THE PRESENT AND FUTURE

STATE-OF-THE-ART REVIEW

Transcatheter Aortic Valve Replacement 2016

A Modern-Day "Through the Looking-Glass" Adventure

Torsten P. Vahl, MD, Susheel K. Kodali, MD, Martin B. Leon, MD

ABSTRACT

Transcatheter aortic valve replacement (TAVR) has become a safe and effective therapy for patients with severe aortic stenosis (AS). In recent trials, the hemodynamic performance and clinical outcomes of the latest generation of TAVR devices demonstrated at least parity with surgical outcomes in patients of similar risk. Many initial obstacles with TAVR have largely been overcome, including frequent access site complications and concerns about strokes and paravalvular leaks. Using a multidisciplinary heart team approach, patient selection, procedural planning, and device implantation have been refined and optimized such that clinical outcomes are generally predictable and reproducible. Future research will focus on the durability of TAVR devices, further enhancements in clinical outcomes, and adjunctive therapies. On the basis of initial results from ongoing clinical trials, the indication for TAVR will likely expand to lower-risk patients. This review provides an overview of recent progress in this field, and highlights future opportunities and directions. (J Am Coll Cardiol 2016;67:1472–87) © 2016 by the American College of Cardiology Foundation.

When Alice ventured "through the looking glass" in the well-known Lewis Carroll sequel to *Alice's Adventures in Wonderland*, she encountered a fantastical world of celebrated characters, concluding in a final poem that "Life, what is it but a dream?" (1). In the past several years, the fantastical conversion from open surgery to catheter-based aortic valve replacement has shared many dream-like elements, having exceeded even the most optimistic projections in this modern-day medical adventure.

Surgical aortic valve replacement (SAVR) has evolved over the past 50 years as the standard-of-care in patients with severe symptomatic aortic stenosis (AS). However, global aging has contributed to a growing dilemma; that is, the increased frequency of severe AS in elderly patients with multiple comorbidities, who are not good candidates for surgery and are either denied surgery or are at high risk for complications and protracted recovery (2,3). In the last decade, a less-invasive, catheter-based approach to aortic valve replacement for patients with severe AS has been strategically developed, studied in rigorously conducted clinical trials, and made available to the worldwide clinical community. Since the first proof-of-concept case performed by Alain Cribier in 2002 (4), transcatheter aortic valve replacement (TAVR) has now been fully integrated into the therapeutic armamentarium for managing AS in patients who are at high risk for conventional surgery, with >200,000 procedures having been performed in >65 countries. TAVR is a novel therapy that qualifies as a

TABLE 1　Summary of Recommendations for AS: Choice of Surgical or Transcatheter Intervention

	COR	LOE
SAVR is recommended in patients who meet an indication for AVR with low or intermediate surgical risk	I	A
For patients in whom TAVR or high-risk SAVR is being considered, members of a Heart Valve Team should collaborate to provide optimal patient care	I	C
TAVR is recommended in patients who meet an indication for AVR for AS who have a prohibitive surgical risk and a predicted post-TAVR survival >12 months	I	B
TAVR is a reasonable alternative to SAVR in patients who meet an indication for AVR and who have high surgical risk	IIa	B
Percutaneous aortic balloon dilation may be considered as a bridge to SAVR or TAVR in severely symptomatic patients with severe AS	IIb	C
TAVR is not recommended in patients in whom existing comorbidities would preclude the expected benefit from correction of AS	III: No benefit	B

Adapted from Nishimura et al. (5).

AS = aortic stenosis; AVR = aortic valve replacement; COR = Class of Recommendation; LOE = Level of Evidence; SAVR = surgical aortic valve replacement; TAVR = transcatheter aortic valve replacement.

ABBREVIATIONS AND ACRONYMS

ACC = American College of Cardiology

AHA = American Heart Association

AS = aortic stenosis

CAD = coronary artery disease

CT = computed tomography

MR = mitral regurgitation

PVR = paravalvular regurgitation

SAVR = surgical aortic valve replacement

STS = Society of Thoracic Surgeons

TAVR = transcatheter aortic valve replacement

TEE = transesophageal echocardiography

TR = tricuspid regurgitation

"breakthrough technology" in medicine for the following reasons: 1) it addresses an unmet clinical need in an important area of medicine not well served by current therapies; 2) it is an innovative device concept that has challenged traditional standards; 3) the clinical benefits have been carefully validated by evidence-based medicine clinical research; 4) the application has been "generalized" to the practicing medical community (sufficiently user-friendly); and 5) it has become elevated beyond territorial subspecialty medicine and resonates as a significant sociomedical cultural advance (e.g., the multidisciplinary "heart team" popularized by TAVR is now the preferred approach for the management of patients with complex cardiovascular disease).

The purpose of the present paper is to provide a selective update on the rapidly changing field of TAVR therapy. Although past achievements and current issues will be discussed, the main goal is to expand our vision and focus a lens on future expectations and possibilities for TAVR as an expanding therapy for patients with aortic valve disease.
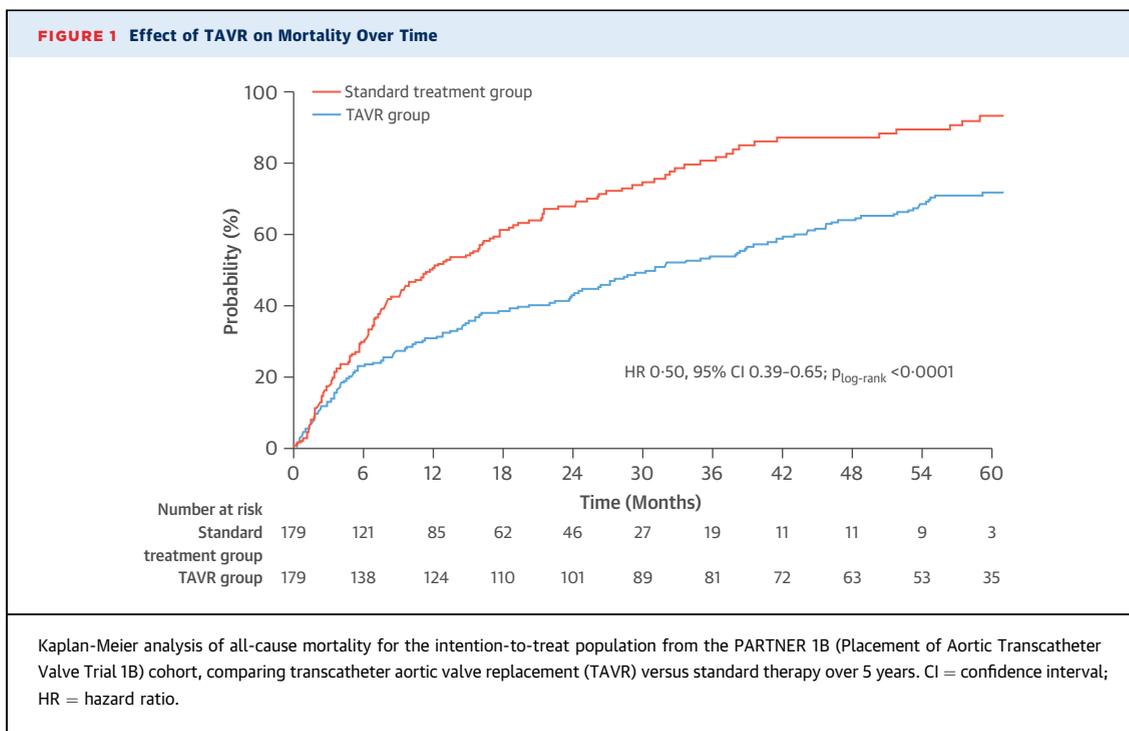
PAST ACHIEVEMENTS

