Transcatheter Aortic Valve Replacement: A Review

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KEYWORDS

• Transcatheter aortic valve replacement • Surgical aortic valve replacement
• Aortic stenosis • Valvular heart disease • Catheter

KEY POINTS

- The treatment of aortic stenosis is changing and being treated more with catheter-based technology: inoperable, high risk, and intermediate risk are now approved.
- Gated multislice CT angiogram has emerged as the gold standard for assessment of valve anatomy and sizing of the transcatheter heart valve.
- Long-term results are needed before its use in lower risk categories.

Video content accompanies this article at http://www.surgical.theclinics.com/.

INTRODUCTION

With the recent approval of the intermediate-risk category for transcatheter aortic valve replacement (TAVR), medicine is undergoing a dramatic paradigm shift in the way aortic valve stenosis is treated. At this time, cardiac surgeons with their expertise in valve replacement remain the gatekeepers for TAVR; however, cardiac surgeons are no longer the sole providers for the advanced treatment of aortic stenosis (AS). The Centers for Medicare and Medicaid Services (CMS) in conjunction with the Food and Drug Administration (FDA) developed detailed criteria to ensure the best adoption of this new technology. A threshold of surgical experience and structural heart procedural experience was required to be a TAVR center.[1] Not only did CMS and the FDA selectively choose centers based on experience, they required a collaborative, multidisciplinary team approach to treatment decision making and participation in the

Disclosures: None.

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Surg Clin N Am 97 (2017) 899–921
http://dx.doi.org/10.1016/j.suc.2017.03.011 surgical.theclinics.com
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Transcatheter Valve Therapy (TVT) Registry. This national registry was created in collaboration between the Society of Thoracic Surgery (STS) and American College of Cardiology (ACC), which mirrors the collaborative approach mandated by CMS and the FDA.

HISTORY

The paradigm shift in treatment of AS did not occur overnight but started in the laboratory with catheter-based concepts that transformed into catheter-based interventions and eventually translated into clinical trials. The first catheter-based therapy was performed in September 1977 in Switzerland by Andreas Gruentzig,[2,3] ushering in the era of interventional cardiology for the treatment of coronary disease. Within 10 years, the first balloon valvuloplasty was performed on a child for treatment of pulmonic stenosis.[4] In 1985, Cribier and coworkers[5] performed the first in-human balloon aortic valvuloplasty on an inoperable 77-year-old man. Cribier and coworkers[6,7] later went on to create the first percutaneous valve, which was subsequently acquired by Edwards Lifesciences (Irvine, CA). The Cribier-Edwards valve was further refined to become the Sapien, balloon expandable transcatheter heart valve (THV).

The Initial Registry of Endovascular Implantation of Valves in Europe[8] and the Registry of Endovascular Critical Aortic Stenosis Treatment were the first trial registries that evaluated feasibility of TAVR. The initial TAVR procedures were done on a compassionate basis. An antegrade approach with transseptal puncture was used for implantation. Although less than perfect, the results demonstrated that patients suffering from severe AS could be helped with a catheter-based procedure. The next several years were spent on refining the devices and implantation technique to produce a safer, more successful procedure.

THE HEART VALVE TEAM

The heart valve team approach has become the standard of care for the treatment of aortic valve stenosis, more specifically TAVR, in the United States.[9,10] CMS has mandated that a team of professionals have joint treatment decision making for these patients. This mandate by CMS clearly puts the patient at the center of the care model.

There are many stakeholders within the multidisciplinary heart valve team. A typical valve team consists of one or more each of the following physicians: cardiothoracic surgeon, interventional cardiologist, imaging specialist/radiologist, cardiac anesthesiologist, and noninvasive cardiologist. However, the most important stakeholder within the team is not one of these physicians but rather is the valve clinical coordinator. The coordinator is typically a registered nurse or advanced practice nurse that understands and oversees all processes within the valve clinic and aims to keep the patient at the center of care. This individual is responsible for overseeing the patient from the initial referral into the valve clinic through the entirety of the diagnostic process. The coordinator also oversees and coordinates the procedural process. He or she is available for coordination of hospital care and ensures all aspects of the follow-up care are arranged. The valve clinical coordinator is responsible for managing and collecting information for the TVT Registry.

The heart valve team should also include other ad hoc members for special, patient-specific circumstances, such as an oncologist for newly diagnosed malignancies, a gerontologist to help address complex medical issues, or a neuropsychologist for evaluation of cognitive impairment. Backup with additional cardiac and noncardiac services, such as a heart failure team, a vascular surgery team, and social services, is a force multiplier and only serves to strengthen the program.[11]

Once the TAVR work-up is completed (discussed next), all members of the multidisciplinary heart valve team meet to review and discuss all of the patient's diagnostic imaging and clinical evaluations. All unresolved issues or concerns are addressed and the team agrees on a treatment plan including THV selection, route of implantation, anesthesia method, and postoperative anticoagulation regimen. The decisions are disseminated to all team members. The decision is also communicated to the patient's other care providers including referring provider, primary care provider, and primary cardiologist.

The multidisciplinary heart valve team develops an expertise over time. With this expertise, the rhythm of patient care is perfected as the team dynamics change and strengthen. It is important that the heart valve team perform robust internal audits of their data and use this information to proactively change procedural and nonprocedural processes for the betterment of the program leading to improved patient outcomes.[12]

TRANSCATHETER AORTIC VALVE REPLACEMENT WORK-UP

The pre-TAVR work-up is best accomplished in a systematic fashion; however, it is well known and understood that the sequence of the diagnostic evaluations may not always be linear and follow the same path. Patients enter the valve clinic at different stages of evaluation. It is important to develop tools to help organize the evaluation process and ensure key diagnostics are not missed (**Fig. 1**).

There are certain key diagnostic procedures and clinical evaluations that every TAVR patient undergoes. There are some diagnostic procedures and clinical evaluations that are performed as needed on a patient-specific basis (**Table 1**).

Key Diagnostic Evaluations

Transthoracic echocardiogram

This is used to diagnose severe AS. Both aortic valve anatomy and aortic valve hemodynamics are assessed. The presence of concomitant mitral, tricuspid, and/or pulmonic valve disease is also determined. This examination is typically performed before referral into the valve clinic but may be repeated if the heart valve team determines the quality of the study is not satisfactory or specific diagnostic criterion are missing.

Coronary angiography

This is performed to determine the presence of coronary artery disease. If significant coronary artery disease is noted, this can add to the surgical risk if both coronary artery bypass grafting and aortic valve replacement are indicated. The team determines if percutaneous revascularization is necessary before TAVR.

Right and left heart catheterization

This is performed at the same time as coronary angiography. It confirms the presence of severe AS. It also serves as a baseline for invasive hemodynamics.

