

Smaller Is Better

A comparison of the Sapien and the Sapien XT transcatheter aortic valve prostheses.

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The PARTNER I trial signaled the start of new era in the treatment of severe symptomatic aortic stenosis. The PARTNER I trial involved two cohorts of patients. In cohort A, patients at high risk for surgical aortic valve replacement (SAVR) were randomized to transcatheter aortic valve replacement (TAVR) with a balloon-expandable, stent-mounted bovine pericardial bioprosthesis versus SAVR. TAVR proved noninferior to SAVR, although there was a higher incidence of vascular complications and stroke with TAVR.¹ In cohort B, inoperable patients were randomized to TAVR versus medical therapy, and TAVR was found to be superior to medical therapy.² Based on the results of the PARTNER I trial, the Food & Drug Administration (FDA) approved TAVR with the Sapien transcatheter heart valve (Edwards Lifesciences) for high-risk and inoperable patients in 2011. Since that time, transcatheter valve technology has hurtled forward, with a particular focus on developing lower-profile devices, smaller sheaths, and better delivery systems to minimize the risk of complications.

There is evidence linking lower-profile devices to reduced vascular and bleeding complications. In a retrospective analysis of 375 consecutive patients undergoing transfemoral TAVR, 204 of which were treated with low-profile devices (14–18 F) and 171 of which were treated with larger devices (19–24 F), lower-profile devices were associated with fewer major vascular complications (0.5% vs 10.5%; $P < .001$) and lower rates of major bleeding (3.4% vs 8.3%; $P = .038$).³ Numerous lower-profile devices are currently under investigation, including the Portico valve (St. Jude Medical) as well as the Lotus valve (Boston Scientific Corporation). Earlier this year, the CoreValve (Medtronic, Inc.), a

self-expanding, nitinol, stent-mounted porcine bioprosthesis delivered via an 18-F sheath, gained FDA approval based on the results of the CoreValve US Pivotal Trial.⁴ Most recently, on June 16, 2014, the FDA approved the second-generation Edwards balloon-

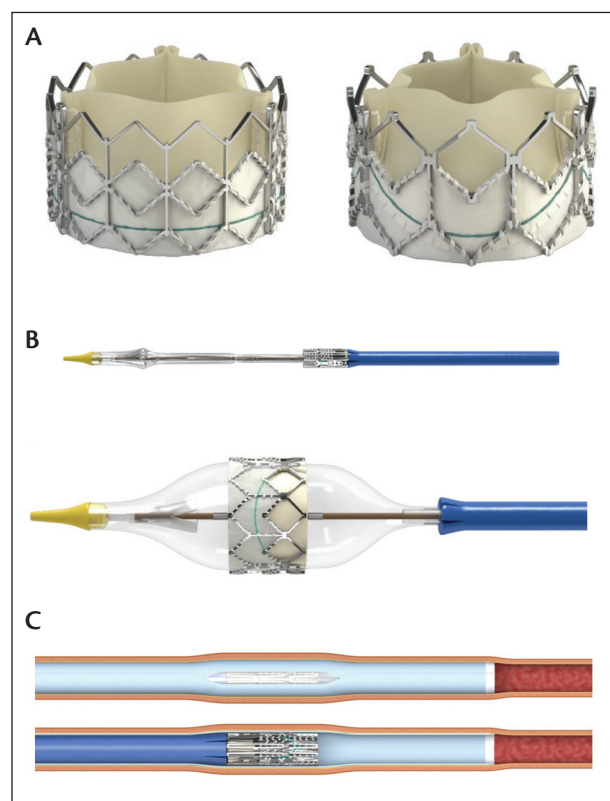


Figure 1. The Sapien (A; left panel) and Sapien XT (A; right panel) valves. The Sapien XT delivery system (B; NovaFlex) (C; expandable sheath).

(courtesy of Edwards Lifesciences)

