

EXPERT CONSENSUS DOCUMENT

2012 ACCF/AATS/SCAI/STS Expert Consensus Document on Transcatheter Aortic Valve Replacement

Developed in collaboration with the American Heart Association, American Society of Echocardiography, European Association for Cardio-Thoracic Surgery, Heart Failure Society of America, Mended Hearts, Society of Cardiovascular Anesthesiologists, Society of Cardiovascular Computed Tomography, and Society for Cardiovascular Magnetic Resonance

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Preamble

This document has been developed as an Expert Consensus Document (ECD) by the American College of Cardiology Foundation (ACCF), American Association for Thoracic Surgery (AATS), Society for Cardiovascular Angiography and Interventions, and the Society of Thoracic Surgeons in collaboration with the American Heart Association (AHA), American Society of Echocardiography, European Association for Cardio-Thoracic Surgery, Heart Failure Society of America, Society of Cardiovascular Computed Tomography, Society of Cardiac Magnetic Resonance, Society of Cardiovascular Anesthesiologists, and Mended Hearts. ECDs are intended to inform practitioners, payers, and other interested parties of the opinion of ACCF and document cosponsors concerning evolving areas of clinical practice and/or technologies that may be widely available or may be new to the practice community. Topics chosen for coverage by ECDs are so designed because the evidence base, the experience with technology, and/or clinical practice are not considered sufficiently well developed to be evaluated by the formal ACCF/AHA Practice Guidelines process. Often the topic is the subject of considerable ongoing investigation. Thus, the reader should view the ECD as the best attempt of the ACCF and document cosponsors to inform and guide clinical practice in areas where rigorous evidence may not yet be available or evidence to date is not widely applied to clinical practice. When feasible, ECDs include indications or contraindications. Some topics covered by ECDs will be addressed subsequently by the ACCF/AHA Practice Guidelines Committee.

To avoid actual, potential, or perceived conflicts of interest that may arise as a result of industry relationships or personal interests among the writing committee, all members of the writing committee, as well as peer reviewers of the document, are asked to disclose all current healthcare-related relationships, including those existing 12 months before initiation of the writing effort. The ACCF Task Force on Clinical Expert Consensus Documents (TF CECD) reviews these disclosures to determine what companies make products (on market or in development) that pertain to the document under development. Based on this information, a writing committee is formed to include a majority of members with no *relevant* relationships with industry or other entity (RWI), led by a chair with no *relevant* RWI. Authors with *relevant* RWI are not permitted to draft or vote on text or recommendations pertaining to their RWI. RWI is reviewed on all conference calls and updated as changes occur. Author and peer reviewer RWI pertinent to this document are disclosed in Appendices 1 and 2, respectively. Additionally, to ensure complete transparency, authors'

comprehensive healthcare-related disclosure information—including RWI not pertinent to this document—is available online (see Online Appendix 3). Disclosure information for the ACCF TF CECD is also available online at www.cardiosource.org/ACCF/About-ACCF/Leadership/Guidelines-and-Documents-Task-Forces.aspx, as well as the ACCF disclosure policy for document development at www.cardiosource.org/Science-And-Quality/Practice-Guidelines-and-Quality-Standards/Relationships-With-Industry-Policy.aspx.

The work of the writing committee was supported exclusively by the ACCF without commercial support. Writing committee members volunteered their time to this effort. Conference calls of the writing committee were confidential and attended only by committee members.

*Robert A. Harrington, MD, FACC
Chair, ACCF Task Force on Clinical Expert Consensus Documents*

1. Introduction

1.1. Document Development Process

1.1.1. Writing Committee Organization

The Writing Committee consisted of a broad range of members representing 12 societies and the following areas of expertise: cardiothoracic surgery, interventional cardiology, general cardiology, geriatric cardiology, echocardiography, cardiac anesthesiology, cardiac computed tomography (CT), cardiac magnetic resonance (CMR), cardiac nursing, heart failure, neurology, valvular heart disease, structural heart disease, and the consumer perspective. Geographic distribution of members crossed most U.S. time zones and included international representation. Members with expertise using this new and emerging technology and those with expertise in their content area, but not in the procedure discussed herein, served on the committee to provide appropriate balance of perspectives.

This writing committee met the College's disclosure requirements for relationships with industry as described in the Preamble. Important to note, if an author works in an institution that serves as a TAVR trial site but has no *direct* relationship with the trial sponsor or other relevant company (that produces [competing] products or services discussed in this document) or *institutional* relationship as defined by the ACCF Disclosure Policy for Document Development, the trial site information was not deemed relevant to this writing effort and is not included in the table of relevant author disclosures (Appendix 1). For example, if an author works in an institution where TAVR is performed, but he/she: 1) does not personally perform the procedure; or 2) performs the procedure but has no direct relationship to the trial (e.g., principal investigator, investigator, steering committee member, consultant) and does not oversee funds related to the trial, then the relationship is not included in the table of relevant disclosures. In these

situations, these relationships do not even need to be disclosed. However, in the spirit of full disclosure, this information is recorded in the online disclosure table containing all author healthcare relationships.

1.1.2. Document Development and Approval

The Writing Committee convened by conference call and e-mail to finalize the document outline, develop the initial draft, revise the draft per committee feedback, and ultimately sign off on the document for external peer review. All participating organizations participated in peer review, resulting in 48 reviewers representing 1,087 comments. Comments were reviewed and addressed by the writing committee. A member of the ACCF TF CECD served as lead reviewer to ensure that all comments were addressed adequately. Both the Writing Committee and TF CECD approved the final document to be sent for board review. The ACCF Board of Trustees, AATS Council, SCAI Board of Directors, and STS Board of Directors reviewed the document, including all peer review comments and Writing Committee responses, and approved the document in January 2012. The AHA, ASE, EACTS, HFSA, Mended Hearts, SCA, SCCT, and SCMR endorsed the document in January 2012. This document is considered current until the TF CECD revises or withdraws it from publication.

1.2. Purpose of This Document

Transcatheter aortic valve replacement (TAVR) offers new and potentially transformational technology for patients with severe aortic valvular stenosis who are either extremely high-risk candidates or inoperable for surgical aortic valve replacement (AVR) or who are inoperable by virtue of associated comorbidities. In the future, this technology may be utilized in lower risk surgical candidates. An estimated 40,000 patients have received TAVR worldwide. Multiple single and multicenter registries, and a single randomized trial, have documented favorable outcomes using a wide spectrum of endpoints, including survival, symptom status, quality of life, and need for repeat hospitalization. The implementation of TAVR into the flow of patient care is complex, involving consideration of several key factors such as clinical site selection, operator and team training and experience, patient selection and evaluation, procedural performance and complication management, and postprocedural care. Collaborative stakeholder involvement is required in the management of this high-risk patient population with extensive coexistent medical conditions. A previously published document by ACCF and STS identified a high-level series of issues to be addressed regarding this technology (1). This current collaborative expert consensus document, which involves 12 professional societies, addresses these issues in greater detail with the intent to examine the current state of the evidence, facilitate the integration of this technology into the armamentarium of therapeutic options for patients with aortic valvular stenosis, and to enable responsible adoption and diffusion of this

promising technology. This document has focused on published data; it must be remembered that there is only 1 single completed randomized trial, although others are in progress or planned; much of the data in this expert consensus document is based upon information from studies and registries, both surgical and TAVR, which are frequently retrospective and include self-reported clinical events rather than adjudicated events.

2. Background and Historical Aspects

The most common cause of valvular aortic stenosis (AS) in adults is calcification of a normal trileaflet or congenital bicuspid valve (2–4). Calcific AS is characterized by lipid accumulation, inflammation, fibrosis, and calcification (5,6) and is common in the United States. It typically presents in older individuals (i.e., >75 years) in contrast to bicuspid AS, which presents a decade or more earlier. Rheumatic AS, uncommon in the Western world, occurs due to fusion of the commissures with scarring and calcification of the cusps, and retraction of the leaflets resulting in the valve being both regurgitant and stenotic.

2.1. Pathophysiology and Clinical Course

In adults with valvular AS, the obstruction develops gradually, typically over many years during which the left ventricle (LV) adapts to the systolic pressure overload with progressive concentric hypertrophy that results in diastolic dysfunction (4,7,8), reduced coronary reserve (9,10), myocardial ischemia (11), and eventually, depressed contractility resulting in LV systolic dysfunction (12–14). Ultimately, in some patients, heart failure or sudden death occurs. Typically, patients with AS are free from cardiovascular symptoms (i.e., angina, syncope, and heart failure) until late in the course of the disease. However, once symptoms manifest, the prognosis is poor, with the interval from the onset of symptoms to the time of death being approximately 2 years in patients with heart failure, 3 years in those with syncope, and 5 years in those with angina (15). Gardin et al. reported that among symptomatic patients with moderate-to-severe AS treated medically, mortality rates after the onset of symptoms were approximately 25% at 1 year and 50% at 2 years (16), with approximately 50% of deaths being sudden. In the elderly high-risk patients in the PARTNER (Placement of Aortic Transcatheter Valve) trial who were treated medically (Cohort B), the survival at 1 year was only 50% (15).

The natural history of AS has changed since the publication of the seminal paper by Morrow and colleagues in 1968 (17). The original data were derived largely from patients with rheumatic AS or AS due to a bicuspid aortic valve, with an average age of death of 63 years. On the contrary, patients being considered for TAVR on a trileaflet valve present much later in life, typically in their late 70s or older, and have dominantly fibrocalcific AS. Although now

occurring later in life, the onset of symptoms still heralds a rapid decline with medical therapy alone (15).

2.2. Diagnosis

2.2.1. Echocardiography Versus Catheterization

Assessment of the severity of stenosis does not differ in TAVR patients compared with the general AS population, and decisions should therefore be based upon established guidelines (18). Although invasive cardiac catheterization has historically been the standard for quantification of AS, this function has been largely replaced by echocardiography (19).

Echocardiographic diagnosis is made by the observation of a calcified valve with restricted leaflet opening by two-dimensional (2D) echocardiography with quantification of the peak and mean AV gradient made by applying the simplified Bernoulli equation ($\Delta p = 4v^2$) to the maximal velocity recorded through the aortic valve by continuous-wave Doppler. Multiple imaging windows (apical 4-chamber and long-axis, right parasternal, suprasternal notch, and subcostal views) should be obtained to assure acquisition of the maximal velocity and to avoid angle-related errors. Although aortic valve area (AVA) can be measured by planimetry, it is more accurately assessed by application of the continuity equation, using pulsed-wave Doppler in the left ventricular outflow tract (LVOT) and continuous-wave Doppler across the valve. Severe stenosis is defined in the guidelines as a peak velocity >4.0 m/s (corresponding to a peak gradient of 64 mm Hg), a mean gradient >40 mm Hg, OR valve area <1.0 cm² when LV systolic function is normal. To account for patient size, the valve area is often indexed to body surface area, with 0.6 cm²/m² considered to be the threshold for severe AS. An important exception is when the gradient suggests less severe stenosis than the valve area, most commonly due to low stroke volume, either in dilated ventricles with low ejection fraction (EF) or small ventricles with normal EF. In this setting, a dobutamine stress study (maximum stress dose 20 mcg/kg/min), may be helpful. If the maximum jet velocity rises over 4 m/s with the dobutamine-induced increase in stroke volume whereas the AVA remains less than 1.0 cm², then the valve is truly severely stenotic. On the other hand, if stroke volume increases with little rise in gradient (causing valve area to increase substantially), then the AS is only mild to moderate in severity, and the LV dysfunction is due to causes other than AS (20–22).

Occasionally, the AVA appears larger than the elevated gradient would suggest, usually due to elevated stroke volume from aortic regurgitation (AR), anemia, fever, or hyperthyroidism. Sometimes, though, it reflects a technical error in applying the continuity equation, when the blood accelerates within the LVOT due to an upper septal bulge, which may result in an overestimation of valve area. To avoid this, one can try to measure the LVOT area at the point of maximal velocity, though the geometry is often

quite distorted in this region, making estimation of the LVOT area difficult. Alternatively, one can use the LV stroke volume (from 2D or three-dimensional [3D] measurements of the LV, ideally with contrast infusion) or right ventricular (RV) stroke volume (from RV outflow tract) as the input into the continuity equation. Dividing this stroke volume by the time velocity integral of the AV continuous-wave Doppler will also yield the AVA, independent of any distortion in the LVOT.

Despite the convenience and wide-spread applicability of transthoracic echocardiography (TTE), there are occasions when invasive measurements are needed, such as in patients with a discrepancy between clinical and echocardiographic assessments. In such cases, catheterization should generally be performed with dual catheters, 1 placed in the LV, the other in the proximal aorta to obtain simultaneous pressure measurements and obtain the most accurate assessment of the gradient. Infusion of dobutamine may allow assessment of low-output, low-gradient AS in the catheterization laboratory (23). Other adjunctive testing used in quantifying AS includes transesophageal echocardiography (TEE) (24), CT scanning (dynamic or gated during systole) (25), and CMR (26).

2.2.2. Stress Testing

The presence or absence of symptoms should guide the management of AS patients, yet in many cases, this important clinical benchmark is difficult to establish, owing to the subjective nature of the symptoms and comorbid conditions such as chronic lung disease in this patient population. In general, stress testing is contraindicated when symptoms are present because of the potential for complications in these patients. However, in patients with equivocal symptoms, stress testing, and in particular stress echocardiography, can be very helpful (27). Simple determination of functional capacity may help show limitations of which a patient may be unaware. Isolated echocardiographic (ECG) changes during the stress test without symptoms or change in blood pressure should not be interpreted as a positive indicator of severe AS. Other potential markers for AS severity include signs of LV dysfunction on exercise echo or a rise in left atrial or right ventricular pressure (28,29).

2.3. Special Considerations

2.3.1. Symptom Status

With severe, symptomatic, calcific AS, AVR is the only effective treatment that improves symptoms and prolongs survival (30,31). These results are partly dependent on LV function. In the setting of LV dysfunction caused by afterload mismatch, survival is still improved, although improvement in LV function and resolution of symptoms might be incomplete after AVR. Age itself is a risk factor for adverse outcome, but it is not a contraindication to AVR even in the very elderly (32,33).

2.3.2. Associated Coronary Artery Disease

In patients with moderate AS, who are undergoing coronary artery bypass graft surgery (CABG), AVR should be performed at the time of revascularization irrespective of symptoms related to moderate AS (34,35). There are no data to support performing AVR for mild AS at the time of CABG. Patients undergoing surgical AVR with significant stenoses (>50% to 70% stenosis) in major coronary arteries should be treated with concomitant CABG. Options in patients with combined AS and CAD continue to grow with the use of hybrid procedures where PCI is followed by valve surgery. It is possible that such a strategy could be performed in the setting of TAVR (36,37).

2.3.3. Associated Lesions—AR, MR, Pulmonary Hypertension, TR

Patients with severe AS often have additional associated significant valvular heart disease. Treatment of these lesions in patients undergoing AVR should be undertaken using standard criteria. However, treatment of associated valvular lesions may increase the risk of AVR (38). A special circumstance is that of pulmonary hypertension (PH) either primary or secondary (reactive or related to increased LV end-diastolic pressure). Both conditions may increase the risk of AVR and must be taken into consideration in the risk/benefit ratio.

PH can be present in patients with severe AS, either from the transmission of increased LV diastolic and/or left atrial pressures, associated mitral regurgitation (MR), or from a secondary increase in pulmonary vascular tone. The prevalence of PH in patients with AS is undefined, varying widely on the definition used and the population studied (39,40). Clinically, PH associated with critical AS portends a poor prognosis and is associated with an increased risk of sudden cardiac death (41). Consistent with the surgical valve implant experience, PH after TAVR is a predictive factor for both early (30-day) and late (1-year) mortality, similar in risk to major access site complications and renal insufficiency (39,42–46). The presence of PH makes patients more susceptible to any hemodynamic and electrical instability related to the procedure and may increase the risk of postprocedural complications. In addition, PH may result in right heart failure and severe tricuspid regurgitation (TR), both of which complicate management and increase risks.

In the setting of severe AS and PH several treatment strategies have been used (47). Persistently elevated left-sided cardiac filling pressures increase the risk of pulmonary edema when challenged with a pulmonary vasodilator. Pulmonary vasodilators, such as nitric oxide, prostacyclin, and sildenafil, have been administered during and following cardiac surgery with improved hemodynamic effects (48–50). However, their overall clinical utility in improving late survival in the surgical population and their role in TAVR remains unclear. Further investigation is needed to deter-

mine the optimal procedural and periprocedural management of patients with AS and PH undergoing TAVR.

2.3.4. Low Gradient–Low EF

As mentioned, the combination of overt congestive heart failure and low aortic valve gradient is relatively common. This may be a consequence of excessive afterload (despite left ventricular hypertrophy [LVH]) or reduced contractile function (51) likely due to increased myocardial fibrosis (52). When there is overt heart failure due to low forward flow and a low transvalvular gradient (mean gradient ≤ 30 mm Hg), both mechanisms may be present. Because of reduced contractility in the low-flow/low-gradient AS patient, prognosis with surgical AVR is adversely affected with operative mortality as high as 20%. However the 5-year survival is still reported to be better in patients treated surgically (53,54). When the primary reason for poor LV performance is excessive afterload, the prognosis following surgical AVR is usually good (14). In general, patients with low gradient, low EF who have the best prognosis are those with inotropic reserve (shown by an increase in stroke volume with dobutamine infusion), who have limited coronary disease and a mean gradient that although low, still exceeds 20 mm Hg (53).

2.3.5. Basal Septal Hypertrophy—Outflow Tract Gradients

Although infrequent, proximal septal bulging with LVOT obstruction may present unique issues in the presence of AS. While this can be readily addressed during AVR via myomectomy, such an approach would not be possible with TAVR. Thus, careful preprocedural echocardiographic screening is recommended to specifically avoid this scenario in patients being considered for TAVR.

3. Current Treatment Options

3.1. Surgical AVR

AVR is the only effective treatment considered a Class I recommendation by ACCF/AHA and ESC guidelines in adults with severe symptomatic AS (28,29). Not only does it offer symptomatic relief, the operation improves long-term survival. Since 1960, when AVR was first introduced, advancement in prosthetic technology including improved hemodynamics, durability and thromboresistance, and techniques in cardiac surgery such as cardioplegia, management of the small aortic root, resection of associated subvalvular disease, and replacement of associated aortic aneurysm have resulted in improvements in both operative and long-term results.

3.1.1. Valve Type

Current AVR options include mechanical, bioprosthetic, and in specific situations homograft and autograft techniques. Each has their advantages and drawbacks, but the

trend in some centers in the recent era has been toward tissue valve replacement in a majority of patients because of improved durability and the lack of requirement for anticoagulation therapy.

3.1.1.1. MECHANICAL VALVES

Mechanical valves are now extremely durable, have excellent hemodynamics, and are minimally thrombogenic with adequate anticoagulation. Current anticoagulation is mostly based on Vitamin K antagonists. Newer agents such as oral direct thrombin inhibitors and factor Xa inhibitors have been studied in other patient populations, mainly atrial fibrillation, and have been found to be associated with decreased bleeding risk and minimum drug or food interaction (55). They have not been well studied in patients with AVR. With warfarin there is a risk of serious thromboembolism of approximately 0.5% a year and a similar risk of major hemorrhage annually (56). Mechanical valves are typically preferred in younger patients given their reliable long-term durability.

3.1.1.2. BIOPROSTHETIC VALVES

Compared with mechanical valves, bioprosthetic valves do not require anticoagulation with warfarin, and thus have a lower risk of bleeding. However, long-term durability varies substantially with age for these valves. Structural valve degeneration leading to symptoms or reoperation, commonly associated with calcification of the biologic leaflets, occurs at an average of 10 to 12 years in younger patients and 15 to 18 years in older patients. Actuarial freedom from reoperation following implant of a modern bioprosthetic valves is approximately 95% at 5 years, 90% at 10 years, but drops to 70% at 15 years (57). Thus, bioprosthetic valves are generally preferred in older patients who are unlikely to tolerate bleeding risk associated with anticoagulation treatment and in whom a 15-year durability is reasonable. In patients with bioprosthetic valves, if prosthetic dysfunction occurs, TAVR may play an important role in solving the clinical issues in the future.

3.1.2. Procedural Hazards

Current data from the Society of Thoracic Surgeons (STS) registry documents a mortality that is under 3% for all patients undergoing AVR. As with any procedure, operative mortality is strongly correlated with the severity of the disease and comorbidity of patients. The operative risks can be estimated with online risk calculators from the STS (<http://209.220.160.181/STSTWebRiskCalc261/>) and the European System for Cardiac Operative Risk Evaluation (www.euroscore.org) (58,59). In selected patients with minimal comorbidity, mortality and major morbidity are under 1% each in many centers. In general, perioperative stroke rates are 1.5% (with major life-debilitating stroke being somewhat less) and other major complications are relatively rare. Renal failure, pulmonary failure, and gastrointestinal complications are not common. As older, more frail patients with extensive comorbidities undergo AVR, the risk of

death and morbidity as well as length of hospitalization increases significantly (60,61). In addition to comorbidity, preoperative functional performance is also a maker of postoperative morbidity/mortality.

A recent study reviewed the results of high-risk surgical AVR in 4 centers with significant experience. The patients were a mean age of 76 and the mean STS predicted risk of mortality was 16.3%. Complications included stroke in 4.4%, new permanent pacemaker in 5%, multisystem organ failure in 6.9%, pneumonia in 7.5%, and dialysis in 8.2%. Postoperative length of stay was 12.6 days and in-hospital mortality was 16.4%. One-, 3- and 5-year survival was 70.9%, 56.8%, and 47.4%. This study was performed between 2002 and 2007 in 4 centers before participation in the PARTNER Trial commenced and therefore serves as a reasonable baseline for comparing the results of TAVR (62).

3.1.3. Patient Selection

Patient selection for AVR for AS is well outlined by ACCF/AHA and ESC guidelines (29,63). Problems arise when the clinicians and patients note significant symptoms and significant structural disease that are complicated by the presence of significant comorbidity. Although current STS risk score and EuroSCORE give information concerning short-term operative risks and benefits, they are not able to predict symptom resolution, quality-of-life improvement, or return to independent living.

3.1.3.1. USE OF STS AND EUROSCORE MODELS IN PATIENT SELECTION FOR CONVENTIONAL AVR

Although a number of risk algorithms for cardiac surgery have been developed, the STS and logistic EuroSCORE are the most commonly used. Although both are accurate in low-risk patients, accuracy is less in higher-risk subsets. These 2 scores include different covariates. The logistic EuroSCORE is based on 12 covariates derived from 14,799 patients undergoing all types of cardiac operations (mostly coronary bypass) in 8 European countries in 1995. On the other hand, the STS risk predictor is based on 24 covariates derived from 67,292 patients undergoing isolated AVR only in the United States over a relatively more contemporary period between 2002 and 2006. The STS model is the standard most commonly used in the United States.

3.1.3.2. PATIENT RISK OF AVR

Information from the STS National Database shows that the operative mortality for isolated AVR has declined from 3.4% in 2002 to 2.6% today (<http://www.sts.org/sites/default/files/documents/20112ndHarvestExecutiveSummary.pdf>). The most important preoperative patient risk factors are the need for emergency surgery, the presence of endocarditis, and a history of previous cardiac surgery. The present models do not include some risk factors that may be particularly important in the prediction of outcomes for very high-risk populations including frailty, PH, porcelain aorta, and the presence of hepatic dysfunc-

tion, although all have been added to a recent upgraded version (64,65).

It should be emphasized that risk models serve as 1 aspect of patient selection, but need to be considered in concert with clinical judgment and the other methods of risk assessment. In the final analysis, patient risk and benefit is determined, not by statistical models, but by the experience, knowledge, and expertise of the physicians charged with rendering care.

3.1.3.2.1. SPECIFIC SURGICAL RISKS

3.1.3.2.1.1. Stroke. Although ischemic stroke can result from many causes after AVR, a major concern is the role of thromboembolism. The risks of thromboembolism are usually greater in the first few days and months after bioprosthetic AVR implantation before the sewing ring of the prosthesis is endothelialized (66); risks after mechanical AVR continue. The risk of stroke within 30 days among 67,292 cases of AVR in the STS Registry was 1.5%; this data set was used to develop a model for predicting 30-day stroke risk (61). Within the STS database among 108,687 AVR operations between 1996 through 2006, the risk of in-hospital permanent stroke decreased 21% from 1.7% to 1.3% (67). It is important to note, however, that independent neurological assessment was not done in these patients, so the actual stroke incidence in these patients may be underestimated. Overall, embolic stroke risks are greater with mechanical valves, which require long-term oral anticoagulation, than with bioprosthetic valves, which have a 0.7% per year risk of thromboembolism in patients with normal sinus rhythm without warfarin anticoagulation (68).

Of note, many AVR patients are older, with other comorbid cardiac conditions that increase stroke risk, including atrial fibrillation, cardiomyopathy, and carotid stenosis or aortic arch atheroma (69). However, even carefully selected octogenarians can safely undergo AVR with a 2% incidence of stroke (32,70).

Because of the risk of stroke, the 2006 ACC/AHA guidelines for the management of patients with valvular heart disease include a variety of recommendations regarding the use of antithrombotic therapy to reduce thromboembolism risk after AVR (63). The choice of antithrombotic agents include warfarin with target international normalized ratios (INRs) typically in the range from 2.0 to 4.0 depending on the specific prosthesis, aspirin 75 mg to 325 mg per day, and clopidogrel 75 mg per day, as well as combinations. Recommendations depend upon the type of valve, timing after surgery, presence or absence of risk factors such as atrial fibrillation, and ability of the patient to take warfarin or aspirin (63).

Given the greater risk of thromboembolism, particularly stroke, which usually occurs within the first 72 hours post-procedure, many centers start heparin (target aPTT 55 s to 70 s) as soon as the risk of surgical postoperative bleeding is acceptable, which is usually within 48 hours of

surgery. Heparin can be discontinued when warfarin therapy reaches a therapeutic INR usually above 2.0 (63).