Gated multislice computed tomography angiography of the chest/abdomen/pelvis

This is considered the gold standard for aortic annulus measurements for preprocedural TAVR assessment. Specific acquisition protocols are performed and vary depending on scanner platform. It determines overall suitability for TAVR. It also determines access method and prosthesis size by using the following:

- Suitability of the peripheral access vessels (ileofemoral, subclavian, and aorta) including size, amount, and distribution of calcium and tortuosity
- Dimensions of the ascending aorta, aortic root, and aortic annulus
- Distribution of calcium within the aortic valve
- Annular plane for intraprocedural[11,13] fluoroscopy images

TAVR WORKUP CHECKLIST

Referring Provider: _____
Primary Cardiologist: _____

Key Clinical Evaluations	Name	Date
Interventional Cardiologist:		
CV Surgeon #1:		
CV Surgeon #2:		

	Date
VC Coordinator:	
Education	
Functional Assessment	
TVT Registry	
Patient Database	
CTA Uploaded for Reconstruction	
Reconstructions Received	

Key Testing	Date	Sig Findings
TTE		
Coronary/Heart Cath		
CTA chest/abdomen/pelvis		
Dental Clearance		
Team Discussion		
PRN Testing/Evaluation		
TEE		
PFT		
Carotid Duplex		
DSE		
Neuropsychology		
Pulmonology		
Gerontology		
Other		
Other		

Fig. 1. Check list for TAVR work-up at Marshfield Clinic.

Table 1
Pre-TAVR evaluations

Key Evaluations	As Needed Evaluations
Transthoracic echocardiogram	Transesophageal echocardiogram
Coronary angiography	Pulmonary function tests
Right and left heart catheterization	Carotid duplex
Two cardiothoracic surgery evaluations	Dobutamine stress echo
Interventional cardiology evaluation	Neuropsychology
Valve clinical coordinator evaluation and education	Pulmonology
Computed tomography angiogram of chest/abdomen/pelvis	Gerontology
Functional/frailty assessment	Other
Multidisciplinary team discussion	

Key Clinical Evaluations

Valve clinic interventional cardiologist

This team member is mandated by the CMS national coverage decision to be a stakeholder in the heart valve team. They review diagnostic evaluations, confirm the presence of symptomatic heart disease secondary to severe AS, and evaluate for contraindications to a TAVR procedure.[14]

Valve clinic cardiothoracic surgeon

It is mandated by the CMS national coverage decision that two cardiac surgeons independently examine the patient face-to-face and evaluate the patient's suitability for surgical aortic valve replacement (SAVR). They document risk category (low, intermediate, high, or prohibitive) and rationale in medical record, and provide to the entire heart valve team.[14]

Valve clinical coordinator

This member was initially seen in collaboration with the valve clinic interventional cardiologist and valve clinic cardiothoracic surgeon. They provide ongoing evaluation and discussion with patient and family as need arises, and pivotal patient and family education and coordination of care. They collaborate with all multidisciplinary providers involved in the patient's care.

Personal dentist or oral surgeon

Clinical guidelines recommended evaluation before surgical cardiac procedures to reduce the rates of infective endocarditis. There are no specific studies or guideline recommendations for TAVR. Whether dental procedures should delay the definitive cardiac treatment has been questioned and should be determined on a patient-specific basis.[15]

As-Needed Diagnostic Evaluations

Three-dimensional transesophageal echocardiogram

This may be completed before referral into the valve clinic and is used along with computed tomography (CT) to determine suitability for TAVR and aortic annulus measurements. In the presence of degenerated surgical aortic valve, it determines the cause of degeneration and hemodynamic abnormalities on transthoracic echocardiogram.

Pulmonary function tests

These are not routinely performed but consideration should be given to complete on all patients because many patients have some level of abnormality documented even when lung disease was not initially suspected. Consideration should be given to perform on all patients with documented pulmonary abnormalities on CT scan. Consideration should be given to perform in patients with known lung disease if not previously completely within 1 year.[16]

Carotid duplex

There has been no significant correlation between amount of carotid artery disease and periprocedural stroke documented. It is typically left to the surgeon's discretion. Higher consideration could be given in patients with suspected symptomatic disease.[17]

Dobutamine stress echocardiogram

This is performed when patients are diagnosed with stage D2 severe AS (symptomatic low-flow/low-gradient, severe AS with reduced left ventricular ejection fraction [LVEF]) to confirm presence of severe AS with a Vmax greater than 4.0 m/s or mean gradient greater than or equal to 40 mm Hg at any level of dobutamine infusion. Special

attention should be paid to baseline hemodynamic numbers because baseline evaluation may confirm the presence of stage D1 or stage D3 severe AS.[9]

As-Needed Clinical Evaluations

Pulmonologist

Consideration for referral for preprocedural optimization should be given in patients with documented severe pulmonary disease. Consideration should be given for referral for patients with newly diagnosed moderate-severe pulmonary disease.

Gerontologist

Consideration should be given for referral in patients with multiple comorbid conditions to assist with determination of suitability for TAVR and for management of medical issues before the procedure.

Neuropsychologist

Consideration should be given for referral in patients with abnormal neurologic evaluation (montreal cognitive assessment or mini–mental state examination) to assist with determination of suitability for TAVR, of the patient's ability to understand the brevity of the medical situation, and of the patient's ability to participate in necessary care following procedure.

Other specialties

As the patients move through the pre-TAVR work-up, often abnormalities, either suspected or incidental, are noted. This may require consultation with other subspecialties for further evaluation and/or treatment.

METHODS OF IMPLANTATION

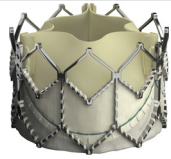
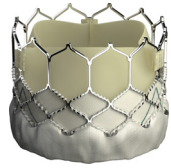
The valve implants are done with either retrograde or antegrade approach and the selection of the approach is based on the patient's vascular anatomy and diameters (Tables 2 and 3).

For the retrograde approach, most of the procedures are performed via percutaneous transfemoral (TF) approach. In the absence of femoral access, transaortic (TAo) or transsubclavian (TS) accesses are more common. Transcarotid and transcaval accesses can be considered but are significantly less common at the current time. Most of the TF procedures are performed under monitored anesthesia care or conscious sedation. All other types of retrograde and antegrade implant procedures are mini-surgical procedures and require general anesthesia. They are usually performed with transesophageal echocardiogram guidance.

All TAVR procedures (retrograde and antegrade) require a temporary pacemaker for rapid burst pacing (for Edwards Lifesciences) or rhythm override (for Medtronic, Dublin, Republic of Ireland). A pigtail catheter is also needed for aortic root injections to guide valve implantation. For Edwards Lifesciences, it is placed in the right cusp and for Medtronic it is placed in the noncoronary cusp. The pigtail catheter is inserted thru femoral, radial, or brachial arterial access. The temporary pacemaker is usually inserted via femoral or internal jugular venous access.

