Transcatheter aortic valve replacement in patients with severe aortic stenosis who are at high risk for surgical complications: Summary assessment of the California Technology Assessment Forum

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Background: The California Technology Assessment Forum is dedicated to assessment and public reporting of syntheses of available data on medical technologies. In this assessment, transcatheter aortic valve replacement (TAVR) was evaluated for patients with severe aortic stenosis (AS) who are at high risk for complications.

Methods and Results: In this assessment, 5 criteria were used: Regulatory approval, sufficient scientific evidence to allow conclusions on effectiveness, evidence that the technology improves net health outcomes, evidence that the technology is as beneficial as established methods, and availability of the technology outside investigational settings. In this assessment, all 5 criteria were judged to have been met. The primary benefit of TAVR is the ability to treat AS in patients who would otherwise be ineligible for surgical aortic valve replacement. It may also be useful for patients at high surgical risk by potentially reducing periprocedural complications and avoiding the morbidity and recovery from undergoing heart surgery. Potential harms include the need for conversion to an open procedure, perioperative death, myocardial infarction, stroke, bleeding, valve embolization, aortic regurgitation, heart block that requires a permanent pacemaker, renal failure, pulmonary failure, and major vascular complications such as cardiac perforation or arterial dissection. Potential long-term harms include death, stroke, valve failure or clotting, and endocarditis. As highlighted at the February 2012 California Technology Assessment Forum meeting, the dispersion of this technology to new centers across the United States must proceed with careful thought given to training and proctoring multidisciplinary teams to become new centers of excellence.

Conclusions: TAVR is a potentially lifesaving procedure that may improve quality of life for patients at high risk for surgical AVR. However, attention needs to be paid to appropriate patient selection, their preoperative evaluation, surgical techniques, and postoperative care to preserve and improve on the results attained in the Placement of Aortic Transcatheter Valve trial. Specialty societies are collaborating to ensure that this happens in a rational and comprehensive manner. (J Thorac Cardiovasc Surg 2014;148:482-91)

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The California Technology Assessment Forum (CTAF) is dedicated to assessment and public reporting of syntheses of available data on medical technologies. Reports are used by health plans, providers, and patients to guide health care decisions and inform health policy initiatives. The CTAF is managed by Blue Shield of California Foundation (BSCF),

which is a separate nonprofit organization that receives funding from the Blue Shield of California health plan, but is governed by its own board of trustees. CTAF and BSCF are not revenue-generating organizations or consultant organizations; they do not endorse specific technologies, advocacy organizations, or organizations that determine health plan benefit coverage. CTAF technology assessments are available at <http://www.ctaf.org>.

The assessment process involves a thorough literature review and determination of comparative effectiveness and value of different care options. In the assessment of transcatheter aortic valve replacement (TAVR) for patients with severe aortic stenosis (AS) who are at high risk for complications, 5 criteria were used: regulatory approval, sufficient scientific evidence to allow conclusions on effectiveness, evidence that the technology improves net health outcomes, evidence that the technology is as beneficial as established methods, and availability of the technology outside investigational settings.

Drafts of technology assessments are posted for public comment and reviewed at an open forum where input is taken from consumers, payors, industry representatives, and relevant health care provider organizations. The American Association of Thoracic Surgery (AATS) has

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Abbreviations and Acronyms	
AS	= aortic stenosis
CI	= confidence interval
CTAF	= California Technology Assessment Forum
DARE	= Database of Abstracts of Reviews of Effects
EuroSCORE	= European System for Cardiac Operative Risk Evaluation
FDA	= US Food and Drug Administration
ICU	= intensive care unit
KCCQ	= Kansas City Cardiomyopathy Questionnaire
MI	= myocardial infarction
NYHA	= New York Heart Association
OR	= odds ratio
PARTNER	= Placement of Aortic Transcatheter Valve Trial
SAVR	= surgical aortic valve replacement
SF-12	= Short Form 12
STS PROM	= Society of Thoracic Surgeons Predicted Risk of Mortality
TAVR	= transcatheter aortic valve replacement

been an active participant in the reviews relevant to our specialty, and the following technology assessment of TAVR was approved by the AATS representative, Dr Frank Sellke, as well as the AATS Council.

The primary benefit of TAVR is the ability to treat AS in patients who would otherwise be ineligible for surgical aortic valve replacement (SAVR). It may also be useful for patients at high surgical risk by potentially reducing periprocedural complications and avoiding the morbidity and recovery from undergoing heart surgery. Potential harms include the need for conversion to an open procedure, perioperative death, myocardial infarction (MI), stroke, bleeding, valve embolization, aortic regurgitation, heart block that requires a permanent pacemaker, renal failure, pulmonary failure, and major vascular complications such as cardiac perforation or arterial dissection. Potential long-term harms include death, stroke, valve failure or clotting, and endocarditis. The focus of this statement is a high-risk cohort of patients with AS, rather than inoperable patients.

TECHNOLOGY ASSESSMENT

Technology Assessment Criterion 1: The Technology Must Have Final Approval From the Appropriate Government Regulatory Bodies

On November 2, 2011, the SAPIEN Transcatheter Heart Valve model 9000TFX (Edwards Lifesciences, Irvine,

Calif), sizes 23 mm and 26 mm, received US Food and Drug Administration (FDA) premarket approval for transfemoral delivery in patients with severe, symptomatic, native, aortic valve stenosis who have been determined to be inoperable by a cardiac surgeon. On October 19, 2012, the SAPIEN Transcatheter Heart Valve model 9000TFX, sizes 23 mm and 26 mm, received FDA premarket approval for transfemoral and transapical delivery in patients with severe, symptomatic, native, aortic valve stenosis who have been determined to be at high risk defined as a Society of Thoracic Surgeons predicted operative risk score of 8% or higher or are judged by the heart team to be at 15% or higher risk of operative mortality.

