



TITLE: Transcatheter Aortic Valve Implantation In Patients With Severe Aortic Stenosis Who Cannot Undergo Surgery

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PUBLISHER: California Technology Assessment Forum

DATE OF PUBLICATION: February 8, 2012

PLACE OF PUBLICATION: San Francisco, CA

TRANSCATHETER AORTIC VALVE IMPLANTATION IN PATIENTS WITH SEVERE AORTIC STENOSIS WHO CANNOT UNDERGO SURGERY

A Technology Assessment

INTRODUCTION

The California Technology Assessment Forum (CTAF) was asked to assess the evidence for the use of transcatheter aortic valve implantation for the treatment of patients with aortic stenosis who are not surgical candidates. Aortic stenosis is treated medically until the valve area decreases to a critical point or the patient becomes symptomatic. Because valvular aortic stenosis is primarily a disease of aging, many patients with aortic stenosis have significant co-morbidities that preclude surgical intervention. The FDA recently approved an aortic valve replacement device that can be implanted without requiring a thoracotomy and cardioplegia.

BACKGROUND

Valvular aortic stenosis

Aortic stenosis (AS) is a decrease in the effective area of the aortic valve leading to increased resistance to the flow of blood across the valve.^{1,2} It is relatively common in the elderly with a prevalence between 4% and 5% among people over the age of 75 years.^{3,4} The disease tends to progress slowly until symptoms occur.⁵⁻⁷ The cardinal symptoms of aortic stenosis are angina, congestive heart failure, and syncope. Classically these occur during exercise because the left ventricle is unable to push sufficient blood across the stenotic valve to meet the demands of the heart and the rest of the body. Surgery is indicated once someone becomes symptomatic because average survival without surgery is only two to three years.^{2,8,9}

The signs of aortic stenosis on physical exam include a systolic murmur, usually loudest at the right upper sternal border, that peaks late and radiates to the right carotid artery.¹⁰ The carotid artery pulse is classically *parvus et tardus*: weak and late. Finally the second heart sound may be reduced in intensity.

There are three main forms of aortic valve disease: congenital abnormalities, such as a bicuspid valve that leads to premature calcification; calcification of the normal trileaflet valve; and rheumatic valve disease. In the United States about a third of aortic stenosis is caused by rheumatic disease, a third by calcification of a

unicuspid or bicuspid valve, and a third by calcification of a normal trileaflet valve.¹¹⁻¹⁴ Calcific aortic valve disease is characterized by progressive aortic valve leaflet thickening and calcification that results in a valve that does not fully open and thus partially obstructs the flow of blood from the left ventricle into the aorta during systole.

The normal aortic valve area when open is between 3 and 4 cm². There is no significant obstruction to flow until the valve area has decreased by 50%. As the valve narrows, the velocity of blood crossing the valve increases to compensate. The degree of stenosis is usually assessed by measuring the jet velocity with Doppler echocardiography. The normal aortic jet velocity is less than 2.5 m/sec. Symptoms usually do not occur in patients until the gradient of the aortic jet is greater than 4.0 m/sec and the valve area is less than 1.0 cm². The ACC/AHA guidelines define the degree of aortic stenosis as mild, moderate, or severe based on aortic jet velocity, the mean pressure gradient across the valve, and the valve area (see Table 1).⁸

Table 1: Severity of aortic stenosis

	Valve area, cm²	Pressure gradient, mm Hg	Jet velocity, m per second
Mild	≥ 1.5	< 25	< 3.0
Moderate	1.0 to 1.5	25 to 40	3.0 to 4.0
Severe	< 1.0	> 40	> 4.0

Surgical aortic valve replacement

Once someone with aortic stenosis becomes symptomatic, they are usually referred for surgery. Indications for surgery include symptomatic severe aortic stenosis, severe aortic stenosis in someone undergoing coronary artery bypass grafting or other open heart surgery, and severe aortic stenosis in someone with a left ventricular ejection fraction of less than 50%.⁸ Surgical aortic valve replacement is associated with a significant risk of operative mortality, defined as any death within 30 days of the surgery. The operative mortality is commonly reported to be between 3% and 7%,¹⁵ but has been decreasing over time despite an increase in the average age and operative risk of patients.^{16,17} In the Society for Thoracic Surgeons National Cardiac Surgery Database operative mortality for isolated aortic valve replacement decreased from 3.4% in 1997 to 2.6% in 2006 while the predicted mortality increased from 2.8% to 3.2% and the average age increased from 66 years to 68 years.¹⁶ The incidence of stroke also decreased from 1.7% to 1.3%.¹⁶ The

improvements were largest in the oldest patients. For example, for patients 85 to 89 years old, operative mortality fell from 7.8% to 4.1% and the stroke rate decreased from 4.1% to 2.4%.¹⁶ These numbers represent reasonable benchmarks that novel therapeutic approaches need to match at a minimum.

Patients with symptomatic aortic stenosis are generally elderly and often have other significant medical illnesses putting them at high risk for perioperative complications including death. There are two risk scores that are widely used to assess patient's risk prior to surgery. The European System for Cardiac Operation Risk Evaluation (EuroSCORE) is widely used in Europe. It was developed based on 19,000 cardiac surgeries performed in Europe in 1995.^{18,19} A more precise version, the logistic EuroSCORE is now more widely used.²⁰ It calculates the predicted operative mortality for a patient undergoing cardiac surgery. However recent studies suggest that it over-predicts the risk of death in patients undergoing valve surgery.²¹⁻²⁴

The Society of Thoracic Surgeons Predicted Risk of Mortality (STS) score was developed from a large US National database in 1994.²⁵⁻²⁷ Similar to the EuroSCORE, it uses a large number of risk factors to predict the risk of death within 30 days of cardiac surgery. Recent validation studies suggest that it may predict the risk from isolated valve surgery more accurately than the EuroSCORE.²⁸⁻³⁰

Despite the poor prognosis without valve replacement and the relatively good outcomes from surgical aortic valve replacement, between 30% and 40% of patients with symptomatic aortic stenosis do not undergo valve replacement.^{31,32} Even with the EuroSCORE and the STS score, there are no clear guidelines defining which patients are inoperable. However, the majority of patients with severe aortic stenosis (AS) who do not undergo surgery are determined to have co-morbidities or an overall risk for poor outcomes that makes them inoperable. Transcatheter aortic valve implantation is a potential life-saver for these patients.

