REVIEW

Current Key Issues in Transcatheter Aortic Valve Replacement Undergoing a Paradigm Shift

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As a new technology in the management of valvular heart disease, transcatheter aortic valve replacement (TAVR) has drawn much attention since its emergence. To date, numerous studies have investigated the safety and efficacy of TAVR in patients of various risk profiles with severe aortic stenosis (AS) and demonstrated comparable or superior outcomes of TAVR when compared with surgical aortic valve replacement (SAVR). The favorable outcomes of TAVR in inoperable patients, as well as in high- and intermediate-risk patients, are endorsed in current guidelines, and trials of low-risk patients have shown non-inferior or even superior results of TAVR than for SAVR, suggesting that the clinical indications of TAVR can be expanded to low-risk patients. Moreover, a therapeutic role of TAVR has been suggested in various aortic valve (AV) diseases, such as bicuspid AV, moderate AS with heart failure, aortic regurgitation, and bioprosthetic valve failure. In this review, we summarize the current issues of TAVR in various patient populations and discuss the expanding clinical indications of TAVR, which are driving a major paradigm shift in the management of AV disease.

Key Words: Aortic stenosis; Surgical aortic valve replacement; Transcatheter aortic valve implantation; Transcatheter aortic valve replacement; Valve-in-valve

New technologies, according to the Gartner hype cycle theory, have 5 phases from conceptual presentation to generalized adoption.[1] The introduction and distribution of transcatheter aortic valve replacement (TAVR), or transcatheter aortic valve implantation (TAVI), demonstrated similar patterns (**Figure 1**), but since its emergence, TAVR has been attracting much attention as an alternative to surgical aortic valve replacement (SAVR). Given the potential benefits of this noninvasive procedure and the unmet clinical need in real-world practice, clinicians and researchers imposed huge expectations and enthusiasm on TAVR ("peak of inflated expectations"), which was then criticized for the risk of complications and uncertainties about device durability and long-term prognosis ("trough of disillusionment"). These concerns were then rebutted with numerous studies from clinical trials and registries that reported favorable outcomes of TAVR, compared with SAVR ("slope of enlightenment"), and it is expected that ongoing trials with constructive discussion will clarify the optimal treatment strategy for applying TAVR in various AV diseases ("plateau of productivity").

Currently, there are active debates regarding the clinical role, long-term durability, risk of complications, and expanding indications of TAVR in patients with low surgical risk, bicuspid AV, moderate aortic stenosis (AS) with heart failure (HF), and bioprosthetic valve failure. In this article, we summarize the current issues in TAVR, and review the expectations for expanding the clinical indications of TAVR with supporting evidence.

Current Treatment Strategy Guided by Surgical Risk Score

TAVR vs. SAVR or Standard Therapy According to Risk Scores

Early in the introduction of TAVR, its clinical role was demonstrated among inoperable patients with severe AS (Society of Thoracic Surgeons [STS] score >15%) and those with high surgical risk (STS score, 10–15%) (**Table 1**).[2–5] Among intermediate-risk patients (STS score, 4–10%) with severe AS, large trials reported that TAVR resulted in similar, or even better, outcomes in terms of the risks of death and disabling stroke, hemodynamic parameters, hospital stay, and quality of life, compared with SAVR (**Table 1**).[6–8] These findings indicate that TAVR was a reasonable alternative to SAVR for intermediate-risk patients with severe AS.[2]
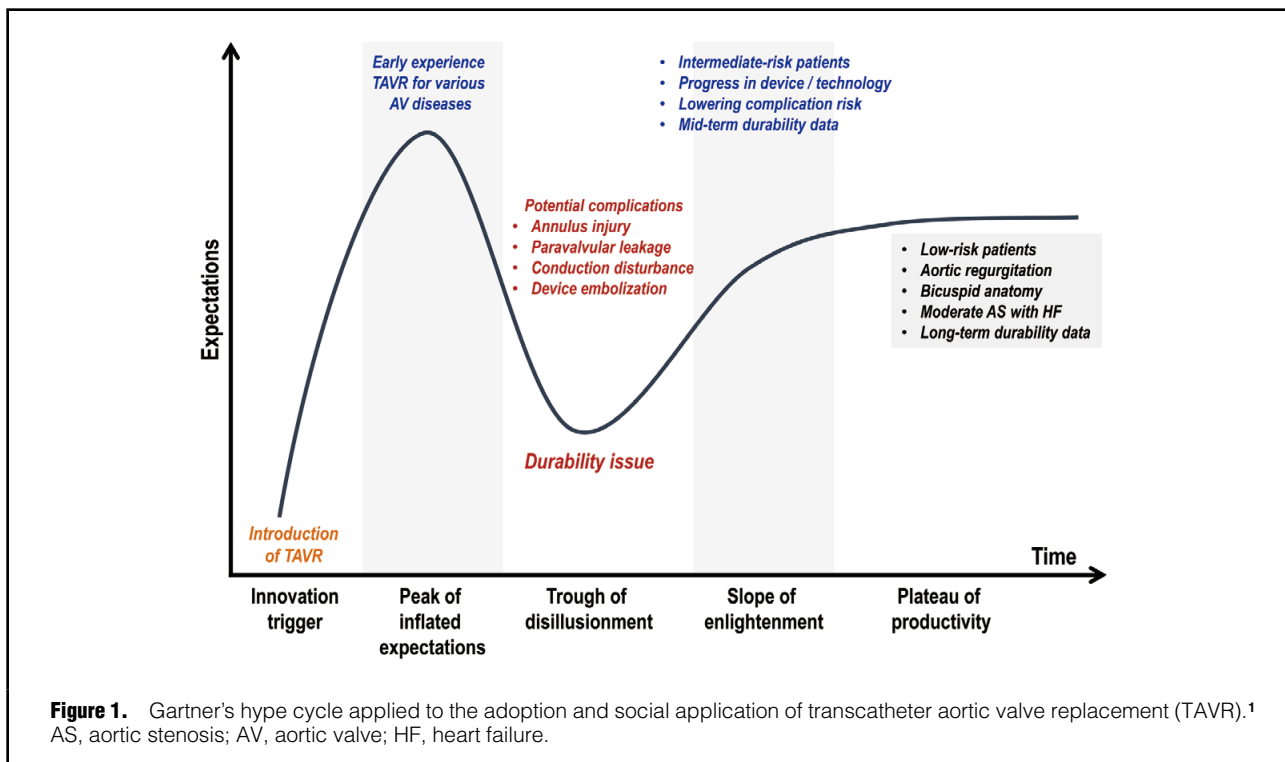
Subsequently, the attentions at the front line of clinical practice turned to low-risk patients, and several studies showed acceptable outcomes in the low-risk patients that render optimistic expectations (**Table 1**).[9–11] Although the outcomes of TAVR in low-risk patients had been questioned, the Evolut Low Risk trial showed that TAVR with Evolut-R was non-inferior to SAVR in terms of a composite of death or disabling stroke at 24 months among more than 1,400 patients with an average STS score of 1.9%.[12]

Figure 1. Gartner's hype cycle applied to the adoption and social application of transcatheter aortic valve replacement (TAVR).[1] AS, aortic stenosis; AV, aortic valve; HF, heart failure.

