Aortic Stenosis:
Modern Therapy for a Venerable Disease

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This is to acknowledge the Sarah K. Gualano, MD, has disclosed that she does not have any financial interests or other relationships with commercial concerns related directly or indirectly to this program. Dr. Gualano will be discussing off-label uses in her presentation.

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Interests: Dr. Gualano is an interventional cardiologist, focusing on catheter based treatment of coronary artery and structural heart disease. Dr. Gualano's primary interest is transcatheter valvular heart disease therapy, and is a member of the UT Southwestern TAVR team.

Purpose: The purpose of this presentation is to review the treatment of severe symptomatic aortic stenosis with transcatheter aortic valve replacement, highlighting initial randomized clinical trial data, as well as patient selection and periprocedural management.

Educational Objectives:

1. Understand the natural history of severe symptomatic aortic stenosis.
2. Review FDA approved transcatheter aortic valve replacement options.
3. Learn about patient selection and evaluation prior to transcatheter aortic valve replacement.
4. Understand post-valve replacement management of these patients.

Aortic stenosis is the most common valve disorder in the world, and one third of the United States elderly population has varying degrees of aortic valve sclerosis on echocardiography. At least two percent of patients over 60 years of age will require intervention for severe symptomatic stenosis at some point in their lifetime. Surgical aortic valve replacement, through median sternotomy requiring cardiopulmonary bypass, remains the gold standard for the treatment of severe symptomatic aortic stenosis in most patients. In the past ten years, the development and refinement of transcatheter valve therapies has provided patients who may have otherwise not been treated an alternative to surgical therapy. The purpose of this presentation is to explore transcatheter valve replacement and the future of non-surgical therapy for severe symptomatic aortic stenosis.

Natural History of Aortic Stenosis

Epidemiology and Natural History.

The known risk factors for the development of aortic calcification are familiar, with significant overlap in known causes of atherosclerosis. Age, male gender, type II diabetes, tobacco use, dyslipidemia and hypertension may all contribute to the development of calcification of the aortic valve. Progressive calcification, predominately of the aortic surface of the valve leaflets, ultimately leads to reduced leaflet excursion, and narrowing of the valve orifice, and typically by the seventh or eighth decade of life, the valve may become severely narrowed. Progressive narrowing of the aortic valve leads to an increased pressure load on the left ventricle, and ultimately when the valve orifice is severely narrowed, a patient may manifest symptoms such as angina, heart failure, syncope, or sudden cardiac death. In symptomatic patients, the mortality rate may reach as high as 25% per year in patients who are not treated. Other conditions, such as a bicuspid aortic valve, may be associated with an accelerated calcification, but the focus of this presentation will be calcific aortic stenosis of a trileaflet valve.

Mechanisms.

Though the natural history of aortic stenosis is well described, the molecular and cellular mechanisms behind aortic calcification are less well understood. In addition to the traditional atherosclerotic risk factors, genetic factors exist for the development of aortic valve calcification. Mutations in genes such as Notch1, the vitamin D receptor gene, and the apoliporotein E2 allele all predispose individuals to the development of aortic calcification [1]. The sequence of events from inflammatory infiltration of the aortic valve tissue, fibroproliferation, neovascularization, cartilage formation, and finally endochondral ossification is similar to the process seen in skeletal bone formation.

The presence of inflammation in signaling pathways in the development of aortic stenosis provide a natural target for potential pharmacotherapy to reduce the progression of aortic stenosis. To date, trials examining statins as a therapy to impact the inflammatory process, such as SALTIRE [2] and RAAVE [3], have failed to show any impact of statins on the rate of aortic calcification. Medical therapy to treat aortic calcification and subsequent stenosis remains elusive, and thus the treatment for patients with severe aortic stenosis remains focused on the surgical therapy for this mechanical disease state.

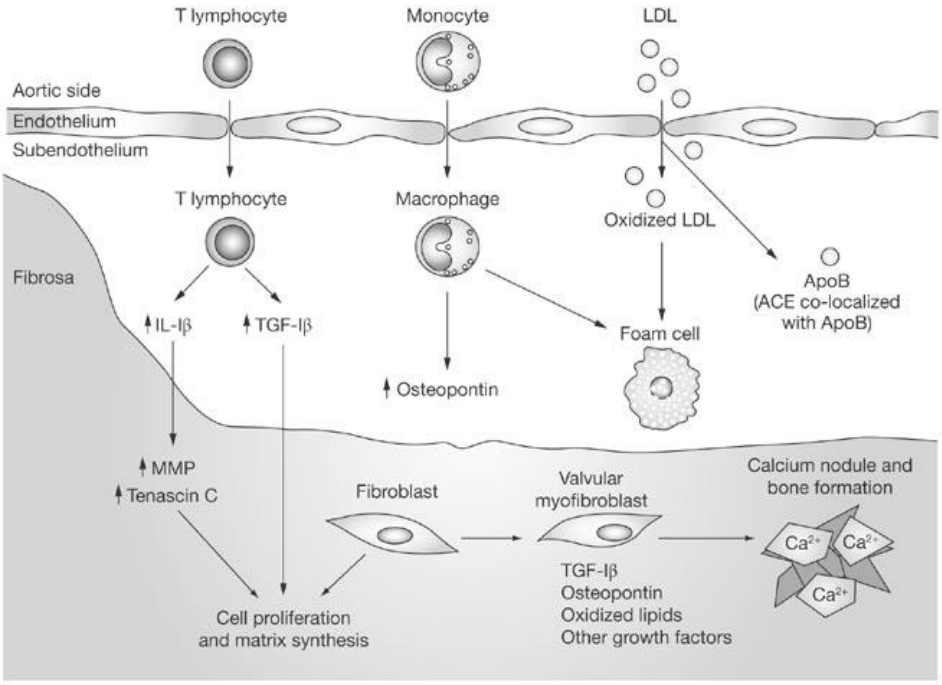

Figure 1. Potential pathways depicting inflammatory cytokine activation of aortic valve calcification. Activation of these inflammatory signaling pathways contributes to the development of this disease process. ACE = angiotensin-converting enzyme; ApoB = apolipoprotein B; IL-1β = interleukin 1β; MMP = metalloproteinase; TGF-1β = transforming growth factor β. [4]

Surgical Aortic Valve Replacement

Surgical Aortic Valve Replacement.

Current ACC/AHA guidelines provide specific echocardiographic parameters for grading the severity of aortic valve disease [5].

