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Review Article

Clinical Research on Transcatheter Aortic Valve Replacement for Bicuspid Aortic Valve Disease: Principles, Challenges, and an Agenda for the Future

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ABSTRACT

Bicuspid aortic valve disease (BAVD) is present in up to half of all patients referred for surgical aortic valve replacement (SAVR) yet was an exclusion criterion for all randomized controlled trials (RCTs) comparing transcatheter aortic valve replacement (TAVR) to SAVR. Nonetheless, approximately 10% of patients currently treated with TAVR have BAVD and available observational data for performing TAVR in these patients are limited by selection bias. Many in the cardiovascular community have advocated for RCTs in this population, but none have been performed. The Heart Valve Collaboratory (HVC) is a multidisciplinary community of stakeholders with the aim of creating significant advances in valvular heart disease by stimulating clinical research, engaging in educational activities, and advancing regulatory science. In December 2020, the HVC hosted a Global Multi-disciplinary workshop involving over 100 international experts in the field. Following this 2-day symposium, working groups with varied expertise were convened to discuss BAVD, including the need for and design of RCTs. This review, conducted under the auspices of the HVC, summarizes available data and knowledge gaps regarding procedural therapy for BAVD, outlining specific challenges for trials in this population. We also propose several potential studies that could be performed and discuss respective strengths and weaknesses of each approach. Finally, we present a roadmap for future directions in clinical research in TAVR for BAVD with an emphasis both on RCTs and also prospective registries focused on disease phenotyping to develop parameters and risk scores that could ultimately be applied to patients to inform clinical decision-making.

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ABBREVIATIONS

BAVD, bicuspid aortic valve disease; CTA, computed tomography angiography; HVC, Heart Valve Collaboratory; LVOT, left ventricular outflow tract; RCT, randomized controlled trial; SAVR, surgical aortic valve replacement; TAVR, transcatheter aortic valve replacement; TVT, Transcatheter Valve Therapy.

BAVD affects 1% to 2% of the population[1] and is thought to be present in up to half of all adult patients referred for surgical aortic valve replacement (SAVR).[2] Approximately 60% of patients undergoing SAVR aged 60 to 80 years have BAVD, but among patients aged 80 years or over, the proportion falls to 20%.[3] BAVD was an exclusion criterion for all randomized controlled trials (RCTs) comparing TAVR vs. SAVR across the spectrum of surgical risk.[4-9] Nonetheless, it is estimated that ~10% of patients currently treated by TAVR have a bicuspid aortic valve.[10] Most surveyed cardiac surgeons and cardiologists agree that the optimal treatment of BAVD is an important clinical question that should be answered with a prospective study; and there is equipoise between TAVR and SAVR that would justify enrollment in an RCT.[11] However, randomized trials assessing procedural strategies in this population are challenging and have not been performed.

Current Landscape

Challenges of TAVR Therapy for Patients With BAVD

There are several anatomical and clinical factors that make TAVR for BAVD distinct and inherently more challenging compared with the use of TAVR in trileaflet aortic valves (Table 1). First, bicuspid valves typically exhibit more severe cusp calcification than tricuspid valves, and the calcification is often asymmetric and not uncommonly extending into the aortic annulus and left ventricular outflow tract (LVOT).[12] Second, rather than the tubular shape generally seen with tricuspid valves, the annular and supraannular portions of the bicuspid aortic valve complex are often more elliptical and eccentric with significant tapering from the outflow tract to the annulus.[13] Third, the aortic annulus in patients with BAVD is typically larger than in those with trileaflet valves[14,15] and sometimes falls outside of the range of sizes suitable for on-label treatment with currently available commercial TAVR valves. Fourth, Sievers type 1 and type 2 bicuspid valves frequently have a calcified raphe.[16,17] Finally, patients with BAVD frequently have concomitant aortopathy[15] which may require surgical replacement of the aortic root and/or ascending aorta to minimize the risk of future aortic dissection.[18] All these factors, whether in isolation but particularly in combination, can predispose to an increased risk of annular and aortic root injury as well as higher rates of paravalvular regurgitation (due to less "circularization" of the valve implant) with the use of TAVR in this patient population.[19]

In addition to anatomic factors, there are also clinical factors that complicate the use of TAVR in patients with BAVD. For example, patients with BAVD may present with aortic regurgitation with insufficient amounts of leaflet or annular calcification, making these patients less anatomically suitable for treatment with current commercially available TAVR devices. Patients with BAVD also typically present with severe aortic stenosis younger, in their 50s and 60s, whereas patients with a trileaflet valve generally present in their 70s or 80s.[20] Since bioprosthetic valve longevity may be reduced in younger patients,[21,22] the importance of valve durability and the feasibility of future procedures as considerations for initial treatment selection are amplified in the BAVD population.

