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Current concept on percutaneous aortic valve replacement. Immediate and long-term results

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SUMMARY

Introduction: *Transcatheter aortic valve replacement (TAVR) is a novel percutaneous intervention for the treatment of patients with severe aortic stenosis (AS).* **Purpose of the Study:** *provide current data from which the indications, risks, benefits, and future directions of TAVR are based.* **Methods:** *Literature review and personal experience derived from the results of major randomized trial of TAVR vs. surgical AVR (SAVR) many of them in which I participated are discussed.* **Results:** *The initial PARTNER I trial results demonstrated its value in high-risk patients for SAVR. Subsequent development of new delivery methods and devices including third generation of TAVR valves (i.e., Edwards Sapien 3 and Medtronic Evolut R) resulted in a reduction of the incidence of procedural complications. Further randomized studies of TAVR vs. SAVR in patients with severe AS with intermediate surgical risk (Partner II and Core-Valve intermediate risk) and those with low surgical risk (Partner III and Evolut low risk study) have further support that today TAVR is the standard-of-care procedure for all patients with AS including high, intermediate and low surgical risk. Patients with bicuspid valve anatomy may not get the same benefits from TAVR as they had been excluded from both PARTNER III and Core Valve Low Risk. Finally, the issue remains about the durability of the TAVR valve.* **Conclusions:** *TAVR is a breakthrough technique that has revolutionized the treatment of AS at the start of this century. TAVR is the standard-of-care procedure for all patients with AS including high, intermediate and low surgical risk.*

Key words: *Aortic stenosis, TVAR vs. SAVR, randomized trials of TAVR vs. SAVR in AS, balloon deployment sapien valve, self-spanding stent TAVR.*

Conflict of interest: I was an investigator from the MGH for several of the randomized trials of TAVR vs. SAVR analized and reported in this manuscript.

INTRODUCTION

Aortic stenosis is the most common valvular heart disease in the Western world. About 7 % of the population over age 65 years suffers from degenerative aortic stenosis and is present in more than 20 % of older adults, leading to $1 billion in US health care expenditures. Moreover, critical AS is prevalent in as much as 2 % to 3 % of the North American population older than 75 years of age, and its prevalence is rising as the population ages (1-8).

The prognosis of patients with symptomatic severe aortic stenosis is dismal without valve replacement (1-3). Even though the American and European guidelines recommend surgical aortic valve replacement (SAVR) to treat this condition as a class I recommendation, approximately one

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third of these patients over the age of 75 years are not referred for surgery (1-5).

SAVR has historically been the only durable treatment of patients with symptomatic severe AS and asymptomatic patients with severe AS undergoing another cardiac surgery. Although SAVR is routinely performed with relatively low mortality, up to one-third of patients are precluded from surgery because of advanced age and comorbid conditions, despite a dismal average survival of only 2 to 3 years in patients with symptomatic severe AS who do not undergo surgery (1-5). Percutaneous balloon aortic valvuloplasty (BAV) was the first percutaneous technique performed in patients with acquired severe AS by Cribier in 1985 (4), at which time it was anticipated to be an alternative to SAVR. In the current era, BAV is recommended for the treatment of severe AS in children and young adults, but initial enthusiasm surrounding this technique as an alternative to SAVR in older patients with calcific AS waned because of the perceived failure of the procedure to alter the natural history of calcific severe AS and because of significant initial procedural morbidity (1-3,5-6). Despite data suggesting that technical and procedural advances have decreased procedural complication rates in high-risk patients, prolongation of survival has not been demonstrated (3,5-6). Consequently, today BAV has been reserved only as a palliative procedure for high-risk patients who cannot undergo valve replacement, either surgical or transcatheter, or as a bridge to surgery in hemodynamically unstable patients (1-3,5,9-11).

During the last 18 years, TAVR has gained wide acceptance with good reproducible clinical and safety outcomes. The early results of percutaneous catheter-based valve replacement are promising. The first percutaneous heart valve replacement was performed by Bonhoeffer in 2002 (12) in the pulmonary position and by Allen Cribier in 2002 in the aortic position (TAVR) (13-14). TAVR has evolved to become a valid therapeutic option for patients with severe aortic stenosis who are inoperable or are at very high surgical risk (15-18), and more recently for patients with severe AS with intermedium surgical risk and those with low surgical risk for SAVR (18-21). Several studies have demonstrated that for patients with severe aortic stenosis who are not candidates for surgery, TAVR has significantly reduced mortality compared with standard treatment (Placement of Aortic Transcatheter Valves [PARTNER] trial, cohort B). Technological improvements, better patient selection, the help of the multidisciplinary Heart Team, and the increased operator experience have led to a significant reduction in most procedure-related complications and long-term mortality (23-24). In this review, I provide my Venezuelan colleagues, on one hand with current data in the TAVR field including clinical outcomes from the most recent, major trials in which I participated, and on the other hand, highlight the remaining pitfalls of this treatment and the gaps in evidence that need to be addressed in order to further improve clinical practice and expand its indication.

Current percutaneous valve technolgy

Currently, there are 2 first-generation percutaneous valves in clinical application, a balloon-expandable Edwards SAPIEN and a self-expandable valve (Core Valve System), with several other second-generation new players achieving first-in-human application. Since 2002 when the first TAVR in a human was reported by Cribier et al, percutaneous heart valves have already undergone several modifications from the first-generation devices. Nonetheless, it is inevitable that as technology develops to overcome the present limitations and to result in safer and more effective techniques, percutaneous heart valve replacement will undoubtedly increase in frequency. Other meticulously designed clinical trials must be performed to definitively determine the short- and long-term results of TAVR compared with the gold standard of open SAVR and to define the appropriate patient population who will benefit the most.

Over seven new valves have been developed in order to improve deliverability and outcomes, most of which incorporate self-expanding nitinol stents that are used with the Core Valve. For instance, the Lotus Valve System (Boston Scientific Inc., Natick, Massachusetts, USA) has been designed to open longitudinally, and Direct Flow Valve (Direct Flow Medical Inc., Santa Rosa, California, USA) incorporates a tubular fabric frame inflated with a rapid-setting

polymerizing agent. Acurate (Symetis Inc., Ecublens, Switzerland) and Portico (St. Jude Medical Inc., St. Paul, Minnesota, USA) valves are also similar to Core Valve since they contain a superior- extending meshwork, which allows for supra coronary aortic positioning and support. The Portico valve (St Jude Medical Inc) is a repositionable self-expanding valve which comes in four sizes (23, 25, 27, and 29 mm) and has been also shown to be noninferior to SAVR for high- and extreme-risk patients (left ventricular ejection fraction <20 %), renal insufficiency (creatinine >3 mg/dL), and a life expectancy <12 months). Moreover, Engager (Medtronic), JenaClip (JenaValve Inc., Munich, Germany), and Acurate valves house features that allow for anatomic implantation in alignment with native valve commissures and coronary openings. Several of these valves are constructed using new and improved sealing mechanisms in order to reduce the occurrence of paravalvular leaks after implantation.