Transcatheter aortic valve implantation (TAVI)

Transscatheter aortic valve implantation is a novel way to replace a diseased aortic valve without a thoracotomy. The first human TAVI was performed by Dr. Cribier in 2002.³³ There have been three generations of the Cribier-Edwards SAPIEN valve. The only valve that has FDA approval is the Edwards SAPIEN XT. It is a trileaflet valve made from bovine pericardium in a cobalt chromium frame that is designed to be expanded by a balloon.

The other commercially available valve, not yet approved by the FDA, is the Medtronic CoreValve. It also

has gone through three generations of design improvements. The current generation CoreValve is a trileaflet valve made from porcine pericardium in a self-expanding nitinol frame.

A multidisciplinary team including both interventional cardiologists and cardiac surgeons evaluate patients with aortic stenosis to decide whether the patient should receive a surgical aortic valve replacement, TAVI, or be treated medically. Patients eligible for TAVI require imaging to precisely measure the size of the aortic annulus in order to determine the correct transcatheter valve size. The iliofemoral arterial system is evaluated by angiography to document the extent of atherosclerotic disease in the peripheral vasculature. The transfemoral approach is the preferred route for TAVI, but other approaches can be used if the iliofemoral system is narrowed and heavily calcified. The transapical approach, which is the next most commonly used approach, requires a left lateral thoracotomy and direct puncture of the left ventricular apex. Other approaches include the transaortic, which requires a sternotomy; the subclavian, which requires a surgical cutdown to the left subclavian artery; and the transaxillary, which requires a surgical cutdown to the left axillary artery.

Because of the possible need to convert to an open procedure, TAVI is usually performed in a hybrid catheterization laboratory / operating room, although some institutions perform the procedure in a regular catheterization laboratory that has rapid access to an operating room. The patient is anticoagulated using heparin and the physician threads a catheter across the aortic valve and performs balloon aortic valvuloplasty. The physician then positions the prosthetic valve and expands it by inflating a balloon during rapid ventricular pacing, which is done to temporarily minimize cardiac output and prevent valve embolization. Two videos describing the procedure are available on the New England Journal of Medicine website: <http://www.nejm.org/doi/full/10.1056/NEJMoa1008232>. After implantation of the valve, patients are maintained on dual anti-platelet therapy for at least six months.

The primary benefit of TAVI is the ability to treat AS in patients who would otherwise be ineligible for surgical valve replacement. Potential harms include the need for conversion to an open procedure, perioperative death, MI, stroke, bleeding, valve embolization, aortic regurgitation, heart block that requires a permanent pacemaker, and major vascular complications such as cardiac perforation or arterial dissection. Potential long term harms include death, stroke, valve failure or clotting, and endocarditis.

TECHNOLOGY ASSESSMENT (TA)

TA 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 received FDA PMA approval for transfemoral delivery in patients with severe, symptomatic native aortic valve stenosis who have been determined to be inoperable by a cardiac surgeon.

The FDA approval requires that Edwards Lifesciences conduct two post approval studies.

Post approval study	Objectives
1. Yearly follow up of patients in premarket study through five years post implant	<ul style="list-style-type: none"> • Describe the five-year durability and quality of life outcomes. <ul style="list-style-type: none"> ○ The measure for durability will be the degree of aortic insufficiency as measure via echocardiogram ○ Quality of life will be measure by three instruments – the Kansas City Cardiomyopathy Questionnaire (KCCQ), SF-12, and EuroQol (EQ)-5D Utilities
2. Follow up newly enrolled patients through five years post implant	<ul style="list-style-type: none"> • Evaluate the neurological and vascular outcomes at 30 days and annually through five years post implant. • “Assess the learning curve among surgical teams placing the device at 50 geographically disbursed sites with high, moderate and low volumes of potential patient participation.” • Evaluate the composite safety and effectiveness endpoints at 30 days and annually through five years post implant.

A National Transcatheter Aortic Valve Replacement registry must be developed within four months of the start of the post approval studies to house study data (pre-procedure, peri-procedure, post-procedure, discharge, 30-day, and 1-year follow-up). The registry will be housed jointly by the American College of Cardiology and the Society for Thoracic Surgeons. Finally, the data will be linked to CMS data for long term follow up including annual follow up through five years post implant.