3.1.3.2.1.2. Other Complications. Aside from other surgical complications of renal, hepatic, neurological, and pulmonary disease compromise, a major risk of conventional AVR is sternal wound infection. In most centers, this risk is under 1% for deep infection, but the risk of any type of infection is still present and particularly increased in patients with diabetes, obesity, smoking, immunosuppressive therapy, and prior radiation therapy. With the advent of negative pressure wound therapy and continued advances in surgical technique, these risks are now rarely fatal, but remain morbid. Blood requirement after valve replacement can lead to hepatitis C, human immunodeficiency virus, or other viral infection. These transfusion-acquired infections are now extremely rare due to transfusion guidelines and systems precautions.

3.1.3.3. PROHIBITIVE RISK, EXTREME RISK, INOPERABILITY

Despite substantial contemporary experience with successful AVR in elderly patients, multiple series have documented that 30% to 40% of patients with severe AS do not undergo surgery owing to advanced age, LV dysfunction, multiple coexisting conditions, and patient preference or physician recommendation (71–76).

The definitions used to describe patient populations considered for TAVR vary; for example, prohibitive risk would describe a patient in whom the procedure could be performed from a technical standpoint but would be associated with prohibitively high morbidity and mortality (77). Inoperability might identify a patient group in whom technical success would not be possible; for example, no vascular access. Different trials have used these terms for patient enrollment; for example, the CoreValve Trial identifies extreme risk, whereas the PARTNER (Placement of AoRtic TraNscathetER Valve) Trial used the term *inoperable*. For this document, we prefer the term *prohibitive risk*. This includes some patients in whom surgery might be deemed unsuitable based on the physician's assessment of the patient's risk for surgery; whereas in others, the surgeon may decide that the operation cannot be performed successfully because of technical considerations. Assessment of inoperability is also driven by surgeon and institutional experience and thus varies. The incidence of patients undergoing AVR with an STS predicted risk of mortality >5% is low but vary significantly amongst institutions and may be related to volume and referral patterns. Experience with such patients is pivotal for TAVR teams. Referral to such team and another opinion/consultation is crucial before deeming a patient inoperable. Whereas practice guidelines have been developed to assist physicians and surgeons in determining appropriate use of treatment options (29,63), there are, however, no specific recommendations for defining inoperability. Current ACCF/AHA guidelines acknowledge that special considerations are required for the management of advanced elderly patients with AS, since

age-related and comorbid conditions commonly exist in patients in their 80s and 90s even though AVR is technically feasible even in this group (67,78).

In the absence of literature evidence and guidelines recommendations, the determination of inoperability in any given patient depends on the judgment of the medical team. It is generally agreed that patients with limited life expectancy due to concurrent conditions such as malignancy, dementia, primary liver disease, chronic obstructive pulmonary disease (COPD), among others, are not appropriate for AVR. Frailty and related conditions of debility and deconditioning are known to result in inability to recover from major heart surgery such as AVR, despite operative survival and hospital discharge (65). These conditions can potentially contribute to increased surgical mortality and morbidity in the elderly (79).

Inoperability from the surgeon's judgment may result from technical considerations that preclude safe performance of AVR, such as prior mediastinal irradiation, porcelain aorta or severe periannular calcification, severe aortic atheromatous disease, prior cardiac operations, among others including the internal mammary artery crossing the midline. Although infrequent, aortic valve bypass with a LV apex-to-descending aortic conduit has been used in some patients with severe AS judged to be inoperable via a mediastinal approach and cardiopulmonary bypass (80).

In summary, a substantial percentage of patients with AS are judged to be inoperable for surgery based primarily on the physician's or surgeon's determination of operative risk and survivability. Although some patients may be found to be inoperable for technical and surgical reasons, most inoperable patients are felt to be too ill from associated comorbid conditions.

3.2. Alternatives to AVR

3.2.1. Medical Therapy

There are no proven medical treatments to prevent or delay the disease process in the aortic valve leaflets. However, evaluation and modification of cardiac risk factors is important in patients with aortic valve disease to prevent concurrent coronary artery disease (CAD). The association of AS with risk factors similar to those associated with atherosclerosis (5,6) had suggested that intervention may be possible to slow or prevent disease progression in the valve leaflet (81,82), but prospective, randomized, placebo-controlled trials failed to demonstrate a benefit of statins in reducing the progression of aortic valve stenosis.

Longer-term palliative medical management of symptomatic AS may be appropriate for patients who are either not candidates for aortic valve surgery due to comorbidities or in patients who refuse AVR. The overall goal of medical therapy is to treat coexisting cardiovascular conditions, and treat superimposed diseases that often exacerbate the disease process. Patients should be educated about the effects of sodium intake, change in weight, and other factors that may

lead to clinical decompensation. Medical therapy should be judicious and include treating concurrent cardiovascular conditions such as correction of anemia and fever, and preventative measures such as pneumococcal or influenza vaccination. Given the severe hypertrophy, optimizing hemodynamics by maintaining sinus rhythm may help with symptom stabilization.

Even with optimal care, adults with severe symptomatic inoperable AS will have exacerbations of symptoms and frequent hospitalizations. Palliative care should include end-of-life discussions and counseling as appropriate. Counseling is also indicated regarding true risk of AVR, and the importance of accurate risk prediction cannot be over-emphasized. Many patients may refuse surgery based on misunderstood operative risk.

3.2.2. Balloon Aortic Valvuloplasty

First reported in 1986 (83), balloon aortic valvuloplasty was considered to be a less invasive and safe alternative to AVR, particularly in high surgical risk patients with multiple medical comorbidities. Although balloon aortic valvuloplasty results in immediate hemodynamic improvement with a significant decrease in transvalvular gradients resulting in larger valve area, it does not result in sustained clinical improvement because of high recurrence rates; restenosis or recoil of the aortic valve usually occurs within 6 months. Patients treated with balloon aortic valvuloplasty alone have shown poor prognosis, with survival rates of 50% at 1 year, 35% at 2 years, and 20% at 3 years (15,84–86). In addition, serious complications due to balloon aortic valvuloplasty occur in 15% to 25% of patients (84,87,88). Balloon aortic valvuloplasty, therefore, should not be used as a substitute for AVR in patients who are candidates for surgical AVR. Even as a palliative treatment, balloon aortic valvuloplasty data suggest that there is much uncertainty regarding improved longevity or quality of life after the procedure with a mean duration of symptom improvement of only 1 year (63,89). There has been no significant difference in long-term survival demonstrated between patients undergoing balloon aortic valvuloplasty and those undergoing medical therapy alone (86). Although balloon aortic valvuloplasty as a stand-alone treatment is not recommended (63,87,88), it may still be used in contemporary practice as a bridge to subsequent AVR (both Class IIb, Level of Evidence C recommendation) (28,84,90). In the current era of TAVR, there has been increased interest in balloon aortic valvuloplasty. In this setting, balloon aortic valvuloplasty may be used to assess whether there is initial clinical improvement, in which case, then the patient may be a candidate for TAVR.

4. Transcatheter Aortic Valve Replacement

4.1. Background and History

Given the increased mortality and morbidity of AVR surgery for high-risk patients and the poor long-term results

of balloon aortic valvuloplasty, there has been interest in the development of a percutaneously delivered aortic heart valve (91). As early as 1992, investigators evaluated stent-based porcine bioprostheses delivered to various aortic sites in animal models (92). This early work culminated in 2000 with implantation of a percutaneous heart valve in a 12-year-old patient with a failing right ventricular to pulmonary arterial conduit that had been placed 8 years previously for the treatment of pulmonary atresia and ventricular septal defect. This initial seminal experience was followed in 2002 by the first human TAVR using the antegrade approach to implant a balloon expandable equine pericardial leaflet stent valve (93). Since that early experience, there have been multiple iterations and a number of new designs.

4.2. Device Description

At the present time, the most data available for TAVR are based upon 2 specific devices—the Sapien valve (Figure 1) Edwards Life Sciences, Inc., Irvine, CA) and the CoreValve (Figure 2) (Medtronic, Inc., Minneapolis, MN). The most recent iteration of the former is a trileaflet bovine pericardial valve mounted with a tubular slotted balloon-expandable stent composed of a cobalt chromium alloy. The Sapien valve is available in 23-mm and 26-mm sizes in the United States and 23-mm, 26-mm, and 29-mm sizes in Europe. The initial devices required a 22- or 24-French sheath for delivery of the prosthesis. Recent iterations (NovaFlex) have decreased this to 18-French. The first and second generations of this device have been tested in randomized controlled trials for both transfemoral and transapical implantation.

The second device (CoreValve) is comprised of 3 porcine pericardial tissue leaflets mounted in a self-expanding nitinol frame. It is available in 3 sizes—26 mm, 29 mm, and 31 mm. This valve has also continued to iterate, with the initial devices being 25-French, but now 18-French delivery

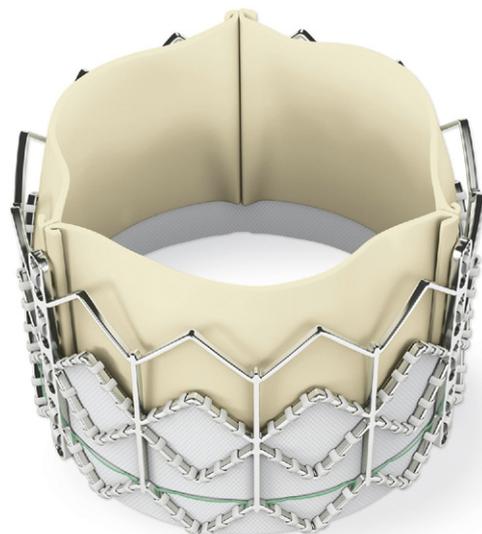


Figure 1. Sapien Valve

Source: Edwards Lifesciences.

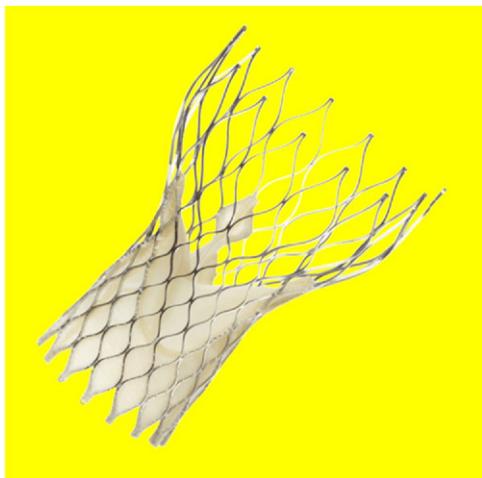


Figure 2. CoreValve

The Medtronic CoreValve System is currently limited to investigational use in the United States. Source: Medtronic, Inc.

sheaths are used. This valve has only been used by a retrograde approach—either via transfemoral, subclavian, or direct aortic access.

A wide range of new devices has been tested with some first-in-man experiences. These devices have been characterized by smaller size, the ability to reposition or even recapture the device after deployment if an optimized device position is not obtained initially, and, modular prosthetic elements to design in situ more optimal conformance to the natural valve and aortic annulus among others.

Specific anatomic issues must be considered in device design. These include the rigid structure of the pattern of valvular calcification and aortic annulus, and the need for as full apposition as possible to the annulus in an attempt to minimize periprosthetic leak which, given sometimes eccentric, bulky calcification, may be difficult. The close proximity to the coronary ostia, the width and height of the sinuses, the membranous ventricular septum with the His bundle and the anterior leaflet of the mitral valve are also important anatomical considerations. In addition, the size and degree of severity of peripheral arterial disease are all factors that could limit catheter size. Other issues include avoidance of central prosthetic leak, leaflet durability, hemodynamic performance, ability to treat both tricuspid and bicuspid valve anatomy, surfaces designed to minimize thrombogenicity, and the need to optimally position the devices and retrieve and reposition when necessary (94).

Fundamental issues for all current and future devices are hemodynamic results, valve durability, and residual or new aortic regurgitation (AR). The initial hemodynamic performance of TAVR valves must be similar or superior to that obtained with surgical AVR. This is crucial because high residual transprosthetic gradients result in less symptomatic improvement and poorer regression of left ventricular mass (95). These transprosthetic gradients are a function of prosthetic size as well as the specific type of prosthesis and

can result in patient–prosthesis mismatch. Typical immediate postprocedural gradients after surgical AVR range from 8 mm Hg to 12 mm Hg, whereas the AV area or effective orifice area (EOA) ranges from 1.4 to 1.9 cm². As documented below in the PARTNER trial, the valve hemodynamics of the TAVR early on are approximately 10% better than the specific surgical aortic prostheses used in that trial.

There are only limited clinical data on the durability of TAVR valves—up to 2 years—in the PARTNER trial and up to 5 years in other registry experiences. Although the absolute number of patients is small, there have been no reports of structural valve deterioration. The fundamental clinical need for durability may depend in part on the specific patient population. In the PARTNER trial, the mean age at implant was 83 years, and serious comorbidities were frequent. In this setting, the need for durability of 20 years is less important than if the patient selection criteria are broadened to include patients in their early to mid 60s who have isolated AS without comorbid conditions. In this latter group, the TAVR valve must have at least equivalent clinical durability to currently available surgically implanted valves.

4.3. Current State of the Evidence

4.3.1. Registry Experience

Registry data provide important information for assessing the role of TAVR in a large number of patients who are not eligible for randomized controlled trials because of strict selection criteria. Several multicenter registries, including Edwards Lifesciences and Medtronic CoreValve (Tables 1 and 2), have reported early and late outcomes with TAVR. However, patient selection criteria varied amongst the different registries; standardized definitions for clinical events such as those described by the Valve Academic Research Consortium (VARC) (96) were not used; and endpoints were not prospectively adjudicated using a blinded clinical event committee.

CoreValve system real-world clinical experience to date is comprised of multiple registries from several participating national sites (97,105–110,115). These study sizes range from 61 to 663 patients, with a combined clinical patient experience of nearly 2,350 patients that includes follow-up of up to 2 years. (See Table 2 for details.)

4.3.1.1. DEMOGRAPHICS

Tables 1 and 2 summarize the major patient characteristics for the Sapien and CoreValve family of registries, respectively. The patients selected for entry are elderly (average age typically over 80 years), with symptomatic severe AS (mean gradient ≥ 45 mm Hg), significant comorbidities, and an average EuroSCORE of ≥ 23 (Sapien) and >16 (CoreValve) (97,105–110), indicating a significant risk with conventional AVR. However, unlike the PARTNER trial, all of these registries used the EuroSCORE risk prediction system for defining high risk and inoperability. EuroSCORE is generally not regarded as valid in high-risk patients for surgical AVR, and surgeon input as to operability was not required in these registries. As a result, the

Table 1. Edwards Sapien Transcatheter Heart Valve Registries

Characteristic	REVIVE, REVIVAL, PARTNER EU (N=222)	SOURCE Registry (TF) (N=920)	France Registry (N=1,137)	Belgium Registry (N=303)	Canada Registry (TF) (N=162)
Demographics					
Age (y)	83	82	83	83	83
Female (%)	55	56	49	46	44
EuroSCORE (mean, %)	26	24	23	29	26
NYHA functional class III/IV (%)	89	76	75	80	93
Aortic valve area (cm ²)	0.59	0.70	0.67	0.60	0.63
Mean gradient (mm Hg)	45	49	48	47	48
Prior CABG (%)	26	15	19	20	30
Ejection fraction (%)	51	52	53	50	55
Outcomes					
30-day mortality (%)	10.4	7.5	7.8	8	9.5
1-y mortality (%)	24	18.9	NR	NR	NR
Stroke (%)	3.3	3.5	3.5	5.0	3.0
Major vascular complications (%)	27.9	11.3	11.3	NR	13.1
Permanent pacemaker (%)	1.8	6.7	8.5	4.0	3.6

CABG indicates coronary artery bypass graft; NR, not reported; NYHA, New York Heart Association; and TF, transfemoral. Data are derived from the Edwards Lifesciences briefing document for the U.S. Food and Drug Administration (FDA) Circulatory Devices Advisory Panel meeting on TAVR on July 21, 2011 (<http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/CirculatorySystemDevicesPanel/ucm240575.htm>).

registry results are difficult to interpret because it is unclear whether the patients who were enrolled in these registries were truly “inoperable” versus “high-risk” (110,111).

4.3.1.2. OUTCOMES

4.3.1.2.1. PROCEDURAL SUCCESS AND HAZARDS. In the SOURCE (SAPIEN Aortic Biosprosthesis European Outcome) registry, procedural success rate (defined as 1 valve implanted, AR <2+, and patient left procedure room alive) was 93% for transfemoral TAVR and 92% for transapical TAVR. The procedural success rate reported for CoreValve is >92% except for 1 study that enrolled very high-risk patients (105). Significant variations between registries were

not observed in terms of deployment, relief of obstruction and avoidance of significant AR (110,111).

4.3.1.2.2. EARLY AND LATE MORBIDITY AND MORTALITY. The early and late major outcomes with Sapien and CoreValve registries are summarized in Tables 1 and 2. The early morbidity of TAVR includes strokes, coronary occlusion, pacemaker implantation, vascular complications, renal failure, cardiac rupture and tamponade, bleeding, aortic dissection, and death. The overall risk of any 30-day major complication ranges from 20% to over 40%. Early mortality ranges from an in-hospital rate of 5% to 8% and a 30-day mortality rate from 8% to 10%. In the SOURCE registry, the incidence of a major bleeding

Table 2. Medtronic CoreValve Transcatheter Heart Valve Registries

Characteristic	Tamburino et al. (109) (N=663)	Milan (107) (N=61)	French (106) (N=66)	Spanish (97) (N=108)	UK/Ireland (108) (N=288)	UK (115) (N=452)	German (110) (N=588)	Buellesfeld et al. (105) (N=126)
Demographics								
Age (y)	82	79	82.5	78.6	81	81.3	81.4	81.9
Female (%)	56	47	51.5	54.6	NR	48	55.8	57.1
EuroSCORE (mean, %)	23	26.6	24.7	16	22	18.1	20.8	23.4
NYHA functional class III/IV (%)	71.5	69	74.6	58.4	74	73.9	88.2	74.6
Mean gradient (mm Hg)	52	54	46	55	NR	NR	48.7	46.8
Outcomes								
Procedural success (%)	98	98.4	92.6	98.1	97.5	98.2	NR	72.6
30-day mortality (%)	5.9	2.2	15.1	7.4	4.7	5.8	12.4	15.2
1-y mortality (%)	15	18.4*	NR	17.7	NR	21.7	NR	38.1**
Stroke (%)	2.5	2.2	4.5	0.0	4.2	4.0	2.8	NR
Major vascular complications (%)	2.0	21.3	7.5	5.6	9.0	6.2	4.0	NR
Permanent pacemaker (%)	19.1	26.1	25.7	35.2	26	24.4	42.5	26.2

*6-month survival, **2-year survival. N indicates number; NR, not reported; and NYHA, New York Heart Association.

event was significantly greater among patients undergoing transapical versus transfemoral TAVR (3.9% vs. 2.3%), whereas the incidence of vascular access-related complications was significantly higher among patients having transfemoral TAVR (major—11.3% vs. 2.0%; minor—10.4% vs. 1.0%) (110–114).

Permanent pacemaker placement is reported in between 1.8% up to 8.5% of patients with Sapien and 19.1% to 42.5% with the CoreValve; renal failure in under 3%; and stroke in 1% to 5%. Registry data reflect an overall mortality rate at 1 year of 19% to 24%. In the SOURCE registry, more than half (51.6%) of deaths up to 1 year had a noncardiac etiology and were related to baseline comorbidities (110,111).

The recent UK TAVR Registry included 452 Medtronic CoreValve implantations (115). In this group, standardized data forms were used and audited. Procedural success was achieved in 98.2% in this high-risk group of patients who had a baseline logistic EuroSCORE of 18.1%. Thirty-day mortality was 5.8%, and 1- and 2-year mortality was 21.7% and 23.9%, respectively. In-hospital stroke occurred in 4% of patients and myocardial infarction in 1.1%. A permanent pacemaker was required in 24.4% (compared with 7.4% with Sapien). Rates of moderate to severe postimplant AR were 17.3% (compared with 9.6% with Sapien). Mortality rates at all time points were significantly lower among patients treated via a transfemoral route as compared with nontransfemoral routes (>85% transapical). In this study, LV function, the presence of moderate/severe AR, and COPD, but not vascular access site, were independent predictors of mortality.

4.3.1.2.3. QUALITY OF LIFE IN REGISTRIES. Quality of life is a key patient-centered outcome. Although death is the lowest possible functional status, for many, survival marked by reduced physical function or independence may be worse than death. The PARTNER EU Registry is a multicenter study of the early European experience in TAVR. Patients undergoing TAVR by transapical or transfemoral approach were followed to 12 months for symptoms by New York Heart Association (NYHA) functional class, and heart failure-related quality of life as assessed by the Kansas City Cardiomyopathy Questionnaire (116). All patients improved, with no significant differences in NYHA functional class improvement noted between transapical or transfemoral approaches.

Several single-center registries have added additional information on quality of life using disease-specific or general surveys (Short Form-36 Health Questionnaire, Short Form-12 Health Questionnaire, Kansas City Cardiomyopathy Questionnaire, Minnesota Living with Heart Failure Questionnaire) and on symptoms (NYHA functional class, and 6-minute walk). Improvements following TAVR in vitality, physical functioning, and general and mental health scores have been identified with physical function demonstrating the greatest improvement. Patients who do not experience improvement are more likely to have comorbidities that contribute to continued symptoms and impair quality of life, such as COPD and reduced EF (Table 3).

4.3.1.2.4. LEARNING CURVE. Each registry has identified a procedural learning curve, but the exact definition of this curve and a clear method to decrease it are not yet clearly reported. This curve has important components such as patient selection, anesthesia, improvement in the equipment over time, and technical decision making regarding valve deployment. The SOURCE registry enrolled 1,038 (Cohort 1) and 1,306 patients (Cohort 2) undergoing TAVR procedures over 2 sequential years. Age and EuroSCORE were not significantly different between the 2 cohorts. Compared with the first year of experience, valve malposition (1.6% vs. 1.2%), and vascular access complications (2.1% vs. 1.8%) were not significantly lower in the second year. However, reductions in the rates of postprocedure AR >2+ (4.5% vs. 2.1%, $p=0.011$) and conversion to open surgery (3.7% vs. 1.5%, $p=0.0315$) were improved (110,111,121). Overall 30-day and 1-year survival was similar in both cohorts despite higher number of patients with heart failure and mitral regurgitation enrolled in Cohort 2.

In summary, the registries demonstrate in high-risk patients that TAVR may be deployed with a high degree of procedural success, predictable risk of stroke, device-dependent high risk of pacemaker implantation (particularly with CoreValve), and a 30-day mortality rate that seems potentially acceptable in a debilitated and ill patient population. Importantly, TAVR seems to alleviate AS to a similar degree as surgical AVR and patients tend to return to Class I or II symptoms with substantial improvements in quality of life.

Future registries should be designed to include contemporary (i.e., VARC) definitions of procedural and quality-of-life outcomes and utilize an independent clinical events committee when possible to standardize event reporting. Longer-term follow-up studies are needed to demonstrate the continued durability of TAVR in the high-risk and inoperable patients.

4.3.2. Randomized Controlled Trial

4.3.2.1. PARTNER TRIAL DESIGN

The PARTNER trial (Figure 3) was a prospective, unblinded, randomized, controlled, multicenter pivotal trial evaluating the safety and effectiveness of the Edwards Sapien THV transcatheter aortic valve; 2 distinct populations were enrolled—inoperable, or Cohort B, and high-risk operable, or Cohort A. Potential candidates were presented on a national conference call for approval for treatment. Randomization was stratified based on operability for AVR surgery and within cohorts by vascular access for transfemoral delivery. Patients who were considered high surgical risk and eligible for transfemoral access were stratified into Cohort A and randomized to treatment (transfemoral AVR) or control (surgical AVR). Cohort A patients who were not eligible for transfemoral access were evaluated as candidates for transapical delivery and, if appropriate, randomized to treatment (transapical AVR) or control (surgical AVR). Nonsurgical candidates were stratified into Cohort B

Table 3. Quality of Life and Symptom Assessment in TAVR Registries

Study Population	NYHA Functional Class	6-Minute Walk	Questionnaire	Other
PARTNER EU Registry; Lefevre et al. (Multicenter; N=130 Sapien) (116)	Improved class at 1 year in 84.5% of patients (85% NYHA functional class III/IV at baseline, 15% NYHA functional class at 1 year); changes noted at 30 days were sustained	NR	KCCQ improvement at 1 year in 72.7% (p<0.0002)	Small improvement in EQ-5D was not significant
Buellesfeld et al. (Multicenter; N=126 CoreValve) (105)	Improved in 80% at 30 days; 74% at 2 years (in 50% by 1 level, in 20% by 2 or more levels)	NR	NR	NR
Krane et al. (Single-center registry; N=99 TAVR) (117)	More class I/II at 3 months (NYHA functional class III/IV from 98% to 2% at 3 months)	NR	Improved SF-36 PF general health and vitality pre/post at 3 months (all p<0.01). No change mental health.	85% would do TAVR again
Ussia et al. (Single-center registry; N=57 TAVR) (118)	More class I/II (average 1.8 NYHA functional class improvement) at 5 months (p<0.001)	NR	SF-12; Improved (p<0.001) physical and mental component scores, return to population norms, greatest change in PF	NR
Bekeredjian et al. (Single-center registry; N=87 TAVR) (119)	Improved class (average of 1.7 NYHA functional class improvement) at 6 months (p<0.001)	NR	SF-36 Improved physical and mental component scores, greatest change in PF	70% average decrease in NT-proBNP levels of 4,000 ng/L (p<0.0001)
Gotzmann et al. (Single-center registry; N=44 TAVR) (120)	Decrease of percentage of NYHA functional class III/IV from 90% to 1.6% at 30 days	Improved walk time at 30 days	MLHFQ; Improved HF-related QOL	Lower average decrease in BNP levels of 400 pg/mL (p<0.005) and 25% increase in 6-minute walk time (p<0.005)

BNP indicates brain natriuretic peptide; EQ-5D, EuroQol Five Dimensions; HF, heart failure; KCCQ indicates Kansas City Cardiomyopathy Questionnaire; LOS, length of stay; MLHFQ, Minnesota Living with Heart Failure Questionnaire; NR, not reported; NYHA, New York Heart Association; PF, physical function; QOL, quality of life; SAVR, surgical aortic valve replacement; SF-12, Short Form 12 Health Questionnaire; SF-36, Short Form 36 Health Questionnaire; and TAVR, transcatheter aortic valve replacement.

and randomized to treatment (transfemoral AVR) or control (“standard” therapy). Inoperability was formally defined as “>50% predicted probability of mortality or serious irreversible complication by 30 days by 1 cardiologist and 2 cardiothoracic surgeons” (15). Cohort B patients who did not meet the criteria for transfemoral delivery were not enrolled in the study because transapical delivery was deemed too risky in Cohort B (Figure 3). Of the 3,105 patients screened, a total of 1,057 subjects (34%) were enrolled at 25 sites in 2 arms—699 patients in Cohort A and 358 patients in Cohort B. There were 2 co-primary endpoints for the inoperable cohort: 1) freedom from death over the duration of the trial with all patients followed for at least 1 year from randomization; and 2) hierarchical composite of death and recurrent hospitalization. In the high-risk cohort, the primary endpoint was freedom from all-cause death at 1 year. Prespecified secondary endpoints included rate of death from cardiovascular causes, NYHA functional class, the rate of repeat hospitalization due to valve-related or procedural-related clinical deterioration, the distance covered during a 6-minute walk test, valve performance (assessed by echocardiography), and the rates of myocardial infarction, stroke, acute kidney injury, vascular complications, and bleeding. All patients were followed

during the index hospitalization; at 30 days, 6 months, and 1 year; and yearly thereafter.