The Edwards SAPIEN Transcatheter Heart Valve, model 9000TFX is the only product approved by the FDA at this time. Edwards will continue to monitor and evaluate the SAPIEN valve and TAVR as a procedure via the national Transcatheter Valve Therapy Registry. Thus, Technology Assessment (TA) Criterion 1 was met. It should be understood that other valves are in clinical trials and in development, but only the SAPIEN valve has, to date, been approved for use in the United States. However, we take the liberty of considering TAVR in a more general sense.

TA Criterion 2: The Scientific Evidence Must Permit Conclusions Concerning the Effectiveness of the Technology Regarding Health Outcomes

The MEDLINE database, EMBASE, Cochrane clinical trials database, Cochrane reviews database, and the Database of Abstracts of Reviews of Effects (DARE) were searched using the key words “transcatheter aortic valve replacement” OR “transcatheter aortic valve implantation” OR “percutaneous aortic valve replacement” OR “Core-Valve” OR “Sapien.” The search was performed for the period from 1945 to January 2012. References were also solicited from the manufacturers and local experts. The abstracts of citations were reviewed for relevance and all potentially relevant articles were reviewed in full. Case series describing at least 100 patients treated with TAVR, comparative studies with surgical therapy, and randomized trials comparing TAVR with medical therapy were included.

The search identified 1356 potentially relevant studies (Figure E1). After elimination of duplicate and nonrelevant references, including reviews and animal studies, the search identified 45 articles describing 16 case series,¹⁻²⁷ 10 comparative trials,²⁸⁻³⁷ and 1 randomized trial.³⁸⁻⁴² An additional 69 early case series and 1 comparative study were excluded because they were too small to provide reliable estimates of the outcomes of interest.^{15,18,20,43-107} Two of the publications included with the case series^{6,7} and 1 of the publications included with the comparative studies³³ were meta-analyses of previous literature

including many of the smaller studies not otherwise described in this assessment. Thus, TA Criterion 2 was met.

TA Criterion 3: The Technology Must Improve Net Health Outcomes

Symptomatic AS has a high short-term mortality so total mortality should be the primary outcome of interest. Treatment of AS is associated with an increased risk for stroke and some patients perceive that their quality of life living with the disabilities of a stroke could be worse than death, so stroke risk is a key outcome. Quality of life and functional status are also major concerns. The New York Heart Association (NYHA) developed the system that is most commonly used to quantify the degree of functional limitation imposed by heart disease.¹⁰⁸ Two more detailed quality of life questionnaires, the Kansas City Cardiomyopathy Questionnaire (KCCQ) and the Medical Outcomes Study Short Form 12 (SF-12) were used in some of the studies. The KCCQ is a validated 23-item questionnaire focusing on 5 domains: symptoms, physical limitation, social limitation, self-efficacy, and quality of life.^{109,110} Other important periprocedural and longer-term outcomes include MI, major bleeding, kidney injury, major vascular complications, and valve dysfunction including aortic regurgitation. A consensus panel published clear definitions for these outcomes in 2011.¹¹¹ Table E1 describes when and where the studies were performed, which valve type was used, and a brief summary of the characteristics of the patients in the studies.

The procedural success rate was generally high, ranging from 95% to 99% in the most recent series. Table E2 summarizes the procedural outcomes and events over 30 days. The most important outcome, 30-day mortality, varied from 6% to 19%, likely due to differences in the underlying risk of the different patient groups studied. The risk of major stroke varied from 1% to 5%. TAVR is known to cause some arrhythmias and 2% and 39% of patients in these case series required insertion of a permanent pacemaker. Case series that evaluated both the CoreValve (Medtronic, Minneapolis, Minn) and the SAPIEN valve suggested that the requirement for a pacemaker is more common with the CoreValve.^{14,18,25} Major vascular complications varied widely (2% to 28%), in part because of differences in what was classified as a vascular complication. Aortic regurgitation, both around and through the implanted valve, is a common complication but most are trivial to mild and unlikely to cause symptoms. However, the prevalence of moderate to severe aortic regurgitation has been reported to be between 2% and 26% in these case series. The rates of MIs, valve embolization, and cardiac tamponade were generally low (<1%). The need for repeat interventions on the implanted valve was between 1% and 3%, but these data were not consistently

reported.^{12,25} Table E3 summarizes the outcomes at 1 year including quality of life outcomes.

Gilard and colleagues⁵ published data from the largest prospective cohort study of TAVR in 2012. The French Aortic National CoreValve and Edwards (FRANCE 2) Registry collected data on 3195 patients treated between January 2010 and October 2011. The average age of the patients was 83 years and half were women. The treating physicians used the SAPIEN valve for 67% of patients and the CoreValve for the remaining 33%. They used the transfemoral approach for 75% of patients and the transapical approach for 18%. The PARTNER randomized trials, as well as observational studies, identified stroke, paravalvular aortic regurgitation, and the need for permanent pacemaker placement as important harms associated with TAVR.¹¹² These outcomes were emphasized in this FRANCE 2 Registry publication.⁵ After 1 year of follow-up in the FRANCE 2 Registry, the incidence of stroke was 4.1%. After 30 days, new pacemakers were placed in 16% of patients and paravalvular leaks were observed in 64% of patients, although only 16% were moderate or severe. New pacemaker placement was more common with the CoreValve than the SAPIEN device (24% vs 12%). Mortality was lower with the transfemoral approach than the transapical approach at 30 days (8.5% vs 14%) and at 1 year (17% vs 22%). In a multivariable analysis adjusting for baseline risk factors, factors associated with an increased mortality at 1 year included, as expected, both a higher logistic EuroSCORE (European System for Cardiac Operative Risk Evaluation) and a higher NYHA functional class, as well as the transapical approach and moderate to severe paravalvular regurgitation. This supports the hypothesis that the transfemoral approach should be the preferred approach if it is technically feasible, and that advances in valve design and delivery that reduce the incidence of paravalvular regurgitation may reduce mortality at 1 year and beyond.