Furthermore, according to the Placement of Aortic Transcatheter Valves (PARTNER) 3 trial, which randomized 1,000 low-risk patients, TAVR with the Sapien 3 resulted in a significantly lower rate of a composite of death, stroke, or rehospitalization at 1 year than SAVR.[13] These "game-changer" trials will expand the clinical indication to low-risk patients.

Risk Scores vs. Frailty as an Independent Prognostic Factor

Based on current evidence, the American Heart Association/American College of Cardiology guidelines recommend TAVR for inoperable patients and those with high surgical risk, and also suggest TAVR for those with intermediate surgical risk (**Figure 2**).[2] However, there are drawbacks to determining treatment strategy based on risk scores alone, because these scores were developed in surgical patients alone, and important comorbidities were overlooked. The European Society of Cardiology/European Association for Cardiothoracic Surgery guidelines adopted similar recommendations based on the calculated surgical risk and provided several aspects to be considered, such as age, severe comorbidity, previous cardiac surgery, frailty, restricted mobility and conditions that may affect the rehabilitation process after TAVR, and any conditions requiring concomitant surgical interventions (**Figure 2**).[3] These recommendations indicate that calculated risk scores should be adjusted by frailty and comorbid conditions, and that the decision on treatment strategy requires comprehensive assessment of the patient.

Most patients undergoing TAVR are frail, which is one of the main reasons for the high mortality rates with TAVR, despite the extremely high procedural success rate. Frailty affects recovery following TAVR, leads to functional decline, and is associated with poor post-TAVR outcomes.[14]

According to the Optimized Catheter Valvular Intervention (OCEAN)-TAVI Japanese multicenter registry, the frailty score affects not only in-hospital outcomes but also post-discharge long-term prognosis.[15] These findings suggest that frail patients have a potential TAVR-related futility. However, it should also be noted that refusal of TAVR, even only once, is associated with worse outcome.[16] Because patients with advanced frailty cannot undergo surgery because of their extremely high peri-operative risk, the only available treatment option for them is TAVR. Therefore, an assessment of frailty in patients undergoing TAVR should not serve as a barrier for the procedure but rather should be used for proper periprocedural management, such as nutritional support or rehabilitation.

Anatomic Complexity and Concerns With TAVR

Implications of AV Calcification

The severity and location of AV calcification are important contributing factors to post-TAVR paravalvular leakage (PVL), because a heavily calcified native AV may prevent complete expansion of the device, even after balloon post-dilation.[17] A study of 150 patients who underwent TAVR suggested that eccentricity of AV calcification (EoC) is associated with PVL risk.[17] In that study, EoC at the AV leaflets was assessed using the maximum difference in calcification between any 2 adjacent leaflet sectors. This "leaflet-based EoC" might seem to be intuitive, but does not reflect true EoC in several situations that are common in severe AS patients. In this regard, our group developed a novel protocol for the assessment of EoC, called "bipartition EoC", which indicates the maximum absolute difference in calcium volume between 2 sectors divided by a cutting line that passes through the center of the AV cusps.[18] This method provides a simple but comprehensive

reflection of the true EoC, especially in patients with balanced calcification at 2 or more leaflets, those with significant commissural calcification, and those for whom delineation of the AV leaflets is difficult (**Figure 3**). The bipartition EoC has a better predictive value for the occurrence of PVL, and response to balloon post-dilation, compared with conventional leaflet-based EoC.[18] These findings highlight the importance of AV calcification and its eccentricity in determining the prosthesis type, device size, and whether to perform pre- and/or post-dilation during TAVR.[17,18]

It is expected that the new-generation devices will reduce the PVL risk, because they are mounted with outside fabric that can fill the gap between the device and AV calcification (**Figure 4**). These evolutionary changes provide optimism for a reduction in PVL without increasing the risk of aortic

root injury. However, the use of balloon-expandable valves still requires attention, because of the need for high-pressure inflation during deployment, especially in patients with heavy AV calcification.[19]

Bicuspid AV

Because of the anatomic characteristics of bicuspid AV, the application of TAVR in bicuspid AS raised negative expectations in terms of elliptical expansion of the device and the risks of coronary obstruction, residual PVL, and aortic root injury, which are attributable to structural characteristics (**Supplementary Figure 1**). Because of the fusion or raphe between AV leaflets, the actual size of the native AV opening is smaller than that of the aortic root, and device selection based on the aortic annulus can result in oversizing. Furthermore, the burden of AV calcification

