients with preserved left ventricular ejection fraction (LVEF >30%, class of recommendation I, level of evidence B) with valve repair being the preferred treatment approach. Surgery is further indicated in asymptomatic patients with left ventricular dysfunction as mirrored by a reduced left ventricular systolic function [LVEF ≤60%] or increased left ventricular dimensions (left ventricular end-systolic diameter ≥45 mm, class of recommendation I, level of evidence B), and should be considered in patients with new onset of atrial fibrillation or increased pulmonary pressures (systolic pulmonary pressure ≥50 mmHg, class of recommendation IIa, level of evidence B), and flail leaflet or significant left atrial dilatation (class of recommendation IIa, level of evidence C) (10). Percutaneous edge-to-edge repair may be considered by the Heart Team for symptomatic patients at high surgical risk (class of recommendation IIb, level of evidence C). Currently, there is no indication to intervene for moderate mitral regurgitation.

In patients with severe secondary mitral regurgitation, optimal guideline-recommended heart failure therapy, including optimal medical therapy and coronary revascularization or cardiac resynchronization as indicated, is of particular importance (10, 38). For the treatment of severe secondary mitral regurgitation, a class I recommendation for mitral valve surgery with valve repair being the method of first choice exists in patients undergoing coronary artery bypass graft surgery, when LVEF is preserved (level of evidence C). In symptomatic patients with reduced left ventricular systolic function (LVEF <30%), surgery should be considered when coronary revascularization is indicated (class of recommendation IIa, level of evidence C). When there is no option for coronary revascularization, mitral valve surgery may be considered in patients with preserved LVEF and low surgical risk (class of recommendation IIb, level of evidence C). A percutaneous edge-to-edge procedure may be considered when echocardiographic criteria of eligibility are met and surgical risk deemed prohibitive (class of recommendation IIb, level of evidence C). Although transcatheter percutaneous mitral valve procedures were shown to substantially reduce the degree of mitral regurgitation, beneficially affect left ventricular reverse remodeling, and significantly decrease the symptomatic burden (15, 39–41), it remains uncertain whether survival benefits are achieved. Emerging interventional procedures such as transcatheter annuloplasty or transapical valve replacement complement the therapeutic armamentarium for severe mitral

TABLE 2 | Recommendations for the treatment of chronic mitral regurgitation according to the 2017 European Society of Cardiology (ESC) and European Association for Cardio-Thoracic Surgery (EACTS) guidelines for the management of valvular heart disease.

Recommendations	Class of recommendation	Level of evidence
PRIMARY MITRAL REGURGITATION		
Mitral valve repair is the treatment of choice when durable results are expected.	**I**	C
Mitral valve surgery is indicated in patients with **severe symptomatic** mitral regurgitation and preserved left ventricular systolic function (LVEF >30%).	**I**	B
Mitral valve surgery is indicated in asymptomatic patients with severe mitral regurgitation and left ventricular dysfunction **(LVEF ≤60% or LVESD ≥45 mm)**.	**I**	B
Mitral valve surgery should be considered in asymptomatic patients with **atrial fibrillation** or **pulmonary hypertension** (systolic pulmonary pressure at rest >50 mmHg)	**IIa**	B
Mitral valve surgery should be considered in asymptomatic patients with low surgical risk, preserved left ventricular function (LVEF >60%) and LVESD between 40 and 44 mm, when durable repair is likely and there is a **flail leaflet** or **left atrial dilatation** (LAVI >60 ml/m2)	**IIa**	C
Mitral valve repair should be considered in **symptomatic** patients with low surgical risk and **severe left ventricular dysfunction** (LVEF <30% and/or LVESD >55 mm) refractory to optimal heart-failure therapy when **successful repair is likely**	**IIa**	C
Mitral valve replacement may be considered in **symptomatic** patients with low surgical risk and **severe left ventricular dysfunction** (LVEF <30% and/or LVESD >55 mm) refractory to optimal heart-failure therapy when **likelihood of repair is low**	**IIb**	C
Percutaneous edge-to-edge repair may be considered by the **Heart Team** in patients with symptomatic severe mitral regurgitation, who meet the echocardiographic criteria of eligibility and are deemed at **high or prohibitive surgical risk**	**IIb**	C
SECONDARY MITRAL REGURGITATION		
Mitral valve surgery is indicated in patients with **severe** mitral regurgitation undergoing **CABG**	**I**	C
Mitral valve surgery should be considered in patients with **severe symptomatic** mitral regurgitation and left ventricular dysfunction (**LVEF <30%**) with an option for **coronary revascularization**	**IIa**	C
Mitral valve surgery may be considered in patients with low surgical risk, preserved left ventricular systolic function (LVEF >30%) and **severe symptomatic** mitral regurgitation refractory to optimal heart-failure therapy	**IIb**	C
Percutaneous edge-to-edge repair may be considered in patients deemed at **high or prohibitive surgical risk** with no option for coronary revascularization, who have **severe symptomatic** mitral regurgitation refractory to optimal heart-failure therapy and meet the echocardiographic criteria of eligibility	**IIb**	C
Percutaneous edge-to-edge repair or valve surgery may be considered by the Heart Team in patients deemed at **high or prohibitive surgical risk** with no option for coronary revascularization and **severe left ventricular dysfunction** (LVEF <30%), who have **severe symptomatic** mitral regurgitation refractory to optimal heart-failure therapy and meet the echocardiographic criteria of eligibility	**IIb**	C

Adapted from Baumgartner et al. (10). CABG, coronary artery bypass grafting; LAVI, left atrial volume index; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter.

regurgitation in high risk patients. Experience with these procedures is, however, still limited and guideline-based recommendations lacking.

TAVR and Natural Course of Mitral Regurgitation

Most studies report on a significant improvement of mitral regurgitation after AVR, which has mostly been attributed to reverse left ventricular remodeling and improved left ventricular function. Indeed, in a meta-analysis including 8,927 patients undergoing TAVR, the severity of mitral regurgitation significantly improved in about 60% of patients (42). In the PARTNER trial, moderate to severe mitral regurgitation was observed in 21% of SAVR and 20% of TAVR patients, and improvement was reported in 69% of SAVR and 58% of TAVR patients at 30 days (2). Similar results were reported in other studies (32, 43, 44). These effects may be particularly predominant in patients with secondary mitral regurgitation as structural valve alterations obviously persist after TAVR. A significant improvement in mitral regurgitation severity is more likely to occur in patients without severe pulmonary hypertension and atrial fibrillation (31) Interestingly, acute improvement in mitral regurgitation has been reported following TAVR and was related to immediate post-procedural

changes in left ventricular hemodynamics and improved mitral leaflet tethering (45). Whether the design of the implanted transcatheter heart valve influences the post-procedural course of mitral regurgitation needs to be delineated in future studies. Observational studies point toward a greater degree of reduction of mitral regurgitation in patients treated with balloon-expandable as compared to self-expandable transcatheter heart valves (28).

Combined TAVR and Transcatheter Mitral Valve Procedure

In comparison to a single valve procedure, surgical double valve replacement/repair is associated with increased morbidity and mortality (36, 46). Indeed, mortality rates of about 10% have been reported for double valve aortic and mitral surgery as compared to 3% for isolated SAVR (36). Over the last decades, transcatheter techniques have evolved and offer less-invasive treatment alternatives to double valve surgery in patients deemed at high or prohibitive surgical risk. Transcatheter mitral valve replacement (TMVR) offers a less invasive treatment alternative to redo cardiac surgery, particularly in high-risk patients with degenerated mitral bioprostheses and failed annuloplasty rings (47). Clinical experience with bivalvular transcatheter procedures, however, is still limited (48, 49). The success of a combined approach with transcatheter mitral valve repair performed at the time of TAVR has been reported in several studies (50, 51). Different transcatheter mitral valve repair technologies may be used in this context such as the MitraClip® device (Abbott Vascular Inc., Menlo Park, CA, USA), the Carillon Mitral Contour System® (Cardiac Dimensions, Kirkland, WA, USA), and the Cardioband® (Valtech, Edwards Lifescience Corp, Irvine, CA, USA) (52) An overview of current devices for transcatheter mitral valve repair is provided in **Table 3**.

The most advanced percutaneous mitral valve repair system is the MitraClip® device which allows for introducing a V-shaped clip on the mitral valve leaflets via a transseptal approach under transesophageal echocardiographic and fluoroscopic guidance (**Figure 1**). Thereby, a double or multiple orifice is created (14–16). High procedural success rates of percutaneous edge-to-edge mitral valve repair have not only been reported for primary, but also secondary mitral regurgitation (41, 53), and safety and efficacy was also demonstrated in patients who did not meet the key echocardiographic eligibility criteria as determined by the EVEREST (Endovascular Valve Edge-to-Edge Repair) studies (54).

Percutaneous indirect mitral annuloplasty was developed to improve leaflet coaptation by reducing mitral annular dimensions using dedicated transcatheter devices such as the Carillon Mitral Contour System®. The Carillon Mitral Contour System® consists of anchors at both ends, which are connected by a curved nitinol ribbon connector. The device is implanted within the coronary sinus to reduce the severity of mitral regurgitation by annular placation (14, 55). Safety and feasibility of the procedure, along with clinical benefits in terms of heart failure symptoms, quality of life, and exercise tolerance have been shown for patients with dilated cardiomyopathy and functional mitral regurgitation in different studies such as the AMADEUS (the Carillon Mitral Annuloplasty Device European Union Study) and the TITAN (Transcatheter Implantation of Carillon Mitral Annuloplasty Device) trials (40, 55). The direct annuloplasty Cardioband® system represents a similar interventional transseptal approach for the treatment of secondary mitral regurgitation (56) The annuloplasty band is implanted around the posterior mitral annulus, aiming at reducing mitral regurgitation by decreasing septolateral annular dimensions.

Besides minimally invasive surgical valve repair or replacement, TMVR has emerged as less-invasive treatment alternative for patients deemed at high or prohibitive surgical risk, with several prostheses already introduced in clinical practice (57–59). Although feasibility and safety of valve-in-valve, valve-in-ring, and valve-in-native ring procedures have been demonstrated for transcatheter heart valve implantation in the mitral position (60), future randomized studies are needed to determine the role of TMVR in patients with severe mitral regurgitation.

TAVR and Staged Transcatheter Mitral Valve Procedure

As significant improvements in mitral regurgitation severity have been observed after AVR (26, 43, 44), a staged approach may be favored over a combined procedure with the aortic valve being addressed first and the mitral valve treated only in patients who remain symptomatic in spite of successful TAVR (50, 61). Patients with prior AVR undergoing transcatheter mitral valve repair, however, represent a complex patient subgroup with a high comorbid burden at increased risk of adverse events. One-year survival in these patients was reported to be below 50% (62).

Given the lack of randomized comparisons between surgical and transcatheter double valve interventions vs. medical management of mitral regurgitation in the context of severe aortic stenosis, evidence-based recommendations on patient selection and optimal timing of interventions cannot be made. For predominantly secondary mitral regurgitation, when no major structural mitral valve defects exist, a staged approach may be reasonable to tailor mitral interventions to patients with persistent symptomatic mitral regurgitation, who may benefit most. Bivalvular interventions may be advocated when concomitant predominantly primary mitral regurgitation is present.

Based on our experience, we strongly advocate a stepwise approach in this high-risk patient population, with TAVR being performed first and percutaneous mitral valve repair considered by the Heart Team only when severe mitral regurgitation persists after TAVR. A close clinical and echocardiographic follow-up of these patients following TAVR is mandatory, with functional tests used when grading of mitral regurgitation is challenging.

Cost-Effectiveness of Transcatheter Valve Procedures

Although procedural costs of TAVR exceed those of SAVR, cost-effectiveness of TAVR in patients at increased surgical

TABLE 3 | Overview of devices for transcatheter mitral valve repair.

Device	Principle	Characteristics
MitraClip (Abbot Vascular)	Edge-to-edge repair	- V-shaped clip is placed on the mitral valve leaflets via transseptal approach - Device produces a double mitral valve orifice
Pascal (Edwards Lifescience)	Edge-to-edge repair	- Central spacer with two paddles is placed on the mitral valve leaflets via transseptal approach - Device produces a double mitral valve orifice
Carillon (Cardiac Dimensions)	Indirect annuloplasty	- Anchors at both ends are connected by a curved nitinol ribbon connector - Device is implanted within the coronary sinus to decrease annular dimensions
Cardioband (Valtech, Edwards Lifescience)	Direct annuloplasty	- Annuloplasty band implanted around the posterior mitral annulus - Device decreases septolateral annular dimensions
Mitralign (Mitralign Inc.)	Direct annuloplasty	- Pledget delivery system with retrograde aortic access - Reduction of the annular circumference is achieved by two pairs of pledgets placed at opposite sites of the annulus and producing tissue plication
NeoChord DS 1000 (NeoChord Inc.)	Chordal repair	- Artificial chord-based system implanted via transapical access, secured to the leaflet and anchored to the left ventricular apex
Harpoon TSD-5 (Edwards Lifescience)	Chordal repair	- Artificial chord-based system implanted via transapical access, secured to the leaflet and anchored to the left ventricular apex

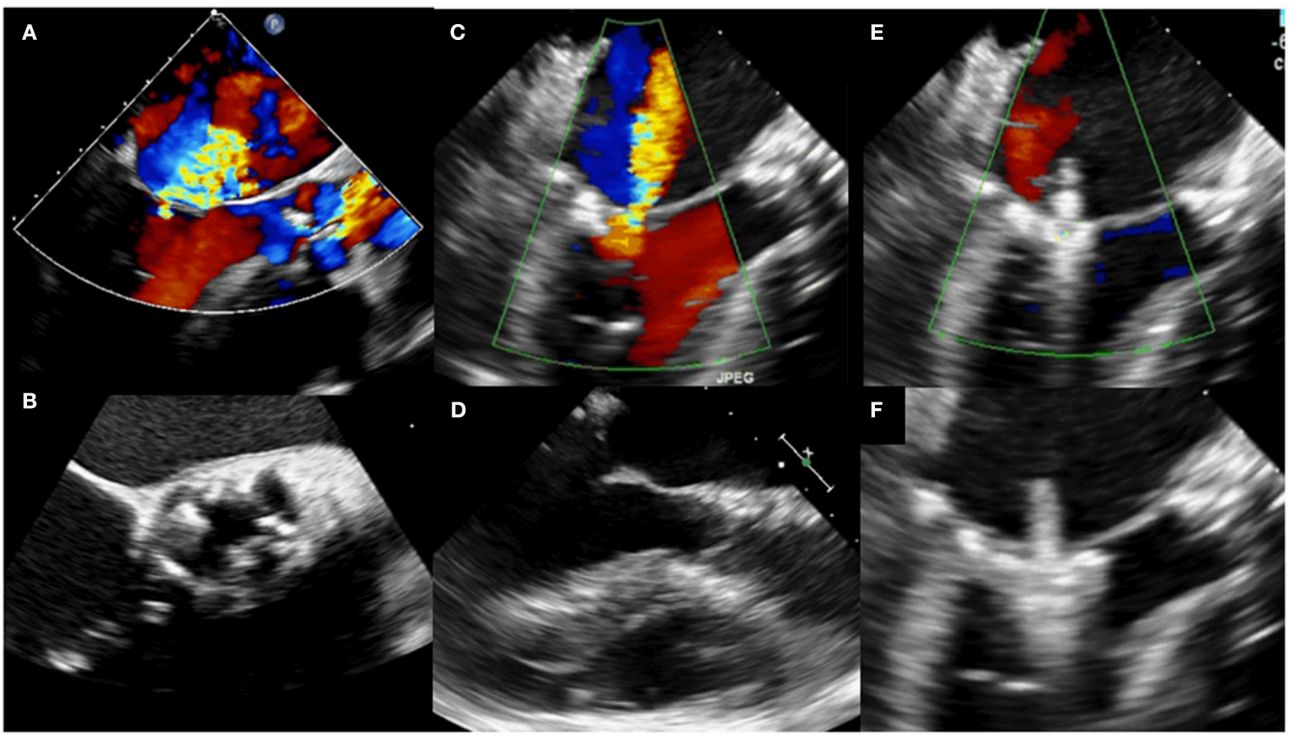

FIGURE 1 | Pre- and post-procedural transesophageal echocardiography in a patient undergoing staged transcatheter aortic valve replacement (TAVR) and edge-to-edge mitral valve repair with the MitraClip® system. **(A)** Transesophageal color Doppler echocardiography at baseline (three-chamber view) showing severe aortic stenosis and concomitant severe mitral regurgitation. **(B)** Transesophageal echocardiography at baseline (aortic valve short-axis view) showing severe aortic stenosis. **(C)** Two-dimensional transesophageal color Doppler echocardiography (three chamber view) showing persistent severe mitral regurgitation following TAVR. **(D)** Two-dimensional transesophageal echocardiography (three chamber view) following TAVR. **(E)** Two-dimensional transesophageal color Doppler echocardiography (three-chamber view) during staged percutaneous edge-to-edge mitral valve repair with the MitraClip® system (grasping). **(F)** Two-dimensional transesophageal echocardiography (three-chamber view) during staged percutaneous edge-to-edge mitral valve repair with the MitraClip® system (grasping).

risk has been demonstrated when shorter hospital stay and reduced need for post-acute rehabilitation services are taken into account, particularly when a transfemoral access is suitable (63–66). In heart failure patients with moderate-to-severe mitral regurgitation, therapy with the MitraClip® device was shown to be cost-effective compared to medical management alone (67). Direct economic comparisons between different transcatheter mitral valve repair systems and mitral valve surgery are, however, lacking. A staged approach with TAVR performed first and percutaneous mitral valve repair tailored to patients who do not experience any improvement in mitral regurgitation following TAVR seems to be cost-effective, as thereby the number of mitral valve interventions is reduced in comparison to simultaneous procedures.

CONCLUSION

Risk assessment and optimal patient selection, along with a personalized treatment approach defined by the Heart Team, is important to ensure best patient care in symptomatic aortic stenosis and concomitant mitral regurgitation. Given the heterogeneity and complexity of mitral valve disease in these high-risk patients, individualized treatment concepts are needed. Although the feasibility and safety of bivalvular transcatheter procedures have been demonstrated, the treatment of first choice—TAVR only, staged TAVR and transcatheter mitral valve procedures, or combined bivalvular transcatheter therapy vs. minimally-invasive surgical treatment—remains to be determined. Randomized trials investigating benefits of mitral valve procedures vs. guideline-based heart failure therapy in TAVR patients with concomitant mitral regurgitation will help to define optimal treatment approaches. Refinements of transcatheter mitral valve concepts including the combination of different approaches will probably enter clinical practice in near future and further improve patient outcomes.

AUTHOR CONTRIBUTIONS

BS analysis and interpretation of the literature, drafting of the manuscript. BS, MR, DL, UL, and AL revising the manuscript critically for important intellectual content, final approval of the manuscript submitted. AL analysis and interpretation of the literature.

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REVIEW
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TAVI and Post Procedural Cardiac Conduction Abnormalities

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Transcatheter aortic valve implantation (TAVI) is a worldwide accepted alternative for treating patients at intermediate or high risk for surgery. In recent years, the rate of complications has markedly decreased except for new-onset atrioventricular and intraventricular conduction block that remains the most common complication after TAVI. Although procedural, clinical, and electrocardiographic predisposing factors have been identified as predictors of conduction disturbances, new strategies are needed to avoid such complications, particularly in the current TAVI era that is moving quickly toward the percutaneous treatment of low-risk patients. In this article, we will review the incidence, predictive factors, and clinical implications of conduction disturbances after TAVI.

Keywords: transcatheter aortic valve implantation, pacemaker, left bundle branch block, right bundle branch block, aortic stenosis

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INTRODUCTION

As transcatheter aortic valve implantation (TAVI) evolves toward treating patients with lower surgical risk and greater life expectancy (1), a significant effort should be directed at a better understanding of common complications following this procedure.

New-onset conduction disturbances are common after TAVI, occurring in as much as 34.8% of patients at hospital discharge (2), and with left bundle branch block (LBBB) being the most common significant conduction disturbance after TAVI (10.5%) (2, 3). Although many studies investigated this topic, indications for permanent pacemaker implantation (PPI) are still unclear, often resulting in overtreatment.

The aims of the present review are to elucidate the anatomical and pathophysiological basis of these complications, to systematically illustrate currently available data, and to highlight unclear areas that clinical research still need to unveil.

ANATOMY AND PATHOPHYSIOLOGY

A high incidence of conduction disturbances occurs not only following TAVI, but also after surgical aortic valve replacement (4), mainly because of the close anatomical relationship between the aortic valve and fundamental structures of the heart conduction system. The atrioventricular (AV) node lies within the apex of the triangle of *Koch*, at the convergence of the tendon of *Todaro* and of the attachment of the tricuspid septal leaflet in the right atrium. It continues as the bundle of His, piercing the membranous septum and penetrating through the central fibrous body to the left. Three major variants of AV nodes have been described, with 50% of individuals exhibiting a

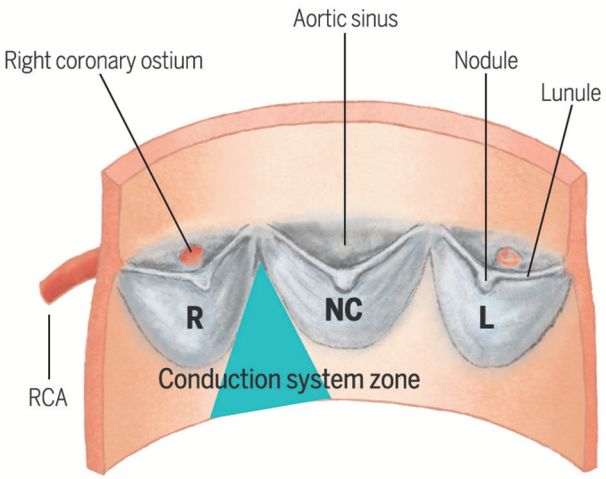


FIGURE 1 | Spatial relationship between the three cusps of the aortic valve and the zone where the left bundle branch emerges beneath the membranous septum. L, Left cusp; NC, Non-Coronary cusp; RCA, Right Coronary Artery.

relatively right-sided AV bundle and 30% with a left-sided AV bundle, whereas in about 20% of patients the bundle courses under the membranous septum just below the endocardium (5). The last 2 above-described variants may expose patients to a higher risk of TAVI-induced conduction disturbances, especially in patients with a short membranous septum (5).

The left bundle branch emerges immediately beneath the membranous septum and is positioned superficially on the crest of the interventricular septum, and is intimately related to the base of the interleaflet triangle separating the non-coronary and right coronary leaflets of the aortic valve (3) (**Figure 1**). Consequently, when operating on the aortic valve, the risk exists to mechanically damage the nearby conductive system. TAVI may acutely expose the conduction system to an ischemic and inflammatory damage, in conjunction with a subacute process of healing (6), which may account for later and overall rarer conduction disturbances. Technical aspects of TAVI procedures, especially self- vs. balloon-expandable valve deployment system (7) and depth of implantation (8), are major factors in directly determining this acute mechanical damage to the conduction system. Furthermore, especially when treating intermediate-risk patients with greater life expectancy, a balance might exist between higher pre- and post-dilation pressures, needed to reduce paravalvular leak and the risk of a direct mechanical damage to the conduction system.

Finally, the close anatomical relationship with the aortic valve could also account for a certain degree of senile calcium deposition on the conduction system, which has been associated with the occurrence of LBBB and advanced atrioventricular block (AVB) in patients with aortic stenosis (9).

Abbreviations: AV, Atrioventricular; AVB, Advanced Atrioventricular Block; EF, Ejection Fraction; LBBB, Left Bundle Branch Block; OR, Odds Ratio; PPI, Permanent Pacemaker Implantation; TAVI, Transcatheter Aortic Valve Implantation.

LEFT BUNDLE BRANCH BLOCK

Overall the most common conduction alteration post-TAVI is new-onset LBBB (8), whose timing varies consistently and reflects different entities and reversibility of damage to the conduction system (**Table 1**); results of studies are summarized in **Table 2**. For the sake of clarity, we will refer to *new onset LBBB* as all LBBB which developed after TAVI, to *persistent LBBB* as all those who did not resolve at the time of discharge, while those patients who did not present LBBB will be referred to as *LBBB-free*.

Onset and Self-Resolution

Urena et al. analyzed a cohort of 202 patients undergoing TAVI with a balloon-expandable valve and with no previous conduction disturbance or PPI, and showed that of the 61 (30.2%) who developed LBBB during hospital stay, 85.2% recovered normal conductive function (59% at 7-day median discharge and 26.2% at long-term follow-up) (8); these findings were in concordance with other studies (6, 16, 17) and demonstrates that most of the new-onset LBBB are transient and do not require PPI implantation. In a cohort of 91 patients undergoing TAVI with self-expandable valve and with no exclusion of patients with previous conduction disturbances and/or PPI, Piazza et al. observed a higher incidence of 54% new-onset LBBB and of 45% at 6-month follow-up (7). These findings, corroborated by other studies (10), further suggest that self-expandable valves may cause a more severe mechanical injury to the conduction system as compared to balloon-expandable valves. Moreover, it was suggested that by not excluding patients with previous conduction disturbances and/or PPI, a higher rate of persistent LBBB might be observed (8).

Impaired Function Recovery and Reverse Remodeling

Historically, the unfavorable effect of LBBB on systolic function is attributed to alterations in global and regional contraction and was proven both in otherwise normal subjects (18) and in hypertensive patients (19); furthermore, an adverse effect on diastolic function (19) and worse prognosis in comorbid patients (20) were also observed. Consequently, concerns were raised that in patients undergoing TAVI who develop persistent LBBB, a reduced EF recovery and therefore reduced benefits from the procedure might be observed.

Nazif et al. showed that in such cases a detrimental effect exists, with less or no EF recovery as compared to LBBB-free patients (58.1% vs. 52.8% at follow-up; $p = 0.001$) (2), independently of baseline EF. Carrabba et al. further elucidated that patients with new-onset LBBB lacked not only EF improvement, but also left ventricular remodeling (13). Urena et al. showed a decreased EF in patients with persistent LBBB at 1-year follow-up ($\Delta = 4.75 \pm 8.02\%$, $p = 0.031$) (8), and Tzikas et al. reported similar findings also in patients treated with self-expandable valves (14). In another study by Urena et al., the only predictors of a lack of EF recovery were higher baseline EF and new onset LBBB (6).

TABLE 1 | Timing of new-onset conduction abnormalities after TAVI.

	Onset	Proposed mechanisms	Incidence	Resolution	Clinical implication	References
LBBB	Intraprocedural (before valve implantation)	Guide wire insertion and balloon pre-dilation	46.5%			(10)
	Post-procedural (early)	Acute mechanical injury (ischemia, inflammation)	10.5–28.2%	• At hospital discharge: 18.1% self-resolves; 40.1–57.4% persists and 11.5 evolves toward complete AVB	The most frequent occurrence of LBBB after TAVI	(2, 6–8, 10)
	Post-procedural (late)		2–6.2%	• At long-term follow-up: 57.4% self-resolves; 14.8% persists and 18% evolves toward complete AVB • With self-expandable TAVI a higher rate of persistent LBBB (45%) was observed at follow-up.		
	At follow-up	Subacute damage (ischemia, healing)	0–2.9%		This represents a rare phenomenon	

TAVI, Transcatheter Aortic Valve Implantation; LBBB, left bundle branch block; AVB:

Impact on Survival and Functional Class

There was no evidence of an impact of new-onset LBBB on patients survival after-TAVI (2, 6, 8, 13, 21) in all but one study by Houthuizen et al., which included patients with high logistic EuroSCORE (21%), therefore more prone to higher mortality rate (28.3%), regardless of whether the new-onset LBBB resolved spontaneously or not. No impact on rehospitalization was observed at 1-year follow-up (6, 8, 21) and no sudden death was reported in patients with new-onset LBBB and no PPI (8). The lack of increased mortality persisted also after a landmark analysis at 30-days (6).

Nonetheless, a poorer New York Heart Association class was observed at follow-up (18% vs. 7% in class II or higher, $p = 0.015$) (6, 8). Testa et al. failed to prove such a difference, although, when considering the high PPI rate in LBBB-free group (17 vs. 18%), it might be attributable to a worse-than-normal mechanical function also in the LBBB-free group (21). Therefore, in patients with persistent LBBB after TAVI, a strategy of early resynchronization seems reasonable, especially in patients with reduced LVEF.

Finally, new-onset persistent LBBB was also associated with an increased risk of AVB and need of PPI at follow-up (13.9 vs. 3.0%, $p = 0.001$, median time to PPI: 12 months) (6, 8). Although further studies are needed in order to confirm these findings, in this setting it might be reasonable to implement a strategy of close (24–48 h) ECG monitoring during the first months after TAVI or after systematic electrophysiology study (8).

Predictors of Left-Bundle Branch Block After TAVI

Common limitations of studies investigating this topic are the inclusion of patients with pre-TAVI conduction disturbances and not taking in due consideration of the role of self- vs. balloon-expandable valves (3, 7), which led to controversial results in the past (6) (**Table 3**). When all these factors were taken into account, predictors of new-onset persistent LBBB were ventricular depth of the prosthesis (odds ratio [OR] = 1.37 for each increase of 1 mm) and baseline QRS duration (OR= 1.24 for each increase of 4 ms) (8); no predictors of transient LBBB were found (8) (**Table 4**).

While a longer QRS duration may be related to baseline conduction system damage and increased vulnerability (8), increased risk of new onset LBBB with lower valve implantation might reflect a more permanent damage to the conduction system with a more ventricular positioning (6). Moreover, this risk factor is consistent also when self-expandable valves are considered (42–44), suggesting that it might be intrinsic of the TAVI procedure.

ADVANCED CONDUCTION DISTURBANCES AFTER TAVI AND PPI

A high rate of new AV and intraventricular conduction delays is observed within the first 48 h of TAVI, with a significant resolution by 30 days. About 22% of patients undergoing TAVI develop a post-operative new-onset AV block after balloon valvuloplasty or after valve deployment. These patients have a 5-fold higher risk of permanent AV block requiring a PPI (45). However, most of the complete AV block as well as the new-onset LBBB and AV blocks tends to disappear within the first days after TAVI: in a cohort of patients implanted with CoreValve, 19.7% had an absolute indication to PPI secondary to the development of advanced II degree AV-block and/or III degree AV block; however half of the advanced conduction delays resolved beyond the periprocedural period, waiting for more than 24 h following TAVI (46).

Incidence of PPI After TAVI

The overall rate of PPI after TAVI ranges from 2 to 51% in a meta-analysis including 41 studies. The rate of PPI implant was

TABLE 2 | Evidences on the clinical impact of LBBB after TAVI.

References	N	TAVI type	New onset LBBB, n (%)	Results	Other
(2)	1151	Balloon-expandable	121 (10.5)	• No difference in mortality (both overall and heart-related) at 30-days and 1-year follow-up • Higher PPI in LBBB group at 1-year follow-up ($p = 0.001$) • Lower EF in the LBBB group at 1-year follow-up (53.4% vs. 57.4%; $p = 0.02$)	All patients were included in the PARTNER trial; †
(11)	202	Balloon-expandable	61 (30.2)	• No difference in mortality at 1-year follow-up • No EF recovery at 1-year follow-up (53 ± 13% vs. 62 ± 9%; $p = 0.0014$) in the persistent LBBB group • Higher PPI in LBBB group (34.2 vs. 4.3%; $p = 0.001$) • No sudden death in patients with persistent LBBB and no PPI at discharge, but higher rates of syncope (16.0 vs. 0.7%; $p = 0.001$) and need for PPI (20.0 vs. 0.7%; $p = 0.001$) at 1-year follow-up • Worse NYHA class at 1-year follow-up ($p = 0.034$)	†
(12)	668	Balloon-expandable	128 (19.2)	• No difference in mortality at 13-month follow-up, even after stratifying for several risk factors; a landmark analysis at 30-d confirmed this finding • No association at 13-month follow-up with rehospitalization, both for all causes and for heart failure • Worse NYHA functional class at 6- month and 1-year follow-up ($p = 0.015$) • No EF recovery (55% vs. 60%; $p = 0.014$) at 13-month follow-up	Four participating centers; †
(13)	92	Self-expandable	34 (37)	• No difference in mortality and/or rehospitalization at 1-year follow-up • Higher PPI in LBBB who developed complete AVB • No EF recovery at 6-month follow-up ($\Delta = 7.39 \pm 9.05\%$ vs. $-0.46 \pm 5.63\%$, $p = 0.0001$) No reverse remodeling at 1-year follow up (ESV 54.5 mL vs. 46 mL, $p < 0.05$; EDV 104 mL vs. 89 mL, $p < 0.05$)	†
(14)	27	Self-expandable	14 (52)	• EF decreased after TAVI in patients with new conduction abnormalities (47 ± 12% to 44 ± 10% vs. 49 ± 12% to 54 ± 12%) • No data on follow-up available	Patients with previous conduction disturbances were included in the analysis
(15)	679	Balloon-expandable (43%) and self-expandable (57%)	233 (34.3)	Increased all-cause mortality in LBBB group (26.6% vs. 17.5%; $p = 0.006$) Strongest predictive factors for all-cause mortality were: TAVI-induced LBBB (HR = 1.54; 95% CI = 1.12–2.10) and COPD (HR = 1.56; 95% CI = 1.15–2.10) A higher number of LBBB were observed after the implantation of a self-expandable valve (51.1% vs. 12%; $p = 0.001$)	Eight participating centers; †

TAVI, Transcatheter Aortic Valve Implantation; LBBB, Left Bundle Branch Block; PPI, Permanent Pacemaker Implantation; EF, Ejection Fraction; NYHA, New York Heart Association; HR, Hazard Ratio; CI, Confidence Interval; †Patients with previous conduction disturbances or PPI were excluded from the analysis. When available, only predictors that persisted at multivariable analysis were reported.

TABLE 3 | Rate of advanced conduction disturbances requiring PPI.

Valve type	References	Design of the study	FU lenght	N	Rate of PPI	Comments
Evolut R	(22)	Retrospetive, multi-center	30-days	120	21.9% ($n = 19$)	Only Evolut R 34 mm included
	(23)	Retrospective, sigle center	1-year	188	25% ($n = 29$)	Only 3 patients had AVB, the remaining had a prophylactic PPI
	(24)	Prospective, multi-center	1-year	1,038	19.3% ($n = 175$)	Unknown rate of AVB
	(25)	Prospective, multi-center	30-days	241	16.4% ($n = 39$)	Unknown rate of AVB
Sapien 3	(26)	Prospective, multi-center	1-year	1,946	11.5% ($n = 195$)	Unknown rate of AVB
	(27)	Propensity-matched cohort	1-year	622	15.5% ($n = 87$)	Cohort compared with ACURATE Neo, higher PPI implant in the Sapien 3 group
	(28)	Randomized trial	1-year	583	16.8% ($n = 96$)	PPI was required in 14.5% of HR patients and in 21.3% of inoperable patients
	(29)	Randomized trial	1-year	1,067	12.4%	Sapien 3 implant in intermediate-risk cohort
Lotus	(30)	Prospective, multi-center	1 year	1,041	34.6%	30.7% of PPI at 30 days, 3.9% after 30 days
	(30)	Multicenter, prospective	1 year	250	36% ($n = 81$)	Cohort of high-risk patients, unknown rate of AVB.
ACURATE neo Symetis	(27)	Propensity-matched cohort	1-year	311	9.9% ($n = 28$)	Cohort compared with Sapien 3, higher PPI implant in the Sapien 3 group
	(31)	Prospective, multicenter	1-year	1,000	8.3% ($n = 83$)	Unknown rate of AVB.

PPI, Permanent Pamaceker Implant; AVB, advanced atrio-ventricular block; HR, high risk.

5 times more frequent in patients receiving a self-expandable Medtronic CoreValve (25–28%) compared to those who received a balloon-expandable Edwards Sapien/Sapien XT valve (5–7%) (47).

This increased risk of PPI with the CoreValve system was confirmed in the CHOICE randomized trial (Comparison of Transcatheter Heart Valves in High Risk Patients With Severe Aortic Stenosis), in which the rate of new PPI in the CoreValve group was 38% while in the Sapien XT group was 23.4% ($p = 0.001$) (48). The SURTAVI trial also confirmed high rates of PPI with both old generation CoreValve (25.5%) and new generation Evolut R (26.7%), despite the inclusion of intermediate-risk patients (49).

Focusing only on the latest-generation transcatheter heart valves, the incidence of PPI ranged between 2.3 and 36.1%. For balloon-expandable prostheses, the PPI rate was between 4.0 and 24.0% when using the new-generation Sapien 3 device, and a similar figure was observed with the previous generation Sapien XT device (ranging between 2.3 and 28.2%). For self-expandable prostheses, the PPI rates were higher with the early generation CoreValve device (16.3–37.7%), and despite a reduction in PPI rates with the new Evolut R, the rates remained relatively higher (14.7–26.7%) (50). These data are confirmed also in the latest experience with the new Evolut R device: among 1,038 patients, the rate of PPI was 17.8%. Similarly, the experience with the latest-generation Evolut PRO valve reports a rate of PPI of 11.8%; however, these results are limited by the low number of patients included in this early feasibility trial ($n = 60$) (51). A low incidence of PPI has been reported in case of Acurate *neo* implantation: in a recent large experience collected in 1,000 patients, the overall incidence of PPI was 8.3% (26); these data are confirmed in a recent propensity matched analysis comparing the Acurate *neo* and the Sapien 3: a high success rates was achieved for both valves, and the clinical and procedural results were comparable. However, Acurate *neo* required less frequently a PPI (9.9% vs. 15.5%; $p = 0.02$). Finally, the Lotus valve has been associated with higher rates of PPI than other devices (31.9–41.0%) (28, 52–54); this could partially be attributable to its peculiar design, including Adaptive Seal technology, which guarantees less paravalvular leak, but might poses a major risk toward the conduction system. Recently introduced strategies for higher implants (including the Lotus Edge Depth Guard Technology) might reduce the aforementioned stress on the conduction system and lead to lower PPI rates.

The prevalence of PPI among the most widely commercially available valves is reported in **Figure 2.** Although a clear trend can be observed, a huge variability in PPI was observed amongst different registries, even when the same valve was involved (**Figure 2)** (1, 22–25, 27, 29–31, 49, 51–75).

As reported by Auffret et al. (76), 2 main factors should be taken into account when evaluating the real incidence of PPI among different studies: first of all, indications to PPI are not uniform and do not always follow the canonic indication reported in the guidelines. As an example, some teams undertook prophylactic PPI in patients with new-onset LBBB after TAVR, which in turn resulted in an increased rate of PPI after TAVI. Moreover, the shorter period of observation after TAVI can underestimate the real incidence of PPI after the procedure. As demonstrated, a reduction in PPI rates has been observed with a strict adherence to Class I and

TABLE 4 | Predictors of conduction disturbances, pacemaker implantation and dependency after TAVI.

Pre-procedural	References	Intra-procedural	References
PREDICTORS OF LBBB			
Baseline QRS duration	(4)	Depth of prostheisis implantation	(4)
PREDICTORS OF AV BLOCK			
Male sex	(32)	New LBBB or RBBB	(32)
Short membranous septum	(33)	QRS > 128 ms	(34)
		Insufficient difference between membranous septum lenght and depth of implantation	
PREDICTORS OF PPI			
Male sex	(35)	New heart block	(35)
1st degree AV block	(35)	Self-expandable valve (vs. balloon-expandable)	(35)
Left anterior hemiblock	(35)	Depth of prosthesis implantation	(36)
Right bundle branch block	(35)	Valve oversizing	(37, 38)
Calcifications (aortic valve, LVOT, mitral valve, membranous septum)	(33, 39, 40)	Insufficient difference between membranous septum lenght and depth of implantation	(33)
PREDICTORS OF PACEMAKER DEPENDENCY			
Baseline LBBB	(41)	PR change after TAVI	(41)
PR duration before TAVI	(41)		
Porcelain Aorta	(41)		

II indications as recommended by clinical guidelines (12). Moreover, as experience, confidence and knowledge grows, a trend toward less PPI in single center registries has been observed (77).

As already mentioned, many of the newly developed advanced AV block resolves spontaneously, therefore according to the European Society of Cardiology guidelines, a prophylactic implantation of PPI after TAVI should be avoided and reserved only to those patients with recurrent AVB after an appropriate period of clinical observation with ECG monitoring (Class I, Level of Evidence C). **Table 3** reports currently available data about the rate of advanced conduction disturbances requiring PPI.

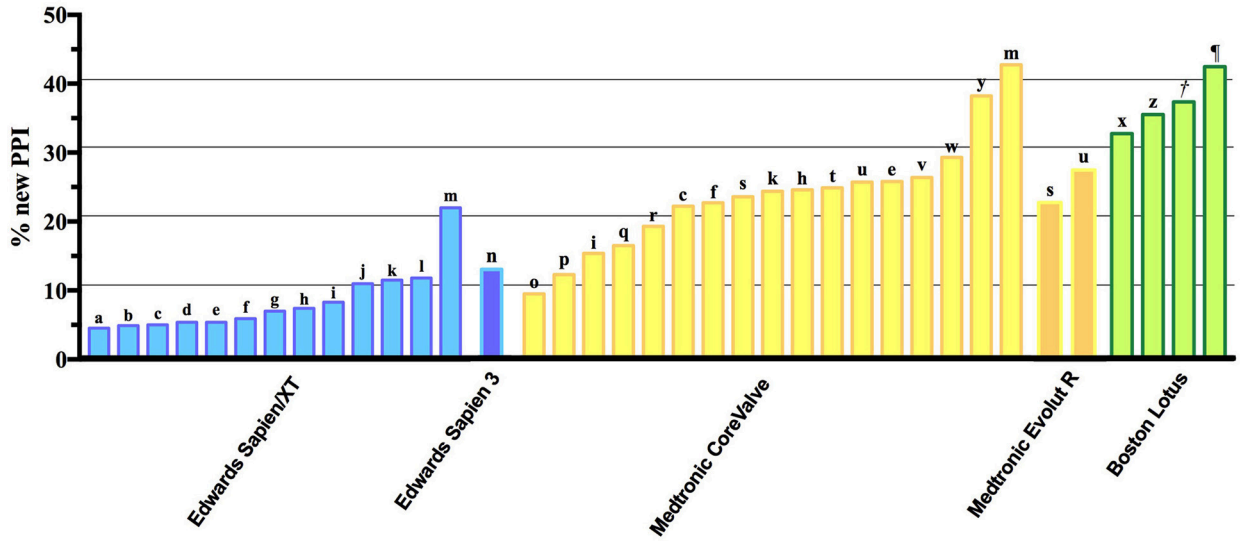
Finally, the real incidence of PPI can be altered in some studies where patients with prior implant of PPI were included in the denominator, although not being exposed to the risk of new PPI implant.