Comparative studies with SAVR. Ten studies compared the outcomes in high-risk patients with symptomatic AS referred for TAVR with patients who were treated with SAVR.²⁸⁻³⁷ The patient characteristics and the primary outcomes of the studies are summarized in Tables E1 to E3. Most of these studies were retrospective. The investigators used a variety of approaches to attempt to account for baseline differences between patients treated with TAVR and those treated with SAVR (n = 1008) including matching, multivariable regression, and propensity score techniques both for adjustment and matching. The results of the earliest study by Piazza and colleagues³⁴ are instructive. Patients in the TAVR group (n = 114) were significantly older, had higher NYHA class, and were at much higher operative risk according to the logistic EuroSCORE than those in the SAVR group (n = 1008). As would be expected based on those differences, the 30-day mortality was substantially higher

in the TAVR group (9.6% vs 2.3%; odds ratio [OR], 4.6; 95% confidence interval [CI], 2.2-9.6). Using different logistic regression models to control for confounding gave a range for results from 1 analysis suggesting that TAVR may be superior to SAVR (adjusted OR, 0.60; 95% CI, 0.11-3.36) to another suggesting that outcomes with TAVR may be much worse (adjusted OR, 7.6; 95% CI, 0.9-63). Using propensity scores, the models ranged from an adjusted OR of 0.35 (95% CI, 0.04-2.7) to an adjusted OR of 3.2 (95% CI, 0.3-32). All the confidence intervals included 1 but the confidence intervals were wide and the adjusted ORs varied widely by the choice of modeling technique. This highlights the difficulty in appropriately and fully adjusting for confounding in observational studies like this and demonstrates why it was appropriate to require randomized trials to evaluate the relative benefits and harms of TAVR both for inoperable and high-risk patients.

Jilaihawi and colleagues³³ published a meta-analysis comparing outcomes in 5025 high-risk patients with severe AS treated with TAVR (16 studies) to those of 3512 patients treated with SAVR (19 studies). Although the number of patients is impressive, the investigators simply pooled the data from these disparate studies without appropriate meta-analytical techniques. Undoubtedly, there was significant heterogeneity between the studies that were pooled as was described in the meta-analysis by Genereux and colleagues.⁶ Furthermore, patients from the 2 groups most often were not treated at the same institution or even in the same country. It is difficult to draw any meaningful conclusions from this study.

Four of the studies^{30-32,36} used propensity scores to match patients treated with SAVR with those treated with TAVR and 1 matched on baseline characteristics³⁵ (age, logistic EuroSCORE, coronary artery disease, valvular heart disease). In general, these studies found that patients in the TAVR group had shorter procedural times, spent fewer days in the intensive care unit, and had shorter hospital stays. There were no significant differences in 30-day mortality and stroke rates. Patients in the TAVR group required permanent pacemakers more often and had a higher incidence of paravalvular aortic regurgitation.

Randomized clinical trials. *The Placement of Aortic Transcatheter Valve Trial.* The PARTNER (Placement of Aortic Transcatheter Valve Trial)¹¹³ included 2 parallel, randomized clinical trials, 1 in operable, high-risk patients (PARTNER A)³⁸⁻⁴² and 1 in patients ineligible for surgery (PARTNER B).¹¹³⁻¹¹⁵ This technology assessment focuses on the PARTNER A trial because our February 2012 CTAF assessment¹¹² focused on the PARTNER B trial and the use of TAVR for patients ineligible for SAVR.

Patients were considered at high risk for operative complications or death if they had a predicted probability of death within 30 days of surgery of at least 15% as

determined by surgeons at each center.⁴² A Society of Thoracic Surgeons (STS) predicted risk of mortality (PROM) score of at least 10% was used as a guideline for high risk. Patients were required to have severe AS defined by either an aortic valve area of less than 0.8 cm², an aortic valve gradient of at least 40 mm Hg, or a peak aortic jet velocity of at least 4.0 m/s. They also were required to have NYHA class II, III, or IV symptoms. Patients were excluded if they had a bicuspid or noncalcified aortic valve, acute MI, coronary artery disease requiring revascularization, left ventricular ejection fraction less than 20%, severe mitral or aortic regurgitation, transient ischemic attack or stroke in the previous 6 months, or severe renal insufficiency (creatinine >3.0 mg/dL or preoperative renal replacement). Eligible patients were randomized to receive the Edwards SAPIEN heart valve system (transfemoral or transapical) or SAVR. The primary end point of the trial was death from any cause.

The study characteristics and findings are summarized in [Tables E1 to E3](#). In brief, 348 patients were randomized to the TAVR group and 351 to the SAVR group. Follow-up was 100% complete over 2 years and the primary analysis was done according to strict intention-to-treat principles. No blinding was reported and no sham procedure was performed.