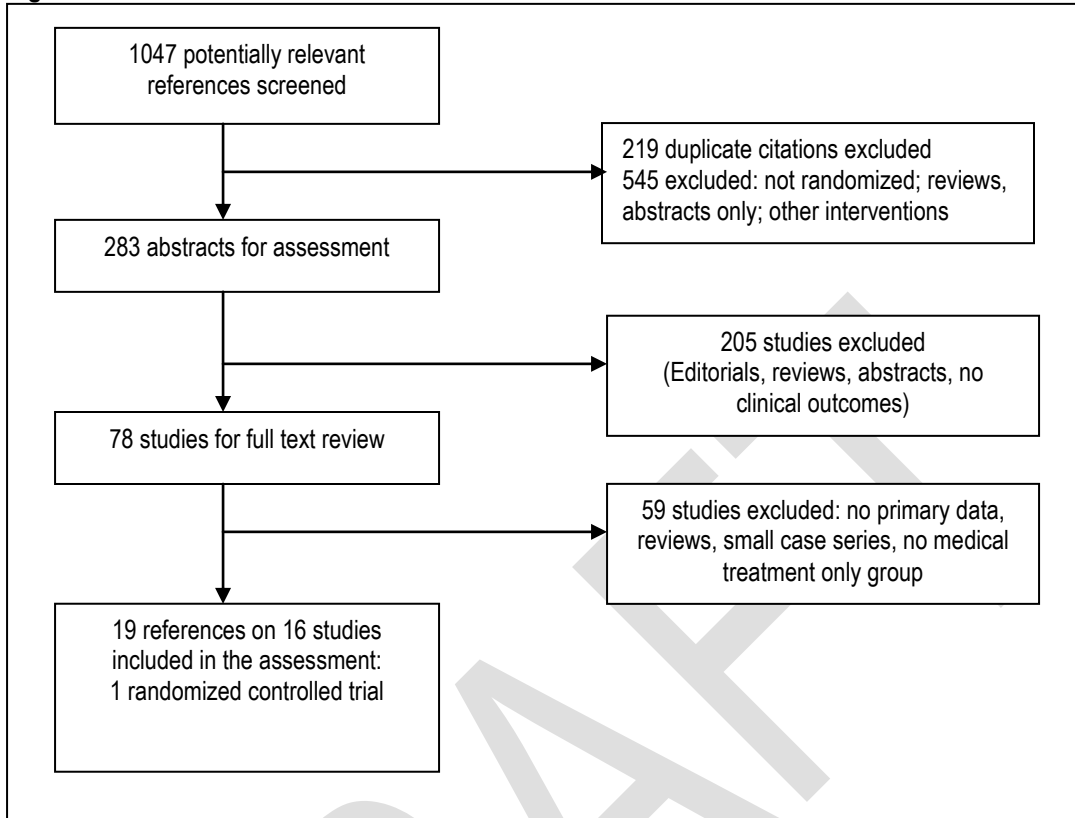
TA Criterion 1 is met.

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 implantation” OR “percutaneous aortic valve implantation” OR “CoreValve” OR “Sapien.” The search was performed for the period from 1945 through December 2011. The detailed search criteria are shown in the Appendix. The bibliographies of systematic reviews and key articles were manually searched for additional references. 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. We included case series describing at least 100 patients treated with TAVI, comparative studies with medical therapy, and randomized trials comparing TAVI to medical therapy.

The search identified 1047 potentially relevant studies (Figure 1). After elimination of duplicate and non-relevant references including reviews and animal studies the search identified 19 articles describing thirteen case series³⁴⁻⁴⁸, two small comparative trials^{49,50} and one randomized trial.^{51,52} An additional 42 early case series were excluded because they were too small to provide reliable estimates of the outcomes of interest.^{33,53-93} Seven comparative studies were excluded because they compared TAVI to surgery and not to medical therapy.⁹⁴⁻¹⁰⁰

Figure 1: Selection of studies for inclusion in review



Level of Evidence: 1, 3, and 5.

TA Criterion 2 is met.

TA Criterion 3: The technology must improve net health outcomes.

Symptomatic aortic stenosis has a high short-term mortality so total mortality should be the primary outcome of interest. Treatment of aortic stenosis is associated with an increased risk for strokes 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 major concern. Clearly quality of life and functional ability are also major concerns. The New York Heart Association developed the system that is most commonly used to quantify the degree of functional limitation imposed by heart disease.¹⁰¹ This system assigns patients to one of four functional classes, depending on the degree of effort needed to elicit symptoms: patients may have symptoms of HF at rest (class IV), on less-than-ordinary exertion (class III), on ordinary exertion (class II), or only at levels of

exertion that would limit normal individuals (class I). 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 five domains: symptoms, physical limitation, social limitation, self-efficacy, and quality of life.^{102,103} It is scored on a 100 point scale with higher scores representing higher functioning and better quality of life. A change of more than five points is considered clinically significant.^{104,105} The SF-12 includes both physical and mental health summary scores with higher scores representing better health-related quality of life.¹⁰⁶ A change of greater than two points is considered clinically significant.¹⁰⁷ Other important peri-procedural and longer term outcomes include myocardial infarction, major bleeding, kidney injury, major vascular complications, and valve dysfunction including aortic regurgitation. A consensus panel published clear definitions for these outcomes in 2011.¹⁰⁸ Prior to that time, the definitions for these outcomes varied somewhat between studies.

Case series

These larger case series are useful for defining the expected range of benefits and harms from the use of TAVI.³⁴⁻⁴⁸ Table 2 describes when and where the studies were performed, which valve type was used, and a brief summary of the characteristics of patients in the studies. Several studies separated the data into groups based on whether the valve was implanted using a transfemoral approach (TF) or a transapical approach (TA). Data for the SAPIEN valve deployed using the transfemoral approach is most relevant for this assessment because the current FDA indication is for this delivery approach. Patients requiring a transapical approach usually have significant peripheral vascular disease that precludes a transfemoral approach and concomitantly more atherosclerosis in the cerebrovascular and coronary circulation, putting them at higher risk for procedural complications and death.

The valves used in these studies were implanted from 2005 through 2010. Both the CoreValve and the SAPIEN valve have gone through several generations of development over that time period based on insights gained during the early case series. About half of the participants in these studies were women and their average age was slightly greater than 80 years. The predicted risk for operative mortality varied from 19% to 34% using the EuroSCORE and from 9% to 19% using the STS score. When both scores were reported, the EuroSCORE was consistently higher than the STS score.