CLINICAL INDICATIONS FOR TAVR. On the basis of current clinical evidence, TAVR has been accepted by the American Heart Association (AHA)/American College of Cardiology (ACC) guidelines (5) as a Class I indication in patients with severe symptomatic AS

and a predicted survival of >1 year who are not candidates for SAVR (Table 1). The characterization of these so-called "inoperable" patients (variously described as extreme- or prohibitive-risk patients) has been problematic, but a widely agreed upon descriptor has been the likelihood of >50% mortality at 30 days or irreversible morbidity after SAVR; this classification includes both patients with extensive medical comorbidities and those with anatomic factors (e.g., porcelain aorta or "hostile" chest) precluding standard surgery. The clinical data supporting this indication derive from several European registries (6–8), the randomized PARTNER 1B (Placement of Aortic Transcatheter Valve Trial 1B) study (9), and the CoreValve (Medtronic, Minneapolis, Minnesota) extreme-risk registry (10). The PARTNER 1B study compared an early version of the balloon-expandable TAVR technology versus standard therapy in 358 inoperable patients. All-cause mortality at 1 year, the primary endpoint, was reduced from 50.7% with standard therapy to 30.7% after TAVR (p < 0.001). Similarly, there was a significant reduction in repeat hospitalizations and an improvement in cardiac symptoms. Importantly, the 5-year follow-up from this randomized trial (11) indicated a sustained >20% absolute reduction in mortality (Figure 1) and no evidence of structural deterioration of the bioprosthesis.

The current guidelines also recommend that TAVR, as a Class IIa indication, should be an alternative to conventional surgery in patients with severely symptomatic AS who are at high risk for mortality and complications after SAVR (5,12). The clinical evidence for this recommendation was also derived from multiple large European country registries, several smaller single-center studies, and 2 important randomized trials from the United States comparing TAVR versus conventional surgery: the PARTNER 1A (Placement of Aortic Transcatheter Valve Trial 1A) study using a balloon-expandable TAVR system (13) and the CoreValve High-Risk study using a self-expanding TAVR platform (14). In PARTNER 1A, which enrolled 699 patients with AS between 2007 and 2009, patient characteristics clearly reflected a high surgical risk cohort: mean age of 84 years; mean Society of Thoracic Surgeons (STS) score of almost 12%; and >90% were in New York Heart Association functional class III or IV. At 1 year, death from any cause was 24.2% after TAVR, compared with 26.8% after SAVR, which met the predefined primary non-inferiority endpoint of the trial. These results were maintained over the following 5 years, with similar

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        Future Expectations and Barriers for TAVR

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FIGURE 1 Effect of TAVR on Mortality Over Time

HR 0·50, 95% CI 0·39–0·65; p_log-rank <0·0001

Number at risk										
Standard treatment group	179	121	85	62	46	27	19	11	11	9	3
TAVR group	179	138	124	110	101	89	81	72	63	53	35

Kaplan-Meier analysis of all-cause mortality for the intention-to-treat population from the PARTNER 1B (Placement of Aortic Transcatheter Valve Trial 1B) cohort, comparing transcatheter aortic valve replacement (TAVR) versus standard therapy over 5 years. CI = confidence interval; HR = hazard ratio.

all-cause mortality in both groups (**Figure 2A**) and a median survival for TAVR patients of 44.5 months compared with 40.6 months for SAVR patients (p = 0.76) (15). Striking early and sustained functional improvements occurred after both TAVR and SAVR, such that 85% of TAVR patients and 81% of SAVR patients remained in New York Heart Association functional class I or II after 5 years. Because the durability of TAVR systems has been a concern, the 5-year echocardiographic studies analyzed by an independent core laboratory were reassuring; hemodynamic improvements, which were equivalent to surgery at 1 year, were sustained for the duration of the study. Specifically, at 5 years, the mean gradient across the transcatheter valve remained stable at 10.7 mm Hg and the mean aortic valve area was 1.6 cm², with no signs of structural deterioration.
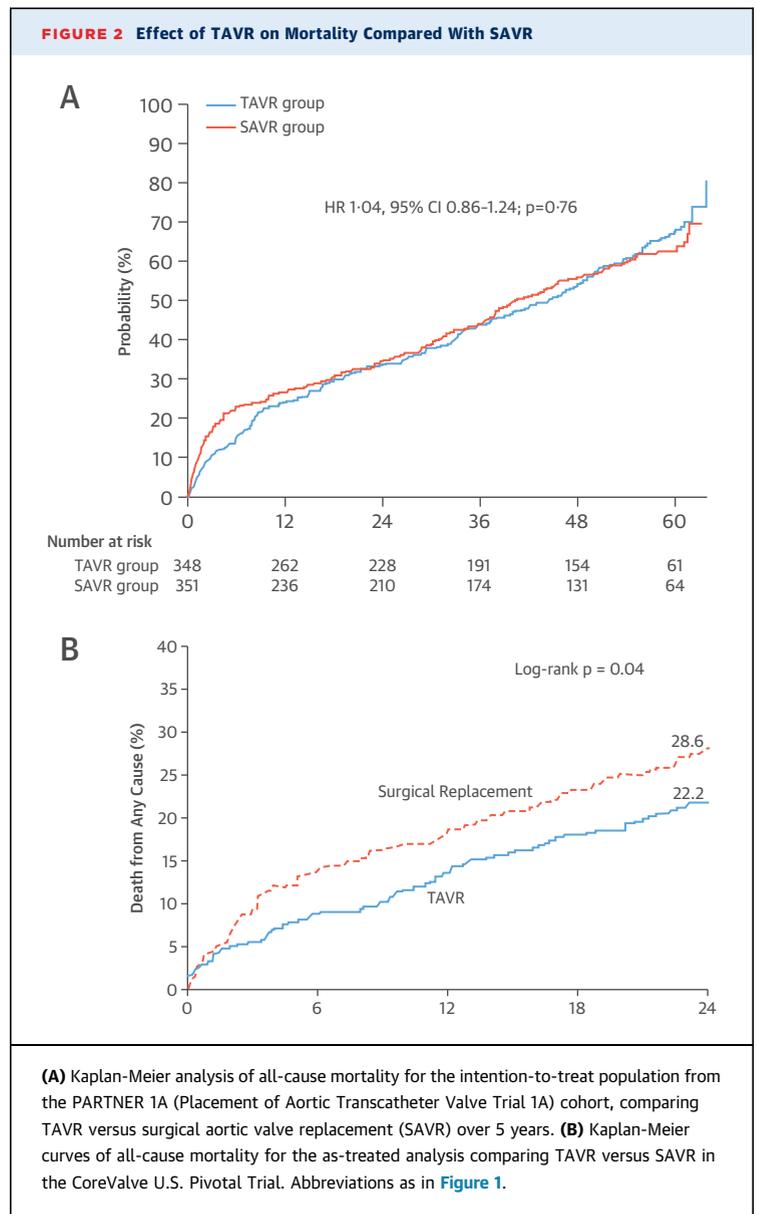
More recently, the CoreValve U.S. Pivotal Trial compared the outcomes of patients with symptomatic severe AS at increased risk for surgery who underwent TAVR with a self-expanding prosthesis versus the outcomes of those who underwent SAVR (14). This study demonstrated an all-cause mortality benefit associated with TAVR at 1 year (absolute mortality difference 4.9%) (**Figure 2B**), which persisted after 2 years of follow-up (absolute mortality difference 6.4%; p = 0.04) (16). Moreover, strokes were also less frequent in the TAVR patients after 2 years (10.9% vs. 16.6%; p < 0.05).