The average age of the participants was 84 years and 43% were female. Their predicted operative mortality by the logistic EuroSCORE was 28% and by the STS PROM score was 12%. There were no significant differences between the 2 groups on 26 potential confounders at baseline although there was a trend towards more patients with an increased creatinine level in the TAVR group (11% vs 7%, $P = .06$). An increased creatinine level has been associated with higher mortality in observational studies of aortic valve replacement so this difference would tend to bias results against TAVR.

TAVR was successful for 95% of patients in the TAVR group. Three patients died during the procedure and it was aborted or converted to open surgery in 16 patients (4.6%). More than 1 transcatheter valve was implanted in 7 patients. The reasons for the use of multiple valves included valve embolization (2 patients) and residual aortic regurgitation (5 patients). Three of these 7 patients died. Valve embolization occurred in 7 additional patients. The procedure was aborted in 2 patients and converted to an open procedure in the remaining 7. As expected, the procedure time was shorter for TAVR (133 minutes vs 230 minutes, P values not reported) as was the average stay in the intensive care unit (ICU) after the procedure (3 days vs 5 days, P values not reported) and the length of the initial hospitalization (8 days vs 12 days, P values not reported).

At 30 days, there were no differences in death from any cause (3.4% vs 6.5%, $P = .07$), major strokes (3.8% vs

2.1%, $P = .20$), or the combination of the two (6.9% vs 8.2%, $P = .52$). The TAVR group did have more neurologic events including transient ischemic attacks and minor strokes (5.5% vs 2.4%, $P = .04$). The TAVR group had more major vascular complications defined as aortic dissection, left ventricular perforation, embolization resulting in permanent damage, vascular injury requiring surgical intervention or causing death, permanent disability, or blood transfusion of at least 3 units (11.0% vs 3.2%, $P < .001$). However, the TAVR group had fewer major bleeding episodes defined as bleeding leading to death or prolonged hospitalization requiring surgical intervention or blood transfusions of at least 3 units (9.3% vs 19.5%, $P < .001$). The TAVR group also had fewer episodes of new onset atrial fibrillation (8.6% vs 16.0%, $P = .006$). There were no differences in the rate of MIs, new pacemakers, or the need for dialysis. The prevalence of paravalvular aortic regurgitation was more common after TAVR for both minimal disease (65% vs 25%, $P < .001$) and moderate to severe regurgitation (12.1% vs 0.9%, $P < .001$). More patients in the TAVR group reported NYHA class II or lower symptoms at 30 days (~72% vs ~59%, $P < .001$).⁴²

At 1 year the outcomes were similar. There were no differences in death from any cause (24.2% vs 26.8%, $P = .44$), major strokes (5.1% vs 2.4%, $P = .07$), or the combination of the two (26.5% vs 28.0%, $P = .68$). The difference in mortality at 1 year between the 2 groups (−2.6%, 95% CI, −9.3% to +4.1%) was within the prespecified noninferiority boundary of 7.5% ($P = .001$ for noninferiority). The differences in neurologic outcomes, major vascular complications, and major bleeding persisted. The prevalence of paravalvular aortic regurgitations remained more common after TAVR for minimal disease (60% vs 20%, $P < .001$) and moderate to severe regurgitation (6.8% vs 1.9%, $P < .001$).

One of the major concerns raised when CTAF considered TAVR for inoperable patients was the lack of longer-term follow-up. The investigators published the 2-year follow-up for the PARTNER trials in 2012.^{39,114} There were no cases of structural valve deterioration and valve area was preserved as assessed by echocardiography. There continued to be no differences in overall mortality at 2 years (35.0% vs 33.9%, $P = .78$), as well as no significant differences in the rate of stroke or rehospitalization. The Kaplan-Meier curves did not diverge at all between 2 and 3 years of follow-up suggesting that the result is likely to be similar over at least 3 years.

Quality of life indicators were better in the TAVR group at 1 month but not at 6 or 12 months.⁴¹ This likely reflects a decrement in quality of life associated with median sternotomy. Quality of life improvements were nearly identical in the 2 groups at 6 and 12 months as measured by the KCCQ, the SF12, the EQ-5D, and their related subscales.

As noted earlier, this was a high-quality randomized trial with remarkable 100% follow-up of all patients for 2 years. There were no significant baseline differences between the TAVR and SAVR groups and the only borderline difference would be expected to bias the results against the TAVR group. The primary methodological concern centers on the 42 patients who were not treated as randomized. Only 4 (1.1%) were in the TAVR group and 38 (10.8%) were in the SAVR group ($P < .001$). This could introduce selection bias. To address this, the investigators performed a strict intention-to-treat analysis and reported this as the primary result. They also performed as-treated analyses for all the major outcomes and none of the conclusions were changed. The other concern was that the time from randomization to treatment was longer for the surgical group (10.6 days vs 15.6 days, $P < .001$). This may explain why there were more pre-procedural deaths in the surgical group (3 vs 10 deaths). At 30 days, there still would be fewer deaths in the transcatheter group (adding 7 additional deaths to that group) but at 1 year there would have been slightly more deaths in the transcatheter group (84 + 7 = 91 vs 89 deaths). Thus, it does not seem that accounting for the difference in pre-procedure deaths would change the conclusion of the study.