Table 1. Clinical Trials Comparing TAVR and SAVR, and Other Important Trials

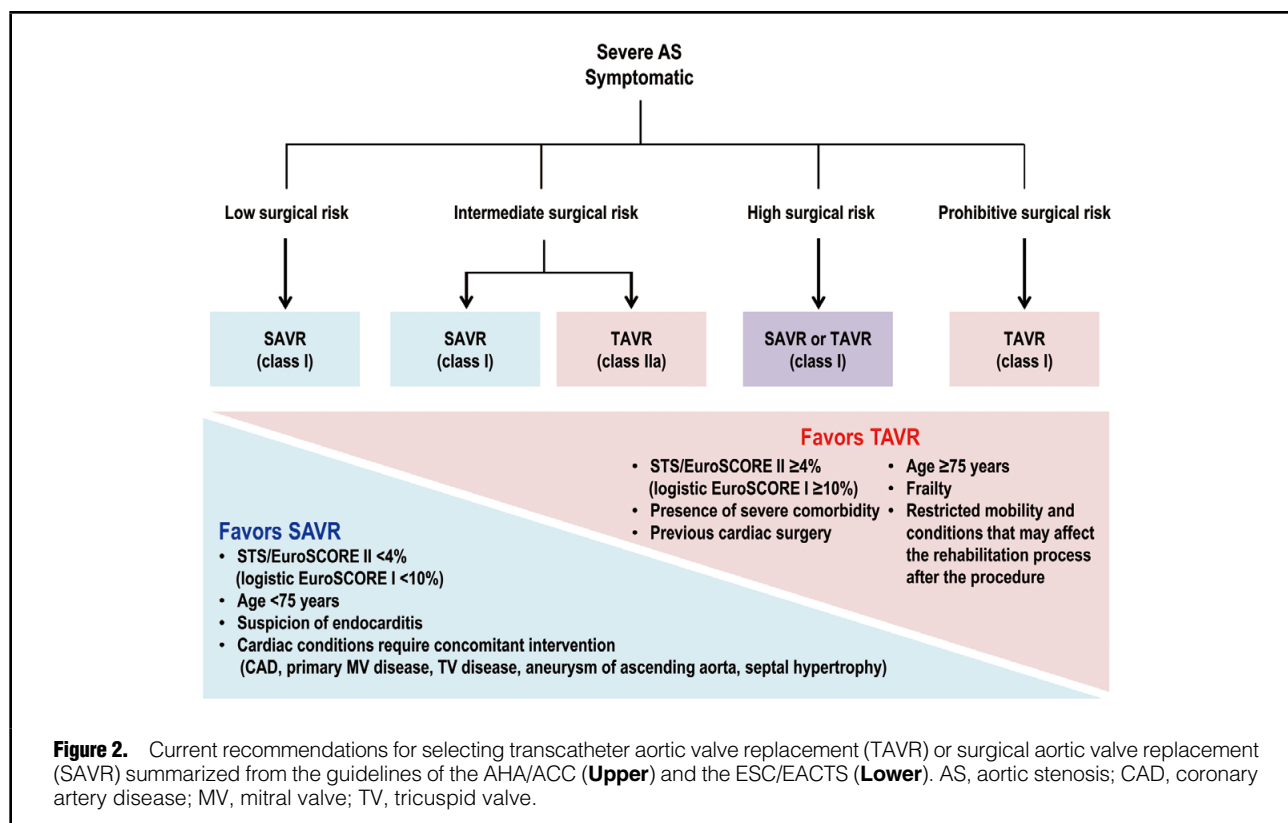| Surgical risk	Clinical trial	Study size	Design	Device	Primary endpoint	Short-term outcomes	Mid- to long-term outcomes
Clinical trials comparing TAVR and SAVR according to calculated risk scores							
Inoperable	PARTNER 1B[4]	358	TAVR vs. standard therapy	Sapien	All-cause death	1-year outcome - TAVR: 30.7% - Standard therapy: 50.7% (P<0.001)	5-year outcome - TAVR: 71.8% - Standard therapy: 93.6% (P<00001)
High	PARTNER 1A[5]	699	TAVR vs. SAVR	Sapien	All-cause death	1-year outcome - TAVR: 24.2% - SAVR: 26.8% (P=0.44)	5-year outcome - TAVR: 67.8% - SAVR: 62.4% (P=0.76)
Intermediate	PARTNER 2A[6]	2,032	TAVR vs. SAVR	Sapien XT	All-cause death or disabling stroke	2-year outcome - TAVR: 19.3% - SAVR: 21.1% (P=0.25) [transfemoral access cohort] - TAVR: 16.8% - SAVR: 20.4% (P=0.05)	–
	SURTAVI[8]	1,746	TAVR vs. SAVR	CoreValve Evolut-R	All-cause death or disabling stroke	2-year outcome - TAVR: 19.3% - SAVR: 21.1% (P=0.25)	–
	CoreValve US Pivotal trial[7]	797	TAVR vs. SAVR	CoreValve	All-cause death	2-year outcome - TAVR: 22.2% - SAVR: 28.6% (P<0.05)	–
Low	NOTION All Comer[9,11]	280	TAVR vs. SAVR	CoreValve	All-cause death	2-year outcome (total) - TAVR: 8.0% - SAVR: 9.8% (P=0.54) [Composite endpoint in low-risk patients] - TAVR: 14.7% - SAVR: 16.8% (P=0.59)	6-year outcome - TAVR: 42.5% - SAVR: 37.7%
	Low Risk TAVR[10]	200 (TAVR)*	TAVR vs. historical SAVR control	Sapien 3 or Evolut-R	All-cause death at 30 days	30-day death - TAVR: 0% - SAVR: 1.7%	–
	PARTNER 3[13]	1,000	TAVR vs. SAVR	Sapien 3	All-cause death, all strokes, and rehospitalization	1-year outcome - TAVR: 8.5% - SAVR: 15.1% (P=0.001)	–
	Evolut Low Risk[12]	1,468	TAVR vs. SAVR	Evolut-R	All-cause death or disabling stroke	2-year outcome - TAVR: 5.3% - SAVR: 6.7%	–
	NOTION 2 [NCT02825134]	992	TAVR vs. SAVR	Any approved device	All-cause death, MI, and stroke	Estimated primary completion date: June 2020	

(**Table 1** continued the next page.)

Important trials of expansion or refinement of the clinical role of TAVR

Topic	Clinical trial	Study size	Design	Device	Primary endpoint	Details
Moderate AS with HF	TAVR UNLOAD [NCT02661451]	600	TAVR vs. optimal HF therapy	Sapien 3	All-cause death, disabling stroke, hospitalization related to HF, AV disease or non-disabling stroke, KCCQ	Estimated primary completion date: January 2020
Asymptomatic severe AS	EARLY TAVR [NCT03042104]	1,109	TAVR vs. clinical surveillance	Sapien 3	All-cause death, all strokes, and unplanned cardiovascular hospitalizations	Estimated primary completion date: December 2021
	EVoLVeD trial [NCT03094143]	1,000	Early intervention (TAVR or SAVR) vs. routine care vs. no follow-up	Any approved device	All-cause death or unplanned AS-related hospitalization	Estimated primary completion date: July 2022 Screening for LV decompensation: troponin or ECG Confirmation of LV decompensation with CMR: mid-wall fibrosis - Intervention: early intervention with TAVR or SAVR (group A) - Comparator #1: routine care (groups B and C) - Comparator #2: no further follow-up (group D)
Antithrombotic therapy	ARTE[51]	222	DAPT vs. SAPT (aspirin)	Sapien XT	All-cause death, MI, ischemic stroke/TIA or life-threatening/major bleeding	3-month composite endpoint - DAPT: 15.3% - SAPT: 7.2% (P=0.065)
	GALILEO [NCT02556203]	1,644	NOAC (rivaroxaban) vs. DAPT	Any approved device	Death, first thromboembolic event, first bleeding event	Prematurely halted in October 2018[†] - Intervention: rivaroxaban+aspirin - Comparator: DAPT followed by SAPT (aspirin alone) [Preliminary analysis] Death or 1st thromboembolic event - Rivaroxaban: 11.4% - DAPT: 8.8% All-cause death - Rivaroxaban: 6.8% - DAPT: 3.3% Primary bleeding - Rivaroxaban: 4.2% - DAPT: 2.4%
	ATLANTIS [NCT02664649]	1,510	NOAC (apixaban) vs. standard of care (VKA or DAPT)	Any approved device	Composite of death, thromboembolic event, bleeding event	Estimated primary completion date: May 2020 - Stratum 1 (Indication for anticoagulation): apixaban vs. VKA - Stratum 2 (no indication for anticoagulation): apixaban vs. DAPT (followed by SAPT)
	ENVISAGE-TAVI AF [NCT02943785]	1,400	NOAC (edoxaban) vs. VKA	Any approved device	Composite of death, thromboembolic event, bleeding event	Estimated primary completion date: May 2020 - Intervention: edoxaban with or without APT - Comparator: VKA with or without APT
	Low Risk TAVR [NCT03557242]	300	VKA with aspirin vs. SAPT (aspirin)	Any approved device	All-cause death, all stroke, life-threatening and major bleeding, major vascular complications, hospitalization for valve-related symptoms or worsening HF, hypo-attenuated leaflet thickening, at least moderately restricted leaflet motion, hemodynamic dysfunction	Estimated primary completion date: July 2023 - Intervention: VKA with aspirin - Comparator: aspirin monotherapy - Registry arm: indication for anticoagulation