Table 1
Clinical and anatomic factors that make transcatheter aortic valve replacement (TAVR) challenging in patients with bicuspid aortic valve disease as compared to patients with trileaflet aortic valves

Clinical factors
• Patients present at younger age (longer subsequent lifetime with an aortic prosthesis)
• Presence of concomitant aortopathy
• More likely to present with predominant aortic regurgitation or mixed aortic valve disease with insufficient calcification for device anchoring
Anatomic factors
• Larger annuli (sometimes outside the recommended range for treatment with commercial transcatheter heart valves)
• Increased cusp calcification, which is often bulky and asymmetrical, and not infrequently extends into the aortic annulus
• Eccentric, nontubular shape of aortic valve complex (tapered or flared)
• Presence of calcified raphe(s)
• Increased frequency of coronary anomalies (including left-dominant coronary circulation, anomalous coronary takeoffs)
• Longer leaflets with increased frequency of calcified leaflets (predisposing to coronary occlusion with TAVR)
• Increased frequency of horizontal aorta
• Aortic root and ascending aorta dilation

Observational Data for TAVR in BAVD

Initial experience with the older generations of balloon-expandable (Sapien XT, Edwards Lifesciences, Irvine, California) and self-expanding (CoreValve, Medtronic, Minneapolis, Minnesota) platforms demonstrated feasibility of TAVR in selected BAVD patients. However, rates of procedural mortality (3.6%), valve embolization (2.2%), post-TAVR aortic regurgitation (28.4%), and conversion to open surgery (2.2%) were higher than those that had been observed with TAVR for trileaflet valves.[23]

In contrast, several more recent studies have suggested that newer generation devices appear to perform well in the BAVD population. Analysis of the Bicuspid aortic stenosis (AS) TAVR multicenter registry demonstrated that TAVR in patients with bicuspid aortic stenosis was associated with an increased rate of conversion to open surgery (2.0% vs. 0.2%), implantation of a second valve (4.8% vs. 1.5%), aortic root injury (1.6% vs. 0%), and moderate or severe paravalvular regurgitation (10.4% vs. 6.8%) as compared with TAVR for trileaflet AS.[24] However, when this analysis was restricted to patients receiving newer-generation TAVR devices (Sapien 3 [Edwards], Evolut R [Medtronic], or Lotus [Boston Scientific, Natick, Massachusetts]), there were no significant differences in any of these procedural complications. Using the third generation balloon-expandable Sapien 3 valve or the self-expanding Evolut R/PRO valve, propensity-matched analyses from the Society of Thoracic Surgeons/American College of Cardiology Transcatheter Valve Therapy (TVT) Registry have demonstrated that there are no significant differences in mortality, valve hemodynamics, or paravalvular regurgitation between patients with bicuspid or tricuspid AS undergoing TAVR at 30 days or 1 year.[25,26] Moreover, when observational studies of TAVR have been restricted to patients at low surgical risk, there were no significant differences in 30-day or 1-year outcomes after treatment with newer-generation balloon expandable valves between patients with bicuspid or tricuspid aortic stenosis.[27]

While these retrospective studies using the most recent generation TAVR systems are encouraging, these analyses have numerous limitations including the lack of a control group undergoing surgical valve replacement and reliance on site-reported clinical outcomes and adverse events. In addition, the use of a clinical registry to evaluate TAVR as a treatment strategy for BAVD is subject to selection bias since patients included in the registry were determined to be suitable for TAVR by the local Heart Team, while patients whose technical results were expected to be poor were likely to be excluded. Furthermore, it can be difficult for the practicing clinician to extrapolate registry findings to their own practice, particularly as these study designs also lack prospective systematic TAVR computed tomography angiography (CTA) data analysis to help guide other

physicians on the appropriate anatomic criteria and definitions of bicuspid morphology to guide patient selection for TAVR.

Some of the limitations of retrospective analyses can be overcome with a prospective study design. Prospective registry studies of TAVR for bicuspid AS are summarized in Table 2. The first study to evaluate clinical outcomes in low-risk bicuspid patients undergoing TAVR was the Low Risk TAVR trial.[28] An independent screening committee evaluated all participants to ensure clinical and anatomical eligibility for TAVR, and postprocedural imaging studies were reviewed by an independent core laboratory. The primary endpoint was all-cause mortality at 30 days. A total of 61 TAVR patients were included, of whom 74% received a balloon-expandable valve, and 26% received a self-expanding valve. At 30 days, there were no deaths or disabling strokes in any of the patients—results that were comparable to a matched SAVR cohort from the same sites. Moreover, no patients required conversion to open surgery, and only 1 patient had moderate paravalvular leak (PVL) at 30 days.