Table 3 summarizes the procedural outcomes and events through thirty days. The procedural success rate was generally high, ranging from 95% to 99% in the most recent series. The most important outcome, 30-

day mortality, varied from 6% to 13%, likely due to differences in the underlying risk of the different patient groups studied. The risk of major stroke varied from 1% to 5%. TAVI is known to cause a number of arrhythmias and 2% and 39% of patients in these case series required insertion of a permanent pacemaker. Case series that evaluated both the CoreValve and the SAPIEN valve suggested that the requirement for a pacemaker is more common with the CoreValve.^{36,41,47} 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 is 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 42% in these case series. The rates of MIs, valve embolization, and cardiac tamponade were generally low (<1%).

Table 4 summarizes the outcomes at one year including quality of life outcomes. Many of the studies did not have sufficient follow-up to report one-year outcomes. One-year mortality ranged from 15% to 28% reflecting the age and comorbidity burden of patients with symptomatic AS. The rate of major stroke ranged from 4% to 10%. The majority of surviving patients reported NYHA Class I or II symptoms. In the one study reporting quality of life using the KCCQ, there were large improvements in the summary score and in a second quality of life measure, the EuroQoL.⁴⁰ The need for repeat interventions on the implanted valve was between 1% and 3%, but these data were not consistently reported.^{45,47}

One study, the UK TAVI registry, reported two-year outcomes in addition to one-year outcomes.⁴¹ Their one year survival was 79% and their two year survival was 74%, suggesting that patients who survive the first year continue to do well. The authors note that 61% of patients had paravalvular aortic regurgitation (AR) that would not have been considered acceptable following surgical aortic valve replacement (SAVR) and that moderate to severe AR was a significant predictor of mortality at one year (hazard ratio 1.7, 95% confidence interval 1.1 to 2.5). The authors suggest that design improvements aimed at reducing AR may lead to better long-term outcomes following TAVI.

Case series are useful for defining important clinical outcomes to evaluate in comparative studies, but are not useful for comparing the effectiveness of TAVI to surgical AVR or to medical therapy. The incidence of the major outcomes varied widely between studies. This likely represents a range of causes including variations in the underlying patient populations studied, skills of the team deploying the device, improvements in device design over time, and variation in the definitions used for the outcomes. The wide variation in the incidence of important outcomes was highlighted in a systematic review that included many of the smaller, early studies.¹⁰⁹ The 30-day mortality ranged from 0% to 25%, MI from 0% to 15%,

conversion to surgery 0% to 8%, moderate to major paravalvular leaks from 3% to 35%, and 30-day major cardiovascular and cerebral events from 3% to 35%, and six-month mortality from 18% to 48%. These large differences in event rates between studies precludes any meaningful conclusions about the role of TAVI based on case-series data. Either large, high quality comparative trials or randomized trials are needed to clearly define the relative risks and benefits of TAVI in well characterized patient populations.

Comparative studies

Two studies comparing outcomes in high risk patients with symptomatic AS referred for TAVI who either were treated with TAVI or were managed medically are also summarized in Tables 2 through 4.^{49,50} Both studies reported much higher mortality in the patients who received medical therapy (44% versus 22% and 28% versus 13%). However, both studies were small and neither attempted to adjust for differences between the medical and TAVI groups. In one of the studies, the authors explicitly state that 28% of the patients were in the no intervention group because of “mortality before definitive treatment because of limitations in the number of patients who could be enrolled for” TAVI.⁴⁹ Thus, all patients who died quickly were by design included in the medical treatment group – clearly biasing the findings of the study. Large comparative studies using sophisticated techniques like propensity score matching to adjust for confounding by indication have the potential to say something meaningful about the role of TAVI, but these two small studies made no attempt to adjust for potential confounders. They suggest that there may be a role for TAVI, but add little to the evaluation of comparative effectiveness.

Table 2: Characteristics of the larger published studies of transcatheter aortic valve implantation

Study	Group	Location	N	Time frame	Valve type	Follow-up (months)	Age, years	Sex, % female	Log EuroSCORE	STS score
Uncontrolled cohorts										
Grube 2008	TAVI	Sieborg, Germany	136	2005-2008	CoreValve	NR	82	58	23	9
Piazza 2008	TAVI	Multicenter	646	2007-2008	CoreValve	NR	81		23	NR
Webb 2009	TAVI	Vancouver, Canada	168	2005-2008	SAPIEN	NR	84	48	29	9
Rodes-Cabeau 2010	TAVI	Canada - 6 centers	339	2005-2009	SAPIEN	8	81	55	NR	10
Bosmans 2011	TAVI	Multicenter Belgium	328	?-2010	CoreValve, SAPIEN	NR	83	54	28	NR
D'Onofrio 2011	TAVI	Multicenter Italy	504	2008-2010	SAPIEN	9	81	61	26	11
Eltchaninoff 2011	TAVI	Multicenter France	244	2009	CoreValve, SAPIEN	1	82	43	26	19
Gurvitch 2011	TAVI	Vancouver, Canada	270	NR	SAPIEN	1	83	50	NR	10
Lefevre 2011	TAVI TF TAVI TA	Multicenter Europe	61 69	2007-2008	SAPIEN	12	82 82	61 51	26 34	11 12
Moat 2011	TAVI	Multicenter UK	870	2007-2009	CoreValve, SAPIEN	NR	82	48	19	NR
Tamburino 2011	TAVI	Multicenter Italy	663	2007-2009	CoreValve	18	81	56	23	NR
Thomas 2010, 2011	TAVI TF TAVI TA	Multicenter Europe	463 575	2007-2009	SAPIEN	12	82 81	55 56	26 29	NR
Zahn 2011	TAVI	Multicenter Germany	697	2009	CoreValve, SAPIEN		81	56	21	NR
Comparative studies										
Kapadia 2009	TAVI Medical	Cleveland, Ohio	18	2006-2007		9	81	33	28	11
			36			6		53		25
Rajani 2010	TAVI Medical	Brighton, UK	38	2007-2009	CoreValve	7	83	45	24	NR
			47					81		
Randomized trials										
Leon 2010	TAVI Medical	Multicenter, US, Germany, Canada	179 179	2007-2009	SAPIEN	19	83	54	28	12