	Mild	Moderate	Severe
Jet Velocity (m/s)	< 3.0	3.0 – 4.0	> 4.0
Mean Gradient (mmHg)	< 25	25 – 40	> 40
Valve Area (cm^2)	> 1.5	1.0 – 1.5	< 1.0
Valve Area Index (cm^2/m^2)	N/A	N/A	< 0.6

Table 1. ACC/AHA guidelines grading the severity of aortic stenosis.

The guidelines also designate aortic valve replacement with a class I indication for patients with severe aortic stenosis and symptoms such as angina, heart failure, or syncope. Many surgical series have demonstrated that AVR improves long-term survival for patients with severe symptomatic AS [6]. Aortic valve replacement is the second most common cardiac surgical procedure performed, next to coronary artery bypass grafting. As the US population ages, the annual number of aortic valve

replacements performed has increased. The rate of in-hospital and 30 day mortality in a study of Medicare beneficiaries undergoing AVR from 1999 to 2011 has steadily declined. Alternatives to traditional AVR with median sternotomy also exist, and many patients undergoing isolated AVR may choose from a less invasive, mini-AVR, with a less extensive incision and sternal splitting.

	1999	2001	2003	2005	2007	2009	2011
No of patients	24 568	26 598	28 186	28 687	28 039	30 418	31 380
In-hospital mortality %	7.1	6.7	6.5	5.5	5.1	4.9	3.8
30 d mortality %	7.6	7.3	7.1	6.0	5.5	5.5	4.2

Table 2. Outcomes of Medicare beneficiaries undergoing aortic valve replacement surgery, 1999-2011. [7]

***Risk Calculators*.**

The Society of Thoracic Surgeons (STS) developed a national database beginning in 1989 as a quality improvement initiative, and with this data has developed a model to calculate the risk of operative mortality and major morbidities for patients undergoing cardiac surgery, including AVR. The calculators are available online and are a simple tool for a practitioner to provide a more educated estimate of risk to patient considering AVR [8]. Data fields such as type of surgery to be performed, patient demographics, comorbidities such as lung disease and cerebrovascular disease, prior cardiac surgical history, and urgency of the procedure are entered online, and risk of mortality as well as complications such as prolonged ventilation and renal failure are calculated.

The EuroScore is another risk algorithm often used to estimate a patient's risk of mortality at the time of surgery [9]. Though the EuroScore calculator is contains fewer variables, the calculated risk of death may be somewhat higher than the STS score, and rates of potential morbidities are not calculated.

Both risk scores may be a helpful tool, but do not capture all comorbid conditions which may affect the risk of surgery. Cirrhosis, porcelain aorta, pulmonary hypertension, hostile chest from radiation are all comorbidities which make the risk of surgical AVR prohibitive, and are not captured in any risk model widely used to date.

Un-operated Patients

Despite the reassuring outcomes of traditional surgical aortic valve replacement, many studies have demonstrated a large proportion of patients may not undergo aortic valve replacement. Several studies in Europe in the early 2000s reported only half of patients with a class I indication for AVR may actually undergo the procedure [10]. There are similar rates of un-operated patients in the US. In a 2009 University of Michigan study across three practice settings, a university hospital, private hospital, and Veterans Administration hospital, nearly half of patients with severe symptomatic AS remained un-operated, with the decision against surgery driven by perceived prohibitive risk of surgical AVR [11]. This treatment gap drove innovation in catheter based therapies for patients with severe aortic stenosis

Percutaneous Treatment of Aortic Stenosis

Balloon Aortic Valvuloplasty and First in Man Transcatheter Replacement.

In the mid-1980s, balloon aortic valvuloplasty was viewed as a potential alternative therapy for patients too ill to undergo surgical AVR. Unfortunately, the procedure was associated with a high (2%) rate of stroke, and the results only durable for 6 -12 months, and thus the procedure was quickly relegated to a niche procedure and not widely performed.

Even as far back as the 1960s, attempts were made to replace the aortic valve via a catheter, but it was Alain Cribier in 2001 who performed the first transcather aortic valve replacement (TAVR) [12]. The valve was composed of 3 bovine pericardial leaflets, sewn into a stainless steel balloon expandable stent. The first patient was a 57 year old man with calcific aortic stenosis, in cardiogenic shock, with comorbidities or peripheral atherosclerosis with prior peripheral bypass, subacute leg ischemia, chronic pancreatitis, silicosis and prior lung cancer, previously undergone balloon aortic valvuloplasty but with developed recurrent aortic stenosis. After the valve was crimped on a balloon, inserted through the femoral vein, and transeptal into the left atrium, was then manipulated into the aortic position. Under rapid ventricular pacing, the balloon was expanded and valve deployed, similar to a coronary stent. Since that time, many improvements were made to not only the valve itself, but also the delivery system and approach. After initial CE Mark was achieved in Europe, and registry data was promising, the landmark clinical trial began enrollment in May 2007.

Clinical Trials

Partner Trial.

After registry data from Europe suggested TAVR would be an acceptable alternative to surgical AVR, the first randomized clinical trial for transcatheter heart valve replacement was completed. Patients were enrolled into one of two arms: (1) a high risk patient cohort, randomized to surgical AVR versus TAVR from a trans-femoral or transapical route, and (2) an inoperable cohort, randomized to transfemoral TAVR or medical therapy. The high risk cohort was defined as patients with high risk of death of at least 15% at 30 days, with a guideline STS score of at least 10%. Inoperable patients were defined as patients with an expected 30 day risk of death of 50% or greater, agreed upon by at least two cardiac surgeons.

The results were groundbreaking. Data from the inoperable cohort B group were released first, and are summarized in the figure below. Though the overall rate of mortality in the TAVR arm and medical therapy arms of the PARTNER B trial were quite high, reflecting the comorbidities which made patients ineligible for surgery, there was a dramatic reduction in overall mortality in patients treated with TAVR. Secondary endpoints of the trial included a dramatic reduction in NYHA class in TAVR treated patients and durable valve performance with no significant change in gradients across the prosthetic valve. The rate of stroke was significantly higher in the TAVR treated arm, in part due to the intra-procedural embolization of valve material, but also subacute cerebral events, presumed due to thromboembolism arising from the compressed native valve material. Not surprisingly, patients undergoing TAVR patients experienced major vascular complications, due to the large 22 French or 24 French delivery systems used in the femoral artery. With these randomized data proving the superiority of TAVR to medical therapy in inoperable patients, the FDA approved the Edwards SAPEIN transcatheter heart valve in November 2011.

