# EXPERT REVIEW

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# New Frontiers in Aortic Therapy: Focus on Current Trials and Devices in Transcatheter Aortic Valve Replacement

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**The first decade of clinical experience with transcatheter aortic valve replacement since 2002 saw the development of 2 main valve systems, namely the Edwards Sapien balloon-expandable valve series and the Medtronic self-expanding CoreValve. These 2 valve platforms now have achieved commercial approval and application worldwide in patients with severe aortic stenosis whose perioperative risk for surgical intervention is high or extreme. In the second decade of transcatheter aortic valve replacement, clinical experience and refinements in valve design have resulted in clinical drift towards lower patient risk cohorts. There are currently 2 major trials, PARTNER II and SURTAVI, that are both evaluating the role of transcatheter aortic valve replacement in intermediate-risk patient cohorts. The results from these landmark trials may usher in a new clinical paradigm for transcatheter aortic valve replacement in its second decade.**


***KEY WORDS: transcatheter aortic valve replacement, surgical aortic valve replacement, Society of Thoracic Surgeons, quality of life, frailty, Kansas City Cardiomyopathy Questionnaire, balloon-expandable Sapien valve, Sapien XT valve, Sapien 3 valve, self-inflating CoreValve, Valve Academic Research Consortium, PARTNER I trial, PARTNER II trial, SURTAVI trial***

TRANSCATHETER AORTIC VALVE REPLACEMENT (TAVR) has revolutionized the therapeutic approach to aortic stenosis in elderly patients at high risk for surgical aortic valve replacement with cardiopulmonary bypass (SAVR).[1–3] The leading TAVR devices (Fig 1) in the current era are the balloon-expandable Edwards Sapien valves (Edwards Lifesciences Corp, Irvine, CA) and the self-inflating Medtronic CoreValve (Medtronic Inc, Minneapolis, MN).[4–6] Although successful TAVR first was described in 2002, rapid progress since then has resulted in accelerated clinical development of new devices and trials in the setting of a multidisciplinary team.[6–8] In an effort to standardize clinical trials in TAVR, the Valve Academic Research Consortium recently has defined and refined clinical endpoints for TAVR.[9,10] This expert review will survey the latest developments in this exciting area of perioperative cardiovascular practice, which has evolved in a little more than a decade from conception to a mainstream clinical therapy worldwide.[11]

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## ADVANCES IN RISK SCORING FOR CLINICAL STRATIFICATION IN TAVR

The landmark placement of aortic transcatheter valve (PARTNER) I TAVR trials stratified high-risk patients with severe aortic stenosis into 2 groups: Cohort A and cohort B.[5,8,12] Cohort A was defined as patients with severe aortic stenosis at high risk for SAVR, with a calculated perioperative mortality risk of at least 10% according to the Society of Thoracic Surgeons (STS) risk score.[7,8,12] The PARTNER I trial demonstrated that TAVR with the balloon-expandable Edwards Sapien valve was a reasonable alternative to SAVR in cohort-A patients.[12] Cohort B was defined as patients with severe aortic stenosis at excessive risk for SAVR, with a calculated STS perioperative mortality risk $> 15\%$.[5,7–8] The PARTNER I trial highlighted that TAVR with the balloon-expandable Sapien valve in cohort-B patients was significantly superior to medical management, including balloon aortic valvuloplasty.[5] Recently, cohort C has been defined as a subset of inoperable patients with aortic stenosis who have relatively poor survival and quality of life, despite TAVR.[8] Comorbidities that may define cohort C include frailty, malnutrition, cachexia, recent malignancy, stroke, dementia, and dialysis.[8] Cohort-C patients have debilitating conditions that make a return to semi-independent living very unlikely after TAVR; these patients succumb with aortic stenosis, but not from aortic stensosis.[8]

The advent of TAVR has refined risk assessment in high-risk patients with aortic stenosis who tend to be elderly with multiple comorbidities. In an effort to boost accuracy and reliability of risk calculation in this setting, recent updates to the STS risk score include frailty as graded by the 5-meter walk test, porcelain aorta, previous radiation therapy, oxygen therapy, and liver disease as graded by the model for end-stage liver disease.[8]