Table 3: Procedural and 30 day benefits and harms of transcatheter aortic valve implantation

Study	Group	Procedural success, %	Death, %	Major Stroke, %	Major vascular complication	Pacemaker placement, %	Mod-severe aortic regurgitation, %	MI, %	Tamp, %	Major bleeding, %	Need for hemodialysis, %
Uncontrolled cohorts											
Grube 2008	TAVI	86	12	1	NR	25	26	2	1	NR	NR
Piazza 2008	TAVI	97	8	2	2	9	NR	1	1	0	NR
Webb 2009	TAVI	94	11	4	8	5	42	1	2	12	2
Rodes-Cabeau 2010	TAVI	93	10	2	13	5	6	1	0	NR, > 1.4	3
Bosmans 2011	TAVI	97	11	5	NR	NR	NR	NR	NR	NR	NR
D'Onofrio 2011	TAVI	99	8	3	NR	5	NR	2	NR	NR	6
Eltchaninoff 2011	TAVI	98	13	4	7	12			2	NR	2
Gurvitch 2011	TAVI	95	10	3	7	6	NR	NR	2	9	3
Lefevre 2011	TAVI TF	96	8	3	28	2	NR	3	NR	5	0
	TAVI TA	95	19	2	5	4		6		12	6
Moat 2011	TAVI	97	7	4	6	16	14	1	NR	NR	NR
Tamburino 2011	TAVI	98	6	1	2	17	21	0	1	3	NR
Thomas 2010, 2011	TAVI TF	95	6	2	11	7	2	NR	NR	NR	1
	TAVI TA	93	10	3	2	7	2				7
Zahn 2011	TAVI	98	12	3	17	39	Severe AR 2.3%	1	2	NR	NR
Comparative studies											
Kapadia 2009	TAVI	NR	5%	0	NR	6	NR	0	NR	NR	NR
	Medical	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Rajani 2010	TAVI	NR	8	3	3	34	NR	NR	3	NR	3
	Medical	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Randomized trials											
Leon 2010	TAVI	97	5	5	16	3	12	0	NR	17	1
	Medical	100	3	1	1	5	-	0	NR	4	2

Table 4: Benefits and harms of transcatheter aortic valve implantation at one year

Study	Group	Death	Major Stroke	NYHA Heart Failure Class	Quality of life KCCQ	Quality of life SF-12
Uncontrolled cohorts						
Grube 2008	TAVI	18	4	3.3 to 1.7	NR	NR
Piazza 2008	TAVI	NR	NR	NR	NR	NR
Webb 2009	TAVI	26	4	78% Class I or II	NR	NR
Rodes-Cabeau 2010	TAVI	24	NR	NR	NR	NR
Bosmans 2011	TAVI	21	NR	NR	NR	NR
D'Onofrio 2011	TAVI	19	NR	NR	NR	NR
Eltchaninoff 2011	TAVI	NR	NR	NR	NR	NR
Gurvitch 2011	TAVI	NR	NR	NR	NR	NR
Lefevre 2011	TAVI TF TAVI TA	21 51	7 10	86% Class I or II 80% Class I or II	50 to 68 50 to 77	NR
Moat 2011	TAVI	21	NR	NR	NR	NR
Tamburino 2011	TAVI	15	3	> 50% Class I or II	NR	NR
Thomas 2010, 2011	TAVI TF TAVI TA	19 28	5 5	78% Class I or II 69% Class I or II	NR	NR
Zahn 2011	TAVI	NR	NR	NR	NR	NR
Comparative studies						
Kapadia 2009	TAVI Medical	~22% ~44%	NR	NR	NR	NR
Rajani 2010	TAVI Medical	~13% ~28%	NR	NR	NR	NR
Randomized trials						
Leon 2010	TAVI Medical	31 50	8 4	75% Class I or II 42% Class I or II	+32 +4	+7 +2

Randomized clinical trials

The Placement of Aortic Transcatheter Valves (PARTNER) Trial

The PARTNER trial⁵¹ included two parallel, randomized clinical trials, one in operable, high risk patients with transfemoral access (PARTNER A) and one in patients ineligible for surgery (PARTNER B). This assessment will only consider the PARTNER B trial as TAVI does not have FDA approval for use in patients who are eligible for surgical aortic valve replacement.

Inoperable patients were expected to have a predicted probability of death or permanent disability of at least 50% and the agreement of two cardiac surgeons that they were not suitable candidates for surgery. Patients were required to have severe aortic stenosis 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 per second. They also were required to have at NYHA class II, III, or IV symptoms. Patients were excluded if they did not have transfemoral access or had a bicuspid or non-calcified aortic valve, acute myocardial infarction, coronary artery disease requiring revascularization, left ventricular ejection fraction less than 20%, severe mitral or aortic regurgitation, transient ischemic attack or stroke in the prior six months, or severe renal insufficiency.

Eligible patients were randomized to receive the second-generation Edwards SAPIEN heart-valve system or usual care. Patients randomized to TAVI group received heparin therapy during the procedure and dual antiplatelet therapy with aspirin and clopidogrel for six months following the procedure. The primary endpoint of the trial was death from any cause.

The study characteristics and findings are summarized in Tables 2 through 4. In brief, 179 patients were randomized to each group. Follow-up was 100% complete through one year and the primary analysis was done according to strict intention to treat principles. No blinding was reported and no sham procedure was performed. It is unclear if endpoint ascertainment and adjudication were blinded.

