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Transcatheter Aortic Valve Implantation in the Elderly: Who to Refer?

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Abstract

In recent years, experience with transcatheter aortic valve implantation has led to improved outcomes in elderly patients with severe aortic stenosis (AS) who may not have previously been considered for intervention. These patients are often frail with significant comorbid conditions.

As the prevalence of AS increases, there is a need for improved assessment parameters to determine the patients most likely to benefit from this novel procedure. This review discusses the diagnostic criteria for severe AS and the trials available to aid in the decision to refer for aortic valve procedures in the elderly.

Keywords

Aortic Stenosis; Transcatheter Aortic Valve Replacement; Surgical Aortic Valve Replacement; Elderly; Frailty; Referral; Quality of Life; Risk Stratification

Introduction

Aortic stenosis (AS) has become a major cause of morbidity and mortality among a growing population of older adults.(1) In response to this clinical challenge, transcatheter aortic valvular implantation (TAVI) has rapidly evolved. Since the initial approval in Europe in 2007, the number of TAVI procedures has exponentially increased with over 100,000 valves placed worldwide.(1–4) The vast majority of these valves were implanted in older adults (the average age of TAVI in the US is ~84 years).(5)

It has become critically important for physicians caring for senior adults with AS to understand the risks and benefits of TAVI placement. The decision to refer for TAVI requires careful consideration of numerous factors including severity of disease, individual patient anatomy, comorbidity, overall prognosis, quality of life, and patient preference. The purpose

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of this review is to discuss AS in elderly patients and to evaluate the factors that can aid in the decision to refer for TAVI.

Epidemiology, Pathophysiology, and Natural History

AS is a disease of the elderly. The largest epidemiologic study from the United States used echocardiographic data from 11,911 patients in three preventive trials from the National Heart, Lung, and Blood Institute. The study demonstrated a prevalence of moderate to severe AS of 2.8% in patients >75 years of age, compared to only 0.2% in patients age 18–45.(6) The European Heart Survey evaluated 5,001 patients in 25 countries. In this cohort, 56% of patients with AS were greater than 70 years of age and 36% had at least one other comorbidity.(7, 8)

The classic description of AS by Morrow in 1968 defined a disease affecting primarily people in their fifth or sixth decade of life with a history of congenital bicuspid aortic valve or rheumatic valvular disease.(9, 10) Over the past half-century, the demographics of AS have changed due to an increase in life-expectancy and a dramatic decrease in the prevalence of rheumatic heart disease. Today, the primary form of AS is fibrocalcific disease. The second leading cause is bicuspid valve disease, typically manifesting in patients <70 years of age.(3, 7, 11, 12)

AS is an obstruction that develops insidiously with progressive calcification, inflammation, and lipid deposition on the valve.(13–19) Risk factors for the development of fibrocalcific AS are similar to those that increase the risk of atherosclerotic coronary disease; i.e. age, smoking, hypertension, and elevated cholesterol.(12) It has also been hypothesized that abnormal shear stress across the valve escalates the rate of calcium and lipid deposition. In bicuspid aortic valves, the increased shear forces lead to the development of significant obstruction approximately ten years earlier than patients with trileaflet AS.(3)

As the degree of obstruction increases in AS, left ventricular (LV) pressure increases, resulting in hypertrophy, fibrosis, and diastolic dysfunction. This can lead to decreased coronary reserve, increased myocardial ischemia, and eventually cause progressive LV dysfunction. In their 1968 paper, Ross and Braunwald famously hypothesized that with progressive pressure overload, the LV loses compensatory reserve causing symptoms to develop with a very poor overall prognosis.(20) The classically described symptoms of AS are angina, syncope, and congestive heart failure. When these symptoms develop, a characteristic, rapid progression of the disease process is seen.(20, 21) Without intervention, the two year mortality of AS is estimated to be as high as 50–80%.(22, 23) The most recent randomized data of high-risk patients with severe AS deemed to be inoperable candidates revealed a mortality of 50% at 1 year, demonstrating that the original hypothesis of Ross and Braunwald remains relevant today.

Diagnosis Using Echo Data

The decision to refer for TAVI starts with proper diagnosis of AS in a patient with correlating symptoms. Echocardiographic diagnosis is made based on several criteria. The valve should appear calcified and thickened with restricted leaflet opening on standard

transthoracic echocardiography. The peak and mean gradient can then be calculated using the simplified Bernoulli equation with the maximal velocity obtained by continuous wave (CW) Doppler. The highest velocity is obtained from multiple imaging positions to reduce the risk of underestimating the peak gradient across the valve. The gradient is then used to calculate the aortic valve area (AVA) using the continuity equation (which requires the measurement of the LV outflow tract (LVOT) velocity time integral (VTI) with pulse wave (PW) Doppler, the aortic valve VTI with CW, and the LVOT area). Based on these measurements, severe AS is defined as an AVA <1 cm^2 (critical <0.8 cm^2), a mean gradient > 40 mm Hg, or a peak velocity > 4 m/s.(24, 25).†

Low Flow and Low gradient AS

Frequently, in patients of advanced age, the criteria for severe AS (see table 1) is complicated by a low AVA (<1 cm^2) with a lower than expected aortic gradient (mean <40 mm Hg). This condition is designated low gradient AS and is commonly seen in patients with low LV ejection fraction (EF). Patients may also have low stroke volume due to severe diastolic dysfunction and are classified as low flow AS.

