Edwards Lifesciences

Edwards SAPIEN XT
Transcatheter Heart Valve with the Ascendra+ Delivery System

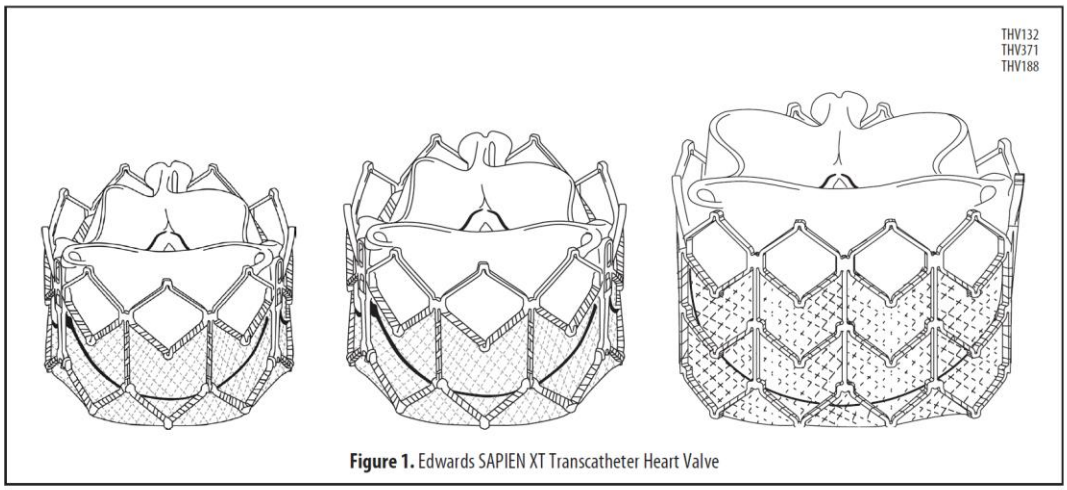

Figure 1. Edwards SAPIEN XT Transcatheter Heart Valve

Instructions for Use

Caution: Federal (USA) law restricts this device to sale by or on the order of a physician.

Implantation of the transcatheter heart valve should be performed only by physicians who have received Edwards Lifesciences training. The implanting physician should be experienced in balloon aortic valvuloplasty.

Please verify that you have the latest version of the instructions for use prior to using the device by visiting http://THVIFU.edwards.com or by calling 1.800.822.9837. In order to access the instructions for use, an IFU Code will be required.

STERILE: The valve is supplied sterilized with glutaraldehyde solution. The delivery system is supplied sterilized with ethylene oxide gas.

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1.0 Device Description

- Edwards SAPIEN XT Transcatheter Heart Valve – Model 9300TFX (Figure 1)

The Edwards SAPIEN XT transcatheter heart valve is comprised of a balloon-expandable, radiopaque, cobalt-chromium frame, trileaflet bovine pericardial tissue valve, and a polyethylene terephthalate (PET) fabric skirt. The leaflets are treated according to the Carpentier-Edwards ThermaFix process.

Table 1

Valve Size	Height
23 mm	14.3 mm
26 mm	17.2 mm
29 mm	19.1 mm

Table 2

Native Valve Annulus Size (TEE)	Native Valve Annulus Size (CT)		Valve Size
	Area	Area Derived Diameter	
18-22 mm	314 – 415 mm^2	20-23 mm	23 mm
21-25 mm	415 – 530 mm^2	23-26 mm	26 mm
24-27 mm	530 – 660 mm^2	26-29 mm	29 mm
Valve size recommendations are based on native valve annulus size, as measured by transesophageal echocardiography (TEE) or computed tomography (CT). Patient anatomical factors and multiple imaging modalities should be considered during valve size selection. Note: Risks associated with undersizing and oversizing should be considered.			

For transcatheter valve-in-surgical valve procedures, size recommendations for surgical bioprostheses with **internal orifice diameters** are shown in Table 3.

Table 3

Bioprosthesis Internal Orifice Diameter	SAPIEN XT Valve Size
18-21 mm	23 mm
21-23.5 mm	26 mm
23.5-27 mm	29 mm

NOTE: The internal orifice diameter of the surgical bioprosthesis must be determined so that the appropriate valve size can be implanted. The bioprosthesis internal diameter of the primary implanted device is best determined by using computed tomography, magnetic resonance imaging, and/or transesophageal echocardiography to perform the necessary measurements. The internal orifice diameter is a directly measured or area derived diameter measurement of the internal opening of the failed surgical valve.

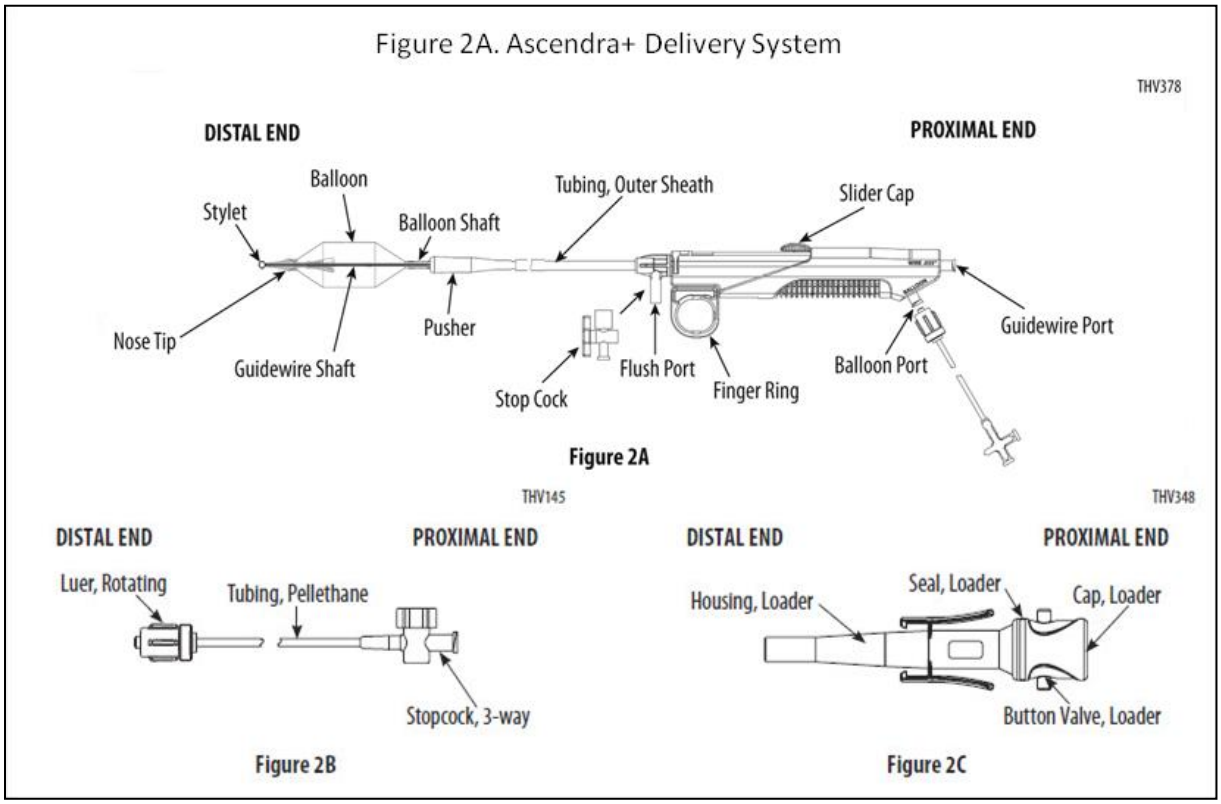
NOTE: Exact volume required to deploy the valve may vary depending on the bioprosthesis internal orifice diameter. Do not exceed the rated burst pressure. See Table 4 for inflation parameters.

- **Ascendra+ Delivery System (Figures 2a, 2b, 2c)**

The Ascendra+ delivery system (useable length 55 cm) is used for delivery of the Edwards SAPIEN XT transcatheter heart valve. The delivery system has radiopaque markers for visualization under fluoroscopy and a balloon for deployment of the valve. A balloon inflation hub, a guidewire hub, and a pusher retraction feature are housed in the handle assembly. The handle is labeled “BALLOON” at the balloon inflation hub and “WIRE 0.035"” at the guidewire hub. The system also comes with a loader that is used to cover the valve during delivery. An extension tube is supplied for use with the delivery system during inflation.

Table 4

Model	Nominal Balloon Diameter	Nominal Inflation Volume	Rated Burst Pressure (RBP)
9355AS23	23 mm	16 mL	7 atm
9355AS26	26 mm	20 mL	7 atm
9355AS29	29 mm	30 mL	7 atm



2.0 Indications

The Edwards SAPIEN XT transcatheter heart valve, model 9300TFX, and accessories are indicated for relief of aortic stenosis in patients with symptomatic heart disease due to severe native calcific aortic stenosis who are judged by a Heart Team, including a cardiac surgeon, to be at intermediate or greater risk for open surgical therapy (i.e., predicted risk of surgical mortality ≥ 3% at 30 days, based on the Society of Thoracic Surgeons (STS) risk score and other clinical co-morbidities unmeasured by the STS risk calculator).

The Edwards SAPIEN XT transcatheter heart valve and accessories are also indicated for patients with symptomatic heart disease due to failure (stenosed, insufficient, or combined) of a surgical bioprosthetic aortic valve who are judged by a heart team, including a cardiac surgeon, to be at high or greater risk for open surgical therapy (i.e., STS operative risk score ≥ 8% or at a ≥ 15% risk of mortality at 30 days).

3.0 Contraindications

The valve and delivery system are contraindicated in patients who cannot tolerate an anticoagulation/antiplatelet regimen or who have active bacterial endocarditis or other active infections.

4.0 Warnings

- Observation of the pacing lead throughout the procedure is essential to avoid the potential risk of pacing lead perforation.
- There may be an increased risk of stroke in transcatheter aortic valve replacement procedures, as compared to balloon aortic valvuloplasty or other standard treatments in high or greater risk patients.
- The devices are designed, intended, and distributed for single use only. **Do not resterilize or reuse the devices.** There are no data to support the sterility, nonpyrogenicity, and functionality of the devices after reprocessing.
- Care should be exercised when sizing the native annulus or surgical valve; implanting a valve that is too small may lead to paravalvular leak, migration or embolization, whereas implanting a valve that is too large may lead to residual gradient (patient-prosthesis mismatch) or annular rupture.
- Accelerated deterioration of the valve may occur in patients with an altered calcium metabolism.
- Prior to delivery, the valve must remain hydrated at all times and cannot be exposed to solutions other than its shipping storage solution and sterile physiologic rinsing solution. Valve leaflets mishandled or damaged during any part of the procedure will require replacement of the valve.
- Caution should be exercised in implanting a valve in patients with clinically significant coronary artery disease.
- Patients with pre-existing mitral valve devices should be carefully assessed prior to implantation of the valve to ensure proper valve positioning and deployment.
- Patients presenting with combination AV low flow, low gradient should undergo additional evaluation to establish the degree of aortic stenosis.
- Do not use the valve if the tamper evident seal is broken, the storage solution does not completely cover the valve, the temperature indicator has been activated, the valve is damaged, or the expiration date has elapsed.
- Do not mishandle the Ascendra+ delivery system or use it if the packaging or any components are not sterile, have been opened or are damaged (e.g. kinked or stretched), or the expiration date has elapsed.
- Care should be exercised in patients with hypersensitivities to cobalt, nickel, chromium, molybdenum, titanium, manganese, silicon, and/or polymeric materials.
- The procedure should be conducted under fluoroscopic guidance. Some fluoroscopically guided procedures are associated with a risk of radiation injury to the skin. These injuries may be painful, disfiguring, and long-lasting.

- Valve recipients should be maintained on anticoagulant/antiplatelet therapy, except when contraindicated, as determined by their physician. This device has not been tested for use without anticoagulation.
- Do not add or apply antibiotics to the storage solution, rinse solutions, or to the valve.

5.0 Precautions

- Long-term durability has not been established for the valve. Regular medical follow-up is advised to evaluate valve performance.
- Glutaraldehyde may cause irritation of the skin, eyes, nose and throat. Avoid prolonged or repeated exposure to, or breathing of, the solution. Use only with adequate ventilation. If skin contact occurs, immediately flush the affected area with water; in the event of contact with eyes, seek immediate medical attention. For more information about glutaraldehyde exposure, refer to the Material Safety Data Sheet available from Edwards Lifesciences.
- To maintain proper valve leaflet coaptation, do not overinflate the deployment balloon.
- Appropriate antibiotic prophylaxis is recommended post-procedure in patients at risk for prosthetic valve infection and endocarditis.
- Safety, effectiveness, and durability have not been established for transcatheter valve in transcatheter valve procedures.
- Safety and effectiveness have not been established for patients with the following characteristics/comorbidities:
    - Non-calcified aortic annulus
    - Severe ventricular dysfunction with ejection fraction < 20%
    - Congenital unicuspid or congenital bicuspid aortic valve
    - Mixed aortic valve disease (aortic stenosis and aortic regurgitation with predominant aortic regurgitation > 3+)
    - Pre-existing prosthetic ring in any position
    - Severe mitral annular calcification (MAC), severe (> 3+) mitral insufficiency, or Gorlin syndrome
    - Blood dyscrasias defined as: leukopenia (WBC < 3,000 cells/mL), acute anemia (Hb < 9 g/dL), thrombocytopenia (platelet count < 50,000 cells/mL), or history of bleeding diathesis or coagulopathy
    - Hypertrophic cardiomyopathy with or without obstruction (HOCM)
    - Echocardiographic evidence of intracardiac mass, thrombus, or vegetation
    - A known hypersensitivity or contraindication to aspirin, heparin, ticlopidine (Ticlid™), or clopidogrel (Plavix™), or sensitivity to contrast media, which cannot be adequately premedicated
    - Excessive calcification of vessel at access site
    - Bulky calcified aortic valve leaflets in close proximity to coronary ostia
    - A concomitant paravalvular leak where the surgical bioprosthesis is not securely fixed in the native annulus or is not structurally intact (e.g. wireform frame fracture)
    - A partially detached leaflet of the surgical bioprosthesis that in the aortic position may obstruct a coronary ostium

- The safety and effectiveness have not been established for implanting the transcatheter valve inside a stented bioprosthetic valve < 21 mm (labeled size) or an unstented bioprosthetic aortic valve.
- Residual mean gradient may be higher in a “TAV-in-SAV” configuration than that observed following implantation of the valve inside a native aortic annulus using the same size device. Patients with elevated mean gradient post procedure should be carefully followed. It is important that the manufacturer, model and size of the preexisting surgical bioprosthetic aortic valve be determined, so that the appropriate valve can be implanted and a prosthesis-patient mismatch be avoided. Additionally, pre-procedure imaging modalities must be employed to make as accurate a determination of the internal orifice as possible.

6.0 Potential Adverse Events

Potential risks associated with the overall procedure including potential access complications associated with standard cardiac catheterization, balloon valvuloplasty, the potential risks of conscious sedation and/or general anesthesia, and the use of angiography:

- Death
- Stroke/transient ischemic attack, clusters or neurological deficit
- Paralysis
- Permanent disability
- Respiratory insufficiency or respiratory failure
- Hemorrhage requiring transfusion or intervention
- Cardiovascular injury including perforation or dissection of vessels, ventricle, myocardium or valvular structures that may require intervention
- Pericardial effusion or cardiac tamponade
- Embolization including air, calcific valve material or thrombus
- Infection including septicemia and endocarditis
- Heart failure
- Myocardial infarction
- Renal insufficiency or renal failure
- Conduction system defect which may require a permanent pacemaker
- Arrhythmia
- Retroperitoneal bleed
- Arteriovenous (AV) fistula or pseudoaneurysm
- Reoperation
- Ischemia or nerve injury
- Restenosis
- Pulmonary edema
- Pleural effusion
- Bleeding
- Anemia

- Abnormal lab values (including electrolyte imbalance)
- Hypertension or hypotension
- Allergic reaction to anesthesia, contrast media, or device materials
- Hematoma
- Syncope
- Pain or changes at the access site
- Exercise intolerance or weakness
- Inflammation
- Angina
- Heart murmur
- Fever

Additional potential risks associated with the use of the valve, delivery system, and/or accessories include:

- Cardiac arrest
- Cardiogenic shock
- Emergency cardiac surgery
- Cardiac failure or low cardiac output
- Coronary flow obstruction/transvalvular flow disturbance
- Device thrombosis requiring intervention
- Valve thrombosis
- Device embolization
- Device migration or malposition requiring intervention
- Valve deployment in unintended location
- Valve stenosis
- Structural valve deterioration (wear, fracture, calcification, leaflet tear/tearing from the stent posts, leaflet retraction, suture line disruption of components of a prosthetic valve, thickening, stenosis)
- Device degeneration
- Paravalvular or transvalvular leak
- Valve regurgitation
- Hemolysis
- Device explants
- Nonstructural dysfunction
- Mechanical failure of delivery system, and/or accessories
- Non-emergent reoperation

7.0 Directions for Use

7.1 Required Equipment

Table 5

Product Name	23 mm System (9355ASP23A)	26 mm System (9355ASP26A)	29 mm System (9355ASP29A)
	Model		
Edwards SAPIEN XT Transcatheter Heart Valve	9300TFX (23 mm)	9300TFX (26 mm)	9300TFX (29 mm)
Ascendra+ Delivery System*	9355AS23	9355AS26	9355AS29
Ascendra+ Introducer Sheath Set	9350IS23	9350IS26	9350IS29
Ascendra Balloon Aortic Valvuloplasty Catheter	9100BAVC		
Inflation devices provided by Edwards Lifesciences			
Edwards Crimper	9350CR		
* Includes the Crimp Stopper			

Additional Equipment:

- 20 cc syringe or larger (x2)
- 50 cc syringe or larger
- Standard cardiac catheterization lab equipment
- Fluoroscopy (fixed, mobile or semi-mobile fluoroscopy systems appropriate for use in percutaneous coronary interventions)
- Transesophageal or transthoracic echocardiography capabilities
- Exchange length 0.035 inch (0.89 mm) extra-stiff guidewire
- Temporary pacemaker (PM) and pacing lead
- Sterile rinsing basins, physiological saline, heparinized saline, 15% diluted radiopaque contrast medium
- Sterile table for valve and device preparation

7.2 Valve Handling and Preparation

Follow sterile technique during device preparation and implantation.

7.2.1 Valve Rinsing Procedure

Before opening the valve jar, carefully examine for evidence of damage (e.g., a cracked jar or lid, leakage, or broken or missing seals).

CAUTION: Valves from containers found to be damaged, leaking, without adequate sterilant, or missing intact seals must not be used for implantation.

Step	Procedure
1	Set up two (2) sterile bowls with at least 500 mL of sterile physiological saline to thoroughly rinse the glutaraldehyde sterilant from the valve.