Although guidelines remain vague and clear indications for PPI are still missing, many multicenter and literature-based decisional algorithms exist. In a recent state-of-the-art review, Auffret et al. proposed (76):

- ECG continuous monitoring until discharge for all patients who undergo TAVI;
- Same day PPI in all patients with a class I/II indication for PPI before TAVI;
- Temporary pacemaker for 24 h if new-onset LBBB and up to 48 h if new advanced AVB;
- PPI if new-onset LBBB persists 48 h after TAVI and QRS duration > 160 msec; consider loop recorder and/or electrophysiological studies and/or 30 days ECG monitoring in all other cases;
- PPI if advanced AV block persists 48 h after TAVI or recur before discharge (28, 54, 55, 57, 58, 78–82).

Predictors of PPI After TAVI

In a recent meta-analysis of 41 studies including 11,210 TAVI recipients, male sex, first-degree AV block, left anterior hemiblock, and right bundle-branch block (RBBB) were identified as pre-procedural predictors of PPI, whereas the presence of intraoperative heart block and the use of a self-expandable prosthesis were the procedural predictors (35). In that study, the implantation of a CoreValve system was associated with a 2.5-fold higher risk of PPI, which was confirmed in another systematic review and in the recent report of the Society of Thoracic Surgeons Transcatheter Valve Therapy registry. Baseline RBBB is probably the strongest, most consistent clinical predictor of PPI; it has been identified in more than half of the studies evaluating multivariable predictors of PPI. Calcifications of the aortic valve (39), LVOT, and mitral annulus (40) and depth of prosthesis implantation (36) have been associated with PPI after TAVI. Proposed cut-off values for valve implantation depth predicting new-onset LBBB or PPI were 7 mm or 25% of the stent frame in the LVOT with the Sapien valve (37) and ranged from 6 to 7.8 mm with the CoreValve system (83) and from 5 to 6.7 mm with the Lotus valve (37). Values of 10 to 15% of valve oversizing have been associated with an increased risk of PPI with first-generation devices (37, 38). Concerning the post-procedural management of TAVI recipients, of particular interest are the predictors of delayed AVB after TAVI. In a larger series of 1,064 patients (45% with self-expandable valves), of whom 71 (6.7%) presented with delayed AVB (occurring 24 h after TAVI), Toggweiller et al. identified male sex and the presence of LBBB or



	Registry [ref]	Edwards Sapien/XT	Edwards Sapien 3	Medtronic Corevalve	Medtronic Evolut R	Boston Lotus		Registry [ref]	Edwards Sapien/XT	Edwards Sapien 3	Medtronic Corevalve	Medtronic Evolut R	Boston Lotus
a	*Partner I* [42]	4.5					*q*	*Italian* [55]			9.3		
b	*Canadian* [43]	4.9					*r*	*Italian* [56]			12.1		
c	*Belgian national* [44]	5.0		22.0			*s*	*Italian* [57]			16.3		
d	*I-TA* [45]	5.4					*t*	*Italian* [58]			19.1		
e	*FRANCE TAVI* [46]	5.4		25.6			*u*	*SWISS TAVI* [59]			23.4	22.1	
f	*PRAGMATIC Plus* [47]	5.9		22.5			*v*	*Italian* [60]			24.7		
g	*SOURCE* [48]	7.0					*z*	*SURTAVI* [26]			25.5	26.7	
h	*UK TAVI* [49]	7.4		24.4			*j*	*German* [61]			26.2		
i	*WIN-TAVI* [50]	8.3		15.2			*k*	*ADVANCE* [62]			29.1		
l	*SOURCE XT* [51]	11.0					*x*	*NOTION* [63]			38		
m	*FRANCE 2* [52]	11.5		24.2			*y*	*REPRISE II* [39]					31.9
n	*Partner II* [53]	11.8					*w*	*RESPOND* [33]					34.6
o	*German TAVI* [54]	22.0		42.5			†	*REPRISE I* [64]					36.4
p	*SOURCE 3* [36]		12				¶	*REPRISE III* [32]					41.4

FIGURE 2 | Summary of major trials and registries involving different types (both self-expandable and balloon-expandable) of valve and reporting incidence of new PPI. PPI, Permanent Pacemaker Implantation.

RBBB after TAVI as independent predictors of delayed AVB (32). Mouillet et al. also proposed a post-TAVI QRS duration cutoff of >128 ms as a predictor of the evolution to AVB 24-h after TAVI (34). Baseline RBBB, PR interval duration before and after TAVI, PR interval change (>28 ms) within 3 days of TAVI, and porcelain aorta have been highlighted as independent predictors of pacemaker dependency at 1 year after TAVI (41). Finally, the membranous septum length, a surrogate for the distance between the aortic ring and the piercing bundle of His, has been proven as a major pre-intervention predictors of advanced AV block and PPI (33). In fact, mechanical compression of the emerging conduction tissue is easier if the membranous septum is too short and insufficient difference between this measure and the depth of implantation is achieved during TAVI.

Prognostic Impact of PPI After TAVI

Right ventricular apical pacing results in a left ventricular electrical activation sequence resembling left bundle-branch block. The resulting electrical asynchrony is manifest in a prolonged QRS duration due to slow myocardial conduction. Consequently, left ventricular contraction is altered, and significant interventricular and intraventricular dyssynchrony may occur (84) as result of a non-physiological activation. Ventricular desynchronization imposed by right ventricular apical pacing causes chronic left ventricular remodeling (85), including asymmetric hypertrophy and redistribution of cardiac mass, mitral regurgitation (86), increased left atrial diameter and reduced ejection fraction (87).

These adverse effects on ventricular structure and function likely explain the association of right ventricular pacing with increased risks of atrial fibrillation and heart failure in randomized clinical trials of pacemaker therapy. The MOST (Mode Selection Trial) demonstrated that heart failure during conventional cardiac pacing can be explained by complex interactions between substrate and promoters (11). Substrate is represented by clinical variables including atrial rhythm, AV conduction, ventricular conduction, ventricular function, symptomatic heart failure, and myocardial infarction. The promoters of heart failure are specific to the implementation of cardiac pacing and contain 2 constituents: ventricular desynchronization and AV desynchronization. Based on this model, patients with a very high-risk substrate (low ejection fraction, history of heart failure) are more likely to receive a negative impact from chronic right ventricular pacing (88).

TABLE 5 | Principal studies on PPI and outcome after TAVI.

References	N	Type of valve	PPI recipients n, (%)	FU length	FU Mortality (PPI vs. no-PPI)	FU Hospitalization (PPI vs. no-PPI)
(79)	1,347	SEV	$n = 33.7\%$	30-days	NA	18.7 vs. 21.7% ($p = 0.39$)
(78)	275	SEV	$n = 66$ (24%)	1-year	12.5% vs. 11.8% ($p = 0.9$)	NA
(80)	2,559	BEV	$n = 173$ (8.8%)	1-year	7.6 vs. 9.0% ($p = 0.52$)	23.9 vs. 18.2% ($p = 0.05$)
(81)	9,785	BEV, SEV	$n = 651$ (6.7%)	1-year	24.1 vs. 19.6% ($p = 0.003$)	37.3 vs. 28.5% ($p = 0.162$)
(77)	1,556	BEV, SEV	$n = 239$ (15.4%)	36 months	36.1 vs. 31.5% ($p = 0.73$)	9.6 vs. 6.2% ($p = 0.25$)
(89)	1,629	BEV,SEV	$n = 322$ (19.8%)	4-years	48.5 vs. 42.9% ($p = 0.15$)	59.6 vs. 51.9% ($p = 0.011$)

SEV, self expanding valve, BEV, balloon expanding valve, PPI, permanent pacemaker implant, FU, follow-up, NA, not available.

The negative impact of PPI in TAVI patients has been largely explored in observational and retrospective studies (6). PPI after TAVI has been linked to and increased risk of recurrent hospitalizations for cardiovascular reasons and less recovery of left ventricular EF among patients with baseline impaired left ventricular function (89). In a meta-analysis published by Regueiro et al., the authors demonstrated a trend trough a reduction of cardiovascular deaths associated with the implantation of the PPI. The reason could be linked to the protective effect of pacing against the progression toward complete AV block and sudden death after TAVI. Conversely, the negative impact of PPI implant on mortality after TAVI was showed in a large patient population of 9,785 subjects. After multivariate adjustment, the authors found that PPI in TAVI patients was associated with a 31% increased risk for 1-year mortality and a 33% increased risk for a composite of mortality or heart failure admission at 1-year. Moreover, PPI was found to be associated with a prolonged length of stay in hospital (7 days vs. 6 days; $p < 0.001$) and in the intensive care unit (56.7 vs. 45.0 h; $p < 0.001$) (90). A smaller recent study of 1,973 patients from the PARTNER trial (91) and an international multicentre registry noted a trend toward increased 1-year mortality in patients with new PPI, but it did not reach statistical significance (92). Similarly, in a small study conducted on a cohort of patients treated with first-generation CoreValve, PPI was not associated with increased mortality at 1-year follow-up (93). Actually, only the large experience from the Society of Thoracic Surgeons/American College of Cardiology TVT registry demonstrated a negative influence of PPI on clinical outcome (90). Notably, PPI after TAVI has also been found to be protective against sudden death (92). The results of the most important studies on PPI and outcomes in TAVI patients are reported in **Table 5** (89–94).

The heterogeneity of data regarding PPI after TAVI can be interpreted in the light of the following points:

1) The negative effects of chronic right ventricular pacing may be difficult to demonstrate in the sicker TAVI population with a reduced life expectancy. A longer follow-up period is necessary to demonstrate the detrimental effect of chronic pacing.
2) The negative impact of chronic pacing could have a prognostic importance mainly in patients with reduced left ventricular EF.
3) The impact of right apical pacing on left ventricular EF is dependent both on the percentage of pacing and on pacing modality (i.e., DDD vs. VVI). Only few patients after TAVI have evidence of pacemaker-dependency, so that the negative impact of PPI implant becomes hard to be demonstrated.
4) The negative effect of chronic pacing is counterbalanced by the protective effect that PPI has at follow-up after TAVI. Patients with baseline RBBB and those with long LBBB (QRS length >160 ms) are at higher risk of death after discharge probably due to the development of AVB (92, 95). In this setting, PPI should be protective against the risk of suddendeath.

FUTURE PERSPECTIVES

As TAVI becomes a widespread technology, it is becoming a safe and valid alternative for the treatment of aortic stenosis also in patients at intermediate surgical risk. The development of new transcatheter valves has led to a reduction in significant perivalvular leaks, but with a milder impact in the rate of PPI after TAVI. One of the main challenges in the TAVI field will be the reduction of advanced conduction disturbances needing PPI. This goal could be achieved through a better understanding of the clinical and procedural factors implicated in the development of conduction disturbances after TAVI and through a careful monitoring of patients developing conduction delays in order to avoid futile PPI. In this context, further

studies should investigate the optimal timing for PPI after TAVI and evaluate factors associated with the development and recovery of conduction disturbances. Moreover, considering the aforementioned difference in PPI amongst different devices, it is reasonable to expect advancements in technology that could minimize the need of PPI especially when TAVI will be expanded to low-risk patients.

AUTHOR CONTRIBUTIONS

All the authors contributed to the manuscript production and in the final revision. AM, CM, MP, and OD structured the manuscript giving contribute to table, figures and text editing. AC, LT, and AL revisited the article implementing the final manuscript form.

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Expanding TAVI to Low and Intermediate Risk Patients

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TAVI has become the standard treatment in patients at increased surgical risk and is increasingly being performed in patients at intermediate to low surgical risk. While non-inferiority has been demonstrated in intermediate risk patients, several challenges—particularly with regard to valve durability—need to be addressed before expansion to lower risk and younger patients can be recommended on a broad basis. Current trends, trials results, and remaining challenges are summarized and discussed in the light of updated treatment guidelines.

Keywords: TAVI, TAVR, intermediate risk, low risk, aortic valve stenosis

INTRODUCTION

Severe aortic valve stenosis (AS) represents the most common valvular heart disease in developed countries. Since its prevalence is associated with increasing age, a growing disease burden is expected in the future considering an aging patient population (1). Surgical aortic valve replacement (SAVR)—the traditional standard of care for patients with severe symptomatic AS—is increasingly complemented by transcatheter aortic valve implantation (TAVI). After the first TAVI procedure in 2002 (4), the number of procedures has increased exponentially in the past years and has recently outperformed the number of isolated SAVR per year in Germany (5). Several prospective randomized trials demonstrated non-inferiority for TAVI compared to SAVR in patients at high surgical risk (6, 7). More recently, three additional trials reported non-inferiority of TAVI in intermediate-risk patients (**Figure 1**, **Table 1**) (8–10). Current debates focus on the expansion of TAVI as the standard of care for the treatment of patients with AS and low to intermediate operative risk.

ASSESSMENT OF OPERATIVE RISK

What are criteria and cutoffs for low to intermediate operative risk? Objective risk estimation remains the Achilles' heel for the evaluation of individual treatment options and overall comparison of clinical trial results. A multitude of relevant clinical and anatomical factors effectively influence operative complexity, complicating precise risk calculation in these patients. All of the widely-used risk stratification tools (STS-PROM, logistic EuroSCORE, EuroSCORE II) entail significant limitations in predicting operative mortality (11, 12). In the absence of a perfectly reliable risk model, the STS-PROM has mostly been applied for individual risk assessment and for comparison of trials results. In the past, operative risk was classified as high (STS-PROM >8%), intermediate (STS-PROM of 4–8%), and low (STS-PROM <4%).

Abbreviations: AS, Aortic stenosis; LogES, Logistic EuroSCORE; PVL, Paravalvular leakage; SAVR, Surgical aortic valve replacement; STS-PROM, Society of Thoracic Surgeons' Predicted Risk of Operative Mortality; TAVI, Transcatheter aortic valve implantation; THV, Transcatheter heart valve.

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FIGURE 1 | Evolution of operative risk in major trials**.** Decline in operative risk, as assessed by the STS-PROM score, in major randomized trials comparing TAVI and SAVR (6–10) and anticipated low to intermediate risk of currently active trials (CoreValve LR, DEDICATE, NOTION 2, PARTNER 3). SAVR, surgical aortic valve replacement; STS-PROM, Society of Thoracic Surgeons' Predicted Risk of Operative Mortality; TAVI, transcatheter aortic valve implantation.

However, important additional factors, e.g. active malignancy, frailty, porcelain aorta, chest wall radiation, liver cirrhosis, or neurological impairment, were not comprehensively integrated in these risk models. In addition, treatment decisions may differ in elderly patients without comorbidities (low operative risk despite advanced age) and young patients with significant comorbidities (increased operative risk despite young age). The 2017 ESC/EACTS guidelines for the management of valvular heart disease incorporate these difficulties and opt for a more differentiated approach to operative risk and choice of treatment modality (13).

TREATMENT SELECTION ACCORDING TO CURRENT GUIDELINES

To help navigate the choice of treatment modality in patients with low to intermediate surgical risk, European (13) and American (14) guidelines were recently updated. In general, the indication for TAVI was expanded to intermediate risk patients in both versions on the basis of three major trials (8–10). American guidelines in its current version consider TAVI a reasonable alternative to SAVR in patients at intermediate operative risk (STS-PROM ≥4%), depending on patient-specific procedural risks, values, and preferences (14). European guidelines emphasize, that the treatment selection (TAVI or SAVR) in patients at increased surgical risk (STS-PROM ≥4%, logistic EuroSCORE ≥10% or risk factors not considered in these algorithms) should be made by the Heart Team on an individualized basis (13). According to the guideline's authors, factors in favor of a catheter-based approach include patient age ≥75 years, prior cardiac surgery, frailty, restricted mobility or anticipated prolonged rehabilitation, favorable transfemoral access, prior chest radiation, porcelain aorta, severe chest deformation, or expected prosthesis-patient mismatch. Other aspects, e.g. patient age <75 years, suspicion of endocarditis, unfavorable anatomy for TAVI (access, low coronary take-off, unfavorable aortic root, valvular, or annular anatomy), and concomitant cardiac conditions that require additional surgical treatment favor SAVR. Overall, SAVR remains the standard therapy for patients <75 years of age with low surgical risk at current as long-term durability data for THV remain insufficient. In the absence of a perfect risk assessment, both guidelines emphasize the integral role of the interdisciplinary heart team in patient evaluation, assessment of technical suitability, and identification of the appropriate treatment modality (13, 14).

EVIDENCE FROM INTERMEDIATE-RISK TRIALS OR REGISTRIES

Essential evidence for the expansion of TAVI for the treatment of intermediate risk patients stems from three prospective randomized trials and reports from major contemporary registries.

Registries

Several large-scale nationwide registries evaluated outcomes and trends in the treatment of aortic valve stenosis. Long before first results from prospective randomized intermediate-risk trials were available, large registries had already reported a paradigm shift of TAVI towards lower risk patients: According to the

TABLE 1 | Results of major prospective randomized trials on TAVI vs. SAVR in high and intermediate to low risk patients.

	PARTNER 1A (6)			**CoreValve HR** (7)			**PARTNER 2A** (10)			**NOTION** (9)			**SURTAVI** (8)		
Time of recruitment	**May 2007–August 2009**			**February 2011–December 2012**			**December 2011 –November 2013**			**December 2009–April 2013**			**June 2012 –June 2016**		
THV	**SAPIEN**			**CoreValve**			**SAPIEN XT**			**CoreValve**			**CoreValve**		
Primary endpoint	**All-cause death at 1 year**			**All-cause death at 1 year**			**All-cause death or diasbling stroke at 2 years**			**All-cause death, disabling stroke or myocardial infarction at 1 year**			**All-cause death or disabling stroke at 2 years**		
	TAVI	**SAVR**	**p**	**TAVI**	**SAVR**	**p**	**TAVI**	**SAVR**	**p**	**TAVI**	**SAVR**	**p**	**TAVI**	**SAVR**	**95% CI**
Number of randomized pts.	348	351	n/a	394	401	n/a	1,011	1,021	n/a	145	135	n/a	864	796	n/a
Age	83.6 ± 6.8	84.5 ± 6.4	0.07	83.2 ± 7.1	83.5 ± 6.3	n/a	81.5 ± 6.7	81.7 ± 6.7	n/a	79.2 ± 4.9	79.0 ± 4.7	n/a	79.9 ± 6.2	79.7 ± 6.1	n/a
Male gender	57.8%	56.7%	0.82	53.6%	52.9%	n/a	54.2%	54.8%	n/a	53.8%	52.6%	n/a	57.6%	55.0%	n/a
STS-PROM (%)	11.8 ± 3.3	11.7 ± 3.5	0.61	7.3 ± 3.0	7.5 ± 3.2	n/a	5.8 ± 2.1	5.8 ± 1.9	n/a	2.9 ± 1.6	3.1 ± 1.7	n/a	4.4 ± 1.5	4.5 ± 1.6	n/a
Log. EuroSCORE (%)	29.3 ± 16.5	29.2 ± 15.6	0.93	17.6 ± 13.0	18.4 ± 12.8	n/a	n/a	n/a	n/a	8.4 ± 4	8.9 ± 5.5	n/a	11.9 ± 7.6	11.6.8.0	n/a
Transfemoral access	70.1%	–	–	n/a	–	–	76.3%	–	–	96.5%	–	–	93.6%	–	–
Primary endpoint	24.2%	26.8%	0.44	14.2%	19.1%	0.04	19.3%	21.1%	0.25	13.1%	16.3%	0.43	12.6%	14.0%	−5.2 to 2.3
All-cause mortality (30 days)	3.4%	6.5%	0.07	3.3%	4.5%	n/a	3.9%	4.1%	0.78	2.1%	3.7%	0.43	2.2%	1.7%	−0.9 to 1.8
All-cause mortality (1 year)	24.2%	26.8%	0.44	14.2%	19.1%	0.004	12.3%	12.9%	0.69	4.9%	7.5%	0.38	6.7%	6.8%	−2.7 to 2.4
All-cause mortality (2 years)	33.9%	35.0%	0.78	22.2%	28.6%	0.04	16.7%	18.0%	0.45	8.0%	9.8%	0.54	11.4%	11.6%	−3.8 to 3.3
Stroke (30 days)	3.8%	2.1%	0.2	4.9%	6.2%	0.46	5.5%	6.1%	0.57	1.4%	3.0%	0.37	3.4%	5.6%	−4.2 to−0.2
Myocardial infarction (30 days)	0	0.6%	0.16	0.8%	0.8%	0.92	1.2%	1.9%	0.22	2.8%	6.0%	0.2	0.9%	1.0%	−1.0 to 0.9
Major vascular complications (30 days)	11.0%	3.2%	<0.001	5.9%	1.7%	0.003	7.9%	5.0%	0.008	5.6%	1.5%	0.1	6.0%	1.0%	3.2 to 6.7
Major or life-threatening bleeding (30 days)	9.3%	3.2%	<0.001	13.6%	35.0%	<0.001	10.4%	43.4%	<0.001	11.3%	20.9%	0.03	12.2%	9.3%	−0.1 to 5.9
New permanent pacemaker (30 days)	3.8%	3.6%	0.89	19.8%	7.1%	<0.001	8.5%	6.9%	0.17	34.1%	1.6%	<0.001	25.9%	6.6%	15.9–22.7

(Continued)

TABLE 1 | Continued

	PARTNER 1A (6)			**CoreValve HR** (7)			**PARTNER 2A** (10)			**NOTION** (9)			**SURTAVI** (8)		
Time of recruitment	**May 2007–August 2009**			**February 2011–December 2012**			**December 2011 –November 2013**			**December 2009–April 2013**			**June 2012 –June 2016**		
THV	**SAPIEN**			**CoreValve**			**SAPIEN XT**			**CoreValve**			**CoreValve**		
Primary endpoint	**All-cause death at 1 year**			**All-cause death at 1 year**			**All-cause death or diasbling stroke at 2 years**			**All-cause death, disabling stroke or myocardial infarction at 1 year**			**All-cause death or disabling stroke at 2 years**		
	TAVI	**SAVR**	**p**	**TAVI**	**SAVR**	**p**	**TAVI**	**SAVR**	**p**	**TAVI**	**SAVR**	**p**	**TAVI**	**SAVR**	**95% CI**
New-onset atrial fibrillation (30 days)	8.6%	16.0%	0.006	11.7%	30.5%	<0.001	9.1%	26.4%	<0.001	16.9%	57.8%	0.001	12.9%	43.3%	−34.7 to −26.4
Acute kidney injury (30 days)	1.2%	1.2%	0.95	6.0%	15.1%	<0.001	1.3%	3.1%	0.006	0.7%	6.7%	0.01	1.7%	4.4%	−4.4 to −1.0
Moderate or severe PVL (1 year)	6.8%	1.9%	<0.001	6.1%	0.5%	<0.001	3.4%	0.4%	<0.001	15.7%	0.9%	0.001	5.3%	0.6%	n/a
Rehospitalization (2 years)	24.7%	21.7%	0.41	n/a	n/a	–	19.6%	17.3%	0.22	n/a	n/a	–	13.2%	9.7%	0.1–7.0
Endocarditis (2 years)	1.5%	1.0%	0.61	0.9%	1.7%	0.35	1.2%	0.7%	0.22	n/a	n/a	–	n/a	n/a	–
AV reintervention (2 years)	n/a	n/a	–	2.5%	0.4%	0.02	1.4%	0.6%	0.09	n/a	n/a	–	2.7%	0.7%	0.6–3.4

AV, aortic valve; CI, confidence interval; LogES, logistic EuroSCORE; PVL, paravalvular leakage; SAVR, surgical aortic valve replacement; STS-PROM, Society of Thoracic Surgeons predicted risk of operative mortality; TAVI, transcatheter aortic valve intervention; THV, transcatheter heart valve. Values are given as mean ± standard deviation or frequencies and percentages.

compulsory German quality assurance registry on aortic valve replacement (AQUA), the number of annual TAVI procedures in Germany increased 20-fold from 2008 to 2014 while the number of SAVR procedures slowly declined (15). Interestingly, operative risk, as assessed by the logistic EuroSCORE, decreased significantly over the years with a larger percentage of patients at low to intermediate risk in the later years (logES<10%: 18.9% [2012] vs. 25.9% [2014]). This was followed by a drop in hospital mortality after TAVI during the observation period (2008: 10.4%, 2014: 4.2%) (15).

Similar trends were observed in the German Aortic Valve Registry (GARY), which included a total of 15,964 patients undergoing TAVI between 2011 and 2013 (16). Over the years, a significant regression in risk profiles (logES 20.2% [2011] to 16.9% [2013]; STS-PROM: 5.2% [2011] to 4.9 [2013], both $p < 0.001$), periprocedural complications and in-hospital mortality (5.9% [2011] to 4.9% [2013], $p = 0.078$) were observed (16).

The Society of Thoracic Surgeons (STS)/American College of Cardiology Transcatheter Valve Therapy (TVT) Registry collected data from 54,782 TAVI procedures performed in the United States from 2012 to 2015. The volume of annual TAVI procedures increased from 4,627 to 24,808 in this time window (17). While the median STS-PROM decreased from 7.1 to 6.3% (2012 vs. 2015, $p < 0.001$), a subsequent decline of 30-day mortality (7.5% [2012] vs. 4.6% [2015], $p < 0.0001$), stroke (2.3% [2012] vs. 1.9% [2015], $p = 0.0264$), or moderate/severe PVL (2012:10.8% [2012] vs. 6.2% [2015], $p < 0.0001$) was observed (17).

A shift in patients' disease severity and advancements in procedural and technical aspects over the past years have most likely contributed to these consistent improvements of outcomes after TAVI. However, a comparison of treatment modalities from these registries' results is impeded by very different risk profiles in the treatment groups, calling for appropriate randomized trials.

Randomized Trials

In addition to several real-world registries, few comprehensive—but highly selective—industry-sponsored trials evaluated outcomes after TAVI in different risk categories (see **Table 1** for selected results, Figure for risk profile). Results of intermediate risk trials are discussed in the following.

The first randomized trial to evaluate TAVI in low to intermediate risk patients was the Nordic STACCATO trial. It started patient recruitment as early as 2008 and aimed to compare transapical TAVI to SAVR in operable patients ≥75 years of age (18). Due to an excess of serious adverse events in the transapical TAVI arm, the study was prematurely terminated after inclusion of 70 patients. The trial was heavily criticized for its design, including only a transapical TAVI arm.

One year later, the NOTION (Nordic Aortic Valve Intervention) trial (9) started recruitment. NOTION randomized 280 patients ≥70 years of age with severe aortic stenosis to TAVI with the Medtronic CoreValve THV or SAVR at three Nordic centers (TAVI:145 patients; SAVR: 135 patients). Mean STS-PROM was 2.9 ± 1.6% in TAVI and 3.1 ± 1.7% in SAVR patients. The access route was transfemoral in 96.5% of TAVI cases. The composite primary endpoint (all-cause mortality, stroke or myocardial infarction) and all-cause mortality were similar in both groups (13.1% [TAVI] vs. 16.3% [SAVR] and 4.9% [TAVI] vs. 7.5% [SAVR], $p = 0.38$). Periprocedural complications differed according to treatment arm with an access of major/life-threatening bleeding (11.3% [TAVI]) vs. 20.9 [SAVR]), acute kidney injury stage 3 (0.7% [TAVI] vs. 6.7% [SAVR]), and new-onset or worsening atrial fibrillation (16.9 [TAVI] vs. 57.8% [SAVR], $p < 0.001$) in the SAVR arm. Rates of permanent pacemaker implantation (34.1% [TAVI] vs. 1.6% [SAVR], $p < 0.001$) and PVL (moderate/severe at 1 year: 15.7% [TAVI] vs. 0.9% [SAVR]) were observed more frequently in patients treated with TAVI. At the same time, transvalvular gradients and effective orifice areas were in favor of TAVI treatment. Recent 5-year data confirmed non-inferiority of TAVI compared to SAVR regarding the composite endpoint (TAVI: 39.2%; SAVR 35.8%; $p = 0.78$) (2) and the 5-year all-cause mortality of 27.7% was the lowest 5-year mortality rate ever reported in a TAVI population. NOTION was the first prospective randomized trial to generate data on TAVI in intermediate to low risk patients. However, the small sample size and the large rate of screening failures challenge the "all-comers" character of the trial.

At a larger scale, the PARTNER 2A trial randomized 2,032 patients with intermediate surgical risk (STS-PROM score 4–8% and heart team consensus) to either TAVI with the balloon-expandable SAPIEN XT or SAVR (10). The mean STS-PROM was 5.8% and almost twice as high as in the NOTION trial. The composite endpoint at 2 years (all-cause death or disabling stroke) was non-inferior in patients treated with TAVI compared to SAVR (TAVI: 19.3%, SAVR: 21.1%, $p = 0.25$). A subsequent subgroup analysis even demonstrated superiority for the transfemoral cohort compared to SAVR (16.3 vs. 20%, $p = 0.04$). At 2 years of follow-up, a higher incidence of life-threatening/disabling bleeding (47.0 vs. 17.3%, $p < 0.001$), acute kidney injury stage 3 (6.2 vs. 3.8%, $p = 0.02$), and new onset atrial fibrillation (27.3 vs. 11.3%, $p < 0.001$) were reported after SAVR while patients after TAVI had a higher risk for major vascular complications (8.6 vs. 5.5%, $p = 0.006$). Interestingly, rates of permanent pacemaker implantations were not significantly different in both groups in this trial. An overall faster recovery and shorter hospitalization (in-hospital: median 6 vs. 9 days, ICU: median 2 vs. 4 days, $p < 0.001$ for both) were observed after TAVI. While lower transprosthetic gradients were reported in the TAVI arm, the rate of moderate/severe PVL was significantly higher compared to SAVR (8.0 vs. 0.6%, $p < 0.001$) and a trend towards more aortic valve re-interventions was observed after TAVI at 2 years (1.4 vs. 0.6%, $p = 0.09$). This observation has to be followed closely as the TAVI indication is expanded to younger patients. Of note, 14.5% of patients in the SAVR arm underwent concomitant coronary artery bypass graft surgery for significant coronary artery disease.

After a recruitment period of almost 4 years, the SURTAVI trial (8) recently reported results of 1,764 patients at intermediate surgical risk (predicted 30-day operative mortality 3–15%). The mean STS-Score was 4.5 ± 1.6% and thus in between the PARTNER 2A and NOTION trials. Patients were randomized 1:1 to TAVI with the self-expanding CoreValve or CoreValve Evolut

R prostheses and SAVR. The primary endpoint, a composite of all-cause death and disabling stroke at 2 years, was similar in both treatment arms (12.6% [TAVI] vs. 14% [SAVR], 95%CI −5.2 to 2.3%). Again, higher rates of acute kidney injury (4.4 vs. 1.7%), new onset atrial fibrillation (43.4 vs. 12.9%), and transfusion requirements (41.1 vs. 12.5%) were observed after SAVR. While hemodynamic measures were in favor of TAVI (transprosthetic gradients, effective orifice area), the incidence of PVL (moderate/severe at 1 year: 5.3 vs. 0.6%) and the need for pacemaker implantation (25.9 vs. 6.6%) were lower after SAVR. Quality of life at 2 years was similar in both groups. Aortic valve reintervention was reported more often after TAVI (2.7 vs. 0.7% at 2 years), although no structural valve deterioration was found in either group.

Currently Active Intermediate to Low Risk Trials

Building on the results of intermediate-risk trials and registries named above, several prospective randomized trials are currently active, either recruiting patients or in follow-up, to evaluate outcomes after TAVI in patients at low to intermediate operative risk. The results of these trials will determine future guideline recommendations on the treatment of aortic stenosis in low to intermediate risk patients (see **Table 2** for major characteristics of these trials).

The PARTNER 3 trial (clinicaltrials.gov NCT02675114) randomly assigns 1,328 patients with low surgical risk (STS-PROM<4%) to TAVI with the Sapien 3 device or SAVR. Patients will be followed for 10 years and the primary endpoint is a composite of all-cause mortality, stroke and rehospitalization at 1 year. Results of the primary endpoint are expected to be presented in 2019.

The Medtronic TAVR low risk trial (clinicaltrials.gov NCT02701283) includes 1,200 patients with an STS-PROM<3%. Patients are randomized to TAVI with the CoreValve or CoreValve Evolut R self-expandable THV or SAVR. Patients will be followed for 10 years and the primary endpoint is a composite of all-cause mortality or disabling stroke at 2 years.

While both studies are industry-sponsored and limited to one THV, two additional investigator-initiated trials have been initiated:

The Nordic NOTION-2 trial (clinicaltrials.gov NCT02825134) aims to randomize 992 low risk patients (STS<4%, ≤75 years) to TAVI with any CE-marked device or SAVR. Due to the exclusion of elderly patients, this trial will particularly gain important insights into outcomes of TAVI in younger patients at low risk. Interestingly, combined procedures (SAVR and concomitant CABG or TAVI and PCI) are also included in the trial. The primary endpoint is a composite of all-cause mortality, stroke or myocardial infarction at 1 year. The trial is investigator-initiated but industry-funded.

The DEDICATE trial (DEDICATE-DZHK6, clinicaltrials.gov NCT03112980) is multicenter investigator-initiated and industry-independent study. It is funded by the DZHK (German Center for Cardiovascular Research), the Deutsche Herzstiftung e.V., and supported by German health insurance providers. Overall 1,600 patients at low to intermediate surgical risk (STS-PROM 2–6%) will be included. As opposed to previous trial designs, DEDICATE aims to investigate a true all-comers patient population and evaluate real-world outcomes. After 1:1 randomization to either TAVI or SAVR, the remaining treatment decisions (e.g. access route, THV type, periprocedural treatment, etc.) are left to the interdisciplinary heart team. All CE-marked devices can be utilized to avoid any potential device-based bias. To account for the increasing importance of long-term data in low risk patients, the primary endpoint was chosen as overall survival after 5 years. Low to intermediate risk patients undergoing aortic valve treatment at the study sites who are not included in the randomized trial will be captured in a nested registry to evaluate an all-comers population.

All of these active trials will add significantly to the current evidence for TAVI in intermediate to low risk patients and allow first insights into long-term results on a broad basis.

REMAINING CHALLENGES

Within the last decade, TAVI has become the standard of care for high-risk patients with severe and symptomatic AS. It has increasingly been performed in intermediate and also low-risk patients more recently. Particularly for younger and low-risk patients, additional challenges need to be addressed:

Valve Durability and Function

The unresolved issue of long-term valve durability is probably the key challenge in expanding TAVI to lower risk and younger age patients. Longitudinal echocardiographic evaluation of the PARTNER trials (PARTNER 1A, 1B, and continued access) demonstrated stable hemodynamic results after TAVI over 5 years of follow-up (19). Similar results were reported in other series and for self-expanding transcatheter heart valves (20). Recently results from the Nordic NOTION trial confirmed not only robust hemodynamic data over 5 years of follow-up but also favorable hemodynamics after TAVI compared to SAVR (2). Particularly in patients with smaller aortic annuli, TAVI may yield a lower incidence of patient-prosthesis mismatch, compared to SAVR. However, increased rates of PVL were consistently observed after TAVI compared to SAVR. Due to an adverse effect of significant paravalvular leakage on survival (10), reduction of residual regurgitation will be essential to improve long-term outcomes. Although progress has been made to reduce residual AR after TAVI in recent studies with next-generation devices (21), further improvements will be required to match data from SAVR cohorts.

Additionally, subclinical leaflet thrombosis, its effects on hemodynamic and clinical results need to be evaluated due to a significantly higher incidence after TAVI compared to SAVR (22). Overall, the incidence of structural valve degeneration and aortic valve re-intervention were low but will naturally become an issue as follow-up length and patient numbers increase. Recently published definitions of prosthesis degeneration may aid comprehensive analysis of this important topic (23, 24). To eliminate durability concerns after TAVI, very solid durability data available for surgical bioprostheses over the course of more than a decade will need to be matched (25).

TABLE 2 | Overview of currently active randomized trials on TAVI vs. SAVR in low to intermediate risk patients with severe aortic stenosis.

	DEDICATE	NOTION 2	PARTNER 3	CoreValve low risk
Reference/NCT number	Clinicaltrials.gov/NCT03112980	Clinicaltrials.gov/NCT02825134	Clinicaltrials.gov/NCT02675114	Clinicaltrials.gov/NCT02701283
Study start date	2017	2016	2016	2016
Study status	Recruiting	Recruiting	Recruiting	Recruiting
Estimated study completion date	2024	2024	2027	2026
Patients' risk profile	STS-PROM 2-6%	Patient age ≤75 years and STS-PROM <4%	STS-PROM <4%	Operative risk <3%
Study arms	TAVI* vs. SAVR* (1:1 randomization)	TAVI* vs. SAVR* (1:1 randomization)	TAVI (SAPIEN 3) vs. SAVR* (1:1 randomization)	TAVI (CoreValve Evolut R) vs. SAVR* (1:1 randomization)
Estimated enrollment	1,600	992	1,328	1,200
Primary Outcome	• Efficacy endpoint: Overall survival at 5 years • Safety endpoint: Overall survival at 1 year and 196 deaths (event-driven)	All-cause mortality, myocardial infarction or stroke at 1 year	All-cause mortality, stroke, or re-hospitalization at 1 year	All-cause mortality or disabling stroke at 2 years
Follow up time	5 years	1 year	10 years	10 years
Listed location countries	Germany	Denmark, Finland, Iceland, Norway, Sweden	Australia, Canada, Japan, New Zealand, United States	Australia, Canada, France, Netherlands, New Zealand, Switzerland, United States
Study sponsor and collaborators	• University Medical Center Hamburg-Eppendorf • German Center for Cardiovascular Research (DZHK)	Rigshospitalet, Denmark Symetis SA, Boston Scientific Corporation, St. Jude Medical	Edwards Lifesciences	Medtronic Cardiovascular

*SAVR, surgical aortic valve replacement; STS-PROM, Society of Thoracic Surgeons predicted risk of operative mortality; TAVI, transcatheter aortic valve intervention; *Any commercially available or CE marked device. Information up-to-date as available on clinicaltrials.gov on June 10th, 2018.*

Nevertheless, degeneration of THV will occur at some point in patient life, leading to either surgical valve replacement or valve-in-valve procedures. Valve-in-valve procedures have demonstrated encouraging results in patients with degenerated surgical aortic bioprostheses (26). Whether these results can be systematically achieved for valve-in-valve procedures in degenerated THV needs to be demonstrated. Different design features of THV may yield variable results after valve-in-valve implantation, for example with regard to coronary access in degenerated supra-annular THV.

While moving towards younger patients, the prevalence of biscuspid aortic valve disease will inevitably increase. Data from retrospective registries demonstrated lower procedural success and higher residual PVL after TAVI in patients with bicuspid compared to tricuspid aortic valve disease (27–30). Implantation of new-generation devices yielded improved outcomes, giving rise to hope that TAVI may become a valid treatment option in bicuspid aortic valve disease in the future (30). Due to the paucity of data, guidelines favor SAVR in these patients at current (13).

Morbidity and Mortality

After early reports of increased stroke rates after TAVI (6), more recent trials have consistently demonstrated similar outcomes for mortality and stroke after TAVI or SAVR. However, distinct complication patterns have repeatedly been reported for both treatment options (see **Table 1**). These need to be weighed against the individual patient's risk profile when choosing the optimal treatment modality. These include a higher incidences of acute kidney injury, bleeding events, and atrial fibrillation after SAVR. TAVI was associated with faster recovery and shorter index hospitalization but a higher rate of re-interventions or heart failure were documented during follow-up. Long-term results will be essential to gain further insights into these important first observations. While major vascular complications were common after transfemoral TAVI with first-generation devices (31), a significant decrease was observed in recently reported intermediate-risk trials (8–10). A shift in patients' risk and device refinements with smaller delivery systems and improved vascular closure devices may be responsible for this decline. Permanent pacemaker implantation remains a concern after TAVI, particularly with self-expanding THV. Although data remain ambiguous regarding the association of pacemaker implantation and outcome after TAVI at current (32, 33), this issue requires in-depth evaluation, particularly in the treatment of younger patients.

Although a major advantage of TAVI relates to the less invasive procedure compared to SAVR, the risk for rare but life-threatening complications after TAVI (e.g., annular rupture, valve migration, or coronary obstruction) requiring bail-out emergency cardiac surgery must be taken into account. Recently

published data from the European Registry on Emergent Cardiac Surgery during TAVI (EuRECS-TAVI) reported an incidence of emergent cardiac surgery of 0.7% in recent years. Most common causes were left ventricular guidewire perforations (28.3%) and annular ruptures (21.2%). Most of these complications occurred during the procedure and mortality remained high despite emergent cardiac surgery (34). While these serious procedure-related complications were more frequent in the early TAVI era and have become very rare events at this stage (35), expansion of TAVI towards younger and low-risk patients requires an even more critical appraisal and all measures need to be taken to prevent these complications.