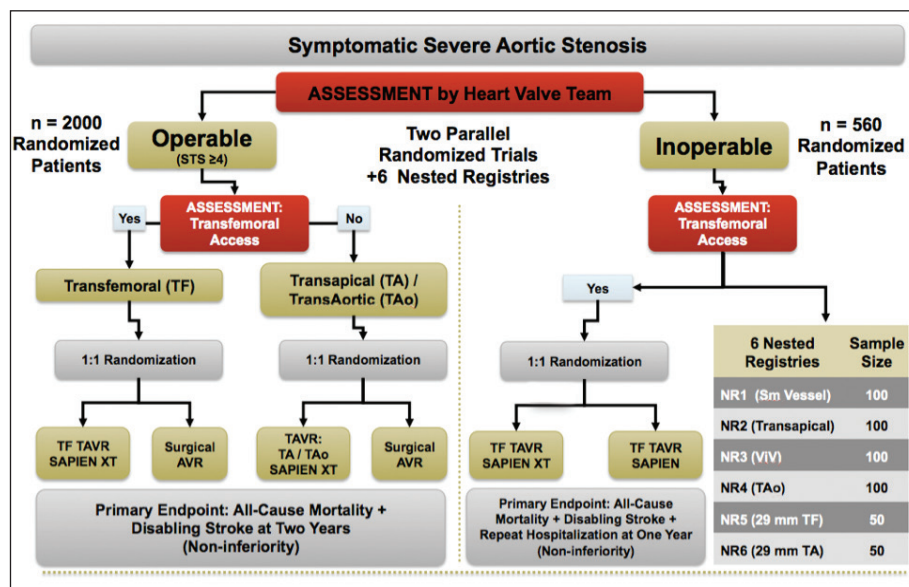


Figure 2. Design of the PARTNER II trial. (From Leon MB. A randomized evaluation of the Sapien XT transcatheter valve system in patients with aortic stenosis who are not candidates for surgery: PARTNER II, Inoperable Cohort. ACC 2013.)

expandable, stent-mounted bovine pericardial prosthesis (Sapien XT) for high-risk and inoperable patients.

KEY FEATURES

The Sapien XT transcatheter heart valve (Edwards Lifesciences) represents further improvements in balloon-expandable, stent-mounted bovine pericardial technology and offers a number of novel features, including the benefit of being markedly lower in profile

than the original Sapien balloon-expandable system. Whereas the Sapien system (Retroflex 3) requires a 22-F sheath to deliver a 23-mm valve and a 24-F sheath to deliver a 26-mm valve, the Sapien XT system (NovaFlex/NovaFlex+) requires only a 16-F sheath to deliver a 23-mm valve or an 18-F sheath to deliver a 26-mm valve. There is also a 29-mm Sapien XT valve delivered via a 20-F sheath, which allows for the treatment of patients with larger aortic annulus areas.

A number of changes in the design of the valve itself, as well as the delivery system, facilitate the reduction in profile. First, the

Sapien XT stent is made of a cobalt-chromium alloy rather than stainless steel. Furthermore, the strut design involves less metal and more open cells, allowing for a lower crimping profile. In addition, the semiclosed leaflet design further facilitates crimping. Alterations in the delivery catheter and sheath also contribute to the slender profile of the Sapien XT. Unlike the Sapien Retroflex 3 delivery system, which required ex vivo mounting of the stent onto the balloon, the Sapien XT

TABLE 1. VASCULAR AND BLEEDING EVENTS AT 30 DAYS

		Sapien (n = 271)		Sapien XT (n = 282)		
Events		n	%	n	%	P Value
Vascular						
	Major	42	15.5	27	9.6	.04
	Minor	20	7.4	14	5.0	.23
Bleeding						
	Disabling	34	12.6	22	7.8	.06
	Major	44	16.4	44	15.7	.84
	Patients with transfusions	80	29.5	73	25.9	.40

(From Leon, MB. A randomized evaluation of the Sapien XT transcatheter valve system in patients with aortic stenosis who are not candidates for surgery: PARTNER II, inoperable cohort. ACC 2013.)

TABLE 2. VASCULAR COMPLICATION CATEGORIES AT 30 DAYS

Events	Sapien (n = 271)		Sapien XT (n = 282)		P Value
	n	%	n	%	
Perforation	13	4.8	2	0.4	.003
Dissection	25	9.2	12	4.3	.03
Hematoma	16	5.9	10	3.6	.23

(From Leon, MB. A randomized evaluation of the Sapien XT transcatheter valve system in patients with aortic stenosis who are not candidates for surgery: PARTNER II, inoperable cohort. ACC 2013.)

NovaFlex system mounts the valve onto the delivery balloon in vivo. Furthermore, the Sapien XT sheath is an expandable sheath that dilates to allow valve passage but subsequently reverts to its original size (Figure 1). This allows for a lower entry and exit profile with only transient expansion of the vessel for a brief interval as the delivery system passes through the sheath. This design both reduces radial force on the vessel as well as linear stretching, thereby minimizing vessel trauma during the procedure.

All of these features contribute to a significant reduction in profile. Whereas a 26-mm Sapien valve required a minimal arterial diameter of 8 mm, a 26-mm Sapien XT valve requires a minimal arterial diameter of only 6.5 mm. The reduction in profile allows more patients

to be candidates for more minimally invasive valve replacement via femoral artery access.