Considerable efforts have been directed to develop rigorous methodology for clinical research with TAVR. The Valve Academic Research Consortium is an independent group with representation from multiple cardiology and surgery societies, academic research organizations, and independent experts, who have helped to create consensus endpoint definitions that are now widely applied and have improved the quality and consistency of clinical research with TAVR (17,18). The acceptance of TAVR as a meaningful new therapy has been an evidence-based medicine journey, demonstrated by the Valve Academic Research Consortium initiative and the previously described high-quality clinical trials. A balanced interpretation of the literature and the prevailing sentiment from experts worldwide indicate that TAVR is now the preferred therapy and the standard-of-care for patients with severe symptomatic AS who are not candidates for surgery. In AS patients who are at high surgical risk, the aforementioned randomized trials taken together (and validated by other available evidence) indicate that TAVR should be elevated to a Class I recommendation, as the preferred alternative to conventional surgery in those patients (especially the elderly) who are good candidates for TAVR.
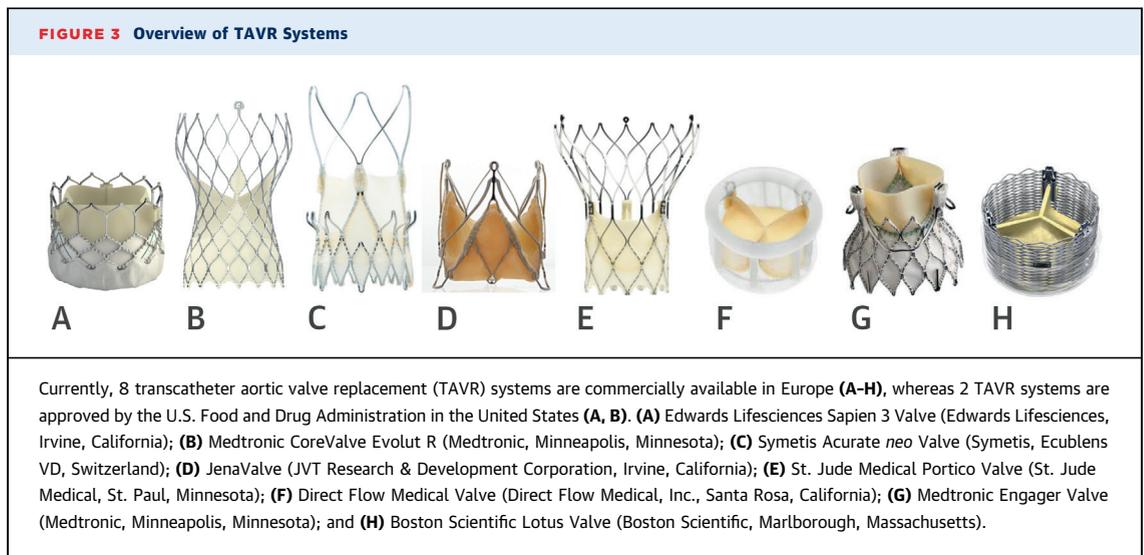
THE HEART VALVE TEAM CONCEPT. Before the TAVR era, a disciplined multidisciplinary team approach had

been used sporadically and inconsistently to manage patients with cardiovascular disease. However, the complexity of diagnosing and managing patients with severe symptomatic AS and multiple comorbidities in an elderly population has required the combined efforts of multiple subspecialties, which renders a single specialty-based care model anachronistic. The clinical care pathway begins with precise diagnosis; it then requires a thoughtful determination of the optimal management strategy (medical therapy, TAVR, or SAVR) and finally a transition to careful post-procedural management. At various times during this pathway, subspecialists are used as members of the heart valve team, including clinical cardiologists, cardiac surgeons, interventional cardiologists, imaging experts (echocardiography and computed tomography [CT]), anesthesiologists, geriatricians, intensivists, and other medical specialists (e.g., neurologists, nephrologists). In addition, a vital component of the heart valve team involves a dedicated and custom-trained group of nonphysician health care specialists, such as hospital administrators, nurse coordinators, nurse practitioners and physician assistants, physical therapists, social service experts, and clinical research personnel. The advantages of a well-designed and functional heart valve team are: 1) improved medical decision making (especially risk vs. benefit determinations) with collaborative input from multiple physicians on essentially every case; 2) improved patient and family communication, leading to greater satisfaction with the knowledge of a multidisciplinary team approach; 3) physician benefit by sharing the burden and liability during intense patient care experiences; 4) improved access to and enrollment in clinical research studies; and 5) overall improvement in team morale, active collaboration, and efficiencies in executing complex clinical care plans. Perhaps one of the greatest achievements of TAVR has been the widespread endorsement of the heart team concept as the fundamental vehicle for obtaining optimal clinical outcomes. Importantly, the routine use of a heart valve team (in essentially every case) is now the guideline-recommended approach for TAVR and is a Class I indication in both the ACC/AHA and the European Society of Cardiology guidelines (5,12).

TECHNOLOGY ENHANCEMENTS. The dramatic evolution of TAVR technology since the early proof-of-concept cases has contributed importantly to the widespread clinical acceptance of this new, less-invasive therapy. There are now 8 commercially available TAVR systems in Europe (**Figure 3**), including several with iterative changes. Most devices can be

FIGURE 2 Effect of TAVR on Mortality Compared With SAVR

A — TAVR group / SAVR group

HR 1·04, 95% CI 0·86–1·24; p=0·76

Probability (%) vs. time (0, 12, 24, 36, 48, 60)

Number at risk

	0	12	24	36	48	60
TAVR group	348	262	228	191	154	61
SAVR group	351	236	210	174	131	64

B — Death from Any Cause (%) vs. time (0, 6, 12, 18, 24)

Log-rank p = 0.04

Surgical Replacement 28.6
TAVR 22.2

(A) Kaplan-Meier analysis of all-cause mortality for the intention-to-treat population from the PARTNER 1A (Placement of Aortic Transcatheter Valve Trial 1A) cohort, comparing TAVR versus surgical aortic valve replacement (SAVR) over 5 years. **(B)** Kaplan-Meier curves of all-cause mortality for the as-treated analysis comparing TAVR versus SAVR in the CoreValve U.S. Pivotal Trial. Abbreviations as in **Figure 1**.

delivered via the transfemoral arterial approach, in addition to other routes (e.g., transapical, axillary-subclavian, direct aortic) when necessary. The main advantages of the new TAVR systems include: 1) markedly lower profiles (catheter and delivery systems), which are >40% reduced in diameter compared with the early devices; 2) improved operator ease-of-use; 3) increased range of valve sizes to accommodate smaller and larger aortic annulus dimensions; 4) more precise and predictable valve positioning; 5) retrievable and repositionable features to insure optimal safety and accuracy of valve positioning; and 6) reduced paravalvular regurgitation (PVR). Importantly, the newest generation of TAVR

FIGURE 3 Overview of TAVR Systems

A   B   C   D   E   F   G   H

Currently, 8 transcatheter aortic valve replacement (TAVR) systems are commercially available in Europe **(A–H)**, whereas 2 TAVR systems are approved by the U.S. Food and Drug Administration in the United States **(A, B)**. **(A)** Edwards Lifesciences Sapien 3 Valve (Edwards Lifesciences, Irvine, California); **(B)** Medtronic CoreValve Evolut R (Medtronic, Minneapolis, Minnesota); **(C)** Symetis Acurate *neo* Valve (Symetis, Ecublens VD, Switzerland); **(D)** JenaValve (JVT Research & Development Corporation, Irvine, California); **(E)** St. Jude Medical Portico Valve (St. Jude Medical, St. Paul, Minnesota); **(F)** Direct Flow Medical Valve (Direct Flow Medical, Inc., Santa Rosa, California); **(G)** Medtronic Engager Valve (Medtronic, Minneapolis, Minnesota); and **(H)** Boston Scientific Lotus Valve (Boston Scientific, Marlborough, Massachusetts).