The Evolut Low Risk Bicuspid Study was a prospective single-arm study which demonstrated promising outcomes with the use of self-expanding TAVR valves to treat bicuspid AS.[29] An important feature of this study was that the screening committee recorded the reasons for patient exclusion. A total of 19 patients were excluded on the basis of anatomical size, either of the sinuses or the aortic annulus; 9 were excluded for the presence of aortopathy; and only 1 was excluded for prohibitive calcification of the LVOT. With this careful screening process, and also potential selection bias by sites with regards to which patients they were willing to enroll, outcomes were favorable. At 30-day follow-up, rates of death (0.7%) and stroke (4.0%) were low. Only 1 patient of 150 (0.7%) required conversion to open surgery, while 3.3% of patients had more than 1 valve implanted. These favorable procedural results were sustained through short-term 1-year follow-up.[30] Similar findings were noted with balloon-expandable devices in a propensity-matched analysis of 148 patients enrolled in the Placement of Aortic Transcatheter Valves (PARTNER) 3 bicuspid registry compared with matched patients undergoing TAVR for tricuspid AS within the PARTNER 3 trial.[31]

It should be acknowledged that these prospective studies of newer-generation TAVR devices have relatively small sample sizes and therefore attendant wide confidence estimates for the event rates. They are also performed in highly selected patient populations, reflecting the expert assessment of the Heart Teams at participating sites.

Potential Explanations for Improving TAVR Outcomes

As noted, the observational studies have suggested improving outcomes with TAVR for bicuspid AS over time. It is likely that advances in device technology, imaging, and implantation techniques have all played a role in these findings. These advances include the addition of sealing skirts to reduce paravalvular regurgitation on newer generation TAVR prostheses; widespread use of CTA for valve sizing with an emphasis on more reproducible annular sizing for bicuspid cases[32]; reduced implant depth so as to mitigate the risk of new pacemakers[33,34]; and more liberal use of predilatation to facilitate complete expansion of the transcatheter valve.

Another potential explanation for these secular trends is a better understanding of favorable (and unfavorable) bicuspid anatomies for TAVR, leading to more appropriate patient selection. Yoon and colleagues demonstrated the impact of bicuspid valve morphology on outcomes achieved with TAVR.[17] This study was based on a collaborative registry that followed 1034 patients with BAVD who underwent TAVR with newer generation devices at 24 centers across 8 countries. All patients underwent core laboratory CTA analysis of the valve complex, in which valve morphology was assessed using the Sievers classification system and further characterized according to the extent of calcification of the raphe, LVOT, and aortic valve leaflets. Calcified raphe and excess leaflet calcification (defined as calcium volume greater than the median value in the study data set) were identified as anatomical features associated with increased mortality. Patients with both heavily calcified leaflets and a calcified raphe had the highest mortality when compared with patients who had only 1 or none of these features (25.7% vs. 9.5% vs. 5.9%). Moreover, patients with both features were also more likely to experience aortic root injury and had more severe paravalvular regurgitation after TAVR. Although this analysis provided useful information on how the morphology of the bicuspid aortic valve impacts clinical outcomes, it is limited by the lack of external validation as well as the inability to prospectively apply these criteria in practice given subjective assessment and lack of specific applicable thresholds (i.e., excess leaflet calcification was determined as greater than the median of the sample included within this study).

A newer classification system for bicuspid aortic valves has recently been developed,[35] which delineates 3 BAV types. The first is the fused bicuspid aortic valve type, which accounts for 90 to 95% of cases and is characterized by 2 of the 3 cusps appearing fused with each other within 3 distinct aortic sinuses. This phenotype has a raphe in 70% of cases. The second type is the 2-sinus bicuspid aortic valve type, which accounts for 5% to 7% of cases. In this phenotype, there are 2 distinct cusps which are roughly equal in size and shape–each of which occupies ~180 degrees of the aortic annulus. This type of bicuspid anatomy is also associated with 2 sinuses but no raphe. Finally, the third phenotype is a partial fusion bicuspid aortic valve type, where the aortic valve appears trileaflet with 3 symmetrical cusps but on closer inspection there is fusion between 2 cusps at the base of the commissure, leading to the formation of a "mini-raphe."

Current Knowledge Gaps

Currently, there are 4 main issues with the available evidence base for TAVR in BAVD. First, all of the available studies are observational in nature and most of these are derived from retrospective analyses of large registries, while the few prospective studies are limited by selection bias and small sample sizes. In previous studies, this selection bias occurs at the site level (where the treating clinical teams recruit only patients they feel will do well with TAVR) and at the level of the formal screening committee (where central case review boards may further review all clinical and imaging data before permitting entry into the study).