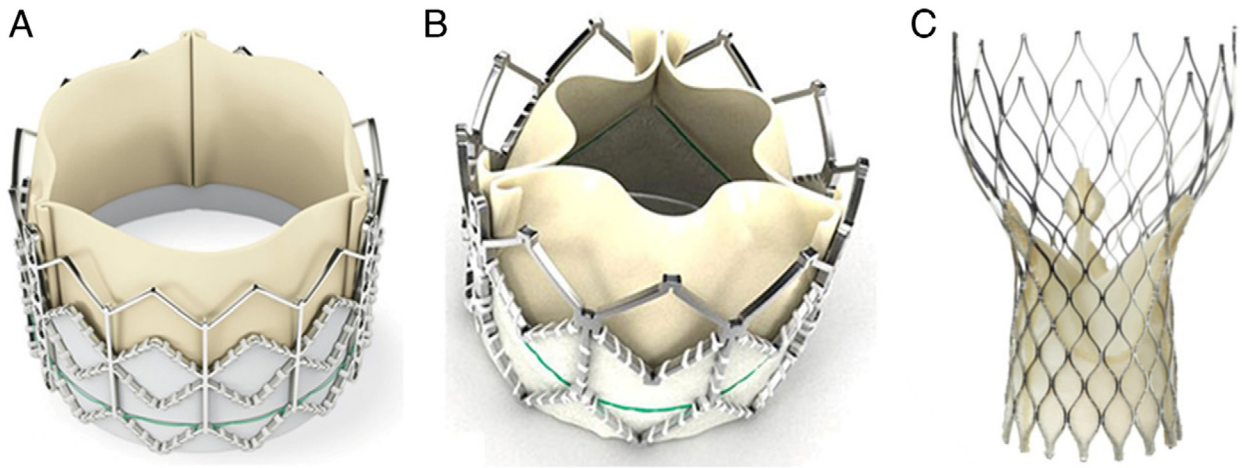


**Fig 1. Current transcatheter heart valves. (A) The Sapien balloon-expandable valve has a stainless steel frame, 3 bovine pericardial leaflets and a fabric sealing cuff. (B) The Sapien XT valve has a cobalt chromium frame, 3 bovine pericardial leaflets, and a fabric sealing cuff and is compatible with lower profile delivery systems. (C) The CoreValve has a self-expandable nitinol frame, 3 porcine pericardial leaflets, and a pericardial seal.[31]**

A novel modified Fried frailty index was developed and tested in TAVR at Columbia University.[13] According to this index, frailty is defined as 2 or more of the following: Impairment in more than 2/6 activities of daily living; serum albumin less than 3.5 g/dL; grip strength less than 30 kg for men or less than 18 kg for women; and a 15-foot walk test greater than 6 seconds.[13] Each variable of this modified frailty index has a maximum score of 3, with the range for a total score being from 0-12 (12 is the most frail). A clinical trial (N = 159: mean age 86 ± 8 years; STS risk score 12 ± 4%) conducted at Columbia University demonstrated that patients with a frailty score > 5 on this scale had a significant increase in mortality within a year after TAVR (hazard ratio 3.5; 95% confidence interval 1.4-8.5; p = 0.007).[13] The same group of investigators also have demonstrated that slow gait speed in this geriatric population significantly correlated with dependent functional status (odds ratio 1.52 for every 0.1 m/s decrease in gait speed; 95% confidence interval 1.21-1.91; p = 0.0003).[14] Another clinical trial also demonstrated that multidimensional geriatric assessment significantly predicted mortality and cardiovascular events after TAVR, especially in the setting of cognitive impairment (odds ratio 2.98; 95% confidence interval 1.07-8.31), malnutrition (odds ratio 6.72; 95% confidence interval 2.04-22.17), mobility impairment (odds ratio 6.65; 95% confidence interval 2.15-20.52), limitations in activities of daily living (odds ratio 3.63; 95% confidence interval 1.29-10.23), and frailty index (odds ratio 3.68; 95% confidence interval 1.21-11.19).[15]

The clinical importance of frailty in this setting has prompted a multicenter trial involving 14 medical centers in the United States and Canada to test 7 frailty assessment tools for prediction of 30-day mortality and major morbidity in adults older than 70 years with severe aortic stenosis undergoing either SAVR or TAVR (NCT01845207: Full details available at www.clincialtrials.gov, last accessed September 2, 2014). The target enrollment is 800 (400 in each study arm). Mortality has been defined as death from any cause. Major morbidity has been defined as an aggregate of composite clinical endpoints defined by VARC and the STS. This landmark trial currently is enrolling: It is estimated that the study will be completed by the end of 2015. It is likely that the findings from this trial will significantly influence the future integration of frailty scores into operative risk calculation for both SAVR and TAVR because it remains an ongoing priority to further refine performance of current risk calculators worldwide.[16,17]

This focus on refined risk assessment resulted in a recent multivariate analysis (N = 2,137) of the PARTNER trials to test for predictors of poor outcome after TAVR.[18] In this trial, a minimum acceptable outcome after TAVR was defined as survival for at least 6 months with a reasonable quality of life, as defined by a standardized instrument such as the Kansas City Cardiomyopathy Questionnaire (KCCQ: scored from 0-100).[18,19] A poor outcome at 6 months after TAVR was defined as any of the following: Death; KCCQ score < 45 (that corresponds to class-IV heart failure symptoms as defined by the New York Heart Association);[20] and a decrease in KCCQ score of at least 10 points from baseline.[18] A poor outcome at 12 months after TAVR was defined as any of the following: Death; KCCQ score < 60 (that corresponds to class-III heart failure symptoms as defined by the New York Heart Association);[20] and a decrease in KCCQ score of at least 10 points from baseline.[18] According to the 6-month definition, 33% of patients had a poor outcome.[18] A final predictive model was also derived consisting of 10 factors: Male sex, diabetes mellitus, major arrhythmia, serum creatinine, mean arterial pressure; body mass index; oxygen-dependent lung disease; mean aortic valve gradient; mini-mental status examination; and 6-minute walk test distance.[18] Overall, this model demonstrated moderate predictive performance, with a c-index of 0.66. According to the 1-year definition, 50% had a poor outcome.[18] The final predictive model consisted of the same predictors for the 6-month model minus diabetes mellitus and mean arterial blood pressure. Overall, this model also demonstrated moderate predictive performance, with a c-index of 0.66.

Although these predictive models demonstrated only moderate performance, they highlighted the prognostic importance of functional status, frailty, renal dysfunction, and cardiorespiratory reserve.[18]