PATIENT SELECTION AND POPULATION

The Sapien XT system has undergone clinical testing in the PARTNER II trial that, like its predecessor PARTNER, was a randomized, controlled clinical trial with two cohorts (Figure 2).⁵

In the PARTNER IIA arm, 2,000 patients with severe symptomatic aortic stenosis deemed to be at intermediate risk for SAVR were randomized to TAVR versus SAVR. Intermediate risk was defined based on the assessment of the heart valve team with a Society of Thoracic Surgeons (STS) predicted risk of mortality of approximately 4% to 8%. Multiple routes of access were available

in the TAVR arm, ranging from transfemoral to transapical to transaortic. The primary endpoint was all-cause mortality plus major stroke at 2 years powered as a noninferiority trial. In the PARTNER IIB arm of the trial, 560 inoperable patients with transfemoral access were randomized to transfemoral TAVR with the Sapien XT device versus transfemoral TAVR with the FDA-approved Sapien system. Inoperability was defined as a risk of death or serious irreversible morbidity exceeding 50% at surgical AVR, as determined by the heart valve team (one cardiologist and two cardiothoracic surgeons). The purpose of the IIB arm

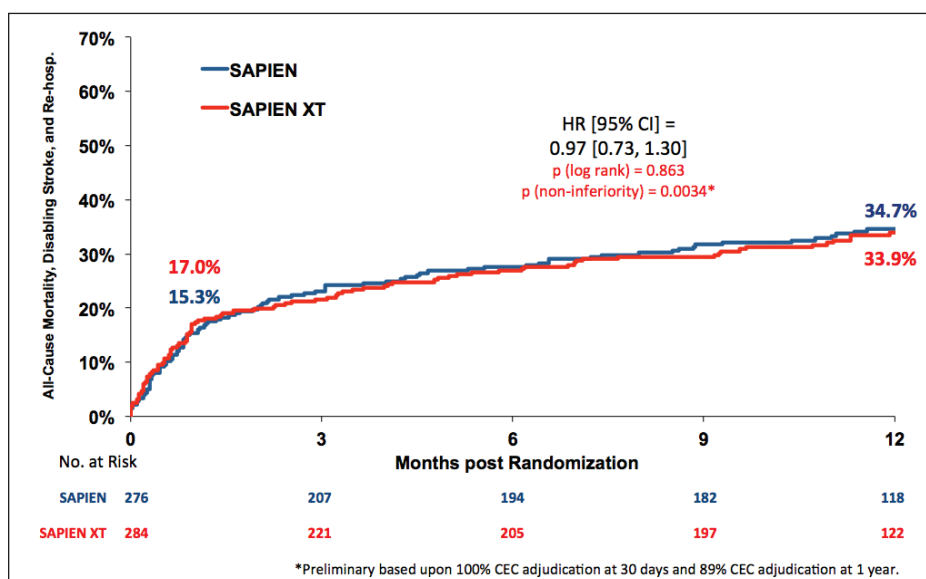


Figure 3. One-year results showing no significant difference between Sapien XT and Sapien in terms of the combined end-point of all-cause mortality, disabling stroke, and rehospitalization. (From Leon MB. A randomized evaluation of the Sapien XT transcatheter valve system in patients with aortic stenosis who are not candidates for surgery: PARTNER II, Inoperable Cohort. ACC 2013.)