In summary, a high-risk surgical patient with severe AS who was randomized to TAVR had a similar risk of dying over 2 years of follow-up compared with SAVR. The rates of stroke and rehospitalization were also equivalent, although when all neurologic events were counted, there was a slight excess in the TAVR group. Patients in the TAVR group experienced more major vascular events and more paravalvular aortic regurgitation. Patients in the SAVR group experienced more major bleeding and required longer stays in the ICU and hospital after the valve replacement procedure. Quality of life improved more rapidly in the TAVR group, likely related to the need for a median sternotomy in the SAVR group. However, quality of life improvements were comparable in both groups at 6 and 12 months. There are differences in terms of vascular complications, major bleeding, strokes, atrial fibrillation, and aortic regurgitation but they seem to balance each other and do not have an impact on the medium-term outcomes over 2 to 3 years. Some uncertainty remains about the long-term viability of the transcatheter valves so the outcomes of the studies over 5 years of follow-up should be closely monitored. Thus, TA Criterion 3 was met.

TA Criterion 4: The Technology Must Be as Beneficial as Any Established Alternatives

The established alternative to TAVR for patients with severe AS is SAVR. Because patients with severe AS are generally older and have multiple comorbidities, they are at high risk for complications during and after SAVR, including death.

The randomized PARTNER A trial, described in detail earlier, directly compared TAVR with SAVR. As discussed

under TA Criterion 3, over 2 years of complete follow-up there were no statistically or clinically significant differences between the 2 groups in death from any cause, repeat hospitalizations, strokes, the combination of death from any cause and repeat hospitalization, or the combination of death from any cause and stroke.³⁹ There was an absolute difference of 8% more patients having major vascular complications with TAVR and an absolute difference of 10% more patients having major bleeding complications with SAVR. There were no differences between the groups in quality of life after 1 month or in the incidence of MI, new pacemakers, renal failure, endocarditis, or structural valve deterioration. There was an excess of mild and moderate paravalvular aortic regurgitation in the TAVR group at 30 days and 1 year, which has been associated with an increased risk for death in previous studies. The survival curves remained overlapping for years 1 to 3 of follow-up but there still may be longer-term problems that arise either from the valves themselves or from the paravalvular leaks. This should be watched in continued long-term follow-up given that almost two thirds of the patients in both groups were still alive at 2 years. That said, the data are convincing that TAVR is equivalent to SAVR in high-risk patients for all important outcomes over 2 years. However, the longer-term results remain to be established. Indeed, either paravalvular or valvular aortic insufficiency, which are increased in the TAVR group, are associated with diminished long-term survival.

The definition of high risk is an essential part of this conclusion. The FDA indication for the Edwards SAPIEN device uses essentially the same definition as that used in the inclusion criteria for the PARTNER trial: patients should have an STS PROM score of at least 10 or have at least a 15% risk of death within 30 days as determined by at least 1 surgeon. There are ongoing randomized trials evaluating the relative risks and benefits of TAVR versus SAVR in lower-risk patients. Therefore, TA Criterion 4 was met.

TA Criterion 5: The Improvement Must Be Attainable Outside the Investigational Setting

TAVR is a technically difficult procedure with a steep learning curve. In the Vancouver single center case series, outcomes improved over time.¹⁶ The investigators compared results in the first 135 patients with the results in the subsequent 135 patients. The overall success rate increased from 93% to 98% and the 30-day mortality decreased from 13% to 6%. There were fewer cases of device embolization, coronary occlusion, stroke, and major vascular injury in the second half of their case series.¹⁶ Some of the improvement may reflect changes in the design of the valvular implants and their delivery systems. In addition, patients in the second half of the case series

were at significantly lower risk for poor outcomes (STS PROM score 8.5 vs 10.5, $P < .01$). Clearly, care must be taken to ensure adequate training and proctoring of physicians performing TAVR. Thus, although equivalent outcomes in the investigational and noninvestigational setting are likely, subsequent studies and analysis will be required to confirm this.

Consensus recommendations have been made jointly by the American College of Cardiology Foundation and the STS.¹¹⁶ In brief, they recommend that programs using TAVR should be performed at a limited number of specialized heart centers with multidisciplinary teams that include at least 1 interventional cardiologist and 1 cardiac surgeon. All personnel should receive appropriate training and credentialing and follow standard protocols set up by expert consensus groups for evidence-based patient selection, procedural details, and complication management. A registry has been established to track appropriate use and patient outcomes.¹¹⁶ Outcomes data from the first year of the registry should be published in 2013 with additional data on whether the outcomes achieved in the PARTNER trial can be replicated in clinical practice in the United States. If followed, these recommendations should ensure that appropriate patients are selected and that highly skilled teams perform the procedure. Thus, TA Criterion 5 was met.

CONCLUSIONS

AS is common in the elderly and when symptoms arise, about half of these patients die within 2 years. SAVR is an effective therapy for AS that can be performed with relatively low morbidity and mortality given the age and comorbidity of most patients with AS. To address the need for additional treatment options for patients with AS who are inoperable or very high risk for surgical treatment, 2 aortic valves (Medtronic's CoreValve and the Edwards SAPIEN valve), which can be implanted using catheters, have been developed. In observational studies, the success rate for transcatheter aortic valve implantation has been greater than 95%, but the 30-day mortality ranged from 6% to 13%. In addition, up to 39% of patients required a permanent pacemaker, up to 28% of patients experienced major vascular complications, and up to 42% developed moderate to severe AS. The case series data and the comparative studies gave inadequate information to fully understand the relative benefits and harms of TAVR compared with standard surgical valve replacement.

