



Edwards Lifesciences

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

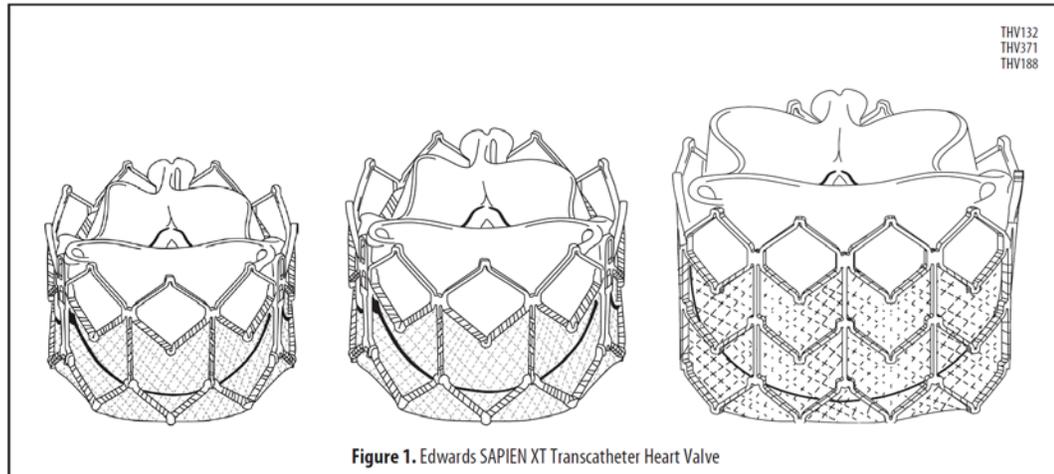


Figure 1. Edwards SAPIEN XT Transcatheter Heart Valve

### 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 THV is supplied sterilized with glutaraldehyde solution. The delivery system is supplied sterilized with ethylene oxide gas.

---

Edwards Lifesciences, the stylized E logo, Edwards, Edwards SAPIEN, Edwards SAPIEN XT, SAPIEN XT, Ascendra, Ascendra+, Carpentier-Edwards, Thermafix, PARTNER and PARTNER II are trademarks of Edwards Lifesciences Corporation.

All other trademarks are the property of their respective owners.

## 1.0 Device Description

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

The Edwards SAPIEN XT transcatheter heart valve (THV) 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)		THV Size
	Area	Area Derived Diameter	
18-22 mm	314 – 415 mm <sup>2</sup>	20-23 mm	23 mm
21-25 mm	415 – 530 mm <sup>2</sup>	23-26 mm	26 mm
24-27 mm	530 – 660 mm <sup>2</sup>	26-29 mm	29 mm

THV 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 THV size selection. Note: Risks associated with undersizing and oversizing should be considered.

For THV-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 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 THV 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.**

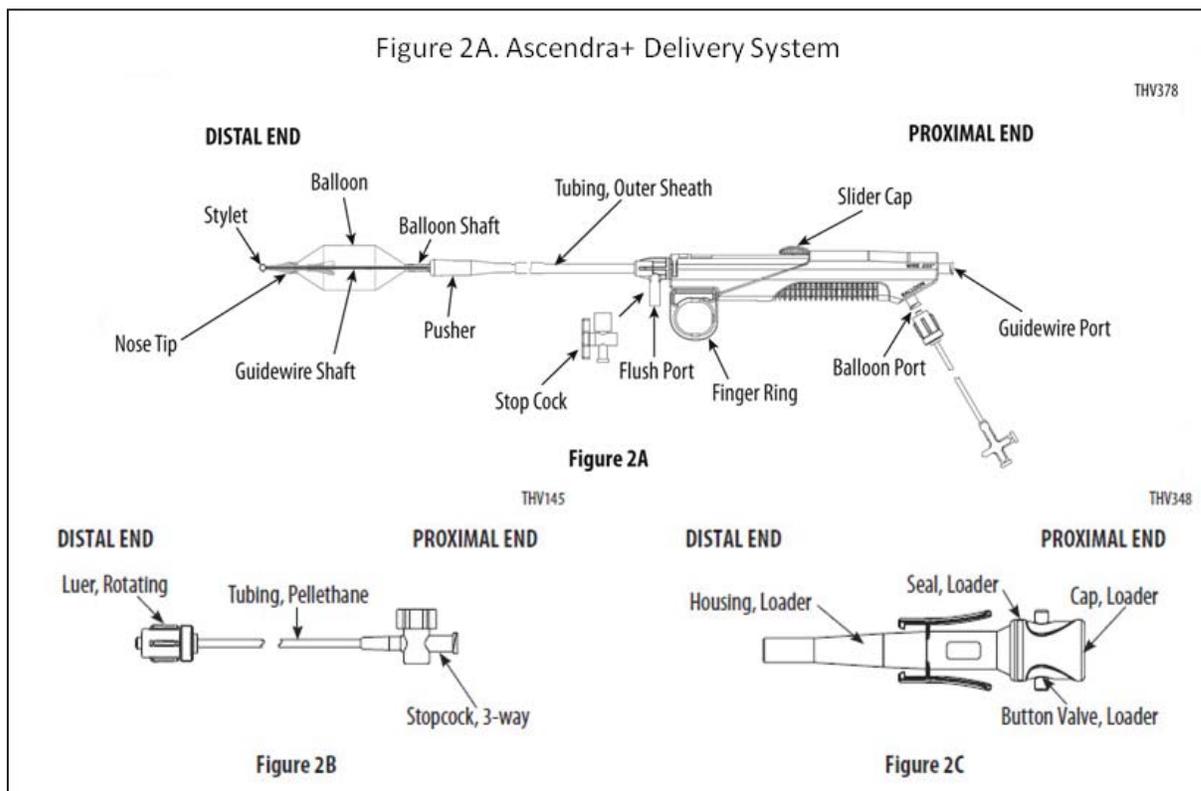
**NOTE: Exact volume required to deploy the THV may vary depending on the bioprosthesis internal orifice diameter. Do not exceed the rated burst pressure. See Table 4 for inflation parameters.**

- **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 THV. 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 THV 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 is indicated for use in patients with symptomatic heart disease due to either severe native calcific aortic stenosis or 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., Society of Thoracic Surgeons operative risk score  $\geq 8\%$  or at a  $\geq 15\%$  risk of mortality at 30 days).

## 3.0 Contraindications

The THV 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 is an increased risk of stroke in transcatheter aortic valve replacement procedures, as compared to balloon aortic valvuloplasty or other standard treatments.
- 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 THV that is too small may lead to paravalvular leak, migration or embolization, whereas implanting a THV that is too large may lead to residual gradient (patient-prosthesis mismatch) or annular rupture.
- Accelerated deterioration of the THV may occur in patients with an altered calcium metabolism.
- Prior to delivery, the THV must remain hydrated at all times and cannot be exposed to solutions other than its shipping storage solution and sterile physiologic rinsing solution. THV leaflets mishandled or damaged during any part of the procedure will require replacement of the THV.
- Caution should be exercised in implanting a THV in patients with clinically significant coronary artery disease.
- Patients with pre-existing mitral valve devices should be carefully assessed prior to implantation of the THV to ensure proper THV 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 THV if the tamper evident seal is broken, the storage solution does not completely cover the THV, the temperature indicator has been activated, the THV 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.
- THV 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 THV.

## 5.0 Precautions

- Long-term durability has not been established for the THV. Regular medical follow-up is advised to evaluate THV 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 THV in THV 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 < 3000 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 THV 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 THV 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 THV 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

- 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 THV, 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 THV and device preparation

### 7.2 THV Handling and Preparation

Follow sterile technique during device preparation and implantation.

#### 7.2.1 THV 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: THVs 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 THV.