Step	Procedure
2	Carefully remove the valve/holder assembly from the jar without touching the tissue. Verify the valve serial identification number with the number on the jar lid and record in the patient information documents. Inspect the valve for any signs of damage to the frame or tissue.
3	Rinse the valve as follows: Place the valve in the first bowl of sterile, physiological saline. Be sure the saline solution completely covers the valve and holder. With the valve and holder submerged, slowly agitate (to gently swirl the valve and holder) back and forth for a minimum of 1 minute. Transfer the valve and holder to the second rinsing bowl of physiological saline and gently agitate for at least one more minute. Ensure the rinse solution in the first bowl is not used. The valve should be left in the final rinse solution until needed to prevent the tissue from drying. **CAUTION: Do not allow the valve to come into contact with the bottom or sides of the rinse bowl during agitation or swirling in the rinse solution. Direct contact between the identification tag and valve is also to be avoided during the rinse procedure. No other objects should be placed in the rinse bowls. The valve should be kept hydrated to prevent the tissue from drying.**

7.2.2 Prepare the Components

Step	Procedure
1	Visually inspect all components for damage.
2	Refer to Ascendra+ Introducer Sheath Set and Crimper instructions for use on device preparation and handling.
3	Ensure the delivery system pusher is in the distal locked position using the slider cap. If the stopcock is not attached to the delivery system, attach stopcock to the flush port. Flush delivery system at the flush port with heparinized saline and close stopcock to delivery system.
4	Carefully remove distal balloon cover.
5	Flush loader through the distal end with heparinized saline and insert the delivery system (with proximal balloon cover on) into loader until loader is completely proximal.
6	Fully retract slider cap and rotate into proximal slot.
7	Slide the proximal balloon cover onto the balloon shaft and carefully peel off the proximal balloon cover from the delivery system.
8	Flush and attach balloon extension tube to the balloon inflation hub.
9	Prepare a 50 cc or larger luer-lock syringe with diluted contrast solution (15:85 contrast to heparinized saline) and attach to the extension tubing.
10	Completely fill the inflation device provided by Edwards with diluted contrast and attach to the extension tubing stopcock. Ensure there are no air bubbles in the balloon. If an air bubble is detected, eliminate it while deflating the balloon. Close the stopcock to the delivery system.
11	Remove excess contrast medium from the inflation device provided by Edwards into the syringe to achieve the appropriate volume required to deploy the valve per the following. Then lock the inflation device: **Delivery System** / **Valve** / **Inflation Volume** Model 9355AS23 / 23 mm / 16 mL Model 9355AS26 / 26 mm / 20 mL Model 9355AS29 / 29 mm / 30 mL **Note: Correct balloon sizing is critical to successful valve deployment and valve function.**

Step	Procedure
12	Close the stopcock to the 50 cc or larger syringe and remove the syringe. **CAUTION: Maintain the inflation device provided by Edwards in the locked position until valve deployment.**

7.2.3 Mount and Crimp the Valve onto the Delivery System

Step	Procedure
1	Rotate the crimper until the aperture is fully opened.
2	Remove the valve from the holder and remove ID tag using sterile scissors.
3	Place valve into crimper aperture and partially crimp so that it fits loosely over the prepared balloon.
4	Remove the valve from the crimper and place it on the delivery system with the inflow (fabric cuff end) of the valve proximally towards the pusher if accessing antegrade. If accessing retrograde, place the valve on the delivery system with the inflow (fabric cuff end) of the valve towards the distal end away from the pusher. Ensure that the valve is aligned between the radiopaque markers.
5	Place the valve/balloon assembly in crimper aperture and gradually crimp. Periodically open crimper to verify correct placement of valve during crimping. Completely crimp until the handle contacts the crimp stopper. **CAUTION: The implanting physician must verify correct mounting/orientation of the valve prior to its implantation.**
6	Advance the slider cap distally to allow the tip of the pusher to align with the proximal end of the crimped valve.
7	Advance the loader onto crimped valve until it reaches the balloon shoulder and the valve is fully covered.
8	While holding the loader in place, fully retract the slider cap and rotate into locked position. Flush through the flush port to fill the loader and hydrate the valve. Once the valve is hydrated, advance the slider cap and rotate into distal locked position. Be sure to maintain position of the crimped valve between the radiopaque markers during hydration. Close the flush port stopcock to the delivery system. **Note: To facilitate flushing, keep the delivery system straight.** **CAUTION: To prevent possible leaflet damage, the valve should not remain in the loader over 30 minutes.**
9	Ensure the slider cap is locked in the distal position and that the valve is still centered between radiopaque markers and fully inside the loader. **Note: Keep valve hydrated until ready for implantation.**
10	Remove the stylet and flush the guidewire lumen of the delivery system. **CAUTION: The implanting physician must verify correct orientation of the valve prior to its implantation.**

7.3 Valvuloplasty and Valve Delivery

Valvuloplasty and valve delivery should be performed under general anesthesia with hemodynamic monitoring in a catheterization lab/hybrid operating room with fluoroscopic and echocardiographic imaging capabilities.

The following table shows the minimum required distances from the native valve annulus to the distal tip of the Ascendra+ sheath to allow the Ascendra+ delivery system balloon to inflate properly during valve deployment. These distances should be considered during the transaortic approach when

selecting the access site on the ascending aorta and determining the insertion depth of the Ascendra+ sheath into the aorta.

Delivery System	Valve	Minimum Required Distance From Annulus to Sheath Tip
Model 9355AS23	23 mm	5.0 cm
Model 9355AS26	26 mm	5.5 cm
Model 9355AS29	29 mm	6.0 cm

Administer heparin to maintain the ACT at ≥ 250 sec.

CAUTION: Contrast media use should be monitored to reduce the risk of renal injury.

7.3.1 Baseline Parameters

Step	Procedure
1	Perform an angiogram with fluoroscopic view perpendicular to the valve.
2	Evaluate the height between the inferior aspect of the annulus and the inferior aspects of the lowest coronary ostium for subsequent prosthetic aortic valve implantation.
3	Introduce a pacemaker (PM) lead until its distal end is positioned in the right ventricle.
4	Set the stimulation parameters, and test pacing.

7.3.2 Valvuloplasty

Refer to Ascendra Balloon Aortic Valvuloplasty Catheter Instructions for Use (IFU) for information on device preparation and handling for a stenotic aortic valve.

Note: Rapid ventricular pacing should be performed when using the Ascendra balloon aortic valvuloplasty catheter for valvuloplasty prior to transcatheter valve implantation.

After placement of the balloon at the intended site, begin rapid ventricular pacing. Once the blood pressure has decreased to 50 mmHg or below, balloon inflation can commence.

CAUTION: Valve implantation should not be carried out if the balloon cannot be fully inflated during valvuloplasty.

7.3.3 Valve Delivery

Step	Procedure
1	Insert the introducer sheath. Refer to the Ascendra+ Introducer Sheath Set IFU for additional information on device preparation and handling.
2	Advance delivery system over guidewire. Engage loader into introducer sheath housing while maintaining a firm grip. Tap lightly on the introducer sheath housing to release air to the proximal end of the loader. Lightly depress button valves on loader to aspirate the loader.
3	Cross the native aortic valve or bioprosthesis and position the transcatheter valve within the valve.
4	Retract pusher by rotating slider cap out of distal locked position and moving it proximally to ensure that the tip of the pusher is retracted completely on to the balloon shaft. **CAUTION: The pusher must be pulled back completely on the balloon shaft for proper balloon inflation and valve deployment.**
5	Verify the correct position of the valve with respect to the valve.

Step	Procedure
6	Begin valve deployment: • Unlock the inflation device. • Begin rapid pacing; once arterial blood pressure has decreased to 50 mmHg or below, balloon inflation can commence. • Deploy the valve by inflating the balloon with the entire volume in the Inflation device provided by Edwards Lifesciences, hold for 3 seconds and confirm that the barrel of the inflation device is empty to ensure complete inflation of the balloon. When the balloon catheter has been completely deflated, turn off the pacemaker. • Retract the delivery system into the introducer sheath.
7	Disengage loader from sheath and remove delivery system and loader.
8	Remove sheath when the ACT level is appropriate (e.g. reaches < 150 sec). Close access site.

8.0 How Supplied

STERILE: The valve is supplied sterilized with glutaraldehyde solution. The delivery system is supplied sterilized with ethylene oxide gas.

8.1 Storage

The valve must be stored at 10 °C to 25 °C (50 °F to 77 °F). Each jar is shipped in an enclosure containing a temperature indicator to detect exposure of the valve to extreme temperature.

The delivery system should be stored in a cool, dry place.

9.0 MR Safety

MR Conditional

Non-clinical testing has demonstrated that the Edwards SAPIEN XT transcatheter heart valve is MR Conditional. A patient with this device, when implanted in the native valve or a failed surgical bioprosthesis, can be scanned safely, immediately after placement of this device under the following conditions:

- Static magnetic field of 1.5 tesla or 3 tesla
- Maximum spatial gradient field of 2500 gauss/cm (25 T/m) or less
- Maximum MR system reported, whole body averaged specific absorption rate (SAR) of 2 W/kg (Normal Operating Mode)

Under the scan conditions defined above, the SAPIEN XT transcatheter heart valve is expected to produce a maximum temperature rise of 2.6 °C after 15 minutes of continuous scanning.
In non-clinical testing, the image artifact caused by the device extends as far as 14.5 mm from the implant for spin echo images and 30 mm for gradient echo images when scanned in a 3.0 T MRI system. The artifact obscures the device lumen in gradient echo images. The implant has not been evaluated in MR systems other than 1.5 or 3.0 T. For valve-in-surgical valve implantation or in the presence of other implants, please refer to MRI safety information for the surgical valve or other devices prior to MR imaging.

10.0 Patient Information

Patient education brochures are provided to each site and should be given to the patient to inform them of the risks and benefits of the procedure and alternatives in adequate time before the procedure to be read and discussed with their physician. A copy of this brochure may also be obtained from Edwards Lifesciences by calling 1.800.822.9837. A patient implant card request form is provided with each transcatheter heart valve. After implantation, all requested information should be completed on this form. The serial number may be found on the package and on the identification tag attached to the transcatheter heart valve. The original form should be returned to the Edwards Lifesciences address indicated on the form and upon receipt, Edwards Lifesciences will provide an identification card to the patient.

11.0 Recovered valve and Device Disposal

The explanted valve should be placed into a suitable histological fixative such as 10% formalin or 2% glutaraldehyde and returned to the company. Refrigeration is not necessary under these circumstances. Contact Edwards Lifesciences to request an Explant Kit.

Used delivery system may be disposed of in the same manner that hospital waste and biohazardous materials are handled. There are no special risks related to the disposal of these devices.

12.0 Clinical Studies

The PARTNER II Cohort B Registries

Cohort B of The Placement of Aortic Transcatheter Valves Trial II (PARTNER II) included registries for the transapical and transaortic delivery of the SAPIEN XT valve. These registries include the following:

- NR1: Inoperable Transapical (TA) Registry – transapical delivery of the 23 mm or 26 mm SAPIEN XT valve.
- NR3: Registry for Transcatheter Heart Valve in Aortic Surgical Valve Implantation (THV-SV). Patients with failing aortic bioprosthetic surgical valve with a surgical mortality or major morbidity ≥ 50% and meeting the sizing requirements for 23 mm or 26 mm SAPIEN XT valve.
- NR4: Inoperable Transaortic (TAo) Registry – transaortic delivery of the 23 mm or 26 mm SAPIEN XT valve.
- NR6: Inoperable Transapical Registry for the delivery of 29 mm SAPIEN XT valve in patients that did not have eligible transfemoral access.

Following completion of enrollment in the nested registries, the FDA approved continued access enrollment in the nested registries (CANRs).

SOURCE Registry XT:

SOURCE Registry XT is an international multi-center prospective, consecutively enrolled, observational registry. Consecutive patient data have been collected at discharge, 30 days, and 12 months post-implant, and will be collected annually thereafter up to 5 years post-implant.

Results of PARTNER II Cohort B Registries (NR1, NR4 and NR6)

A total of 265 patients were treated in PARTNER II Cohort B Nested Registries 1, 4, and 6. The primary safety and effectiveness endpoint was freedom from all-cause mortality at 1 year. The KM estimate at 30 days involving freedom from all-cause mortality was 92.0 ± 1.7%.

There were 1.9% major strokes, no incidence of endocarditis, 1.5% myocardial infarction, 5.7% major vascular complications, 11.3% disabling bleeding events, 3.0% cardiac intervention, and 4.5% new pacemaker at 30 days.

NYHA went from 3.2 ± 0.61 at baseline to 1.9 ± 0.88 at 30 days. The mean change was -1.3 ± 1.10. Device success was observed in 69.6% of patients (165/237). The mean hospitalization stay was 11.1 ± 8.96 days which included 4.5 ± 7.12 days in the ICU. The mean EOA was 0.7 ± 0.19 cm^2 at baseline and 1.6 ± 0.43 cm^2 at 30 days, and the average mean gradient decreased from 41.2 ± 12.17 mmHg at baseline to 8.6 ± 3.59 mmHg at 30 days. The mean peak gradient decreased from 73.2 ± 21.51 mmHg at baseline to 17.7 ± 7.30 mmHg at 30 days.

Results of SOURCE XT

A total of 2688 patients were enrolled. The vast majority of patients (96%) were treated with either the transapical (TA) or transfemoral (TF) approach. Only a small proportion of patients were treated with transaortic (TAo) or subclavian approaches. The implant approach was 62.7% for TF, 33.3% for TA, 3.76% for TAo and 0.3% for subclavian. The results only include the TF, TA and TAo approaches (n = 2680).

Using K-M event rates at 30 days post implant for the TF, TA/TAo population, 6.2% of patients had died, 3% due to a cardiac death, 3.6% of patients had suffered a stroke, and 6.6% had a major vascular complication. Major/life threatening bleeding had occurred in 14.9% of patients, major bleeding in 10.2%, and renal failure or AKI in 17.8%. Permanent pacemakers were implanted in 9.5% of patients. Using K-M event rates at 1 year post implant for the TF, TA/TAo population, 19.5% of patients had died, 9.5% of these from cardiac death, and 6.3% of patients had suffered a stroke. Major/life-threatening bleeding had occurred in 17.3% of patients, major bleeding in 12%, major vascular complications in 7.2%, renal failure or AKI in 20.5% and 11% of patients had a new pacemaker implanted.

Of the 2688 patients that were enrolled, fifty-seven (57) of these patients had the SAPIEN XT valve implanted into a failing surgical prosthesis. The TF approach was used in 23 patients, and the TA/TAo approach was used in 34 patients. The implanted valve size was 23 mm in 38 patients (66.7%), 26 mm in 14 patients (24.6%), and 29 mm in 5 patients (8.8%).

No deaths, no strokes, no major vascular complications, no life threatening bleedings, one (1) renal failure, and no new permanent pacemakers were reported at 30 days post implant for the TF population. At 1 year post implant, 3 deaths were reported for the TF population.

In the TA/TAo population, 3 deaths, 1 (major) stroke, 2 major vascular complications, 3 life threatening bleedings, and 4 new permanent pacemakers were reported at 30 days. At 1 year post implant, 4 additional deaths, 1 additional (minor) stroke, 1 additional major vascular complication, and 1 additional new permanent pacemaker were reported for the TA/TAo population.

The PARTNER II Cohort B Aortic Valve-in-Valve Registry (NR3/CANR3)

A clinical study was performed to establish a reasonable assurance of safety and effectiveness of transcatheter aortic valve replacement with the Edwards SAPIEN XT valve in patients with a failing surgical bioprosthetic aortic valve (i.e., “TAV-in-SAV”). The study was carried out as a single-arm registry nested (i.e., the PARTNER II Trial), which was designated as “NR3.” NR3 was originally approved for 100 patients and later expanded under a Continued Access Protocol (CAP). Data from the original NR3 cohort and the NR3 CAP (CANR3) cohort were pooled at 30 days and 1 year data was available for the NR3 cohort only.

Patients were treated at 40 investigational sites between June 12, 2012 and December 10, 2013. The database for this PMA supplement reflected data collected through February 26, 2015 and included 199 patients (2 patients withdrew prior to treatment). By the last database extract performed on February 26, 2015, all of these patients were included in the 30-day data analysis, and 97 patients were included in the 1-year analysis.

The NR3 study was a single arm, prospective, observational, descriptive study without formal hypothesis testing. The patients were limited to those who were deemed by a heart team to have a mortality or major morbidity rate of ≥ 50% for replacement of a failing surgical aortic valve and met the sizing requirements for the 23 mm or 26 mm SAPIEN XT valve. The specific sizing requirements were imposed because the 29 mm SAPIEN XT valve was not available when the study was initiated.

Contractors were utilized for analysis and interpretation of the clinical data, including an independent Data Safety Monitoring Board (DSMB) that was instructed to notify the applicant of any safety or compliance issues, a Clinical Event Committee (CEC) that was responsible for adjudicating endpoint-related events reported during the trial per definitions established *a priori*, an Electrocardiography (ECG) Core Lab for independent analysis of rhythm and occurrence of myocardial infarction, and an Echocardiography Core Lab for independent analysis of all echocardiograms.

Results of PARTNER II Cohort B Aortic Valve-in-Valve Registry (NR3/CANR3)

Since identical protocols were used in the pivotal and CAP cohort investigations, data from the two cohorts were pooled.

The “Attempted Implant” population consisted of all screen success patients for whom the index procedure was started. The “Valve Implant” population consisted of those patients for whom the valve implant process was completed. A total of 199 patients were screened for study participation. Two

patients withdrew consent prior to treatment; therefore, there were 197 “Attempted Implant” patients. Two “Attempted Implant” patients were excluded from the “Valve Implant” population, because in one patient, intra-procedural TEE demonstrated a low transvalvular jet velocity (2.6 m/s) and gradient of 24 mmHg which did not meet the inclusion criteria, and in the other patient, the procedure was aborted due to inability to place the purse string sutures for transapical access. The patient disposition is summarized in Table 12.

The demographics of the pooled study population are summarized in the Table 13. The mean age was 78.5 years, and 60.4% were male. A high proportion of patients had significant comorbidities, frailty, and prior cardiac interventions. The mean STS score was 9.7, and 95.4% of all patients were in NYHA classes III or IV.

Table 14 provides a summary of the failed surgical valves treated, which consisted of 94.4% bioprosthesis, 4.6% homografts, and 1.0% other valve types. Aortic stenosis was the predominant cause of prosthetic failure (54.2%), followed by mixed lesion (23.4%) and insufficiency/regurgitation (22.4%).

The primary endpoint of all-cause mortality, all stroke, moderate or severe obstruction, or moderate or severe paravalvular leak was 16.9% at 30 days and 38.0% at 1 year, as shown in Table 15.

No unanticipated adverse device effects (UADEs) were reported throughout the trial. Three explants have been reported to date; one explant occurred at autopsy, and two during surgical aortic valve replacement due to severe aortic insufficiency on postoperative day 5 and day 18, respectively. No CEC adjudicated endocarditis was reported.

The key safety outcomes adjudicated by the CEC for this study are presented in Table 16 through Table 18.

Valve hemodynamics as assessed by echocardiography is summarized in Table 19 and Figure 11 through Figure 15. The mean DVI increased from 0.27 ± 0.10 at baseline to 0.37 ± 0.09 at 30 days and 0.39 ± 0.11 at 1 year. The mean gradient decreased from 36.1 ± 16.38 mmHg at baseline to 17.4 ± 7.37 mmHg at 30 days, which was maintained at 1 year. The mean peak gradient decreased from 65.0 ± 26.76 mmHg at baseline to 32.7 ± 12.90 mmHg at 30 days, which was maintained at 1 year. Moderate/severe aortic regurgitation was present in 43.7% of subjects at baseline, which decreased to 2.5% at 30 days and 1.9% at 1 year. Moderate/severe paravalvular leak was present in 6.8% of subjects at baseline, 2.5% at 30 days, and 1.9% at 1 year.

It is important to note that although mean and peak gradients were significantly reduced as compared to baseline for the “TAV-in-SAV” procedure, the residual mean and peak gradients were numerically higher than those observed for TAVR procedures performed for native valve stenosis.