The PARTNER A trial is the pivotal randomized trial that helps us understand the balance of risks and harms of TAVR compared with SAVR.³⁸⁻⁴² In the trial, 348 patients with severe AS were randomized to the TAVR group (Edwards SAPIEN valve via the transfemoral or transapical approach) and 351 patients were randomized to the surgical therapy group. Mortality over 2 years

was virtually identical at 35% and there was no excess of stroke, pacemaker placement, valve failure, or rehospitalization in the TAVR group. Quality of life measures improved faster in the TAVR group but were essentially the same in the 2 groups by 6 months. The excess of major vascular complications in the TAVR group was balanced by an excess of major bleeding episodes in the surgical group. Other features that weigh in favor of TAVR include avoiding a median sternotomy, a shorter stay in the ICU, and a shorter hospitalization. The major remaining concern is the excess of paravalvular aortic regurgitation in the TAVR group compared with the surgical group.

The trial was not methodologically perfect. Forty-two patients were not treated as randomized and all but 4 of them were in the surgical group. This may have introduced some selection bias because it represents more than 10% of the patients randomized to the surgical group. In addition, the time from randomization to procedure was significantly longer in the surgical group. This may in part explain why 10 patients randomized to the surgical group died before their procedure whereas only 3 patients in the TAVR group died before their procedure. Intention-to-treat analyses, per protocol analyses, and sensitivity analyses suggest that these problems are not large enough to invalidate the conclusion that the 2 treatments are equally beneficial, but others may judge differently.

Patient selection is essential to ensure that the results of the PARTNER trial apply to patients treated in the community. A multidisciplinary team that includes at a minimum 1 cardiac surgeon, a general cardiologist, and an interventional cardiologist should agree that a patient is high risk before offering TAVR. Patients must be informed of the upfront risks of death, stroke, pacemaker placement, and major vascular complications (11% in the PARTNER A trial). Patients also need to be informed that some uncertainty remains about the durability of percutaneous aortic valves beyond 3 years. There is a high prevalence of moderate to severe aortic regurgitation, which may lead to recurrent symptoms or unforeseen problems with the valve. As was highlighted at the February 2012 CTAF meeting, the dispersion of this technology to new centers across the United States must proceed with careful thought given to training and proctoring multidisciplinary teams to become new centers of excellence. Attention needs to be paid to appropriate patient selection, their preoperative evaluation, surgical techniques, and postoperative care to preserve and improve on the results attained in the PARTNER trial. As described under TA Criterion 5, the specialty societies are collaborating to ensure that this happens in a rational and comprehensive manner.¹¹⁶

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FIGURE E1. Selection of studies for inclusion in the review.

TABLE E1. Characteristics of the larger published studies on transcatheter aortic valve replacement

Study	Group	Location	N	Time frame	Valve type	Follow-up (months)	Age (years)	Sex (% female)	Log EuroSCORE	STS score
Uncontrolled cohorts										
Grube 2008	TAVR	Sieborg, Germany	136	2005-2008	CoreValve	NR	82	58	23	9
Piazza 2008	TAVR	Multicenter	646	2007-2008	CoreValve	NR	81		23	NR
Rodes-Cabeau 2010	TAVR	Canada, 6 centers	339	2005-2009	SAPIEN	8	81	55	NR	10
Bosmans 2011	TAVR	Multicenter Belgium	328	?-2010	CoreValve, SAPIEN	NR	83	54	28	NR
D'Onofrio 2011, 2012	TAVR	Multicenter Italy	566	2008-2011	SAPIEN	10	81	61	26	12
Eltchaninoff 2011	TAVR	Multicenter France	244	2009	CoreValve, SAPIEN	1	82	43	26	19
Gurvitch 2011	TAVR	Vancouver, Canada	270	NR	SAPIEN	1	83	50	NR	10
Humphries 2011; Webb 2009	TAVR	Vancouver and Quebec, Canada	641	2005-2011	CoreValve, SAPIEN	10	83	51	NR	8
Lefevre 2011	TAVR TF	Multicenter	61	2007-2008	SAPIEN	12	82	61	26	11
	TAVR TA	Europe	69				82	51	34	12
Moat 2011	TAVR	Multicenter UK	870	2007-2009	CoreValve, SAPIEN	NR	82	48	19	NR
Tamburino 2011	TAVR	Multicenter Italy	663	2007-2009	CoreValve	18	81	56	23	NR
Thomas 2010, 2011	TAVR TF	Multicenter Europe	463	2007-2009	SAPIEN	12	82	55	26	NR
	TAVR TA		575				81	56	29	
Zahn 2011	TAVR	Multicenter Germany	697	2009	CoreValve, SAPIEN	1	81	56	21	NR
Eggebrecht 2012	TAVR	MA 53 studies	10,037	2004-2011	CoreValve, SAPIEN	1	82	53	25	NR
Genereux 2012	TAVR	MA 16 studies	3519	2008-2010	CoreValve, SAPIEN	12	NR	NR	23	9
Gilard 2012	TAVR	Multicenter France	3195	2010-2011	CoreValve, SAPIEN	12	83	49	22	14
Comparative studies										
Kapadia 2009	TAVR	Cleveland, Ohio	18	2006-2007	SAPIEN	9	81	33	28	11
	Medical		36			6	83	53	25	13
Rajani 2010	TAVR	Brighton, UK	38	2007-2009	CoreValve	7	83	45	24	NR
	Medical		47				81	52	13	NR
Piazza 2009	TAVR	2 European centers	114	2006-2008		1				
	Surgical		1008							
Zierer 2009	TAVR	Frankfurt, Germany	21	2006-2007	SAPIEN	12	85	71	38	NR
	Surgical		30				82	63	35	NR
Clavel 2010	TAVR	Multicenter Canada, Austria	83	2006-2008	SAPIEN	12	81	41	32	12
	Surgical	Germany	200				70	19	18	6
Walther 2010	TAVR	Leipzig, Germany	100	2006-2008	SAPIEN	12	83	77	29	15
	Surgical		100	1996-2008			82	70	30	NA
Higgins 2011	TAVR	British Columbia, Canada	46	2005-2010	SAPIEN	1	78	80	NR	NR
	Surgical		46	2001-2009			78	79	NR	NR
Stohr 2011	TAVR	Aachen, Germany	175	2008-2010	CoreValve, SAPIEN	1	80	40	21	NR
	Surgical		175				79	24	17	NR
Ben-Dor 2012	TAVR	PARTNER	159	2007-2011	SAPIEN	13	84	57	42	12
	Surgical	nonrandomized	146			24	79	49	27	8
	Medical		595			7	82	55	43	12
Conradi 2012	TAVR	Hamburg, Germany	82	2009-2010	SAPIEN	6	82	63	24	9
	Surgical		82				82	58	24	9
Fusari 2012	TAVR	Italy	106	2008-2009	SAPIEN	21	81	68	22	8.4
	Surgical		81			22	78	67	8.5	2.8
Jilaihawi 2012	TAVR	MA 35 studies	5024	Before 2010	CoreValve, SAPIEN	24	81	54	25	NR
	Surgical		3512				82	56	18	NR