Third-generation valves have been developed by Medtronic and Edwards. Medtronic developed the Evolut R, which is a new TAVR valve that keeps the same nitinol stent frame as the predecessors, while it has been associated with a 10 % reduction in length on the portion of the stent that settles on the outflow tract. The sealing skirt remains unchanged in order to reduce paravalvular leak, and catheter sizes include a smaller 14-18 F sheath. Edwards developed the SAPIEN 3 valve, which differs from the previous versions due to its newly developed cobalt chromium stent frame. The lower part of the stent frame is covered similar to the SAPIEN XT, while it also includes a polyethylene terephthalate skirt to reduce paravalvular leak. As delivered with 14-16 F catheter sizes, this valve has been shown to be more effective in the reduction of vascular complications compared to its predecessors. However, it has been associated with the increased incidence of permanent pacemaker placement after TAVR deployment.

Modes of delivery

Currently, there are six main routes for the insertion of TAVR, as follows: transfemoral, transapical, trans-subclavian, transaortic, trans-carotid, and transcaval routes. Approximately 10 % - 20 % of patients have small or tortuous femoral arteries due to peripheral vascular diseases, precluding the use of the old 18-25 F delivery systems. While the Core Valve could be inserted via the subclavian artery, the SAPIEN valve should bypass the calcified aortic arch by transapically moving through the left ventricular apex. However, since this procedure requires surgical intervention, it has been associated with higher risk of other complications, such as postoperative hemorrhage.

Randomized trials of TAVR vs SAVR in patients with severe aortic stenosis

Encouraging results have been reported with both the Edwards Sapien and the Core Valve systems (15-22).

High risk patients for SAVR (STS > 10 %)

The pivotal PARTNER I trial is the first randomized (1:1), controlled, multicenter study assessing the effectiveness and safety of TAVR in patients with severe, symptomatic aortic stenosis who are at high risk for conventional surgery 15-17). The study device (Edwards SAPIEN) for this trial was available in 23- and 26-mm valve sizes and was delivered via a 22 F or 24 F sheath for the transfemoral approach or a 26F sheath for the transapical route. The balloon-expandable bioprosthesis is composed of a stainless-steel frame inside of which a trileaflet bovine pericardial valve is mounted. In the PARTNER trial, the criteria used to define severe degenerative aortic valve stenosis were an aortic valve area of <0.8 cm^2 (or aortic valve area index <0.5 cm^2/m^2), a mean aortic gradient of >40 mm Hg, or a peak aortic jet velocity of >4 m/s. All patients had a New York Heart Association functional class ≥2. Some of the exclusion criteria included recent acute myocardial infarction (≤1 month), recent stroke or transient ischemic attack (within 6 months), congenital unicuspidal or bicuspid aortic valves, a preexisting prosthetic heart valve in any position, severe ventricular dysfunction (left ventricular ejection fraction < 20 %).

Subjects enrolled in the PARTNERS I trial

were separated into 2 groups A and B), and each cohort was separately powered and analyzed. In the cohort B, which was composed of patients who were deemed to be unsuitable candidates for surgery, TAVR was compared with standard medical therapy (15). Inoperability was judged by a cardiac interventionist and 2 separate surgical investigators and was based on a 30-day probability of death or serious, irreversible condition >50 % after surgical valve replacement. In cohort A, TAVR was compared with SAVR in high-risk surgical candidates who were characterized by a Society of Thoracic Surgeons risk score >10 % and the presence of comorbidities resulting in a ≥15 % predicted 30-day mortality as assessed by a cardiac surgeon (16). Depending on their eligibility for transfemoral access, cohort A patients were further assigned to either the transfemoral or transapical arm of the trial. Within each arm, patients were randomized between TAVR and SAVR. The primary end point was all-cause mortality at 1 year, but patients were followed up for at least 5 years (17).

The PARTNERS Trial Cohort A was composed of 699 patients with severe, symptomatic aortic stenosis deemed at high risk for traditional open-heart surgery (16). Patients were evenly randomized to receive either the Edwards SAPIEN valve with transfemoral or transapical delivery or traditional open-heart surgery. As shown in Table 1 and Figure 2, the study achieved its primary end point at 1 year, concluding that survival of patients treated with the Edwards SAPIEN transcatheter aortic valve was equivalent to the survival of those treated with surgical AVR. In this cohort, the study found that TAVI was noninferior to surgical AVR for all-cause mortality at 1 year,

