Edwards SAPIEN 3, SAPIEN 3 Ultra, and SAPIEN 3 Ultra RESILIA Transcatheter Heart Valve System

Edwards SAPIEN 3, Edwards SAPIEN 3 Ultra, and Edwards SAPIEN 3 Ultra RESILIA Transcatheter Heart Valve

Edwards Commander Delivery System

Instructions for Use

CAUTION: Federal (USA) law restricts these devices 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 SAPIEN 3 and SAPIEN 3 Ultra valves are supplied sterilized with glutaraldehyde solution. The SAPIEN 3 Ultra RESILIA valve, delivery system, sheath, and crimper are supplied sterilized with ethylene oxide gas.

1.0 Device Description

Edwards SAPIEN 3, SAPIEN 3 Ultra, and SAPIEN 3 Ultra RESILIA Transcatheter Heart Valve System

The Edwards SAPIEN 3, SAPIEN 3 Ultra, and SAPIEN 3 Ultra RESILIA Transcatheter Heart Valve (THV) system consists of the Edwards SAPIEN 3, SAPIEN 3 Ultra, and SAPIEN 3 Ultra RESILIA transcatheter heart valves and delivery systems.

- **Edwards SAPIEN 3 Ultra RESILIA Transcatheter Heart Valve - (Figure 1)**

The Edwards SAPIEN 3 Ultra RESILIA transcatheter heart valve is comprised of a balloon-expandable, radiopaque, cobalt-chromium frame, trileaflet RESILIA bovine pericardial tissue valve, and polyethelyne terephthalate (PET) inner and outer fabric skirts.

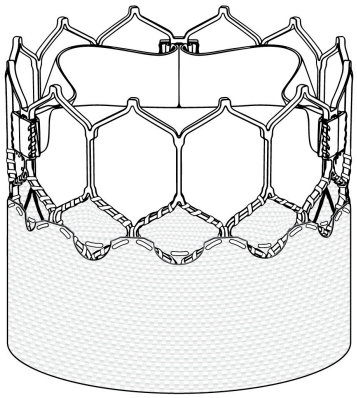
RESILIA Tissue: RESILIA tissue is created with a novel technology called Edwards Integrity Preservation. The technology incorporates a stable capping anti-calcification process, which blocks residual aldehyde groups that are known to bind with calcium. The technology also incorporates tissue preservation with glycerol, which replaces the traditional storage in liquid-based solutions such as glutaraldehyde. The storage method eliminates tissue exposure to the residual unbound aldehyde groups commonly found in glutaraldehyde storage solutions.

- **Edwards SAPIEN 3 Ultra Transcatheter Heart Valve - (Figure 2)**

The Edwards SAPIEN 3 Ultra transcatheter heart valve is comprised of a balloon-expandable, radiopaque, cobalt-chromium frame, trileaflet bovine pericardial tissue valve, and polyethylene terephthalate (PET) inner and outer fabric skirts. The leaflets are treated according to the Carpentier-Edwards ThermaFix process.

- **Edwards SAPIEN 3 Transcatheter Heart Valve - (Figure 3)**

The Edwards SAPIEN 3 transcatheter heart valve is comprised of a balloon-expandable, radiopaque, cobalt-chromium frame, trileaflet bovine pericardial tissue valve, and polyethylene terephthalate (PET) fabric skirt. The leaflets are treated according to the Carpentier-Edwards ThermaFix process.

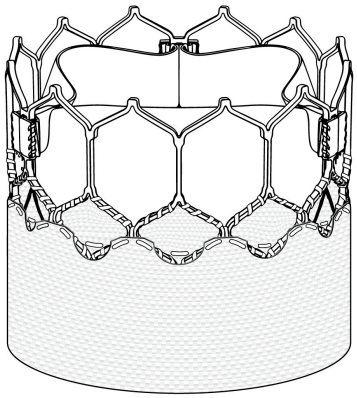


9755RSL

Table 1

Valve Size	Valve Height
20 mm	15.5 mm
23 mm	18 mm
26 mm	20 mm
29 mm	22.5 mm

Figure 1: Edwards SAPIEN 3 Ultra RESILIA Transcatheter Heart Valve

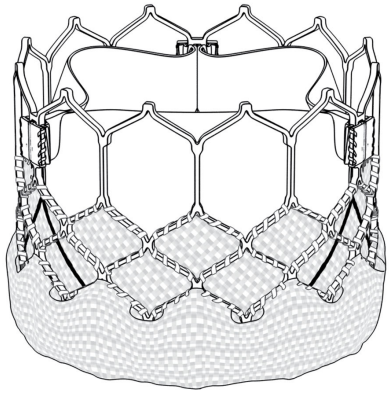


9750TFX

Table 2

Valve Size	Valve Height
20 mm	15.5 mm
23 mm	18 mm
26 mm	20 mm

Figure 2: Edwards SAPIEN 3 Ultra Transcatheter Heart Valve



9600TFX

Table 3

Valve Size	Valve Height
20 mm	15.5 mm
23 mm	18 mm
26 mm	20 mm
29 mm	22.5 mm

Figure 3: Edwards SAPIEN 3 Transcatheter Heart Valve

Sizing recommendations for implanting the Edwards SAPIEN 3, SAPIEN 3 Ultra, and SAPIEN 3 Ultra RESILIA transcatheter heart valves in a native annulus are provided in the table below:

Table 4

Native Valve Annulus Size (TEE)	Native Valve Annulus Size (CT)		THV Size
	Area	Area Derived Diameter	
16 - 19 mm	273 - 345 mm^2	18.6 - 21 mm	20 mm
18 - 22 mm	338 - 430 mm^2	20.7 - 23.4 mm	23 mm
21 - 25 mm	430 - 546 mm^2	23.4 - 26.4 mm	26 mm
24 - 28 mm	540 - 683 mm^2	26.2 - 29.5 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.

Sizing recommendations for implanting the Edwards SAPIEN 3, SAPIEN 3 Ultra, and SAPIEN 3 Ultra RESILIA transcatheter heart valves in a failing surgical bioprosthesis, except for the INSPIRIS RESILIA aortic valve sizes 19 - 25 mm, are provided in the table below:

Table 5

Surgical Valve True Inner Diameter (ID)[1]	THV Size
16.5 - 19.0 mm	20 mm
18.5 - 22.0 mm	23 mm
22.0 - 25.0 mm	26 mm
25.0 - 28.5 mm	29 mm

Note: Surgical valve 'True ID' may be smaller than the labeled valve size. For THV-in-THV, the native valve annulus size should be considered to determine the appropriate THV size to implant. For a failing stentless bioprosthesis, consider sizing recommendations for a native annulus. The dimensions of the failed bioprosthesis should be determined so that the appropriate THV size can be implanted; and is best determined by using computed tomography, magnetic resonance imaging, and/or transesophageal echocardiography.

Sizing recommendations for implanting the Edwards SAPIEN 3, SAPIEN 3 Ultra, and SAPIEN 3 Ultra RESILIA transcatheter heart valves in a failing INSPIRIS RESILIA aortic surgical bioprosthesis in sizes 19 - 25 mm are provided in the table below:

Table 6

INSPIRIS RESILIA Aortic Valve (model 11500A)* Labeled Size	THV Size
19 mm	20 mm or 23 mm
21 mm	23 mm or 26 mm
23 mm	26 mm
25 mm	29 mm

*INSPIRIS RESILIA aortic valve model 11500A sizes 19 - 25 mm incorporate VFit technology which consists of expandable bands and fluoroscopically visible size markers designed for potential future valve-in-valve procedures. Clinical data are not currently available on the INSPIRIS RESILIA aortic valve Model 11500A valve-in-valve procedure or expansion feature. The impact of tissue ingrowth on the expansion feature of the INSPIRIS RESILIA aortic valve has not been assessed.

WARNING: Do not perform stand-alone balloon aortic valvuloplasty procedures in the INSPIRIS RESILIA aortic valve for the sizes 19 - 25 mm. This may expand the valve causing aortic incompetence, coronary embolism or annular rupture.

Note: INSPIRIS RESILIA aortic valve model 11500A sizes 27 - 29 mm do not incorporate VFit technology and therefore follow the surgical valve True ID sizing provided in Table 5.

Sizing recommendations for implanting the Edwards SAPIEN 3, SAPIEN 3 Ultra, and SAPIEN 3 Ultra RESILIA transcatheter heart valves in a failing native mitral valve with an annuloplasty ring are provided in the table below:

Table 7

CT Orifice Area		SAPIEN 3, SAPIEN 3 Ultra, and SAPIEN 3 Ultra RESILIA
Min Value	Max Value	
280 mm^2	350 mm^2	23 mm
350 mm^2	450 mm^2	26 mm
450 mm^2	600 mm^2	29 mm
Note that the size 20 mm SAPIEN 3, SAPIEN 3 Ultra, and SAPIEN 3 Ultra RESILIA THV is not included due to its size being too small for the mitral position.		

WARNING: Transcatheter valve replacement in mitral annuloplasty rings is not recommended in cases of partial annuloplasty ring dehiscence due to high risk of PVL.

WARNING: Transcatheter valve replacement in mitral annuloplasty rings is not recommended in cases of partial (incomplete) annuloplasty rings in the absence of annular calcium due to increased risk of valve embolization.

WARNING: Transcatheter valve replacement in mitral annuloplasty rings is not recommended in cases of rigid annuloplasty rings due to increased risk of PVL or THV deformation.

Note: Exact volume required to deploy the THV may vary depending on the prosthesis inner diameter. Factors such as calcification and pannus tissue growth may not be accurately visualized in imaging and may reduce the effective inner diameter of the failing prosthesis to a size smaller than the 'True ID'. These factors should be considered and assessed in order to determine the most appropriate THV size to achieve nominal THV deployment and sufficient anchoring. Do not exceed the rated burst pressure. See Table 8 for inflation parameters.

- **Edwards Commander Delivery System - (Figure 4)**

The Edwards Commander delivery system facilitates the placement of the bioprosthesis. It consists of a flex catheter to aid in valve alignment to the balloon, tracking, and positioning of the valve. The delivery system includes a tapered tip to facilitate crossing of the valve. The handle contains a flex wheel to control flexing of the flex catheter, and a balloon lock and fine adjustment wheel to facilitate valve alignment and positioning of the valve within the target location. A stylet is included within the guidewire lumen of the delivery system. The balloon catheter has radiopaque valve alignment markers defining the working length of the balloon. A radiopaque center marker in the balloon is provided to help with valve positioning. A radiopaque triple marker proximal to the balloon indicates the flex catheter position during deployment. The inflation parameters for valve deployment are:

Table 8

Model	Nominal Balloon Diameter	Nominal Inflation Volume	Rated Burst Pressure (RBP)
9600LDS20 9750CM20	20 mm	11 ml	7 atm
9600LDS23 9750CM23	23 mm	17 ml	7 atm
9600LDS26 9750CM26	26 mm	23 ml	7 atm
9600LDS29 9750CM29	29 mm	33 ml	7 atm

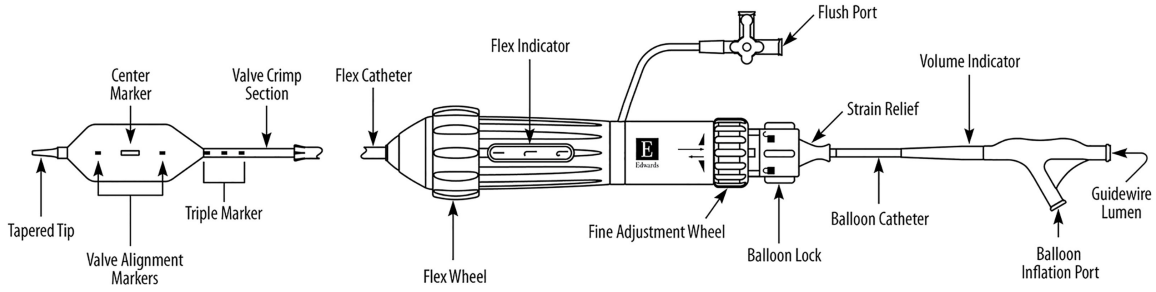


Figure 4: Edwards Commander Delivery System

Additional Accessories

Figure 5: Loader

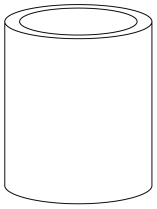


Figure 6: Qualcrimp Crimping Accessory

- **Loader**

The loader allows for the delivery of the crimped valve through the hemostasis valves of the sheath.

- **Edwards Sheath**

Refer to the provided Edwards sheath instructions for use for device description.

- **Edwards Crimper**

Refer to the Edwards Crimper instructions for use for device description.

2.0 Indications

1. The Edwards SAPIEN 3, SAPIEN 3 Ultra, and SAPIEN 3 Ultra RESILIA Transcatheter Heart Valve system is indicated to reduce the risks associated with progression from asymptomatic to symptomatic severe native calcific aortic stenosis in patients who are judged by a heart team to be appropriate for transcatheter heart valve replacement therapy.
2. The Edwards SAPIEN 3, SAPIEN 3 Ultra, and SAPIEN 3 Ultra RESILIA Transcatheter Heart Valve system is 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 appropriate for the transcatheter heart valve replacement therapy.
3. The Edwards SAPIEN 3, SAPIEN 3 Ultra, and SAPIEN 3 Ultra RESILIA Transcatheter Heart Valve system is indicated for patients with symptomatic heart disease due to a failing (stenosed, insufficient, or combined) surgical or transcatheter bioprosthetic aortic valve, or a native mitral valve with an annuloplasty ring who are judged by a heart team, including a cardiac surgeon, to be at high or greater risk for open surgical therapy (i.e., predicted risk of surgical mortality ≥ 8% at 30 days, based on the Society of Thoracic Surgeons (STS) risk score and other clinical co-morbidities unmeasured by the STS risk calculator).
4. The Edwards SAPIEN 3, SAPIEN 3 Ultra, and SAPIEN 3 Ultra RESILIA Transcatheter Heart Valve system is indicated for patients with symptomatic heart disease due to a failing (stenosed, insufficient, or combined) surgical bioprosthetic mitral valve 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 ≥ 4% at 30 days, based on the Society of Thoracic Surgeons (STS) risk score and other clinical co-morbidities unmeasured by the STS risk calculator).

3.0 Contraindications

The Edwards SAPIEN 3, SAPIEN 3 Ultra, and SAPIEN 3 Ultra RESILIA THV System are contraindicated in patients who cannot tolerate an anticoagulation/antiplatelet regimen, who have active bacterial endocarditis or other active infections, or who has significant annuloplasty ring dehiscence.

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.
- Incorrect sizing of the valve may lead to paravalvular leak, migration, embolization, residual gradient (patient-prosthesis mismatch) and/or annular rupture.
- Accelerated deterioration of the valve due to calcific degeneration may occur in children, adolescents, or young adults and 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 prostheses should be carefully assessed prior to implantation of the valve to ensure proper valve positioning and deployment.
- Do not use the valve if the tamper evident seal is broken, the storage solution does not completely cover the valve (SAPIEN 3 and SAPIEN 3 Ultra only), the temperature indicator has been activated, the valve is damaged, or the expiration date has elapsed.
- Do not mishandle the 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.
- Use of excessive contrast media may lead to renal failure. Measure the patient's creatinine level prior to the procedure. Contrast media usage should be monitored.
- Patient injury could occur if the delivery system is not un-flexed prior to removal.
- 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 (SAPIEN 3 and SAPIEN 3 Ultra only), rinse solutions, or to the valve.
- Balloon valvuloplasty should be avoided in the treatment of failing bioprostheses as this may result in embolization of bioprosthesis material and mechanical disruption of the valve leaflets.

5.0 Precautions

- Long-term durability has not been established for the valve. Regular medical follow-up is advised to evaluate valve performance.
- Limited clinical data are available for transcatheter aortic valve replacement in patients with a congenital bicuspid aortic valve who are deemed to be at low surgical risk. Anatomical characteristics should be considered when using the valve in this population. In addition, patient age should be considered as long-term durability of the valve has not been established.
- Data on TAVR in patients with asymptomatic severe aortic stenosis are based on study of predominantly low surgical risk patients. Limited clinical data to inform benefit-risk considerations are available for TAVR in patients with asymptomatic severe aortic stenosis who are deemed to be at intermediate or greater surgical risk.
- 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.
- If a significant increase in resistance occurs when advancing the catheter through the vasculature, stop advancement and investigate the cause of resistance before proceeding. Do not force passage, as this could increase the risk of vascular complications. As compared to SAPIEN 3, system advancement force may be higher with the use of SAPIEN 3 Ultra/SAPIEN 3 Ultra RESILIA THV in tortuous/challenging vessel anatomies.
- 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.
- Additional precautions for transseptal replacement of a failed mitral valve bioprosthesis include, presence of devices or thrombus or other abnormalities in the caval vein precluding safe transvenous femoral access for transseptal approach; presence of Atrial Septal Occluder Device or calcium preventing safe transseptal access.
- Special care must be exercised in mitral valve replacement to avoid entrapment of the subvalvular apparatus.
- 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 aortic valve
  - Pre-existing prosthetic ring in the tricuspid position
  - Severe mitral annular calcification (MAC), severe (> 3+) mitral insufficiency, or Gorlin syndrome
  - Blood dyscrasias defined as: leukopenia (WBC < 3000 cells/µL), acute anemia (Hb < 9 g/dL), thrombocytopenia (platelet count < 50,000 cells/µL), 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
  - Significant aortic disease, including abdominal aortic or thoracic aneurysm defined as maximal luminal diameter 5 cm or greater; marked tortuosity (hyperacute bend), aortic arch atheroma (especially if thick [> 5 mm], protruding, or ulcerated) or narrowing (especially with calcification and surface irregularities) of the abdominal or thoracic aorta, severe "unfolding" and tortuosity of the thoracic aorta
  - Access characteristics that would preclude safe placement of the Edwards sheath, such as severe obstructive calcification or severe tortuosity
  - Bulky calcified aortic valve leaflets in close proximity to coronary ostia
  - A concomitant paravalvular leak where the failing prosthesis is not securely fixed in the native annulus or is not structurally intact (e.g., wireform frame fracture, annuloplasty ring dehiscence)
  - A partially detached leaflet of the failing bioprosthesis that in the aortic position may obstruct a coronary ostium

- For Left axillary approach, a left subclavian takeoff angle ~ ≥ 90° from the aortic arch causes sharp angles, which may be responsible for potential sheath kinking, subclavian/axillary dissection and aortic arch damage.
- For left/right axillary approach, ensure there is flow in Left Internal Mammary Artery (LIMA)/Right Internal Mammary Artery (RIMA) during procedure and monitor pressure in homolateral radial artery.
- Residual mean gradient may be higher in a "THV-in-failing prosthesis" 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 prosthesis 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 inner diameter as possible.
- Post-procedure and follow-up assessment of TAVR device performance by Doppler echocardiography may be impacted by inherent limitations in the Bernoulli equation used to determine measurements such as mean gradient, EOA, and prosthesis-patient mismatch. These limitations may lead to an overstating or understating of valve performance measurements after TAVR implantation. Therefore, a post-TAVR echocardiogram should be used to establish a baseline from which future follow-up visits are compared to. Confirmatory direct pressure measurement via cardiac catheterization may be considered, when indicated, prior to reintervention.

6.0 Patient Selection and Counseling

6.1 Patient Selection

Patient selection should be performed by the multi-disciplinary heart team. Use of the SAPIEN 3, SAPIEN 3 Ultra, and SAPIEN 3 Ultra RESILIA THV system should be considered an option for asymptomatic patients with severe aortic stenosis. Specific factors that need to be considered include the following:

- Overall medical status, including conditions which might preclude the safety of a percutaneous, transcatheter procedure including severe tortuosity of the anatomy, native aortic annulus size unsuitable for transcatheter valves sizes 20, 23, 26, 29 mm based on 3D imaging, and left ventricular outflow tract calcification that would increase the risk of annular rupture or significant paravalvular leak (PVL) post- TAVR.
- Inability to tolerate or condition precluding treatment with anti-thrombotic therapy or anticoagulation
- Hypertrophic cardiomyopathy with obstruction
- Need for cardiac surgery for other reasons
- Bicuspid valve with unfavorable features for TAVR
- Renal insufficiency and/or renal replacement therapy
- Life expectancy and considerations for future interventions

6.2 Patient Counseling

Care decisions for an asymptomatic patient should be made by the multi-disciplinary heart team and patient in light of all the circumstances presented. The process should use tools for shared decision-making in which patient values, preferences, and associated conditions and co-morbidities, as well as the risks and benefits associated with the treatment options and potential future procedures, are considered.

The patient should be counseled with respect to their disease, expected disease progression and treatment options, including the following information:

- An explanation of heart valve disease and severe aortic stenosis and the progressive and unpredictable nature of the condition which will ultimately result in the need for valve replacement
- Discussion of the available options while the patient is asymptomatic to include the risk associated with waiting or undergoing TAVR and include a discussion of the benefits. Specifically, the risks of early TAVR are permanent pacemaker implantation and bleeding.
- Discussion of the need for blood-thinning medication and/or aspirin as recommended.
- Provide and review the patient brochure

7.0 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, atrium, septum, myocardium or valvular structures that may require intervention
- Pericardial effusion or cardiac tamponade
- Thoracic bleeding
- 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 or brachial plexus 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 (e.g., wound infection, hematoma, and other wound care complications) 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
- Left ventricular outflow tract obstruction
- 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

8.0 Directions for Use

8.1 System Compatibility

Table 9

Product Name	20 mm System	23 mm System	26 mm System	29 mm System
	Model			
Edwards SAPIEN 3 Ultra RESILIA Transcatheter Heart Valve	9755RSL20	9755RSL23	9755RSL26	9755RSL29
Edwards Commander Delivery System	9750CM20	9750CM23	9750CM26	9750CM29
Sheath provided by Edwards Lifesciences				
Inflation device, Qualcrimp crimping accessory, crimp stopper and loader provided by Edwards Lifesciences				
Edwards Crimper	9600CR			

Table 10

Product Name	20 mm System	23 mm System	26 mm System
	Model		
Edwards SAPIEN 3 Ultra Transcatheter Heart Valve	9750TFX20	9750TFX23	9750TFX26
Edwards Commander Delivery System	9750CM20	9750CM23	9750CM26
Sheath provided by Edwards Lifesciences			
Inflation device, Qualcrimp crimping accessory, crimp stopper and loader provided by Edwards Lifesciences			
Edwards Crimper	9600CR		

Table 11

Product Name	20 mm System	23 mm System	26 mm System	29 mm System
	Model			
Edwards SAPIEN 3 Transcatheter Heart Valve	9600TFX20	9600TFX23	9600TFX26	9600TFX29
Edwards Commander Delivery System	9600LDS20	9600LDS23	9600LDS26	9600LDS29
Sheath provided by Edwards Lifesciences				
Inflation device, Qualcrimp crimping accessory, crimp stopper and loader provided by Edwards Lifesciences				
Edwards Crimper	9600CR			

Additional Equipment:

- Balloon catheter, per the discretion of the physician
- 20 cc syringe or larger (x2)
- 50 cc syringe or larger
- High-pressure 3-way stopcock (x2)

- 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
- Instrumentation for transseptal access and septostomy, as applicable
- Sterile rinsing basins, physiological saline, heparinized saline, 15% diluted radiopaque contrast medium
- Sterile table for valve and device preparation

8.2 Valve Handling and Preparation

Maintain sterile technique during device preparation and implantation.

SAPIEN 3 Ultra RESILIA Transcatheter Heart Valve

The SAPIEN 3 Ultra RESILIA transcatheter heart valve is provided sterile and nonpyrogenic. The packaging consists of a carton containing a foil pouch. Within the foil pouch is a tray that is sealed with a Tyvek lid. Inside of the tray is the valve holder which contains the valve.

1. Remove the tamper evident label to open the carton.
2. Remove the foil pouch from the carton in the non-sterile field. Before opening, examine the package for evidence of damage and broken or missing seals. Open pouch and remove tray in the non-sterile field.

   WARNING: Do not open foil pouch into sterile field. Foil pouch is a protective cover only. Only the valve holder may be introduced into the sterile field.
3. The tray is labeled with the model, size, and serial number. The model, size, and serial number should be confirmed with the number on the valve package and valve implant data card.
4. Near the sterile field, hold the base of the tray and peel the lid from the tray.
5. The valve holder and contents are sterile. Transfer the valve holder to the sterile field.

   CAUTION: The contents of the valve holder must be handled using a sterile technique. Take care when removing the valve holder from the tray to ensure there is no contact with the nonsterile adhesive on the lip of the tray.

8.2.1 Valve Soaking/Rinsing Procedure

8.2.1.1 SAPIEN 3 Ultra RESILIA Transcatheter Heart Valve

1. Setup one (1) sterile bowl with at least 500 ml of sterile physiological saline to soak the valve.
2. Open the valve holder by holding the base and lifting the lid. Carefully remove the valve from the valve holder without touching the tissue. Inspect the valve for any signs of damage to the frame or tissue.
3. Place the valve in the sterile bowl of sterile physiological saline. Be sure that the sterile physiological saline completely covers the valve for at least two minutes to hydrate the leaflets. The valve should be left in the sterile physiological saline to prevent the tissue from drying.

   CAUTION: No other objects should be placed in the soak bowl. The valve should be kept hydrated to prevent the tissue from drying.

8.2.1.2 SAPIEN 3 and SAPIEN 3 Ultra Transcatheter Heart Valve

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.

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.
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 sterile 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.

8.2.2 Prepare the Components

Refer to the Edwards sheath, Edwards Crimper and Edwards Balloon Catheter instructions for use for device preparation.

1. Visually inspect all components for damage. Ensure the Edwards Commander delivery system is fully unflexed and the balloon catheter is fully advanced in the flex catheter.

   WARNING: To prevent possible damage to the balloon shaft, ensure that the proximal end of the balloon shaft is not subjected to bending.
2. Flush the flex catheter.
3. Carefully remove the distal balloon cover from the delivery system.
4. Remove the stylet from the distal end of the guidewire lumen and set aside. Flush the guidewire lumen with heparinized saline and insert the stylet back into the distal end of the guidewire lumen.

   NOTE: Failure to insert the stylet back into the guidewire lumen may result in damage to the lumen during crimping process.
5. Place the delivery system into the default position and make sure that the flex catheter tip is covered by the proximal balloon cover. Unscrew the loader cap from the loader tube and flush the loader cap. Place the loader cap over the proximal balloon cover and onto the flex catheter with the inside of the cap oriented towards the distal tip.
6. Fully advance the balloon catheter in the flex catheter.
   Peel off the proximal balloon cover over the blue section of the balloon shaft.
7. Attach a 3-way stopcock to the balloon inflation port. Partially fill a 50 cc or larger syringe with 15 - 20 ml diluted contrast medium and attach to the 3-way stopcock.
8. Fill the inflation device provided by Edwards Lifesciences with excess volume relative to the indicated inflation volume. Lock the inflation device and attach to the 3-way stopcock.
9. Close the 3-way stopcock to the inflation device provided by Edwards Lifesciences and de-air the system using the 50 cc or larger syringe. Slowly release the plunger and leave zero-pressure in the system.

   WARNING: Ensure there is no residual fluid left in the balloon to avoid potential difficulty with valve alignment during the procedure.
10. Close the stopcock to the delivery system. By rotating the knob of the inflation device provided by Edwards Lifesciences, transfer the contrast medium into the syringe to achieve the appropriate volume required to deploy the valve.
11. Close the stopcock to the 50 cc or larger syringe. Remove the syringe. Verify that the inflation volume is correct and lock the inflation device provided by Edwards Lifesciences.

    CAUTION: Maintain the inflation device provided by Edwards Lifesciences in the locked position until valve deployment.

8.2.3 Mount and Crimp the Valve on the Delivery System

1. Set up two (2) additional sterile bowls with at least 100 ml of sterile physiological saline to thoroughly rinse the Qualcrimp crimping accessory.
2. Completely submerge the Qualcrimp crimping accessory in the first bowl and gently compress it to ensure complete saline absorption. Slowly swirl the Qualcrimp crimping accessory for a minimum of 1 minute. Repeat this process in the second bowl.
3. Remove the valve from the soaking/rinsing bowl. When using the SAPIEN 3 or SAPIEN 3 Ultra valve remove the valve from the holder and remove the ID tag.
4. Attach the 2-piece crimp stopper to the base of the crimper and click into place.
5. With the crimper in the open position, gently place the valve into the crimper aperture. Gradually crimp the valve until it fits into the Qualcrimp crimping accessory.
6. Place the Qualcrimp crimping accessory over the valve making sure the valve is parallel to the edge of the Qualcrimp crimping accessory.
7. Place the valve and Qualcrimp crimping accessory in crimper aperture. Insert the delivery system coaxially within the valve on the Valve Crimp Section (2-3 mm distal to the balloon shaft) with the orientation of the valve on the delivery system as described below:

   Antegrade approach: Inflow (outer skirt end) of the valve towards the proximal end of the delivery system.

Retrograde approach: Inflow (outer skirt end) of the valve towards the distal end of the delivery system.

8. Crimp the valve until it reaches the Qualcrimp Stop located on the 2-piece Crimp Stopper.
9. Gently remove the Qualcrimp crimping accessory from the valve. Remove the Qualcrimp Stop from the Final Stop, leaving the Final Stop in place.
10. Fully crimp the valve until it reaches the Final Stop and hold for 5 seconds.

    Note: Ensure that the Valve Crimp Section remains coaxial within the valve. Ensure that the valve is fully within the crimper jaws during crimping.
11. Repeat the full crimp of the valve two more times for a total of three full crimps for 5 seconds each.
12. Pull the balloon shaft and lock in the default position.
13. Flush the loader with heparinized saline. Immediately advance the valve into the loader until it is completely inside the loader.

    CAUTION: To prevent possible leaflet damage, the valve should not remain fully crimped and/or in the loader for over 15 minutes.
14. Attach the loader cap to the loader, re-flush the delivery system through the flush port and close the stopcock to the delivery system.

    Remove the stylet and flush the guidewire lumen of the delivery system.

    CAUTION: Keep the valve hydrated until ready for implantation.

    CAUTION: The physician must verify correct orientation of the valve prior to its implantation.

8.3 Valvuloplasty and Valve Delivery

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

Administer heparin to maintain the ACT at ≥ 250 sec during the procedure.

Balloon valvuloplasty should be avoided in the treatment of failing bioprostheses as this may result in embolization of bioprosthesis material and mechanical disruption of the valve leaflets.

CAUTION: Use of excessive contrast media may lead to renal failure. Measure the patient's creatinine level prior to the procedure. Contrast media usage should be monitored.

CAUTION: Procedure may require an arterial cut-down with surgical closure of the puncture site due to the size of the arteriotomy.

8.3.1 Baseline Parameters

1. Perform an angiogram with fluoroscopic view perpendicular to the valve.
2. Evaluate the distance of the left and right coronary ostia from the aortic annulus in relation to the valve frame height.
3. Introduce a pacemaker (PM) lead and position appropriately.
4. Set the stimulation parameters to obtain 1:1 capture, and test pacing.

8.3.2 Valvuloplasty

Pre-dilate the native aortic valve, per the discretion of the physician, according to the instructions for use for the selected balloon aortic valvuloplasty catheter.

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

8.3.3 Valve Delivery

1. Gain access using standard catheterization techniques.
2. Prepare and insert the Edwards sheath. Refer to the Edwards sheath IFU for information on device preparation and handling.
3. Insert the loader into the sheath until the loader stops.
4. Advance the Edwards Commander delivery system, with the Edwards logo in the proper orientation (the delivery system articulates in a direction opposite from the flush port), through the sheath until the valve exits the sheath.

    Note: Maintain the proper orientation of the flex catheter throughout the procedure. The delivery system articulates in a direction opposite from the flush port.

    CAUTION: For iliofemoral access, the valve should not be advanced through the sheath if the sheath tip is not past the bifurcation.

    CAUTION: To prevent possible leaflet damage, the valve should not remain in the sheath for over 5 minutes.

5. In a straight section of the vasculature, initiate valve alignment by disengaging the balloon lock and pulling the balloon catheter straight back until part of the warning marker is visible. Do not pull past the warning marker.

   WARNING: To prevent possible damage to the balloon shaft, ensure that the proximal end of the balloon shaft is not subjected to bending.

   Engage the balloon lock.

   Use the fine adjustment wheel to position the valve between the valve alignment markers.

   CAUTION: Do not turn the fine adjustment wheel if the balloon lock is not engaged.

   WARNING: Do not position the valve past the distal valve alignment marker. This will prevent proper valve deployment.

   CAUTION: Maintain guidewire position during valve alignment.

   WARNING: If valve alignment is not performed in a straight section, there may be difficulties performing this step which may lead to delivery system damage and inability to inflate the balloon. Utilizing alternate fluoroscopic views may help with assessing curvature of the anatomy. If excessive tension is experienced during valve alignment, repositioning the delivery system to a different straight section of the vasculature and relieving compression (or tension) in the system will be necessary.
6. Advance the catheter and use the flex wheel, if needed, to cross the valve or annuloplasty ring.

   Note: Verify the orientation of the Edwards logo to ensure proper articulation. The delivery system articulates in a direction opposite from the flush port.
7. Disengage the balloon lock and retract the tip of the flex catheter to the center of the triple marker. Engage the balloon lock.
8. Verify the correct position of the valve with respect to the target location.
9. As necessary, utilize the flex wheel to adjust the co-axiality of the valve and the fine adjustment wheel to adjust the position of the valve.
10. Before deployment, ensure that the valve is correctly positioned between the valve alignment markers and the flex catheter tip is over the triple marker.
11. Begin valve deployment:
    - Unlock the inflation device provided by Edwards Lifesciences.
    - Begin rapid pacing; once systolic 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.
    - Deflate the balloon. When the balloon catheter has been completely deflated, turn off the pacemaker.

8.3.4 System Removal

1. Unflex the delivery system while retracting the device, if needed. Verify that the flex catheter tip is locked over the triple marker. Retract the loader to the proximal end of the delivery system and remove the delivery system from the sheath.

   Note: For subclavian-axillary approach, keep delivery system inside sheath until ready to remove all devices as one unit.

   CAUTION: Patient injury could occur if the delivery system is not unflexed prior to removal.
2. Remove all devices when the ACT level is appropriate. Refer to the Edwards sheath instructions for use for device removal.
3. Close the access site.

9.0 How Supplied

STERILE: The SAPIEN 3 and SAPIEN 3 Ultra valves are supplied sterilized with glutaraldehyde solution. The SAPIEN 3 Ultra RESILIA valve and Edwards Commander delivery system are supplied sterilized with ethylene oxide gas.

9.1 Storage

The valve must be stored at 10 °C to 25 °C (50 °F to 77 °F). Each valve 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.

10.0 Magnetic Resonance (MR) Safety Information

MRI Safety Information

A person with the SAPIEN 3, SAPIEN 3 Ultra, or SAPIEN 3 Ultra RESILIA transcatheter heart valve implant may be safely scanned under the following conditions. Failure to follow these conditions may result in injury.	
Device Name	Edwards SAPIEN 3 transcatheter heart valve Edwards SAPIEN 3 Ultra transcatheter heart valve Edwards SAPIEN 3 Ultra RESILIA transcatheter heart valve
Static Magnetic Field Strength (B0)	1.5 T or 3.0 T
Maximum Spatial Field Gradient	25 T/m (2,500 gauss/cm)
RF Excitation	Circularly Polarized (CP) / Multichannel-2 (MC-2)
RF Transmit Coil Type	There are no Transmit Coil restrictions
Operating Mode	Normal Operating Mode
Maximum Whole-Body SAR	2 W/kg
Scan Duration	2 W/kg whole-body average SAR for 60 minutes of continuous RF (a sequence or back to back series/scan without breaks)
MR Image Artifact	The presence of this implant may produce an image artifact.
For valve-in-prosthesis 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.	

11.0 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.

12.0 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.

13.0 Clinical Studies

13.1 SUMMARY OF PRIMARY CLINICAL STUDY

THE PARTNER II TRIAL OVERVIEW, SAPIEN 3 VALVE

SAPIEN 3 High Risk and Inoperable Cohort: The SAPIEN 3 High Risk and Inoperable Cohort of the PARTNER II trial (PIIS3HR) was a single arm, non-randomized, historical-controlled study to compare the third generation Edwards SAPIEN 3 system with the first generation Edwards SAPIEN valve system in patients who either have high risk for surgery or cannot undergo surgery (inoperable). The valve sizes used in the PIIS3HR trial included only the 23, 26 and 29 mm sizes. The 20 mm valve size was introduced into the trial after enrollment was completed with the three larger sizes, thus a separate nested registry, NR7, with identical inclusion/exclusion criteria as the PIIS3HR Cohort except for the aortic annulus diameter, was created to collect data for

the 20 mm valve. Data from the PIIS3HR Cohort and NR7 are pooled for the statistical analyses. For convenience, this combined cohort is referred to as "PIIS3HR" hereafter.

The database included 583 eligible patients enrolled at 29 investigational sites in the U.S.

The PIIS3HR study used an independent Data Safety Monitoring Board (DSMB) that was instructed to notify Edwards Lifesciences of any safety or compliance issues, a Clinical Events Committee (CEC) that was responsible for adjudicating endpoint related events reported during the trial per *a priori* established VARC 2 definitions[2], an ECG core laboratory for independent analysis of rhythm, and an echocardiographic core laboratory for independently analyzing all echocardiograms.

SAPIEN 3 Post Approval Study, High Risk and Inoperable Cohort: The post approval study consisted of continued follow-up of the patients enrolled in the PARTNER II High Risk and Inoperable Cohort and the nested registry for the 20 mm valve size (NR7). A database extract was performed on February 01, 2021, which yielded 664 operable high risk and inoperable patients that had been treated with an Edwards SAPIEN 3 transcatheter heart valve. The patients were treated between October 1, 2013 and August 11, 2015. The procedure was performed in 40 sites, 39 in the US and 1 in Canada.

Clinical Inclusion and Exclusion Criteria

Patients in the trial received a SAPIEN 3 transcatheter heart valve for symptomatic heart disease due to severe native calcific aortic stenosis who were deemed to be at high risk or inoperable for surgical aortic valve replacement (complete inclusion and exclusion criteria are available at https://www.accessdata.fda.gov/cdrh_docs/pdf14/P140031b.pdf).

Follow-up Schedule

Patients in the post approval study were followed-up annually through five years.

Clinical Endpoints

The endpoints analyzed in this application included death rate, adjudicated adverse events (stroke, aortic valve reinterventions, prosthetic valve dysfunction, rehospitalization from symptoms of aortic stenosis and/or complications of the valve procedure, and endocarditis), key site reported adverse events, valve performance based on echocardiographic data, New York Heart Association (NYHA) classification, length of hospitalization, and the Kansas City Cardiomyopathy Questionnaire (KCCQ) score.

SAPIEN 3 Intermediate Risk Cohort: The PIIS3i Cohort of the PARTNER II trial was a single arm, non-randomized, historical-controlled study to compare TAVR with the Edwards SAPIEN 3 system to the surgical aortic valve replacement (SAVR) arm from the previous PARTNER II trial Cohort A (PIIA-SAVR) in patients who were judged by a heart team to be at intermediate risk for open surgical therapy. The valve sizes used in the PIIS3i study included the 20, 23, 26, and 29 mm sizes.

Patients in PIIS3i were treated between February 2014 and September 2014. Patients in PIIA-SAVR were treated between January 2012 and November 2013. The database reflected data collected through December 10, 2015 and included 1,078 patients in PIIS3i enrolled at 51 investigational sites in the U.S. and 1,021 patients in PIIA-SAVR enrolled at 57 investigational sites in the U.S.

The PIIS3i 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 pre-established definitions, which were primarily Valve Academic Research Consortium-1 VARC-2 definitions[2], with the following exceptions:

- Prosthetic valve dysfunction was adjudicated per VARC-1
- Aortic valve reintervention was adjudicated per protocol definition
- Rehospitalization for symptoms of aortic stenosis and/or complications of the valve procedure were adjudicated using the protocol and VARC-2 definitions as guidelines

The events in the PIIA-SAVR cohort were adjudicated by the CEC in accordance with the pre-specified, primarily VARC-1 definitions, with the following exceptions:

- Acute Kidney Injury (AKI) was adjudicated with a modified VARC-1 definition in which the CEC applied the 72-hour staging window to any AKI event that occurred within 30 days
- Aortic valve reintervention was adjudicated per the 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

An electrocardiogram (ECG) core laboratory was used for independent analysis of rhythm, an echocardiographic core laboratory for echocardiograms, and a computerized tomography (CT) core laboratory for baseline CTs for annulus dimensions.

Clinical Inclusion and Exclusion Criteria

Patients in the trial received a SAPIEN 3 transcatheter heart valve for symptomatic heart disease due to severe native calcific aortic stenosis who were deemed to be at intermediate risk for surgical aortic valve replacement (complete inclusion and exclusion criteria are available at https://www.accessdata.fda.gov/cdrh_docs/pdf14/P140031S010b.pdf).

Follow-up Schedule

Patients in the post approval study will be followed annually through ten years.

SAPIEN 3 Post Approval Study, Intermediate Risk Cohort: The post approval study consisted of continued follow-up of the patients enrolled in the PIIS3i study. A database extract was performed on April 01, 2024, which yielded 512 intermediate risk TAVR patients and 458 SAVR patients.

THE PARTNER 3 TRIAL OVERVIEW, SAPIEN 3 VALVE

Patients were enrolled between March 2016 and June 2018. The database reflected data collected through December 21, 2018 and included 1000 patients. There were 71 investigational sites in the U.S, Australia, Canada, New Zealand, and Japan.

The PARTNER 3 trial was a prospective, randomized (1:1), controlled, multicenter study to compare TAVR with the Edwards SAPIEN 3 THV to SAVR. A subset of patients were enrolled in a computed tomography (CT) substudy to investigate the prevalence of Hypoattenuated Leaflet Thickening (HALT) and reduced leaflet mobility.

The PARTNER 3 trial used an independent Data Safety Monitoring Board (DSMB) that was instructed to notify the applicant 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 Valve Academic Research Consortium-2 (VARC-2) definitions[2]. A CT core laboratory was used for assessment of baseline CTs for annulus dimensions and the CT images acquired in the CT substudy.

SAPIEN 3 Post Approval Study, Low Risk Cohort: The post approval study consisted of continued follow-up of the patients enrolled in the PARTNER 3 Low Risk Trial. A database extract was performed on June 05, 2023, which yielded 418 low risk TAVR patients and 359 SAVR patients.

Clinical Inclusion and Exclusion Criteria

Patients in the trial received a commercially available SAPIEN 3 transcatheter heart valve and surgical valves for symptomatic heart disease due to severe native calcific aortic stenosis who were deemed to be at low risk for surgical aortic valve replacement (complete inclusion and exclusion criteria are available at https://www.accessdata.fda.gov/cdrh_docs/pdf14/P140031S085B.pdf).

Follow-up Schedule

Patients in the post approval study will be followed annually through ten years.

Clinical Endpoints

The endpoints analyzed in this application included: death rate, adjudicated adverse events (stroke, TIA, and aortic valve reinterventions, rehospitalization), key site reported adverse events, atrial fibrillation, length of index hospitalization, valve performance based on echocardiographic data, New York Heart Association (NYHA) classification, 6-minute walk test, and the Kansas City Cardiomyopathy Questionnaire (KCCQ) score. The analyses in the application focused on the 30-day and/or one-year time points. At 5 years, the analyses included death rate, adjudicated adverse events (stroke, TIA, and aortic valve reinterventions, rehospitalization), key site reported adverse events, atrial fibrillation, length of index hospitalization, valve performance based on echocardiographic data, New York Heart Association (NYHA) classification, and the Kansas City Cardiomyopathy Questionnaire (KCCQ) score.