In patients with a small AVA and a gradient less than 40 mm Hg, the clinician must determine if the aortic valve is truly stenotic; or if instead, the limited valve opening is due to a weak LV that is unable to generate the force needed to open the valve (termed pseudo-stenosis). Understanding the approach to these patients is important, as this problem may be seen in up to 5–10% of patients with AS.(10, 26, 27)

Dobutamine stress echo (DSE) is usually used to assess the presence of pseudo-stenosis in low-gradient AS. On echocardiographic evaluation, patients with pseudo-stenosis, when challenged with dobutamine, have an increase in AVA with little to no change in aortic valve gradient (AVA will generally improve to > 1.2 cm^2).(28) Patients undergoing DSE who experience an increased transvalvular gradient with no improvement in AVA are more likely to require aortic valve replacement. In patients in this “true” stenosis group, DSE can be additionally valuable by assessing contractile reserve. Contractile reserve is defined as an increase in stroke volume by 20% and has been associated with a lower operative mortality. (27, 29)

Patients with low-gradient severe AS carry as much as 20% greater operative morbidity and mortality with surgical aortic valve replacement (SAVR) than those patients with high gradient severe AS. However, five-year mortality outcomes still favor treatment.(30, 31) Le Ven et al. analyzed patients with low-flow, low gradient severe AS compared to patients with high gradient AS undergoing TAVI. Patients with low-flow severe AS were seen to have a markedly higher 30-day mortality (11.4% vs. 5.9% respectively p=0.01). On univariate analysis, low EF in patients with low gradient AS was correlated with higher cumulative mortality [HR 1.61 (95% CI 1.19 to 2.49, p=0.002)].(32) Low gradient AS has also been shown to correlate with greater frequency of other comorbidity; i.e. pulmonary hypertension,

†Of note there remains debate over the optimal cut-off for AVA defining severe AS. Many experienced clinicians advocate for an echocardiographic cut-off of 0.8 cm^2 and a cardiac catheterization lab cut-off of 1.0 cm^2 for severe AS based on differences in the quantitative hemodynamics used to make the AVA calculation. (24)

PAD, severe mitral regurgitation (MR), and coronary artery disease (CAD).(33, 34) The results of the True or Pseudo Severe Aortic Stenosis (TOPAS) registry will aid in further understanding outcomes in low flow AS patients.

Medical Management of Severe AS

No effective medical therapy has been shown to affect mortality in AS. Medical treatment is primarily used to optimize CV status and alleviate symptoms in conjunction with aortic valve replacement or for palliation of symptoms. While awaiting surgery, lifestyle modification, such as limiting physical exertion, is generally recommended. In those patients who are not SAVR or TAVI candidates, medical therapy to improve preload and afterload can be attempted. The main goals of medical therapy include volume status optimization and hypertension management. (35)

While hypertension has been associated with the development of symptoms at an earlier stage, blood pressure reduction entails intrinsic risks.(36, 37) Diuretics can decrease afterload by reducing overall blood volume; however, they can also diminish necessary preload needed to maintain cardiac output in the setting of severe AS. Beta blockade can reduce contractility and is generally contraindicated. Vasodilators such as hydralazine and nifedipine, while reducing additional afterload, will not greatly affect the fixed obstruction at the level of the valve and can lower systemic blood pressure and coronary perfusion pressure.

In critically ill patients awaiting surgery or TAVI, balloon valvuloplasty (BAV) may be attempted. BAV can result in short term symptomatic improvement. However, in the ensuing months after BAV, the stenosis tends to re-occur; and survival is not improved when compared to medical therapy (3-year survival of only 17% in the BAV group in one study). (38) Additionally, the risk of vascular complications, bleeding, and stroke are significant post-BAV.(39)

Outcomes without invasive management in AS have been very poor. A classic study of patients with severe AS who were recommended for surgery but refused showed a three year mortality of 79% in the medically treated group.(21) Modern data from the Placement of Aortic Transcatheter Valve Trial (PARTNER) studies in patients who were not surgical candidates showed similarly high two-year mortality rates (mortality of 68% in the medical treatment arm).(22)

SAVR

The 2008 ACC guidelines for valvular heart disease give three class I recommendations for SAVR (see table 2).(40) In the elderly, SAVR is generally reserved for those with severe symptomatic AS and who are reasonable operative candidates. Surgeons frequently use validated risk scores such as the Society of Thoracic Surgeons score (STS) or the EuroSCORE as an objective way to assess risk.(41, 42) No specific guidelines address which patients are of prohibitive risk; however, in clinical trials, an STS score of 8–15% predicited mortality has been used as the risk cut-off for SAVR. A larger database review shows that the majority of patients receiving SAVR have an STS of < 5%.(10)