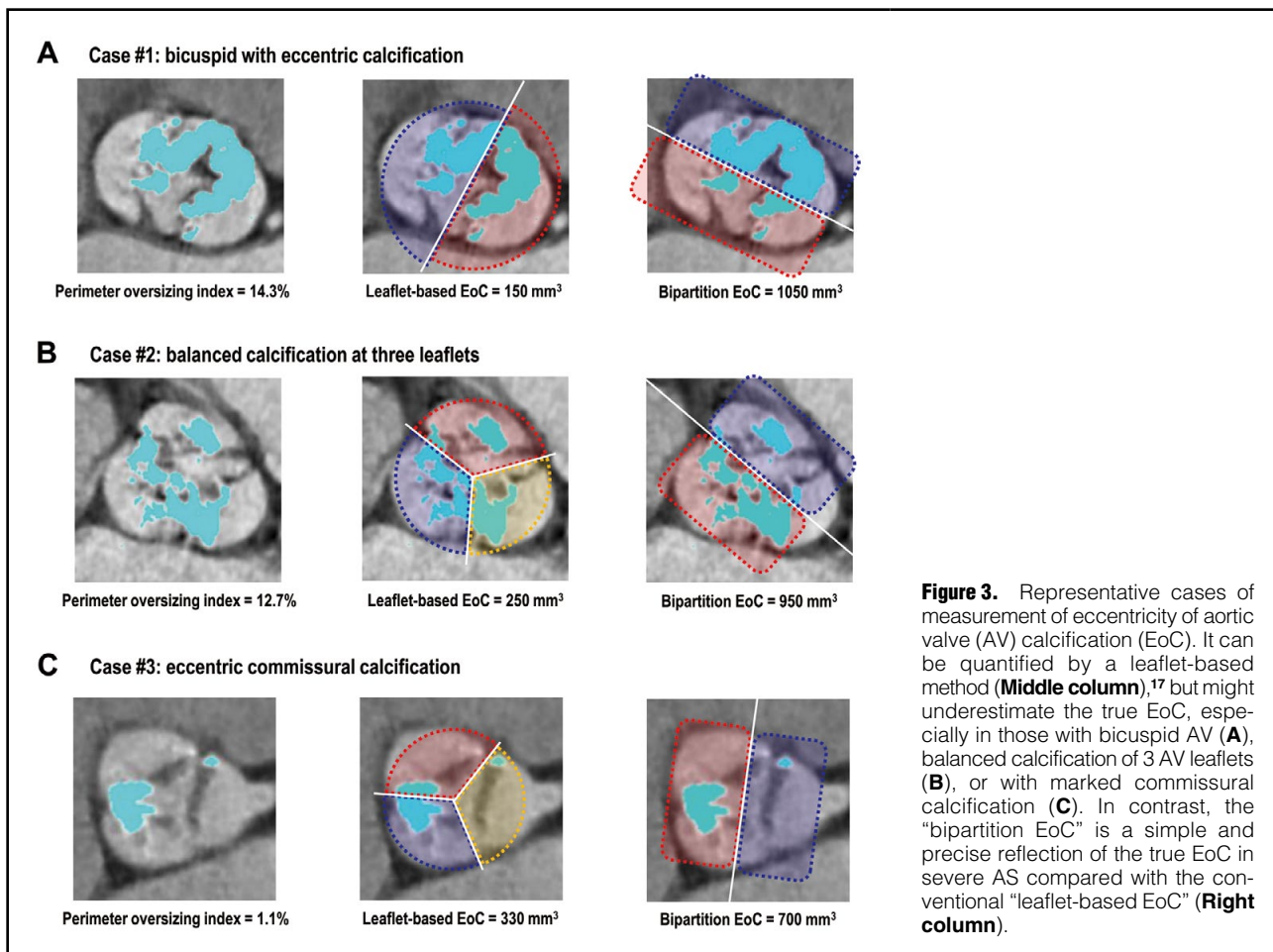(**Table 1** continued the next page.)

Topic	Clinical trial	Study size	Design	Device	Primary endpoint	Details
	POPular-TAVI [NCT02247128]	1,000	DAPT vs. SAPT (aspirin) vs. OAC with clopidogrel vs. OAC	Any approved device	All bleeding complications, non-procedure-related bleeding complications	Estimated primary completion date: January 2019 - Cohort A: DAPT - Cohort B: aspirin monotherapy - Cohort C: OAC with clopidogrel - Cohort D: OAC monotherapy
	ADAPT-TAVR [NCT03284827]	220	NOAC (edoxaban) vs. DAPT	Any approved device	Leaflet thrombosis documented by cardiac CT Imaging	Estimated primary completion date: June 2019
	AVATAR [NCT02735902]	170	VKA vs. VKA with aspirin	Any approved device	All-cause death, MI, all stroke, valve thrombosis, hemorrhage ≥2 as defined by the VARC 2	Estimated primary completion date: April 2020 - Intervention: VKA monotherapy - Comparator: VKA with aspirin

*The Low Risk TAVR trial enrolled 200 low-risk patients with symptomatic severe AS and compared outcomes with an inverse probability weighting-adjusted control cohort of 719 patients who underwent SAVR at the same institutions using the STS database.[10] †The GALILEO trial [NCT02556203] was designed to compare standard DAPT vs. apixaban in TAVR patients without atrial fibrillation. However, the trial was prematurely halted in October 2018, because of concerns regarding the bleeding risk. APT, antiplatelet therapy; AS, aortic stenosis; AV, aortic valve; CT, computed tomography; DAPT, dual antiplatelet therapy; HF, heart failure; MI, myocardial infarction; NOAC, non-vitamin K antagonist oral anticoagulant; SAPT, single antiplatelet therapy; SAVR, surgical aortic valve replacement; TAVR, transcatheter aortic valve replacement; TIA, transient ischemic attack; VARC, Valve Academic Research Consortium; VKA, vitamin K antagonist.