Step	Procedure
2	Carefully remove the THV/holder assembly from the jar without touching the tissue. Verify the THV serial identification number with the number on the jar lid and record in the patient information documents. Inspect the THV for any signs of damage to the frame or tissue.
3	Rinse the THV as follows: Place the THV in the first bowl of sterile, physiological saline. Be sure the saline solution completely covers the THV and holder. With the THV and holder submerged, slowly agitate (to gently swirl the THV and holder) back and forth for a minimum of 1 minute. Transfer the THV 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 THV should be left in the final rinse solution until needed to prevent the tissue from drying.  <b>CAUTION: Do not allow the THV 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 THV is also to be avoided during the rinse procedure. No other objects should be placed in the rinse bowls. The THV should be kept hydrated to prevent the tissue from drying.</b>

### 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 THV per the following. Then lock the inflation device: <table border="1" data-bbox="293 1528 935 1724"> <thead> <tr> <th>Delivery System</th> <th>THV</th> <th>Inflation Volume</th> </tr> </thead> <tbody> <tr> <td>Model 9355AS23</td> <td>23 mm</td> <td>16 mL</td> </tr> <tr> <td>Model 9355AS26</td> <td>26 mm</td> <td>20 mL</td> </tr> <tr> <td>Model 9355AS29</td> <td>29 mm</td> <td>30 mL</td> </tr> </tbody> </table> <p><b>Note: Correct balloon sizing is critical to successful valve deployment and valve function.</b></p>	Delivery System	THV	Inflation Volume	Model 9355AS23	23 mm	16 mL	Model 9355AS26	26 mm	20 mL	Model 9355AS29	29 mm	30 mL
Delivery System	THV	Inflation Volume											
Model 9355AS23	23 mm	16 mL											
Model 9355AS26	26 mm	20 mL											
Model 9355AS29	29 mm	30 mL											
12	Close the stopcock to the 50 cc or larger syringe and remove the syringe.  <b>CAUTION: Maintain the inflation device provided by Edwards in the locked position until THV deployment.</b>												

### 7.2.3 Mount and Crimp the THV onto the Delivery System

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

### 7.3 Valvuloplasty and THV Delivery

Valvuloplasty and THV 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 THV 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	THV	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  $\geq$  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: THV implantation should not be carried out if the balloon cannot be fully inflated during valvuloplasty.**

### 7.3.3 THV 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 THV 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. <b>CAUTION: The pusher must be pulled back completely on the balloon shaft for proper balloon inflation and THV deployment.</b>
5	Verify the correct position of the THV with respect to the valve.
6	Begin THV deployment: <ul style="list-style-type: none"> <li>• Unlock the inflation device.</li> <li>• Begin rapid pacing; once arterial blood pressure has decreased to 50 mmHg or below, balloon inflation can commence.</li> <li>• Deploy the THV 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.</li> <li>• Retract the delivery system into the introducer sheath.</li> </ul>
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 THV is supplied sterilized with glutaraldehyde solution. The delivery system is supplied sterilized with ethylene oxide gas.

## 8.1 Storage

The THV 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 THV 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 THV is MR Conditional. A patient with this device, when implanted in the native valve or a failed surgical bioprosthesis, can be safely scanned in an MR system meeting the following conditions:

- Static magnetic field of 1.5 tesla (T) or 3.0 T.
- 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 the 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 THV and Device Disposal

The explanted THV 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 THV. These registries include the following:

- NR1: Inoperable Transapical (TA) Registry – transapical delivery of the 23mm or 26mm SAPIEN XT THV.
- 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  $\geq$  50% and meeting the sizing requirements for 23mm or 26mm SAPIEN XT THV.

- NR4: Inoperable Transaortic (TAo) Registry – transaortic delivery of the 23mm or 26 mm SAPIEN XT THV.
- NR6: Inoperable Transapical Registry for the delivery of 29mm SAPIEN XT 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  $92.0 \pm 1.7\%$ .

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  $3.2 \pm 0.61$  at baseline to  $1.9 \pm 0.88$  at 30 days. The mean change was  $-1.3 \pm 1.10$ . Device success was observed in 69.6% of patients (165/237). The mean hospitalization stay was  $11.1 \pm 8.96$  days which included  $4.5 \pm 7.12$  days in the ICU. The mean EOA was  $0.7 \pm 0.19$  cm<sup>2</sup> at baseline and  $1.6 \pm 0.43$  cm<sup>2</sup> at 30 days, and the average mean gradient decreased from  $41.2 \pm 12.17$  mmHg at baseline to  $8.6 \pm 3.59$  mmHg at 30 days. The mean peak gradient decreased from  $73.2 \pm 21.51$  mmHg at baseline to  $17.7 \pm 7.30$  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 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 23mm in 38 patients (66.7%), 26mm in 14 patients (24.6%), and 29mm 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 THV 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  $\geq 50\%$  for replacement of a failing surgical aortic valve and met the sizing requirements for the 23 mm or 26 mm SAPIEN XT THV. The specific sizing requirements were imposed because the 29 mm SAPIEN XT THV 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 7.

The demographics of the pooled study population are summarized in Table 8. 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 9 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 10.

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 11 through Table 13.

Valve hemodynamics as assessed by echocardiography is summarized in Table 14 and Figure 9 through Figure 15. The mean DVI increased from  $0.27 \pm 0.10$  at baseline to  $0.37 \pm 0.09$  at 30 days and  $0.39 \pm 0.11$  at 1 year. The mean gradient decreased from  $36.1 \pm 16.38$  mmHg at baseline to  $17.4 \pm 7.37$  mmHg at 30 days, which was maintained at 1 year. The mean peak gradient decreased from  $65.0 \pm 26.76$  mmHg at baseline to  $32.7 \pm 12.90$  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  $49.8 \pm 169.9$  meters from baseline to 30 days and  $86.1 \pm 142.0$  meters from baseline to 1 year.

The mean hospitalization stay among the Attempted Implant population was  $7.9 \pm 7.0$  days, which included  $2.9 \pm 5.0$  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 15. The mean KCCQ summary score among the Attempted Implant population improved from  $45.5 \pm 21.8$  at baseline to  $68.0 \pm 22.0$  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  $> 1.2 \text{ cm}^2$  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  $\geq 20$  mmHg or peak velocity  $\geq 3$ m/s was observed in 62 cases and moderate/severe aortic regurgitation in 5 cases.

## **PARTNER II Cohort B Registries Clinical Data**

<b>Clinical Table 1: Cohort B (Inoperable) Baseline Characteristics and Echocardiographic Findings for NR1, NR4 and NR6 (AT Population)*</b>	
	<b>SAPIEN XT (TA/TAo)</b>
Characteristic	(N = 265)
Age - yr	82.0 ± 7.79
Male sex — no. (%)	141/265 (53.2%)
STS score <sup>†</sup>	10.3 ± 5.51
Logistic EuroSCORE <sup>‡</sup>	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 <sup>§</sup> — 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 <sup>2</sup>	0.7 ± 0.19
Mean aortic-valve gradient — mmHg	41.2 ± 12.17
Mean LVEF — %	52.5 ± 13.37
Moderate or severe mitral regurgitation <sup>**</sup> — no./total no. (%)	70/232 (30.2%)
<p>* 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.</p> <p><sup>†</sup> 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.</p> <p><sup>‡</sup> 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.</p> <p><sup>§</sup> Frailty was determined by the surgeons according to prespecified criteria.</p> <p>** Moderate or severe mitral regurgitation was defined as regurgitation of grade 3+ or higher.</p>	

