Chapter 8: Diagnostic workup and evaluation: eligibility, risk assessment, FDA guidelines.

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Risk assessment

Heart Team Evaluation

One of the key requirements of a successful TAVR program is a multidisciplinary Heart Valve team, composed of cardiologists, interventional cardiologists, cardiothoracic surgeons, radiologists, anesthesiologists as well as other clinical staff. (see Chapter 5: The Role of the Heart Team)

The responsibilities of the Heart Team are to review the patient's medical condition and the severity of the valve abnormality; determine which interventions are indicated, technically feasible, and reasonable; and discuss benefits and risks of these interventions with the patient and family, keeping in mind their values and preferences.

Ideally, the Heart Team should meet periodically and frequently enough to ensure that all appropriate patients can be reviewed in a timely manner so that action plans for further evaluations or definitive therapy can be determined.

Risk Scores

The standard scoring systems utilized for assessment and risk stratification for TAVR patients have traditionally been the Society of Thoracic Surgeons risk score (STS; riskcalc.sts.org/) and European System for Cardiac Operative Risk Evaluation (EuroSCORE; www.euroscore.org). Both scoring systems are derived from surgical data, they primarily are used to calculate risk of morbidity and mortality after cardiac surgery, and have had limited validation in the TAVR population. The STS score does not include indices of frailty and degree of disability in elderly patients. Despite its limitations, the STS score is the most widely used.

Operative risk is defined as low if the predicted perioperative mortality rate is <4%, intermediate when the rate is 4-8%, and high when the rate is >8%. Patients with perioperative mortality rates >15% are generally considered “inoperable” or to have prohibitive risk. It is well recognized that such scoring systems, while very helpful, do not capture all the key comorbidities or consider patient frailty, which might also impact clinical decision making. Furthermore, they also do not consider regional or local institutional experiences and resources that might suggest a benefit of one potential therapy over another.

OBSERVANT is a novel risk score that is a simplified model using seven clinical variables (GFR, critical state, pulmonary hypertension, diabetes mellitus, New York Heart Failure IV, history of prior balloon aortic valvuloplasty and LVEF < 40%)[2]. This model demonstrated good discrimination and

validation cohorts in prediction of 30-day mortality with improved risk prediction compared with the EuroSCORE.

The Kansas City Cardiomyopathy Questionnaire-Overall Summary (KCCQ-OS) score was designed to quantify quality of life in heart failure patients. This score system was used in the PARTNER 1 Trial with the purpose of defining poor outcome after TAVR considering both survival and quality of life. Poor outcome 6 months after TAVR was defined as any of the following: death, KCCQ-OS score <45, or decrease of 10 points in the KCCQ-OS score from baseline to 6 months.[3]

The American College of Cardiology offers a TAVR In-Hospital Risk App that can be used as a reference for estimation the risk of in hospital mortality for patients that are assessed for TAVR: http://www.acc.org/tools-and-practice-support/mobile-resources/features/tavr-in-hospital-mortality-risk-app

Frailty and disability

While difficult to define, frailty is associated with poor outcomes. In a single-high volume TAVR center, frailty was assessed using the following criteria:

- >2 of 6 activities of daily living impairment
- serum albumin <3.5g/dL
- grip strength <30kg for male and <18kg for female
- 15 feet walk test > 7 seconds.

Each criterion is scored from 0-3. Total score ranges from 0 to 12, 12 being the highest degree of frailty. In one population, a frailty score >5 was associated with a 3-fold increase in 1 year mortality after TAVR.[4]

Additional assessment can be performed with scales like the Canadian Study of Health and Aging Scale, performance-based assessments like the "Up and Go" test and chair stands, the Rockwood Frailty Index, or frailty phenotype scales like the Cardiovascular Health Study Frailty Scale or Edmonton Frail Scale[5]. The FRAILTY-AVR Study[6] compared the predictive value of different frailty scales to predict outcome of TAVR or SAVR, and found that the Essential Frailty Toolset (based on lower extremity weakness, cognitive impairment, anemia and hypoalbuminemia) was the strongest predictor of 1-year mortality and disability.

Due to the advanced age of patients, comorbidities and life expectancy must be assessed prior to embarking on this choice of therapy. TAVR should not be offered to patients who have non-cardiac illnesses that are the predominant cause of their symptoms, or who have a life expectancy of less than twelve months due to non-cardiac illnesses[9].