Figure 2. Current recommendations for selecting transcatheter aortic valve replacement (TAVR) or surgical aortic valve replacement (SAVR) summarized from the guidelines of the AHA/ACC (**Upper**) and the ESC/EACTS (**Lower**). AS, aortic stenosis; CAD, coronary artery disease; MV, mitral valve; TV, tricuspid valve.

is larger in bicuspid AV than in tricuspid AV, the height of coaptation of bicuspid AV can be higher than that of usual tricuspid AV, and the degenerative changes in bicuspid AV result in fibrosis and calcification of the redundant AV cusps, further increasing the cusp height.[20] It means that the main radial resistance from the bicuspid AV leaflets does not directly affect the level of prosthetic AV annulus level but rather the level 4–5 mm higher than the annulus. Therefore, determining the device size and deployment procedures

(i.e., balloon pre- or post-dilation) in bicuspid AS should be different from the usual pre-TAVR planning for tricuspid AS: the supra-annular structure, together with the actual opening size of native bicuspid AV leaflets, should be considered. For short devices, prosthetic AV leaflets are to be placed at the same level as the native AV annulus, through a direct tear of the bicuspid AV leaflets. However, for long self-expanding devices, such as Evolut-R and Evolut-PRO, the sizing of the device needs special consider-

Figure 3. Representative cases of measurement of eccentricity of aortic valve (AV) calcification (EoC). It can be quantified by a leaflet-based method (**Middle column**),[17] but might underestimate the true EoC, especially in those with bicuspid AV (**A**), balanced calcification of 3 AV leaflets (**B**), or with marked commissural calcification (**C**). In contrast, the "bipartition EoC" is a simple and precise reflection of the true EoC in severe AS compared with the conventional "leaflet-based EoC" (**Right column**).

ations, given the anatomic characteristics of bicuspid AV.[20]

In contrast to these concerns, several studies have demonstrated non-inferior procedural outcomes in selected patients with bicuspid AS compared with tricuspid AS, especially when the procedure was performed with new-generation devices that resulted in less PVL risk and higher device success rates.[21,22]

Patient-Prosthesis Mismatch

Compared with SAVR, the remaining calcified AV structures after TAVR raise concern regarding the risk of patient-prosthesis mismatch (PPM). An analysis of the STS/ACC registry reported that severe and moderate PPM following TAVR were 12% and 25%, respectively.[23] However, landmark studies showed that a lower incidence of PPM incidence after TAVR than after SAVR, even when performed with a sutureless device.[24,25]

Because PPM incidence is associated with the size of both the aortic annulus and bioprosthesis, there has been a concern regarding PPM in patients with a small aortic annulus, especially in the Asian population. However, the mean transaortic pressure gradient after TAVR is similar between patients with a smaller aortic annulus and those with a larger aortic annulus.[26] Recent analyses from the OCEAN-TAVI registry showed that PPM prevalence in Asian patients is low, and that the post-TAVR prognosis is acceptable, even in those with an extremely small aortic annulus.[27,28] Therefore, the risk of PPM following TAVR
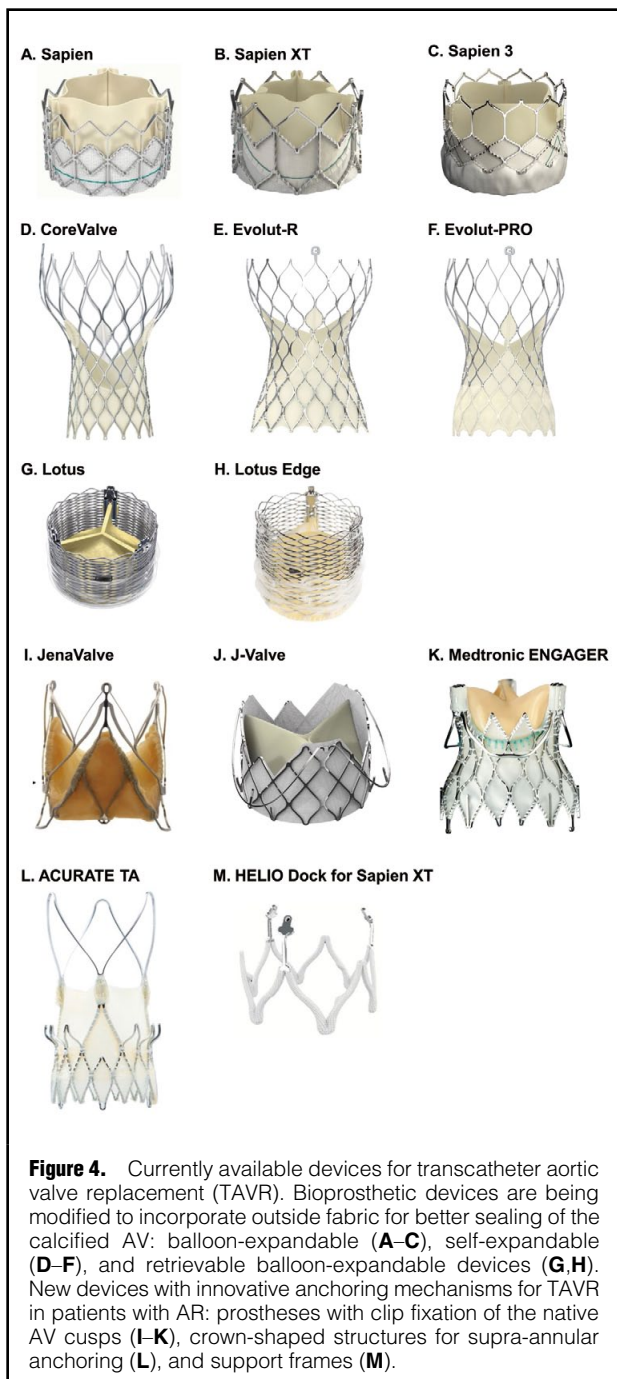
in patients with a small aortic annulus or in Asian patients has been addressed and should not serve as a barrier against TAVR.

Novel Indications of TAVR

TAVR for AR

Although several case reports and small studies suggested the feasibility of TAVR for aortic regurgitation (AR), early studies showed lower success rate and higher mortality risk compared with the outcomes of SAVR, because of the anatomic differences between AS and AR.[29] In patients with AS, heavy deposition of calcium on native AV leaflets and commissures serve to anchor the prosthesis. In contrast, patients with AR have minimal or absent calcification of AV leaflets, and have a dilated aortic root and ascending aorta. These anatomic features are obstacles to TAVR procedures, including suboptimal visualization of AV on fluoroscopy during the procedure and insufficient device anchoring, leading to a higher risk of device dislocation and residual AR.