4.3.2.2. DEMOGRAPHICS AND OTHER BASELINE CHARACTERISTICS

The mean age was about 83 years in Cohort B and 84 in Cohort A; slightly more patients were female (53.6%) in Cohort B, and slightly more patients were male (57.2%) in Cohort A; and most were Caucasian (Table 4). Over 92% in both cohorts were NYHA functional class III or IV, and 60% of patients in both cohorts had undergone prior CABG or PCI. Overall, the groups were balanced in most baseline characteristics in Cohort A; however, there were some imbalances in Cohort B (15). Patients in both cohorts had relatively preserved LV systolic function.

Patients in Cohort B had greater frequency of coexisting conditions that contributed to the surgeons’ determination of inoperability, including an extensively calcified (porcelain) aorta (15.1%), chest-wall deformity or prior chest-wall irradiation (13.1%), oxygen-dependent respiratory insufficiency (23.5%), and frailty, according to prespecified criteria (23.1%).

4.3.2.3. PARTNER TRIAL RESULTS

In the inoperable Cohort B patients with symptomatic severe AS, TAVR substantially reduced all-cause mortality

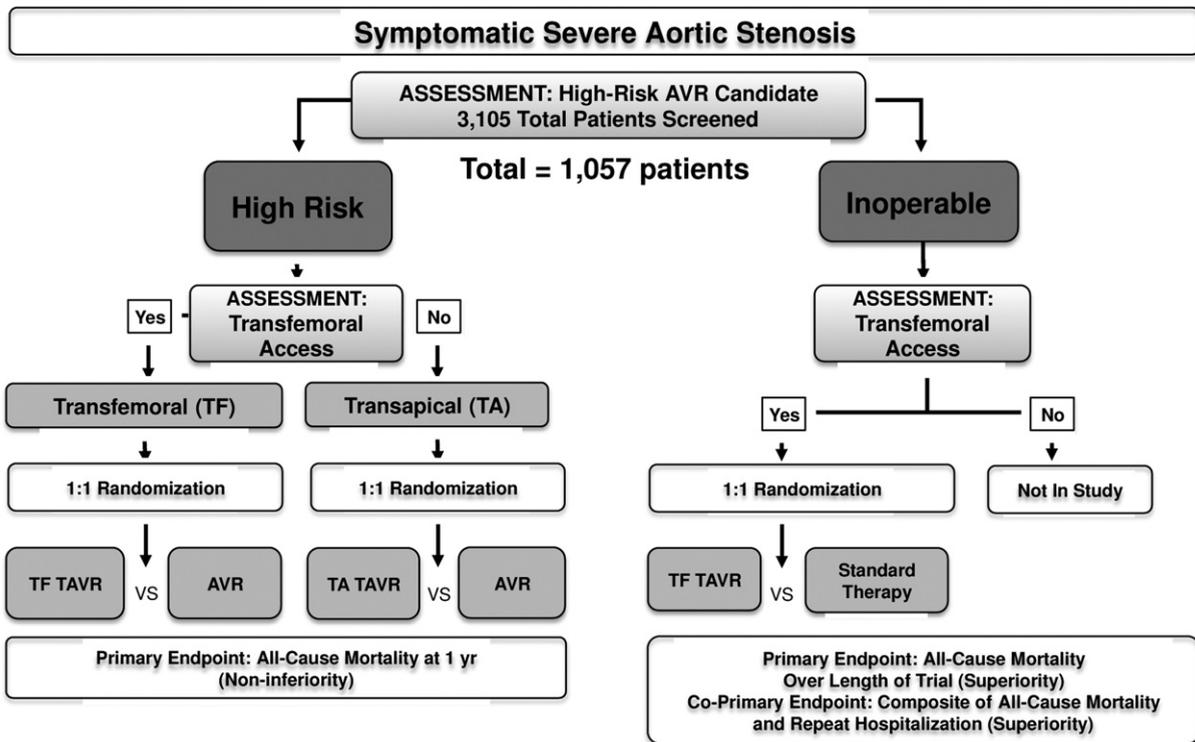


Figure 3. PARTNER Trial Design

by nearly 50% and the composite of all-cause mortality and repeat hospitalization by 55% compared with standard therapy at 1-year follow-up (Table 5). In addition, all key secondary endpoints including patient function significantly improved at 30 days and 1 year. TAVR was associated with an increased risk for stroke and procedure-related adverse events such as bleeding and vascular complications. Sensitivity analyses of patients as they were treated all favored TAVR. Overall, the benefit from TAVR in inoperable patients with symptomatic severe AS greatly exceeds the risk.

In the high-risk Cohort A patients, TAVR was noninferior to AVR for all-cause mortality at 1 year (24.2% vs. 26.8%, hazard ratio: 0.93, 95% confidence interval: 0.71 to 1.22, $p=0.001$ for noninferiority) (Table 6). AVR mortality at 30 days (6.5%) was lower than expected operative mortality (11.8%). Whether this discrepancy can be attributed to chance alone (ideal outcomes with expert surgeons within the idealized environment of a randomized trial) or due to “calibration drift” as surgical outcomes improve over time is not clear. All neurological events (30-day major stroke, 3.8% vs. 2.1%) and vascular complications (30-day, 11.1% vs. 3.2%) were more frequent with TAVR. By contrast, major bleeding and new-onset atrial fibrillation were more frequent with AVR. Improvements in echocardiographic findings were similar in both groups, although paravalvular regurgitation was increased with TAVR. The data from this cohort further support TAVR as an accept-

able alternative to surgical AVR in selected high-risk operable patients.

Of note, the 30-day mortality (generally thought to be procedure-related) in Cohort A (3.4%) and Cohort B (5.0%) was lower than the published SOURCE registry mortality (8.5%), despite a relatively lower-risk patient population enrolled in the latter (1-year mortality of 30.7% in Cohort B, 22.2% in Cohort A, and 18.9% in SOURCE). This arguably raises questions about the generalizability of the randomized trial data to clinical practice.

4.3.2.3.1. QUALITY OF LIFE. The quality-of-life results from Cohort B arm, the inoperable cohort, TAVR patients had improvement in the 6-minute walk performance compared with baseline ($p=0.002$), whereas standard therapy patients did not ($p=0.67$) (15). In addition, TAVR patients were less symptomatic (New York Heart Association class), had reduced hospitalization stay, and improved physical functioning compared with standard therapy. In the high-risk cohort, both New York Heart Association class and 6-minute walk test favored TAVR at 30 days, but the differences were not significant at 1 year. TAVR patients had shorter index hospitalization length of stay (8 vs. 12 days, $p<0.001$). Quality of life as assessed by disease-specific measures (Kansas City Cardiomyopathy Questionnaire [KCCQ]) and by general health-related quality of life (Short Form-12 Health Questionnaire) improved at 1, 6, and 12 months in the TAVR group and were significantly higher than in the control arm ($p<0.001$). This supports

Table 4. Demographic and Other Baseline Characteristics of the PARTNER Trial (Cohort B Data First)

Characteristic	Cohort B			Cohort A		
	TAVR (N=179)	Standard Rx (N=179)	p Value	TAVR (N=348)	AVR (N=351)	p Value
Demographics						
Age (y)	83.1 ± 8.6	83.2 ± 8.3	0.95	83.6 ± 6.8	84.5 ± 6.4	0.07
Male (%)	45.8	46.9	0.92	57.8	56.7	0.82
STS score	11.2 ± 5.8	11.9 ± 4.8	0.21	11.8 ± 3.3	11.7 ± 3.5	0.61
Logistic EuroSCORE	26.4 ± 17.2	30.4 ± 19.1	0.04	29.3 ± 16.5	29.2 ± 15.6	0.93
NYHA functional class III or IV (%)	92.2	93.9	0.68	94.3	94.0	0.79
O ₂ -dependent COPD (%)	21.2	25.7	0.38	9.2	7.1	0.34
Frailty (%)	18.1	28	0.09	15.6	17.6	0.58
Porcelain aorta (%)	19	11.2	0.05	0.6	1.1	0.69
Chest wall radiation (%)	8.9	8.4	1.00	0.9	0.9	1.00
Chest wall deformity (%)	8.4	5.0	0.29	0	0.3	1.00
Echocardiographic Characteristics						
AV area (cm ²)	0.6 ± 0.2	0.6 ± 0.2	0.97	0.7 ± 0.2	0.6 ± 0.2	0.13
Mean AV gradient (mm Hg)	44.5 ± 15.7	43.0 ± 15.3	0.39	42.7 ± 14.6	43.5 ± 14.3	0.45
Mean LV EF (%)	53.9 ± 13.1	51.1 ± 14.3	0.06	52.5 ± 13.5	53.3 ± 12.8	0.45

Cohort B includes only nonsurgical candidates in whom “inoperability” was formally defined as greater than 50% predicted probability of mortality or serious irreversible complication by 30 days by 1 cardiologist and 2 cardiothoracic surgeons.

Cohort A includes patients determined to be at high operative risk defined as predicted operative mortality of ≥15% and/or an STS risk score of ≤10%. The STS risk algorithm is based on the presence of coexisting illnesses in order to predict 30-day operative mortality.

AV indicates aortic valve; AVR, aortic valve replacement; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; Rx, therapy; STS, Society of Thoracic Surgeons; and TAVR, transcatheter aortic valve replacement.

Data are derived from the Edwards Lifesciences’ briefing document for the U.S. FDA Circulatory Devices Advisory Panel meeting on TAVR on July 21, 2011 (http://www.accessdata.fda.gov/cdrh_docs/pdf10/P100041b.pdf) and may show some discrepancies compared with the published manuscripts.

that general and disease-specific quality of life are improved with TAVR to 1 year over standard care among inoperable patients (122) (Table 7). The quality of life results from the Cohort A arm of the PARTNER trial were presented in November 2011. The preliminary conclusions were that among patients with severe AS who were at high risk for standard valve replacement, both surgical and transcatheter AVR resulted in substantial improvement in disease-specific

and generic health-related quality-of-life assessment over 1-year follow-up, including KCCQ Summary Scale, SF-12 Physical, and SF-12 Mental tests. The benefits were greater at earlier time points in the transfemoral TAVR group and were equivalent at 1 year (123).

4.3.2.3.2. CONTINUED-ACCESS PROTOCOL. Upon completion of the randomized PARTNER trial, patients have been allowed to have access to TAVR under a continued-access

Table 5. Major Outcomes at 30 Days and 1 Year in Cohort B of the PARTNER Trial

Characteristic	30 Days			1 Year		
	TAVR (N=179)	Standard Rx (N=179)	p Value	TAVR (N=179)	Standard Rx (N=179)	p Value
All-cause death (%)	5.0	2.8	0.41	30.7	49.7	<0.001
All-cause death or rehospitalization (%)	11.2	12.3	0.74	43.6	70.4	<0.001
Event-free MACCE (%)	90.5	94.4	NR	65.4	47.1	0.003
All stroke (%)	7.3	1.7	0.02	11.2	4.5	0.03
Major stroke (%)	5.6	1.1	0.04	8.4	3.9	0.12
All-cause death or major stroke (%)*	8.4	3.9	0.12	33.0	50.3	0.001
Major vascular complications (%)	16.8	1.1	<0.0001	17.3	2.2	<0.0001
Major bleeding (%)	20.6	3.9	<0.0001	28.4	14.4	<0.001
Pacemaker insertion (%)	3.4	5.0	0.60	4.5	7.8	0.27
Echocardiographic Endpoints						
AV area (EOA) (cm ²)	1.5 ± 0.4	0.8 ± 0.2	<0.0001	1.6 ± 0.5	0.7 ± 0.32	<0.0001
Mean AV gradient (mm Hg)	11.1 ± 6.6	33.0 ± 12.5	<0.0001	12.5 ± 10.3	44.4 ± 15.7	<0.0001

Cohort B includes only nonsurgical candidates in whom “inoperability” was formally defined as greater than 50% predicted probability of mortality or serious irreversible complication by 30 days by 1 cardiologist and 2 cardiothoracic surgeons.

*All-cause death or major stroke was not a predefined endpoint.

AV indicates aortic valve; EOA, effective orifice area; MACCE, major adverse cardiac and cerebrovascular events; NR, not reported; Rx, therapy; and TAVR, transcatheter aortic valve replacement.

Data are based on Edwards Lifesciences’ briefing document for the U.S. FDA Circulatory Devices Advisory Panel meeting on TAVR on July 21, 2011 (http://www.accessdata.fda.gov/cdrh_docs/pdf10/P100041b.pdf), and may show some discrepancies compared with the published manuscripts.

Table 6. Major Outcomes at 30 Days and 1 Year in Cohort A of the PARTNER Trial

Characteristic	30 Days			1 Year		
	TAVR (N=348)	Surgical AVR (N=351)	p Value	TAVR (N=348)	Surgical AVR (N=351)	p Value
Clinical Outcomes						
All-cause death (%)	3.4	6.5	0.07	24.2	26.8	0.44
All-cause death or rehospitalization (%)	7.2	9.7	0.24	34.6	35.9	0.73
All stroke (%)	5.5	2.4	0.04	8.3	4.3	0.04
Major stroke (%)	3.8	2.1	0.20	5.1	2.4	0.07
All-cause death or major stroke (%)*	6.9	8.2	0.52	26.5	28.0	0.68
Major vascular complications (%)	17.0	3.8	<0.01	18.0	4.8	<0.01
Major bleeding (%)	9.3	19.5	<0.01	14.7	25.7	<0.01
Atrial fibrillation (%)	8.6	16.0	<0.01	12.1	17.1	0.07
Pacemaker insertion (%)	3.8	3.6	0.89	5.7	5.0	0.68
Echocardiographic Endpoints						
AV area (EOA) (cm ²)	1.7 ± 0.5	1.5 ± 0.4	0.001	1.6 ± 0.5	1.4 ± 0.5	0.002
Mean AV gradient (mm Hg)	9.9 ± 4.8	10.8 ± 5.0	0.16	10.2 ± 4.3	11.5 ± 5.4	0.008

Cohort A includes patients determined to be at high operative risk defined as predicted operative mortality of ≥15% and/or an STS risk score of ≥10%. The STS risk algorithm is based on the presence of coexisting illnesses in order to predict 30-day operative mortality.

*All-cause death or major stroke was not a predefined endpoint.

AV indicates aortic valve; AVR, aortic valve replacement; EOA, effective orifice area; and TAVR, transcatheter aortic valve replacement.

protocol. Enrollment in the randomized continued-access cohort was initiated following completion of the enrollment for PARTNER cohort B trial. From March to September 2009, 91 inoperable patients were enrolled—41 were randomized to TAVR and 50 to standard care. Both short-term (30 days) and long-term (6 months to 1 year) results have been reported (<http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/CirculatorySystemDevicesPanel/UCM262935.pdf>). However, between-group analyses were not conducted due to the small sample size. Enrollment in nonrandomized continued-access cohort was initiated in September 2009 after both cohorts of PARTNER had completed randomized enrollment. Over 600 patients with transfemoral TAVR are being followed currently in this cohort.

4.3.2.4. TAVR-SPECIFIC CLINICAL ISSUES

4.3.2.4.1. STROKE. Stroke is one of the major adverse events associated with TAVR. Standardized criteria for the defi-

nition of stroke endpoints for TAVR clinical trials have been published by the VARC (Table 8). The incidence of stroke depends on the assessment technique used for ascertainment. In the PARTNER Cohort A, the risk of clinically apparent “major” stroke defined as modified Rankin score ≥2 was 3.8% at 30 days and 5.1% at 1 year among the TAVR group compared with 2.1% and 2.4%, respectively, in the surgical group (124). In the PARTNER Cohort B, the stroke risk was 5% with TAVR compared with 1.1% with standard therapy at 30 days and 8.4% versus 3.9% at 1 year (15). Using magnetic resonance imaging-diffusion weighted imaging (MRI-DWI) studies, the incidence of cerebral ischemic lesions post-TAVR has been reported to be as high as 68% to 84% in some studies, although clinically apparent stroke was reported in >4% of cases (125–128). Thus, the clinical significance of these new CMR-defined lesions post-TAVR is not clear.

Most stroke cases are due to thromboembolism from the valve site or due to atherothrombotic emboli originating

Table 7. Quality of Life and Symptom Assessment in TAVR Trials

Study Population	NYHA Functional Class	6-Minute Walk	Questionnaire	Other
PARTNER B (Trial) TAVR vs. placebo (multicenter; N=358) (15,122)	More class I, II with TAVR at 1 year (74.8% vs. 42.0%)	TAVR improved walk time pre/post at 1 year; no change in no-TAVR group	KCCQ; Marked improvement with TAVR at 1 year; SF12; improvement in physical and mental HRQOL with TAVR	TAVR had fewer rehospitalizations at 1 year
PARTNER A (Trial) TAVR vs. SAVR (multicenter; N=699) (124)	More class I, II with TAVR at 30 days; No difference between TAVR and SAVR at 1 year	TAVR improved walk time at 30 days compared with SAVR; No difference between TAVR and SAVR at 1 year	NR	Shorter LOS with TAVR

HRQOL indicates health-related quality of life; KCCQ indicates Kansas City Cardiomyopathy Questionnaire; LOS, length of stay; NR, not reported; QOL, quality of life; SAVR, surgical aortic valve replacement; and TAVR, transcatheter aortic valve replacement.

Table 8. Stroke

Stroke Diagnostic Criteria

Rapid onset of a focal or global neurological deficit with at least 1 of the following: change in level of consciousness, hemiplegia, hemiparesis, numbness or sensory loss affecting 1 side of the body, dysphasia or aphasia, hemianopia, amaurosis fugax, or other neurological signs or symptoms consistent with stroke

Duration of a focal or global neurological deficit ≥ 24 h; **OR** < 24 h, if therapeutic intervention(s) were performed (e.g., thrombolytic therapy or intracranial angioplasty); **OR** available neuroimaging documents a new hemorrhage or infarct; **OR** the neurological deficit results in death

No other readily identifiable nonstroke cause for the clinical presentation (e.g., brain tumor, trauma, infection, hypoglycemia, peripheral lesion, pharmacological influences)*

Confirmation of the diagnosis by at least 1 of the following:

Neurology or neurosurgical specialist

Neuroimaging procedure (MR or CT scan or cerebral angiography)

Lumbar puncture (i.e., spinal fluid analysis diagnostic or intracranial hemorrhage)

Stroke Definitions

Transient ischemic attack:

New focal neurological deficit with rapid symptom resolution (usually 1 to 2 h), always within 24 h

Neuroimaging without tissue injury

Stroke: (diagnosis as above, preferably with positive neuroimaging study)

Minor—Modified Rankin score < 2 at 30 and 90 days†

Major—Modified Rankin score ≥ 2 at 30 and 90 days

*Patients with nonfocal global encephalopathy will not be reported as a stroke without unequivocal evidence based upon neuroimaging studies.

†Modified Rankin score assessments should be made by qualified individuals according to a certification process. If there is discordance between the 30- and 90-day Modified Rankin scores, a final determination of major versus minor stroke will be adjudicated by the neurology members of the clinical events committee.

CT indicates computed tomography; and MR, magnetic resonance.
Reprinted with permission from Leon et al. (96).

from ulcerative plaque in the great vessels such as the aortic arch. Such particles can be dislodged during catheter manipulation and embolize to the carotids or vertebrals to cause occlusions of distal intracerebral branch arteries. Other potential causes include hypotension associated with rapid ventricular pacing or hemodynamic instability during the procedure, and rarely due to aortic dissection complicating TAVR. It is important to recognize that many patients who have AS may also have other causes for an ischemic stroke such as age, hypertension, diabetes, or other cardiac conditions, including atrial fibrillation, which is a potent risk factor for cardioembolic stroke (69). Differentiating the cause of the stroke is not always easy, but most trials and registries define strokes within 30 days of an interventional procedure as attributable to the procedure. After 30 days, other comorbid risk factors may account for stroke, which might, therefore, not be attributable to the prosthetic valve. Diagnostic evaluations are needed to assess the neck and cerebral vessels, cardiac function, and other potential causes of stroke in order to differentiate the stroke subtype and embark on the best treatment to prevent a recurrent stroke (129,130). Nearly two thirds of the strokes related to TAVR at 1 year occurred within the first 30 days in PARTNER Cohort B (13/20), suggesting that most events were likely procedure-related (15). The incidence of stroke may lessen as patient selection becomes more refined, delivery systems improve in their profile, and embolic protection devices and protocol-driven antithrombotic regimens are routinely used during TAVR.

4.3.2.4.2. CONDUCTION DEFECTS. Atrioventricular conduction disturbances after TAVR are associated with many patient-related and procedural-related factors, including preoperative comorbid status, the degree and bulkiness of aortic valve and annular calcification, interventricular septal thickness, pre-existing electrocardiogram abnormalities, the depth of prosthesis implantation, and the profile of the implanted prosthesis (131,132). Unlike conventional AVR, where there may be localized trauma due to decalcification of the annulus and/or suture placement in the proximity of the AV node or the bundles, TAVR may cause conduction abnormalities through mechanical impingement of the conduction system by the prosthesis.

The incidence of new left bundle-branch block and complete heart block after TAVR ranges from 14% to 83% and 19% to 22%, respectively. Patients with pre-existing right bundle-branch block may be at the highest risk for the development of complete heart block and the need for subsequent pacing (133). The majority of conduction abnormalities occur prior to actual valve implantation, with 46% occurring during balloon aortic valvuloplasty, 25% during balloon/prosthesis positioning and wire-crossing of the aortic valve, and the remaining 29% during prosthesis expansion (134). The incidence of complete heart block requiring permanent pacemaker implantation has been higher with the CoreValve (19.2% to 42.5%) than with the Sapien valve (1.8% to 8.5%), potentially due to its larger profile and extension low into the LV outflow tract. In the most recent UK Registry, pacemakers were implanted in 24.4% of patients receiving the CoreValve.

Overall, permanent pacemaker implantation rates with the CoreValve, but not Sapien valve, are higher than conventional surgical AVR rates of 1% to 10%. The need for permanent pacemaker implantation occurs early postprocedure and rarely after hospital discharge. The need for permanent pacemaker implantation has no effect on survival, both early at 30 days postprocedure and late at 1 year (135). Continuous postoperative electrocardiogram monitoring should be performed in all patients early after TAVR procedures. Patients with pre-existing or new conduction abnormalities and those receiving the CoreValve device may require longer monitoring.

4.3.2.4.3. VASCULAR COMPLICATIONS. Vascular complications are the most frequent adverse outcome of TAVR and are especially common with transfemoral approach (136). These complications relate to the large-caliber sheaths necessary for device deployment, as well as severe atherosclerosis of the arteries, which is common (137). Center/operator experience, the degree and location of vascular calcification, vascular tortuosity, and sheath-to artery ratio are predictors of major vascular complication (137,138). Major vascular complications are classified in accordance with the definitions provided by the VARC and include aortic dissection, perforation, rupture, or bleeding requiring significant blood transfusions, or additional percutaneous or surgical intervention (96). Incidence of major vascular complications ranges from 2% to 26% with transfemoral access and is related to vessel size, tortuosity, and degree of aortoiliac occlusive disease and from 5% to 7% with transapical access (107,109,111,116,139).

Subclavian access may represent an alternative approach in some patients in whom transfemoral or transapical direct aortic access cannot be utilized. Subclavian artery injury is rare with such access although transient brachial plexus neuropathy has been reported with this approach (140). As delivery systems improve in their profile, the incidence of these complications will lessen (136,141). Of note, left subclavian arterial access for TAVR may not be appropriate in patients with prior CABG with left internal thoracic arterial graft because temporary interruption of blood flow in the left internal thoracic artery may cause coronary insufficiency.