The NYHA class by visit is shown in Figure 16. About 89% of subjects were in NYHA I/II at 30 days and 84% at 1 year as compared to 5% at baseline.

The mean improvement in 6MWD among the Attempted Implant population was 49.8 ± 169.9 meters from baseline to 30 days and 86.1 ± 142.0 meters from baseline to 1 year.

The mean hospitalization stay among the Attempted Implant population was 7.9 ± 7.0 days, which included 2.9 ± 5.0 days in the ICU.

The QoL at different time points as measured by the Kansas City Cardiomyopathy Questionnaire (KCCQ) clinical summary score is shown in Figure 17. The mean KCCQ summary score among the Attempted Implant population improved from 45.5 ± 21.8 at baseline to 68.0 ± 22.0 at 30 days and 70.4 at 1 year.

Device success was defined as successful vascular access, delivery and deployment and retrieval of delivery system; correct positioning, intended performance (aortic valve area > 1.2 cm^2 and mean aortic valve gradient < 20 mmHg or peak velocity < 3 m/s, without moderate or severe prosthetic valve aortic regurgitation. It was achieved in 61.5% of patients. In the vast majority of device failure subjects, the failure was due to unintended performance of the valve; specifically, mean gradient ≥ 20 mmHg or peak velocity ≥ 3 m/s was observed in 62 cases and moderate/severe aortic regurgitation in 5 cases.

PARTNER II Cohort B Registries Clinical Data

Table 6:
Cohort B (Inoperable)
Baseline Characteristics and Echocardiographic Findings for NR1, NR4 and NR6 (AT Population)*

	SAPIEN XT Valve (TA/TAo)
Characteristic	(N = 265)
Age - yr	82.0 ± 7.79
Male sex — no. (%)	141/265 (53.2%)
STS score†	10.3 ± 5.51
Logistic EuroSCORE‡	13.2 ± 11.96
NYHA class — no. (%):	
I/II	24/264 (9.1%)
III/IV	240/264 (90.9%)
Coronary artery disease — no./total no. (%)	194/265 (73.2%)
Previous myocardial infarction — no./total no. (%)	56/265 (21.1%)
Previous intervention — no./total no. (%)	
CABG	118/265 (44.5%)
PCI	107/265 (40.4%)
Balloon aortic valvuloplasty	72/265 (27.2%)
Peripheral vascular disease — no./total no. (%)	150/265 (56.6%)
COPD — no./total no. (%):	
Any	101/265 (38.1%)
Oxygen-dependent	41/265 (15.5%)
Creatinine > 2 mg/dL (177 µmol/liter) — no./total no. (%)	28/265 (10.6%)
Atrial fibrillation — no./total no. (%)	95/265 (35.8%)
Permanent pacemaker — no./total no. (%)	43/265 (16.2%)
Pulmonary hypertension — no./total no. (%)	34/254 (13.4%)
Frailty§ — no./total no. (%)	97/254 (38.2%)
Extensively calcified aorta — no./total no. (%)	42/254 (16.5%)
Chest-wall deformity — no./total no. (%)	6/254 (2.4%)
Liver disease — no./total no. (%)	9/265 (3.4%)
Echocardiographic findings	
Aortic-valve area — cm^2	0.7 ± 0.19
Mean aortic-valve gradient — mmHg	41.2 ± 12.17
Mean LVEF — %	52.5 ± 13.37
Moderate or severe mitral regurgitation** — no./total no. (%)	70/232 (30.2%)

* Plus–minus values are mean ± SD. To convert the value for creatinine to micromoles per liter, multiply by 88.4. AT denotes As Treated population, CABG denotes coronary-artery bypass grafting, COPD chronic obstructive pulmonary disease, LVEF left ventricular ejection fraction, NYHA New York Heart Association, PCI percutaneous coronary intervention, and TAVR transcatheter aortic-valve implantation.

† The Society of Thoracic Surgeons (STS) score measures patient risk at the time of cardiovascular surgery on a scale that ranges from 0% to 100%, with higher numbers indicating greater risk. An STS score higher than 10% indicates very high surgical risk.

‡ The logistic European System for Cardiac Operative Risk Evaluation (EuroSCORE), which measures patient risk at the time of cardiovascular surgery, is calculated with the use of a logistic-regression equation. Scores range from 0% to 100%, with higher scores indicating greater risk. A logistic EuroSCORE higher than 20% indicates very high surgical risk.

§ Frailty was determined by the surgeons according to prespecified criteria.

** Moderate or severe mitral regurgitation was defined as regurgitation of grade 3+ or higher.

Table 7:
Cohort B (Inoperable) Clinical Outcomes at 30 days for NR1, NR4 and NR6 (AT Population)*

Outcome[a]	SAPIEN XT Valve (N = 265)
Death from any cause	21/265 (7.9%)
Major Stroke	5/265 (1.9%)
Repeat hospitalization[b]	8/265 (3.0%)
Death from any cause or major stroke or repeat hospitalization	31/265 (11.7%)
Myocardial Infarction	4/265 (1.5%)
Major Vascular Complications	15/265 (5.7%)
Renal Failure[c]	7/265 (2.6%)
Disabling Bleeding Event[d]	30/265 (11.3%)
Cardiac Reintervention[e]	8/265 (3.0%)
Endocarditis	0/265 (0.0%)
New Atrial Fibrillation[f]	9/167 (5.4%)
New pacemaker	12/265 (4.5%)

* AT = As Treated, NA = not applicable, TAVR = transcatheter aortic valve replacement. Data presented as n/N (%) of patients.
a. CEC adjudicated.
b. Repeat hospitalizations were included if they were due to aortic stenosis or complications of the valve procedure (e.g., TAVR).
c. Renal failure is defined as stage III acute kidney injury: Increase in serum creatinine to ≥ 300% (3 x increase compared with baseline) or serum creatinine of ≥ 4 mg/dl (≥ 354 µmol/L) with an acute increase of at least 0.5 mg/dl (44 µmol/L).
d. Disabling bleeding: Fatal bleeding OR bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, or pericardial necessitating pericardiocentesis, or intramuscular with compartment syndrome OR bleeding causing hypovolemic shock or severe hypotension requiring vasopressors or surgery OR overt source of bleeding with drop in hemoglobin of ≥ 5 g/dL or whole blood of packed red blood cells (RBC) transfusion ≥ 4 units.
e. Cardiac reintervention includes any intervention that repairs, alters or replaces a previously operated valve OR balloon aortic valvuloplasty OR Surgical aortic valve replacement OR valve in valve
f. Based on 167 patients at 30 days.

Table 8:
Conduction Disturbance Requiring Pacemaker to 30 Days for NR1, NR4 and NR6 (CEC Adjudicated) (AT Population)

	SAPIEN XT Valve (TA/TAo) (N = 265)	
Event	**Events**	**Patients with Event**
New Permanent Pacemaker- All Patients[1]		
0-30 Days	12	12/265 (4.5%)
New Permanent Pacemaker – Patients without pre-procedural pacemaker[2]		
0-30 Days	12	12/222 (5.4%)

[1] Subjects with pacemaker or ICD at baseline are included (all patients included in denominator).
[2] Subjects with pacemaker or ICD at baseline are excluded (patients with baseline pacemaker/ICD subtracted from denominator).
Note: The patients who received a new pacemaker in both rows are the same patients. The only difference is the denominators.

Figure 3:
All-Cause Mortality, Major Stroke or Re-Hospitalization to 30 Days, NR1, NR4, and NR6 – TA/TAo (AT Population)

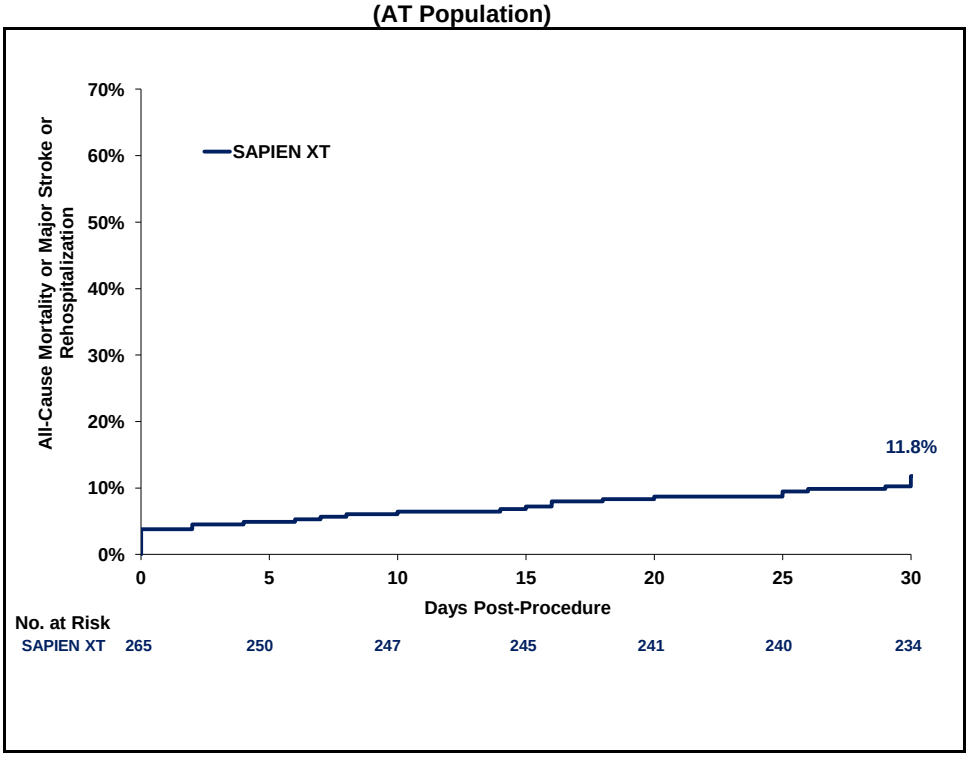


Figure 4:
All-Cause Mortality to 30 Days, NR1, NR4, and NR6 – TA/TAo

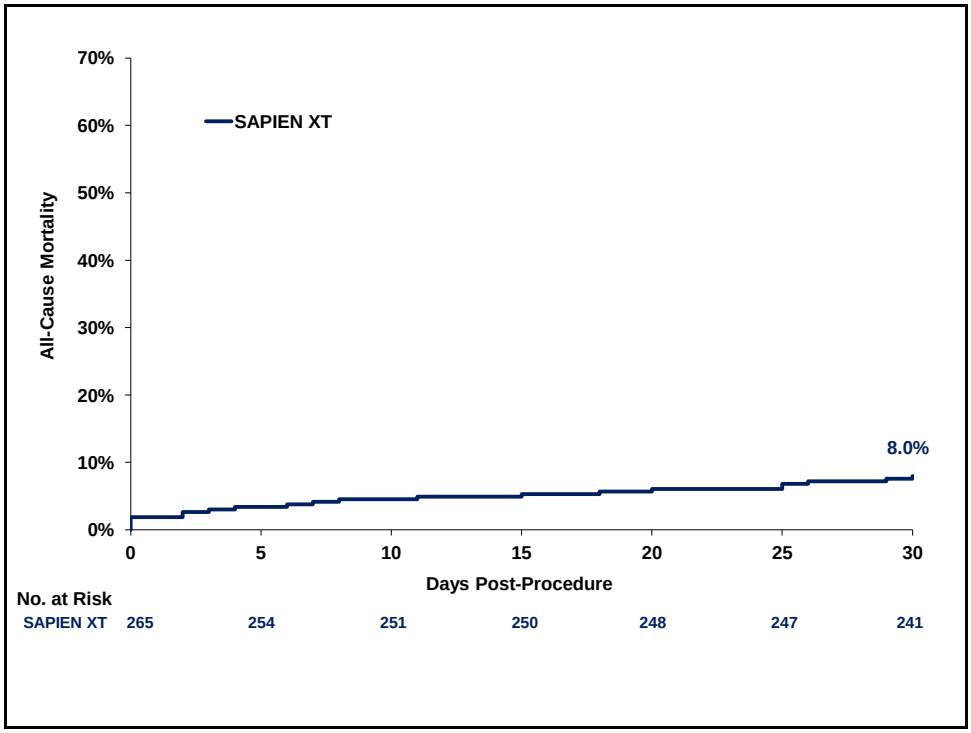


Figure 5:
Major Stroke at 30 Days, NR1, NR4, and NR6 – TA/TAo (AT Population)

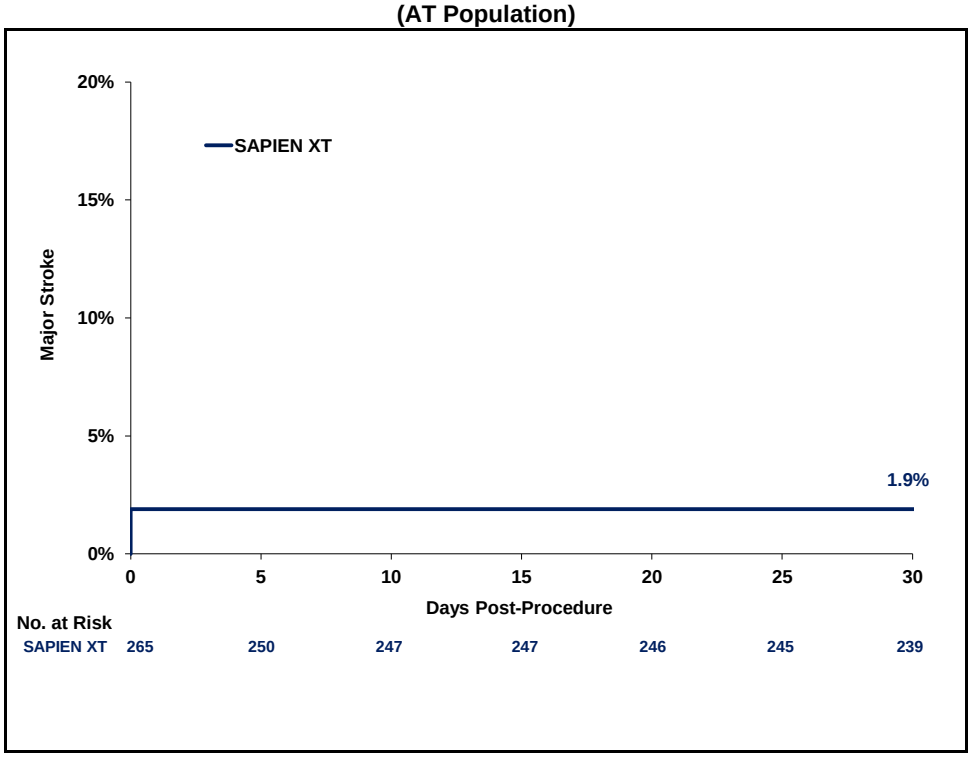


Figure 6:
Re-Hospitalization at 30 Days, NR1, NR4, and NR6 –TA/TAo
(AT Population)

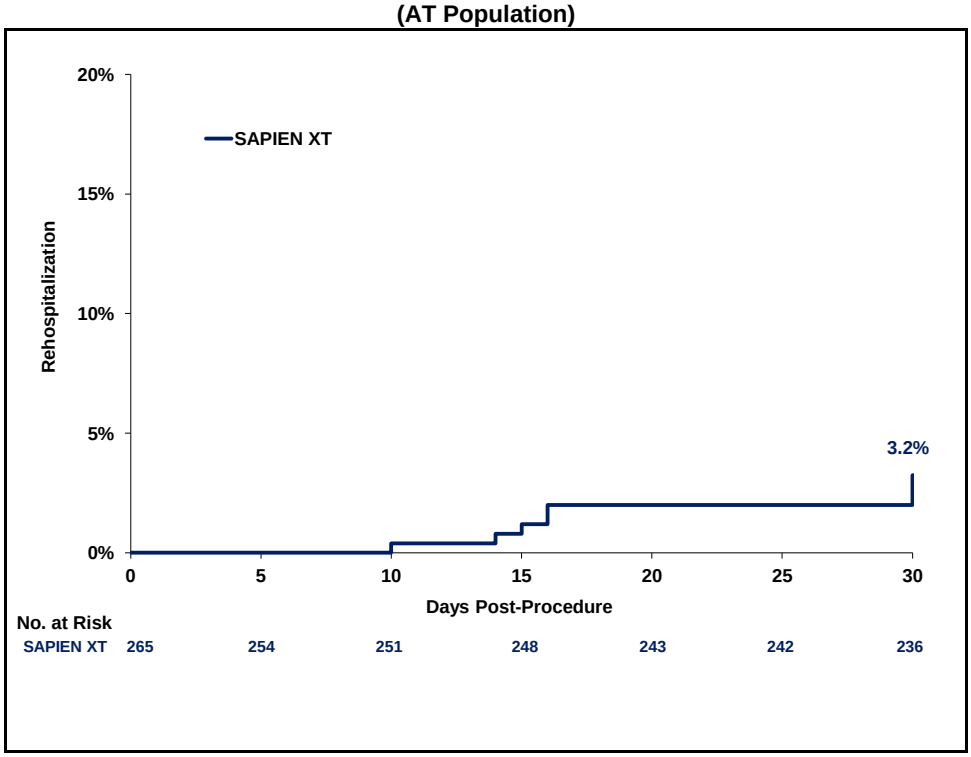


Figure 7:
Effective Orifice Area, NR1, NR4, and NR6 – TA/TAo
(Valve Implant Population)

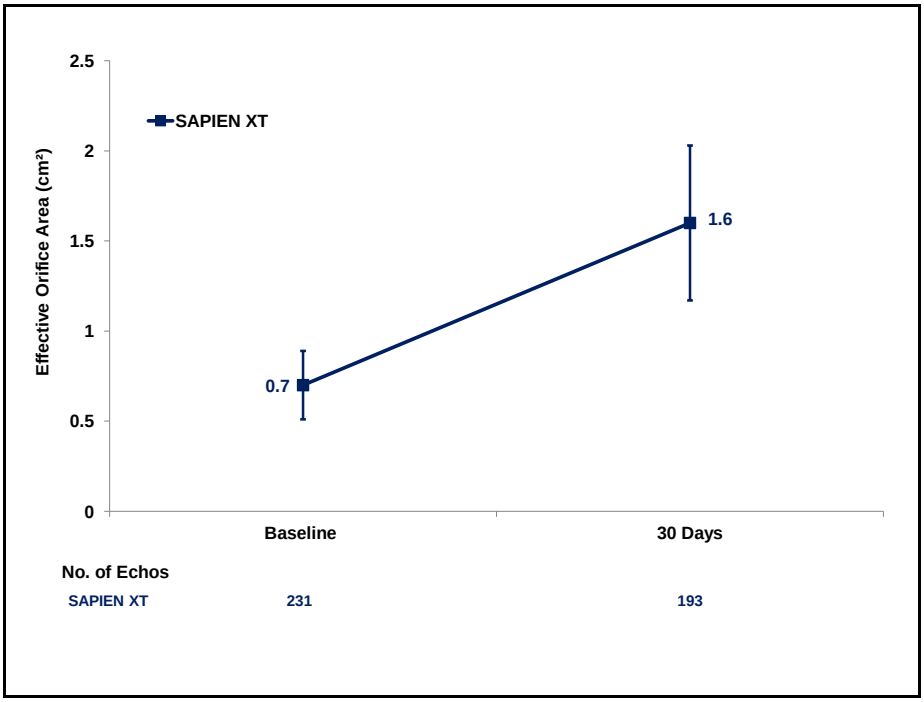


Figure 8:
Mean Gradient, NR1, NR4, and NR6 – TA/TAo
(Valve Implant Population)