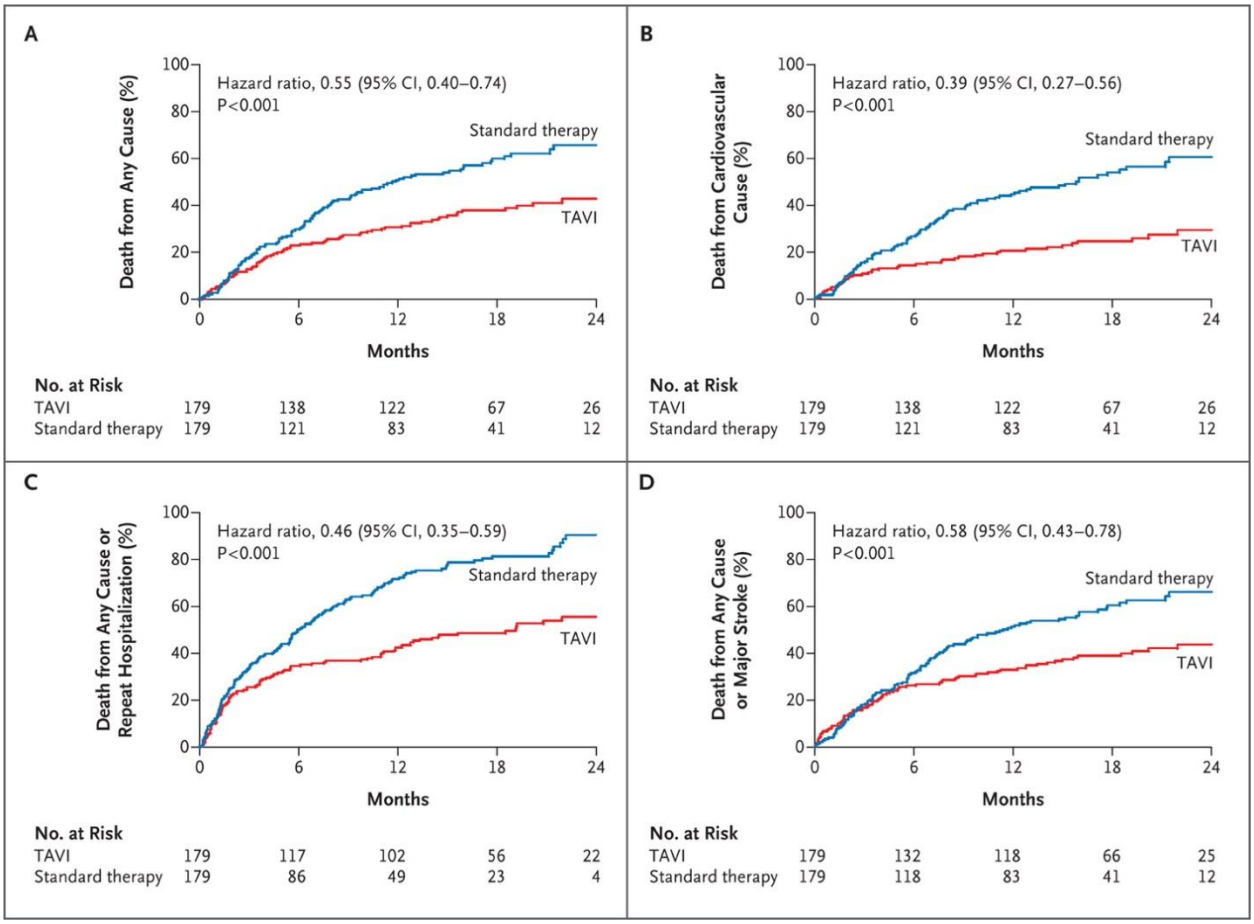

Figure 2. Time-to Event Curves for the primary endpoint and other selected end points; Partner B cohort [13].

One year later, the results of the cohort A, surgical AVR versus TAVR arm were released, with equal enthusiasm. In the PARTNER A cohort of high risk severe AS patients, TAVR was non-inferior to surgical AVR for the primary endpoint of death from any cause. Once again the rate of stroke was somewhat higher in patients treated with TAVR, and there were major bleeding rates seen with TAVR. But in October 2012, the SAPIEN valve was approved to treat high risk patients with severe symptomatic AS.