4.3.2.4.4. PATIENT PREFERENCES. Informed consent requires the patient and/or support system be appropriately informed of the procedure benefits and risks, possess personal decision-making capacity, and ultimately be able to make a voluntary decision. Older adults often rely on trusted physicians, family, or friends to participate and guide medical decision making at the point of medical care. A central goal in this interaction is the exchange of relevant, detailed information about treatment strategies delivered in terminology that is understood by the patient and family. This patient-centric educational effort is essential in providing the patient and family information to facilitate interaction with the healthcare team, and promote personalized decision making for each patient. It is important to remem-

ber that risk tolerance and patient expectations vary across many patient populations. Thus, a thorough review of personalized risk/benefit profile is essential for each patient undergoing an invasive procedure.

4.3.2.4.5. BENEFIT/RISK ASSESSMENT. The complex task of balancing the benefit and risk of TAVR depends upon accurate information regarding prognosis for survival, morbidity, and expected quality of life. Ideally, an accurate validated model that predicts both in-hospital and long-term outcome should guide this analysis, help educate patients and their families, and effectively manage safety tradeoffs and healthcare expenditure. Such a model would include some assessment of the relative role of severe AS versus comorbidity (e.g., COPD in the etiology of symptoms such as dyspnea). Although several risk models have been developed for prognostication after cardiac surgery, they are limited by modest performance with regards to discriminatory ability, calibration, and face validity. It is not clear whether these models for conventional cardiac surgery are similarly predictive of outcome of patients being considered for TAVR. An additional important issue relates to the lack of a formal assessment of other aspects of treatment risk and benefit (e.g., gait, cognition, frailty) in these risk models. Thus, better performing risk models are needed that include a wide spectrum of prognostic variables using contemporary data in relevant populations for a TAVR-specific risk algorithm.

In TAVR candidates, the benefits of avoidance of sternotomy and cardiopulmonary bypass with its attendant complications and prolonged recovery/hospitalization by applying TAVR appear to come at the price of potentially serious vascular and technical complications and increased hazards of stroke and paravalvular AR (Figure 4). For prohibitively high-risk inoperable patients, such a tradeoff is

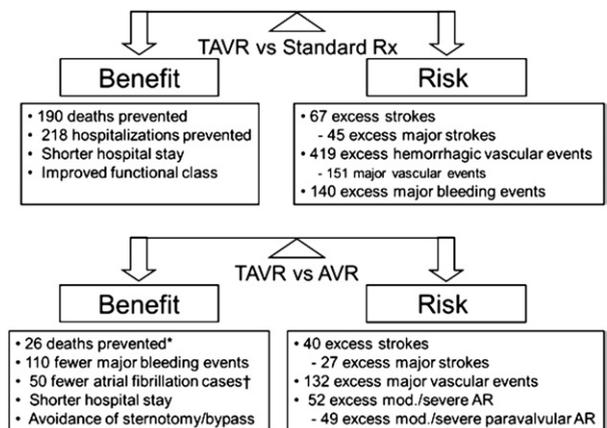


Figure 4. Benefit/Risk Balance in the PARTNER Trial

Data are shown for every 1,000 patients treated with TAVR instead of standard treatment in Cohort B (above) or standard AVR in Cohort A (below). The excesses listed are not mutually exclusive, because some patients had more than 1 event. Only data with statistically significant differences at 1 year of follow-up are shown except for deaths* (p=0.44) and atrial fibrillation† (p=0.07) in Cohort A. AR indicates aortic valvular regurgitation; AVR, surgical aortic valve replacement; and TAVR, transcatheter aortic valve replacement.

acceptable given the documented statistically-significant and clinically-important mortality benefit and functional improvement. For high surgical risk patients in whom mortality benefit has not been proven, the findings present a dilemma, given that the irreversible effects of stroke might be of greater potential clinical significance in terms of long-term disability, permanent dependency, and increased societal costs than the complications of sternotomy and bleeding. Although bleeding occurs acutely, is often overt, and has immediate clinical impact leading to increased length of stay and resource utilization, a “causal link” to adverse long-term clinical outcome remains unproven. Ultimately, the relative weights both patients and physicians assign to the utility associated with these periprocedural hazards is likely to impact individual case-based benefit/risk assessment and decision making. Cost considerations are also likely to materially impact the adoption of TAVR in treatment algorithms for AS.

4.3.2.5. MEDTRONIC COREVALVE U.S. PIVOTAL TRIAL

The U.S. pivotal trial with the Medtronic CoreValve self-expanding valve is currently enrolling patients at 40 sites (NCT # 01240902). Patients are allocated into either an Extreme Risk cohort, similar to Cohort B inoperable patients in the PARTNER trial or a High Risk cohort analogous to PARTNER Cohort A. There will be 487 patients enrolled in the extreme-risk group with an additional 100 patients with inadequate iliofemoral access placed in a nested registry of alternative access with either subclavian or direct aortic approaches. The High Risk cohort will enroll 790 patients in a 1:1 randomization between TAVR and surgical AVR.

5. Integration of TAVR Into Clinical Practice

5.1. Patient Evaluation and Management

5.1.1. Multidisciplinary Team

The creation of a multidisciplinary team that includes the patient in the decision process in choosing the most appropriate form of treatment for AS including AVR (i.e., surgical or percutaneous) is essential. It is similar in concept to the “heart team” approach for CAD (142). Factors such as sex, race, availability, experience, and institutional commitment to managing very high-risk patients, technical skills, local results, referral patterns, and patient preference all may have an impact on the decision-making process and should be taken into account by this multidisciplinary team. Ideally, such a team would be comprised of the patient’s primary cardiologist, cardiac surgeon, interventional cardiologist, echocardiographer, imaging specialists—CT or CMR, heart failure and valve disease specialist, cardiac anesthesiologist, nurse practitioner, and cardiac rehabilitation specialists. Such a strategy would result in input from multiple skill sets with the goal being the best possible

course of therapy leading to the best possible clinical outcome for the specific patient.

Localization of a heart team working together in a valve clinic will help optimize the functions of the valve team. Such a clinic should combine clinical cardiac care, advanced imaging capability, and surgical consultation to provide centralized assessment and treatment options for complex valve disorders. Patients referred to a valve clinic should be assessed by a cardiologist and a cardiovascular surgeon to discuss the options for surgical intervention if indicated. Prior diagnostic studies should be reviewed and additional diagnostic imaging (echocardiography, TEE, MDCT [multidetector computed tomography], CMR) performed as clinically indicated. Overall, a valve clinic should offer patients a personalized approach for the evaluation and treatment of complex valve disorders with the availability of a cardiologist and a cardiac surgeon specializing in valve disorders.

5.1.2. Patient Selection

5.1.2.1. INCLUSION/EXCLUSION CRITERIA

TAVR is appropriate currently only for a highly select population and the valve team should systematically identify the characteristics that define that population with most benefit and acceptable risk. These identification criteria should be operationalized into practice and may evolve over time with this new technology as new data become available.

The inclusion and exclusion criteria in extant randomized studies are generally appropriate for use in clinical practice (Table 9). These vary somewhat, but there are some criteria common to most studies. Some criteria can be precisely identified with objective measurements, but many require subjective estimates based on clinical judgment. These subjective assessments are at least as important as the objective determinations and necessarily create some variability in the process of patient selection. The criteria presented here are based on current technology and experience. As technology improves and experience is gained, it is likely that many of these criteria will change to expand TAVR to different populations that will be optimally treated with the next generation of devices. In addition, the arbitrary criteria such as qualifying aortic AVA measurement within 45 days within the procedure will be modified and made more flexible.

5.1.2.2. SPECIFIC PATIENT SUBSETS

5.1.2.2.1. PORCELAIN AORTA, FRIABLE AORTIC ATHEROMA, RADIATION HEART DISEASE. Occasionally, otherwise fairly healthy candidates for AVR will have local factors such as prior radiation therapy to their mediastinum and/or severe calcific changes within their ascending aorta (“porcelain aorta”) that add significant risk to a traditional open AVR. Rarely, transesophageal echocardiography will reveal advanced atherosclerosis with mobile and pedunculated atheromata that also increase risk for stroke or a major embolic event with traditional TAVR. Cases such as these are

Table 9. Patient Selection: Inclusion and Exclusion Criteria in Clinical Trials

Inclusion Criteria

1. Patient has calcific aortic valve stenosis with echocardiographically derived criteria: mean gradient >40 mm Hg or jet velocity >4.0 m/s *and* an initial AVA of <0.8 cm² or indexed EOA <0.5 cm²/m². Qualifying AVA baseline measurement must be within 45 days of the date of the procedure.
2. A cardiac interventionalist and 2 experienced cardiothoracic surgeons agree that medical factors either preclude operation or are high risk for surgical AVR, based on a conclusion that the probability of death or serious, irreversible morbidity exceeds the probability of meaningful improvement. The surgeons' consult notes shall specify the medical or anatomic factors leading to that conclusion and include a printout of the calculation of the STS score to additionally identify the risks in the patient. At least 1 of the cardiac surgeon assessors must have physically evaluated the patient.
3. Patient is deemed to be symptomatic from his/her aortic valve stenosis, as differentiated from symptoms related to comorbid conditions, and as demonstrated by NYHA functional class II or greater.

Exclusion Criteria (candidates will be excluded if any of the following conditions are present)

1. Evidence of an acute myocardial infarction ≤1 month (30 days) before the intended treatment (defined as: Q-wave MI, or non-Q-wave MI with total CK elevation of CK-MB ≥ twice normal in the presence of MB elevation and/or troponin level elevation [WHO definition])
2. Aortic valve is a congenital unicuspid or congenital bicuspid valve, or is noncalcified
3. Mixed aortic valve disease (aortic stenosis and aortic regurgitation with predominant aortic regurgitation >3+)
4. Hemodynamic or respiratory instability requiring inotropic support, mechanical ventilation, or mechanical heart assistance within 30 days of screening evaluation
5. Need for emergency surgery for any reason
6. Hypertrophic cardiomyopathy with or without obstruction
7. Severe left ventricular dysfunction with LVEF <20%
8. Severe pulmonary hypertension and RV dysfunction
9. Echocardiographic evidence of intracardiac mass, thrombus or vegetation
10. A known contraindication or hypersensitivity to all anticoagulation regimens, or inability to be anticoagulated for the study procedure
11. Native aortic annulus size <18 mm or >25 mm as measured by echocardiogram*
12. MRI confirmed CVA or TIA within 6 months (180 days) of the procedure
13. Renal insufficiency (creatinine >3.0 mg/dL) and/or end-stage renal disease requiring chronic dialysis at the time of screening
14. Estimated life expectancy <12 months (365 days) due to noncardiac comorbid conditions
15. Severe incapacitating dementia
16. Significant aortic disease, including abdominal aortic or thoracic aneurysm defined as maximal luminal diameter 5 cm or greater; marked tortuosity (hyperacute bend), aortic arch atheroma [especially if thick (>5 mm), protruding or ulcerated] or narrowing (especially with calcification and surface irregularities) of the abdominal or thoracic aorta, severe "unfolding" and tortuosity of the thoracic aorta
17. Severe mitral regurgitation

*The boundaries of annulus size will continue to change in concert with changing device size.

AVA indicates aortic valve area; AVR, aortic valve replacement; CK, creatine kinase; CVA, cerebrovascular accident; EOA, effective orifice area; LVEF, left ventricular ejection fraction; MB, MB isoenzyme; MI, myocardial infarction; MRI, magnetic resonance imaging; NYHA, New York Heart Association; RV, right ventricular; STS, Society of Thoracic Surgeons; TIA, transient ischemic attack; and WHO, World Health Organization.

approached individually and the correct approach is at best an educated judgment on the part of the surgical team. TAVR offers an alternative for the treatment of AS when there is severe circumferential calcification (porcelain aorta) or heavy atherosclerotic disease burden in the ascending aorta (143). Patients with extensive atherothrombotic burden involving the ascending aorta should be approached very carefully irrespective of whether either a transapical or transfemoral procedure because of the potential for embolization.

5.1.2.2.2. VERY ELDERLY. Advanced age has important implications, as typically these patients have several comorbid conditions (in addition to advanced age) that increase the risk of AVR or TAVR. Functional status and comprehensive assessment of comorbidities including CAD, history of transient ischemic attack or stroke, chronic kidney disease, and dementia should be performed. Finally, risk and benefit, including prognosis of existing conditions, should be thoroughly discussed with the patient and family as part of the initial meeting with the TAVR team and should include a

review of postprocedural complications that may extend hospitalization. On the other hand, successful procedures result in improvement in dyspnea, a heightened energy level, and an overall improved quality of life. Life expectancy can be prolonged, since the mortality of medically-treated symptomatic severe AS carries a high mortality.

As noted above, symptoms usually improve following valve replacement, but a caveat exists for elderly patients regarding dyspnea and the presence of LVH. LVH is seen in 54% of men and 81% of women with severe AS (144–147) whereas men more often have less LVH, some LV chamber enlargement, and some reduction in EF. Occasionally women will have such severe diastolic dysfunction that even when the afterload stress is relieved by TAVR, elevated LV filling pressures may result in persistent symptoms of shortness of breath. Since LVH may eventually regress following TAVR, shortness of breath may also eventually improve over several months following valve replacement. Men, who tend to have a greater degree of LV

myocardial fibrosis and abnormal LV collagen network patterns (148), may have more inherent reduced contractility, so that relieving afterload with TAVR may also not result in early or marked symptomatic improvement. When discussing TAVR with the very elderly, they should be made aware that symptomatic improvement may be delayed or minimal in some cases.

5.1.2.2.3. FRAILTY AND FUTILITY VERSUS UTILITY. As previously discussed, the concepts of frailty and futility will assume central importance in patient selection for TAVR by virtue of the extensive comorbidities present in this population. Frailty is an important and frequent condition in elderly patients and should be considered when dealing with invasive care in older adults (149). Although it can have significant overlap with disability and comorbidity, it is a distinct syndrome and is characterized by a vicious cycle of decreasing muscle mass, energy expenditure, and malnutrition culminating in vulnerability to adverse events (150). In the PARTNER trial, frailty was present in as many as 23% of patients in Cohort B and 16% in Cohort A. Besides comorbidities, and frequently in combination with them, it is likely to play a role in the assessment of the individual's candidacy for invasive care and therefore in withholding any intervention in nearly one half of high-risk patients with AS (151). It is important to consider that frailty may be a reversible physiological phenotype in some cases, and therefore it is premature to consider this a permanent characteristic of the individual patient. To the extent that AS may contribute to the declining health state, AVR or TAVR may reverse frailty. In this case, frailty may be a marker for treatment benefit. Conversely, if the individual is frail from multiple other organ system declines, frailty may be a marker of treatment risk.

The impact of frailty on the clinical course and outcome of patients presenting with severe AS is beginning to be investigated but is difficult to assess because of its multidimensional phenotype and the lack of a clear and agreed-upon assessment. The definition of frailty used in recent studies ranges from the qualitative “eyeball test” to more quantitative scores such as the Fried Frailty Index (150). A simple test for defining frailty is a timed gait speed over 5 m. In a recent Canadian study (152), a time of >6 seconds as a measure of frailty was found to be an independent predictor of mortality compared with the STS risk algorithm alone. As such, it has recently been added to the STS database upgrade (Version 2.73, July 1, 2011) and will be uniformly collected in patients undergoing cardiac surgery (152). Future studies should aim at developing more reliable and reproducible ways of identifying frailty, as well as incorporating these assessments in development of risk and benefit prediction.

Futility is also an important consideration for TAVR. There may be some patients in whom this procedure should not be performed because the clinical condition is too far advanced; in these patients, even a successful technical procedure is futile and does not improve health outcomes.

Therapeutic futility may be determined based upon: 1) lack of medical efficacy, as judged by the patient's physician; or 2) lack of a meaningful survival, as judged by the personal values of the patient (153,154). Although therapeutic futility may be invoked to justify denial, limitation, or withdrawal of care, the threshold for defining it is unclear, controversial, and often viewed differently by different stakeholders. In the PARTNER trial, the criterion for inoperability—used as a surrogate for futility with regards to surgical intervention—was an estimate of probability of death or serious, irreversible morbidity $\geq 50\%$ by a cardiologist and 2 experienced cardiothoracic surgeons (15). Despite successful correction of AS leading to an absolute 20% survival advantage, there was still 30% mortality in the TAVR treatment arm at 1 year, mainly due to noncardiac causes. The key to treatment in this group of “inoperable” patients is to define the “futility versus utility” treatment paradigm. Clearer definition of comorbid conditions that adversely affect survival despite successful valve implementation as well as quality of life and health economic assessment in those “inoperable” patients is crucial so that this therapy is appropriately used in patients likely to benefit (utility) compared with those unlikely to benefit despite successful therapy (futility). Although some might argue that it is inappropriate and misleading to say that treatment is futile simply because the probability that it will succeed is small, especially given the substantial uncertainty in our ability to prognosticate in individual patients and lack of validated tools that universally discriminate survivors from nonsurvivors of critical illness, it is nonetheless important to define meaningful cutoff points. This is particularly true when, in the course of a progressive illness, continued use of resources other than measures for comfort, is no longer reasonable, practical, or appropriate. Ultimately, these decisions must be guided by what our society considers to be the inherent value of human life and the resultant financial burden society is willing to bear for the provision of modern public health care (155).

5.1.3. Care Plan in Candidates for TAVR

The healthcare team needs to be intimately involved in discussions on risk/benefits including detailed information on individualized risks for each patient and alignment of quality-of-life expectations. Failure to understand and comply with a plan of care may account for dissatisfaction with procedural outcomes and potential rehospitalizations (156,157). One critical intervention to ensure effective care coordination and transition is that of comprehensive plan of care and educational material given to patient and/or caregivers prior to the planned procedures, and again during and after hospitalization. This process may encourage full participation of the patient and family about adherence to medication therapy and activity recommendations. Transitions of care and follow-up will be improved by discussion and written instructions reviewed with each patient including medications, timely follow-up with the various health-

care professionals involved with the patient's ongoing care, and appropriate postprocedural activities. The ongoing care and coordination with the cardiovascular care team may decrease likelihood of readmission and improve overall adherence. Healthcare providers should pay close attention to psychosocial and socioeconomic issues that the patient and family face, including access to care, risk of depression, and healthcare disparities (158–160).

5.1.4. Imaging Assessment

Imaging plays an essential role in patient selection and procedural planning, performance, and follow-up (161). In each of these steps, optimal imaging can help to enhance successful outcome. There is variability in the specific imaging protocols preferred in individual institutions. This variability is the result of institutional and individual experience and equipment, as well as the specific patient characteristics to be considered.

5.1.4.1. ECHOCARDIOGRAPHY

The following general recommendations can be made for echo assessment of patients being considered for TAVR. More detailed instructions can be found in a recent expert consensus statement from the American Society of Echocardiography and the European Society of Echocardiography (161).

5.1.4.1.1. ANNULUS SIZE AND CUSP AND ROOT ANATOMY. Accurate assessment of annular size is critical. Underestimation of annular size could lead to selection and deployment of a valve which is too small, with risks of poor hemodynamics, paravalvular regurgitation, and valve migration and embolism. Overestimation of annular size and placement of a valve that is too large can lead to other adverse outcomes, including incomplete deployment (with both valvular and paravalvular regurgitation) or catastrophic annular rupture. In general, all TAVRs are designed to be deployed in annuli that are slightly smaller than the prosthesis size. This oversizing is required because the valves are sutureless and depend on radial force to prevent dislodgement. For the initial Sapien valves, the 23-mm valve was designed for 18-mm to 22-mm annuli, whereas the 26-mm prosthesis was designed for 21-mm to 25-mm annuli. The Sapien XT valve, with 23-mm, 26-mm, and 29-mm sizes, is designed for annuli from 18 mm to 27 mm. The CoreValve has 26-mm, 29-mm, and 31-mm prosthesis sizes (using a different sizing convention from the Sapien valve) designed for annuli from 20 mm to 23 mm for the 26-mm prosthesis, 24 mm to 27 mm for the 29-mm prosthesis, and 26 mm to 29 mm for the 31-mm annuli. Annular dimensions can be measured with either TTE or TEE (162). With either modality, the annular anteroposterior diameter is measured from a long-axis view. Care must be taken to identify the true annulus, not overlying calcium. Measurements are made in systole at the hinge point of the leaflets into the LVOT with a trailing edge to leading edge convention. Because the annulus is often elliptical, optimal assessment should include measurement of the transverse (coronal)

diameter, using the short-axis view, ideally with biplane TEE approach or CT, which allows simultaneous long- and short-axis interrogation of the annular plane.

5.1.4.1.2. AORTIC ROOT DISEASE AND ASCENDING AORTIC DIMENSIONS. Assessment of cusp and root anatomy is also critical. The PARTNER trial excluded all patients with bicuspid aortic valves for concern that such valves might distort the prosthesis, leading to paravalvular regurgitation. Thus, TAVR in any nontricuspid valve would be considered an off-label use, though successful treatment of bicuspid valves has been reported (163). It is often difficult to determine cusp anatomy in the densely calcified valves commonly treated by TAVR. In this setting, CT or review of old echocardiograms may allow better assessment of the underlying anatomy. Pathology reviews have demonstrated progressive increase with age in the proportion of trileaflet valves in severe AS patients, from 15% in those under 60 years to 60% over 70 years (72% for those over 80 years) (2). Of note, this study showed that even pathological examination cannot determine cusp anatomy in some heavily distorted valves.

Several issues must be considered in assessing root anatomy and pathology. Care must be taken to assure that valve deployment will not compromise the coronary ostia, either from the device itself or from cusp calcification being shifted and displaced into the coronary. In general, CT scanning provides a more comprehensive assessment of the relationship of the coronary arteries to the annulus and valve leaflets, demonstrating an average annular–left coronary artery distance of 13.4 ± 3.2 mm and annular–right coronary artery distance of 13.6 ± 2.8 mm (164). Nevertheless, echo, particularly TEE, can measure the distance from the aortic valve annulus to the right coronary ostium. Since the left coronary does not lie in a standard TEE or TTE imaging plane that intersects the annulus, measurement from 3D datasets may be a feasible approach for this.

Accurate assessment of the aortic root and tubular portion is also important. The CoreValve Revalving System is designed with a supra-annular location of the porcine pericardial valve, located in the sinus of Valsalva. As a result, the CoreValve nitinol frame has a longer length than conventional surgical valves, ranging from 52 mm (for the 31-mm valve) to 55 mm (for the 26-mm valve) including its deployment hooks. It is recommended that the upper dimensions of the tubular aorta measured at 45 mm above the annulus be 40 mm for the 26-mm valve and 43 mm for the 29-mm and 31-mm CoreValve prostheses.

Preprocedural assessment of AR in TAVR candidates should be governed by guidelines from the American Society of Echocardiography (165). This assessment is based on multiple parameters, including LV size, AR jet size and morphology, AR pressure half-time, and diastolic flow reversal in the aortic arch. Patients with >3+ AR were excluded from the PARTNER trial and should be considered relatively contraindicated for TAVR.

5.1.4.1.3. THREE-DIMENSIONAL ECHOCARDIOGRAPHY. Real-time 3D TEE is an important modality for preprocedural

Table 10. Potential Approaches for Imaging in TAVR

Preprocedural Assessment

1. Assessment of aortic annular size and shape (CT, CMR, 2D and 3D echocardiography)
2. Assessment of aortic valve for number of cusps, degree of calcification and valve area by planimetry (CT, CMR, 2D and 3D echocardiography)
3. Measurement of the distance between annulus and coronary ostia (CT, CMR, 2D and 3D echocardiography)
4. Planning for precise coaxial alignment of the stent-valve along the centerline of the aortic valve and aortic root (CT)
5. Assessment of aortic dimensions (2D and 3D echocardiography, CT or CMR) and atherosclerosis (echocardiography, CT, or CMR)
6. Assessment of dimensions and atherosclerosis of iliofemoral vessels (CT, MR, angiography)

Postprocedural Assessment

1. Assessment of degree of aortic regurgitation (echocardiography or CMR)
2. Assessment of cerebral embolization (cerebral MRI)

2D indicates 2-dimensional; 3D, 3-dimensional; CMR, cardiac magnetic resonance; CT, computed tomography; MRI, magnetic resonance imaging; and TAVR, transcatheter aortic valve replacement.

and intraprocedural assessment of TAVR patients (166,167). Similar to MDCT and CMR, it can help with precise assessment of the aortic root and annulus, potentially helping reduce the chance for prosthesis-sizing error in patients. However, multiple studies have demonstrated significant differences in dimensions of the aortic root and annulus measured by 2D TTE, 2D TEE, 3D TEE, and MDCT (166,167). Hence, it is imperative to realize that the imaging technique utilized might impact TAVR size selection and strategy. TEE, including real-time 3D TEE can help evaluate the extent of and precisely locate the jet of AR following prosthesis implantation.

5.1.4.2. TOMOGRAPHIC IMAGING

5.1.4.2.1. RATIONALE FOR TOMOGRAPHIC IMAGING. Optimizing outcome relies heavily on image guidance for patient selection, preprocedural planning, and intraoperative decision making (168). Correct positioning of the prosthesis

relative to the annulus is critical. If valve deployment is too high, increased risk of paravalvular regurgitation, aortic injury, coronary occlusion, or embolization of the prosthesis can occur. If positioning is too low, mitral valve dysfunction, heart block, paravalvular regurgitation, or embolization into the left ventricular cavity can occur (169). In addition, the relatively large delivery catheters currently required for valve insertion are associated with the risk of vascular complications, necessitating assessment of iliofemoral vasculature. This has led to the application of 3D imaging approaches for TAVR, including CT, CMR, 3D echocardiography, and C-arm CT (162,166,170,171) (Table 10).

