Sapien Valve: Past, Present, and Future

A look at how the Sapien family of valves continues to evolve to treat a range of patients seeking transcatheter aortic valve replacement.

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Aortic stenosis (AS) remains the most common form of adult-acquired valvular heart disease in developed countries, which increases in prevalence with age.[1] Surgical aortic valve replacement (SAVR) has been the standard therapy for patients with severe symptomatic AS, improving survival and symptoms. However, since treating the first patient with a catheter-based prosthesis in 2002, the field of transcatheter aortic valve replacement (TAVR) has grown exponentially. With two commercially available prostheses in the United States (ie, the Sapien family of valves [Edwards Lifesciences] and the CoreValve device [Medtronic]) and multiple others in clinical trials, the field continues to expand. This article describes the current state and future iterations of the Sapien family of prostheses.

SAPIEN VALVE

The Sapien valve is a trileaflet bioprosthesis made of bovine pericardium that is mounted on a balloon-expandable stainless steel stent (Figure 1A). The stent frame has an inner polyethylene terephthalate (PET) fabric skirt placed on the ventricular side covering half of the frame, limiting stent expansion and decreasing paravalvular insufficiency. Due to the lack of a sewing ring, the valve is oversized to the aortic annulus to ensure postdeployment stability. It is available in two sizes: a 23-mm valve with a 14.5-mm stent height, and a 26-mm valve with a 16-mm stent height. In benchtop testing, its durability has been shown for more than 10 years. The Sapien valve provides a larger effective orifice area and better hemodynamic profile than corresponding surgically implanted valves, but has a higher incidence of paravalvular insufficiency.[2] It is delivered via a transfemoral (TF) approach with the retroflex catheter or via a transapical (TA) approach with the Ascendra delivery system. It has been thoroughly evaluated in multiple international registries and a large randomized clinical trial. The results of some important trials are summarized below.

PARTNER Trial

The PARTNER US multicenter randomized trial[3] led to US Food and Drug Administration approval of the Sapien valve (Figure 2). The primary endpoint of the PARTNER trial was death from any cause at 1 year. Between May 2007 and August 2009, patients from 25 centers with severe symptomatic AS were enrolled in two treatment arms: (1) cohort A, which randomized 699 patients with an elevated surgical risk (Society of Thoracic Surgeons score > 10%) to traditional SAVR or TAVR (TA or TF); and (2) cohort B, which randomized

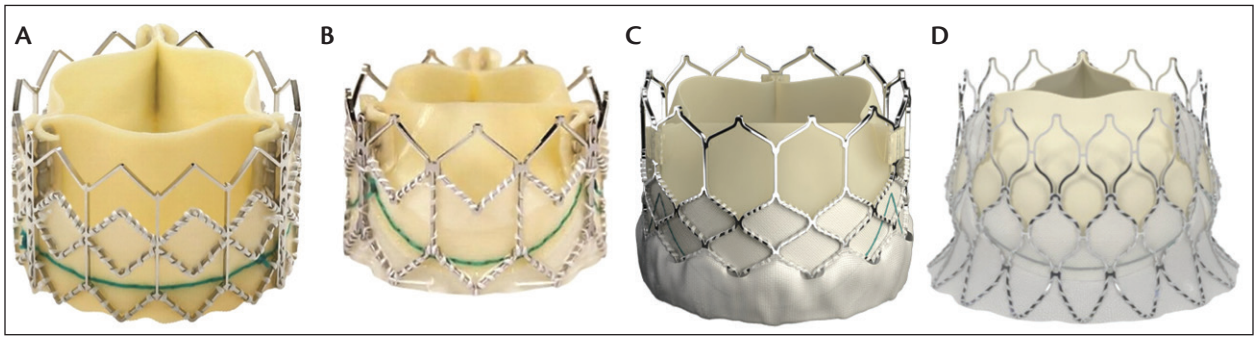

Figure 1. Sapien valve (A); Sapien XT valve (B); Sapien 3 valve (C); Centera valve (Edwards Lifesciences) (D).