The STS database shows the mortality for isolated SAVR has improved by about 1% over the past decade and is currently estimated as 2.6%. When concomitant procedures are required, the operative risk is increased. For example, the mortality risk of SAVR plus bypass surgery in 2011 was 4.7%, and SAVR plus mitral replacement was 7.1%.(43)

Transcatheter Aortic Valve Implantation

Despite the strikingly high mortality with symptomatic AS, a large percentage (30–40%) of patients evaluated for SAVR were deemed inoperable or refused the surgical procedure.(40, 44, 45) Age was the most frequently sited co-morbidity prohibiting surgical intervention.(6, 8, 46) TAVI was developed as an alternative therapeutic option for this group of patients. The first, major randomized trials performed to prove the efficacy and safety of TAVI were done in a series of publications by the PARTNER group.

The initial trial of TAVI in 2010 by Leon et al. was performed in patients who were considered too high-risk to undergo surgery.(47) Three hundred fifty-eight patients with symptomatic, severe AS defined as AVA < 0.8 cm^2, mean aortic gradient > 40 mm Hg, or a peak velocity of > 4 m/s were evaluated and deemed to be inoperable by two surgeons using an STS score > 10% or a coexisting condition that would be associated with a >50% predicted probability of death within 30 days of surgery.

In this trial, a one-year mortality of 30.7% was seen in the TAVI arm -- compared to 50.7% in the medical arm ($p<0.001$). The results at two years demonstrated a mortality of 34% in the TAVI group and 68% in the standard therapy group ($p<0.001$) with corresponding cardiac death 31% and 62% respectively ($p<0.001$).(22)

TAVI vs. SAVR

The 2011 PARTNER trial evaluated patients considered acceptable, although high-risk surgical candidates, and randomized them in a 1:1 fashion to TAVI vs. SAVR.(48) Six hundred ninety-nine high-risk patients with severe symptomatic AS were randomized. At thirty days, the rate of death from any cause was 2.4% in the transcatheter group and 6.5% in the surgical group ($p=0.07$). Mortality was 24.2% and 26.8% at 1 year respectively ($p=0.44$), meeting criteria for non-inferiority ($p=0.001$).

Although there were comparable mortality rates in the trial, significant differences in the frequency of major complications after TAVI were seen. The proportion of major stroke at 30 days was slightly higher in the TAVI group: 3.8% vs. 2.1% ($p= 0.07$). Vascular complications were significantly higher in TAVI at 30 days (11% vs. 3.2%, $p<0.001$). Surgical patients experienced more post-procedural bleeding (9.3% vs. 19.5%, $p<0.001$) and new onset atrial fibrillation (8.6% vs. 16.0%, $p=0.006$). The need for post-procedural pacemaker placement was similar between the 2 groups (3.8 vs. 3.6 %, $p=0.89$).

The two-year outcome in this high-risk cohort was recently published showing a mortality of 34% in TAVI and 35% in SAVR ($p=0.78$).(49) At 30 days, the risk of stroke was not significantly higher with TAVI than with SAVR (4.6 vs. 2.4%, $p=0.12$). Post-operative AVA was similar between the two groups. Paravalvular aortic regurgitation (AR) was more

frequent after TAVI; and importantly, even mild paravalvular AR was strongly associated with increased late mortality (p<0.001).

Anticoagulation and Bleeding in SAVR and TAVI in the Elderly

The need for adjunctive antiplatelet and antithrombotic treatment after TAVI and SAVR must also be considered, particularly in elderly patients at increased bleeding risk during and after the procedure. Peri-procedural bleeding has been shown to be significantly higher with SAVR than TAVI (19.5% vs. 9.3%, p<0.001).(48) Major bleeding events have been associated with increased morbidity and mortality with both procedures (adjusted HR 2.49, 95% CI 1.85–3.37; p<0.001) and have been linked with increased rates of acute kidney insufficiency requiring dialysis in SAVR.(50)

Anticoagulation choice after TAVI has largely been empirically determined as clinical evidence is lacking. The current recommendations by the ACCF/AATS/SCAI/STS consensus document state that patients who are post-TAVI should be placed on aspirin and clopidogrel therapy. However, no recommendation of the duration of clopidogrel therapy was given nor was the loading dose specified.

The choice of anti-thrombotic therapy in patients receiving SAVR varies according to center, patient comorbidities (i.e. concomitant atrial fibrillation), and valve type. The STS database of prosthetic SAVR showed that 49% of patients are discharged on aspirin alone, 12% on warfarin alone, and 23% with warfarin plus aspirin. A 2012 document comparing 25,656 patients post-SAVR showed an individual risk of stroke or bleeding event of 1% on aspirin monotherapy at 3 months.(51) The cohort placed on aspirin plus coumadin had a lower risk of embolic stroke but had a significantly higher risk of bleeding when compared to patients on aspirin monotherapy (relative risk of bleeding: 2.80, 95% CI: 2.18 to 3.60, p<0.0001).