SAPIEN 3 THV IN BICUSPID AORTIC VALVE FOR PATIENTS AT INTERMEDIATE OR GREATER SURGICAL RISK - STS/ACC TRANSCATHETER VALVE THERAPY REGISTRY (TVTR) ANALYSIS

A database extract was performed on November 15, 2017, which yielded 545 patients with bicuspid aortic valves that had been treated with an Edwards SAPIEN 3 transcatheter heart valve. The patients were treated between July 14, 2015 and August 15, 2016. The procedure was performed in 225 participating hospitals.

Adjudications were completed per the TVT Registry Coder's Data Dictionary by the Duke Clinical Research Institute (DCRI) for three adverse events: stroke, transient ischemic attack (TIA), and aortic valve reinterventions.

Clinical Inclusion and Exclusion Criteria

Patients in the database extract received a commercially available SAPIEN 3 transcatheter heart valve for symptomatic heart disease associated with a bicuspid aortic valve. The patients were treated based on clinical judgement of their treating physicians.

Follow-up Schedule

All patients were followed post implantation according to their local standards of care. The TVT Registry collects follow-up data at discharge, 30 days, and 1 year.

Clinical Endpoints

Data entered into the TVT Registry were collected through standardized data collection forms. The endpoints analyzed in this application included: death rate, adjudicated adverse events (stroke, TIA, and aortic valve reinterventions), key site reported adverse events, valve performance based on echocardiographic data, New York Heart Association (NYHA) classification, 5-meter walk test, and the Kansas City Cardiomyopathy Questionnaire (KCCQ) score. The analyses in the application focused on the 30-day and one-year time points.

SAPIEN 3 THV IN BICUSPID AORTIC VALVE FOR PATIENTS AT LOW SURGICAL RISK - PARTNER 3 BICUSPID REGISTRY ANALYSIS

Under the PARTNER 3 trial, a prospective, single-arm, registry was enrolled to establish a reasonable assurance of safety and effectiveness of TAVR with the Edwards SAPIEN 3 THV in patients with severe, native, calcific, aortic stenosis of a bicuspid aortic valve who are judged by a heart team to be at low risk for open surgical therapy. Patients were enrolled between October 2017 and May 2018, and data was collected through August 28, 2019 for 75 patients.

The data safety monitoring board and clinical events committee described in the PARTNER 3 trial above were also used in this registry.

Clinical Inclusion and Exclusion Criteria

Patients in the trial received a commercially available SAPIEN 3 transcatheter heart valve for symptomatic heart disease due to severe native calcific aortic stenosis of a bicuspid aortic valve who were deemed to be at low risk for surgical aortic valve replacement.

Follow-up Schedule

Patients were followed-up at discharge, 30 days, and 1 year, and will continue to be followed up to 10 years.

Clinical Endpoints

The clinical endpoints were the same as those listed above in the PARTNER 3 trial.

SAPIEN 3 THV Valve-in-Valve - STS/ACC Transcatheter Valve Therapy Registry (TVTR) Analysis

A database extract was performed on August 4, 2016, which yielded 314 patients that had been treated with an Edwards SAPIEN 3 transcatheter heart valve placed in a failed surgical aortic bioprosthesis (i.e., aortic valve-in-valve) and 311 patients that had been treated with an Edwards SAPIEN XT transcatheter heart valve (N = 241) or SAPIEN 3 THV (N = 70) placed in a failed surgical mitral bioprosthesis (i.e., mitral valve-in-valve). Patients who presented with an existing valve-in-valve that was failing were excluded from the database extract. The SAPIEN XT transcatheter heart valve was included in the database extract for the mitral valve-in-valve uses because there were fewer SAPIEN 3 transcatheter heart valve cases in the registry due to its relatively shorter commercial use history and the SAPIEN XT THV data were considered to be generally applicable to the SAPIEN 3 transcatheter heart valve due to their similarities in design.

The aortic valve-in-valve patients were treated between July 23rd, 2015 and June 29th, 2016 at 130 participating hospitals; the mitral valve-in-valve patients were treated at 112 participating hospitals between July 10th, 2014 and June 27th, 2016 for the SAPIEN XT transcatheter heart valve and between June 23rd, 2015 and June 15th, 2016 for the SAPIEN 3 transcatheter heart valve.

Adjudications were completed per the TVT Registry Coder's Data Dictionary by the Duke Clinical Research Institute (DCRI) for three adverse events: readmission for heart failure, stroke/transient ischemic attack (TIA), and aortic and mitral valve reinterventions.

Clinical Inclusion and Exclusion Criteria

Patients in the database extract received a commercially available SAPIEN 3 transcatheter heart valve (for both aortic and mitral valve-in-valve) or SAPIEN XT transcatheter heart valve (for mitral valve-in-valve only) for symptomatic heart disease associated with a failed (stenosed, insufficient, or combined) surgical bioprosthetic aortic or mitral valve. They were deemed to be at high or greater risk for open surgical therapy and were treated off-label based on the clinical judgement of their treating physicians.

Follow-up Schedule

All patients were followed post implantation according to their local standards of care. The TVT Registry collects follow-up data at discharge, 30 days, and 1 year.

Clinical Endpoints

Data entered into the TVT Registry were collected through standardized data collection forms. The endpoints analyzed in this application included: death rate, adjudicated adverse events (readmission for heart failure, stroke/TIA, and valve reinterventions), key site reported adverse events, valve performance based on echocardiographic data, New York Heart Association (NYHA) classification, 6-minute or 5-meter walk test, and the Kansas City Cardiomyopathy Questionnaire (KCCQ) score. The analyses in the application focused on the discharge and 30-day time points.

SAPIEN 3 and SAPIEN 3 Ultra THV THV-in-THV - STS/ACC Transcatheter Valve Therapy Registry (TVTR) Analysis

A database extract was performed on August 9, 2019. Patients were excluded if their previous transcatheter aortic valve replacement (TAVR) procedure was performed prior to April 23, 2007 (first implant in the US under the PARTNER trial). The database extract yielded 404 patients that had undergone a THV-in-THV procedure with an Edwards SAPIEN 3 (N=402) or Edwards SAPIEN 3 Ultra (N=2) transcatheter heart valve. These patients were treated between August 4, 2015 and July 11, 2019 at 188 participating hospitals.

To obtain more complete 1-year follow-up data, a treatment cutoff date of June 9, 2018 was then applied to the data set obtained above, which yielded 263 patients (SAPIEN 3 THV only) treated at 138 participating hospitals. The cutoff date was 14 months before the database extract date, which included a +60-day window for the 1-year visit. These 263 patients constituted the clinical data set used to support this application.

Clinical Inclusion and Exclusion Criteria

The initial database extract included all patients who received a commercially available Edwards SAPIEN 3 or Edwards SAPIEN 3 Ultra transcatheter heart valve in an aortic THV-in-THV procedure. The final data set was a subset of the initial database extract as described above.

Follow-up Schedule

All patients were followed post-implantation according to their local standards of care. The TVT Registry collects follow-up data at 30 days and 1 year.

Clinical Endpoints

Data entered into the TVT Registry were collected through standardized data collection forms. The endpoints analyzed in this application included: death, stroke/transient ischemic attack (TIA), valve reinterventions, key site reported adverse events, valve performance based on echocardiographic data, New York Heart Association (NYHA) classification, and the Kansas City Cardiomyopathy Questionnaire (KCCQ) score. The analyses in the application focused on 30-day and 1-year time points.

SAPIEN 3 Valve in Ring - STS/ACC Transcatheter Valve Therapy Registry (TVTR) Analysis & Mitral Implantation of Transcatheter Valves (MITRAL) Study Overview

A database extract from the TVT Registry was performed of all eligible patients in the registry on May 29, 2020, with a treatment cutoff date of May 28, 2019. This yielded 206 patients (SAPIEN 3 THV only) treated at 90 participating hospitals, which was pooled with 30 additional patients treated at 11 participating hospitals between February 2016 and October 2017 in the "valve in ring" arm of the MITRAL study, a sponsor-investigator IDE. While a formal poolability analysis was not conducted, the two datasets were deemed poolable because both included patients with comparable baseline characteristics, functional status, and clinical comorbidities, with similar risk for open surgical therapy. These 236 patients constituted the clinical dataset used to support this application.

Clinical Inclusion and Exclusion Criteria

The analysis population consists of all patients with a failing native mitral valve with an annuloplasty ring who had a procedure to implant the Edwards SAPIEN 3 THV by May 28, 2019 in the TVTR mitral module and patients from the "valve in ring" arm of the MITRAL study (complete inclusion and exclusion criteria are available at https://www.accessdata.fda.gov/cdrh_docs/pdf14/P140031S125B.pdf). The baseline characteristics of these patients show a morbid population at high surgical risk with no other good options, as evidenced by an STS score of 9.4 ± 6.4 and 81% of the patients being in New York Heart Association (NYHA) class of III/IV.

Follow-up Schedule

All patients were followed post-implantation according to their local standards of care. The TVT Registry collects follow-up data at 30 days and 1 year. All patients enrolled in the MITRAL study were scheduled for follow-up examinations at discharge, 30 days, 6 months, 1 year, and annually thereafter to a minimum of 5 years post-procedure.

Preoperative and post-operative assessments included physical assessment and patient interview, laboratory measurements, imaging tests, and health status/quality of life (QoL) questionnaire. Adverse events and complications were recorded at all visits.

Clinical Endpoints

The endpoints analyzed included: death, stroke/TIA, valve reinterventions, key site reported adverse events, valve performance based on echocardiographic data, NYHA classification, and the Kansas City Cardiomyopathy Questionnaire (KCCQ) score. The analyses focused on the 30-day and 1-year time points and were carried out descriptively.

SAPIEN 3 Ultra Confirmatory Study Overview

A prospective, single-arm, multicenter clinical study was conducted to confirm the procedural safety and effectiveness of the SAPIEN 3 Ultra system in patients with severe, calcific aortic stenosis (AS) who are at intermediate operative risk for surgical aortic valve replacement (SAVR).

The study enrolled 40 patients in Canada and United Kingdom.

It utilized an echocardiographic core laboratory for echocardiograms.

Follow-up Schedule

All patients were followed post implantation at discharge and 30 days, and will continue to be followed at 6 months, 1 year and annually thereafter for a minimum of 5 years.

Clinical Endpoints

The endpoints analyzed were procedure success (defined as freedom from mortality, conversion to surgery and moderate or severe paravalvular regurgitation at exit from the procedure room), key site reported adverse events, valve performance, and New York Heart Association (NYHA) classification.

SAPIEN 3 Valve in Valve Intermediate Risk Overview - STS/ACC Transcatheter Valve Therapy Registry (TVTR) & Partner 3 Mitral Valve in Valve (P3 MVIV) Study Overview

A database extract from the TVT Registry was performed on January 27, 2023, yielding 452 patients at intermediate risk with a mitral valve-in-valve procedure completed with a SAPIEN 3 or SAPIEN 3 Ultra valve. In addition, there were 50 patients that were treated with a SAPIEN 3 or SAPIEN 3 Ultra valve in the PARTNER 3 mitral valve in valve study who were at intermediate surgical risk and prospectively enrolled in the multicenter study. The patient populations were pooled (N = 502) for analysis in addition to analysis of the patients in the study alone (N = 50).

The mitral valve-in-valve study used an independent Data Safety Monitoring Board (DSMB) that was instructed to notify the applicant of any safety or compliance issues and a Clinical Events Committee (CEC) that was responsible for adjudicating endpoint-related events reported during the trial.

Clinical Inclusion and Exclusion Criteria

Patients in the database extract received a commercially available SAPIEN 3 or SAPIEN 3 Ultra transcatheter heart valve for symptomatic heart disease associated with a failing surgical mitral valve implant. Fifty patients in the registry received a SAPIEN 3 valve (complete inclusion and exclusion criteria are available at https://www.accessdata.fda.gov/cdrh_docs/pdf14/P140031S162B.pdf).

Follow-up Schedule

All patients were followed post implantation according to their local standards of care. The TVT Registry collects follow-up data at discharge, 30 days, and 1 year. The study cohort was followed at discharge, 30 days, 6 months and 1 year and will be followed yearly thereafter for ten years.

Clinical Endpoints

The endpoints analyzed for the pooled cohort in this application included: co-primary endpoints of all cause death or all stroke at 30-days and all cause death at one year; also presented were site-reported adverse events, valve performance based on echocardiographic data, New York Heart Association (NYHA) classification, 6-minute walk test, and the Kansas City Cardiomyopathy Questionnaire (KCCQ) score. The analyses in the application focused on the 30-day and one-year time points.

THE EARLY-TAVR TRIAL OVERVIEW, SAPIEN 3 and SAPIEN 3 Ultra THV

Patients were enrolled between July 2017 and December 2021. The database reflected data collected through April 1, 2024 and included 901 patients. There were 75 investigational sites in the US and Canada.

The EARLY TAVR trial was a prospective, randomized (1:1), controlled, multicenter study to compare TAVR with the Edwards SAPIEN 3 or SAPIEN 3 Ultra THV to clinical surveillance (CS).

The EARLY TAVR trial used an independent Data Safety Monitoring Board (DSMB) that was instructed to notify the applicant 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 Valve Academic Research Consortium-2 (VARC-2) definitions and some events were re-adjudicated per VARC-3 definitions. A Biomarker core lab was used for assessment of N-terminal pro-B-type natriuretic peptide (NT-proBNP).

Clinical Inclusion and Exclusion Criteria

Patients in the trial received a commercially available SAPIEN 3 or SAPIEN 3 Ultra transcatheter heart valve or were treated with clinical surveillance for asymptomatic heart disease due to severe native calcific aortic stenosis (complete inclusion and exclusion criteria are available at https://clinicaltrials.gov/study/NCT03042104).

Follow-up Schedule

Patients in the TAVR arm will be followed through 5-years. Patients treated with clinical surveillance will be followed through 10-years. Patients in the CS arm who undergo AVR prior to 5-years will be followed through 5-years post-procedure.

Clinical Endpoints

The endpoints analyzed included: death, stroke, unplanned cardiovascular hospitalization, adjudicated adverse events (intervention/reintervention, hospitalization), time to delayed AVR, key site-reported adverse events, valve performance and left ventricular function based on echocardiographic data, Kansas City Cardiomyopathy Questionnaire (KCCQ) score, New York Heart Association (NYHA) classification, 6-minute walk test, N-Terminal Prohormone of Brain Natriuretic Peptide (NT-proBNP) assessment and length of index hospitalization. The analyses focused on all available data used for the primary endpoint and data to 2-year follow-up.

13.2 PARTNER II SAPIEN 3 HIGH-RISK/INOPERABLE COHORT

Patient Accountability

All 583 eligible patients were successfully implanted with a SAPIEN 3 valve, which constitutes the Valve Implant (VI) population. Among the VI population, 491 patients were implanted via the transfemoral (TF) access route, and 92 patients via the transapical (TA) or transaortic (TAo) access route.

Table 12: Patient Accountability

	SAPIEN 3 Valve Overall	SAPIEN 3 Valve Transfemoral Access	SAPIEN 3 Valve Non-Transfemoral Access
Eligible Patient Population (EPP)	583	491	92
Valve Implant (VI) Population	583	491	92

Eligible Patient Population (EPP) consists of all enrolled patients who received treatment assignment from the database and entered into the catheterization laboratory/hybrid suite and who remained eligible to receive the implant.

Valve Implant (VI) Population consists of all enrolled patients who received a SAPIEN 3 valve, and retained the valve upon leaving the catheterization laboratory/hybrid suite.

Study Population Demographics and Baseline Parameters

The demographics of the study population are summarized in Table 13, which are typical of a TAVR study performed in the U.S.

Table 13: Patient Demographics and Baseline Characteristics – PIIS3HR VI Population

Characteristic	SAPIEN 3 Valve Overall (N = 583)	SAPIEN 3 Valve Transfemoral Access (N = 491)	SAPIEN 3 Valve Non-Transfemoral Access (N = 92)
Age, yr	82.6 ± 8.1	82.8 ± 8.2	81.7 ± 7.5
Male sex, no. (%)	338 (58.0%)	277 (56.4%)	61 (66.3%)
STS score	8.6 ± 3.7	8.4 ± 3.5	10.0 ± 4.3
New York Heart Association (NYHA) class, no. (%):			
I/II	58 (9.9%)	51 (10.4%)	7 (7.6%)
III/IV	525 (90.1%)	440 (89.6%)	85 (92.4%)
Coronary artery disease, no. (%)	444 (76.2%)	360 (73.3%)	84 (91.3%)
Previous myocardial infarction, no. (%)	117 (20.1%)	87 (17.7%)	30 (32.6%)
Previous intervention, no. (%)			
Coronary-artery bypass grafting (CABG)	193 (33.1%)	145 (29.5%)	48 (52.2%)
Percutaneous coronary intervention (PCI)	199 (34.1%)	163 (33.2%)	36 (39.1%)
Prior aortic valvuloplasty	62 (10.6%)	49 (10.0%)	13 (14.1%)
Cerebral vascular accident (CVA), no. (%)	64 (11.0%)	53 (10.8%)	11 (12.0%)
Peripheral vascular disease, no. (%)	205 (35.2%)	155 (31.6%)	50 (54.3%)
Chronic obstructive pulmonary disease (COPD), no. (%):			
Any	259 (44.6%)	216 (44.1%)	43 (47.3%)
Oxygen-dependent	68 (11.8%)	58 (11.9%)	10 (11.0%)
Atrial fibrillation, no. (%)	255 (43.7%)	212 (43.2%)	43 (46.7%)
Permanent pacemaker, no. (%)	95 (16.3%)	78 (15.9%)	17 (18.5%)
Severe pulmonary hypertension, no. (%)	30 (5.1%)	24 (4.9%)	6 (6.5%)
Frailty, no. (%)	180 (30.9%)	162 (33.0%)	18 (19.6%)
Chest deformities that preclude an open chest procedure, no. (%)	4 (0.7%)	3 (0.6%)	1 (1.1%)
Cirrhosis, no. (%)	11 (1.9%)	9 (1.8%)	2 (2.2%)
Echocardiographic findings			
Effective Orifice Area (EOA), cm^2	0.7 ± 0.2	0.7 ± 0.2	0.7 ± 0.1
Mean aortic-valve gradient, mmHg	45.5 ± 14.3	45.7 ± 14.4	44.0 ± 13.2
Mean left ventricular ejection fraction (LVEF), %	56.4 ± 14.8	57.0 ± 14.5	53.2 ± 15.9
Moderate or severe mitral regurgitation, no./total no. (%)	69/541 (12.8%)	63/461 (13.7%)	6/80 (7.5%)

Safety and Effectiveness Results

Primary Endpoint

The composite rate of all-cause mortality, all stroke, and AI ≥ moderate at 30 days was 6.7% in the SAPIEN 3 cohort and 15.6% in the SAPIEN cohort, as shown in Table 14. The resulting proportion difference in the average treatment effect on the treated (ATT; [3]) was -6.9% (90% CI:[-13.3%, -0.5%]). Since the upper limit of the CI was < 7.5%, the non–inferiority was met.

Table 14: Primary Endpoint Analysis – Non-Inferiority Test SAPIEN 3 Valve (PIIS3HR VI Population) vs. SAPIEN Valve

Event at 30 days	SAPIEN 3 Valve (N = 583)	SAPIEN Valve (N = 326)	Weighted Proportion Difference in Average Treatment Effect on the Treated (ATT)
Composite of Death, Stroke and AI ≥ Moderate	6.7% [5.1%, 8.6%][1]	15.6% [12.6%, 19.5%][1]	-6.9% [-13.3%, -0.5%][2]
[1]For each individual study, the two-sided 90% stratified Wilson confidence interval was provided. [2]The Wald-type two-sided 90% confidence interval using weighted mean and SD is provided.			

The Kaplan-Meier (K-M) estimates for all-cause mortality, cardiac mortality, and all stroke at 30 days for the SAPIEN 3 cohort and the SAPIEN cohort are provided in Table 15.

Table 15: Death and Stroke at 30 Days – SAPIEN 3 Valve vs. SAPIEN Valve (VI Population)

	SAPIEN 3 Valve (N = 583)			SAPIEN Valve (N = 326)		
Event at 30 Days	No. Events	No. Pts with Events	K-M Estimated Event Rate[1] (95% CI)	No. Events	No. Pts with Events	K-M Estimated Event Rate (95% CI)
Death	13	13	2.2% ([1.3%, 3.8%])	15	15	4.6% ([2.8%, 7.5%])
Cardiac Death	8	8	1.4% ([0.7%, 2.7%])	10	10	3.1% ([1.7%, 5.7%])
All Stroke	9	9	1.6% ([0.8%, 3.0%])	14	14	4.3% ([2.6%, 7.2%])
[1]Kaplan-Meier (K-M) estimates at 30 days used time to first event for each patient. Events occurring after 30 days were not included in this analysis.						

Secondary Endpoints

Aortic insufficiency by visit is provided in Figure 7.

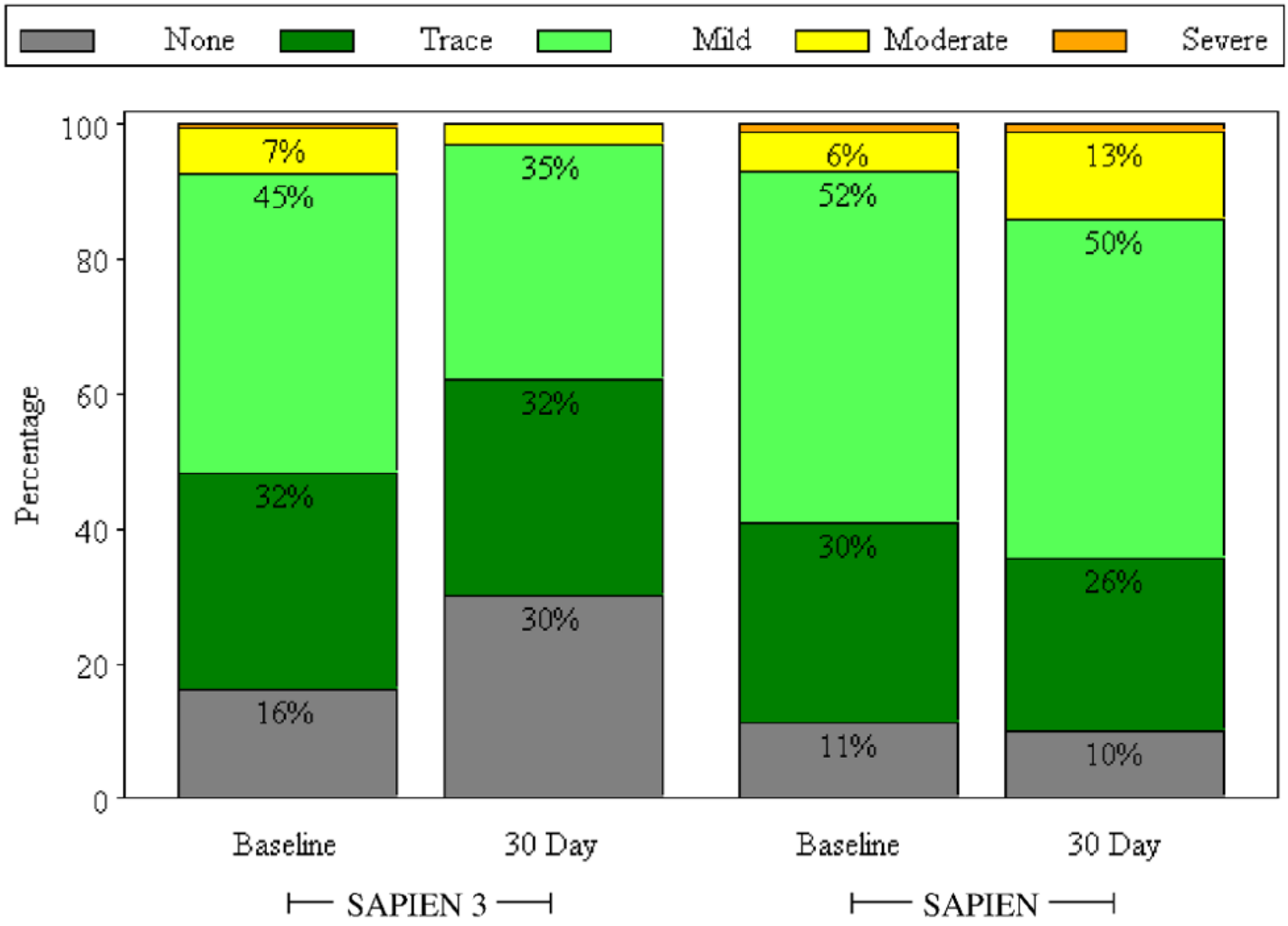


Figure 7: Aortic Insufficiency by Visit – SAPIEN 3 Valve (PIIS3HR VI Population) vs. SAPIEN Valve

The proportion of patients with AI ≥ moderate at 30 days was 3.0% in the SAPIEN 3 cohort and 14.3% in the SAPIEN cohort, which were found to be statistically significantly different (p=0.0051; Table 16).

Table 16: Aortic Insufficiency at 30 Days (SAPIEN 3 Valve vs. SAPIEN Valve VI Population)

Event at 30 Days	SAPIEN 3 Valve (N = 583)	SAPIEN Valve (N = 326)	Weighted Proportion Difference in Average Treatment Effect on the Treated (ATT)	P-value
AI ≥ Moderate, n/Total no. (%) [95% CI]	16/532 (3.0%) [1.7%, 4.8%][1]	40/280 (14.3%) [10.4%, 18.9%][1]	-13.1% [-22.2%, -3.9%][2]	0.0051

[1]95% Clopper-Pearson Exact confidence interval.
[2]The Wald-type two-sided 90% confidence interval using weighted mean and SD is provided.

The rate of major vascular complications at 30 days post implantation is shown in Figure 8. The rate was 5.0% for the SAPIEN 3 cohort and 10.1% for the SAPIEN cohort, which were found to be not statistically significantly different (p=0.0578; Table 17).

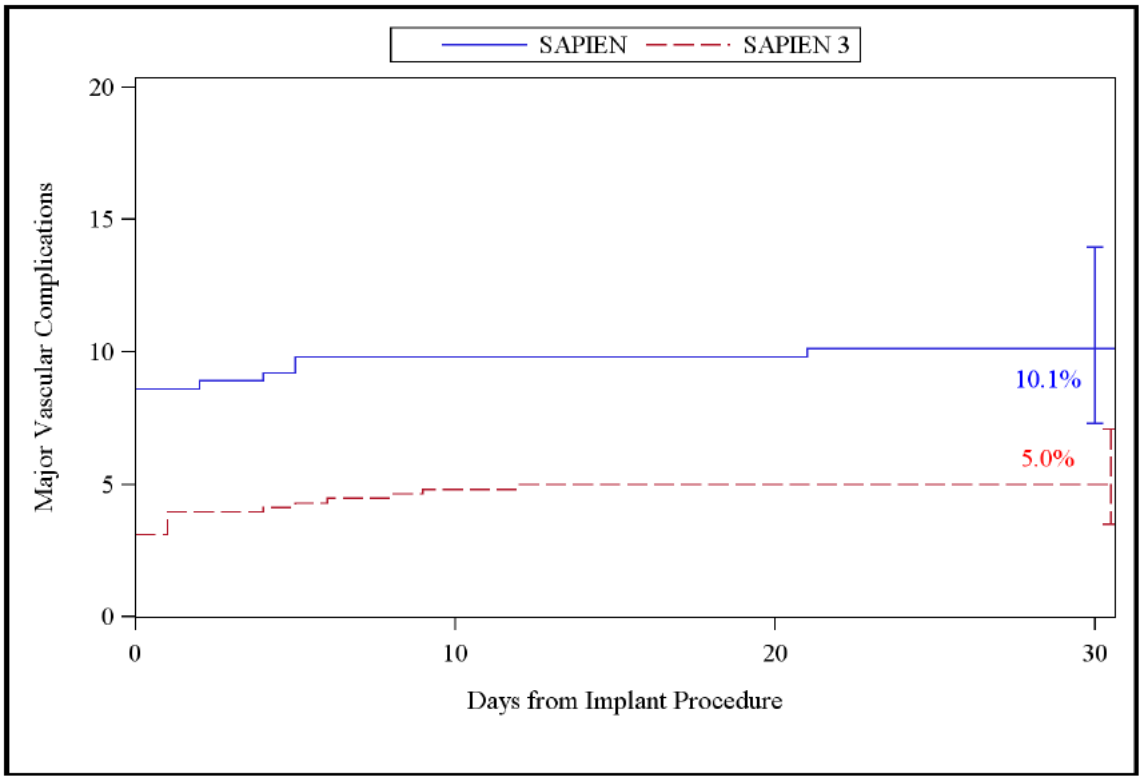


Figure 8: Major Vascular Complications at 30 Days – SAPIEN 3 Valve vs. SAPIEN Valve (VI Population)

Table 17: Major Vascular Complications at 30 Days – SAPIEN 3 Valve vs. SAPIEN Valve (VI Population)

Event at 30 Days	SAPIEN 3 Valve (N = 583)	SAPIEN Valve (N = 326)	Weighted Proportion Difference in Average Treatment Effect on the Treated (ATT)	P-value
Major Vascular Complications, n/ Total no. (%) [95% CI]	29/583 (5.0%) [3.4%, 7.1%]	33/326 (10.1%) [7.1%, 13.9%][1]	-8.0% [-16.2%, 0.3%][2]	0.0578

[1]95% Clopper-Pearson Exact confidence interval.
[2]The Wald-type two-sided 90% confidence interval using weighted mean and SD is provided.

Table 18 lists the hypothesis testing of the two secondary endpoints conducted with p-values in descending order for the Hochberg multiplicity adjustment steps. The largest p-value (p=0.0578 from major vascular complications) was greater than 0.05. As such, the null hypothesis was not rejected for the testing of major vascular complications at 30 days. The subsequent testing of AI ≥ moderate at 30 days had a p-value of 0.0051, which was less than 0.025. As such, the null hypothesis was rejected for AI ≥ moderate at 30 days, indicating that the SAPIEN 3 cohort was superior over the SAPIEN cohort in regards to AI ≥ moderate at 30 days.

Table 18: Secondary Endpoints for Labeling – SAPIEN 3 Valve vs. SAPIEN Valve (VI Population)

Endpoints	Original p-value	Inference
Major Vascular Complications at 30 Days	0.0578	> 0.05; reject the alternative hypothesis. Proceed to the rest of testing
AI at 30 Days	0.0051	< 0.025; claim superiority

Adverse Events

The key CEC adjudicated adverse events at 30 days are presented in Table 19.

Table 19: CEC Adjudicated Adverse Events at 30 Days (PIIS3HR VI Population)

30-Day Adverse Events	SAPIEN 3 Valve Overall	SAPIEN 3 Valve Trans-femoral Access TF	SAPIEN 3 Valve Non-Transfemoral Access
Composite Event Rate of Death, All Stroke and AI ≥ Moderate, n/N (%)	37/545 (6.8%)	27/463 (5.8%)	10/82 (12.2%)
Death			
From any cause, n/N (%)	13/583 (2.2%)	8/491 (1.6%)	5/92 (5.4%)
From cardiovascular cause, n/N (%)	8/583 (1.4%)	5/491 (1.0%)	3/92 (3.3%)
Stroke, n/N (%)	9/583 (1.5%)	8/491 (1.6%)	1/92 (1.1%)
AI ≥ moderate, n/N (%)	16/532 (3.0%)	12/455 (2.6%)	4/77 (5.2%)
Myocardial Infarction, n/N (%)	3/583 (0.5%)	2/491 (0.4%)	1/92 (1.1%)
Major Vascular Complications, n/N (%)	29/583 (5.0%)	26/491 (5.3%)	3/92 (3.3%)
Acute Kidney Injury, Stage III, n/N (%)	6/583 (1.0%)	4/491 (0.8%)	2/92 (2.2%)
Disabling Bleeding Event, n/N (%)	37/583 (6.3%)	27/491 (5.5%)	10/92 (10.9%)
Aortic Valve Re-Intervention, n/N (%)	6/583 (1.0%)	4/491 (0.8%)	2/92 (2.2%)
Endocarditis, n/N (%)	1/583 (0.2%)	1/491 (0.2%)	0/92 (0.0%)
Conduction Disturbance Requiring Permanent Pacemaker, n/N (%)	76/583 (13.0%)	65/491 (13.2%)	11/92 (12.0%)

Other Results

Procedural Information

Overall, the mean duration in the catheterization laboratory/hybrid suite was 192.8 ± 59.3 min, the mean total procedure time was 86.3 ± 44.2 min, and the mean total anesthesia time was 193.7 ± 62.9 min. These duration times were slightly shorter in the TF patients. General anesthesia was used in the vast majority of cases; 15.9% of the TF patients had conscious sedation. Correct positioning of the valve was achieved in 99.1% of the patients. Five patients (0.9%; including 3 TF patients) were implanted with a second valve. One patient (0.2%) experienced valve embolization following rupture of the delivery balloon on annular calcium. This patient was converted to surgical aortic valve replacement and later died from aortic dissection.

Valve Performance

The mean EOA increased from 0.7 ± 0.2 cm^2 at baseline to 1.6 ± 0.4 cm^2 at 30 days, as shown in Figure 9.

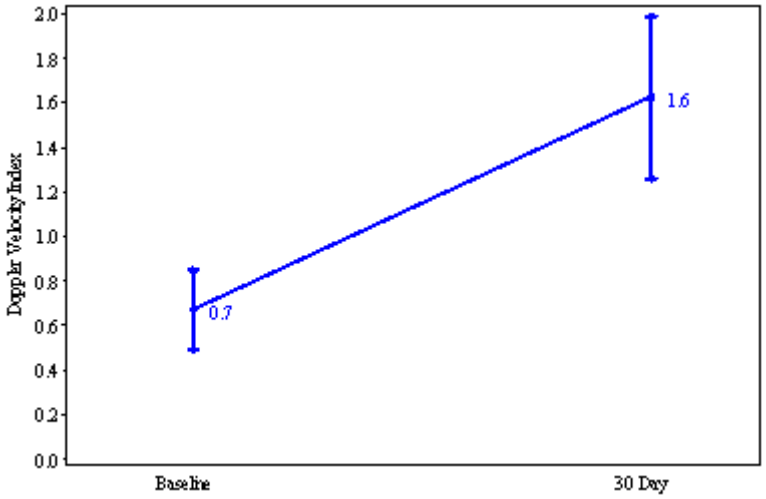


Figure 9: Effective Orifice Area (PIIS3HR VI Population)

The average mean gradient decreased from 45.5 ± 14.3 mmHg at baseline to 11.1 ± 4.5 mmHg at 30 days, as shown in Figure 10.

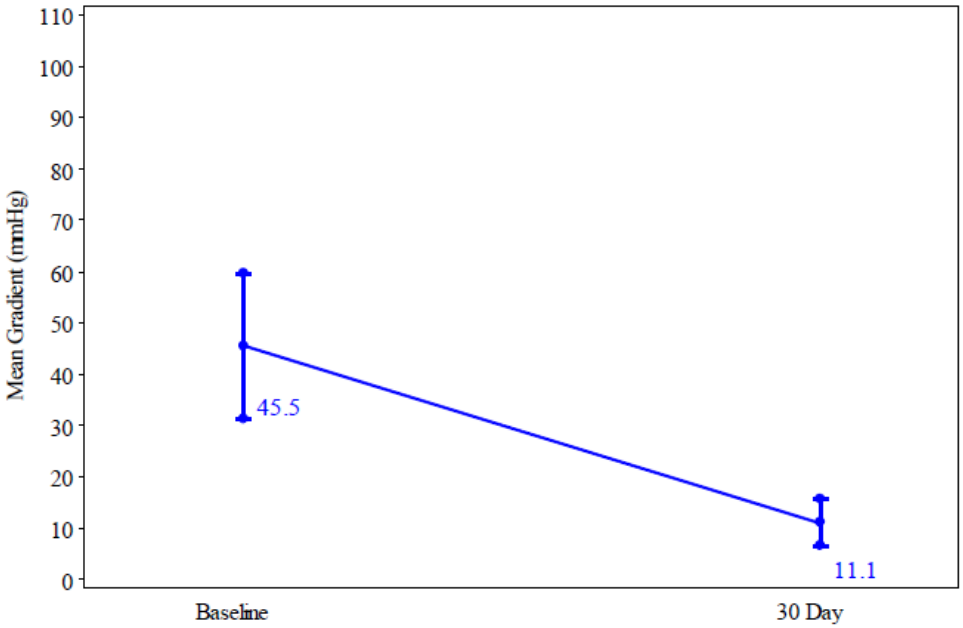


Figure 10: Mean Gradient (PIIS3HR VI Population)

The mean peak gradient decreased from 75.8 ± 22.6 mmHg at baseline to 21.2 ± 8.5 mmHg at 30 days, as shown in Figure 11.

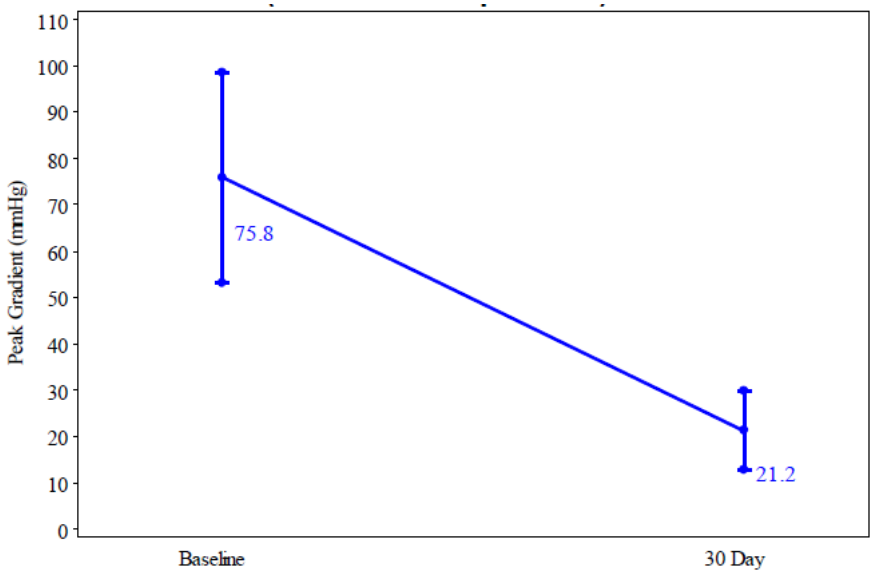


Figure 11: Peak Gradient (PIIS3HR VI Population)

The proportion of patients with AI ≥ moderate was 7.3% at baseline and 3.0% at 30 days, as shown in Figure 12.

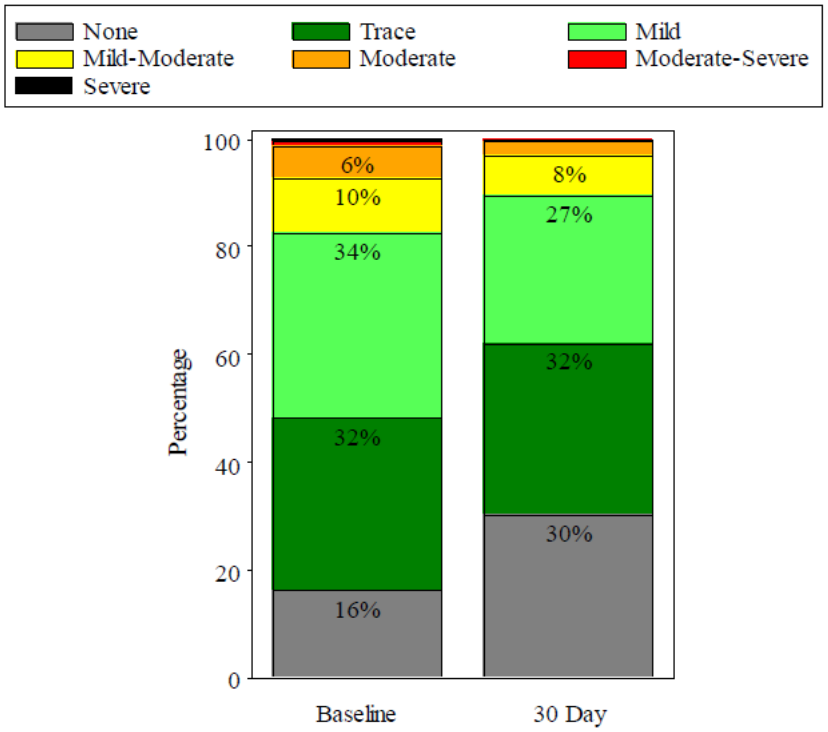


Figure 12: Aortic Insufficiency (PIIS3HR VI Population)

The proportion of patients with aortic paravalvular leak (PVL) ≥ moderate was 2.9% at 30 days, as shown in Figure 13.

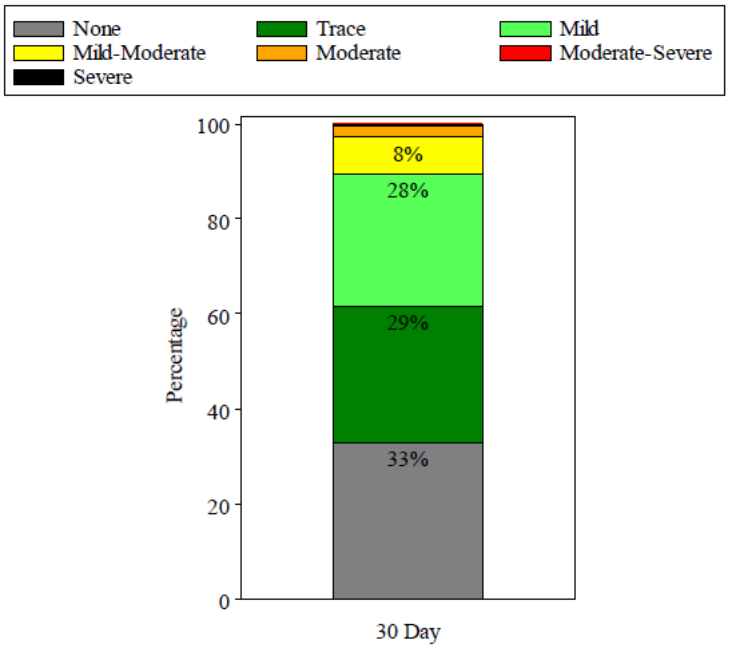


Figure 13: Aortic Paravalvular Leak (PIIS3HR VI Population)

New York Heart Association

The NYHA class by visit is shown in Figure 14. For all patients, the mean NYHA class was 3.2 ± 0.6 at baseline and 1.7 ± 0.7 at 30 days.