A core team is identified for the valve implant procedure. At our institution, this team includes a cardiovascular surgeon (first operator), an interventional cardiologist (second operator), hemodynamic technician (to operate the pacemaker), and an anesthesiologist. If a second interventional cardiologist is available, he or she acts as an assistant. For implantation of the Edwards Lifesciences THV, the first operator is responsible for the finer adjustment of the delivery system. The second operator is

Table 2
Current Edwards Lifesciences transcatheter heart valves

Valve		Valve Size (mm)	Annulus Size (mm^2)	Access	Sheath Size (French catheter)
Sapien (first-generation)		23	18–22 mm (diameter)	TF	22
				TA	26
		26	21–25 mm (diameter)	TF	24
				TA	26
Sapien XT (second-generation)		23	338–430	TF	16
				TAo, TA	24
		26	430–546	TF	18
				TAo, TA	24
		29	540–683	TF	20
				TAo, TA	26
Sapien 3 (third-generation)		20	273–345	TF, TAo, TS	14
		23	338–430	TF, TAo, TS	14
				TA	18
		26	430–546	TF, TAo, TS	14
				TA	18
		29	540–683	TF, TAo, TS	16
				TA	21

Abbreviations: TA, transapical; TAo, transaortic; TF, transfemoral; TS, transsubclavian.

Table 3
Current Medtronic transcatheter heart valves

Valve		Valve Size (mm)	Annulus Size (Diameter)	Access	Sheath Size (French catheter)
CoreValve		26	20–23	TF, SC, TAo	18
		29	23–27		
		31	26–29		
CoreValve Evolut R		23	18–20	TF, SC, TAo	14
		26	20–23		
		29	23–26		
		34	26–30	TF, SC, TAo	16

Abbreviations: SC, subclavian, TAo, transaortic; TF, transfemoral.

in-charge of initiating the implant sequence and is responsible for aortography and inflating balloon to deploy the valve. For implantation of the Medtronic THV, the responsibilities remain the same; however, the second operator is also responsible to unsheath the valve. The valve team is constantly in sync with each other throughout the procedure. It is essential to check the orientation of the valve before inserting into the sheath. It is also important to standardize the valve implantation sequence with the team and practice it multiple times before the real procedure.

Anticoagulation is maintained with a target activated clotting time of 300 $\pm$ 25 seconds. Rapid burst pacing is kept to the minimum for patients with compromised left ventricular (LV) function. At our institution, we try to maintain systolic blood pressure of approximately 110 to 120 mm of Hg before the valve implantation sequence.

For TAo and transapical (TA) accesses, a shorter delivery system is used thru a larger 24F catheter sheath. Apart from the access site management, the valve deployment sequences remain the same. The only change in TA access is the orientation of the mounted valve, which is exactly opposite to the valve mounted for the retrograde access (**Figs. 2** and **3**, Videos 1–4).

EVOLUTION OF THE TRANSCATHETER HEART VALVE

Currently there are only two companies that offer commercially available THVs: Edwards Lifesciences and Medtronic.

EDWARDS LIFESCIENCES

Edwards Lifesciences was the first company to market with a commercial THV, in November 2011, the Sapien THV. The Edwards Sapien THV was comprised of a balloon-expandable, stainless steel frame, three bovine pericardial tissue leaflets and a polyethylene terephthalate (PET) fabric skirt. The PET fabric skirt was sewn on the inner portion of the bottom of the stent frame to help seal the aortic annulus

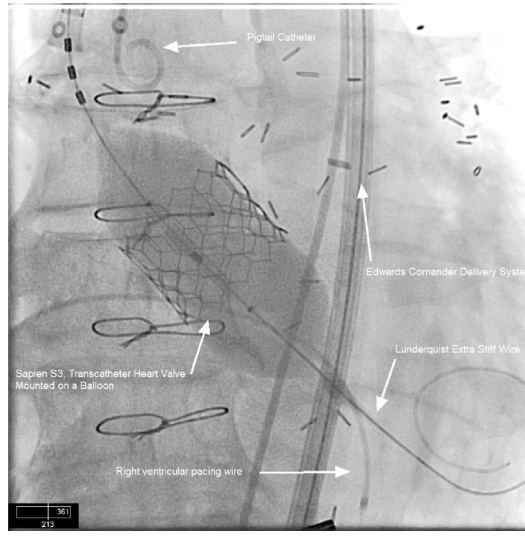


Fig. 2. Annotated TF Sapien S3 valve.

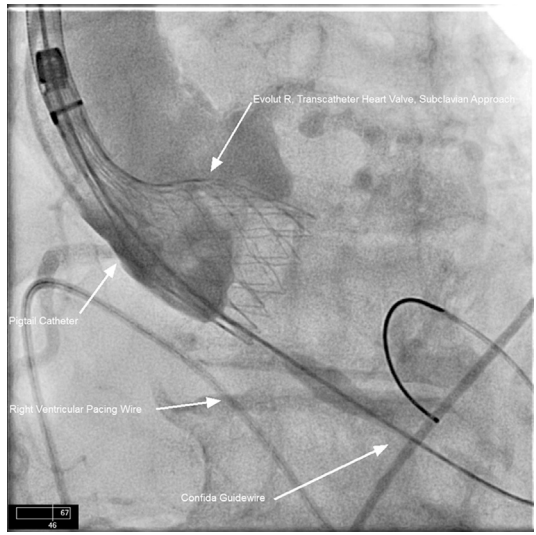


Fig. 3. Annotated TS: Evolut R, valve, aortogram.

and reduce the amount of paravalvular leak (PVL). The leaflets were treated according to the Carpentier-Edwards ThermaFix process, which is intended to reduce the buildup of calcium overtime. The Sapien THV is currently no longer available for implantation but was available in two sizes, 23 mm and 26 mm. The 23-mm valve was delivered through a 22F catheter sheath if placed using TF access or a 26F catheter sheath if delivered using TA access. The 26-mm valve was delivered through a 24F catheter sheath if placed using TF access or 26F catheter is placed using TA access.

In March of 2010 Sapien XT, Edwards Lifesciences second-generation THV, received CE mark for approval. The Sapien XT THV also consists of a balloon-expandable frame; however, the frame is constructed using cobalt-chromium instead of stainless steel. Three bovine pericardial leaflets treated with the Carpentier-Edwards ThermaFix process and an inner PET fabric skirt were also used. The improvements seen in the Sapien XT THV allows for expanded annular size coverage, smaller sheath sizes, and expanded access routes to include TAo. Four sizes of Sapien XT THV are available: 20 mm, 23 mm, 26 mm, and 29 mm. When delivered using TF access, a sheath size of either 16F, 18F, or 20F catheter is used. When delivered using TAo or TA access, a 24F catheter sheath for the 23-mm or 26-mm valve is used and a 26F catheter sheath for the 29-mm valve is used.