Cost-Effectiveness

With the rapid growth of TAVI volume, its implications on healthcare systems and its cost-effectiveness will become even more important, particularly while expanding TAVI indications to lower risk patients (36). An early analysis from the Netherlands demonstrated higher 1-years costs of TAVI vs. SAVR in intermediate-risk patients (37). This cost difference was mainly driven by the difference in device prices. A recent cost-effectiveness analysis from the Partner 2A and Sapien 3 trials reported lower costs at 2 years after TAVI (3). Higher procedural costs were compensated for by shorter hospitalization and substantially lower costs during follow-up. Regional and national differences in reimbursement and device costs impede generalization of these results. However, health economic analyses will gain importance as the field expands.

CONCLUSION

TAVI has become the standard treatment in patients at increased surgical risk and is increasingly being performed in patients at intermediate to low risk at current. Non-inferiority has been demonstrated in different intermediate risk cohorts. However, before broad expansion to lower risk and younger patients can be recommended, several challenges—particularly with regard to valve durability—need to be addressed. Several randomized trials are under way to investigate these issues and will determine future guideline recommendations. For now, distinct risks should be weighed into the decision of TAVI vs. SAVR, incorporating each patient's individual risk profile and personal preferences. Shared-decision making will increasingly become a crucial element in this process. Preferences of the informed patient should be discussed, balanced, and weighed into the joint treatment decision of the interdisciplinary heart team to select the appropriate treatment for every individual patient while expanding TAVI to intermediate and low risk operative patients.

AUTHOR CONTRIBUTIONS

LV: literature research, drafted the manuscript; MS: literature research, critical revision of the manuscript.

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REVIEW
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Access Sites for TAVI: Patient Selection Criteria, Technical Aspects, and Outcomes

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During the last ten years, transcatheter aortic valve implantation (TAVI) has become a reliable and valid alternative treatment for elderly patients with severe symptomatic aortic valve stenosis requiring valve replacement and being at high or intermediate surgical risk. While common femoral arteries are the access site of choice in the vast majority of TAVI patients, in up to 15–20% of TAVI candidates this route might be precluded due to the presence of diffuse atherosclerotic disease, tortuosity or small vessel diameter. Therefore, in order to achieve an antegrade or retrograde implant, several alterative access routes have been described, namely trans-axillary, trans-aortic, trans-apical, trans-carotid, trans-septal, and trans-caval. The aim of this paper is to give a concise overview on vascular access sites for TAVI, with a particular focus on patient's selection criteria, imaging, technical aspects, and clinical outcome.

Keywords: TAVI, trans-axillary, trans-aortic, trans-apical, trans-carotid, trans-septal, trans-caval, access

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INTRODUCTION

Transcatheter aortic valve implantation (TAVI) has gained prime time as the preferred treatment for elderly patients suffering from severe symptomatic aortic valve stenosis and at high or intermediate risk for standard surgery (1). During the last decade, cardiac centers have faced a continuously increasing number of TAVI procedures that overtook, in some countries, the number of standard surgical aortic valve replacements (2).

Experience acquired in this setting suggests that procedural success is achieved through an accurate pre-procedural evaluation, a perfect matching between commercially available prostheses and the peculiar anatomical characteristics of TAVI patients, technical implant skills of the TAVI team and a tailored choice of access options, the latter representing one of the most critical points.

The trans-femoral access represents the preferred route in the vast majority of TAVI patients because of its minimal invasiveness and the possibility to perform the procedure under conscious sedation without intubation. Increased expertise and technical advancements lead to a significant reduction of major access site-related vascular complications that occur, nowadays, in <10% of cases.

Due to its wide diffusion and feasibility, the trans-femoral access is the preferred route in the majority of the clinical trials and is recommended as first choice by all guidelines and consensus documents (1–5).

Nonetheless, data from randomized clinical trials (3–7) and registries (8–14) clearly show that the trans-femoral access might be precluded in up to 25–30% of TAVI patients due to the

presence of severe arterial disease (**Figure 1**). In particular, obstructive peripheral vascular disease, femoro-iliac tortuosity, aortic atheromas, or the presence of previously implanted arterial grafts can seriously limit the possibility of a transfemoral access (**Figure 2**).

Beside technical aspects, the choice of the access in TAVI seems to be independently associated with an impact on prognosis, in particular in the case of the trans-apical approach, when manipulation of the left ventricular apex is needed (14, 15). This evidence highlights the priority of an appropriate access route selection in TAVI. So far, several alternative options for antegrade or retrograde TAVI procedures have been described, namely the trans-femoral, trans-axyllarian, trans-aortic, trans-apical, trans-carotid, trans-septal, and trans-caval. Nonetheless, no randomized comparisons are so far available, thus the choice is often based on data derived from retrospective analyses of national registries as well as on local experience.

In this report we give a concise overview on accesses for TAVI, with a particular focus on patient's selection criteria, technical aspects and clinical outcome.

FEMORAL ACCESS

The common femoral artery represents the preferred access in the vast majority of TAVI procedures. This route allows a fully-percutaneous TAVI under conscious sedation/local anesthesia. Careful procedural planning and accurate choice of the proper site for vascular puncture are keys for procedural success.

Patient's Selection and Planning

While obtaining the femoral access is technically easy, planning a successful procedure through this route might be demanding and time consuming. Unplanned (or angio-only guided) femoral access should be avoided whenever possible, this representing a potential risk of severe vascular complications. A detailed reconstruction of the arterial route along with precise aortic annular dimensions can be obtained at CT scan analysis, adding invaluable data about the feasibility of different approaches.

As a standard protocol in our center, patients referred for TAVR undergo an angio CT-scan and a 3D reconstruction extending from the aortic annulus to the superficial femoral artery with commercially available software packages (e.g., 3mensio structural Heart, Pie Medical Imaging, Maastricht, The Netherlands). The relationship of the vessels, in particular of the bifurcation, with the femoral head should be carefully evaluated. In selected cases, the angiographic reconstruction will help to perform a fluoro-guided puncture of the artery with no or minimal contrast injection (**Figure 3**).

While analyzing the common femoral and iliac arteries, particular attention should be paid to their caliber (that has to exceed at least 5.5 mm, ideally 6.5 mm for a 18F delivery system) and to the presence and extension of atherosclerotic plaques, calcifications as well as to the degree and extension of tortuosity. When calcifications are concentric, located anywhere from the aorto iliac bifurcation to the femoral bifurcation, even in the presence of vessels of good caliber, this could represent a potential contraindication for the trans-femoral access and the need for alternative accesses should be discussed within the Heart Team. A good estimation of the caliber of the iliac artery is of paramount importance in balloon size selection when transient occlusion is needed in bailout situations.

Beside detailed analysis of the iliiac-femoral arteries, a cautious exploration of the aorta should be performed as well in order to identify potential challenges such as tortuosity, presence of aneurysms, thrombotic appositions, or aortic arch calcifications. All these anatomic features are potential sources of embolization or causes of vascular rupture/dissection when large catheters are inserted and, therefore, can be considered as relative contraindications for a transfemoral approach.

Technical Aspects

When deemed suitable for transcutaneous access, an optimal puncture site is then identified (**Figures 3A,B**) in the segment of the common femoral artery extending between the inferior epigastric artery and the distal portion of the common femoral artery, ideally 1 cm above the femoral bifurcation (**Figure 3C**). In case of vascular complications, the most common being failure of the vascular closure device; having enough distance from the femoral bifurcation will allow the placement of a covered stent or, in alternative, a safe surgical isolation and repair.

In presence of an anterior calcification of the femoral artery, attention should be paid when percutaneous suture-based vascular closure devices (e.g., Perclose, Prostar, both from Abbot medical) are meant to be used, because their efficacy might be reduced. In those cases, surgical cut down with or without surgical endarterectomy or alternative access, should be considered.

When performing a transcutaneous femoral artery puncture for TAVR, we almost invariably try to roadmap the route. For this purpose a selective angiography with a pigtail inserted by the contralateral access through a cross-over technique is used (**Figures 4A–C**). Then, the needle is directed toward the middle of the pigtail, and the arterial wall is punctured on its anterior aspect (**Figure 4D**). This will minimize the risk of vascular injury and enhance the success rate of percutaneous closure devices as well. While in the first TAVI series the Prostar was widely adopted, nowadays vascular preclosure with two Perclose/Proglide (Abbot Medical) devices inserted on the medial (2 o'clock) and lateral (11 o'clock) aspect of the arterial wall are used in the vast majority of transfemoral cases. When using this technique, attention should be paid in removing the contralateral pigtail before the insertion of the closure devices in order to prevent the entrapment of the catheter, a complication requireing surgical removal (**Figure 4E**). In some centers, omolateral injections using micropuncture needles (3F) are used to identify the optimal site. In obese patients with deep femoral arteries (i.e., >8 cm from the skin) as well as in cases with anterior calcifications, surgical cut down or alternative accesses should be considered. At case completion, when doubting about the efficacy of the preclosure devices implanted, a good tip to keep in mind is to perform a crossover from the contralateral femoral artery before removing the main sheath. This will allow to position a safety wire in the iliac/femoral artery that could be used rapidly for balloon occlusion and, eventually, to deliver a covered stent.

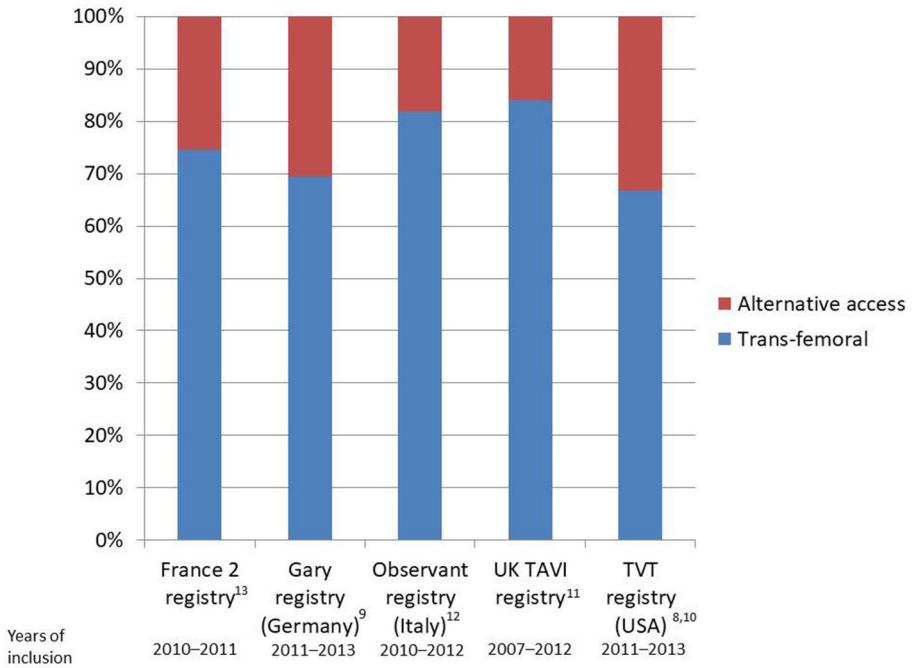

FIGURE 1 | Bar plot reporting rates of transfemoral implants as compared to alternative accesses in national registries.

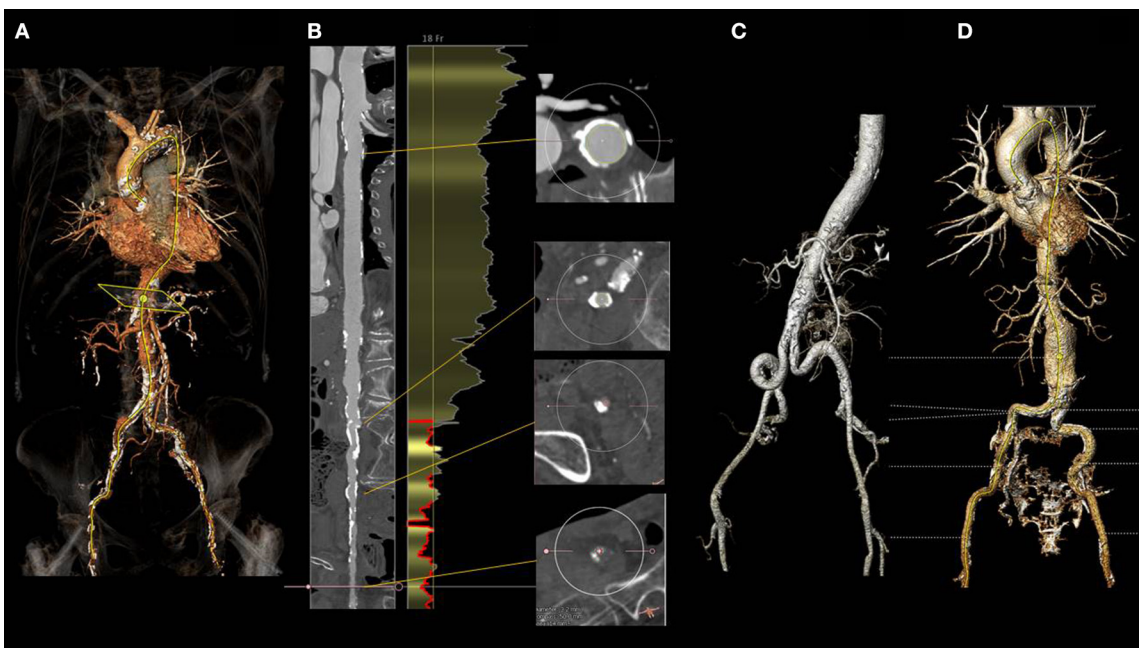

FIGURE 2 | Three dimensional angio CT reconstruction obtained with the 3mensio software in a patient with severe aortic stenosis referred for TAVI **(A)**. Snake view of the aorta and right iliacofemoral arteries **(B)** clearly shows diffuse calcific atherosclerotic disease precluding trans-femoral route. **(C)** shows diffuse tortuosity of the iliac arteries, while **(D)** the incidental finding of an infrarenal abdominal aneurysm. All the above mentioned findings might preclude a transfemoral approach.

Outcome Data

Increased awareness of operators regarding the intrinsic difficulties of the femoral access in TAVI associated with technological advancements such as the progressive reduction of the caliber of the vascular sheaths and delivery systems has led to a perceivable reduction in the occurrence of major vascular

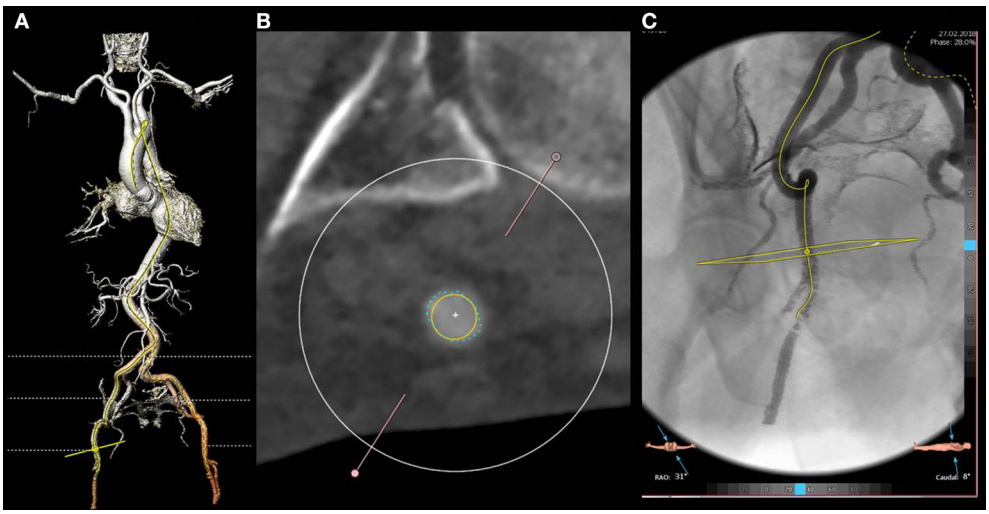

FIGURE 3 | Three dimensional reconstruction of the arterial system **(A)** and cross section of the common right femoral artery at the optimal puncture site **(B)**. The artery shows a good caliber (exceeding 6.5 mm as evident from the yellow circle) and no calcifications. Moderate tortuosity of the superficial iliac artery is evident at both 3 D and angio reconstruction **(C)**. In particular, the angio reconstruction allows for the fluoro guided detection of the optimal access site, based on its relationship with the femoral head.

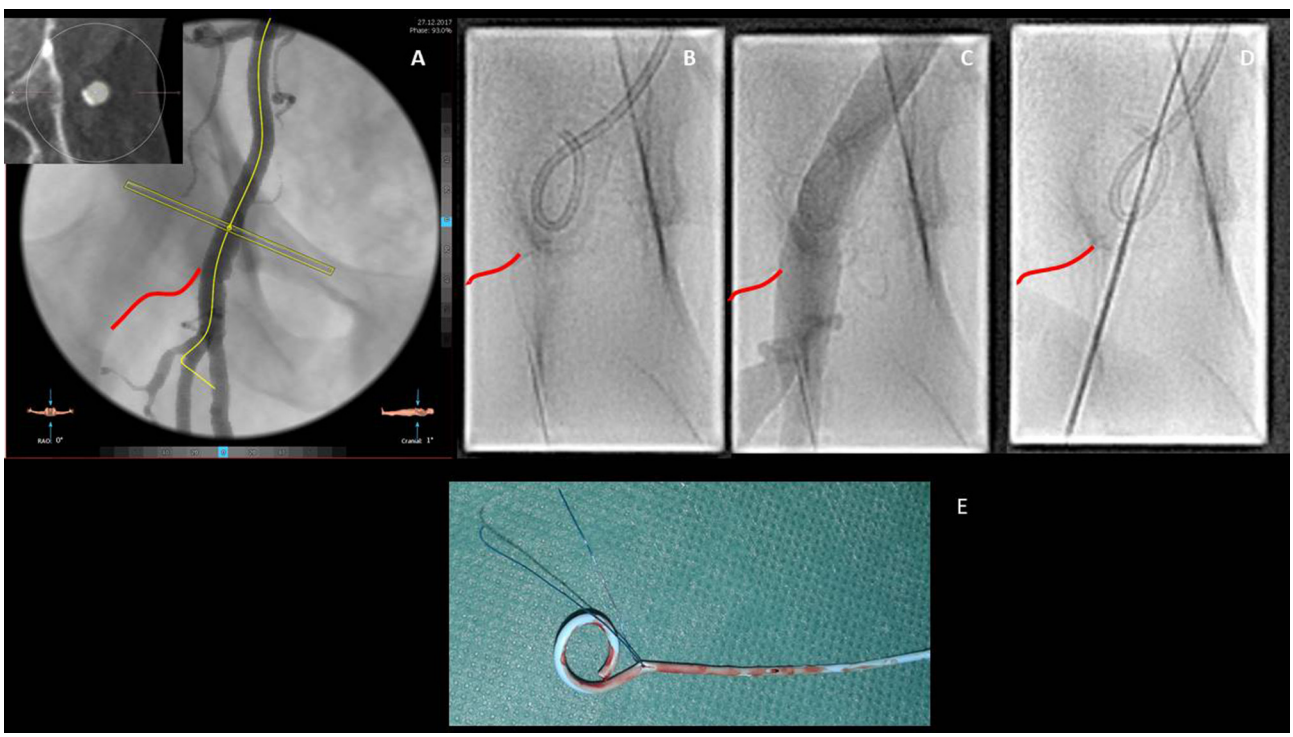

FIGURE 4 | Step by step approach for the transfemoral access. Once the common femoral artery has been deemed suitable for a trans-femoral approach due to the good caliber and the lack of anterior calcifications, the relationships with the femoral head (inferior border of the femoral head is highlighted in red), observed at the angio reconstruction, have to be described **(A)**. Through a contralateral crossover, the pigtail is inserted in the common right femoral artery **(B)** and its position confirmed by contrast injection **(C)**. Vessel puncture aiming at the anterior aspect of the femoral artery is then performed **(D)**. Particular attention has to be paid in removing the pigtail before inserting the suture based closure devices with the consequent risk of catheter jailing and need for surgical removal **(E)**.

complications, declined from above 10% in early PARTNER trials to about 6% in the more recent SURTAVI, NOTION and COREVALVE high risk trials (3–7). These data are in line with real-life data reported from national registries [(8–14), **Table 1**].

TRANS-AXILLARY/TRANS-SUBCLAVIAN ACCESS

The subclavian artery is the terminal branch of the brachiocephalic artery. For the purpose of a retrograde TAVI implant, the right axillary/subclavian artery is rarely (if not ever) used due to the anatomy of the vessel leading to an unfavorable implantation angle. The left subclavian artery arises as the third branch of the aortic arch after the left common carotid artery, and exits the thorax from the superior thoracic aperture between the anterior and middle scalene muscles before passing between the first rib and the clavicle. At the lateral border of the first rib it continues as the axillary artery. The proximal third of the axillary artery (i.e., between the lateral border of the first rib and the medial border of the pectoralis minor) represents the ideal target for both surgical and percutaneous approaches (**Figures 5A,B**).

Patient's Selection and Planning

Trans-axillary approach represents a valid option in 5–10% of patients referred for transarterial retrograde TAVI (32) and, in many centers, is considered the second option when trans-femoral TAVI is not feasible. Currently available software for CT-scan analysis allows a semi-automated 3D reconstruction of the axillary and subclavian arteries. As for the femoral approach, caliber (>6.5 mm), calcifications, tortuosity and anatomical relationships with side branches have to be taken into account. Particular attention should be paid to the aortic take-off of the subclavian artery, a typical site of atherosclerotic calcific plaque apposition.

Worth to mention is the different histological structure of the axillary and subclavian arteries when compared to the femoral artery. In fact, the subclavian, and axillary arteries are of the elastic type while the femoral is of the muscular type with a media containing smooth muscle cells instead of elastic fibers and a thicker, and more fibrous, adventitia (33). Those characteristics predispose this access to vascular complications such as ruptures or dissections. For these reasons, in the presence of a patent right internal mammarian artery to left anterior descending artery, the use of this access has been questioned due to the increased risk of vascular complication leading to the potentially lethal acute graft occlusion.

Technical Aspects

Transaxillarian approach was usually performed through a surgical cut down (**Figure 5C**), but the feasibility of a full percutaneous approach has been demonstrated (33).

When performing a surgical cut down, a 6–7 cm incision 1 cm below and parallel to the clavicle from the mid clavicular line to the axillary line is performed. Then, the pectoralis major muscle is dissected along its fibers, the pectoralis minor is retracted, and vessels are exposed. Attention is required to not damage to the nervous structures of the brachial plexus. Once isolated, a single or double purse string suture is placed on the subclavian artery and access to lumen is achieved by means of a direct puncture. In selected cases, a 10–12 cm Dacron vascular graft can be anastomosed end-to-side to the subclavian artery with and a standard large femoral sheath (>18F), custom modified by cutting the distal portion in order to allow to accommodate the sheath inside the vascular graft without extending its distal edge into the subclavian artery (34) (**Figures 5D,E**). This modified technique avoids extensive manipulation of the artery in case of borderline vascular diameter allowing a safe implantation even in patients with patent left internal mammary artery to the left anterior descending coronary artery.

A fully percutaneuos approach was described by Schäfer et al. in 2012 as the "Hamburg Sankt Georg Approach" (33). The axillary artery was landmarked with a regular J-wire and punctured below the clavicula to allow manual compression and reduce the risk of pneumothorax. Subsequently, the procedure was carried out as for the trans-femoral access. In their report, vascular complications significantly decreased when two Proglide (Abbott Vascular Devices) were used instead of a ProStar (Abbott

TABLE 1 | Procedural outcomes according to the access site.

Access	Procedural success(%)	30 D mortality	Major and life-threatening bleeding	Neurological events (TIA/Stroke)	New pacemaker implantation (%)
Trans-femoral (3–14)	95–100	2.1–5%‡ 5.2–9.7%†	9.3–28.1%‡ 3.5–11.4%†	1.4–6.7% (30 days stroke) 2.3–4.1% (1 year stroke)	3.4–34.1 5.9–20.1
Trans-axyllarian (16)	97.9	5.7%	7.8% life threatening 36.2% major bleeding	2.1%	24.7
Trans-Aortic (17–24)	87–100	6.1–13%	0.3–12%	0–3.2%	0–14
Trans-Apical (13, 25–28)	90–96	4.6–14%	3.6–6.1%	1.3–4.1%	5.4–11.0
Trans-Carotid (29)	100	6.3%	4.2%	3.1% (all TIAs, stroke not reported)	26.5
Trans-Caval (30, 31)	100	8%	12% (6% transcaval related)	5%	16

‡*Data derived from Partner A, Partner B, Partner II, Notion and SURTAVI trials.*
†*Data derived from TVT, Gary, UK TAVI, Observant and France2 registries.*

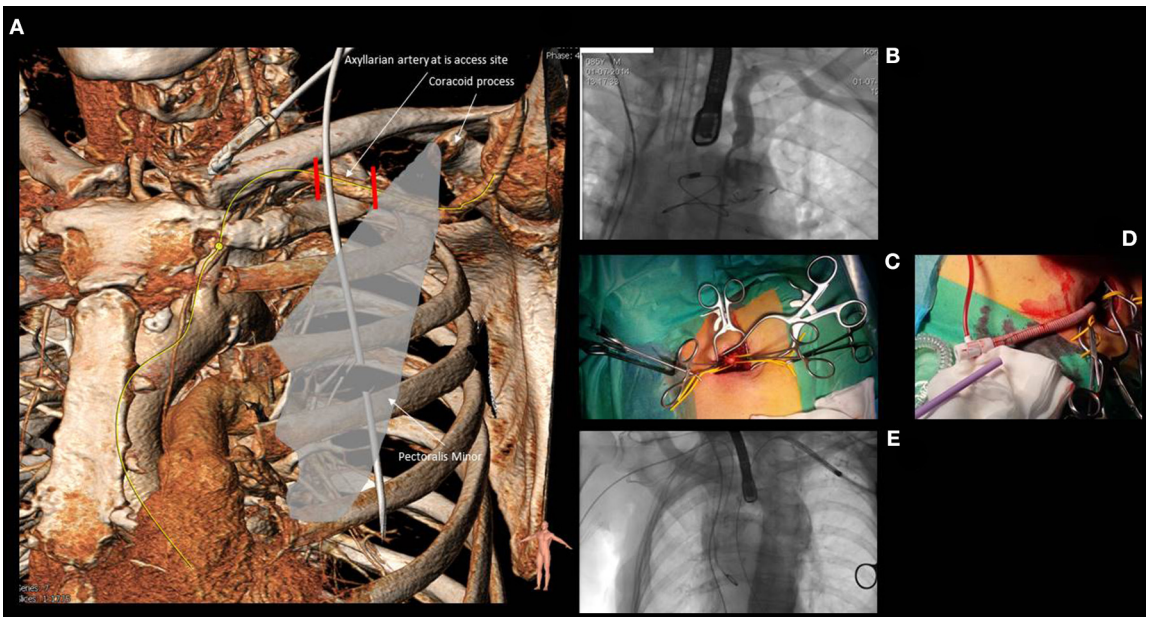

FIGURE 5 | Anatomy of the subclavian and axillary artery **(A)** and its relationship with the clavicle, the first rib and the medial border of the pectoralis minor. The first segment of the axillary artery (comprised between the two red lines) is usually the target for both surgical or percutaneous approaches. **(B)** shows the angiographic anatomy of the subclavian and axillary artery. **(C)** reports the surgical cut down for axillary artery with the vessel isolated by two yellow rubber bands. **(D)** shows a "Chimney approach" performed by means of a 15 cm × 8 mm GelwaveTM prosthesis, a gelatin sealed woven polyester peripheral vascular graft and a Check-FloVR PerformerTM 18 F Cook sheath (length 35 cm), routinely used for the transfemoral modified by cutting the distal portion in order to obtain an approximate length of 10–12 cm that could allow to accommodate the sheath inside the vascular graft without extending its distal edge into the axillary artery. **(E)** shows the navigation of a Medtronic Corevalve delivery system through the left subclavian artery.

Vascular Devices, Redwood City, California). At completion of the case, closure of the axillary artery was achieved with the pre-implanted vascular closure devices, while a peripheral balloon was always advanced in the subclavian artery to control possible bleedings.

Self-expandable prostheses are chosen in the vast majority of cases performed through this access, mainly the Medtronic Corevalve, while balloon expandable devices have been used only in selected cases.

Outcome Data

Trans-axillary approach has shown to be non-inferior to the femoral approach in terms of procedural and medium-term results in a propensity matched comparison derived from the Italian national registry (16). Both groups showed comparable rates of procedural success (subclavian 97.9 vs. femoral 96.5%, p = ns), major vascular complications (5.0 vs. 7.8%, p = ns) and life-threatening bleeding (7.8 vs. 5.7%, p = ns). Freedom from cardiovascular death as well as survival at 2 years was also comparable between the two groups, providing strong support to the use of this approach as a valid alternative to the trans-femoral access.

DIRECT TRANSAORTIC ACCESS

The direct transaortic TAVI has been originally reported by Bapat in 2012 (17, 18). The new concept behind this first report was the use of the short transapical TAVI delivery system for the retrograde TAVI implant through the ascending aorta. Since its advent, the trans-aortic technique was well accepted by heart teams and it has become a valid option in case of severe vascular disease impeding trans-femoral TAVI (19–24). Both balloon-expandable and self-expandable prostheses are currently used with good results. Some dedicated delivery systems are commercially avaliable, but standard trans-femoral systems can be used, adopting some tricks in room set-up (long delivery systems requiring good support).

Patient's Selection and Planning

Most of the patients selected for TAVI are in fact eligible for a direct trans-aortic access with few exclusions, basically represented by the presence of thorax deformities, very short ascending aorta, porcelain aorta and the presence of a patent venous coronary artery bypass graft with proximal anastomosis on the ascending aorta at risk of damage. When facing a severely atherosclerotic aortic arch (with a good ascending portion), the direct aortic access might represent a good choice. This will allow to avoid extensive manipulation of an atherosclerotic aortic arch with the consequent risk of hembolization. In case a trans-aortic TAVI is planned, a careful evaluation of the quality of the aortic wall area where the purse string sutures will be placed (free of calcium for at least 1 square cm) is mandatory (**Figures 6A,B**). This is usually performed at CT-scan analysis, and for this purpose, a native contrast-free scan can be enough.

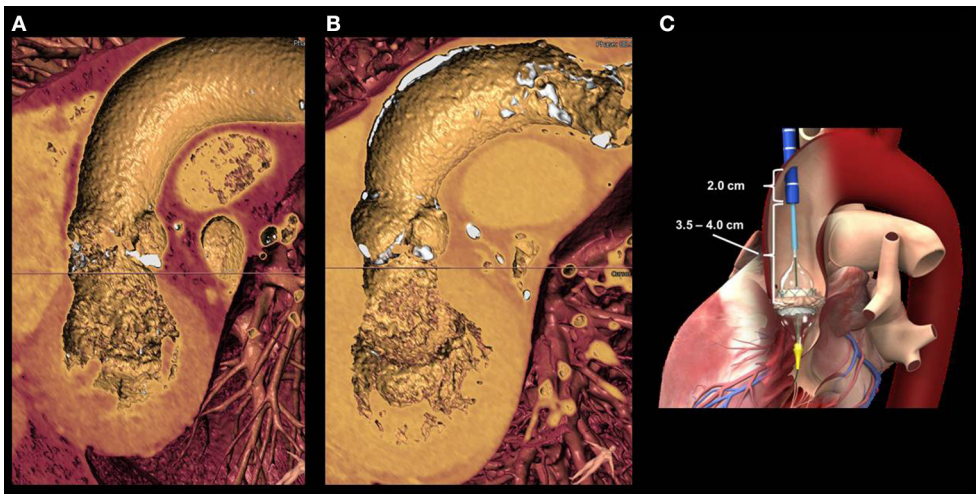

FIGURE 6 | (A) shows a 3D reconstruction of the left ventricle, aortic valve and ascending aorta in a patient with severe aortic stenosis. Lack of anterior calcifications of the aortic walls allowed for a transaortic approach. **(B)** shows an a case of a patients with extensive anterior aortic calcifications, a potential contra-indication for trans-aortic puncture. **(C)** the distance between the aortic entry site and the aortic valve annulus is of paramount importance for the valve release. A minimal distance of 6 cm is required for small delivery systems. The larger the valve size, the longer will be the length for delivery system retrieval.

Then, the trajectory between the entry site and the aortic valve annulus has to be considered in order to allow a perfect alignment between the delivery system and the native aortic valve. An "horizontal" ascending aorta (i.e., with an angle $>70°$) requires more banding of the delivery system with the subsequent risk of valve malalignment. Additionally, in order to allow the complete release of the valve, the aortic entry should be at least 6 cm between the above the aortic annulus (**Figure 6C**).

Technical Aspects

The right antero-lateral mini-thoracotomy at second intercostal space and the direct trans-aortic TAVI through an upper mini-sternotomy requires a different set-up of the cath lab as compared to the traditional trans-femoral access. First, the fluoroscopy arm is placed at patient's left side with cardiac surgeon and cardiologist standing together at the patient's right side. Compared to the mini-sternotomy, the advantage of the right mini-thoracotomy is represented by a lateral entry site into aortic lumen (right side) allowing for a straight trajectory of the delivery system through the stenotic aortic, with a consequent reduced risk of aortic damage.

Trans-aortic TAVI can be successfully performed with the Edwards Sapien balloon-expandable valve, using the dedicated trans-apical delivery system (valve mounted with the tissue skirt toward the tip of the delivery system) as well as with the Corevalve system (19–24). Other devices such as the trans-femoral Boston Lotus, the trans-femoral Accurate Neo Symetis and the St Jude Portico valve systems have been rarely used by the trans-apical route.

Due to the invasiveness of the approach, procedures are invariably performed under general anesthesia and the mechanical ventilation is obtained with a single or a double lumen endotracheal tube.

In the case the right antero-lateral mini-thoracotomy is choosen, a 5–8 cm long incision is usually performed at the right second intercostal space, parallel to the right clavicle, and muscles are gently dissected. If possible, mammary vessels should not be damaged. The pleural space is opened and the lung is either deflated (with a double-lumen tube) or displaced in order to identify the pericardium at the level of the ascending aorta. Ribs are retracted, the pericardium is opened and stay sutures are placed to expand the surgical field and pull the ascending aorta toward the operators. To identify the entry site, the ascending aorta is gently manipulated for calcium detection or a Doppler probe is used for the same purpose. The distance between the entry site and the aortic annulus is confirmed with a graduated pigtail catheter placed against the non-coronary aortic cusps under fluoroscopy. Two 3-0 or 4-0 polypropylene purse-string sutures reinforced by pledgets are placed at the entry site on the lateral wall of the ascending aorta. The ascending aorta is then punctured within the purse-string sutures and a soft guidewire is advanced toward the aortic valve, allowing for a standard valve implant. In case the trans-aortic TAVI is performed through an upper mini-sternotomy, the incision (5–8 cm) is carried out along the mid line of the thorax and the upper part of the sternum is sawed to reach the cranial portion of the ascending aorta. Once a sternal spreader is in place and the pericardium is opened, placement of the purse string sutures follows the same rules of the mini-thoracotomy but entry site is at a more more anterior. The advantage of an upper mini-sternotomy is that pleural spaces are not open. Full sternotomy is usually performed in high-risk patients requiring combined procedures such as off-pump coronary artery bypass grafting and/or tricuspid valve repair on cardiopulmonary bypass and beating heart can be considered in selected cases (35–37). The device insertion is similar to the upper mini-sternotomy.

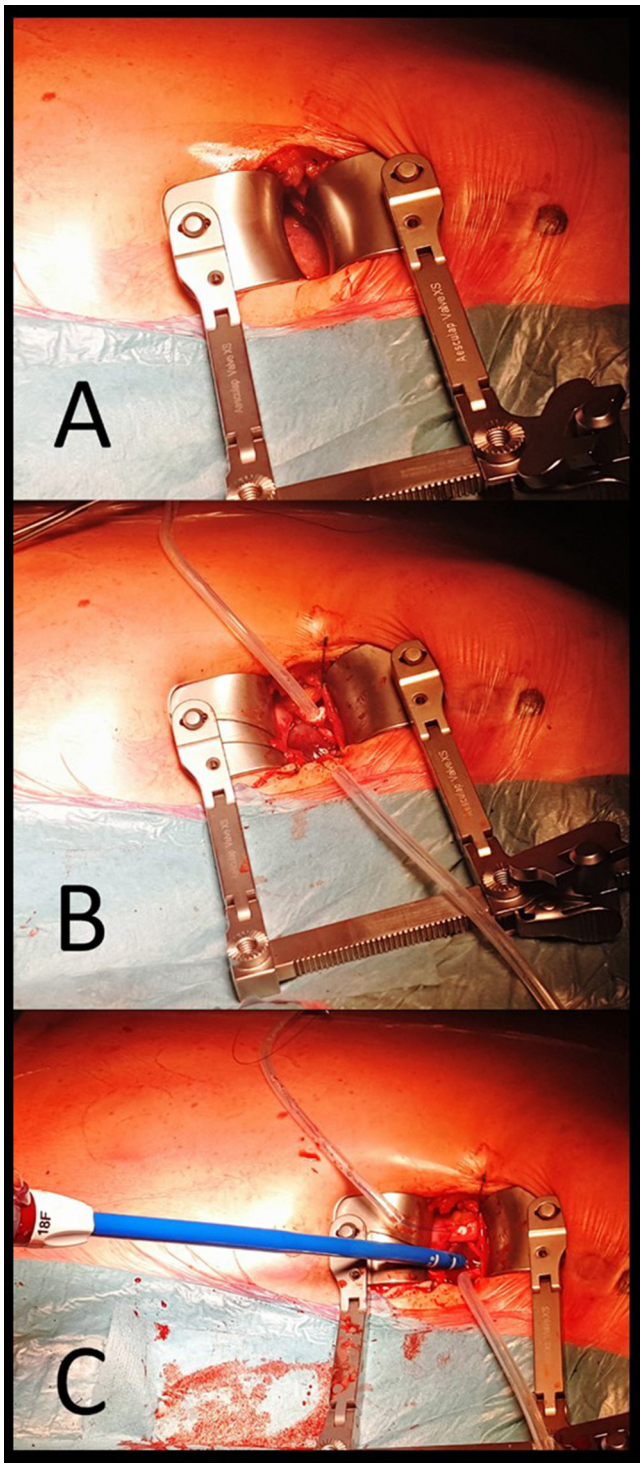

FIGURE 7 | Procedural steps in trans-apical approach. **(A)** surgical incision at the left fifth intercostal space and, after placement of a rib retractor and opening pericardium the apex is exposed. **(B)** Purse-string sutures reinforced by pledgets are placed at the apex and stabilized with a Tourniquet. **(C)** after apex is punctured within the purse-string sutures and a soft guidewire is advanced with an antegrade approach toward the aortic valve and positioned in the ascending aorta. Then, a conventional 18F sheath is advanced in the left ventricular cavity.

Clinical Results

While trans-apical can be at risk of apical bleeding and major access related complications in frail elderly patients (38, 39), the transaortic TAVI can be a valid alternative in preventing apical manipulations and peripheral vascular injuries, with satisfactory clinical results. Procedural success rates of above 90% have been reported in the vast majority of series, with a 30 days mortality ranging from 6.1 to 13%. In a recently published review comparing trans-aortic vs. trans-apical TAVI procedures, Dunne et al. (40) reported similar 30-day outcomes: mortality of 7.9% (TAO) and 9.7% (TA); procedural success of 95% for both; rate of conversion to surgical aortic valve replacement of 2.1% (TAO) and 1.1% (TA); rate of new pacemaker implantation of 5.5% (TAO) and 5.9% (TA). A trend toward a lower rate of stroke in the trans-aortic TAVI group was also evident (0.9% in TAO vs 2.1% in TA).

Compared to the transapical TAVI, avoidance of apical incision with the related myocardial scar reduces the risk of apical aneurysm formation, ventricular rupture and late arrhythmias (35).

TRANSAPICAL ACCESS

The transapical access represents the historical alternative to the trans-femoral TAVI and can be performed in all patients with contraindications to the transfemoral TAVI (13, 25–28).

Patient's Selection and Planning

The approach requires a left mini-thoracotomy andgeneral anesthesia. Contraindications to the transapical access route are a few, basically represented by a severely reduced left ventricular function and the presence of apical thrombus. Preoperative CT-scan images, can be useful in identifying the ventricular apex and its relationship with the thorax wall while transthoracic echocardiogram right before the procedure helps in identifying the apex and guiding the mini-thoracotomy. With regards to the commercially available transcatheter aortic valves and delivery systems, the transapical TAVI requires short dedicated delivery catheters. So far only the Edwards Sapien balloon-expandable valve and the self-expandable Symetis valve provide such possibility.

Technical Aspects

A left antero-lateral mini-thoracotomy at the fifth intercostal space requires a different set-up of the cath lab as compared to the trans-femoral and the transaortic accesses. The fluoroscopy arm is placed at patient's right side with cardiac surgeon and cardiologist standing together at the patient's left side. Due to the invasiveness of the approach, the transapical TAVI is performed under general anesthesia and the mechanical ventilation is obtained with a single lumen endotracheal tube. A 5–8 cm long incision is performed at left fifth intercostal space and muscles are gently dissected (**Figure 7A**). The pleura space is opened. After the placement of a rib retractor the pericardium is opened and stay sutures are placed to expand the surgical field and pull apex toward the operators. Two concentric 3-0 or 4-0 polypropylene

purse-string sutures reinforced by pledgets are placed at the apex (**Figure 7B**). Then, the apex is punctured within the purse-string sutures and a soft guidewire is advanced toward the aortic valve and the ascending aorta (**Figure 7C**). The valve is placed and delivered following standard techniques. Once implant is achieved, the delivery system and the sheath are gently removed and sutures are secured. In order to lower the intraventricular pressure during this phase, a short period of rapid pacing can be useful.