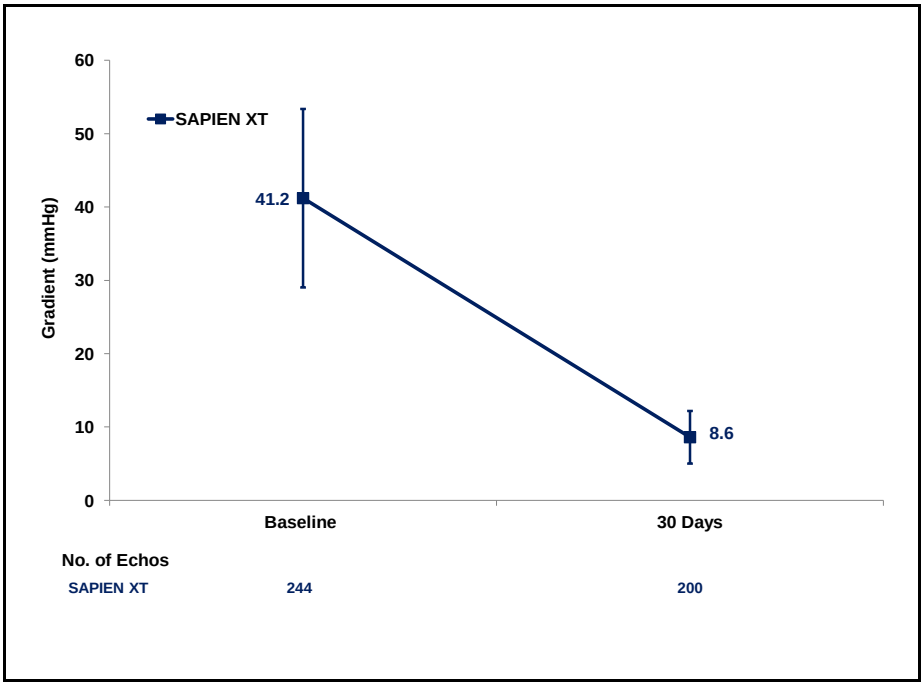


Table 9: NYHA Functional Class By Visit for NR1, NR4 and NR6 (AT Population)					
	SAPIEN XT Valve (N = 265)				
Visit	I	II	III	IV	Total
Baseline	1	23	158	82	264
30 Days	84	88	45	12	229

Figure 9:
NYHA Class by Visit, NR1, NR4, and NR6 – TA/TAo
(Intent-to-Treat Population)

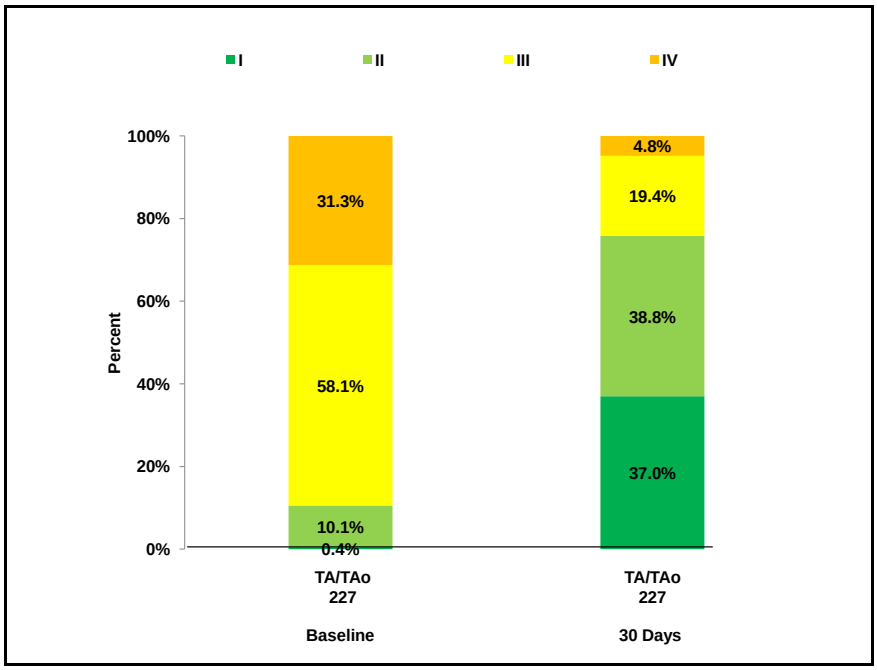
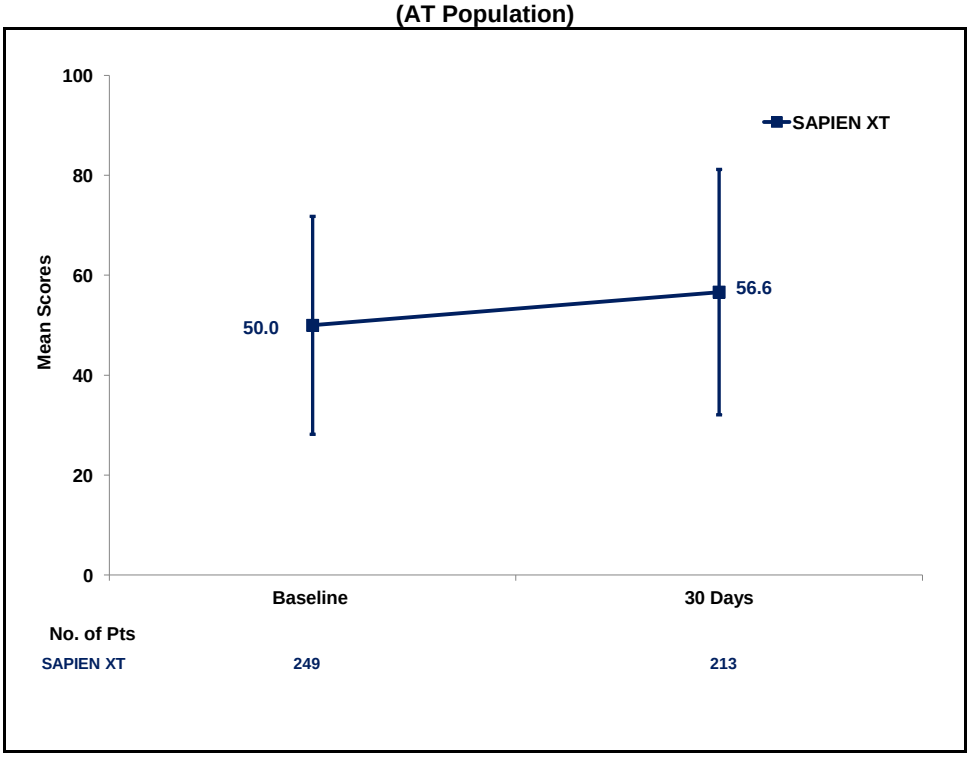


Figure 10:
KCCQ Clinical Summary Score, NR1, NR4, and NR6 – TA/TAo
(AT Population)



SOURCE XT Clinical Data

Table 10:
SOURCE XT (High Risk) Baseline Characteristics of the Patients and Echocardiographic Findings (AT Population)*

	Transfemoral	TA/TAo Pooled
Characteristic	(N = 1685)	(N = 995)
Age - yr	82.0 ± 6.5	80.3 ± 6.5
Male sex — no. (%)	600 / 1685 (35.6%)	536 / 995 (53.9%)
STS score†	8.0 ± 6.8	7.9 ± 6.2
Logistic EuroSCORE‡	19.8 ± 11.6	21.6 ± 13.7
NYHA class		
I/II — no./total no. (%)	377 / 1676 (22.5%)	242 / 992 (24.4%)
III/IV — no./total no. (%)	1299 / 1676 (77.5%)	750 / 992 (75.6%)
Coronary artery disease — no./total no. (%)	667 / 1685 (39.6%)	518 / 995 (52.1%)
Previous myocardial infarction — no./total no. (%)	205 / 1685 (12.2%)	197 / 995 (19.8%)
Previous intervention		
CABG — no./total no. (%)	204 / 1685 (12.1%)	226 / 995 (22.7%)
PCI — no./total no. (%)	460 / 1685 (27.3%)	355 / 995 (35.7%)
Balloon aortic valvuloplasty — no./total no. (%)	128 / 1685 (7.6%)	66 / 995 (6.6%)
Cerebral vascular disease — no./total no. (%)	191 / 1685 (11.3%)	143 / 995 (14.4%)
Peripheral vascular disease — no./total no. (%)	248 / 1684 (14.7%)	320 / 995 (32.2%)
COPD		
Pulmonary Artery Disease COPD — no./total no. (%)	327 / 1684 (19.4%)	218 / 995 (21.9%)
Pulmonary Artery Disease Oxygen Dependent — no./total no. (%)	31 / 1684 (1.8%)	11 / 995 (1.1%)
Creatinine > 2 mg/dL (177 µmol/liter) — no./total no. (%)	104 / 1681 (6.2%)	114 / 994 (11.5%)
Atrial fibrillation — no./total no.	395 / 1678 (23.5%)	289 / 990 (29.2%)
Permanent pacemaker — no./total no. (%)	170 / 1685 (10.1%)	134 / 995 (13.5%)
Pulmonary hypertension — no./total no. (%)	440 / 1684 (26.1%)	204 / 995 (20.5%)
Frailty§ — no./total no. (%)	896 / 932 (96.1%)	548 / 579 (94.6%)
Extensively calcified aorta — no./total no. (%)	71 / 1684 (4.2%)	103 / 995 (10.4%)
Chest-wall deformity — no./total no. (%)	18 / 1684 (1.1%)	6 / 995 (0.6%)
Liver disease — no./total no. (%)	52 / 1685 (3.1%)	27 / 995 (2.7%)
Echocardiographic findings		
Aortic-valve area — cm^2	0.7 ± 0.21	0.7 ± 0.21
Mean aortic-valve gradient — mmHg	49.2 ± 16.54	45.0 ± 15.43
Mean LVEF — %	55.1 ± 12.48	53.2 ± 12.50
Moderate or severe mitral regurgitation** — no./total no. (%)	345 / 1633 (21.1%)	174 / 976 (17.8%)

* Plus–minus values are means ± SD. To convert the value for creatinine to micromoles per liter, multiply by 88.4. AT denotes as treated population, CABG denotes coronary-artery bypass grafting, COPD chronic obstructive pulmonary disease, LVEF left ventricular ejection fraction, NYHA New York Heart Association, PCI percutaneous coronary intervention, and TAVR transcatheter aortic-valve implantation.
† The Society of Thoracic Surgeons (STS) score measures patient risk at the time of cardiovascular surgery on a scale that ranges from 0% to 100%, with higher numbers indicating greater risk. An STS score higher than 10% indicates very high surgical risk.
‡ The logistic European System for Cardiac Operative Risk Evaluation (EuroSCORE), which measures patient risk at the time of cardiovascular surgery, is calculated with the use of a logistic-regression equation. Scores range from 0% to 100%, with higher scores indicating greater risk. A logistic EuroSCORE higher than 20% indicates very high surgical risk.
§ Frailty was determined by the surgeons according to prespecified criteria.
** Moderate or severe mitral regurgitation was defined as regurgitation of grade 3+ or higher.

Table 11:
SOURCE XT (High Risk) Clinical Outcomes[a] at 30 days and 1 year (AT Population)*

	30 Days		1-Year	
	Transfemoral	**TA/TAo**	**Transfemoral**	**TA/TAo**
Outcome	**(N = 1685)**	**(N = 995)**	**(N = 1685)**	**(N = 995)**
All Cause Death	71 (4.2%)	96 (9.7%)	248 (15.0%)	266 (27.0%)
Cardiac Death	28 (1.7%)	51 (5.2%)	106 (6.7%)	132 (14.4%)
Stroke				
All Stroke	56 (3.4%)	39 (4.1%)	90 (5.6%)	66 (7.6%)
Major Stroke	34 (2.0%)	27 (2.8%)	55 (3.5%)	44 (5.0%)
Repeat hospitalization[b]	80 (4.9%)	83 (9.0%)	396 (25.5%)	314 (36.7%)
Myocardial Infarction	7 (0.4%)	9 (0.9%)	23 (1.5%)	21 (2.5%)
Major Vascular Complications	132 (7.9%)	43 (4.4%)	139 (8.3%)	52 (5.5%)
Renal Failure[d]/AKI	197 (11.9%)	270 (28.0%)	240 (14.7%)	292 (30.6%)
Life-threatening bleeding[c]	63 (3.8%)	84 (8.6%)	74 (4.5%)	101 (10.6%)
Endocarditis	2 (0.1%)	2 (0.2%)	15 (1.0%)	10 (1.2%)
New Atrial Fibrillation	54 (3.3%)	83 (8.8%)	89 (5.6%)	109 (12.0%)
New pacemaker	145 (8.7%)	105 (10.8%)	165 (10.0%)	120 (12.7%)

* AT = As Treated, TAVR = transcatheter aortic valve replacement. Data presented as n (%) of patients where % is the Kaplan-Meier event rate at 30-days and 1-year respectively.
a. CEC adjudicated
b. Repeat hospitalizations were included if they were due to aortic stenosis or complications of the valve procedure (e.g., TAVR).
c. Disabling bleeding: Fatal bleeding OR bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, or pericardial necessitating pericardiocentesis, or intramuscular with compartment syndrome OR bleeding causing hypovolemic shock or severe hypotension requiring vasopressors or surgery OR overt source of bleeding with drop in hemoglobin of ≥ 5 g/dL or whole blood of packed red blood cells (RBC) transfusion ≥ 4 units
d. Renal failure is defined as stage III acute kidney injury: Increase in serum creatinine to ≥ 300% (3 x increase compared with baseline) or serum creatinine of ≥ 4 mg/dL (≥ 354 µmol/L) with an acute increase of at least 0.5 mg/dL (44 µmol/L)

PARTNER II Nested Registry 3/ Continued Access Nested Registry 3 (NR3/CANR3) (Aortic Valve-in-Valve)

Table 12:
Patient Disposition

	Attempted Implant[1]	Valve Implant[2]
Number of Patients	197	195

[1]Attempted Implant: All screen success patients for whom the Index Procedure was started. Patients were analyzed according to the valve used in the initial implant attempt.
[2] Valve Implant: This population was a subset of the Attempted Implant group, consisting of those patients for whom the valve implant process was completed.

Table 13: Demographic and Baseline Characteristics Attempted Implant Population	
Characteristic	**Results[1] (N = 197)**
Age – yr	78.5 ± 11.00[1]
Male sex	119/197 (60.4%)
STS score	9.7 ± 5.09
New York Heart Association (NYHA) class	
I/II	9/197 (4.6%)
III/IV	188/197 (95.4%)
Coronary artery disease	139/197 (70.6%)
Previous myocardial infarction	25/197 (12.7%)
Previous intervention	
Coronary artery bypass grafting (CABG)	97/197 (49.2%)
Percutaneous coronary intervention (PCI)	39/197 (19.8%)
Prior aortic valvuloplasty	17/197 (8.6%)
Cerebral vascular accident (CVA)	29/197 (14.7%)
Peripheral vascular disease	49/197 (24.9%)
Chronic obstructive pulmonary disease (COPD)	
Any	65/197 (33.0%)
Oxygen-dependent	14/197 (7.1%)
Creatinine > 2 mg/dL (177 µmol/liter)[2]	25/197 (12.7%)
Atrial fibrillation	98/197 (49.7%)
Permanent pacemaker	51/197 (25.9%)
Pulmonary hypertension	26/197 (13.2%)
Frailty[3]	65/197 (33.0%)
Extensively calcified aorta	12/197 (6.1%)
Chest-wall deformity	4/197 (2.0%)
Liver disease	14/197 (7.1%)
Reason for Valve Replacement	
Mixed Lesion	45/192 (23.4%)
Insufficiency/regurgitation Only	43/192 (22.4%)
Stenosis Only	104/192 (54.2%)
Echocardiographic findings	
Doppler Velocity Index (DVI)[4]	0.27 ± 0.10
Mean aortic-valve gradient — mmHg	35.9 ± 16.42
Mean left ventricular ejection fraction (LVEF) — %	49.8 ± 13.87
Moderate or severe mitral regurgitation[5]	62/171 (36.3%)

[1]Quantitative data are expressed as mean ± SD (n). Categorical data are expressed as no./total no. (%).
[2]To convert the value for creatinine to micromoles per liter, multiply by 88.4.
[3]Frailty was determined by the surgeons according to pre-specified criteria.
[4]DVI is a flow-dependent measure of orifice stenosis. A DVI < 0.25 suggests significant stenosis.
[5]Moderate or severe mitral regurgitation was defined as regurgitation of grade 3+ or higher.

Table 14:
Summary of Failed Bioprosthetic Surgical Valves
Attempted Implant Population

	Results[1] (N = 197)
Type of Failed Surgical Valve	
Bioprosthesis	184/195 (94.4%)
Homograft	9/195 (4.6%)
Other[2]	2/195 (1.0%)
Reason for Valve Replacement	
Mixed Lesion	45/192 (23.4%)
Insufficiency/regurgitation Only	43/192 (22.4%)
Stenosis Only	104/192 (54.2%)

[1] Categorical data are expressed as no./total no. (%).
[2] Other includes an unidentified manufactured tissue valve and a St. Jude mechanical composite.

Table 15:
All-Cause Mortality, All Stroke, Moderate or Severe Obstruction, or Moderate or Severe Paravalvular Leak
Valve Implant Population

	30 Days (N = 195)		1 Year (N = 96)	
Events	**Patients with Event**	**95% Confidence Interval[3]**	**Patients with Event**	**95% Confidence Interval**
Composite Event[1]	28/166 (16.9%)	[11.5%, 23.4%]	27/71 (38.0%)	[26.8%, 50.3%]
All-Cause Mortality	8/195 (4.1%)	[1.8%, 7.9%]	19/96 (19.8%)	[12.4%, 29.2%]
All Stroke	5/195 (2.6%)	[0.8%, 5.9%]	3/96 (3.1%)	[0.6%, 8.9%]
Moderate or Severe Obstruction[2]	12/169 (7.1%)	[3.7%, 12.1%]	6/54 (11.1%)	[4.2%, 22.6%]
Moderate or Severe PV Leak	4/162 (2.5%)	[0.7%, 6.2%]	1/53 (1.9%)	[0.0%, 10.1%]

[1] Composite of all-cause mortality, all stroke, moderate or severe obstruction, moderate or severe paravalvular leak. Mortality and stroke are calculated at 30 days. The moderate or severe obstruction and paravalvular leak use the Echo core lab's determination at the 30-day follow-up visit.
[2] Doppler velocity index (DVI) < 0.25 per the echo core lab read.
[3] Confidence intervals calculated using exact binomial calculations. The confidence intervals are calculated without multiplicity adjustment. The adjusted confidence intervals could be wider than presented here. As such, confidence intervals are provided to illustrate the variability only and should not be used to draw any statistical conclusion.