In June 2015, Edwards Lifesciences received FDA approval for their third-generation THV: Sapien 3. This valve also consists of a balloon-expandable cobalt chromium frame; however, the frame's geometry was altered to allow for lower delivery height and reduction in delivery profile. There are still three bovine pericardial leaflets, which are also treated with the Carpentier-Edwards ThermaFix process. A PET fabric outer skirt was added in addition to the PET fabric inner skirt to further seal the aortic annulus and further reduce the amount of PVL. The Sapien 3 THV has been approved for TF, TA, TAo, or TS. When delivered using TF, TAo, or TS access, a 14F catheter sheath is used for the placement of a 23-mm or 26-mm valve and a 16F catheter sheath is used for the placement of a 29-mm valve. When delivered using TA access, an 18F catheter sheath is used for the 23-mm or 26-mm valve and a 21F catheter sheath for the 29-mm valve (see **Table 2**).

MEDTRONIC

In January of 2014, Medtronic announced FDA approval of its CoreValve THV, making it the second commercially available system on the market. The second-generation Medtronic THV, CoreValve Evolut R, was approved by the FDA in June of 2015. Both the CoreValve and CoreValve Evolut R THV systems are comprised of three porcine leaflets and an inner porcine skirt sutured to a self-expanding nitinol frame. Both the CoreValve and CoreValve Evolut R have "three distinct segments: the base portion which exerts a high radial force that expands and pushes aside the calcified leaflets [of the native valve]; the central portion which carries the valve; and the top portion which flares to fixate and stabilize the valve in the ascending aorta".[18] The Evolut R features an improved design to the nitinol frame with a lower delivery height, reduced delivery profile, and expanded sealing skirt to further reduce the amount of PVL. The other significant improvement in the CoreValve Evolut R is the ability to recapture the THV once partially deployed allowing for repositioning within the annulus. The CoreValve THV is available in three sizes: 26 mm, 29 mm, and 31 mm fitting annular dimensions ranging from 20 mm to 30 mm using an 18F catheter sheath. The CoreValve Evolut R THV is available in four sizes: 23 mm, 26 mm, 29 mm, and 34 mm fitting annular dimension ranging from 18 mm to 30 mm using a 14F catheter sheath for the 23 mm, 26 mm, or 29 mm and a 16F catheter sheath for the 34 mm. Both the CoreValve and CoreValve Evolut R THV are delivered using TF, TAo, or TS access (see **Table 3**).

CURRENT INDICATIONS FOR TRANSCATHETER AORTIC VALVE REPLACEMENT

TAVR using all commercially available THV has an indication for use in patients with symptomatic heart disease caused by severe, calcific native, or prosthetic AS who meet an indication for SAVR but are considered to have at least intermediate surgical risk for implantation of the Edwards Lifesciences S3 or Sapien XT THVs or high to prohibitive surgical risk for the Medtronic CoreValve and CoreValve Evolut R THVs.

DEFINITION OF SEVERE AORTIC STENOSIS

According to the American Heart Association (AHA)/ACC Guidelines for the Management of Patients with Valvular Heart Disease,[9] which was updated most recently in 2014, severe AS is broken down into three stages: D1, D2, and D3. Patients must qualify for one of these three stages to be considered for TAVR.

Stage D1 Severe Aortic Stenosis

Stage D1 AS is defined as "severe symptomatic severe high-gradient AS."[9] Echocardiographic valve anatomy findings reveal leaflet calcification with reduced leaflet motion. Hemodynamic findings of the aortic valve typically reveal an aortic valve area of less than or equal to 1.0 cm^2 (may be larger with mixed AS/aortic regurgitation), an aortic Vmax of greater than 4.0 m/s, or a mean gradient greater than or equal to 40 mm Hg.

Stage D2 Severe Aortic Stenosis

Stage D2 AS is defined as "symptomatic severe low-flow/low-gradient AS with reduced LVEF less than 50%."[9] Echocardiographic valve anatomy findings reveal leaflet calcification with reduced leaflet motion. Hemodynamic findings of the aortic valve typically show an aortic valve area of less than or equal to 1.0 cm^2 with a resting aortic Vmax less than 4.0 m/s or mean gradient less than 40 mm Hg. Dobutamine

stress echocardiogram shows aortic valve area less than or equal to 1.0 cm^2 and an aortic Vmax greater than or equal to 4.0 m/s or a mean gradient greater than or equal to 40 mm Hg at any flow rate of dobutamine.

Stage D3 Severe Aortic Stenosis

Stage D3 AS is defined as "symptomatic severe low-gradient AS with normal LVEF ≥50%."[9] Echocardiographic valve anatomy findings reveal leaflet calcification with reduced leaflet motion. Hemodynamic findings of the aortic valve show an aortic valve area of less than or equal to 1.0 cm^2 with an aortic Vmax less than or equal to 4 m/s or mean gradient less than or equal to 40 mm Hg and an indexed stroke volume of less than 35 mL/m^2 (**Table 4**).

SURGICAL RISK EVALUATION

Initially, when TAVR was first approved by the FDA, it was indicated only for patients with prohibitive/high surgical risk. Since that time, the level of surgical risk needed for TAVR indication has decreased. Operative mortality is typically calculated using a scoring system or tool. Two of the most common cardiovascular surgical risk estimators are the euroSCORE II and the STS Risk Score. The STS risk model is the more widely used of the two and is referred to in the AHA/ACC Guidelines for the Management of Patients with Valvular Heart Disease and was also used to determine risk in all of the major TAVR clinical trials. The STS offers a free online STS risk calculator tool.[19] The STS predicted risk of operative mortality (PROM) correlates to surgical risk category as follows: high risk = STS PROM greater than 8%, intermediate risk = STS PROM 4% to 8%, and low risk = STS PROM less than 4%.

Using only the STS Risk Score has limitations because it does not take into consideration other patient-specific factors, such as frailty, comorbid conditions with major organ system compromise, or surgical procedure barriers (**Table 5**). These factors should also be considered when determining risk.