Clinical Results

The transapical TAVI can be an alternative to the transfemoral TAVI in case of severe vascular disease. Also in this case, reported procedural success rate are above 90% with 30 days mortality rate ranging from 4 to 14%.

According to data derived from the German GARY registry, trans-apical access is an independent predictor of 1 year mortality in TAVI patients. While this effect is related to the impact of apical manipulation or associated to the increased co-morbidities of those patients is still widely debated (14, 15).

OTHER ACCESSES

Starting from the original description of the first in human case of a percutaneous transcatheter implantation of an aortic valve prosthesis performed by Alain Cribier in April 2002 (41), access's choice seems to represent an intrinsic challenge of this technique. In their ground-breaking report, the procedure was performed through an antegrade approach from the right femoral vein. Access to the left atrium was obtained by trans-septal puncture, then the stenotic aortic valve was crossed on an antegrade fashion creating a venous arterial loop to allow the advancement and the stability of the percutaneous valve. Apart from this pioneering description, the antegrade transeptal approach is nowadays not considered as an option in patients unsuitable for other conventional accesses.

Rarely, the trans-carotid approach can be considered as an alternative option in patients unsuitable for trans-femoral, trans-subclavian or surgical trans-aortic/apical approaches.

While pro's are represented by avoidance of chest opening and the possibility to perform the procedure under local anesthesia, cons are mainly related to the necessity of a complex pre procedural planning with carotid and vertebral doppler to exclude significant atheromatosis, and cerebral MRI to confirm patency of the circle of Willis that could limit the cerebral perfusion during the carotid occlusion. While both common carotid arteries can be chosen, usually the left one is preferred given the straight pathway to the aortic valve. From a practical perspective, a 2 cm incision above the left clavicle allows the surgical exposure of the common carotid artery. Attention to avoid injury to the vagus nerve has to be paid. The arterial lumen is then accessed by direct puncture and surgical closure is performed at case completion. To the best of our knowledge, percutaneous access was not reported in this setting due to the complex management of potential bleedings and vascular damage. Mylotte et al. reported the feasibility and the safety of this trans-carotid approach in 96 patients enrolled in 3 different French sites (42). In their series, no major bleedings nor vascular complications related to the access site occurred, while only three transient ischemic attacks and no strokes were reported. No direct or propensity matched comparisons to trans-femoral TAVI are available so far.

The trans-caval approach, described by Greenbaum et al. in 2014 (29) is considered as the last resort in patients not qualifying for any other vascular access. Procedural planning requires a baseline CT-scan to identify a calcium free target on the right abdominal aortic wall allowing for a safe passage from the inferior vena cava to the aortic lumen of the large bore sheath. After having obtained a femoral venous access, the inferior vena cava is punctured by means of a stiff CTO wire (usually a Confianza PRO 12) mounted over a microcatheter and a standard RCA or IMA guiding catheter. The caval and aortic walls are perforated by using electrocautery applied at the distal end of the wire. Once obtained access to the aortic lumen, the wire is snared and both the microcatheter and the guiding catether are advanced into the abdominal aorta. This allows for the placement of a stiff "0.035" wire and the advancement of a large introducer sheath from the femoral vein into the aortic lumen for conventional retrograde aortic valve replacement. At case completion, heparin is reversed, and the aortic perforation is closed using a conventional vascular, duct or ventricular septal defect occluder device. The authors recently reported the 30-day outcomes of the first 100 patients from the prospective multicentre study (30). Device success, defined as successful trans-caval access and deployment of a closure device without death or emergent surgery was obtained in 98% of cases. Nonetheless, VARC-2 major or life threatening bleedings were evident in 12 patients, retroperitoneal hematomas were found at post procedural CT-scans in 24% of patients, while in 8 cases implant of an aortic covered stent was deemed necessary during the index procedure or in the early post procedural phase. Thus, so far, based on the above mentioned data, this approach should be considered as a proof of concept rather than as an effective alternative option to standard TAVI access routes and should only be considered in patients without alternative treatment options.

CONCLUSIONS

Retrograde trans-femoral TAVI is the access of choice in the vast majority of patients with severe aortic stenosis deemed at intermediate or high operative risk for traditional surgical aortic valve replacement, and current guidelines highlight that the feasibility of a transfemoral approach should be considered as a determinant aspect favoring TAVI in the decision making process when choosing between percutaneous or surgical procedures. In line with current recommendations, also in our clinical experience, the transfemoral access is always considered as the first option. Nonetheless, in a discrete percentage of cases, this access might be precluded. This implies that several different options have been proposed as alternatives, each of them with unique features, pros and cons. The availability of different, mainly surgical accesses, should be seen as a possibility for

the patients to be treated with a trans-catheter approach and for the involved heart team as a concrete opportunity to increase even more the collaboration between cardiac experts with interventional or surgical skills. So far, no randomized head to head comparisons between different access options are available, and if ever obtainable, several local factors and patient's characteristics should be considered when choosing an alternative approach. Future extension of TAVI to lower risk patients will probably result in a relative increase of transfemoral procedures. Nonetheless, in those higher risk patients in which the femoral approach is precluded, alternative routes, either percutaneously or surgically achieved might represent a concrete opportunity. When willing to avoid either general anesthesia and/or sternum/rib opening with pulmonary deflation, an option that could result as a game changer in the post op management of elderly patients allowing early mobilization and discharge, the axillary (either surgically or percutaneously performed) and trans-carotid access can be considered as a second option. On the other hand, local expertise might favor trans-aortic or trans-apical approaches due to their wide availability.

Surely, while no clear indications are still available, TAVI operators are called to a tailored decision making. Comprehensive patient's evaluation as well as extensive discussion within the heart team will represent the key points to achieve good procedural and long term outcomes.

AUTHOR CONTRIBUTIONS

LB conceived, drafted and finalized the manuscript. EF wrote the sections regarding transapical and transaortic access. GP, FF, TM, FP, and MM critically reviewed the manuscript.

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REVIEW
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TAVI: Simplification Is the Ultimate Sophistication

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Since its introduction in 2002, TAVI has evolved dramatically and is now standard of care for intermediate risk patients when the femoral approach can be implemented safely. The development of innovative transcatheter heart valves (THVs) and refinement of technical skills have contributed to the decrease in complication rates associated with TAVI[4]. Increased experience, smaller sheaths, rigorous pre-procedural planning and improved vascular closing techniques have resulted in markedly lower rates of vascular complications. The next step is the simplification of the procedure, which should contribute to a further decrease in complications, and also reduce procedural time, hospital stay as well as staff workload and costs. Moving to conscious sedation, no predilatation, no temporary pace maker and use of the radial approach as the contralateral approach are all instrumental in achieving this ultimate refinement.

Keywords: TAVI, simplification, minimalist, vascular complications, temporary pace maker, hospital stay duration

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INTRODUCTION

Since the first successful procedure was carried out in 2002 (1), transcatheter aortic valve implantation (TAVI) has gradually been established as an alternative to conventional surgery in patients with severe aortic stenosis contra-indicated to surgery or at high surgical risk (2). In 2017, during the last ESC meeting, TAVI indications were extended to intermediate risk patients when the transfemoral approach (TFA) is feasible (3).

Improvements in technique, devices, operator's experience, and patient selection have contributed to a dramatic decrease in procedural complications, thus allowing further technical simplification at every step of the procedure (4–9). In this paper, our aim is to describe how to simplify the technique at each stage of the procedure in order to turn it into a "PCI-like" procedure and to discuss how this may improve TAVI outcomes.

PRE-PROCEDURAL EVALUATION AND PROCEDURAL SETTING

Patient clinical and anatomical criteria may influence per- and post- procedural outcomes. Therefore, a truly minimalist approach should be considered only when femoral access is possible. Recently, Barbalios et al. compared minimalist TAVI performed in the catheterization laboratory to standard TAVI performed in the hybrid room demonstrating shorter procedure and intensive care unit time, as well as reduced hospitalization duration and costs in the minimalist approach group without differences in terms of short- and long-term survival (10).

Multislice CT (MSCT) is instrumental in procedural simplification. Image quality and optimal analysis are therefore crucial for anticipating the potential difficulty of the procedure as well as for optimal valve selection and working view. The role of MSCT has also been central in allowing a shift from general anesthesia to conscious sedation by obviating the need for transesophageal echocardiography (TOE) during the procedure. MSCT became the gold standard for evaluation of the aortic root in our center in 2009.

The use of the TRA for preprocedural evaluation of the coronary arteries is also part of the simplification process. It helps not only to reduce the risk of vascular complications related to the screening phase, but also to assess femoral access by performing a selective bilateral iliac injection using a long multipurpose catheter. Recently, screening of coronary artery disease and ad hoc percutaneous coronary intervention (PCI) during TAVI has been described by Barbanti et al. showing to be feasible without increased periprocedural complications (11).

A minimalist approach can be performed in routine practice with two operators, two nurses and an anesthesiologist (**Figure 1**). A cardiac surgeon and an echocardiographist are not mandatory in the room but should be available.

FROM GENERAL ANESTHESIA TO CONSCIOUS SEDATION

Although the first in-man TAVI cases in Rouen were initially performed on conscious sedation (1), the procedure was commonly carried out under general anesthesia between 2002 and 2008 in Europe. It remains standard practice in the majority of cases in North America (12). However, it was Alain Cribier's idea that TAVI should be a "PCI- like" procedure. Potential advantages of general anesthesia are patient's procedural comfort, possibility of using TOE and rapid conversion to surgery when complications occur (13–15). Conversely, many issues are related to general anesthesia such as hemodynamic instability, higher need for inotropic drugs, higher risk of bleeding, increased risk of pulmonary infection, extubation difficulty or delay in patients with chronic pulmonary disease, late complication identification such as stroke or aortic complications and finally, longer procedural duration, hospital stay, higher staff workload, and global costs (16–18). In the France 2 and the France TAVI registries, the adoption of local anesthesia with conscious sedation has progressively increased from 30% in 2010 to 70% in 2017 (15, 19). In a recent meta-analysis, outcomes of both approaches were similar with respect to in-hospital mortality, conversion to open-heart surgery, major vascular complications, acute kidney failure and stroke (17). Cross-over to general anesthesia was observed in only 6%. Conversely, catecholamine requirement and transfusion were less frequent in patients on conscious sedation, and duration of intensive care unit and global hospital stay was also shorter (17, 20, 21). No difference concerning neurocognitive outcomes was highlighted between both approaches (21).

Data from registries demonstrated the feasibility, safety, and cost-effectiveness of local anesthesia with conscious sedation in comparison to general anesthesia, with potential advantages in terms of bleeding and hospitalization length. It has been adopted as the default approach in our center since April 2009.

FROM SURGICAL CUT DOWN TO PERCUTANEOUS ACCESS

Initially, TAVI procedures were performed exclusively via surgical cut down (1). Over the past decade, sheath diameter has been gradually reduced to 14–16 French with the last generation percutaneous heart valves (**Figure 2**). TFA is currently the default access route, with superior outcomes than transapical route and other transvascular approaches as carotid, aortic, axillary, and caval-aortic. Alternative transvascular routes may be considered anly in case of unsuitable femoral access (22).

Percutaneous closure has been progressively adopted in routine practice in most centers for TF TAVI procedures (23). Indeed, even though the surgical approach has been reported to be associated with a low rate of vascular complications and to provide a more direct control of haemostasis (24), percutaneous closure is a less invasive technique and may result in shorter hospital stay (25). With the refinement of the TAVI procedure, better patient preprocedural screening, increased operator experience, and device improvement, the percutaneous approach has become more simple, less time consuming, thus allowing a reduction in staff workload. The Prostar technique was introduced in our center in 2009 and we moved progressively to Proglide (Abbott Vascular Devices, Redwood City, CA, United States) preclosing in 2015-2016 (26) because this technique was simpler and less costly. In 2016, a lower risk of vascular complications was reported with the use of 2 Proglide devices in comparison with Prostar (27). New collagen-based closure devices were recently described in TAVI procedure as the MANTA closure device with similar results than suture based closure devices (28).

In addition to the selection of the most appropriate percutaneous device, the percutaneous technique should be rigorous in order to limit access site complications. Indeed, the common femoral artery puncture site should be carefully selected on the CT-scan or angiography before the procedure. During the procedure, puncture should be performed under angiographic or ultra-sound guidance at the center of the anterior arterial wall (29). Percutaneous closure devices should be subsequently deployed as previously described (30).

Thus, percutaneous transfemoral access is as safe as the surgical approach and feasible in the majority of cases with a very high rate of success after the learning phase. Most vascular complications can be managed percutaneously. It is an essential component of TAVI's simplification process allowing early discharge.

Abbreviations: BAV, balloon aortic valvuloplasty; CCU, conventional cardiology unit; ICU, intensive care unit; LV, left ventricle; MP, multipurpose; MSCT, multislice CT; PCI, percutaneous coronary intervention; TAVI, transcatheter aortic valve implantation; TFA, transfemoral approach; TOE, transesophagal echocardiography; TRA, transradial approach.

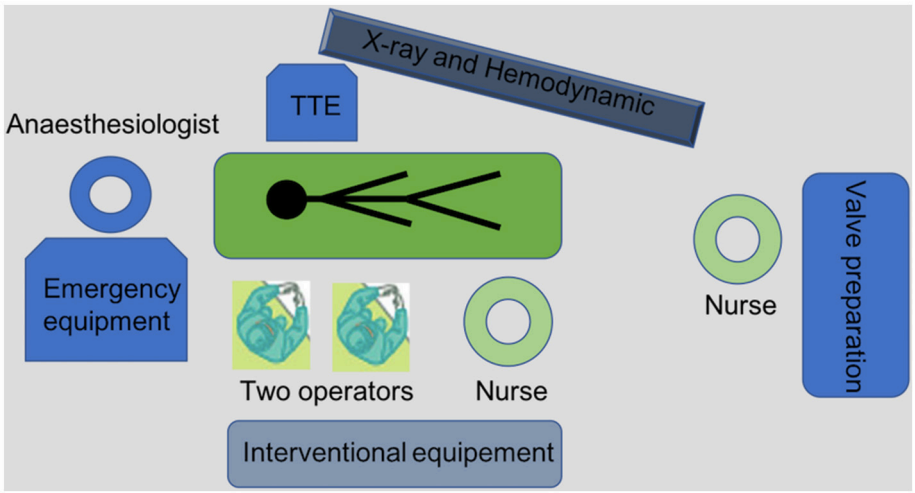

FIGURE 1 | Equipment and procedural set-up for a "minimalist" TAVI procedure.

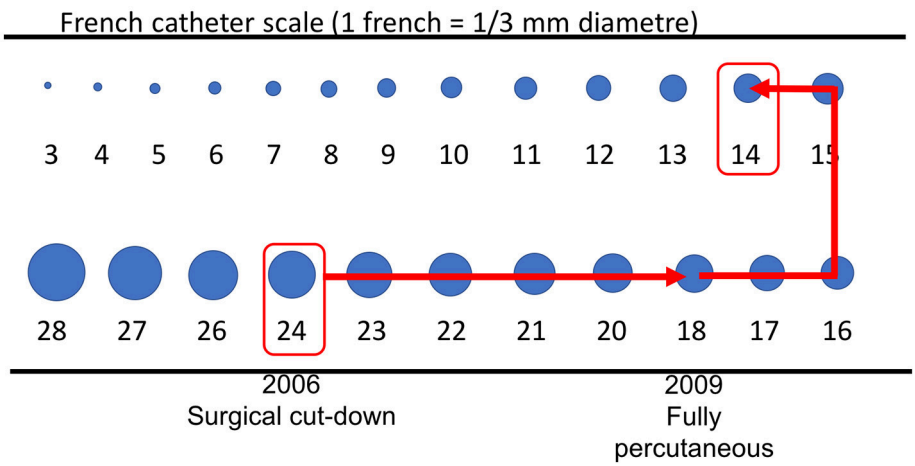

FIGURE 2 | Sheath size from first to last generation devices.

FROM CONTRALATERAL FEMORAL ACCESS TO RADIAL ACCESS

Although vascular complications dramatically decreased in parallel with enhanced operator experience, availability of low profile sheaths and better patient selection, 25–30% of these complications occurred at the contralateral femoral access site, (9). Therefore, using the TRA as a secondary access appears to be very promising (29–31). We have been using this approach since 2016 and have observed a 50% reduction in vascular complications. The radial artery (right or left) is punctured and a 40 cm 6 Fr hydrophilic sheath with a side port for blood pressure measurement is subsequently inserted through the radial artery. A 125 4 or 5 Fr multipurpose (MP) catheter is advanced over a standard 0.35 guide wire to the common iliac artery in order to obtain a reference image and guide the puncture. After the puncture, the MP catheter is retrieved and a pig-tail is advanced in the ascending aorta via the 0.35 guide wire to perform aortography before and after TAVI. At the end of the procedure, prior to access closure, the MP catheter is re-advanced to the common femoral artery in order to check the final result of the closure (29). In cases of vascular complication, a long 120 cm 5 Fr catheter (Optimed, Germany) can be positioned in the common femoral artery to perform femoral artery balloon inflation or stent implantation. In rare cases where a covered stent is needed, a larger balloon can be used through the Optimed catheter in order to close temporarily the iliac or femoral artery, while a cross-over femoral approach is implemented (29). Indeed, in our practice, even if the radial secondary access is our default approach, the controlateral femoral access should be available immediately in case of failure or emergent need of cross-over.

Therefore, by reducing contralateral vascular complications and simplifying the procedure, TRA will probably follow the predominant tendency observed in other interventional

cardiology settings and become the gold standard contralateral approach for TAVI.

FROM VENOUS STIMULATION TO LV GUIDE WIRE PACING

During balloon valvuloplasty (BAV) or balloon expandable TAVI procedures, rapid ventricular pacing is mandatory. Traditionally, rapid pacing is performed through a venous access with temporary pacemaker implantation (1). However, this technique may be challenging in anatomic variations and may lead to increased X-ray exposure and complications (32) such as hematoma, arterio-venous fistula, thrombosis or right ventricle perforation. Recently, rapid ventricular pacing through the left ventricle guide wire has been described as a way of simplifying the procedure by eliminating the need for additional vascular access during TAVI (33). This approach was adopted in 2016 in our center. Briefly, a 22 G needle is inserted subcutaneously near the femoral sheath. Alligator clips are then connected to the left ventricle guide wire (negative clip) and to the needle (positive clip) following insertion of the delivery system close to the aortic valve. The rapid pacing is then tested using maximal output and minimal sensitivity (**Figure 3**). Valve implantation is then carried out under rapid pacing. In the presence of high-degree conduction disturbance, stimulation can be performed with this technique while a temporary pacemaker is inserted through a venous access, more frequently through brachial vein access to limit femoral vascular complications.

This new technique has been shown to be feasible and safe, allowing stable stimulation with a low rate of complications and a potential reduction in procedural time. A randomized trial comparing left ventricle guide wire rapid pacing to conventional pacing (Easy TAVI) is ongoing in France (NCT02781896).

VALVE IMPLANTATION WITHOUT PREDILATION

In the early days of TAVI, BAV was considered a mandatory step. However BAV have been shown to be associated with a higher risk of cerebral embolization, and severe acute aortic regurgitation may occur after predilatation in up to 3% of cases. TAVI without BAV was evaluated for the first time in 2011 by Grübe et al. (34) and was shown to be feasible in non-randomized studies (35, 36). Currently, improvements in new generation devices including paravalvular skirts, the ability of repositioning of the valve, lower profile of delivery system, and of the prosthesis provide more favorable outcomes (22). Therefore, BAV seems no longer essential during TAVI procedures, and consequently, TAVI without predilation is routinely implemented in many centers.

We moved progressively to this approach between 2012 and 2015 in our center. Today, more than 90% of cases are performed without predilatation. Only very complex anatomies or highly calcified valves are predilated before valve deployment (5–10%). Post dilatation is performed mainly after self-expandable valve deployment in the presence of significant paravalvular leak or transvalvular gradient (10–15%).

Thus, avoiding balloon predilatation may reduce complication rates, decrease the need for permanent pacemaker and reduce procedural time. A large randomized trial (37) with the Sapien 3 valve is on-going in France (NCT02729519).

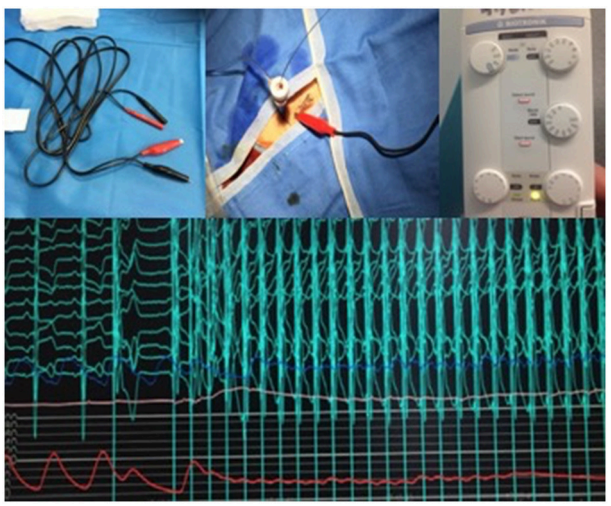

FIGURE 3 | From left to right and up to down: Alligator clips with negative clip (black) and positive clip (red). After insertion of Sheath, a 22G needle is inserted subcutaneously through the skin, close to the femoral sheath and the positive clip is connected to the needle while the negative clip is connected to the guidewire. Setting of the temporary pacemaker with maximal output and minimal sensitivity. Pacing efficacy at 180 beats per minute with the LV wire and drop in blood pressure.

TABLE 1 | Current outcomes of early discharge after TAVI.

Study	Patients	Early discharge, n (%)	Timing of early discharge	30-days mortality, n (%)	Rehospitalization within 30-days, n (%)
Durand et al. (40)	337	121 (36)	Within 3 days	0 (0)	4 (3.3)
Noad et al. (41)	120	26 (21.7)	Same/next day	0 (0)	1 (3.84)
Serletis-Bizios et al. (42)	130	76 (59)	Within 3 days	1 (1.3)	3 (3.94)
Lauck et al. (43)	393	150 (38.2)	Within 2 days	1 (0.7)	12 (8)

POST-PROCEDURE MANAGEMENT:

From Intensive Care Unit (ICU) to Conventional Cardiology Unit (CCU)

After TAVI, systematic close monitoring with special attention to hemodynamic and cardiac rhythm is mandatory to allow early detection of periprocedural complications. In many centers, monitoring is performed for at least 12 to 24 h in the ICU before transferring the patient to a CCU after clinical and paraclinical status re-assessment. Recently, TAVI without subsequent ICU admission has been evaluated and has been shown to be feasible and safe in selected patients after rigorous preprocedural and postprocedural evaluation (38). Indeed, this new strategy adopted in our center in 2017 may obviate ICU admission in up to one third of cases and should be considered a part of the "minimalist" approach.

Short Hospitalization

Early discharge was evaluated in the literature demonstrating safety in patients with hospitalization duration shorter than 48 h (39). Indeed, the median length of hospitalization was 1 day in the early discharge group with no differences between early discharge and discharge after 48 h in terms of 1-month mortality, stroke and readmission. A "minimalistic" TAVI procedure with local anesthesia, no predilatation, urinary catheter avoidance and early removal of temporary pacemaker was predictive of early discharge in this study. Current outcomes of early discharge after TAVI are summarized in **Table 1.** Shortening hospital stay is also an essential component of the TAVI simplification process with a potential reduction in procedural costs and need for rehabilitation but may be studied in large studies to ensure safety without increased risk of outcomes or readmission.

CONCLUSION

TAVI simplification has already been adopted in routine practice in experienced centers, resulting in a low rate of complications, shorter procedural time, improved patient comfort, as well as decreased costs and staff workload. However, rigorous patient selection, and risk stratification are key factors in ensuring successful "PCI-like" procedures. On-going randomized trials may confirm preliminary results, thus leading to a "simple" but not "simpler" procedure in the near future with lower profile devices.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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Transcatheter Treatment of Bicuspid Aortic Valve Disease: Imaging and Interventional Considerations

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Patients with bicuspid aortic valve disease have systematically been excluded from large randomized clinical trials investigating transcatheter aortic valve implantation (TAVI) due to their younger age, lower surgical risk and complex aortic anatomy. The asymmetric nature of the bicuspid valve orifice often accompanied by heavy regional calcification has led to concerns regarding valve positioning and expansion. Bicuspid aortic valve disease patients are at heightened risk of TAVI-related complications including coronary occlusion, aortic dissection and annular rupture, as well as the known risks of progressive aortopathy in these patients. These unique anatomical characteristics pose challenges for TAVI operators. However, with recent and ongoing refinements in implantation technique, improvements in pre-procedural imaging and iterations in device design, TAVI is emerging as a safe and feasible treatment option in this population. Paravalvular aortic regurgitation and high pacemaker rates have been the Achilles Heel for TAVI in bicuspid valve patients, yet newer generation devices are yielding promising results. Further studies are required before TAVI ultimately emerges as a viable option in low and intermediate surgical-risk patients with bicuspid valve disease. This review comprehensively summarizes the epidemiology, pathology and current evidence for TAVI in patients with bicuspid aortic valve disease. We also outline some practical tips for performing TAVI in these patients.

Keywords: TAVI, bicuspid valve disease, CT, treatment, bicuspid aortic valve

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INTRODUCTION

The transcatheter aortic valve implantation (TAVI) revolution for severe tricuspid aortic valve stenosis (AS) is well-recognized as an alternative to surgical aortic valve replacement (SAVR) for severe aortic stenosis. This has been established in the randomized clinical trials for balloon-expandable and self-expanding valves (1–4). TAVI is now regarded as the standard of care for patients with severe symptomatic AS that are considered inoperable or in patients at high surgical risk. More recently randomized clinical trials have shown non-inferiority when TAVI has been compared with SAVR in patients at intermediate or low surgical risk (5–7). Bicuspid aortic valve (BAV) has largely been excluded from seminal randomized clinical trials involving TAVI. This was due to concerns about (i) valve positioning and expansion due to the asymmetrical nature of the leaflets and heavy calcification leading to severe paravalvular leak (PVL), (ii) aortic annulus rupture and risk of coronary occlusion, (iii) concomitant aortopathy associated with BAV increasing

the risk of spontaneous and iatrogenic aortic dissection and rupture, and (iv) concerns regarding the long-term durability of Transcatheter Heart Valves (THV), particularly in a younger BAV population. There is clear data on the safety and efficacy of TAVI in patients with tricuspid valve severe AS (1–10), and despite encouraging data from registries including BAV disease patients (11–14), TAVI has yet to establish itself in this patient cohort.

This review summarizes the evidence for TAVI in bicuspid aortic valve disease, the role of multi-slice computed tomography (MSCT) to aid procedural planning, and technical considerations to undertake when performing TAVI in BAV.

EPIDEMIOLOGY

BAV disease is a common congenital cardiac abnormality seen in adults and is frequently associated with AS (15). The estimated incidence of bicuspid aortic valves is 0.4–2.25% in the general population. The most frequent complication of BAV is AS, often requiring aortic valve replacement surgery. BAV is commonly associated with aortopathy leading to asymptomatic dilatation of the ascending aorta in the initial stages followed by aneurysm formation of the aorta and the potential life-threatening complication of aortic dissection (16–20). In a large population based study involving nearly 200 patients with a mean follow-up of 15 years, 13% developed severe AS requiring SAVR. In this cohort of patients, the main indication for surgery was severe AS; performed at a younger age group compared with the general population (21).

Registry data has shown that 37% of BAV patients have moderate-to-severe AS at the time of their initial echocardiogram (22). The prevalence of bicuspid aortic valve disease in patients undergoing surgical aortic valve replacement has been reported to be as high as 50% in some surgical series, 27.5% amongst octogenarians, and up to 41.7% of septuagenarians (23). In an Asian transcatheter aortic valve implantation (TAVI) population, BAV has been reported in upto 50%, potentially posing unique challenges for percutaneous treatment options in the Asian landscape (24).

PATHOLOGY

BAV disease is frequently associated with valvular stenosis, valvular regurgitation, aortic coarctation, aortic dilatation, aneurysms, and dissection. It is essential that pre-procedural imaging assesses the thoracic aorta in BAV patients. Aortic root dilatation occurs in 50–60% of patients with a normally functioning bicuspid valve, increasing the risk of aortic dissection nine-fold (25). The etiology of ascending aortic dilatation may be due to genetic and hemodynamic factors that affect the aortic wall elasticity and strength. Genetic mutations in smooth muscle cells α actin (ACTA2) and transforming growth factor β receptor (TGFBR1 and TGFBR2) have been linked with aortopathy in BAV disease (26). A genetic link between aortic dilatation and BAV can be substantiated by the fact there is greater incidence of aortopathy in first degree relatives with BAV disease, and not infrequently we see progressive aortic root dilatation in patients post SAVR with BAV disease (27).

Abnormalities in wall shear stress can arise due to the asymmetrical nature of the orifice in BAV patients. Studies using flow-sensitive MRI and four-dimensional (4D) cardiovascular MRI have looked at abnormalities in wall shear stress and flow patterns in the aortic wall for different BAV fusion patterns, which in turn has been linked with adverse remodeling within the aortic root wall (28, 29). The right and left cusp fusion variant of BAV is associated with asymmetrically elevated wall shear stress in the ascending aorta (30, 31). Phenotypic variations in BAV fusion patterns may need to be considered when assessing patients, especially if TAVI is to be extended to low-risk patients. As highlighted certain BAV fusion patterns are predictors of increased wall shear stress and aortic root dilatation (**Figure 1**).

CLASSIFICATION SYSTEMS FOR BICUSPID AORTIC VALVE DISEASE

Different classification systems exist for the varying BAV morphologies; based on the presence and characteristics of the raphe, commissural position, description of the cusp and its size and the aortic sinus characteristics (15, 21). The most widely used classification is by Sievers and Schmidtke; due to its simplicity and user friendliness (33). Valve morphology is classified according to the number of cusps and the presence of raphes, as well as the position and symmetry of the cusps. Type 0 has 2 symmetric leaflet/cusps and 1 commissure without evidence of a raphe, Type 1 has a single raphe due to fusion of the left coronary cusp with either the right or non-coronary cusp, and Type 2 arises when 2 raphes are present with fusion of both the right and non-coronary cusps (**Figure 2**). A functional (bicuspid) valve are classified as tricuspid valves with no raphe present, but there is fixation of the commissure between 2 cusps due to degenerative processes. Mylotte et al. used a modified Sievers classification system and observed higher rates of PVL in Sievers type 1 morphology (34.2%) than in Sievers type 0 (13.3%), possibly due to incomplete THV expansion due to calcified raphe and leaflet asymmetry (14).

Jilaihawi et al. proposed a classification system for BAV and described 3 subtypes, tricommissural, bicommisural raphe type, and bicommisural non-raphe type (11). The classification enabled a greater understanding of the interaction of the valve with the aortic-valvular complex at both the basal leaflet plane (presence or absence of a raphe) and at the commissural level (presence of 2 or 3 commissures). It was noted that the presence of a calcified raphe may impact on TAVI expansion and device apposition at the annulus. Tricommisural BAV type was not found to be associated with aortopathy and has widely been termed functional or acquired BAV disease. Tricommisural BAV arises from rheumatic, fibrotic, or calcific processes leading to focal commissural fusion (11). Tricommisural BAV disease is different from tricuspid valve aortic stenosis and may account for the higher incidence of PPM after TAVI. Interestingly, there were marked geographical differences between the subtypes of BAV. Non-raphe type bicommisural bicuspid AS was more

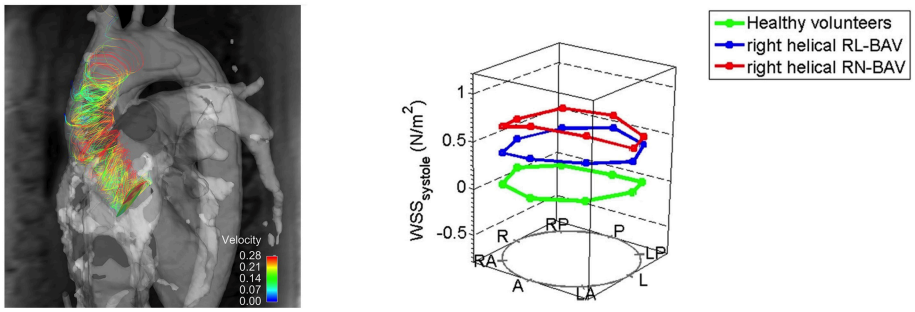

FIGURE 1 | Altered right-handed helical aortic flow patterns in patients with bicuspid aortic valve disease. Patients with right and non-coronary cusp fusion BAV had higher wall shear stress patterns in the ascending aorta [Reproduced with permission from the Bissell et al. (32)].

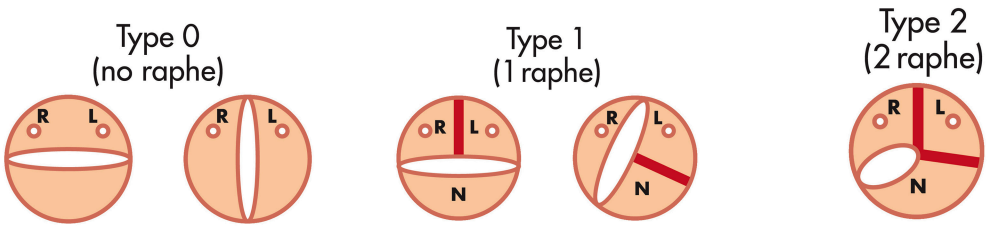

FIGURE 2 | The Sievers and Schmidtke classification system for bicuspid aortic valve [Adapted from Sievers et al. (33)].

common in Asia, but not in North America or Europe. The classification system did not predict the rates of moderate or severe PVL (tricommisural 19%, bicommisural raphe type 19.5%, and bicommisural non-raphe subtype 15%). Thirty-day mortality rates according to the BAV subtypes were not found to be statistically different (tricommisural 4.2%, bicommissural raphe subtype 2.7%, and bicommisural non-raphe subtype 9.5%). There was also no difference in new permanent pacemaker implantation rates between the BAV subtypes.

CURRENT REGISTRY DATA ON BICUSPID AORTIC VALVE DISEASE

Our current understanding of the safety and efficacy of treating BAV patients with TAVI is largely based on small registries, most of which used older generation THVs (14, 34, 35). A multi-center study raised concerns regarding an excess of bioprosthetic PVL in bicuspid aortic valve disease patients undergoing TAVI (14). This was a retrospective registry of 139 patients across 12 centers collecting clinical, procedural, and follow-up data. Procedural mortality was 3.6%, with THV embolization occurring in 2.2% with a 1-year mortality of 17.5%. MSCT-based TAVI sizing was used in 63.5% of patients. AR grade 2+ post-TAVI was not infrequent at 28.4% which decreased to 17.4% when CT-sizing and planning algorithms were used. This series demonstrated that pre-procedural MSCT imaging can minimize PVL in TAVI for BAV disease by more accurately sizing the annulus. In a registry using a newer generation SAPIEN 3 valve, 51 patients with BAV disease from 8 centers were evaluated (13). The incidence of trivial and no AR post-TAVI was 63% and mild AR was 37%. The 30-day mortality rate was reported at 3.9%.

In a study of 130 patients with severe AS and BAV from 14 centers undergoing TAVI (11), the 30-day outcomes were comparable with those reported in patients with tricuspid valve stenosis (1, 2, 7, 36, 37). There was however an excess of new pacemaker implantation which was similar for balloon expandable and self-expanding valves (**Table 1**). An increase in significant PVL was not observed in this study as compared with tricuspid valve stenosis patients undergoing TAVI. Once again, PVL rates were lower in this study if MSCT data was used for sizing.

The Bicuspid AS TAVI multicentre registry is the largest study to date evaluating 546 patients with either bicuspid or tricuspid AS who were propensity scored matched (12). Patients were recruited from Europe, North America and the Asia specific region. The patients with bicuspid severe AS had lower STS scores and represented an intermediate risk profile population, and furthermore the use of a large prostheses was more commonly associated with bicuspid AS patients. The major findings of this study were bicuspid severe AS patients had more frequent conversion to open surgery and a significantly lower device success rate as compared with propensity matched tricuspid AS patients. There were no significant between-group differences in procedural complications such aortic root injury and moderate-to-severe PVL when new generation devices were used. All-cause mortality at 2-year follow-up was comparable between the bicuspid and tricuspid groups.

TABLE 1 | Summary of 30-day outcomes in the main TAVI trials in patients with bicuspid aortic stenosis.

Study	Patients (n)	BE (%)	SE (%)	ME* (%)	Death (%)	All CVE (%)	Valve embolization (%)	PVL > Mild (%)	New PPM (%)	Conversion to surgery (%)	Need for second valve (%)	References
Yoon et al.	546	58	34	8	3.7	2.9	NA	10.4	15.4	2.0	4.8	(12)
Perlman et al.	51	100	0	0	3.9	1.9	0	0	23.5	0	0	(13)
Jilaihawi et al.	130	54	46	0	1.5	3.2	1.5	18.1	26.2	3.1	3.1	(11)
Mylotte et al.	139	34	66	0	5.0	2.2	2.2	28.4	23.2	2.2	3.6	(14)

ME, mechanical expanding valve LOTUS valve; NA, not available; CVE, cerebrovascular event, stroke, or transient ischemic attack.*

PROSTHESIS CHOICE IN BICUSPID VALVE DISEASE

Operators need to be cognisant of the potential advantages and disadvantages of balloon-expandable and self-expanding devices in the BAV space. Balloon-expandable valves exert greater radial force as compared with self-expanding devices and may circularize the native annulus minimizing potential sites for paravalvular leaks. Mylotte et al. (14) reported outcomes on both balloon-expandable and self-expanding devices observing a greater incidence of PVL $\geq$2 with self-expanding valves (19.6% with Sapien XT and 32.2% with CoreValve). This may be attributable to the reduced radial strength in self-expanding devices increasing the likelihood of residual PVL. Conversely, when comparisons are made using newer generation balloon-expandable and self-expanding devices which feature an external sealing skirt there were no significant differences between the two general valve designs (38).

Rates of annular rupture have been reported to be as high as 5.3% in some series using the balloon-expandable Sapien XT valve (38). This may have been largely driven by a degree of oversizing required for device anchoring to prevent significant PVL. With improvements in design of the newer-generation balloon expandable valves there is sufficient anchoring with less oversizing which has led to acceptable rates of PVL and annular rupture (39, 40). When sizing is guided by CT annular measurements a degree of oversizing (7–13% for the S3 THV design) appears to be safe with newer generation valves, leading to a reduction in AR in patients with bicuspid valve disease.

In a series of 51 patients who underwent TAVI in bicuspid AS using the new generation balloon expandable S3 valve, device success rate was reported to be 98% with no cases of moderate to severe aortic regurgitation (13). Improvements in design of the newer generation S3 THVs have resulted in a lower profile device with more accurate positioning, and improved sealing with its polyethylene terephthalate outer skirt. The Lotus mechanical expanding valve has an outer adaptive seal with the ability to be repositioned and retrieved. Promising results were also demonstrated with regards device success when this device was used to treat bicuspid AS patients (38).

NEW PERMANENT PACEMAKER IMPLANTATION RATES FOR TAVI IN BICUSPID VALVE DISEASE

One of the main limitations of TAVI in tricuspid valve severe AS compared with SAVR is the high incidence of conduction abnormalities. New permanent pacemaker implantation has emerged to be an important short-term complication; reported to be around 6.0% for balloon expandable valves and up to 28.0% for self-expanding valves (41, 42). There are no specific design advances that have been incorporated in the newer generation THVs to reduce the risk of permanent pacemaker implantation. Moreover, there has been a reported increase in conduction abnormalities with newer generation devices (43). Mauri et al. identified technical and anatomical factors predisposing to new permanent pacemaker implantation (44). In this study using the new generation SAPIEN 3 THV, 33 of 229 patients received a pacemaker following TAVI. Pre-existing RBBB, left ventricular outflow tract calcification and an implantation depth defined as >25.5% of the stent frame below the annulus were each found to be important predictors of new permanent pacemaker implantation. This study highlighted important technical factors such as reducing the depth of the valve implant by a mere 3 mm reduced the need for permanent pacemaker implantation by 52%. TAVI operators will need to consider such technical aspects to reduce pacing rates, yet balance these with the risk of THV embolization with higher implants (45).

For bicuspid valve severe AS, pacemaker implantation rates were similar for balloon expandable (BE) and self-expanding (SE) THVs (11, 14). Jilaihawi et al. reported pacing rates of 25.5% for balloon expanding valves and 26.9% for self-expanding valves (11). Mylotte et al. also reported higher than expected pacing rates (16.7% for balloon expanding and 26.7% for self-expanding valves) in TAVI patients (14).

It has been postulated that the higher incidence of PPM implantation rates in BAV patients is related to asymmetric THV expansion due to resistant calcified raphe and leaflet fusion. There may be preferential expansion posteriorly to the non-coronary cusp which lies adjacent to the atrioventricular node. In tricuspid valve disease or incomplete raphe type BAV, there may be a more symmetrical expansion of THVs, thus diverting tissue away from the AV node (11). The presence of bulky calcification in the Sievers L-R Type 1 BAV may cause protrusion

toward the membranous part of the interventricular septum leading to atrioventricular and intraventricular conduction block (46). The higher pacemaker rates may thus be associated with difficulty in valve positioning due to irregular leaflet shape and inability to achieve a coaxial position during valve deployment. This can often lead to lower implantation depths, known to be associated with higher pacing rates. Patients with BAV disease also tend to be younger, and as TAVI moves to intermediate and the low-risk, complications such as pacemaker implantations will be important. Understanding the factors contributing to new permanent pacemaker implantation need to be addressed with particular focus on implantation depth and important calcification in the left ventricular outflow tract.