The average age of the participants was 83 years and a little more than half were female. Their predicted operative mortality by the logistic EuroSCORE was 28% and by the STS score was 12%. Notably, the logistic EuroSCORE risk was significantly lower in the TAVI group (26.4% versus 30.4%, p=0.004) and the STS score was also lower, but not significantly lower (11.2% versus 12.1%, p=0.14). Thus, despite randomization, the TAVI group was at lower risk for operative mortality than the standard care group. In addition, the TAVI group had less COPD (41.3% versus 52.5%, p=0.04), less atrial fibrillation (32.9% versus 48.8%, p=0.04), and a trend towards better left ventricular function (ejection fraction 53.9% versus 51.1%,

p=0.06).

TAVI was successful for 97% of patients in the TAVI group, but 16% experienced major vascular complications (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), 17% had major bleeding (causing death or prolonged hospitalization or requiring surgical intervention or at blood transfusion of at least 3 units), and 11.8% had moderate or severe paravalvular aortic regurgitation. In the first 30 days there were no MIs in either group, but there was a non-significant trend toward more deaths from any cause (5.0% versus 2.8%, p=0.41) and major strokes (5.0% versus 1.1%, p=0.06) in the TAVI group. Interestingly, there was a trend towards placement of fewer permanent pacemakers (3.4% versus 5.0%, p=0.60) and less need for dialysis (1.1% versus 1.7%, p=1.00) in the TAVI group.

At one year outcomes clearly favored the TAVI group. There were significantly fewer deaths from any cause (30.7% versus 49.7%, p<0.001), fewer hospitalizations (22.3% versus 41.9%, p<0.001), and fewer deaths or hospitalizations (42.5% versus 70.4%, p<0.001) in the TAVI group. There was still a trend towards more major strokes in the TAVI group (7.8% versus 3.9%, p=0.18) but it was not statistically significant. In the TAVI group, there were few re-interventions at the valve. Three patients had a repeat TAVI within 24 hours of the initial procedure, two had surgical aortic valve replacement and one had a balloon aortic valvuloplasty. In the standard therapy group, four patients received TAVI off protocol at other institutions, 17 patients had surgical aortic valve replacement, and 150 (84%) had at least one balloon aortic valvuloplasty with 30 having a second valvuloplasty during the first year of follow-up.

The quality of life outcomes at one year also favored the TAVI group. The proportion of patients reporting NYHA class I or II symptoms was higher in the TAVI group (74.8% versus 42.0%, p<0.001).⁵¹ In the TAVI group, the KCCQ summary score increased from 36.2 at baseline to 69.4 at one year (p<0.001), while the standard therapy group summary score only increased from 34.4 to 47.0 (p=0.20).⁵² The between group differences were clinically and statistically significantly different (p<0.001) at one, six and twelve months follow-up for the summary score and for all five domains of the KCCQ. At one year, patients in the TAVI group also reported significant increases in both the physical and mental health domains of the SF-12 (p<0.001), while no significant increases were found in the standard therapy group.

It is also noteworthy that the 30-day mortality in the PARTNER B trial was lower than that reported in any of the 13 large case series summarized in Table 2 even though most of the case series had lower average risk scores by both the EuroSCORE and STS models. For instance, the European PARTNER cohort⁴⁰ had a 30-

day mortality of 8.5%, much higher than the 2.8% mortality in the PARTNER B randomized trial. The opposite was true at one year: the mortality in the TAVI group in the PARTNER B randomized trial was higher than that reported by any of the case series except for the subgroup of patients in the European PARTNER case series⁴⁰ treated using the transapical approach. This apparent paradox may reflect the fact that all of the TAVI procedures in the randomized trial were done via the lower risk transfemoral approach while many of the case series were a mix of patients treated using the transfemoral and transapical approaches. It also could be due to the technical skill and experience of the centers involved in the PARTNER B trial. The higher one-year mortality may be due to a higher comorbidity burden among the patients who were eligible for inclusion in this randomized trial of “inoperable” patients. However, these findings, combined with the baseline differences in risk scores in the two groups, suggest that real world outcomes are unlikely to be as impressive as those reported in the PARTNER B randomized trial.

The 50% one-year mortality in the standard therapy group was also remarkably high. There may be some element of selection bias despite randomization given the significant higher EuroSCORE and STS score in the standard therapy group. However, the absolute differences in the risk scores were not large enough to explain the 19% absolute difference in the one-year risk of death. In addition, the analysis was done by strict intention to treat and follow-up was 100% at one year, so there should be no additional selection bias due to loss to follow-up.

Finally, follow-up in the trial is relatively short. Problems with valve failure may not show up in short term clinical trials. A good example is one of the early heart valves: the Bjork-Shiley valve approved by the FDA in 1979, but withdrawn from the market in 1986 after it became clear that this version of the valve was prone to strut failures that caused death in two-thirds of the cases of failure. There are case series data beyond one-year of follow-up, but the number of patients followed is relatively low. Additional long-term follow-up will be essential to prove the durability of the one-year results of the PARTNER B trial.

In summary, inoperable patients randomized to TAVI had a significant lower risk of dying at one year compared to usual care and were less likely to be readmitted to the hospital. However, patients in the TAVI group experienced more major strokes and major vascular events. In spite of these harms, patients in the TAVI group had markedly better quality of life as assessed by NYHA class, the KCCQ, and the SF-12. An important concern that has been raised with these results is that 84% of patients in the control group received aortic valvuloplasty during follow-up.¹¹⁰ As Dr. Redberg noted in her letter, the ACC and AHA consider aortic valvuloplasty as “not useful and may be harmful” when used as primary therapy for aortic stenosis.⁸ The procedure does not appear to change the natural history of AS and is associated with a high

incidence adverse events.¹¹¹⁻¹¹³ However, the ACC and AHA also concluded that balloon valvuloplasty may be considered for palliation in patients for whom surgery is not an option.⁸ And the patients in the PARTNER B trial were considered inoperable. Furthermore, the magnitude of harms following aortic valvuloplasty are not large enough to explain the 19% absolute difference in total mortality between the TAVI group and the standard therapy group at one year. In the authors reply to Dr. Redberg, the investigators reported that there was only one death and two strokes within 7 days of balloon valvuloplasty among the 150 patients in the standard therapy group who were treated with that procedure.¹¹⁴

TA Criterion 3 is met.