Predicting Optimal Patients for TAVI

The prototypical tenet of geriatric care of “start low and go slow” and “less is more” contrasts the approach implied by the data in the PARTNER trials, which demonstrate improved outcomes with an aggressive invasive approach. The inherent risks associated with invasive procedures in this population make it vitally important that providers identify the subsets of older adults who will benefit from TAVI or SAVR. Selecting patients to achieve a high benefit-to-risk ratio is a substantial clinical challenge. The remainder of the document will evaluate the data available to guide the clinician through this process. Table 2 offers a summary of referral criteria for each of the different treatment modalities for severe AS.

Perioperative Risk Assessment

Given the complexity of the decision to refer for SAVR or TAVI, objective risk calculators have been developed to estimate surgical risk. The STS score was specifically designed to analyze the risk of aortic valve surgery and remains the most commonly used score in the evaluation TAVI and SAVR patients in North America.(41) It contains 24 covariates derived from testing 67,292 patients undergoing isolated SAVR between 2002 and 2006. Emergency

surgery, history of endocarditis, and history of previous cardiac surgery are the most heavily weighted variables in the score.

It is important to recognize the STS score does not incorporate several key risk factors; i.e., aortic anatomy, cirrhosis, and pulmonary hypertension. It fails to consider several features that are crucial to the elderly population: frailty, cognitive functioning, nutritional status, and quality of life metrics.(52)

As part of the recent SURgical replacement and Transcatheter Aortic Valve Implantation trial (SURTAVI), a novel risk-stratification process was used to include the risk factors that are missing from the STS score. To construct an alternative score, Van Mieghem et al. chose age plus ten risk factors: concomitant CAD, frailty, LV dysfunction with EF < 35%, baseline neurologic dysfunction, pulmonary disease, peripheral arterial disease (PAD), renal disease, history of sternotomy, diabetes, and pulmonary hypertension.(53, 54) The SURTAVI assessment model has not been validated in a large prospective fashion, but may prove to be a reasonable addition to the STS score in aiding in the decision of TAVI vs. SAVR.

The STS risk score and alternative available risk scores (i.e. EuroSCORE) have been criticized for poor risk prediction in the highest risk patients (the group of patients in which accurate risk assessment is most vital).(33) The recognized need for a TAVI specific risk score has resulted in the development of a risk model based on registry data. The model is currently undergoing evaluation and is yet to be published.

Predictors of Morbidity and Mortality in the PARTNER Trials

In the 2-year analysis of all participants in the inoperable (very high-risk) PARTNER cohort, Makkar et al. performed several key inquires of the comorbid conditions associated with morbidity and mortality after TAVI. First, stratification of 2-year mortality based on tertile of STS risk (<5%, 5–14.9% and ≥15%) was performed. Those patients in with an STS score ≤ 14.9% had a significantly lower mortality with TAVI than with those with STS ≥ 15% (HR 0.58; CI =0.41–0.81).(22) (See figure 1.) The study also found several other comorbidities that were statistically linked to death, including body mass index (HR per unit increase 0.95; 95% CI, 0.91 to 0.98; p=0.005); history of stroke (HR 2.99; 95% CI, 1.19 to 7.51; p=0.01); and chronic obstructive pulmonary disease (COPD).

Kodali et al. performed a two-year analysis of the high-risk cohort receiving TAVI vs. SAVR.(49) The trial showed similar multivariate predictors of increased mortality as was seen in the inoperable cohort (see table 3). Body mass index, stroke, liver disease, STS score, and mitral regurgitation were associated with increased mortality. Pre-procedural creatinine level, prior vascular surgery, and a mean aortic gradient increase of > 10 mm Hg after TAVI were independently associated with increased mortality in the TAVI group but not in the SAVR group. History of coronary artery bypass grafting, STS score, liver disease and degree of mitral regurgitation were associated with worse outcomes with SAVR.

Quality of Life and Disability

TAVI has been associated with improved quality of life in high-risk patients in multiple studies. For the elderly, this is frequently paramount as the quality of life often supersedes

the quantity of life.(49, 55–62). Several metrics have been used to assess quality of life before and after TAVI. These include Medical Outcomes Study Short-Form 36 Health Survey (SF-36), New York Heart Association (NYHA) class, frequency of re-hospitalization, and 6-minute walk test.

In the inoperable (very high-risk) cohort of the PARTNER trial, objective quality of life metrics favored TAVI over medical therapy. A NYHA class I or II symptom rating was seen in 83% of the TAVI treatment arm compared to 43% in the standard therapy arm. The rate of re-hospitalization for cardiac reasons was lower after TAVI, as was the median number of days alive and out of the hospital (699 days vs. 355 days, $p<0.001$).