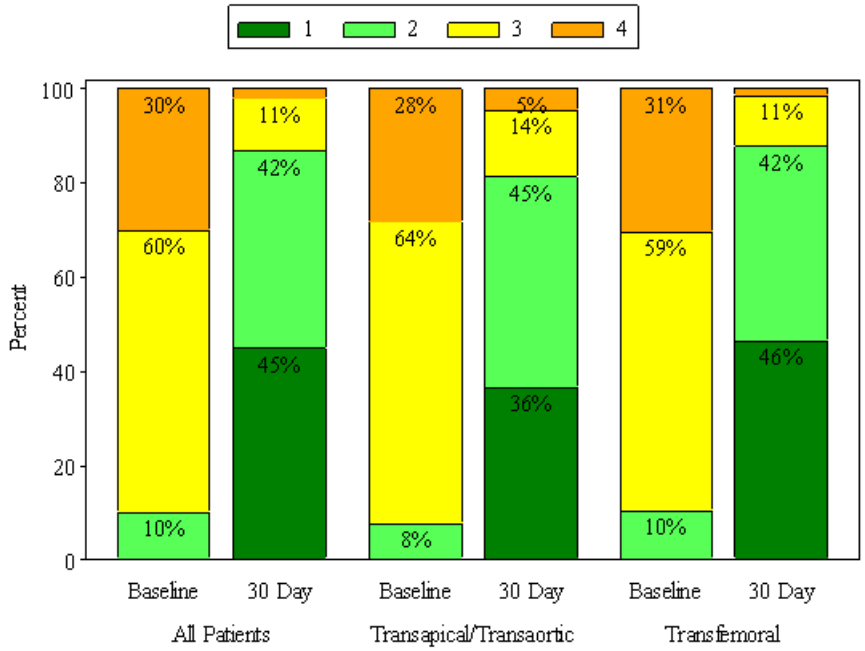


Figure 14: NYHA Class by Visit (PIIS3HR VI Population)

Six Minute Walk Test (6MWT)

The improvement in mean 6MWT distance was 38.5 ± 110.2 meters from baseline to 30 days for all patients, 42.6 ± 107.8 meters for all TF patients, and 15.9 ± 121.2 meters for all TA/TAo patients.

Length of Stay (LoS)

The overall mean LoS was 6.8 ± 4.8 days, which included 3.0 ± 2.7 days in the ICU. The mean LoS was 6.1 ± 4.3 days (including 2.7 ± 2.3 days in the ICU) for the TF patients and 10.4 ± 5.4 days (including 4.8 ± 3.9 days in the ICU) for the TA/TAo patients.

Quality of Life (QoL)

QoL was measured using the visual analog scale (VAS) of the EuroQoL (EQ-5D) measure. The VAS is a self-assessment in which patients rate their well-being on a scale from 0 to 100 where 0 is the worst state they can imagine and 100 is the best state. During the trial, the mean improvement in VAS scale from baseline to 30 days was 14.6 ± 22.2 for all patients, 15.1 ± 21.5 for the TF patients, and 11.5 ± 25.7 for the TA/TAo patients.

Additional QoL instruments

The mean overall Kansas City Cardiomyopathy Questionnaire (KCCQ) summary score was 46.9 ± 22.6 at baseline, and 67.5 ± 22.6 at 30 days for the entire VI population. Except for self-efficacy which showed a small improvement, moderate to large improvements were observed in all other subscores at 30 days. In general, improvements in the TF patients were slightly larger compared to those observed in the TA/TAo patients.

Using the SF-36 norm based questionnaire, the physical component score for all patients improved from 32.0 ± 8.9 at baseline to 37.1 ± 9.7 at 30 days, and the mental component score improved from 46.9 ± 12.8 at baseline to 50.0 ± 12.5 at 30 days. In the TF patients, the physical component score improved from 31.8 ± 8.7 at baseline to 37.3 ± 9.8 at 30 days, and the mental component score improved from 46.8 ± 13.1 at baseline to 50.5 ± 12.2 at 30 days. In the TA/TAo patients, the physical component score improved from 32.9 ± 10.0 at baseline to 35.9 ± 9.4 at 30 days, and the mental component scores were 47.2 ± 11.1 at baseline and 47.2 ± 14.0 at 30 days.

13.3 SUMMARY OF SUPPLEMENTAL CLINICAL INFORMATION

Supplemental Clinical Study Design

Supplemental clinical data came from a study (referred to as "S3OUS" hereafter) conducted in Europe and Canada.

The S3OUS study was a non-randomized, prospective, multi-center study in inoperable, high surgical risk, and intermediate surgical risk patients who underwent implantation of the 23, 26, or 29 mm SAPIEN 3 valve.

Except the intermediate surgical risk patients, the inclusion/exclusion criteria of the S3OUS trial were largely similar to those of the PIIS3HR trial. The S3OUS study had a minimum age requirement (≥ 75 years) and the upper limit for AVA was higher (<1 cm^2 instead of ≤ 0.80 cm^2). Additionally, the S3OUS study included BAV within 30 days of the procedure (unless BAV was a bridge to procedure), patients with planned concomitant surgical or transcatheter ablation for atrial fibrillation, hemodynamic or respiratory instability requiring inotropic support, mechanical ventilation or mechanical heart assistance within 30 days of screening; and the need for emergency surgery for any reason. Furthermore, the exclusion criteria in the S3OUS study excluded senile dementia and any neurologic disease which severely affected the ability to walk or perform everyday activities, and shortened the time interval regarding confirmed stroke or TIA (within 3 months instead of 6 months of the procedure). The follow-up periods were discharge or 7 days, whichever comes first, 30 days, 1 year, and annually thereafter to a minimum of 5 years post procedure.

Patient Accountability

Patients were treated at 14 investigational sites. Note that the intermediate risk patients enrolled in the S3OUS study were excluded from the analysis presented herein. The database included 102 "all treated" (AT) inoperable and high surgical risk patients. "All treated" population is defined to include all patients who were enrolled in the trial and for whom the study valve implantation procedures were started (i.e., the anesthesia was started).

One patient was excluded from the VI population. This patient experienced an aortic root rupture caused by displacement of a large lump of calcium with sharp edges through the native aortic annulus following balloon expansion of the SAPIEN 3 valve. The patient was subsequently converted to SAVR. After the patient was weaned off cardio-pulmonary bypass, bleeding in the region of the dorsal root occurred, and the patient died on the operating table.

A total of 56 patients were successfully implanted with a SAPIEN 3 valve via the transfemoral access route, and 45 via the transapical/transaortic access route, as shown in Table 20.

Table 20: Patient Accountability (S3OUS)

SAPIEN 3 Valve Overall		SAPIEN 3 Valve Transfemoral Access		SAPIEN 3 Valve Non-Transfemoral Access	
All Treated (AT) Population	**Valve Implant (VI) Population**	**All Treated (AT) Population**	**Valve Implant (VI) Population**	**All Treated (AT) Population**	**Valve Implant (VI) Population**
102	101	57	56	45	45

All Treated (AT) Population consists of all patients who were enrolled in the trial and for whom the study valve implantation procedures were started (i.e., anesthesia was started).

Valve Implant (VI) Population consists of all enrolled patients who received a SAPIEN 3 valve, and retained the valve upon leaving the catheterization laboratory/hybrid suite.

Study Population Demographics and Baseline Parameters

The demographics of the S3OUS study population are shown in Table 21.

Table 21: Patient Demographics and Baseline Characteristics (S3OUS AT Population)

Demographics and Baseline Characteristics	SAPIEN 3 Valve Overall (N = 102)	SAPIEN 3 Valve Transfemoral Access (N = 57)	SAPIEN 3 Valve Non-Transfemoral Access (N = 45)
Age, yr	84.1 ± 5.0	85.1 ± 4.6	83.0 ± 5.3
Male sex, no.(%)	40 (39.2%)	23 (40.4%)	17 (37.8%)
STS score	8.0 ± 4.7	8.2 ± 4.2	7.9 ± 5.2
Logistic EuroSCORE	24.1 ± 13.0	22.3 ± 11.3	26.4 ± 14.7
New York Heart Association (NYHA) class, no.(%):			
I/II	11 (10.8%)	6 (10.5%)	5 (11.1%)
III/IV	91 (89.2%)	51 (89.5%)	40 (88.9%)
Coronary artery disease, no.(%)	68 (66.7%)	36 (63.2%)	32 (71.1%)

Demographics and Baseline Characteristics	SAPIEN 3 Valve Overall (N = 102)	SAPIEN 3 Valve Transfemoral Access (N = 57)	SAPIEN 3 Valve Non-Transfemoral Access (N = 45)
Previous myocardial infarction, no.(%)	20 (19.6%)	7 (12.3%)	13 (28.9%)
Previous intervention, no.(%)			
Coronary-artery bypass grafting (CABG)	24 (23.5%)	10 (17.5%)	14 (31.1%)
Percutaneous coronary intervention (PCI)	34 (33.3%)	16 (28.1%)	18 (40.0%)
Prior aortic valvuloplasty	10 (9.8%)	8 (14.0%)	2 (4.4%)
Stroke, no.(%)	7 (6.9%)	4 (7.0%)	3 (6.7%)
Peripheral vascular disease, no.(%)	27 (26.5%)	10 (17.5%)	17 (37.8%)
Chronic obstructive pulmonary disease (COPD), no.(%):			
Any	25 (24.5%)	13 (22.8%)	12 (26.7%)
Oxygen-dependent	1 (1.0%)	1 (1.8%)	0 (0%)
Atrial fibrillation, no.(%)	48 (47.1%)	22 (38.6%)	26 (57.8%)
Permanent pacemaker, no.(%)	15 (14.7%)	7 (12.3%)	8 (17.8%)
Severe pulmonary hypertension, no.(%)	10 (9.8%)	6 (10.5%)	4 (8.9%)
Severe liver disease / Cirrhosis, no.(%)	1 (1.0%)	1 (1.8%)	0 (0%)
Echocardiographic findings			
Effective Orifice Area (EOA), cm^2	0.6 ± 0.2	0.6 ± 0.2	0.6 ± 0.1
Mean aortic-valve gradient, mmHg	44.8 ± 15.3	45.2 ± 14.7	44.2 ± 16.1
Mean left ventricular ejection fraction (LVEF), %	56.7 ± 9.1	57.7 ± 9.3	55.3 ± 8.7
Moderate or severe mitral regurgitation, no./total no. (%)	23/85 (27.1%)	9/48 (18.8%)	14/37 (37.8%)
Plus–minus values are means ± SD.			

Safety and Effectiveness Results

Key Adverse Events

Key adverse events as adjudicated by the CEC are presented in Table 22.

Table 22: CEC Adjudicated Adverse Events at 1 Year (S3OUS AT Population)

Outcomes	30 Days			1 Year		
	SAPIEN 3 Valve Overall	SAPIEN 3 Valve Transfemoral Access	SAPIEN 3 Valve Non-Transfemoral Access	SAPIEN 3 Valve Overall	SAPIEN 3 Valve Transfemoral Access	SAPIEN 3 Valve Non-Transfemoral Access
Composite Event Rate of Death, All Stroke and AI ≥ Moderate, n/N (%)	13/88 (14.8%)	3/50 (6.0%)	10/38 (26.3%)	25/82 (30.5%)	9/47 (19.1%)	16/35 (45.7%)
Death						
From any death, n/N (%)	8/102 (7.8%)	2/57 (3.5%)	6/45 (13.3%)	20/102 (19.6%)	7/57 (12.3%)	13/45 (28.9%)
From cardiovascular cause, n/N (%)	7/102 (6.9%)	2/57 (3.5%)	5/45 (11.1%)	9/102 (8.8%)	2/57 (3.5%)	7/45 (15.6%)
Stroke, n/N (%)	3/102 (2.9%)	1/57 (1.8%)	2/45 (4.4%)	5/102 (4.9%)	2/57 (3.5%)	3/45 (6.7%)

Outcomes	30 Days			1 Year		
	SAPIEN 3 Valve Overall	SAPIEN 3 Valve Transfemoral Access	SAPIEN 3 Valve Non-Transfemoral Access	SAPIEN 3 Valve Overall	SAPIEN 3 Valve Transfemoral Access	SAPIEN 3 Valve Non-Transfemoral Access
Aortic Insufficiency (AI) ≥ Moderate, n/N (%)	3/81 (3.7%)	1/49 (2.0%)	2/32 (6.3%)	1/62 (1.6%)	1/40 (2.5%)	0/22 (0.0%)
Disabling Stroke, n/N (%)	0/102 (0.0%)	0/57 (0.0%)	0/45 (0.0%)	1/102 (1.0%)	1/57 (1.8%)	0/45 (0.0%)
Myocardial Infarction, n/N (%)	2/102 (2.0%)	2/57 (3.5%)	0/45 (0.0%)	3/102 (2.9%)	2/57 (3.5%)	1/45 (2.2%)
Major Vascular Complications, n/N (%)	5/102 (4.9%)	1/57 (1.8%)	4/45 (8.9%)	N/A	N/A	N/A
Acute Kidney Injury - Stage III, n/N (%)	0/102 (0.0%)	0/57 (0.0%)	0/45 (0.0%)	N/A	N/A	N/A
Disabling Bleeding Event, n/N (%)	6/102 (5.9%)	3/57 (5.3%)	3/45 (6.7%)	N/A	N/A	N/A
Valve Dysfunction Requiring Intervention, n/N (%)	0/102 (0.0%)	0/57 (0.0%)	0/45 (0.0%)	N/A	N/A	N/A
Prosthetic Valve Endocarditis, n/N (%)	0/102 (0.0%)	0/57 (0.0%)	0/45 (0.0%)	1/102 (1.0%)	0/57 (0.0%)	1/45 (2.2%)
Conduction Abnormality Requiring Pacemaker, n/N (%)	14/102 (13.7%)	7/57 (12.3%)	7/45 (15.6%)	14/102 (13.7%)	7/57 (12.3%)	7/45 (15.6%)

The composite adverse event rate involving all-cause mortality, all stroke, and AI ≥ moderate at 30 days for all patients is higher in the S3OUS cohort than PIIS3HR cohort (14.8% vs. 6.8%). This disparity is due to the composition of the study populations, specifically the S3OUS cohort comprises 44.1% TA/TAo patients vs. 15.8% TA/TAo patients in the PIIS3HR cohort. Note, the composite adverse event rate at 30 days for TF patients was similar, specifically, 6.0% in the S3OUS cohort and 5.8% in the PIIS3HR cohort.

The K-M estimates for all-cause mortality for all patients, the TF patients, and the TA/TAo patients are shown in Figure 15.

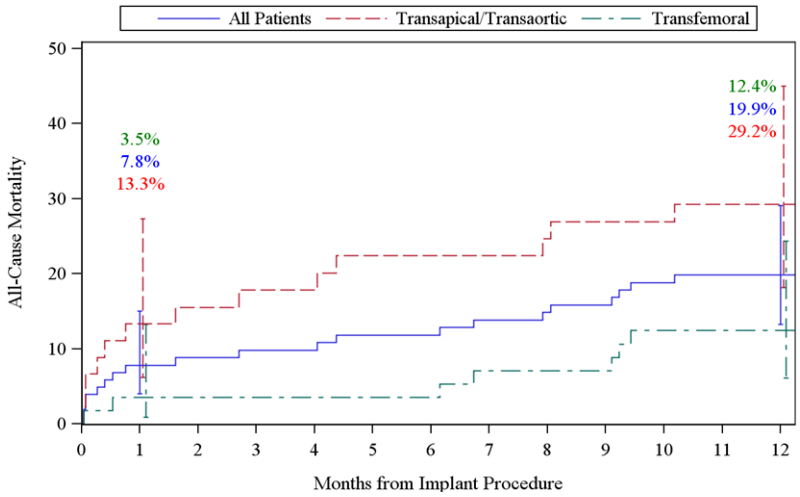


Figure 15: All-Cause Mortality at 1 Year (S3OUS AT Population)

Note: 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.

The K-M estimates for the stroke rate for all patients, the TF patients, and the TA/TAo patients are shown in Figure 16.

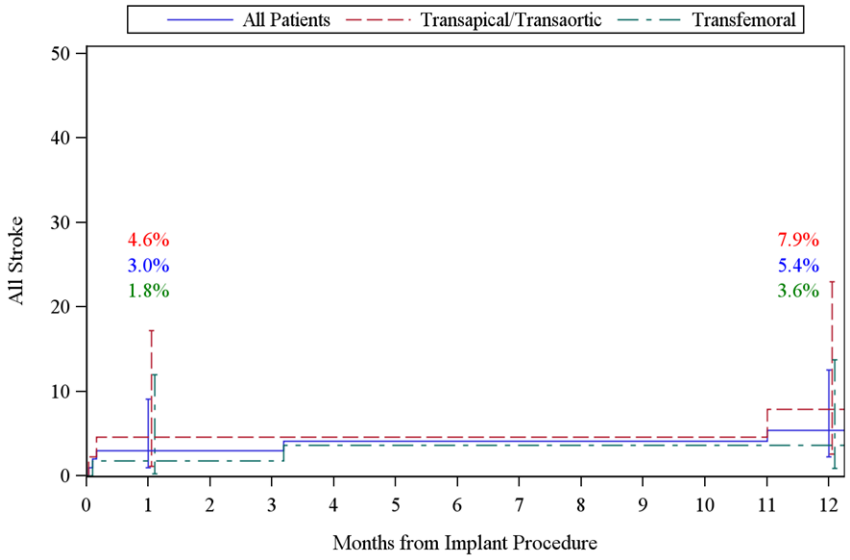


Figure 16: All Stroke at 1 Year (S3OUS AT Population)

Note: 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.

Valve Performance

The mean EOA increased from 0.6 ± 0.2 cm^2 at baseline to 1.5 ± 0.4 cm^2 at 30 days and 1.4 ± 0.4 cm^2 at 1 year, as shown in Figure 17.

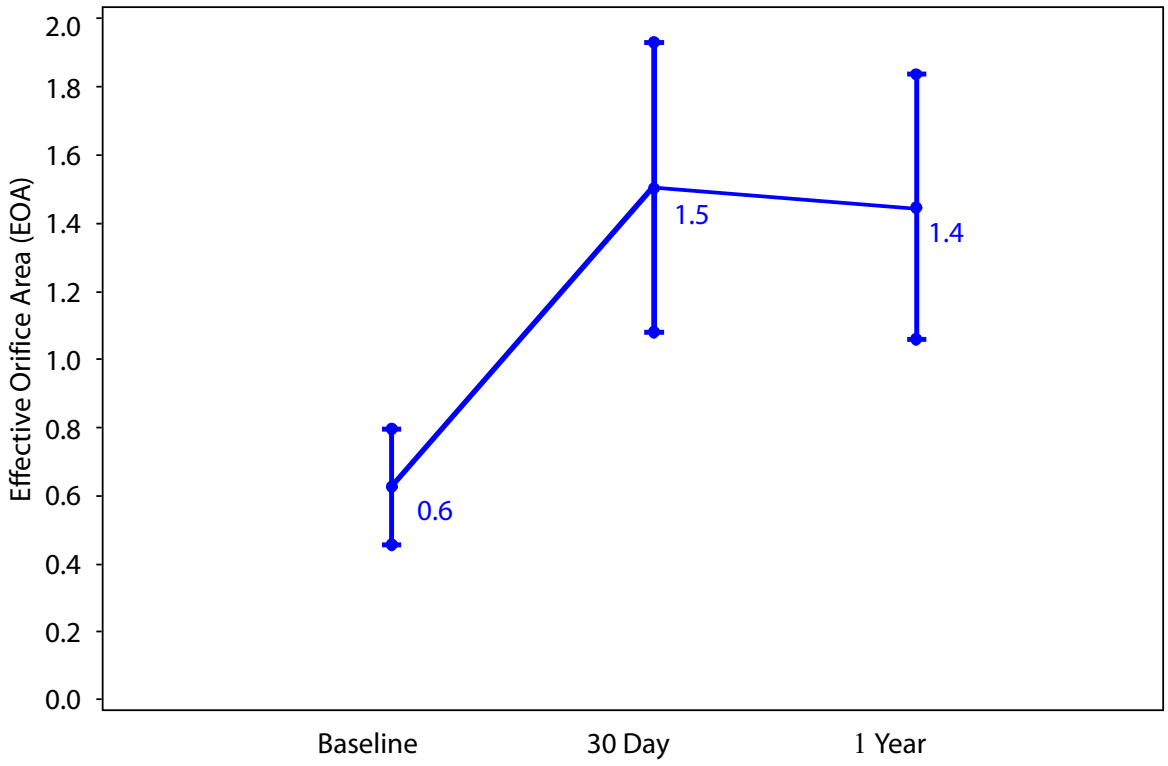


Figure 17: Effective Orifice Area (S3OUS VI Population)

The average mean gradient decreased from 44.8 ± 15.4 mmHg at baseline to 10.4 ± 4.1 mmHg at 30 days and maintained at 10.7 ± 4.1 mmHg at 1 year, as shown in Figure 18.

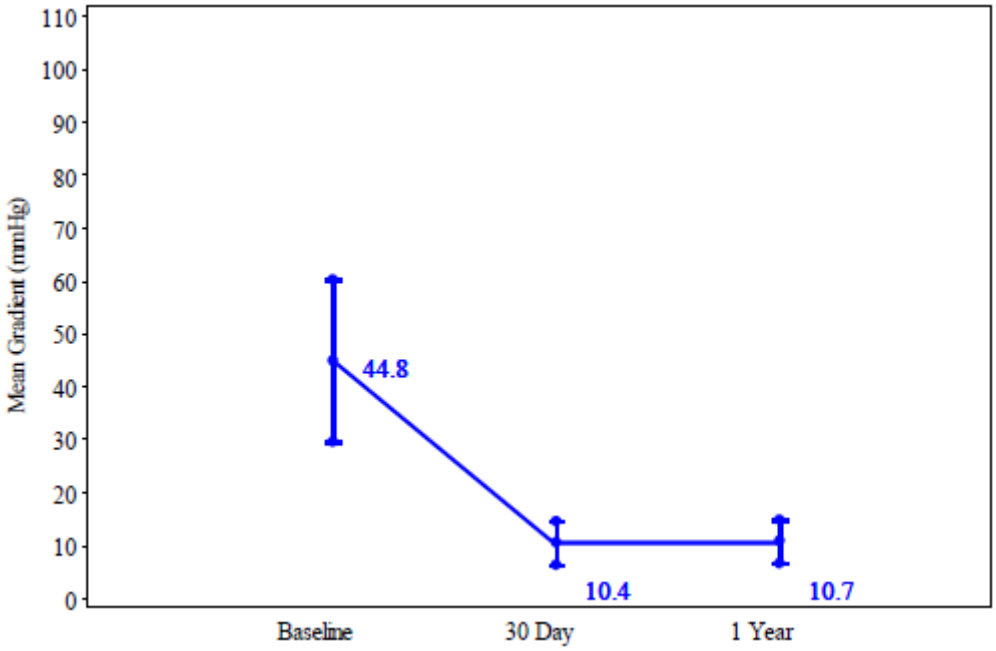


Figure 18: Mean Gradient (S3OUS VI Population)

The mean peak gradient decreased from 77.5 ± 24.9 mmHg at baseline to 21.0 ± 7.7 mmHg at 30 days, and maintained at 21.5 ± 8.2 mmHg at 1 year, as shown in Figure 19.

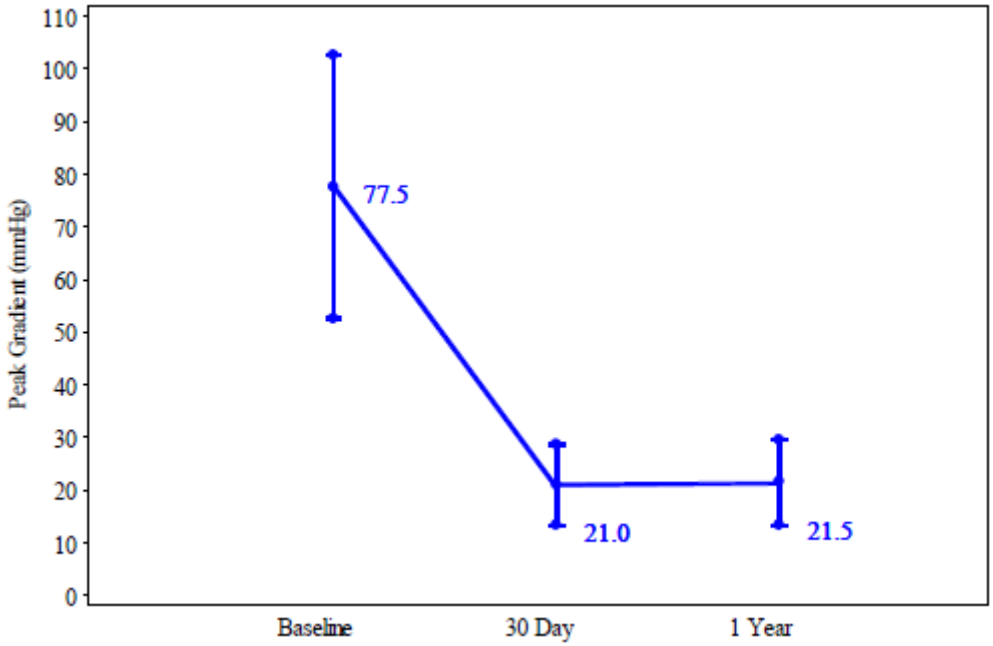


Figure 19: Peak Gradient (S3OUS VI Population)

The proportion of patients with aortic insufficiency ≥ moderate was 9.8% at baseline, 3.7% at 30 days, and 1.6% at 1 year, as shown in Figure 20.

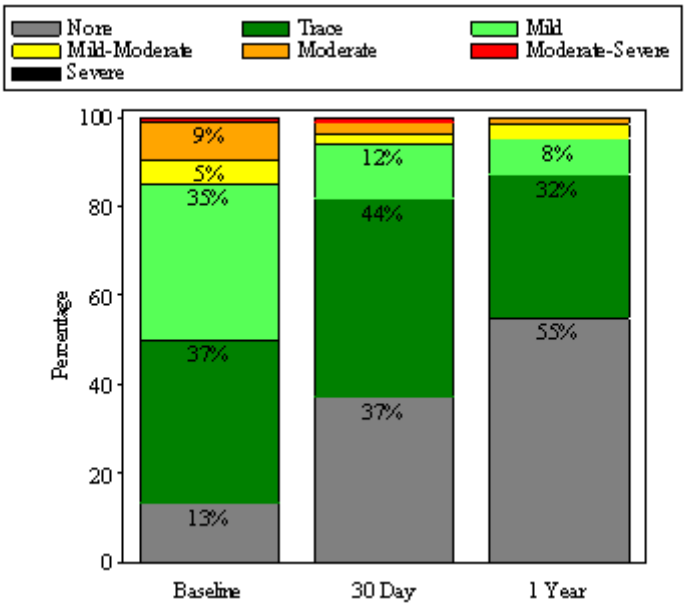


Figure 20: Aortic Insufficiency (S3OUS VI Population)

The proportion of patients with aortic PVL ≥ moderate was 3.7% at 30 days, and 1.6% at 1 year, as shown in Figure 21.

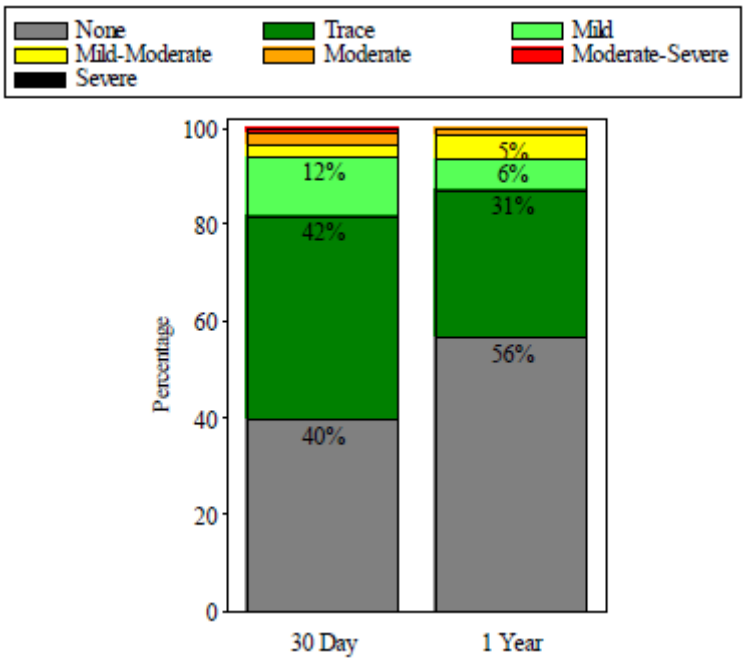


Figure 21: Aortic Paravalvular Leak (S3OUS VI Population)

New York Heart Association

The NYHA class by visit is shown in Figure 22. For all patients, the mean NYHA class decreased from 3.0 ± 0.5 at baseline to 1.6 ± 0.7 at 30 days and 1.8 ± 0.6 at 1 year.

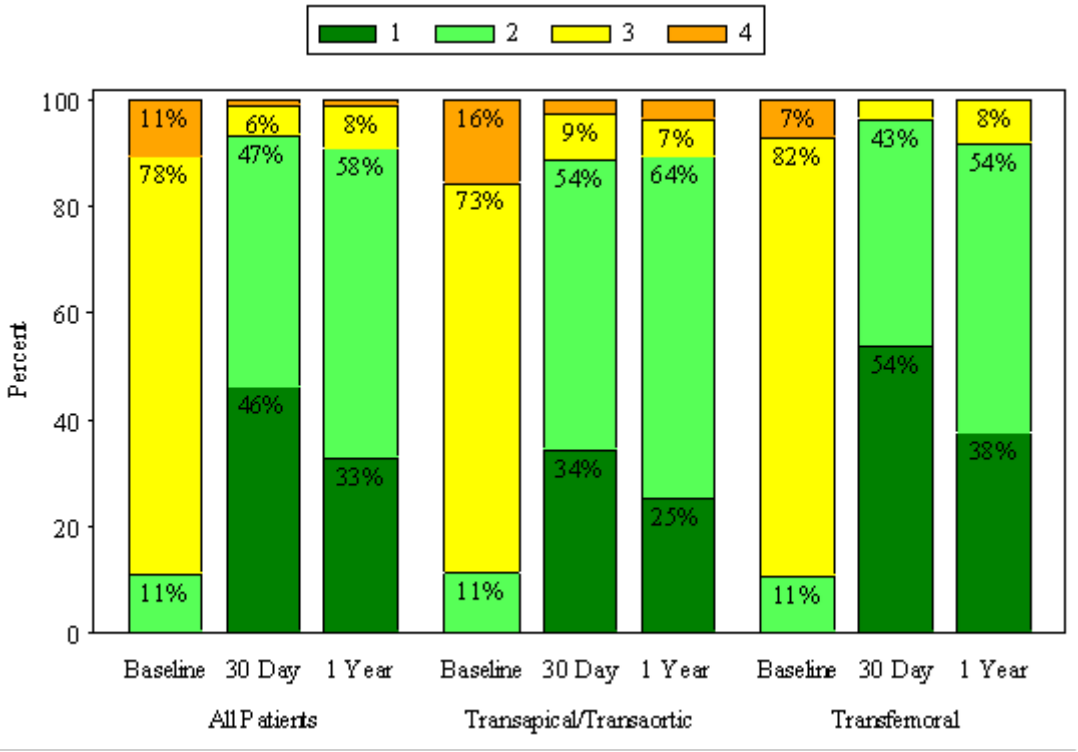


Figure 22: NYHA Class by Visit (S3OUS AT Population)

13.4 PARTNER II POST APPROVAL STUDY OVERVIEW SAPIEN 3 VALVE

Patient Accountability

At the time of database extract, 216 of 664 high risk and inoperable patients were eligible for the 5-year visit and 186 (86.1%) completed the visit within the 30-day follow-up window. A detailed summary of the patient accountability at 30 days to 5 years is shown in Table 23.

Table 23: Patient Accountability (VI Population N= 664)

	30 Days	6 Months	1 Year	2 Years	3 Years	4 Years	5 Years
The patients with known visit accountability*	664 (100.0%)	664 (100.0%)	664 (100.0%)	664 (100.0%)	664 (100.0%)	664 (100.0%)	664 (100.0%)
On study at follow-up visit	647	601	555	465	389	303	216
Follow-up visit completed	644 (99.5%)	574 (95.5%)	540 (97.3%)	446 (95.9%)	363 (93.3%)	280 (92.4%)	186 (86.1%)
Missed Visit	3 (0.5%)	27 (4.5%)	15 (2.7%)	19 (4.1%)	26 (6.7%)	23 (7.6%)	30 (13.9%)
Discontinued prior to follow-up visit†	17	63	109	199	275	361	448
Death	17	59	99	180	241	310	376
Withdrawal	0	4	7	12	22	34	43
Lost to follow-up	0	0	1	3	7	12	24
Exit with other reason	0	0	2	4	5	5	5
Visit pending‡	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

*The patients with known accountability is calculated as follows: (Number with FU visit + those with missed visit + those who have exited the study before the upper limit of the visit window) / the total population

†This includes all patients who exited the study prior to the end of the follow-up visit window and who have not had the visit.

‡Patients are not yet due or are within the follow-up visit window, but have not completed the follow-up visit yet.

The "Attempted Implant (AI)" population consisted of all patients in the dataset. The "Valve Implant (VI)" population consisted of those patients for whom the valve implant procedure succeeded. The numbers of patients in these two analysis populations are shown in Table 24.

Table 24: Analysis Populations

Analysis Population	Number of Patients
Attempted implant population	671
Valve implant population	664

Study Population Demographics and Baseline Characteristics

Patient demographics and baseline characteristics, as shown in Table 25, present an elderly, multimorbid cohort of patients, consistent with the high operative risk of the populations.

Table 25: Demographics and Baseline Characteristics (VI Population)

Demographics and Baseline Characteristics	Summary Statistics*
Age - years	82.9 ± 8.07 (664)
Male sex	51.1% (339/664)
Society of Thoracic Surgeons (STS) score	8.7 ± 3.75 (664)
New York Heart Association (NYHA) class	
Class I/II	12.0% (80/664)
Class III/IV	88.0% (584/664)
Previous myocardial infarction	18.2% (121/664)
Previous intervention	
Coronary artery bypass grafting (CABG)	31.2% (207/664)
Percutaneous coronary intervention (PCI)	33.0% (219/664)
Cerebrovascular accident (CVA)	11.4% (76/664)
Peripheral vascular disease (PVD)	35.2% (234/664)
Atrial fibrillation	42.2% (280/664)
Atrial flutter	5.6% (37/664)
Permanent pacemaker	15.5% (103/664)
Echocardiographic findings (Valve Implant Population)	
Valve area (cm^2)	0.66 ± 0.166 (622)
Mean gradient (mmHg)	45.9 ± 14.22 (649)
Peak gradient	76.4 ± 22.48 (649)
*Continuous measures - Mean ± SD (Total no.); Categorical measures % (no./Total no.)	

Safety and Effectiveness Results

Safety Endpoints

The composite rate of death, all-stroke, and moderate or greater aortic insufficiency (AI) is presented in Table 26.

Table 26: Composite Event Rate of Death, All Stroke and AI ≥ Moderate (VI Population N = 664)

Outcome	30 Days	1 Year	2 Years	3 Years	4 Years	5 Years
Death, All Stroke and Aortic Insufficiency (AI) ≥ Moderate	42/627 (6.7%)	126/551 (22.9%)	208/553 (37.6%)	275/535 (51.4%)	344/507 (67.9%)	400/532 (75.2%)

The Kaplan-Meier estimates of CEC-adjudicated adverse events through five years are presented in Table 27. The all-cause mortality rate was 61.9% at 5 years, including a cardiovascular mortality rate of 42.3%.

Table 27: CEC-Adjudicated Adverse Events (VI Population N = 664)

CEC-Adjudicated Adverse Events	30 Days	1 Year	2 Years	3 Years	4 Years	5 Years
All-Cause Death	15, 15 (2.3%)	97, 97 (14.7%)	177, 177 (27.2%)	243, 243 (37.8%)	308, 308 (48.8%)	375, 375 (61.9%)
Cardiovascular Death	9, 9 (1.4%)	58, 58 (9.1%)	102, 102 (16.7%)	141, 141 (24.1%)	177, 177 (31.9%)	216, 216 (42.3%)
All Stroke	11, 11 (1.7%)	26, 26 (4.2%)	47, 43 (7.4%)	62, 55 (10.2%)	68, 60 (11.6%)	77, 69 (15.0%)
Major Stroke	5, 5 (0.8%)	13, 13 (2.1%)	30, 27 (4.8%)	42, 36 (6.8%)	45, 38 (7.4%)	54, 47 (10.8%)
Minor Stroke	6, 6 (0.9%)	13, 13 (2.1%)	47, 43 (7.4%)	62, 55 (10.2%)	68, 60 (11.6%)	77, 69 (15.0%)
Rehospitalization from Symptoms of Aortic Stenosis and/or Complications of the Valve Procedure	55, 52 (7.9%)	165, 126 (19.8%)	214, 151 (24.3%)	250, 172 (28.8%)	280, 186 (32.4%)	301, 197 (36.3%)
Kaplan-Meier estimate - no. of events, no. of subjects with the event (%)						

The percentage of subjects with moderate or greater aortic insufficiency (AI) through five years is presented in Table 28. At five years, moderate or greater AI was reported in 2.1% of subjects.

Table 28: Aortic Insufficiency through 5 Years (VI Population N = 664)

Outcome	1 Year	2 Years	3 Years	4 Years	5 Years
Aortic Insufficiency (AI) ≥ Moderate	10/449 (2.2%)	4/369 (1.1%)	5/286 (1.7%)	10/192 (5.2%)	3/146 (2.1%)

Kaplan-Meier estimates of site-reported adverse events through five years are presented in Table 29.

Table 29: Site Reported Adverse Events (VI Population N = 664)

Outcomes	1 Year	2 Years	3 Years	4 Years	5 Years
Bleeding	35.1% (297, 229)	38.5% (336, 247)	41.9% (372, 263)	46.5% (411, 280)	48.6% (433, 286)
Vascular Complication	11.3% (81, 75)	11.3% (81, 75)	11.5% (82, 76)	11.8% (84, 77)	11.8% (84, 77)
Myocardial Infarction	2.7% (19, 17)	4.5% (31, 26)	6.1% (38, 33)	7.8% (45, 39)	9.0% (49, 42)
New Permanent Pacemaker	16.2% (106, 106)	17.2% (111, 111)	18.4% (116, 116)	20.9% (126, 125)	21.8% (128, 127)
New onset Atrial Fibrillation	7.4% (53, 48)	8.6% (61, 54)	9.5% (65, 58)	11.0% (70, 63)	12.8% (74, 67)
Kaplan-Meier estimate - % (no. of events, no. of subjects with the event)					

Effectiveness Endpoints

Valve Performance

The echocardiographic valve performance results are shown in Figure 23 through Figure 27. The effective orifice area increased from 0.66 cm^2 at baseline to 1.60 cm^2 at 1 year, which was maintained through 5 years (1.54 cm^2). The mean gradient decreased from 45.8 mmHg at baseline to 12.1 mmHg at 1 year, which was maintained through 5 years (11.8 mmHg). Peak gradient decreased from 76.4 mmHg at baseline to 22.6 mmHg at 1 year, which was maintained through 5 years (21.4 mmHg). At five years, 92.5% of subjects had mild or less total AR. No subjects had severe total AR. At five years, 94.5% of subjects had mild or less paravalvular regurgitation. No subjects had severe paravalvular AR.

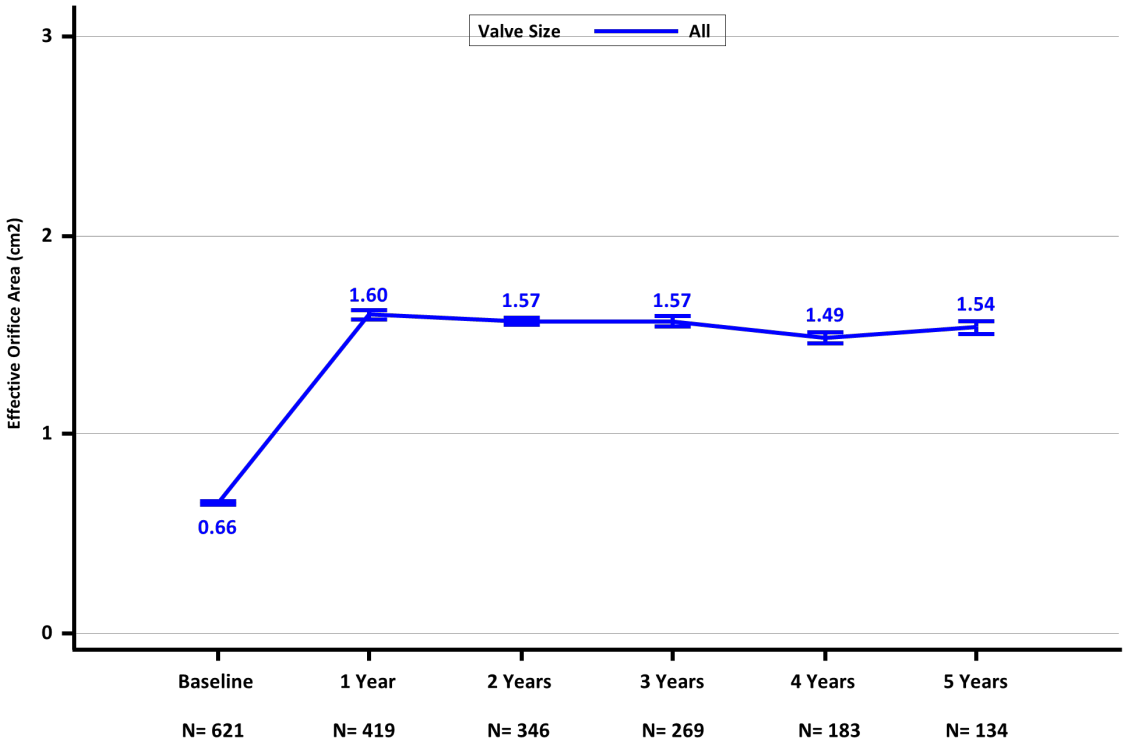


Figure 23: Effective Orifice Area by Visit (VI Population)

Note: Line plot with mean and standard error. The total number of patients at each visit time point only counted the patients with valid values.