(Continued)

TABLE E1. Continued

Study	Group	Location	N	Time frame	Valve type	Follow-up (months)	Age (years)	Sex (% female)	Log EuroSCORE	STS score
Randomized trials										
PARTNER B (inoperable)	TAVR	Multicenter, United States, Germany, Canada	179	2007-2009	SAPIEN	19	83	54	28	12
Leon 2010	Medical		179							
PARTNER A (high risk)	TAVR	Multicenter, United States, Germany, Canada	348	2007-2009	SAPIEN	24	84	43	29	12
Smith 2011	Surgical		351							
Kodali 2012										

TAVR, Transcatheter aortic valve replacement; NR, not reported; TF, transfemoral; TA, transapical; NA, not available; STS, Society of Thoracic Surgeons; EuroSCORE, European System for Cardiac Operative Risk Evaluation; MA, meta-analysis; PARTNER, Placement of Aortic Transcatheter Valve Trial.

TABLE E2. Procedural and 30-day benefits and harms of transcatheter aortic valve replacement

Study	Group	Procedural success (%)	Death (%)	Major stroke (%)	Major vascular complication	Pacemaker placement (%)	Moderate to severe aortic regurgitation (%)	MI %	Tamponade (%)	Major bleeding (%)	Need for hemodialysis (%)
Uncontrolled cohorts											
Grube 2008	TAVR	86	12	1	NR	25	26	2	1	NR	NR
Piazza 2008	TAVR	97	8	2	2	9	NR	1	1	0	NR
Rodes-Cabeau 2010	TAVR	93	10	2	13	5	6	1	0	NR, >1.4	3
Bosmans 2011	TAVR	97	11	5	NR	NR	NR	NR	NR	NR	NR
D'Onofrio 2011, 2012	TAVR	99	8	3	NR	5	NR	2	NR	NR	6
Elchaninoff 2011	TAVR	98	13	4	7	12			2	NR	2
Gurvitch 2011	TAVR	95	10	3	7	6	NR	NR	2	9	3
Humphries 2011;	TAVR	Failures excluded	9	2	9	6	NR	NR	NR	17	NR
Webb 2009											
Lefevre 2011	TAVR TF	96	8	3	28	2	NR	3	NR	5	0
	TAVR TA	95	19	2	5	4		6		12	6
Moat 2011	TAVR	97	7	4	6	16	14	1	NR	NR	NR
Tamburino 2011	TAVR	98	6	1	2	17	21	0	1	3	NR
Thomas 2010, 2011	TAVR TF	95	6	2	11	7	2	NR	NR	NR	1
	TAVR TA	93	10	3	2	7	2				7
Zahn 2011	TAVR	98	12	3	17	39	Severe 2.3	1	2	NR	NR
Eggebrecht 2012	TAVR	NR	8	3	NR	NR	NR	NR	NR	NR	NR
Genereux 2012	TAVR	92	8	4	12	14	7	1	3	16	NR
Gilard 2012	TAVR	97	10	2	5	16	17	NR	NR	4	NR
Comparative studies											
Kapadia 2009	TAVR	NR	5	0	NR	6	NR	0	NR	NR	NR
	Medical	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Rajani 2010	TAVR	NR	8	3	3	34	NR	NR	3	NR	3
	Medical	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Piazza 2009	TAVR		10								
	Surgical		2								
Zierer 2009	TAVR	85	14	0	NR	0	NR	NR	NR	NR	0
	Surgical	100	10	3	NR	3	NR	NR	NR	NR	10
Clavel 2010	TAVR	NR	19	NR	NR	NR	6	NR	NR	NR	NR
	Surgical	NR	12	NR	NR	NR	0	NR	NR	NR	NR
Walther 2010	TAVR	97	10	0	NR	10	NR	NR	NR	NR	NR
	Surgical	100	15	2	NR	NR	NR	NR	NR	NR	NR
Higgins 2011	TAVR	NR	13	0	NR	NR	NR	NR	NR	NR	NR
	Surgical	NR	9	4	NR	NR	NR	NR	NR	NR	NR
Stohr 2011	TAVR	100	12	1	NR	15	3	NR	NR	NR	4
	Surgical	100	8	0.5	NR	2	0	NR	NR	NR	14
Ben-Dor 2012	TAVR	NR	12	NR	NR	NR	NR	NR	NR	NR	NR
	Surgical	NR	13	NR	NR	NR	NR	NR	NR	NR	NR
	Medical	NR	10	NR	NR	NR	NR	NR	NR	NR	NR
Conradi 2012	TAVR	96	7	2	NR	4	1	NR	NR	NR	NR
	Surgical	100	9	2	NR	2	0	NR	NR	NR	NR
Fusari 2012	TAVR	100	2	1	4	6	NR	1	1	2	5
	Surgical	100	4	2	0	1	NR	1	0	5	5
Jilaihawi 2012	TAVR	NR	8	3	7	12	12	1	1	NR	4
	Surgical	NR	9	2	NR	6	NR	NR	NR	NR	2