systems approved by the U.S. Food and Drug Administration in the United States, the balloon-expandable Sapien 3 (Edwards Lifesciences, Irvine, California) and the self-expanding CoreValve Evolut-R (Medtronic), incorporate most of the attributes described previously and have helped to transform TAVR into a routine, low-risk procedure with predictable clinical outcomes.
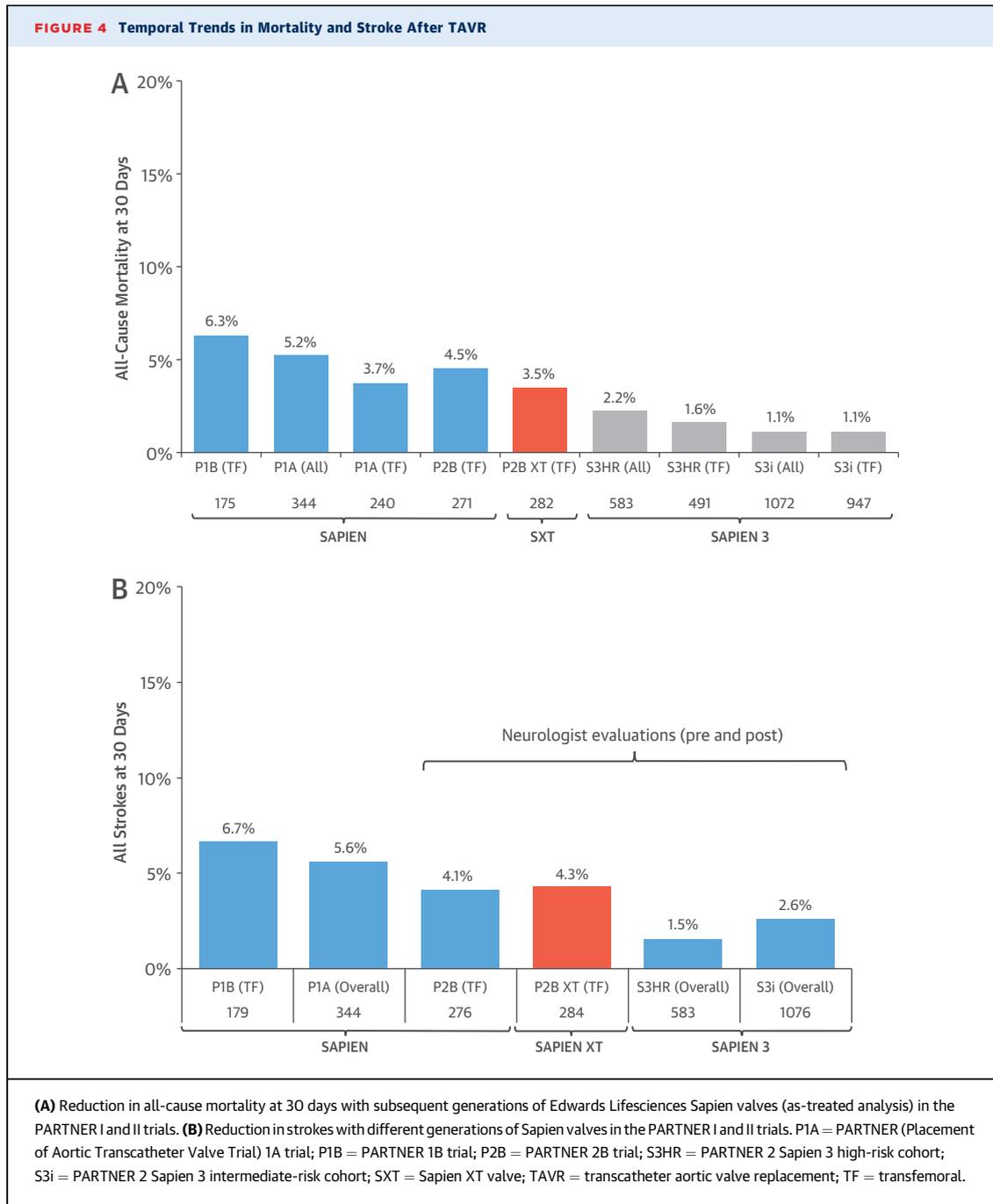
IMPROVED CLINICAL OUTCOMES. In parallel with technology enhancements, patients have also benefited from increased operator experience, more refined case selection, and improved procedural methods. The cumulative impact of these favorable changes over time has resulted in a significant improvement in clinical outcomes. Comparing mortality and stroke outcomes from the earliest PARTNER randomized trials (which began enrollment in 2007) versus the most recent results from the Sapien 3 studies (reported in 2015 in similar risk cohorts) (19) indicates a reduction in 30-day mortality from 6.3% to 2.2% (**Figure 4A**) and a reduction in strokes from 6.7% to 2.6% (**Figure 4B**). The very low periprocedural adverse event rate in the Sapien 3 registry resulted in a 1-year survival rate of 87.3% for high-risk patients and a stroke rate of 2.4% (20). Similarly, a large meta-analysis from 25 multicenter registries and 33 single-center studies found an important reduction in strokes after TAVR; these findings were associated with increased operator experience and technology advancement (21). Other TAVR-related complications, such as vascular injury, bleeding, and PVR, have also declined significantly with the use of lower profile TAVR systems, rigorous vascular management techniques, more sophisticated valve-sizing algorithms incorporating routine pre-procedure CT

angiography, and valve design modifications. Because the main procedure-related predictors of early and late mortality after TAVR are strokes, major vascular complications, bleeding events, and moderate to severe PVR, the reduction of these complications by a variety of means has helped to establish modern-day TAVR as a relatively safe procedure, with mortality rates at least as low as conventional surgery under most circumstances.

CURRENT ISSUES

PROCEDURAL DEVELOPMENTS. As TAVR technology has improved, procedural factors have also undergone substantive transformation. Using the heart team model as the organizational framework, pre-procedural diagnostic evaluations have been standardized, and intraprocedural technical steps have been systematically developed. As a result, there is less variability (from case to case) in procedural methods, which has helped to achieve consistent intersite clinical outcomes.

Minimalist strategy. Remarkably, the first TAVR procedure, reported by Alain Cribier in 2002 (4), was performed with conscious sedation, local anesthesia, and without the guidance of transesophageal echocardiography (TEE). Thereafter, in an effort to optimize safety with early-stage devices and to train practitioners, it was advisable to uniformly apply procedural "safeguards," including general anesthesia and intraprocedural TEE. More recently, as TAVR has become standardized with high procedural success and reduced complications, the focus has shifted toward simplification of the procedure; this strategy is now described as the "minimalist"

FIGURE 4 Temporal Trends in Mortality and Stroke After TAVR

(A) Reduction in all-cause mortality at 30 days with subsequent generations of Edwards Lifesciences Sapien valves (as-treated analysis) in the PARTNER I and II trials. **(B)** Reduction in strokes with different generations of Sapien valves in the PARTNER I and II trials. P1A = PARTNER (Placement of Aortic Transcatheter Valve Trial) 1A trial; P1B = PARTNER 1B trial; P2B = PARTNER 2B trial; S3HR = PARTNER 2 Sapien 3 high-risk cohort; S3i = PARTNER 2 Sapien 3 intermediate-risk cohort; SXT = Sapien XT valve; TAVR = transcatheter aortic valve replacement; TF = transfemoral.

approach. The components of a minimalist TAVR strategy include percutaneous transfemoral vascular access, monitored anesthesia control (i.e., conscious sedation) without general anesthesia, reduction or elimination of intraprocedural TEE guidance, reduction or elimination of balloon pre-dilation before valve implantation, and pre-specified care plans to encourage rapid ambulation and early hospital discharge. Some high-volume centers are already promoting a minimalistic strategy with conscious sedation and without routine use of TEE as the standard approach for most TAVR patients (22-24). More commonly, patient triaging has resulted in a "hybrid" strategy in most centers, favoring a minimalist approach in straightforward cases with adequate imaging windows for transthoracic echocardiography, and a more conventional approach in either high-risk or ambiguous cases, wherein the virtues of TEE guidance would be especially advantageous. This hybrid strategy requires careful

pre-operative assessment of comorbidities and identification of high-risk anatomic features with CT angiography to optimally risk-stratify patients.