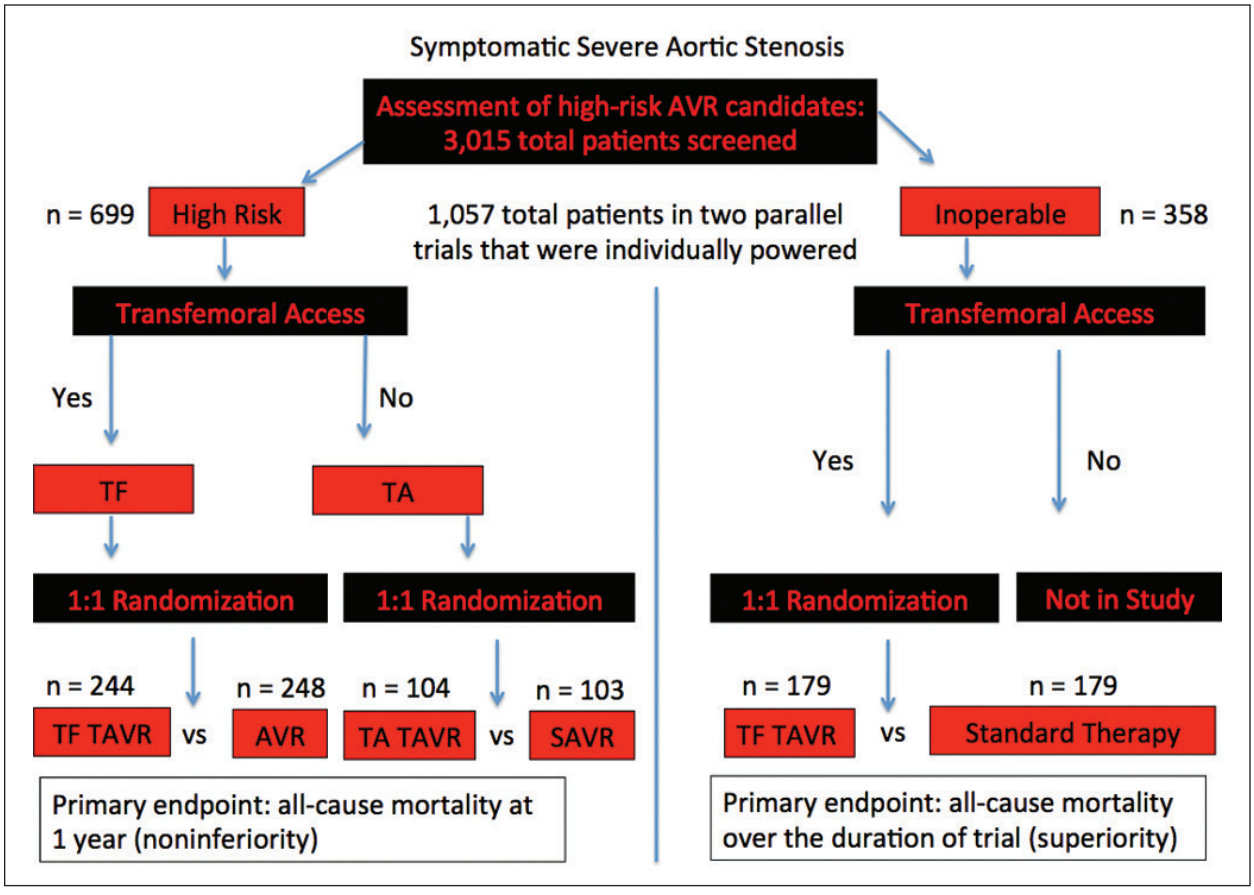

Figure 2. PARTNER trial design. A total of 1,057 patients were enrolled in the study, and 699 high-surgical-risk patients were randomized to undergo TF TAVR, TA TAVR, or SAVR; 358 patients were deemed surgically inoperable and were randomized to medical therapy versus TF TAVR.