5.1.4.2.2. MULTIDETECTOR COMPUTED TOMOGRAPHY. MDCT provides comprehensive assessment of the aortic root, atherosclerotic burden, and course of the thoracoabdominal aorta and its iliofemoral branches (Figure 5). MDCT in the

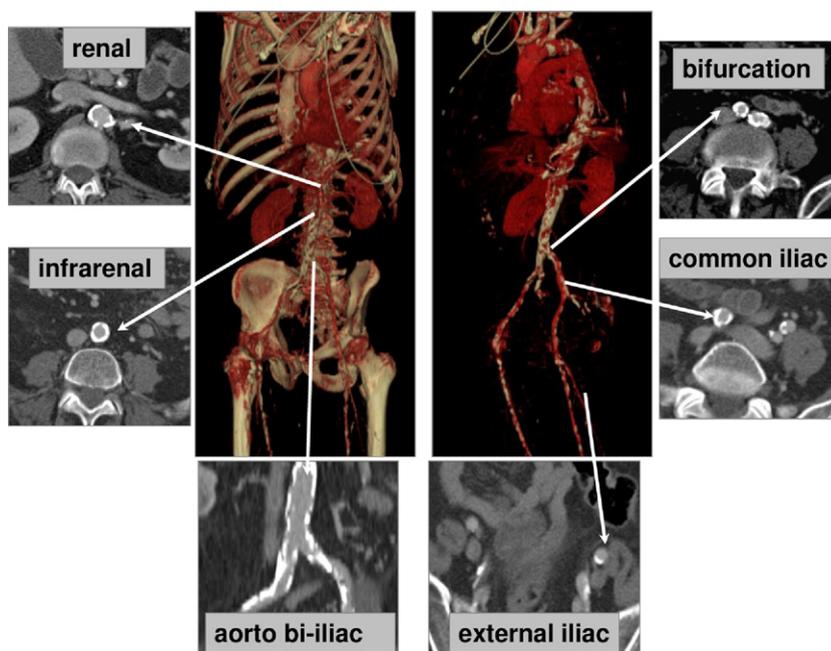


Figure 5. Reconstructed Multidetector Computed Tomographic Images of the Abdominal Aorta and Its Pelvic Branches Demonstrating Tortuosity and Extensive Calcific Atherosclerosis

The extent and degree of peripheral arterial disease is essential in determining the feasibility and safety of transfemoral approaches. In some patients with extensive disease, alternative approaches such as direct aortic, subclavian, or transapical procedures should be considered.

context of TAVR eligibility assessment has become routine in many large-volume centers (172).

MDCT systems with at least 64 detectors and a spatial resolution of 0.5 mm to 0.6 mm are recommended. The specific scan protocols used for assessment vary but generally include imaging of the aortic root and the thoracoabdominal aorta and its iliofemoral branches. ECG-synchronized imaging of the aortic root is important to avoid image quality degradation due to motion artifacts, and image reconstruction is performed at the desired phase of the cardiac cycle (e.g., a systolic 30% to 40% phase for valve area and annular assessment). Using the retrospectively ECG-gated helical acquisition, CT data can be acquired throughout the entire cardiac cycle, enabling 4D image reconstructions for evaluation of valvular function, albeit at the expense of a higher radiation dose (173). Alternatively, prospectively ECG-triggered axial CT data acquisition requires much less radiation; however, images are acquired during a prespecified phase of the cardiac cycle and reconstruction in other phases or 4D cine loops may not be reconstructible (174). However, protocols with newer generation scanners allow prospective acquisition at a lower radiation dose with subsequent display of cine loops (175). Although radiation exposure is important to consider with any CT acquisition, it is less a concern in the elderly patients currently considered for TAVR.

Because a standard bolus of 80 mL to 120 mL of low-osmolar iodinated contrast is necessary, the benefits versus risks of iodinated contrast need to be carefully weighed (176). An alternative approach involves a pelvic scan after intra-arterial contrast injection into the infrarenal abdominal aorta (catheter left in place after cardiac catheterization) using a very low dose (15 mL) of contrast (177). If contrast administration is not feasible, a noncontrast scan, although not optimal, still allows the assessment of overall vessel size, calcification, and tortuosity.

As previously mentioned, analysis and measurement of the annulus size and shape are crucial for procedural success. Typical annulus measurements, obtained using 2D TTE or TEE provide a single diameter measurement, assuming a circular annular orifice (178). In contrast, 3D CT systolic reconstruction of the annulus orthogonal to the center-axis of the LVOT allows for the assessment of minimal and maximal diameter, circumference, and area measurements (162,164,166,179–183). Indeed, these studies have demonstrated that the LVOT is often oval, rather than circular. Hence, multimodality imaging might improve the accuracy of AV measurements and reduce the chance for prosthesis-sizing errors in patients considered for TAVR.

Complete coronary assessment with MDCT is obviously limited in the current population evaluated for TAVR because of the very high prevalence of advanced calcified disease, precluding precise assessment of luminal stenosis. However, MDCT allows measurement of the distance between annulus and coronary ostia, which identifies patients at risk for coronary occlusion during TAVR. Al-

though no definite criteria exist to exclude patients, a <10 mm distance might identify increased risk of coronary ostial occlusion (184). In this setting, placement of a guidewire or balloon catheter in the left main artery could be considered to ensure access in case of complications.

Although echocardiography is used extensively to assess the aortic valve, cine MDCT can provide incremental value in its assessment, including number of cusps, especially in cases of heavy calcification, where echocardiography can be difficult. Also, cine MDCT can be used to perform planimetry of the aortic valve (180,185).

Optimal coaxial alignment of the stent valve along the centerline of the aortic valve and aortic root is important during positioning. Ascertainment of the right height to avoid too high or too low placement is important to avoid AR and optimize valve function (169). Although traditional assessment of root orientation is performed using multiple invasive aortograms in 1 or 2 orthogonal planes, double-oblique multiplanar MDCT reconstruction allows preprocedural prediction of the aortic root angle (186,187). This potentially decreases the number of aortograms required during the procedure, therefore shortening both procedure time and contrast usage, and improves precision of deployment. The emergence of C-arm CT would further allow the incorporation of fusion imaging in the catheterization laboratory (170).

5.1.4.2.3. CARDIAC MAGNETIC RESONANCE. Similar to MDCT, CMR can also potentially provide comprehensive assessment of the aortic valve, annulus, aortic root, course of the thoracoabdominal aorta and luminal caliber of the iliofemoral branches, without the ionizing radiation. 2D ECG-gated noncontrast cine CMR sequences across the aortic valve (even avoiding the calcium blooming commonly seen on CT) and aortic root can provide a detailed assessment of LV function, aortic annulus, valve, root, and coronary ostia, similar to that obtained on MDCT (188). In addition, free-breathing noncontrast navigator-gated 3D whole-heart acquisition can also be obtained to mimic the volumetric acquisition of a CT image (171). It also enables assessment of the aortic root in addition to assessing the LVOT–aortic root angulation and predicting imaging planes. The use of 3D gadolinium-enhanced magnetic resonance imaging can provide precise luminal dimensions of the thoracoabdominal aorta and its iliofemoral branches (189). In cases with renal insufficiency, a navigator-gated, free-breathing, 3D noncontrast steady-state free precession sequence can be used to assess luminal dimensions. However, CMR is not optimal for assessment of aortic wall changes, especially dense aortic calcifications, because it would lead to signal voids and hence, appear dark. Postprocedural assessment of residual aortic insufficiency by quantitative CMR might have a potential role in TAVR patients (190). However, CMR is a time-intensive technique, which could be a limiting factor, particularly in older patients. In patients with tenuous renal function, the benefits of gadolinium administration have to be balanced against the risks

of nephrogenic systemic fibrosis (191). In addition to the above-mentioned constraints, CMR is not recommended in patients with pacemakers, defibrillators, or intracranial aneurysm clips, although the currently used valves are CMR compatible.

5.2. Procedural Performance

5.2.1. Role of Surgeon and/or Cardiologist

The central position of the heart team in optimizing TAVR patient evaluation, procedure performance, and outcomes has been emphasized. Candidacy for TAVR should be determined together by both the surgeon and cardiologist, ideally in an established valve or structural heart disease clinic. During procedural performance, both cardiologist and surgeon should be active participants. There are several specific tasks to be considered among others: 1) gaining access to the vascular tree by either various transarterial sites or by the transapical route; 2) crossing the stenotic aortic valve; 3) balloon aortic valvuloplasty; 4) optimal positioning and deployment of the aortic prosthesis; 5) achieving secure vascular closure; 6) assessment and treatment of procedural-related complications, which encompasses vascular access, cardiac structure, coronary artery anatomy, and electrophysiology issues; and 7) considerations for access for hemodynamic support and the need for cardiopulmonary bypass need to be determined by the cardiovascular (CV) surgeon and team. Each of these tasks contains within it multiple component parts, e.g., the need for rapid ventricular pacing during either balloon aortic valvuloplasty or prosthetic deployment, and identifying the optimal fluoroscopic position to be used.

The above-mentioned tasks often require different skill sets. In the future, as training programs evolve with integration of cardiovascular surgery and interventional cardiology, the roles of either or both specialties may change. However, at the present time and for the foreseeable future, both a surgeon and an interventional cardiologist should be integrally involved with each procedure. Prior to the start of each procedure, a specific team leader should be identified, either the surgeon or the interventional cardiologist. That individual should have overall supervision for the specific case to optimize the procedure. The specific person identified will depend on the operator experience as well as the unique characteristics and challenges of each individual case; for example, the cardiovascular surgeon should be the primary team member responsible for the surgical aspects of transapical and transaortic procedures or if a subclavian cutdown is to be required. Interventional cardiologists usually assume the lead operator position in transfemoral procedures, whereas cardiothoracic surgeons usually lead transapical procedures. The specific roles of the other individuals involved should be identified. Some will be shared, e.g., deciding what specific angle identifies the optimal fluoroscopic view for visualizing the plane of the aortic valve for deployment. Other roles will involve just 1

individual, e.g., taking the team through the pre-and post-procedure checklists and selection of the specific pacing algorithm for deployment. It is important for all members of the team to be present for all stages of the procedure.

The most important considerations are team-based care, identification of a specific team leader, close communication, and preplanning for outlining management of potential complications. Likewise postprocedure care is optimally delivered on a multispecialty team care service similar to a transplant service where all specialties are participatory to achieve optimal patient outcomes.

5.2.2. Procedural Location

Procedural location will vary from institution to institution related to several factors including resources currently available in the facility. The specific location has important physical implications, as well as personnel and equipment implications. Optimal equipment requirements include a state-of-the-art, large-field-of-view fluoroscopic imaging system—preferably a fixed overhead or floor-mounted system that has positioning capability rather than a portable C-arm system. This system needs to have the ability to store and review images and accommodate varying patient sizes. A potentially important adjunct for this is the availability of either biplane imaging or imaging programs that can automatically help aid in the selection of orthogonal views for imaging during positioning of the valve. Integration of TEE echocardiographic images, particularly 3D capabilities, is helpful; the availability of CT or CMR is a significant advantage, particularly if image overlay is possible, which will become more widely used in the future. Full catheterization laboratory hemodynamic capability is also required for hybrid rooms. Other resources required include present cardiopulmonary bypass machines, perfusionists, and related ancillary supplies with an inventory of interventional cardiology equipment for balloon aortic valvuloplasty, coronary balloons, stents, and 0.014-inch wires if coronary occlusion occurs as a complication of device deployment. As vascular access is critical, a variety of peripheral arterial balloons and covered stents for treatment of peripheral vascular complications such as iliac rupture, and a variety of vascular closure devices are also important for completion of the procedure. The procedure location should also be fully capable of providing anesthesia services including advanced airway management, general anesthesia, full hemodynamic monitoring, and administration of vasoactive agents into the central circulation.

As can be seen, these requirements mandate specific room sizes and configurations. Such a hybrid room may be situated in a surgical suite or may be in a large modified catheterization laboratory (approximately ≥ 800 square feet) with appropriate air handling and air exchange modifications. In the future, as procedures for the treatment of a variety of structural heart and endovascular disease procedures increase, it is anticipated that hybrid rooms will become more standard of care for these team-based therapies.

Personnel requirements are also of great importance. Personnel who are trained to deal with complicated hemodynamics, the specific equipment to be used, and complication management are critical. This has significant implications. For example, if the procedures are carried out in a modified cardiac catheterization laboratory staffed by cardiac laboratory personnel, although there would be expert experience with percutaneous procedures and vascular complications, if urgent cardiopulmonary bypass was required, there may be undue treatment delays related to inexperience with that specific procedure. On the other hand, if the procedures are carried out in an operating room with limited catheterization laboratory capabilities and personnel, the ability to promptly address and treat a coronary or a vascular complication requiring immediate attention may be compromised. Team-based training and care that includes complication management remain a cornerstone.

5.2.3. Anesthetic Considerations for TAVR

Patients undergoing TAVR are at a high risk for procedural complications, including hemodynamic collapse. Careful planning and intraoperative anesthetic management can mitigate risk (67,192,193). During the preoperative evaluation, special attention is paid to factors that may predict higher risk of intraprocedural instability, in particular: depressed EF, elevated pulmonary pressures, significant MR, incomplete revascularization, collateral dependent coronary circulation, COPD, HF, and acute/chronic kidney disease. In patients least likely to tolerate rapid ventricular pacing and hypotension, preventive measures may be instituted (194) and steps taken to allow for rapid institution of cardiopulmonary bypass. Rarely, elective bypass may be utilized. Routine surgical antibiotic prophylaxis administered prior to surgical incision or vascular access is warranted to decrease the risk of wound infection and endocarditis.

TAVR is typically performed under general anesthesia with central monitoring, using a pulmonary artery catheter and transesophageal echocardiography. Single-lung ventilation is not necessary for TA procedures. Although a temporary ventricular pacing wire can be placed through a hemodynamic catheter, more commonly, a temporary transvenous lead is passed through the femoral or subclavian vein or, in the case of transapical procedures, sewn directly on the epicardial surface. After a ventricular wire is passed, thresholds are checked at a pacing of rate 10 to 20 beats/min higher than the patients intrinsic rates. For placement of the CoreValve, rapid pacing for device placement is not required. Arterial pressure monitoring may be done via the radial artery, but in the case of ipsilateral axillary bypass, a plan must be made for additional monitoring either from the contralateral radial or femoral artery. At least 1 large-volume line is obtained peripherally or centrally. Immediate access to a defibrillator device is necessary because ventricular fibrillation can occur with manipulation of catheters within the heart or with rapid ventricular pacing. This may

be best accomplished with preapplied defibrillator pads connected to the defibrillator before starting the procedure.

Steps are required to prevent significant hypothermia, and these are often similar to those used in off-pump CABG. The room is heated, fluid warmers are used, and some type of underbody heating system (either forced air or fluid) is generally used. This is important because a limiting step in early extubation of these patients is often the time needed to warm them following the procedure.

Communication in this multidisciplinary approach is the key word for intraoperative success. The importance of training a dedicated team cannot be overemphasized. Frequent changes of personnel will dilute the learning curve. Standard doses of anesthetic, sedative, and narcotic analgesic agents may need to be reduced on the basis of the age and frailty of the patient (195). Intraoperative challenges may be encountered even before induction. Use of ultrasound for venous access is beneficial to prevent hemorrhage and complications associated with placement of central line.

Unless otherwise indicated, volume status needs to be supplemented as the patients in this age group are usually volume depleted. Generally, 1.0 L to 1.5 L of fluid are required, but a combination of pulmonary artery pressures, central venous pressure, and echocardiographic evaluation can guide tailored therapy. Severely underfilled ventricles may pose an additional problem to guidewire/applicator device insertion in these hypertrophied ventricles. Patients with severe concentric LV hypertrophy and intravascular volume depletion may exhibit a rapid and sustained deterioration of hemodynamic status in response to ventricular pacing, rapid ventricular pacing, intracardiac guidewire or catheter manipulations, or balloon aortic valvuloplasty. In patients with low cardiac output and those with more than moderate PH, inotropes such as milrinone or dobutamine may be considered prior to the procedure, with the goal of obtaining a cardiac index of at least 1.8 L/min/m². Inhaled nitric oxide or inhaled epoprostenol should be available for the treatment of severe PH and right ventricular failure.

Avoidance of prolonged hypotension is perhaps the most important step in preventing hemodynamic collapse. The cycle of hypotension, subendocardial ischemia, low output and further hypotension with ultimate ventricular fibrillation is best avoided as treatment is difficult once these events occur. Maintenance of a mean pressure of >75 mm Hg (or systolic of at least 120 mm Hg) is advisable before initiation of rapid ventricular pacing. The frequency and duration of rapid ventricular pacing episodes may need to be limited to allow enough time between episodes to permit recovery of circulatory function in patients with limited hemodynamic reserve. In patients with a slow recovery of spontaneous circulation after ventricular pacing, pre-emptive therapy with vasopressor therapy such as norepinephrine, epinephrine, or phenylephrine as an intravenous infusion or as incremental intravenous boluses may be important to treat hypotension and facilitate recovery after rapid ventricular pacing. Hypertension may be dangerous and increase the

risk of bleeding and ventricular rupture, especially during transapical TAVR.

Anticoagulation therapy is usually initiated after insertion of the regular sheaths and prior to placement of the large sheath into the vasculature, and repeated to maintain an activated clotting time (ACT) of >300 seconds. Heparin anticoagulation can be reversed by the administration of protamine sulfate on a milligram to milligram neutralization dose, although it may not be necessary to reverse heparin anticoagulation for transfemoral TAVR if there is a minimal risk of surgical bleeding. A transvenous pacing wire should be secured in position in patients with postprocedural interventricular conduction abnormalities, at high risk for heart block, or with heart block until it is determined whether a permanent pacemaker is necessary (196).

Although general anesthesia is generally used for transapical procedures, some experienced institutions are performing transfemoral implantation with conscious sedation (197). With this approach, with conscious sedation, the patient is awake and spontaneously breathing without an artificial airway. Intraoperative TEE for procedural guidance may be difficult or impossible if TAVR is performed under conscious sedation. Adequacy of ventilation and oxygenation should be continuously assessed during conscious sedation and qualified personnel and equipment to perform intubation of the trachea, provide airway protection, and administer mechanical ventilatory support should be immediately available to detect and treat acute respiratory failure in patients managed during TAVR with conscious sedation.

5.2.4. Vascular Access

Placement of TAVR is accomplished via femoral artery, subclavian artery, or the aorta. The Sapien valve may be deployed by major transvascular access as well as transapically, whereas the CoreValve uses only major transvascular access (110). Careful evaluation of the patient's atherosclerotic load and location, arterial size and tortuosity, and presence of mural thrombus are required for the best possible delivery site. There are specific advantages and disadvantages to each vascular access approach. Selection of the optimal route requires consideration of specific patient anatomy and the specific device to be used.

5.2.4.1. CARDIOPULMONARY BYPASS REQUIREMENT

Cardiopulmonary bypass is infrequently (<5%) required for support during the valve implantation due to cardiac decompensation as a consequence of cardiac tamponade, coronary occlusion, severe acute AR, aortic rupture, or acute aortic dissection. With experience, and excellent hemodynamic and anesthetic management, this requirement is rarely necessary. Accessory cannulation sites in the femoral vessels or with an adjunctive axillary graft and venous cannula should be considered if femoral access sites are not suitable. Risk of vascular compromise, injury, or particulate embolism should be weighed with the risk of cardiac support needs.

5.2.4.2. PERCUTANEOUS OR CUTDOWN ACCESS

Both percutaneous and cutdown access approaches are used; there are advantages and disadvantages to each. Complications with access in this high-risk and generally older population are frequent. Decisions about access technique and site depend on the degree and severity of atherosclerosis, vessel size, specific prosthetic device to be used, and the heart team's experience (136–138,198). Use of percutaneous approaches preferentially occurs when access sites are relatively large and free of significant atherosclerotic disease. Less favorable vessels may require cutdown, often with placement of axillary, iliac, or aortic insertion grafts or conduits to provide access sites. Percutaneous insertions are occasionally converted to open repair or hybrid repairs, utilizing percutaneous closure devices and surgical techniques as needed (199).

5.2.4.3. DEPLOYMENT TECHNIQUE

The goals of deployment are to avoid hemodynamic compromise while obtaining a stable valve, positioned without coronary obstruction, interference of mitral valve function, conduction system impingement, or overhanging native aortic leaflets, and avoidance of aortic root complications (rupture and dissection). There are several approaches to the aortic valve, which can be broadly categorized as retrograde or antegrade.

Retrograde passage is generally performed via the femoral artery. There are obvious limitations in patients with peripheral arterial disease or small vessels. Additional, reported retrograde options include the axillary approach and direct ascending aortic puncture. A femoral approach is used in the vast majority of retrograde deployments, starting with either a standard percutaneous femoral arterial access or a surgical exposure of the artery. A series of dilators is employed, under fluoroscopic vision, to reach the size of the deployment sheath. The sheath is passed into the body of the thoracoabdominal aorta. Crossing the aortic valve is accomplished using standard interventional techniques, and a stiff wire exchange is performed, with redundancy in the LV cavity to prevent loss of position. Care must be taken to avoid damage to the LV, resulting in perforation.

The transapical approach is the only currently available antegrade approach, and equipment is only available for this approach for the Sapien valve. Access is obtained via a left anterior thoracotomy, which is made after localization of the apex by fluoroscopy or TTE. After entering the pleural space, digital inspection can further localize the position of the apex and a 2-inch to 3-inch segment of rib may be resected to facilitate exposure. To reduce postoperative pain, soft tissue retractors are preferred to heavy metal retraction. The proper site of puncture is on the left ventricular apex, which is more anterior and proximal than the anatomic cardiac apex. TEE is of great value in helping to localize the apex of the LV. Either 2 concentric purse-string sutures or 2 mattress sutures are placed with felt buttress. Puncture is made and a 0.035-inch guidewire is passed through the

native valve. A balloon catheter may help facilitate wire placement by avoiding the mitral subvalvular apparatus. After the guide wire is placed in the ascending aorta, a coronary catheter such as a JR-4 can be used to guide the wire into the descending aorta, and the wire is exchanged for a stiffer wire (super or extra stiff). The deployment sheath is then passed to a depth of 3 cm to 4 cm, following which, balloon aortic valvuloplasty of the native valve is performed prior to valve implantation.

A more recent approach that has gained interest and acceptance is the direct aortic or transaortic approach. This approach is being employed with both the balloon expandable and self-expanding techniques. The access is through either an upper partial sternotomy or a second or third right intercostal space minithoracotomy. Concentric felt pledgeted reinforced purse-string sutures are placed in the ascending aorta at least 5 cm above the valve. A guidewire is then placed retrograde across the valve, and balloon aortic valvuloplasty and valve deployment performed similar to the other access techniques. The advantages of this approach include the short distance from the aortic valve, allowing optimal control and enhanced surgeon comfort level with a technique they are already using routinely for cardiopulmonary bypass cannulation as compared with the left ventricular apex approach. Another possible advantage is a less painful incision than with a left anterior thoracotomy at a lower interspace. Disadvantages include manipulation of the ascending aorta with possible embolization of atherosclerotic debris when disease is present. Current-generation delivery systems are being modified for this approach (200).

5.2.4.4. BALLOON EXPANDABLE VERSUS SELF-EXPANDING PROSTHESES

There are significant differences between the balloon-expandable and self-expanding valves. Balloon-expandable valves, such as the Sapien, cannot be collapsed once expanded. Self-expanding, nitinol-based valves such as the CoreValve can be partially deployed and repositioned to some extent. The promise of recapture and repositioning newer nitinol-based valves offer significant potential advantages in reducing complications from malpositioning. Both valves must be “oversized,” but the CoreValve in particular seems to work best when the valve is somewhat underexpanded. Risks of overaggressive sizing include leaflet dysfunction and annular or aortic rupture (110).

5.2.5. Imaging During TAVR

The mainstay of intraprocedural imaging is fluoroscopy and angiography for device placement. TEE is an important adjunct to this and is used at the operator’s discretion. The role of intraoperative rotational CT scan is currently in evolution. TEE is used for both transfemoral and transapical deployment, but with transfemoral procedures increasingly being performed under local anesthesia combined with conscious sedation (197), the role of TEE in this setting may decrease, though imaging around the time of valve deployment in this setting is possible (201) and transnasal

TEE with smaller probes may allow prolonged monitoring without general anesthesia, though clearly with significant compromise in comparison to standard TEE. TTE may also be used for guidance, though image quality is limited. Similarly, intracardiac echocardiography has been reported for TAVR guidance, though imaging capabilities are much less than TEE (202). Personnel performing TEE guidance of TAVR, whether cardiologists or anesthesiologists, must be fully trained in the full spectrum of transesophageal and intraoperative echo with special emphasis on the aortic valve and associated structures (203). Training guidelines indicate the need for involvement in 300 intraoperative studies, 150 as an operator (203). Additional training is necessary to become familiar with the specifics of TAVR. Frequent changes of the personnel performing TEE guidance dilutes the learning curve and is not recommended. Patients undergoing TAVR tend to be elderly, unstable, and have multiple comorbidities, and thus attention must not be diverted from critical anesthesia management. It is possible for the attending anesthesiologist to provide echocardiographic procedural guidance, but in many situations, such guidance will need to be provided by a dedicated cardiologist or anesthesiologist not distracted by clinical anesthesia needs.

5.2.5.1. RECOMMENDATIONS FOR TEE GUIDANCE FOR PATIENTS UNDERGOING TAVR

The following brief recommendations can be made for TEE guidance of patients undergoing TAVR. More detailed instructions of procedural echocardiography can be found in a recent expert consensus statement from the American

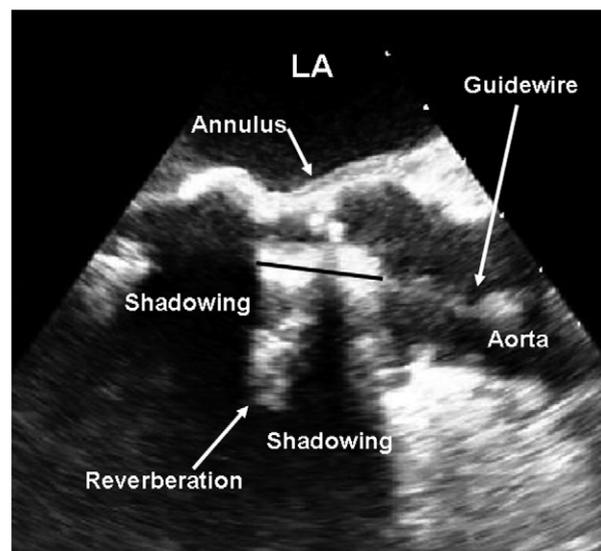


Figure 6. Midesophageal Long-Axis TEE View Showing the Proper Positioning of a Sapien Valve (black line*) Across the Aortic Annulus Prior to Balloon Deployment

Note that approximately half the valve is above and below the annulus. Note also the difficulty of imaging due to shadowing from the prosthesis and annular and mitral valve calcification, as well as a prominent reverberation artifact, emphasizing the need for thorough training prior to providing procedural guidance. LA indicates left atrium. *Visible as black line.