Specific scenarios that would favor intraprocedural TEE include patients at high risk for coronary occlusion or annulus rupture, problematic valve sizing situations that can be clarified with TEE measurements, and other high-risk scenarios (e.g., chronic kidney disease) in which TEE valve placement guidance can reduce radiocontrast exposure and the risk of acute kidney injury. There are 2 other situations in which selective use of TEE guidance during TAVR can be of great value: assessment and treatment of post-implant PVR and rapid diagnosis to direct management after potentially catastrophic complications (25,26). Several studies have indicated that significant PVR after TAVR is associated with increased late mortality (27-30), resulting in the need for accurate PVR assessment and corrective treatment algorithms (31). Although analysis of hemodynamics should be routinely performed, and contrast aortography may be helpful, TEE determination of the severity and location of PVR is the most worthwhile intraprocedural modality to direct further therapy. TEE guidance and appropriate use of post-dilation have been shown to reduce significant PVR after TAVR (32,33).

The immediate causal analysis of rare but life-threatening complications can also be greatly facilitated by TEE. During cases of sudden severe hypotension during TAVR, TEE can rapidly distinguish among the differential diagnoses of annulus or ventricular rupture, coronary occlusion, severe aortic or mitral regurgitation (MR), bleeding, or left ventricular outflow tract obstruction (25,26). Nonetheless, because serious complications and significant PVR have been progressively reduced with greater operator experience and new TAVR devices, variations of the minimalist strategy have become prevalent in most high-volume TAVR centers. The pervasive need to develop more cost-effective interventional therapies has also promoted this approach, which reduces resource consumption. In one study (34), after careful triaging, the use of a minimalist transfemoral strategy was shown to reduce hospital length of stay by 40% and total inpatient costs by $10,000 per case compared with a standard approach using general anesthesia and TEE guidance, without negatively affecting clinical outcomes or PVR.

In parallel to a minimalistic implantation approach, many experienced TAVR centers are currently developing early discharge programs. In a retrospective analysis of 500 high-risk or inoperable patients from Italy who underwent transfemoral

TAVR, >20% were discharged within 72 h, and, importantly, there were no differences in 30-day outcomes between the 2 groups (35). The concept of early discharge after TAVR is being further assessed in the 3M (Multidisciplinary, Multimodality, But Minimalist) TAVR study, in which good candidates for uncomplicated TAVR are discharged the day after undergoing TAVR. Preliminary data from the pilot 3M study suggest that appropriately selected patients can be discharged safely the day after TAVR, despite a mean age of 83 years and an average STS score of 8.3% (36).

Valve sizing and positioning. A particular area of continued frustration and controversy has been establishing the optimal valve sizing guidelines to match the aortic annulus dimensions for each TAVR system. After initial efforts to measure the aortic annulus using 2-dimensional echocardiography, the current accepted gold standard has transitioned to CT angiography with standardized methodology and focusing on either area or perimeter measurements of the usually eccentric annulus (37,38). Some degree of valve to annulus oversizing is usually required, especially for self-expanding nitinol-based TAVR designs. In addition to annulus measurements, it is essential to examine the entire aortic valvular complex, including the left ventricular outflow tract, the sinuses, the origin of the coronaries, and the sinotubular junction. The importance of optimal valve sizing cannot be overemphasized, as it has an impact on complications (e.g., valve embolization, annulus rupture), valve positioning, valve hemodynamics, and PVR. Several studies have shown that optimizing valve sizing with CT angiography (or 3-dimensional TEE) is instrumental in reducing the likelihood of PVR (37-39). Because each TAVR frame design has unique geometry and expansion characteristics, the proper valve-sizing recommendations are specific for each TAVR system. Not infrequently, either the imaging studies are imprecise or the CT measurements fall in a border zone between 2 valve sizes, requiring the use of other modalities, such as TEE or balloon sizing (40), to make final decisions regarding valve size.

Another critical procedural issue is accuracy of valve placement within the aortic annulus. In the early period of TAVR, valve movement during deployment was a frequent event for both balloon-expandable and self-expanding platforms, despite stabilizing maneuvers such as rapid ventricular pacing. Imprecise valve positioning of only a few millimeters can result in valve embolization, significant PVR (mismatch of the valve "seal zone" and the anatomic annulus), coronary obstruction, or

conduction system abnormalities requiring new permanent pacemakers. Fortunately, in the current era of TAVR systems, valve positioning accuracy has improved dramatically due to both design enhancements (which have improved valve stability during deployment) and the availability of retrievable and repositionable delivery systems with newer versions of self-expanding TAVR devices.

DEVICE VERSUS DEVICE CONSIDERATIONS. After a decade of technical developments and established clinical indications, it is natural to question whether all TAVR systems have similar clinical results or if specific TAVR devices have design features that favor improved outcomes. This issue is especially relevant because most TAVR devices are distinctly different from the standpoint of frame geometry and material composition, valve tissue properties (both fixation and placement within the frame), and delivery system characteristics. Based on the original 2 clinical devices, TAVR systems had usually been categorized according to deployment methods, as either balloon-expandable with metal frames (either stainless steel or cobalt alloys) or self-expanding frames made of a super-elastic metal alloy (nitinol). More recently, additional TAVR designs and deployment methods have been created with other distinctive features, such as the nonmetallic fully polymeric Direct Flow Medical valve (Santa Rosa, California) (41,42), the nitinol mesh-design mechanically expanded Lotus valve (Boston Scientific, Marlborough, Massachusetts) (43,44), and the self-expanding JenaValve (JVT Research & Development Corporation, Irvine, California), which "clips" to the native aortic leaflets for positioning and retention (45,46). Because the preponderance of available clinical data has been with either the balloon-expandable Sapien valve or the self-expanding CoreValve, these 2 TAVR devices have been most commonly compared; however, most of these comparisons have largely been subjective and inferential, as there has never been a large, properly designed randomized trial comparing Sapien versus CoreValve. The CHOICE study was a small randomized trial (241 patients) in which clinically indicated TAVR patients were randomized to receive either the Sapien valve or the CoreValve and be followed up at 30 days (47) and 1 year (48). Although treatment with the CoreValve was associated with a higher frequency of PVR and new pacemakers, there were no significant differences between the 2 TAVR systems in 1-year clinical outcomes (death, stroke, repeat hospitalizations, vascular or bleeding events, and acute kidney injury). These results are consistent