358 patients with severe AS who were deemed inoperable to optimal medical treatment (including balloon aortic valvuloplasty) or TF TAVR. In the inoperable cohort, all-cause mortality (30.7% vs 50.7%; *P* < .001), cardiovascular mortality (19.6% vs 41.9%; *P* < .001), repeat hospitalization (22.3% vs 44.1%; *P* < .001), and the composite endpoint of death or repeat hospitalization (42.5% vs 71.6%; *P* < .001) were seen less often in patients who were randomized to TAVR. During follow-up, there was no evidence of degeneration of the valvular prosthesis or restenosis at 2 years.[4] At 5-year follow-up, the advantage of TAVR over medical therapy persisted.[5] Heart failure symptoms were less severe in patients treated with TAVR, but they also had a higher incidence of major vascular complications (16.2% vs 1.1%; *P* < .001), major bleeding (22.3% vs 11.2%; *P* < .001), as well as major strokes (5.0% vs 1.1%; *P* = .06). As a result of this trial, TAVR became the new standard of care in patients with severe AS who are not suitable for SAVR.

The results of the high-risk operative cohort[2] demonstrated a statistically nonsignificant difference in all-cause mortality at 30-day (3.4% vs 6.5%; *P* = .07), 1-year (24.2% vs 26.8%), 2-year (33.9% vs 35%), and 3-year (44.2% vs 44.8%) follow-up.[6,7] Although the rates of all neurologic events were higher after TAVR at 30 days and 1 year (5.5% vs 2.4% and 8.3% vs 4.3%, respectively; *P* < .05), rates of major strokes were not significantly different between TAVR and SAVR at 30 days (3.8% vs 2.1%; *P* = .2) or at 1 year (5.1% vs 2.4%; *P* = .07). Of note, the stroke rate was higher in the TA TAVR cohort, as these patients had severe peripheral vessel disease and hence were at increased risk of stroke.[8] There were other important differences in periprocedural risks between the two groups, including more major vascular complications at 30 days after TAVR (11% vs 3.2%; *P* < .001) and more major bleeding (19.5% vs 9.3%; *P* < .001) and new-onset atrial fibrillation (16% vs 8.6%; *P* = .006) after SAVR. The improvement of symptoms was similar after TAVR and SAVR and was sustained at 3 years in both groups.[9]

TABLE 1. SIZING CHARTS FOR THE SAPIEN XT AND SAPIEN 3 VALVES				
SAPIEN XT VALVE SIZING CHART				
	23 mm	**26 mm**	**29 mm**	
Annulus diameter (mm)	18–22	21–25	24–27	
Annulus area (mm^2)	332–395	425–596	528–660	
Expanded length (mm)	14	17	19	
SAPIEN 3 VALVE SIZING CHART				
	20 mm	**23 mm**	**26 mm**	**29 mm**
Annulus diameter (mm)	16–19	18–22	21–25	24–28
Annulus area (mm^2)	273–345	338–430	430–546	540–680
Expanded length (mm)	15.5	18	20	22.5

From these results, TAVR emerged as a viable alternative to SAVR in high-risk patients, the choice being guided by the decision of the interdisciplinary heart team.

Canadian Registry

The Canadian multicenter experience of 339 patients who underwent TAVR between 2005 and 2009 was published in 2012.[10] Among the 335 patients who underwent TAVR, four received the Cribier-Edwards valve, 275 received the Sapien valve, and seven received the Sapien XT valve. At a mean follow-up of 42 ± 15 months, a total of 188 patients (55.5%) had died; 36 (10.4%) died within 30 days after the procedure, and 152 (44.8%) died during the follow-up period. Chronic obstructive pulmonary disease, chronic kidney disease, atrial fibrillation, and frailty were univariate predictors of late mortality. There was no structural or hemodynamic deterioration of the valve. This registry highlighted that the valve was durable for the follow-up period of 4 years and that patient-specific characteristics predicted late mortality. Mild aortic regurgitation was stable and did not affect left ventricular function. Finally, 89% of patients had no or minimal symptoms (New York Heart Association [NYHA] class I/II) during follow-up.

SOURCE Registry

The SOURCE (Edwards Sapien Aortic Bioprosthesis European Outcome) registry, which included 1,123 consecutive high-risk patients who underwent TF and TA TAVR in 32 centers across Europe, was created for post-marketing surveillance. Overall procedural success was 93.8%, with 30-day mortality rates of 6.3% and 10.3% for the TF and TA approaches, respectively. During follow-up, there was marked improvement in functional status, symptoms, and survival. The results from the registry supported the gradual expansion of this technology to centers that were appropriately trained and equipped.[11]