<b>Clinical Table 2: Cohort B (Inoperable) Clinical Outcomes at 30 days for NR1, NR4 and NR6 (AT Population)*</b>	
<b>Outcome<sup>a</sup></b>	<b>SAPIEN XT (N = 265)</b>
Death from any cause	21/265 (7.9%)
Major Stroke	5/265 (1.9%)
Repeat hospitalization <sup>b</sup>	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 <sup>c</sup>	7/265 (2.6%)
Disabling Bleeding Event <sup>d</sup>	30/265 (11.3%)
Cardiac Reintervention <sup>e</sup>	8/265 (3.0%)
Endocarditis	0/265 (0.0%)
New Atrial Fibrillation <sup>f</sup>	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  $\geq 300\%$  (3 x increase compared with baseline) or serum creatinine of  $\geq 4$  mg/d ( $\geq 354$   $\mu\text{mol/L}$ ) with an acute increase of at least 0.5 mg/dl (44  $\mu\text{mol/L}$ )

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  $\geq 5$  g/dL or whole blood of packed red blood cells (RBC) transfusion  $\geq 4$  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

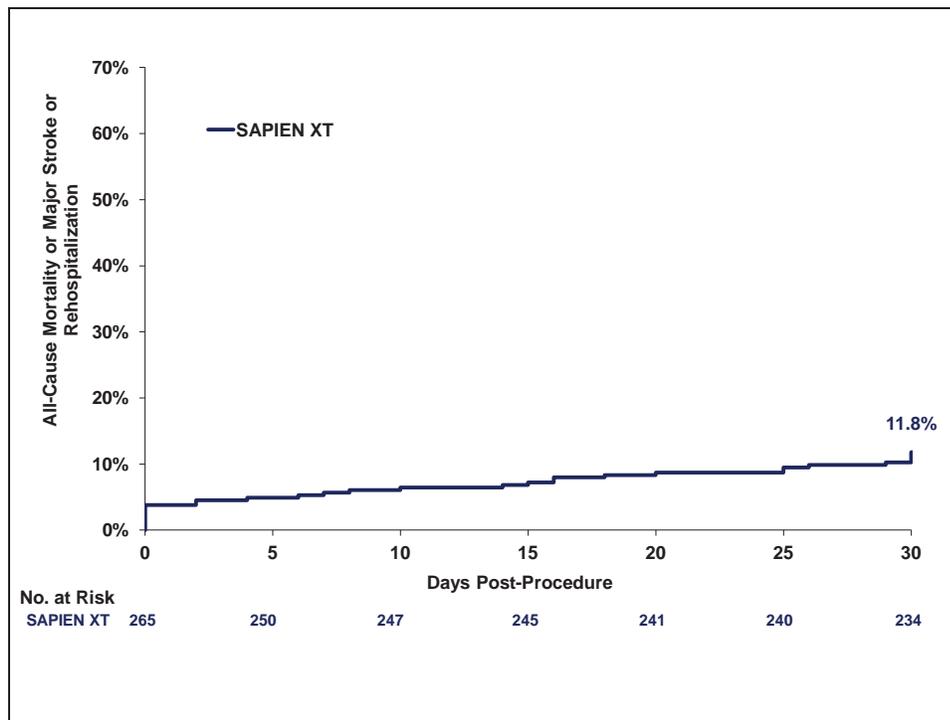
f. Based on 167 patients at 30 days

<b>Clinical Table 3: Conduction Disturbance Requiring Pacemaker to 30 Days for NR1, NR4 and NR6 (CEC Adjudicated) – AT Population</b>		
<b>Event</b>	<b>SAPIEN XT (TA/TAo)(N = 265)</b>	
	<b>Events</b>	<b>Patients with Event</b>
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%)

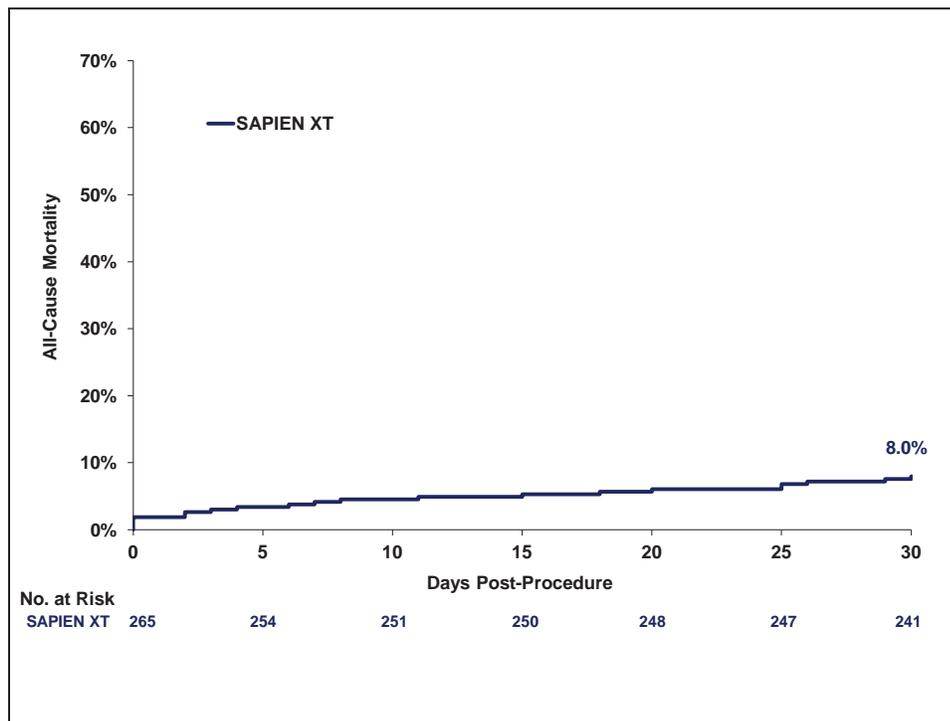
[1] Subjects with pacemaker or ICD at baseline are included (all patients included in denominator).

[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 (AT Population)**

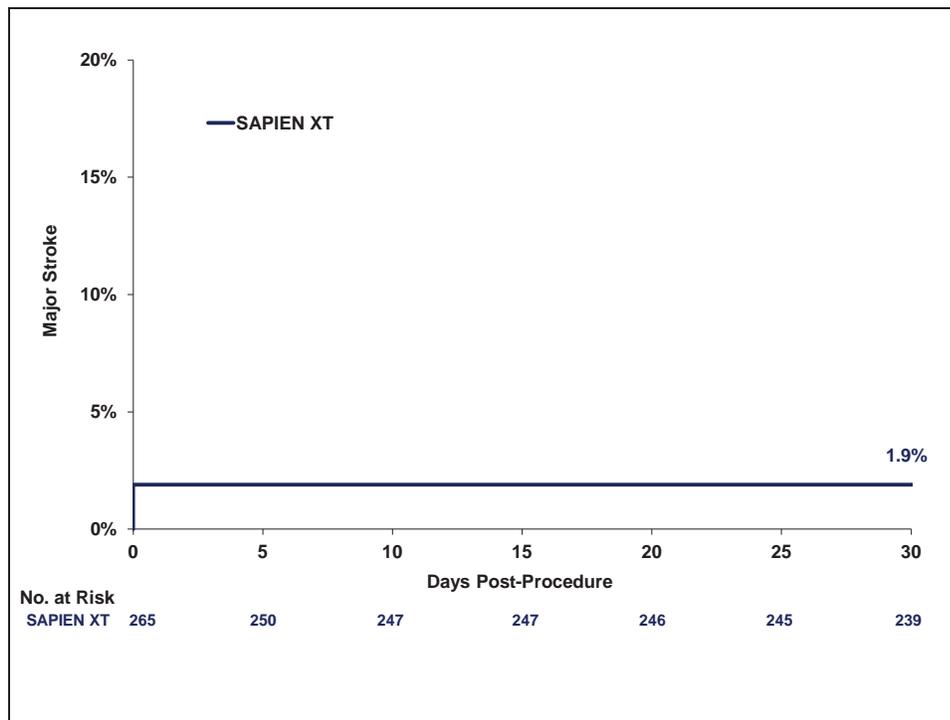


Figure 5: Major Stroke at 30 Days, NR1, NR4, and NR6 – T/TAo (AT Population)