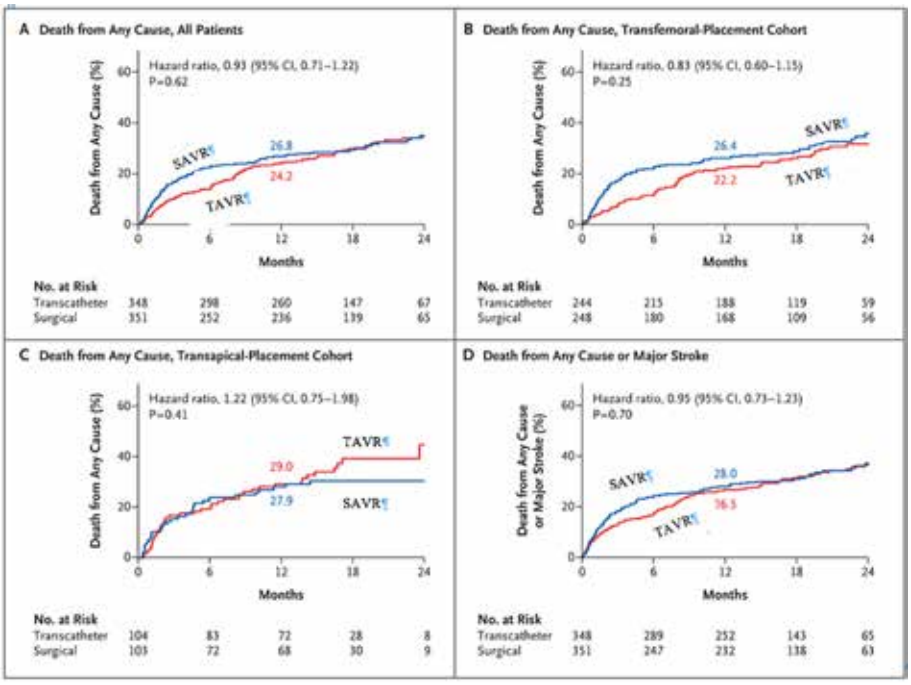

Figure 1. **Partner I (A).** Time-to-event curves are shown for death from any cause in all patients (Panel A), in the transfemoral-placement cohort (Panel B), and in the transapical-placement cohort (Panel C) and for a composite of death or major stroke (Panel D) among patients who were randomly assigned to undergo either transcatheter aortic-valve replacement (TAVR) or surgical aortic-valve replacement (AVR). The event rates were calculated with the use of Kaplan–Meier methods and compared with the use of the log-rank test. Modified from Leon MB, Smith CR, Mack M, Miller C, Moses JW, Svensson LG, Tuzcu EM, Webb JG, Fontana GP, Makkar RR, Brown DL, Block PC, Guyton RA, Pichard AD, Bavaria JE, Herrmann HC, Douglas PS, Petersen JL, Akin JJ, Anderson WN, Wang D, Pocock S; PARTNER Trial Investigators. Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. N Engl J Med. 2010;363:1597-1607.

Table 1

Combined death and disable stroke

Trial	TAVR	SAVR	P-value
Partner I A	30.7 %	49.7 %	<0.001
Partner I B	26.5 %	28.0 %	0.68
Partner II	34.6 %	33.9 %	0.75
Partner III (low risk)	8.5 %	15.1 %	0.001
Core Valve	14.2 %	19.1 %	0.04
Core Valve (low risk)	5.3 %	6.7 %	No inferiority

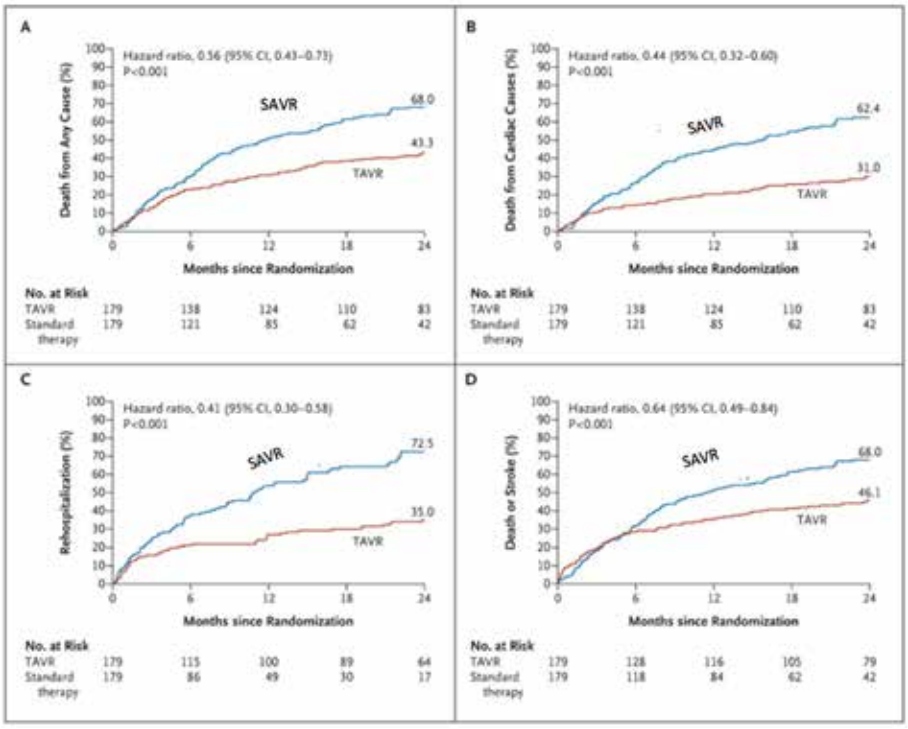

Figure 2. **Partner I (B). Time-to-Event Analyses of Key End Points during 2 Years of Follow-up.** Panel A shows the rate of death from any cause, Panel B the rate of death from cardiac causes, Panel C the rate of rehospitalization, and Panel D the rate of death or stroke. Event rates were calculated with the use of Kaplan–Meier methods and were compared with the use of the log-rank test. Deaths from unknown causes were assumed to be deaths from cardiac causes. TAVR denotes transcatheter aortic-valve replacement. SAVR denotes surgical aortic-valve replacement. Modified from Smith CR, Leon MB, Mack MJ, Miller DC, Moses JW, Svensson LG, Tuzcu EM, Webb JG, Fontana GP, Makkar RR, Williams M, Dewey T, Kapadia S, Babaliaros V, Thourani VH, Corso P, Pichard AD, Bavaria JE, Herrmann HC, Akin JJ, Anderson WN, Wang D, Pocock SJ; PARTNER Trial Investigators. Transcatheter versus surgical aortic-valve replacement in high-risk patients. N Engl J Med. 2011;364:2187-2198.

24.2 % versus 26.8 %, respectively. At 1 year, the rate of death resulting from any cause was 30 % with TAVI versus 50.7 % with standard treatment. However, TAVR patients had a higher incidence of strokes and major vascular complications compared with standard treatment. The rate of major strokes was 3.8 % in the TAVR arm versus 2.1 % in the SAVR arm at 30 days and 5.1 % versus 2.4 % at 1 year, a difference that was not statistically significant (P=0.20 at 30 days and P=0.07 at 1 year). However, when strokes and transient ischemic attacks were considered together, there was a statistically significant benefit favoring surgery at both 30 days and 1 year (P=0.04). Quality-of-life data analysis showed that high-risk, surgery-eligible patients treated via a transfemoral route in PARTNER A cohort had substantial quality-of-life benefits compared with surgery in the early weeks after the procedure. This was not the case for patients treated via a transapical route. In this latter group of patients, there was no benefit of transcatheter AVR over surgical AVR at any time point; in fact, quality of life tended to be better with surgical replacement at both 1 and 6 months.