SAPIEN XT VALVE

The new-generation device, Sapien XT (Figure 1B), is a modified and improved version of the Sapien prosthesis that was commercialized in Europe in 2009 and approved in the United States in June 2014. It consists of a cobalt chromium, balloon-expandable stent with an integrated trileaflet bovine tissue valve and an inner fabric skirt on the ventricular side. Changes in the stent material and design, as well as the ability to mount the valve on the deployment balloon inside the abdominal aorta, allowed for a smaller delivery system. TF valve implantation utilizes the NovaFlex catheter, which allows safe passage around the aortic arch with its deflectable nose cone and utilizes an expandable sheath (e-sheath) that minimizes the arteriotomy size. TA and transaortic delivery is possible by the Ascendra+ delivery system, which is optimized for a single operator. The Sapien XT prosthesis is available in three valve sizes: 23, 26, and 29 mm, allowing the treatment of patients with aortic annuli ranging from 18 to 27 mm (Table 1). The results from major publications are summarized in the following sections.

PARTNER II Trial

The aim of the PARTNER II trial is to compare the safety and effectiveness of the Sapien XT valve with the NovaFlex delivery system versus the Sapien valve in a randomized controlled trial. It has two arms: (1) an inoperable cohort, which randomized patients to Sapien XT versus Sapien via a TF approach; and (2) a moderate-

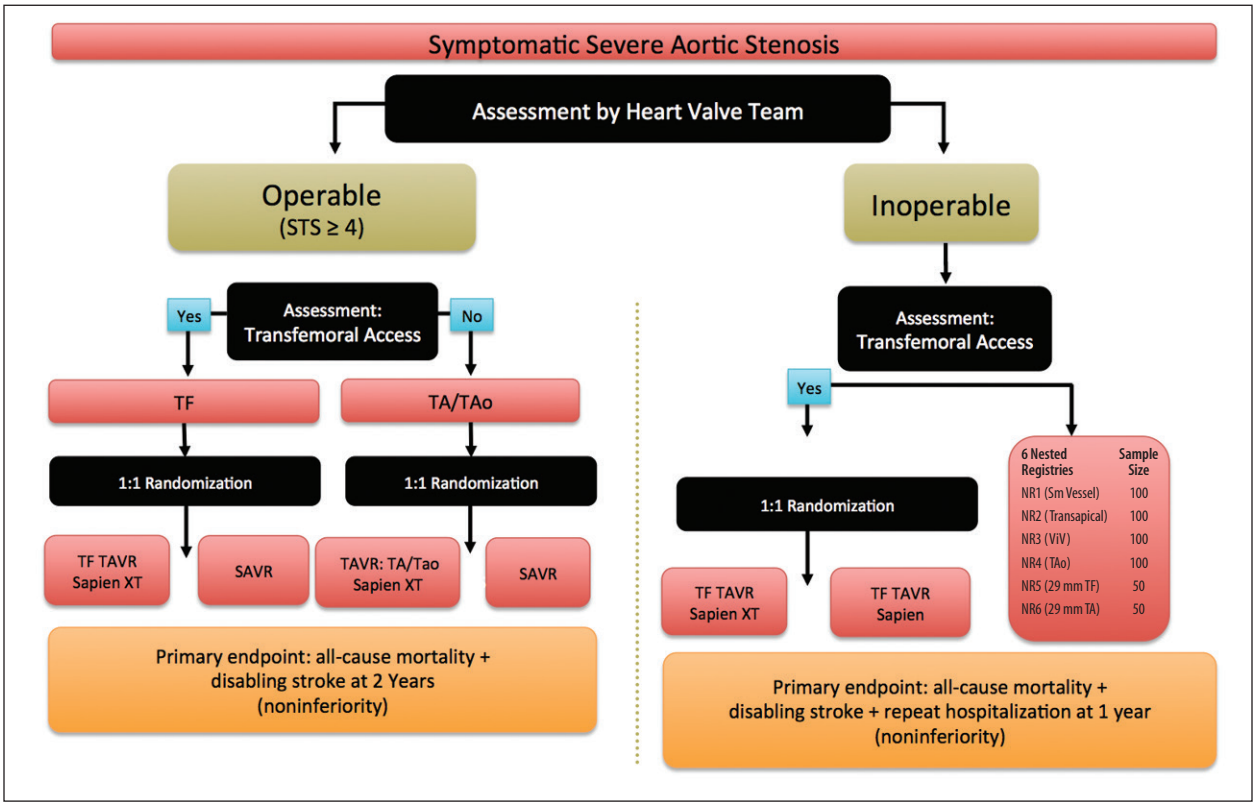

Figure 3. PARTNER II study design. The PARTNER II study was designed to compare Sapien XT with the Sapien valve in surgically inoperable patients. The second arm randomized patients in the intermediate-surgical-risk category to undergo TAVR versus SAVR. TAo, transaortic.