TA Criterion 4: The technology must be as beneficial as any established alternatives.

For truly inoperable patients with severe symptomatic aortic stenosis, there is no established alternative to TAVI. The ACC/AHA guidelines do not recommend balloon aortic valvuloplasty in adults who are candidates for surgical aortic valve replacement, though it may be appropriate for palliation in some inoperable patients.⁸ The procedure is associated with a moderate reduction in the pressure gradient across the aortic valve, but the valve area rarely increases to greater than 1.0 cm².^{115,116} Serious complications (stroke, aortic regurgitation, MI) occur in more than 10% of patients^{112,113,116,117} and restenosis usually occurs within six to 12 months.^{115,116,118} Most importantly, the natural history of patients with aortic stenosis who are treated with balloon aortic valvuloplasty is the same as that of untreated aortic stenosis.^{111,113,118}

The PARTNER B trial compared TAVI to “standard therapy,” which in the context of this trial was valvuloplasty as 60% of patients in the standard therapy group received valvuloplasty within one month of randomization and an additional 24% received valvuloplasty during follow-up. As discussed under TA criterion 3, very few patients in the standard therapy group experienced serious adverse events within one week of valvuloplasty (one death, two strokes). Thus the marked decrease in total mortality and large improvements in quality of life in the TAVI arm of the PARTNER B trial at one year compared to standard therapy demonstrated that TAVI is more beneficial than established alternatives as long as patients are aware of the short term increased risk of death, stroke, aortic regurgitation, and major vascular events and long-term uncertainties about valve durability.

The key assumption underlying this reasoning is that patients receiving TAVI are truly inoperable. This was clearly not the case for all patients in the PARTNER B trial. Twelve patients in the standard therapy group

had surgical aortic valve replacement during follow-up. In spite of their prohibitively high operative risk, their one-year mortality was only 33%. This was much lower than the remainder of the standard therapy group and about equivalent to the one-year mortality of the TAVI group. The PARTNER B trial demonstrated that TAVI is at least as beneficial as medical therapy or valvuloplasty, but only in truly inoperable patients. Care must be taken to ensure that appropriate patients are selected to receive TAVI.

TA Criterion 4 is met.

TA Criterion 5: The improvement must be attainable outside of the investigational setting.

TAVI is a technically difficult procedure with a steep learning curve. In the Vancouver single center case series, outcomes improved over time.³⁹ The investigators compared results in the first 135 patients to 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.³⁹ 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 score 8.5 versus 10.5, $p < 0.01$). In fact, in the much larger, multicenter UK TAVI registry, there was no significant difference between proctored and non-proctored cases or between the first twenty cases at a center and the subsequent cases.⁴¹ However, a large Italian study did show significantly higher 30-day mortality in the first third of the cases in their series.⁴⁴ Clearly care must be taken to ensure adequate training and proctoring of physicians performing TAVI.

There are consensus recommendations that have been made jointly by the American College of Cardiology and the Society of Thoracic Surgeons.¹¹⁹ In brief, they recommend that programs utilizing TAVI should be performed by a limited number of specialized heart centers with multidisciplinary teams that include at least one primary cardiologist, one interventional cardiologists, and one 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. Finally, a registry should be established to track appropriate use and patient outcomes.¹¹⁹ If followed, these recommendations should ensure that appropriate patients are selected and that highly skilled teams perform the procedure.

TA Criterion 5 is met.

CONCLUSION

Aortic stenosis is common in the elderly and when symptoms arise about half of patients die within two years. Surgical aortic valve replacement is an effective therapy for aortic stenosis that can be performed with relatively low morbidity and mortality given the age and co-morbidity of most patients with aortic stenosis. However, approximately one third of patients with symptomatic aortic stenosis are considered inoperable. Until recently, there have been no effective alternative therapies to surgical aortic valve replacement for these patients.

Scientists have developed two aortic valves (Medtronic CoreValve, Edwards SAPIEN) that can be implanted using catheters rather than open-heart surgery. A large number of case-series demonstrated successful implantation of transcatheter aortic valves in more than 95% of patients, 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 aortic stenosis. The case-series data and the small comparative studies gave inadequate information to fully understand the relative benefits and harms of TAVI compared with standard therapy.

The PARTNER B trial is the pivotal randomized trial to date that helps us understand the risks and benefits of TAVI.^{51,52} In the PARTNER B trial, 179 patients with severe AS were randomized to the TAVI group (Edwards SAPIEN valve via the transfemoral approach) and 179 patients were randomized to the standard therapy group. The 30-day mortality in the TAVI group was only 5% and only 3% of the TAVI group required a permanent pacemaker. The stroke rate was higher in the TAVI group (5% versus 1%), but by one year the overall outcomes strongly favored the TAVI group. Mortality was significantly lower (31% versus 50%) and quality of life was much higher by three different instruments.

The trial was not methodologically perfect. Neither the patients nor outcome assessment was blinded. There were baseline differences between the two groups indicating that the TAVI group had a lower overall risk and fewer important comorbidities, such as COPD. Concerns have been raised because 64% of patients in the standard therapy group received aortic valvuloplasty within 30 days of randomization and an additional 20% after 30 days. However, none of these issues are of sufficient magnitude to explain the large one-year mortality difference between the two groups.