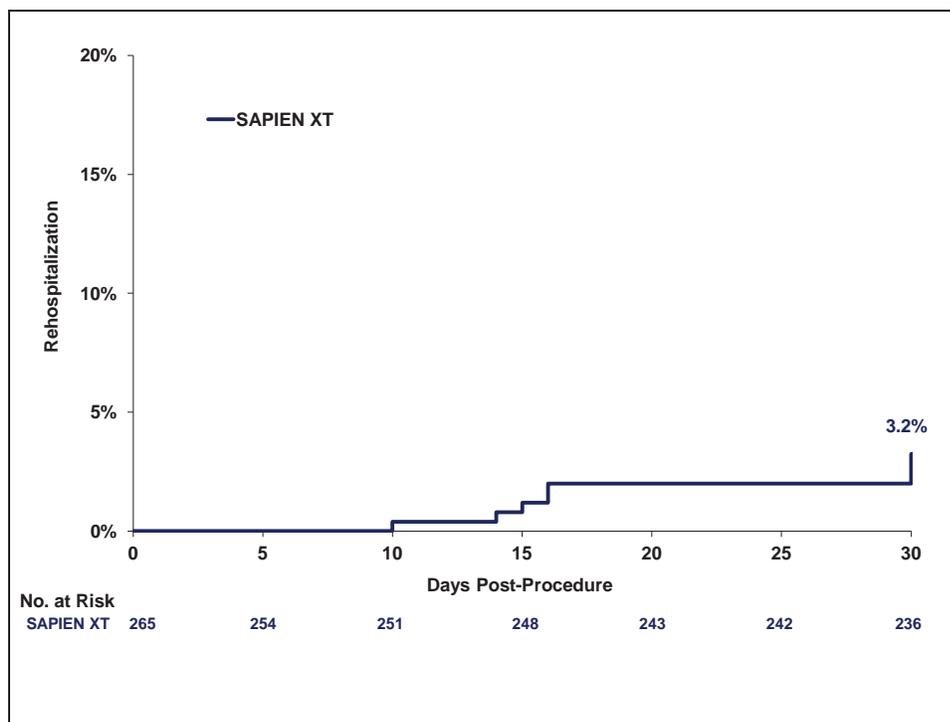
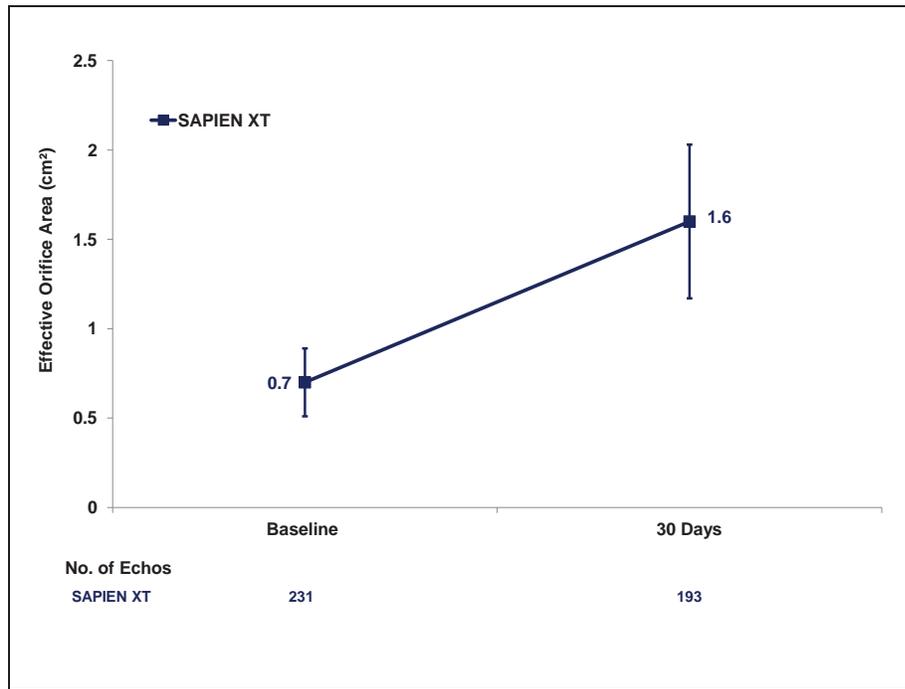
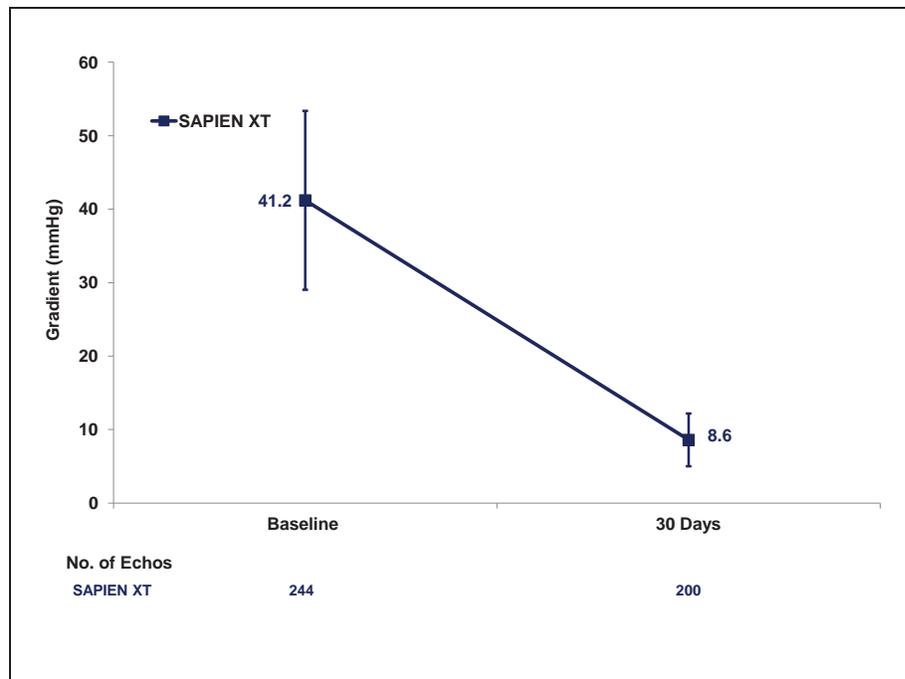


Figure 6: Re-Hospitalization at 30 Days, NR1, NR4, and NR6 – T/TAo (AT Population)



**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)**

Clinical Table 4: NYHA Functional Class By Visit for NR1, NR4 and NR6 (AT Population)					
	SAPIEN XT (N = 265)				
Visit	I	II	III	IV	Total
Baseline	1	23	158	82	264
30 Days	84	88	45	12	229

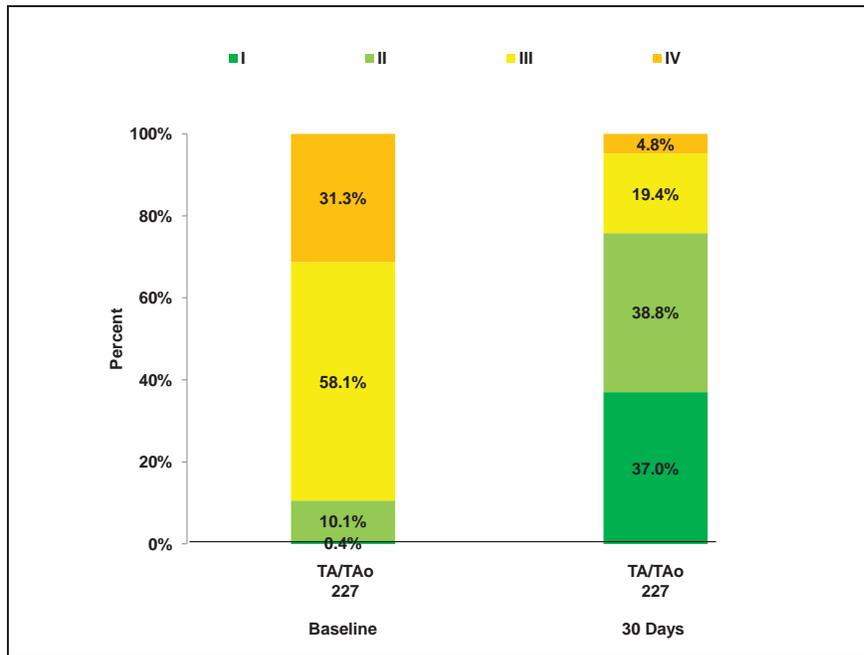


Figure 9: NYHA Class by Visit, NR1, NR4, and NR6 – TA/TAo (Intent-to-Treat Population)