According to the ACC/AHA Guidelines,[9] the following are examples of major organ system compromise:

- Cardiac: LV systolic dysfunction, LV diastolic dysfunction, right ventricular (RV) dysfunction, or pulmonary hypertension
- Renal: chronic kidney disease stage 3 or more
- Pulmonary: moderate or greater restrictive or constrictive lung disease based on pulmonary function test analysis
- Neurologic: dementia of any type, significant cognitive dysfunction, Parkinson disease, stroke with persistent deficit
- Gastrointestinal: Crohn's disease, ulcerative colitis, nutritional impairment with serum albumin less than 3
- Gastrointestinal (liver specific): cirrhosis, variceal bleeding
- Oncologic: active malignancy

Some of the surgical procedure barriers that could be encountered that would increase risk of surgical AVR are presence of tracheostomy, calcification in the ascending aorta (porcelain aorta), radiation damage, chest structure malformation, coronary anatomy/grafts adherent to the chest wall, or coronary bypass grafts crossing midline.[9]

Frailty is a state of vulnerability to poor resolution of homoeostasis after a stressor event and is a consequence of cumulative decline in many physiologic systems during a lifetime. This cumulative decline depletes homoeostatic reserves until minor stressor

Table 4
Stage of symptomatic severe aortic stenosis

		D: Symptomatic Severe AS		
D1	Symptomatic severe high-gradient AS	• Severe leaflet calcification or congenital stenosis with severely reduced leaflet opening	• Aortic Vmax $\geq$4 m/s or mean ΔP $\geq$40 mm Hg • AVA typically $\leq$1.0 cm^2 (or AVAi $\leq$0.6 cm^2/m^2) but may be larger with mixed AS/AR	• LV diastolic dysfunction • LV hypertrophy • Pulmonary hypertension may be present	• Dyspnea or decreased exercise tolerance • Angina • Syncope/presyncope
D2	Symptomatic severe low-flow/low-gradient AS with reduced LVEF	• Severe leaflet calcification with severely reduced leaflet motion	• AVA $\leq$1.0 cm^2 with resting aortic Vmax <4 m/s or mean ΔP <40 mm Hg • Dobutamine stress echocardiography shows AVA $\leq$1.0 cm^2 with Vmax $\geq$4 m/s at any flow rate	• LV diastolic dysfunction • LV hypertrophy • LVEF <50%	• HF • Angina • Syncope/presyncope
D3	Symptomatic severe low-gradient AS with normal LVEF or paradoxic low-flow severe AS	• Severe leaflet calcification with severely reduced leaflet motion	• AVA $\leq$1.0 cm^2 with aortic Vmax <4 m/s or mean ΔP <40 mm Hg • Indexed AVA $\leq$0.6 cm^2/m^2 and • Stroke volume index <35 mL/m^2 • Measured when patient is normotensive (systolic BP <140 mm Hg)	• Increased LV relative wall thickness • Small LV chamber with low stroke volume • Restrictive diastolic filling • LVEF $\geq$50%	• HF • Angina • Syncope/presyncope

Abbreviations: AR, aortic regurgitation; AVA, aortic valve area; AVAi, aortic valve area indexed to body surface area; BP, blood pressure; HF, heart failure; Vmax, maximum aortic velocity; ΔP, pressure gradient.

From Nishimura RA, Otto CM, Bonow RO, et al. 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association task force on practice guidelines. J Thorac Cardiovasc Surg 2014;148(1):e17–8; with permission.

Table 5
Risk assessment combining STS risk estimate, frailty, major organ system dysfunction, and procedure-specific impediments

	Low Risk (Must Meet ALL Criteria in This Column)	Intermediate Risk (Any One Criterion in This Column)	High Risk (Any One Criterion in This Column)	Prohibitive Risk (Any One Criterion in This Column)
STS PROM[a]	<4% AND	4%–8% OR	>8% OR	Predicted risk with surgery of
Frailty[b]	None AND	1 index (mild) OR	≥2 indices (moderate to severe) OR	death or major morbidity (all-cause) >50% at 1 y OR
Major organ system compromise not to be improved postoperatively[c]	None AND	1 organ system OR	No more than 2 organ systems OR	≥3 Organ systems OR
Procedure-specific impediment[d]	None	Possible procedure-specific impediment	Possible procedure-specific impediment	Severe procedure-specific impediment

Abbreviations: CKD, chronic kidney disease; CNS, central nervous system; CVA, stroke; $DLCO_2$, diffusion capacity for carbon dioxide; FEV_1, forced expiratory volume in 1 s; GI, gastrointestinal; INR, international normalized ratio; RV, right ventricular; VKA, vitamin K antagonist.

[a] Use of the STS PROM to predict risk in a given institution with reasonable reliability is appropriate only if institutional outcomes are within one standard deviation of STS average observed/expected ratio for the procedure in question.

[b] Seven frailty indices: Katz Activities of Daily Living (independence in feeding, bathing, dressing, transferring, toileting, and urinary continence) and independence in ambulation (no walking aid or assist required or 5-m walk in <6 s). Other scoring systems can be applied to calculate no, mild-, or moderate-to-severe frailty.

[c] Examples of major organ system compromise: cardiac—severe LV systolic or diastolic dysfunction or RV dysfunction, fixed pulmonary hypertension; CKD stage 3 or worse; pulmonary dysfunction with FEV_1 less than 50% or $DLCO_2$ less than 50% of predicted; CNS dysfunction—dementia, Alzheimer disease, Parkinson disease, CVA with persistent physical limitation; GI dysfunction—Crohn's disease, ulcerative colitis, nutritional impairment, or serum albumin less than 3.0; cancer—active malignancy; and liver—any history of cirrhosis, variceal bleeding, or elevated INR in the absence of VKA therapy.

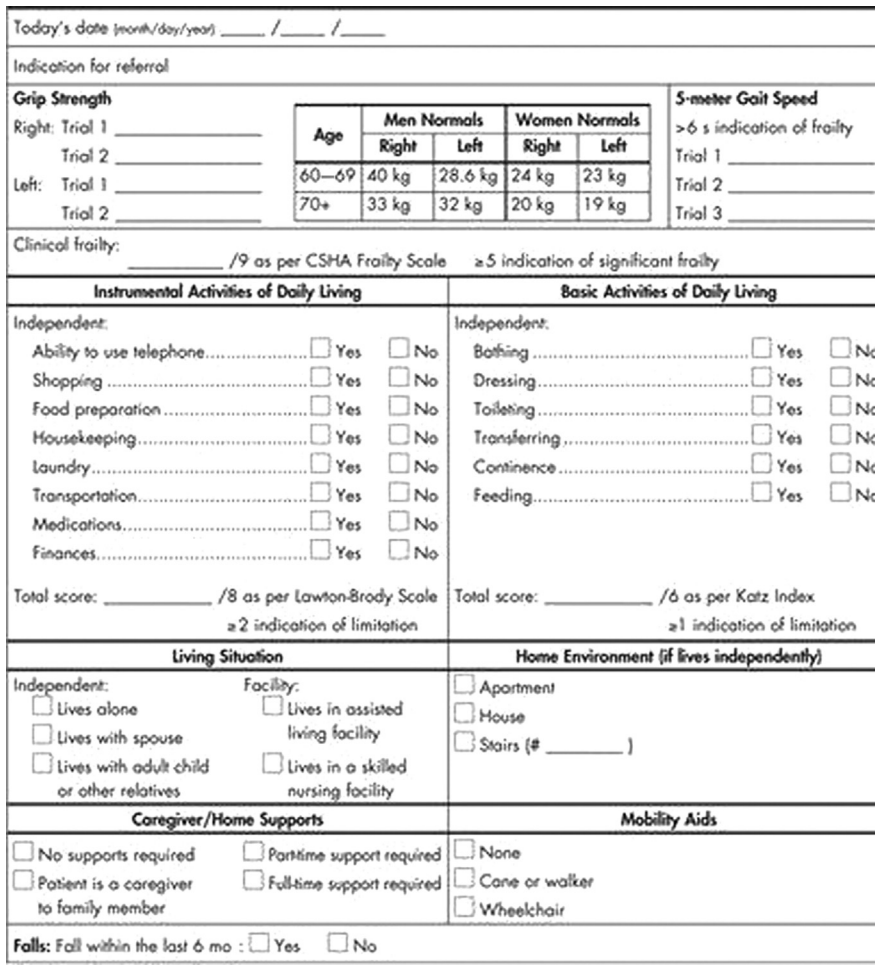
[d] Examples: tracheostomy present, heavily calcified ascending aorta, chest malformation, arterial coronary graft adherent to posterior chest wall, or radiation damage.