(Continued)

TABLE E2. Continued

Study	Group	Procedural success (%)	Death (%)	Major stroke (%)	Major vascular complication	Pacemaker placement (%)	Moderate to severe aortic regurgitation (%)	MI %	Tamponade (%)	Major bleeding (%)	Need for hemodialysis (%)
Randomized trials											
PARTNER B	TAVR	97	5	5	16	3	12	0	NR	17	1
Leon 2010	Medical	100	3	1	1	5	-	0	NR	4	2
PARTNER A	TAVR	95	3.4	3.8	11.0	3.8	12.2	0	NR	9.3	2.9
Smith 2011	Surgical	99	6.5	2.1	3.2	3.6	0.9	0.6	NR	19.5	3.0
Kodali 2012											

MI, Myocardial infarction; TAVR, transcatheter aortic valve replacement; NR, not reported; TF, transfemoral; TA, transapical; PARTNER, Placement of Aortic Transcatheter Valve Trial.

TABLE E3. Benefits and harms of transcatheter aortic valve replacement at 1 year

Study	Group	Death	Major stroke	NYHA heart failure class	Quality of life KCCQ	Quality of life SF-12
Uncontrolled cohorts						
Grube 2008	TAVR	18	4	3.3 to 1.7	NR	NR
Piazza 2008	TAVR	NR	NR	NR	NR	NR
Rodes-Cabeau 2010	TAVR	24	NR	NR	NR	NR
Bosmans 2011	TAVR	21	NR	NR	NR	NR
D'Onofrio 2011, 2012	TAVR	17	NR	NR	NR	NR
Eltchaninoff 2011	TAVR	NR	NR	NR	NR	NR
Gurvitch 2011	TAVR	NR	NR	NR	NR	NR
Humphries 2011; Webb 2009	TAVR	83 F, 73 M	NR	NR	NR	NR
Lefevre 2011	TAVR TF	21	7	86% Class I or II	50 to 68	NR
	TAVR TA	51	10	80% Class I or II	50 to 77	
Moat 2011	TAVR	21	NR	NR	NR	NR
Tamburino 2011	TAVR	15	3	>50% Class I or II	NR	NR
Thomas 2010, 2011	TAVR TF	19	5	78% Class I or II	NR	NR
	TAVR TA	28	5	69% Class I or II		
Zahn 2011	TAVR	NR	NR	NR	NR	NR
Eggebrecht 2012	TAVR	NR	5	NR	NR	NR
Genereux 2012	TAVR	22	NR	NR	NR	NR
Gilard 2012	TAVR	24	2	90% Class I or II	NR	NR
Comparative studies						
Kapadia 2009	TAVR	~22%	NR	NR	NR	NR
	Medical	~44%				
Rajani 2010	TAVR	~13%	NR	NR	NR	NR
	Medical	~28%				
Piazza 2009	TAVR	NR	NR	NR	NR	NR
	Surgical	NR	NR	NR	NR	NR
Zierer 2009	TAVR	24	NR	NR	NR	NR
	Surgical	17	NR	NR	NR	NR
Clavel 2010	TAVR	NR	NR	NR	NR	NR
	Surgical	NR	NR	NR	NR	NR
Walther 2010	TAVR	27	NR	NR	NR	NR
	Surgical	31	NR	NR	NR	NR
Higgins 2011	TAVR	NR	NR	NR	NR	NR
	Surgical	NR	NR	NR	NR	NR
Stohr 2011	TAVR	NR	NR	NR	NR	NR
	Surgical	NR	NR	NR	NR	NR
Ben-Dor 2012	TAVR	21	NR	NR	NR	NR
	Surgical	21	NR	NR	NR	NR
	Medical	36	NR	NR	NR	NR
Conradi 2012	TAVR	NR	NR	NR	NR	NR
	Surgical	NR	NR	NR	NR	NR
Fusari 2012	TAVR	12	NR	~86% Class I or II	NR	NR
	Surgical	10	NR	~84% Class I or II	NR	NR
Jilaihawi 2012	TAVR	23	NR	NR	NR	NR
	Surgical	18	NR	NR	NR	NR
Randomized trials						
PARTNER B	TAVR	31	8	75% Class I or II	+32	+7
Leon 2010	Medical	50	4	42% Class I or II	+4	+2
Reynolds 2011						
PARTNER A	TAVR	24	5	~63% Class I or II	+29	+6.5
Smith 2011	Surgical	27	2	~63% Class I or II	+25	+5.6
Kodali 2012						

NYHA, New York Heart Association; KCCQ, Kansas City Cardiomyopathy Questionnaire; SF-12, Short Form 12; TAVR, transcatheter aortic valve replacement; NR, not reported; TF, transfemoral; TA, transapical; PARTNER, Placement of Aortic Transcatheter Valve Trial.