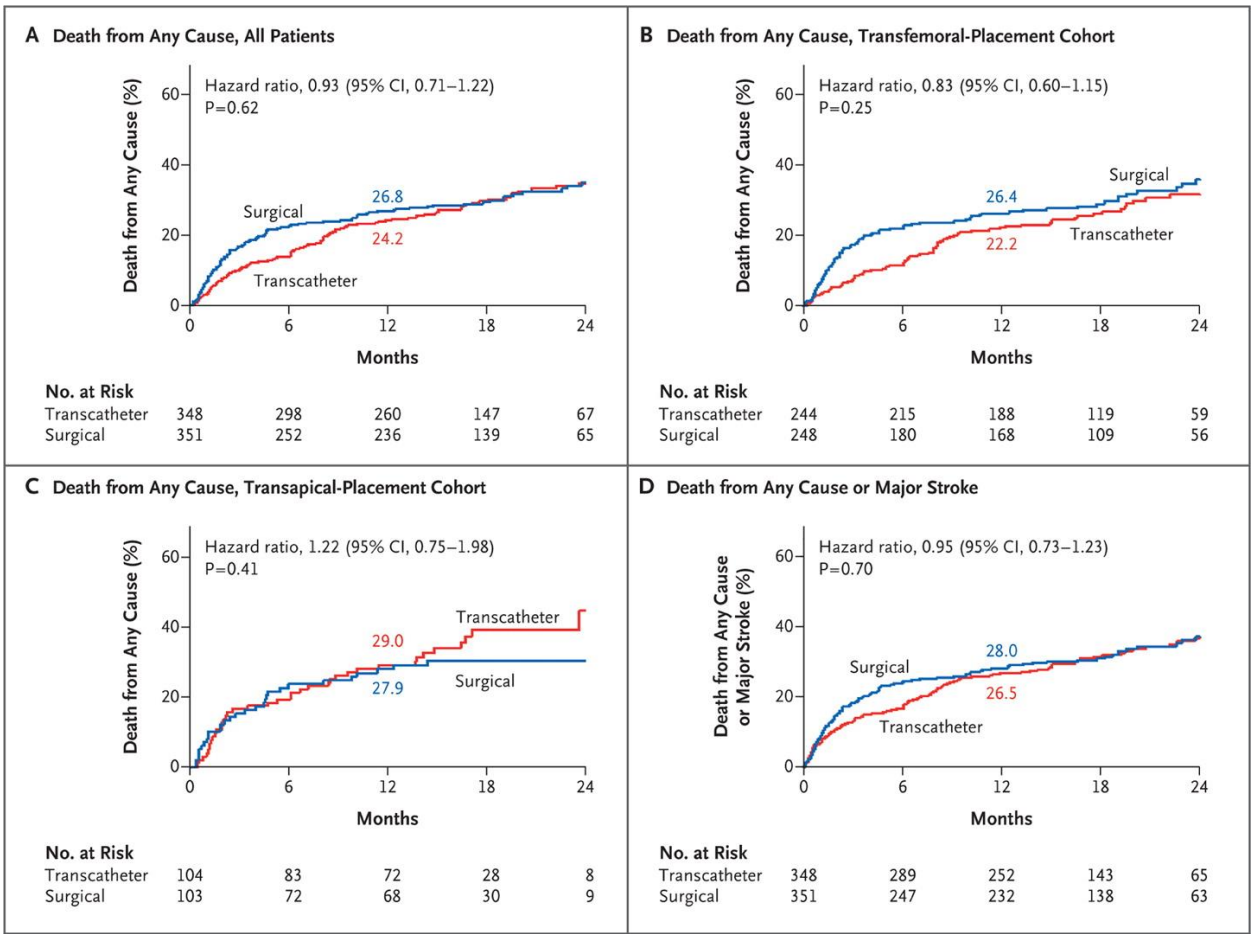

Figure 3. Time-to-event curves for the primary endpoint and other selected end points; Partner A cohort [14].

CoreValve.

The Medtronic CoreValve, the second transcatheter heart valve widely used throughout the world, was also rigorously tested in a clinical trial setting. Similar to the PARTNER trial, enrolled patients were divided into a “high risk” and “extreme risk” groups. Though the extreme risk study was initially designed to randomize patients to either CoreValve or medical therapy, with the approval of the SAPEIN device, the protocol was modified, replacing the control medical therapy group with a performance goal. The objective performance goal was constructed from a meta-analysis of contemporary balloon valvuloplasty series, and 12 month PARTNER B all cause mortality and stroke rate, with the most conservative estimate of even rate calculated to be 43%.

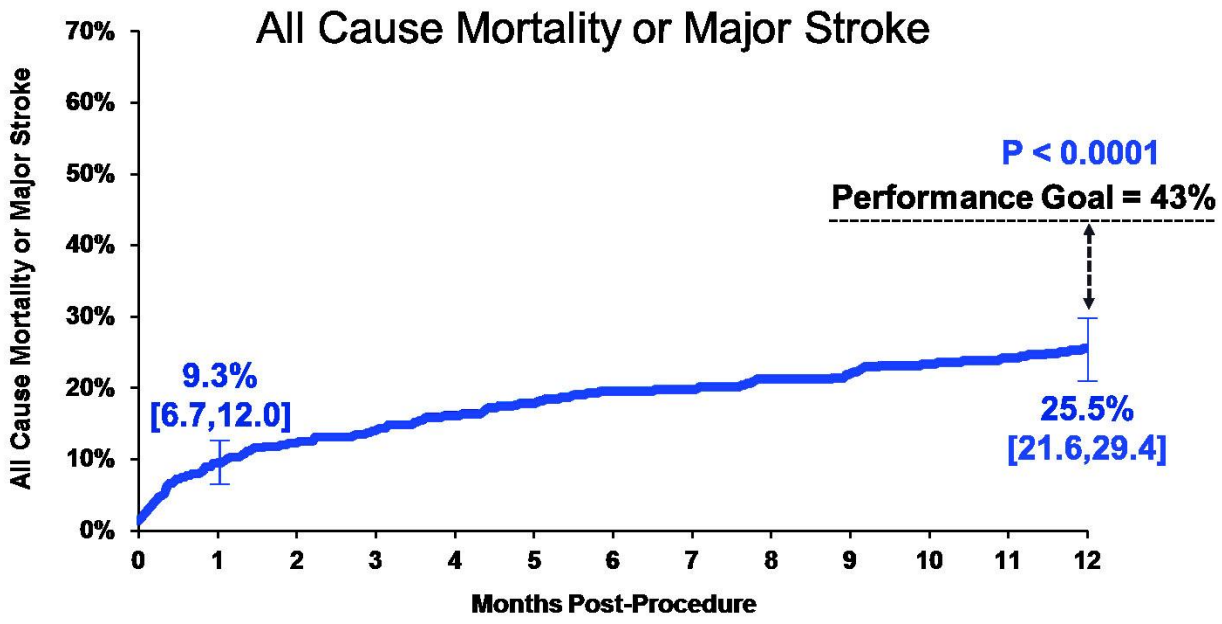

Figure 4. CoreValve extreme risk iliofemoral study, primary endpoint [15].

The rate of stroke seen in this study was similar to those seen in the PARTNER trial. Patients also experienced a significant improvement in NHYA class compared to baseline at study enrolled. One notable difference between the valves is the higher need for pacemaker in the CoreValve trial, where 22% required pacemaker implant one month post-procedure. This is likely due to the continued pressure exerted by the self-expanding valve on the conduction system adjacent to the left ventricular outflow tract. After an expedited review of this promising data, the CoreValve was approved by the FDA on January 17, 2014, for extreme risk patients with symptomatic severe AS.

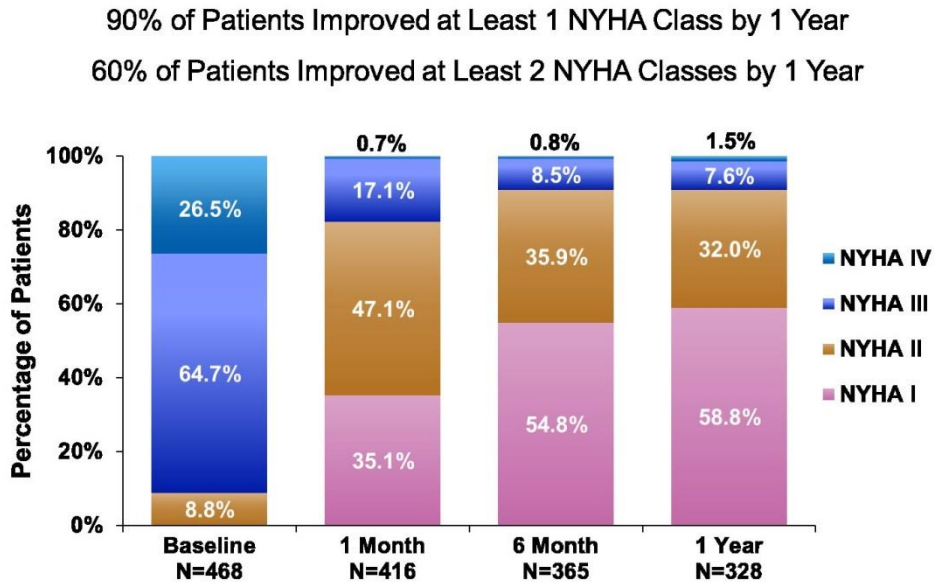

Figure 5. CoreValve extreme risk iliofemoral study, survivor NYHA class [15].