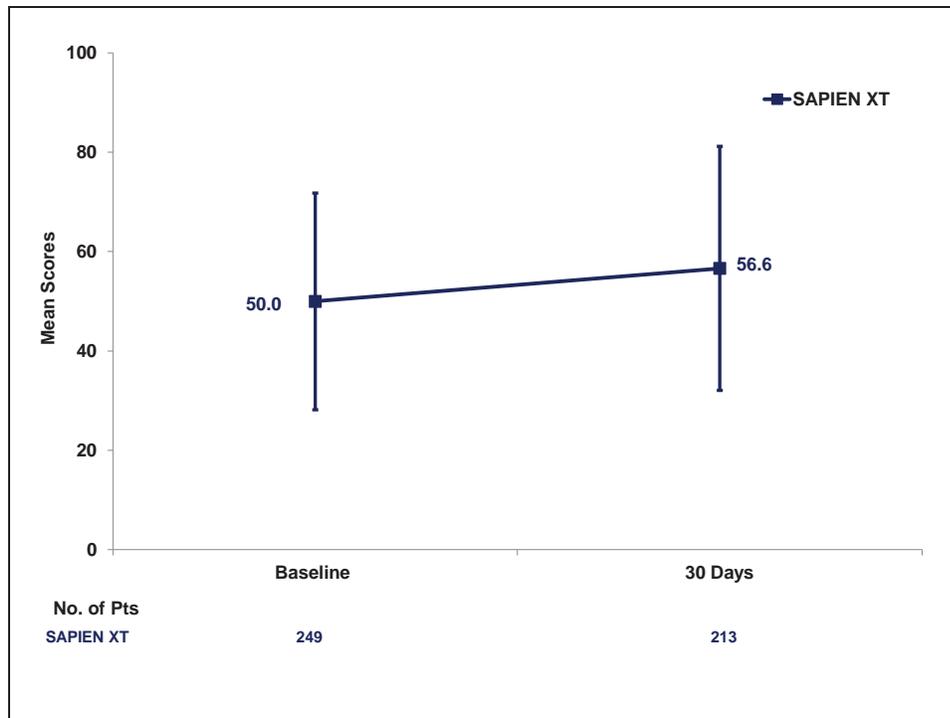


Figure 10: KCCQ Clinical Summary Score, NR1, NR4, and NR6 – TA/TAo (AT Population)

**SOURCE XT Clinical Data**

<b>Clinical Table 5: SOURCE XT (High Risk) Baseline Characteristics of the Patients and Echocardiographic Findings (AT Population)*</b>		
	<b>Transfemoral</b>	<b>TA/TAo Pooled</b>
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 <sup>†</sup>	8.0 ± 6.8	7.9 ± 6.2
Logistic EuroSCORE <sup>‡</sup>	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 <sup>§</sup> — 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 <sup>2</sup>	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.

<sup>†</sup> 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.

<sup>‡</sup> 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.

<sup>§</sup> Frailty was determined by the surgeons according to prespecified criteria.

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

<b>Clinical Table 6: SOURCE XT (High Risk) Clinical Outcomes<sup>a</sup> at 30 days and 1 year (AT Population)*</b>				
	<b>30 Days</b>		<b>1-Year</b>	
	<b>Transfemoral</b>	<b>TA/TAo</b>	<b>Transfemoral</b>	<b>TA/TAo</b>
<b>Outcome</b>	<b>(N = 1685)</b>	<b>(N = 995)</b>	<b>(N = 1685)</b>	<b>(N = 995)</b>
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 <sup>b</sup>	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 <sup>d</sup> /AKI	197 (11.9%)	270 (28.0%)	240 (14.7%)	292 (30.6%)
Life-threatening bleeding <sup>c</sup>	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  $\geq 5$  g/dL or whole blood of packed red blood cells (RBC) transfusion  $\geq 4$  units

d. Renal failure is defined as stage III acute kidney injury: Increase in serum creatinine to  $\geq 300\%$  (3 x increase compared with baseline) or serum creatinine of  $\geq 4$  mg/d ( $\geq 354$   $\mu\text{mol/L}$ ) with an acute increase of at least 0.5 mg/dl (44  $\mu\text{mol/L}$ )

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

**Table 7: Patient Disposition**

	Attempted Implant <sup>1</sup>	Valve Implant <sup>2</sup>
Number of Patients	197	195

<sup>1</sup>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.

<sup>2</sup>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 8: Demographic and Baseline Characteristics – Attempted Implant Population**

Characteristic	Results <sup>1</sup> (N=197)
Age – yr	78.5 ± 11.00 <sup>1</sup>
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) <sup>2</sup>	25/197 (12.7%)
Atrial fibrillation	98/197 (49.7%)
Permanent pacemaker	51/197 (25.9%)
Pulmonary hypertension	26/197 (13.2%)
Frailty <sup>3</sup>	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) <sup>4</sup>	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 <sup>5</sup>	62/171 (36.3%)

<sup>1</sup> Quantitative data are expressed as mean ± SD (n). Categorical data are expressed as no./total no. (%).

<sup>2</sup> To convert the value for creatinine to micromoles per liter, multiply by 88.4.

<sup>3</sup> Frailty was determined by the surgeons according to pre-specified criteria.

<sup>4</sup> DVI is a flow-dependent measure of orifice stenosis. A DVI < 0.25 suggests significant stenosis.

<sup>5</sup> Moderate or severe mitral regurgitation was defined as regurgitation of grade 3+ or higher.

**Table 9: Summary of Failed Bioprosthetic Surgical Valves Attempted Implant Population**

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

<sup>1</sup> Categorical data are expressed as no./total no. (%).

<sup>2</sup> Other includes an unidentified manufactured tissue valve and a St. Jude mechanical composite

**Table 10: All-Cause Mortality, All Stroke, Moderate or Severe Obstruction, or Moderate or Severe Paravalvular Leak – Valve Implant Population**

Events	30 Days (N=195)		1 Year (N=96)	
	Patients with Event	95% Confidence Interval <sup>3</sup>	Patients with Event	95% Confidence Interval
Composite Event <sup>1</sup>	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 <sup>2</sup>	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%]

<sup>1</sup> 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.

<sup>2</sup> Doppler velocity index (DVI) < 0.25 per the echo core lab read.

<sup>3</sup> 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 11: CEC Adjudicated Adverse Events – Attempted Implant Population**

Adverse Events	Rate (no./total no. (%))	
	30 Days (N=197)	1 Year (N=97)
Death <sup>1</sup>		
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 <sup>2</sup>	2/197 (1.0%)	N/A
Disabling Bleeding <sup>3</sup>	19/197 (9.6%)	16/97 (16.5%)
Cardiac Reintervention <sup>4</sup>	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%)

<sup>1</sup> Deaths from unknown causes were assumed to be deaths from cardiovascular causes.