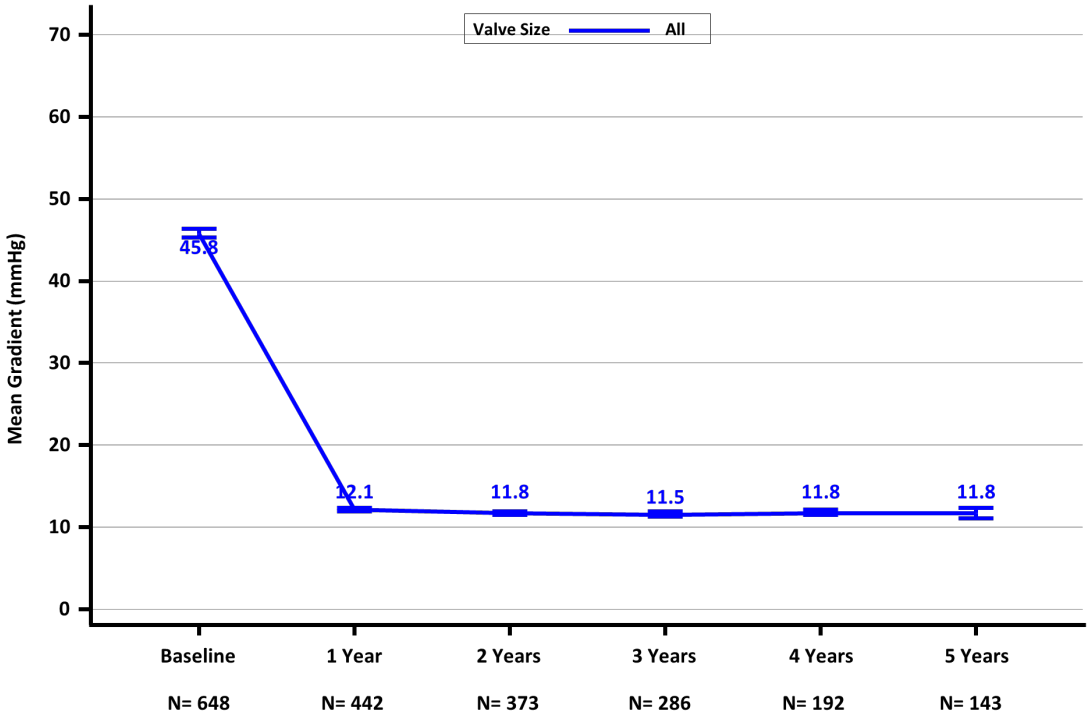


Figure 24: Mean Gradient by Visit (VI Population)

Note: Line plot with mean and standard error. The total number of patients at each visit time point only counted the patients with valid values.

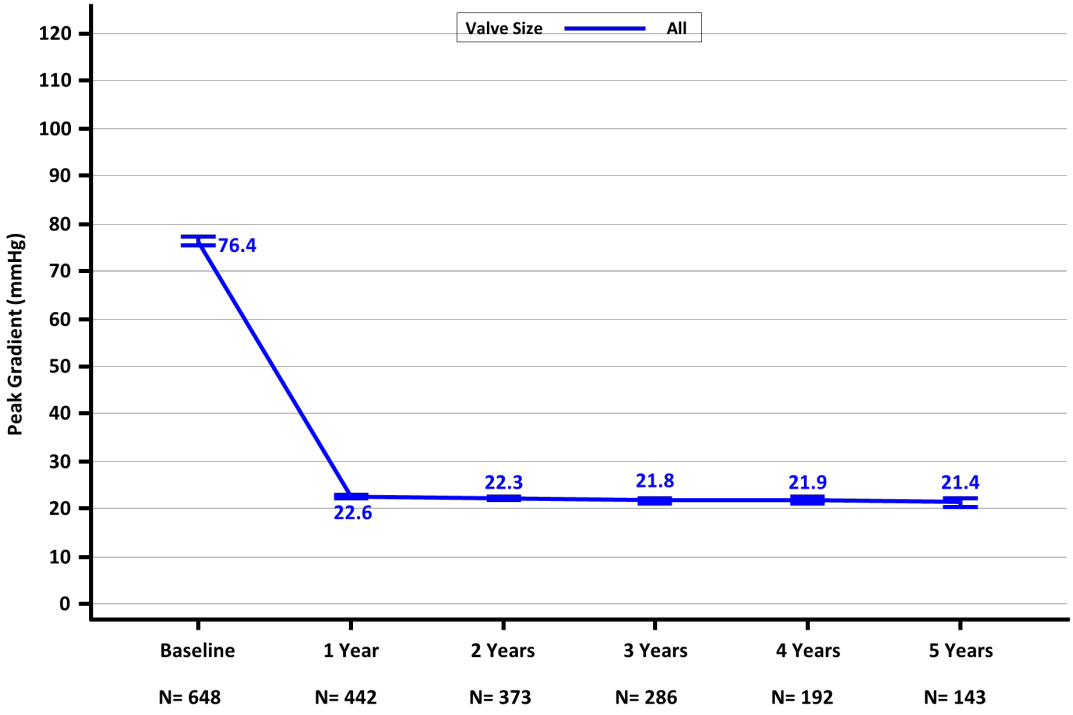


Figure 25: Peak Gradient by Visit (VI Population)

Note: Line plot with mean and standard error. The total number of patients at each visit time point only counted the patients with valid values.

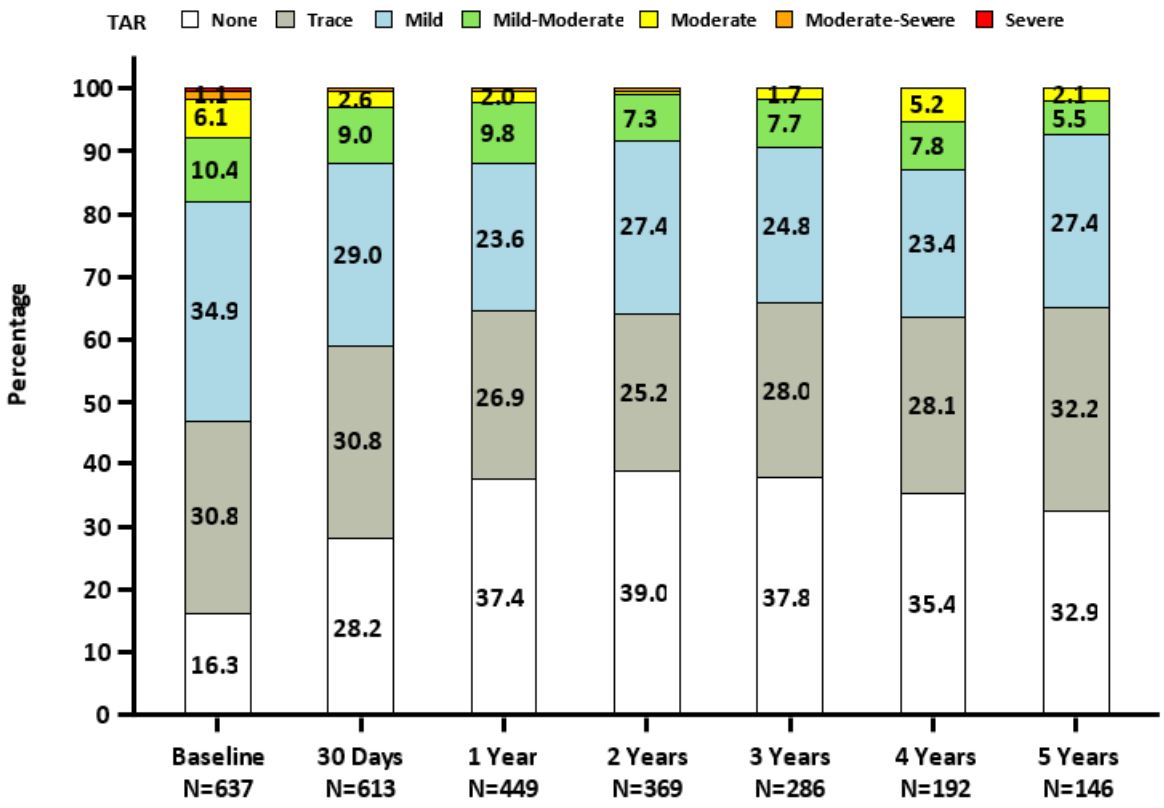


Figure 26: Total Aortic Regurgitation (VI Population)

Note: Line plot with mean and standard error. The total number of patients at each visit time point only counted the patients with valid values.

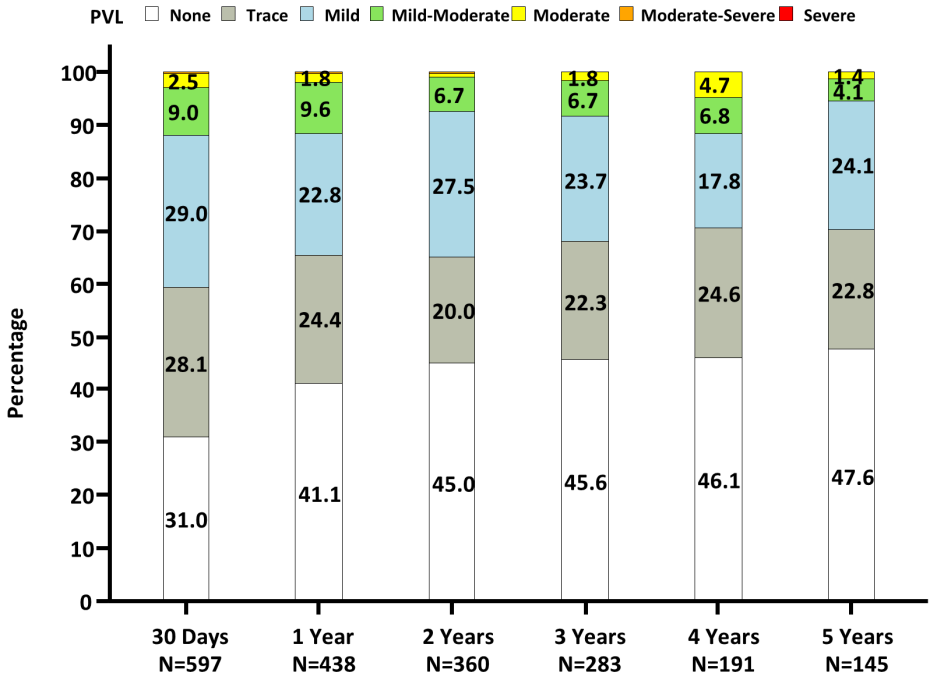


Figure 27: Paravalvular Aortic Regurgitation (VI Population)

Note: Line plot with mean and standard error. The total number of patients at each visit time point only counted the patients with valid values.

Kaplan-Meier estimates for structural valve deterioration (SVD) through five years are presented in Table 30. At five years, the rate of SVD was 1.2%. Five events of SVD were reported for 5 patients.

Table 30: Structural Valve Deterioration through 5 Years (VI Population N = 664)

Outcomes	1 Year	2 Years	3 Years	4 Years	5 Years
Structural Valve Deterioration	0.3% (2, 2)	0.5% (3, 3)	0.7% (4, 4)	0.7% (4, 4)	1.2% (5, 5)
Kaplan-Meier estimate - % (no. of events, no. of subjects with the event)					

New York Heart Association Functional Class

The NYHA functional class distributions by visit are presented in Figure 28. At baseline, 88.1% of patients were in NYHA III/IV. At 5 years, the majority (88.3%) of patients were in NYHA I/II.

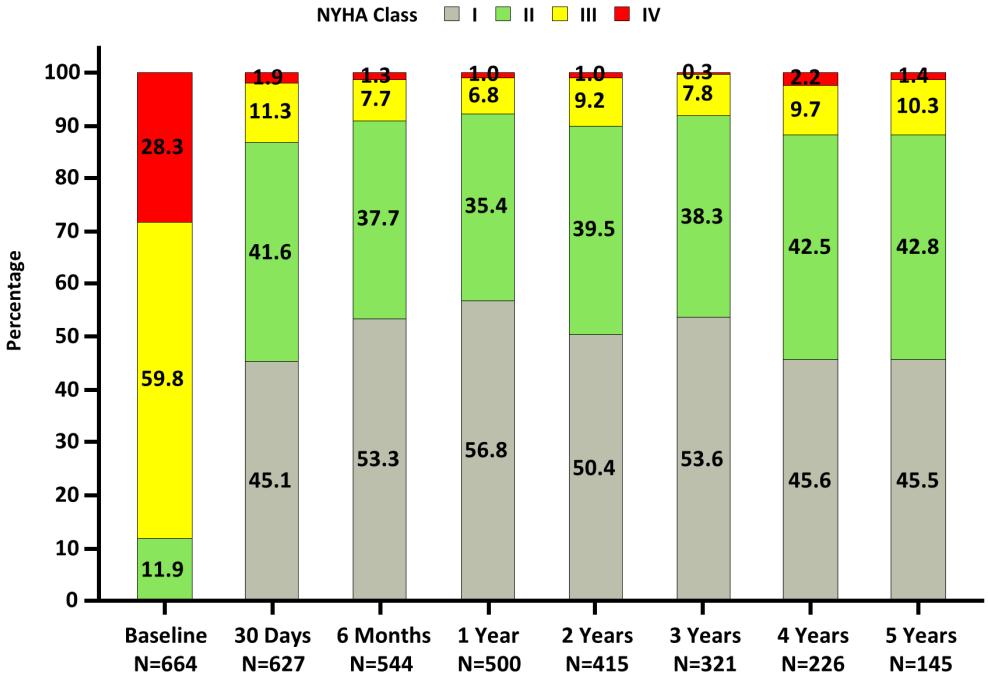


Figure 28: NYHA Class by Visit (VI Population)

Length of Stay

The mean index hospitalization stay was 6.8 days, which included an average of 3.0 days spent in the intensive care unit (ICU), as shown in Table 31.

Table 31: Index Hospitalization (VI Population)

Index Hospitalization	Length in Days*
Index hospitalization duration	6.8 ± 4.75 (664)
Intensive care stay	3.0 ± 2.84 (664)
*Mean ± SE (Total no.)	

Quality of Life

The results for the KCCQ overall summary score are presented in Figure 29. The mean score increased from 47.5 at baseline to 72.3 at 1 year, which was maintained through 5 years (69.0).

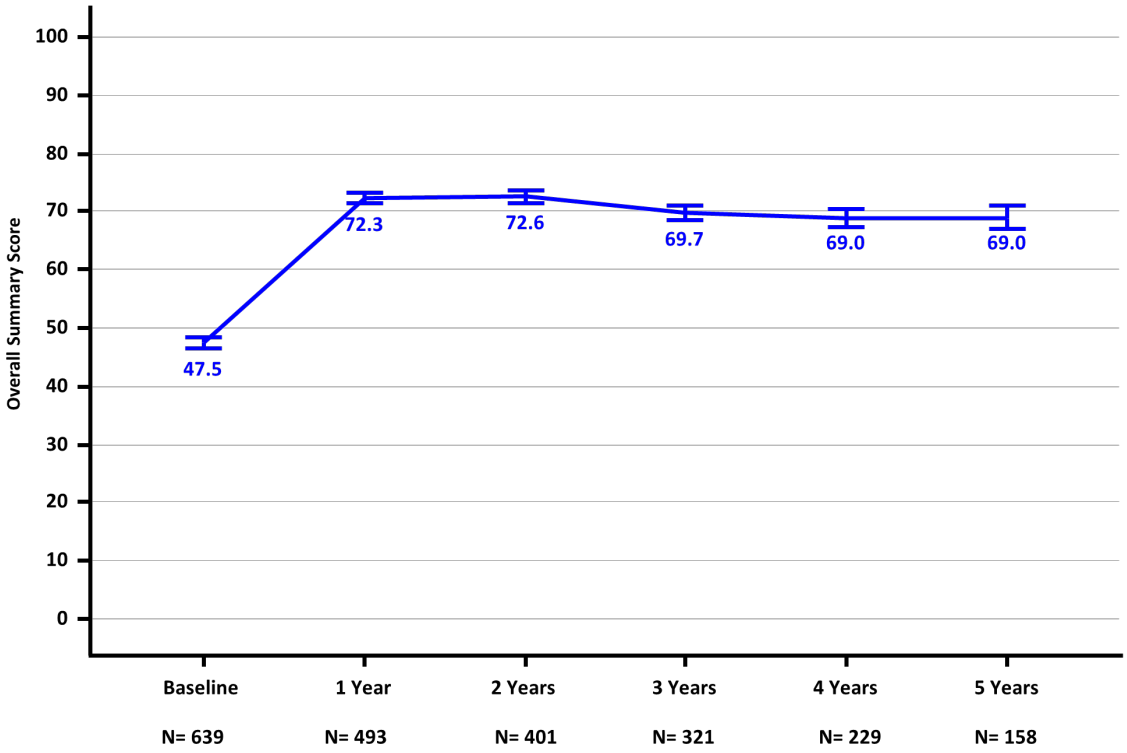


Figure 29: KCCQ Overall Summary Score (VI Population)

Note: Line plot with mean and standard error. The total number of patients at each visit time point only counted the patients with valid values.

Other Study Observations

Procedural Information

The procedural information is summarized in Table 32. General anesthesia was used in the majority (86.1%) of patients. Conversion to open heart surgery occurred in one patient due to device embolization.

Table 32: General Procedure Data (VI Population)

Procedural Data Summary	Summary Statistics (N=664)
Total procedure time (minute)	86.0 ± 44.09 (649)
Implanted valve size (mm)	
20	13.9% (92/664)
23	30.1% (200/664)
26	34.2% (227/664)
29	21.8% (145/664)
Total anesthesia time (minutes)	192.2 ± 63.06 (571)
Type of anesthesia used	
General	86.1% (572/664)
Conscious Sedation	13.9% (92/664)
Arterial site access	
Percutaneous	81.5% (539/661)
Surgical Cut-Down	14.2% (94/661)

Procedural Data Summary	Summary Statistics (N=664)
Conduit	0.2% (1/661)
None	4.1% (27/661)
Fluoroscopy time (minutes)	18.6 ± 9.88 (655)
Final position of the functioning transcatheter heart valve	
Acceptable - correct at intended site	99.2% (659/664)
Too ventricular	0.8% (5/664)
Too aortic	0.0% (0/664)
Valve not deployed	0/664 (0.0%)
Post-dilatation	16.3% (108/664)
Number of post-dilatation performed	
1	90.7% (98/108)
≥ 2	9.3% (10/108)
Valve in valve procedure performed (THV-in-THV)	1.1% (7/664)
Concomitant procedure(s) performed	2.4% (16/664)
Conversion to open heart surgery	
Valve dislodged	(0.2% (1/664)
*Continuous measures - mean ± SD (n); categorical measures - % (no./Total no.)	

Study Strength and Weaknesses

Data collected from the single-arm post approval study demonstrates acceptable clinical, functional, and hemodynamic long-term outcomes, and supports the safety and effectiveness of the SAPIEN 3 for the treatment of high risk subjects with severe symptomatic aortic stenosis. While efforts were made to ensure all treated subjects were followed through study completion, compliance with all follow-up requirements was difficult to obtain due to the existing comorbidities in this elderly, high surgical risk population, and their inabilities to attend in-office visits.

13.5 PARTNER II SAPIEN 3 INTERMEDIATE RISK COHORT

Patient Accountability

At the time of database lock, of the 1078 patients enrolled in the PMA study (PIIS3i), 99.2% (1069) patients are available for analysis at the completion of the study, the 1-year post-operative visit. Table 33 presents patient accountability in the PIIS3i and PIIA-SAVR cohorts. Of the 1,074 eligible patients (Eligible Patient or EP Population) in PIIS3i, 1,069 were successfully implanted with a SAPIEN 3 valve and constitute the PIIS3i Valve Implant (VI) population. Among the VI population, 943 patients were implanted via the transfemoral (TF) access route, and 126 patients via a non-transfemoral (non-TF; mainly transapical and transaortic) access route. Of the 938 eligible patients in the PIIA-SAVR cohort, 936 were successfully implanted with a surgical valve and constitute the PIIA-SAVR VI population.

Table 33: Patient Accountability

	All Enrolled Patients	Eligible Patient (EP) Population*	Valve Implant (VI) Population†
SAPIEN 3 Cohort	1078	1074	1069
TF	952	948	943
Non-TF	126	126	126
PIIA SAVR	1021	938	936

	All Enrolled Patients	Eligible Patient (EP) Population*	Valve Implant (VI) Population†

*Eligible Patient (EP) Population consists of all enrolled patients who were determined eligible after screening, entered into the catheterization laboratory and remained eligible to receive the assigned implant.

†Valve Implant (VI) Population is a subset of the EP Population who received the assigned valve, and retained the valve upon leaving the catheterization laboratory.

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, as summarized in Table 34 for the PIIS3i and PIIA-SAVR EP populations.

Table 34: Patient Demographics and Baseline Characteristics of the EP Population

Demographics & Characteristics*	SAPIEN 3 Valve			PIIA-SAVR (N = 938)
	Overall (N = 1074)	TF Only (N = 948)	Non-TF Only (N = 126)	
Age – years	81.9 ± 6.60	82.1 ± 6.57	80.7 ± 6.69	81.6 ± 6.73
Male sex	662/1074 (61.6%)	577/948 (60.9%)	85/126 (67.5%)	514/938 (54.8%)
Society of Thoracic Surgeons (STS) score	5.3 ± 1.29	5.3 ± 1.29	5.6 ± 1.28	5.8 ± 1.92
New York Heart Association (NYHA) class				
I/II	294/1074 (27.4%)	262/948 (27.6%)	32/126 (25.4%)	225/937 (24.0%)
III/IV	780/1074 (72.6%)	686/948 (72.4%)	94/126 (74.6%)	712/937 (76.0%)
Coronary artery disease	748/1074 (69.6%)	652/948 (68.8%)	96/126 (76.2%)	623/938 (66.4%)
Previous myocardial infarction	172/1074 (16.0%)	133/948 (14.0%)	39/126 (31.0%)	166/938 (17.7%)
Previous intervention				
Coronary artery bypass grafting (CABG)	301/1074 (28.0%)	248/948 (26.2%)	53/126 (42.1%)	241/938 (25.7%)
Percutaneous coronary intervention (PCI)	344/1074 (32.0%)	299/948 (31.5%)	45/126 (35.7%)	254/938 (27.1%)
Prior aortic valvuloplasty	55/1074 (5.1%)	51/948 (5.4%)	4/126 (3.2%)	45/938 (4.8%)
Cerebral vascular accident (CVA)	97/1074 (9.0%)	81/948 (8.5%)	16/126 (12.7%)	96/938 (10.2%)
Peripheral vascular disease	304/1074 (28.3%)	231/948 (24.4%)	73/126 (57.9%)	301/938 (32.1%)
Chronic obstructive pulmonary disease (COPD)				
Any	321/1072 (29.9%)	270/946 (28.5%)	51/126 (40.5%)	279/932 (29.9%)
Oxygen-dependent	53/1067 (5.0%)	46/942 (4.9%)	7/125 (5.6%)	26/925 (2.8%)
Atrial fibrillation	385/1074 (35.8%)	342/948 (36.1%)	43/126 (34.1%)	326/938 (34.8%)
Permanent pacemaker	142/1074 (13.2%)	121/948 (12.8%)	21/126 (16.7%)	113/938 (12.0%)
Severe pulmonary hypertension	25/1074 (2.3%)	19/948 (2.0%)	6/126 (4.8%)	N/A
Frailty	92/1074 (8.6%)	86/948 (9.1%)	6/126 (4.8%)	15/938 (1.6%)
Porcelain aorta	1/1074 (0.1%)	1/948 (0.1%)	0/126 (0.0%)	0/938 (0.0%)
Chest deformities that preclude an open chest procedure	1/1074 (0.1%)	1/948 (0.1%)	0/126 (0.0%)	0/938 (0.0%)
Cirrhosis	4/1074 (0.4%)	4/948 (0.4%)	0/126 (0.0%)	4/938 (0.4%)
Echocardiographic findings (Valve Implant Population)				
Effective orifice area (EOA) - cm^2	0.7 ± 0.17	0.7 ± 0.16	0.7 ± 0.18	0.7 ± 0.20

Demographics & Characteristics*	SAPIEN 3 Valve			PIIA-SAVR (N = 938)
	Overall (N = 1074)	TF Only (N = 948)	Non-TF Only (N = 126)	
Mean aortic-valve gradient - mmHg	46.1 ± 12.63	46.1 ± 12.66	45.8 ± 12.47	44.7 ± 12.55
Mean left ventricular ejection fraction (LVEF) %	58.5 ± 13.36	58.8 ± 13.24	56.0 ± 14.05	55.4 ± 11.75
Moderate or severe mitral regurgitation	91/1033 (8.8%)	87/909 (9.6%)	4/124 (3.2%)	153/841 (18.2%)

*Continuous measures - Mean ± SD; Categorical measures – n/total no. (%)

Safety and Effectiveness Results

Primary Endpoints

The primary endpoint was a composite of all-cause death, stroke, and AI ≥ moderate at 1 year. The weighted proportion difference of the primary endpoint was -9.2% (90% CI: [-12.4%, -6.0%]) using the average treatment effect on the treated (ATT) method[3], as shown in Table 35 and Figure 30. Since the upper limit of the CI was < 7.5%, non–inferiority was met.

Table 35: Primary Endpoint Non-Inferiority Test (VI Population)

	Observed Event rate		Propensity Score Quintile Pooled Proportion Difference (ATT Method*) [90% CI]†	Margin	Conclusion for Non-Inferiority Test
	SAPIEN 3 Valve (N = 1069)	PIIA-SAVR (N = 936)			
Composite of all-cause death, all stroke, and aortic insufficiency (AI) ≥ moderate at 1 year	13.0%	23.2%	-9.2% [-12.4%, -6.0%]	7.5%	Pass

*ATT: average treatment effect on the treated
†Two-sided 90% Wald-type confidence interval

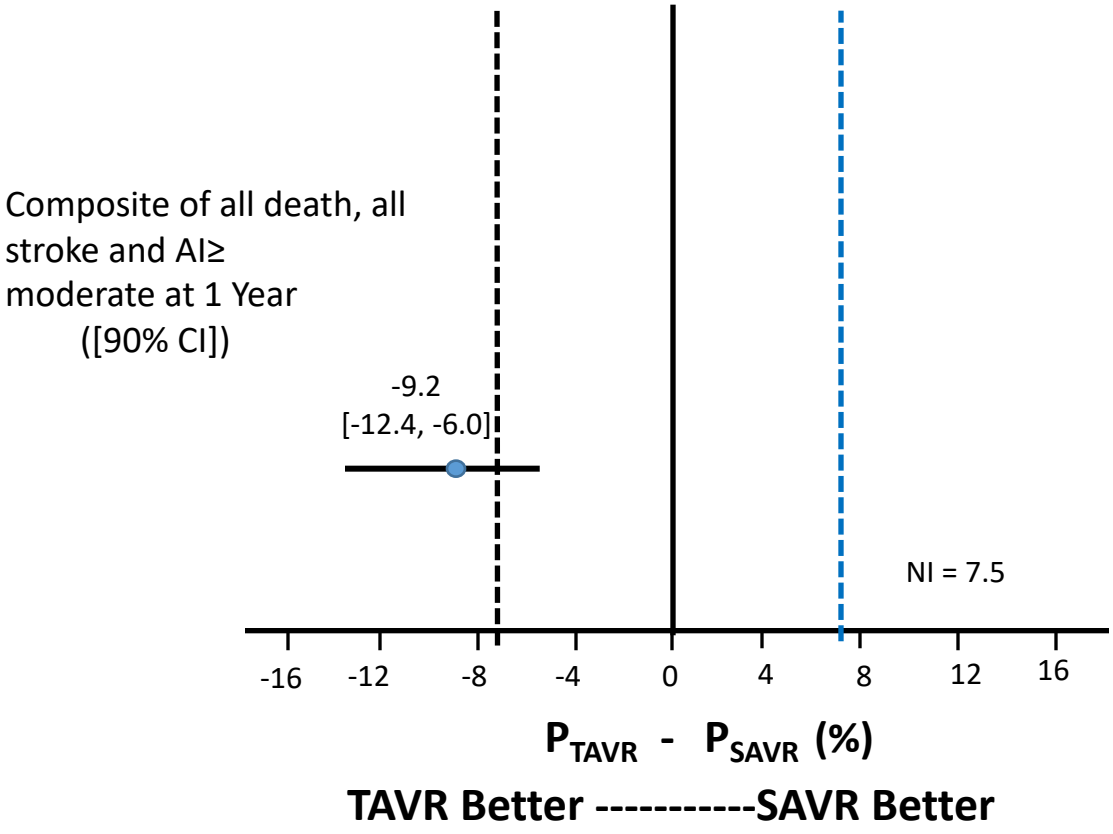


Figure 30: Forest Plot – Composite of All Death, All Stroke and AI ≥ Moderate (VI Population)

The Kaplan-Meier (KM) estimates for all-cause death and all stroke at 1 year for the PIIS3i cohort and the PIIA-SAVR cohort are provided in Table 36, as well as Figure 31 and Figure 32, respectively.

Table 36: All-Cause Death and All Stroke at 1 Year (VI Population)

Endpoints	SAPIEN 3 Valve (N = 1069)			PIIA-SAVR (N = 936)			Propensity Score Quintile Pooled Proportion Difference (ATT Method†)
	Observed Event Rate	Kaplan-Meier Event Rate*		Observed Event Rate	Kaplan-Meier Event Rate*		
		Point Estimate	Standard Error		Point Estimate	Standard Error	
All-cause death at 1 year	7.0%	7.1%	0.79%	12.4%	12.6%	1.09%	-5.2%
All stroke at 1 year	4.5%	4.6%	0.65%	7.9%	8.1%	0.91%	-3.5%

*Kaplan-Meier estimates were calculated at 365 days and included only the first event for each patient. Events occurring after 365 days were not included in this analysis.
†ATT: average treatment effect on the treated

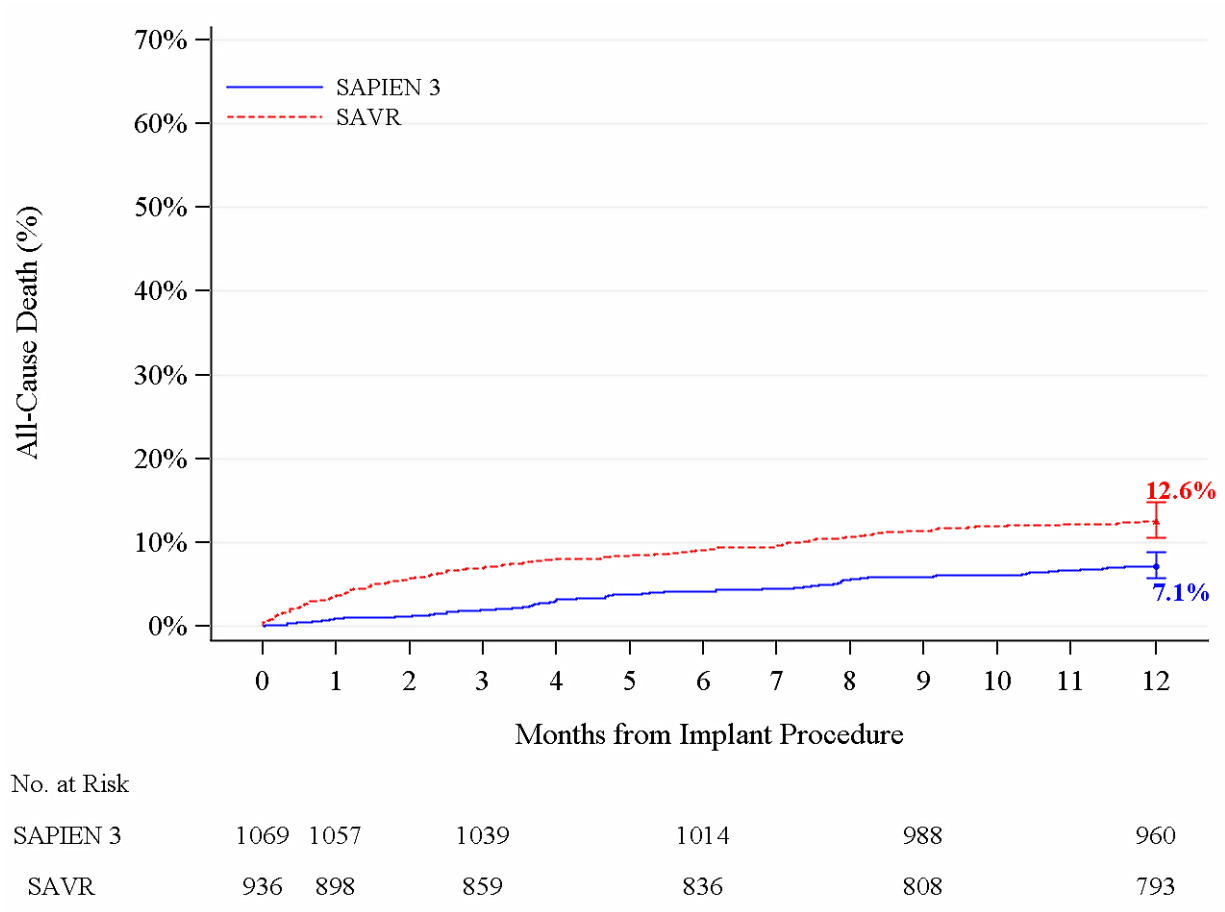


Figure 31: All-Cause Death through 1 Year (VI Population)

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

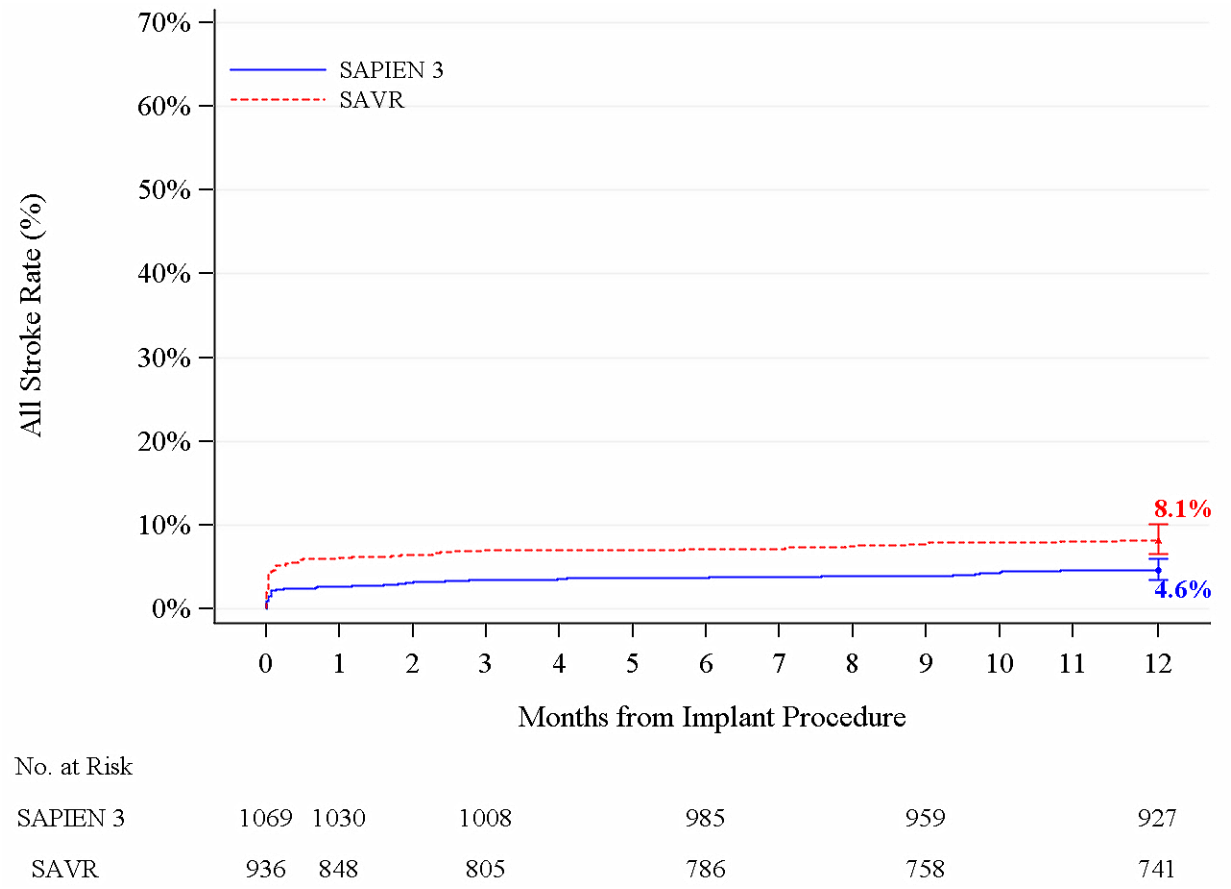


Figure 32: All Stroke through 1 Year (VI Population)

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

The proportion of patients with AI ≥ moderate at 1 year was 1.6% for the PIIS3i cohort and 0.3% for the PIIA-SAVR cohort, as shown in Table 37.

Table 37: Aortic Insufficiency (AI) ≥ Moderate at 1 Year (VI Population)

	Observed Event Rate		Propensity Score Quintile Pooled Proportion Difference (ATT Method*)
	SAPIEN 3 Valve (N = 1069)	SAVR (N = 936)	
Aortic insufficiency (AI) ≥ moderate	1.6%	0.3%	1.2%
*ATT: average treatment effect on the treated			

Secondary Endpoints

The secondary endpoints were examined in a pre-specified order adjusted for the propensity quintiles using the ATT method. Table 38 summarizes the statistical conclusions on the non-inferiority hypothesis testing of the five secondary endpoints for labeling that were evaluated using a gatekeeping/hierarchical multiplicity adjustment procedure to control the overall type I error to 0.05. For each secondary endpoint, the upper limit of the confidence interval was less than the respective non-inferiority margin. Therefore, for each of the secondary endpoints for labeling, the SAPIEN 3 valve was non-inferior to SAVR.

Table 38: Secondary Endpoints for Labeling – Gatekeeping/Hierarchical Method (VI Population)

Pre-Specified Order for Gatekeeping/ Hierarchical Method	Endpoints	Observed Event Rate		Weighted Proportion Difference in Average Treatment Effect on the Treated [90% CI][†]	Margin	Conclusion for Non-Inferiority Test
		SAPIEN 3 Valve (N = 1069)	PIIA-SAVR (N = 936)			
No. 1	Composite of all death, all strokes, life threatening (disabling)/ major bleeding and major vascular complication at 30 days	18.3%	79.4%	-60.5% [-63.5%, -57.4%]	7.5%	Pass
No. 2	Major vascular and access complications through 30 days	5.8%	5.3%	0.3% [-1.5%, 2.0%]	5.0%	Pass
No. 3	Life threatening (disabling)/ major bleeding through 30 days	14.6%	78.2%	-63.2% [-66.2%, -60.2%]	5.0%	Pass
No. 4	All-cause death through 30 days	0.9%	3.7%	-2.7% [-3.9%, -1.5%]	2.5%	Pass
No. 5	All stroke through 30 days	2.6%	6.1%	-3.2% [-4.7%, -1.6%]	2.5%	Pass

[†]Two-sided 90% Wald-type confidence interval.

The forest plots for all-cause death and all stroke at 30 days are provided in Figure 33 and Figure 34, respectively.

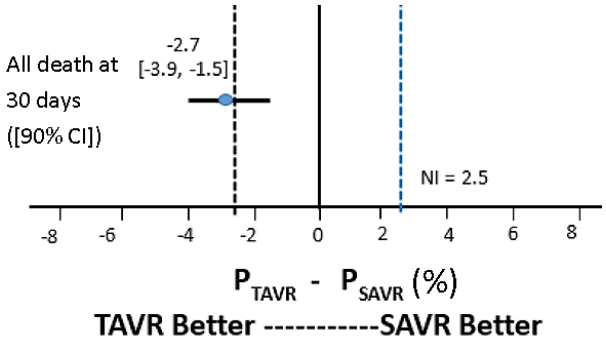


Figure 33: Forest Plot – All-Cause Death at 30 Days (VI Population)

Note: As part of a pre-specified hierarchy, the hypothesis for this endpoint was tested using a hierarchical gatekeeping approach. The confidence interval shown here was not adjusted for multiplicity per the gatekeeping approach.

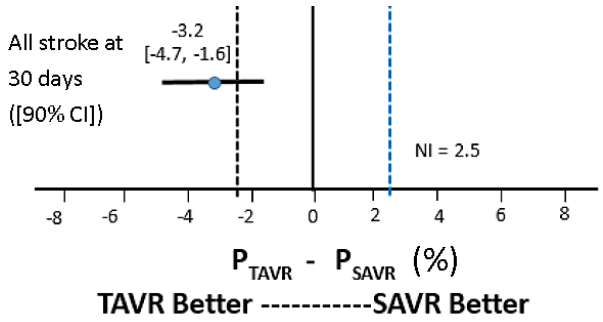


Figure 34: Forest Plot – All Stroke at 30 Days (VI Population)

Note: As part of a pre-specified hierarchy, the hypothesis for this endpoint was tested using a hierarchical gatekeeping approach. The confidence interval shown here was not adjusted for multiplicity per the gatekeeping approach.

Adverse Events

The key CEC-adjudicated adverse events through 1 year for the EP population are presented in Table 39.

Table 39: CEC-Adjudicated Adverse Events through 1 Year (EP Population)

Event*	SAPIEN 3 Valve			PIIA-SAVR
	Overall	TF Only	Non-TF Only	
7 Days				
Acute kidney injury: Stage III	5/1074 (0.5%)	3/948 (0.3%)	2/126 (1.6%)	N/A
30 Days				
Death	12/1074 (1.1%)	10/948 (1.1%)	2/126 (1.6%)	35/938 (3.7%)
Cardiac death	10/1074 (0.9%)	9/948 (0.9%)	1/126 (0.8%)	26/938 (2.8%)
Non-cardiac death	2/1074 (0.2%)	1/948 (0.1%)	1/126 (0.8%)	9/938 (1.0%)
Stroke	29/1074 (2.7%)	24/948 (2.5%)	5/126 (4.0%)	57/938 (6.1%)
Major (disabling) stroke	11/1074 (1.0%)	7/948 (0.7%)	4/126 (3.2%)	41/938 (4.4%)
Minor (non-disabling) stroke	18/1074 (1.7%)	17/948 (1.8%)	1/126 (0.8%)	16/938 (1.7%)
Myocardial infarction	3/1074 (0.3%)	3/948 (0.3%)	0/126 (0.0%)	17/938 (1.8%)
Major vascular complication	65/1074 (6.1%)	60/948 (6.3%)	5/126 (4.0%)	50/938 (5.3%)
Life threatening (disabling) or major bleeding	159/1074 (14.8%)	112/948 (11.8%)	47/126 (37.3%)	733/938 (78.1%)
Aortic valve re-intervention	1/1074 (0.1%)	1/948 (0.1%)	0/126 (0.0%)	0/938 (0.0%)
Any endocarditis	2/1074 (0.2%)	2/948 (0.2%)	0/126 (0.0%)	0/938 (0.0%)
Rhythm disturbance requiring permanent pacemaker	108/1074 (10.1%)	99/948 (10.4%)	9/126 (7.1%)	68/938 (7.2%)
1 Year				
Death	79/1074 (7.4%)	61/948 (6.4%)	18/126 (14.3%)	117/938 (12.5%)
Cardiac death	47/1074 (4.4%)	37/948 (3.9%)	10/126 (7.9%)	70/938 (7.5%)
Non-cardiac death	32/1074 (3.0%)	24/948 (2.5%)	8/126 (6.3%)	47/938 (5.0%)
Stroke	49/1074 (4.6%)	40/948 (4.2%)	9/126 (7.1%)	74/938 (7.9%)
Major (disabling) stroke	24/1074 (2.2%)	16/948 (1.7%)	8/126 (6.3%)	53/938 (5.7%)
Minor (non-disabling) stroke	25/1074 (2.3%)	24/948 (2.5%)	1/126 (0.8%)	22/938 (2.3%)

Event*	SAPIEN 3 Valve			PIIA-SAVR
	Overall	TF Only	Non-TF Only	
Aortic valve re-intervention	6/1074 (0.6%)	6/948 (0.6%)	0/126 (0.0%)	4/938 (0.4%)
Any endocarditis	8/1074 (0.7%)	7/948 (0.7%)	1/126 (0.8%)	6/938 (0.6%)
*Categorical measures - n. / total no. (%).				