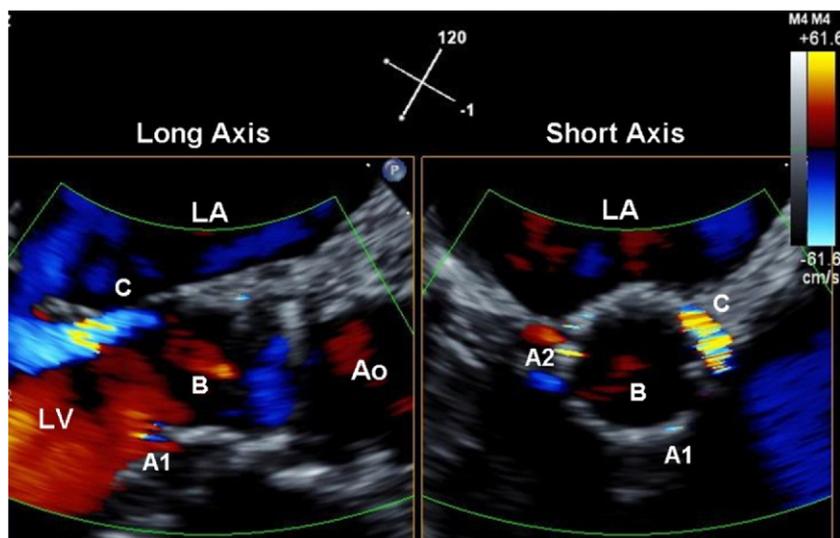


Figure 7. Mixed AR

Central and paravalvular AR following TAVR deployment in a biplane long- and short-axis TEE view. A1 and A2 are trivial paravalvular leaks, whereas B is a trivial central regurgitation, all of which are negligible. C is a more severe paravalvular leak, which was ameliorated by a second valve inflation. Ao indicates aorta; AR, aortic regurgitation; LA, left atrium; and LV, left ventricle.

Society of Echocardiography and the European Society of Echocardiography (161).

1. **Guidewire placement:** After confirming annular size for proper device selection, TEE can help with guidewire placement. This is particularly important in transapical TAVR, where manual dimpling of the apex can be visualized and guidewire passage through the AV can be confirmed, avoiding the submitral apparatus or the hypertrophied septum.

Valve placement: TEE can be very helpful in the correct placement of the valve prosthesis, though fluoroscopy is commonly used for localization. It is critical to understand the landmarks of the valve when mounted on the guiding catheter. For the Sapien valve, roughly half of the device should be above and below the aortic annulus (Figure 6). For the CoreValve, TEE should confirm that the nitinol stent is well within the borders of the calcified native annulus. Visualizing the valve during the time of rapid pacing and balloon inflation (for the Sapien valve) or deployment of the CoreValve provides an immediate verification of correct valve placement. If the valve is placed using fluoroscopic guidance, the TEE probe must be partially retracted during that time to facilitate positioning or the fluoroscopic view can be changed.

2. **Postdeployment assessment:** A particular concern for periprocedural imaging relates to assessment of AR that is complicated by the common frequency of paravalvular leaks and shadowing from the prosthesis (Figures 7 and 8). This assessment must be made very rapidly in the procedure room (to allow possible reballoning or even deployment of a second valve if the AR is severe and cannot be controlled otherwise). It is critical to distinguish between valvular and paravalvular regurgitation and to determine whether it is severe enough to require immediate intervention. Small paravalvular leaks are often visualized due to the widespread irregular calcification in the native valves that leave gaps between the annulus and the prosthesis. If the leaks are punctate in cross section, with jets that do not extend beyond the LVOT and without visible proximal convergence zones above the prosthesis or flow reversal in the aortic arch, then no intervention is needed (Figure 7, jets A1 and A2). If not, and

velocity aliasing is seen superior to the prosthesis with AR extending beyond the LVOT, then reballoning or a valve-in-valve approach may be appropriate (Figure 7, jet C).

Mild central valvular regurgitation is commonly seen after valve deployment, which frequently resolves with removal of the guidewire and/or a rise in central aortic pressure (Figure 7, jet B). An inadequately deployed transcatheter valve may have crimped leaflets with more significant valvular AR, which dictates reballoning. Rarely, 1 of the leaflets may remain stuck in the open position, resulting in torrential AR with marked aortic flow reversal and a short pressure half-time (Figure 8) (204). In such a case, gentle probing with a soft guidewire or catheter may free up the stuck leaflet; if not, immediate placement of a second transcatheter valve should be considered. This will be less of an issue with newer generation valve designs.

Postdeployment echocardiography commonly discloses small areas of paravalvular or central valvular leak. Most commonly, these originate around areas of extreme leaflet calcification, particularly at the commissural areas. If significant, these may be treated with repeat ballooning of the prosthesis to further expand it to close paravalvular leaks or inadequate noncircular deployment. A small additional amount of fluid (1 mL) may be added to the system prior to reballoning to insure complete inflation (110,205–210). For CoreValve, indications are similar—significant paravalvular leak with AR and underexpanded prosthesis (assessed by TEE and/or fluoroscopy).

There are a number of other complications that must be recognized immediately after TAVR if poor clinical outcome is to be averted. Persistent hypotension may result from occlusion of a coronary artery by the device or displaced calcium. This can be recognized by characteristic regional hypokinesis, best appreciated from the transthoracic view and possibly by evaluating flow in the coronary arteries themselves. Global dysfunction with preserved coronary flow may reflect persistent depression from rapid pacing and balloon inflation, requiring inotropes and possibly intra-aortic counterpulsation or full bypass. Finally, hypotension may result from LVOT

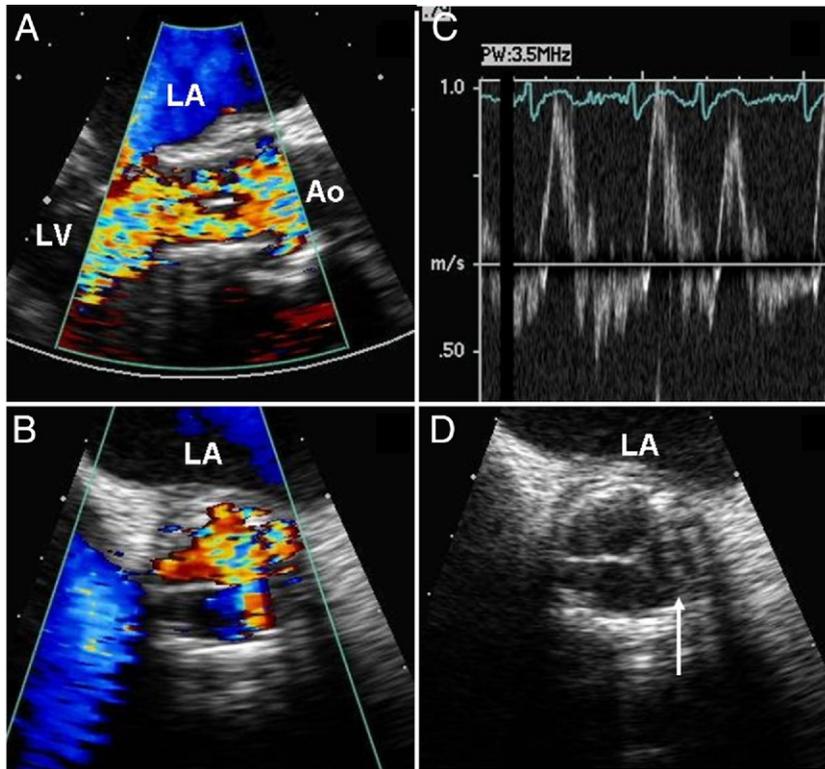


Figure 8. Severe AR

Long-axis TEE view showing severe AR following TAVR deployment (Panel A), confirmed by flow reversal in the descending aorta (Panel B). Short axis imaging (Panels C and D) demonstrates that this is due to failure of the leaflet in the left coronary position (arrow) to close in diastole, ultimately treated by deploying a second valve inside this one. Ao indicates aorta; AR, aortic regurgitation; LA, left atrium; and LV, left ventricle.

obstruction following the abrupt fall in afterload, requiring volume, negative inotropes, and vasopressors. Other etiologies such as severe MR, dislodgement of the AV prosthesis, pericardial tamponade, RV perforation from the pacemaker lead, air embolism, vascular access bleeding, and aortic dissection must be considered. Although TEE is very helpful for initial device placement and deployment, it is in the setting of hemodynamic instability that TEE is essential to rapidly diagnose these complications.

5.2.5.2. BALLOON DILATION AND SIZE

Prior to passage of the valve, predilation of the annulus is performed. Standard techniques of percutaneous balloon aortic valvuloplasty are employed, with rapid pacing during inflation. Radiographic contrast opacification of the root during maximal inflation may provide useful information when the location of the coronary ostia in relation to the annulus and the leaflet calcification or any other aortic root pathology requires further delineation. The valvuloplasty balloon size used is generally 20 mm to 23 mm, depending on the size of the annulus (110,211,212).

5.2.5.3. RAPID PACING

Rapid ventricular pacing is generally required for deployments with balloon-expanding devices. The goal is to create a transient reversible decrease in ventricular ejection, thereby reducing forces leading to valve migration during deployment. Typically, this requires pacing at a rate of 160 to 220 beats/min. Ideally, there should be a decrease in

systolic pressure to <70 mm Hg, with a pulse pressure <20 mm Hg. Pacing is accomplished by either transvenous or, less frequently, epicardial electrodes. Reducing the number and duration of pacing runs is important in this tenuous patient population to prevent instability (110,213).

5.2.5.4. EXPERIENCE WITH TAVR

An important issue in evaluating the results of TAVR is standardization of definitions for success, as well as efficacy. The VARC Consortium has proposed the definitions for device success, combined safety endpoint at 30 days, and the combined efficacy endpoint at 1 year or longer (Table 11) (96). Application of these standard definitions will facilitate comparability and analysis of outcome between different registries and studies. Another important issue on outcomes as well as learning curves relates to the experience of the center, patient selection criteria, and the expert onsite technical support provided by the companies in each case. For example, the UK TAVR experience documented similar results with proctored and nonproctored cases, as well as the first 20 cases versus continued cases in each center. This finding must be considered in light of the fact that the review of potential cases is influenced by the experience that other operators and centers have gained. The presence of the industry representatives in the procedures is also an invaluable asset in recognizing the potential for complications and treatment of same. These 2 background issues

Table 11. Composite Endpoints

Device Success

- Successful vascular access, delivery and deployment of the device and successful retrieval of the delivery system
- Correct position of the device in the proper anatomical location
- Intended performance of the prosthetic heart valve (aortic valve area 1.2 cm² and mean aortic valve gradient, 20 mm Hg or peak velocity, 3 m/s, without moderate or severe prosthetic valve AR)
- Only 1 valve implanted in the proper anatomical location

Combined Safety Endpoint (at 30 Days)

- All-cause mortality
- Major stroke
- Life-threatening (or disabling) bleeding
- Acute kidney injury—Stage 3 (including renal replacement therapy)
- Periprocedural MI
- Major vascular complication
- Repeat procedure for valve-related dysfunction (surgical or interventional therapy)

Combined Efficacy Endpoint (at 1 Year or Longer)

- All-cause mortality (after 30 days)
- Failure of current therapy for AS, requiring hospitalization for symptoms of valve-related or cardiac decompensation
- Prosthetic heart valve dysfunction (aortic valve area 1.2 cm² and mean aortic valve gradient \geq 20 mm Hg or peak velocity \geq 3 m/s, OR moderate or severe prosthetic valve AR)

AR indicates aortic regurgitation; and AS, aortic stenosis.
Reprinted with permission from Leon et al (96).

enhance the chance of success and may have contributed to the accelerated learning curve (115).

Compared with patients who underwent TAVR early after its introduction, patients treated more recently have benefited from shared experiences, more careful patient selection, advances in equipment and technique, and expanded operator experience. Prior reports have demonstrated a steep learning curve with TAVR using the CoreValve and Sapien valves (214–217). Whether improved operator experience alone can improve certain outcomes more than others remains unclear.

Since its introduction, increasing experience with the CoreValve TAVR revealed a trend of improved combined safety endpoint at 30 days from 30% to 17%, predominately driven by a reduction in life-threatening periprocedural bleeding complications occurring from TAVR (215). The most recent UK experience (115) identified a 30-day mortality of 5.8%. Furthermore, there was a significant reduction in cerebrovascular complications. Despite these trends, all-cause and CV mortality at 1 and 2 years remain high. Experience using the Edwards Sapien valve, on the other hand, revealed that, in 1 analysis, procedural experience was an independent predictor of 30-day mortality (214). The overall combined 30-day mortality decreased with increased experience, 10.5% to 8.5%. Procedural success rates also improved from 92.6% to 97.8% with time, predominately in the transfemoral approach, 89.3% to 98.8%.

Overall, consistent with other percutaneous therapies, the evidence demonstrates that procedural success and mortality rates improve with experience, whereas periprocedural complications are reduced. The introduction of smaller valve platforms introduces some uncertainty in defining whether the improved outcomes are solely related to the operator's experience. Nonetheless operational volumes of given indi-

viduals and centers are critical to consider. Current training protocols attempt to accelerate the learning curve by utilizing experienced proctors and didactic teaching, represented in both the PARTNER and CoreValve trials. If the learning curve can be truncated, procedural outcomes may continue to improve even as more operators enter this clinical arena. Specific criteria regarding operator and center training and experience are the focus of a multisocietal credentialing document (218).

5.3. Complication Management

Complications with TAVR are fairly common due to both the complexity of the procedure, as well as the morbidity of the patients being treated (Table 12). This has led to development of new tools and techniques to manage these complications (219).

5.3.1. Shock, Low Cardiac Output Post-TAVR

The noncompliant hypertrophied ventricles in these patients are very susceptible to myocardial ischemia. The combination of anesthesia, rapid pacing, volume shifts, and brief periods of no cardiac output have made hemodynamic shock and low cardiac output a not infrequent occurrence during and immediately after deployment.

The need for careful management of systemic pressure, inotropic support, and optimal ventilation to avoid and mitigate PH is clear. In patients at extreme risk for hemodynamic instability (i.e., those with low EF, collateral dependent coronary circulation, or PH), elective cardiopulmonary bypass (CPB) has been used to facilitate the procedure. Not infrequently, IABP support may be required to bridge these patients to adequate cardiac output. Also rare, but reported, is occlusion of coronary ostia by deployment (approximately 1% of cases). These may be addressed

Table 12. TAVR Complications and Management

Complication	Management Options Depending on the Clinical Condition, Hemodynamic Status, and Number of Options Available
Shock, low cardiac output	<ul style="list-style-type: none"> Careful systemic pressure management, inotropic support, IABP, or CPB
Occlusion of coronary ostia	<ul style="list-style-type: none"> PCI or CABG
Significant annular rupture	<ul style="list-style-type: none"> Pericardial drainage, autotransfusion, conversion to open surgical closure. If no other options, care and sedation
Ventricular perforation	<ul style="list-style-type: none"> Pericardial drainage, autotransfusion, conversion to open surgical closure.
Paravalvular aortic regurgitation	<ul style="list-style-type: none"> Postdeployment balloon dilation
Central valvular aortic regurgitation	<ul style="list-style-type: none"> Usually self-limited, but may require gentle probing of leaflets with a soft wire or catheter Delivery of a second TAVR device
Heart block	<ul style="list-style-type: none"> Pacemaker implantation
Device malposition	<ul style="list-style-type: none"> Deployment of overlapping 2nd valve
Device embolization	<ul style="list-style-type: none"> Urgent endovascular or surgical management
Atrial fibrillation	<ul style="list-style-type: none"> Rate control, rhythm control via pharmacological or electrical cardioversion
Major ischemic stroke	<ul style="list-style-type: none"> Catheter-based, mechanical embolic retrieval
Minor ischemic stroke	<ul style="list-style-type: none"> Aspirin, anticoagulants
Hemorrhagic stroke	<ul style="list-style-type: none"> Reversal of anticoagulation, correction of coagulopathy
Major bleeding	<ul style="list-style-type: none"> Hemodynamic support, blood transfusion
Vascular complications	<ul style="list-style-type: none"> Urgent endovascular repair/surgery
Acute kidney injury	<ul style="list-style-type: none"> Supportive care Maintain optimal fluid status

Each of the management options mentioned should be at least considered in the treatment of these complications.

CABG indicates coronary artery bypass graft; CPB, cardiopulmonary bypass; IABP, intra-aortic balloon pump; and PCI, percutaneous coronary intervention.

at times percutaneously, but may require CPB support for brief periods to allow recovery. Using a combination of these techniques, cardiac failure as a cause of death in TAVR has been rare (109,220–224). Rarely, “suicide” LV can occur and must be looked for. This occurs in patients with combined AS and subaortic stenosis or severe LV hypertrophy and cavity obliteration (109,224,225). The situation is exacerbated by diuresis and inotropes and is instead managed with volume expansion and beta blockade.

5.3.2. Annular Rupture

Annular rupture is a rare but devastating complication of TAVR. Predisposing factors include bulky and dense calcification, small sinotubular junction, smaller annular size, aggressive balloon predilation, and possibly porcelain aorta. Once seen, mortality is high. Management can include decisions for comfort care and sedation, attempts at medical management with pericardial drainage and autotransfusion of smaller leaks, and emergent conversion to open operation, which makes it even more important to define and plan

for or against this possibility in patients in a “high-risk” substrate (226).

5.3.3. Post-TAVR Aortic Regurgitation

Post-TAVR AR must be characterized as to its location, severity, and cause and should integrate both central and paravalvular origins to estimate overall volumetric impact. Central regurgitation is generally a result of improper valve deployment or sizing. Heavy guidewires through the valve can cause a substantial leak by holding a leaflet open, and full evaluation of central leak can only be undertaken once these wires are removed. Overhanging leaflet material can change the diastolic flow pattern and lead to improper leaflet closure. Damage to the leaflets can occur during crimping; significant central AR requires rapid consideration of a valve-in-valve deployment.

Paravalvular leaks of varying degrees are common. These are generally caused by inadequate inflation of the prosthesis or by calcific deposits that prevent the valve unit to properly seat and seal within the annulus. Acute leaks may respond to repeat ballooning the valve to obtain a better seal and more expansion. Predisposing factors include eccentric calcification and heavy irregular calcific deposits within the annular area, and incorrectly sized prostheses. In addition, an increased LVOT angulation in relation to the aorta, and a valve seated less deeply in the annulus predispose to paravalvular leak. Paravalvular regurgitation is quite common immediately post-TAVR, occurring at an incidence of 85%. At 1 year, up to 75% still have mild or more paravalvular regurgitation, and one third have more than mild regurgitation.

The incidence of residual mild or moderate AR (+1 and +2) is significantly higher in TAVR patients compared with surgical procedures, whereas hemodynamically severe postprocedural AR (+3 and +4) is rare. Experience has demonstrated that aortic paravalvular regurgitation after self-expanding TAVR devices can be reduced by sufficient balloon aortic valvuloplasty prior to deployment of a percutaneous prosthesis for self-expanding valves. Occasionally in heavily calcified valves, repeat balloon dilation after valve deployment is needed to fully expand the prosthesis. Post-valve dilation can be performed safely with a slightly oversized balloon, without causing significant structural damage to the prosthesis. Appropriate preprocedural planning utilizing both echocardiography and CT for annular analysis is important in order to avoid undersizing of the valve compared with the annulus because this can also cause significant paravalvular regurgitation.

Acute postprocedural regurgitation requires continued surveillance because regurgitation may change in the subsequent days post-TAVR. The self-expanding properties of the stent in the CoreValve prosthesis may reduce the grade of paravalvular AR or recoil from the compressive forces of the heavy calcification on either prosthesis may worsen the degree (227,228). Clinical concern about the impact of paravalvular regurgitation after TAVR is prudent, given the findings that after surgical AVR, patients with moderate-

severe or severe AR develop chronic volume overload that can lead to left ventricular remodeling/dysfunction and increase the risk for hemolysis. At the present time, there is not sufficient long-term follow-up after TAVR to understand the clinical significance of paravalvular regurgitation and whether the severity of paravalvular regurgitation progresses with time. However, it is clear that postprocedural regurgitation is associated with adverse outcomes (109,225). There are no reported cases of hemolysis with TAVR despite paravalvular AR.

5.3.4. Post-TAVR Heart Block

TAVR is associated with a variable incidence of complete heart block and/or need for pacemaker implantation (132,227–231). This is much more common in CoreValve recipients (227–231). Preoperative conduction delay is associated with an increased incidence of permanent pacemaker implantation as well. Although heart block occurs usually early after TAVR, it may be delayed up to 30 days. Enhanced surveillance for this complication is important, particularly if the patients are dismissed early following the procedure.

5.3.5. Post-TAVR Device Migration/Malposition

Rarely, TAVR devices will become malpositioned or migrate. In the self-expanding models, they can be moved to some degree until fully deployed. The balloon-expandable models do not enjoy this degree of flexibility with positioning. A malpositioned valve may be “unstable” or may embolize. If the valve is unstable, rapid placement of a second overlapping valve may salvage the procedure. Valves embolizing distally may occasionally be extracted in the aorta and a second device implanted. Ventricular embolization requires urgent surgery (185,232,233).

5.3.6. Ventricular and Vascular Perforation

Ventricular perforation is a rare complication of transfemoral TAVR. Its management is similar to that for this complication during percutaneous balloon aortic valvuloplasty, with pericardial drainage and autotransfusion or conversion to open closure. Large-vessel aortoiliac injury similarly is uncommon, but if present, can be managed in most cases by introduction of a covered stent. Some operators place a guidewire down the leg from the contralateral femoral artery for rapid access and control. Readiness for vessel rupture with occlusion balloon cannot be overemphasized. Preparation for this complication is critical with preplanning. It is best managed by avoiding it. Careful maintenance of a good wire position and use of a stiff wire with a soft tip are helpful in prevention of perforation during TAVR (234).

5.4. Postprocedural Care

5.4.1. Postprocedural Recovery

Designated units for postprocedural recovery are imperative for optimal care and better outcome of this group of high-risk patients undergoing TAVR (221). Although the

particulars of postprocedural care will vary from institution to institution and country to country, as well as with the maturity of the TAVR program, the principles of care remain the same that these complex patients should be treated in postprocedural units experienced with both cardiac surgical and interventional cardiology procedures.

5.4.1.1. RECOMMENDATIONS FOR PROCEDURAL CARE AFTER TAVR

1. Immediate or early extubation, early mobilization, and meticulous attention to the many potential complications in this elderly, frail group of patients.
2. Post-anesthetic care unit (PACU) or intensive care unit (ICU). There should be a common care pathway with all patients cared for in the same setting so that the care team is conversant with the care pathway. The criteria for weaning in a fast-track concept are as follows:
 - a. Adequate core temperature of $>36^{\circ}\text{C}$
 - b. Hemodynamically stable
 - c. No active bleeding from drainage site
3. The care is somewhat different for transapical and transfemoral patients. Prevention of postoperative hypertension and hypertension upon tracheal extubation is crucial in patients undergoing transapical TAVR to decrease the risk of bleeding or ventricular rupture. Patients undergoing transapical TAVR also require postoperative analgesia for thoracotomy incisional pain and management of thoracostomy tube drainage and subsequent thoracostomy tube removal. Transfemoral TAVR patients require supine positioning until femoral vascular access sheaths are removed and hemostasis has been achieved. Patients undergoing direct aortic and subclavian approaches also need to be carefully monitored for any mediastinal/thoracic bleeding with particular attention paid to avoiding postoperative hypertension.
4. The monitoring includes vital parameters including fluid balance therapy, renal status, and atrioventricular conduction system. Adequate hydration and avoidance of early diuretic administration is important to minimize renal failure. Completion of perioperative surgical antibiotic prophylaxis, resuming preoperative medications such as beta blockers, and initiation of prophylaxis for venous thromboembolism should be addressed within the first 24 hours after operation. A pain management regimen should be initiated immediately if necessary after operation in the postprocedural unit and may consist of intercostal nerve block, infiltration of the wound with local anesthetics, narcotics, or non-narcotic analgesics. Epidural analgesia is not normally required for transapical TAVR because the thoracotomy incision is limited and satisfactory postoperative pain control can be achieved with parenteral or patient-controlled analgesics. Patients undergoing transfemoral TAVR should be evaluated for lower extremity vascular insufficiency, groin hematoma, retroperitoneal bleeding, and femoral artery pseudoaneurysm formation in the instrumented limb.
5. When stable, patients should be transferred to a telemetry unit with hemodynamic and electrocardiographic monitoring capability. The duration of monitoring will depend on the patients response to TAVR and the specific prosthesis used. There are differences in the need for permanent pacemaker implantation between the Edwards Sapien and Medtronic CoreValve device with rates being lower with the former; accordingly, longer electrocardiographic monitoring may be required after implantation of the latter (132). Depending on institutional protocols, patients should be discharged from the hospital after a final examination with TTE. Antiplatelet therapy

with aspirin and clopidogrel is recommended to decrease the risk of thrombotic or thromboembolic complications if there are no contraindications to these medications (235).