Table 1: Risk Assessment Combining STS Risk Estimate, Frailty, Major Organ System Dysfunction, and Procedure-Specific Impediment[7]

	Low	**Intermediate**	**High Risk**	**Prohibitive Risk**

	Risk (must meet all criterion)	**Risk (any 1 criterion in this column)**	**(any 1 criterion in this column)**	**(any 1 criterion in this column)**
STS predicted risk of operative mortality*	<4%	4% to 8%	>8%	Predictive risk with surgery of death or major morbidity (all cause) >50% at 1 year.
Frailty ¶	None	1 Index (mild)	>2 Indices (moderate to severe)	
Major organ system compromise not to be improved postoperatively Δ	None	1 Organ system	No more than 2 Organ systems	>3 Organ systems
Procedure-specific impediment ◊	None	Possible procedure specific impediment	Possible procedure specific impediment	Severe procedure specific impediment.

*Use of the Society of Thoracic Surgeons Predicted Risk of Mortality to predict risk in a given institution with reasonable reliability is appropriate only if institutional outcomes are within one standard deviation of STS average observed/expected ratio for the procedure in question.

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

Δ Examples of major organ system compromise: Cardiac-severe LV systolic or diastolic dysfunction or RV dysfunction, fixed pulmonary hypertension; CKD stage 3 or worse; pulmonary dysfunction with FEV1 <50% or $DLCO_2$ <50% of predicted; CNS dysfunction (dementia, Alzheimer's disease, Parkinson's disease, CVA with persistent physical limitation); GI dysfunction-Crohn's disease, ulcerative colitis, nutritional impairment, or serum albumin <3.0; cancer-active malignancy; and liver-any history of cirrhosis, variceal bleeding, or elevated INR in the absence of VKA therapy.

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

Diagnostic work-up and evaluation

History and physical exam

The most common symptom of aortic stenosis is exertional dyspnea or decreased exercise tolerance. The symptoms of aortic stenosis associated with poor prognosis are angina, syncope and heart

failure. Increased flow velocity and turbulent flow across the narrowed valve result in a systolic crescendo decrescendo ejection murmur heard loudest over the proximal ascending aorta in the right parasternal third and fourth intercostal space, with the peak of the murmur occurring later in systole as the stenosis becomes more severe. The murmur usually radiates to the clavicles and carotids. A slow rising carotid upstroke (pulsus tardus) and reduced carotid pulse amplitude (pulsus parvus) are often encountered on physical exam in severe aortic stenosis. A soft (or absent) A2 can also be a sign of a more severely stenotic aortic valve. No single physical examination finding has both high sensitivity and high specificity for the diagnosis of severe aortic stenosis.

The history is particularly important, especially considering the progression of symptoms over time and the degree of impairment. It is also critical to separate symptoms of valvular disease from other significant co-morbidities, such as pulmonary disease, generalized deconditioning, neurologic/orthopedic disorders, or even under-treated coronary disease or arrhythmias that potentially might not improve despite correction of an underlying valvular problem. There must be a low threshold for addition non-cardiac diagnostic testing or referral for a specialist's evaluation (especially if there are opportunities for additional medical optimization).

Multimodality imaging assessment

The goals of the pre-procedural assessment are to confirm the diagnosis of severe AS, evaluate for concomitant cardiac pathologies, determine the potential contraindications or technical feasibility for either TAVR or SAVR, select the appropriate size of the aortic prosthesis, and to evaluate the feasibility of various access sites or surgical approaches**.** The Heart Valve team should coordinate these studies in order to obtain high quality information. Consideration should be given to identifying key clinicians with interest and expertise in each imaging modality to insure the highest quality and consistency in interpreting the studies with the focus on the specific anatomical questions that the Heart Team might have.