Referral of Patients to a TAVR Center

Since the approval of the Edwards SAPIEN valve in late 2011, over 200 hospitals have developed TAVR programs. The team approach required to evaluate and manage these elderly and chronically ill patients is vital to the success of the procedure. The current process of establishing a patient's candidacy for TAVR usually begins with a referral to a TAVR center, and evaluation by two surgeons and an interventional cardiologist. Review of the patient's echo for aortic anatomy and stenosis severity, left ventricular function, concomitant valvular disease, and right heart function are particularly important in the decision making process. The patient then undergoes a dedicated CT angiogram, evaluating both the aortic valve complex with precise measurements to choose a particular size valve, as well as the peripheral vasculature to determine by which route the valve should be implanted. Finally, a right heart cardiac catheterization to evaluate cardiac output and presence of pulmonary hypertension, and coronary angiography to both detect and potentially treat significant coronary stenosis prior to the TAVR procedure. Once these steps are made, and any significant active comorbid conditions addressed, then the patient may proceed with TAVR.

The patient evaluation process is complicated, and one key component of the TAVR team is the valve clinic coordinator, who has the challenging role of coordinating the extensive pre-operative testing, and arranging for detailed post-TAVR follow up. This individual works closely with the implanting physicians to track pre- and post-implant patients. As part of the CMS coverage guidelines, all TAVR centers must report patient data to the ACC/STS TVT registry, including pre-procedural patient characteristics, intraprocedure findings and complications, and one month and yearly follow-up. Patients post-implant receive undergo and echo at one and 12 months, and their functional status is measured with the Kansas City Cardiomyopathy Questionnaire during these visits.

Post-Approval Data

TVT Registry.

Initial data is now available from the TVT registry, which suggests the real world outcomes of TAVR cases in the US is near the outcomes seen in the PARTNER trial though not identical.

Table 5. In-Hospital and 30-Day Mortality in the STS/ACC TVT Registry Compared With Previous Studies

	Mortality, No./Total (%)											
	STS/ACC TVT Registry			PARTNER Trial[5,6]				SOURCE[20]		GARY[21]		
	Inoperable	High-Risk		Inoperable	High-Risk							
	TF	TF	TA	TF	TF	TA	FRANCE 2[19]	TF	TA	TF	TA	UK SATIRE[22]
In-hospital	61/139 (5.4)	146/3833 (3.8)	190/2318 (8.2)	NR	NR	NR	NR	NR	NR	138/2694 (5.1)	62/870 (7.1)	NR
30-Day	30/489 (6.1)	77/1687 (4.6)	112/1147 (9.8)	9/179 (5.0)	9/244 (3.7)	9/104 (8.7)	293/3195 (9.2)	29/463 (6.3)	59/575 (10.3)	NA	NA	91/1181 (7.1)

Abbreviations: NR, data not reported; STS/ACC TVT, Society of Thoracic Surgeons/American College of Cardiology Transcatheter Valve Therapy; TA, transapical; TF, transfemoral.

Table 3. In-hospital and 30 day mortality from the STS/ACC TVT registry.

Though an STS score of 8% or greater was an inclusion criteria for the PARTER trial, the median STS score in the TVT registry was only 7%, suggesting off-label use of transcatheter heart valves. Whether the downward drift of risk score is due to patients with comorbidities not captured in the STS calculator undergoing TAVR, or increased TAVR treatment of medium risk patients, remains to be seen [16].

Frailty.

The best means to quantify and characterize frailty continues to be elusive. Though many metrics and questionnaires are available to a practitioner to assess frailty, a 5 meter walk test may be used in conjunction with the STS score to provide a more accurate picture of a patient's functional status and risk. Based on recent data represented in the figures below, gait speed and STS score do not always track together, and a seeming moderate risk patient based on STS score may be frail once the 5 m walk test is performed. A slow gait speed may be predictive of increased risk, and in conjunction with the STS score, may be a powerful tool in the decision making process for treatment of severe AS patients.

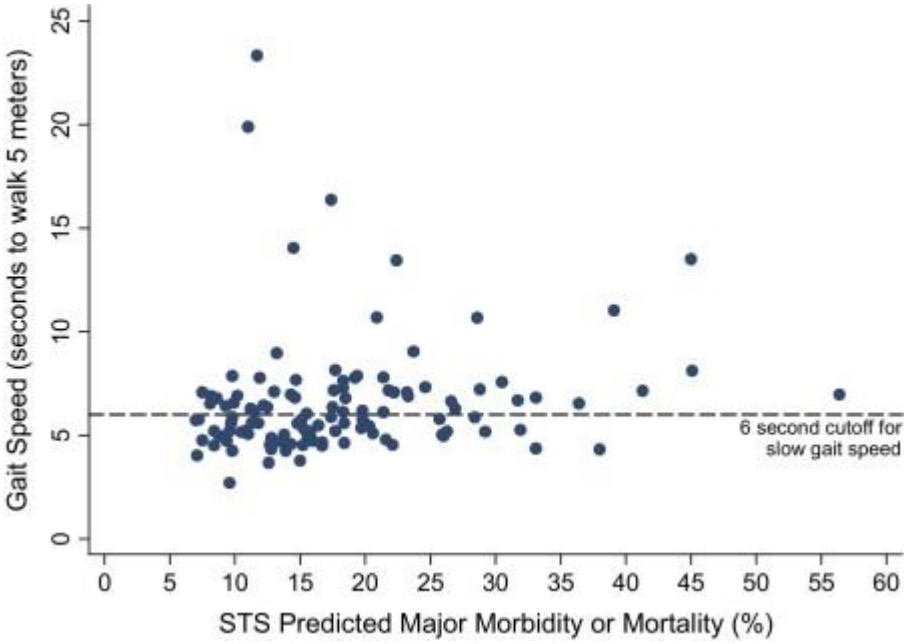

Figure 6. Lack of correlation between gait speed and Society of Thoracic Surgeons (STS) score (R = 0.14, p = 0.13), showing that gait speed represents a distinct domain. In addition, there was no correlation between gait speed and age or left ventricular ejection fraction [17].