<sup>2</sup> Acute kidney injury, stage III is defined as an increase in serum creatinine to  $\geq 300\%$  (3 x increase compared with baseline) or serum creatinine of  $\geq 4$  mg/d ( $\geq 354$   $\mu\text{mol/L}$ ) with an acute increase of at least 0.5 mg/dl (44  $\mu\text{mol/L}$ ) within 72 hours of the procedure (per the VARC-1 definition).

Adverse Events	Rate (no./total no. (%))	
	30 Days (N=197)	1 Year (N=97)

<sup>3</sup>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  $\geq 5$  g/dL or whole blood of packed red blood cells (RBC) transfusion  $\geq 4$  units (Life-threatening per VARC-1 definitions).

<sup>4</sup>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 12: Kaplan-Meier (KM) Event Rate for CEC Adjudicated Major Vascular Complications, Major Stroke, Minor Stroke, TIA, and Acute Kidney Injury – Attempted Implant Population**

VARC Event <sup>1</sup>	30 Days (N=197)				1 Year (N=97)			
	Events	Patients with Event	KM Estimate <sup>2</sup>	95% CI <sup>3</sup>	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)				

<sup>1</sup>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.

<sup>2</sup>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.

<sup>3</sup>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 13: 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 <sup>1</sup>	3	3/197 (1.5%)	1	1/97 (1.0%)
New Permanent Pacemaker – Patients without preexisting pacemaker <sup>2</sup>	3	3/146 (2.1%)	1	1/70 (1.4%)

<sup>1</sup>Subjects with pacemaker or ICD at baseline were included (all patients included in denominator).

<sup>2</sup>Subjects with pacemaker or ICD at baseline were excluded (patients with baseline pacemaker/ICD subtracted from denominator).

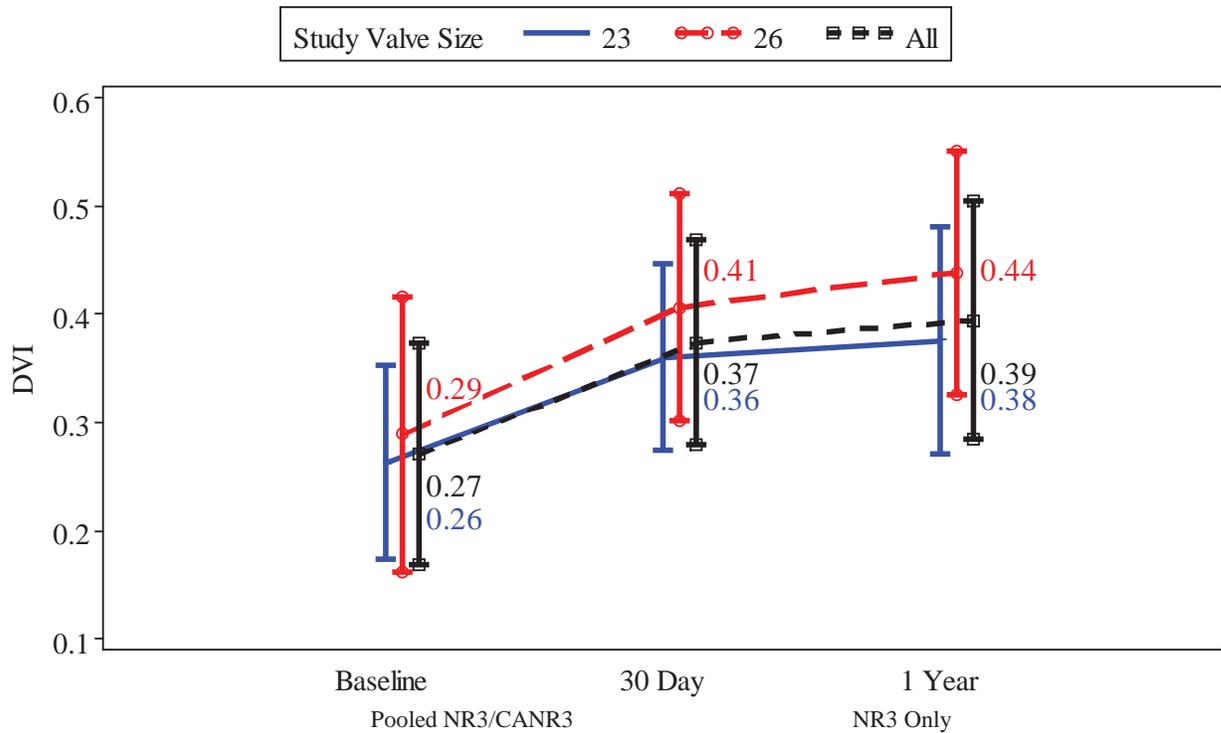
Note: The patient who received a new pacemaker in both rows is the same patient. The only difference is the denominators.

**Table 14: Valve Hemodynamics Measured by Echocardiography - Valve Implant Population**

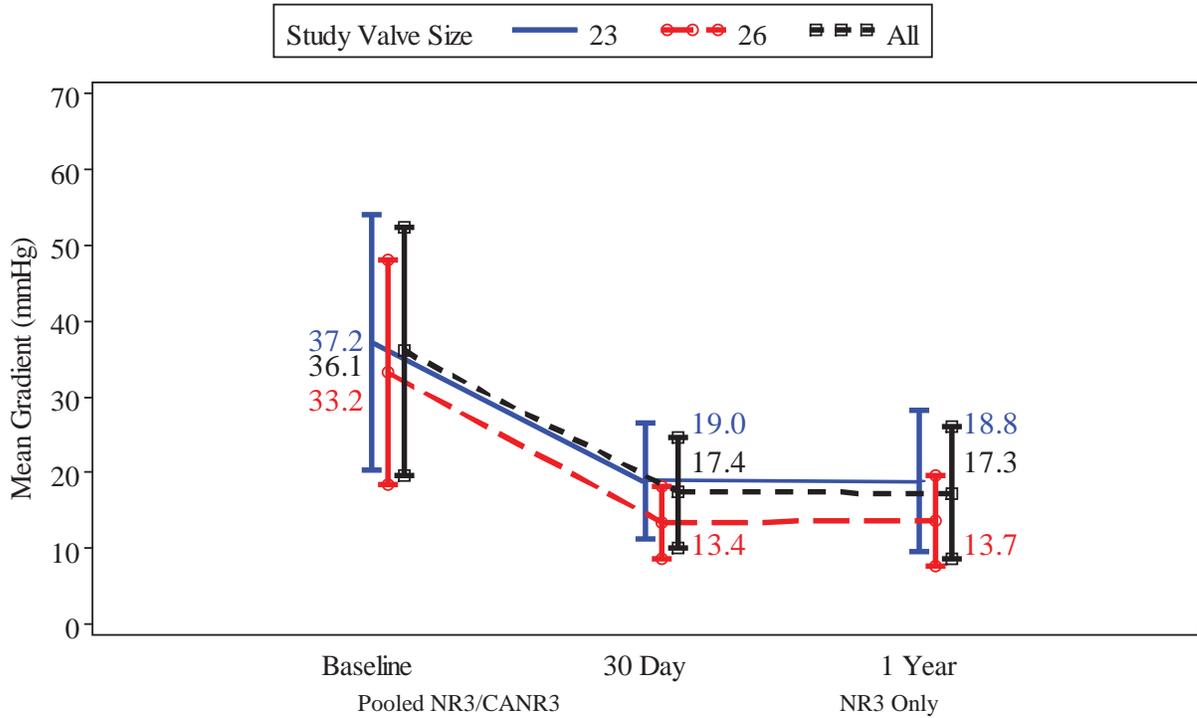
	<b>Baseline (N=195)</b>	<b>Discharge (N=195)</b>	<b>30 Days (N=195)</b>	<b>1 Year (N=96)</b>
<b>Doppler Velocity Index - mean ± SD (n)</b>				
All Valve Sizes	0.27 ± 0.10 (173)	0.37 ± 0.09 (161)	0.37 ± 0.09 (169)	0.39 ± 0.11 (54)
23 mm (N=140)	0.26 ± 0.09 (123)	0.36 ± 0.10 (114)	0.36 ± 0.09 (118)	0.38 ± 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)
<b>Mean Gradient (mmHg) - mean ± SD (n)</b>				
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)
<b>Peak Gradient (mmHg) - mean ± SD (n)</b>				
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)
<b>Total Aortic Regurgitation - no./total no. (%)</b>				
<b>All Valve Sizes</b>				
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%)
<b>23 mm</b>				
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%)
<b>26 mm</b>				
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%)
<b>Paravalvular Leak - no./total no. (%)</b>				
<b>All Valve Sizes</b>				
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%)
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%)