risk cohort, which randomized patients to SAVR versus TAVR with the Sapien XT and included the TA, transaortic, or TF approach (Figure 3). In addition to these populations, there are other nonrandomized nested registries for the inoperable population: inoperable small vessel, inoperable TA, valve in valve, transaortic, 29-mm Sapien XT TF, 29-mm Sapien XT TA, and 20-mm Sapien 3. The primary endpoint of the inoperable cohort is a composite endpoint of death, disabling stroke, and repeat hospitalization. At 30 days, there was no significant difference in the incidence of the composite endpoint (P = .6) with Sapien XT; however, major vascular events were more common with the Sapien valve (15.5% vs 9.6%; P = .04). Sapien XT was noninferior compared to the Sapien valve and showed similar hemodynamic performance.[12] The 29-mm prosthesis had a similar performance in the nonrandomized registries.

SOURCE XT

In the SOURCE XT registry, 2,166 patients underwent TAVR using the Sapien XT valve at 93 sites in 17 European countries. In the registry, the access routes used were: 62.7% TF, 33.3% TA, 3.7% transaortic, and 0.3% transsubclavian. The all-cause 1-year mortality rate was 16.7%. The majority of the patients had trace to mild aortic regurgitation, and only 6% had moderate/severe AR. The majority were also in NYHA class I/II and had improvement in quality-of-life indexes.

SAPIEN 3 VALVE

The Sapien 3 valve is the newest iteration of the Sapien family of valves designed to minimize aortic insufficiency and reduce the diameter of the delivery system. The inflow portion of the valve has a PET fabric cuff in addition to an internal skirt to minimize paravalvular leak. It has a smaller crimped profile and a longer stent frame compared to the first- and second-generation Sapien valves. The longer length of the frame prevents native leaflet prolapse and better positioning during deployment. It has a cobalt chromium frame with wide strut angles providing a low delivery profile and an enhanced frame geometry for greater radial strength (Figure 1C). It is available in four sizes (20, 23, 26, and 29 mm), thus widening the range of patients eligible for TAVR. The 20-, 23-, and 26-mm devices are delivered using a 14-F e-sheath, and the 29-mm device is delivered by

TABLE 2. OUTER DIAMETER OF SHEATH AND MINIMUM VESSEL DIAMETER REQUIRED FOR THE SAPIEN FAMILY OF VALVES

Valve Name	Valve Size (mm)	Sheath Outer Diameter (mm)	Minimum Vessel Diameter (mm)	Sheath Sizes (F)
Sapien	23	8.4	7	22
	26	9.2	8	24
Sapien XT	23	6.7	6	16
	26	7.2	6.5	18
	29	8	7	20
Sapien 3	20	6	5	14
	23	6	5.5	14
	26	6	5.5	14
	29	6.7	6	16

a 16-F e-sheath. The delivery system for the TF route (Commander) is more flexible than NovaFlex+ and has a distal flex point that allows more coaxial alignment of the valve, especially in horizontal aortic root. The balloon has a central marker that is positioned at the annular plane during deployment. The new Certitude system for the transaortic and TA approach is more ergonomically designed for single-operator use and better control during valve deployment. It uses an 18-F sheath for the 23- and 26-mm valves and a 21-F sheath for the 29-mm valve (Table 2).