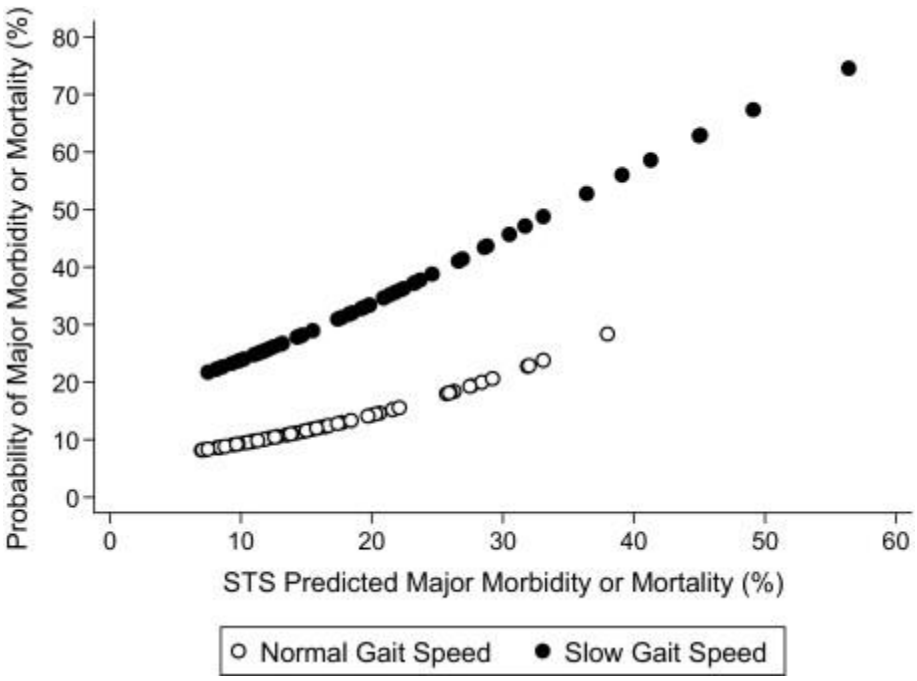

Figure 7. Predicted probability of mortality or morbidity according to gait speed and the STS risk score. Slow gait speed conferred a 2- to 3-flod increase in risk for any given level of STS predicted mortality or major morbidity compared with normal gait speed. The adjusted odds ratio for mortality or major morbidity was 3.05 (95% confidence interval: 1.23 to 7.54)[17].

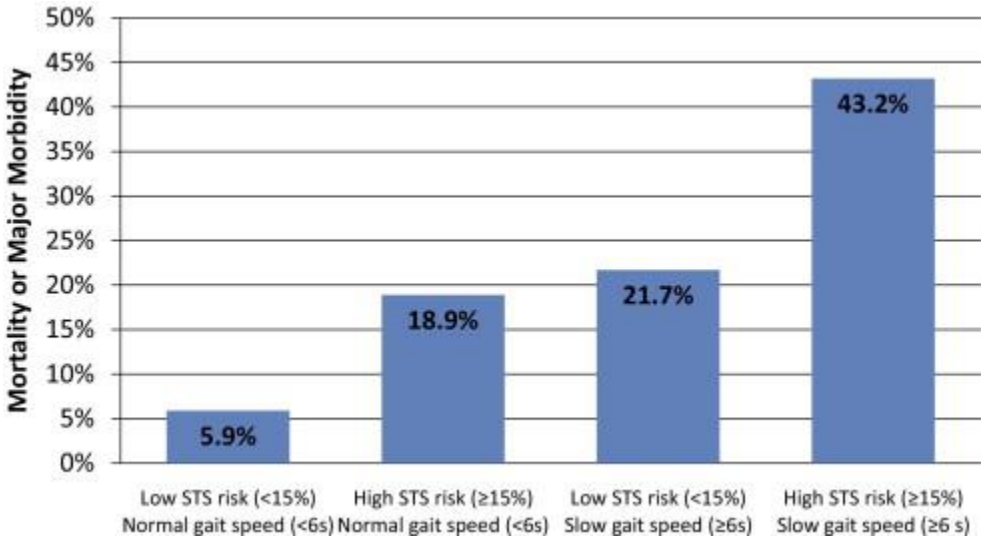

Figure 8. Mortality or major morbidity according to gait speed and the STS risk score. The dual risk factors of slow gait speed (≥6 s to walk 5 m) and high STS score (≥ 15% predicted mortality or major morbidity) identified patients at highest risk. Among those with the dual risk factors, 43.2% experienced a major morbidity or mortality compared with only 5.9% of those without either risk factor [17].

Periprocedural Management of Patients

Stroke Prevention.

The success of the PARTNER and CoreValve clinical trials has led fairly rapid dissemination of TAVR technology. These studies also highlight important areas of further study to continue to improve of the procedure as well as post-procedure care. One of the most vital area of focus is the further reduction of the peri-TAVR risk of stroke. To address the issue of thromboembolism during valve deployment, many new valves have been designed, as well as ancillary catheters to protect cerebral perfusion. Most of these innovative devices are inserted percutaneously, and deploy a net or filter above the great vessels in an attempt to catch debris before it may travel to the brain.

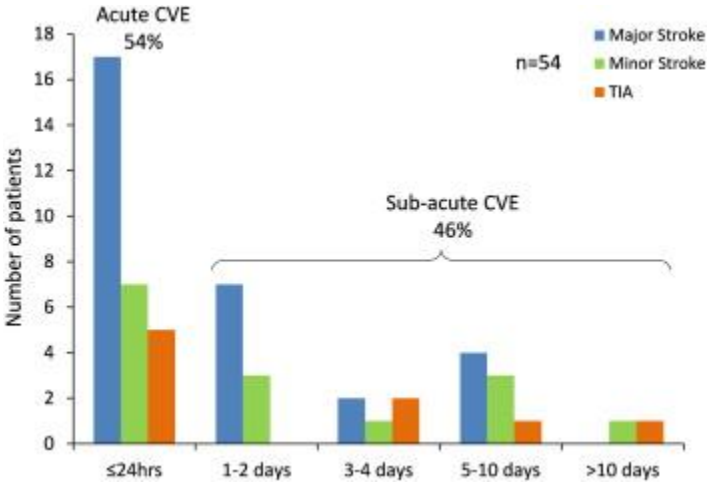

Figure 9. Timing of cerebrovascular events within 30 days after TAVR [18].