Table 2
Prospective studies reporting outcomes after TAVR for bicuspid aortic valve disease

Study name	First author	Year	N	Valve type	Primary outcome	Maximum follow-up	Main results
Low Risk TAVR	Waksman	2020	61	74.0% balloon-expandable and 16.0% self-expanding	All-cause mortality at 30-d	30-d	No deaths and no disabling strokes at 30-d
Low Risk Bicuspid Study	Forrest	2020	150	Evolut R or Evolut PRO	All-cause mortality or disabling stroke at 30-d	1-y	1.3% death or disabling stroke at 30-d; when propensity matched to patients with tricuspid AS, no difference in outcomes at 1-y
PARTNER 3 Bicuspid Registry	Williams	2021	148	Sapien 3	All-cause death, all stroke, and cardiovascular hospitalization at 1-y	1-y	No difference in primary endpoint when compared to patients with tricuspid AS; 0.7% mortality at 1-y in bicuspid patients

TAVR, transcatheter aortic valve replacement.

Additionally, these studies are limited to relatively short-term comparisons (e.g., 1 year), which is a major deficiency given the importance of long-term outcomes among the 50- to 60-year-old patients who are typically affected by BAVD.

A second major issue is the lack of data comparing outcomes of TAVR with those of SAVR for bicuspid AS. To our knowledge, there are only 2 studies that include a SAVR comparator group. The first is a propensity-matched analysis derived from the National Inpatient Sample between 2012 and 2016.[36] This study is limited, however, by the use of administrative databases and the fact that only in-hospital outcomes were available. The second study utilized the Nationwide Readmission Database to study 1393 propensity matched pairs who underwent TAVR and SAVR, of which 848 pairs had 6-month follow-up.[37] This study suggested that TAVR was associated with reduced in-hospital mortality compared with SAVR, but 6-month outcomes were similar. This study was also limited by its dependence on an administrative database with attendant potential for coding errors and lack of granular imaging, procedural and follow-up data. Both studies are also susceptible to confounding by indication, whereby patients offered TAVR are likely to be those who are felt to be unsuitable for surgery.

To date, there is limited available comparative data on quality-of-life outcomes for bicuspid patients after TAVR vs. SAVR. Understanding long-term health status among such patients is important since potential complications of TAVR treatment for patients with BAVD (e.g., pacemaker implantation, PVL) may impact late quality of life as well as long-term survival.

Another critical limitation of the available data is the lack of well-defined and validated imaging criteria for patient selection for TAVR. As described, the imaging features that have been proposed for risk stratification for TAVR in BAVD are based on a single multicenter study that has not been replicated. As such, there is a lack of clearly defined, prospective, advanced imaging phenotyping using TAVR CTA for imaging markers that can inform therapeutic decision-making. Beyond bicuspid leaflet morphology, CTA phenotyping should also encompass other anatomical variants or anomalies known to be associated with BAVD such as cusp length, coronary artery origin, and ostia heights. Finally, recent large-scale registry-based studies reflect only those patients with BAVD who were felt to be appropriate for TAVR (due to anatomic or clinical factors, or both) and thus suffer from serious unmeasured selection bias. Specifically, the clinical utility of an intervention can be defined both by its effect on the population receiving treatment, and also from the effect that withholding therapy has on patients who are not treated. Since the majority of available CTA and clinical data on BAVD are derived from patients who underwent TAVR, we have little understanding of those factors that led to the treatment decisions. Moreover, little is known about the outcomes of patients deemed not suitable for TAVR either on the basis of clinical or anatomical factors, and whether they were then treated with surgery or no intervention.

Specific Challenges for Clinical Trials of TAVR for BAVD

Although much of the treatment evidence base for trileaflet AS with TAVR is derived from RCTs, conducting meaningful randomized trials for BAVD poses several key challenges. The most obvious challenge is perceived lack of equipoise. Both patients and physicians may be reluctant to enroll in a RCT where the alternative is SAVR, since TAVR for bicuspid AS is currently both approved by the US FDA and reimbursed by Medicare. It should be stated once again, however, that BAVD patients were excluded from previous SAVR vs. TAVR randomized trials. The quality of data supporting TAVR use in BAVD patients is therefore relatively low and equipoise between these 2 options is justified.