Krane et al. used the SF-36 survey to assess 99 patients after TAVI. SF-36 scores increased across several domains with TAVI: physical functioning score 34.7 vs. 48.5, $p< 0.001$, general health score 7.1 vs. 54.1, $p<0.01$, vitality score 37 vs. 46.1, $p<0.01$, and physical heath summarized score 31.2 vs. 38.6, $p<0.001$.(61)

Six minute walk testing is an intuitive way to assess functional capacity after TAVI. The original PARTNER trials evaluated 6-minute walk in both cohorts. Compared to medical therapy, TAVI had a significant improvement in 6 minute walk distance ($p=0.02$). When compared to surgery, the TAVI group had better walking distance at one month ($p=0.002$), but there was no difference observed at one year ($p=0.67$). Another study of TAVI from Europe showed that patients were able to walk significantly farther after TAVI than before the procedure: 266 meters vs. 204 meters ($p<0.001$).(57)

Cognitive Function and Stroke

The risk of impairing cognitive function after TAVI due to stroke or prolonged delirium is a key consideration in the elderly. In the PARTNER inoperable cohort, the rate of stroke at 2 years was markedly higher in the TAVI group than in the medically managed group (13.8% vs. 5.5%, $p=0.01$). Strokes within the first 30 days were mainly ischemic (12 ischemic and 1 hemorrhagic); however, from 30 days to 2 years, the rate of hemorrhagic strokes increased (5 ischemic strokes and 4 hemorrhagic stokes in the TAVI arm vs. 1 hemorrhagic and 4 ischemic strokes in the medical therapy arm).(63) The increased rate of hemorrhagic stroke is likely attributable to the standard dual antiplatelet therapy used with TAVI.

Alternatively, in the high-risk cohort of the PARTNER trial, the stroke rate was seen to be much lower: 2.1% in the SAVR group and 3.8% in the TAVI group at 30 days. Overall risk of stroke and TIA at one year was also higher in the transcatheter group (2.4% vs. 5.5%, $p=0.04$).

It must be noted that with the improvement in interventional techniques and operator skill, the TAVI associated stroke risk has decreased. In recent registry data from November 2011-May 2013, the Edwards Sapien transcatheter valve (Edwards Lifescience, Irvine, CA) showed a TAVI stroke risk of only 2%.(5)

There has been only limited study of cognitive function before and after TAVI. A study by Ghanem et al. assessing the frequency of cerebral emboli with diffusion weighted magnetic resonance imaging (MRI) showed that up to 64% of patients studied had evidence of emboli.

Only 5.4% (5 of 111 patients) developed diagnosable early cognitive decline and even less, 2.7% (3 of 111) experienced late cognitive decline. Only patient age (p=0.012) was associated with increased risk of diminished cognitive status after TAVI. History of stroke, use of cerebral embolic protection devices, and baseline cognitive status were not significantly correlated with increased risk of early cognitive impairment.(64)

Frailty

Frailty is a state of vulnerability in which a patient has decreased physiologic reserve resulting in a poor outcome when a stressor is applied. Fried et al. completed seminal work that defined frailty based on unintentional weight loss, walking speed, and low physical activity. Her later work added other markers to our understanding of the condition; i.e. wasting, weakness, low albumin levels, and inability to perform the activities of daily living (ADLs).(65, 66)

Frailty is an extremely common problem in patients undergoing TAVI evaluation. Stortecky et al. described 100 patients in Sweden undergoing TAVI. Approximately 50% of patients were considered frail based on a derived frailty index score.(33, 67) In another study of 102 patients undergoing assessment for TAVI, 79% of those evaluated were considered frail based on the sole parameter of gait speed.(68)

Several groups have attempted evaluate the relationship between frailty and mortality with TAVI. In Stortecky et al., a frailty index score was derived based on mini mental status examination, a “Get Up and Go” test, disability scores, and a nutritional assessment. The score was not associated with greater mortality post-TAVI, but was significantly linked to subsequent CV and cerebrovascular events (OR: 4.17; 95% CI 1.37–12.72; p=0.01).

Green et al. defined a multi-modality frailty score based on ADL disability, serum albumin, gait speed, and grip strength. The study showed that a higher score in the model correlated with a shorter predicted survival after TAVI (HR 3.51; 95% CI, 1.43–8.62; p=0.006).(68)

Frailty in TAVI is an active area of ongoing research. The multicenter Frailty-AVR study will assess outcomes in 400 SAVR and 400 TAVI patients over age 70, using 7 different frailty assessment tools. This study will define which components of a frailty evaluation are most predictive of major morbidity and mortality, as well as determining the degree of frailty that would warrant TAVI inclusion over SAVR.(69)

Active Research: Novel Technologies

Industry has been aggressively developing new valve technology to improve outcomes in TAVI. Several ongoing clinical trials have been developed to address the shortcomings of the first generation valves; i.e. large catheter size leading to vascular complications, high incidence of paravalvular AR, and frequent post-procedural complete heart block requiring pacemaker placement.(70)