Table 16:
CEC Adjudicated Adverse Events
Attempted Implant Population

Adverse Events	Rate (no./total no. (%))	
	30 Days (N = 197)	1 Year (N = 97)
Death[1]		
From any cause	8/197 (4.1%)	19/97 (19.6%)
From cardiovascular cause	7/197 (3.6%)	15/97 (15.5%)
Major Stroke	5/197 (2.5%)	3/97 (3.1%)
Myocardial Infarction	5/197 (2.5%)	3/97 (3.1%)
Major Vascular Complications	8/197 (4.1%)	6/97 (6.2%)
Acute Kidney Injury, Stage III[2]	2/197 (1.0%)	N/A
Disabling Bleeding[3]	19/197 (9.6%)	16/97 (16.5%)
Cardiac Reintervention[4]	4/197 (2.0%)	2/97 (2.1%)
Endocarditis	0/197 (0.0%)	0/97 (0.0%)
New Atrial Fibrillation	4/135 (3.0%)	2/45 (4.4%)
New Pacemaker	3/197 (1.5%)	1/97 (1.0%)

[1] Deaths from unknown causes were assumed to be deaths from cardiovascular causes.

[2] Acute kidney injury, stage III is defined as an increase in serum creatinine to ≥ 300% (3 x increase compared with baseline) or serum creatinine of ≥ 4 mg/dL (≥ 354 µmol/L) with an acute increase of at least 0.5 mg/dL (44 µmol/L) within 72 hours of the procedure (per the VARC-1 definition).

[3] Disabling bleeding: Fatal bleeding OR bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, or pericardial necessitating pericardiocentesis, or intramuscular with compartment syndrome OR bleeding causing hypovolemic shock or severe hypotension requiring vasopressors or surgery OR overt source of bleeding with drop in hemoglobin of ≥ 5 g/dL or whole blood of packed red blood cells (RBC) transfusion ≥ 4 units (Life-threatening per VARC-1 definitions).

[4] Cardiac reintervention includes any intervention that repairs, alters or replaces a previously operated valve OR balloon aortic valvuloplasty OR Surgical aortic valve replacement OR valve in valve.

Table 17:
Kaplan-Meier (KM) Event Rate for CEC Adjudicated Major Vascular Complications, Major Stroke, Minor Stroke, TIA, and Acute Kidney Injury
Attempted Implant Population

	30 Days (N = 197)				1 Year (N = 97)			
VARC Event[1]	**Events**	**Patients with Event**	**KM Estimate[2]**	**95% CI[3]**	**Events**	**Patients with Event**	**KM Estimate**	**95% CI**
Major Vascular Complications and/or Major Stroke and/or Minor Stroke and/or TIA and/or Acute Kidney Injury, Stage III	15	14	0.071	(0.043, 0.117)	14	12	0.127	(0.074, 0.213)
Major Vascular Complications	8	8	0.041	(0.021, 0.080)	6	6	0.062	(0.029, 0.134)
Major Stroke	5	5	0.025	(0.011, 0.060)	5	3	0.032	(0.010, 0.096)
Minor Stroke	0	0	0.000	N/A	0	0	0.000	N/A
TIA	0	0	0.000	N/A	1	1	0.013	(0.002, 0.089)
Acute Kidney Injury, Stage III	2	2	0.010	(0.003, 0.040)				

[1] Standardized endpoint definitions for transcatheter aortic valve implantation clinical trials consensus from the Valve Academic Research Consortium (VARC). Events with missing or incomplete onset dates were excluded from the analysis.
[2] Kaplan-Meier estimates used the first event per patient. Events occurring after day 30 and day 365 were not included in the analysis of the 30-day and 1-year results, respectively.
[3] Confidence intervals calculated using Greenwood's formula. The confidence intervals are calculated without multiplicity adjustment. The adjusted confidence intervals could be wider than presented here. As such, confidence intervals are provided to illustrate the variability only and should not be used to draw any statistical conclusion.

Table 18:
Conduction Disturbance Requiring New Permanent Pacemaker
Attempted Implant Population

	30 Days (N = 197)		1 Year (N = 97)	
	Events	**Patients with Event**	**Events**	**Patients with Event**
New Permanent Pacemaker – All Patients[1]	3	3/197 (1.5%)	1	1/97 (1.0%)
New Permanent Pacemaker – Patients without preexisting pacemaker[2]	3	3/146 (2.1%)	1	1/70 (1.4%)

[1] Subjects with pacemaker or ICD at baseline were included (all patients included in denominator).
[2] Subjects with pacemaker or ICD at baseline were excluded (patients with baseline pacemaker/ICD subtracted from denominator).
Note: The patient who received a new pacemaker in both rows is the same patient. The only difference is the denominators.

Table 19:
Valve Hemodynamics Measured by Echocardiography
Valve Implant Population

	Baseline (N = 195)	Discharge (N = 195)	30 Days (N = 195)	1 Year (N = 96)
Doppler Velocity Index - mean ± SD (n)				
All Valve Sizes	0.27 ± 0.10 (173)	0.37 ± 0.09 (161)	0.37 ± 0.09 (169)	0.39 ± 0.11 (54)
23 mm (N = 140)	0.26 ± 0.09 (123)	0.36 ± 0.10 (114)	0.36 ± 0.09 (118)	0.38 ± 0.11 (38)
26 mm (N = 55)	0.29 ± 0.13 (50)	0.40 ± 0.08 (47)	0.41 ± 0.11 (51)	0.44 ± 0.11 (16)
Mean Gradient (mmHg) - mean ± SD (n)				
All Valve Sizes	36.1 ± 16.38 (179)	18.2 ± 7.79 (168)	17.4 ± 7.37 (176)	17.3 ± 8.76 (56)
23 mm (N = 140)	37.2 ± 16.86 (129)	19.5 ± 8.19 (120)	19.0 ± 7.64 (125)	18.8 ± 9.32 (40)
26 mm (N = 55)	33.2 ± 14.84 (50)	15.0 ± 5.51 (48)	13.4 ± 4.79 (51)	13.7 ± 5.91 (16)
Peak Gradient (mmHg) - mean ± SD (n)				
All Valve Sizes	65.0 ± 26.76 (179)	34.3 ± 13.67 (168)	32.7 ± 12.90 (176)	32.8 ± 15.58 (56)
23 mm (N = 140)	66.9 ± 27.49 (129)	36.5 ± 14.36 (120)	35.4 ± 13.30 (125)	35.2 ± 16.80 (40)
26 mm (N = 55)	60.1 ± 24.34 (50)	29.0 ± 10.05 (48)	26.2 ± 9.09 (51)	26.7 ± 10.04 (16)
Total Aortic Regurgitation - no./total no. (%)				
All Valve Sizes				
None	22/174 (12.6%)	74/164 (45.1%)	86/163 (52.8%)	34/53 (64.2%)
Trace	34/174 (19.5%)	64/164 (39.0%)	58/163 (35.6%)	15/53 (28.3%)
Mild	42/174 (24.1%)	21/164 (12.8%)	15/163 (9.2%)	3/53 (5.7%)
Moderate	47/174 (27.0%)	4/164 (2.4%)	3/163 (1.8%)	1/53 (1.9%)
Severe	29/174 (16.7%)	1/164 (0.6%)	1/163 (0.6%)	0/53 (0.0%)
23 mm				
None	21/124 (16.9%)	55/116 (47.4%)	63/115 (54.8%)	23/37 (62.2%)
Trace	29/124 (23.4%)	43/116 (37.1%)	39/115 (33.9%)	12/37 (32.4%)
Mild	32/124 (25.8%)	14/116 (12.1%)	10/115 (8.7%)	2/37 (5.4%)
Moderate	29/124 (23.4%)	3/116 (2.6%)	2/115 (1.7%)	0/37 (0.0%)
Severe	13/124 (10.5%)	1/116 (0.9%)	1/115 (0.9%)	0/37 (0.0%)
26 mm				
None	1/50 (2.0%)	19/48 (39.6%)	23/48 (47.9%)	11/16 (68.8%)
Trace	5/50 (10.0%)	21/48 (43.8%)	19/48 (39.6%)	3/16 (18.8%)
Mild	10/50 (20.0%)	7/48 (14.6%)	5/48 (10.4%)	1/16 (6.3%)
Moderate	18/50 (36.0%)	1/48 (2.1%)	1/48 (2.1%)	1/16 (6.3%)
Severe	16/50 (32.0%)	0/48 (0.0%)	0/48 (0.0%)	0/16 (0.0%)
Paravalvular Leak - no./total no. (%)				
All Valve Sizes				
None	121/162 (74.7%)	76/164 (46.3%)	91/162 (56.2%)	35/53 (66.0%)
Trace	18/162 (11.1%)	66/164 (40.2%)	56/162 (34.6%)	15/53 (28.3%)
Mild	12/162 (7.4%)	17/164 (10.4%)	11/162 (6.8%)	2/53 (3.8%)

Table 19: Valve Hemodynamics Measured by Echocardiography Valve Implant Population				
	Baseline (N = 195)	**Discharge (N = 195)**	**30 Days (N = 195)**	**1 Year (N = 96)**
Moderate	8/162 (4.9%)	4/164 (2.4%)	3/162 (1.9%)	1/53 (1.9%)
Severe	3/162 (1.9%)	1/164 (0.6%)	1/162 (0.6%)	0/53 (0.0%)
23 mm				
None	92/121 (76.0%)	55/116 (47.4%)	68/114 (59.6%)	24/37 (64.9%)
Trace	15/121 (12.4%)	47/116 (40.5%)	36/114 (31.6%)	11/37 (29.7%)
Mild	10/121 (8.3%)	10/116 (8.6%)	7/114 (6.1%)	2/37 (5.4%)
Moderate	2/121 (1.7%)	3/116 (2.6%)	2/114 (1.8%)	0/37 (0.0%)
Severe	2/121 (1.7%)	1/116 (0.9%)	1/114 (0.9%)	0/37 (0.0%)
26 mm				
None	29/41 (70.7%)	21/48 (43.8%)	23/48 (47.9%)	11/16 (68.8%)
Trace	3/41 (7.3%)	19/48 (39.6%)	20/48 (41.7%)	4/16 (25.0%)
Mild	2/41 (4.9%)	7/48 (14.6%)	4/48 (8.3%)	0/16 (0.0%)
Moderate	6/41 (14.6%)	1/48 (2.1%)	1/48 (2.1%)	1/16 (6.3%)
Severe	1/41 (2.4%)	0/48 (0.0%)	0/48 (0.0%)	0/16 (0.0%)