The higher rate of stroke is seen not only in the operating room, but also post-operatively. Current guidelines recommend 6 months of therapy post-TAVR, typically with aspirin and clopidogrel, or in patients with an indication for anticoagulation with warfarin, aspirin and warfarin. These recommendations are based on the strategies used in the PARTNER trial, derived from post-procedure medical regimens after surgical AVR and stenting. Single center data may suggest that a single agent may be adequate, but to date, no randomized data exist comparing alternative strategies. Future trials exploring rates of bleeding and stroke in patients treated with varying medical regimens should shed light on this area.

Anticoagulation post-procedure.

	PARTNER	ACC/STS	CCS
Pre-procedural	Aspirin 80 mg Clopidogrel 300 mg		
Procedural	Unfractionated Heparin Goal ACT 250 s Protamine optional	Unfractionated Heparin Goal ACT 300 s Protamine advised	
Post-procedural	Aspirin 81mg Q day indefinitely Clopidogrel 75 mg daily for 90 days	Aspirin 81 mg Q day indefinitely Clopidogrel 75 mg daily for 3 – 6 months If indication for warfarin (AF) no clopidogrel	Low dose aspirin daily Thienopyridine for 1 – 3 months If oral anticoagulant indicated, avoid triple therapy if possible

Table 4. Current recommendations for antithrombotic agents and strategies for TAVR. AC C = American College of Cardiology; ACT = activated clotting time; AF = atrial fibrillation; CCS = Canadian Cardiovascular Society; STS = Society for Thoracic Surgeons [18].

Paravalvular Leak.

Another key procedural outcome at the time of TAVR is the degree of paravalvular leak. Though operators initially were less concerned about moderate leak around the aortic prosthesis, the degree of paravalvular leak is now one of the most important immediate, post-implant findings. Mid and long term outcomes of patients undergoing TAVR is so impacted by the degree of paravalvular leak, efforts to reduce the potential for leak have shaped design and development of future valves. In the PARTNER era, valve sizing was performed based on single plane transthoracic and transesophageal measurements, resulting in implantation of undersized valves. Without adequate seal within the annulus, a patient might experience a significant paravalvular leak. While severe leak was treated with either post-dilation or implantation of an additional valve, moderate degrees of regurgitation were generally accepted.

A post-hoc analysis of 2 year PARTNER data revealed that patients with moderate or even mild paravalvular leak were at increased risk of death compared to those with trivial to no leak. This has contributed to the widespread use of CT angiography in annulus sizing and valve prosthesis selection, and a 10% oversizing of valves to ensure adequate seal against the native annulus and valve.

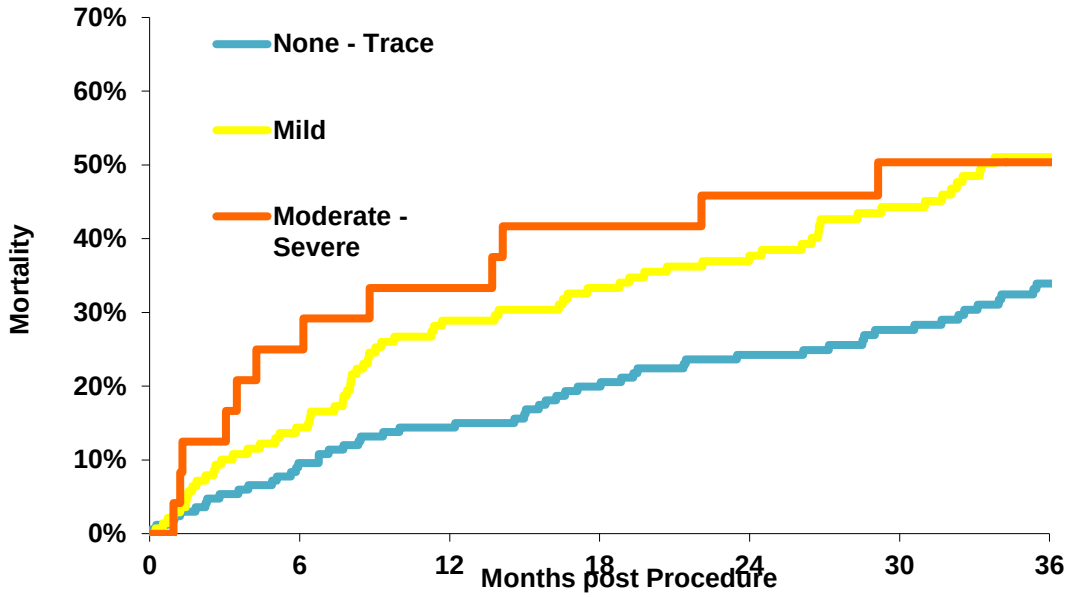

Figure 10. Impact of paravalvular leak on mortality [19].

Future Considerations

Moderate Risk Patients.

Once clinical trial evidence supported the treatment of high risk or inoperable patients with severe aortic stenosis with TAVR, a natural next step was the consideration for treatment of moderate risk patients with TAVR rather than surgery. Registry data from Europe is promising, but randomized clinical trial data is yet to be released. The PARTNER IIA trial has completed enrollment assessing moderate risk patients (STS score 4 – 8%) who undergo TAVR with the next generation SAPIEN XT valve for time until death or disabling stroke. The SurTAVI trial similarly enrolled moderate risk patients (age greater than 75 or STS 2 – 10%), randomized to either CoreValve or surgical AVR, with a primary outcome of death or disabling stroke at 2 years. Data from both trials is expected by 2015. If these trials demonstrate the positive outcomes physicians are hoping for when, the pool of patients as potential TAVR candidates would increase dramatically. For example, a white non-obese 78 year old man with prior coronary bypass, normal left ventricular systolic function, and mild COPD, would have an STS score of 3.1%, making this theoretical individual a moderate risk patient for AVR.

Degenerative Bioprosthetic Valves.

Though randomized data is lacking, off-label use of the Edwards SAPIEN valve to treat a degenerative surgical bioprosthetic valve has also expanded. As long as the previously implanted valve is a 23 mm or larger prosthesis, this can be performed relatively easily, as the surgical valve ring provides an excellent landing zone for the transcatheter valve. One arm of the upcoming PARTNER II trial should provide more data regarding the efficacy of using transcatheter valves in this position.

Aortic Insufficiency and Bicuspid Valves.

Treatment of aortic insufficiency in high risk patients may be another off-label use of transcatheter valves. Balloon expandable valves such as the Edwards SAPIEN require the calcium of the stenotic aortic valve to act as an anchor, and may not be ideal for use in aortic insufficiency, which is typically associated with less calcification but rather annulus dilation. The CoreValve may be a better candidate for use in aortic insufficiency, as the self-expanding stent may better secure the valve within a minimally calcified annulus.