In addition, site-reported new-onset atrial fibrillation was 5.9% in the PIIS3i EP population and 29.2% in the PIIA-SAVR EP population.

Bleeding Rate

The bleeding rates utilizing the number of units transfused are presented in Table 40.

Table 40: Bleeding Rate Using Site-Reported Units Transfused (EP Population)

Event*	SAPIEN 3 Valve (N = 1074)	PIIA-SAVR (N = 938)
Transfusion units ≥ 2 and < 4	47/1074 (4.4%)	184/938 (19.6%)
Transfusion units ≥ 4	18/1074 (1.7%)	218/938 (23.2%)
*Site-reported Transfusion at Day 0 or Day 1; Categorical measures - n. / total no. (%)		

Other Results

Procedural Information

In the PIIS3i EP population the mean duration in the catheterization laboratory was 187.3 ± 53.2 minutes, the mean total procedure time was 84.2 ± 40.7 minutes, and the mean total anesthesia time was 186.9 ± 61.1 minutes, all of which were slightly shorter in the TF group. General anesthesia was used in the vast majority of cases; 18.9% of the TF patients had conscious sedation. Correct positioning of the valve was achieved in 99.3% of the patients. Four (4) patients (0.4%, all TF patients) were implanted with a second valve. One (1) patient (0.1%) experienced valve embolization and two (2) patients (0.2%) experienced annular rupture.

In the PIIA-SAVR EP population, the mean duration in the operating room was 333.2 ± 96.4 min, the mean total procedure time was 237.5 ± 86.58 min, and the mean anesthesia time was 333.5 ± 108.42 min. General anesthesia was used in all patients.

Valve Performance

The measurements of EOA, mean gradient, peak gradient, total aortic regurgitation (AR), and aortic paravalvular leak (PVL) are presented in Figure 35 to Figure 39. The increase in EOA and decrease in gradient were sustained at 1 year. In PIIS3i, the proportion of patients with total AR ≥ moderate was 6.2% at baseline, 3.9% at 30 days, and 1.6% at 1 year, while in PIIA-SAVR, the proportion of patients with total AR ≥ moderate was 12.0% at baseline, 0.7% at 30 days, and 0.3% at 1 year. The proportion of patients with aortic PVL ≥ moderate was 3.8% at 30 days and 1.5% at 1 year in PIIS3i, as compared to 0.5% at 30 days and 0.3% at 1 year in PIIA-SAVR.

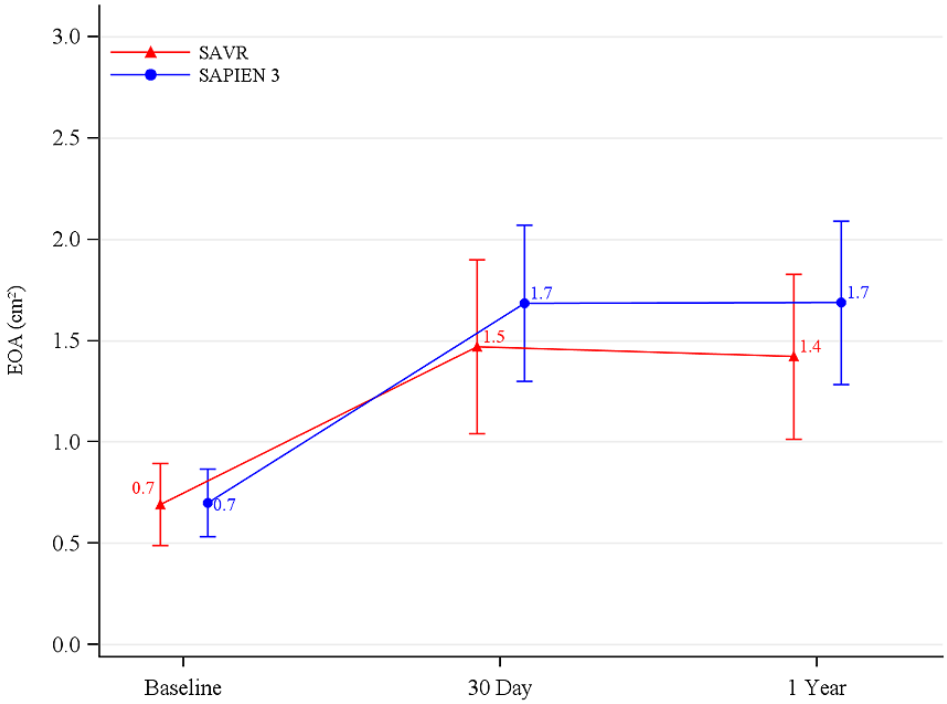


Figure 35: Effective Orifice Area (VI Population)

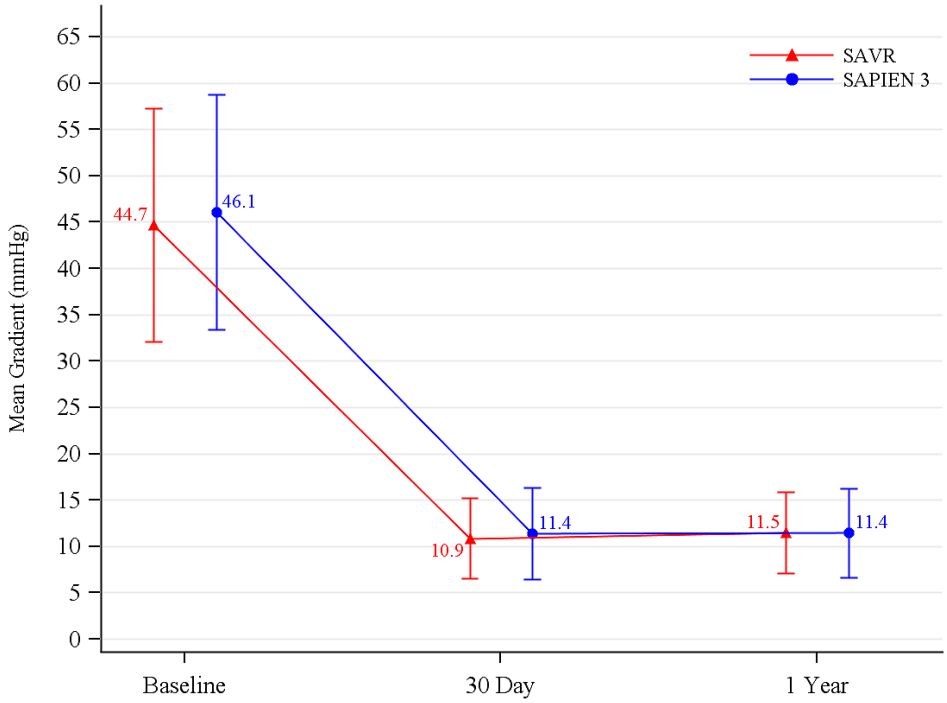


Figure 36: Mean Gradient (VI Population)

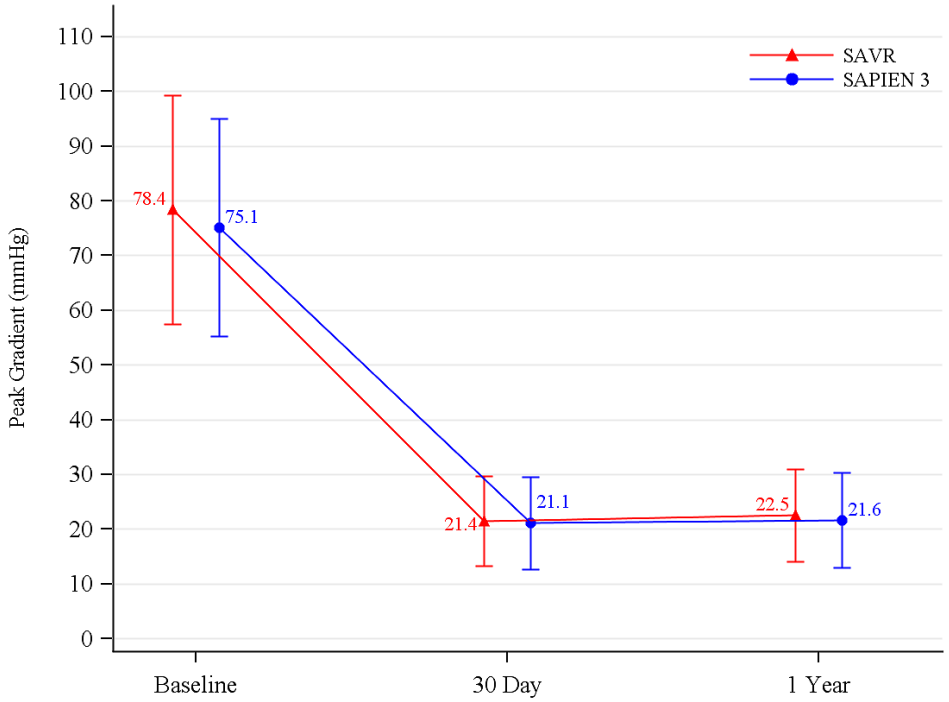


Figure 37: Peak Gradient (VI Population)

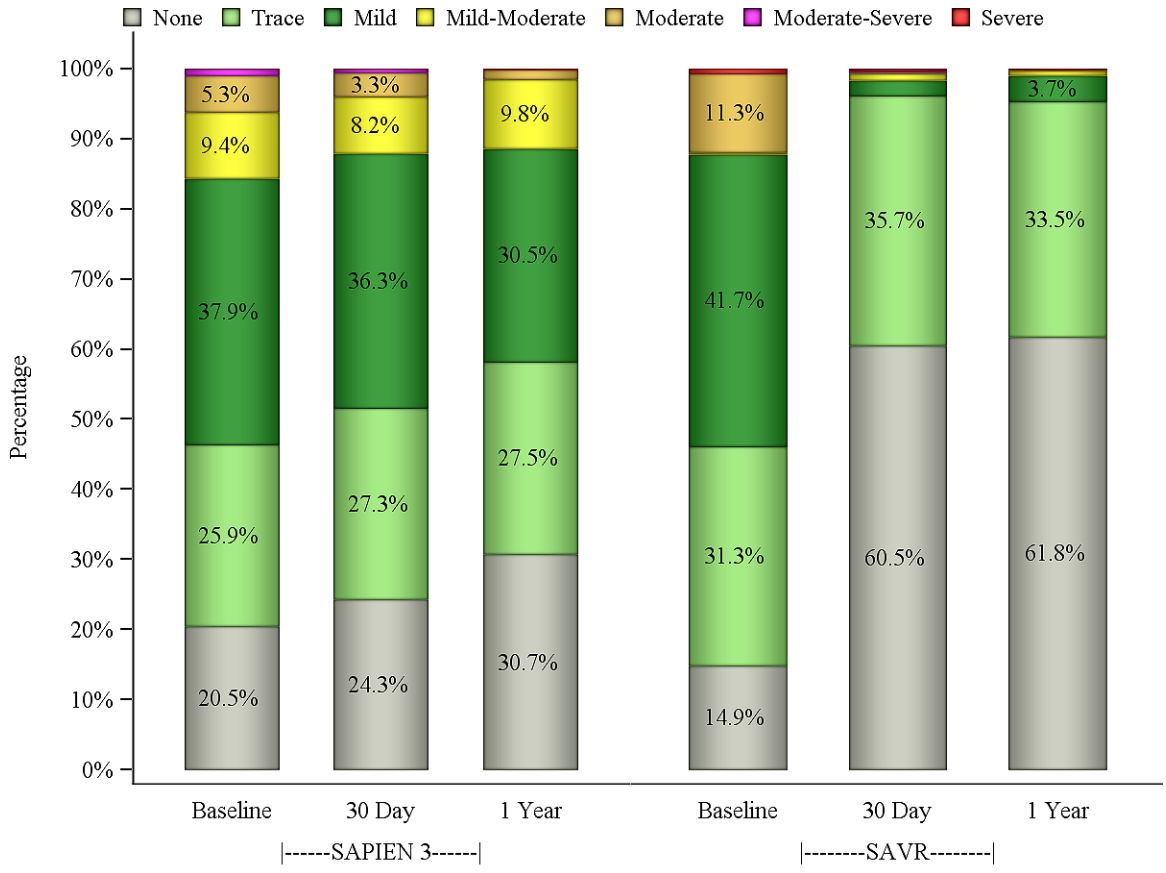


Figure 38: Total Aortic Regurgitation (VI Population)

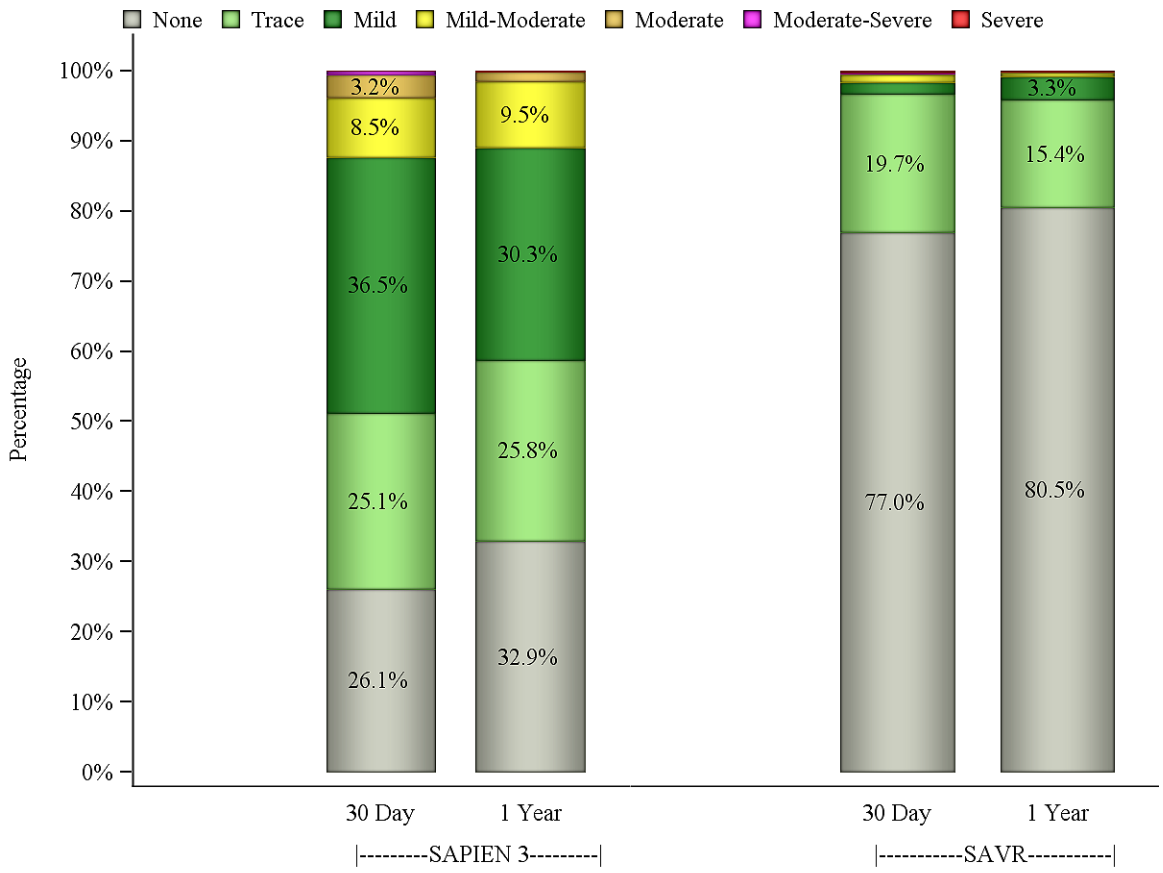


Figure 39: Aortic Paravalvular Leak (VI Population)

New York Heart Association

The NYHA classifications by visit are presented in Figure 40. In PIIS3i, 72.6% of the patients were in NYHA Class III or IV at baseline, which reduced to 6.3% at 30 days and 6.7% at 1 year, while in PIIA-SAVR, the percentage of patients in NYHA Class III or IV was 76.0% at baseline, 13.6% at 30 days, and 6.7% at 1 year. A side-by-side comparison of the results by access approach is presented in Figure 41.

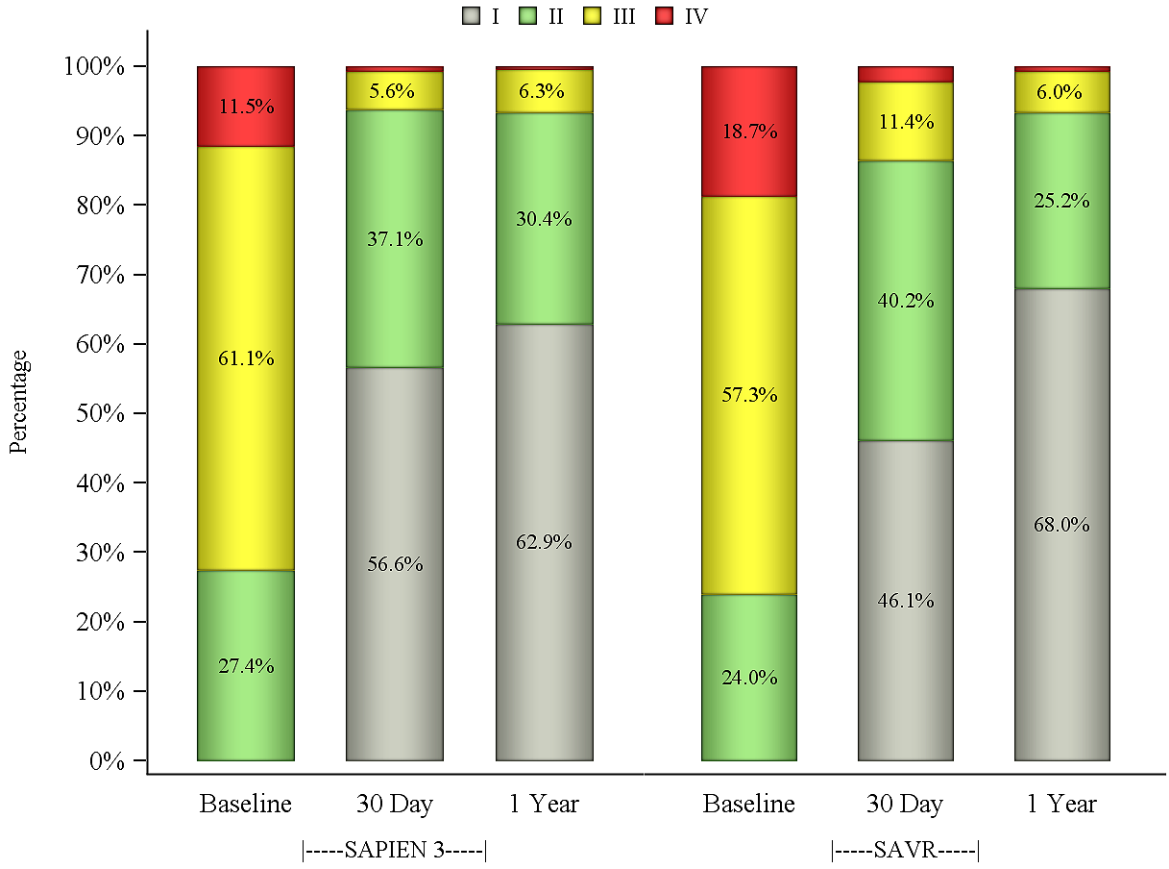


Figure 40: NYHA Class by Visit (EP Population)

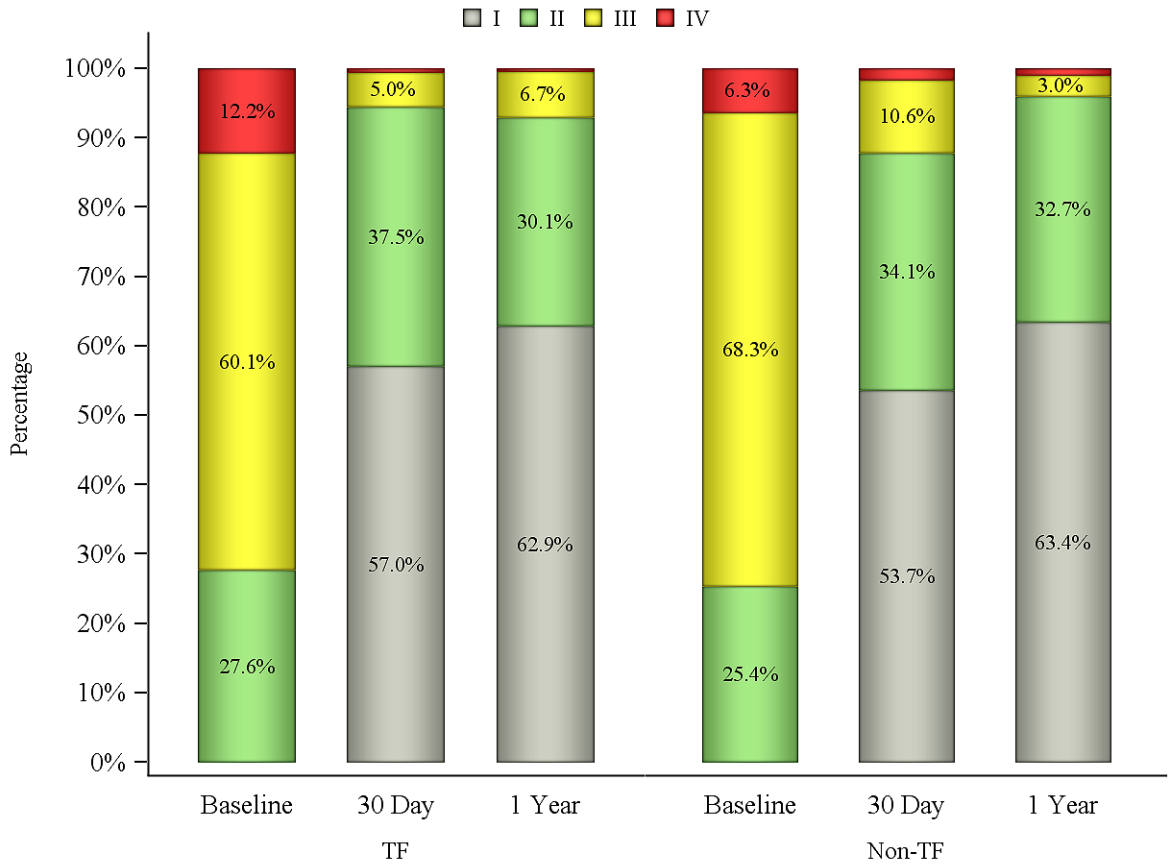


Figure 41: NYHA Class by Visit – TF versus non-TF Access (EP Population)

Six-Minute Walk Test (6MWT)

The improvements in mean 6MWT distance are presented in Table 41. The SAPIEN 3 valve patients had a similar increase in mean 6MWT distance from baseline to 1 year as the PIIA-SAVR patients.

Table 41: 6MWT Distance (EP Population)

6MWT Distance (m)*	SAPIEN 3 Valve			PIIA-SAVR
	All	TF	Non-TF	
Baseline	193.9 ± 118.1	194.1 ± 117.2	192.5 ± 125.5	179.3 ± 123.2
30 days	230.6 ± 126.1	234.6 ± 123.6	199.0 ± 140.6	166.7 ± 126.4
1 year	227.7 ± 134.7	230.6 ± 133.6	202.8 ± 142.1	219.2 ± 133.8
*Plus–minus values are means ± SD.				

Length of Stay (LoS)

The results for LoS are presented in Table 42. Overall, the SAPIEN 3 valve patients had shorter LoS than the PIIA-SAVR patients.

Table 42: Length of Stay (EP Population)

Length of Stay (days)*	SAPIEN 3 Valve			PIIA-SAVR
	All	TF	Non-TF	
Overall	5.5 ± 5.7	5.0 ± 5.2	9.3 ± 7.7	11.9 ± 7.6
ICU	2.7 ± 3.0	2.5 ± 2.6	4.2 ± 4.9	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 42. Except for self-efficacy which showed a small improvement, moderate to large improvements were observed in all other subscores at 30 days and were sustained at 1 year in the PIIS3i EP population. A side-by-side comparison of the results by access approach is presented in Figure 43. In general, improvements in the TF group were slightly larger as compared to those observed in the Non-TF group.

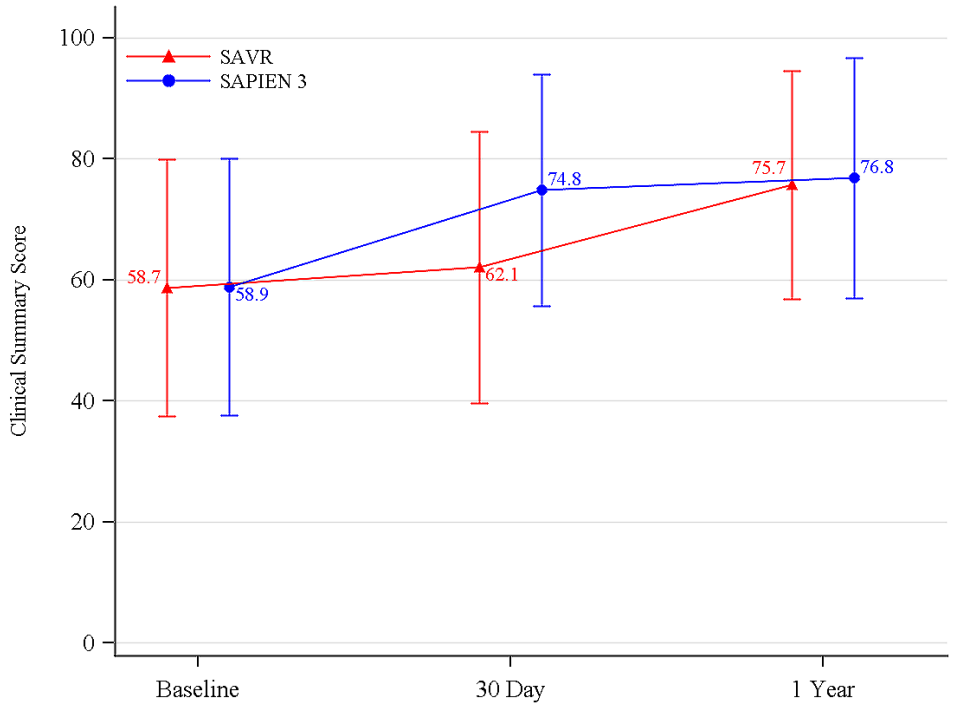


Figure 42: KCCQ Clinical Summary Score (EP Population)

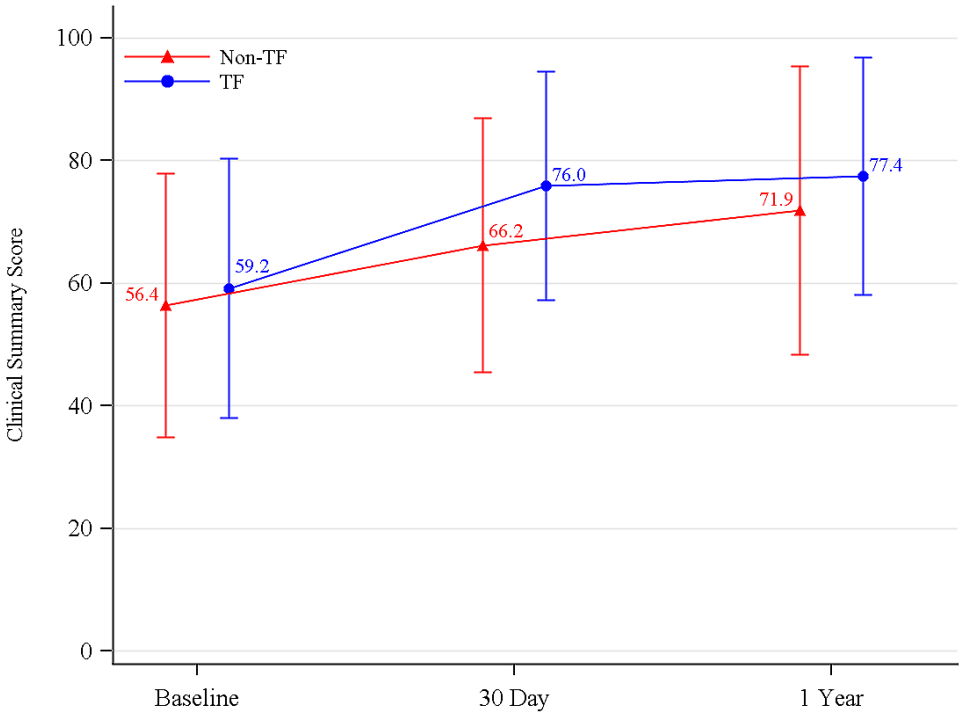


Figure 43: KCCQ Clinical Summary Score - TF versus non-TF Access (EP Population)

Additional QoL instruments

QoL was also measured using the visual analog scale (VAS) of the EuroQoL (EQ-5D) measure and the SF-36 Health Status Questionnaire. The VAS is a self-assessment in which patients rate their well-being on a scale from 0 to 100 where 0 is the worst state they can imagine and 100 is the best state. 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 Table 43 and Table 44, respectively.

Table 43: EQ-5D Visual Analog Scale (EP Population)

EQ-5D Visual Analog Scale*	SAPIEN 3 Valve			PIIA-SAVR
	All	TF	Non-TF	
Baseline	60.3 ± 20.0	61.0 ± 19.8	55.1 ± 20.7	59.5 ± 20.5
30 days	74.0 ± 16.6	74.8 ± 16.6	68.5 ± 16.2	67.2 ± 19.5
1 year	74.4 ± 17.2	74.7 ± 17.1	71.8 ± 17.8	74.3 ± 16.7

*Plus–minus values are means ± SD.

Table 44: SF-36 Health Status Questionnaire Score (EP Population)

SF-36 Health Status Questionnaire Score*	SAPIEN 3 Valve			PIIA-SAVR
	All	TF	Non-TF	
Physical Component Score				
Baseline	34.7 ± 9.1	35.0 ± 9.1	33.1 ± 8.5	34.3 ± 9.0
30 days	39.7 ± 9.8	40.3 ± 9.7	34.8 ± 9.2	34.5 ± 8.4
1 year	40.0 ± 10.3	40.4 ± 10.2	37.0 ± 10.8	39.5 ± 10.4
Mental Component Score				
Baseline	48.0 ± 11.8	48.1 ± 11.8	47.0 ± 12.3	48.0 ± 12.3
30 days	51.8 ± 10.6	52.3 ± 10.4	47.8 ± 11.3	45.5 ± 13.3
1 year	52.5 ± 10.7	52.7 ± 10.8	50.7 ± 10.1	52.0 ± 11.3

*Plus–minus values are means ± SD.

13.6 SAPIEN 3 POST APPROVAL STUDY, INTERMEDIATE RISK COHORT OVERVIEW

Overall Study Compliance

At the time of database extract, 970 patients were eligible for the 5 year visit, and 890 completed the visit within the 60-day follow-up window. A detailed summary of the overall study compliance at 30 days to 5 years is shown in Table 45.

Table 45: Overall Study Compliance (EP Population)

	30-day Visit		1-Year Visit		5-Year Visit	
	SAPIEN 3 (N=1074)	SAVR (N=938)	SAPIEN 3 (N=1074)	SAVR (N=938)	SAPIEN 3 (N=1074)	SAVR (N=938)
Total patients	1074	938	1074	938	1074	938
Non-eligible	13	38	99	136	562	480
-Death	13	35	79	115	404	367
-Withdrawal	0	3	16	19	97	74
-Lost to follow-up	0	0	4	2	60	34
-Exit with other reason	0	0	0	0	1	5
Eligible	1061	900	975	802	512	458
-Follow-up visit completed	99.5% (1056)	98% (882)	99.3% (968)	96.5% (774)	89.5% (458)	94.3% (432)
-Missed visit	0.5% (5)	2.0% (18)	0.7% (7)	3.5% (28)	10.5% (54)	5.7% (26)

Safety and Effectiveness Results

The Kaplan-Meier (KM) rates for all-cause death in the TAVR cohort was 7.1% at 1 year and 41.2% at 5 years and for all stroke was 4.6% at 1 year and 12.9% at 5 years. The KM rates for all-cause death in the SAVR cohort was 12.7% at 1 year and 43% at 5 years and for all stroke was 8.1% at 1 year and 12.4% at 5 years. The KM rates are provided in Figure 44 and Figure 45.

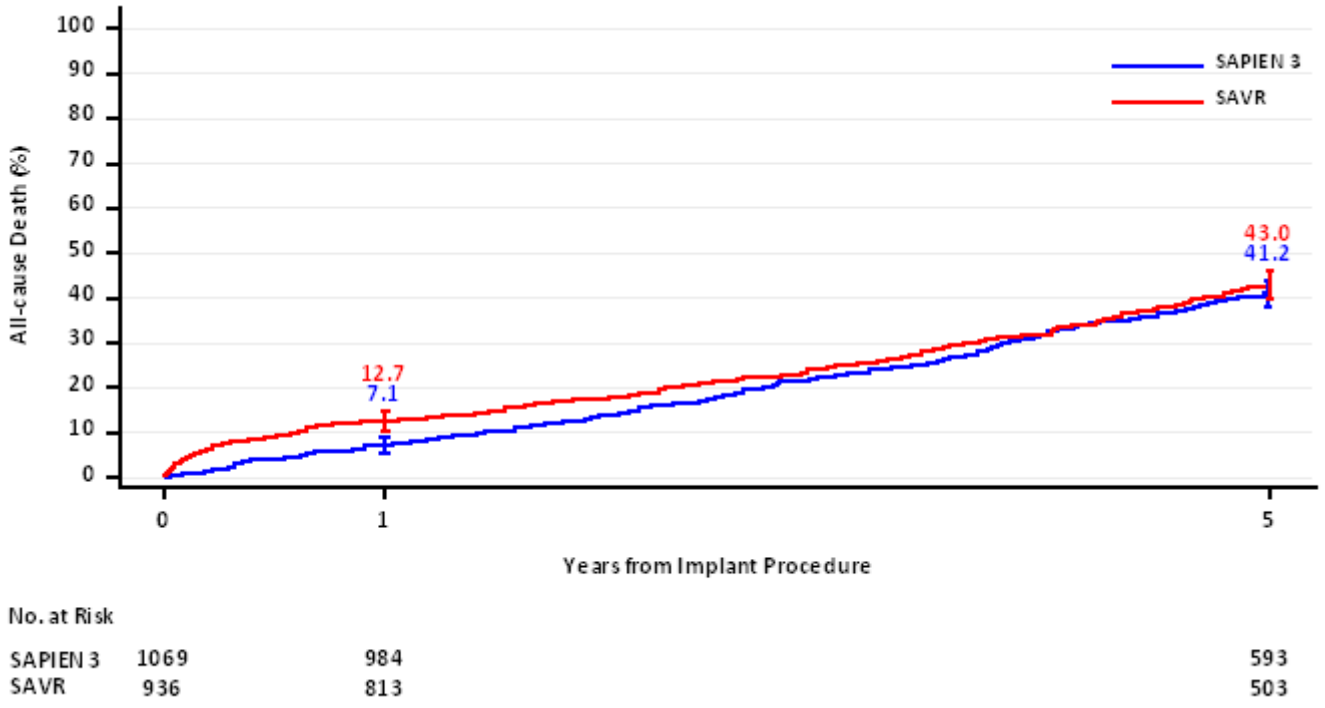


Figure 44: All-cause Death to 5 Years (VI Population)

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

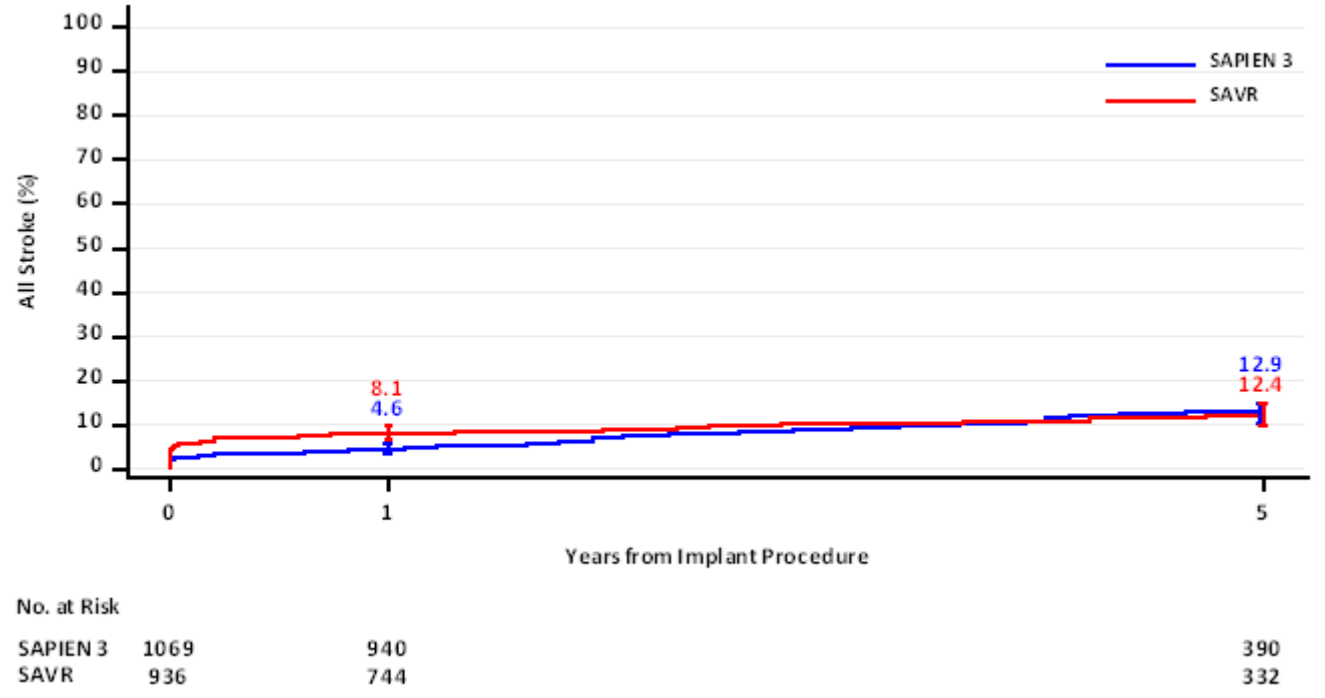


Figure 45: All Stroke to 5 Years (VI Population)

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

Valve Performance

The effective orifice area (EOA), mean aortic gradient, total aortic regurgitation (AR), and paravalvular regurgitation values obtained over time for the TAVR and SAVR patients are shown in Figure 46 through Figure 48, respectively. The increase in EOA and decrease in gradient were sustained through 5 years in both cohorts. In the TAVR cohort, the proportion of patients with total AR ≥ moderate was 0.6% at 30 days, 0.0% at 1 year and 0.5% at 5 years, while in the SAVR cohort, the corresponding proportion was 1.7% at 30 days, 1.0% at 1 year and 0.1% at 5 years. The proportion of patients with paravalvular regurgitation ≥ moderate was 0.5% at 30 days, 1.4% at 1 year and 0.5% at 5 years in the TAVR cohort, as compared to 1.6% at 30 days, 0.8% at 1 year, and 1.4% at 5 years in the SAVR cohort.

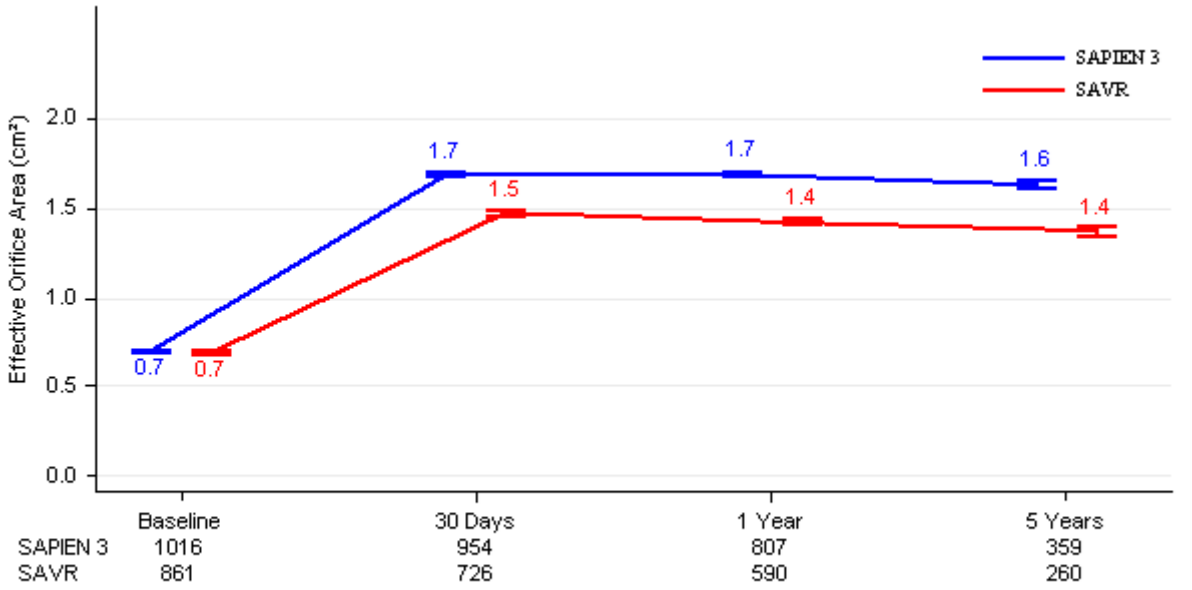


Figure 46: Effective Orifice Area (VI Population)

Note: Line plot with mean and standard error. The total number of patients at each visit timepoint only counted the patients with valid values.

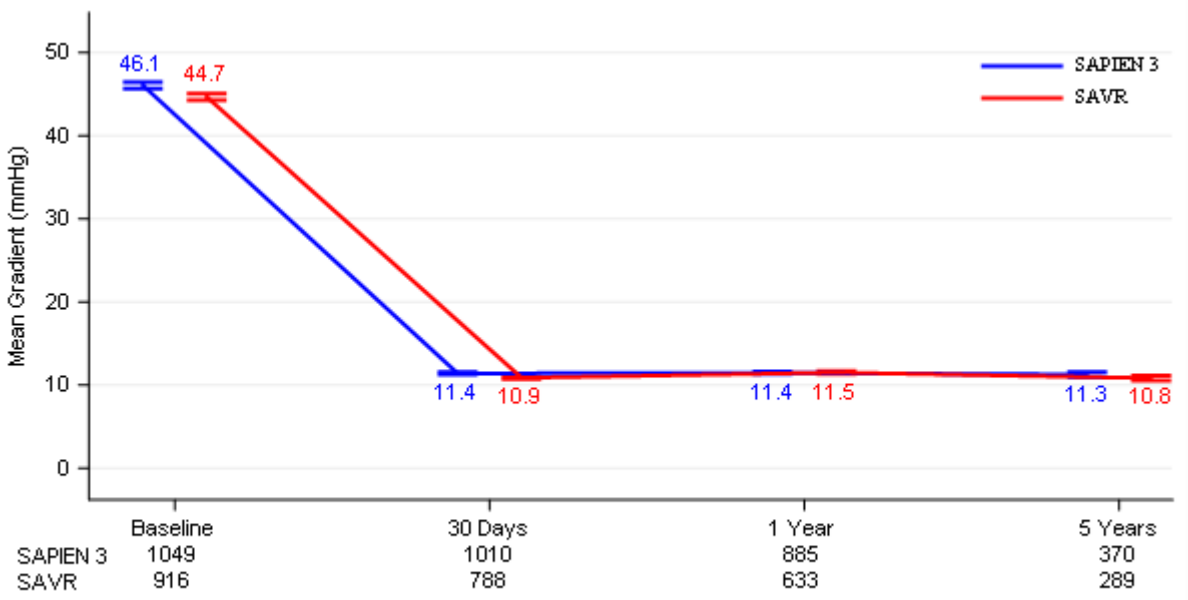


Figure 47: Mean Gradient (VI Population)

Note: Line plot with mean and standard error. The total number of patients at each visit timepoint only counted the patients with valid values.