From Nishimura RA, Otto CM, Bonow RO, et al. 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association task force on practice guidelines. J Thorac Cardiovasc Surg 2014;148(1):e14; with permission.

events trigger disproportionate changes in health status.[20] Frailty is an important factor as surgical risk prediction and is classified as either mild (one abnormal index), moderate (two abnormal indices), or severe (three or more abnormal indices).[9]

At our facility frailty assessment is initiated with the initial evaluation in the valve clinic and is documented on a frailty/functional assessment form (Fig. 4). This form is placed in the electronic medical record and is immediately available to all members of the valve team for review. The following indices are measured:

- Grip strength. A functional measurement to determine muscle strength. Muscle weakness has been shown to increase the risk of 1-month functional decline and need for new social help.[21]
- 5-m gait speed. An average gait speed greater than or equal to 6 seconds is considered slow and is an indication of frailty. The test is performed with any patient able to walk 5 m. The following guidelines should be used. (1) Accompany the patient to the designated area that has been marked at 0 and 5 m. (2) Position the patient with his/her feet behind and just touching the 0-m start line. (3) Instruct


Today's date (month/day/year) ____ /____ /____

Indication for referral

Grip Strength

Right: Trial 1 ____
Trial 2 ____
Left: Trial 1 ____
Trial 2 ____

Age	Men Normals		Women Normals	
	Right	Left	Right	Left
60—69	40 kg	28.6 kg	24 kg	23 kg
70+	33 kg	32 kg	20 kg	19 kg

5-meter Gait Speed

>6 s indication of frailty
Trial 1 ____
Trial 2 ____
Trial 3 ____

Clinical frailty: ____ /9 as per CSHA Frailty Scale ≥5 indication of significant frailty

Instrumental Activities of Daily Living

Independent:
Ability to use telephone ☐ Yes ☐ No
Shopping ☐ Yes ☐ No
Food preparation ☐ Yes ☐ No
Housekeeping ☐ Yes ☐ No
Laundry ☐ Yes ☐ No
Transportation ☐ Yes ☐ No
Medications ☐ Yes ☐ No
Finances ☐ Yes ☐ No

Total score: ____ /8 as per Lawton-Brody Scale
≥2 indication of limitation

Basic Activities of Daily Living

Independent:
Bathing ☐ Yes ☐ No
Dressing ☐ Yes ☐ No
Toileting ☐ Yes ☐ No
Transferring ☐ Yes ☐ No
Continence ☐ Yes ☐ No
Feeding ☐ Yes ☐ No

Total score: ____ /6 as per Katz Index
≥1 indication of limitation

Living Situation

Independent:
☐ Lives alone
☐ Lives with spouse
☐ Lives with adult child or other relatives

Facility:
☐ Lives in assisted living facility
☐ Lives in a skilled nursing facility

Home Environment (if lives independently)

☐ Apartment
☐ House
☐ Stairs (# ____)

Caregiver/Home Supports

☐ No supports required
☐ Patient is a caregiver to family member
☐ Part-time support required
☐ Full-time support required

Mobility Aids

☐ None
☐ Cane or walker
☐ Wheelchair

Falls: Fall within the last 6 mo : ☐ Yes ☐ No

Fig. 4. Frailty tool at Marshfield Clinic.

the patient to "Walk at your comfortable pace" until a few steps past the 5-m mark (the patient should not start to slow down before the 5-m mark). (4) Begin each trial on the word "Go." (5) Start the timer with the first step after the 0-m line. (6) Stop the timer with the first step after the 5-m line. (7) Repeat three times, allowing sufficient time for recuperation between trials. (8) Record the times in seconds on the data collection form. The patient may use a walking aid (cane, walker). If the patient is receiving an intravenous drip, he/she should perform the test without the intravenous drip if possible.[22]

- Canadian Study of Health and Aging frailty scale. The Clinical Frailty Scale has been shown to be an effective measure of frailty and can provide predictive information similar to that of other established tools.[23]
- Lawton-Brody Instrumental Activities of Daily Living Scale. This is an instrument used to assess independent living.[24] The instrument is most useful for identifying how a person is functioning at the present time. Requiring assistance in more than one functional domain represents limitation.
- Katz Index of Independence in Activities of Daily Living. This is an instrument used to identify a patient's ability to perform basic activities of daily living. Requiring assistance in any one or more functional domain represents limitation.[25]
- Montreal Cognitive Assessment. "Poorer Montreal Cognitive Assessment scores were significantly correlated with the higher likelihood of being frail, independent of age, sex, education, drinking, smoking, living alone, Independence in Activities of Daily Living and a history of comorbidities."[26]
- Psoas muscle area. Sarcopenia has been defined as progressive loss of skeletal muscle mass, strength, and power, and is regarded as a key component of frailty.[27] A reduced psoas muscle area is one way to determine presence of sarcopenia.[28] This is easily calculated and is determined with images available from the gated multislice CT scan already performed.

RANDOMIZED TRIALS

In 2010 the PARTNER investigators reported on the treatment of TAVR in high-risk patients with AS not believed to be candidates for conventional surgery.[29] Cohort B was the first multicenter trial that randomized 385 patients with critical AS to either a new balloon expandable transcatheter aortic valve versus the best in medical therapy, which also included balloon aortic valvuloplasty. The results from this trial lead the FDA to approve and CMS to pay for a commercially available THV for the treatment of symptomatic, severe AS in patients believed to have prohibitive risk for surgical treatment.

At 1 year, the rate of death from any cause (Kaplan-Meier analysis) was 50.7% with standard therapy and 30.7% with TAVR ($P<.001$). The rate of the composite end point of death from any cause or repeat hospitalization was 42.5% with TAVR as compared with 71.6% with standard therapy (hazard ratio, 0.46; 95% confidence interval, 0.35–0.59; $P<.001$). Among survivors at 1 year, the rate of cardiac symptoms (New York Heart Association class III or IV) was lower among patients who had undergone TAVR than among those who had received standard therapy (25.2% vs 58.0%; $P<.001$). At 30 days, TAVR, as compared with standard therapy, was associated with a higher incidence of major strokes (5.0% vs 1.1%; $P = .06$) and major vascular complications (16.2% vs 1.1%; $P<.001$). In the year after TAVR, there was no deterioration in the functioning of the bioprosthetic valve, as assessed by evidence of stenosis or regurgitation on an echocardiogram. The Sapien valve was found to be superior to medical management in cohort B.