For those patients and providers who have equipoise between TAVR and SAVR for bicuspid AS, several other important trial design questions will need to be addressed. First, what are the specific clinical and anatomical characteristics of the ideal BAVD population to study? In contrast to trileaflet aortic stenosis, which is relatively uniform from both a pathologic and anatomic standpoint, BAVD represents a very heterogenous group of patients with varying anatomical phenotypes, at the level of not just the leaflet, but annular, coronary, and aortic root levels, with additional associated comorbidities. In particular, concomitant aortopathy is present in 20 to 30% of patients with BAVD.[38] As noted previously, the presence of aortopathy poses several challenges for TAVR[1]: although aortopathy cannot be treated by TAVR, small series with intermediate follow-up have not shown significant interval growth[2]; the TAVR procedure may be technically more challenging due to eccentric dilatation causing angulation and a horizontal valve plane; and[3] there may be increased procedural risk related to aortic injury during valve advancement or deployment. The presence of aortopathy also affects potential trial designs, as a threshold of root dilatation would need to be agreed upon as an exclusion criterion. Beyond aortopathy, the heterogeneity of BAVD also has implications for trial design. There may be certain anatomic phenotypes that are not best treated with TAVR and therefore should not be included in a clinical trial, but these anatomic parameters would have to be agreed upon and defined as part of the trial design. Patients with predominant aortic regurgitation or mixed aortic valve disease, which can occur commonly in BAVD, would also present a similar challenge.

Another critical challenge in designing clinical trials for treatment of BAVD is the optimal duration of follow-up. Patients with significant BAVD tend to be younger than patients with trileaflet aortic valves, which necessitates longer-term follow-up with attendant increases in trial cost and complexity. If, for example, there are subtle differences between TAVR and SAVR in outcomes such as mild paravalvular regurgitation or increased risk of structural valve deterioration due to asymmetrical valve expansion, these issues may not impact valve durability or mortality until 10 years or longer. As a result, long-term follow-up in a trial of TAVR in BAVD is likely to be even more important than in the pivotal low-risk RCTs in patients with trileaflet AS, in which the average age at enrollment was 73 to 74 years.[6,9] Additionally, the need for long-term follow-up carries with it the risk of trial obsolescence. If there are significant advances in TAVR device technology or technique in the 10+ years it takes to complete a trial, the trial results may have limited impact on clinical practice by the time they are available.

The final issue for BAVD trials is the need to manage bioprosthetic valve failure (both surgical and transcatheter) over the patient's lifetime. Unless the trial is limited to older patients, it is likely that many BAVD patients will need at least 1 and possibly 2 repeat valve procedures in their lifetime. Given the known complexities associated with valve-in-valve procedures, clinical trials of TAVR for BAVD will therefore need to thoroughly capture subsequent valve replacement procedures in order to assess how the short- and long-term outcomes of the "second valve" are influenced by the initial therapeutic strategy.

Proposed Study Designs for Treatment of BAVD

In this section, we describe 5 potential clinical trials to address current knowledge gaps regarding the role of TAVR in the management of severe AS due to BAVD (Table 3). For each trial, we propose study objectives, endpoints, and discuss the advantages and disadvantages of the particular design with respect to practicality and knowledge generation.

Study 1: Conventional "Regulatory Trial"

The first potential study is a conventional RCT with a noninferiority design—similar to the trials that led to approval of TAVR for treatment of severe trileaflet AS across the surgical risk spectrum. The control strategy would be SAVR, and the primary endpoint would be a composite of all-cause death, disabling stroke, and heart failure rehospitalization (including hospitalization for management of complications related to the valve prosthesis such as PVL and structural valve deterioration), which would be assessed at 10-year follow-up. This trial design would

Table 3
Potential study designs for clinical trials to address current knowledge gaps in the treatment of patients with severe aortic stenosis due to bicuspid aortic valve disease