The PARTNER I cohort B was composed of 358 patients with severe, symptomatic aortic stenosis deemed inoperable for traditional open-heart surgery. Patients were evenly randomized to receive either the Edwards SAPIEN valve or standard therapy. Although the 30-day rates of stroke (3.8 % versus 2.1 %; P=0.20) and vascular complications (11 % versus 3.0 %; P<0.001) were higher in the TAVR group, as shown in Table 1 and Figure 2 survival at 1 year was dramatically higher in patients receiving the valve compared with those who received best medical therapy (69.3 % versus 49.3 %; P<0.001). Furthermore, patients who received the valve had repeat hospitalizations and better symptoms relief than those receiving standard medical care. Two-year outcomes in the PARTNER I B trial showed that survival curves are continuing to separate, and the number needed to treat to save 1 life dropped from 5 at 1 year to 4 at 1 years (17). The Food and Drug Administration approved the SAPIEN valve for the US market on the basis of the PARTNER B results. Two-year follow-up data continue to support the role of TAVI as the standard of care for symptomatic patients with aortic stenosis who are not surgical candidates (17).

Two-year follow-up data from the PARTNERS I trial were reported by Kodali et al (17). They reported that outcomes between TAVR and surgery were comparable at 2 years of follow-up. Nevertheless, further follow-up of this data is required because the main unanswered question concerns the duration or longevity of the percutaneous valve. The more important news to address duration or longevity of TAVR will probably come from 4- or 5-year follow-up studies. The point that there is more aortic insufficiency with TAVR is valid. The fact that risk for stroke was not significantly different at 2 years is still not completely reassuring because it looks like more strokes occurred with TAVR than with surgical AVR (8 versus 12 strokes).

Intermediate risk patients for SAVR (STS > 4 % and < 10 %)

A second prospective, randomized, multicenter trial, the PARTNER II trial, was designed to investigate the procedural clinical performance and outcomes after TAVR with a next-generation Edwards SAPIEN XT THV and the new 18F Nova Flex system (Edwards Lifesciences) (18). The newer SAPIEN XT valve has several key differences from the previous-generation device, including a cobalt chromium frame and modified leaflet design that may improve durability. The PARTNER II cohort B includes patients with severe aortic stenosis deemed to be inoperable. In this trial cohort, the old device versus new device noninferiority trial was designed. The primary end point is a composite of death, stroke, and repeat hospitalization at 1 year. In addition, cohort A of the PARTNER II trial randomized patients between TAVR with the SAPIEN XT valve and surgical AVR in moderate- to high-risk patients. This trial enrolled patients with an intermedius surgical risk for SAVR (STS >4 % and less than 10 %) than the patients in the PARTNER I trial had. As shown in Table 1 and Figure 3, this study (Partner II) demonstrated that among patients with symptomatic severe AS who are intermediate-risk surgical candidates, TAVR was noninferior to surgical AVR with respect to all-cause mortality and disabling stroke at 2 years. The frequency and severity of paravalvular aortic regurgitation were greater after TAVR than after surgery. In the TAVR group at 30 days, mild paravalvular

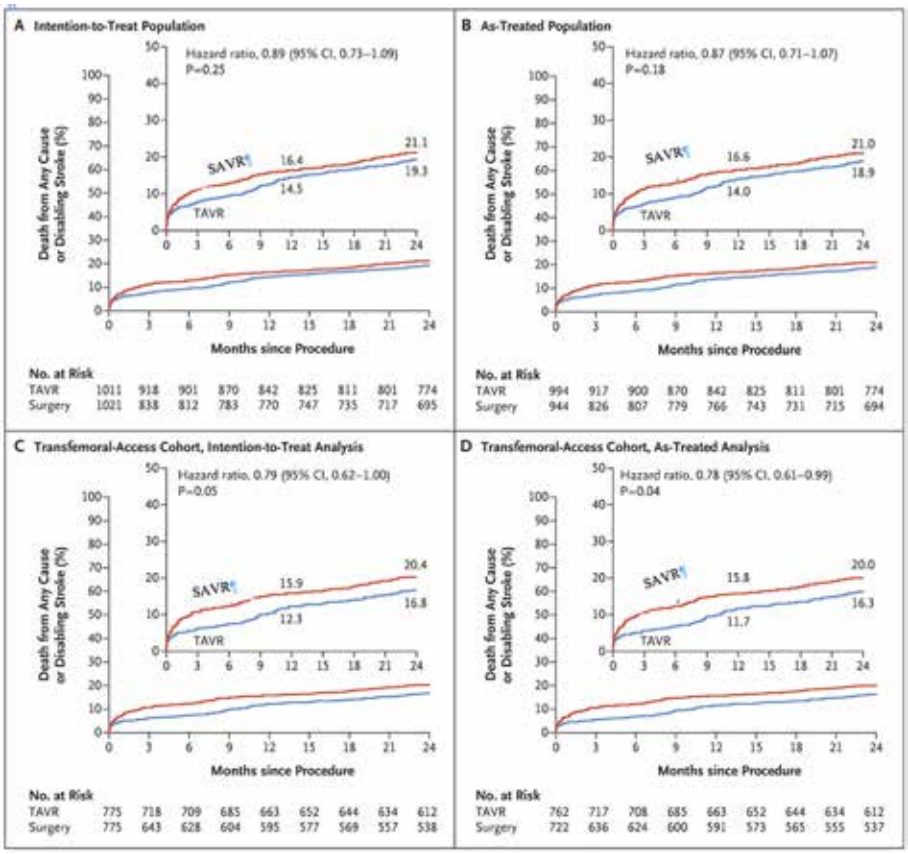

Figure 3. **Partner II. Time-to-Event Curves for the Primary Composite End Point.** The insets show the same data on an enlarged y axis. TAVR denotes transcatheter AVR. SAVR denotes surgical AVR. Modified from Leon, M; Smith CR, Mack MJ, Makkar RR, Svensson LG, Kodali SK, Thourani VH, Tuzcu EM, Craig Miller D, Herrmann HC, Doshi D, Cohen DJ, M.D.Transcatheter or Surgical Aortic-Valve Replacement in Intermediate-Risk Patients. N Engl J Med. 2016;374:1609-1620.

aortic regurgitation was observed according to the standard classification scheme in 22.5 % of patients, and moderate or severe paravalvular aortic regurgitation in 3.7 %. Patients in the TAVR group who had moderate or severe, but not mild, paravalvular aortic regurgitation (according to either the standard or expanded classification scheme) at 30 days had higher mortality during 2 years of follow-up than did patients who had no or trace regurgitation (P<0.001).