Figure 11:
Doppler Velocity Index by Visit
Valve Implant Population

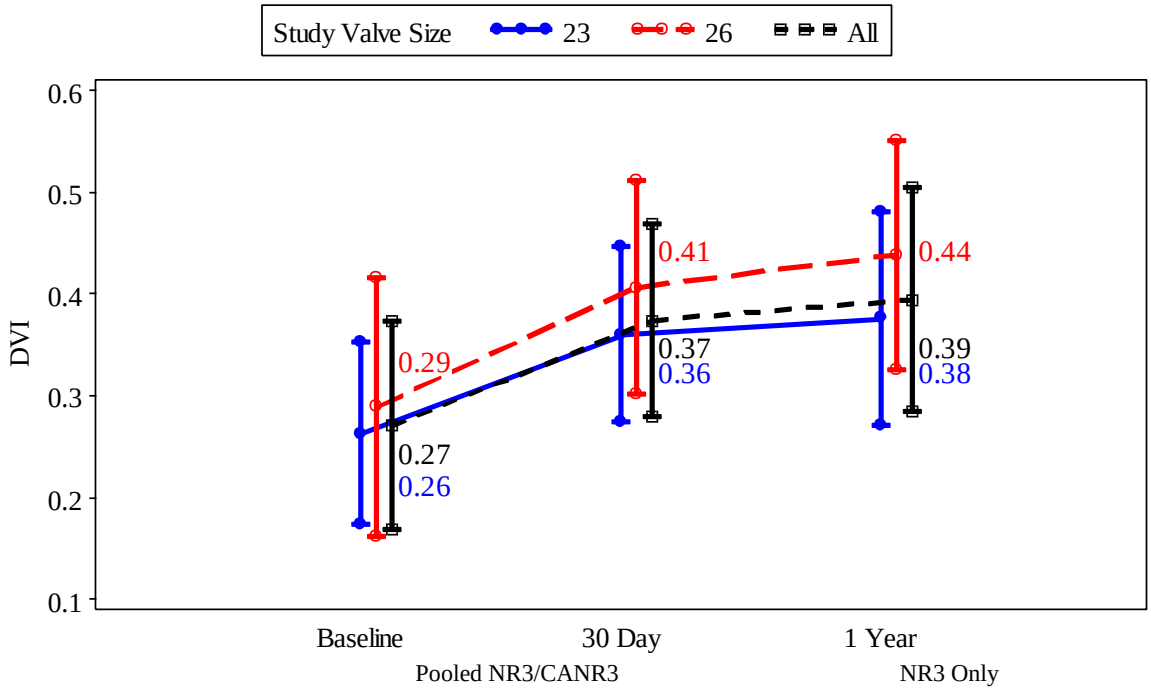


Figure 12:
Mean Gradient by Visit
Valve Implant Population

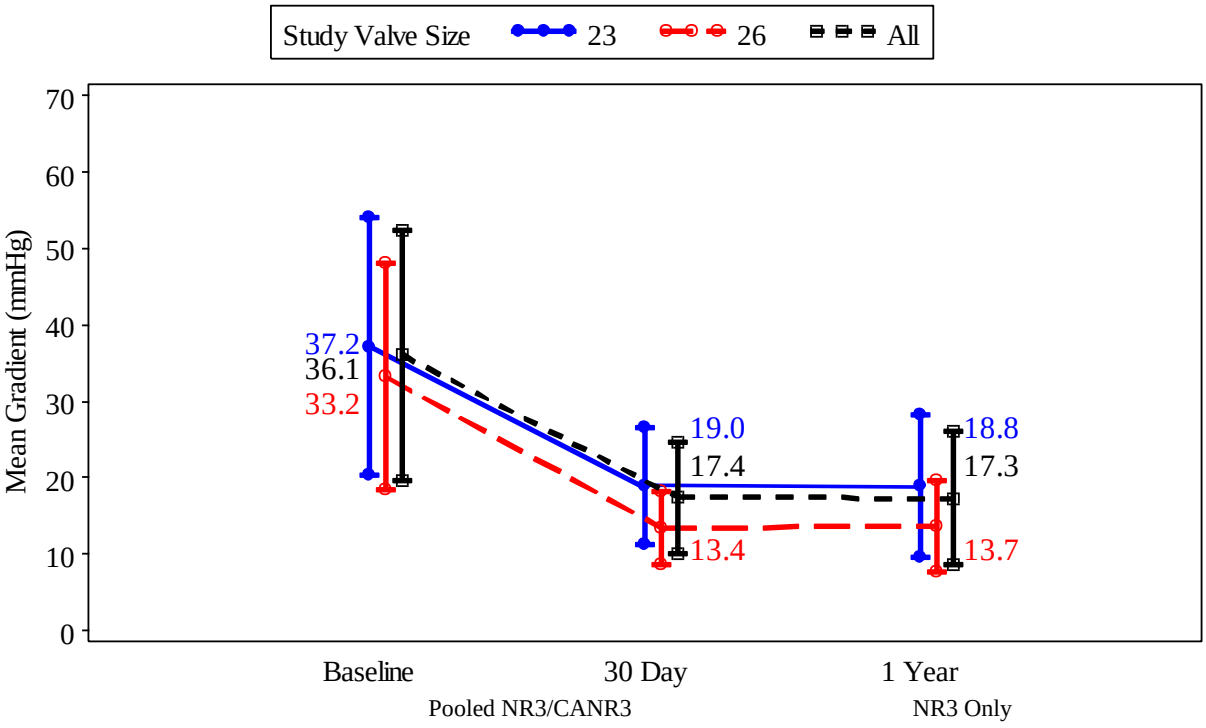


Figure 13:
Peak Gradient by Visit
Valve Implant Population

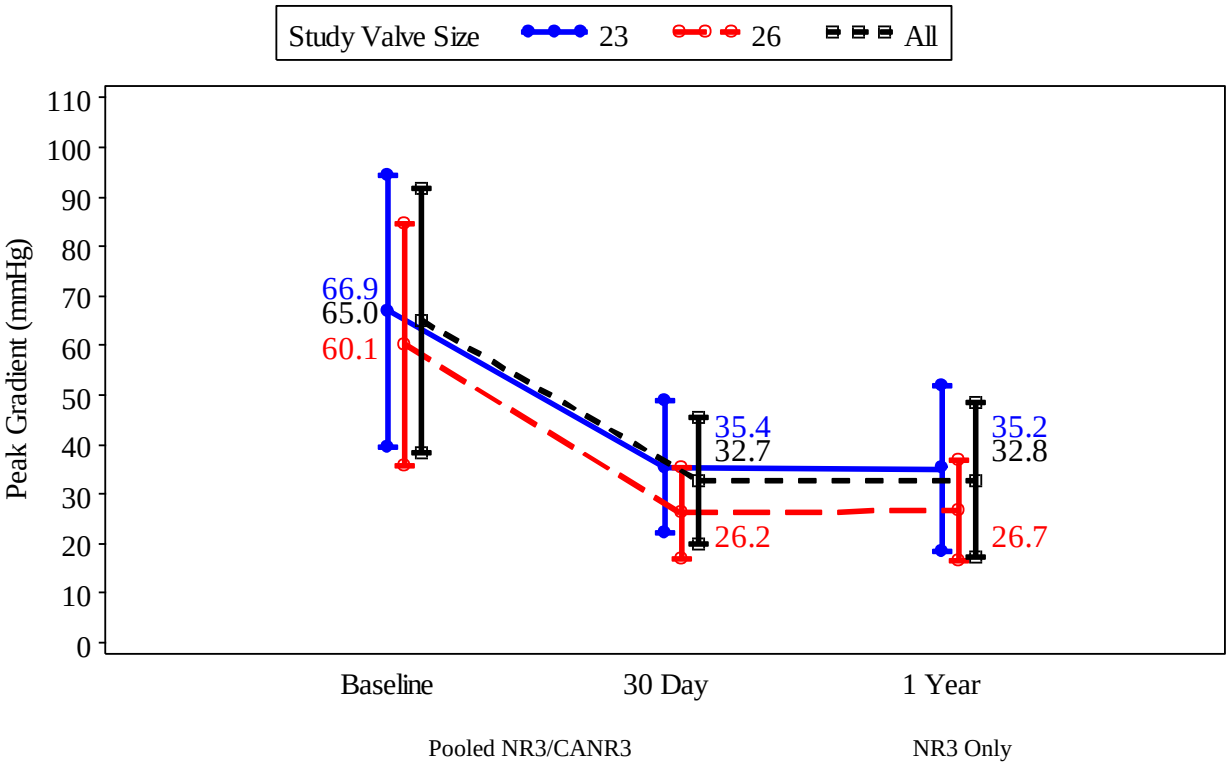


Figure 14:
Total Aortic Regurgitation by Visit
Valve Implant Population

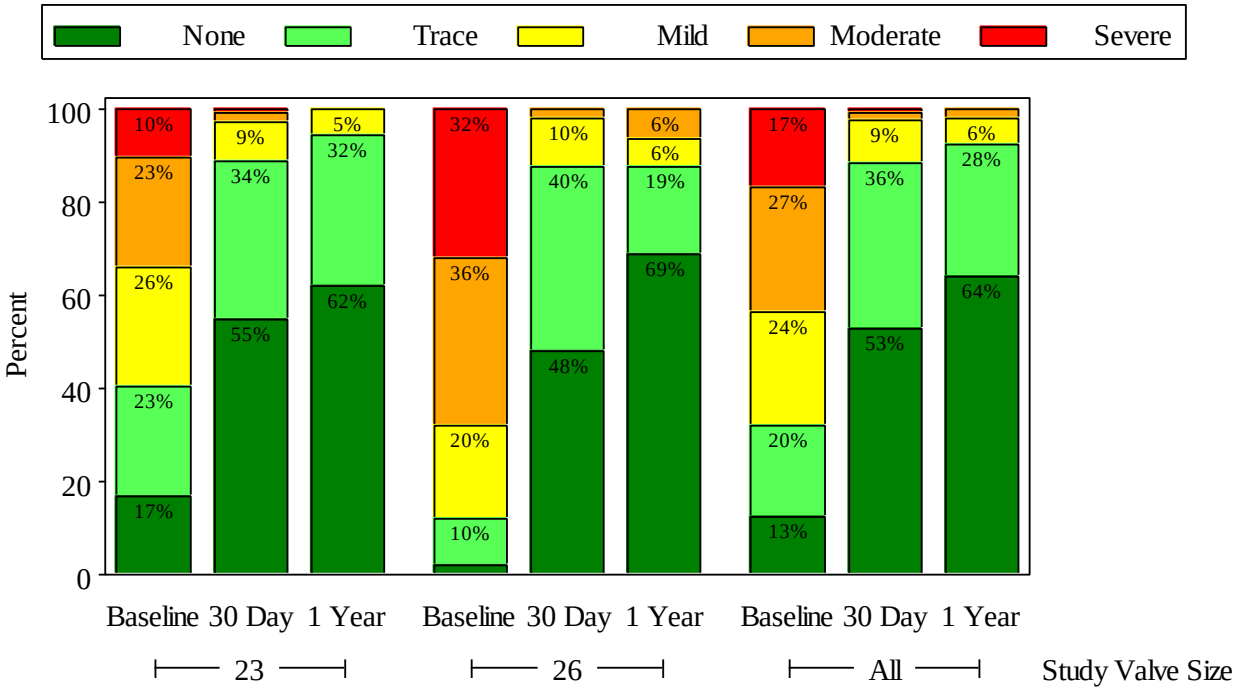


Figure 15:
Paravalvular Leak by Visit
Valve Implant Population

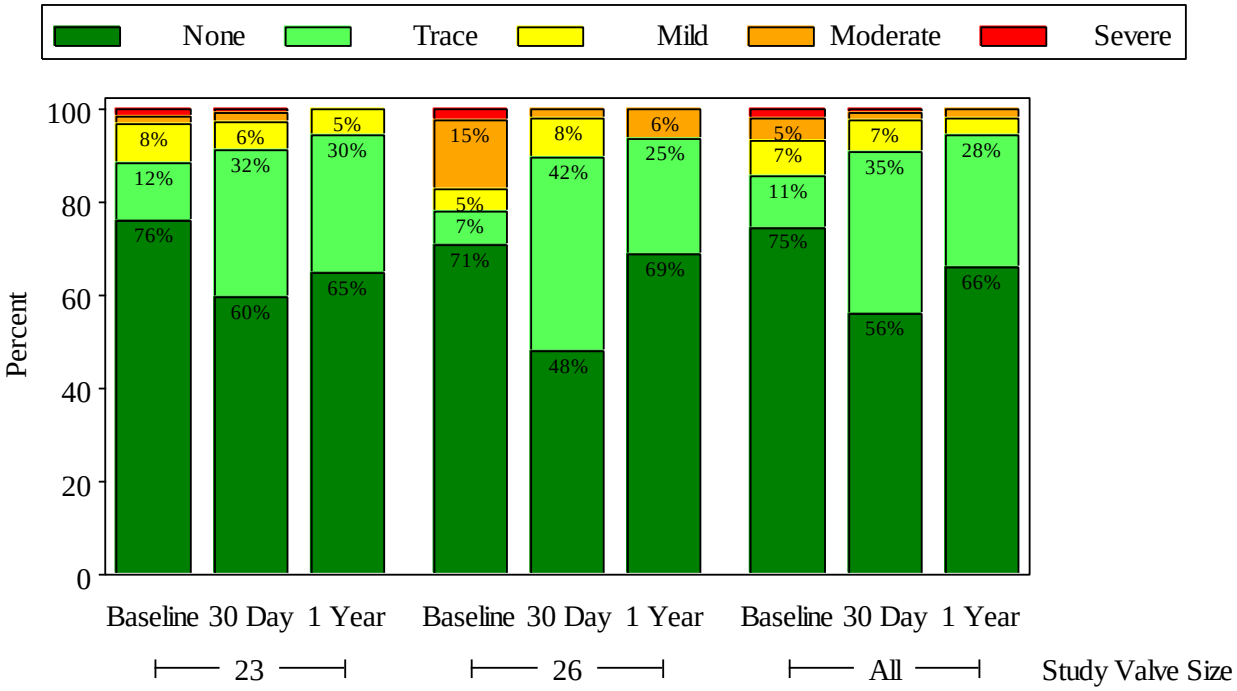


Figure 16:
NYHA Class by Visit
Attempted Implant Population

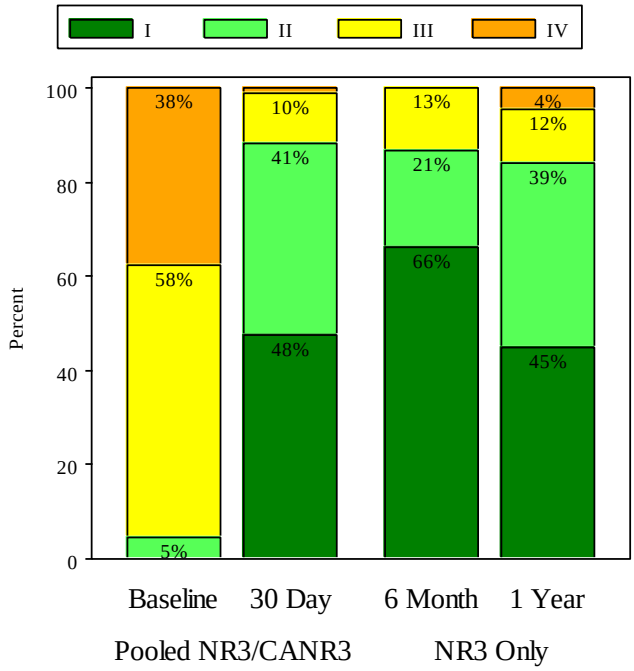


Figure 17:
KCCQ Clinical Summary Score
Attempted Implant Population

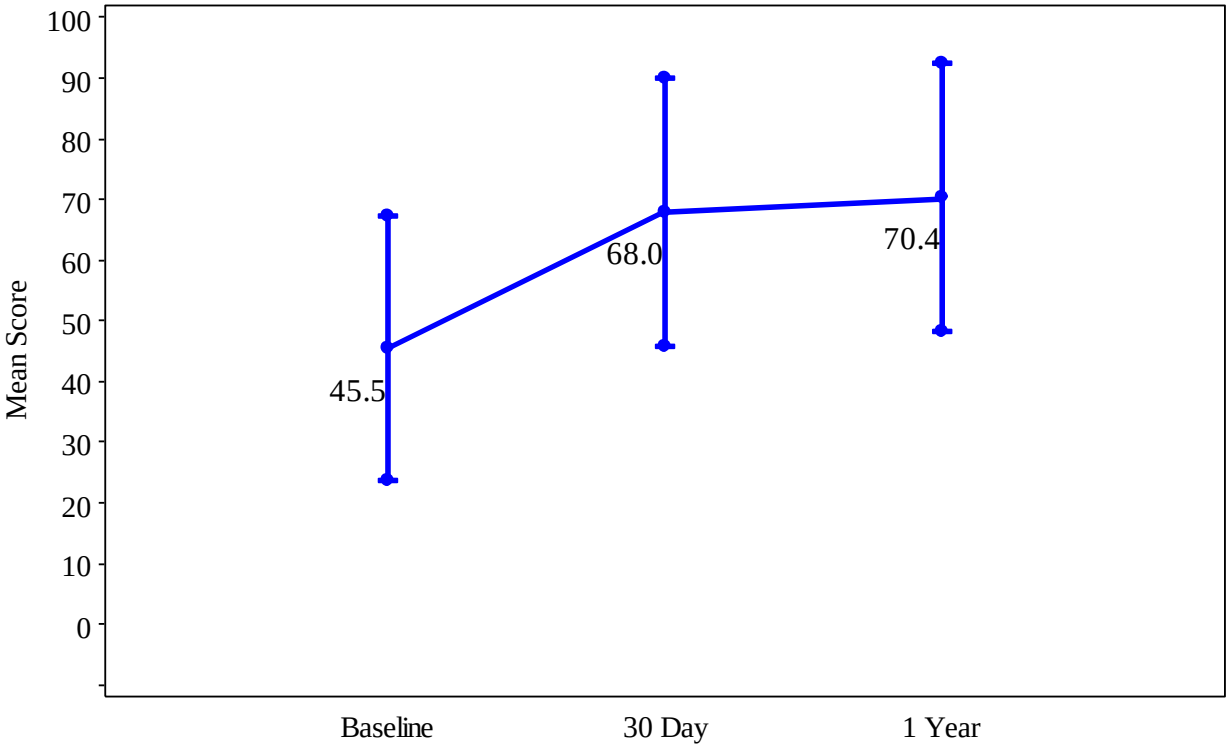


Table 20: Device Success and Reason for Device Failure Valve Implant Population	
Device Success[1]	**Rate[2]**
Success	115/187 (61.5%)
Failure	72/187 (38.5%)
Factor 1: Unsuccessful access, delivery, deployment, or retrieval of delivery system	11/72 (15.3%)
Factor 2: Position - Too Aortic or Too Ventricular	2/72 (2.8%)
Factor 3a: mean gradient ≥ 20 mmHg or peak velocity ≥ 3 m/s	62/70 (88.6%)
Factor 3b: Moderate/ Severe Aortic Regurgitation	5/71 (7.0%)
Factor 4: More than 1 valve implanted	3/72 (4.2%)
[1] Device success was defined as successful vascular access, delivery and deployment and retrieval of delivery system; correct positioning of the valve, intended performance (mean aortic valve gradient < 20 mmHg or peak velocity < 3 m/s, without moderate or severe prosthetic valve AR), only one valve implanted. Each participant who failed could experience a failure in more than one factor. If a patient failed one factor, the device was considered a failure even if other factors were undetermined due to missing data. [2] The results are expressed as no. / total no. (%). The denominator for each factor was equal to the patients with an overall failure and non-missing data for that factor.	

The PARTNER IIA Study Design

PIIA was a 1:1 randomized, controlled study independently powered to compare the results of TAVR with the SAPIEN XT valve to traditional, open-heart aortic valve surgery (i.e., surgical aortic valve replacement or SAVR). The SAPIEN XT valve was available in sizes 23 mm, 26 mm, and 29 mm.

Patients were treated from December 2011 to November 2013. The database reflected data collected through February 1, 2016 and included 1,011 patients in the SAPIEN XT arm and 1,021 patients in the SAVR arm at 57 investigational sites in the U.S. and Canada.

The study used an independent Data Safety Monitoring Board (DSMB) that was instructed to notify Edwards Lifesciences of any safety or compliance issues and a Clinical Events Committee (CEC) that was responsible for adjudicating endpoint related events reported during the trial. The CEC adjudicated the events per definitions established *a priori*, which were primarily VARC-1 definitions with the following exceptions:

- AKI was adjudicated with a modified VARC-1 definition in which the CEC identified the peak creatinine within 30 days of the index procedure, 30 days to 1 year, and 1 year to 2 years to determine if it met the definition of AKI.
- Aortic valve reintervention, hemolysis, and pericarditis were adjudicated per Protocol definition.
- Rehospitalization for symptoms of AS and/or complications of the valve procedure were adjudicated using the Protocol and VARC-1 as guidelines.
- Bleeding events were adjudicated irrespective of whether there was an identifiable, overt source of bleeding and could be adjudicated based on transfusion or hemoglobin drop alone.

Also, an ECG core laboratory was used for independent analysis of rhythm, and an echocardiographic core laboratory for independently analyzing all echocardiograms.

A. Accountability of the PMA Cohort

At the time of database lock, of the 2032 patients enrolled in the PMA study, 73.5% (1494) patients are available for analysis at the completion of the study, the 2 year post-operative visit. Table 21 presents patient accountability in the PIIA trial. The SAPIEN XT valve patients had either a transfemoral (TF) or non-transfemoral (non-TF) access.

Table 21:
Patient Accountability

	Intent to Treat Population[a]	As Treated Population[b]	Valve Implant Population[c]
SAPIEN XT Valve	1011	994	974
Transfemoral	775	762	749
Non-Transfemoral	236	232	225
SAVR	1021	944	936

a. Intent to Treat (ITT): All randomized patients
b. As Treated (AT): All enrolled/randomized patients for whom the Index Procedure is started. Patients were analyzed according to the valve used in the initial implant attempt.
c. Valve Implant (VI): All As Treated patients whose valve implant process is completed.

In the SAPIEN XT valve ITT population, 187 patients exited the study prior to the 2-year visit. Of the remaining 824 patients who were due for the 2-year visit, 784 patients (95.1%) completed the 2-year visit, and 40 patients (4.9%) missed the 2-year visit.

In the SAVR ITT population, 216 patients exited the study prior to the 2-year visit. Of the remaining 805 patients who were due for the 2-year visit, 710 patients (88.2%) completed the 2-year visit, and 95 patients (11.8%) missed the 2-year visit.

B. Study Population Demographics and Baseline Parameters

The demographics of the study population are typical for an aortic stenosis valve replacement study performed in the US. The demographics and baseline characteristics of the ITT population are presented in Table 22. Among the SAPIEN XT valve population, 775 patients were implanted via the transfemoral (TF) access route and 236 patients via the non-TF access route, including transapical (TA) or transaortic (TAo) access.

Table 22:
Demographics and Baseline Characteristics
(ITT Population)

Demographics & Characteristic	SAPIEN XT Valve			SAVR (N = 1021)
	All (N = 1011)	TF only (N = 775)	Non-TF Only (N = 236)	
Age (years)	81.5±6.7	81.8±6.7	80.6±6.6	81.7±6.7
Male Sex	548/1011 (54.2%)	426/775 (55.0%)	122/236 (51.7%)	560/1021 (54.8%)
Society of Thoracic Surgeons (STS) score	5.8±2.1	5.8±2.1	6.0±2.1	5.8±1.9
New York Heart Association (NYHA) class				
I/II	229/1011 (22.7%)	174/775 (22.5%)	55/236 (23.3%)	244/1020 (23.9%)

Table 22:
Demographics and Baseline Characteristics
(ITT Population)

Demographics & Characteristic	SAPIEN XT Valve			SAVR (N = 1021)
	All (N = 1011)	TF only (N = 775)	Non-TF Only (N = 236)	
III/IV	782/1011 (77.3%)	601/775 (77.5%)	181/236 (76.7%)	776/1020 (76.1%)
Coronary Artery Disease	700/1011 (69.2%)	531/775 (68.5%)	169/236 (71.6%)	679/1021 (66.5%)
Previous Myocardial Infarction	185/1011 (18.3%)	137/775 (17.7%)	48/236 (20.3%)	179/1021 (17.5%)
Previous Reintervention				
Coronary Artery Bypass Grafting	239/1011 (23.6%)	179/775 (23.1%)	60/236 (25.4%)	261/1021 (25.6%)
Percutaneous coronary intervention	274/1011 (27.1%)	202/775 (26.1%)	72/236 (30.5%)	282/1021 (27.6%)
Prior aortic valvuloplasty	51/1011 (5.0%)	35/775 (4.5%)	16/236 (6.8%)	50/1021 (4.9%)
Cerebral vascular accident	103/1011 (10.2%)	67/775 (8.6%)	36/236 (15.3%)	104/1021 (10.2%)
Peripheral vascular disease	282/1011 (27.9%)	167/775 (21.5%)	115/236 (48.7%)	336/1021 (32.9%)
Chronic obstructive pulmonary disease				
Any	321/1011 (31.8%)	228/775 (29.4%)	93/236 (39.4%)	306/1021 (30.0%)
Oxygen-dependent	34/1011 (3.4%)	20/775 (2.6%)	14/236 (5.9%)	32/1021 (3.1%)
Atrial fibrillation	313/1011 (31.0%)	245/775 (31.6%)	68/236 (28.8%)	359/1021 (35.2%)
Permanent pacemaker	118/1011 (11.7%)	91/775 (11.7%)	27/236 (11.4%)	123/1021 (12.0%)
Pulmonary hypertension	29/1011 (2.9%)	25/775 (3.2%)	4/236 (1.7%)	25/1019 (2.5%)
Frailty	12/1011 (1.2%)	11/775 (1.4%)	1/236 (0.4%)	15/1019 (1.5%)
Porcelain aorta	0/1011 (0.0%)	0/775 (0.0%)	0/236 (0.0%)	1/1019 (0.1%)
Chest deformities that preclude an open chest procedure	0/1011 (0.0%)	0/775 (0.0%)	0/236 (0.0%)	0/1019 (0.0%)
Cirrhosis	0/1011 (0.0%)	0/775 (0.0%)	0/236 (0.0%)	5/1019 (0.5%)
Echocardiographic findings (VI Population)				
Effective orifice area (EOA) - cm^2	0.7±0.2	0.7±0.2	0.7±0.2	0.7±0.2
Mean aortic valve gradient - mmHg	45.0±13.3	45.0±13.6	44.7±12.3	44.7±12.6
Moderate or severe mitral regurgitation	146/875 (16.7%)	116/677 (17.1%)	30/198 (15.2%)	153/841 (18.2%)
Continuous measures – Mean ± SD; Categorical measures – n/Total no. (%)				

C. Safety and Effectiveness Results

a. Primary Endpoint

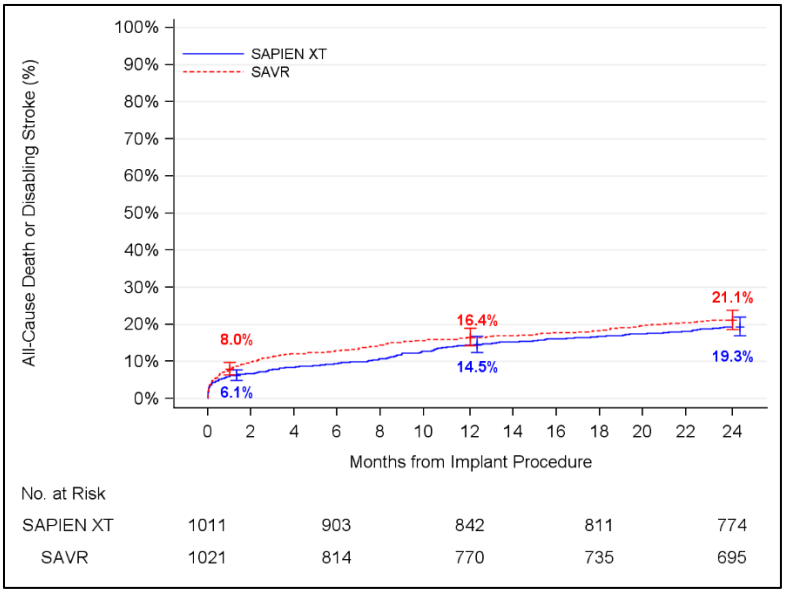
The results of the composite primary endpoint of all-cause death or disabling (major) stroke at 2 years and each component are presented for the ITT population in Table 23 and Figures 18-20. The K-M estimate of the composite event for SAPIEN XT cohort was found to be non-inferior to that for SAVR (19.3% vs. 21.1%; p = 0.0014).