The designs of the second-generation valves have mainly focused on decreasing the profile of the device to allow for delivery through an 18 French (Fr) or smaller sheath. The Edwards

Sapien 3, Sapien XT, and Medtronic (Minneapolis, MN) CoreValve Evolut all tout significantly smaller Fr delivery systems. The Sapien-3 has increased radial force compared to the Sapien-XT to allow for decreased paravalvular AR. It has slightly increased height compared to the first generation heart valve for improved positioning but has been associated with a greater incidence of complete heart block when compared to Sapient XT.(71)

TAVI Care Coordination and Cardiac Rehabilitation

Transitioning care after TAVI is a crucial issue. The expert consensus document on TAVI suggests a careful transition back to the primary cardiologist after the first month post-procedure. A clear plan should be agreed upon for management of co-morbid conditions that may have been uncovered during the pre-TAVI evaluation as well as treatment of complications that arose during the procedure. Further research is required to determine the proper intervals of routine imagining after valve insertion as well as the type and duration of anti-thrombotic needed to reduce the risk of stroke.

There has been very limited research into the effects of cardiac rehabilitation (CR) on post-TAVI patients. The largest study to date by Voller et al. showed that CR is efficacious in improving 6-minute walk times and exercise capacity in both TAVI and SAVR.(72) Another small trial comparing early CR effects on SAVR and TAVI patients demonstrated similar improvements in 6-minute walk time and exercise capacity on cardiopulmonary exercise testing. There was no difference in improvement between post-TAVI vs. post-SAVR patients. (73) Further study is needed to optimize the effects of CR in this cohort, to determine the geriatric interventions most likely to confer benefit, and to elicit the cost effectiveness of CR programs in the post-procedural setting.

Conclusions

In the elderly, AS is an increasingly common problem encountered in clinical practice. The development of symptoms heralds extremely high short-term mortality and compels the patients' physician to consider intervention options in an otherwise frail population. Prior to the advent of TAVI, the physician was forced to recommend SAVR in high-risk patients and as many as 30% were denied surgery due to frailty and comorbidity.(74)

With the advent of TAVI, dramatic improvements in outcome have occurred; i.e., decreased mortality, reduced hospitalizations, improved quality of life, and diminished disability rates. Simultaneously, overall surgical morbidity and mortality has significantly decreased. However, despite the marked benefits observed in the randomized PARTNER trials, the risk of major complications including stroke, vascular events, and mortality are considerable. While adverse events related to TAVI and SAVR are steadily improving, the uncertainty when weighing the risks and benefits of these aggressive clinical strategies in high-risk patients remains significant. The available data provokes the question: how can we best define the patients most likely to benefit from the procedure with the lowest likelihood of a complication, prolonged hospitalization, or insidious subclinical cognitive decline?

The studies mentioned above describe the factors that aid in overall risk assessment for TAVI (see table 4). Additionally, anatomical and echo characteristics can also alter the individual

patient risk, i.e. PAD and low-flow AS. More recently, several groups have added frailty scores to traditionally used risk calculators. Although further validation is required, these risk factors will likely have an increasingly important role in correctly individualizing valve therapy in the near future.(53, 67)

The knowledge of increased risk from enhanced prognostic tools is definitely important. However, even more imperative is the physician's clinical response once these risk factors are identified. For example, when frailty is identified in the pre-operative phase, clinicians should preemptively attempt to reduce disability, weakness, and improve nutritional status prior to TAVI. Strength training, nutritional supplementation and testosterone therapy have been the major therapies studied to-date. (75–77) However, significant physical exertion in severe AS can lead to worsening symptoms and potentially cause pulmonary edema. Testosterone therapy has recently been associated with increased CV events.(78) This leaves nutritional support as a major means of improving geriatric functioning prior to TAVI and should be routinely incorporated into TAVI program services.

The value of the doctor-patient relationship is the last major consideration. A candid discussion with the patient and the patient's family during the evaluation of severe symptomatic AS is essential. Interventionalists and surgeons treating patients with AS must have a thorough knowledge of geriatric principles as part of a clinical standard. Understanding these elderly patients' goals and wishes are crucial when weighing the risks and benefits of this major procedure. This can be particularly challenging when patients and their families have varying degrees of health literacy.

As the technology and experience with TAVI grows, complications and mortality will continue to decline. Given the dramatic benefits seen in the PARTNER randomized trials, recommending against TAVI in elderly patients has become progressively more difficult. There is an enduring need for larger scale studies to elucidate patients who are most likely to suffer serious complications and to establish guideline based cut-offs to guide TAVI referral in the elderly.