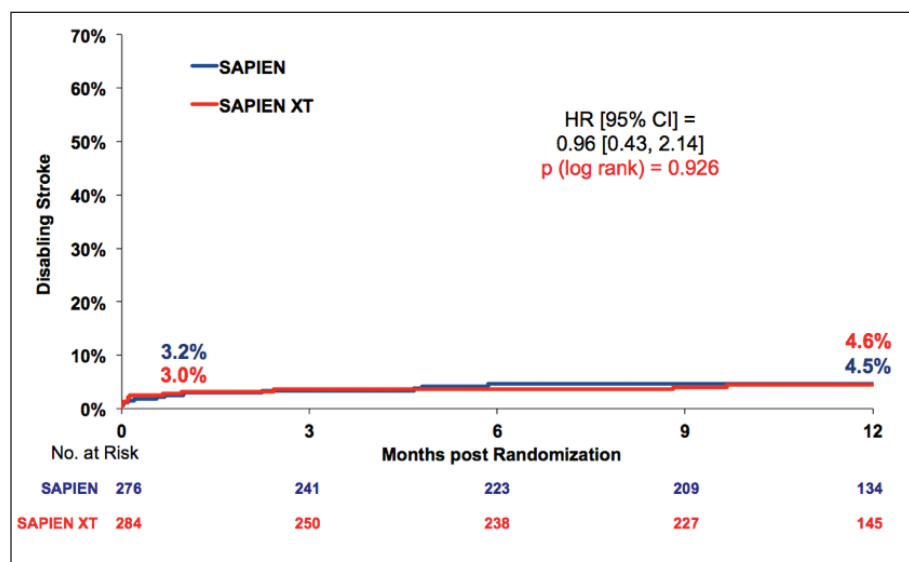


Figure 4. Kaplan-Meier curves show no significant difference in stroke rate between Sapien XT and Sapien at 30 days and 1 year. (From Leon MB. A randomized evaluation of the Sapien XT transcatheter valve system in patients with aortic stenosis who are not candidates for surgery: PARTNER II, Inoperable Cohort. ACC 2013.)

was to compare the safety and efficacy of the Sapien XT system against the FDA-approved Sapien system. The IIB arm also included a series of nested registries for the examination of Sapien XT's performance in situations ranging from alternative access (transapical or transaortic) to valve-in-valve implantation. The B arm was also powered as a noninferiority trial with the primary endpoint being a composite of all-cause mortality, disabling stroke, and repeat hospitalization within 1 year.

Key inclusion criteria included the presence of severe aortic stenosis defined as an echo-derived aortic valve area $< 0.8 \text{ cm}^2$ with a peak velocity of $> 4 \text{ m/s}$, or a mean

gradient $> 40 \text{ mm Hg}$ with at least NYHA class II or more symptoms. Key exclusion criteria included left ventricular systolic function $< 20\%$, end-stage renal disease, unrevascularized coronary artery disease, myocardial infarction within the past month, cerebrovascular accident within the past 6 months, and insufficient or excessive aortic annulus size. Although the preliminary data from the PARTNER IIA arm remain under analysis, data from the IIB arm were presented by Dr. Martin Leon at the ACC meeting in March 2013.⁵ In the inoperable cohort, 276 patients were randomized to Sapien, whereas 284 patients were randomized to Sapien XT. Both groups were evenly matched in terms of demographic characteristics, comorbidities, severity of heart disease, and severity of aortic stenosis. With respect to procedural factors, Sapien XT was associated with shorter anesthesia times, fewer multivalve implantations, fewer aborted procedures, and less need for hemodynamic support with an intra-aortic balloon pump. At 1 year, however, there was no significant difference between Sapien XT and Sapien in terms of the combined endpoint of all-cause mortality, disabling stroke, and repeat hospitalization (Figure 3).

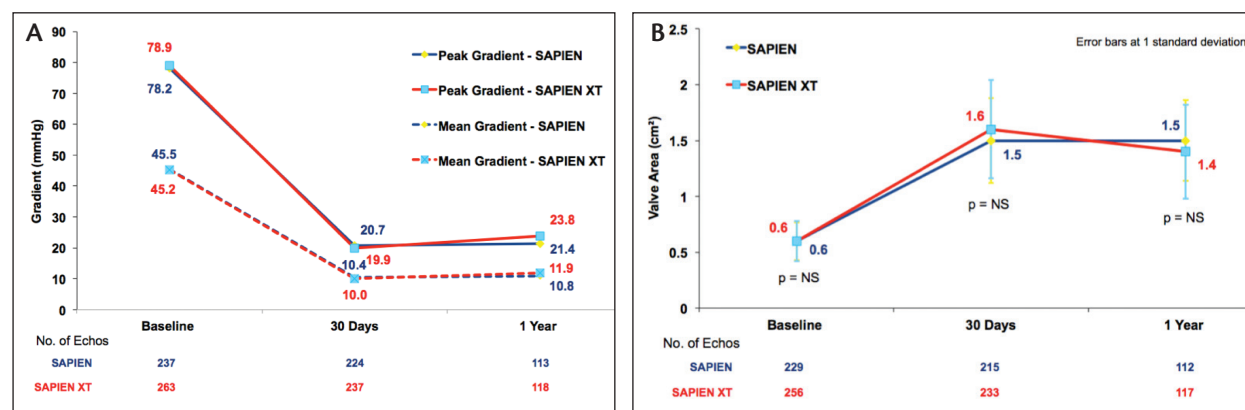


Figure 5. There was no significant difference between the two devices in calculated valve area (A) or mean gradient (B) by echo at 30 days or 1 year. (From Leon MB. A randomized evaluation of the Sapien XT transcatheter valve system in patients with aortic stenosis who are not candidates for surgery: PARTNER II, Inoperable Cohort. ACC 2013.)

Data from the PARTNER IIB trial demonstrate that Sapien XT is noninferior to Sapien with respect to hemodynamic performance . . .