CORONARY OCCLUSION AND ANNULAR RUPTURE

The data on acute coronary occlusion during TAVI stems from isolated case reports and case series. The incidence is reported to be <1% and is a rare yet potentially life-threatening (4, 47–52). Randomized control trials of patients with tricuspid severe AS; report an acute coronary obstruction incidence of 0.1–1.2%. Data from bicuspid TAVI registry data report a similar 0–1.5% incidence of acute coronary obstruction (11–14, 38). Certain factors may increase the risk of coronary obstruction post-TAVI such as female sex, coronary ostia height of <10 mm, sinus of Valsalva dimensions and the presence of severe valve calcification (53). Most reported cases of coronary obstruction post-TAVI received a balloon-expandable THV.

Recent reports have arisen of the development of delayed coronary obstruction (DCO) occurring hours or days following TAVI. In a recently published international registry of 17,092 patients undergoing TAVI, the reported incidence of delayed coronary obstruction was 0.22% (54). DCO can be divided into early (0–7 days) and late (>7 days) post-TAVI. The etiology of DCO relates to a number factors such as a narrow sinuses of Valsalva, low coronary heights, excessive calcification, valve-in-valve TAVI and pharmacological factors such as antiplatelet and anticoagulation (54). Aortic root injury and annulus rupture likewise is a rare complication in BAV undergoing TAVI; reported to have an incidence ranging from 0 to 2% in the reported literature (11–14, 38).

COMPARISON OF OUTCOMES BETWEEN OLD AND NEWER GENERATION THVS IN BAV

THV device iteration significantly addressed the shortcomings of earlier generation THVs which were limited by PVL. Significant PVL post-TAVI has been shown to correlate with increased mortality (37, 55–57). PVL rates have improved significantly with newer-generation devices for patients with tricuspid AS patients, and has also been seen when newer-generation THVs are used in BAV patients (13). In a recently reported BAV registry comparing older versus newer generation THVs in BAV, moderate or severe paravalvular leak was significantly less frequent with new-generation devices compared to early generation devices (0.0 vs. 8.5%; $p = 0.002$), which resulted in a higher device success rate (92.2 vs. 80.9%; $p = 0.01$) (38). When compared with TAVI in tricuspid valve stenosis, there were no differences in procedural related complications with new generation devices. This was true for cumulative mortality at 2 years which were similar for tricuspid and bicuspid valves with newer generation devices (12). This has also been seen in several other registries using the SAPIEN 3 valve in tricuspid AS (58–61). Improvements in PVL have largely been made by developing a poly-ethylene terephthalate sealing skirt along with more accurate positioning. With the Lotus valve, the incidence of moderate to severe PVL has been reported to be as low as 2.0%, largely due to the adaptive seal and optimal positioning due to device retrievability and repositionability (62).

TECHNICAL CONSIDERATIONS FOR TAVI IN BAV

BAV disease poses many technical challenges for TAVI operators. Selection of the optimal angiographic projection and visualization of the aortic annulus can be difficult due to the asymmetric shape of the cusps and sinus of Valsalva. Calcium distribution throughout the aorto-annular complex is frequently asymmetric, along with raphe resistant to pre-dilatation and aortic root dilatation. These variations may promote poor valve expansion and thus adversely affect valve hemodynamics and durability which in turn can lead to high transvalvular gradients, PVL, device malpositioning, and higher permanent pacemaker rates post-TAVI (11, 12, 14, 63). The aortic annulus is often elliptical in shape, larger in size, and associated with a dilated and horizontal aorta, (64) further giving rise to difficulties in device positioning and expansion. The native valve leaflets can be capacious due to leaflet fusion resulting in longer leaflets increasing the risk of coronary obstruction (34, 65).

Himbert et al. reported on the use of self-expanding devices in 15 patients with BAV disease (66). The device was associated with non-circular expansion at the annular level which was less frequent when the device was implanted lower in the left ventricular outflow tract. In another series of 21 patients who had post-procedural MSCT imaging, non-circular expansion of the valve was seen more commonly with self-expanding valves due to the asymmetrical nature of the bicuspid valve orifice and resistant raphe (67). With balloon-expandable valves there have been reports of asymmetric longitudinal valve expansion, however further assessment is required for both self-expanding and balloon-expandable valves to ascertain if this ultimately affects leaflet motion and durability (13).

Imaging for TAVI in Bicuspid-Aortic Valve Disease

Sizing of THVs can be difficult due to multiple anatomical considerations including a large and eccentric annulus, calcified raphe, horizontal aorta, complex calcification, and aortic root

dilatation. Each of these variables can interplay and make TAVI implantation technically challenging. MSCT has enabled operators to have a better understanding of the anatomy of BAV disease, critical for procedural planning pre-TAVI to minimize complications (68).

Due to the percutaneous nature of TAVI, operators lack the ability to expose the surgical field and directly visualize the aortic valve, annulus and structures around it. MSCT is used to provide a comprehensive 3-dimensional data-set of the aortic valve anatomy and identification of concomitant aortopathy. MSCT provides anatomical measurements of the aortic annulus, detail of the aortic valve, calcium burden, aortic root ("sinus of Valsalva"), coronary ostia and access site, all of which are essential to minimize complications and improve procedural outcomes. In BAV, MSCT is key to providing information on leaflet morphology, symmetry of the valve leaflets, presence of raphe and the location of calcification all of which can influence the type and size of THV selected (**Figure 3**) (69).

In a study using MSCT which looked at the shape and size of the annulus in bicuspid ($n = 200$) and tricuspid valves ($n = 200$), the aortic annulus was found to be less elliptical in bicuspid than tricuspid valves (ellipticity index 1.24 vs. 1.29, respectively). This study also highlighted that biscuspid valve patients had large annular areas compared with tricuspid valves (5.21 vs. 4.63 cm^2) (27). Reports from recent large series of bicuspid patients indicate that annular dimensions still fall within the valve sizing recommendations for current commercially available THVs (13, 14, 67).

THV oversizing can lead to distortion and poor expansion of the valve prosthesis leading to PVL. This can be improved with intra-procedural post-dilatation, however there is a risk of annular rupture, aortic root haematoma and heart block with subsequent post-dilatations. A self-expanding THV may minimize the risk of annular rupture, however when compared with balloon expandable THVs, there is a greater incidence of PVL and heart block in BAV disease patients (38, 70).

Balloon Sizing

Other techniques can be used to help with valve sizing such as fluoroscopic balloon sizing of the aortic valve annulus pre-TAVI (71). Balloon sizing can complement MSCT especially when there is ambiguity regarding valve sizing and when measurements fall in the "gray zone" between two valve sizes. In the presence of bulky cusps or long leaflets, balloon sizing can mimic valve implantation and also identify patients at risk of coronary obstruction. It provides additional information that is not available from MSCT or transoesphageal echocardiography (TEE) and can help predict how situations such as severe, eccentric calcification may behave and the complications that can arise from it.

Commonly in BAV disease the abnormal geometry at the annular level and unequal-sized leaflets makes alignment of the two or three hinge points (depending on BAV type) difficult. MSCT is useful in tricuspid valve disease to find the optimal implantation projection of the aortic root and an orthogonal alignment of the native annulus. This however, is often found to be unhelpful in BAV disease. Techniques have been described using the pigtail catheter and altering the fluoroscopic projection to find an optimal view for implantation; "follow the right cusp rule" (72) and the "Right cusp rule, Part II" (73).

Valve Crossing

Crossing the stenotic BAV may be challenging and time-consuming, increasing the risk of embolic cerebral complications. Careful interrogation of the MSCT can identify the fused cusps in BAV disease and may help with predicting the location of valve opening and maximize the chance of the wire to cross. Frangieh et al. (68) have described a step by step approach to crossing a stenotic BAV. Wire movement should start from the non-fused leaflet ("single cusp") which has no raphe and then with careful rotation direct the wire in small steps toward the fused cusps. If starting in the NCC rotate clockwise, or anticlockwise if starting in the LCC. In BAV with no raphe, there are only two anatomical cusps and the guide wire should be slowly manipulated between each cusp carefully interrogating the opening between the leaflets. In more angulated aortic roots, catheters with a bigger curve such as an Amplatz-2 (AL-2) may help with retrograde crossing, and/or softer hydrophilic coated wires such as the Glidewire. In extreme circumstances when conventional retrograde wire crossing of the BAV is not possible, *ad hoc* trans-septal puncture followed

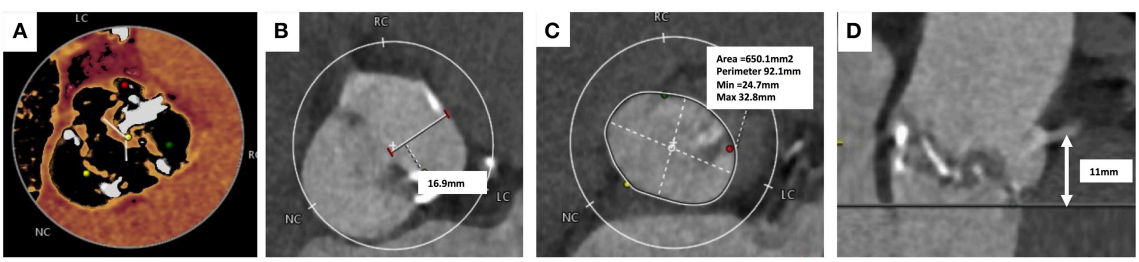

FIGURE 3 | Computer Tomography Imaging of bicuspid aortic valve. **(A)** Sievers Type 1 Raphe-type bicuspid aortic valve (BAV) with mixed cusp fusion (left-right). **(B)** Large bulky cusps measuring 16.9 mm maximum diameter. **(C)** Asymmetric large annulus. **(D)** Low lying coronary ostia at 11 mm combined with large bulky leaflets indicate a risk of coronary occlusion during TAVI.

by wire delivery into the left ventricular apex, anterograde aortic valve crossing, wire externalization and subsequent aorto-venous loop creation can be undertaken. A catheter of choice (i.e., AL) can then be placed retrogradely across the stenotic BAV thus facilitating regular fully percutaneous transfemoral TAVI (**Figure 4**) (74, 75).

HOW TO PERFORM TAVI IN BICUSPID AORTIC VALVE DISEASE

Historically, patients with BAV disease with severe AS were referred for SAVR. However, there is an increasing tendency for some younger patients to opt for a less invasive percutaneous

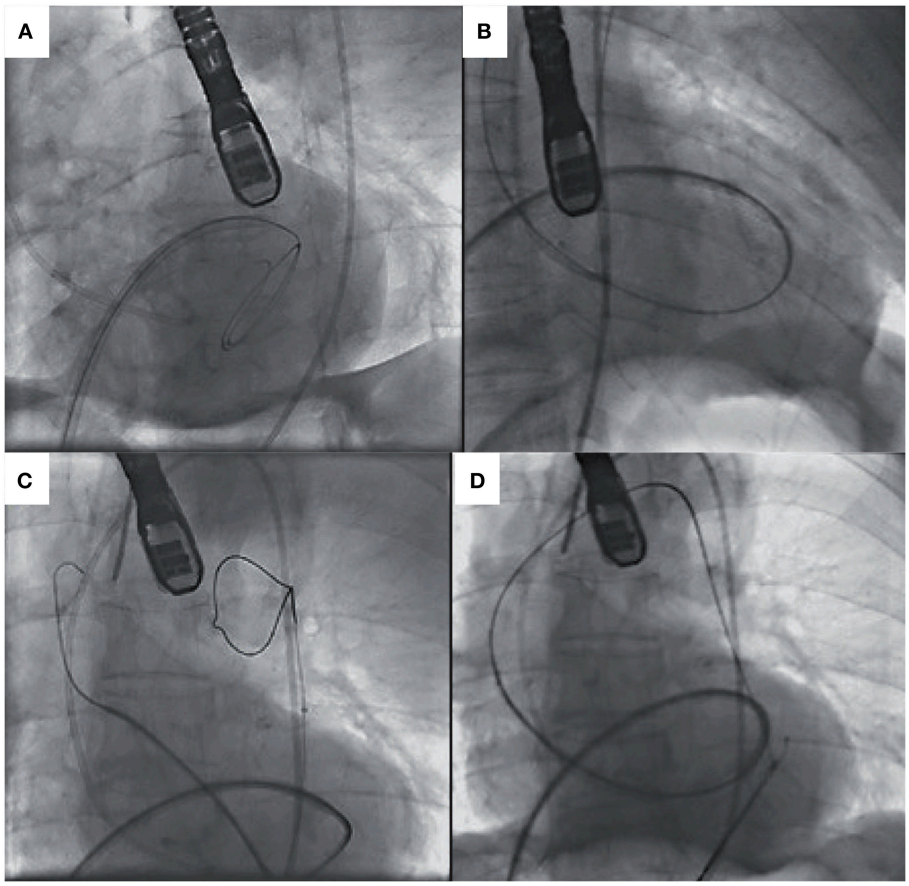

FIGURE 4 | (A) Transeptal puncture and positioning of hydrophilic wire and Judkins Right in the left ventricle. **(B)** Anterograde crossing of the aortic valve and wire changed for exchange wire. **(C)** Amplatz Goose Neck Snare used to snare the exchange wire. **(D)** Exchange wire then externalized via the left femoral artery [Adapted with permission from the Rodríguez-Olivares et al. (75)].

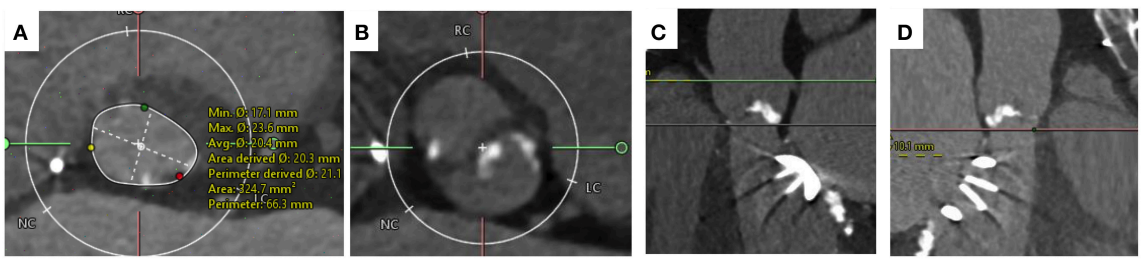

FIGURE 5 | MSCT imaging of bicuspid aortic valve. **(A)** Annulus measurement with minimum diameter of 17 mm and maximum diameter of 24 mm and area of 325 mm^2. **(B)** Cross-sectional view taken 4 mm above the level of the annulus. The valve is a Type 0 Sievers BAV with no raphe. **(C)** Distance to coronary ostia >10 mm. **(D)** The distance from the aortic annulus to the mitral valve ring measures 10.1 mm acceptable for TAVI implantation.

procedure, particularly in the presence of significant co-morbidity or prior cardiac surgery. The selection of the type and size of the valve can be challenging due to the anatomical reasons outlined above, with MSCT playing an important role in THV device selection and implantation technique. Sizing and implantation technique is key to success in TAVI in bicuspid valve disease. Due the asymmetric nature of the aortic annulus, eccentric heavy calcification and raphe resistant to dilation, THV valves are implanted higher and anchored at the tightest part of the commissural. This has in part led to sizing of valves at +4 mm above the annulus at the intercommisural space. The final implantation depth are often higher due to the anchoring effect of the calcification at the level of the commisures with <4 m for CoreValve, <3 mm for CoreValve Evolute R (Medtronic, Minneapolis, Minnesota) and atrio-ventricular ratio of 60/40 for Sapien XT/S3 (Edwards Lifesciences, Minnesota). Here we present 2 illustrative cases of how to perform TAVI in BAV.

Case 1

A 67-year old female with acute respiratory failure due to severe AS was referred for consideration of TAVI. She underwent ventricular septal defect repair at the age of 10. At the age of 57 she presented with progressive breathlessness secondary to severe mitral regurgitation and underwent a mitral valve replacement with a 27 mm Carpentier Edwards Magna Valve. Six years later she developed further progressive dyspnoea and underwent an urgent redo mitral valve replacement for a stenotic prosthetic mitral valve. A 33 mm Carbomedics Valve was inserted into the mitral position. She has end-stage renal disease requiring haemodialysis.

Transthoracic echocardiography showed a degenerated bicuspid aortic valve with a peak velocity of 5.2 m/s (peak gradient 108 mmHg; mean gradient 68 mmHg, area of 0.43 cm^2). The mitral valve prosthesis was functioning normally. Invasive coronary angiography revealed normal coronary arteries. Following a Heart team discussion, it was decided to perform TAVI due to her previous mitral and redo mitral valve replacement. The aortic valve was a Sievers Type 0 bicuspid valve. The aortic annulus minimum diameter was 17 mm, maximum diameter 24 mm, perimeter 69 mm, and an area of 355 mm^2 (**Figure 5**). The common femoral arteries measured 6 mm bilaterally. A technical concern regarding TAVI in this lady was the interaction of the TAVI valve with the mitral valve prosthesis and the risk of valve embolization

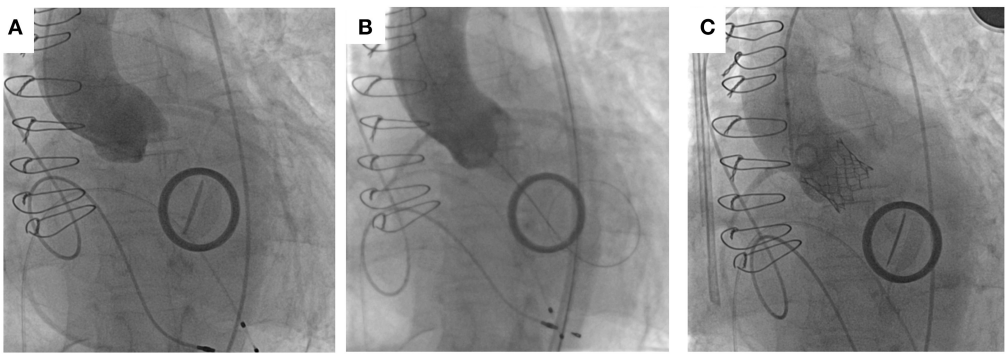

FIGURE 6 | Implantation of SAPIEN 3 in patient with bicuspid aortic valve with previous mitral valve replacement. **(A)** Aortogram for root alignment with pigtail catheter in the right coronary cusp. **(B)** Balloon sizing with 20 mm balloon touching hinge points with simultaneous aortogram showing filling of coronary arteries. **(C)** Successful deployment of 23 mm SAPIEN 3 valve with no paravalvular leakage.

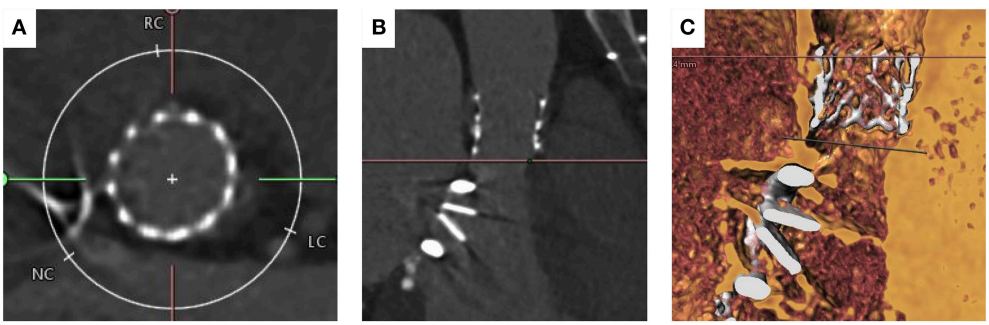

FIGURE 7 | MSCT imaging of the aortic annulus post TAVI implantation with 23 mm Edwards Sapien Valve. **(A)** shows circular deployment of the transcatheter heart valve. **(B)** Left ventricular outflow tract view showing bi-leaflet mitral valve prosthesis and TAVI valve post deployment. **(C)** Volume rendered imaging confirming there is no interaction between the base of the TAVI valve and mitral valve prosthesis.

during deployment. The MSCT identified the rim between the mitral valve prosthesis and the aortic annulus to measure 10 mm, which was felt to provide an adequate landing zone for the THV, with the risk of valve embolization deemed to be small.

The right femoral artery was cannulated and a 14 French E-sheath was introduced. The annulus area was felt to be between two valve sizes (23and 26 mm Sapien S3 valves). The valve was crossed retrogradely using an Amplatz Left1 diagnostic catheter and a "straight" standard wire. The wire was then exchanged with a pre-shaped small Safari wire (Boston Scientific, Natick, MA, USA). A balloon aortic valvuloplasty was performed and simultaneous aortogram was performed. An aortogram confirmed that during inflation the 20 mm balloon adequately filled the aortic annulus and was in contact with the hinge points (**Figure 6**). Coronary filling was also visualized. It was therefore decided to implant a 23 mm Edwards Sapien S3 Valve. Careful attention was given during valve positioning ensuring the valve skirt was positioned just below the hinge points. The valve was confirmed to be well positioned with good hemodynamics without paravalvular regurgitation. Following valve deployment, MSCT was performed confirming circular expansion of the valve and no infringement on the mitral valve prosthesis (**Figure 7**).

In cases of BAV, large aortic annuli pose a challenge for the TAVI operator as large annular dimensions fall outside the recommended sizing ranges for currently available THVs. There are concerns regarding significant paravalvular leakage post TAVI deployment in this group of patients. In certain cases with large annuli the inter-commisural space can be used for the landing zone with good effect. Improvements in THV design (in particular the sealing skirt) and technical considerations such as landing the valve in the inter-commisural space means that these patients can be treated with good outcomes. This forms the rationale of some TAVI operators who suggest to size and land the THV 4 mm above the measured annulus.

Case 2

A 58 year-old male with end stage renal disease due to IgA nephropathy who had previously undergone a renal transplant which had failed was declined for redo renal transplantation. He had progressive dyspnoea and a history of syncope on exertion. The transthoracic echocardiogram confirmed severe stenosis of a BAV with a peak velocity of 3.9 m/s (peak gradient 61 mmHg, mean gradient of 39 mmHg and area of 0.89 cm^2). There was also the presence of moderate aortic regurgitation. Coronary angiography revealed non-flow limiting coronary artery disease. MSCT confirmed a Sievers Type 1 bicuspid valve with a partial raphe between the right and left cusps. The aortic annulus was large with a perimeter measuring 98 mm, mean Sinus of Valsalva diameter of 40 mm and an inter-commisural distance of 29 mm (**Figure 8**). Both common femoral arteries were of large caliber and measured 8 mm on the left and 9 mm on the right. Following discussion by the Heart team and careful analysis of the MSCT it was felt that TAVI was technically possible if deployed at the inter-commisural space.

TAVI was performed under local anesthetic and the right femoral artery was cannulated and a 20 Fr sheath was inserted. The left femoral artery was cannulated and a 7 Fr sheath was inserted. The left femoral vein was used for insertion of a temporary pacemaker lead. The bicuspid aortic valve was crossed retrogradely using a Amplatz Left 1 diagnostic catheter and a hydrophilic coated straight tipped Glidewire. This was exchanged for a pre-shaped Safari wire and placed in the left ventricular apex. A balloon valvuloplasty was performed using a 25 mm balloon and a simultaneous aortogram was performed. The aortogram revealed a leak of contrast into the left ventricular cavity during balloon aortic valvuloplasty and felt to be an inadequate seal. A 34 mm Evolut CoreValve was deployed at the level of the leaflet tips, with hemodynamics and echocardiography confirming a good result with no significant PVL. The peak velocity across the TAVI valve was 1.8 m/s, peak gradient of 14 mmHg and area of 1.11 cm^2.

CONCLUSIONS

Despite encouraging data, especially with newer generation THVs for BAV disease, caution needs to be taken as patients with bicuspid AS are more likely to be younger (12, 38, 76) and therefore concerns regarding significant PVL and high permanent pacemaker implantation rates need to be

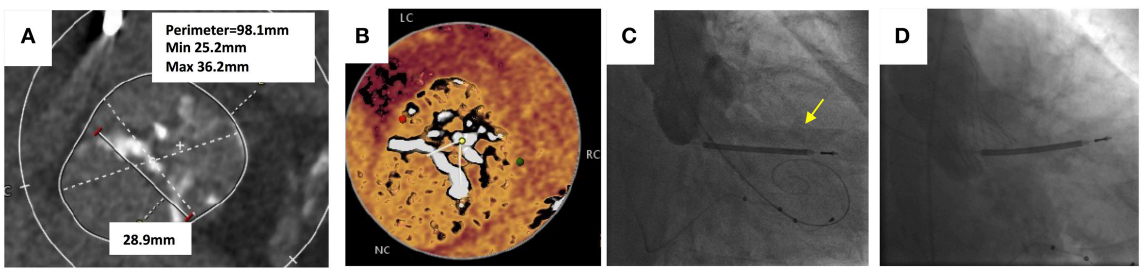

FIGURE 8 | Transcatheter aortic valve replacement in bicuspid aortic valve. **(A)** Sievers Type 1 bicuspid valve with partial raphe between the right and left cusps. Large annulus with perimeter measuring 98.1 mm and an intercommisural distance of 28.9 mm. **(B)** "Hockey puck" view of the bicuspid valve shows partial raphe between left and cusps. **(C)** Balloon valvuloplasty with 25 mm balloon for sizing prior to TAVI implantation. Yellow arrow shows leak of contrast into left ventricle during simultaneous aortogram indicating inadequate seal. **(D)** 34 mm Evolute R deployed at leaflet tips with no paravalvular leak.

addressed before offering it to younger and lower operative risk patients. With improvements in the design of the sealing skirts of THVs, PVL rates have reduced and the ability to reposition and retrieve the devices have led to more technical success with TAVI in selected patients with BAV disease. Procedural success is high and the survival rates are similar to those in patients with tricuspid valve AS undergoing TAVI. However, complications such as moderate or severe PVL and aortic root dissection are more common in BAV disease compared to tricuspid aortic valve patients. As the indications for TAVI expands with data supporting its use in the younger and intermediate risk group patients, the proportion of patients with BAV is expected rise. Specifically designed prospective studies are required to provide further evidence on durability, anatomical selection criteria and long-term success before it becomes a viable option for patients with BAV.

AUTHOR CONTRIBUTIONS

RD and RP wrote the manuscript and provided substantial contribution to the discussion and content. All the authors researched data for the article, and reviewed and/or edited the manuscript before submission.

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The authors can confirm that full written informed consent was obtained from the patients for publication of the case reports included in this review.

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REVIEW
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Cerebrovascular Events After Transcatheter Aortic Valve Implantation

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Transcatheter aortic valve implantation (TAVI) has emerged as an alternative less invasive treatment for patients with symptomatic severe aortic stenosis. Despite the technological development and knowledge improvement in recent years, neurological complications remain a concern, especially with the expansion of the technique toward younger and lower risk patients. Clinical cerebrovascular events have an important impact on patients' morbidity and mortality with a multifactorial origin. While cerebral microembolizations during TAVI is a universal phenomenon and embolic protection devices have been developed in an attempt to reduce them, their clinical utility remains unclear. We review the current evidence on cerebrovascular events associated with TAVI and potential preventive strategies.

Keywords: TAVI, cerebrovascular event, stroke, aortic valve stenosis, transcatheter aortic valve implantation, transcatheter aortic vave replacement

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INTRODUCTION

Transcatheter aortic valve implantation (TAVI) has been established as the therapy of choice in patients with severe aortic stenosis of high or prohibitive risk, and in the last years as a valid alternative to surgery (SAVR) in patients with intermediate risk (1–4). Despite the great technological advances, cerebrovascular events (CVE) remain one of the most feared complications, increasing the risk of morbidity and mortality at short and long term (5, 6). The incidence of CVE following TAVI varies according to definition ranging from 1 to 11% (7) and with a similar frequency compared to SAVR in randomized clinical trials (4, 8). However, it exceeds any other daily percutaneous cardiac intervention especially in the acute period to decrease later in the following months (6, 9). Despite clinically strokes represents only a small proportion of patients, silent cerebral embolisms are an almost universal finding associated with this procedure. Furthermore, the real impact of these micro emboli on patients' cognitive function and development of future cerebral complications remain unclear. We present a review of the current knowledge about CVE following TAVI and insights about potential preventive strategies and future implications.

CLASSIFICATION AND DEFINITION OF CEREBROVASCULAR EVENTS

In an effort to unify the discrepancies in the stroke definition used across the studies, the Valve Academic Research Consortium (VARC-I) in 2012 recommended to use the definitions of transient ischemic attack (TIA) and stroke (10). TIA was defined as a neurological deficit that resolves

TABLE 1 | The modified Rankin Scale for classification of stroke severity.

Severity	Degree of neurological damage
Level 0	No disability: no restriction of usual activities
Level 1	No significant disability: able to carry out all usual activities despite neurologic deficits
Level 2	Slight disability: able to look after own affairs without assistance but is unable to carry out all previous activities
Level 3	Moderate disability: requires some help but is able to walk without any assistance
Level 4	Moderately severe disability: cannot to attend to own bodily needs without assistance or requires assistance to walk
Level 5	Severe disability: requires constant nursing care and attention
Level 6	Death

Adapted from Sacco et al. (11).

TABLE 2 | Cerebrovascular events definitions according to the Neurological Academic Research Consortium (2017).

NEUROARC NEUROLOGICAL EVENT DEFINITIONS		
Type 1	Overt injury	Ischemic stroke
		Cerebral / Subarachnoid hemorrhage
		Hipoxic Injury
Type 2	Covert injury	CNS Infarction
		CNS Hemorrhage
Type 3	Symptoms without injury	TIA
		Delirium
CLASSIFICATION OF NEUROLOGICAL EVENT TIMING		
Periprocedural	<30 days post-intervention	
Late	>30 days post-intervention	

CNS, central nervous system. Adapted from Lansky et al. (12).

rapidly, in <24 h, without evidence of tissue injury in neuroimaging study. Stroke was defined as a new focal or global neurological deficit that persisted more than 24 h, or <24 h associated with cerebral injury in neuroimaging study, or if the neurological deficit resulted in death. The severity of stroke is usually categorized according to the modified Rankin Scale (mRS), classifying it into disabiling (major stroke mRS ≥2) and non-disabiling (minor stroke mRS <2) (**Table 1**). This criteria have been recently complemented by the Neurologic Academic Research Consortium in 2017 after the preparation of a consensus document where they established a new classification and also defined the endpoints applicable to clinical trials (12) (**Table 2**).

INCIDENCE OF CLINICAL CEREBROVASCULAR EVENTS

Cerebrovascular complications related to TAVI showed a significant variability between centers and studies, ranging from 1 to 11% (7). Rates of 30-day CVE in randomized trials and national registries are shown in **Figure 1**. This variability might be explained depending on the definition used, study design, diagnostic methods, patient risk-profile, site-specific factors, and systematic evaluation by a neurologist (13–15). The stroke incidence reported in most studies was generally a combination of non-disabling (*minor*) and disabling (*major*) stroke, while TIA is less frequently reported. The studies that categorized the stroke severity, suggested that disabling stroke had a higher incidence (58%) than non-disabling (26%) and transient ischemic attack (16%) (16). However, this data could be influenced by a lack of adequate and systematic neurological assessment to detect minor stroke or TIA in observational and randomized studies.

Initially, the results from PARTNER I trial (both cohorts A and B) showed greater stroke incidence in the group undergoing TAVI (1, 3, 17). Later, in the Corevalve trial with high-risk patient, patients undergoing TAVI had a numerically lower stroke rate at 30-day and 1-year compared to SAVR (2). In the recent randomized trials with intermediate risk patients, the results of the NOTION I, PARTNER-2, and SURTAVI trials showed a 1.4, 5.5, 3.4% 30-day stroke rate in the TAVI arm, compared to 3.0% ($p = 0.37$), 6.1% ($p = 0.57$), and 5.6% (95%CI −4.2 to 0.3) in the surgical arm, respectively. In addition, in the propensity matched comparison of the surgical arm from PARTNER 2 with the observational cohort of Sapien 3 study, the 30-day stroke rate was lower in the TAVI group (−3.5, 95% CI: −5.9 to −1.1, $p = 0.004$) (18). Thus, the initial fear of higher CVE rates in the TAVI arm has changed over time and now there is enough evidence to support that clinical CVE incidence is at least similar to the surgical arm (4, 8, 19).

Several meta-analyses, including mostly observational studies, have determined the incidence of stroke following TAVI (6, 7, 20). Eggebrecht et al. (with 10,037 patients from 53 studies) reported a 30-day stroke rate of 3.3 ± 1.8%, with the majority being major strokes (2.9 ± 1.8%). More recently, Muralidharan et al. (with 29,043 patients from 34 studies) and Auffret et al. (with 72,318 patients from 64 studies) reported a median 30-day stroke rate of 3.1 and 3.3%, respectively (9, 18).

TEMPORAL PRESENTATION AND PATHOPHYSIOLOGY OF CEREBROVASCULAR EVENTS

Cerebrovascular events have been also classified according to the temporal pattern in acute (≤24 h), sub-acute (1–30 days), and late (>1 month) events. Several studies have shown that stroke incidence following TAVI has a peak in the immediate period after the procedure (24–48 h), reaching in some studies, half of the total events within 1 month (5, 21). Patients remain vulnerable for a period of up to 2 months after the procedure to subsequently decrease and stay stable over time. Temporal distribution of the CVE is closely related to their mechanism (**Figure 2**) (5).

Acute Cerebrovascular Events

Most Acute CVE after TAVI are related to an ischemic origin, with <5% reported as hemorrhagic stroke (16). Most of this ischemic CVE are related to an embolic source. Due

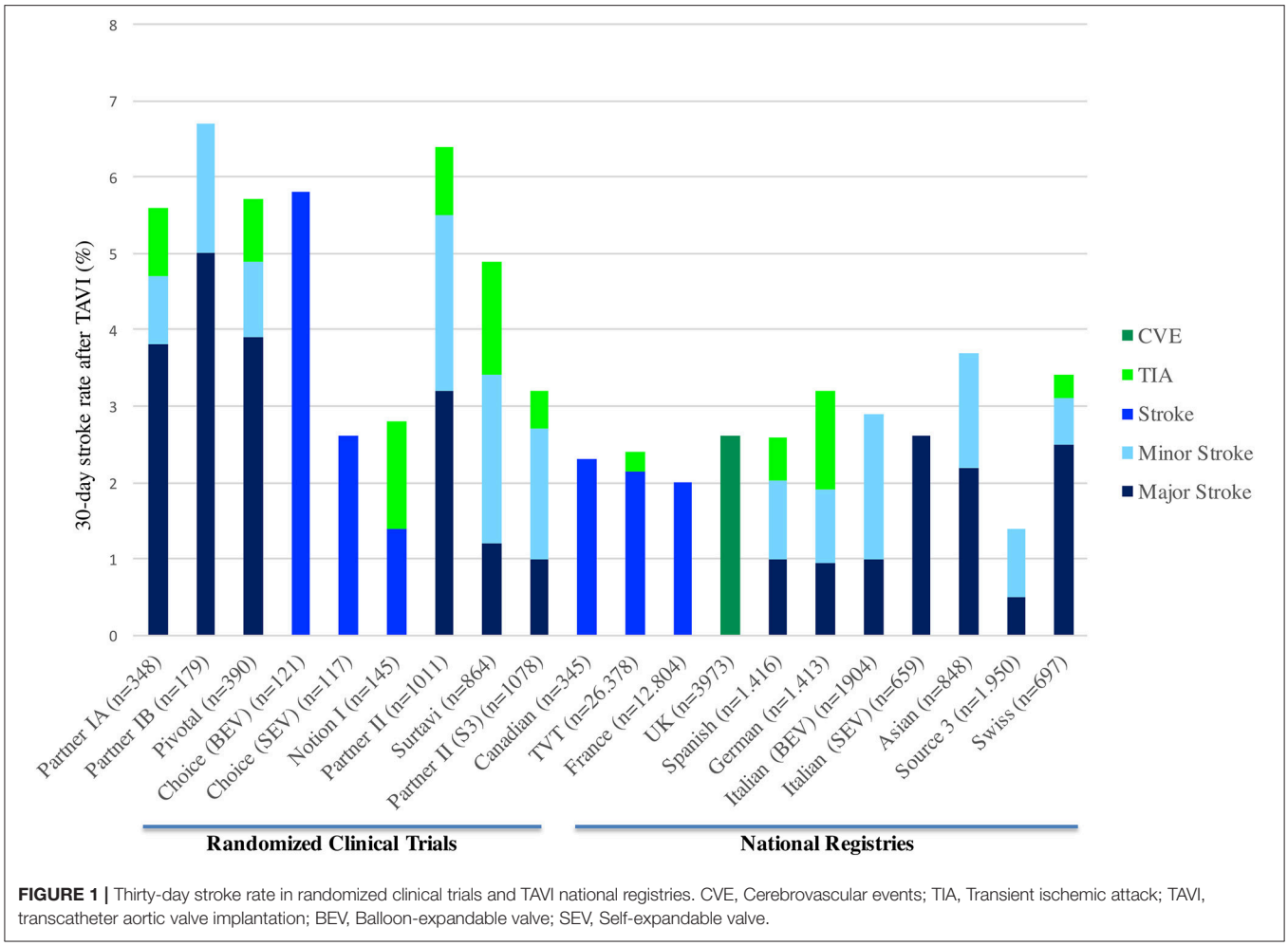

FIGURE 1 | Thirty-day stroke rate in randomized clinical trials and TAVI national registries. CVE, Cerebrovascular events; TIA, Transient ischemic attack; TAVI, transcatheter aortic valve implantation; BEV, Balloon-expandable valve; SEV, Self-expandable valve.

to the constitution of the calcified aortic valve and the walls of the aorta, its manipulation with rigid and large delivery catheters, balloon valvuloplasty or the interaction of the stent valve during the positioning or valve release will inevitably generate embolic material (22). This fact is supported by several different findings (**Figure 3**): Firstly, studies with diffusion-weighted magnetic resonance imaging (DW-MRI) demonstrated that between 60 and 90% of patients had new silent cerebral lesions after TAVI, independently of the vascular access or device type (22, 25, 26). These lesions were generally multiple, diffuse, distributed in both cerebral hemispheres and from both cerebral vascular territories (anterior and posterior) in most patients, suggesting an embolic nature. Secondly, procedural transcranial doppler studies confirmed that there were high intensity signals (HITS) in the middle cerebral artery in almost all the phases of the procedures, but especially during valve positioning and implantation (24). Interestingly, it has been suggested that valve design and implantation process could be associated with different temporal pattern of the HITS. While balloon expandable valve produces more emboli during valve positioning, self-expandable valve has greater amount of HITS during valve deployment (24). Thirdly, Van Mieghen et al., extensively examined the incidence and the histopathology of embolic debris retained in an embolic protection device during TAVI (27) (**Figure 3**). In the majority of cases (>85%), debris was obtained after the procedure, with a median size of 1 mm (IQR 0.6–1.6 mm). The nature of these emboli was varied. The most frequent was fibrin and thrombotic material (74% of the patients) (**Figure 4**) that were found in similar proportion in balloon and self-expanding valve. The wires and catheters used are known to be prothrombotic, associated with suboptimal anticoagulation during the procedure could be a potential source of thrombus formation. Additionally, damage to endothelium secondary to catheters manipulation, may cause platelet activation and the coagulation cascade, resulting in thrombus generation. Tissue-derived debris was present in 63% of the patients, with higher proportion in patients with balloon-expandable valve and higher degree of oversizing. This proportion of debris and its histopathology nature has been confirmed in more recent studies (27–31) (**Figure 4**). In this line, another study reported that total atheroma volume in the aorta was associated with higher risk of acute CVE (32). Another possible source of CVE during the procedure was air embolisms, especially associated with large delivery catheters and contrast injection. However, air

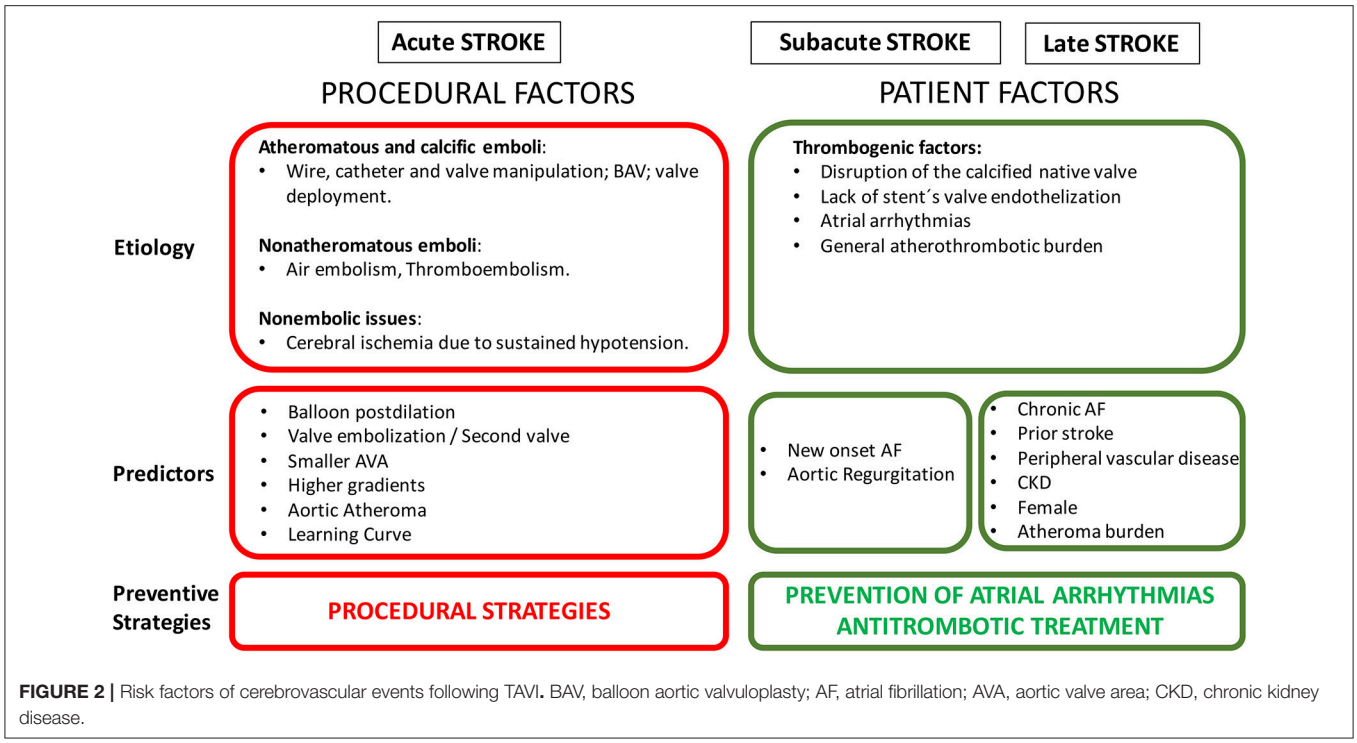

FIGURE 2 | Risk factors of cerebrovascular events following TAVI**.** BAV, balloon aortic valvuloplasty; AF, atrial fibrillation; AVA, aortic valve area; CKD, chronic kidney disease.

embolisms are usually considered temporary and are difficult to detect.