Considering that anchoring of the device is the key issue in TAVR for AR, several new-generation devices with innovative anchorage mechanisms demonstrate promising results (**Figure 4**). With the use of these new-generation devices, TAVR for severe AR might be a technically feasible treatment option.[29,30]

Figure 4. Currently available devices for transcatheter aortic valve replacement (TAVR). Bioprosthetic devices are being modified to incorporate outside fabric for better sealing of the calcified AV: balloon-expandable (**A**–**C**), self-expandable (**D**–**F**), and retrievable balloon-expandable devices (**G**,**H**). New devices with innovative anchoring mechanisms for TAVR in patients with AR: prostheses with clip fixation of the native AV cusps (**I**–**K**), crown-shaped structures for supra-annular anchoring (**L**), and support frames (**M**).

TAVR for Moderate AS With HF

In patients with moderate AS, AVR is not routinely recommended because the mortality risk of moderate AS is lower than that of severe AS, and the expected surgical risk cannot meet the net benefit of AVR.[2,3] However, patients with moderate AS have a higher risk of death when accompanied by LV dysfunction. A recent study of patients with moderate AS and LV systolic dysfunction demonstrated 48% all-cause death or HF hospitalization at 4-year follow-up,[31] inferring that these patients may need early AVR (**Supplementary Figure 2**). However, it should be also noted that the peri-operative risk markedly increases with the presence of LV dysfunction. For example, postoperative 30-day mortality of patients with low-flow low-gradient (LFLG)-AS ranges from 5% to 30%, although these studies included younger patients with lower risk profiles.[32,33] Therefore, minimally invasive TAVR can be a potential treatment option for patients with LFLG-AS. The True of Pseudo-severe Aortic Stenosis (TOPAS) registry provided convincing evidence of the benefit of TAVR in patients with AS and LV systolic dysfunction: among 287 patients with LFLG-AS, the mortality rates were 3.8%, 20.1%, and 32.3% at 30 days, 1 year, and 2 years, respectively.[34] These outcomes were slightly better than those in previous studies of TAVR in patients with LFLG-AS, and comparable to those in studies of TAVR in high- to prohibitive-risk patients. An ongoing study, Transcatheter Aortic Valve Replacement to Unload the Left ventricle in patients with Advanced heart failure (TAVR UNLOAD) trial [NCT02661451], will clarify whether TAVR is an effective alternative treatment in patients with moderate AS and LV systolic dysfunction, compared with SAVR (**Table 1**).

Durability Issues

Long-Term Durability of Bioprosthetic Valves

The overall structure of the valve leaflets of the prosthesis is similar between SAVR and TAVR, and the leaflets' material properties are identical. However, there are important structural and procedural differences that could result in a difference in durability: (1) leaflet thickness, (2) presence of native AV calcification, and (3) oval-shaped annulus.[35] In order to allow transcatheter delivery, TAV leaflets are thinner (~0.25 mm) than the SAV leaflets (~0.4 mm).[36] Moreover, higher stress and strain are applied to the TAV leaflets during the procedure compared with SAV leaflets. The remaining heavy calcification of the AV and non-circular, asymmetric stent-frame deployment may further increase the stress on the TAV leaflets. Computational tissue-fatigue models suggest that the peak stress on TAV leaflets is higher than that for SAV, and the simulated durability of TAV is approximately 7.8 years, which is shorter than the expected 15 years of durability for SAV.[36] TAV durability can be further decreased if implanted in an elliptical annulus or under-expanded, which can be overcome by a supra-annular design of the TAV for an elliptical annulus or proper sizing and post-dilation using a balloon for under-expansion.

However, recent studies show an acceptable mid-term durability of TAVR: reintervention was performed in 0.8% of patients after TAVR and in 0.3% after SAVR during a 5-year follow-up.[5,37] Studies with follow-up duration >5 years also report favorable durability of TAVR, with the rate of structural valve deterioration ranging from 1.4% to 4.8%.[11,38,39] The extrapolation of currently available data enables an optimistic expectation of the long-term durability of TAVR.

Leaflet Thrombosis

Durability issues for TAVR also include the development of leaflet thrombosis. Makkar et al collected CT scan images of 55 patients who underwent TAVR from an ongoing trial and of 132 patients from registries of either TAVR or SAVR and found that 40% of patients from the trial and 13% of patients from the registries had reduced leaflet motion on CT.[40] An analysis of CT images of 890 patients

Table 2. Special Considerations for Valve-in-Valve Procedure for Failed Surgical Bioprosthesis

Important features of surgical bioprosthesis	Details
Type of transcatheter device	• Balloon-expandable devices are favored • Self-expandable devices need caution because of long frame
Manufacturer sizing and labeling	• Bioprosthesis from different manufacturers often have different internal/external diameters even with the same labeled size
Mechanism of failure	• Regurgitant valve: leaflet tears with relatively larger internal diameters • Stenotic valve: prominent pannus or calcification with reduced internal diameters
Limited use of balloon predilation	• Balloon predilation may cause embolization of debris from bulky and friable degenerated surgical bioprosthesis
Positioning and deployment	• ViV-TAVR should target the overlapping of the new bioprosthesis at the surgical valve annular sewing ring • Radio-opaque structures of the surgical bioprosthesis can be used as markers • Stentless surgical bioprosthesis: use of anatomic or reference markers with root aortography
Small bioprosthesis	• For small (internal diameter <20 mm) surgical bioprosthesis, a self-expanding device can be an effective option, using high implantation
Potential complications	• Coronary ostial obstruction, lack of full expansion, and PPM • Need for permanent pacemaker implantation is lower in ViV-TAVR than in TAVR for native AV