Table 23:
All-Cause Death or Disabling (Major) Stroke at 2 Years
(ITT Population)

	SAPIEN XT Valve (N = 1011)					SAVR (N = 1021)				
Event	No. of Events*	Patients with Event	No. Patients at Risk	K-M Estimate†		No. of Events*	Patients with Event	No. Patients at Risk	K-M Estimate†	
				Point Estimate	Standard Error				Point Estimate	Standard Error
All-cause death or disabling stroke at 2 years	229	192	774	19.3%	1.3%	235	202	695	21.1%	1.3%
All-cause death at 2 years	166	166	798	16.7%	1.2%	170	170	719	18.0%	1.3%
Disabling stroke at 2 years	63	59	774	6.2%	0.8%	65	61	695	6.4%	0.8%

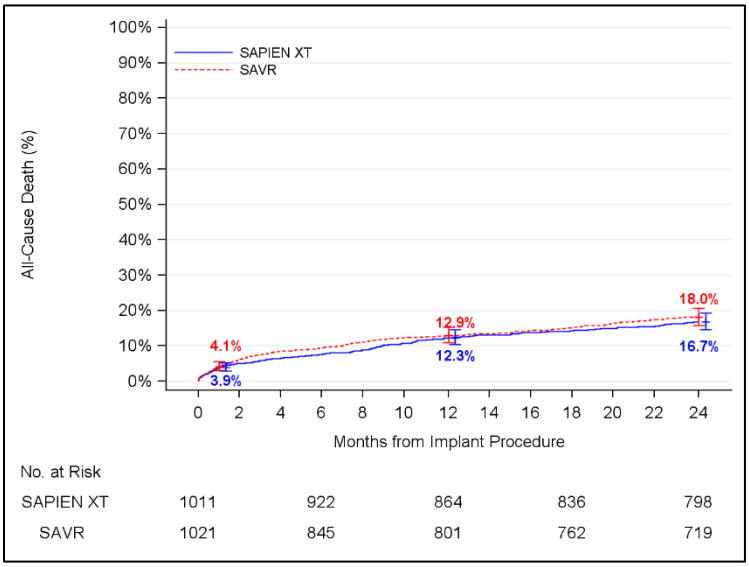
*Events with missing or incomplete onset dates are excluded from the analysis.
†K-M estimates are provided at 2 years (day 730) and use the first event per patient. Events occurring after 730 days are not included in the analysis.

Figure 18:
All-Cause Death or Disabling (Major) Stroke through 2 Years
(ITT Population)



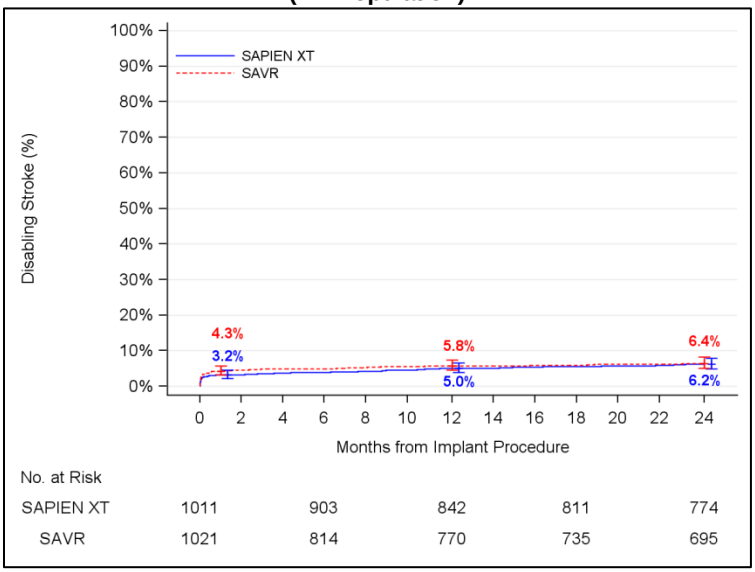
Note: The confidence intervals at 30 days and 12 months were calculated without multiplicity adjustment. The adjusted confidence intervals could be wider than presented here. As such, confidence intervals are provided to illustrate the variability only and should not be used to draw any statistical conclusion.

Figure 19:
All-Cause Death through 2 Years
(ITT Population)



Note: The confidence intervals were calculated without multiplicity adjustment. The adjusted confidence intervals could be wider than presented here. As such, confidence intervals are provided to illustrate the variability only and should not be used to draw any statistical conclusion.

Figure 20:
Disabling (Major) Stroke through 2 Years
(ITT Population)



Note: The confidence intervals were calculated without multiplicity adjustment. The adjusted confidence intervals could be wider than presented here. As such, confidence intervals are provided to illustrate the variability only and should not be used to draw any statistical conclusion.

The results for the primary endpoint and its components for the SAPIEN XT valve ITT population by access approach are presented in Table 24. The TF access had clinically lower all-cause death and disabling (major) stroke rates than did the non-TF access.

Table 24:
All-Cause Death or Disabling (Major) Stroke to 2 Years by Access Approach
(SAPIEN XT valve ITT Population)

	TF (N = 775)					Non-TF (N = 236)				
Event	No. of Events*	Patients with Event	No. Patients at Risk	K-M Estimate†		No. of Events*	Patients with Event	No. Patients at Risk	K-M Estimate†	
				Point Estimate	Standard Error				Point Estimate	Standard Error
All-cause death or disabling stroke at 2 years	151	128	612	16.8%	1.4%	78	64	162	27.7%	3.0%
All-cause death at 2 year	108	108	630	14.2%	1.3%	58	58	168	25.2%	2.9%
Disabling stroke at 2 years	43	39	612	5.3%	0.8%	20	20	162	9.1%	1.9%

*Events with missing or incomplete onset dates are excluded from the analysis.
†Kaplan-Meier estimates are provided at 2 years (day 730) and use the first event per patient. Events occurring after 730 days are not included in the analysis.

b. Key Secondary Endpoints

The results for the six (6) key secondary endpoints using the Hochberg's step-up method for multiple tests are presented for the ITT population in Table 25 and for the as-treated (AT) population in Table 26. SAPIEN XT valve was found to be non-inferior to SAVR in NYHA class at 2 years, DAOH to 2 years, 6MWT distance at 2 years, and EOA at 2 years. The 6MWT distance at 2 years was superior to that at baseline in the SAPIEN XT valve patients. However, the result failed to reject the null hypothesis that the mean total AR in the SAPIEN XT arm was worse than that in the SAVR arm by a margin of 0.25.

Table 25:
Key Secondary Endpoints Comparisons Using the Hochberg Method
(ITT/VI Population)

Endpoint	Summary Statistics*		Difference†	p-value	Reference α	Statistical Inference
	SAPIEN XT Valve	SAVR				
Total AR at 2 years§ (VI)	1.2±1.0 (606)	0.5±0.7 (520)	0.8 (0.67, 0.86)	> 0.9999	0.05	Fail to reject null hypothesis and move on to next line
Change in 6MWT distance from baseline to 2 years (SAPIEN XT valve only; ITT)	14.5±128.7 (604)	NA	NA	0.0057	0.025	Reject null hypothesis and conclude non-inferiority for the rest of endpoints
NYHA class at 2 years (ITT)	1.5±0.7 (737)	1.4±0.6 (649)	0.1 (0.0, 0.2)	< 0.0001		
DAOH to 2 years (ITT)	637.5±203.2 (960)	619.0±223.1 (885)	18.6 (-1.0, 38.1)	< 0.0001		
6MWT distance at 2 years (ITT)	203.2±132.4 (615)	209.8±153.5 (513)	-6.6 (-23.5, 10.3)	< 0.0001		
EOA at 2 years (VI)	1.5±0.4 (567)	1.4±0.4 (488)	0.1 (0.09, 0.19)	< 0.0001		

*Mean ± SD (n)
†Difference (95% CI)
§Total AR was graded as: none = 0, trace =1, mild and mild-moderate = 2, moderate and moderate-severe = 3, and severe = 4. It was treated as a continuous variable and compared using the t-test.

Table 26:
Key Secondary Endpoints Comparisons Using the Hochberg Method
(AT/VI Population)

Endpoint	Summary Statistics*		Difference†	p-value	Reference α	Statistical Inference
	SAPIEN XT Valve	SAVR				
Total AR at 2 years§ (VI)	1.2±1.0 (606)	0.5±0.7 (520)	0.8 (0.7, 0.9)	> 0.9999	0.05	Fail to reject null hypothesis and move on to next line
Change in 6MWT distance from baseline to 2 years (SAPIEN XT valve only; AT)	14.5±128.7 (604)	NA	NA	0.0057	0.025	Reject null hypothesis and conclude non-inferiority for the rest of endpoints
NYHA at the 2-year visit (AT)	1.5±0.7 (737)	1.4±0.6 (649)	0.1 (0.0, 0.2)	< 0.0001		
DAOH to 2 years (AT)	638.8 ± 201.5 (958)	619.5 ± 222.4 (883)	19.2 (-0.2, 38.7)	< 0.0001		
6MWT distance at the 2-year visit (AT)	203.2±132.4 (615)	209.8±153.5 (513)	-6.6 (-23.5, 10.3)	< 0.0001		

Table 26:
Key Secondary Endpoints Comparisons Using the Hochberg Method
(AT/VI Population)

Endpoint	Summary Statistics*		Difference†	p-value	Reference α	Statistical Inference
	SAPIEN XT Valve	SAVR				
EOA at 2 years (VI)	1.5±0.4 (567)	1.4±0.4 (488)	0.14 (0.09, 0.20)	< 0.0001		

*Mean ± SD (n)
†Difference (95% CI)
§Total AR was graded as: none = 0, trace = 1, mild and mild-moderate = 2, moderate and moderate-severe = 3, and severe = 4. It was treated as a continuous variable and compared using the t-test.

Adjunctive Secondary Endpoints

The results for the first adjunctive secondary composite endpoint of 14 pre-specified site-reported events are presented in Tables 27 and 28.

Table 27:
Composite Endpoint of 14 Pre-specified Site-Reported Events to 30 Days or Discharge
(AT Population)

Adverse Event	SAPIEN XT Valve (N = 994)		SAVR (N = 944)		Relative Risk SAPIEN XT Valve versus SAVR
	Events*	Patients with Event	Events*	Patients with Event	
Composite event to 30 days or discharge†	573	378/994 (38.0%)	714	493/944 (52.2%)	0.73

*Imputed dates are used for events with incomplete onset dates.
†The composite event consists of all stroke and TIA; myocardial infarction; vascular complications; life-threatening bleeding; reoperation for catheter-based intervention for valve thrombosis, valve displacement, or other valve- or procedure-related complication; pericarditis; hemolysis; mediastinitis; endocarditis; aortic insufficiency; aortic stenosis; permanent pacemaker implantation; mitral valve injury or insufficiency; or renal insufficiency.

Table 28:
Composite Endpoint of 14 Pre-specified Site-Reported Events from Day 31 to 2 Years
(AT Population)

Adverse Event	SAPIEN XT Valve (N = 994)		SAVR (N = 944)		Relative Risk SAPIEN XT Valve versus SAVR
	Events/Patients with Event/No. at Risk*	K-M Estimate (Standard Error)	Events/Patients with Event/No. at Risk*	K-M Estimate (Standard Error)	
Composite event from day 31 to 2 years†	428/284/594	31.0% (1.53%)	344/225/568	26.5% (1.52%)	1.17

*Events with missing or incomplete onset dates and those occurring before day 31 or after day 730 are excluded from the analysis.
†The composite event consists of all stroke and TIA; myocardial infarction; vascular complications; life-threatening bleeding; reoperation for catheter-based intervention for valve thrombosis, valve displacement, or other valve- or procedure-related complication; pericarditis; hemolysis; mediastinitis; endocarditis; aortic insufficiency; aortic stenosis; permanent pacemaker implantation; mitral valve injury or insufficiency; or renal insufficiency.

The result for the second adjunctive secondary composite endpoint of CEC-adjudicated all stroke, major vascular complications, or aortic valve reinterventions at 2 years is presented in Table 29 for the AT population.

Table 29:
All Stroke, Major Vascular Complications, or Aortic Valve Reintervention to 2 Years
(AT Population)

Event	SAPIEN XT Valve (N = 994)		SAVR (N = 944)		Relative Risk SAPIEN XT Valve vs SAVR
	Events/Patients with Event/No. at Risk*	K-M Estimate (Standard Error)	Events/Patients with Event/No. at Risk*	K-M Estimate (Standard Error)	
All stroke, major vascular complications, or reinterventions at 2 years	210/176/684	18.1% (1.24%)	156/132/644	14.4% (1.16%)	1.26

*Events with missing or incomplete onset dates and those occurring before day 31 or after day 730 are excluded from the analysis.

The result for the third adjunctive secondary composite endpoint of all-cause mortality, disabling stroke, or rehospitalization at 2 years is presented in Table 30 for the AT population.

Table 30:
All-Cause Death, Disabling (Major) Stroke, or Rehospitalization to 2 Years
(AT Population)

Event	SAPIEN XT Valve (N = 994)		SAVR (N = 944)		Relative Risk SAPIEN XT Valve vs SAVR
	Events/Patients with Event/No. at Risk*	K-M Estimate (Standard Error)	Events/Patients with Event/No. at Risk*	K-M Estimate (Standard Error)	
All-cause death, disabling stroke, or rehospitalization at 2 years	486/313/655	31.7% (1.48%)	428/298/600	32.0% (1.53%)	0.99

*Events with missing or incomplete onset dates and those occurring before day 31 or after day 730 are excluded from the analysis.

c. Adverse Events

Results for some key CEC-adjudicated adverse events through 2 years are presented in Table 31 for the ITT population.

Table 31:
Key CEC-Adjudicated Adverse Events
(ITT Population)

Event*	SAPIEN XT Valve			SAVR (N = 1021)
	Overall (N = 1011)	TF Access (N = 775)	Non-TF Access (N = 236)	
30 Days				
Acute kidney injury	192 (19.0)	106 (13.7)	86 (36.4)	327 (32.0)
Stage III	13 (1.3)	4 (0.5)	9 (3.8)	31 (3.0)
Death	39 (3.9)	23 (3.0)	16 (6.8)	41 (4.0)
Cardiac death	33 (3.3)	21 (2.7)	12 (5.1)	32 (3.1)
Non-cardiac death	6 (0.6)	2 (0.3)	4 (1.7)	9 (0.9)
Stroke	55 (5.4)	32 (4.1)	23 (9.7)	61 (6.0)
Disabling stroke	32 (3.2)	18 (2.3)	14 (5.9)	43 (4.2)
Non-disabling stroke	23 (2.3)	14 (1.8)	9 (3.8)	18 (1.8)
Myocardial infarction	12 (1.2)	5 (0.6)	7 (3.0)	19 (1.9)
Major vascular complication	80 (7.9)	66 (8.5)	14 (5.9)	51 (5.0)
Life threatening/disabling bleeding	105 (10.4)	52 (6.7)	53 (22.5)	442 (43.3)
Aortic valve reintervention	4 (0.4)	3 (0.4)	1 (0.4)	0 (0.0)
Endocarditis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Rhythm disturbance requiring permanent pacemaker	85 (8.4)	62 (8.0)	23 (9.7)	68 (6.7)
2 Years				
Acute kidney injury	326 (32.2)	206 (26.6)	120 (50.8)	404 (39.6)
Stage III	36 (3.6)	18 (2.3)	18 (7.6)	57 (5.6)
Death	166 (16.4)	108 (13.9)	58 (24.6)	170 (16.7)
Cardiac death	97 (9.6)	67 (8.6)	30 (12.7)	105 (10.3)
Non-cardiac death	69 (6.8)	41 (5.3)	28 (11.9)	65 (6.4)
Stroke	91 (9.0)	62 (8.0)	29 (12.3)	85 (8.3)
Disabling stroke	59 (5.8)	39 (5.0)	20 (8.5)	61 (6.0)
Non-disabling stroke	33 (3.3)	24 (3.1)	9 (3.8)	27 (2.6)
Myocardial infarction	33 (3.3)	21 (2.7)	12 (5.1)	37 (3.6)
Major vascular complication	86 (8.5)	69 (8.9)	17 (7.2)	55 (5.4)
Life threatening/disabling bleeding	169 (16.7)	101 (13.0)	68 (28.8)	471 (46.1)
Aortic valve reintervention	13 (1.3)	9 (1.2)	4 (1.7)	5 (0.5)
Endocarditis	11 (1.1)	10 (1.3)	1 (0.4)	6 (0.6)
Rhythm disturbance requiring permanent pacemaker	114 (11.3)	85 (11.0)	29 (12.3)	96 (9.4)

*Categorical measures - n/Total no. (%);Events with missing or incomplete onset dates are excluded from the analysis.

d. Other Results

Procedural Information
Overall, in the SAPIEN XT valve AT population the mean duration in the catheterization laboratory was 209.0 ± 59.5 min, the mean total procedure time was 102.7 ± 51.4 min, and the mean total anesthesia time was 207.1 ± 64.7 min. These duration times were slightly shorter in the TF group. General anesthesia was used in the vast majority of cases; 7.8% of the TF patients had conscious sedation. Correct positioning of the valve was achieved in 98.5% of the patients. Nineteen (19) patients (1.7% of TF patients and 2.6% of non-TF patients) were implanted with a second valve. Two (2) patients (0.5%) experienced valve dislodgement. Three (3) patients (0.3%) experienced annular rupture.

In the SAVR AT population, the mean duration in the operating room was 332.3 ± 96.9 min, the mean total procedure time was 236.8 ± 86.9 min, and the mean anesthesia time was 333.0 ± 108.6 min. General anesthesia was used in all patients. It was difficult to wean 26 patients (2.8%) from cardiopulmonary bypass, which was terminated in the majority of cases with intra-aortic balloon pump and/or inotropes.