5.4.2. Hemodynamic Assessment

Echocardiographic assessment early after TAVR generally reveals a favorable hemodynamic response, with the presence of a significantly lower mean transvalvular gradient and a larger effective orifice area (EOA), usually ≤ 10 mm Hg and >1.5 cm², respectively. Techniques used for assessment of aortic valve performance vary. The use of measurements of the left of the LVOT diameter and velocity immediately proximal to the stent has been emphasized (236). At short- and long-term follow-up, percutaneously implanted valves provide sustained improvements in hemodynamic performance with slightly lower mean transvalvular gradients and larger EOAs than surgically implanted valves, either stented or stentless (237).

Postprocedure hemodynamic assessment is particularly important to exclude potential prosthesis complications. Transcatheter aortic valves differ, not only in design, but also in implantation technique from surgical AVR. TAVR preserves the native calcified aortic valve compared with surgical AVR, which requires that the native valve be removed prior to prosthesis implantation. The native valve and annular calcification may potentially prevent the adherence of the prosthesis to the aortic wall, whereas low prosthesis deployment into the LV outflow tract may lead to incomplete and/or irregular expansion of the prosthesis, as well as paravalvular prosthetic leak.

An additional concern is severe patient-prosthesis mismatch, which is defined as an effective orifice area index ≤ 0.65 cm²/m² (238). Patient-prosthesis mismatch in surgical AVR is associated with a reduction in functional status and increased morbidity and mortality at short-term and long-term follow-up (239,240). The stent in TAVR prosthesis is thinner than that of the stented valves employed for surgical AVR, minimizing the obstruction to blood flow and reducing the incidence of patient-prosthesis mismatch. Whether reduced rates of patient-prosthesis mismatch will translate to improved functional status and improved survival remains to be defined.

5.4.3. Atrial Fibrillation

The incidence of new-onset atrial fibrillation (AF) after successful TAVR ranges from 0.6% to 8.6% (15,124,132,241). However, over 25% of patients undergoing TAVR have pre-existing AF. Continuous postprocedural electrocardiogram monitoring should be performed for at least 3 days in all patients after transcatheter therapy. Management of atrial fibrillation post-TAVR is based on the ACC/AHA/ESC guidelines for management of atrial fibrillation (242).

5.4.4. Treatment of Stroke

The treatment of a stroke will depend on the subtype of stroke diagnosed by brain imaging, timing of the event after any procedure, and the severity of the neurological deficit. A

large intracerebral hemorrhage could call for reversal of any anticoagulants and correction of any coagulopathy with fresh-frozen plasma or other transfusions (243). The diagnosis of an acute ischemic stroke with moderate to severe neurological deficits may require thrombolysis or mechanical clot retrieval depending on the size, location, and whether any major intracerebral artery is occluded. An in-hospital stroke within 8 hours of the onset of neurological symptoms usually requires urgent consultation by a stroke neurologist or neurosurgeon. Angiography and stroke intervention may be recommended for large and/or disabling strokes. These treatments are generally available at comprehensive stroke centers. Typical embolic strokes in this setting are the result of calcific emboli. If the stroke is the result of thromboembolism, local rt-PA may be considered although bleeding risk in this elderly population is very high.

Minor strokes, small infarcts on brain imaging, or the absence of any evidence of any major cerebral vessel occlusions can usually be treated with aspirin (244). If atrial fibrillation is present, then institution of an oral anticoagulant program is warranted (129). If any intracardiac thrombus is detected, then early institution of heparin followed by oral anticoagulants is suggested (63). When the patient is stable, other diagnostic evaluations should be done to evaluate for other potential causes of stroke, including vascular imaging to detect any extracranial carotid or vertebral stenosis or intracranial occlusive disease, echocardiography, and Holter monitoring. If no definite source of cardiac embolism is detected, then long-term treatment with antiplatelet options to prevent recurrent stroke may be instituted, which include aspirin, extended-release dipyridamole, and clopidogrel (129).

5.5. Long-Term Care

5.5.1. Role of Primary Cardiologist

The long-term care of the patient after TAVR will be mainly guided by the primary referring cardiologist. In contrast to patients undergoing surgical AVR, patients undergoing TAVR tend to be older, with more severe comorbidities and lower functional status, mandating more frequent cardiology follow-up.

The role of the primary cardiologist is to:

1. Prescribe and monitor medical therapy for concurrent cardiovascular disease, including hypertension, atrial fibrillation, heart failure, CAD, and peripheral and cerebrovascular disease, as well as diabetes and dyslipidemia.
2. Prescribe and monitor antithrombotic and/or antiplatelet therapy as recommended for the prosthetic aortic valve and concurrent conditions such as coronary stents or atrial fibrillation.
3. Monitor cardiac and TAVR function with periodic clinical evaluation and echocardiography.
4. Surveillance for and treatment of early and late procedural-related complications

5. Maintain close communication with the implanting physicians if complications occur that may be related to the procedure.

5.5.2. Follow-Up Visits

The patient should be followed closely by the implanting physician team for the first 30 days after TAVR to diagnose and follow any procedural complications. Evaluations should include a post-TAVR baseline echocardiogram and ECG (to document any conduction abnormalities) occurring during that time period. After 30 days, a suggested schedule for follow-up by the primary cardiologist is noted in Table 13.

Follow-up is then continued at the first 6 months, at 1 year, and annually thereafter. The frequency of follow-up evaluations should be increased if there is significant post-TAVR paravalvular leak or any change in clinical status or echocardiographic findings. As experience grows with TAVR, the frequency of echocardiography assessment will likely decrease towards that of surgical AVR, deemed appropriate every 3 years (245). Additional diagnostic studies may be considered as clinically warranted, including evaluation for coronary disease if symptoms are present.

5.5.3. Hemodynamic Evaluation

Hemodynamic evaluation should be performed by echocardiography as indicated in Section 5.5.2 above. Invasive measurement of LV and aortic pressure is not routinely needed unless there are unresolved questions, discrepancies between echocardiographic and physical examination findings, or other unresolved clinical issues.

5.5.4. Interaction of Co-Treatments

Given the frequency of coexisting conditions, multiple antiplatelet or anticoagulant strategies may be required. For example, some patients may be receiving antiplatelet therapy for a coronary stent or antithrombotic therapy for atrial fibrillation. This is complicated by the fact that most patients undergoing TAVR are elderly and often have comorbidities that increase bleeding risk. It is prudent to avoid, if possible, the use of multiple anticoagulant therapies. In patients treated with warfarin, a direct thrombin inhibitor, or Factor Xa inhibitor, it is reasonable to continue low-dose aspirin, but other antiplatelet therapy should be avoided, if possible.

Table 13. Recommended Patient Follow-Up Post-TAVR

Timing Post-TAVR	Clinical Evaluation	Echocardiography
30 days	X	X
6 months	X	
1 year	X	X
Annually thereafter	X	X

TAVR indicates transcatheter aortic valve replacement.

5.5.5. Management of AR

AR after TAVR typically is paravalvular and most often only mild or mild to moderate in severity. At 1-year follow-up, 13% of patients have no AR, with only trace or mild regurgitation in 80% of patients (15,124). These patients do not require any specific therapy for AR other than medical therapy for concurrent hypertension and periodic echocardiography monitoring as described above.

Moderate or severe AR is present after TAVR (even after interventions during the procedure to reduce AR severity) in about 12% of patients at 30 days and 7% at 1-year follow-up (15,124).

5.5.5.1. RECOMMENDATIONS FOR MANAGING SEVERE AR AFTER TAVR

1. When severe AR is present after TAVR, treatment is similar to native valve AR as detailed in the ACCF/AHA valvular heart disease guidelines (63).
2. With acute severe AR or chronic severe AR with symptoms of heart failure, surgical AVR may be considered if the patient is a surgical candidate and surgical risk is acceptable. Other options include placement of a second TAVR within the leaking prosthesis ("valve-in-valve").

6. Technology Evolution

Next-generation devices promise the potential for improvements, offering expanded clinical utility with advances that include: lower profile delivery catheters, more accurate positioning, reduced paravalvular leak, and ability to either reposition or even retrieve (Table 14) (246). Many of the new device technologies utilize a self-expandable, high radial strength repositionable prosthesis consisting of pericardial tissue on a nitinol frame. Two additional valves have recently received approval for commercial sale in Europe. The JenaValve (JenaValve Technology, Munich, Germany) and Acurate Valve (Symetis, Inc., Lausanne, Switzerland) are both delivered currently via a transapical approach.

Other valve designs currently in early clinical studies include Portico Valve (St. Jude Medical, St. Paul, MN), Direct Flow Medical (Direct Flow Medical, Santa Rosa, CA), and Sadra Lotus Valve (Sadra Medical, Los Gatos, CA). Other new designs include flexible sealing membranes aimed at more optimal conformation to the calcified native annulus to reduce paravalvular leaks. New valve designs and materials can also provide the possibility of new prosthesis technology. The Lutter valve was created in an effort to create a more physiological heart valve by utilizing tissue engineering (247). The PercValve (Advanced Bioprosthetic Surfaces, San Antonio, TX) uses nanotechnology in its elastic nitinol frame and leaflets. These leaflets are designed to allow for the growth of endothelial cells, essentially converting it to a tissue valve. Initial animal studies have shown complete endothelialization of the e-nitinol leaflets within 10 days and may eliminate the need for anticoagulation (248). A final novel approach involves anchoring the prosthesis by using an injectable polymer that cures in

Table 14. TAVR Valve Types and Qualities

Device	Company	Expansion Mechanism	Valve Material	Stent Material	Repositionable	Retrievable	Clinical Trials	FIM	CE Mark	French Size
Colibri Heart Valve	Endoluminal Technology Research	Balloon- and self-expandable	Pericardium	Stainless steel/ Nitinol	No	No	No	2003	No	Balloon: 16 Self: 12
Direct Flow	Direct Flow Medical	Polymer-injected	Pericardium	Polymer	Yes	No	No	2006	No	22
Lotus	Sadra Medical	Self-expandable	Pericardium	Nitinol	Yes	No	No	2007	No	21
JenaValve	JenaValve Technology	Self-expandable	Pericardium	Nitinol	Yes	No	No	2007	Yes	28
Heart Leaflet	Heart Leaflet Technologies	Self-expandable	Pericardium	Nitinol	Yes	Yes	No	N/A	No	16
Lutter	N/A	Self-expandable	Tissue engineered	Nitinol	No	No	No	N/A	No	N/A
PercValve	Advanced Bioprosthetic Surfaces	Self-expandable	e-Nitinol	e-Nitinol	No	No	No	N/A	No	10
Portico	St. Jude	Self-expandable	Pericardium	Nitinol	Yes	Yes	Yes	2011	No	22
Accurate	Symetis	Self-expandable	Pericardium	Nitinol	Yes	Yes	Yes	2009	Yes	28

CE indicates Conformité Européenne, a mandatory conformity for products placed on the market in the European Economic Area; FIM, first in man; N/A, not applicable; and TAVR, transcatheter aortic valve replacement. Modified from Chiam and Ruiz (94).

position to maintain the implant permanently in place. The outcome with these new technologies will be the focus of multiple registries and then randomized trials.

7. Applications in New Patient Populations and New Study Designs

As experience is gained and technology evolves, the patient population best served with TAVR is likely to change, and 3 areas that merit specific consideration are the “valve-in valve” technique for patients with dysfunctional aortic bioprostheses, the use of TAVR in patients with stenotic bicuspid aortic valves, and application to lower-risk surgical patients. Other patient populations, such as those with chronic or end-stage renal disease, may also be candidates for this technology and will be the subject of future investigations.

7.1. Valve-in-Valve

Patients with dysfunction of a conventional aortic prosthesis present therapeutic challenges. Although repeat operation can be considered, an attractive option is to use a TAVR procedure in which the device is deployed within the previously placed bioprosthesis (209,249–254). In multiple small series, transcatheter aortic valve-in-valve implantation appears to be a safe option for the management of bioprosthetic valve failure in patients at high risk for reoperative conventional AVR. In this setting, coronary anatomy should be carefully defined in order to minimize the possibility of coronary obstruction by the transcatheter prosthesis (209,220,250,255). In addition, valve-in-valve procedures require a large enough bioprosthetic valve inserted at the index operation to prevent patient prosthetic mismatch with the TAVR valve.

7.2. Bicuspid Aortic Valve

The asymmetric valvular anatomy often seen with a bicuspid aortic valve theoretically predisposes to a noncircular expansion of the TAVR device, thereby creating an increased risk of paravalvular regurgitation (256).

Because of this concern, the presence of a bicuspid aortic valve is considered a relative contraindication to TAVR. Since bicuspid aortic valve patients have generally been excluded from major TAVR trials, there is little clinical experience in this area. Several centers, however, have achieved reasonable success in selected bicuspid aortic valve patients with AS (163,256,257). It should be noted that in the Canadian bicuspid aortic valve experience, moderate paravalvular leaks occurred in 2 of 11 patients, and another patient experienced late device migration (256). Bicuspid aortic valve patients with bulky leaflets, markedly asymmetric valvular anatomy, and significant aortic incompetence appear to have a higher risk of suboptimal device seating. Whether new valve designs, perhaps those with self-sealing membranes, will improve device performance in this group remains to be determined.

7.3. Lower-Risk Populations

Data from the STS Registry indicate that approximately 10% of patients undergoing AVR have an STS score ≥ 8 and therefore would be potential candidates for TAVR using current selection criteria. There has been interest in expanding the potential group of candidates for TAVR to include patients with an STS score ≥ 4 . This would broaden to 25% the number of patients who might be treated with TAVR rather than AVR. There has been concern about the potential for “selection creep,” with more lower-risk patients treated with TAVR. This should be avoided until more evidence-based data become available on the outcome of TAVR versus AVR in these patients. The planned and ongoing trials evaluating both the Sapien and the CoreValve in lower-risk populations will be of central importance in identifying subsequent utilization of this technology in expanded patient groups.

8. Introduction of TAVR Into Practice: U.S. Versus European Perspective

8.1. U.S. Perspective

The U.S. perspective reflects the fact that TAVR approval required a randomized controlled trial, the full extent of which has just now been published (124). This contrasts with Europe where 5 new valves or iterations of current valves are already in relatively widespread clinical use. Accordingly, from the U.S. perspective, the rollout of this technology is a key issue. This rollout is influenced by the societal beliefs in a free market; convenient and timely access to medical care; patient and physician expectations; as well as return on investment by companies and institutions alike. These latter issues have led to the proliferation of advanced cardiovascular facilities, which could complicate the rollout of new-device strategies such as TAVR. For example, the state of California alone has 125 facilities that perform percutaneous coronary intervention, the county/city of Los Angeles has 33 cardiovascular surgical and primary ST-elevation myocardial infarction centers. The Dallas–Fort Worth Metropolitan region also has 33 full-service cardiovascular surgical centers. To plan for each of these centers in either Los Angeles or the Dallas–Fort Worth region to offer TAVR would result in the dilution of concentrated experience. Thus, for a complicated procedure such as TAVR, which is applied in some of the highest-risk patients treated for cardiovascular disease, such as those enrolled in the PARTNER and CoreValve trials, setting up specialized centers of excellence should be a top consideration for optimizing patient care and outcomes.

The concept of development of these specialized heart centers is likely to be somewhat controversial, given the expectation in the United States that each hospital with experienced personnel should be able to perform any and all indicated procedures. However, results of TAVR are likely to be optimal when performed by a heart team of experi-

enced surgeons, structural interventional cardiologists, and CV imaging specialists working together in high-volume tertiary care centers with ancillary support services capable of dealing with very complex patients with advanced comorbid conditions. For detailed recommendations, please refer to the Multisocietal Position Statement on Operator and Institutional Requirements for TVRR (218). The specific details of the U.S. rollout and reimbursement for this procedure are as yet to be fully determined. The criteria for regulatory approval and reimbursement by appropriate federal agencies should be based upon expertise; high, adjudicated procedure volumes; and documentation of a healthcare team approach. In addition, mandatory enrollment in structural heart disease registries should be required so that short- and longer-term outcomes can be assessed and updated with new evolving data.

8.2. European Perspective

Adoption of TAVR has been rapid, and the changing trends in Europe have escalated; in selected centers in Germany, TAVR accounts for over 30% of all AVRs. For example, 1 single center has an experience of more than 1,300 TAVRs and has trained more than 360 doctors in over 32 centers from more than 30 countries. Germany itself has approximately 87 centers performing TAVR. The miniaturization of the applicator device, the option to implant newer valves from different manufacturers, and the need for high-quality intraoperative imaging are challenges consistent with the high costs involved with these procedures. Reimbursement varies in different countries. In general, at present, the insurance providers in Europe are bearing the high costs involved in these operative procedures which may be questioned in the future, unless outcomes of improved long-term survival are available. The United Kingdom approach to the development of active TAVR centers has recently been described and can serve as a model for other countries. This rollout included 2 specific technologies (i.e., Medtronic CoreValve and Edwards Sapien). The development of this program consisted of didactic session, simulator training, observation of cases at experienced centers, and proctoring at new centers. Core essentials of the program included a multidisciplinary team process for patient selection and for procedural performance. All patients undergoing TAVR were entered into a Central Cardiac Audit Database, which included clinical as well as administrative data using standardized data elements and definitions. This approach has the advantage of including all patients with either of the 2 devices, monitoring the potential of changing patient selection criteria, the ability to document learning curve and the opportunity to evaluate the outcome of patients treated with each of the devices. Particularly relevant findings include the observation that: 1) 30-day and mid-term mortality was equivalent in proctored and nonproctored cases; and 2) the fact that outcomes in the first 20 cases were similar to subsequent cases in each of the 25 centers involved.

9. Role of Registries

Post-marketing data collection for medical device evaluation is an essential component in the assessment of device performance and its benefit/risk balance throughout the product life cycle. In addition to confirmation of data observed in pre-approval studies, post-marketing studies provide information regarding ‘real world’ use in patient subsets not fully tested in pre-market clinical trials. Registries offer an important platform for post-marketing device evaluation. For example, the STS National Database and ACC’s National Cardiovascular Data Registry (NCDR®) that have traditionally focused on national benchmarking, quality improvement, and research, are rapidly emerging to fulfill this important role. The ability to link clinical registry data with administrative data opens an untapped resource for monitoring and predicting both short- and potentially long-term outcomes. In general, the short-term clinical information can be used for risk stratification and identification of important clinical subgroups, whereas the administrative data can be used to track patterns of use and ultimately long-term events.

In the past, device monitoring has typically been carried out through industry-supported trials and post-approval studies. It has been necessary for industry to undertake the very expensive and time-consuming task of developing data registries. In the development of these registries, there has been little coordination with existing societal registries to harmonize definitions or data specifications. An unfortunate byproduct of this approach has led to the well-recognized inconsistencies seen in cardiovascular data reporting. In addition, there is the unavoidable potential for a conflict of interest that might arise from a manufacturer conducting studies of its own device.

The use of clinical registries can address many of these concerns. Registries such as the STS Database and ACC’s NCDR® have a high degree of national participation, so the data represents a true national experience. These registries have a well-established protocol for data collection, with trained abstractors and onsite rigorous audits to ensure high data quality and completeness of entry. Database definitions are generally regarded as national standards, and there is a high degree of harmonization between terms common to these registries. These definitions should be based upon consensus documents; for example, VARC definitions of stroke (96). Furthermore, each registry can be linked to administrative databases in order to obtain long-term outcome information. These facts demonstrate the ability of the national cardiovascular registries to serve as the foundation for comprehensive device registries. In the last few years, the FDA has collaborated with various organizations to use registry data to investigate several important device-related studies. Although there is no specific legislative mandate to use clinical registries, FDA leadership does actively encourage the use of registries for device surveillance.

Registries offer distinct theoretical advantages in this field, but it should be remembered that practical application presents uncharted waters. Perhaps 1 major challenge lies in the fact that a successful program will require close cooperation between multiple organizations. For example, the STS and ACCF have a long history of cooperation and collaboration on registry-related projects, holding monthly conference calls devoted to registry coordination, thus laying the foundation for collaborative projects such as device surveillance. Similar collaborations will require the need for contractual agreements to address issues such as data ownership, data access, and governance of linked registries. Sophisticated statistical analysis will be a central feature of surveillance projects, so coordination with an analytic center will also be necessary. Certainly, FDA input will be central to any device-related project, and coordination with the Centers for Medicare and Medicaid Services (CMS) may be necessary as well. The device manufacturer will have an essential role, especially in post-approval studies, so coordination with industry will be a key element of any project.

Device surveillance will require fundamental changes in the clinical database operations. Presently, there is no provision for timely data entry, but post-approval studies will require exactly that in order to capture adverse events as they occur. Likewise, post-approval studies require long-term follow-up of information that cannot be obtained from administrative databases. Provision must be made to capture information such as echocardiographic findings and quality-of-life data months to years after device insertion. It should also be noted that the use of CMS MedPAR data may have limited usefulness in this context because of the inability to acquire contemporary data limited to only those patients >65 years. (In general, the most current available MedPAR data are 2 years old.) Additional challenges include standardized rigorous methodology adapted for sparse data and standardized reporting formats modeled after the CONSORT (Consolidated Standards of Reporting Trials) guidelines for randomized trials, PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) guidelines for meta-analyses, or STROBE (STrengthening the Reporting of Observational studies in Epidemiology) guidelines for observational studies (182,258–260). It should be emphasized that the registry should capture data on all devices that are placed. Specific post-approval studies may focus on a smaller, more select population, but a comprehensive registry should collect information on all devices for complete analyses independent of industry-sponsored studies. A potential incentive for participation in the device registry might be linking it to CMS coverage criteria or other form of federal legislation.

Funding the device registries requires innovative consideration. Despite the fact that federal agencies encourage the use of clinical registries, funding for such projects is not available for device-related projects. Although industry funding for studies related to their specific product offers the

most straightforward approach other models rely upon centers to pay a fee in return for registry participation.

As registries are developed, a “silo” construction must be avoided. It is critically important to keep an eye on the future so that present plans fit seamlessly with the vision for future initiatives. This means that a device-specific registry should be designed to serve as a building block for the next generation of registries. Planning for interoperability, resource sharing, and avoidance of duplication will be necessary to create the system of integrated, coordinated registries that will be the hallmark of registries for the next decade.

10. Summary and Recommendations

There are a number of potential treatment recommendations for patients with AS (Table 15). Consideration of the risk/benefit of each option needs to be carefully evaluated

and discussed with the patient and family. The involvement of the heart team in decision making is also essential.

The approval of TAVR represents a fundamental change in the management of aortic valvular heart disease by offering an alternative to traditional surgical aortic valve replacement in carefully selected patients. The penetration of this technology in the broad group of patients with AS remains to be determined and will depend on the continued evolution of the technology and the results of clinical trials conducted in these patients. At the present time, several observations and recommendations can be made.

1. *Complex Technology*: Although the technique and equipment continue to evolve, TAVR is a complex procedure with many interlocking steps that require meticulous attention to achieve optimal results and minimize complications.
2. *Team-Based Approach*: A foundational requirement of TAVR is a team-based approach to patient care. Given the high-risk profile of patients, who often have

Table 15. Current Treatment Recommendations for Patients With Aortic Stenosis

Treatment	Indication	Major Complications
Surgical Aortic Valve Replacement	<ul style="list-style-type: none"> • Symptomatic severe AS (Class I, LOE: B) • Severe AS undergoing CABG, aortic surgery or other valve surgery (Class I, LOE: C) • Symptomatic moderate AS undergoing CABG, aortic surgery or other valve surgery (Class IIa, LOE: C) • Asymptomatic severe AS with hypotensive response to exercise (Class IIb; LOE: C) • Asymptomatic extremely severe AS (AVA <0.6 cm², mean gradient >50 mm Hg, or jet velocity >5 m/s) (Class IIb, LOE: C) 	<ul style="list-style-type: none"> • Mortality (3%) • Stroke (2%) • Prolonged ventilation (11%) • Thromboembolism and bleeding • Prosthetic dysfunction • Perioperative complications are higher when surgical AVR is combined with CABG
Transcatheter Aortic Valve Replacement	<ul style="list-style-type: none"> • TAVR is recommended in patients with severe, symptomatic, calcific stenosis of a trileaflet aortic valve who have aortic and vascular anatomy suitable for TAVR and a predicted survival >12 months, and who have a prohibitive surgical risk as defined by an estimated 50% or greater risk of mortality or irreversible morbidity at 30 days or other factors such as frailty, prior radiation therapy, porcelain aorta, and severe hepatic or pulmonary disease. • TAVR is a reasonable alternative to surgical AVR in patients at high surgical risk (PARTNER Trial Criteria: STS ≥8%*) 	<ul style="list-style-type: none"> • Mortality (3% to 5%) • Stroke (6% to 7%) • Access complications (17%) • Pacemaker insertion <ul style="list-style-type: none"> ○ 2% to 9% (Sapien) ○ 19% to 43% (CoreValve) • Bleeding • Prosthetic dysfunction • Paravalvular AR • Acute kidney injury • Other <ul style="list-style-type: none"> ○ Coronary occlusion ○ Valve embolization ○ Aortic rupture
Balloon Aortic Valvuloplasty	<ul style="list-style-type: none"> • Reasonable for palliation in adult patients with AS in whom surgical AVR cannot be performed because of serious comorbid conditions (Class IIb, LOE: C) • Bridge to surgical AVR (Class IIb, LOE: C) 	<ul style="list-style-type: none"> • Mortality • Stroke • Access complications • Restenosis
Medical Therapy	<ul style="list-style-type: none"> • No specific therapy for asymptomatic AS • Medical therapy not indicated for symptomatic severe AS • Appropriate control of blood pressure and other risk factors as indicated • Statins not indicated for preventing progression of AS • Diuretics, vasodilators and positive inotropes should be avoided in patients awaiting surgery because of risk of destabilization 	<ul style="list-style-type: none"> • Hemodynamic instability

Class I: Conditions for which there is evidence for and/or general agreement that the procedure or treatment is beneficial, useful, and effective; Class II: Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a procedure or treatment; Class IIa: Weight of evidence/opinion is in favor of usefulness/efficacy; Class IIb: Usefulness/efficacy is less well established by evidence/opinion; LOE B: Data derived from a single randomized trial or nonrandomized studies; LOE C: Only consensus opinion of experts, case studies, or standard-of-care. *The original PARTNER protocol specified inclusion criteria as a minimum STS-predicted risk of mortality of ≥10. During the trial enrollment phase, the minimum STS-predicted risk of mortality was changed to ≥8. In both instances, 2 surgeons had to document that the true predicted risk of mortality was ≥15.