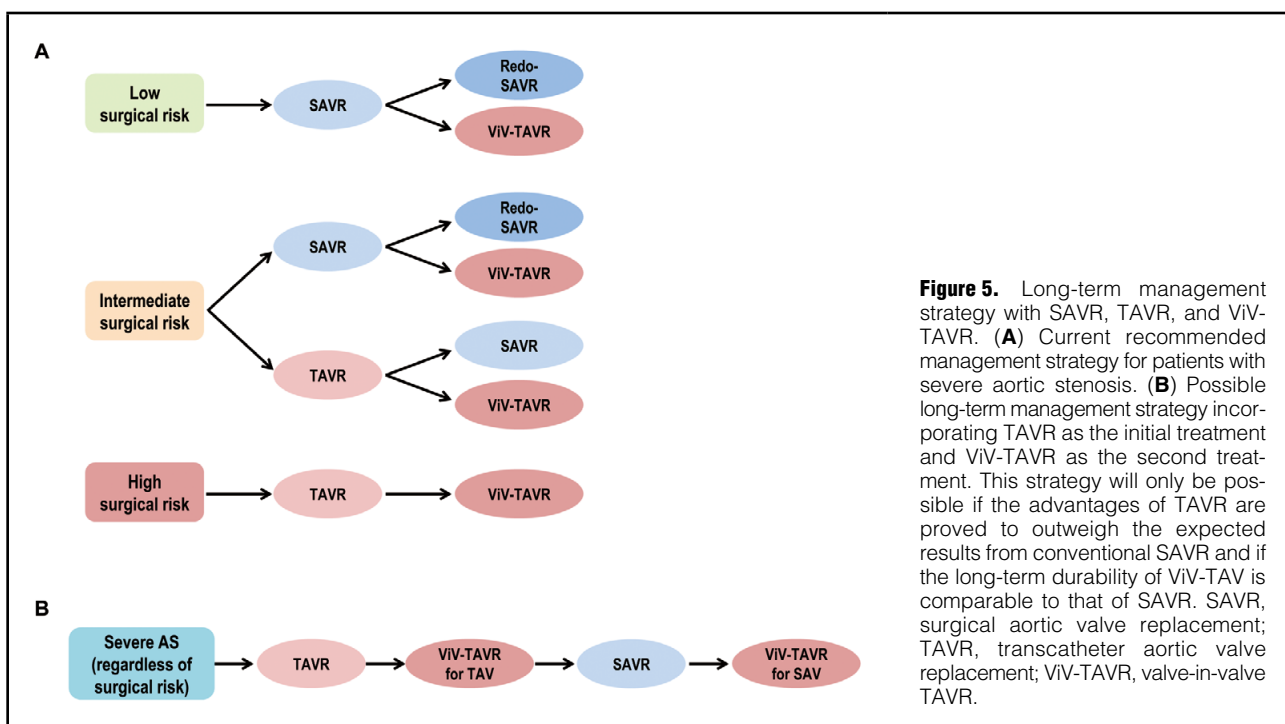AV, aortic valve; PPM, patient-prosthesis mismatch; TAVR, transcatheter aortic valve replacement; ViV, valve-in-valve.

Figure 5. Long-term management strategy with SAVR, TAVR, and ViV-TAVR. (**A**) Current recommended management strategy for patients with severe aortic stenosis. (**B**) Possible long-term management strategy incorporating TAVR as the initial treatment and ViV-TAVR as the second treatment. This strategy will only be possible if the advantages of TAVR are proved to outweigh the expected results from conventional SAVR and if the long-term durability of ViV-TAV is comparable to that of SAVR. SAVR, surgical aortic valve replacement; TAVR, transcatheter aortic valve replacement; ViV-TAVR, valve-in-valve TAVR.

with a bioprosthetic AV reported that the incidence of subclinical leaflet thrombosis was 4% in SAV and 13% in TAV.[41] Compared with complete resection of native leaflets and uniform expansion of the bioprosthesis in SAVR, the transcatheter procedure may cause traumatic injury to the pericardial leaflets and incomplete expansion or overexpansion of the device, resulting in a higher incidence of subclinical leaflet thrombosis.

From the studies that reported subclinical leaflet thrombosis after TAVR, there was an interesting finding that anticoagulant use, compared with dual antiplatelet therapy, was associated with a lower risk of thrombosis development.[40,41] That finding suggested a preventive effect of anticoagulation against the development of leaflet throm-

bosis and overt valve dysfunction after TAVR. Several ongoing trials will provide concrete evidence on the appropriate antithrombotic treatment after TAVR (**Table 1**). Furthermore, because the development of leaflet thrombosis is one of the main concerns regarding durability, the results of these trials will contribute to an improvement of the durability of TAV.

Valve-in-Valve Procedures and Long-Term Management Strategy

Age and Deciding Between TAVR and SAVR
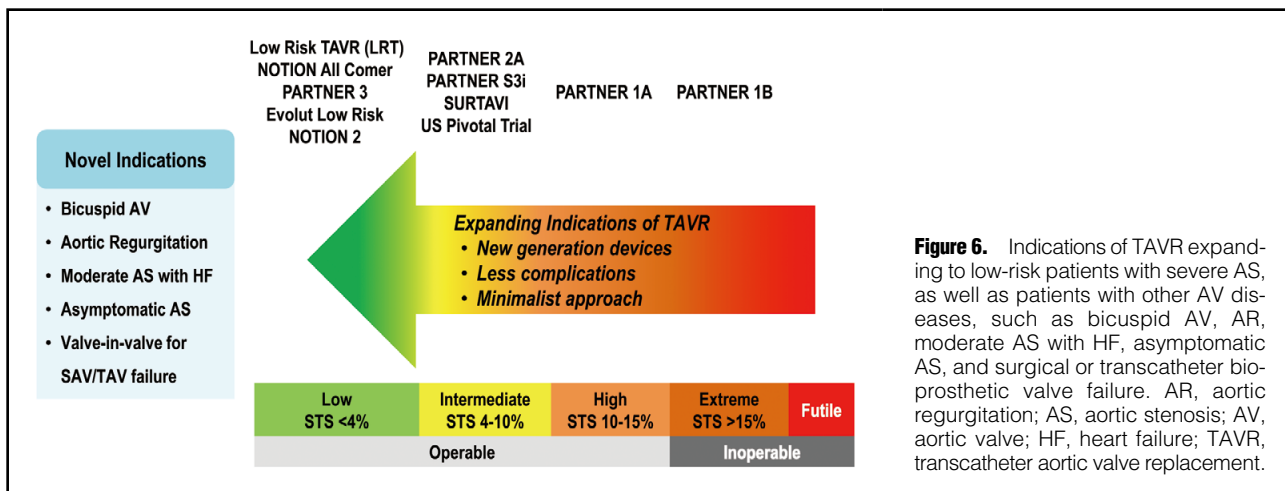The therapeutic strategy for severe AS can be summarized as the ratio between life expectancy and valve durability.[35]

Figure 6. Indications of TAVR expanding to low-risk patients with severe AS, as well as patients with other AV diseases, such as bicuspid AV, AR, moderate AS with HF, asymptomatic AS, and surgical or transcatheter bioprosthetic valve failure. AR, aortic regurgitation; AS, aortic stenosis; AV, aortic valve; HF, heart failure; TAVR, transcatheter aortic valve replacement.