However, given the lower profile of the Sapien XT, the number of major vascular complications and disabling bleeding events at 30 days was significantly reduced. In particular, there were significantly fewer perforations and dissections. Tables 1 and 2 summarize these differences.

The importance of reducing vascular complications should not be underestimated. Although 9.6% of the Sapien XT arm and 15.5% of the Sapien arm suffered major vascular complications, in a Cox regression model, major vascular complications with either system were equally associated with increased all-cause mortality at 1 year.⁶ Minimizing major vascular complications, therefore, indirectly impacts outcomes.

Although Sapien XT's lower profile resulted in fewer vascular complications, this did not translate into fewer strokes. The Kaplan-Meier curves show no significant difference in stroke rate at either 30 days or 1 year between Sapien XT and Sapien (Figure 4). This result proves disappointing in that stroke remains a relative disadvantage of TAVR relative to SAVR (5.6% vs 2.3%; $P < .04$) based on the results of the PARTNER I trial.¹

The hemodynamic performance of Sapien XT proved noninferior to Sapien. There was no significant difference between the two devices in mean gradient or calculated valve area by echo at 30 days or 1 year (Figure 5). Rates of moderate or greater aortic insufficiency after TAVR were, however, similar with Sapien XT versus Sapien (24.8% vs 21.3%; $P = .29$).⁵ Paravalvular aortic regurgitation remains an Achilles heel of TAVR, as the relatively rare occurrence of moderate or more paravalvular regurgitation has been associated with increased mortality after TAVR.⁷

FUTURE DIRECTIONS

The Sapien XT balloon-expandable, stent-mounted bovine pericardial transcatheter valvular bioprosthesis is lower in profile than its predecessor Sapien. Preliminary data from the PARTNER IIB trial demonstrate that Sapien XT is non-inferior to Sapien with respect to hemodynamic performance and the composite endpoint of mortality, disabling stroke, and rehospitalization. Sapien XT's lower profile does, however, translate into fewer vascular and bleeding

complications, particularly fewer iliac dissections and perforations. Review of the data from the PARTNER IIA arm comparing Sapien XT to surgical AVR in intermediate-risk patients is currently ongoing. In the meantime, the PARTNER II trial has moved on to testing the Sapien 3 balloon-expandable transcatheter heart valve, a lower-profile device deliverable via a 14-F sheath in the majority of patients. There is no question that the rapid improvement in transcatheter valve technology has led to the rapid proliferation of TAVR. Whether the dissemination of TAVR proves valuable from the standpoint of health care economics, however, remains an open question. Given the high cost of the technology, the long track record of value with SAVR, and ongoing concerns about relative disadvantages with TAVR, such as stroke and paravalvular regurgitation, there is an imperative need for further objective randomized data comparing TAVR against SAVR in a variety of populations.⁸ For those practicing in the field of valvular and structural heart disease these rapid improvements in technology provide both a challenge and an opportunity to improve health care outcomes and patient care. ■

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1. Smith CR, Leon MB, Mack MJ, et al. Transcatheter versus surgical aortic valve replacement in high-risk patients. *N Engl J Med*. 2011;364:2187-2198.
2. Leon MB, Smith CR, Mack MJ, et al. Transcatheter aortic valve implantation for aortic stenosis in patients who cannot undergo surgery. *N Engl J Med*. 2010;363:1597-1607.
3. Barbanti M, Binder RK, Freeman M, et al. Impact of low profile sheaths on vascular complications during transfemoral transcatheter aortic valve replacement. *Eurointervention*. 2013;9:929-935.
4. Adams DH, Popma JJ, Reardon MJ, et al. Transcatheter aortic valve replacement with a self-expanding prosthesis. *N Engl J Med*. 2014;370:1790-1798.
5. Leon MB. A randomized evaluation of the Sapien XT transcatheter valve system in patients with aortic stenosis who are not candidates for surgery: PARTNER II, inoperable cohort. Presented at the ACC annual meeting; San Francisco, CA; March 9-11, 2013.
6. Pichard A, Doshi D, Kodali S. A randomized comparison of vascular complications after TAVR comparing the Sapien versus the lower-profile Sapien XT system in "inoperable" aortic stenosis patients: a PARTNER 2 substudy analysis. *J Am Coll Cardiol*. 2014;63(12S).
7. Lerakis S, Hayek SS, Douglas PS. Paravalvular aortic leak after transcatheter aortic valve replacement: current knowledge. *Circulation*. 2013;127:397-407.
8. Feldman AM, Disesa VJ. Transcatheter aortic valve replacement: flattening the cost curve. *JAMA*. 2014;312:25-26.