with a balanced interpretation of the literature comparing the Sapien valve and the CoreValve: 1) similar mortality, strokes, and other clinical endpoints; 2) greater need for new pacemakers after CoreValve implantation; 3) similar valve hemodynamics and valve durability; and 4) more frequent rare, but important complications after the Sapien valve implantation, including annulus rupture (49,50) and coronary occlusions (51). Currently, it seems that the majority of patients with AS who are candidates for TAVR can be treated with similar excellent clinical outcomes by using either Sapien or CoreValve devices. However, it is important to note that in a minority of patients, attention to specific anatomic factors or clinical circumstances might reasonably favor one or another device design. For instance, CoreValve is more difficult to implant in horizontal aortas and, due to the higher rates of new pacemakers, may be less favorable in patients with heart failure and reduced left ventricular function. Conversely, in patients with concerns regarding risk of annulus rupture due to severe calcification of the aortic valvar complex, the self-expanding CoreValve may be preferable. In addition, there are currently 3 large randomized trials in the United States (each including approximately 1,000 patients) comparing new TAVR devices versus devices approved by the U.S. Food and Drug Administration (either CoreValve or Sapien); these studies should provide further interesting direct comparison data among the different TAVR designs. A final consideration relates to the importance of operator learning curves and experience with each TAVR system. Unlike other commonly used interventional technologies (e.g., balloon dilation catheters or stents), TAVR expertise requires intensive device-specific training for correct valve sizing, accurate valve placement, and avoidance of complications. Consequently, in the future, it seems likely that even high-volume operators will restrict their TAVR device use to no more than 3 or 4 different systems.

ADJUNCTIVE PHARMACOTHERAPY. Perhaps the area of greatest confusion, with insufficient evidence to guide clinicians, is the most appropriate adjunct pharmacotherapy during and after TAVR procedures. Complicating matters further is the difficulty in managing an elderly patient population with frequent atrial fibrillation (AF; approximately 40% in most studies) at high risk for both strokes and bleeding complications. Bleeding events, early and late after TAVR, are frequently observed and have been highlighted as an important predictor of mortality (52,53). Most studies, including the PARTNER and CoreValve

pivotal trials (9,10,13,14), have used a pharmacotherapy approach consisting of intraprocedural heparin and post-procedure dual antiplatelet therapy (aspirin and clopidogrel) for 3 or 6 months, as tolerated, at the physician's discretion, and combined with warfarin, as indicated. This generic approach potentially exposes some patients to increased bleeding risks and may not provide optimal protection to reduce the risk of embolic strokes and valve thrombosis. Alternative pharmacologic regimens have included the use of intraprocedural bivalirudin instead of heparin (54), single antiplatelet agents for shorter durations, and exploratory studies with novel anticoagulant agents instead of warfarin and/or antiplatelet agents (e.g., Galileo trial; NCT02556203). Clearly, additional studies, including several newly proposed randomized trials, will be required to develop a rational and customized strategic approach to balance the bleeding risks of new drug therapies and their antithrombotic value in preventing important valve-related thrombotic events.

FUTURE EXPECTATIONS

CLINICAL OUTCOMES AND PROCEDURAL BENCHMARKS.
Looking forward, a progressive attitude to encourage optimal clinical outcomes after TAVR would favor the application of quality benchmarks. As an example, an optimal quality TAVR center in the future should be able to achieve the following outcomes in high-risk AS patients: 1) all-cause mortality of approximately 2% to 3% at 30 days and <10% at 1 year; 2) significant strokes at 30 days in <2%; 3) major vascular complications in <5%; 4) new permanent pacemakers in <10%; and 5) moderate or severe PVR in <5%. Similar attempts to establish other procedural standards are an important component to minimize clinical outcome variability and achieve best clinical practices.

EXPANDING CLINICAL INDICATIONS. An area of
particular excitement in the immediate future is the expansion of TAVR to many other patient populations, some currently being treated with SAVR and others representing uncharted clinical territories. Appropriate evidence-based medicine verification is currently underway in several of these expansion clinical categories. However, in some instances, clinical practice has superseded clinical research, and important knowledge gaps remain.
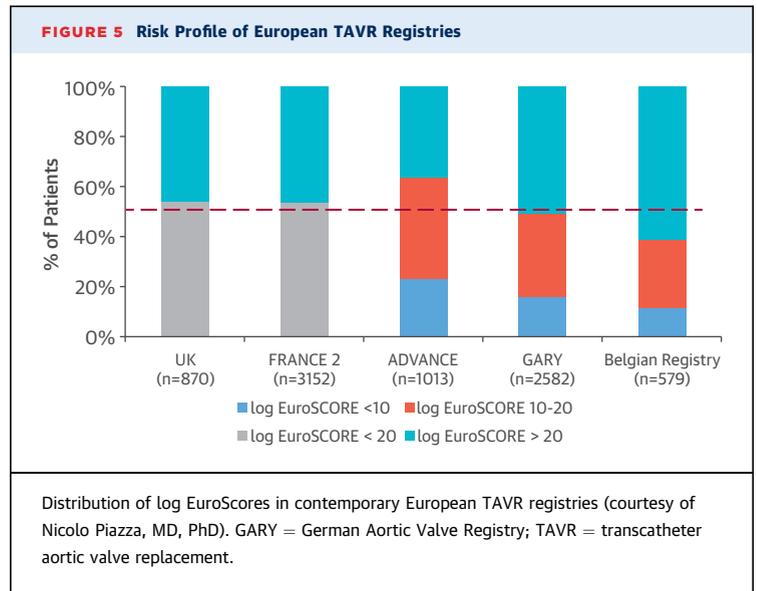
Lower risk patients. In the most recent AHA/ACC guidelines for the management of patients with AS (5), there are 8 class I or IIa recommendations for SAVR, all of which are Level of Evidence B or C and without randomized clinical trial validation.

Interestingly, for the most part, none of these recommendations was based on clinical risk stratification. Recognizing that TAVR was a new and unproven therapy, the imposition of risk strata to select the earliest patients for treatment was appropriate, considering the high frequency of periprocedural complications and the unknown durability of transcatheter bioprosthetic valves. A decade later, with >1,000 centers around the world routinely performing TAVR, marked reductions in TAVR-related complications, and evidence for good "midterm" valve durability (11,15), there is less justification for imposing strict limitations on TAVR use based on clinical risk stratification. Moreover, the current delineation of specific risk categories has been confusing and subjective, with significant site-to-site variation, in part due to local surgical results and comparative experiences with TAVR. Clearly, the sole use of STS mortality scores is insufficient to characterize surgical risk, as there are many high-risk factors not represented in the STS risk algorithm, including radiation-induced chest wall abnormalities, anatomic chest wall deformities, chest wall adherent and patent internal mammary surgical bypass graft conduits, severely calcified proximal aorta precluding safe surgery, severe liver disease, severe dementia, severe obstructive or restrictive pulmonary disease, and frailty. The AHA/ACC guidelines (5) have attempted to broaden the risk classification schema by incorporating 4 considerations to determine surgical risk: STS mortality score; frailty; clinical comorbidities; and procedure-related factors (vascular access and annulus calcification patterns, among others). Nevertheless, surgical and TAVR risk assessment remains an imprecise process, subject to the best intentions of individual heart team impressions and opinions. In the future, when more data in lower-risk patients are accumulated, it is likely that TAVR use will not be constrained by risk stratification but will be influenced more by specific anatomic and clinical factors.