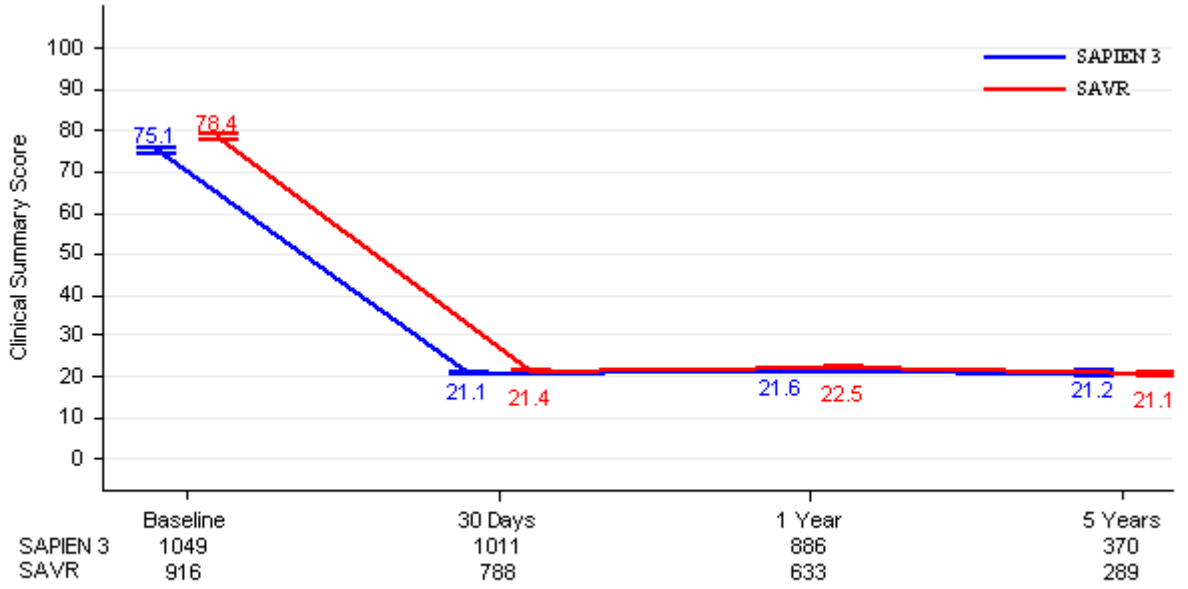


Figure 48: Peak Gradient (VI Population)

Note: Line plot with mean and standard error. The total number of patients at each visit timepoint only counted the patients with valid values.

New York Heart Association (NYHA) Functional Class

The NYHA classifications by visit are presented in Figure 49. At baseline, 72.6% of TAVR patients and 76% of SAVR patients were in NYHA III/IV. At 1 year the majority (93%) of TAVR and SAVR patients were in NYHA Class I/II. At 5 years the majority (91%) of TAVR and (93%) SAVR patients were in NYHA Class I/II. A side-by-side comparison of the results by access approach is presented in Figure 52.

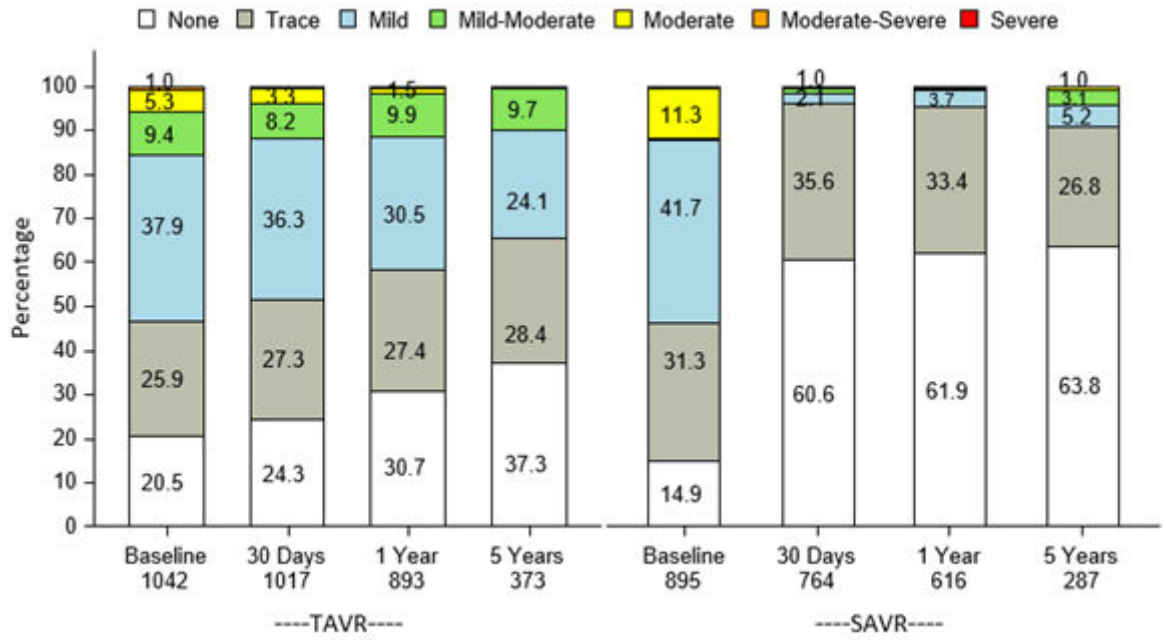


Figure 49: Total Aortic Regurgitation by Visit (VI Population)

Note: The total number of patients at each visit time point only counted the patients with valid values.

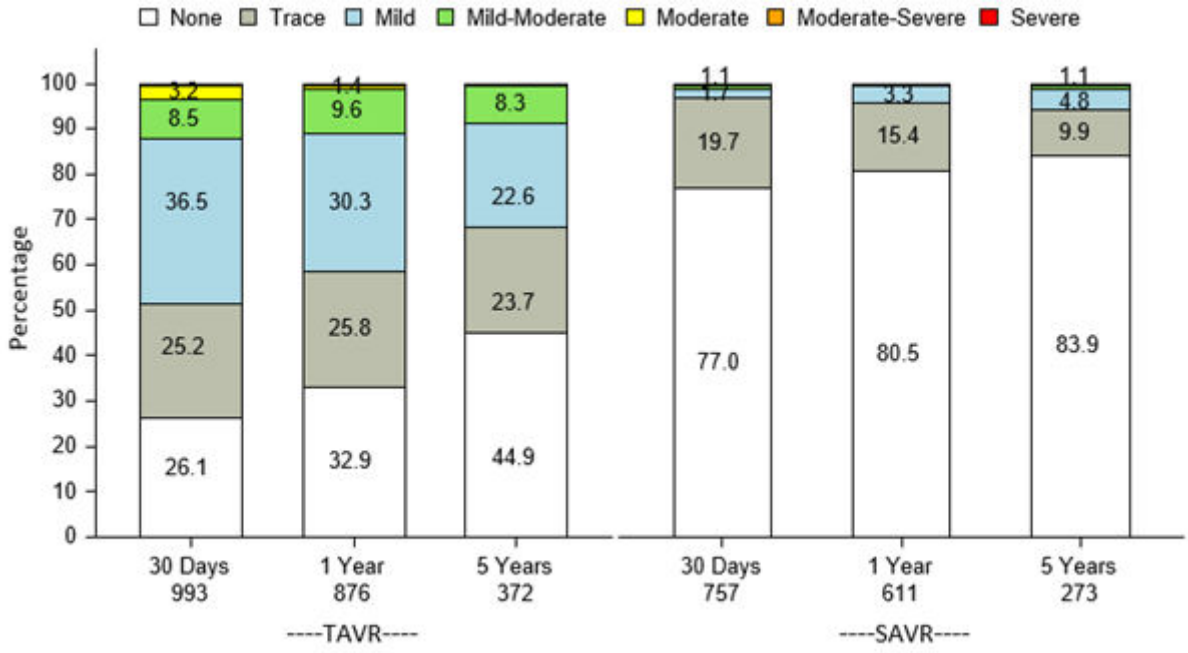


Figure 50: Paravalvular Aortic Regurgitation by Visit (VI Population)

Note: The total number of patients at each visit time point only counted the patients with valid values.

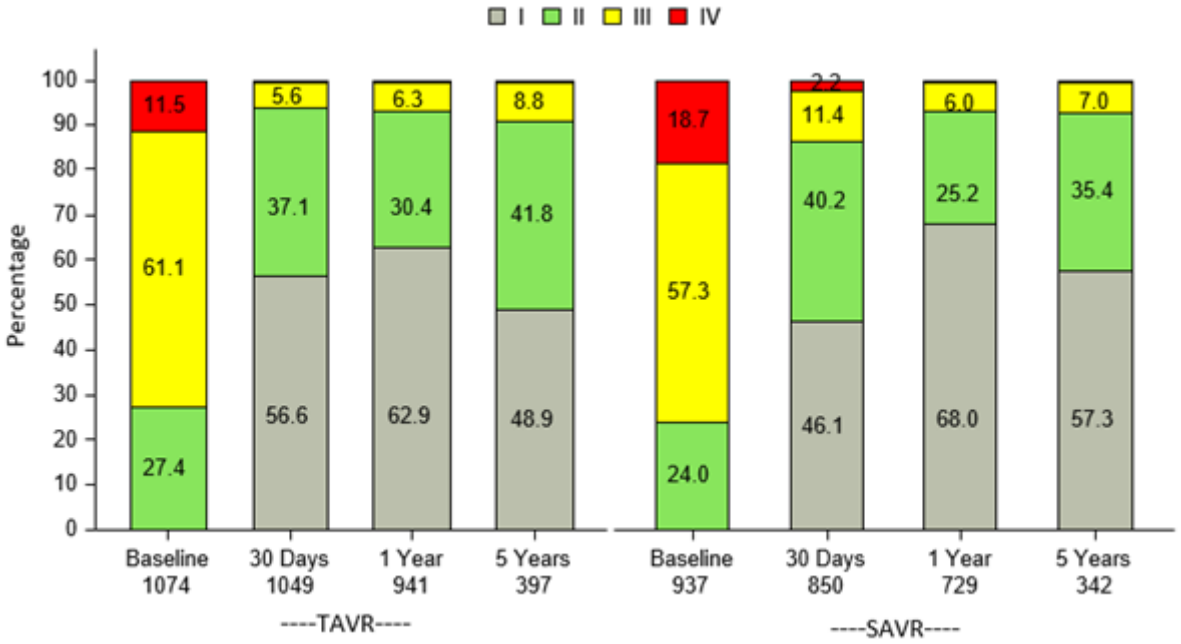


Figure 51: NYHA Class by Visit (EP Population)

Note: The total number of patients at each visit time point only counted the patients with valid values.

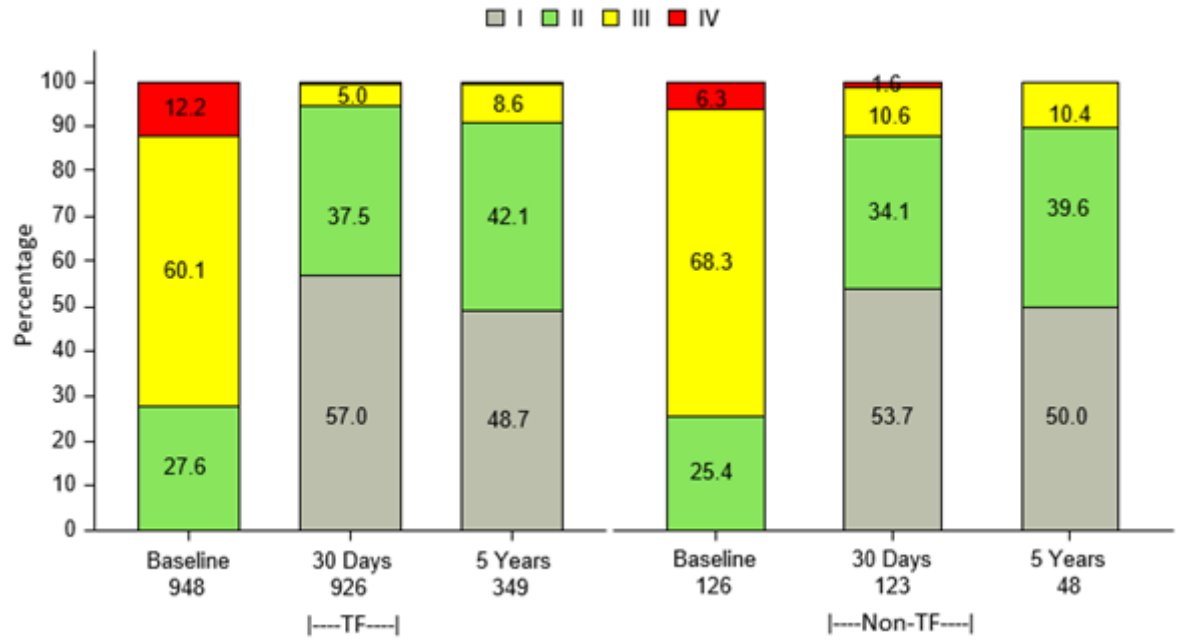


Figure 52: NYHA Class by Visit - TF versus non-TF Access S3I (EP Population)

Note: The total number of patients at each visit time point only counted the patients with valid values.

Quality of Life (QoL)

KCCQ

The results for the KCCQ overall summary score are presented in Figure 53. The mean score increased from 58.9 at baseline to 74.8 at 30 days, 76.8 at 1 year and 71.3 at 5 years in TAVR patients and from 58.7 at baseline to 62.1 at 30 days 75.7 at 1 year, and 71.2 in SAVR patients. A side-by-side comparison of the results by access approach is presented in Figure 54. In general, improvements in the TF group were slightly larger as compared to those observed in the Non-TF group.

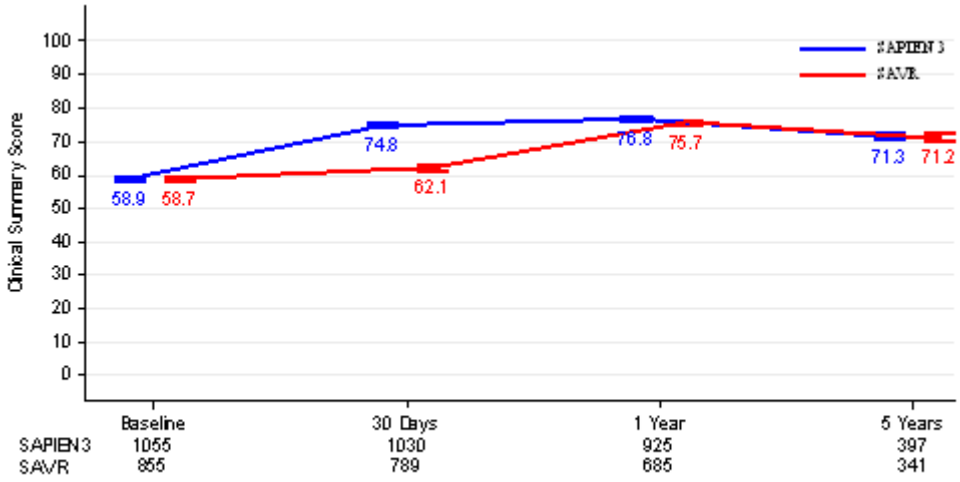


Figure 53: KCCQ Clinical Summary Score (EP Population)

Note: Line plot with mean and standard error. The total number of patients at each visit time point only counted the patients with valid values.

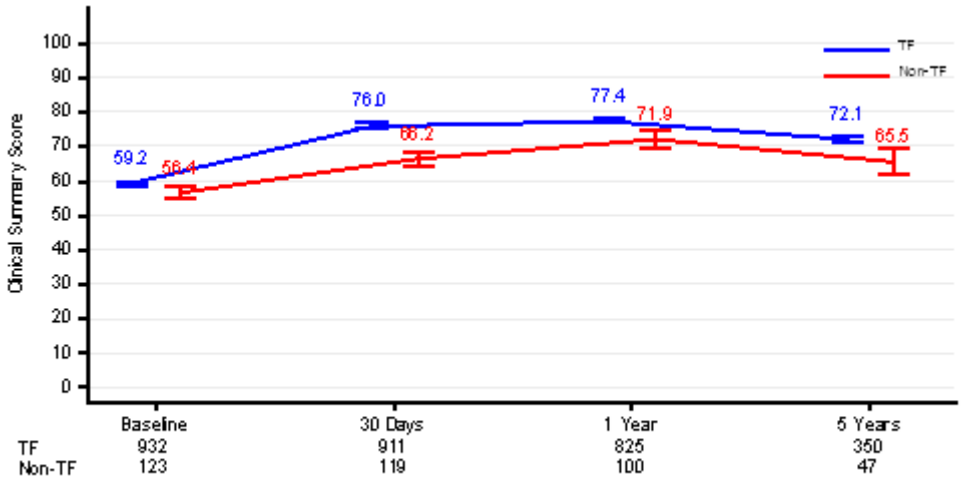


Figure 54: KCCQ Clinical Summary Score - TF versus non-TF Access (EP Population)

Note: Line plot with mean and standard error. The total number of patients at each visit time point only counted the patients with valid values.

Adverse Events

The Kaplan-Meier rates of the CEC-adjudicated adverse events through 5 years are presented in Table 46.

Table 46: CEC-Adjudicated Adverse Events through 5 Year (EP Population)

Event	Kaplan-Meier Rate*			
	SAPEIN 3 Valve			
	Overall	TF Only	Non-TF Only	PIIA-SAVR
30 Days				
All-Cause Death	1.1% (12, 12)	1.1% (10, 10)	1.6% (2, 2)	3.8% (36, 36)
Cardiac Death	0.9% (10, 10)	1.0% (9, 9)	0.8% (1, 1)	2.8% (26, 26)

Event	Kaplan-Meier Rate*			
	SAPEIN 3 Valve			
	Overall	TF Only	Non-TF Only	PIIA-SAVR
Non-Cardiac Death	0.2% (2, 2)	0.1% (1, 1)	0.8% (1, 1)	1.0% (9, 9)
Stroke	2.7% (30, 29)	2.5% (24, 24)	4.0% (6, 5)	6.1% (59, 57)
Major (disabling) stroke	1.0% (12, 11)	0.7% (7, 7)	3.2% (5, 4)	4.4% (42, 41)
Minor (non-disabling) stroke	1.7% (18, 18)	1.8% (17, 17)	0.8% (1, 1)	1.7% (17, 16)
Aortic valve re-intervention	0.1% (1, 1)	0.1% (1, 1)	0.0% (0, 0)	0.0% (0, 0)
Any endocarditis	0.2% (2, 2)	0.2% (2, 2)	0.0% (0, 0)	0.0% (0, 0)
Myocardial infarction	0.3% (3, 3)	0.3% (3, 3)	0.0% (0, 0)	1.8% (17, 17)
Major vascular complication	6.1% (68, 65)	6.3% (63, 60)	4.0% (5, 5)	5.3% (54, 50)
Life threatening (disabling) or major bleeding	14.9% (165, 160)	11.9% (117, 113)	37.3% (48, 47)	79.1% (767, 742)
Rhythm disturbance requiring permanent pacemaker ‡	10.1% (108, 108)	10.5% (99, 99)	7.2% (9, 9)	7.3% (68, 68)
1 Year				
All-Cause Death	7.5% (80, 80)	6.6% (62, 62)	14.4% (18, 18)	12.8% (120, 120)
Cardiac Death	4.5% (47, 47)	4.0% (37, 37)	8.2% (10, 10)	7.7% (70, 70)
Non-Cardiac Death	3.1% (32, 32)	2.6% (24, 24)	6.8% (8, 8)	5.3% (47, 47)
Stroke	4.6% (51, 49)	4.3% (41, 40)	7.4% (10, 9)	8.1% (78, 74)
Major (disabling) stroke	2.3% (26, 24)	1.7% (17, 16)	6.6% (9, 8)	5.8% (55, 53)
Minor (non-disabling) stroke	2.4% (25, 25)	2.6% (24, 24)	0.8% (1, 1)	2.4% (23, 22)
Aortic valve re-intervention	0.6% (6, 6)	0.7% (6, 6)	0.0% (0, 0)	0.5% (5, 4)
Any endocarditis	0.8% (8, 8)	0.8% (7, 7)	0.9% (1, 1)	0.7% (6, 6)
5 Years				
All-Cause Death	41.4% (432, 432)	41.5% (382, 382)	40.6% (50, 50)	43.0% (399, 399)
Cardiac Death	25.5% (225, 225)	25.6% (198, 198)	25.0% (27, 27)	27.2% (214, 214)
Non-Cardiac Death	20.0% (172, 172)	20.1% (152, 152)	19.8% (20, 20)	19.8% (147, 147)
Stroke	12.9% (127, 115)	12.8% (112, 101)	13.5% (15, 14)	12.4% (116, 102)
Major (disabling) stroke	7.9% (74, 69)	7.7% (62, 58)	9.9% (12, 11)	9.3% (83, 76)
Minor (non-disabling) stroke	5.7% (53, 51)	6.0% (50, 48)	3.7% (3, 3)	3.8% (33, 31)

*Kaplan-Meier rate (no. of events, no. of patients with the event).

‡Patients with pacemaker or ICD at baseline were not counted as new events.

13.7 PARTNER 3 SAPIEN 3 LOW RISK COHORT

A. Accountability of the PMA Cohort

At the time of database lock, a total of 1000 subjects were randomized in the study, including 503 TAVR patients and 497 SAVR patients.

There were three different analysis populations defined in the protocol: Intention-to-Treat (ITT), As Treated (AT), and Valve Implant (VI), as summarized in Table 47 and Figure 55. The primary analysis was the AT analysis.

Table 47: Analysis Populations

Analysis Population	Definition	Number of Patients	
		TAVR	SAVR
Intention-To-Treat (ITT)	All randomized patients.	503	497
As Treated (AT)	All ITT patients for whom the index procedure was begun, whether or not the index procedure was completed.	496	454
Valve Implant (VI)	All AT patients who received and retained the intended valve during the index procedure.	495	453

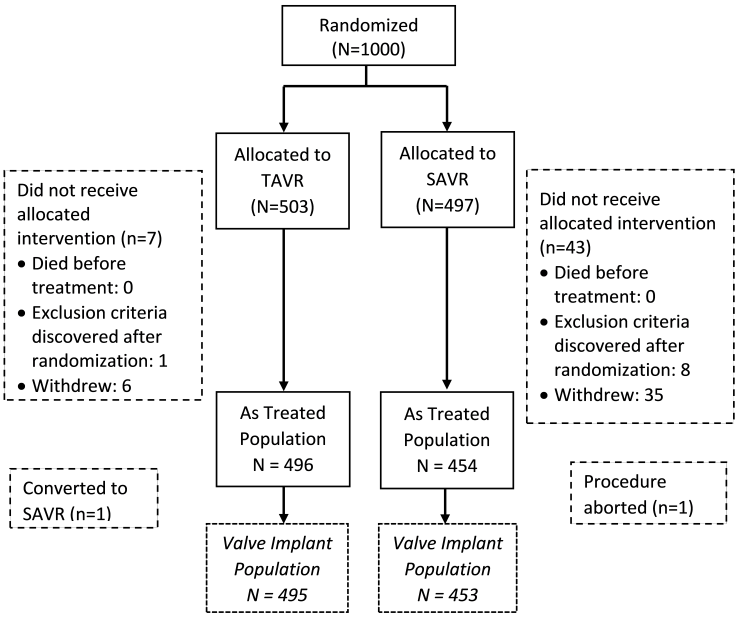


Figure 55: Patient Population Flowchart

The overall follow-up compliance of the trial is summarized in Table 48.

Table 48: Overall Study Compliance (AT Population)

Patient Accountability	30-day Visit		1 Year Visit	
	TAVR (N=496)	SAVR (N=454)	TAVR (N=496)	SAVR (N=454)
Total patients	496	454	496	454
Non-eligible	2	11	6	30
Death	2	6	5	11
Withdrawal	0	3	0	12
Lost to follow-up	0	0	0	1
Exit with other reason	0	2	1	6
Visit not yet due	0	0	0	0
Eligible	494	443	490	424
Follow-up visit completed	96.5% (493)	96.5% (438)	97.8% (485)	91.2% (414)
Missed visit	0.2% (1)	1.1% (5)	1.0% (5)	2.2% (10)

B. Study Population Demographics and Baseline Characteristics

The demographics and baseline characteristics of the study population are typical for a TAVR study performed in the U.S., as shown in Table 49. The treatment cohorts were generally well balanced with respect to age, gender, and STS risk score.

Table 49: Patient Demographics and Baseline Characteristics (AT Population)

Demographics and Baseline Characteristics	Summary Statistics*	
	TAVR (N = 496)	SAVR (N = 454)
Age - years	73.3 ± 5.8	73.6 ± 6.1
Male sex	67.5% (335/496)	71.1% (323/454)
Society of Thoracic Surgeons (STS) score	1.9 ± 0.7	1.9 ± 0.6
New York Heart Association (NYHA) class		
I/II	68.8% (341/496)	76.2% (346/454)
III/IV	31.1% (155/496)	23.8% (108/454)
Previous myocardial infarction	5.7% (28/495)	5.8% (26/452)
Previous intervention		
Coronary artery bypass grafting (CABG)	3.0% (15/494)	1.8% (8/451)
Percutaneous coronary intervention (PCI)	18.8% (93/494)	16.2% (73/452)
Stroke or cerebrovascular accident (CVA)	3.4% (17/496)	5.1% (23/453)
Peripheral vascular disease (PVD)	6.9% (34/494)	7.3% (33/453)
Atrial fibrillation	15.7% (78/496)	18.8% (85/453)
Atrial flutter	3.0% (15/496)	2.4% (11/452)
Permanent pacemaker or defibrillator	2.4% (12/496)	2.9% (13/454)
Hostile chest	0.0% (0/496)	0.0% (0/454)
Echocardiographic findings (Valve Implant Population)		
Valve area (cm^2)	0.8 ± 0.2 (459)	0.8 ± 0.2 (424)
Mean gradient (mmHg)	49.4 ± 12.8 (484)	48.3 ± 11.8 (442)
Mean left ventricular ejection fraction (LVEF) %	65.7 ± 9.0 (472)	66.2 ± 8.6 (436)
Moderate or severe aortic regurgitation	3.9% (19/484)	2.5% (11/446)
Moderate or severe mitral regurgitation	1.3% (6/477)	3.2% (14/437)
* Continuous measures - Mean ± SD (Total no.); Categorical measures % (no./Total no.)		

C. Safety and Effectiveness Results

1. Primary Endpoint

The primary endpoint results are presented in Table 50 and Figure 56. The rate of all-cause death, all stroke, or rehospitalization (valve-related or procedure-related and including heart failure) at 1-year was 8.5% in the TAVR group and 15.1% in the SAVR group. Since the upper limit of the 95% confidence interval for the difference in the primary endpoint event rate was < 6.0%, non–inferiority was achieved.

Table 50: Primary Endpoint Analysis (AT Population)

Event	Kaplan-Meier Rate*		Difference of KM Estimate (TAVR – SAVR)	95% CI* for the Difference	Non-inferiority Criterion
	TAVR (N=496}	SAVR (N=454)			
All-cause death, all stroke, or rehospitalization	8.5% (42)	15.1% (68)	-6.65%	[-10.77%,-2.52%]	Pass
All-cause death	1.0% (5)	2.5% (11)	-1.44%	[-3.13%, 0.24%]	
All stroke	1.2% (6)	3.1% (14)	-1.90%	[-3.77%, -0.02%]	
Rehospitalization	7.3% (36)	11.0% (49)	-3.74%	[-7.45%, -0.02%]	
*Kaplan-Meier estimate - % (no. of subjects with the event)					

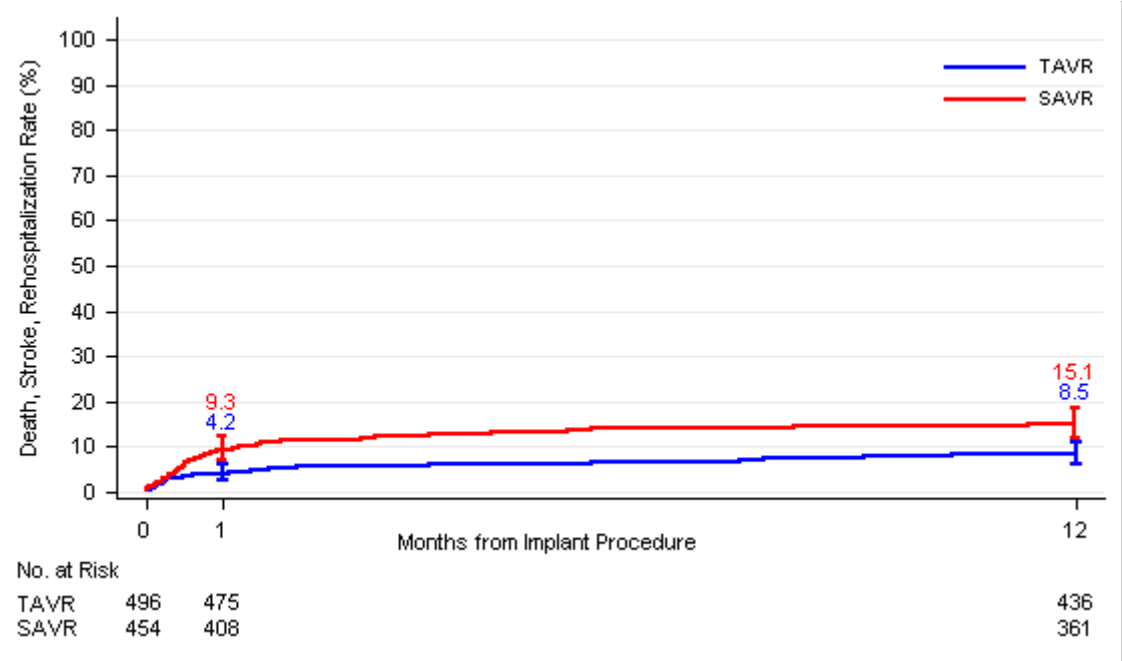


Figure 56: All-Cause Death, All Stroke, and Rehospitalization through 1 Year (AT Population)

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.

2. Secondary Endpoints

Hypothesis testing

Since the primary endpoint passed the non-inferiority testing, the prespecified superiority testing was carried out on the six select secondary endpoints sequentially. TAVR with the SAPIEN 3 valve was found to be superior to SAVR in all six secondary endpoints, as shown in Table 51.

Table 51: Superiority Testing of Select Secondary Endpoints (AT Population)

No.	Endpoint	Summary Statistics*		Difference (TAVR – SAVR)	95% CI for the Difference	p-value (Superiority Test Result)
		TAVR (N=496)	SAVR (N=454)			
1	New onset atrial fibrillation at 30 days†	5.0% (21/417)	39.3% (145/369)	-34.3%	[-39.7%, -28.9%]	<.0001 (pass)

No.	Endpoint	Summary Statistics*		Difference (TAVR – SAVR)	95% CI for the Difference	p-value (Superiority Test Result)
		TAVR (N=496)	SAVR (N=454)			
2	Length of index hospitalization (days)	2.9 ± 0.1 (496)	7.4 ± 0.2 (454)	-4.5	[-4.8, -4.1]	<.0001 (pass)
3	All-cause death, all stroke, or rehospitalization at 1 year	8.5% (42)	15.1% (68)	-6.6%	[-10.8%, -2.5%]	0.0016 (pass)
4	Death, KCCQ < 45 or KCCQ decrease from baseline ≥ 10 points at 30 days	3.9% (19/492)	30.6% (133/435)	-26.7%	[-31.4%, -22.1%]	<.0001 (pass)
5	Death or all stroke at 30 days	1.0% (5/496)	3.3% (15/454)	-2.3%	[-4.2%, -0.4%]	0.0214 (pass)
6	All stroke at 30 days	0.6% (3/496)	2.4% (11/454)	-1.8%	[-3.4%, -0.2%]	0.0284 (pass)

*Continuous measures - Mean ± SE (Total no.); Categorical measures – observed rate, % (no./Total no.), except No. 3 - Kaplan-Meier rate, % (Total no.).
† Patients with pre-procedural atrial fibrillation were excluded from the analysis.

Valve Performance

The effective orifice area (EOA), mean aortic gradient, total aortic regurgitation (AR), and paravalvular regurgitation values obtained over time for the TAVR and SAVR patients are shown in Figure 57 through Figure 60, respectively. The increase in EOA and decrease in gradient were sustained through 1 year in both cohorts. In the TAVR cohort, the proportion of patients with total AR ≥ moderate was 0.8% at 30 days and 1.1% at 1 year, while in the SAVR cohort, the corresponding proportion was 0.4% at 30 days and 0.6% at 1 year. The proportion of patients with paravalvular regurgitation ≥ moderate was 0.8% at 30 days and 0.6% at 1 year in the TAVR cohort, as compared to 0.0% at 30 days and 0.8% at 1 year in the SAVR cohort.

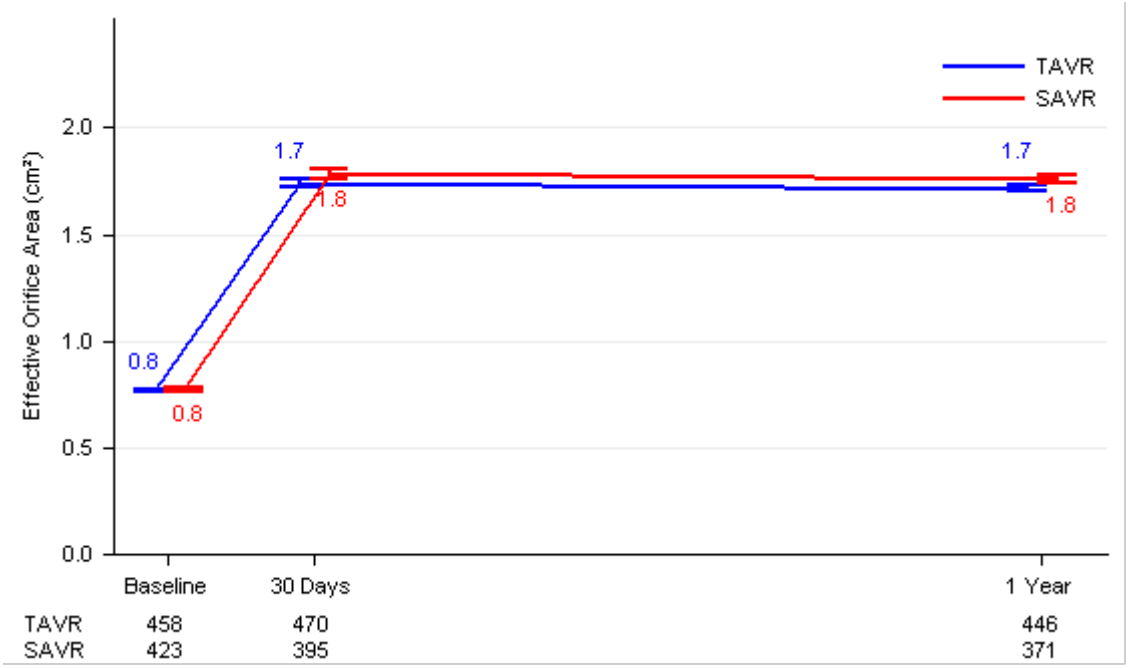


Figure 57: Effective Orifice Area (VI Population)

Note: Line plot with mean and standard error. The total number of patients at each visit time point only counted the patients with valid values.

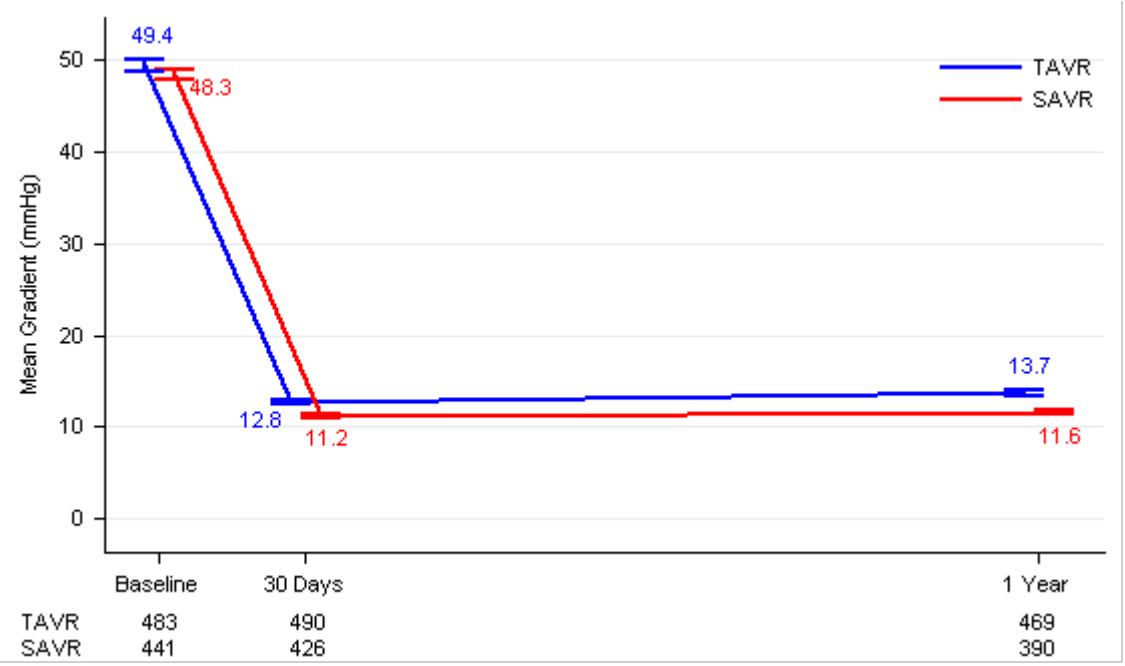


Figure 58: Mean Aortic Gradient (VI Population)

Note: Line plot with mean and standard error. The total number of patients at each visit time point only counted the patients with valid values.

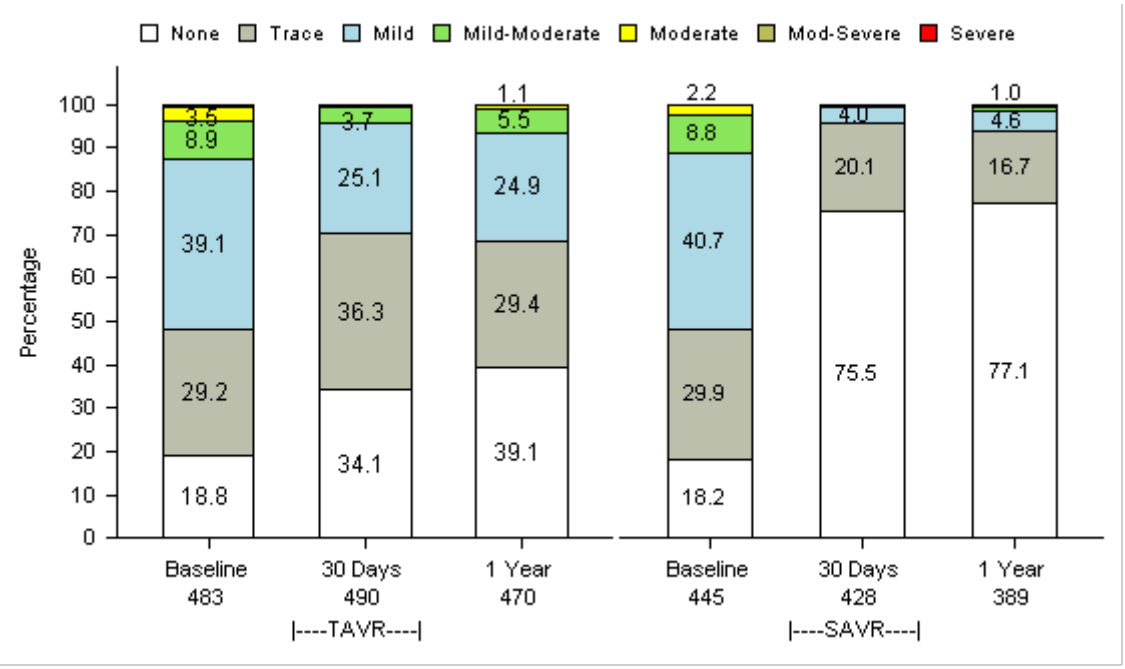


Figure 59: Total Aortic Regurgitation (VI Population)

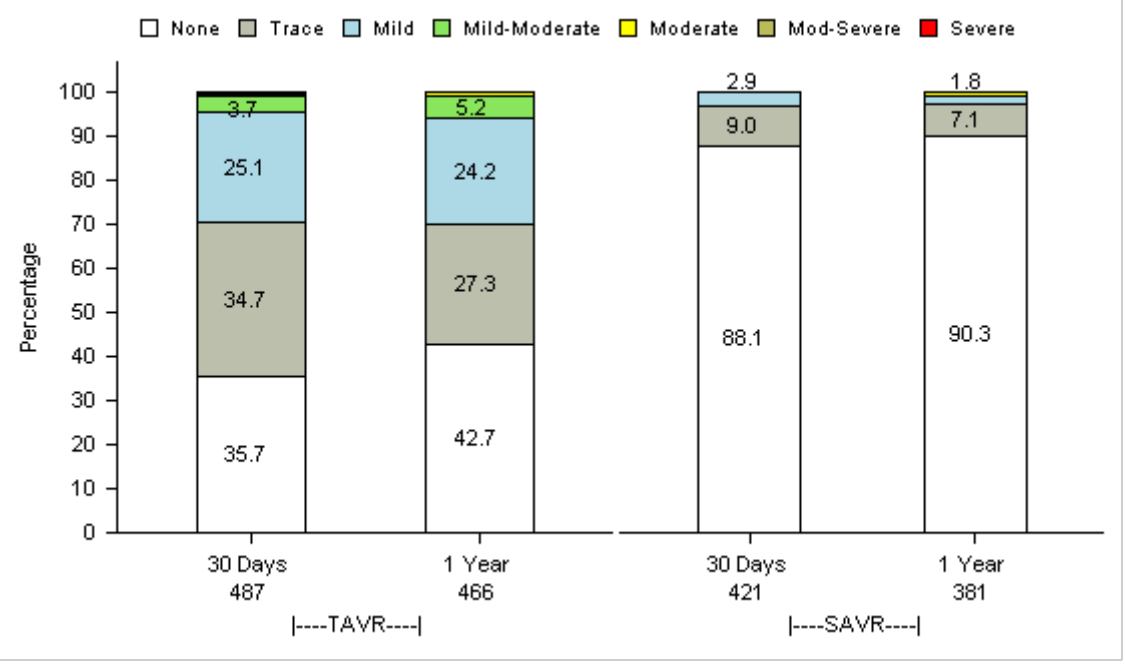


Figure 60: Paravalvular Regurgitation (VI Population)

New York Heart Association (NYHA) Functional Class

The NYHA classifications by visit are presented in Figure 61. At baseline, 31.3% of TAVR patients and 23.6% of SAVR patients were in NYHA III/IV. At 1 year the majority (~99%) of TAVR and SAVR patients were in NYHA Class I/II.