In December 2010, Medtronic began its pivotal US trial designed to evaluate the safety and efficacy of the Core Valve system (19-20). The study enrolled >1300 patients at 40 clinical sites. The trial includes 2 studies in different patient populations: 1 study of patients diagnosed as high risk for aortic valve surgery and a second study of patients diagnosed as extreme risk. Patients deemed at extreme risk were not randomized to optimal medical management; rather, they were evaluated against a performance goal derived from contemporary studies. Patients in the high-risk group were randomized 1:1 to either TAVR with Core Valve vs. surgical AVR. The primary end point was all-cause death or major stroke within 12 months. The SURTAVI trial concluded that TAVR was non-inferior to SAVR with respect to all-cause mortality and disabling stroke at 2 years in patients with severe, symptomatic AS at intermediate surgical risk. SAVR was associated with a marginally higher peri-operative

stroke rate while TAVR was associated with a modest increase in hospitalizations related to aortic valvular disease at 2 years. TAVR was statistically noninferior to surgery in patients who were deemed to be at intermediate surgical risk by a multidisciplinary heart team. They found that the risk of death or disabling stroke at 24 months was 14 % for the SAVR vs. 12.6 % for the TAVR patients in this trial. Surgery was associated with higher rates of acute kidney injury, atrial fibrillation, and transfusion requirements, whereas TAVR had higher rates of residual aortic regurgitation and need for pacemaker implantation. TAVR resulted in better aortic-valve hemodynamics than surgery, and neither TAVR nor surgery showed evidence of structural valve deterioration at 24 months (19-21).

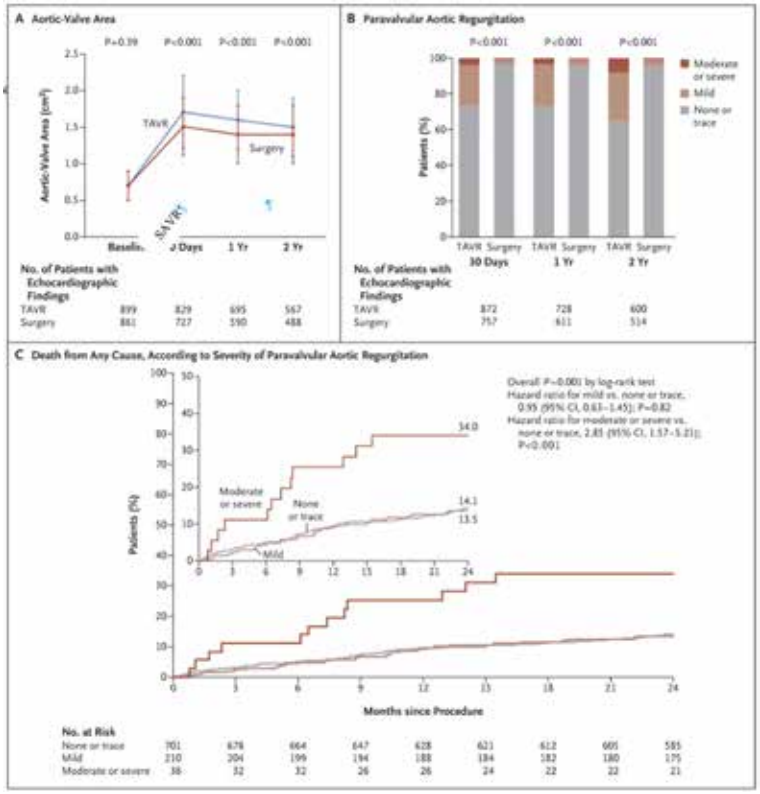

Figure 4. **Partner II. Echocardiographic Findings:** Panel A shows the change in aortic-valve area from baseline to 2 years, and Panel B the percentage of patients with paravalvular aortic regurgitation at 30 days, 1 year, and 2 years after the procedure. Panel C shows time-to-event curves for death from any cause according to the severity of paravalvular aortic regurgitation (post hoc analysis). The inset shows the same data on an enlarged y axis. The frequency and severity of paravalvular aortic regurgitation were greater after TAVR than after surgery. In the TAVR group at 30 days, mild paravalvular aortic regurgitation was observed according to the standard classification scheme in 22.5 % of patients, and moderate or severe paravalvular aortic regurgitation in 3.7 %. Patients in the TAVR group who had moderate or severe, but not mild, paravalvular aortic regurgitation (according to either the standard or expanded classification scheme) at 30 days had higher mortality during 2 years of follow-up than did patients who had no or trace regurgitation (P<0.001). Modified from Leon, M; Smith CR, Mack MJ, Makkar RR, Svensson LG, Kodali SK, Thourani VH, Tuzcu EM, Craig Miller D, Herrmann HC, Doshi D, Cohen DJ, M.D.Transcatheter or Surgical Aortic-Valve Replacement in Intermediate-Risk Patients. N Engl J Med. 2016;374:1609-1620.

Low risk patients for SAVR (STS < 4 %)

The earliest trials evaluated TAVR in the "sickest" patients - many of whom cannot be treated with surgery - with subsequent research moving down the spectrum of risk to include patient at high-risk and intermedium surgical risk for SAVR. The Partner III trial included patients at low surgical risk (STS <4 %), which comprise the majority of patients who are candidates for surgery to have their aortic valve replaced (22). PARTNER III included 1 000 patients with severe aortic stenosis at 71 centers in the U.S. and several other countries with over 95 percent of patients enrolled at U.S. sites. Participants were carefully screened to be low risk for either TAVR or surgery and were randomly assigned to receive the SAPIEN 3 TAVR valve, the newest generation technology, or surgical valve replacement. Compared with the earlier PARTNER trials with intermediate - and high-risk surgical patients, this low-risk group was younger (73 years on average), had fewer co-morbid conditions and had fewer symptoms. There were also more men than women enrolled (67.5 percent vs. 32.5 percent, respectively).

The primary endpoint was the combined rate of all-cause death, any stroke and re-hospitalizations (those related to the valve, the procedure or heart failure) at one year after the procedure. The results of the primary end point are depicted in Table 2 and Figure 5. Taken by themselves, each component of the primary endpoint also favored TAVR, which is confirmatory evidence of the outcome.