Presently, several clinical research studies have acknowledged a downward risk "drift" and have begun to justify the use of TAVR in lower risk patients. In many of the European registries (6-8,55), approximately 50% of TAVR patients had risk profiles with logistic EuroSCOREs <20% (considered low or intermediate risk) (Figure 5). Similarly, in the initial 7,710 patients treated with TAVR from the U.S. post-approval Transcatheter Valve Therapy (TVT) registry, the median overall STS score for high-risk and inoperable patients was only 7% (56). Importantly, in the European registries and in 2 single-center studies (57,58), the observed TAVR mortality at 30 days in

lower-risk patients was significantly lower than in high-risk patients, which is similar to previous findings with SAVR. In addition, 3 propensity-matched, risk-adjusted comparisons of TAVR and surgery were conducted in intermediate-risk patients (59-61), with the results indicating almost identical 30-day mortality in transcatheter and surgically treated patients with AS. The recently published NOTION (Nordic Aortic Valve Intervention) trial (62) randomized 280 "all-comer" patients >70 years of age with AS in 3 Scandinavian centers to undergo conventional surgery versus TAVR with the self-expanding CoreValve. The average age was 79 years, and >80% of patients had an STS score <4%. Mortality (all-cause) and the composite primary endpoint of mortality, myocardial infarction, and strokes were similar in the surgery versus TAVR treatment arms at 30 days, 1 year, and 2 years. In the NOTION trial, hemodynamic valve performance was significantly better in CoreValve-treated patients compared with those treated with surgery. Two large randomized trials are ongoing in approximately 3,500 patients with intermediate-risk AS (STS scores between 3% to 4% and 8%) comparing surgery versus TAVR using either the balloon-expandable Sapien XT platform (PARTNER IIA) or the self-expanding CoreValve device (SurTAVI [Safety and Efficacy Study of the Medtronic CoreValve System in the Treatment of Severe, Symptomatic Aortic Stenosis in Intermediate Risk Subjects Who Need Aortic Valve Replacement]). Results from these important randomized trials in intermediate-risk patients will begin to become available in the next year.

The first large series of patients with intermediate-risk AS treated with a third-generation TAVR system (Sapien 3 valve) was recently presented at the 2015 ACC scientific sessions (19). In 1,076 patients with intermediate-risk profiles (mean age 81.9 years; median STS score 5.2%) treated with Sapien 3, the 30-day mortality was 1.1%, significant strokes occurred in 1.0%, and moderate to severe PVR was present in <4% of patients. These data, combined with the encouraging 5-year valve durability findings previously discussed (11,15), have heightened the enthusiasm for accelerating efforts to extend the recommended use of TAVR as an alternative to surgery for lower risk patients. In the future, clinical risk assessment will be replaced by a more logical approach that relies heavily on the multidisciplinary heart team to determine the choice of intervention, starting with whether the patient is a good candidate for TAVR (the less-invasive intervention) versus SAVR, on the basis of clinical, anatomic, and patient preference factors.

FIGURE 5 Risk Profile of European TAVR Registries

Distribution of log EuroScores in contemporary European TAVR registries (courtesy of Nicolo Piazza, MD, PhD). GARY = German Aortic Valve Registry; TAVR = transcatheter aortic valve replacement.

Valve-in-valve for bioprosthetic valve failure. Currently, the frequency of implanted surgical aortic and mitral bioprosthetic valves exceeds mechanical valve implantations (63). Bioprosthetic valves are often preferred due to reduced thrombogenicity, obviating the need for long-term anticoagulation. Structural deterioration of bioprosthetic valves results in hemodynamic failure (stenosis, regurgitation, or both), typically within 10 to 15 years after implantation, and is somewhat dependent on valve type and patient age. Therefore, the clinical management of bioprosthetic valve failure in patients who are poor candidates for repeat surgical valve replacement is increasingly problematic. Recently, transcatheter valve-in-valve implantation has emerged as a novel, less-invasive therapy for failed bioprosthetic surgical valves (64). On the basis of clinical registry data, the self-expanding CoreValve and the balloon-expandable Sapien XT valve have been approved for use in high-risk patients with aortic bioprosthetic valve failure. In the largest international registry of transcatheter aortic valve-in-valve implants (65), using both balloon-expandable and self-expanding transcatheter valves, early hemodynamics findings were encouraging and 1-year survival was 83.2%. Of note, in this multicenter report, stenotic degeneration of the surgical bioprosthesis and small valve implant size (usually resulting in higher postprocedural gradients) were associated with worse clinical outcomes. From a technical standpoint, compared with native valve TAVR, transcatheter valve-in-valve therapy results in less frequent PVR and new pacemakers but more common coronary

occlusions, particularly in surgical valves, in which the leaflets are sutured outside the stent frame. In smaller surgical valves, the self-expanding CoreValve results in less patient–prosthesis mismatch after valve-in-valve implants due to the supra-annular position of the valve (66). In the future, it is likely that transcatheter valve-in-valve implantation will become the preferred treatment for surgical bioprosthesis valve failure in a broad spectrum of patients, especially if customized devices are developed with improved hemodynamics.

Bicuspid aortic valve disease. In a large surgical series, bicuspid aortic valves have a high prevalence in younger patients with AS, but even in the elderly (>80 years of age), bicuspid valves comprise approximately 20% of the surgical cases (67). The hesitancy to treat stenotic bicuspid valves with TAVR arose from concerns that a more oval annulus shape, unequal leaflet size, heavy and uneven calcification of the leaflets, and the presence of calcified raphes might interfere with optimal TAVR deployment and/or lead to suboptimal hemodynamics with increased PVR. A recent analysis of multislice CT scans (68) revealed that in bicuspid aortic valves compared with tricuspid aortic valves, the annulus was more circular and less elliptical, the annulus area and perimeter were significantly larger, and there was more eccentric calcification. Two other legitimate concerns with treating bicuspid aortic valves using TAVR include heightened valve durability requirements in these younger patients and associated aortic pathologies, including aneurysms, which are more prone to develop aortic dissections.

Thus far, retrospective registry series indicate that only a small fraction of TAVR procedures were performed in bicuspid valves. Recent data from a TAVR-bicuspid valve registry, including 12 high-volume centers (139 patients) in Europe and Canada, support a preliminary finding that TAVR is safe, with a 5% 30-day and 17.5% 1-year mortality (69). However, as predicted, a major concern in patients with bicuspid aortic valves is the higher incidence of PVR; post-implantation aortic regurgitation ≥2 was found in 28.4% of patients. Perhaps new technologies with space-filling designs to prevent PVR will become necessary when treating bicuspid valves. Importantly, dedicated clinical trials in patients with bicuspid AS and next-generation TAVR devices are needed to help determine the most appropriate clinical indications.

AS and concomitant disease (combined therapies). Many patients with severe AS have significant cardiac comorbid conditions that may require treatment in addition to TAVR. These conditions include other valvular lesions (mitral and/or tricuspid regurgitation [TR]), coronary artery disease (CAD), and AF. Management of these concomitant diseases requires clinical insight and creative applications of new technologies in a customized, case-based strategy, using various combinations of medical therapies, other transcatheter devices, or surgery.

MR is a frequent finding in patients with severe AS, and moderate or severe MR has been reported in various registries in as many as 30% of patients undergoing TAVR (70). Although significant MR has been a predictor of reduced survival after TAVR (71,72), the PARTNER trial suggested that the impact of MR on post-procedure mortality was greater after surgery compared with TAVR (73). The severity of baseline MR is reduced in >50% of patients after TAVR (71), especially in patients with functional (vs. organic) MR. In some patients with residual significant MR after TAVR and continued symptoms of heart failure, a new approach is sequential or simultaneous treatment with percutaneous mitral valve repair using the MitraClip system (Abbott Laboratories, Abbott Park, Illinois) (74-76). Undoubtedly, as additional transcatheter mitral valve repair and replacement systems are validated, combination TAVR and mitral valve therapies may become commonplace. Similarly, TR is also commonly found in patients with AS, and the combination of severe TR with right ventricular dysfunction predicts worse outcomes after TAVR (77,78). In the future, several innovative transcatheter TR reduction approaches, including "spacers," and plication or ring annuloplasty devices, may be combined with TAVR in carefully selected patients.