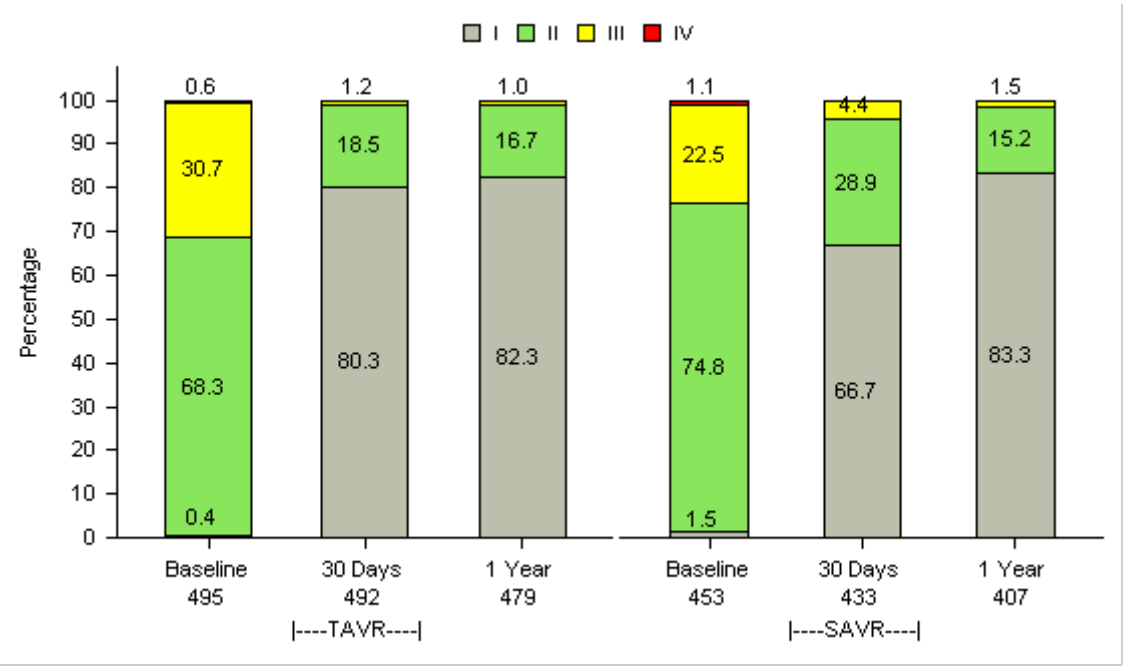


Figure 61: NYHA Class by Visit (VI Population)

Six-Minute Walk Test (6MWT)

The results for the 6MWT distance are presented in Figure 62. The TAVR patients showed an increase in mean 6MWT distance from 331.0 m at baseline to 349.1 m at 30 days, while SAVR patients showed a decrease from 329.4 m at baseline to 314.4 m at 30 days. The two cohorts had similar values at 1 year (347.6 m for TAVR and 351.7 m for SAVR).

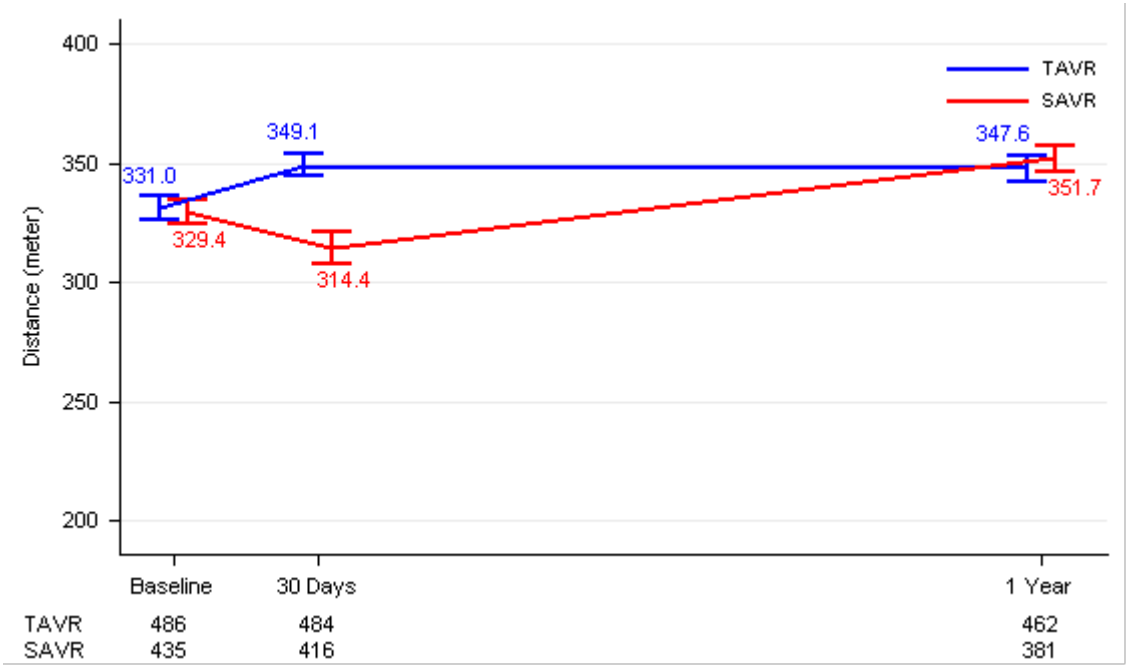


Figure 62: 6MWT Distance (VI Population)

Note: Line plot with mean and standard error. The total number of patients at each visit time point only counted the patients with valid values.

Quality of Life (QoL)

KCCQ

The results for the KCCQ overall summary score are presented in Figure 63. The mean score increased from 70.3 at baseline to 88.9 at 30 days and 89.9 at 1 year in TAVR patients and from 70.1 at baseline to 72.8 at 30 days and 88.1 at 1 year in SAVR patients.

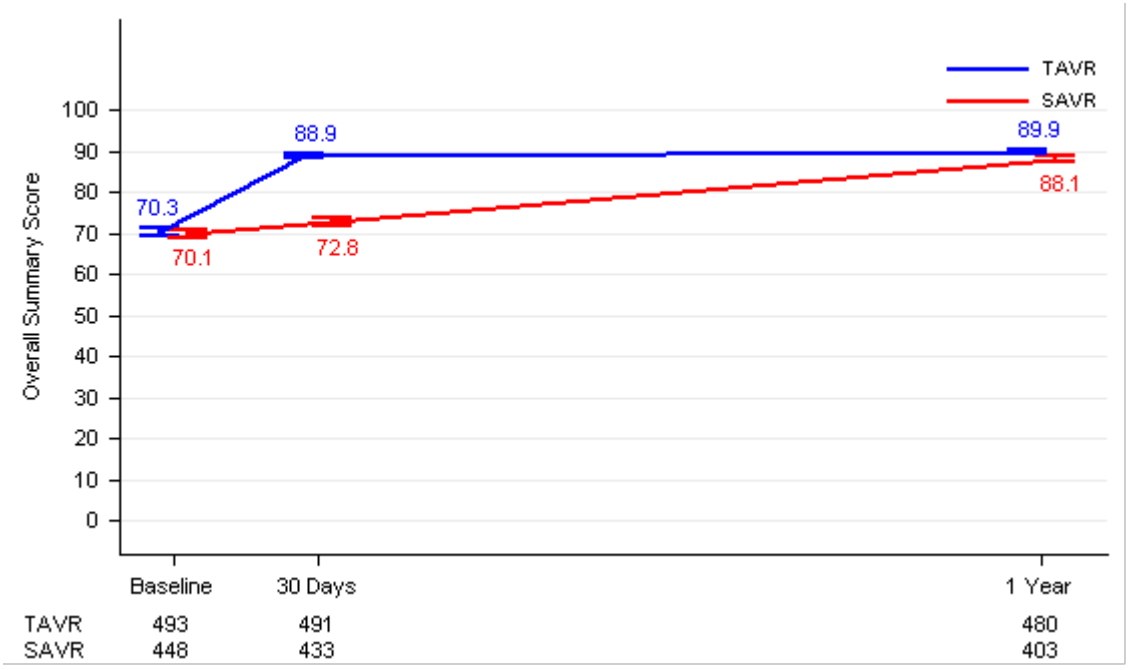


Figure 63: KCCQ Overall Summary Score (VI Population)

Note: Line plot with mean and standard error. The total number of patients at each visit time point only counted the patients with valid values.

EuroQol (EQ-5D)

The results for the EQ-5D visual analog score (VAS) are presented in Figure 64. The mean score was 74.2 at baseline, 85.2 at 30 days, and 84.4 at 1 year in TAVR patients as compared to 75.2 at baseline, 76.5 at 30 days, and 84.7 at 1 year in SAVR patients.

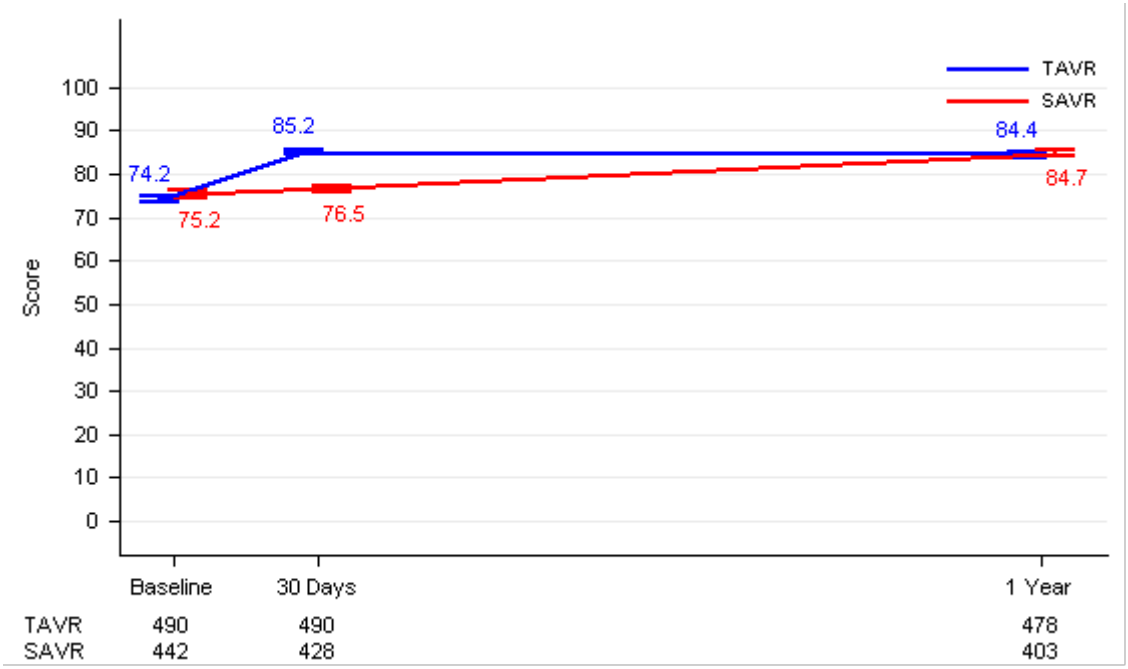


Figure 64: EQ-5D Visual Analog Score (VI Population)

Note: Line plot with mean and standard error. The total number of patients at each visit time point only counted the patients with valid values.

Short Form (SF)-36

The results for the SF-36 physical component summary score and mental component summary score are presented in Figure 65 and Figure 66, respectively.

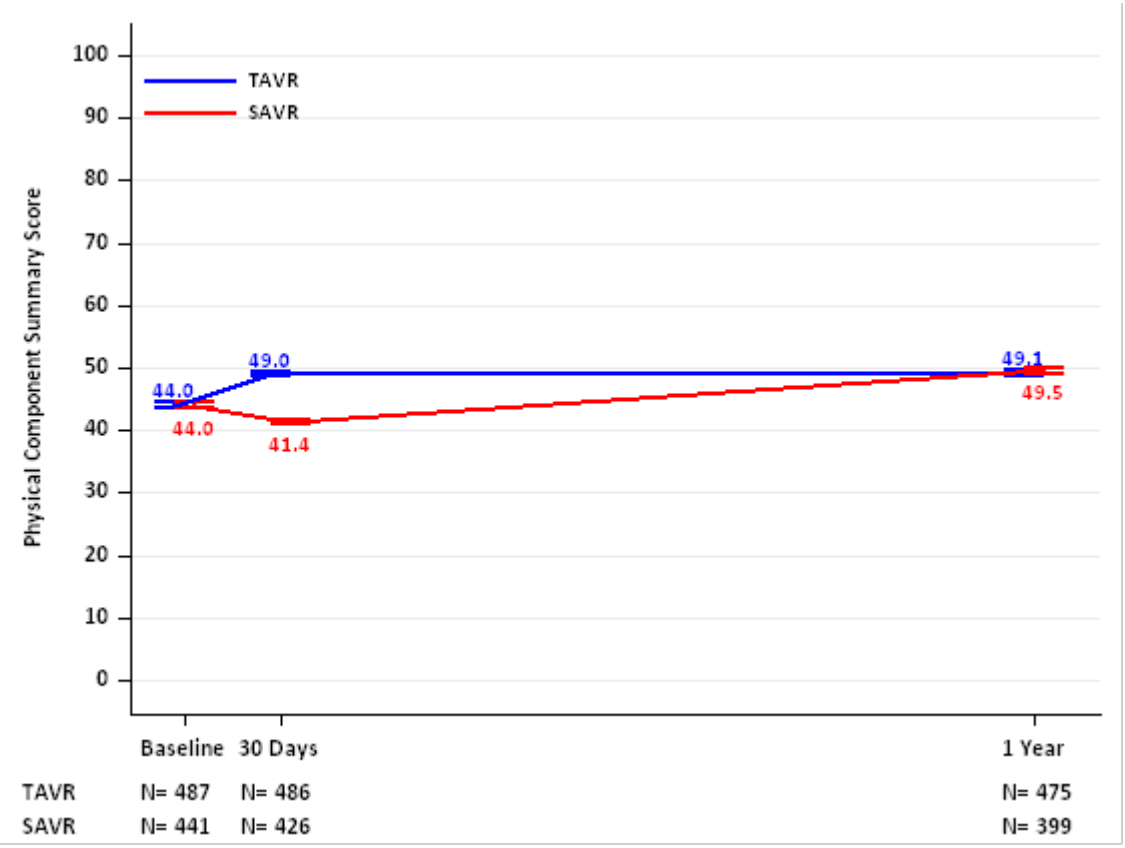


Figure 65: SF-36 Physical Component Summary Score (VI Population)

Note: Line plot with mean and standard error. The total number of patients at each visit time point only counted the patients with valid values.

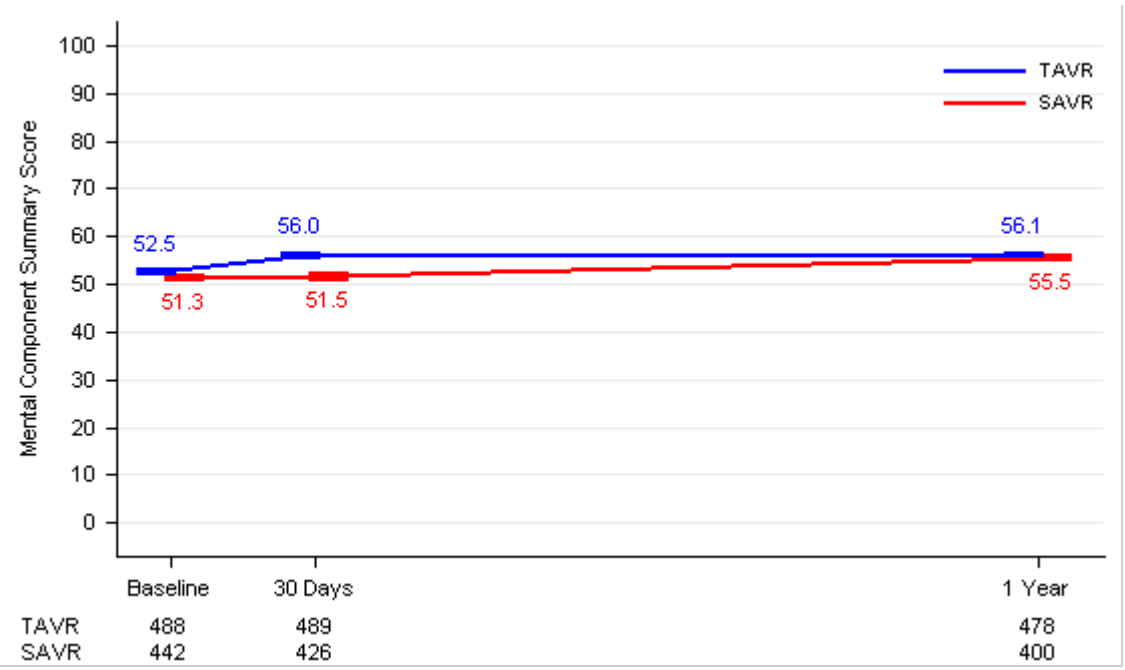


Figure 66: SF-36 Mental Component Summary (VI Population)

Note: Line plot with mean and standard error. The total number of patients at each visit time point only counted the patients with valid values.

3. Adverse Events

The Kaplan-Meier estimates of the CEC-adjudicated adverse events through 1 year are presented in Table 52.

Table 52: CEC-Adjudicated Adverse Events through 1 Year (AT Population)

Event	Kaplan-Meier Rate*			
	30 Days		1 Year	
	TAVR (N=496)	SAVR (N=454)	TAVR (N=496)	SAVR (N=454)
All cause death	0.4% (2, 2)	1.1% (5, 5)	1.0% (5, 5)	2.5% (11, 11)
Cardiovascular death	0.4% (2, 2)	0.9% (4, 4)	0.8% (4, 4)	2.0% (9, 9)
All stroke	0.6% (3, 3)	2.4% (11, 11)	1.2% (6, 6)	3.1% (14, 14)
Disabling stroke	0.0% (0, 0)	0.4% (2, 2)	0.2% (1, 1)	0.9% (4, 4)
Non-disabling stroke	0.6% (3, 3)	2.0% (9, 9)	1.0% (5, 5)	2.2% (10, 10)
Death or stroke	1.0% (5, 5)	3.3% (16, 15)	1.8% (11, 9)	4.9% (25, 22)
Death or disabling stroke	0.4% (2, 2)	1.3% (7, 6)	1.0% (6, 5)	2.9% (15, 13)
Major vascular complications	2.2% (12, 11)	1.5% (8, 7)	2.8% (15, 14)	1.5% (8, 7)
Life-threatening / disabling, or major bleeding	3.6% (22, 18)	24.5% (123, 111)	7.7% (45, 38)	25.9% (132, 117)
Life-threatening / disabling bleeding	1.2% (9, 6)	11.9% (58, 54)	2.8% (17, 14)	12.8% (63, 58)
Major bleeding	2.6% (13, 13)	13.5% (65, 61)	5.3% (28, 26)	14.2% (69, 64)
Myocardial infarction	1.0% (5, 5)	1.3% (6, 6)	1.2% (6, 6)	2.2% (10, 10)
Requirement for renal replacement[†]	0.2% (1, 1)	0.7% (3, 3)	0.2% (1, 1)	0.7% (3, 3)
New permanent pacemaker implantation resulting from new or worsened conduction disturbances[‡]	6.5% (32, 32)	4.0% (18, 18)	7.3% (36, 36)	5.4% (24, 24)
Coronary obstruction requiring intervention	0.2% (1, 1)	0.7% (3, 3)	0.2% (1, 1)	0.7% (3, 3)
New onset atrial fibrillation	5.0% (21, 21)	39.5% (145, 145)	7.0% (29, 29)	40.9% (150, 150)
Rehospitalization[‖]	3.4% (18, 17)	6.5% (30, 29)	7.3% (39, 36)	11.0% (59, 49)

[*]Kaplan-Meier rate (no. of events, no. of patients with the event).
[†]Requirement for renal replacement was based on the site-reported event. All the other events were based on the CEC-adjudicated results.
[‡]Patients with pacemaker or ICD at baseline were not counted as new events.
[‖]Rehospitalization (valve-related or procedure-related and including heart failure).

4. Subgroup Analysis

Gender Analysis

The protocol specified a subgroup analysis on gender. The primary endpoint result stratified by gender is presented in Figure 67.

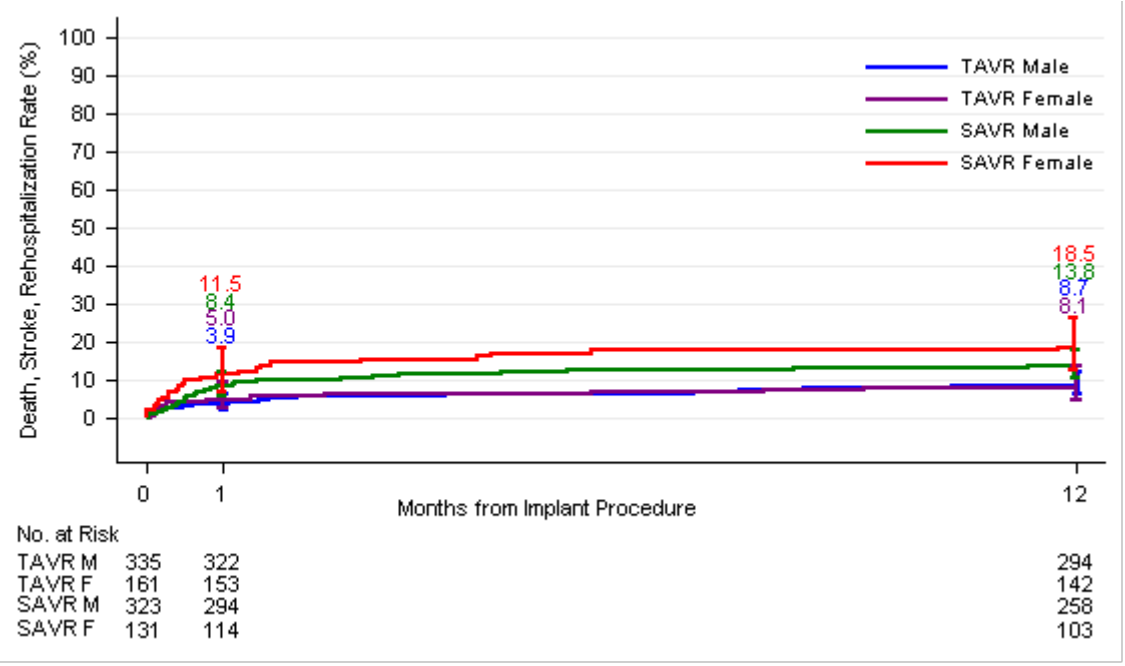


Figure 67: All-Cause Death, All Stroke, and Rehospitalization through 1 Year Stratified by Gender (AT Population)

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.

5. Other Study Observations

Procedural Information

The general procedural data are summarized in Table 53. Conscious sedation was used in the majority of TAVR patients (65.1%). The mean procedure time was significantly lower for TAVR compared to SAVR (58.6 minutes vs. 208.3 minutes). There were less concomitant (planned) procedures performed for TAVR patients compared to SAVR patients (6.9% vs. 26.4%). Additional TAVR and SAVR specific procedural data are presented in Table 54 and Table 55, respectively.

Table 53: General Procedural Data (AT Population)

Variable	Summary Statistics*	
	TAVR (N=496)	SAVR (N=454)
Subject treated according to their treatment assignment	99.8% (495/496)	99.8% (453/454)
Procedure aborted	0	1
Subject was assigned to TAVR but received SAVR	1	0
Procedure time (min)	58.6 ± 1.6 (496)	208.3 ± 2.9 (454)
Anesthesia type		
General	33.3% (165/496)	100.0% (454/454)
Conscious sedation	65.1% (323/496)	NA
Conversion from conscious sedation to general anesthesia during the procedure	1.6% (8/496)	NA
Anesthesia time (min)	138.7 ± 2.20 (496)	309.7 ± 3.7 (454)
Concomitant procedures	6.9% (34/496)	26.4% (120/454)
Annular area (mm^2)	473.5 ± 83.3 (486)	479.6 ± 87.6 (441)

Variable	Summary Statistics*	
	TAVR (N=496)	SAVR (N=454)
*Continuous measures – mean ± SE (n) for procedure and anesthesia time, mean ± SD (n) for annular area; Categorical measures - % (no./Total no.)		

Table 54: TAVR Procedure Data (AT Population)

Variable	Summary Statistics*
	TAVR (N=496)
Valve size	
20 mm	2.2% (11/496)
23 mm	29.2% (145/496)
26 mm	47.6% (236/496)
29 mm	21.0% (104/496)
Successful access, delivery and retrieval of the device delivery system	99.8% (494/495)
Arterial access method	
Left percutaneous	22.2% (109/490)
Right percutaneous	76.7% (376/490)
Left surgical cutdown	0.0% (0/490)
Right surgical cutdown	1.0% (5/490)
Total fluoroscopy time (min)	13.9 ± 0.3 (487)
BAV performed	57.8% (286/495)
Post dilatation performed	20.9% (103/494)
Number of post dilatations	
1	89.3% (92/103)
2	8.7% (9/103)
3	1.9% (2/103)
More than one SAPIEN 3 THV implanted	0.2% (1/495)
*Continuous measures - mean ± SE (n); categorical measures - % (no./Total no.). For patients in whom the procedure was aborted or who were converted to surgery, the rest of the procedure data except valve size were not collected.	

Table 55: SAVR Procedure Data (AT Population)

Variable	Summary Statistics*
	SAVR (N=454)
Procedure aborted†	0.2% (1/454)
Valve size	
19 mm	2.9% (13/453)
21 mm	17.2% (78/453)
23 mm	36.6% (166/453)
25 mm	35.5% (161/453)

Variable	Summary Statistics*
	SAVR (N=454)
27 mm	6.8% (31/453)
29 mm	0.9% (4/453)
Total aortic cross clamp time (min)	74.3 ± 1.3 (453)
Total pump time (min)	97.7 ± 1.6 (453)
SAVR approach	
Sternotomy	95.4% (432/453)
Thoracotomy	0.9% (4/453)
Mini right upper thoracotomy	2.9% (13/453)
Port access	0.2% (1/453)
Other	0.7% (3/453)
Successful implantation of the surgical valve	100.0% (453/453)
*Continuous measures - mean ± SE (n); categorical measures - % (no./Total no.). †For patients in whom the procedure was aborted, the rest of the procedure data were not collected.	

Computed Tomography (CT) Sub-Study

There were 184 TAVR and 162 SAVR patients at 30 days and 160 and 134 patients at 1 year, respectively, who had at least one adequate CT for leaflet assessments. The HALT and leaflet mobility imaging findings are summarized in Table 56, along with the associated mean aortic pressure gradients. The mean aortic pressure gradients at 1 year stratified by HALT and leaflet mobility at 30 days are summarized in Table 57 and Table 58, respectively. The rate of death, stroke or TIA at 1 year stratified by HALT and leaflet mobility at 30 days are summarized in Table 59 and Table 60, respectively. The CT substudy was not powered to compare the relative incidence or the severity of HALT or reduced leaflet mobility between the TAVR and SAVR cohorts, or to determine whether late clinical outcomes were affected by the presence of HALT or reduced leaflet mobility.

Table 56: HALT and Leaflet Mobility Findings and Associated Mean Gradients

Findings	Summary Statistics*			
	30 Days		1 Year	
	TAVR (N=184)	SAVR (N=162)	TAVR (N=160)	SAVR (N=134)
Proportion of patients on oral anticoagulants at time of scan	6.0% (11/184)	21.0% (34/162)	8.1% (13/160)	13.4% (18/134)
HALT†				
No thickening	84.8% (156/184)	95.7% (155/162)	74.4% (119/160)	82.1% (110/134)
Mean gradient (mmHg)	12.5 ± 0.3 (156)	10.8 ± 0.3 (155)	13.7 ± 0.4 (115)	11.7 ± 0.4 (106)
< 25% leaflet length thickened	4.9% (9/184)	1.2% (2/162)	11.3% (18/160)	7.5% (10/134)
Mean gradient (mmHg)	11.4 ± 0.9 (9)	16.5 ± NA (1)	12.9 ± 0.7 (18)	9.3 ± 1.8 (8)
25%-50% leaflet length thickened	3.3% (6/184)	1.9% (3/162)	6.3% (10/160)	5.2% (7/134)
Mean gradient (mmHg)	13.7 ± 1.7 (6)	9.4 ± 1.4 (3)	13.2 ± 1.8 (10)	15.1 ± 2.4 (7)
50%-75% leaflet length thickened	6.5% (12/184)	0.6% (1/162)	5.0% (8/160)	3.7% (5/134)
Mean gradient (mmHg)	15.2 ± 1.9 (12)	9.8 ± NA (1)	16.9 ± 3.3 (8)	16.1 ± 4.0 (5)

Findings	Summary Statistics*			
	30 Days		1 Year	
	TAVR (N=184)	SAVR (N=162)	TAVR (N=160)	SAVR (N=134)
> 75% leaflet length thickened	0.5% (1/184)	0.6% (1/162)	3.1% (5/160)	1.5% (2/134)
Mean gradient (mmHg)	10.2 ± NA (1)	16.8 ± NA (1)	20.2 ± 6.2 (5)	9.0 ± 4.2 (2)
Number of leaflets with HALT	6.7% (37/552)	2.3% (11/486)	12.7% (61/480)	8.2% (33/402)
0 leaflets thickening	156	155	119	110
1 leaflet thickening	21	4	26	15
2 leaflets thickening	5	2	10	9
3 leaflets thickening	2	1	5	0
Leaflet mobility‡				
Unrestricted	85.3% (145/170)	96.8% (149/154)	77.6% (118/152)	83.% (108/129)
Mean gradient (mmHg)	12.2 ± 0.3 (145)	10.7 ± 0.3 (148)	13.3 ± 0.4 (114)	12.0 ± 0.5 (105)
Partially restricted, restriction limited to base	5.3% (9/170)	1.3% (2/154)	11.8% (18/152)	8.5% (11/129)
Mean gradient (mmHg)	11.4 ± 0.9 (9)	14.6 ± 1.9 (2)	12.5 ± 0.6 (18)	9.9 ± 1.6 (9)
Partially restricted (< 50%)	5.3% (9/170)	1.3% (2/154)	3.9% (6/152)	3.1% (4/129)
Mean gradient (mmHg)	15.5 ± 2.4 (9)	10.3 ± 0.5 (2)	14.0 ± 2.8 (6)	15.6 ± 3.0 (4)
Partially restricted (50%-75%)	3.5% (6/170)	0.0% (0/154)	4.6% (7/152)	3.9% (5/129)
Mean gradient (mmHg)	12.8 ± 1.7 (6)	NA	21.8 ± 3.9 (7)	11.3 ± 3.6 (5)
Largely immobile	0.6% (1/170)	0.6% (1/154)	2.0% (3/152)	0.8% (1/129)
Mean gradient (mmHg)	13.3 ± NA (1)	16.8 ± NA (1)	19.5 ± 8.1 (3)	13.1 ± NA (1)
Number of leaflets partially restricted or largely immobile				
0 leaflet	145	149	118	108
1 leaflet	21	2	22	13
2 leaflets	4	2	8	8
3 leaflets	0	1	4	0

*Continuous measures - mean ± SE (n); categorical measures - % (no./Total no.). The analysis population included all the patients enrolled in the CT substudy and had at least one adequate CT for leaflet assessments.

†HALT was defined as: the presence of any hyopattenuated leaflet thickening in any singular leaflet as identified by an independent CT core laboratory. The extent of the hypoattenuated leaflet thickening was graded with regards to the entire leaflet as: None, < 25%, 25-50%, 50-75%, or > 75%. If more than one leaflet had the appearance of HALT, the thickening measure of the most impacted leaflet was used. Presence of any degree of HALT on any one leaflet rendered a finding.

‡Leaflet mobility was determined by an independent CT core laboratory and included: unrestricted, partially restricted mobility limited to the base of a leaflet, partially restricted mobility involving more than the base of the leaflet but less than 50% of the leaflet, partially restricted mobility involving more than 50% of the leaflet but less than 75% of the leaflet, and/or a largely immobile leaflet. Presence of any degree of restriction or immobility on any one leaflet rendered a finding.

Table 57: Mean Aortic Gradient at 1 Year Stratified by HALT at 30 Days

	Summary Statistics*			
	HALT at 30 Days		No HALT at 30 Days	
	TAVR (N=28)	SAVR (N=7)	TAVR (N=156)	SAVR (N=155)
Mean gradient	13.6 ± 1.2 (24)	13.7 ± 2.7 (5)	13.6 ± 0.4 (137)	11.8 ± 0.4 (125)

*Mean ± SE (n). The analysis population included all the patients enrolled in the CT substudy and had an adequate CT for leaflet assessments at 30 days.

Table 58: Mean Aortic Gradient at 1 Year Stratified by Leaflet Mobility at 30 Days

	Summary Statistics*			
	Reduced Leaflet Mobility at 30 Days		Unrestricted at 30 Days	
	TAVR (N=25)	SAVR (N=5)	TAVR (N=145)	SAVR (N=149)
Mean gradient	13.7 ± 1.28 (23)	14.2 ± 3.48 (4)	13.3 ± 0.4 (124)	11.7 ± 0.4 (119)

*Mean ± SE (n). The analysis population included all the patients enrolled in the CT substudy and had an adequate CT for leaflet assessments at 30 days.

Table 59: All-Cause Mortality, All Stroke or TIA at 1 Year Stratified by HALT at 30 Days

1-Year Endpoint	Kaplan-Meier Rate*			
	HALT at 30 Days		No HALT at 30 Days	
	TAVR (N=28)	SAVR (N=7)	TAVR (N=156)	SAVR (N=155)
All-cause mortality	0.0% (0)	0.0% (0)	1.3% (2)	1.4% (2)
All stroke	0.0% (0)	0.0% (0)	0.7% (1)	0.0% (0)
TIA	5.6%(1)	0.0% (0)	1.3% (2)	0.0% (0)
All-cause mortality or all stroke or TIA	5.6% (1)	0.0% (0)	3.3% (5)	1.4% (2)

*Kaplan-Meier rate (no. of patients with event). The analysis population included all the patients enrolled in the CT substudy and had an adequate CT for leaflet assessments at 30 days. The Kaplan-Meier analysis used the CT test date as the start date in determining time to event. Presence of any degree of HALT on any one leaflet rendered a finding and inclusion in the HALT cohort.

Table 60: All-Cause Mortality, All Stroke or TIA at 1 Year Stratified by Leaflet Mobility at 30 Days

1-Year Endpoint	Kaplan-Meier Rate*			
	Reduced Leaflet Mobility at 30 Days		Unrestricted at 30 Days	
	TAVR (N=25)	SAVR (N=5)	TAVR (N=145)	SAVR (N=149)
All-cause mortality	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)
All stroke	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)
TIA	6.3% (1)	0.0% (0)	6.3% (1)	0.0% (0)
All-cause mortality or all stroke or TIA	6.3% (1)	0.0% (0)	3.6% (5)	1.4% (2)

*Kaplan-Meier rate (no. of patients with event). The analysis population included all the patients enrolled in the CT substudy and an adequate CT for leaflet assessments at 30 days. The Kaplan-Meier analysis used the CT test date as the start date in determining time to event. Reduced leaflet mobility included any of the following assessments: partially restricted limited to base, partially restricted involving more than the base but less than 50% of the leaflet, partially restricted involving more than 50% but less than

75% of the leaflet, and/or largely immobile. Presence of any degree of restriction or immobility on any one leaflet rendered a finding and inclusion in the reduced leaflet mobility cohort.

13.8 SAPIEN 3 POST APPROVAL STUDY, LOW RISK COHORT OVERVIEW

Overall Study Compliance

At the time of database extract, 777 patients were eligible for the 5 year visit, and 736 completed the visit within the 45-day follow-up window. A detailed summary of overall study compliance at 30 days to 5 years is shown in Table 61.

Table 61: Overall Study Compliance (AT Population)

	30-day Visit		1 Year Visit		5 Year Visit	
	TAVR (N=496)	SAVR (N=454)	TAVR (N=496)	SAVR (N=454)	TAVR (N=496)	SAVR (N=454)
Total patients	496	454	496	454	496	454
Non-eligible	2	11	6	30	78	95
-Death	2	6	5	11	50	35
-Withdrawal	0	3	0	12	15	42
-Lost to follow-up	0	0	0	1	2	4
-Exit with other reason	0	2	1	6	11	14
-Visit not yet due	0	0	0	0	0	0
Eligible	494	443	490	424	418	359
-Follow-up visit completed	99.4% (493)	96.5% (438)	98.0% (486)	91.2% (414)	79.6% (395)	75.1% (341)
-Missed visit	0.2% (1)	1.1% (5)	0.8% (4)	2.2% (10)	4.6% (23)	4.0% (18)

Safety and Effectiveness Results

1. Primary Endpoint

The primary endpoint results are presented in Figure 68. The rate of all-cause death, all stroke or rehospitalization (valve-related or procedure-related and including heart failure) at 1-year was 8.5% and at 5-years was 22.9% in the TAVR cohort and 15.5% at 1-year and 27.3% at 5-years in the SAVR cohort.

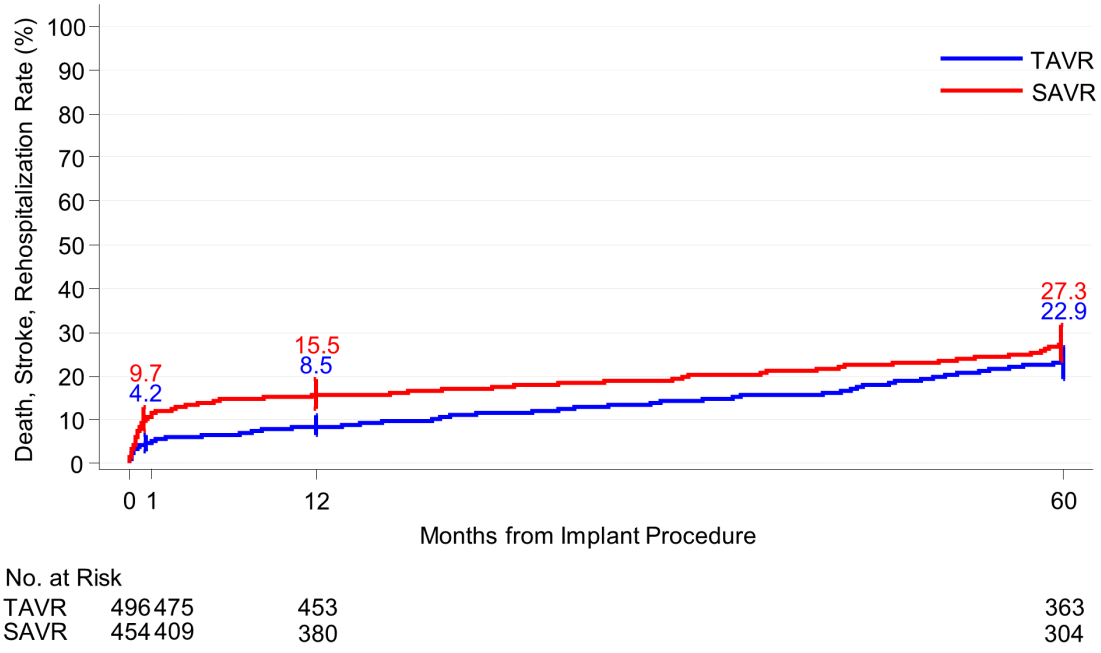


Figure 68: All-Cause Death, All Stroke, and Rehospitalization through 5 Years (AT Population)

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.

Valve Performance

The effective orifice area (EOA), mean aortic gradient, total aortic regurgitation (AR), and paravalvular regurgitation values obtained over time for the TAVR and SAVR patients are shown in Figure 69 through Figure 72, respectively. The increase in EOA and decrease in gradient were sustained through 5 years in both cohorts. In the TAVR cohort, the proportion of patients with total AR ≥ moderate was 0.8% at 30 days, 0.9% at 1 year and 1.9% at 5 years, while in the SAVR cohort, the corresponding proportion was 0.5% at 30 days, 0.5% at 1 year and 0.3% at 5 years. The proportion of patients with paravalvular regurgitation ≥ moderate was 0.8% at 30 days, 0.6% at 1 year and 0.9% at 5 years in the TAVR cohort, as compared to 0.0% at 30 days, 0.8% at 1 year, and 0.0% at 5 years in the SAVR cohort.

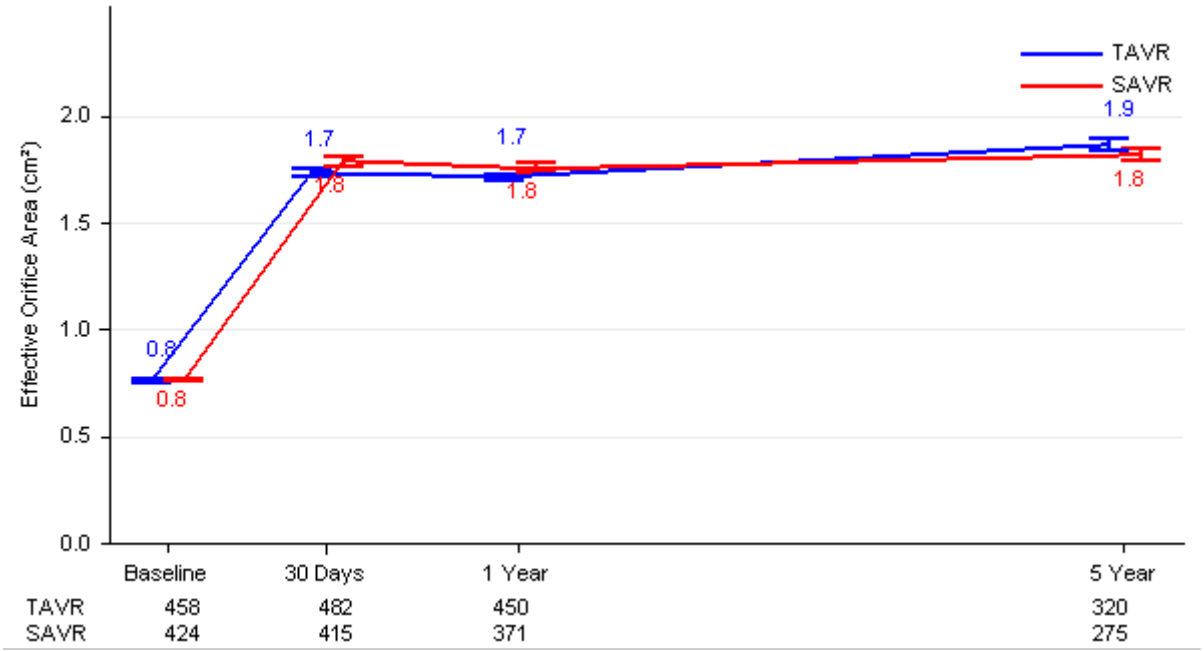


Figure 69: Effective Orifice Area (VI Population)

Note: Line plot with mean and standard error. The total number of patients at each visit time point only counted the patients with valid values.