Systemic hypotension could also develop cerebral hypoperfusion, especially in the border territories supplied by different cerebral arteries, causing a watershed infarct. At least, one ventricular rapid pacing is mandatory in almost every TAVI, either with the valvuloplasty or balloon postdilation (more frequently performed with self-expandable valves) or during valve implantation (with balloon-expandable valves). Rapid pacing causes an impairment of cerebral perfusion but it is usually transitory and well tolerated with a prompt recovery. Patients with very low ejection fraction, especially after a long ventricular rapid pacing, may have a prolonged period of hypotension that requires inotropic support. Additionally, permanent cerebral injury could be caused by maintained systemic hypotension in the setting of hemodynamic instability during any procedural complication (bleeding, cardiac tamponade, severe acute aortic regurgitation…), even when inotropic and mechanical circulatory support are provided. Fortunately, the incidence of such complications has clearly decreased in the later years.

Subacute/Late Cerebrovascular Events

Cerebrovascular events occurring more than 48 h after TAVI are unlikely to be related to the procedure *per se*. The etiology of delayed CVE is less understood and has a multifactorial origin. In the immediate period after valve implantation, several theoretical phenomena may be thrombogenic. Disruption of the calcified native valve with denudation of the endothelium, the stent of the valve before endothelization, and the paravalvular space with the native valve compressed against the aortic wall, are some examples of potential sources of thrombus. Intraartrial thrombus formation related to atrial arrhythmias could be another source of thromboembolism. Intracardiac thrombus, usually detected in left atrial appendage, and spontaneous echo contrast were frequent findings in patients with aortic stenosis (10 and 24%, respectively) (33).

PREDICTORS OF CEREBROVASCULAR EVENTS AFTER TAVI

Based on their mechanism, predictors of CVE following TAVI can be divided in procedural and patient factors related (**Figure 2**). Several studies reported predictors of developing neurological events after TAVI (5, 7, 34). Initially, the PARTNER trial showed that patients with lower aortic valve area had a higher risk of CVE in the early period after TAVI (16). This was related to a more calcified valve, with a plausible mechanism of higher risk of embolization. In this line, Nombela-Franco et al. reported that patients with a higher degree of valve calcification underwent more frequently balloon post-dilation (BPD) to treat paravalvular regurgitation (35). These patients also had a higher rate of acute CVE. However, it was not possible to determine if the independent factor for the acute CVE was the amount of calcium or BPD. Later, other studies highlighted the impact on acute CVE of mechanical procedural factors, such as number of implantation attempts, valve embolization, second valve implantation, or BPD (5, 14, 21).

Attempts have been made to find other risk factors related to CVE following TAVI, such as the presence of porcelain aorta, which in cardiac surgery is a well-established factor with a

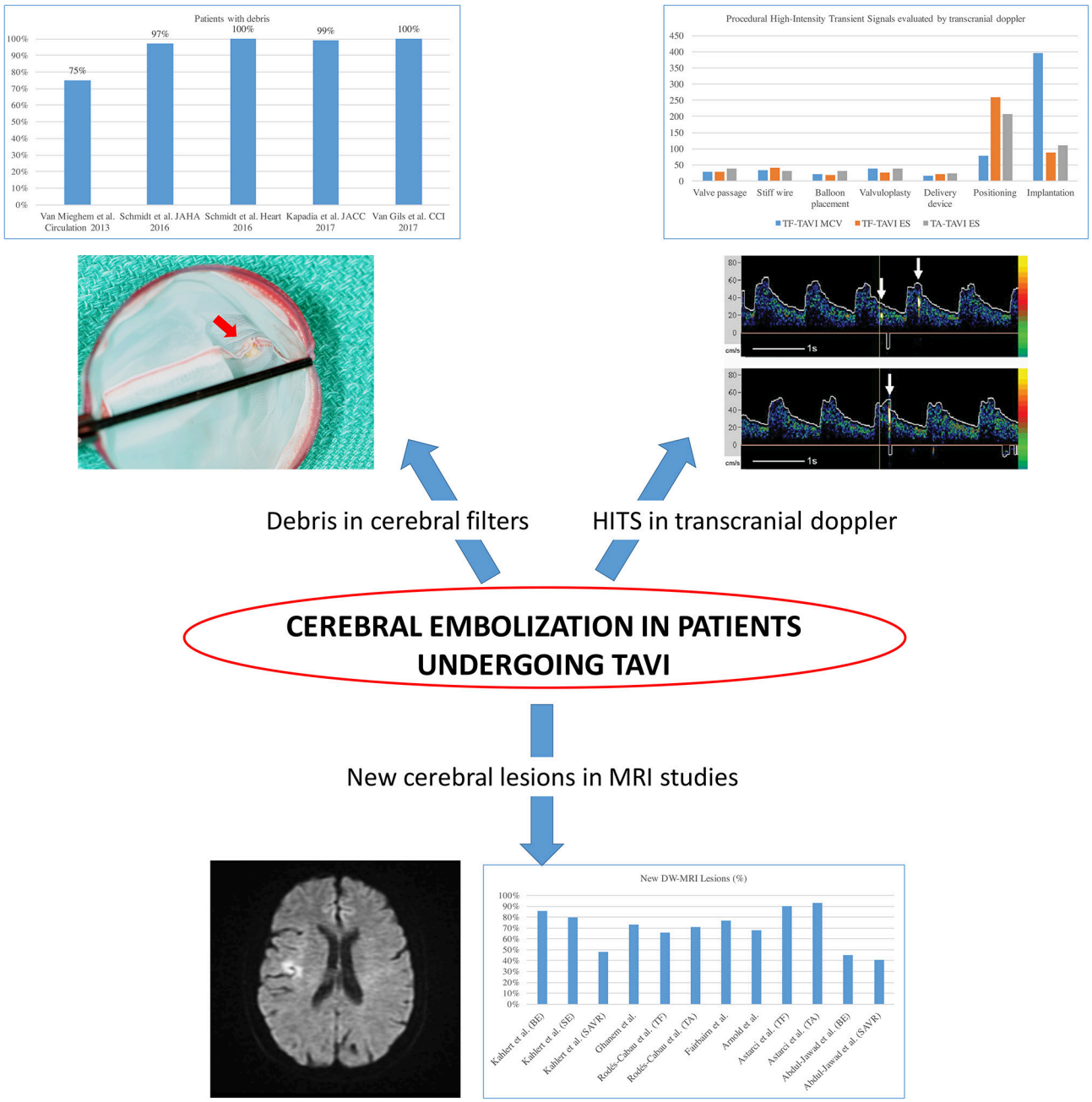

FIGURE 3 | Evidence of cerebral embolization during and after transcatheter aortic valve implantation**.** HITS, high intensity transient signals; TAVI, transcatheter aortic valve implantation; DW-MRI, diffusion-weighted magnetic resonance imaging; TF, transfemoral; TA, transapical. Adapted from Abdul-Jawad Altisent et al. (23) and Kahlert et al. (24).

higher risk of stroke (36). Although porcelain aorta is associated with a greater burden of cardiovascular risk factors (37), and therefore could lead to a higher incidence of late CVE, the currently available evidence have not found a higher incidence of stroke in this group of patients undergoing TAVI compared to patients without porcelain aorta (1.6 vs. 2.5% respectively, $p = 1.0$) (37–39). It would appear reasonable that operator, and center experience may also be predictors of stroke post TAVI. Carroll et al. evaluated the association of hospital TAVI volume and patient outcomes by using data from 42,988 procedures conducted at 395 hospitals from the TVT Registry from 2011 through 2015. High-volume centers had significantly lower in-hospital events, but no difference was found in the stroke rate ($p = 0.14$) (40). However, a greater center experience was associated with lower stroke rates (2.03 vs. 1.66%, $p = 0.01$), similar findings described by Auffret et al. showing 1.55 fold more

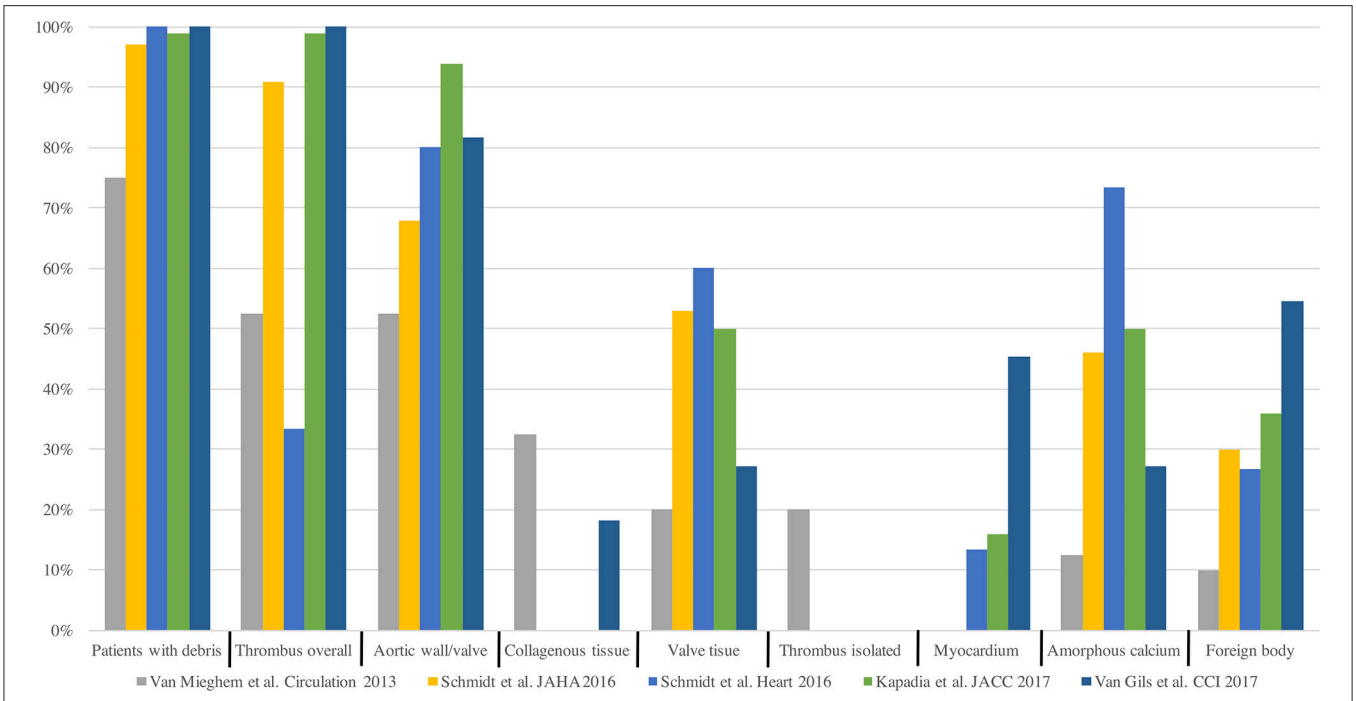

FIGURE 4 | Frequency and distribution of captured debris in histopathologic analysis.

risk of CVE after TAVI during the first half of enrollment (95%CI, 1.16–2.08, $p = 0.003$) (7).

Regarding the access site, no differences were found in MRI studies comparing transfemoral vs. transapical approaches (41). Also, some meta-analysis have revealed that a non-transfemoral approach did not carry a higher stroke risk (RR 1.03, 95%CI 0.83–1.27, $p = 0.81$) (7). Transcarotid approach in terms of stroke risk is more controversial. Non-randomized trials found similar neurological outcomes (3.8% 30-day CVE) compared to an historically transfemoral cohort (42). However, recent evidence with a small number of patients ($n = 22$) showed more than twice the number and total volume of new ischemic lesions evaluated by diffusion-weighted magnetic resonance imaging within the left hemisphere ($p < 0.01$ for both) when performing TAVI through the left carotid artery (43). Therefore, more information is needed to clarify this issue.

In the sub-acute phase after TAVI, the strongest predictor for 30-day CVE found in several studies was NOAF, which usually occurs in an average of 15% of the patients. In a recent meta-analysis NOAF had a 1.85-fold increased 30-day hazard for CVE after TAVI. Although the incidence and definition of NOAF has varied across the studies, some studies reported that even short and transient periods of NOAF may have a significant influence in CVE, especially because some of these patients had a suboptimal anticoagulation regimen (44, 45). The stroke rate of patients with optimal anticoagulation was 2.9% compared to 40% in non-anticoagulated patients (45). Also Nuis et al. found a temporal relation between NOAF and CVE, where NOAF preceded the first signs of neurological impairment in all patients with an ischemic stroke (44). Auffret et al., also found that chronic kidney disease (CKD) defined by an estimated glomerular filtration rate <60 ml/min·1.73 m^2, was an additional factor associated with an increased risk of 30-day CVE (7). Renal disease facilitates chronic inflammation, oxidative stress and atherosclerotic process with an increase in vascular calcification and endothelial dysfunction (46). In general, patients with renal impairment usually have an excess risk of stroke after adjusting for age and other cardiovascular risk factor (47).

PROGNOSIS VALUE ON MORTALITY, MORBIDITY AND NEUROCOGNITIVE FUNCTION OF CEREBROVASCULAR EVENTS AFTER TAVI

Patients with an early CVE (within 30-day) after TAVI had significantly higher mortality at 30-day and 1-year as compared to those without CVE, as shown in several studies (5, 9, 20, 21, 48–50). Eggebrecht et al. also reported a 3.5 times higher 30-day mortality after stroke in a large meta-analysis. One-month mortality was as high as 25% in patients with CVE compared to 7% in patients without CVE. Similarly, in a more recent meta-analysis of 29,034 patients, mortality was six-fold higher in patients with stroke (20). Short and long term mortality risk is incremental according to the severity of the CVE, being significantly higher with major stroke (OR 7.43; 95% CI, 2.45–22.53; $p = 0.001$, and HR 1.75; 95% CI, 1.01–3.04; $p = 0.043$ respectively) (**Figure 5**).

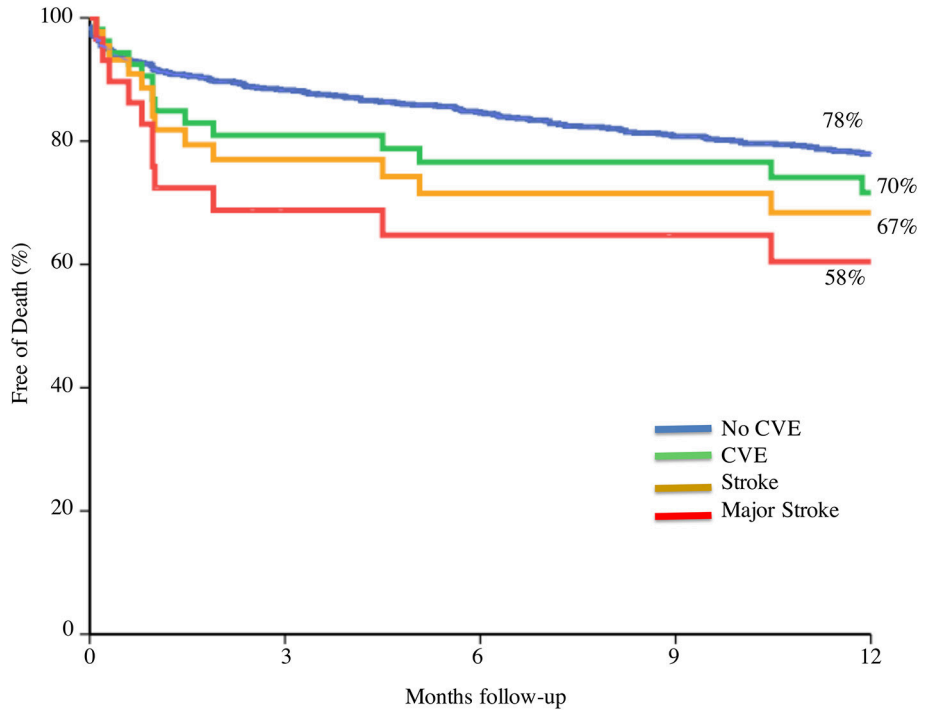

FIGURE 5 | Prognosis value on mortality according to cerebrovascular event severity. CVE, cerebrovascular events. Adapted from Nombela-Franco et al. (5).

In addition, stroke is probably the most feared complication (even more than death) reported by patients (51). Coylewright et al. described that the majority of patients undergoing TAVI wanted to maintain independence and be able to participate in daily hobbies, and only 7% of the patients stated that their main goal was to stay alive after the procedure. Importantly, the total proportion of patients with a permanent disability (modified Rankin scale of 2–5) at 30-day is around 50% of patients with CVE (5, 48). This highlights the impact of major stroke, not only in mortality, but also in patients' quality of life.

Cognitive Function and Cerebral Lesions

As previously commented, new cerebral silent lesions are found in a high (∼75%) percentage of patients undergoing TAVI, and cerebral embolization is almost ubiquitous in studies with filters embolic protection devices. The Rotterdam Scan Study evaluated the presence of silent cerebral infarction in a group of healthy elderly patients, demonstrating 3 times higher risk of stroke, greater decline in cognitive functions and 2 times more risk of dementia after a follow-up of almost 4 years (52, 53). In addition, in SAVR patients, it has been found an association between new cerebral lesions in DWI-MRI studies and cognitive deterioration during follow-up (54). However, the impact of these silent cerebral emboli and its relationship with cognitive deterioration after TAVI is under debate. In one study (n = 111), neurocognitive function declined in 5.4% of patients after TAVI (55) but new cerebral lesions were not associated with cognitive impairment. In a study of 44 consecutive patients with systematic baseline and serial neurologic and cognitive assessments combined with post-procedure DWI-MRI imaging, brain lesions were detected in 94% of the patients (56). Neurologic impairment, assessed by a worsening in the National Institutes of Health Stroke Scale (NIHSS), was detected in 21 and 11% of patients, at discharge and 30-day, respectively, and it was slightly higher in patients with cerebral lesions (23 vs. 15%). In addition, cognitive decline evaluated by the Montreal Cognitive Assessment was identified in 33 and 41% of patients at discharge and 30-day, respectively. However, many studies, failed to find an association between new cerebral lesions post-TAVI and cognitive impairment (57, 58). In more recent studies the volume of these new cerebral lesions had a weak, although statistical significant, correlation with neurocognitive changes (31). These discrepancies across studies could be explained due to the lack of validated models to assess neurocognitive function in TAVI candidates, a certain degree of cognitive dysfunction pre-procedural in some patients and the high prevalence of inter and intra-observer variability for these tests.

Several studies have analyzed the global impact of cognitive function after TAVI, independently of the presence of cerebral lesions. Schoenenberger et al. (n = 229) showed in a prospective analysis that cognitive function, assessed by the Mini-mental State Examination, worsened in 12.7% (n = 29) of patients. Interestingly among the patients with cognitive impairment before the procedure, TAVI was related to an improvement in the cognitive function in 37.5% (n = 18). Baseline smaller aortic valve areas were lower in patients who cognitively improved, suggesting a greater hemodynamic benefit in those

patients (59). Another study evaluated changes of the Montreal Cognitive Assessment score with an improvement at the early stage and remained stable at 1-year (60). This global improvement was more pronounced among the 40% of patients with baseline cognitive impairment. However, early decline in some complex cognitive functions was also observed in 26%, persisting at 1 year in 10% of the patients. Thus, long-term follow up studies are needed to clarify the consequences of this nearly universal cerebral embolism imaging finding post TAVI in regards to neurocognitive impairment and vascular dementia, especially in younger patients with longer life expectancy.

PREVENTION STRATEGIES

As previously commented, the majority of CVE following TAVI have an embolic origin. The strategy to obtain, at least a theoretical reduction of the CVE rate, is: (1) to decrease thrombus formation and debris embolization, and (2) once they have been formed or embolized, to avoid them reaching cerebral vasculature by using mechanical barriers such as embolic protection device (EPD). Regarding the first objective improving device performance and procedural technique (less damage of the aortic wall, less traumatic valve crossing and avoiding multiple recaptures and balloon pre and post-dilation) could lead to a significant reduction of the amount of debris. Another important factor is the antithrombotic therapy before, during and after the procedure.

ANTITHROMBOTIC THERAPY

Antithrombotic treatment in patients undergoing TAVI is currently one of the most important research scenarios in the TAVI field, with several large multicenter randomized clinical trials already ongoing. However, in the initial phase of the TAVI, and until definitive trials results, antithrombotic treatment has been recommended on an empirical basis. Guidelines do not recommend any treatment before the procedure (61, 62) and pre-procedural aspirin plus a loading dose of 300–600 mg of clopidogrel has been adopted from randomized clinical trials in patients undergoing transfemoral TAVI (1, 2, 19). Pre-procedural loading dose of clopidogrel is avoided in non-transfemoral cases. Most of the centers achieved intraprocedural anticoagulation with full-dose of intravenous heparin, although one fourth of the centers do not performed activated clotting time (ACT) measurement to guide anticoagulation (63). One non-randomized retrospective study compared the efficacy and safety of the standard bolus of heparin based on body weight vs. an adjusted dose of heparin guided by a baseline ACT. Interestingly, the ACT-guided group received lower total dose of heparin with no differences in terms of stroke and lower rate of major and life-threatening bleeding (64). The BRAVO trial reported that bivalirudin did not reduce the rates of major bleeding within 48 h or net adverse cardiovascular events at 30 days (65). In the MRI-substudy of the BRAVO trial, new post-procedural cerebral lesions and large lesions (volume $\geq$1,000 mm^3) were also similar in both groups (66). Thus, bivalirudin was considered an alternative procedural anticoagulant in patients unable to receive heparin.

Regarding the antiplatelet treatment after the procedure, dual antiplatelet therapy (DAPT) is the most common antithrombotic treatment prescribed at hospital discharge in patients without AF, but with a high variability of the duration across centers (63), ranging from 1 to 12 months in most centers. Although a minority of centers initially adopted a single antiplatelet treatment, there are 3 small randomized trials suggesting no benefit of DAPT in terms of ischemic events with a higher rate of bleeding complications (67, 68). The CLOE and Popular TAVI trials will determine the efficacy and safety of a less aggressive antiplatelet treatment in patients undergoing TAVI (**Figure 6**). On the other hand, valve thrombosis and its relation to CVE (69), has raised the question whether a more aggressive antithrombotic treatment should be the preferred option in the first months after the procedure. Several on-going trials would help to clarify this issue (**Figure 6**).

In patients with AF, the variability in the antithrombotic treatment across centers is even greater. In an international survey with 250 centers, warfarin alone or combined with either ASA or clopidogrel were used in 28, 39, and 26% of the centers, respectively (63). Triple therapy (warfarin+DAPT, 4.5%) or left atrial appendage closure (0.5%) was marginally used as the standard care in patients with AF undergoing TAVI. Two observational studies showed no differences in terms of stroke, but lower bleeding rates in patients treated with warfarin alone compared to a combination of warfarin with one antiplatelet drug, especially with ASA (70, 71). Another interesting alternative in patients with AF is to mechanically close the left atrial appendage in order to reduce bleeding events without jeopardizing stroke protection (72). The impact of non-vitamin K antagonist oral anticoagulants and left atrial appendage closure would be tested in future randomized trials (**Figure 6**).

EMBOLIC PROTECTION DEVICES

Embolic protection devices have emerged as a potential solution to decrease cerebral embolization and the associated neurological effects. To date, 4 types of EPD have been studied, with differences mainly in terms of design and access routes (**Figure 7**, **Table 3**). Deflectors, represented by the Embrella (Edwards Lifesciences, Irvine, CA) and TriGuard (Keystone Heart Ltd, Caesarea, Israel) devices are released along the external curvature of the aortic arch providing coverage to the innominate artery, common left carotid and in the case of the Triguard also to the left subclavian artery rejecting the embolized material toward the descending aorta. On the other hand, there are filter-type systems represented by Sentinel (Claret Medical Inc., Santa Rosa, CA) and Embol-X (Edwards Lifesciences, Irvine, CA). The first contains filters that are released in the brachiocephalic trunk and the left common carotid, and the second is positioned in the ascending aorta being deployed before

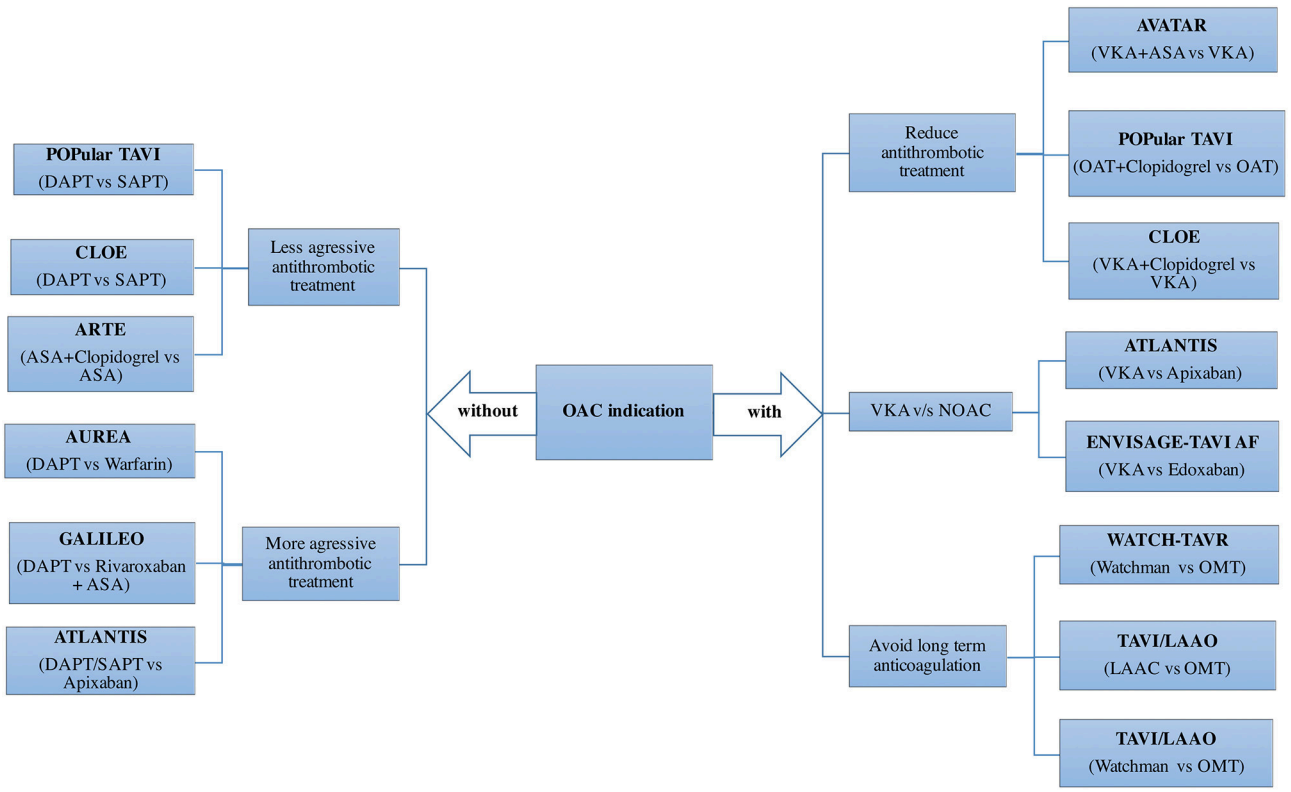

FIGURE 6 | Adjunctive antithrombotic treatment after TAVI: Randomized clinical trials**.** ASA, acetylsalicylic acid; DAPT, dual antiplatelet therapy; LAAO, left atrial appendage occlusion; NOAC, novel oral anticoagulant; OAC, oral anticoagulant; OMT, optimal medical treatment; SAPT, single antiplatelet therapy; TAVI, transcatheter aortic valve implantation; VKA, vitamin K antagonists.

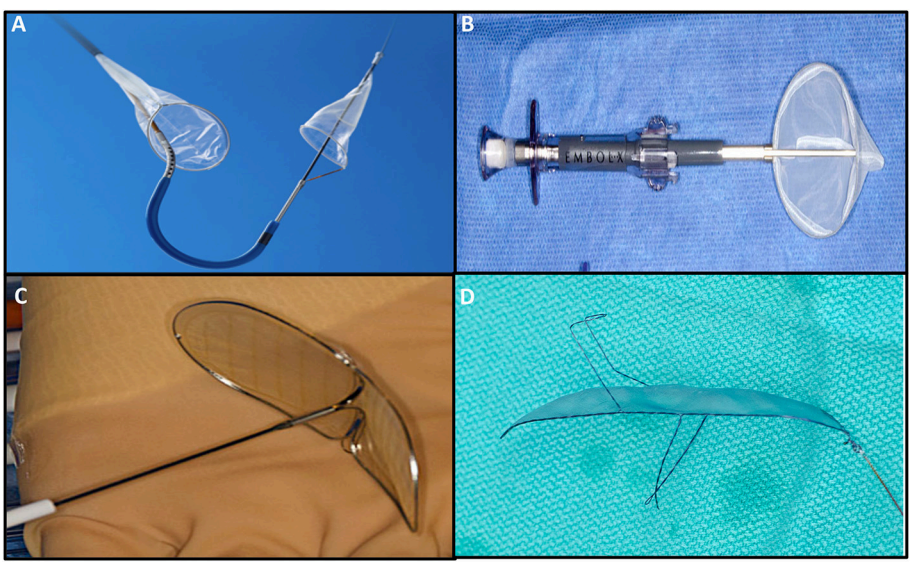

FIGURE 7 | Cerebral embolic protection devices: **(A)** Sentinel (Claret Medical Inc., Santa Rosa, CA; **(B)** Embol-X (Edwards Lifesciences, Irvine, CA); **(C)** Embrella (Edwards Lifesciences, Irvine, CA); **(D)** TriGuard (Keystone Heart Ltd, Caesarea, Israel).

TABLE 3 | Main characteristics of the embolic protection devices.

Device	Manufacturer	Design	access	Delivery	deployment
Embrella	Edwards Lifesciences, Irvine, CA	Deflector	Radial/Brachial	6F	Aortic arch
TriGuard	Keystone Heart Ltd, Caesarea, Israel	Deflector	Femoral	9F	Aortic arch
Sentinel	Claret Medical Inc., Santa Rosa, CA	Filter	Radial/Brachial	6F	1 filter to brachiocephalic trunk and 1 filter to left common carotid
Embol-X	Edwards Lifesciences, Irvine, CA	Filter	Direct aortic	14F	Ascending aorta

Adapted from Steinvil et al. (73).

aortic puncture for transaortic TAVI, providing a full cerebral coverage (73).

Randomized Clinical Trials

The current available evidence in relation to EPD are constituted by a series of observational and 5 randomized studies (31, 58, 74–76), which have been also combined in several meta-analysis (77–80). Main limitations of randomized trials have been the relatively low number of patients included and using surrogate events such as the number and volume of cerebral lesions as the primary endpoint, instead of clinical neurological events.

The Embrella device was evaluated in the prospective non-randomized PROTAVI-C trial ($n = 52$) by DW-MRI (at baseline, 7 and 30 days) and procedural transcranial Doppler. Its implantation was associated with higher total number of HITS than the control group ($p < 0.001$). Both groups presented new brain lesions (100% of patients in each group), however the intervention group showed a lower volume of ischemic lesions compared to the control group ($p = 0.003$) (81).

The DEFLECT III multicenter randomized trial ($n = 85$) evaluated the TriGuard system, with neurocognitive assessment and DW-MRI at baseline, pre-discharge and 30-day. The safety endpoint (death, stroke, major bleeding, acute kidney injury stage 2 or 3, major vascular complication) occurred in 21.7% of the intervention group and in 30.8% of the control group ($p = 0.34$). Patients with a full cerebral coverage (89% in the intervention group), had a greater freedom from new ischemic brain lesions at 30-day (26.9 vs. 11.5%) and lower neurological deficit in NIHSS scale (3.1 vs. 15.4%; $p = 0.16$) (74).

There is very limited evidence in trans-aortic TAVI with the EMBOL-X device in a single randomized trial that included 30 patients (14 patients with filter). In the intervention group, a nonsignificant decrease in new brain lesions (57 vs. 69%; $p = 0.70$) and volume lesions (88 ± 60 mm^3 vs. 168 ± 217 mm^3; $p = 0.27$) in DW-MRI at 7 days post-procedure was found (75).

The MISTRAL-C multicenter randomized trial ($n = 65$) compared the number of new brain lesions evaluated by DW-MRI and neurocognitive function before and after TAVI (average 5 days) using the Claret Sentinel device. The primary endpoint (percentage of patients with new brain lesions) was not reduced in the device group (73 vs. 87%; $p = 0.31$) with a tendency to lower volume of new brain lesions (95 vs. 197 mm^3; $p = 0.171$). A significant reduction in the number of patients with multiple brain lesions (20 vs. 0%; $p = 0.03$) and lower cognitive impairment (4 vs. 27%; $p = 0.017$) was observed. Regarding study limitations, images and neurocognitive tests were obtained in only 57 and 80% of patients with and without EP, respectively (76).

The CLEAN-TAVI randomized trial ($n = 100$) with the Claret Sentinel device, was the first trial to show a positive result in the primary end-point (new brain lesions evaluated by DW-MRI at 2 days after the intervention). The filter group was associated with a significant reduction of new cerebral lesions in the protected territories (4 vs. 10, $p < 0.001$) and in the entire brain (8 vs. 16, $p = 0.002$). Volume of these lesions was also lower in the filter group (466 vs. 800 mm^3; $p = 0.02$), with a total of 5 minor strokes in each treatment arm (54–58, 68–70).

The SENTINEL study ($n = 363$) is the largest randomized study with EPD. The device was successfully implanted in all the patients, and obtained almost universally embolic material, mostly non-thrombotic from the arterial walls. Fluoroscopic time was longer in the device group with a non-inferior rate of the primary safety end-point (7.3% vs. 9.9, $p = 0.41$). Primary efficacy end-point (volume of new cerebral lesions) was similar in both groups (102.8 vs. 178 mm^3; $p = 0.33$) in the DW-MRI performed between 2 and 7 days after the procedure. The stroke rate was numerically lower in the device group (5.6 vs. 9.1%, $p = 0.25$) (31).

Several meta-analyses have combined the results of the observational and randomized studies. Surrogate end-point such as the number and volume of new brain lesions seemed to be reduced in favor of the EPD (77, 80), although differences in the global rate of stroke or death is more controversial. While, some meta-analyses did not show any an statistical differences, other showed a reduction in the combined event of death or stroke using EPD, performing an analysis by the fixed-effects method (79). Finally, a recent single-center observational study, included 280 consecutive patients treated with the Sentinel device and compared them to a historical cohort of patients ($n = 522$) treated in an identical setting but without a filter. After a propensity score matching ($n = 280$ in each group), patients in the filter group had a significant reduction of the stroke rate (1.4 vs. 4.6%, $p = 0.03$), or a combination of death or stroke (2.1 vs. 6.8%, $p = 0.01$) (82). The procedure without an EPD was the only independent predictor ($p = 0.04$) for the occurrence of stroke within 7 days.

Cost Effectiveness Analysis

A stroke can have an unpredictable and devastating impact, not only in terms of mortality but also in terms of its sequelae (50% permanent disability). It is estimated that more than half of

patients with a clinical stroke will be unable to return to work, and 1 in 3 patients will have serious financial problems (83–85). The economic and social impact of presenting a stroke after the implantation of TAVI is a topic to consider. It is estimated that during the index hospitalization, it can increase the costs of the initial hospitalization ∼$25,000, with an average of 7 additional days of hospital stay compared to patients who do not have a stroke (86). This cost can be even higher in patients discharged with a moderate disability, in whom the annual health costs can be increased by up to $60,000 (87). According to meta-analyses from Giustino et al. 22 patients have to be treated to reduce one stroke or death using EPD (79). The Sentinel device has a cost around to $2,800, therefore, making a quick and simplified calculation, a total of $61,600 has to be spent to prevent one stroke or death, a value that may be justifiable given the negative physical, emotional and economic impact of stroke. However proper studies about the cost-effectiveness of EPD are needed to determine the validity of this rough calculation.

CONCLUSIONS

Cerebrovascular events after TAVI had a multifactorial etiology with an incidence about ∼3–4%. This complication has clearly a significant impact on patient's morbidity and mortality, mainly during its acute and subacute phase. Despite the fact that its incidence has slightly decreased in the modern TAVI era with greater knowledge and new technologies, it seems that cerebral embolization is ubiquitous after TAVI, proven by HITS during the procedure; new cerebral lesions on DW-MRI studies and debris captured in cerebral filters devices. The clinical impact of cerebral embolization is still under discussion. The currently available trials with EPD have not been designed to detect clinical CVE and they have assessed neurological damage by surrogate end-points such as rate or volume of new brain lesions. However, the expansion of the technique to younger and low risk patients will force us to look for new and better tools to avoid cerebral embolization.

AUTHOR CONTRIBUTIONS

Each author has contributed to this work as follows: GA and LN-F: conception and design, drafting and revising of manuscript, final approval of the manuscript submitted; GT-C: critical review of the manuscript for important intellectual content; final approval of the manuscript submitted.

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Moderate Aortic Stenosis and Reduced Left Ventricular Ejection Fraction: Current Evidence and Challenges Ahead

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Moderate aortic stenosis (AS) and reduced left ventricular ejection fraction (LVEF) constitute a clinical entity that has been proposed as a therapeutic target for transcatheter aortic valve replacement (TAVR). It is defined by a mean trans-aortic gradient between 20 and 40 mmHg and an aortic valve area between 1.0 and 1.5 cm^2 in patients with LVEF < 50%. Retrospective data suggests a prevalence of 0.8% among patients referred for echocardiographic assessment. These patients are younger and show a higher frequency of previous myocardial infarction than those with severe AS randomized to TAVR in recent trials. In two retrospective studies including patients with moderate AS and reduced LVEF, a one-year mortality rate of 9 and 32% was reported, the latter in patients treated with medical therapy only during follow-up. Echocardiographic diagnosis of moderate AS poses challenges as current guidelines are directed to determine severe AS, and different presentations of moderate and mild AS have been generally neglected. Thus, the nomenclature would need to be revised and a description of possible scenarios is provided in this review. Dobutamine stress echocardiography and computed tomography are promising complementary tools. Likewise, a standardized clinical pathway is needed, in which a high level of suspicion and a low threshold for referral to a heart valve center is warranted. The Transcatheter Aortic Valve Replacement to UNload the Left ventricle in patients with Advanced heart failure (TAVR UNLOAD) trial (NCT02661451) is exploring whether TAVR would improve outcomes in patients receiving optimal heart failure therapy.

Keywords: moderate aortic stenosis, left ventricular ejection fraction, transcatheter aortic valve replacement, surgical aortic valve replacement, structural heart disease, TAVR UNLOAD trial

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INTRODUCTION

Severe aortic stenosis (AS) is the most common indication for valvular interventions in adults. It affects 3% of patients after 75 years of age (1). Earlier stages of the disease have been typically disregarded as targets for aortic valve replacement (AVR) given an unfavorable risk-benefit balance. Specifically, due to the relatively high rates of peri-procedural death or stroke with AVR, and

the lack of evidence of a significant increased risk of events in patients with mild to moderate AS treated medically (2). Better characterization of high risk populations among patients with moderate AS together with advancements of transcatheter aortic valve replacement would identify a niche population potentially benefiting from an earlier intervention (3–5).

In patients with moderate AS and concomitant reduced left ventricular ejection fraction (LVEF < 50%), death or heart failure hospitalization was observed in half of them at 4 years of follow-up (5). It is noteworthy that pathophysiologically LVEF reduction in this population is generally not attributed to AS, but rather to myocardial damage due to ischemic conditions or non-ischemic non-valvular cardiomyopathies. In this setting moderate AS may contribute significantly to the overall ventricular afterload, and contribute to systolic and diastolic dysfunctions and ultimately to a progressive symptomatic status (6, 7). In patients with severe AS and conservative treatment, reduced LVEF has been associated with increased rates of death and heart failure hospitalizations [hazard ratio (HR), 95% confidence interval (CI): 1.82 [1.44–2.28], $p < 0.001$, when compared with LVEF > 70% by the Teichholz or Simpson method] (8). In patients undergoing AVR, reduced EF has also emerged as an independent predictor of mortality at 5 years of follow-up, with an increase of 12% mortality [HR (95% CI) = 0.88 (0.83–0.94), $p < 0.001$] for every 10% decrease in LVEF (9). Among patients with moderate AS and reduced LVEF, male sex, New York Heart Association (NYHA) functional class III and IV, and the peak aortic jet velocity obtained with Doppler ultrasound emerged as independent predictors of worse outcome (5). Advanced heart failure symptoms (NYHA III or IV = 58%, NYHA II = 31%, and NYHA I = 23%, at 2 years) as well as being admitted at the time of diagnosis (60 vs. 34% at 2 years, $p < 0.001$), are associated with increased rate of death, AVR or heart failure hospitalizations (5).