Valve Performance
The measurements of EOA, mean gradient, peak gradient, total aortic regurgitation (AR), and aortic paravalvular leak (PVL) are presented in Figures 21-25. The increase in EOA and decrease in gradient were sustained at 2 years. In the SAPIEN XT arm, the proportion of patients with total AR ≥ moderate was 11.0% at baseline, 3.8% at 30 days, 4.0% at 1 year, and 9.4% at 2 years, while in the SAVR arm, the proportion of patients with total AR ≥ moderate was 12.0% at baseline, 0.7% at 30 days, 0.3% at 1 year, and 0.8% at 2 years. The proportion of patients with aortic PVL ≥ moderate was 3.8% at 30 days, 3.4% at 1 year, and 8.0% at 2 years in the SAPIEN XT arm, as compared to 0.5% at 30 days, 0.3% at 1 year, and 0.6% at 2 years in the SAVR arm**.**

Figure 21:
Effective Orifice Area
(VI Population)

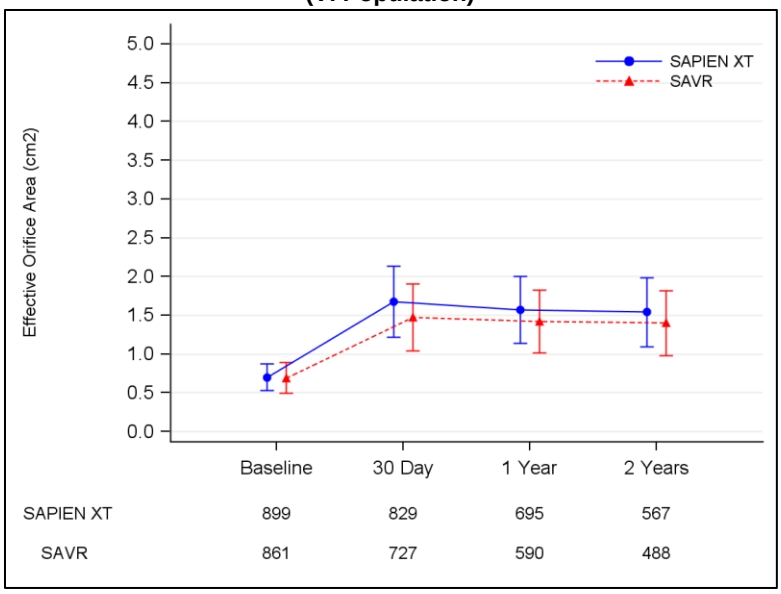


Figure 22:
Mean Gradient
(VI Population)

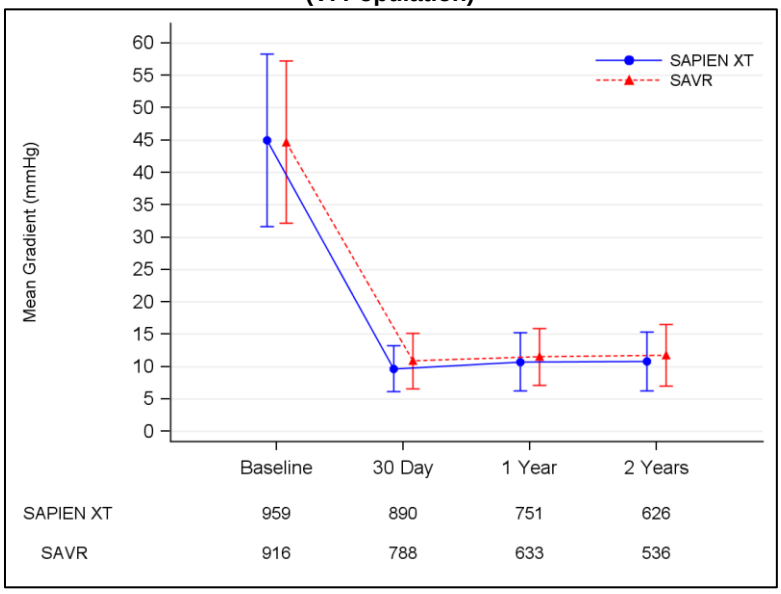


Figure 23:
Peak Gradient
(VI Population)

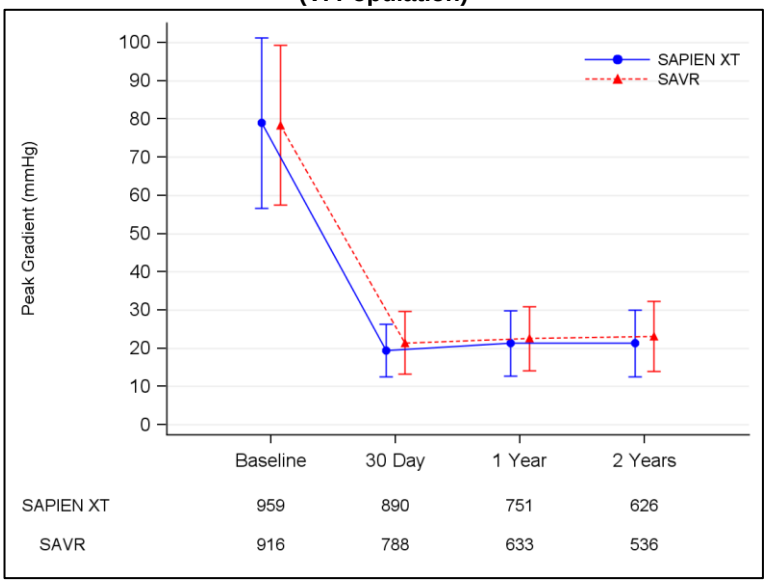


Figure 24:
Total Aortic Regurgitation
(VI Population)

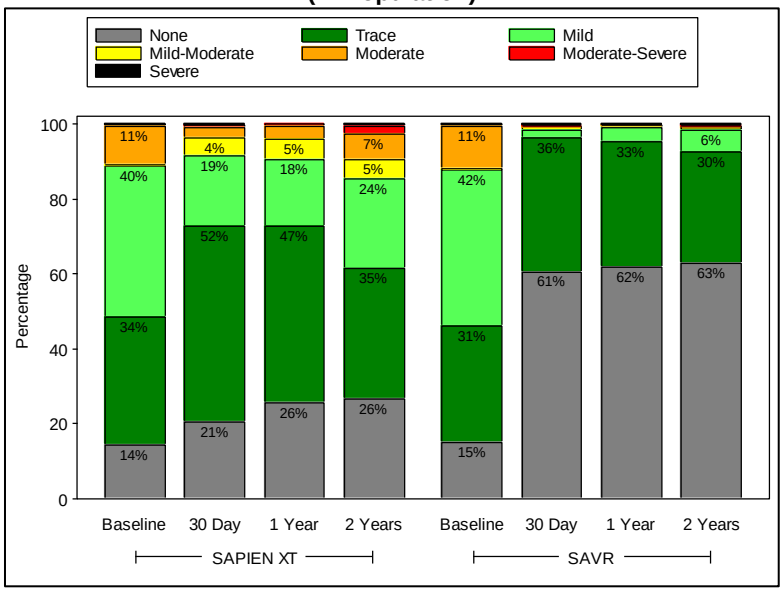
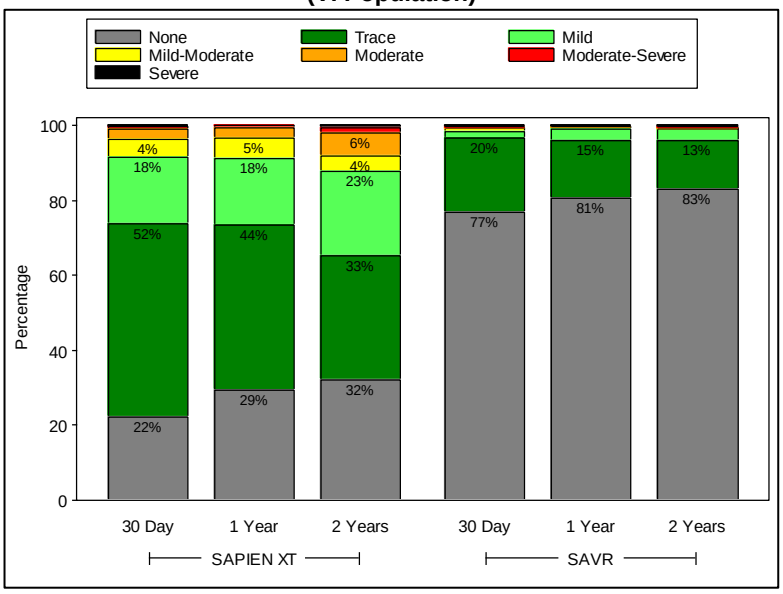


Figure 25:
Aortic Paravalvular Leak
(VI Population)



NYHA

The NYHA classifications by visit are presented in Figure 26. In the SAPIEN XT valve AT population, 78% of the patients were in NYHA Class III or IV at baseline, which reduced to 11% at 30 days, 8% at 1 year, and 10% at 2 years, while in the SAVR AT population, the percentage of patients in NYHA Class III or IV was 76% at baseline, 14% at 30 days, 7% at 1 year, and 7% at 2 years. A side-by-side comparison of the results by access approach is presented in Figure 27.

Figure 26:
NYHA Class
(AT Population)

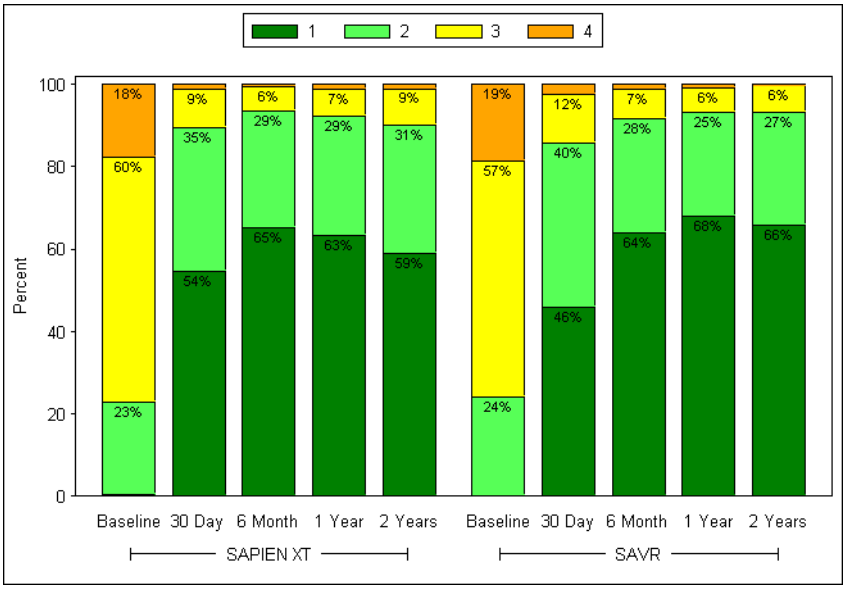
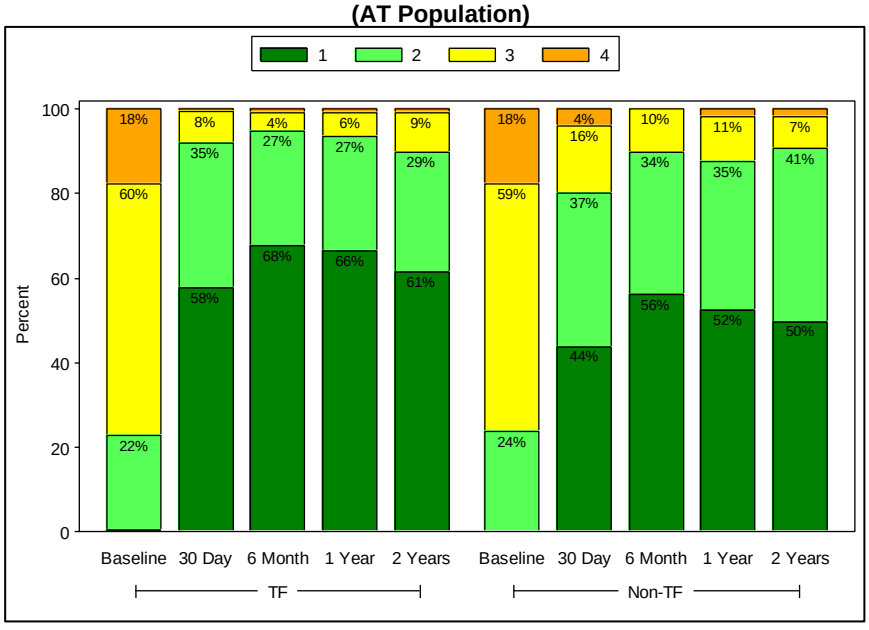


Figure 27:
NYHA Class- TF versus non-TF Access
(AT Population)



Length of Stay (LoS)

The results for LoS are presented in Table 32. Overall, the SAPIEN XT valve patients had shorter LoS than the SAVR patients.

Table 32:
Length of Stay
(AT Population)

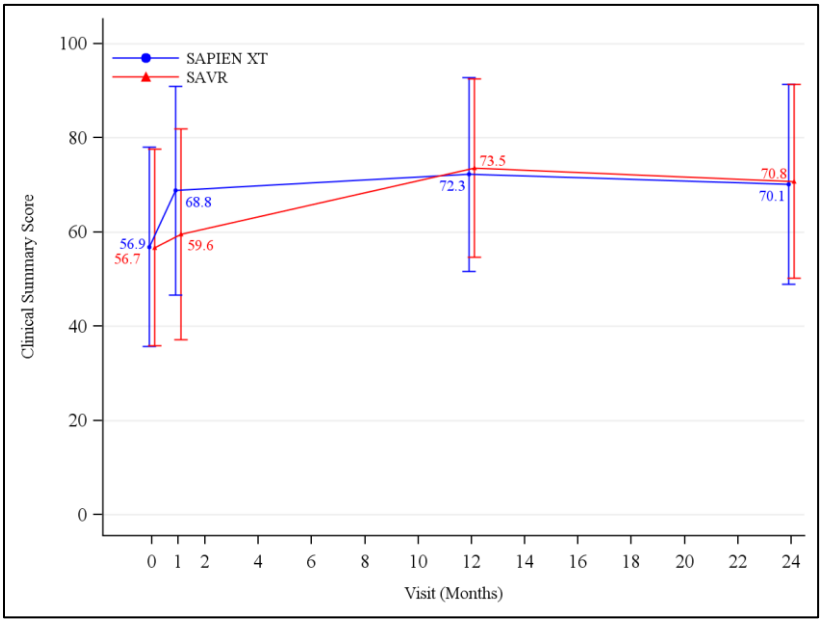
Length of Stay (days)	SAPIEN XT Valve			SAVR
	All	TF	Non-TF	
Overall	7.4±5.6	6.5±4.6	10.3±7.3	11.9±7.6
ICU	3.4±3.5	2.9±2.4	4.9±5.5	5.6±6.1

Plus–minus values are means ± SD.

QoL

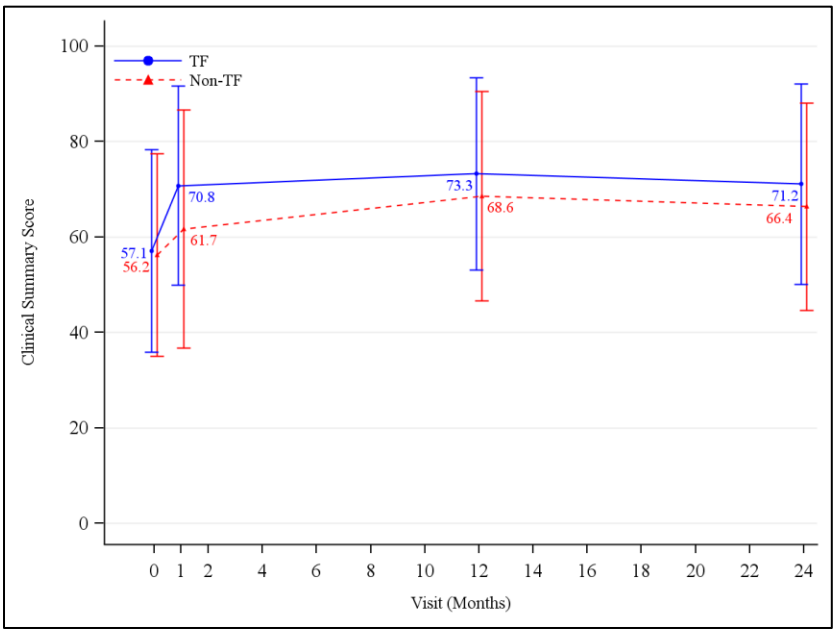
The QoL measurements using the Kansas City Cardiomyopathy Questionnaire (KCCQ) clinical summary score are presented in Figure 28. Improvements were observed in all sub-scores at 30 days and were sustained at 1 and 2 years in the SAPIEN XT valve AT population. A side-by-side comparison of the results by access approach is presented in Figure 29. In general, improvements in the TF group were slightly larger compared to those observed in the non-TF group. Among the SAVR patients, improvements were observed in most sub-scores at 30 days and were sustained at 1 and 2 years, except decreases from baseline to 30 days in KCCQ physical limitations and social limitations.

Figure 28:
KCCQ Clinical Summary Score
(AT Population)



Note: Line Plot with mean and standard deviation

Figure 29:
KCCQ Clinical Summary Score – TF versus non-TF Access
(AT Population)



Additional QoL instruments

QoL was also measured using the utility score of the EuroQoL (EQ-5D) measure and the SF-36 Health Status Questionnaire. The EQ-5D is a measure of self-reported health outcomes that is applicable to a wide range of health conditions and treatments. It consists of 2 parts: a descriptive system and a visual analogue scale (Part II). Part I of the scale consists of 5 single-item dimensions including: mobility, self care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has a 3 point response scale designed to indicate the level of the problem. The overall EQ-5D score from Part I may be converted into a single index value (also known as utilities score) between 0.0 (i.e., death) and 1.0 (perfect health). SF-36 uses 36 questions to measure functional health and well-being from the patient's point of view and is generally reported in two (2) summary scores on a scale from 0 to 100 which evaluate physical (the Physical Summary Score) and mental (the Mental Summary Score) health, with higher scores representing better functional health and well-being. The results of the VAS and SF-36 measures are presented in Tables 33 and 34, respectively.

Table 33:
EQ-5D Utilities Score
(AT Population)

EQ-5D Utilities Score*	SAPIEN XT Valve			SAVR
	All	TF	Non-TF	
Baseline	0.7±0.2	0.7±0.2	0.7±0.2	0.7±0.2
30 days	0.8±0.2	0.8±0.2	0.7±0.2	0.7±0.2
1 year	0.8±0.2	0.8±0.2	0.8±0.2	0.8±0.2
2 years	0.8±0.2	0.8±0.2	0.8±0.2	0.8±0.2

*Plus–minus values are means ± SD.

Table 34: SF-36 Health Status Questionnaire Score (AT Population)

SF-36 Health Status Questionnaire Score*	SAPIEN XT Valve			SAVR
	All	TF	Non-TF	
Physical Component Score				
Baseline	36.1±8.9	36.3±9.0	35.6±8.7	35.9±8.7
30 days	40.0±9.3	41.0±9.2	36.5±8.6	36.1±8.0
1 year	40.6±9.8	40.8±9.9	39.8±9.2	41.0±9.9
2 years	39.4±9.8	39.8±9.8	37.8±9.4	39.1±10.0
Mental Component Score				
Baseline	48.8±11.3	48.7±11.2	49.0±11.7	47.7±11.8
30 days	50.4±11.7	51.4±11.2	46.7±12.6	45.5±12.8
1 year	52.2±10.9	52.4±10.5	51.4±11.9	51.6±10.8
2 years	51.5±10.9	51.5±10.8	51.7±11.3	51.6±10.8

*Plus–minus values are means ± SD.

13.0 References

Bapat, V., I. Mydin, et al. (2013). “A guide to fluoroscopic identification and design of bioprosthetic valves: A reference for valve-in-valve procedure.” Catheter Cardiovasc Interv. 81:853-861.

Ferrari, E. (2011). “Transapical aortic 'valve-in-valve' procedure for degenerated stented bioprosthesis.” Eur J Cardiothorac Surg 41(3): 485-490.

Gurvitch, R., A. Cheung, et al. (2011). “Transcatheter valve-in-valve implantation for failed surgical bioprosthetic valves.” J Am Coll Cardiol 58(21): 2196-2209.

Leon MB, Piazza N, Nikolsky E, Blackstone EH, Cutlip DE, Kappetein AP, et al. Standardized endpoint definitions for transcatheter aortic valve implantation clinical trials: a consensus report from the Valve Academic Research Consortium. J Am Coll Cardiol 2011;57(3):253-69.

Piazza, N., et al. (2011). “Transcatheter aortic valve implantation for failing surgical aortic bioprosthetic valve from concept to clinical application and evaluation (part 1).” JACC Cardiovasc Interv 4(7): 721-732.

These products are manufactured and sold under one or more of the following US patent(s): US Patent No. 6,214,054; 6,547,827; 6,908,481; 7,214,344; 7,510,575; 7,530,253; 7,895,876; 7,993,394; 8,439,970; 8,475,522; 8,764,820; and 8,945,208; and corresponding foreign patents. Additional patents are pending.

08/2016
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