AR indicates aortic regurgitation; AS, aortic stenosis; AVR, aortic valve replacement; CABG, coronary artery bypass graft; LOE, level of evidence; STS, Society of Thoracic Surgeons; and TAVR, transcatheter aortic valve replacement. Source of Class/LOE recommendations: Bonow et al. (28).

multiple comorbidities, as well as the technical complexity of the procedure involved, this team-based care will need to include multiple contributors at different stages in the process but will be mainly centered around the primary cardiologist, the cardiovascular surgeon, and the interventional cardiologist. Patients and families must be included in the care team. Other team members will include cardiac anesthesiologists, heart failure specialists, structural heart disease physicians, imaging specialists and the nursing care team, among others.

3. *Patient Selection:* In adults with severe, symptomatic, calcific stenosis of a trileaflet aortic valve who have aortic and vascular anatomy suitable for TAVR and a predicted survival >12 months:

- TAVR is recommended in patients with prohibitive surgical risk.
- TAVR is a reasonable alternative to surgical AVR in patients at high surgical risk.

Definitions of severe AS have varied between registries, trials, and guidelines. In general, all require severely reduced, calcified leaflet motion, and aortic jet velocity >4.0 m/s OR an AVA <1.0 cm² OR AV index <0.6 cm²/m² OR a mean gradient >40 mm Hg. In the setting of LV systolic dysfunction, severe AS is present when the leaflets are calcified, with reduced systolic motion, and dobutamine stress echocardiography shows an aortic velocity of >4.0 m/s OR mean gradient >40 mm Hg with a valve area <1.0 cm² OR AV index <0.6 cm²/m² at any flow rate.

Prohibitive surgical risk is defined as:

- An estimated 50% or greater risk of mortality or irreversible morbidity at 30 days (as assessed by one cardiologist and 2 cardiothoracic surgeons), or other factors such as frailty, prior radiation therapy, porcelain aorta, and severe hepatic or pulmonary disease.
- Suitable aortic and vascular anatomy is defined as:
- Both aortic annulus size and valve plane to coronary ostium height suitable for placement of an available TAVR.
- Adequate vascular access for passage of the TAVR system (femoral iliac, subclavian, axillary) or suitability for an apical implantation approach.

TAVR is not currently recommended because of limited available information in adults who have:

- An acceptable surgical risk for conventional surgical AVR
- Known bicuspid aortic valve
- Failing bioprosthetic aortic valve
- Severe mitral annular calcification or severe MR
- Moderate AS
- Other (e.g., severe AR and subaortic stenosis)

In these groups, additional scientific data will need to be collected to ascertain risk/benefit ratio prior to integration into routine clinical care.

4. *TAVR Screening:* Screening protocols should be part of every TAVR evaluation. These may vary from institution to institution. Some information may be obtained from referring institutions, whereas some will be obtained within the institution performing the TAVR. In the former case, the information obtained must be of high quality so that optimal recommendations can be formulated. Requisite pieces of information include:

- Data sufficient to calculate STS score
- Measurement of clinical parameters related to the presence of comorbid conditions such as pulmonary function tests in patients with COPD or extent and severity of malignancy if present
- Assessment for the degree of cognitive impairment as appropriate
- Imaging data to confirm
 - Presence and severity of aortic stenosis
 - Presence and severity of associated CAD
 - Left ventricular function
 - Presence and severity of associated valvular heart disease lesions
 - Presence and extent of cerebral vascular disease
- Preprocedural imaging for planning should be done by the institution performing TAVR
 - Assessment of annular size for device selection
 - Assessment of details of arterial anatomy including the peripheral aortoiliac vessels as well as the aortic arch and ascending aorta which may impact on access selection

5. *Site Selection:* Centers should have experience with structural heart disease. All members of the heart team should be available onsite. In addition, a structural heart disease center or clinic, a procedural performance area (either a hybrid surgical room or a specially modified cardiac catheterization laboratory room), a postprocedure care team, and expert imaging using echocardiography and CT should be available. Setting up specialized centers of excellence with convenient access to patients should be a top priority for responsible dissemination of this technology. For more details, please see facility requirements in the “SCAI/AATS/ACCF/STS Multisociety Expert Consensus Statement: Operator & Institutional Requirements for Transcatheter Valve Repair and Replacement; Part 1 TAVR” (218).

6. *Center and Physician Experience:* Expertise with surgical AVR is essential—the number of surgical procedures has been recommended to be 50 within the past 12 months. For the interventional cardiologist, experience with balloon aortic valvuloplasty as well as experience in a team-based care approach is recommended. During the rollout of the procedure, experienced proctors will form part of the heart care team. These physicians will be onsite for the first several cases after a site has been initiated. After the performance of these initial procedures, centers will be eligible to qualify for independent

TAVR. Physician teams need to be experienced with transapical, transarterial, and alternative arterial approaches for TAVR. For detailed information on requirements for interventional cardiologists and surgeons to perform TAVR, please refer to the “SCAI/AATS/ACCF/STS Multisociety Expert Consensus Statement: Operator & Institutional Requirements for Transcatheter Valve Repair and Replacement; Part 1 TAVR.” (218).

7. *Procedural Performance:* TAVR should be performed in either specially modified, large cardiac catheterization laboratories or hybrid rooms. Fixed imaging and intraprocedural echocardiography are required as are capabilities for cardiopulmonary bypass for management of procedural complications. In addition to the valve implantation equipment, peripheral and coronary interventions equipment must be available for urgent treatment of complications. The ability to provide general anesthesia should be available.
8. *Postprocedural Care:* The intensity of postprocedural care depends on the presence of comorbidities, as well as the results of the TAVR itself. Protocols should be defined for routine care, as well as management of specific problems and complications. Ideally, a dedicated recovery area should be established at each site to which all patients should be transferred for optimal postprocedural care. Postdischarge care plans should include consideration of rehabilitation, and home health or other support needed during recovery. In addition, follow-up with the primary care team can ensure successful transitions of care.
9. *Registries:* Participation is recommended in national TAVR registries that include clinical and administrative claims data that will allow careful evaluation of both short-term and long-term risks and benefits and track changes in patient selection criteria, procedural performance, and device iteration. Preferably, registries should also capture demographics and mortality outcome data of surgically and medically treated patients in order to facilitate comparison of different therapeutic strategies to improve identification and selection of optimal therapeutic options.

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Key Words: ACCF Clinical Expert Consensus Document ■ aortic stenosis ■ aortic valve replacement ■ heart team ■ high-risk patients ■ percutaneous valve therapy ■ structural heart disease ■ transcatheter aortic valve implantation ■ transcatheter aortic valve replacement.

**APPENDIX 1. AUTHOR RELATIONSHIPS WITH INDUSTRY AND OTHER ENTITIES (RELEVANT)—
 2012 ACCF/AATS/SCAI/STS EXPERT CONSENSUS DOCUMENT ON TRANSCATHETER AORTIC VALVE
 REPLACEMENT**

Committee Member	Employment	Consultant	Speaker's Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational or Other Financial Benefit	Expert Witness
Arvind Agnihotri*	Massachusetts General Hospital/Harvard Medical School—Cardiac Surgeon	None	None	None	None	• Edwards Lifesciences	None
Karen P. Alexander	Duke University Medical Center—Associate Professor of Medicine/Cardiology	None	None	None	None	None	None

Committee Member	Employment	Consultant	Speaker's Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational or Other Financial Benefit	Expert Witness
Steven R. Bailey*	University of Texas Medical Center—Professor of Medicine and Radiology	None	None	None	<ul style="list-style-type: none"> • Boston Scientific (DSMB) • Palmaz Scientific 	None	None
John H. Calhoun	University of Texas Health Sciences Center—Professor and Chair, Department of CT Surgery	None	None	None	None	None	None
Blase A. Carabello*	Veterans Affairs Medical Center; Baylor College of Medicine—Professor of Medicine	None	None	None	<ul style="list-style-type: none"> • Edwards Lifesciences (DSMB)† • Medtronic† 	None	None
Milind Y. Desai	Cleveland Clinic—Associate Professor of Medicine, Department of Cardiovascular Medicine	None	None	None	None	None	None
Fred H. Edwards	University of Florida—Professor of Surgery; Chief, Cardiothoracic Surgery	None	None	None	None	None	None
Gary S. Francis	University of Minnesota Medical School—Professor of Medicine	None	None	None	<ul style="list-style-type: none"> • Corthera (DSMB) • Novartis (DSMB) 	None	None
Timothy J. Gardner	Christiana Care Health Systems—Medical Director	None	None	None	None	None	None
David R. Holmes, Jr.	Mayo Clinic—Consultant, Cardiovascular Diseases	None	None	None	None	None	None
A. Pieter Kappetein*	Erasmus Medical Center—Department of Thoracic Surgery	None	None	None	None	<ul style="list-style-type: none"> • Boston Scientific† • Medtronic† 	None
Sanjay Kaul	Cedars-Sinai Medical Center—Director, Cardiology Fellowship Training Program	None	None	None	None	None	None
Jane A. Linderbaum	Mayo Clinic; Saint Mary's Hospital—Assistant Professor of Medicine; Director, CV Inpatient Practice	None	None	None	None	None	None
Michael J. Mack*	The Heart Hospital Baylor Plano—Director	None	None	None	<ul style="list-style-type: none"> • Boston Scientific† • Edwards Lifesciences† 	None	None
Chirojit Mukherjee	Heart Center Leipzig University of Leipzig, Germany—Senior Consultant & Director Fellowship Program Anesthesia and Intensive Medicine II	None	None	None	None	None	None
Debabrata Mukherjee	Texas Tech University Health Sciences Center—Chief, Cardiovascular Medicine	None	None	None	None	None	None

Committee Member	Employment	Consultant	Speaker's Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational or Other Financial Benefit	Expert Witness
Catherine M. Otto	University of Washington, Division of Cardiology—Professor of Medicine	None	None	None	None	None	None
Carlos E. Ruiz	Lenox Hill Heart and Vascular Institute of New York—Professor and Chief, Division of Pediatric Cardiology	None	None	None	None	None	None
Ralph L. Sacco	Miller School of Medicine, Jackson Memorial Hospital, University of Miami—Chairman of Neurology, Professor of Neurology, Public Health & Epidemiology, Human Genetics, and Neurosurgery; Executive Director, McKnight Brain Institute	None	None	None	None	None	None
Donnette Smith	Mended Hearts—Consumer Advocate	None	None	None	None	None	None
James D. Thomas	Cleveland Clinic Foundation—Moore Chair of Cardiovascular Imaging	None	None	None	None	None	None

This table represents the relationships of committee members with industry and other entities that were determined to be relevant to this document. These relationships were reviewed and updated in conjunction with all meetings and/or conference calls of the writing committee during the document development process. The table does not necessarily reflect relationships with industry at the time of publication. A person is deemed to have a significant interest in a business if the interest represents ownership of 5% or more of the voting stock or share of the business entity, or ownership of ≥\$10,000 of the fair market value of the business entity; or if funds received by the person from the business entity exceed 5% of the person's gross income for the previous year. Relationships that exist with no financial benefit are also included for the purpose of transparency. Relationships in this table are modest unless otherwise noted. Please refer to <http://www.cardiosource.org/Science-And-Quality/Practice-Guidelines-and-Quality-Standards/Relationships-With-Industry-Policy.aspx> for definitions of disclosure categories or additional information about the ACCF Disclosure Policy for Writing Committees.

According to the ACCF, a person has a *relevant* relationship if: a) the relationship or interest relates to the same or similar subject matter, intellectual property or asset, topic, or issue addressed in the document; or b) the company/entity (with whom the relationship exists) makes a drug, drug class, or device addressed in the document, or makes a competing drug or device addressed in the document; or c) the person or a member of the person's household, has a reasonable potential for financial, professional or other personal gain or loss as a result of the issues/content addressed in the document.

*Recused from writing initial text and voting on document recommendations due to relevant relationships with industry to this document. †No financial benefit.

DSMB indicates Data Safety Monitoring Board.

APPENDIX 2. REVIEWER RELATIONSHIPS WITH INDUSTRY AND OTHER ENTITIES (RELEVANT)— 2012 ACCF/AATS/SCAI/STS EXPERT CONSENSUS DOCUMENT ON TRANSCATHETER AORTIC VALVE REPLACEMENT

Peer Reviewer	Representation	Employment	Consultant	Speaker's Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
David H. Adams	Official Reviewer—AATS	Mt. Sinai Medical Center Department of Thoracic Surgery—Professor and Chair	• Edwards Lifesciences*	None	None	None	• Medtronic	None
Gabriel S. Aldea	Official Reviewer—STS	University of Washington Medical Center—Associate Professor of Medicine	None	None	None	None	None	None
Ottavio Alfieri	Organizational Reviewer—EACTS	San Raffaele University Hospital—Professor, Division of Cardiac Surgery	• Symetis • Valtech	None	None	None	• Edwards Lifesciences	None

Peer Reviewer	Representation	Employment	Consultant	Speaker's Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
Stephen H. Bailey	Content Reviewer	Allegheny General Hospital Department of Cardiovascular Thoracic Surgery	None	None	None	None	None	None
Deepak L. Bhatt	Official Reviewer—ACCF Task Force on Clinical Expert Consensus Documents	VA Boston Health Care System—Chief, Division of Cardiology	None	None	None	• Ethicon* • Medtronic*	None	None
Emmanouil Brilakis	Content Reviewer—ACCF Interventional Scientific Council	UT Southwestern Medical School—Director, Cardiac Catheterization Laboratory, VA North Texas Healthcare System	• St. Jude* • Terumo	None	None	None	• Abbott Vascular* • Infraredx* • Medtronic*	None
James Burke	Content Reviewer—ACCF Interventional Scientific Council	Lehigh Valley Heart Specialists	None	None	None	None	None	None
Shelton Caruthers	Organizational Reviewer—SCMR	Washington University School of Medicine, Cardiovascular MR Labs	None	None	• General Electric • Royal Philips Electronics	• Kereos*	None	None
Albert T. Cheung	Organizational Reviewer—SCA	Hospital of the University of Pennsylvania—Professor of Anesthesiology & Critical Care	None	None	None	None	None	None
Joseph Cleveland	Content Reviewer—ACCF Council on Cardiovascular Care for Older Adults	University of Colorado Denver—Associate Professor	• Baxter Biosurgery	None	None	None	None	None
George Dangas	Content Reviewer—ACCF Interventional Scientific Council	Mount Sinai Medical Center—Program Director, Interventional Cardiology	• Abbott • Boston Scientific • Bracco • Guerbet • Maquet/Datascope • Medtronic • St. Jude Medical	• Astra Zeneca • NCME	None	None	• Abbott Vascular† • Lutonix† • Medtronic† • Ortho McNeil	Plaintiff, stroke, 2011
Larry Dean	Content Reviewer—ACCF Interventional Scientific Council	University of Washington School of Medicine—Professor of Medicine & Surgery	• Emageon • Philips Medical	• Edwards Lifesciences	None	None	None	None
Pamela Douglas	Content Reviewer—ACCF Imaging Council	Duke University Medical Center—Ursula Geller Professor of Research in Cardiovascular Diseases	None	None	None	• Atritech† • Edwards LifeSciences† • Viacor†	None	None
Ted Feldman	Official Reviewer—SCAI	Evanston Hospital Cardiology Division—Director, Cardiac Catheterization Lab	• Abbott • Boston Scientific • Edwards Lifesciences • W.L. Gore	None	None	• Abbott • Boston Scientific† • Edwards Lifesciences† • W.L. Gore†	None	None
David A. Fullerton	Official Reviewer—STS & TVRR Writing Committee	University of Colorado School of Medicine—Head, Cardiothoracic Surgery	None	None	None	None	None	None

Peer Reviewer	Representation	Employment	Consultant	Speaker's Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
Mario J. Garcia	Content Reviewer—ACCF Task Force on Clinical Expert Consensus Documents	Montefiore Medical Center—Albert Einstein College of Medicine—Chief, Division of Cardiology	• MD Imaging	None	• Pfizer	None	None	None
Frederico Gentile	Content Reviewer—ACCF Task Force on Clinical Expert Consensus Documents	Centro Medico Diagnostico	None	None	None	None	None	None
Robert Guyton	Content Reviewer—ACCF Patient-Centered Care Committee	Emory Clinic, Inc.—Professor and Chief, Division of Cardiothoracic Surgery	None	None	None	NIH†	None	Defendant, Cardiac Surgery, 2011
Rebecca T. Hahn	Organizational Reviewer—ASE	Columbia University College of Physicians & Surgeons —Associate Professor of Clinical Medicine	None	None	None	None	None	None
Joerg Hausleiter	Organizational Reviewer—SCCT	Duetsches Herzzentrum Munchen	None	• Abbott	None	None	None	None
Joerg Herrmann	Content Reviewer—ACCF Interventional Scientific Council	Mayo Clinic	None	None	None	None	None	None
Loren Hirtzka	Organizational Reviewer—AHA	Cardiac, Vascular and Thoracic Surgeons, Inc.—Medical Director, Cardiac Surgery	None	None	None	None	None	Defendant, delayed pericardial tamponade after aortic valve surgery, 2004
Philippe H. Kolh	Organizational Reviewer—EACTS	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported
Michael J. Landzberg	Content Reviewer—ACCF Adult Congenital & Pediatric Cardiology Council	BACH Pulmonary Hypertension Serv—Medical Director, Boston Adult Congenital Heart	None	None	None	None	None	None
Catherine Case Larson	Organizational Reviewer—Mended Hearts	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported
Jonathon Leipsic	Organizational Reviewer—SCCT	Providence Health Care; University of British Columbia—Chairman, Department of Radiology; Assistant Professor of Radiology	None	• Edwards Lifesciences • GE Healthcare	None	None	• Edwards Lifesciences*	None
Glenn Levine	Content Reviewer—ACC/AHA Percutaneous Coronary Interventions Guidelines	Baylor College of Medicine— Professor of Medicine	None	None	None	None	None	Defendant, Patient non-responsive after noncardiac surgery, 2010

Peer Reviewer	Representation	Employment	Consultant	Speaker's Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
Jane A. Linderbaum	Content Reviewer—ACCF Task Force on Clinical Expert Consensus Documents	Mayo Clinic; Rochester Saint Mary's Hospital—Assistant Professor of Medicine; Director, CV Inpatient Practice	None	None	None	None	None	None
Ehtisham Mahmud	Content Reviewer—ACCF Interventional Scientific Council	University of California, San Diego—Professor of Medicine and Director, Cardiac Catheterization Laboratory	• Phillips Medical	• Medtronic	None	• Abbott Vascular* • Boston Scientific*	• St. Jude's Medical	None
Margo B. Minissian	Content Reviewer—ACCF Cardiovascular Team Council	Cedars Sinai Heart Institute Women's Heart Center; UCLA School of Nursing—Cardiology Nurse Practitioner; Assistant Clinical Professor	None	None	None	None	None	None
David J. Moliterno	Content Reviewer—ACCF Task Force on Clinical Expert Consensus Documents	University of Kentucky—Chief of Medicine	• Boston Scientific • Symetis	None	None	None	None	None
Srihari Naidu	Content Reviewer—ACCF Interventional Scientific Council	Winthrop University Hospital—Director, Cardiac Cath Lab	• Abbott Vascular	None	None	None	None	None
Hani Najm	Content Reviewer—ACCF Surgeon Scientific Council	National Guard Health Affairs—President, Saudi Heart Association	None	None	None	None	None	None
Rick Nishimura	Content Reviewer—ACC/AHA Valvular Heart Disease Guidelines	Mayo Clinic, Division of Cardiovascular Disease—Judd and Mary Morris Leighton Professor of Medicine	None	None	None	None	None	None
Amit R. Patel	Organizational Reviewer—SCMR	Chicago Department of Medicine—Assistant Professor of Medicine	None	None	None	None	None	None
Stephen Ramee	Official Reviewer—ACC Board of Governors	Ochsner Clinic Foundation—Director, Cardiac Catheterization	None	None	• Access Closure* • Boston Scientific* • Hot Spur*	• Abbott† • Boston Scientific† • Edwards Lifesciences† • Medtronic†	None	None
Pasala Ravichandran	Content Reviewer—ACCF Surgeon Scientific Council & ACCF Heart Failure & Transplant Committee	Oregon Health & Science University—Associate Professor	None	None	None	None	None	None

Peer Reviewer	Representation	Employment	Consultant	Speaker's Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
Jack Shanewise	Organizational Reviewer—SCA	Columbia University College of Physicians & Surgeons—Professor of Clinical Anesthesiology	None	None	None	None	None	Defendant, ruptured pulmonary artery by PA cath, 2011 Defendant, air embolism during heart surgery, 2010 Plaintiff, failed endotracheal tube exchange, 2011
William J. Stewart	Organizational Reviewer—ASE	Cleveland Clinic Foundation—Professor of Medicine	None	None	None	None	• Edwards Lifesciences†	None
Lars G. Svensson	Official Reviewer—AATS	Cleveland Clinic Foundation Department of Thoracic & Cardiovascular Surgery—Director, Center for Aortic Surgery	None	None	• Valve Exchange • Cardiosolutions • Postthorax†	• Edwards Lifesciences†	None	None
E. Murat Tuzcu	Official Reviewer—ACCF Board of Trustees	Cleveland Clinic Foundation—Professor of Medicine	None	None	None	None	None	None
Hector Ventura	Content Reviewer—ACCF Heart Failure & Transplant Committee	Ochsner Clinic Foundation Department of Cardiology—Director, Section of Cardiomyopathy and Heart Transplantation	None	None	None	• PARTNER Trial Executive Committee†	None	None
Robert Vincent	Content Reviewer—ACCF Adult Congenital & Pediatric Cardiology Council	Children's Sibley Heart Center—Co-Medical Director, Heart Transplant; Director, Cardiac Catheterization Laboratory	None	None	None	None	AGA Medical Corp†	Defendant, vascular injury during cath, 2009 Plaintiff, air embolus, 2008 Defendant, cause of dilated cardiomyopathy, 2007
Andrew R. Weintraub	Organizational Reviewer—HFSA	Tufts University School of Medicine—Assistant Professor of Medicine	None	None	None	None	• Cardiva Inc	None
Christopher White	Content Reviewer—ACCF Interventional Scientific Council	Ochsner Clinical Foundation—Chairman, Department of Cardiology	• Baxter	None	None	• St. Jude	None	None
Alan Zajarias	Official Reviewer—SCAI	Washington University School of Medicine—Associate Professor of Medicine	• St. Jude's Medical • Edwards Lifesciences	None	None	• Edwards Lifesciences (PI, PARTNER 2 Trial)†	None	None

This table represents the relationships of reviewers with industry and other entities that were disclosed at the time of peer review and determined to be relevant. It does not necessarily reflect relationships with industry at the time of publication. A person is deemed to have a significant interest in a business if the interest represents ownership of $\geq 5\%$ of the voting stock or share of the business entity, or ownership of $\geq \$10,000$ of the fair market value of the business entity; or if funds received by the person from the business entity exceed 5% of the person's gross income for the previous year. A relationship is considered to be modest if it is less than significant under the preceding definition. Relationships that exist with no financial benefit are also included for the purpose of transparency. Relationships in this table are modest unless otherwise noted. Names are listed in alphabetical order within each category of review.

According to the ACCF/AHA, a person has a *relevant relationship* IF: a) the *relationship or interest* relates to the same or similar subject matter, intellectual property or asset, topic, or issue addressed in the *document*; or b) the *company/entity* (with whom the relationship exists) makes a drug, drug class, or device addressed in the *document*, or makes a competing drug or device addressed in the *document*; or c) the *person or a member of the person's household*, has a reasonable potential for financial, professional or other personal gain or loss as a result of the issues/content addressed in the *document*.

*Significant relationship. †No financial benefit.

AATS indicates American Association for Thoracic Surgery; ACCF, American College of Cardiology Foundation; ACE, Accreditation for Cardiovascular Excellence; AHA, American Heart Association; ASE, American Society of Echocardiography; DCRI, Duke Clinical Research Institute; EACTS, European Association for Cardio-Thoracic Surgery; HFSA, Heart Failure Society of America; NCDR-CARE, National Cardiovascular Data Registry-Carotid Artery Revascularization and Endarterectomy; NIH, National Institutes of Health; PARTNER, Placement of Aortic Transcatheter Valve Trial; PI, principal investigator; SCA, Society of Cardiovascular Anesthesiologists; SCAI, Society for Cardiovascular Angiography and Interventions; SCCT, Society of Cardiovascular Computed Tomography; SCMR, Society for Cardiovascular Magnetic Resonance; and STS, Society of Thoracic Surgeons.

APPENDIX 3. ABBREVIATION LIST

AR = aortic regurgitation	LVOT = left ventricular outflow tract
AS = aortic stenosis	MDCT = multidetector computed tomography
AVA = aortic valve area	NCDR = National Cardiovascular Data Registry
AVR = aortic valve replacement	PARTNER = Placement of Aortic Transcatheter Valve trial
CAD = coronary artery disease	PH = pulmonary hypertension
CMR = cardiac magnetic resonance	RV = right ventricular
COPD = chronic obstructive pulmonary disease	SOURCE = SAPIEN Aortic Biosprosthesis European Outcome registry
CT = computed tomography	STS = Society of Thoracic Surgeons
EF = ejection fraction	TAVR = transcatheter aortic valve replacement
EOA = effective orifice area	TEE = transesophageal echocardiogram
EuroSCORE = European system for cardiac operative risk evaluation	TTE = transthoracic echocardiography
LV = left ventricular	VARC = Valve Academic Research Consortium