This review summarizes the frequency of concomitant reduced LVEF and moderate AS, its natural history, differential patient characteristics when compared with patients with severe AS, diagnostic challenges, and further discusses the rationale of the ongoing Transcatheter Aortic Valve Replacement to UNload the Left ventricle in patients with ADvanced heart failure (TAVR UNLOAD) trial (NCT02661451) (10).

Epidemiology and Natural History

Reduced LVEF is an established predictor of adverse events including heart failure hospitalizations and death, and its severity determines the treatment alternatives for a patient (11). One to Two Percent of adults live with the diagnosis of heart failure, with a lifetime probability of 1:3 to receive this diagnosis after the age of 55 years (11) Reduced LVEF accompanies this clinical syndrome in approximately 50% of cases. Ambulatory patients with symptomatic reduced LVEF have a one year risk of death of 7% and hospitalizations of 32%; whereas the rates increase to 17 and 44% after one hospitalization (11). Less is known for moderate aortic stenosis, since it is not a target of medical therapy, as several attempts to decelerate the progression of disease have failed (12–14). Moreover, surgical aortic valve replacement (SAVR) is considered only when moderate AS is diagnosed as a bystander in a patient undergoing an open heart surgery for other conditions (15). Consequently, in routine clinical practice, this condition is not prospectively ascertained and streamlined for treatment, leading to difficulties in determining its frequency.

An analysis of the Duke echocardiographic database ($N = 132{,}804$) showed that 1.2% of patients would qualify for the diagnosis of moderate or severe AS and reduced LVEF, from which 0.8% had moderate and 0.4% had severe AS (16). In an effort of extrapolation, for a center performing 5,000 echocardiograms per year, this would represent the diagnosis of moderate AS and reduced LVEF in 40 patients per year. More importantly, one third of patients with moderate AS included in the aforementioned analysis did not survive more than one year on medical treatment only (16). More optimistic results were observed in a multi-center retrospective analysis, which showed a one-year mortality rate of 9% in patients with moderate AS and reduced LVEF, partially explained by a 13% rate of AVR at one-year (5). Both studies ought to be contrasted with the 1.4% rate of one-year mortality observed in the Simvastatin and Ezetimibe in Aortic Stenosis (SEAS) trial, which randomized 1,873 patients with *mild-to-moderate* AS to an intensive cholesterol lowering strategy (13). Contrary to the previous higher risk cohorts, the SEAS trial included *asymptomatic* patients with no atherosclerotic conditions, diabetes mellitus, or indication of lipid-lowering therapy. Virtually all patients had LVEF above 50 and 30% had an aortic valve area (AVA) above 1.5 cm^2, consistent with mild AS. This comparison highlights the impact of LVEF and AS severity on clinical outcomes.

The rate of progression of AS has been systemically assessed in the SEAS and other randomized trials investigating the impact of lipid-lowering therapies on the natural history of the disease (12–14). Despite a significant reduction of low-density lipoprotein cholesterol, the disease progression remained comparable among study groups. A meta-analysis of statin trials reported an annual increase in mean trans-aortic gradient of 2.8 ± 3.0 mmHg, and a decrease in aortic valve area of 0.04 ± 0.27 cm^2 (17). Uncertainty remains on individual factors that may accelerate the progression of the disease (e.g., smoking, serum creatinine), and individual variation has been described with mean rates of progression as high as an annual increase of 7 mmHg in mean gradient and decrease of 0.1 cm^2 in AVA (18).

Supportive evidence of the detrimental role of increased trans-aortic gradients stems from research on prosthesis-patient mismatch (PPM) after SAVR. PPM is present when the AVA of the inserted valve is too small in relation to the body size of the patient, which generates higher than expected trans-aortic gradients (6). In a cohort of 2,576 patients who underwent SAVR, severe PPM defined as an indexed AVA (AVAi) ≤ 0.65 cm^2/m^2, was associated with increased late overall and cardiovascular mortality, after adjustment for other known risk factors (6). Importantly, moderate PPM (AVAi > 0.65 but ≤ 0.85 cm^2/m^2) was also associated with increased mortality {HR [95% CI] = 1.21 [1.03–1.41], $p = 0.01$} in patients with reduced LVEF (<50%) only (6). Pathophysiologically, this suggests that patients with impaired systolic function suffer from persistent higher-than-normal afterload. Furthermore, recent evidence suggests that in patients with AS, the decline in LVEF starts before AS is severe

and accelerates after AVA reaches 1.2 cm^2 (19). LVEF < 60% in the presence of moderate AS has been suggested as a predictor of further LVEF deterioration (19).

Hypertension is highly prevalent in patients with moderate AS and reduced LVEF (5). Although not a direct component of the disease, it determines the arterial component of the afterload. The sum of the valvular and arterial components of the afterload represents the valvulo-arterial impedance, (20) which is a strong predictor of mortality in patients in different stages of AS, ranging from moderate to severe asymptomatic patients up to post-TAVR patients (21–23). In elderly patients who typically have a reduced arterial compliance, means to reduce the arterial component of the overall LV afterload with medical therapy i.e., anti-hypertensive drugs, are limited. In this clinical setting AVR for even moderate AS may eventually be the only option to further reduce the valvulo-arterial impedance and improve outcome (10).

Aortic Valve Replacement

Current clinical practice guidelines recommend SAVR in patients with moderate AS undergoing CABG or surgery of the ascending aorta or of another valve (class of recommendation IIa and a level of evidence C) (15, 24) Moreover, Patients undergoing CABG before 70 years of age with a peak gradient above 30 mmHg and a documented yearly progression of 5 mmHg, may benefit from SAVR (2). These represent the only two mentions of moderate aortic stenosis in the ESC/EACTS guidelines for management of valvular heart disease, and are largely supported by retrospective data (15). Such interventions are referred to as "prophylactic SAVR," aiming to avoid a second open-heart procedure. A post-CABG SAVR procedure is exposed to the risk of damaging patent grafts including the internal mammary arteries; is technically challenging due to calcified aortic arches and scarring of the mediastinum; and procedural mortality has been reported in up to 16% of patients (25, 26) In patients with prior CABG that require AVR, TAVR is progressively replacing SAVR (26). In a propensity-matched analysis including 3,880 record in each group, TAVR and SAVR showed similar in-hospital mortality (2.3 vs. 2.4%, $p = 0.71$) but TAVR was associated with lower incidence of procedural complications including myocardial infarction (1.5% vs. 3.4%, $p < 0.001$), stroke (1.4 vs. 2.7%, $p < 0.001$), bleeding (10.6 vs. 24.6%, $p < 0.001$), and acute kidney injury (16.2 vs. 19.3%, $p < 0.001$). Consequently, the rationale of exposing the patient to a prophylactic SAVR in order to avoid a second open-heart surgery is currently challenged (26).

The concept of "therapeutic" TAVR in patients with moderate AS is evolving (10). In a retrospective analysis of 1,090 patients with moderate AS and reduced LVEF, SAVR within 90 days vs. no intervention, was associated with a 41% reduction of all-cause mortality after a median follow-up time of 1.2 years (16). Moreover, this benefit remained in a sub-group of patients with reduced LVEF without coronary artery disease (16).

Patient Characteristics

Patients with moderate AS and reduced LVEF are younger and show a higher frequency of prior acute myocardial infarction than patients with severe AS typically included in randomized trials (see **Table 1**) (3, 5, 16, 29, 32). Importantly, prospective randomized trials comparing TAVR vs. SAVR in bicuspid aortic valve disease may provide guidance on the preferred approach for such sub-group, which has been largely excluded from TAVR studies. Post-TAVR incidence of moderate to severe paravalvular leak and new pacemaker implantation has been more frequently observed in patients with bicuspid anatomy (33). Furthermore, it remains unclear whether there is a preferred device, being a balloon-expandable, self-expandable, or mechanically-expanded transcatheter heart valve, when treating patients in potential need for a re-do procedure due to an expected longer life expectancy (34, 35).

Challenges

Three main challenges exist for promoting "therapeutic" TAVR in patients with moderate AS and reduced LVEF: (1) better understanding of the echocardiographic diagnosis of moderate AS, (2) defining a clinical pathway to identify patients, and (3) evidence from randomized trials supporting TAVR in this population.

Echocardiographic Diagnosis of Moderate Aortic Stenosis

Moderate AS is characterized by a mean trans-aortic gradient between 20 and 40 mmHg and an AVA between 1.0 and 1.5 cm^2. Other findings include a peak velocity of the trans-aortic flow between 3.0 and 4.0 m/s, a velocity ratio between 0.25 and 0.50, and an indexed AVA by body surface area between 0.60 and 0.85 cm^2/m^2 (36). When findings are concordant (e.g., mean gradient between 20 and 40 mmHg and AVA between 1.0 and 1.5 cm^2), the diagnosis is clear-cut. However, discordant findings are frequently observed (e.g., AVA < 1.0 cm^2 and mean gradient between 20 and 40 mmHg; or, AVA between 1.0 and 1.5 cm^2 and mean gradient < 20 mmHg), especially in the context of reduced LVEF.

In **Figure 1** we summarize the different scenarios that could be observed when evaluating a patient with AS. Our understanding of severe AS has increased significantly in the last two decades, and the most recent classification of patients includes sub-groups based on gradient (low-gradient: mean gradient < 40), ejection fraction (abnormal <50%) and flow status (low flow < 35 ml/m^2) (36). All flow-gradient patterns, stratified by LVEF, have been reported in patients with severe AS (36–38). When findings for severe AS are discordant in patients with reduced LVEF (AVA < 1 cm^2 and mean gradient < 40 mmHg) patients are assessed with a low-dose dobutamine stress echocardiogram (DSE) to differentiate among "true severe" AS vs. "pseudo-severe" AS (e.g., moderate AS) (36). Likewise, the difference between mild AS and moderate AS would need to be established through a DSE if therapeutically relevant. For descriptive purposes, **Figure 1** creates AS groups based on the following parameters: (1) AS severity is concordant if the AVA and the mean gradient match the same category (i.e., mild, moderate or severe), and if not, AS severity is defined as discordant; (2) In this description, the gradient is not defined as "high" or "low" gradient, but rather in relationship with the category it applies (i.e., mild, moderate, or severe); (3) sub-groups can be further classed

TABLE 1 | Clinical characteristics in patients with moderate or severe aortic stenosis.

	Moderate AS and reduced LVEF	Moderate AS and reduced LVEF	Severe AS and reduced LVEF	Severe AS inoperable	Severe AS extreme risk	Severe AS high risk	Severe AS high risk	Severe AS intermediate risk	Severe AS intermediate risk	Severe AS all-comers
Age, years	73	73	76	83	83	84	83	82	80	79
Female gender, %	25	31	40	54	52	42	46	46	42	46
Hypertension, %	74	68	67	NA	90	NA	95	NA	93	71
Diabetes, %	38	39	32	NA	42	NA	35	38	34	18
Peripheral vascular disease, %	20	17	14	30	35	43	42	28	31	4
Cerebrovascular disease, %	43	23	21	27	23	29	26	32	13	17
Atrial fibrillation, %	NA	32	32	33	47	41	41	31	28	28
Chronic pulmonary disease, %	25	11	6	NA	NA	43	NA	32	NA	12
Prior myocardial infarction, %	52	39	35	19	31	27	26	18	14	6
Prior PCI, %	36	13	10	31	37	34	34	27	21	8
Prior CABG, %	28	22	19	37	40	43	30	24	16	NA
Ischemic heart disease, %	48	63	64	68	82	75	75	69	63	NA
Patients analyzed	305	403	935	179*	489	348*	394*	1011*	879*	145*
References	van Gils et al. (5)	Samad et al. (16)	Samad et al. (16)	Leon et al. (27)	Popma et al. (28)	Smith et al. (29)	Adams et al. (30)	Leon et al. (3)	Reardon et al. (31)	Thyregod et al. (32)
Study type	Retrospective	Retrospective	Retrospective	RCT	Prospective	RCT	RCT	RCT	RCT	RCT

**Includes subjects randomized to transcatheter aortic valve replacement. AS, aortic stenosis; LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft surgery; NA, not available; RCT, randomized controlled trial.*

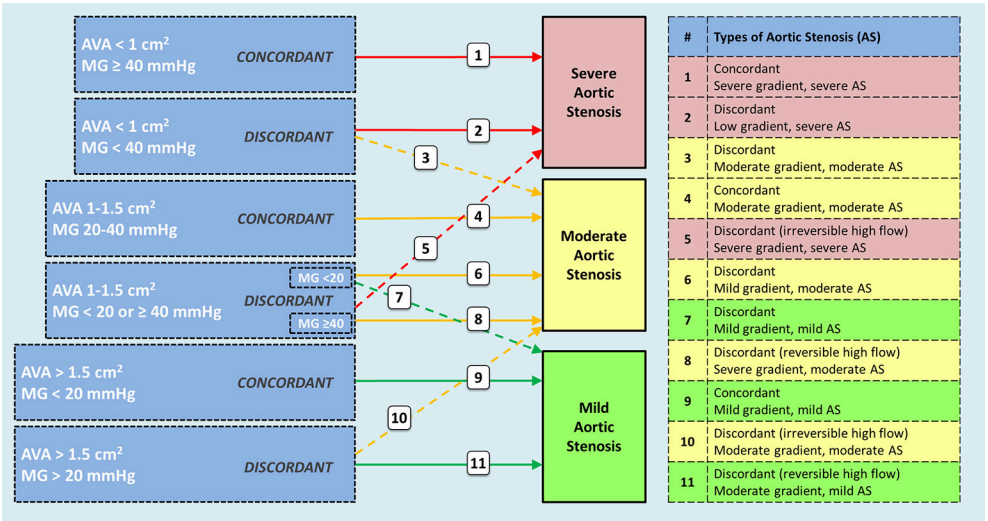

FIGURE 1 | Possible scenarios observed in patients with aortic stenosis including sub-groups according to ejection fraction and flow patterns. Concordant findings between aortic valve area and transvalvular gradient do not pose diagnostic challenges. However, discordant findings require additional tests to define the appropriate category (e.g., dobutamine stress echo, CT-derived aortic valve calcium score, 3D-echo or CT-derived left ventricular outflow tract area). Interpretation of findings are better stablished for categories 2 and 3 (true severe vs. pseudosevere aortic stenosis); however, knowledge is evolving for categories 6 and 7. Patient with high transvalvular flow should be classified after determining if the mechanism of high flow is reversible (e.g., fever, anemia) or irreversible (e.g., concomitant aortic regurgitation). Categories 8 and 11 correspond to reversible causes, and 5 and 10 to irreversible causes. Patients with aortic stenosis can be further categorized based on ejection fraction and flow status. AVA = aortic valve area; MG = mean gradient.

based on LVEF (above or below 50%) and flow status (above or below 35 ml/m^2). With this description, "pseudo-severe AS" would be referred to as "discordant moderate-gradient moderate AS." It is "discordant" because initially the AVA would be compatible with severe AS (<1 cm^2) but the gradient with moderate AS (<40 mmHg). All initially discordant cases need further evaluation in order to be properly classified, especially with concomitant reduced LVEF: (1) make sure that there are no technical pitfalls in the measurement of the mean gradient (e.g., misalignment of the Doppler signal with the direction of the flow, inadvertent recording of mitral regurgitation) or the AVA (e.g., underestimation of the left ventricular outflow tract diameter); (2) if LVEF is the factor that could potentially influence the gradient and aortic valve opening, a low-dose DSE is indicated, starting at 2.5 or 5 μg/kg/min with a progressive increase in the infusion every 3–5 min to a maximum dose of 10–20 μg/kg/min; (36) (3) in the absence of contractile or flow-reserve, the computed tomography aortic valve calcium score helps to determine the likelihood of having severe AS (e.g., likely if ≥ 2000 in men, and if ≥ 1200 in women) (36). Currently, there is insufficient data to differentiate mild from moderate AS based on calcium score; (4) increased gradient due to high trans-valvular flow should be considered as an option in patients with discordant findings. When causes are reversible (e.g., fever or anemia), patients should be reassessed after correcting the causes. When causes are irreversible (e.g., significant aortic regurgitation), patients should be categorized according to the gradient severity and treatment should be offered accordingly.

These concepts open a new era in the diagnosis of aortic stenosis, and registry data as well as retrospective analysis may help us clarify the need for an updated nomenclature, which would require a joint effort of cardiology societies.

Clinical Pathway for Moderate Aortic Stenosis and Reduced LVEF

Offering TAVR to patients with moderate AS and reduced LVEF would be a change of a clinical paradigm. Due to the currently non-existing treatment alternatives apart from established heart failure therapies, these patients do not fall into any specific clinical pathway. If these patients were to be offered TAVR, imaging will play a pivotal role. Patients with moderate AS and reduced LVEF may be referred within the same institution or through other referral institutions due to symptoms, physical exam (e.g., systolic murmur), or screening echocardiogram. Severity of AS in the context of reduced LVEF may need to be confirmed with a DSE (if initial findings are discordant). Moreover, once the diagnosis is confirmed technical plausibility of TAVR needs to be assessed by means of a pre-TAVR multi-slice computed tomography. Current evidence supports the use of transfemoral over non-transfemoral access for TAVR, given a lower rate of procedural complications (e.g., acute kidney injury, need for renal replacement therapy) and lower 1 year mortality (39, 40). Thus, a transfemoral approach should be considered as first option for this high risk population, commonly avoiding the need of general anesthesia. Most patients would have coronary artery disease, and a coronary angiogram would need to be included in the clinical work-up.

It is essential to refer potential candidates to experienced heart valve centers (15). A high grade of suspicion and low threshold for referral would be required from non-interventional

cardiologists and other specialties. Moreover, a systematic echocardiographic assessment of the AVA in all patients with at least mild AS gradient, would potentially help to identify patients with "discordant mild-gradient moderate AS," which would otherwise have been missed. Nevertheless, current evidence recommends watchful waiting and periodic echocardiographic follow-up in patients with moderate AS and reduced LVEF. This approach may significantly change if results of ongoing trials prove to be clinically meaningful.

TAVR UNLOAD Trial

The single most important requirement to promote TAVR as a therapeutic option in patients with moderate AS and reduced LVEF is to create confirmatory prospective evidence that this intervention is clinically meaningful (5, 6, 16). The Transcatheter Aortic Valve Replacement to UNload the Left ventricle in patients with Advanced heart failure (TAVR UNLOAD) trial (NCT02661451) is an international, multicenter, randomized, open-label, clinical trial comparing TAVR with the Edwards SAPIEN 3 Transcatheter Heart Valve in addition to optimal heart failure therapy (OHFT) vs. OHFT alone in patients with moderate AS and reduced LVEF (10). This trial is currently enrolling patients in The Netherlands, Canada, and the United States of America. Screening of patients includes echocardiographic eligibility assessment by an independent Core Laboratory, which centrally confirms the presence of moderate AS and reduced LVEF. Assessment may include a DSE. Importantly, written confirmation of OHFT is provided by a local heart failure specialist. Clinical, imaging, and procedural eligibility are confirmed by a Central Screening Committee before randomization. The primary endpoint, defined as the hierarchical occurrence of all-cause death, disabling stroke, hospitalizations related to HF, symptomatic aortic valve disease or non-disabling stroke, and the change in the Kansas City Cardiomyopathy Questionnaire, will be analyzed at 1 year. Changes in heart failure pharmacologic and device therapies will be monitored. Moreover, echocardiographic endpoints will be assessed up to 2 years. Findings may have a significant impact on the way we diagnose, refer and manage patients with AS.

CONCLUSION

Patients with moderate AS and reduced LVEF are exposed to a significant risk of clinical events including death. Indirect evidence suggests that aortic valve replacement may offer a clinically meaningful benefit. Incorporating this entity as a therapeutic target requires re-assessment of how we diagnose AS and improved strategies of referral. The TAVR UNLOAD trial is investigating whether TAVR could improve clinical outcomes including quality of life in this high risk population.

AUTHOR CONTRIBUTIONS

ES and NVM conceived the manuscript. ES wrote the first draft in collaboration with BR, MG, and NVM. All co-authors critically reviewed and approved the final manuscript.

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REVIEW
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The Role of Cerebral Embolic Protection Devices During Transcatheter Aortic Valve Replacement

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Transcatheter aortic valve replacement is the therapy of choice for patients with severe aortic stenosis who have prohibitive or high surgical risk. However, the benefit of TAVR is attenuated by the occurrence of major disabling stroke which is associated with increased mortality and early-reduced quality of life**.** Despite advances in TAVR technology, stroke remains a serious complication that is associated with significant negative outcomes. The majority of these occur in the acute phase following TAVR where cerebral embolic events are frequent. Cerebral embolic protection devices (CEPD) have been developed to minimize the risk of peri-procedural ischemic stroke during TAVR. CEPD have the potential to reduce intraprocedural burden of new silent ischemic injury. In this review we outline the etiology and incidence of stroke in TAVR population, and systematically review current evidence for cerebral embolic protection devices.

Keywords: stroke, embolic protection devices, aortic stenosis, TAVI, TAVR

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INTRODUCTION

Aortic stenosis (AS) is the most common valvular pathology in the elderly and its prevalence is expected to increase rapidly over the next decade due to an aging population (1, 2). Transcatheter aortic valve replacement (TAVR) has revolutionized the treatment of symptomatic AS with over 300,000 TAVR procedures performed worldwide, to-date. This resulted following a number of registries (3, 4) and randomized controlled trials (5–11) demonstrating mortality benefits of TAVR in inoperable and high-risk surgical patients. However, the benefit of TAVR is attenuated by the occurrence of major disabling stroke which is associated with increased mortality and in the short term reduced quality of life. Despite the evolution in TAVR technology, cerebrovascular events remain one of the most serious complications with long-term negative sequelae. Cerebral embolic protection devices (CEPD) have been developed to minimize the risk of peri-procedural ischemic stroke during TAVR. Furthermore, with the anticipated expansion of TAVR into intermediate risk and younger patients, the prevention of TAVR-related stroke and understanding the role of CEPD in this will become essential (12).

In this review we outline the etiology and incidence of stroke in TAVR population, and systematically review current evidence for cerebral embolic protection devices.

ETIOLOGY

The temporal pattern of stroke following aortic valve intervention is similar between surgical and transcatheter aortic valve replacement. However, the main disparity between these occurs in the acute peri-procedural period with up to half of strokes occurring within the first 24-h after TAVR (13, 14). The PARTNER trial (6) observed a significantly increased risk of peri-procedural stroke (6.7%) compared to medical therapy (1.7%). Subsequent meta-analyses (15, 16) demonstrated 30-days stroke incidence of 3.1–3.3%, and that it confers a 3.5-fold increase in mortality at 1-year. After the initial 2 months, known as the late phase, there is a similar incidence of stroke between surgical and transcatheter aortic valve replacement groups that is likely to reflect the baseline risk profiles of the populations (13, 17).

Acute Stroke

Acute strokes are ischemic in the vast majority (95%) of patients and thought to be secondary to procedural factors (**Table 1**). These peri-procedural strokes occur due to embolization phenomenon arising from disruption of the vasculature, especially the aortic arch, degenerate aortic leaflets, or the left ventricular outflow tract. This causes calcific material or atheromatous plaque embolization (18). The passage of stiff guidewires, large caliber TAVR delivery systems, and prolonged procedural time have previously been associated with cerebral embolization in AS patients (19). Furthermore, repeated attempts to the cross calcified aortic valve, manipulation of the calcified aortic valve annulus, mechanical force of valve deployment, and pre- or post-dilatation may all be associated with further anatomical disruption leading to cerebral embolization. In addition, thrombotic cerebral microembolization has been observed in patients acutely following TAVR, potentially developing on guidewires or catheters. Lastly, CEPD studies have demonstrated the presence of myocardial tissue and plastic from TAVR delivery system as sources of cerebral embolization (18).

Hemodynamic instability occurring during TAVR can lead to systemic hypotension and consequently cerebral hypoperfusion. The effect of cerebral microemboli under these conditions is amplified, due to impairment of clearance and cementation of microemboli within small vessels (20). Rapid ventricular pacing constitutes the greatest risk of hemodynamic instability during TAVR, this is required during balloon valvuloplasty before or after TAVR, and in balloon expandable TAVR prostheses, or in cases where difficultly is encountered in precise positioning of self-expanding TAVR prostheses to minimize the risk of migration/embolization. In general, rapid ventricular pacing is well tolerated however in certain patients this can be associated with greater risk of hemodynamic instability, for example those with impaired left ventricular function or in those with marked left ventricular hypertrophy (17). Hemodynamic instability can also occur as a consequence of anesthetic complications, or secondary to hemorrhage.

SUBACUTE/LATE STROKE

The etiology of delayed stroke after TAVR remains poorly characterized and is probably due to multiple factors, the primary cause thought to be thromboembolic. This can occur due to numerous reasons: valve crimping and balloon dilatation of prosthetic valve leaflets can cause structural damage that result in prothrombotic state with platelet and fibrin aggregation (14); the valve delivery system may scrape the diffuse atherosclerosis inside the aorta and some particles be dislodged later with the increased cardiac output and increased flow; increased risk of thrombus formation on the TAVR prosthesis as endothelialization can take over 1 year (21); and new onset atrial arrhythmias, predominantly atrial fibrillation, have been revealed to confer increased risk of ischemic stroke and mortality (22). In addition, TAVR prothesis leaflet thickening and leaflet thrombus have recently been reported following an acutely successful procedure. Makkar et al. (23) reported on reduced aortic-valve leaflet motion in 55 patients from a clinical trial of TAVR and two single-center registries that included 132 patients who were undergoing either TAVR or surgical aortic-valve bioprosthesis implantation. From the clinical trial arm, reduced leaflet motion was noted in 22 of 55 patients (40%) on computed tomography (CT) imaging approximately 1-month after TAVR. Of note, all the patients with reduced leaflet motion CT had hypoattenuating opacities noted in the corresponding leaflets on two-dimensional CT. The findings on transesophageal echocardiography were consistent with a hyperechogenic, homogeneous mass located on the aortic aspect of the prosthetic leaflets that prevented normal leaflet excursion. There was no significant difference between patients with reduced leaflet motion and those with normal leaflet motion with respect to the mean aortic-valve gradient. Importantly, there was no significant difference in the incidence of stroke or TIA between patients with reduced leaflet motion and those with normal leaflet motion in the clinical trial (2 of 22 patients and 0 of 33 patients, respectively; $P = 0.16$). However, in the pooled registries including surgical aortic valve replacement, a significant difference was detected (3 of 17 patients and 1 of 115 patients, respectively; $P = 0.007$). Chakravarty et al. (24) reported on 890 patients from two large registries who had CT imaging following either TAVR or surgical aortic valve replacement. It was demonstrated that 106 (12%) of 890 patients had subclinical leaflet thrombosis, including five (4%) of 138 with thrombosis of surgical valves vs. 101 (13%) of 752 with thrombosis of transcatheter valves ($p = 0.001$).Subclinical leaflet thrombosis was less frequent among patients receiving anticoagulants. Subclinical leaflet thrombosis resolved in 36 (100%) of 36 patients receiving anticoagulants, whereas it persisted in 20 (91%) of 22 patients not receiving anticoagulants ($p < 0.0001$). Although stroke rates were not different between those with (4·12 strokes per 100 person-years) or without (1.92 strokes per 100 person-years) reduced leaflet motion ($p = 0.10$), subclinical leaflet thrombosis

TABLE 1 | Mechanisms of stroke in TAVR patients.

Stroke timing	Mechanism of stroke	Possible associated factors
Acute (Periprocedural)	Embolization phenomenon	- Wire or catheter manipulation in the aortic arch, ascending aorta or aortic arch - Crossing calcified aortic valve - Balloon aortic valvuloplasy - TAVR device manipulation across aortic root and annulus - TAVR prosthesis deployment - Postdilatation of TAVR
	Global ischemia	- Hemodynamic instability - Rapid ventricular pacing - Anesthetic complication
	Hemorrhagic	- Vascular complication - Anticoagulation (heparin) associated intraprocedurally
Subacute/Late	Thromboembolic	- Atrial fibrillation (new on-set or chronic) - Thromboembolic phenomenon (cardio-embolic)
	Hemorrhagic	- Long-term use of anti-coagulation and/or antiplatelet therapy

was associated with increased rates of transient ischaemic attacks (TIAs; 4.18 TIAs per 100 person-years vs. 0.60 TIAs per 100 person-years; $p = 0.0005$) and all strokes or TIAs (7.85 vs. 2.36 per 100 person-years; $p = 0.001$). Although, CEPD have no role in the prevention of leaflet thrombosis, prosthetic valve thrombosis may potentially have a tangible deleterious effect on rates of cerebrovascular accidents, but further data from the randomized low risk TAVR trials are awaited which should help clarify this issue.

SILENT CEREBROVASCULAR EVENTS

The incidence of subclinical new cerebral ischemic lesions has been identified in as many as 93% of patients post-TAVR and recent pooled analysis reported an incidence of 77.5% (25). These are up to double of that seen in isolated surgical aortic valve replacement (26). Subclinical acute cerebral ischemic lesions can be accurately identified on diffusion-weighted magnetic resonance imaging (DW-MRI) with these regions demonstrating hyperintense signal as a result of reduction in water diffusion rate (27). Hyperintense signals on DW-MRI are well-established surrogate parameters for cerebral embolization and have already been investigated after catheter-based or cardiothoracic surgical interventions (28). In addition, cognitive function testing can be utilized to screen patients to determine those who may have had subclinical strokes (29). In various clinical contexts the occurrence of small brain infarcts has been linked to a higher incidence of stroke (30, 31) or cognitive impairment and dementia (32–34). Cerebral emboli detected on DWI-MRI increases the risk of clinically overt stroke by 2-4 fold and the greater the volume of lesions seen on DW-MRI, the greater the long-term risk of cognitive dysfunction and long-term dementia (32, 35). However, the prognostic significance of these subclinical brain injuries remains contentious and the correlation between new cerebral infarcts post TAVR and long-term cognitive decline or behavioral changes remain uncertain. Performing neurocognitive assessment immediately following TAVR is challenging in elderly patients since results can be influenced by the degree of alertness and fatigue, which is common in elderly patients peri-procedurally especially if sedation or general anesthetic have been administered (36). The BRAVO-3 MRI study investigated the role of intra-procedural parenteral anticoagulation (heparin vs. bivalirudin) during TAVR in reducing risk of cerebral emboli during TAVR (37). In this study, there was no difference in rates of with new cerebral emboli between the bivalirudin (54.5%) and heparin (58.1%) groups. Of note, all patients that presented with clinically overt stroke showed evidence of new emboli on MRI. The total volume of emboli, the volume of single embolus per patient, and the volume of the largest embolus per patient were higher in patients presenting with vs. without stroke at 30-days.

Transcarotid Doppler studies have shown a high incidence of high-intensity transient signal (HITS) throughout the entire TAVR procedure, especially during valve positioning and implantation (38), highlighting the high embolic risk during these phases of the procedure. Therefore, the use of CEPD might play an important role during these at high risk phases of the TAVR procedure. All studies evaluating CEPD have focused on the assessment and characterization of new brain ischemic lesions on DW-MRI as the main efficacy endpoints (39). The relatively small incidence of clinically apparent cerebrovascular events makes them difficult to use as endpoints in clinical trials, shifting the attention to subclinical cerebral injury (17).

CEREBRAL EMBOLIC PROTECTION DEVICES

Cerebral embolic protection devices are filters designed to capture or deflect emboli traveling to the brain during TAVR procedures in order to protect the supra-aortic vessels from embolic debris. These filters are normally positioned across the origin of supra-aortic vessels before the advancement of the TAVR system across the aortic valve and is retrieved at the end of the procedure (**Figure 1**). The positioning of these devices can be challenging particularly if atherosclerotic plaques are located in the vicinity of the ostium of supra-aortic vessels or aortic arch, hampering the implantation and positioning of CEPD which may even promote plaque disruption and consequently cerebral embolization (40). Initial in-human experiences have shown the feasibility and safety of CEPD during TAVR (41, 42). Currently there are three devices commercially available with studies that have evaluated their efficacy (**Table 2**).

EMBRELLA DEVICE

The Embrella Embolic Deflector device (EED) (Edwards Lifesciences; Irvine, California, United States) is a filter designed

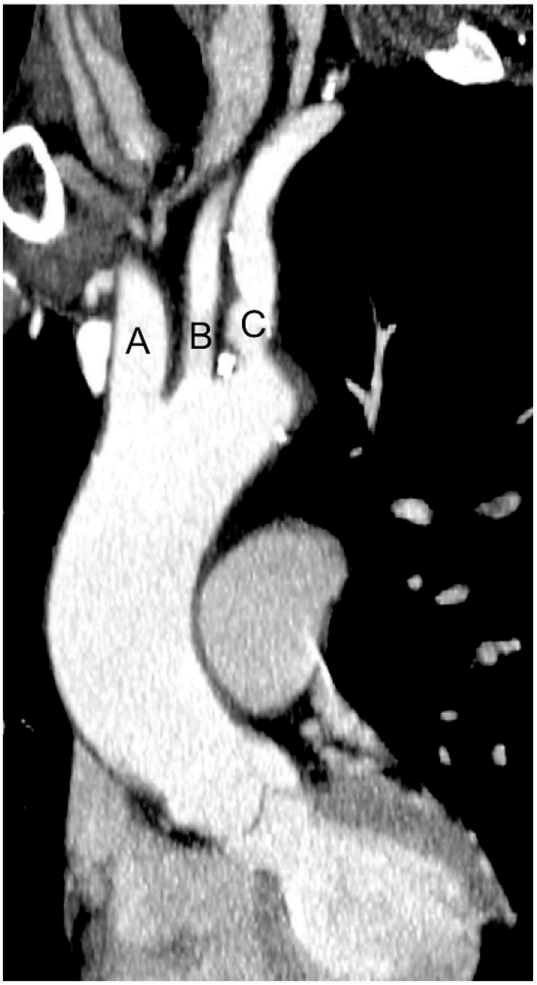


FIGURE 1 | Computed tomography image of ascending aorta and supra-aortic vessels. **(A)** Brachiocephalic artery; **(B)** Left common carotid artery; **(C)** Left subclavian artery.

to deflect debris traveling to the brain during the positioning and implantation of the TAVR valve. The distal end of the deflector consists of an oval shaped nitinol frame (length 59 mm, width 25.5 mm) covered with a porus polyurethane membrane (100 microns pore size). The frame of the device has two opposing petals that are positioned along the greater curve of the aorta, covering the ostia of both the brachiocephalic and the left common carotid arteries (45). The device is inserted via the right radial or brachial approach using a 6-French delivery system. The EED system is deployed at the beginning of the TAVR procedure just before any attempt to cross the native aortic valve. Nietlispach et al. reported the first in-human experience with the EED device showing the feasibility and safety of device implantation in a preliminary series of 4 patients (1 aortic valvuloplasty, 3 TAVR procedures) (41). Subsequently, the PROTAVI-C study (45) evaluated the procedural safety, technical feasibility, and exploratory efficacy of the EED. This prospective non-randomized study included 54 patients, with 42 patients receiving the EED device and 12 patients not receiving it (control group). TAVR procedures were performed by transfemoral approach with Edwards Sapiens XT. The PROTAVI-C study demonstrated that EED use during TAVR is feasible and safe with minimal procedural complications related to the device (1 radial thrombosis with no clinical consequences and 1 pseudoaneurysm of the brachial artery that required surgical repair). The EED system did not prevent the occurrence of cerebral microemboli during TAVR as evaluated by transcranial Doppler during the procedure. The number of HITS was actually higher in the EED group than in the control group, 632 [interquartile range, 347-893] vs. 279 [interquartile range, 0–505], respectively ($p < 0.001$). Therefore, suggesting that EED manipulation may also represent a potential source of embolic debris. In addition, the use of EED had no effect on the occurrence and number of new ischemic lesions as evaluated by DW-MRI at 7 days after the procedure. These ischemic lesions disappeared within few weeks (as evaluated by DW-MRI at around 30 days) and were not associated with any neurological and cognitive impairment. However, the use of a EED was associated with a reduction in lesion volume compared to the control group. Fundamentally, this study was limited by the low number of patients and lack of randomization. However, the EED device is currently not available commercially.

CLARET DEVICE

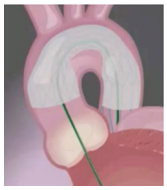
The Claret embolic protection device (CD) (Claret Medical, Inc.; Santa Rosa, California, United States) is designed to capture debris dislodged during TAVR and it is the first device with FDA approval (46). The system consists of a dual filter system deployed via the right radial or brachial approach to the brachiocephalic and left common carotid arteries. It consists of a proximal filter (sized 9–15 mm in diameter) delivered in the brachiocephalic artery covering all areas of the brain supplied by the right vertebral and right carotid artery and a distal filter (sized 6.5–10 mm in diameter) delivered in the left common carotid artery. The left vertebral artery, which usually originates from the left subclavian artery, remains unprotected, as does the cerebral regions fed by this vessel. At the start of the procedure the system is advanced through a 6F sheath and it is deployed in the aortic arch and withdrawn following removal of the TAVR delivery system (42). The CLEAN TAVI study (43) was a single center, blinded, randomized clinical trial that evaluated the efficacy of the Claret device in reducing the number of cerebral lesions in patients undergoing TAVR with Medtronic CoreValve. The primary endpoint was the reduction in number of lesions on DW-MRI at 2 days post-TAVR. The secondary outcome was the difference in volume of new lesions after TAVR in potentially protected territories. The study included 100 patients randomized 1:1 to the control or filter group. This showed a reduction in the number of new ischemic cerebral lesions [difference 5.00 (IQR, 2.00-8.00); $p < 0.001$] and volume of cerebral lesions in the filter group compared to the control group [difference 234 mm^3 (95% CI, 91-406); $p = 0.001$]. These changes were observed largely within cerebral territories that

TABLE 2 | Cerebral protection devices and current evidence base.

	Embrella	**Claret**	**TriGuard**
Manufacturer	Edwards Lifesciences; Irvine, California, United States	Claret Medical, Inc.; Santa Rosa, California, United States	Keystone Heart Ltd., Herzliya, Israel
Structure	Oval shaped nitinol frame (length 59 mm, width 25.5 mm) Covered with a porus polyurethane membrane Pore size: 100 μm	Two oval coned mesh positioned within brachiocephalic (sized 9–15 mm diameter) and left common arteries (sized 6.5–10 mm in diameter) Pore size: 140 μm	Single-wire nitinol frame and mesh filter, maintained by stabilizers in the brachiocephalic artery and the inner curvature of the aortic arch. Pore size: 130 μm
Delivery approach	Radial/brachial artery	Radial/brachial artery	Femoral
Sheath Size	6 French	6 French	9 French
Primary Mechanism	Deflection	Filter and capture	Deflection
Coverage	Brachiocephalic and the left common carotid arteries	Brachiocephalic and the left common carotid arteries	Brachiocephalic, left common carotid, and left subclavian arteries
Most relevant study	PROTAVI-C (41)	SENTINEL (43)	DEFLECT III (44)
Methods	Prospective, non-randomized study. Device $n = 54$ Control $n = 12$	RCT Safety arm $n = 123$ Device arm $n = 121$ Imaging control arm $n = 119$	RCT Device $n = 46$ Control $n = 39$
Patient and procedural characteristics	52% male, median age 83 years. Only balloon expandable TAVR (Edwards Sapien XT) Only Transfemoral TAVR Successful device positioning in 100%	48% male, medial 83 years Balloon expandable TAVR in 70% Transfemoral TAVR in 95% Successful device positioning in 94%	46% male, mean age 82 years Balloon expandable TAVR in 64% Transfemoral TAVR in 97% Successful device positioning in 89%
Outcomes	**DW-MRI:** - Non-significant increase in lesion numbers (8 vs. 4, $P = 0.41$) in device group. - Significantly lower lesion volumes (40% smaller, $P = 0.003$) in device group. **TCD:** - Higher procedural HITS rates in device group.	**DW-MRI:** Protected territories: - 42% reduction in device arm of total lesion volume ($P = 0.33$) - 33% reduction in number ($P = 0.90$). All territories: - 5% reduction of total lesion volume ($P = 0.81$), 40% in number ($P = 0.77$). Neurocognitive: - no difference in overall composite scores at baseline, 30 days, or 90 days. - Change in neurocognitive scores from baseline to 30-day follow-up correlated with median new lesion volume in protected territories	**DW-MRI:** - Device related greater freedom from new cerebral DWI lesions (21.2 vs. 11.5%), - 44% reduction of median lesion size **Neurocognitive**: - Reduction worsening in National Institutes of Health Stroke Scale score from baseline (2.6 vs. 12.1%) in device arm
Ongoing studies	No registered on-going study	Ongoing study powered for efficacy (PROTECT-TAVI Trial; ClinicalTrials.gov Identifier: NCT02895737)	Ongoing study powered for efficacy (REFLECT Trial; ClinicalTrials.gov Identifier: NCT02536196)

were protected by the filter (day 2 post-TAVR: 246 vs. 527 mL, $p = 0.002$). The MISTRAL-C study (47), a multicenter, double-blind, randomized trial that confirmed the efficacy of CD in reducing the number of new ischemic cerebral lesions and the volume of these lesions in 65 patients randomized 1:1 to CD vs. non-CD. The main limitation of this study is that only 57% of the randomized patients underwent follow-up DW-MRI. The SENTINEL trial (48) is the largest randomized clinical trial evaluating the safety and efficacy of a transcatheter CD system during TAVR. The SENTINEL trial enrolled 363 patients, who were randomized 1:1:1 into a safety arm ($n = 123$), an imaging device arm ($n = 121$), and an imaging control arm ($n = 119$). In this study a significant reduction of median total new lesion volume in protected territories, evaluated by DW-MRI 2-7 days after TAVR, was not observed (102.8 mm^3, IQR 36.9-423.2 mm^3 in the device arm vs. 178.0 mm^3, IQR 34.3-482.5 mm3 in the control arm; $p = 0.33$), However, the use of the Sentinel device during TAVR was safely performed and histopathological debris was found within filters in 99% of patients, confirming the embolic risk during TAVR with frequent embolization of non-thrombotic material (vascular material in 94% of cases). Importantly, it was demonstrated for the first time that there is a correlation between new lesion volume and neurocognitive decline. Latib et al. (36) identified some challenges related to this trial that can be extended to other CEPD trials. Firstly, the need of baseline MRI to detect previous neurological damage and their impact on new cerebral lesions. *Post-hoc* multivariable analysis in the SENTINEL trial identified pre-existing lesion volume as main predictor of new lesion volumes. In addition, after adjusting for baseline T2/FLAIR lesion volume, there was a reduction in new lesion volume in both protected and all territories in the device vs. control arms. Secondly, the time

TABLE 3 | Percutaneous cerebral protection devices currently under development or first-in-man study stage.