Patient selection is essential to ensure that the results of the PARTNER trial apply to patients treated in the community. All patients must be eligible for the transfemoral approach. A multidisciplinary team that includes a cardiac surgeon, a general cardiologist, and an interventional cardiologist should agree that a patient is inoperable before offering TAVI. Patients must be informed of the upfront risk of death, stroke, pacemaker placement, and major vascular complications (16% in the PARTNER B trial). Patients also need to be informed that the long-term durability of the percutaneous aortic valves remains unclear. Observational data from one study suggest that patients who survive the first year following TAVI do well during the following year, but more data are needed.⁴¹ There is a high prevalence of moderate to severe AR, which may lead to recurrent symptoms or unforeseen problems with the valve. As was highlighted by Dr. Lazar in his editorial on the PARTNER B trial, given these uncertainties TAVI should not be performed in patients with a long life expectancy until more data are available.¹²⁰ Additional studies are also needed before extending the use of TAVI to other patient groups and to other delivery approaches.

RECOMMENDATION

It is recommended that use of the SAPIEN transcatheter aortic valve meets CTAF TA Criterion 1 through 5 for safety, effectiveness and improvement in net health outcomes when used for the treatment of severe, symptomatic aortic stenosis in patients determined to be inoperable by a cardiac surgeon who can be treated using the transfemoral approach.

February 8, 2011

This is the first review of this technology by the California Technology Assessment Forum.

RECOMMENDATIONS OF OTHERS

Blue Cross Blue Shield Association (BCBSA)

No reports on this technology were found at the BCBSA Technology Evaluation Center website.

Canadian Agency for Drugs and Technologies in Health (CADTH)

CADTH has been tracking and publishing reports on transcatheter aortic valve implantation since 2005; these reports can be found at <http://www.cadth.ca/en/search?q=sapient+valve> . These reports display the evolving TAVI research and findings between June 2005 and October 2011. Of relevance to this assessment are the Rapid Response Reports from October 2011:

1. Report: Rapid Response: Transcatheter Aortic Valve Implantation for Aortic Stenosis: Competency: 20 October 2011. The report stated that there is no evidence-based literature available to help determine the annual number of TAVR procedures required to maintain competency and/or expertise in performing the procedure.
2. Report: Rapid Response: Transcatheter Aortic Valve Implantation for Aortic Stenosis: A Review of the Clinical Effectiveness and Guidelines, 28 October 2011. The report conclusion states that:

“TAVI represents a viable alternative for patients with severe aortic valve stenosis who are not eligible to standard surgery treatment, with statistically significant clinical benefits. However, long-term success and complication rates of the procedure are uncertain at the present time. No evidence that met the study inclusion criteria regarding procedural access points was identified. Existing guidelines and reviews suggested that strict patient selection and procedural considerations following consultation with a multidisciplinary team are vital to the success of TAVI.”

National Institute for Health and Clinical Excellence (NICE)

NICE issued full guidance for TAVR/TAVI for aortic stenosis in June 2008. NICE is reassessing the guidance and underwent a consultation period which closed on August 22, 2011. The 2008 guidance as well as all consultation comments can be found at <http://guidance.nice.org.uk/IPG266> . The Interventional Procedures Advisory Committee (IPAC) is reviewing the guidance and the consultation comments to determine the safety and efficacy of the procedure. The date of publication for the reassessment including outcomes of the consultation period and any changes to the current guidance document is unknown.

Centers for Medicare and Medicaid Services (CMS)

On September 22, 2011, the Society for Thoracic Surgeons (STS) and the American College of Cardiology (ACC) submitted a formal request to CMS to develop a National Coverage Determination (NCD) for TAVR. The proposed decision memo will be released on 3/28/2012 and the expected National Coverage Analysis (NCA) completion date is 6/26/2012. The National Coverage Analysis Tracking Sheet for TAVR can be found at [http://www.cms.gov/medicare-coverage-database/details/nca-tracking-sheet.aspx?NCAId=257&ver=1&NcaName=Transcatheter%20Aortic%20Valve%20Replacement%20\(TAVR\)&bc=AiAAAAAIAAA&](http://www.cms.gov/medicare-coverage-database/details/nca-tracking-sheet.aspx?NCAId=257&ver=1&NcaName=Transcatheter%20Aortic%20Valve%20Replacement%20(TAVR)&bc=AiAAAAAIAAA&) .

American Association for Thoracic Surgery (AATS)

AATS has been invited to provide an opinion on the technology and to send a representative to participate at the meeting.

Society of Thoracic Surgeons (STS)

STR has been invited to provide an opinion on the technology and to send a representative to participate at the meeting.

American College of Cardiology (ACC), CA Chapter

The California Chapter of the ACC has been invited to provide an opinion on the technology and to send a representative to participate at the meeting.

The Society for Cardiac Angiography and Interventions (SCAI)

SCAI has been invited to provide an opinion on the technology and to send a representative to participate at the meeting.

Advanced Medical Technology Association (ADVAMED)

ADVAMED has been invited to provide an opinion on the technology and to send a representative to participate at the meeting.

ABBREVIATIONS

CTAF	California Technology Assessment Forum
DARE	Database of Abstracts of Reviews of Effects
FDA:	US Food and Drug Administration
RCT	Randomized Controlled Trial
NS	Not significant
CI	Confidence Interval
NR	Not reported
COPD	Chronic obstructive pulmonary disease
TAVI	Transcatheter aortic valve implantation
SAVR	Surgical aortic valve replacement
NYHA	New York Heart Association
SF-12	Short form 12
KCCQ	Kansas City Cardiomyopathy Questionnaire
EuroSCORE	European System for Cardiac Operative Risk Evaluation
STS	Society of Thoracic Surgeons predicted risk of mortality
MI	Myocardial infarction
Tamp	Tamponade
CI	Confidence interval
CKD	Chronic kidney disease

HR	Hazard ratio
OR	Odds ratio
NR	Not reported
TF	Transfemoral
TA	Transapical
UK	United Kingdom
US	United States
AR	Aortic regurgitation
ACC	American College of Cardiology
AHA	American Heart Association

DRAFT

APPENDIX: Search strategy

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