Among patients with severe, symptomatic aortic stenosis who were at low surgical risk, TAVR using the SAPIEN 3 valve compared with SAVR significantly reduced the primary endpoint of death, stroke and re-hospitalizations by 46 percent at one year, according to data from the latest PARTNER trial presented at the American College of Cardiology's 68th Annual Scientific Session. In addition, the rates of death from any cause, stroke and repeat hospitalizations independently favored TAVR at 30 days and at one year. There are two major limitations to the PARTNER III trial. First, the data are limited to one-year follow-up and longer-term follow-up is needed to be certain that the transcatheter valves are as durable as surgical valves. The patients in this trial will be followed for 10 years. Second, certain patients were excluded in this study, such as patients with bicuspid aortic valve disease and those with poor anatomy such that the valve couldn't be threaded through the femoral artery in the groin. Trials showing the benefits of TAVR in low-risk patients has been well received, and the question now has shifted to who nowadays, is a candidate for open heart surgery.

TAVR met non-inferiority to surgical aortic valve replacement (SAVR) also in the Core Valve Low Risk Trial and superiority in PARTNER III, with fewer strokes and no significant uptick in paravalvular regurgitation among patients with severe aortic stenosis in either study. Eugene Braunwald, MD, of Brigham and Women's Hospital in Boston, said it was a "historic moment" at the American College of Cardiology (ACC) annual meeting. "The fact that two separate groups using two separate valves have come to very similar conclusions, this not only doubles the acceptability, but it quadruples it. The issue remains about the durability of the TAVR valve and what happens in terms of risk to the patient if there is a need to reoperate, but valve-in-valve could be an option in these patients.

Unresolved issues

Patients with bicuspid valve anatomy may not get the same benefits from TAVR as they had been excluded from both PARTNER III and Core Valve Low Risk trials that evaluated the safety and efficacy of the balloon-expandable Sapien 3 and self-expanding Core Valve devices, respectively. Others who may still need surgery include those with coronary artery disease (who may do better with coronary artery bypass grafting and valve replacement surgery together), and those who can't get transfemoral access for their procedure. Finally, two concerns associated with moderate downsides of TAVR are the higher incidence of paravalvular leakage with both valves, and the pacemaker rate for the self-expanding valve.

The results of the immediate and intermediate long-term outcomes of TAVR in a wide range of surgical risk from low risk to prohibited risk have provided happiness and enthusiasm to interventional cardiologists who felt that they have conquered the percutaneous treatment of calcific aortic stenosis (23-24).

Table 2

Primary endpoint and components Partner III trial (TAVR vs SAVR)

	TAVR (n= 496)	SAVR (n= 454)	P-value
Composite all cause mortality, stroke & rehospitalization	8.5 %	15.1 %	0.001
Stroke	0.6 %	2.4 %	0.02
Death or Stroke	1.0 %	3.3 %	0.01

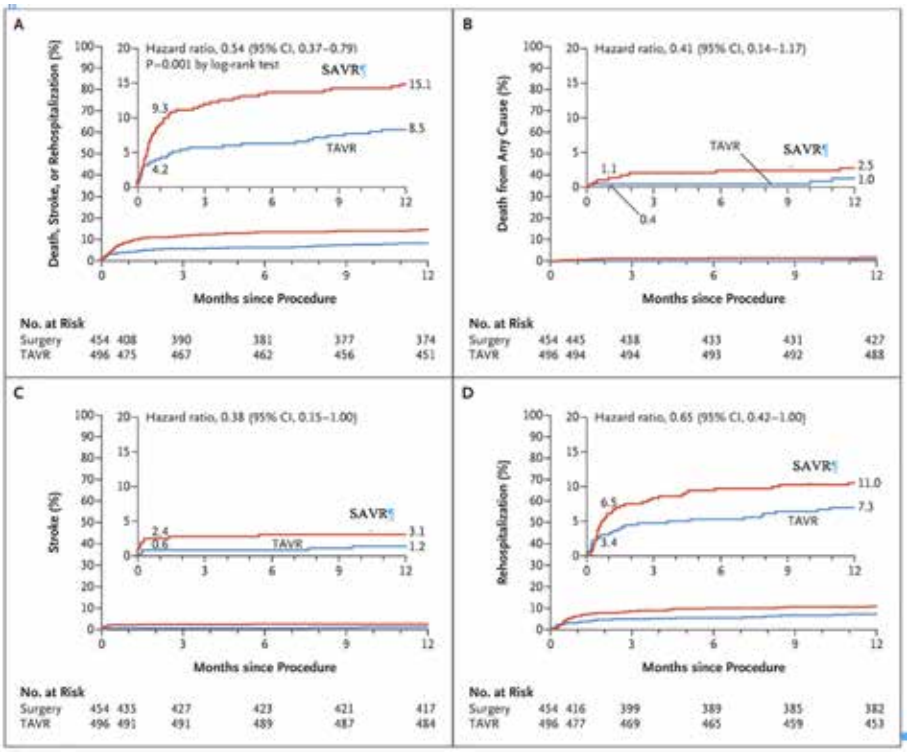

Figure 5. **Partner III. Two years Primary End Point of Partner III (SAVR vs TAVR in low risk patients (STS < 4 %). Time-to-Event Curves for the Primary Composite End Point and the Individual Components of the Primary End Point.** Shown are Kaplan-Meier estimates of the rate primary composite end point (Panel A) and the individual components of the primary end point, which are death from any cause (Panel B), stroke (Panel C), and rehospitalization (Panel D), in patients who any underwent transcatheter aortic-valve replacement (TAVR) and those who underwent surgical aortic-valve replacement (SAVR). The insets show the same data on an enlarged y axis. Modified from Mack MJ, Leon MB, Thourani VH, Makkar R, Kodali ASK, Russo P, Williams MR, McCabe JM, Brown DL, Babaliaros V, Goldman S, Szeto WY, Genereux P, Pershad , Pocock SJ, Alu MC, Webb JG, Smith CR, PARTNER 3 Investigators. Transcatheter aortic valve replacement with a balloon-expandable valve in low-risk patients. N Engl J Med. 2019;380:1695-1705.