It is well known that more than one-half of patients with AS who are >70 years of age also have CAD (79). For decades, the standard approach to patients undergoing surgery for severe AS with concomitant CAD has been simultaneous coronary revascularization. However, in the era of TAVR, these traditional notions have been challenged; selective proximal vessel, clinically driven revascularization is now preferred, rather than the obligatory complete revascularization (80), and percutaneous coronary intervention (PCI) is an alternative to surgery in carefully defined patients. Several considerations must be strategically managed in patients with AS and concomitant CAD treated with TAVR and PCI, including the complexity of coronary lesions (sometimes surgery is preferred), the safety of PCI in the setting of untreated AS (sometimes bridging balloon aortic valvuloplasty is recommended), and the timing of PCI, either before or during the TAVR procedure (in part, determined by the expected

complexity of the PCI). Lessons from the PARTNER and CoreValve trials have helped to develop clinically sensible approaches to managing these issues of AS plus concomitant CAD (13,14), but further dedicated clinical trials are ongoing that should provide more definitive evidence-based guidelines.

In severe AS, AF is present in approximately 40% of patients (13,81), and AF has been associated with increased periprocedural strokes after TAVR as well as reduced long-term survival (82,83). Devising optimal pharmacotherapy regimens in elderly patients with AS and concomitant AF has been problematic, largely due to excessive bleeding complications resulting from the combination of systemic anticoagulation and antiplatelet agents. A novel recent approach in patients with AS and AF who are at high risk for bleeding has been the implantation of a left atrial appendage closure device (84), which obviates the need for anticoagulation therapy. The use of these combination device applications should become commonplace in the future to provide optimal treatment options for patients with complex AS and concomitant cardiovascular problems.

OTHER NEW CLINICAL INDICATIONS. There are many other meaningful clinical indications for TAVR that have been and are being explored in various retrospective subanalyses, ongoing studies, and planned future clinical trials. For instance, carefully conducted studies (85) have examined the safety and efficacy of TAVR in patients with low-flow (and often low-gradient) AS, which has been a confusing entity to diagnose and carries a dire prognosis without valve replacement therapy. The management of patients with severe AS, but without clear cardiac symptoms, has been the subject of debate for decades and will now become a target for new randomized clinical trials. Similarly, patients with moderate AS and clinical heart failure, representing another management dilemma, will be evaluated in a new randomized clinical trial comparing standard medical therapy versus early TAVR. Finally, patients with severe aortic regurgitation and clinical indications for surgical repair or SAVR, but who are high risk for surgery, have already been treated with some TAVR devices (86-88) and will be the subject of a soon-to-begin U.S. early feasibility study. Clearly, the availability of less-invasive (percutaneous), safe (low frequency of early mortality, strokes, and other complications), and effective (excellent hemodynamics and midterm valve durability) TAVR therapies has spawned a resurgence of interest in new clinical indications and treatment options for patients with aortic valve disease.

FURTHER TECHNOLOGY ENHANCEMENTS. The rapid technology evolution from early prototype devices to current-generation TAVR systems with low-profile designs, dedicated user-friendly delivery

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CENTRAL ILLUSTRATION TAVR: Future Expectations and Barriers

FUTURE MANAGEMENT STRATEGIES FOR PATIENTS WITH SYMPTOMATIC SEVERE AORTIC STENOSIS

'Prohibitive risk' patients	Extreme risk or 'inoperable' patients	'High risk' patients	'Lower risk' patients*
✖ Surgical aortic valve replacement (SAVR)	✖ SAVR	✔ SAVR	✔ SAVR (preferred)
✖ Transcatheter aortic valve replacement (TAVR)	✔ TAVR	✔ TAVR (preferred)	✔ TAVR
• Both SAVR and TAVR considered 'futile' • Focus on symptom relief and palliation	• SAVR suboptimal • TAVR expected to improve survival and quality of life (QoL)	• Both SAVR and TAVR expected to improve survival and QoL • TAVR preferred unless age, anatomical or other patient factors make SAVR the superior option	• Both SAVR and TAVR expected to improve survival and QoL • May consider TAVR in absence of anatomic or unfavorable clinical characteristics with emphasis on patient age and valve durability

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Patients with severe aortic stenosis present with a spectrum of comorbidities that influence the treatment options available to them. The heart team will choose the optimal treatment strategy for individual patients based on their age, frailty, and anatomic and clinical characteristics. For patients undergoing transcatheter aortic valve replacement (TAVR), the bar for the performance standard is set by surgical aortic valve replacement (SAVR). TAVR has evolved as the preferred treatment for high-risk and inoperable patients. *Because the durability of transcatheter heart valves and outcomes in lower risk patients require further studies, SAVR remains the treatment of choice for such patients.

systems, heart valves with proven midterm durability, precise positioning during deployment with repositioning and retrieval features, and various concepts for reducing PVR has revolutionized the current practice of TAVR. Predictions for future TAVR systems include even lower profile devices (insuring percutaneous transfemoral access for almost all patients), further refinements of the aforementioned design attributes, and novel technologies, such as tissue-engineered heart valves (89).

Importantly, long-term valve durability concerns have remained a limitation in the expansion of TAVR to lower-risk patients. The 5-year follow-up data from PARTNER (11,15) is reassuring, in that no episodes of structural deterioration requiring replacement were observed, and valve hemodynamics (gradient and effective orifice areas) remained stable. Nevertheless, additional follow-up data in transcatheter valves will be required in the future to declare equivalence with the most durable surgical bioprosthetic valves (90). Perhaps the uncertainty of long-term durability becomes less concerning with the possibility of transcatheter valve-in-valve therapy to extend the duration of nonsurgical valve treatment.

In parallel with TAVR technology developments, advanced imaging systems and accessory devices have been—and will continue to be—dramatically enhanced. Sophisticated CT image work stations for pre-procedure case planning will help to guide correct selection of valve sizes and types. Intraprocedural imaging with new wide-angle 3-dimensional intra-cardiac echocardiography and multimodality co-registration capabilities will improve case-based decision making without adding undo complexity.

Although the frequency of periprocedural major clinical neurological events after TAVR has decreased, lingering questions remain regarding minor neurological events and neurocognitive functional changes. Several cerebral protection devices have been developed to capture or deflect liberated embolic debris during TAVR procedures, and neuroimaging studies have already shown improvements suggesting increased cerebral perfusion with cerebral protection in early randomized clinical trials (91-94). Decisions of systematic versus selective use of such devices in high-risk patients during TAVR remain controversial and await further clinical outcomes data from ongoing randomized clinical trials.

A potpourri of other accessory devices is being optimized to facilitate TAVR procedures. Dedicated pre-shaped guidewires, novel large-hole percutaneous closure devices, improved temporary pacemaker technologies, and new valvuloplasty and valve remodeling systems are presently all in clinical evaluations. The use of new technology refinements must be a balance between increased device costs and demonstrated incremental clinical benefit.

CONCLUSIONS

Over the past decade, TAVR has evolved as an important and mature alternative to SAVR for patients with high or prohibitive surgical risk (**Central Illustration**). Patient screening and procedural techniques have been effectively modified by using a heart team approach, and technical advances were introduced in a rapid fashion to simplify the procedure and reduce complications. In the future, device durability and expansion of clinical indications (supported by clinical evidence) will be important themes. The modern-day medical adventure of TAVR has thus transformed clinical practice and will remain an important contribution in the management of patients with AS.

REPRINT REQUESTS AND CORRESPONDENCE: Dr. Torsten P. Vahl, Columbia University Medical Center, Structural Heart and Valve Center, 177 Fort Washington Avenue, 5th Floor, Room 5C-501, New York, New York 10032. E-mail: tv2193@columbia.edu.

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