Initial Study

Initial feasibility studies showed 100% procedural success and that no patient had greater than mild AI. There were no 30-day bleeding, stroke, death, or vascular complications. One patient (6.4%) required permanent pacemaker implantation. Postprocedure CT scans showed that the valve was consistently symmetrical and circular.[13]

Sapien 3 Trial

The Sapien 3 trial enrolled 150 patients at 15 sites in Europe and Canada. Sixty-four percent of patients underwent TF TAVR, and 36% underwent an alternative access (transaortic or TA). The stroke rate in the alternative access group was 10.8%. There was no vascular access–related mortality during this study. TF TAVR showed the lowest 30-day mortality rate (2.3%), no disabling stroke, and 96% total percutaneous access and closure. Paravalvular regurgitation was absent or trace in 74.3% of patients, mild in 22.1%, and moderate in 3.5%, and none had severe regurgitation. Furthermore, 93.3% of patients were in NYHA class I/II at 30 days. The pacemaker rate (13.3%), however, was higher than that reported with balloon-expandable valves. This was attributed to lower implantation of the valve in early part of the trial (Table 3).[14]

PARTNER II S3i

There are nonrandomized cohorts of the PARTNER II trial that evaluate the Sapien 3 valve in two different subsets: (1) intermediate risk (S3i), in which 1,076 patients in a nonrandomized registry of intermediate-risk patients with severe AS compared with historical data of SAVR; and (2) high risk or inoperable (S3HR), in which 583 patients in a nonrandomized registry of high-risk/inoper-

TABLE 3. OUTCOMES WITH THE SAPIEN FAMILY OF VALVES*

Outcome Endpoints	Sapien	Sapien XT	Sapien 3
Stroke	5.5%–6.7%	4.3%–6.3%	2.7%
Major vascular complication	16%	11%–13%	6%
Procedural success	96%	97%	94%
Trace/no aortic insufficiency	22.6%	64%–78%	72%
Permanent pacemaker	5%	8%–11%	13.3%
Mortality, 30 d	3.4%–6.3%	3.5%–4.2%	2.1%

**The data on Sapien XT and Sapien 3 are based on registry and nonrandomized studies.*

The results of the PARTNER II trial and S3 continued access registry are eagerly awaited to show how this technology compares to the surgical alternative in intermediate-risk patients.

able patients with severe AS are compared with historical data on the Sapien valve.

Thirty-day outcomes of the high- and intermediate-risk cohorts treated with the Sapien 3 valve were presented at the American College of Cardiology meeting in San Diego. The observed 30-day mortality was 2.2% in the high-risk cohort and 1.1% in the intermediate-risk cohort, which was markedly lower than the expected mortality according to the Society of Thoracic Surgeons risk calculator, which were 8.6% and 5.3%, respectively. The stroke rate was the lowest reported in balloon-expandable TAVR trials so far. At 30 days, 3.7% of the patients had greater than mild paravalvular insufficiency.

CENTERA VALVE

The Centera valve (Edwards Lifesciences) is a self-expanding, nitinol-frame, bovine pericardial leaflet valve (Figure 1D) with a PET skirt that is available in 23- and 26-mm sizes. The self-expanding frame allows for partial valve repositioning and retrieval. It can be delivered by a TF or subclavian approach using 14-F e-sheaths. The height of the valve is shorter than other self-expanding valves, allowing self-centering and minimal ventricular protrusion. It can be resheathed and repositioned until 70% of the valve is deployed. The delivery consists of a catheter and detachable motorized handle. The system is designed for controlled valve deployment or retraction by a single operator. The final deployment is done under rapid pacing, and the valve is released by pressing a single button. Binder et al reported using the Centera valve in 15 patients for symptomatic severe aortic stenosis.[15]

The valve was successfully implanted in all the cases, and none required placement of a second valve. Paravalvular regurgitation at 30 days was none or trivial in 23%, mild in 69%, and moderate in 8%. Survival was 87% at 30 days and 80% at 1 year. All patients were in NYHA class I or II at 1 year. However, four patients (27%) required pacemaker implantation, a rate that is comparable to other self-expanding valves. The European CE Mark trial is currently underway.

CONCLUSION

The field of TAVR has greatly evolved. Improvements in valve design, patient selection, and valve sizing have led to a lower incidence of postprocedural stroke, paravalvular insufficiency, and vascular complications. The results of the PARTNER II trial and S3 continued access registry are eagerly awaited to show how this technology compares to the surgical alternative in intermediate-risk patients. As we identify patient and device characteristics that lead to a lower procedural complication rate and improved procedural success, we will be able to individualize the type of prosthesis selected for each patient. ■

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