Study design (number)	Study arms	Primary endpoint	Secondary endpoints	Follow-up duration	Eligibility criteria	Advantages	Disadvantages
Conventional noninferiority regulatory RCT (1)	Treatment group: TAVR with any commercially available valve platform Control group: SAVR	Composite of all-cause death, disabling stroke, and heart failure hospitalization	Exhaustive list of clinical, echocardiographic, and quality-of-life parameters as per the pivotal trials comparing TAVR to SAVR in trileaflet AS	10 y	Severe bicuspid AS across full spectrum of surgical risk deemed eligible by local heart team	Robust methodology with highly granular data with multiple secondary endpoints	Resource intensive with high costs and a long wait until trial results are available; unclear whether clinicians will enroll all patients
Pragmatic RCT using administrative claims data, electronic health records and established clinical registries for follow-up (2)	Treatment group: TAVR with any commercially available valve platform Control group: SAVR Parallel registry of patients not suitable for randomization	Composite of all-cause death, disabling stroke, or heart failure hospitalization	Lean case report forms with more limited follow-up parameters compared with a traditional regulatory trial	10 y	Consecutive patients with severe bicuspid AS across full spectrum of surgical risk; patients unsuitable for randomization followed in nested parallel registries of SAVR and TAVR	Lower costs than traditional RCT; parallel registries for patients not randomized; enrollment of consecutive bicuspid AS patients should aid rapid recruitment; inclusion of parallel registries provides insight into generalizability	Lack of core-lab adjudicated imaging data for all patients; site-reported clinical outcomes without central adjudication; lack of granular quality of life data and other secondary endpoints
Conventional noninferiority RCT in low-risk patients with optimal anatomy for TAVR (3)	Treatment group: TAVR with any commercially available valve platform Control group: SAVR	Composite of all-cause death, disabling stroke, and heart failure hospitalization	Exhaustive list of clinical, echocardiographic, and quality-of-life parameters as per the pivotal trials comparing TAVR to SAVR in trileaflet AS	10 y	More restrictive; only low-risk patients with optimal anatomy for TAVR would be included	Will provide first rigorous randomized data to support current practice patterns; low likelihood of harm for any investigative strategy	Does not truly address an evidence gap; challenges to recruitment since TAVR is already approved for these patients
RCT focusing on quality-of-life outcomes (4)	Treatment group: TAVR with any commercially available valve platform Control group: minimally invasive SAVR	Disease-specific and generic health status at 1-mo follow-up	Echocardiographic parameters, discharge to home, healthcare utilization, and costs	1 y	Low-risk patients suitable for TAVR or minimally invasive SAVR	Modest sample size and shorter duration meaning lower costs and more rapid evidence generation; addresses a question not studied in previous TAVR vs. SAVR RCTs	Not powered for difference in clinical outcomes
Prospective CT-based registry with core-laboratory analysis (5)	All patients with bicuspid AS referred for TAVR	Development of a risk score to predict clinical outcomes and procedural success with TAVR	Understanding of bicuspid anatomies more suitable for balloon-expandable or self-expanding valves	1 y	Consecutive patients with severe bicuspid AS referred for TAVR who have undergone a CTA	Practical design with lower costs and no requirement for randomization; results could help inform design of future trials	No randomized comparison of TAVR to SAVR

CTA, computed tomography angiography; RCT, randomized controlled trial; SAVR, surgical aortic valve replacement; TAVR, transcatheter aortic valve replacement.

include patients across the surgical risk spectrum, with eligibility determined initially by the local heart team. Given the need for concomitant aortic root or ascending aorta replacement, patients with a maximal aortic diameter greater than 4.5 cm would be excluded.[39] Further screening would then be performed by a case review committee, echocardiography core laboratory, and CT core laboratory. A comprehensive set of secondary clinical outcomes would be collected similar to those included in the original TAVR vs. SAVR RCTs, including long-term quality of life measures. In addition, detailed echocardiographic assessments would be performed at multiple timepoints with a focus on paravalvular regurgitation, valve degeneration, and left ventricular function. Finally, CT follow-up would be critical to assess and learn about TAVR device conformation for a given BAVD anatomy including symmetrical frame expansion of the transcatheter valves, leaflet mobility, subclinical leaflet thrombosis, and any consequent effects on valve performance.

- Advantages: Robust methodology; highly granular data from secondary endpoints.
- Disadvantages: High cost; long-term follow-up mandatory, and trial results may be obsolete at completion owing to evolution of TAVR (or SAVR) technology; even with 10-year follow-up, questions regarding lifetime management would persist.

Study 2: Pragmatic "All-Comers" RCT With Parallel Nested Registries

An alternative approach would be to perform a trial similar to Study 1 that would encourage recruitment of all consecutive bicuspid aortic stenosis patients at each site, and use a pragmatic approach to follow-up based on a combination of administrative claims data and electronic health records. Inclusion and exclusion criteria would be identical to Study 1 (i.e., full spectrum of surgical risk, aortic diameter $<$4.5 cm), but the emphasis would be on recruitment of all patients being considered for some form of valve replacement for bicuspid AS. This approach would have the benefit of permitting capture of data for patients for whom the local heart team felt there was not equipoise and would thus be better treated with TAVR or SAVR. These patients would be enrolled into parallel, prospective registries according to treatment selected and their outcomes followed longitudinally. All other patients for whom there was felt to be equipoise would be randomized to TAVR (using any commercially available device) vs. SAVR. Ideally, such a study would incorporate the TVT registry as a mechanism for collection of baseline patient characteristics, technical details, and in-hospital outcomes. Then, similar to the Swedish model (as exemplified by the TASTE and SWEDEHEART studies[40,41]), follow-up would be based on linkage of trial participants to administrative claims through Medicare or private insurance. Similar to Trial 1, the primary endpoint would be a composite of all-cause death, hospitalization for stroke, or heart failure rehospitalization, with a noninferiority design. There would be dedicated echocardiographic and CT imaging substudies for the patients recruited into the RCT component to provide additional insight into patient selection for the RCT and anatomic factors associated with differential outcomes. Lean case report forms with limited collected follow-up parameters would be utilized to help keep costs down.