	Baseline (N=195)	Discharge (N=195)	30 Days (N=195)	1 Year (N=96)
<b>23 mm</b>				
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%)
<b>26 mm</b>				
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%)

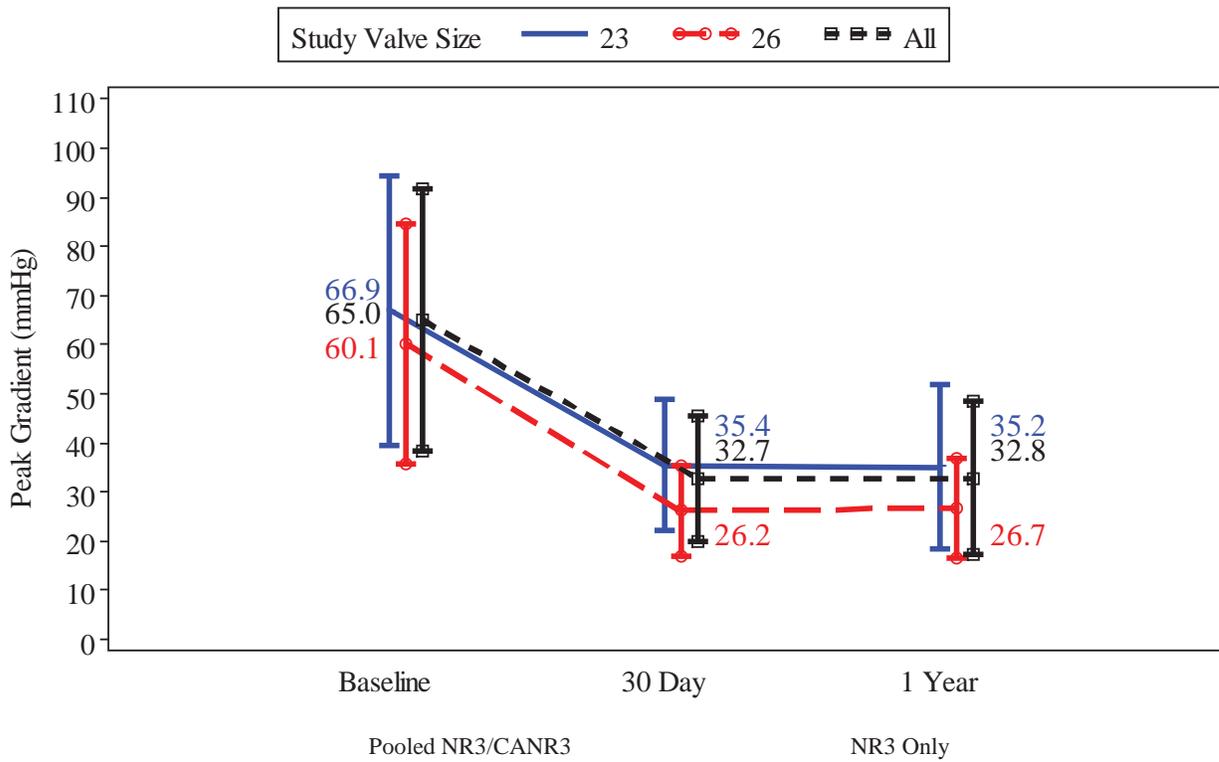
**Figure 11: Doppler Velocity Index by Visit – Valve Implant Population**



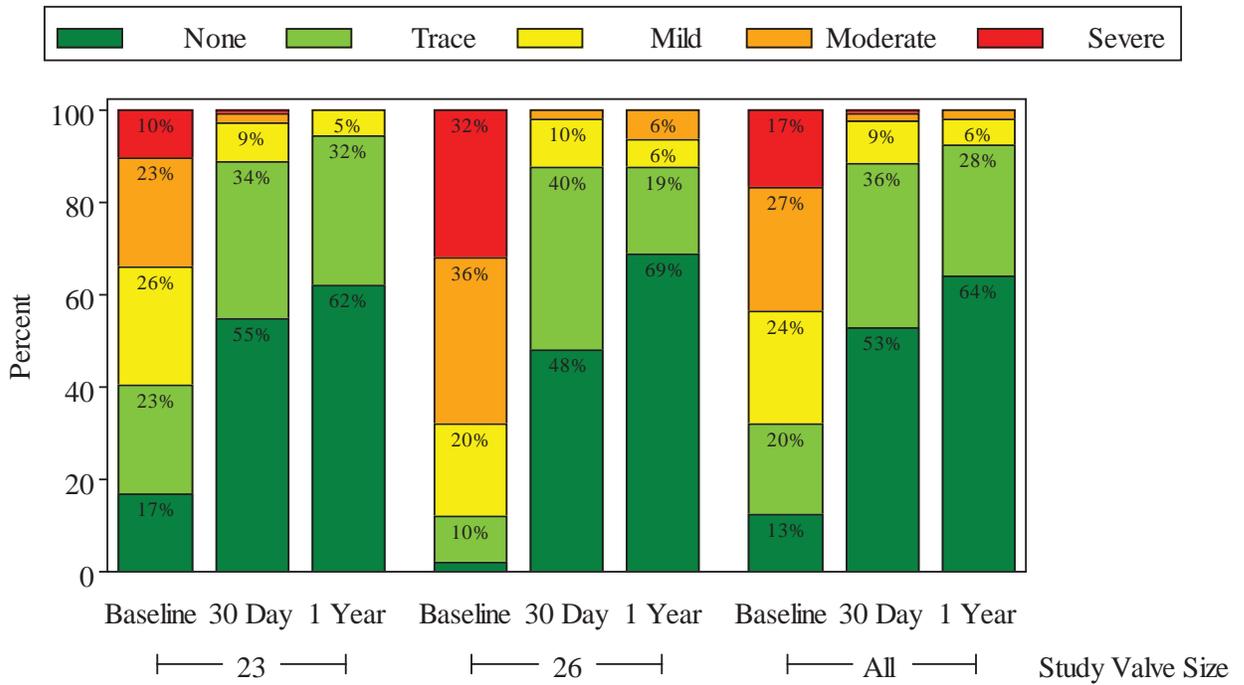
**Figure 12: Mean Gradient by Visit – Valve Implant Population**