The heart team

The heart team is vastly a multidisciplinary team approach, and a collaborative exercise for the heart valve team is necessary for successful program outcomes. Optimal patient selection is critical to a successful TAVR vs. SAVR procedures. This multidisciplinary team is essential during the screening, during the procedure, after the procedure, and during the

follow-up of these patients, and it plays a big role given the multiple areas of expertise. Patients should be screened into a TAVR program by a member of the multidisciplinary team, not by an individual specialist. Selection of candidates for TAVR should involve multidisciplinary consultation between interventional cardiologists, surgeons, echocardiographers, other imaging specialists, anesthesiologists, pulmonologist, and other specialists if necessary. The use of a team approach has been shown to improve outcomes in these types of complex procedures.

TAVR procedure

Transcatheter AVR is performed with either local or spinal anesthesia, with sedation or with general anesthesia in a cardiac catheterization laboratory, or in a hybrid operating room equipped with fluoroscopy and transesophageal echocardiography. TAVR is performed through either the transfemoral or transapical approach. The concept of a hybrid room was developed for this technique and requires a large room equipped with high-resolution fluoroscopy and cineangiography with Dyna CT (Siemens USA, Washington, DC) and transesophageal echocardiography capability. It requires double-ventilation circulation and a readily available heart-lung machine, intra-aortic balloon pump, and pacemaker. The screening tests usually necessary in the evaluation of these patients include clinical evaluation; ECG; transthoracic echocardiography; transesophageal echocardiography; chest, abdominal, and pelvic computed tomography angiography; cardiac catheterization with coronary arteriography; pulmonary function tests; and noninvasive carotid studies. Surgical risk of the patients is assessed by the use of special scoring methods for risk stratification. They include the Euro SCORE, the Society of Thoracic Surgeons score (STS), and the Frailty Score. When tests are completed, the results of the evaluation are discussed openly with the multidisciplinary group to determine the best way forward for each individual patient.

Cardiac and aortic valve imaging

Assessment of the anatomy of the aortic annulus is an important component of case selection. Both manufacturers currently have 4 sizes of bioprosthesis in widespread use to treat a wide range of annuli. The balloon expandable Sapien Edwards valve include 20, 23, 26- and 29-mm diameter valve sizes. The Medtronic Core Valve System comprised of three design iterations; Medtronic core Valve System (1st generation), Evolut R System and Medtronic Core Valve Evolut PRO System (3rd generation). The Medtronic Evolut Pro + includes 23, 26, 29- and 34-mm diameter valve sizes. They have thresholds for sizing of their prostheses for the annular dimensions of a particular patient dictated by estimated need for oversizing.

It is clear that measured dimensions by various imaging modalities used for this purpose vary significantly. Transthoracic echocardiography (TTE) using two-dimensional (2D) imaging, color flow mapping, and spectral Doppler is well-established for the primary assessment of aortic valve disease. However, many advances to this foundational modality have contributed to improved diagnosis and management. Specifically, transesophageal, three-dimensional (3D), strain and stress echocardiography all provide important adjunctive information for aortic valve disease. Computed tomography and magnetic resonance imaging can also be helpful when aortic valve disease severity remains indeterminant with echocardiography. Although transthoracic echocardiography acts as a useful screening tool in this regard, transesophageal echocardiography, sometimes as an immediate pre-TAVR confirmatory evaluation, is regarded as the current standard of care.

Currently computerized tomography is considered as the gold standard for TVAR procedures. It provides additional information on the noncircular nature of the aortic annulus, which is poorly appreciated by echocardiographic modalities. Each manufacturer has set clear boundaries for each bioprosthesis size. The Edwards SAPIEN device requires an annulus of 18 to 21 mm for its smaller 23-mm bioprosthesis and 22 to 25 mm for its larger 26-mm bioprosthesis, with 21 to 22 mm remaining a gray zone, at the operator's discretion. A larger 29-mm Edwards SAPIEN device now approved in Europe and US meets the requirements for larger aortic annulus 24-28 mm). The Medtronic Core Valve device

requires an annulus of 20 to 23 mm for its smaller 23-mm bioprosthesis and 24 to 27 mm for its larger 29-mm bioprosthesis. Although 23 to 24 mm is an unspecified gray zone, the larger bioprosthesis is generally prescribed for these dimensions. A new 34 mm valve is now available for larger aortic annulus (> 24 to 30 mm).

The implantation procedure involves accessing a femoral artery, performing balloon valvuloplasty in some patients, and then advancing the device across the native valve. During rapid right ventricular pacing, a balloon is inflated to deploy the valve and the stent frame. Transfemoral TAVI represents the most commonly used access approach overall. However, the safety of this approach depends heavily on careful iliofemoral assessment by computed tomography angiography. Important aspects of relevance are vessel sizing, assessment of tortuosity, and calcification. The newer version of the Edwards Sapien device is the Sapien 3. After establishing THV valve size, the next step requires access evaluation. For 20 mm, 23 mm and 26 mm S3 THV, the minimum vessel diameter is 5.5mm. The Evolut PRO+ Core Valve system requires a minimal access of 5.0 mm vessel diameter for the 23-29 mm valves.

The femoral access risk ratio, defined as sheath size divided by minimal femoral access diameter, with a threshold of 2.6, has been identified as an independent predictor of major vascular complications. The same study has also shown that excessive calcification at the site of femoral access is an independent risk factor for major vascular complication.

The future

The future of percutaneous TAVR depends on the development of smaller-diameter collapsible, repositionable, and compressible valve prostheses; anti calcification treatment; and adjunctive techniques to decrease the incidence of cerebrovascular embolic events. TAVR is definitely a breakthrough technique that has revolutionized the treatment of aortic stenosis at the start of this century. Although today these techniques were initially targeted to patients at high risk for AVR, today they have extended to the intermedium and lower- surgical risk groups. Since the initial promise holds true after careful evaluation, the road is long and demanding, but the interventionalist dream for percutaneous AVR has become a reality. Further development and improvement of current available TAVR devices are expected to increase success, to decrease complications, and to broaden TAVR indication to larger number of patients. The next generation of devices may help to reduce the frequency of procedure-related complications. In older patients with vascular disease, it is difficult to insert the larger device used in the PARTNER trial. The next-generation devices such as the SAPIEN XT (Edwards) that is 40 % smaller, the Sapien 3 and the approved Evolut Pro+ CoreValve (Medtronic) obviated the vascular complications and reduce the bleeding complications. The SAPIEN valve system initially used has evolved, and current platforms, now fourth generation, have a much smaller diameter (18F) and thus has decreased vascular complication and stroke rates. These complications will be further reduced as operator experience increases and potentially with the routine use of embolic protection devices. If stroke rates are reduced, then certainly TAVR will march even further forward and has recently tested in lower-risk populations with aortic stenosis in whom surgery is indicated. Such optimism should be welcomed by both patients and interventionists alike, but only after the efficacy and longer-term durability of TAVR vs SAVR trial have been rigorous evaluated.