ABBREVIATIONS

ADL	Activities of Daily Living
AR	Aortic Regurgitation
AS	Aortic Stenosis
AVA	Aortic Valve Area
BAV	Balloon Valvuloplasty
CAD	Coronary Artery Disease
COPD	Chronic Obstructive Pulmonary Disease
CR	Cardiac Rehabilitation
CW	Continuous Wave

DSE	Dobutamine Stress Echocardiography
EF	Ejection Fraction
LV	Left Ventricular
LVOT	Left Ventricular Outflow Tract
MR	Mitral Regurgitation
MRI	Magnetic Resonance Imaging
NYHA	New York Heart Association
PAD	Peripheral Arterial Disease
PARTNER	Placement of Aortic Transcatheter Valve
PW	Pulsed Wave
SAVR	Surgical Aortic Valve Replacement
STS	Society Thoracic Surgeons
TAVI	Transcatheter Aortic Valve Implantation
VTI	Velocity Time Integral;

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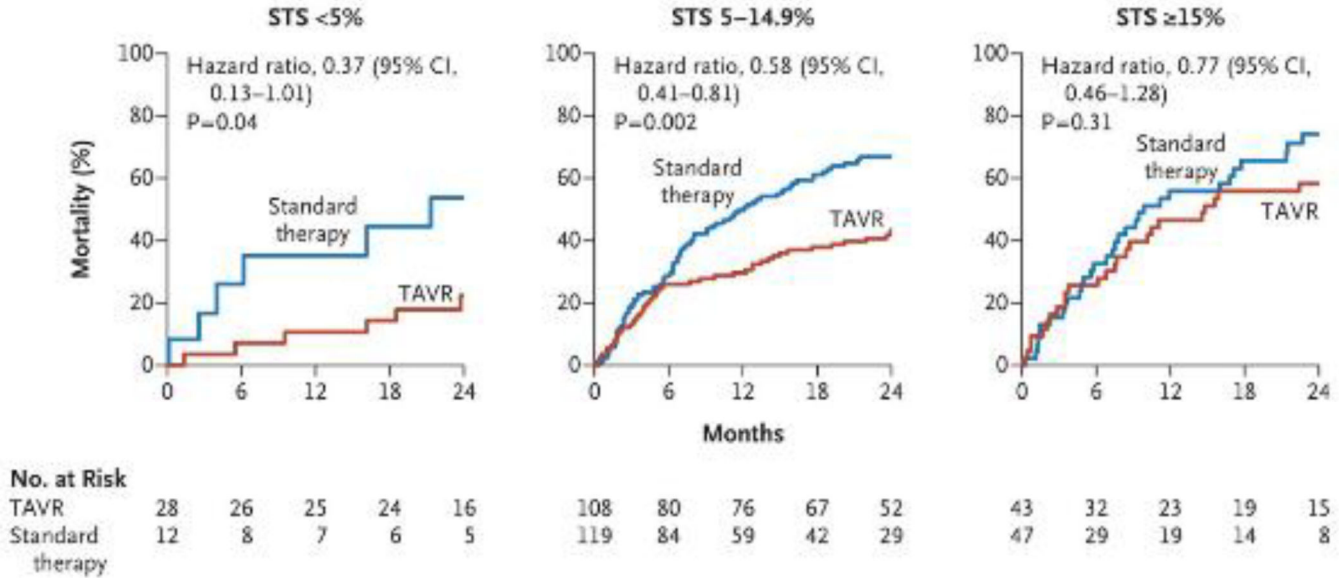

Figure 1. Two Year Mortality Stratified According to the Society of Thoracic Surgeons (STS) Risk Score

Stratification according to STS categories revealed a significant association with 2-year mortality (<5%, 5 to 14.9%, and ≥ 15 - with higher scores indicating greater surgical risk). From Makkar RR, et al. Transcatheter aortic-valve replacement for inoperable severe aortic stenosis.New Engl J Med. 2012 May 3;366(18):1696-704 Reprinted with permission from Massachusetts Medical Society.(22)

Table 1

Echocardiograpic Diagnostic Criteria for AS

Diagnostic Criteria	Echo measurements	Limitations
AVA <1 cm^2	LVOT area *, AV VTI with CW, LVOT gradient with PW	LVOT diameter if incorrect can cause large error in AVA.
AVA index < 0.6 cm^2/m^2	Divide the AVA by BSA	Weight used is not ideal body weight
Peak jet velocity >4 m/s	CW through aortic valve	CW Doppler must be aligned correctly
Mean gradient > 40 mmHg	AV CW using Bernoulli equation	Same as above
Dimension less index (Velocity ratio) < 0.25	Velocity ratio = V·LVOT/V·AS	Cannot take into account individual variations in LVOT size
Aortic valve planimetry	Direct measurement of area on 2D/3D echo	Limited and rarely used in 2D echo due to aortic calcification leading to reverberation of signal.

(AV = aortic valve, BSA = Body surface area, VTI = velocity time integral, LVOT= left ventricular outflow tract, Bernoulli equation is $\Delta P = 4v^2$)

*AVA calculated from LVOT diameter.