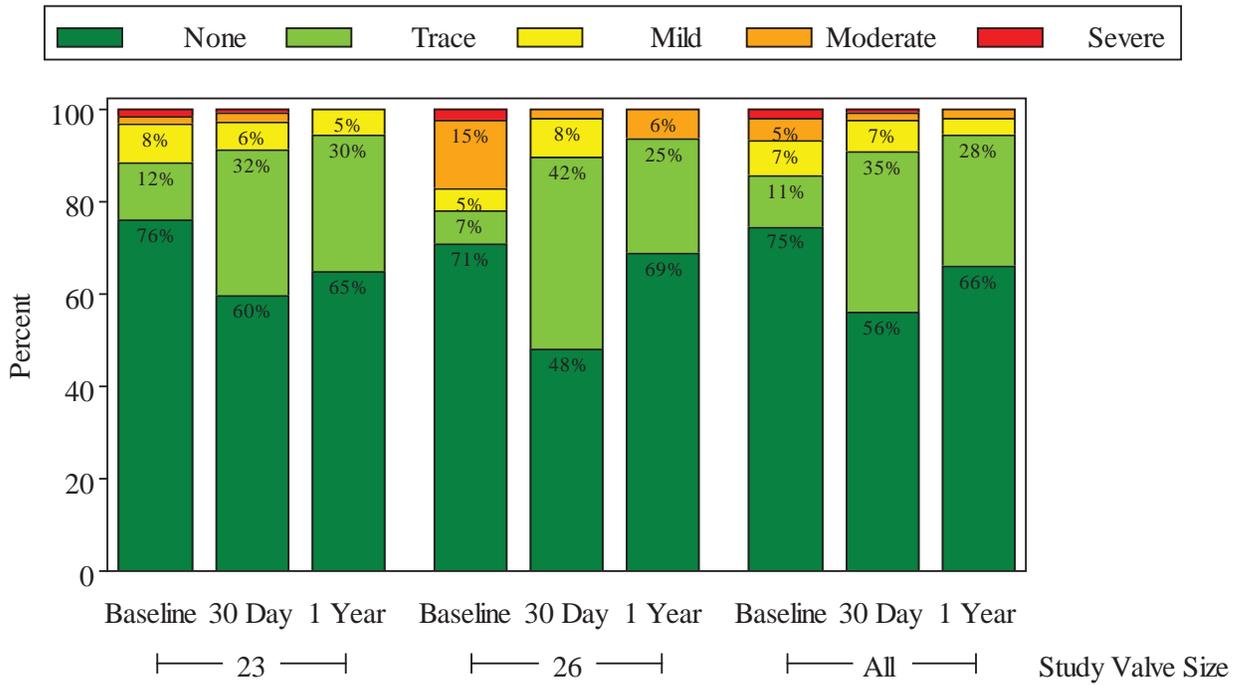
**Figure 13: Peak Gradient by Visit – Valve Implant Population**



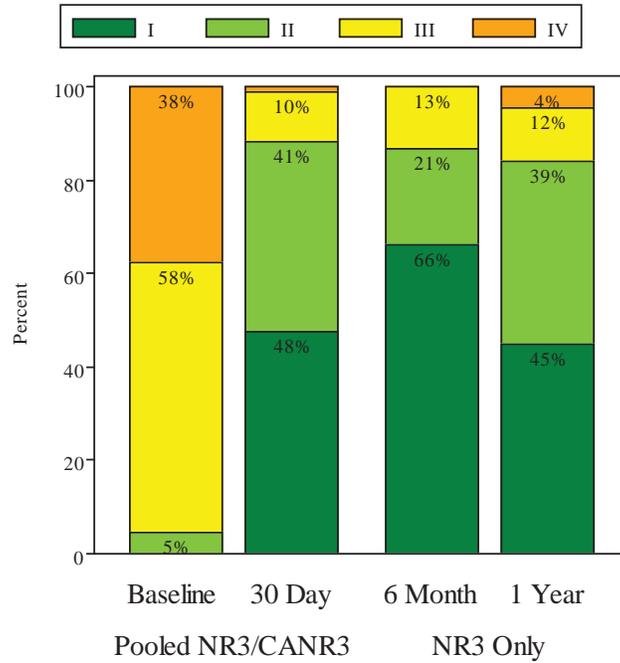
**Figure 14: Total Aortic Regurgitation by Visit – Valve Implant Population**



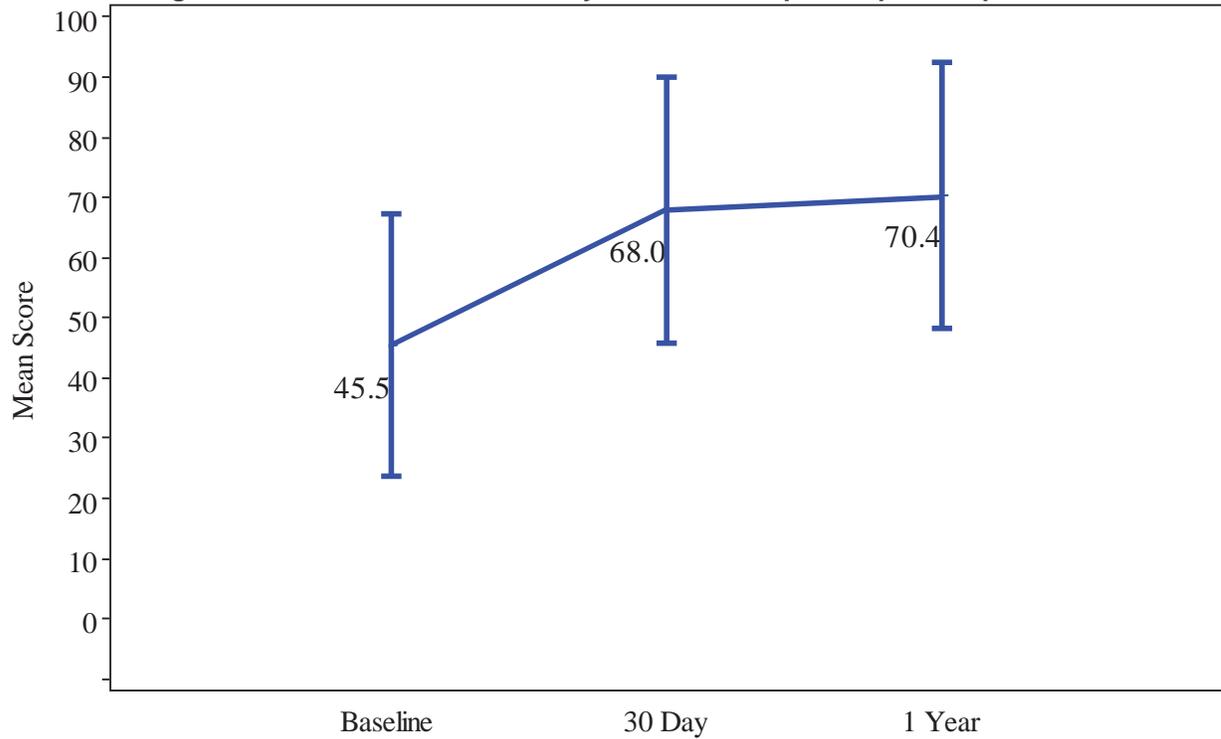
**Figure 15: Paravalvular Leak by Visit – Valve Implant Population**



**Figure 16: NYHA Class by Visit – Attempted Implant Population**



**Figure 17: KCCQ Clinical Summary Score – Attempted Implant Population**



**Table 15: Device Success and Reason for Device Failure - Valve Implant Population**

Device Success	Rate
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 $\geq$ 20mmHg or peak velocity $\geq$ 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%)
<sup>1</sup> Device success was defined as successful vascular access, delivery and deployment and retrieval of delivery system; correct positioning of the THV, intended performance (mean aortic valve gradient < 20 mmHg or peak velocity < 3 m/s, without moderate or severe prosthetic valve AR), only one THV 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. <sup>2</sup> 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.	

### 13.0 Bibliography

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.

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. 5,411,552; 6,214,054; 6,547,827; 6,561,970; 6,908,481; 7,214,344; 7,510,575; 7,530,253; and 7,993,394 and corresponding foreign patents. Additional patents are pending.

The FDA has requested Edwards to increase product surveillance with the SAPIEN XT THV in order to ensure a high-quality product experience. If you have any quality questions or concerns, please immediately call 1-949-250-3612, option 4.



Edwards

10/2015  
©Copyright 2015, Edwards Lifesciences LLC  
All rights reserved.

---

<b>Edwards Lifesciences LLC</b>	Telephone	949.250.2500
One Edwards Way		800.424.3278
Irvine, CA 92614-5688 USA	FAX	949.250.2525
Made in USA		

Web IFU  
158501002D