Complications of TAVR

Through both rapidly increasing clinical experience and progressive improvement in TAVR devices (eg, lower profile systems to reduce vascular complications), TAVR outcomes have improved (24-25). Local vascular complications secondary to arterial sheath insertion such as groin hematoma, vessel rupture, thrombosis, or pseudoaneurysm may occur in 5.5-20 % of patients undergoing TAVR (25). However, these vascular complications have decreased in frequency with the newer valves associated with smaller delivery systems.

Ongoing studies continue to scrutinize the risks of TAVR complications and continuing efforts seek to minimize these risks. Periprocedural complications are related to vascular access

(including injury at the arterial access site, arterial tree trauma, and problems with vascular closure), valve deployment (including improper positioning, coronary compromise and annular rupture), valve function (including paravalvular leak), organ injury (including stroke, myocardial ischemia/injury, and acute kidney injury), and arrhythmic complications (including high degree heart block and atrial fibrillation) and late complications including aortic regurgitation and prosthetic valve thrombosis (24-25). Data from the TVR Registry showed that AVR patients remain an elderly population (mean age 82 years), with multiple comorbidities, reflected by a high mean STS predicted risk of mortality (STS PROM) for surgical valve replacement (8.34 %), were highly symptomatic (New York Heart Association functional class III/IV in 82.5 %), frail (slow 5-m walk test in 81.6 %), and have poor self-reported health status (median baseline Kansas City Cardiomyopathy Questionnaire score of 39.1) (24-25). Procedure performance is changing, with an increased use of moderate sedation (from 1.6 % to 5.1 %) and increase in femoral access using percutaneous techniques (66.8 % in 2014). Vascular complication rates are decreasing (from 5.6 % to 4.2 %), whereas site-reported stroke rates remain stable at 2.2 % (25). The small delivery size leads to less vascular complications. Updates in technology ensure a more precise deployment leading to less PVL. Newer generation valves, such as the SAPIEN 3, Lotus, and EvolutR, are also becoming viable options for patients with bicuspid aortic valves, as studies of first-generation valves showed unacceptable levels of PVL.

During the TAVR procedure the specific mode of anesthesia was typically general, with moderate sedation used in only <5 %, although with a clinically and statistically meaningful increase in use over time (p for trend <0.0001). This has changed with smaller TAVR catheters, so that the use of conscious moderate sedation has become increasingly frequent in selected patients (25). This trend can be expected to increase because it results in a shorter length of hospital stay and improved patient preference and tolerance of the procedure. Performance of cardiopulmonary bypass is infrequent (<5 %) and usually is performed emergently as the result of a complication.

New conduction disturbances induced by TAVR, although markedly less frequent with more recent devices, is still a persistent problem and if untreated, poses a threat for patients who could develop sudden complete heart block. A tradeoff between oversizing the TAVR prosthesis to achieve lesser degrees of perivalvular leak must be balanced against forceful compression of conduction tissue under the valve and inducing conduction abnormalities requiring a pacemaker. Fortunately, post-procedural pacemaker implantation had only a small effect on survival or quality of life after adjusting for pre and periprocedural patient characteristics. New cerebrovascular events including ischemic lesions were detectable by magnetic resonance imaging in up to 84 % of patients, of which only 4 % of those were associated with clinical stroke. The PARTNER 2 trial reflected no difference in rate of stroke or transient ischemic attack compared with AVR at 30 days, 1 year, and 2 years follow-up (20,22). The Sentinel cerebral protection device (a filter placed in the brachiocephalic artery during the procedure to capture debris) can be used to reduce the rate of embolic stroke. The SENTINEL trial demonstrated a numerically lower rate of cerebrovascular events; however, it was not statistically significant. Rare complications of TAVR of less than 1 % incidence rate include myocardial perforation, valve dislodgement, need for valve repositioning, need for valve retrieval, aortic annular rupture, device embolization, and aortic dissection (25)

Predictors of mortality in patients undergoing TAVR

Previous studies, have shown that 30-day mortality rate predictors were age above >90 years, need for dialysis, and use of transapical TAVR approach (24-25). Pre intervention left ventricular dysfunction and mitral regurgitation in patient with severe AS identify a population at high risk for both SAVR and TAVR. We evaluated the effect of baseline LV dysfunction (LVEF > 20 % and < 50 %) on clinical outcomes after TAVR and SAVR and the impact of aortic valve replacement technique on LV functional recovery in high-risk patients with symptomatic severe AS within the randomized Placement of Aortic Transcatheter Valves (PARTNER)

trial (26). There was a borderline association of LV dysfunction with 30-day cardiac death after SAVR and with an increased risk of repeat hospitalization within the first year after TAVR. The lack of influence of LV dysfunction on periprocedural mortality is probably because of the exclusion of patients with severe LV dysfunction (LVEF < 20 %), in whom the bulk of the risk is thought to exit. Nevertheless, our findings confirm the efficacy and safety of TAVR in patients with LV dysfunction and indicate that TAVR should be considered a feasible option in patients with symptomatic severe AS and LV dysfunction who are at high risk for SAVR (25).

CONCLUSION

TAVR is a new method of aortic valve replacement when it meets the criteria of severe aortic stenosis. Since the initial investigation in the PARTNER I trial, TAVR has been shown to play a pivotal role in aortic stenosis therapy. Various methods are available for the deployment of a valve, including trans-femoral, trans-apical, and trans-aortic approaches. In addition, multiple valves could be selected depending on the necessity and mode of delivery (e.g., Edwards Sapien and Core Valve System). While the main limitation of TAVR compared to surgical aortic valve replacement was increased risk of stroke, the incidence rate was found to decrease after the reduction of catheter diameters and development of new TAVR valves. Future directions of TAVR has involved usage in patients with lower STS risk scores, those requiring valve-in-valve techniques, and employment of this modality in hybrid procedures. However, further trials and studies are required in order to support these new therapeutic indications and interventions.

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