- Advantages: Lower costs than a traditional regulatory trial due to use of claims data for follow-up; broad entry criteria and streamlined enrollment process should allow for a large number of study sites for rapid recruitment and potentially improved generalizability of results; parallel registries to permit longitudinal follow-up of patients deemed not suitable for randomization and treated with either TAVR or SAVR, which would provide critical insight into the generalizability of the trial results.
- Disadvantages: Lack of detailed CT or echocardiographic follow-up for all patients; lack of core-lab adjudication of BAVD anatomic phenotyping; clinical outcomes based on site-reported outcomes captured for administrative claims; some secondary outcomes that do not result in hospitalization may not be captured (e.g., quality of life); challenging to follow non-Medicare patients longitudinally in the United States due to changing health plans.

Study 3: RCT of TAVR vs. SAVR for Low-Risk Patients With Optimal Anatomy for TAVR

In contrast to the relatively broad inclusion criteria for the previous 2 study designs, patients would only be enrolled after review of diagnostic studies by CT core laboratory and case review committee for confirmation of optimal anatomy for TAVR. Similar to Studies 1 and 2, this trial would adopt a noninferiority design with a composite primary endpoint of all-cause death, disabling stroke, and heart failure rehospitalization. In contrast to Studies 1 and 2, this trial would be designed to generate focused evidence to support current clinical practice (since these are the patients in whom TAVR is already being performed at many centers).

- Advantages: Study design will provide rigorous data to support current practice patterns; investigator confidence that TAVR can be performed with good technical results in these patients should support recruitment.
- Disadvantages: Does not truly address an evidence gap, since these patients are likely to have TAVR results similar to trileaflet AS; expected event rate low, thus necessitating a large sample size to demonstrate noninferiority; may be challenging to enroll to if many centers are already offering TAVR to these patients.

Study 4: RCT of TAVR vs. Minimally Invasive SAVR

In contrast to the previous studies, all of which were designed to examine long-term clinical outcomes, this would be a short-term RCT with a focus on recovery and early QOL. The SAVR procedures could be performed either via mini-sternotomy or mini-thoracotomy. The primary outcome would be the disease-specific and generic health status at 1-month follow-up (adjusted for baseline). Secondary endpoints would include echocardiographic measures of residual gradient and PVL, discharge to home, length of hospital stay, health care resource utilization, and costs.

- Advantages: Modest sample size and shorter trial duration should minimize time to evidence generation and limit obsolescence of results when primary endpoint is reached.
- Disadvantages: Underpowered to provide meaningful data on clinical events such as mortality or stroke; recruitment limited to sites with experience performing minimally invasive SAVR, which may also limit generalizability.

Study 5: Prospective Single-Arm Registry of Patients With Bicuspid AS Referred for TAVR, With CT Core Laboratory Analysis

The primary objective of this study design would be to identify specific valve phenotypes that are likely to achieve optimal or suboptimal results with TAVR, building on existing imaging databases. By performing detailed phenotypic CT analysis, the study would use a combination of standard statistical analysis and machine learning image processing to develop algorithms to predict technical and clinical outcomes (mortality, stroke, paravalvular regurgitation, or new pacemaker insertion) of TAVR for BAVD. This data set could potentially be combined with existing CT studies on patients with bicuspid AS to serve as validation cohorts for any resulting algorithms. In addition, CT phenotyping could potentially be used to predict clinical outcomes and procedural success (or complications) with balloon-expandable vs self-expanding valves. If successful, these analyses would provide algorithms (or simplified scoring systems) for improved clinical decision-making and procedural planning. Finally, by linkage of this registry with the TVT and Society of Thoracic Surgeons registries as well as claims data, it may be possible to perform a rigorous