Table 2

Criteria for Referral for AVR, TAVI, and BAV

SAVR	**1**	Severe, symptomatic AS
	2	Open heart surgery for another indication AND moderate to severe AS
	3	Severe AS AND LV EF< 50%.
TAVI	**1**	High-risk or prohibitive risk surgical patients with severe, symptomatic, trileaflet AS.
	2	Severe, symptomatic AS with STS score ≥ 8, as an alternative to SAVR. *
	3	Severe, symptomatic AS with anatomy precluding SAVR (i.e. radiation to chest, porcelain aorta)
	4	Severe, symptomatic AS with prohibitive surgical risk (an estimated 50% or greater risk of mortality at 30 days due to significant comorbid conditions **)
BAV	**1**	Extreme risk patients as a bridge to SAVR or TAVI.
	2	Palliative therapy for short to intermediate term symptomatic improvement.

(LV = left ventricular, EF = ejection fraction)

* STS score based on referral criteria for partner trials – initially STS ≥ 10, it was later decreased to ≥8.

** i.e. those comorbid conditions associated with increased mortality with SAVR (liver disease, significant COPD, pulmonary hypertension, etc.)

Table 3

Comorbidities and Risk Factors Contributing to TAVI outcomes of Morbidity or Mortality

Risk Factor	HR/OR, 95% CI, P value	Trial Evaluating
STS score		Dewey et al.(79)
EuroSCORE		Nashef et al.(42)
SURTAVI score		Van Mieghem et al.(53)
BMI *	HR 0.96; CI,0.94 to 0.98; p<0.001	Kodali et al.(49)
Stroke history	HR 2.99; CI, 1.19 to 7.51; p=0.01	Makkar et al.(22)
COPD requiring oxygen	HR 1.69; CI, 1.05 to 2.73; p=0.03	Makkar et al.
Liver disease	HR 2.24; CI, 1.30 to 4.00; p= 0.006	Kodali et al.
Age **	OR 1.09, CI 1.03 to 16 p=0.005	Auffret et al.(80)
Frailty	HR 3.5; CI, 1.4 to 8.5; p<0.007	Green et al.(68)
Cognitive Impairment	OR 2.85 (1.32–6.17) 0.1	Stortecky et al.(67)
Malnutrition ***	OR 1.30 (1.03–1.66) 0.03	Stortecky et al.
Trans-apical approach	OR 3.12; CI, 1.43 to 6.82; p=0.004	Van der Boon et al.(81)
PH ≥ 60 mm Hg	OR 7.56; CI, 2.58 to 22.17; p<0.001	Auffret et al.
Low-Flow	HR 1.48; CI, 1.13 to 1.97; p=0.005	Le Ven et al.(32)
Peri-procedural Cr	HR 1.06; CI, 1.00 to 1.13, p=0.04	Kodali et al.
Prior Vascular surgery	HR 1.85; CI, 1.01 to 3.39, p=0.05	Kodali et al.
Moderate to severe MR	HR 1.36 CI, 1.02 to 1.82, p=0.04	Kodali et al.

HR = Hazard Ratio, OR= Odds Ratio, CI= 95% Confidence Interval, BMI = Body Mass Index, COPD = Chronic Obstructive Pulmonary Disease, PH = Pulmonary Hypertension, Cr= Creatinine, MR = Mitral Regurgitation

* Lower BMI seen to be protective; the hazard ratio represents an increase of 1

** for each increase of 1 year

*** based on mini nutritional assessment (82)

Table 4

Studies Assessing Frailty and Outcome in TAVI vs. Cardiac Surgery.

Study	Parameter(s)	Result	HR/OR; 95% CI, P value*
Green et al.(68)	Gaits speed, grip strength, serum albumin, ADL status in frailty score with **TAVI**	↑ frailty score correlates with ↑ 1 year mortality	HR 3.5; CI: 1.4 to 8.5, p< 0.007
Afialo et al.(83)	Frailty and disability score in **cardiac surgery**	5 meter gait speed and Nagi disability score ≥ 3, ↑ mortality	Gait: OR 2.63; CI, 1.17 to 5.90 Nagi: OR 2.98; CI, 1.35–6.56
De Areza et al.(84)	EuroSCORE + 6 minute walk test for **SAVR**	6 minute walk distance associated with composite CV outcome	HR 0.28; CI, 0.09 to 0.85, p=0.025
Lee et al.(85)	Frailty based on impairment of ADLs, ambulation, or history of dementia in **cardiac surgery**	Frailty - ↑ hospital mortality and ↑ hospital stay	OR 1.8; CI, 1.1 to 3.0 for mortality
Schoenenberger et al.(86)	Frailty index to assess functional decline after **TAVI**	Frailty index strongly predicted functional decline	OR 1.56; CI, 1.20 to 2.04; p= 0.001
Stortecky et al.(67)	Multidimensional Geriatric Assessment (MGA) tool to predict adverse events in **TAVI**	Frailty characteristics-cognitive impairment, malnutrition, mobility impairment, limitations in ADLs - were predictive of increased mortality.	OR 3.29; CI, 1.06 to 10.15; for MGA

ADL = activity of daily living, CV= cardiovascular

*p value given if available.