Echocardiography

Transthoracic echocardiogram is generally the first imaging test ordered. It is used to confirm severe aortic stenosis (aortic valve area of <1 cm^2, peak velocity across the valve >4 m/s and mean gradient >40 mmHg) when LV systolic function is normal. It is also used to assess the degree of aortic incompetence and other valvular pathologies, left ventricular systolic ejection fraction and diastolic dysfunction, as well as to estimate right-sided and pulmonary pressures. If the ejection fraction is <40% and the aortic valve gradients are not within the severe range, then dobutamine stress echocardiography can be done in an attempt to obtain a gradient or flow velocity that meets criteria for severe aortic stenosis. If the maximum jet velocity rises to over 4 m/s with the dobutamine-induced increase in stroke volume while the AVA remains less than 1.0 cm^2, then the valve is truly severely stenotic. 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 likely due to causes other than AS[8].

Three-dimensional transesophageal echocardiography (TEE) can be used to scrutinize other possible cardiac pathologies, and can help provide an accurate assessment of the aortic annulus, which impacts prosthesis size selection. (For more details refer to Chapter 9)

Multidetector Computed Tomography (MDCT)

Cardiac CT is the main imaging modality for assessing vascular anatomy, aortic root anatomy, and aortic annular size. It can also describe the coronary artery height, annular and LV outflow calcifications, and sinotubular and ascending aortic anatomy. For more details refer to Chapter 9.

Computed tomography can accurately evaluate iliofemoral tortuosity, calcium burden, and size. The diameters of the common femoral arteries are measured below the inguinal ligament in the axial projection. The real vessel diameter is defined as the distance between the internal vessel walls. However, in the case of wall calcification the real diameter is the vessel lumen, the internal diameter is often reduced by the calcification. The minimal vessel diameter varies depending on the type and size of valve being used, but in general a minimal diameter of 5.5mm is recommended for transfemoral TAVR. No well-defined cutoff or definition of tortuosity or calcification has been established.

Right Heart Catheterization and Coronary Angiography

Right and left cardiac catheterization is used to evaluate for concomitant pulmonary hypertension or coronary artery disease (CAD) that may require treatment prior to TAVR, especially in cases of triple vessel disease or left main coronary disease. The 2017 ACC Expert Consensus for TAVR in management in adults with severe aortic stenosis indicate that all patients should undergo coronary angiography because coronary artery disease is common in patients undergoing TAVR (40% to 75%).[9]

Percutaneous coronary intervention can be performed in patients with severe AS and significant CAD without an increase in 30-day mortality or procedural complication rate. In a single-center retrospective study of patients with severe AS undergoing PCI for stable angina (24%), unstable angina (41%), NSTEMI (19%) or STEMI (6%), the 30-day mortality and risk of procedural complications were not significantly different than in a propensity-matched cohort without severe AS. However, patients with ejection fraction <30% and patients with STS score >10% are the highest risk of 30-day mortality after PCI.[10]

Crossing the aortic valve during the catheterization and invasive measurement of the left ventricle is not routinely needed unless there are discrepancies between the patient's symptoms, physical exam findings, and echocardiographic findings. If assessment of the aortic valve gradients is required, this is generally done using simultaneous pressure monitoring within the aorta and left ventricle.

Other testing

Standard blood tests including renal function, pulmonary function tests, and carotid ultrasound are recommended. Severe pulmonary disease is defined as oxygen dependence, forced expiratory volume

in 1s < 50% predicted or DLCO < 50% predicted. COPD patients that are oxygen dependent or with poor functional mobility at baseline have poor outcome post TAVR.[11]

Dental evaluation is recommended with treatment of any acute issues prior to TAVR to avoid prosthetic valve endocarditis. Standard antibiotic prophylaxis is the same as for all prosthetic valves.

FDA Approvals

In August 2016, the Edwards Sapien XT and Sapien X3 were approved by the FDA for intermediate risk patients (STS score 4%- 8%). In March 2017, Medtronic received FDA approval for the CoreValve Evolut Pro Valve for patients with severe aortic stenosis with intermediate risk, based on the SURTAVI Clinical Trial.[12]

2017 AHA/ACC Focused Update of Valvular Heart Disease Guidelines[13]

TAVR is recommended for symptomatic patients with severe AS and a prohibitive risk for surgical AVR who have a predicted post-TAVR survival greater than 12 months. (Ia)

TAVR is recommended for symptomatic patients with severe AS and high risk for surgical AVR, depending on patient-specific procedural risks, values, and preferences. (Ia)

TAVR is a reasonable alternative to surgical AVR for symptomatic patients with severe AS and an intermediate surgical risk, depending on patient-specific procedural risks, values, and preferences. (IIa)

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