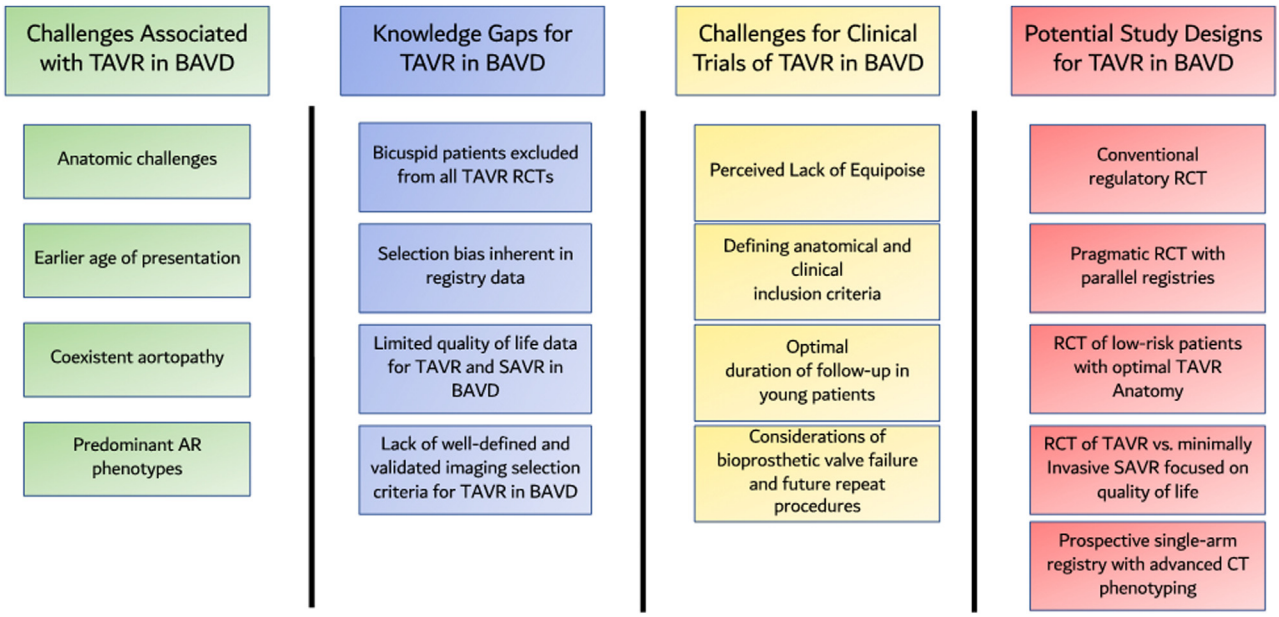

Figure 1. Summary of current considerations and future directions for clinical research on transcatheter aortic valve replacement (TAVR) for bicuspid aortic valve disease (BAVR).
Abbreviations: CT, computed tomography; RCT, randomized controlled trial; SAVR, surgical aortic valve replacement.

observational comparison of SAVR vs. TAVR outcomes while adjusting for standard clinical features as well as valve complex anatomy.

- Advantages: Practical design that does not require randomization; since primary outcomes are short-term, results will be available rapidly; addresses a major evidence gap in identifying features that can be prospectively applied to aid patient selection; the results could be utilized to help inform the design and eligibility criteria of a prospective RCT.
- Disadvantages: Will require large sample size to identify enough complications to support predictive models; not designed to support therapeutic comparisons of TAVR to SAVR.

Current Recommendations: Agenda for Future Clinical Research in TAVR for BAVD

The prospect of a randomized trial comparing TAVR and SAVR for patients with BAVD has been raised and debated for several years. Based on recent surveys, most physicians agree this is an important clinical question that merits careful study and believe there is sufficient equipoise between TAVR and SAVR to justify randomization among selected anatomic subsets. Importantly, the observational data generated to date, both from large retrospective databases and small prospective studies, have significant limitations. Nonetheless, as outlined in this article, there are myriad challenges that make the design and conduct of a traditional RCT in this space more complex than for patients with aortic stenosis and trileaflet valves (Figure 1).

To initiate this dialog, we have outlined 5 different potential study designs involving severe AS due to BAVD and summarized some of the key advantages and disadvantages of each. In order to advance this agenda, we recommend that a multidisciplinary working group be convened to explore the feasibility of performing a pragmatic clinical trial using electronic health records and existing registry infrastructures to compare long-term clinical outcomes of TAVR vs. SAVR for patients with severe AS due to BAVD (study design #2). The inclusion of parallel registries of patients with bicuspid AS who are selected for TAVR or SAVR will be critical to define the "universe" of such patients and to understand how to apply the randomized trial results in practice. Such a trial could be executed at much lower costs than a traditional RCT while still addressing a key knowledge gap that could inform guideline recommendations. And if successful, such a trial could serve as a blueprint for future studies exploring expanded indications for other approved devices.

In parallel, we recommend prioritizing the development of a prospective registry with a focus on advanced CT phenotyping to develop parameters and risk scores that can be prospectively applied to patients to inform clinical decision-making (Study Design #5). This study could build on previous CT data sets and help to generate CT-based risk scores for patients with bicuspid severe AS being considered for TAVR. Although not a randomized trial, this observational study could also serve as the basis for studies identifying the optimal valve type for a particular valve anatomy.

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