There are also case reports of stenotic bicuspid valves, with two only two sinuses of Valsalva, with transcatheter valves. However, the risk of complication such as valve deformation or embolization may be significantly greater due to the distorted aortic valve and root anatomy seen in bicuspid patients. The ideal prosthesis for treatment of these patients is yet to be determined.

Conclusions

The landscape of treatment for severe aortic stenosis has changed dramatically in the past five years. The molecular and cellular mechanisms behind aortic valve calcification are only beginning to be understood, and pharmacotherapy to halt disease progression remains elusive. The gold standard therapy for the treatment of patients with severe symptomatic aortic stenosis remains surgical valve replacement. TAVR is an alternative for patients previously considered inoperable or high risk for complications at the time of surgery. While further study into the appropriate patient selection, design of valves, implantation procedures, and post-operative management of patients is ongoing, physicians can celebrate the initial success of this therapy for a large portion of previously untreated patients.

References

1. Rajamannan NM. Update on the pathophysiology of aortic stenosis. Eur Heart J 2008;10:E4-10.

2. Cowell SJ, Newby DE, Prescott RJ, Bloomfield P, Reid J, Northridge DB, Boon NA. N Engl J Med 2005;352:2389-2397.

3. Moura LM, Ramos SF, Zamorano JL, Barros IM, Azevedo LF, Rocha-Goncalves F, Rajamannan N. Rosuvastatin affecting aortic valve endothelium to slow the progression of aortic stenosis. J Am Coll Cardiol 2007;49:554-561.

4. Freeman RV and Otto CM. Calcific aortic stenosis: an update. Circ 2005;111:3316-3326.

5. Bonow RO, Carabello BA, Chatterjee K, de Leon AC Jr., Faxon DP, Freed MD, Gaasch WH, Lytle BW, Nishimura RA, O'Gara PT, O'Rourke RO, Otto CM, Shah PM, Shanewise JS. 2008 Focused update incorporated into the ACC/AHA 2006 guidelines for the management of patients with valvular heart disease. Circ 2008;188:e523-e661.

6. Brown ML, Pellikka PA, Schaff HV, Scott CG, Mullany CJ, Sundt TM, Dearani JA, Daly RC, Orszulak TA. The benefits of early valve replacement in asymptomatic patients with severe aortic stenosis. J Thorac Cardiovasc Surg 2008;135:308-315.

7. Barreto-Filho JA, Wang Y, Dodson JA, Desai MM, Sugeng L, Geirsson A, Krumholz HM. Trends for aortic valve replacement for elderly patients in the United States 1999 – 2011. JAMA 2013;310:2078-2085.

8. http://riskcalc.sts.org

9. http://www.euroscore.org

10. Iung B, Baron G, Butchart EG, Delahye F, Gohlke-Barwolf C, Levang OW, Tornos P, Vanoverschelde JL, Vermeer F, Boersma E, Ravaud P, Vahanian A. A prospective study of patients with valvular heart disease in Europe: The Euro Heart Survey on Valvular Heart Disease. Eur Heart J 2003;24:1231-1243.

11. Bach DS, Siao D, Girard SE, Duvernoy C, McCallister BD Jr, Gualano SK. Evaluation of patients with severe symptomatic aortic stenosis who do not undergo aortic valve replacement: the potential role of subjectively overestimated risk. Circ Cardiovasc Qual Outcomes 2009;2:533-539.

12. Cribier A, Eltchaninoff H, Bash A, Borenstein N, Tron C, Bauer F, Derumeaux G, Anselme F, Laborde F, Leon MB. Percutaneous transcatheter implantation of an aortic valve prosthesis for calcific aortic stenosis: first human case description. Circ 2002;106:3006-3008.

13. Leon MB, Smith CR, Mack M, Miller DC, Moses JW, Svensson LG, Tuzcu EM, Webb JG, Fontana GP, Makkar RR, DL Brown, Block PC, Guyton RA, Pichard AD, Bavaria JE, Hermann HC, Douglas PS, Peterson JL, Akin JJ, Anderson WN, Wang D, Pocock S. Transcatheter aortic-valve

implantation for aortic stenosis in patients who cannot undergo surgery. N Engl J Med 2010;263:1597-1607.

14. Smith CR, Leon MB, Mack MJ, Miller DC, Moses JW, Svensonn LG, Tuzcu EM, Webb JG, Fontana GP, Makkar RR, Williams M, Dewey T, Kapadia S, Babaliaros V, Thourani VH, Corso P, Pichard AD, Bavaria JE, Hermann HC, Akin JJ, Anderson WN, Wang D, Pocock S. Transcatheter versus surgical aortic-valve replacement in high risk patients. N Engl J Med 2011;364:2187-2198.

15. Popma JJ, on behalf of the CoreVale US Clinical Investigators. Presented at Transcatheter Cardiovascular Therapeutics, San Francisco 2013.

16. Mack MJ, Brennan JM, Brindis R, Carroll J, Edwards F, Grover F, Shahian D, Tuzcu EM, Peterson ED, Rumsfeld JS, Hewitt K, Shewan C, Michaels J, Christensen B, Christian A, O'Brien S, Holmes D. Outcomes following transcatheter aortic valve replacement in the United States. JAMA 2013;310:2069-2077.

17. Afilalo J, Eisenberg MJ, Morin JF, Bergman H, Monette J, Noiseux N, Perrault LP, Alexander KP, Langois Y, Dendukuri N, Chamoun P, Kasparian G, Robichaud S, Gharacholou SM, Boivin JF. Gait speed as an incremental predictor of mortality and major morbidity in elderly patients undergoing cardiac surgery. JACC 2010;56:1668-1676.

18. Rodes-Cabau J, Dauerman HL, Cohen MG, Mehran R, Small EM, Smyth SS, Costa MA, Mega JL, O'Donoghue ML, Ohman EM, Becker RC. Antithrombotic treatment in transcatheter aortic valve implantation: insights for cerebrovascular and bleeding events. JACC 2013;62:2349-2359.

19. Kodali SK, Williams MR, Smith CR, Svensson LG, Webb JG, Makkar RR, Fontana GP, Dewey TM, Thourani VH, Pichard AD, Fischbein M, Szeto WY, Lim S, Greason KL, Teirstein PS, Malaisrie SC, Douglas PS, Hahn RT, Whisenant B, Zajarais A, Wang D, Akin JJ, Anderson WN, Leon MB. Two year outcomes after transcatheter or surgical aortic valve replacement. N Engl J Med 2012;366:1686-1695.