Because of the peri-operative risk, older patients may prefer TAVR, avoiding open heart surgery. In contrast, younger patients may prefer a strategy that can avoid reintervention, placing higher value on long-term durability of the prosthesis. Current guidelines suggest the age of 75 years as a provisional criterion.[3,35] For example, in patients with life expectancy <10 years (i.e., aged ≥75 years), TAVR would be the rational therapeutic approach, because the bioprosthesis has an expected durability of up to 10 years. In contrast, in patients with life expectancy over 15–20 years (i.e., aged <75 years), SAVR can be an appropriate option.[3] However, the age of 75 years is an arbitrary cutoff, as there is limited evidence on the outcomes of TAVR in younger patients. Therefore, blindly following this age cutoff may be inappropriate in a society where life expectancy is exceptionally long (i.e., Japan), or in younger patients who have high surgical risk or have other factors not included in the risk scoring calculators but which may increase the risk of surgery.[42] Several studies show that the outcomes of younger patients (age <75 years) were similar between SAVR and TAVR, despite the higher incidence of comorbidities among those who underwent TAVR.[9,43] These optimistic results require further confirmation in large-scale randomized trials, and the cutoff age of 75 years may be downgraded with ongoing trials addressing the long-term durability of TAVR.

ViV-TAVR as Bailout Strategy for Failed Surgical Bioprosthesis
As a treatment plan for bioprosthetic valve failure, redo-SAVR has long been considered the only available treatment, despite the high risk of mortality and morbidity. However, there has been a breakthrough with valve-in-valve (ViV) TAVR. Generally, SAV has support structures such as a stent or frame, which is attached to a basal ring covered by a fabric sewing cuff (**Supplementary Figure 3**). These structural features should be considered during ViV-TAVR. Unlike the native stenotic AV, the SAV is less elliptical, has a stiffer, non-expandable landing zone because of the stent or frame, a smaller internal diameter, and less consistent friction on the new transcatheter device, which poses a risk of post-deployment movement towards LV or aorta. Therefore, this bailout procedure needs special considerations, as summarized in **Table 2**.

According to registries of high-risk patients who under-

went ViV-TAVR for failed SAV, the 1-month mortality was 2.7–7.6% and the 1-year mortality was 12.4–16.8%.[44,45] As an alternative treatment option for failed SAV, the outcomes of ViV-TAVR should be compared with those of redo-SAVR. A recent meta-analysis demonstrated similar procedural mortality and 30-day mortality between the 2 therapeutic measures.[46] The potential benefits of redo-SAVR over ViV-TAVR were superior echocardiographic outcomes, lower PPM incidence, and lower occurrence of PVL.[46] In contrast, ViV-TAVR showed better outcomes than redo-SAVR in terms of a lower rate of permanent pacemaker implantation, shorter stay in intensive care unit, and shorter hospital stay. Furthermore, a recent study from the STS/ACC registry reported lower mortality rate and less HF hospitalizations in the ViV-TAVR group, compared with those who underwent TAVR for a native valve.[47] Based on these results suggesting that ViV-TAVR is a feasible alternative to redo-SAVR in patients with failed SAV, the ViV-TAVR has been approved in the USA, Europe, and many other countries. In Japan, ViV-TAVR with Evolut-R for failed SAV was approved in 2018.

ViV-TAVR as Rescue of Failed Transcatheter Bioprosthesis
Because TAV can degenerate in a manner similar to that of SAV, ViV application in failed TAV is also a treatment option. Since the early TAVR era, this "Russian doll concept procedure" has been a feasible rescue treatment with high success rates in cases of TAV malposition, moderate or severe PVL, or intravalvular regurgitation. According to a recent study, the late survival rate was 85.1% at a median follow-up of 4.4 years after index TAVR and 1.7 years after ViV-TAVR for TAV, and the hemodynamic outcome was favorable.[48] Considering the acceptable outcomes of ViV-TAVR and the rapidly growing population of patients with TAV, ViV-TAVR holds promise for wider use.

New Paradigm for Young Patients With AS
The clinical role of TAVR is currently being applied in patients for whom previously SAVR was recommended; that is, those with severe AS and low surgical risk; bicuspid AV; moderate AS with HF; severe AR; and bioprosthetic valve failure. Also, given the acceptable outcomes demonstrated in numerous studies, ViV-TAVR will not just

remain as a rescue treatment, but can be incorporated in the management strategies of severe AS, when long-term durability is provided.

Currently, the management strategy for severe AS is mainly determined by the estimated risk scores (**Figure 5A**).[2,3] The initial treatment of choice is SAVR for low-risk patients, SAVR or TAVR for intermediate-risk patients, and TAVR for high surgical risk and inoperable patients. For those with bioprosthetic valve failure, redo-SAVR or ViV-TAVR can be considered. However, if the advantages of TAVR outweigh the expected results from conventional SAVR, it is possible that the overall treatment strategy will change (**Figure 5B**). Given the comparable or even better outcomes of TAVR than SAVR among low-risk patients, the initial treatment of choice would be TAVR regardless of the estimated risk scores, if the long-term durability of TAVR is proved to be comparable to that of SAVR.[12,13] Similarly, if the clinical outcomes of ViV-TAVR are comparable to those of redo-SAVR, then ViV-TAVR can be used instead of redo-SAVR at the time of TAV structural deterioration. Thereafter, patients may need SAVR, followed by ViV-TAVR for SAVR, if the replaced bioprosthesis deteriorates.

To date, there have been several reports in which TAVR was performed for young patients with severe AS, because of multiple previous surgeries for congenital heart disease, or severe comorbid diseases that render the patient inoperable.[49,50] Apart from previous heart surgery or severe comorbid diseases, the treatment of choice for young patients is SAVR, and the above suggested approach (**Figure 5B**) require much more evidence on very long-term outcomes.[2,35] Nonetheless, recent studies supporting TAV durability suggest that TAVR might replace conventional SAVR in certain patients with severe AS regardless of the calculated risk scores.[37,38] The major paradigm shift for TAVR, in terms of replacing the current role of SAVR and incorporating ViV-TAVR procedures into the treatment algorithm, can be considered a reasonable new direction (**Figure 6**).

Conclusions

In this review, we have discussed whether TAVR could play a major therapeutic role as an alternative to SAVR. The efficacy and safety of TAVR have been investigated in numerous studies of patients with severe AS and a wide spectrum of surgical risk. The overall outcomes of TAVR were comparable with, or even superior to, those of SAVR, especially among those with intermediate and high surgical risk. Furthermore, recent trials showed similar or even better outcomes of TAVR in low-risk patients, compared with SAVR. Based on consistent evidence, TAVR is replacing the clinical role of SAVR, and its indications are expanding to various patient populations with AV disease, including bicuspid AS, moderate AS with HF, severe AR, and bioprosthetic valve failure. A major paradigm shift in the treatment of AV disease is already in progress, and future studies are needed to clarify the optimal treatment strategy for applying TAVR in patients with various AV diseases.

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Disclosures

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Supplementary Files

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