A year later, the same PARTNER investigators reported on Cohort A, which randomized 699 high-risk patients with AS to either TAVR or SAVR.[30] TAVR was found not to be inferior to standard SAVR in patients with advanced symptomatic AS who were at high risk for surgical therapy. Each group had statistically the same mortality at 1 year with TAVR and SAVR each demonstrating equivalent 1-year mortality (TAVR, 24.2%; SAVR, 26.8%) and equivalent relief of symptoms at 1 year.

In 2014, US CoreValve clinical investigators reported on 795 patients that were randomized to high-risk surgical procedure versus the first self-expanding THV. This pivotal trial demonstrated a higher rate of survival with the CoreValve at 1 year than SAVR. In this as-treated analysis, the rate of death from any cause at 1 year was significantly lower in the TAVR group than in the surgical group (14.2% vs 19.1%), with an absolute reduction in risk of 4.9% points (upper boundary of the 95% confidence interval, −0.4; $P<.001$) for noninferiority ($P = .04$ for superiority).[31]

In April 2016, PARTNER 2 investigators published their result on patients with intermediate-risk TAVR. Intermediate risk was defined as an STS score 4% to 8%. In this trial, they randomized 2032 patients to SAVR versus TAVR either TF or TAo. At 2 years, the investigators found that TAVR and SAVR had similar results for mortality and disabling stroke. TAVR in essence was found to be noninferior to standard aortic valve surgery.[32] Of note is that the THV used in this study was Edwards Lifesciences' second-generation Sapien XT THV. In a separate propensity-matched observational trial Thourani and colleagues[33] suggested that TAVR might be the preferred treatment alternative in intermediate-risk patients; however, this trial used Edwards Lifesciences' newest THV Sapien 3 not the Sapien XT THV. The Sapien 3 THV system included several design changes believed to improve the procedural technique, safety, and success.

The 5-year results of PARNTER 1 were recently published and demonstrated that high-risk TAVR and SAVR seem to have equivalent overall outcomes.[34] There were no differences in overall mortality, stroke, and readmission to the hospital. There was no valve deterioration in either group and the hemodynamics for each group seemed to be the same with sustained low mean gradient across the valve along with LV mass regression. The slightly higher stroke rate demonstrated in the TAVR group was no longer demonstrated at 5 years. However, the higher PVL rate in the TAVR group still played a major role in a predictor of late mortality. Inherent to the early studies were the limitations of the early technology including the rudimentary understanding of valve sizing and the limited TAVR valve sizes of 23 mm and 26 mm for all patients.

DATABASE AND OBSERVATIONAL STUDIES

Although not randomized data, observational database reviews can reveal and demonstrate real world experiences and how devices and procedures behave in all comers. CE certification occurred many years before FDA approval and real world outcome experience may be informed from these databases. The German Aortic Valve Registry has done just that.[35] Unlike other registries, the German Aortic Valve Registry also includes patients that undergo SAVR along with coronary artery bypass graft. The first study that was published from this group demonstrated two things. First, excellent outcomes are possible on a national level. Second, the total number of aortic valve interventions in Germany increased more than 7% suggesting that more patients were receiving treatment of AS.[35] In addition, patients with intermediate- and low-risk TAVR were reviewed and found to have comparable outcomes to surgical patients. This registry identified patient-specific predictors of early mortality from PVL, such as higher baseline pulmonary artery pressure and the presence of 2+ mitral regurgitation.

The United Kingdom implantation TAVR registry demonstrated favorable survival rates at 3 and 5 years of 61.2% and 45.5%, respectively. Stroke within 30 days was the only procedural predictor of mortality. In addition, the authors believed there were specific underlying disease characteristics that were major factors in determining outcome, such as atrial fibrillation, respiratory dysfunction, ventricular dysfunction, and renal dysfunction.[36] Neither device type nor PVL were seen as a predictor of long-term outcome.

The STS/TVT database recently reported its finding on 26,414 patients with TAVR with procedure dates from 2011 through December 2014. The patients were grouped into two time periods: 2011 through 2012, and 2013 through December of 2014. There were a total of 346 centers that participated. This study provided an overview of current US TVT practice and trends. They compared the first time period (2011–2012) with the second time period (2013–December 2014). First, the data sets noted that these patients were elderly with a mean age 82 and this did not change between the two study periods. Second, patients in the later time period experienced an overall drop in the mean STS score, perhaps reflecting lower risk applications for TAVR. During the second time period, with the evolution of technology and changes in procedural characteristics the data sets noted the following:

- Increase in use of moderate sedation from 1.6% to 5.1%
- Increase in use of percutaneous techniques up to 66.8% in 2014
- Decrease in vascular complications from 5.6% to 4.2%
- Decrease in bleeding complication rates, reflected of lower profile devices

Despite the evolution in technology the stroke rates remained stable at 2.2% during both time periods.[37]

COMPLICATIONS OF TRANSCATHETER AORTIC VALVE REPLACEMENT

Complications associated with TAVR are categorized as early/procedural or late/post-procedural and typically are related to mechanical factors, such as design/type of THV or implantation technique, and independent patient factors, such as age, presence of Peripheral artery disease (PAD), or end-stage renal disease (ESRD).

Common early/procedural complications include the following:

- Bleeding. Mostly related to mechanical factors, such as sheath delivery size leading to vascular complications. Also can be related to the inability to maintain hemostasis at the vascular access points. These bleeds are confounded by the use of anticoagulation or antiplatelet medications.
- Low cardiac output/hypotension. Usually treatable with medications. Rarely needs to be treated with cardiopulmonary bypass. Could consider treatment with intra-aortic balloon pump or Impella device (Abiomed Danvers, MA, USA).[38]
- Coronary obstruction. More common with low ostia heights (<10 mm), small sinuses of Valsalva, and bulky leaflet calcification. Can be treated at the time of TAVR with emergent percutaneous coronary intervention.
- Stroke. Commonly related to manipulation of catheters in diseased vessels. Less commonly related to prolonged episodes of hypotension (hypoperfusion).
- Annular rupture. Rare, but life-threatening. More common with smaller annular size, smaller sinotublar junction size, bulky calcification at the annulus and LV outflow tract (LVOT), implantation of a balloon-expandable device. Can be treated aggressively with conversion to open procedure or with comfort measures. This contingency plan is determined before procedure with patient involvement.