	Emblock	Point-Guard	Emboliner	ProtEmbo	Embolisher	Fliterlex
Device Illustration						
Company	Innovative Cardiovascular Solutions	Transverse Medical	Cardiological Solutions	Protembis	Cardioptimus	Fliterlex
Regulatory status	Feasibility study ongoing	Pre-clinical	Pre-clinical	Feasibility study awaited	Pre-clinical	Pre-clinical
Access	12F Contralateral Transfemoral	Unclear (Assume femoral)	9F Contralateral Transfemoral	6F left Transradial	Contralateral Transfemoral	Ipsilateral Transfemoral
Embolic protection mechanism	Capture and removal	Deflector, capture and removal	Capture and removal	Deflector	Deflector	Deflector
Cerebral Protection	All supra-aortic arteries	All supra-aortic arteries	All supra-aortic arteries	All supra-aortic arteries	All supra-aortic arteries	All supra-aortic arteries
Positioning	Aortic Arch	Aortic arch	Aortic arch	Aortic arch	Aortic arch	Aortic arch and descending aorta
Other features	•Integrated pigtail catheter •Designed to minimize use of contrast	•Sealing technology •Conforms to aortic arch	•Dual-layer Nitinol mesh filter mounted on a 6-Fr catheter	•Deflection of microparticles as tiny as 60 microns to descending aorta		•Full protection: Brain, Aorta and Body (kidney)

points of evaluation of 2–7 days after TAVR might create too much heterogeneity in terms of detected volumes of ischemic lesions because of the time-dependent sensitivity of DW-MRI. As a matter of fact, the time point for performing DW-MRI post-TAVR could affect the sensitivity for detecting silent cerebral infarcts, as these lesions tend to disappear over time, being totally absent at 30 days following the procedure (49, 50). Thirdly, the evaluation of cognitive dysfunction might be misleading in elderly patients in the first few days after TAVR, therefore a simpler and more focused battery of tests may be repeated later in time. Furthermore, the Claret device can only protect completely 9 out of 28 brain territories because of the dual blood supply of the posterior circulation. Thus, if we believe that cerebral protection is important, it is not acceptable that these areas of the brain remain unprotected. The even embolic distribution shown on DW-MRI validates the need of a comprehensive brain protection (51, 52).

TRIGUARD DEVICE

The TriGuard (TG) CEPD (Keystone Heart Ltd., Herzliya, Israel) is a mechanical system designed to deflect cerebral emboli during TAVR while allowing maximal blood flow to the brain and it is the only deflection device that covers all 3 cerebral vessels. The device is a single-wire nitinol frame and mesh filter with pore size of 130 μm and it is positioned across all 3 cerebral vessels and maintained by stabilizers in the innominate artery and the inner curvature of the aortic arch. At the start of the TAVR procedure, a 9 Fr arterial sheath is inserted in the contralateral femoral artery through which the TriGuard device is advanced to the aortic arch and deployed to cover the ostia of the three major cerebral vessel take-offs and it is withdrawn after completion of the TAVR procedure (44).

The DEFLECT I (44) and DEFLECT II (53) studies are single arm studies that confirmed the safety and performance of the first and second generation TriGuard device. In particular, the DEFLECT I formed the basis for TriGuard been granted CE mark in October 2013. The DEFLECT III (54) a prospective, multi-center, single-blind, randomized controlled trial evaluating the safety, efficacy and performance of the TriGuard device in subjects undergoing TAVR. The study included 85 patients randomized 1:1 to CEDP (46) or unprotected TAVR (39). This study showed that embolic protection during TAVR with TriGuard was safe and complete vessel coverage was achieved in 89% of the patients. The safety endpoint (including death, stroke, life-threatening or disabling bleeding, stage 2 or 3 acute kidney injury, or major vascular complications) was not different between the two groups. However, in the intention-to-treat analysis the use of TriGuard was associated with a greater freedom from new cerebral DWI lesions (21.2 vs. 11.5%), a reduction in "new neurologic impairment" defined as worsening in National Institutes of Health Stroke Scale score from baseline (2.6 vs. 12.1%) and a reduction in single and multiple lesions volume, especially for lesion volume of small and medium size (<150 mm^3). Additionally, it showed improved cognitive function in some domain at discharge: in the International

Shopping List Test (a measure of episodic memory), significant differences were observed when patients were evaluated at discharge, favoring the interventional arm (65.4 vs. 30.4%, $p = 0.022$). The main limitations of this study are its lack of statistical power to evaluate the safety and efficacy endpoints and the high loss to follow-up (31% were lost to the post-interventional DWI evaluations and 26% were lost to the post-interventional cognitive and neurologic assessments). Lansky et al. (54) performed a pooled analysis on DEFLECT I, DEFLECT II studies, and the Neuro TAVR registry, this was a registry of 142 patients undergoing TAVR with TriGuard protection ($n = 59$) vs. no protection ($n = 83$). The study reported that TriGuard protection significantly reduced the incidence of in-hospital Valve Academic Research Consortium-2–defined stroke (VARC-2) (0 vs. 6%; $P = 0.05$),the incidence of stroke as defined by worsening National Institutes of Health Stroke Scale (NIHSS) with DW-MRI lesions (0 vs. 19%; $P = 0.002$), brain embolic lesion volume on MRI (315 + 620 mm3 vs. 511 + 893 mm3; $P = 0.04$) and demonstrated improved functioning on cognitive testing post-TAVR. The REFLECT-US (55) trial is an ongoing multicenter, randomized controlled trial evaluating the safety, efficacy, and performance of the TriGuard device in a larger cohort of patients undergoing TAVR compared to previous studies. This trial is including 285 TAVR subjects with 2:1 randomization to TriGuard (190 patients) and unprotected TAVR (95 patients).

NEW CEREBRAL PROTECTION DEVICES

Several new CEPD are currently under development or early first-in-human analysis, these are outlined in **Table 3.** The Emblok Embolic Protection System (Innovative Cardiovascular Solutions, LLC) is one of the devices that has ongoing clinical feasibility study. This device provides full circumferential coverage of the aortic arch, hence protecting all supra-aortic vessels, utilizing a pore size of 125 μm. The system incorporates an integrated 4-Fr radiopaque pigtail catheter which provides constant visualization, from which aortagram can be performed both for CEPD and TAVR deployment. In addition, the radiopaque pigtail catheter aids in defining the non-coronary cusp hence it facilitates precise valve implantation while potentially decreasing contrast injections during TAVR positioning and deployment. The delivery system is 11–Fr compatible and allows two devices (i.e., embolic filter and pigtail catheter) to be deployed through a single access site supported by 0.035 guidewire. Clinical studies are currently underway to establish the safety and efficacy of Emblock in TAVR patient. In addition, there are other CEPD that currently under development or early first-in-human analysis, these are outlined in **Table 3**.

DISCUSSION

Despite advances in TAVR technology, stroke remains a serious complication that is associated with significant negative outcomes. The majority of these occur in the acute phase following TAVR where cerebral embolic events are frequent. CEPD have the potential to reduce intraprocedural burden of new silent ischemic injury. Although individual CEPD studies have not yet demonstrated a reduction in rates of silent cerebral ischemic lesions evaluated by DW-MRI, they have demonstrated reductions in total cerebral ischemic volumes. Giustino et al. (56) performed a meta-analysis on 5 studies evaluating the efficacy of these 3 CEPD. A total of 625 patients were included, 376 with CEPD and 249 without CEPD, the CEPD group showed a lower risk in death or stroke, suggesting that CEPD may be a clinically relevant adjunctive strategy in patients undergoing TAVR. Aufrett e al. meta-analysis (sixty-four studies involving 72,318 patients) reported that female sex, chronic kidney disease, enrollment date, and new-onset atrial fibrillation were predictors of early CVE after TAVR. The main limitation of this meta-analysis is that most of the studies included were not powered for CVEs as main endpoint (57). A very large multicentre study, powered for early CVEs, is needed to identify which are the predictors of such events that will help us tailoring our preventive strategies. Preventing procedure-related cerebral injury remains a significant unmet clinical need with potentially important long-term sequelae. As we move to low-risk patients, the bar to ensuring good TAVR outcomes will become much higher. Hence, CEPD could potentially become standard of care if: (a) we accept as a community that silent cerebral infarction has a negative impact on long-term outcomes and that prevention of these is as important as preventing stroke; (b) CEPD devices are easy to use, safe, provide full protection of supra-aortic arteries during the procedure, and can be rapidly implanted without adding significant time to the procedure or interfering with valve positioning or deployment; (c) specific reimbursement for CEPD during TAVR become available and/or the cost of devices decrease significantly. If the previous conditions are satisfied, a very large multicentre randomized study might be conducted to evaluate the clinical benefit from CEPD devices.

CONCLUSION

Stroke remains one of the most serious complication following TAVR with associated worse outcomes that negate the benefit of TAVR procedure. Although CEPD have been demonstrated to reduce cerebral infarct volume, whether it decreases rates of both silent cerebral ischemic lesions and clinically evident ischemic strokes remains unclear. However, there will be greater emphasis on prevention of cerebral ischemic events as we move to low-risk patients. To elucidate the exact role of CEPD, a large randomized controlled trial with long-term follow-up with baseline and follow-up cerebral MRI imaging, and full neurological clinical evaluation, ideally using a device that protects all supra-aortic arteries, to establish the role of CEPD both in the short and long term.

AUTHOR CONTRIBUTIONS

OD, GI, GW, and AL substantially contributed conception and design of the manuscript. OD and GI wrote the first draft of the manuscript. All authors contributed to manuscript revision, read and approved the submitted version.

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ORIGINAL RESEARCH
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Patient Disposition and Clinical Outcome After Referral to a Dedicated TAVI Clinic

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Introduction: Transcatheter aortic valve implantation (TAVI) is the standard of care for the majority of patients with severe symptomatic aortic stenosis (AS) at excessive-, high- and intermediate-surgical risk. A proportion of patients referred for TAVI do not undergo the procedure and proceed with an alternate treatment strategy. There is scarce data describing the final treatment allocation of such patients. Hence, we sought to evaluate the final treatment allocation of patients referred for TAVI in contemporary practice.

Methods: We performed a single center prospective observational study, including all patients referred to our institution for treatment of severe aortic stenosis between February 2014 and August 2017. Baseline demographic and clinical data were recorded. Patients were categorized according to treatment allocation: TAVI, surgical aortic valve replacement (SAVR) or optimal medical therapy (OMT). Clinical outcomes were adjudicated according to VARC-2 definitions. All patients were discussed at a dedicated Heart Team meeting.

Results: Total of 245 patients were referred for assessment to a dedicated TAVI clinic during the study period. Patients with moderate ($N = 32$; 13.1%) and asymptomatic ($N = 31$; 13.1%) AS were excluded. Subsequently, 53.9% ($N = 132$) received TAVI, 12.7% ($N = 31$) were managed with OMT, and 7.3% ($N = 18$) had SAVR. Reasons for OMT included primarily: patient's preference ($N = 12$; 38.7%); excessive surgical risk ($N = 4$; 12.9%) and severe frailty ($N = 5$; 16.1%). Reasons for surgical referral included low surgical risk ($N = 11$; 61.1%), excessive annulus size ($N = 5$; 27.8%), and aortic root dilatation ($N = 2$; 11.1%). Patients proceeding to SAVR had lower surgical risk than those in either the OMT or TAVI cohorts ($P < 0.001$). Mean STS score in SAVR group was 2.2 ± 1.3 vs. 4.5 ± 2.4 in OMT cohort and 6.1 ± 4.9 in TAVI cohort. Six-month all-cause mortality was 16.7, 19.4, and 9.3% among those receiving SAVR, OMT, and TAVI, respectively.

Conclusions: Almost half of all patients with severe AS referred to a dedicated TAVI clinic did not receive a TAVI. A considerable proportion of patients were reclassified as

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moderate AS (13%), were asymptomatic (13%), or intervention was determined to be futile (13%) due to advanced frailty. Early detection and increased awareness of valvular heart disease are required to increase the number of patients that can benefit from TAVI.

Keywords: aortic stenosis, transcatheter aortic valve implantation, TAVI, patient disposition, surgical aortic valve replacement, SAVR, optimal medical therapy, OMT

INTRODUCTION

Aortic stenosis (AS) is the most common valve disease affecting elderly patients, occurring in ∼3.4% of the population over 75 years of age (1). Transcatheter aortic valve implantation (TAVI) has transformed the management of AS patients and is considered to be the standard of care in elderly patients at excessive-, high- and intermediate-surgical risk. Indeed, TAVI has surpassed surgical aortic valve replacement (SAVR) as the dominant strategy for the treatment of symptomatic severe AS (2). National and regional differences in the availability of TAVI have emerged however and there exist considerable variations in the use of TAVI or SAVR (3).

Societal guidelines suggest that a Heart Team approach should facilitate the determination of the most appropriate therapeutic strategy for AS patients (4, 5). Such patients are usually referred to a dedicated Structural Heart clinic in a TAVI center for consideration of the most appropriate treatment. A proportion of patients with severe AS referred for TAVI are however likely to be more appropriately treated with SAVR due to young age and low operative risk, anatomical challenges, or concomitant coronary artery or mitral valve disease (4). Similarly, some patients at extreme-operative risk may be more appropriately treated conservatively. There is however, little information available on the final treatment allocation of patients referred to dedicated TAVI clinics (6, 7). Such information may have implications for healthcare resource allocation, service development planning, assessment of equitable patient access, and physician training.

We sought to address this knowledge gap by examining the disposition of patients referred to a dedicated TAVI clinic in contemporary clinical practice, to understand the motives for the chosen treatment allocation, and to describe clinical outcomes of various treatment strategies.

METHODS

Patient Population

In this prospective single center study, data was collected on all patients with severe AS referred for assessment to a dedicated out-patient TAVI clinic between February 2014 and August 2017. Patients were referred from community medical practitioners, the general medical service, cardiologists, and cardiothoracic surgeons. The diagnosis of severe AS was reassessed in the clinic and patients with < severe AS were excluded from the study. Demographic, clinical, laboratory, echocardiographic, and procedural data were prospectively collected into a dedicated database. All patients provided informed consent for the procedure and the hospital ethical committee approved the data collection for this study.

Patients were categorized according to treatment allocation: TAVI, SAVR, or optimal medical therapy (OMT). The TAVI and SAVR groups included patients undergoing the respective intervention or those that died awaiting the procedure. The OMT group included patients treated with standard heart failure therapies, and balloon aortic valvuloplasty, but not deemed suitable for TAVI.

Endpoints and Definitions

In all cases, treatment allocation and the rationale for this allocation was documented after Heart Team discussion. Echocardiographic data was defined according to established criteria (8). Severe AS was defined according to standard societal guidelines (mean pressure gradient >40 mmHg, aortic valve area by continuity equation < 1 cm^2). In cases of suspected low-flow low-gradient AS, the diagnosis was confirmed using dobutamine stress echocardiography and/or multislice computed tomography. Severe pulmonary hypertension was defined as pulmonary artery systolic pressure ≥60 mmHg. Chronic kidney disease was defined as estimated glomerular filtration rate <30 mL/min/1.73 m^2, chronic obstructive pulmonary disease as the ratio of forced expiratory volume in one second (FEV1) over forced vital capacity (FVC)–(FEV1/FVC) ≤70%. Obstructive coronary artery disease was defined as visual stenosis of a major epicardial artery ≥70% diameter stenosis.

Surgical risk was calculated using the Society of Thoracic Surgeons predicted risk of mortality (STS-PROM) score and the European System for Cardiac Operative Risk Evaluation (EuroSCORE; logistic EuroSCORE; and EuroSCORE II).

Clinical endpoints included procedural mortality, 30-day mortality, 6-month all-cause mortality, and stroke/transient ischemic attack as well as procedural complications. All outcomes were adjudicated according to the updated VARC-2 criteria (9). Clinical follow-up was performed by patient attendance at out-patient clinic or telephonic interview with patients, family members, and general practitioners. Follow-up time was the time between the procedure and follow-up in patients undergoing TAVI and SAVR or as the time from treatment decision in patients managed with OMT.

Statistical Analysis

Continuous variables are presented as mean and standard deviation or median with interquartile range according to distribution. Normally distributed variables were compared with the Student *t*-test and non-normally distributed variables compared with the Wilcoxon rank-sum test. Categorical variables

are presented as numbers and percentages, and were compared using chi-square or Fisher exact test. Multiple comparisons were analyzed using analysis of variance with Bonferroni correction or with the Kruskal-Wallis test. Survival was depicted using Kaplan-Meier graphs. Due to significant differences in baseline characteristics between treatment groups, we do not present comparative statistics on clinical outcomes. A probability value <0.05 was considered to indicate statistical significance. All analyses were performed with Minitab software version 17.

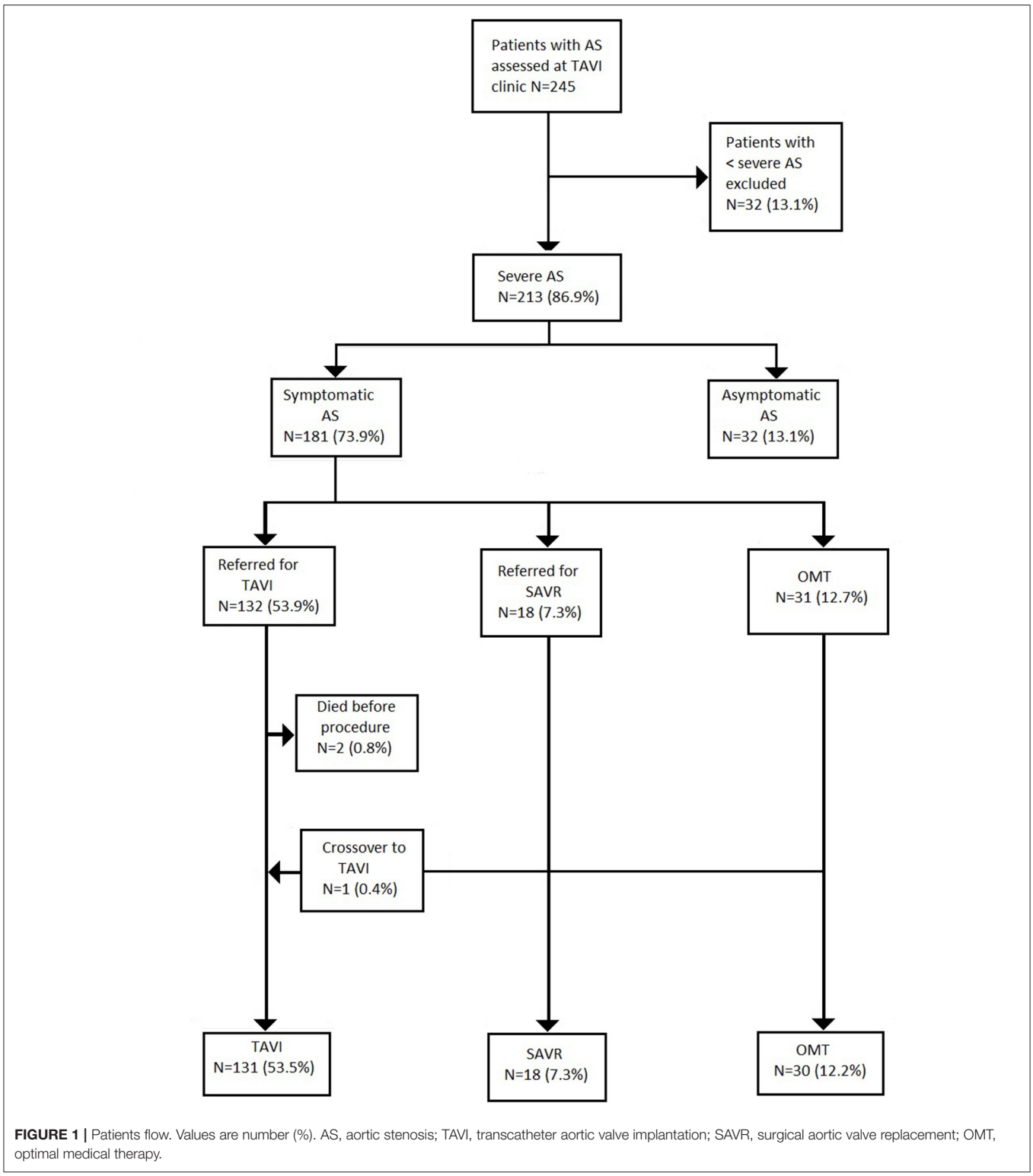

FIGURE 1 | Patients flow. Values are number (%). AS, aortic stenosis; TAVI, transcatheter aortic valve implantation; SAVR, surgical aortic valve replacement; OMT, optimal medical therapy.

RESULTS

Patients and Treatment Allocation

A total of 245 patients with AS were referred for assessment during the study period (**Figure 1**). Moderate AS was determined in 32 (13.1%) cases after careful multimodal imaging assessment. Among 213 patients with severe AS, 31.1% ($N = 32$) did not have symptoms, thus yielding a final study population of 181 patients with severe symptomatic AS. The median age of the study cohort was 83 [IQR 79–87] years and 53% ($N = 96$) were male (**Table 1**).

Treatment allocation after Heart Team discussion was as follows (**Table 1**): TAVI in 132 (53.9%); SAVR in 18 (9.9%); and OMT in 31 (17.1%). One patient initially managed with OMT proceeded to TAVI as a novel large THV (Medtronic, 34 mm Evolut R) became commercially available. Two patients died awaiting TAVI. Surgery was preferred to TAVI in 18 patients (7.3%) due to low surgical risk ($N = 11$; 61.1%)–mean STS score: 2.2%; excessive annulus size for commercially available TAVI devices at the time ($N = 5$; 27.8%); and bicuspid aortic valve morphology with aortic root dilatation ($N = 2$; 11.1%).

TABLE 1 | Baseline characteristics according to treatment allocation.

Demographic characteristics	All ($N = 181$)	TAVI ($N = 132$)	SAVR ($N = 18$)	OMT ($N = 31$)	*p*-value
Age, median [IQR]	83 [79–87]	83.3 [80.5–87]	73 [60–79]	86 [82–88]	<0.001*#$
Male sex	96 (53)	67 (50.8)	12 (66.7)	17 (54.8)	0.4
Symptoms					
NYHA Class III/IV	137 (77.8)	107 (84.3)	12 (66.7)	19 (61.3)	0.01*
Angina	42 (24.4)	35 (28)	4 (22.2)	3 (9.7)	0.1
Syncope	50 (28.4)	42 (33.1)	2 (11.1)	6 (19.4)	0.1
Co-morbid conditions					
Diabetes mellitus	40 (22.3)	29 (22.3)	5 (27.8)	6 (19.3)	0.8
Hypertension	147 (81.2)	116 (87.9)	10 (55.6)	21 (67.7)	<0.001*#
CKD eGFR < 30 mL/min/1.73 m²	24 (13.9)	20 (15.6)	1(5.9)	3 (11.1)	0.4
COPD	26 (14.5)	23 (17.7)	1 (5.6)	2 (6.5)	0.1
PVD	29 (16.2)	28 (21.5)	0 (0)	1 (3.2)	0.001*#
Stroke	34 (19)	27 (20.8)	2 (11.1)	5 (16.1)	0.5
Prior MI	49 (27.7)	37 (28.7)	4 (22.2)	8 (26.7)	0.8
Prior PCI	55 (30.9)	42 (32.6)	4 (22.2)	9 (29)	0.6
Prior CABG	25 (14)	21 (16.2)	1 (5.6)	3 (10)	0.3
Atrial fibrillation	72 (39.8)	50 (38.2)	9 (50)	13 (41.9)	0.6
PASP > 60 mmHg	8 (4.5)	5 (3.9)	0 (0)	3 (9.7)	–
Permanent pacemaker	21 (11.8)	15 (11.5)	0 (0)	6 (20)	0.1
Biological assessment					
Weight, Kg	74.9 ± 16.4	74.7 ± 16	83.4 ± 17.2	70.3 ± 16.7	0.1
eGFR, mL/min/1.73 m²	51 [39–64.5]	50 [38.3–64]	77 [43–86.5]	51 [38–59]	0.02#$
Pre TAVI Coronary angiography,					
Obstructive CAD (>70% visual diameter stenosis)	57 (33.7)	41 (32.5)	5 (27.8)	11 (44)	0.8
PCI	20 (13.8)	23 (22.1)	0 (0)	7 (30.4)	0.01#$
Echocardiography					
Peak gradient, mmHg	75 [65–90]	75 [66–90]	70 [59–78.5]	72 [60–101]	N/A
Mean gradient, mmHg	47.5 [39–57]	48 [40–57.5]	41 [36–49.1]	48 [37.3–63.5]	N/A
AVA, cm²	0.7 [0.5–0.8]	0.6 [0.5–0.8]	0.7 [0.5–1.1]	0.7 [0.6–0.8]	N/A
LVEF, %	55 [50–60]	55 [50–60]	60 [55–60]	55 [40–60]	N/A
PASP, mmHg	35 [28–45]	34 [28–41]	37 [25.8–47]	40 [33.5–49.5]	N/A
MR Grade ≥ 3	32 (18.1)	29 (22.5)	2 (11.1)	1 (3.3)	N/A
Surgical risk					
EuroSCORE II	8.1 ± 8.5	9.2 ± 9.2	2.6 ± 1.6	6.4 ± 6.1	0.004#$
Logistic EuroSCORE	20.3 ± 15.3	22.9 ± 15.9	6.2 ± 3.7	17.8 ± 11.5	<0.001#$
STS PROM score	5.4 ± 4.6	6.1 ± 4.9	2.2 ± 1.3	4.5 ± 2.4	0.001*#$

*Values are number (%), median [interquartile range], or mean ± SD. $p < 0.05$ was used as the level of statistical significance. *Denotes statistical significance in TAVI-OMT pairwise comparison. #Denotes statistical significance in TAVI-SAVR pairwise comparison. $Denotes statistical significance in SAVR-OMT pairwise comparison. COPD, chronic obstructive pulmonary disease; PVD, peripheral vascular disease; MI, myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; PASP, pulmonary artery systolic pressure; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; CAD, coronary artery disease; AVA, aortic valve area; MR, mitral regurgitation; LVEF, left ventricular ejection fraction; STS, Society of Thoracic Surgeons Predicted Risk of Mortality score.*

OMT was preferred in 31 cases (12.7%) due to a patient preference to avoid intervention ($N = 12$; 38.7%); excessive annulus size but too frail for surgery ($N = 4$; 12.9%); severe frailty or immobility ($N = 5$; 16.1%); end-stage pulmonary disease ($N = 3$; 9.7%); severe cognitive impairment ($N = 2$; 6.5%); and end-stage malignancy ($N = 1$; 3.2%). In 4 cases (12.9%), patients died before completion of their out-patient TAVI work-up. One patient (3.2%) did not attend follow-up (**Table 2**).

Demographic Information

Baseline demographic, clinical, biological and echocardiographic characteristics according to treatment allocation are presented in **Table 1**. Patients managed with SAVR were significantly younger than those in either the OMT or TAVI cohorts (73 [IQR 60–79] vs. 86 [IQR 82–88] and 83.3 [IQR 80.5–87], respectively; $P < 0.001$). As expected, SAVR patients had lower STS scores then the other groups (2.2 ± 1.3% vs. 4.5 ± 2.4% and 6.1 ± 4.9% respectively; $P = 0.001$). Patients undergoing SAVR also had higher median left ventricular ejection fraction than those in the OMT or the TAVI group [60% [IQR 55–60] vs. 55% [IQR 40–60] and 55% (50–60), respectively]. The median waiting time for TAVI was 70 [23–160] days, whereas median waiting time for SAVR was 272 [181–361] days ($P < 0.001$).

Clinical Outcome

Clinical outcomes are presented in **Table 3**. SAVR was associated with numerically higher rates of bleeding (27.8% vs. 10.6%) and acute kidney injury (33.3% vs. 4.5%), than TAVI, but with lower rates of new permanent pacemaker insertion (11.1% vs. 28.9%) and vascular complications (0% vs. 9.1%).

When compared to TAVI, SAVR was associated with a numerically higher procedural (5.6% vs. 0.8%) and 30-day mortality (11.1% vs. 2.3%). Six-month follow-up data was available for all patients in the OMT and SAVR group, and for 129 (97.7%) patients in the TAVI cohort. Median follow-up was 14 months [IQR 7–22] in the OMT cohort, 16.5 months [IQR 7.5–27] in the SAVR group and 12 months [IQR 8–21.8] for TAVI patients. Six-month all-cause mortality was highest among patients managed with OMT as compared to SAVR or TAVI (19.4% vs. 16.7% vs. 9.3%, respectively). All-cause mortality is displayed using Kaplan-Meier survival curves in **Figure 2**.

TABLE 2 | Indication for treatment allocation to surgery or medical therapy.

Treatment allocation	*N* (%)
Primary reason for OMT	***N* = 31**
Patient preference	12 (38.7)
Excessive annulus size but too frail for surgery	4 (12.9)
Severe cognitive impairment	2 (6.5)
End-stage malignancy	1 (3.2)
End-stage pulmonary disease	3 (9.7)
Severe frailty / immobility	5 (16.1)
Did not attend clinic	1 (3.2)
Died before work-up complete	4 (12.9)
Primary reason for SAVR	***N* = 18**
Low surgical risk	11 (61.1)
Excessive annulus size	5 (27.8)
Aortic root dilatation	2 (11.1)

Values are number (%). OMT, optimal medical therapy; SAVR, surgical aortic valve replacement.

TABLE 3 | Procedural and clinical outcomes.

Outcomes, *N* (%)	All (*N* = 181)	TAVI (*N* = 132)	SAVR (*N* = 18)	OMT (*N* = 31)
Procedural mortality (*N* = 150)	2 (1.3)	1 (0.8)	1 (5.6)	N/A
30-day mortality	6 (3.3)	3 (2.3)	2 (11.1)	1 (3.2)
6 month all-cause morality	21 (11.8)	12 (9.3)	3 (16.7)	6 (19.4)
Stroke/TIA	6 (3.6)	3 (2.5)	1 (5.6)	2 (7.1)
Procedural complications				
Myocardial Infarction	1 (0.7)	0 (0)	1 (5.6)	N/A
Any bleeding	19 (12.7)	14 (10.6)	5 (27.8)	N/A
Life-threatening bleeding	8 (5.3)	5 (3.8)	3 (16.7)	N/A
Acute kidney injury	12 (8)	6 (4.5)	6 (33.3)	N/A
Any vascular complication	12 (8)	12 (9.1)	0 (0)	N/A
Major vascular complication	6 (4)	6 (4.5)	0 (0)	N/A
New permanent pacemaker	27 (18)	25 (18.9)	2 (11.1)	N/A

Values are number (%). TAVI, transcatheter aortic valve implantation; SAVR, surgical aortic valve replacement; OMT, optimal medical therapy; TIA, transient ischaemic attack.

DISCUSSION

The main findings of our study are that only 53.5% of patients referred to a dedicated clinic for consideration for TAVI went on to receive a transcatheter heart valve. After reassessment of the severity of AS, 13.1% were reclassified as moderate rather than severe AS and among severe AS patients, up to 13.1% were asymptomatic and did not proceed to intervention. Among symptomatic severe AS patients, 20% were unsuitable for TAVI, with 7.3% undergoing SAVR and a further 12.7% of cases were deemed futile and hence managed with OMT. This information has important implications.

It seems striking that in contemporary clinical practice, only one in two patients referred for TAVI actually receive this life-saving therapy. These results are however not unique, and other studies have documented similarly low rates of application of TAVI technology: 59% in an Italian study ($N = 98$) and 39% in a Canadian report (6, 7). These results must be contextualized however: when patients with moderate or asymptomatic AS were excluded, then nearly three-quarters (73%) were treated with TAVI. Further 10% were referred for SAVR.

In our study, more than 1 in 10 (13.1%) patients purportedly with severe AS were reclassified as moderate AS after assessment at a dedicated clinic. These data suggest that societal guidelines and position papers which recommend centralization of complex procedures, such as TAVI, at dedicated tertiary referral centers are appropriate (4, 10, 11). Centralization serves, not only to improve procedural outcome, but also more appropriately select the most appropriate intervention (if any) for a given patient. In AS, ancillary diagnostic capabilities such as transoesophageal and

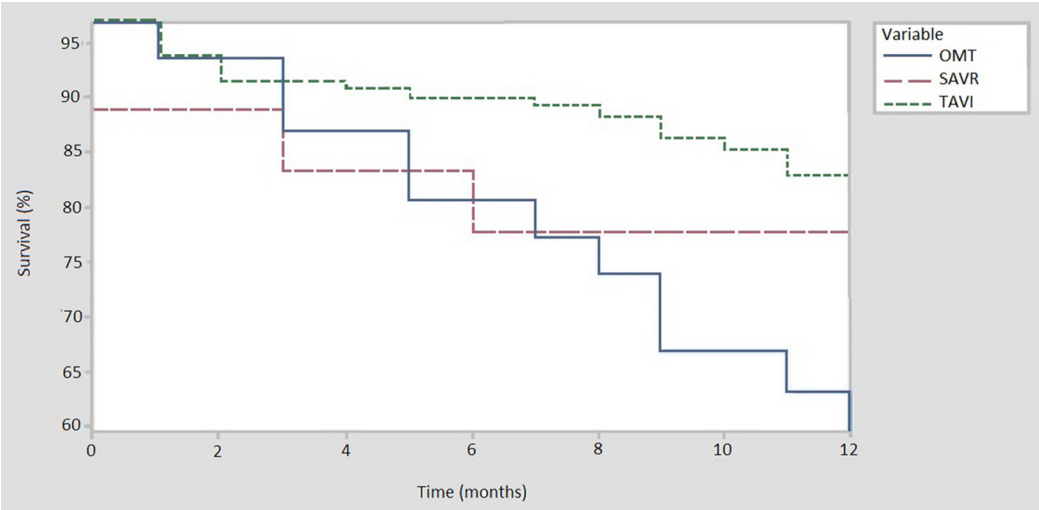

FIGURE 2 | All cause mortality at 12 months. TAVI, trancatheter aortic valve implantation ($N = 131$); OMT, optimal medical therapy ($N = 30$); SAVR, sugical aortic valve replacement ($N = 18$).

dobutamine stress echocardiography, and multislice computed tomography are required. Such techniques may not be readily available in smaller referring centers and could result in patients being misclassified, as demonstrated in our study.

There remain few data describing the prevalence of symptoms in elderly patients with severe AS referred for TAVI (6, 7). In our patient population, quality of life and functional capacity are often more important patient-related outcome measures than mortality (12, 13). Indeed, elderly patients are often reluctant to undertake procedures that confer a mortality advantage if symptomatic benefit is not guaranteed. In the current study, 13.1% of our elderly patients (mean age 84.7 years) with severe AS did not report cardiovascular symptoms. In selected cases, exercise stress testing was performed to confirm the absence of symptoms, but in many cases, additional testing was not performed as the patients were satisfied with their quality of life. Such treatment decisions are appropriate in this elderly population but are less relevant in younger AS patients where the mortality advantage of TAVI is more pertinent.

In patients treated with OMT ($N = 31$), 12 (38.7%) refused the procedure, 4 (12.9%) died before the decision was finalized and 4 (12.9%) did not proceed because of unsuitable anatomy (large annuli) and concomitant frailty. In all other cases, the procedure was deemed futile due to co-morbidities such as end-stage malignancy, excessive frailty, and cognitive impairment. These results are similar to previous studies in which the majority of patients who did not proceed to TAVI either declined the procedure, had unsuitable anatomy for percutaneous approach, or due to significant co-morbidities a symptomatic improvement was viewed as unlikely (6, 7). Patients managed with OMT in our cohort were older than patients in the two other subgroups, but interestingly, the prevalence of co-morbidities was not higher than in patients treated with TAVI or SAVR. The STS score of patients managed with OMT was significantly lower, than the mean STS score in the TAVI cohort (4.5 $\pm$ 2.4 vs. 6.1 $\pm$ 4.9 respectively; $P = 0.04$). As expected, patients referred for SAVR had the lowest STS score (2.2 $\pm$ 1.3; $P < 0.001$). The lower STS score in the OMT group compared to those undergoing TAVI may be attributed to factors that are not accounted for in the traditional surgical risk scores, such as frailty, cognitive impairment, etc. These treatment decisions highlight the important role of a multidisciplinary team (Heart Team) in determining management strategies. Moreover, these data point to the vital importance of considering patient's preference in decision making; nearly 4 in 10 patients treated with OMT refused TAVI. As expected, the prognosis in the OMT group was dismal with all-cause mortality of 19.4% at 6 months.

Despite TAVI now being extended to younger and lower risk populations, almost 1 in 10 patients ($N = 18$; 9.9%) in the current cohort were referred for SAVR. The recent publication of two low risk TAVI randomized trials will change these practices and will result in many younger patients being referred for TAVI in the coming years (14, 15). In our study, surgery was preferential in many cases, irrespective of operative risk, due to the presence of bicuspid aortic valve and dilation of the aortic root or concomitant severe coronary artery disease. Surgery will remain an important treatment option for patients with infective endocarditis, aortic thrombus or other anatomic characteristics that render TAVI unsuitable, or those with coexisting multivalve disease amenable to surgical correction (4). In contrast, the 28% of severe AS patients referred for SAVR due to excessively large aortic annuli not suitable for commercially available TAVI systems at that time would be expected to have TAVI in contemporary practice since larger devices such as the Medtronic Evolut R 34 mm (Medtronic, Minneapolis, Minnesota, USA) or overexpansion of the SAPIEN 3 (Edwards Lifesciences, Irvine, CA, USA) prosthesis have emerged.

In a significant proportion of patients, frailty and cognitive impairment may limit the symptomatic benefit derived from TAVI (16, 17). Intervention in such patients is deemed to

be "futile." It is important to acknowledge however, that in many such cases, a delayed presentation or diagnosis may have contributed to patients being labeled as futile. Opportunistic screening for severe valvular heart disease by general practitioners in the community has the potential to reduce the number of patients presenting late and improve outcome (18). A heart valve disease awareness survey performed among patients above the age of 60 years in nine European countries, found that only 7% of patients could identify symptoms of AS correctly and in 54.2% of cases, their general practitioner did not routinely use a stethoscope to examine their heart (19). It is recommended that all patients age ≥70 years should undergo opportunistic cardiovascular examination for a systolic murmur, symptoms of AS, and a referral for a transthoracic echocardiography if a murmur is detected (20). Community events, such as European Heart Valve Disease Awareness day serve to raise awareness of AS among general population and encourage seeking medical advice at an earlier stage (21).

LIMITATIONS

The current study comprises a single center experience of a small number of patients. Furthermore, changes in the threshold for intervention have evolved during the study enrolment which would have affected the disposition of patients at intermediate risk. Indeed, recent data suggesting extension of TAVI to patients at low operative risk will further impact patient disposition in the future. Consideration will need to be given to valve durability and the risk of paravalvular leak especially in this younger, lower risk cohort. Advancements in TAVI technology and patient screening, and local awareness of the dedicated TAVI clinic are also likely to have impacted the proportion of patients assigned to TAVI or OMT.

Our main objective was to report the ultimate treatment allocation for this patient population. Nevertheless, we also provide clinical outcome data according to the VARC definitions, but we did not present statistical comparisons between treatment groups due to considerable differences in the baseline characteristics of these patient populations. Interpretation of outcome data should be interpreted with caution, since the sample size is small and selection bias was introduced in the screening process.

CONCLUSIONS

Almost half of all patients with severe AS referred to a dedicated clinic for TAVI do not receive a transcatheter heart valve. A considerable proportion of these elderly patients are reclassified as moderate AS, are asymptomatic, or intervention is determined to be futile due to advanced frailty or cognitive impairment. Early detection and increased awareness of valvular heart disease are required to reduce the proportion of patients declined TAVI.

DATA AVAILABILITY STATEMENT

All datasets generated for this study are included in the article/supplementary material.

ETHICS STATEMENT

Ethical approval for this study has been granted by Ethics Committee, Galway University Hospital, Galway, Ireland.

AUTHOR CONTRIBUTIONS

MG was responsible for data collection, statistical analysis, literature review, and write up of the manuscript. CR, GM, and LM were responsible for data collection. AN, FS, BH, DV, AS, and MD were responsible for patient management. EF, FM, NM, KM, and VB were responsible for literature review and review of the manuscript. WW was responsible for review of the manuscript. DM was responsible for patient management, review of the manuscript, and approval of the final version of the manuscript.

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