- Vascular complications. More common with larger delivery sheath size and in patients with PAD.
- Heart block. Occurs in one out of six patients and is believed to be related to inflammation, swelling, or compression of the pacemaker tissue.[39] More common with pre-existing right bundle branch block or left anterior fascicular block, smaller LVOT diameter, and higher ratio of annulus diameter to LVOT diameter. More common with lower delivery height of the THV and in use of self-expanding devices.[40] If a patient at any point following TAVR develops type 2 atrioventricular block or complete Heart block, electrophysiology should be consulted for consideration of permanent pacemaker implantation.[41]
- Aortic regurgitation (paravalvular and central). Often caused by malpositioning of the THV, either too high or too low. Can also be caused by undersizing of the THV.
- Pericardial effusion/tamponade. Can occur from RV perforation from temporary transvenous pacemaker or LV perforation from wires/catheters. Typically treated with pericardiocentesis but may require open procedure.

Common late/postprocedural complications include the following:

- Bleeding. Although less common in this time period, the frequent types of late bleeds are gastrointestinal, neurologic, or traumatic fall-related. These bleeds are confounded by the use of anticoagulation or antiplatelet medications.
- Valve leaflet thrombosis. A more recently documented phenomenon, subclinical valve thrombosis that may lead to a rising AV gradient. Valves placed by TAVR and SAVR have been discovered to contain subclinical thrombus. Four-dimensional CT scan is the best way to document this problem and a trial of anticoagulation should be considered.[42]
- Heart block. In patients who develop a new left branch bundle block or type 1 heart block, close monitoring with an event monitor at the time of discharge may be considered to allow for closer monitoring of potential late atrioventricular block.
- Aortic regurgitation (paravalvular and central). May not be discovered until after the patient has left the procedure room. If PVL is greater than moderate, this is associated with a poorer long-term prognosis at 2 years.[31,32] It is important that all members of the heart care team communicate in the same language and quantify the amount of PVL in a consistent and concise manner. The Valve Academic Research Consortium (VARC) has settled on common language and criteria that should be used.[33,34] If significant by VARC 2 criteria, the implanting physicians should consider a second procedure to “plug” the leak, postdilate the implanted THV, or implant a second THV if believed to be related to malpositioning.
- Patient prosthetic mismatch. Although patient prosthetic mismatch occurs more with SAVR, it is still noted with TAVR. In some patients with patient prosthetic mismatch, symptoms never resolve or worsen. There may not be the typical LV mass regression.[43]
- Prosthetic valve endocarditis. Occurs in 1.13% to 2.3% of patients in large TAVR cohorts. Diagnosed by transthoracic echocardiogram or transesophageal echocardiogram. The bacteria are usually *Staphylococcus*, *Streptococcus*, and *Enterococci*. The onset of endocarditis is early or late. Overall the diagnosis carries a poor prognosis given the inherent population.[44,45]

SPECIAL CIRCUMSTANCES

As the indications for TAVR expand, more patients will be served with this treatment modality leading to use of TAVR in patient populations that may not have been

specifically studied initially. These special circumstances should be evaluated on a case by case basis until more research is available and long-term durability is documented.

End-Stage Renal Disease

Patients with ESRD were excluded from the PARTNER trials but were included in the CoreValve US Expanded Use Study. There has been at least one database/observation study using TVT Registry data that reviewed all patients with renal-replacement therapy. Mack and coworkers[46] reported that patients on renal-replacement therapy were compared with nondialysis patients undergoing TAVR. They found that patient on renal-replacement therapy had higher mean STS PROM scores (13.8% vs 6.8%; $P<.0001$), a higher incidence of bleeding complications (7.7% vs 3.3%; $P<.001$), a higher major vascular complication rate (9.5% vs 6.1%; $P = .006$), and a higher in-hospital mortality (9.7% vs 5.3%; $P = .0002$). The risk of stroke seemed to be the same for both groups. Of note was a lower than expected observed mortality for patients with TAVR and ESRD.

Patients with ESRD in the CoreValve US Expanded Use Study were found to have a higher risk for mortality and complications.[47] Stroke and major vascular injury were infrequent and valve durability was maintained at 1 year.[48]

In summary, TAVR in patients with ESRD carries a higher risk than seen in the general pool of patients undergoing the procedure, but still is offered with caution.[49]

Pregnancy

Women represent close to 50% of all patients undergoing TAVR.[50] Although extremely rare, there have been case reports of pregnant patients undergoing TAVR with successful outcomes.[51] Pre-TAVR work-up may need to be altered to reduce the amount of radiation and contrast exposure to the patient and the baby. The procedural steps should remain as close to routine as possible to help ensure optimal THV placement and patient outcomes.

Incidental Pulmonary Nodules

Single pulmonary nodules (<5 mm in size) are a common finding in elderly patients with AS. With the gated multislice CT angiography performed on all patients during pre-TAVR work-up, incidental findings are bound to be found[52] and may be noted in up to 18% of patients screened.[53] Often these incidental findings include pulmonary nodules. Unless advanced thoracic malignancy is obvious, the reduction of morbidity and mortality by TAVR outweighs potentially harmful delays regarding further diagnostics. Standard, guideline-approved evaluation of single pulmonary nodules is safely performed after TAVR.[54]

THE FUTURE

TAVR and other transcatheter valve therapies are here to stay. Currently in the United States there are only two THVs available for commercial implantation; however, in Europe there are eight THVs for commercial implantations. Some of the valves commercially available in Europe are currently under study in the United States. After the recent approval for TAVR in the intermediate-risk group (PROM 4%–8%), the only group left to be treated with SAVR is the low-risk group (PROM <4%). As new THVs become available and TAVR indications expand, the future of advanced treatment of AS is predicted to shift even further from SAVR to TAVR.

A recent study reported by the Northern New England Cardiovascular Disease Study Group confirmed the longevity of SAVR noting that patients younger than 80 had a median survivorship of 11.5 years, patients between the ages of 80 and 84 had a median survivorship of 6.8 years, and those older than age 85 had a median survivorship of 6.2 years. Knowing the median survival with SAVR, to rationally approve TAVR in the low-risk group, long-term data on valve durability need to be evaluated[55,56] with documentation of freedom from structural valve deterioration that approaches 80% at 20 years for one biologic valve.[57]

History does not repeat itself, but is an important gauge into the future. It is not hard to recall the initial celebration within the surgical community with the results of the first-generation biologic valves at 5 years, only to be met with the sobering results of the 10-year durability data. Many unanswered questions remain about TAVR, such as the effect of PVL on long-term outcomes, the effect of permanent pacemaker implant in this subset of patients on mortality, and of course the 10- or 20-year THV durability data. However, it is important that the modern cardiac surgeon take a page from vascular surgery colleagues and continue to acquire endovascular skills. For the modern cardiac surgeon with the appropriate skill sets,[58] the future is bright.

SUPPLEMENTARY DATA

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.suc.2017.03.011.

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