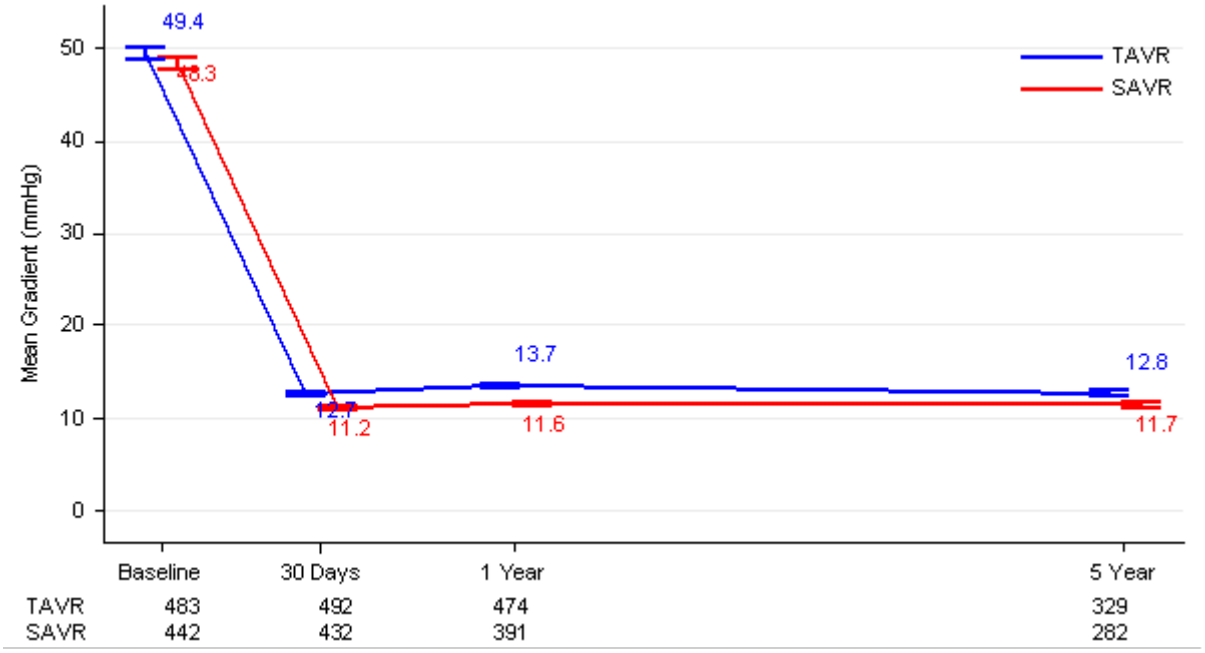


Figure 70: Mean Aortic Gradient (VI Population)

Note: Line plot with mean and standard error. The total number of patients at each visit time point only counted the patients with valid values.

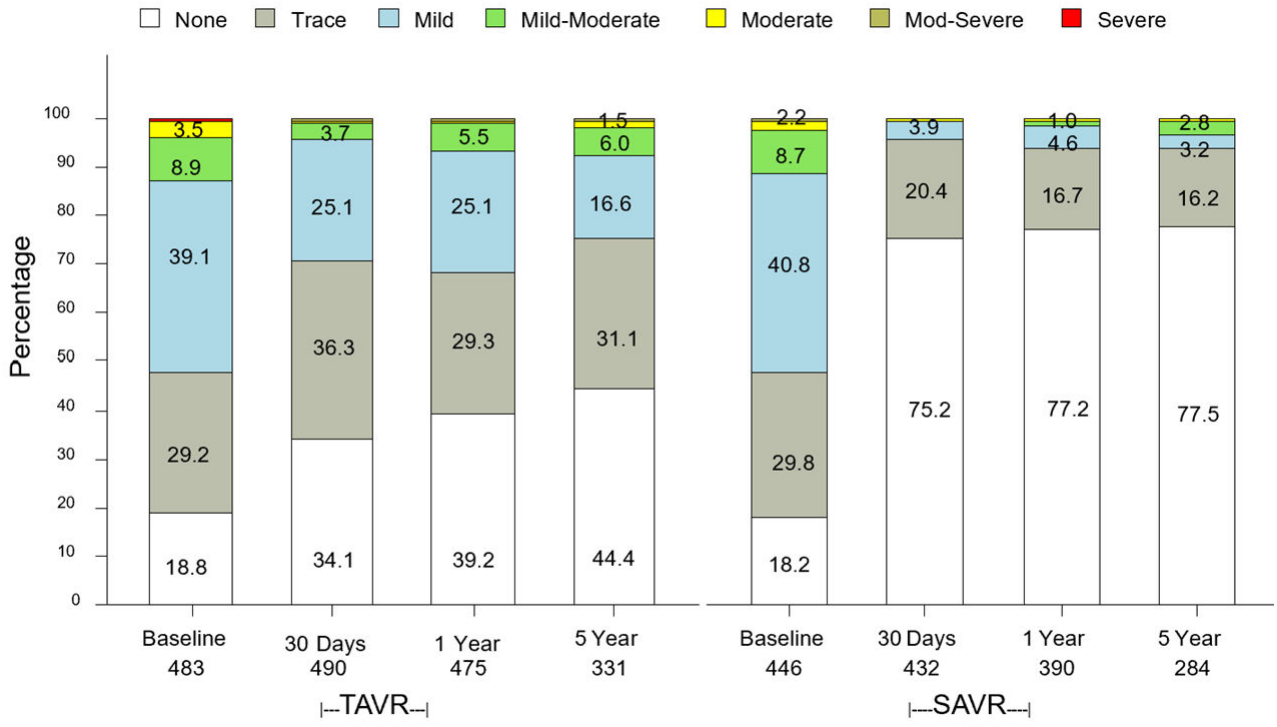


Figure 71: Total Aortic Regurgitation (VI Population)

Note: The total number of patients at each visit time point only counted the patients with valid values.

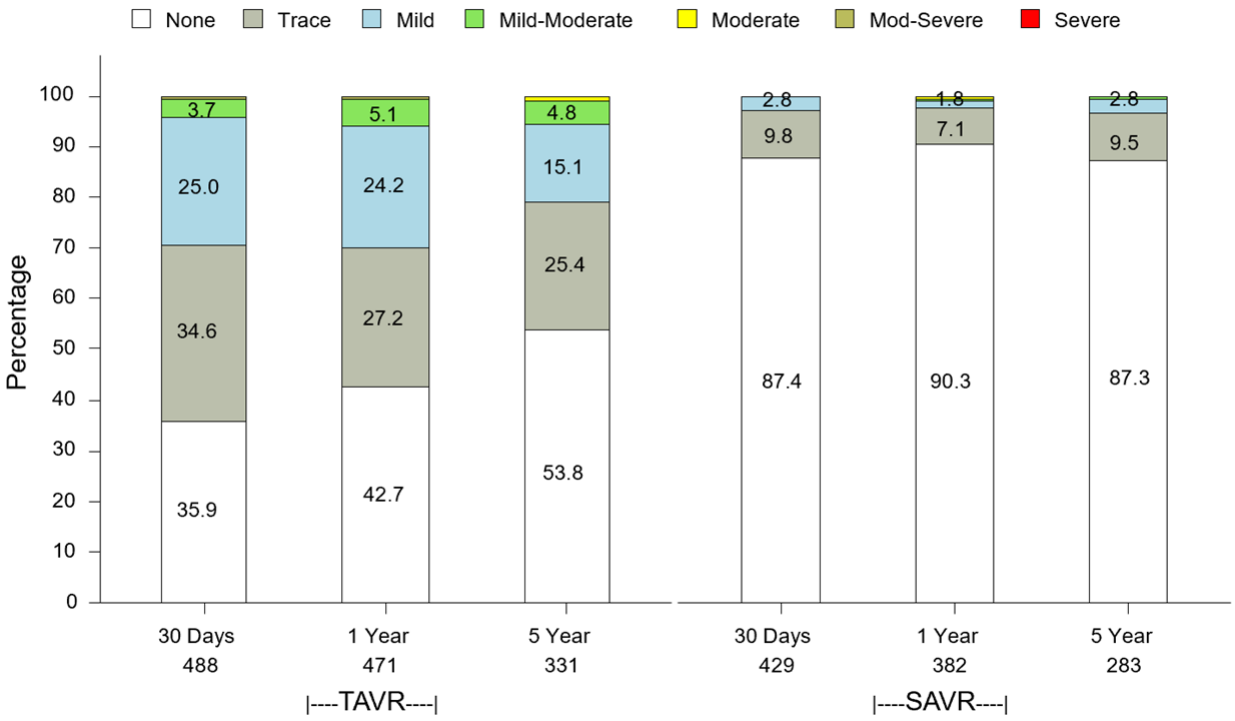


Figure 72: Paravalvular Regurgitation (VI Population)

Note: The total number of patients at each visit time point only counted the patients with valid values.

New York Heart Association (NYHA) Functional Class

The NYHA classifications by visit are presented in Figure 73. At baseline, 31.3% of TAVR patients and 23.6% of SAVR patients were in NYHA III/IV. At 1 year the majority (~99%) of TAVR and SAVR patients were in NYHA Class I/II. At 5 years the majority (~96%) of TAVR and SAVR patients were in NYHA Class I/II.

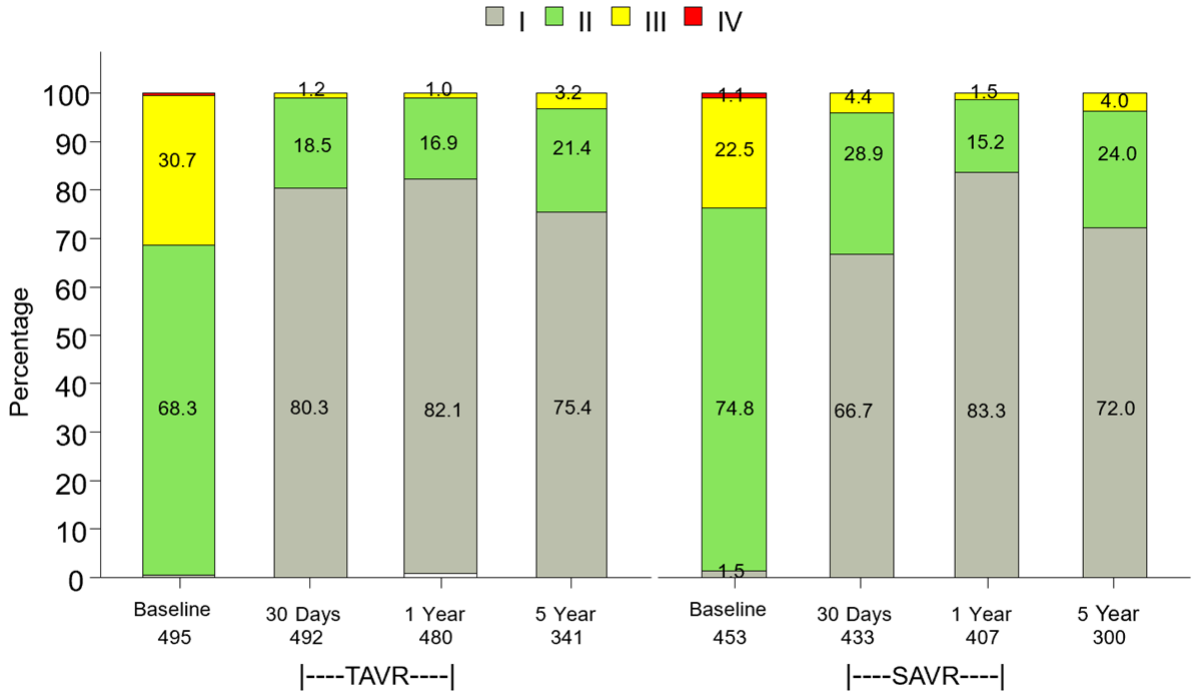


Figure 73: NYHA Class by Visit (VI Population)

Note: The total number of patients at each visit time point only counted the patients with valid values.

Quality of Life (QoL)

KCCQ

The results for the KCCQ overall summary score are presented in Figure 74. The mean score increased from 70.3 at baseline to 88.9 at 30 days, 89.9 at 1 year and 86.2 at 5 years in TAVR patients and from 70.1 at baseline to 72.8 at 30 days 88.1 at 1 year, and 85.9 in SAVR patients.

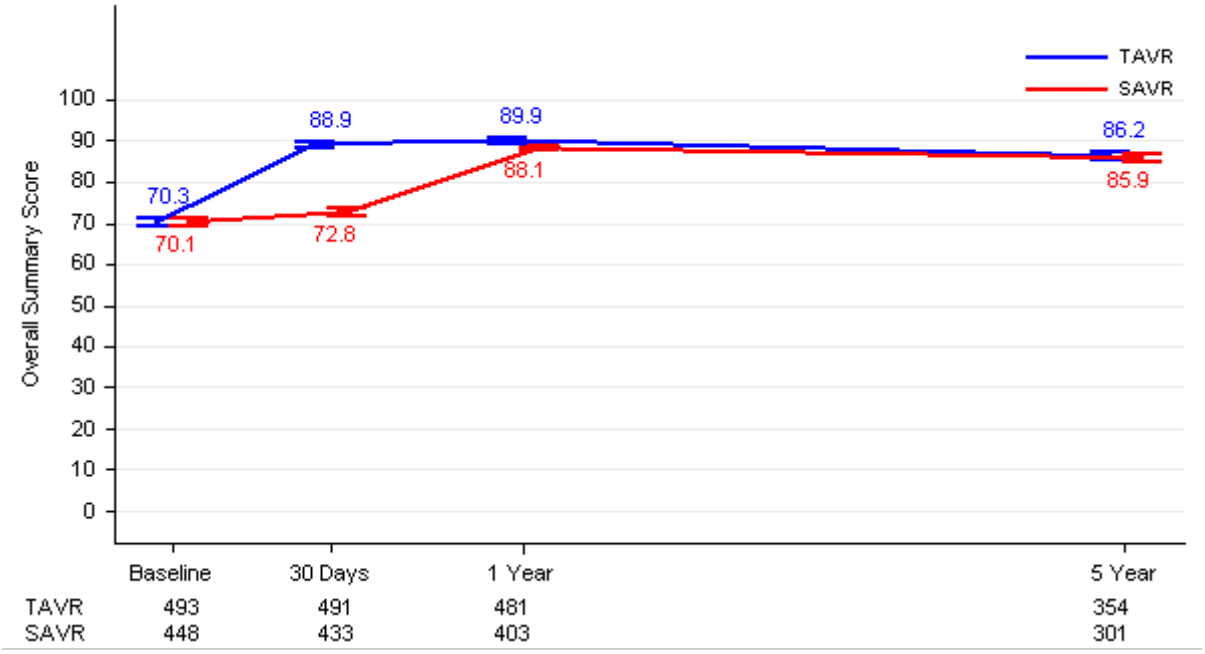


Figure 74: KCCQ Overall Summary Score (VI Population)

Short Form (SF)-36

The results for the SF-36 physical component summary score and mental component summary score are presented in Figure 75 and Figure 76, respectively.

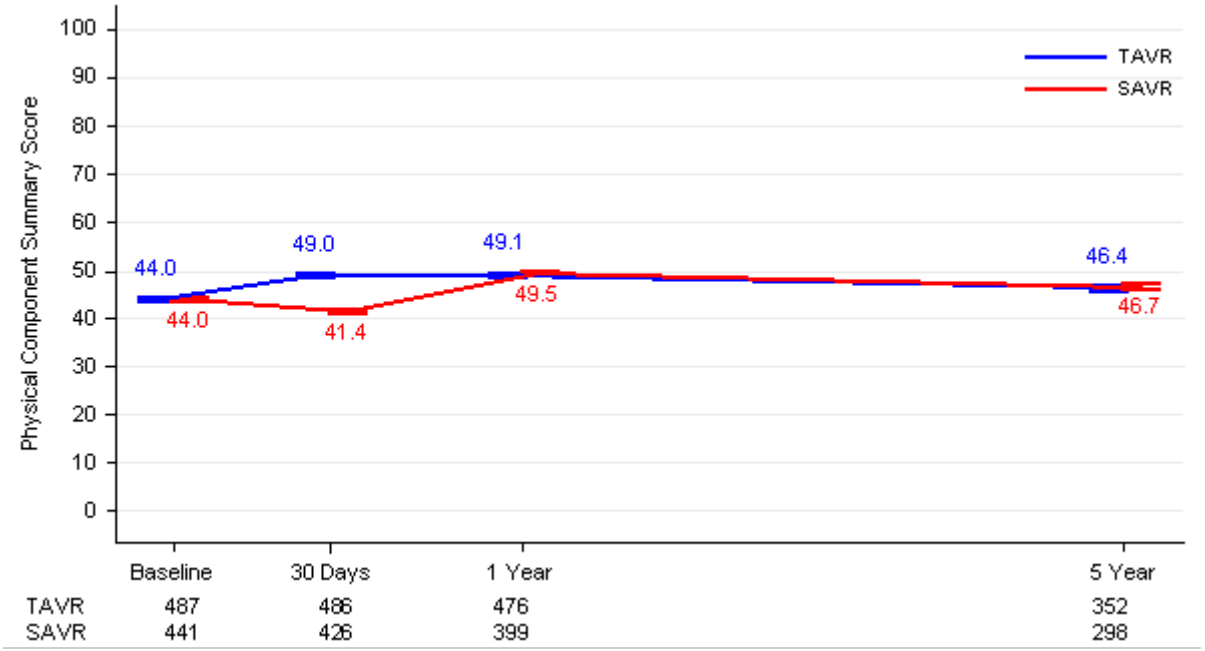


Figure 75: SF-36 Physical Component Summary Score (VI Population)

Note: Line plot with mean and standard error. The total number of patients at each visit time point only counted the patients with valid values.

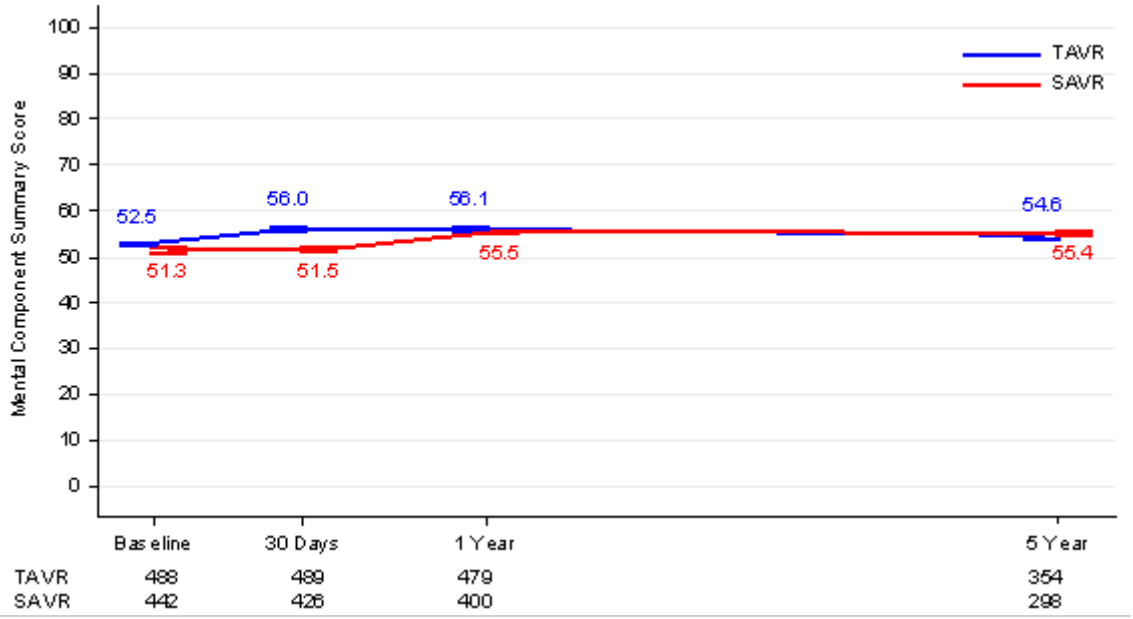


Figure 76: SF-36 Mental Component Summary (VI Population)

Note: Line plot with mean and standard error. The total number of patients at each visit time point only counted the patients with valid values.

3. Adverse Events

The Kaplan-Meier rates of the CEC-adjudicated adverse events through 1 year are presented in Table 62.

Table 62: CEC-Adjudicated Adverse Events through 5 Year (AT Population)

Event	Kaplan-Meier Rate*					
	30 Days		1 Year		5 Year	
	TAVR (N=496)	SAVR (N=454)	TAVR (N=496)	SAVR (N=454)	TAVR (N=496)	SAVR (N=454)
All cause death	0.4% (2, 2)	1.1% (5, 5)	1.0% (5, 5)	2.4% (11, 11)	10.2% (49, 49)	9.0% (39, 39)
Cardiovascular death	0.4% (2, 2)	0.9% (4, 4)	0.8% (4, 4)	2.0% (9, 9)	4.9% (23, 23)	5.1% (21, 21)
All stroke	0.6% (3, 3)	2.7% (12, 12)	1.2% (6, 6)	3.3% (15, 15)	5.8% (32, 27)	6.4% (27, 27)
Disabling stroke	0.0% (0, 0)	0.7% (3, 3)	0.2% (1, 1)	1.1% (5, 5)	2.9% (17, 13)	2.7% (11, 11)
Non-disabling stroke	0.6% (3, 3)	2.0% (9, 9)	1.0% (5, 5)	2.2% (10, 10)	3.2% (15, 15)	3.7% (16, 16)
Death or stroke	1.0% (5, 5)	3.5% (17, 16)	1.8% (11, 9)	5.1% (26, 23)	13.9% (80, 67)	13.3% (61, 56)
Death or disabling stroke	0.4% (2, 2)	1.5% (8, 7)	1.0% (6, 5)	3.1% (16, 14)	11.5% (65, 55)	9.8% (45, 41)
Major vascular complications	2.2% (12, 11)	1.5% (8, 7)	2.8% (15, 14)	1.5% (8, 7)	NA	NA
Life-threatening / disabling, or major bleeding	3.6% (22, 18)	24.5% (123, 111)	7.7% (45, 38)	25.9% (132, 117)	NA	NA

Event	Kaplan-Meier Rate*					
	30 Days		1 Year		5 Year	
	TAVR (N=496)	SAVR (N=454)	TAVR (N=496)	SAVR (N=454)	TAVR (N=496)	SAVR (N=454)
Life-threatening / disabling bleeding	1.2% (9, 6)	11.9% (58, 54)	2.8% (17, 14)	12.8% (63, 58)	NA	NA
Major bleeding	2.6% (13, 13)	13.5% (65, 61)	5.3% (28, 26)	14.1% (69, 64)	NA	NA
Myocardial infarction	1.0% (5, 5)	1.3% (6, 6)	1.2% (6, 6)	2.2% (10, 10)	NA	NA
Requirement for renal replacement†	0.2% (1, 1)	0.7% (3, 3)	0.2% (1, 1)	0.7% (3, 3)	NA	NA
New permanent pacemaker implantation resulting from new or worsened conduction disturbances ‡	6.5% (32, 32)	4.0% (18, 18)	7.3% (36, 36)	5.4% (24, 24)	NA	NA
Coronary obstruction requiring intervention	0.2% (1, 1)	0.7% (3, 3)	0.2% (1, 1)	0.7% (3, 3)	NA	NA
New onset atrial fibrillation	5.3% (22, 22)	39.5% (145, 145)	7.2% (30, 30)	40.9% (150, 150)	NA	NA
Rehospitalization‖	3.4% (18, 17)	6.7% (31, 30)	7.3% (39, 36)	11.2% (60, 50)	13.7% (80, 65)	17.4% (106, 74)

*Kaplan-Meier rate (no. of events, no. of patients with the event).

†Requirement for renal replacement is based on the site-reported event.

‡Patients with pacemaker or ICD at baseline were not counted as new events.

‖Rehospitalization (valve-related or procedure-related and including heart failure)

Subgroup Analysis

Gender Analysis

The protocol specified a subgroup analysis on gender. The primary endpoint result stratified by gender is presented in through 5 years in Figure 77.

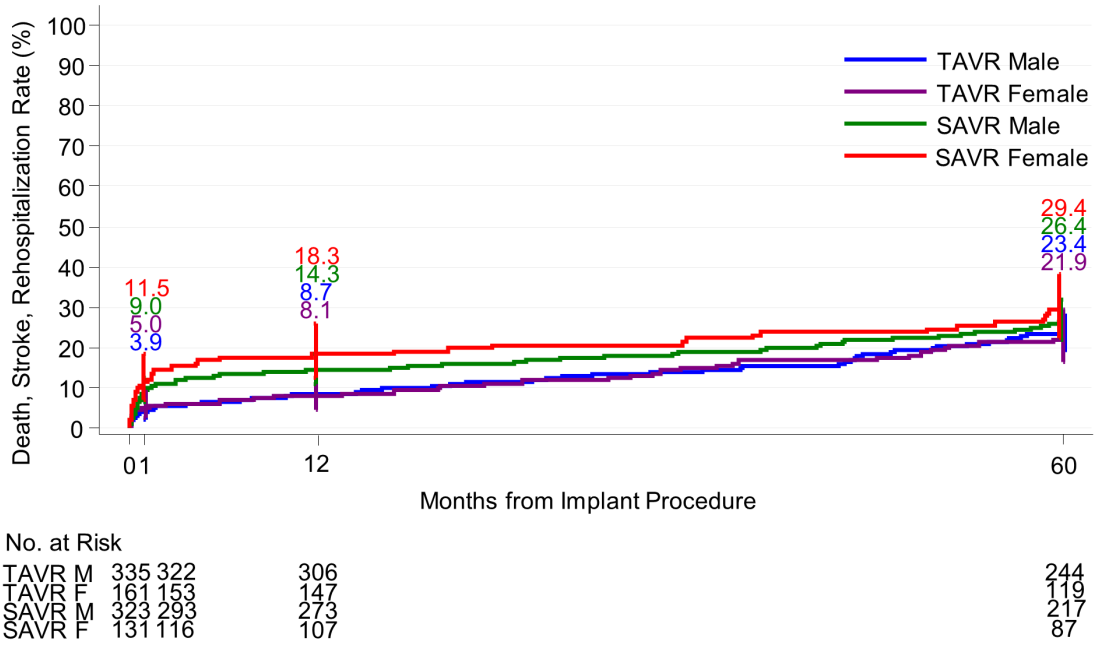


Figure 77: All-Cause Death, All Stroke, and Rehospitalization through 5 Year Stratified by Gender (AT Population)

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.

Small Valve Analysis

Study Population Demographics and Baseline Characteristics

The demographics and baseline characteristics of the study population areas shown in Table 63.

Table 63: Patient Demographics and Baseline Characteristics - 23mm or Smaller Valve Size (AT Population)

	Summary Statistics*		
Demographics and Baseline Characteristics	**TAVR**	**SAVR**	**ALL**
Age - years	73.3 ± 5.23 (156)	73.5 ± 5.92 (257)	73.4 ± 5.66 (413)
Male sex	36/156 (23.1%)	135/257 (52.5%)	171/413 (41.4%)
Society of Thoracic Surgeons (STS) score	2.1 ± 0.69 (156)	2.0 ± 0.61 (257)	2.0 ± 0.64 (413)
New York Heart Association (NYHA) class			
I/II	104/156 (66.7%)	199/257 (77.4%)	303/413 (73.4%)
III/IV	52/156 (33.3%)	58/257 (22.6%)	110/413 (26.6%)
Previous myocardial infarction	8/155 (5.2%)	16/257 (6.2%)	24/412 (5.8%)
Previous intervention			
Coronary artery bypass grafting (CABG)	1/155 (0.6%)	5/254 (2.0%)	6/409 (1.5%)
Percutaneous coronary intervention (PCI)	14/155 (9.0%)	43/255 (16.9%)	57/410 (13.9%)
Stroke or cerebrovascular accident (CVA)	6/156 (3.8%)	11/256 (4.3%)	17/412 (4.1%)

	Summary Statistics*		
Demographics and Baseline Characteristics	**TAVR**	**SAVR**	**ALL**
Peripheral vascular disease (PVD)	11/156 (7.1%)	13/256 (5.1%)	24/412 (5.8%)
Atrial fibrillation	13/156 (8.3%)	41/257 (16.0%)	54/413 (13.1%)
Atrial flutter	2/156 (1.3%)	5/257 (1.9%)	7/413 (1.7%)
Permanent pacemaker or defibrillator	1/156 (0.6%)	10/257 (3.9%)	11/413 (2.7%)
Hostile chest	0/156 (0.0%)	0/257 (0.0%)	0/413 (0.0%)
Echocardiographic findings (Valve Implant Population)			
Valve area (cm^2)	0.7 ± 0.13 (146)	0.7 ± 0.16 (241)	0.7 ± 0.15 (387)
Mean gradient (mmHg)	51.7 ± 13.22 (154)	48.0 ± 12.20 (251)	49.4 ± 12.71 (405)
Left ventricular ejection fraction (LVEF) %	68.1 ± 8.64 (150)	68.1 ± 7.94 (248)	68.1 ± 8.20 (398)
Moderate or severe aortic regurgitation	8/151 (5.3%)	4/251 (1.6%)	12/402 (3.0%)
Moderate or severe mitral regurgitation	1/149 (0.7%)	7/245 (2.9%)	8/394 (2.0%)

Safety and Effectiveness Results

The rate of all-cause death stratified by valve size through 5 years is presented in Figure 78.

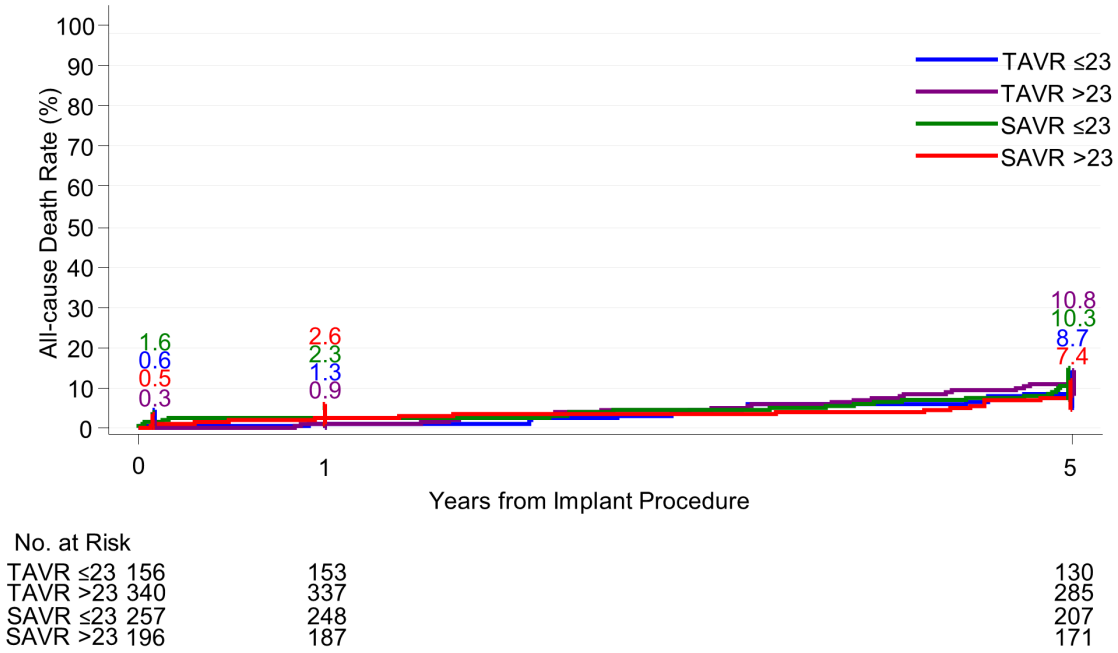


Figure 78: All-Cause Death through 5 Year Stratified by Valve Size (AT Population)

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.

13.9 SAPIEN 3 THV IN BICUSPID AORTIC VALVE FOR PATIENTS AT INTERMEDIATE OR GREATER SURGICAL RISK – STS/ACC TRANSCATHETER VALVE THERAPY REGISTRY (TVTR) ANALYSIS

Patient Accountability

At the time of database extract, of the 545 patients in the bicuspid aortic valve cohort, 527 patients were eligible for the 30-day visit, and 486 (92.2%) patients paid a visit within the 30-day follow-up window defined as the period between 21 and 75 days post-procedure. Of the 465 patients eligible for the 1-year visit, 309 (66.5%) paid a visit within the 1 year follow-up window defined as the period between 305 and 425 days post-procedure. A detailed summary of the patient accountability at 30 days and 1 year is shown in Table 64.

Table 64: Patient Visit Accountability

	30-day Visit	1-year Visit
Total patients	545	545
Non-eligible[*]	18	80
-Death	14	43
-Withdrawal	2	8
-Lost to follow-up	2	29
-Visit not yet due[‡]	0	0
Eligible	527	465
-Follow-up visit completed	486 (92.2%)	309 (66.5%)
-Missed visit[†]	41 (7.8%)	156 (33.5%)

[*]This includes all patients who exited the study prior to the end of the follow-up visit window and those who have not had the visit.
[‡]Patients have not reached the end of the visit window and have not completed the follow-up visit yet.
[†]Data extract date has exceeded the end of the visit window and the patients have not reported the visit data.

The "Attempted Implant" population consisted of all patients entered into the registry with a bicuspid aortic valve. The "Valve Implant" population consisted of those patients for whom the valve implant procedure has started and a "No" was indicated for both "procedure aborted" and "conversion to open heart surgery." The "Valve Implant" population consists of 540 patients as 5 patients were converted to open heart surgery and did not receive the SAPIEN 3 transcatheter heart valve.

Patient Demographics and Baseline Characteristics

The demographics and baseline characteristics of bicuspid aortic valve patients, as shown in Table 65, present a multimorbid cohort of patients with a mean STS score of 5.5 ± 4.0.

Table 65: Patient Demographics and Baseline Characteristics - Bicuspid Population (Attempted Implant Population)

Demographics and Baseline Characteristics	Summary Statistics[*]
Age - years	73.4 ± 11.1 (545)
Male sex	349 / 545
Society of Thoracic Surgeons (STS) score	5.5 ± 4.0 (538)
New York Heart Association (NYHA) class	
I/II	106 / 535 (19.8%)
III/IV	429 / 535 (80.2%)
Previous myocardial infarction	119 / 544 (21.9%)
Previous intervention	
Coronary artery bypass grafting (CABG)	101 / 543 (18.6%)

Demographics and Baseline Characteristics	Summary Statistics*
Percutaneous coronary intervention (PCI)	138 / 545 (25.3%)
Prior aortic valvuloplasty	34 / 545 (6.2%)
Cerebrovascular accident (CVA)	56 / 545 (10.3%)
Peripheral vascular disease	128 / 544 (23.5%)
Atrial fibrillation	183 / 545 (33.6%)
Permanent pacemaker	54 / 545 (9.9%)
Porcelain aorta	12 / 545 (2.2%)
Hostile chest	44 / 545 (8.1%)
Echocardiographic findings (Valve Implant Population)	
Valve area - cm^2	0.7 ± 0.2 (524)
Mean aortic valve gradient - mmHg	44.9 ± 15.5 (535)
Mean left ventricular ejection fraction (LVEF) %	52.9 ± 15.5 (534)
Moderate or severe aortic regurgitation	91 / 536 (17.0%)
Moderate or severe mitral regurgitation	101 / 438 (23.1%)
*Continuous measures - Mean ± SD (Total no.); categorical measures - n. / Total no. (%).	

Safety and Effectiveness Results

Safety Endpoints

The mortality rates at discharge, 30 days, one-year and the Kaplan-Meier curve for all-cause mortality are shown in Table 66 and Figure 79, respectively. There were a total of 12 deaths reported at 30 days and 43 deaths reported at one year.

Table 66: Death Rate - Bicuspid Population (Attempted Implant Population)

	Discharge*	30 Days†	1 Year†
All-cause death‡	1.8% (10)	2.3% (12)	10.3% (43)
Cardiac death	1.1% (6)	1.3% (7)	3.0% (13)

*Observed rate - % (n).
†Kaplan-Meier estimate - % (n)
‡Includes all deaths reported in TVTR and identified through CMS linkage.

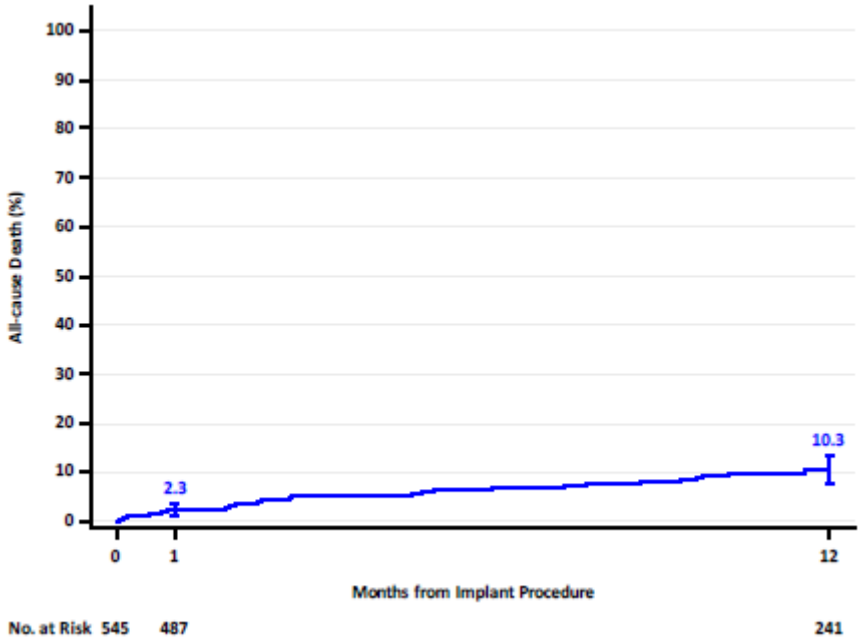


Figure 79: All-Cause Death Rate - Bicuspid Population (Attempted Implant Population)

The DCRI adjudicated events, including all strokes, TIAs and aortic valve reinterventions at discharge, 30 days and one year are shown in Table 67.

Table 67: Duke Clinical Research Institute Adjudicated Events - Bicuspid Population (Attempted Implant Population)

Events	Discharge*	30 Days†	1 Year†
All strokes	1.5% (8, 8)	1.9% (10, 10)	2.7% (13, 13)
Ischemic stroke	1.5% (8, 8)	1.9% (10, 10)	2.7% (13, 13)
Hemorrhagic stroke	0.0% (0, 0)	0.0% (0, 0)	0.0% (0, 0)
Transient ischemic attack (TIA)	0.2% (1, 1)	0.2% (1, 1)	0.2% (1, 1)
Aortic valve reintervention	0.2% (1, 1)	0.2% (1, 1)	0.8% (3, 3)

*Observed rate - % (no. of events, no. of subjects with the event)
†Kaplan-Meier estimate - % (no. of events, no. of subjects with the event)

Note: At the time of this extract, there is one stroke and one aortic valve reintervention that are pending adjudication.

Site Reported Adverse Events

The site reported adverse events at discharge, 30 days and one year for the bicuspid population are shown in Table 68.

Table 68: Site Reported Adverse Events - Bicuspid Population (Attempted Implant Population)

Events	Discharge*	30 Days†	1 Year†
Non-valve related readmission	N/A‡	8.7% (50, 45)	26.8% (164, 110)
Conduction/native pacer disturbance req pacer	7.3% (40, 40)	8.6% (46, 46)	9.7% (50, 50)
Minor vascular complication	4.6% (25, 25)	5.0% (28, 27)	5.0% (28, 27)
Unplanned vascular surgery or intervention	3.5% (19, 19)	3.5% (19, 19)	3.8% (20, 20)
Cardiac arrest	2.9% (16, 16)	3.0% (16, 16)	3.0% (16, 16)
Atrial fibrillation	2.4% (13, 13)	2.4% (13, 13)	2.4% (13, 13)
Hematoma at access site	2.2% (12, 12)	2.2% (12, 12)	2.2% (12, 12)

Events	Discharge*	30 Days†	1 Year†
Ischemic Stroke	1.5% (8, 8)	2.0% (11, 11)	2.6% (13, 13)
Other bleed	2.0% (12, 11)	2.0% (12, 11)	2.0% (12, 11)
Unplanned other cardiac surgery or intervention	1.3% (7, 7)	1.9% (10, 10)	3.3% (16, 15)
Bleeding at access site	1.8% (10, 10)	1.8% (10, 10)	1.8% (10, 10)
Major vascular complication	1.1% (6, 6)	1.1% (6, 6)	1.1% (6, 6)
Perforation with or w/o tamponade	1.1% (6, 6)	1.1% (6, 6)	1.1% (6, 6)
Myocardial infarction	0.7% (4, 4)	0.9% (5, 5)	1.5% (7, 7)
Percutaneous coronary intervention (PCI)	0.7% (5, 4)	0.9% (6, 5)	1.2% (7, 6)
Valve Related Readmission	N/A‡	0.8% (5, 4)	2.1% (12, 9)
Coronary Compression or Obstruction	0.7% (4, 4)	0.7% (4, 4)	0.7% (4, 4)
New requirement for dialysis	0.4% (2, 2)	0.6% (3, 3)	0.9% (4, 4)
Major Bleeding Event	N/A‡	0.4% (2, 2)	1.3% (6, 5)
Conduction/native pacer disturbance requiring implantable cardioverter defibrillator (ICD)	0.2% (1, 1)	0.4% (2, 2)	1.6% (6, 6)
Genitourinary (GU) Bleed	0.4% (2, 2)	0.4% (2, 2)	0.4% (2, 2)
Annular Dissection	0.4% (2, 2)	0.4% (2, 2)	0.4% (2, 2)
Aortic Valve Reintervention	0.2% (1, 1)	0.2% (1, 1)	1.0% (4, 4)
Transient Ischemic Attack	0.2% (1, 1)	0.2% (1, 1)	0.2% (1, 1)
Aortic Dissection	0.2% (1, 1)	0.2% (1, 1)	0.2% (1, 1)
Device recapture or retrieval	0.2% (1, 1)	0.2% (1, 1)	0.2% (1, 1)
Retroperitoneal bleeding	0.2% (1, 1)	0.2% (1, 1)	0.2% (1, 1)
Endocarditis	0.0% (0, 0)	0.0% (0, 0)	0.6% (2, 2)
Device Thrombosis	0.0% (0, 0)	0.0% (0, 0)	0.2% (1, 1)
Undetermined Stroke	0.0% (0, 0)	0.0% (0, 0)	0.3% (1, 1)

*Observed rate - % (no. of events, no. of subjects with the event)
† Kaplan-Meier estimate - % (no. of events, no. of subjects with the event)
‡ N/A = Event not collected on case report form at the time period. % (no. of events, no. of subjects with the event)

Effectiveness Endpoints

Valve Performance

The bicuspid aortic valve echocardiographic performance data are summarized in Figure 80 to Figure 82. The mean gradients 44.9 ± 15.5 mmHg at baseline to 12.0 ± 5.2 mmHg at 30 days and 13.4 ± 9.6 mmHg at one year. Moderate/severe PVL was observed in 4.8% of the patients at 30 days and 5.1% of the patients at one year.

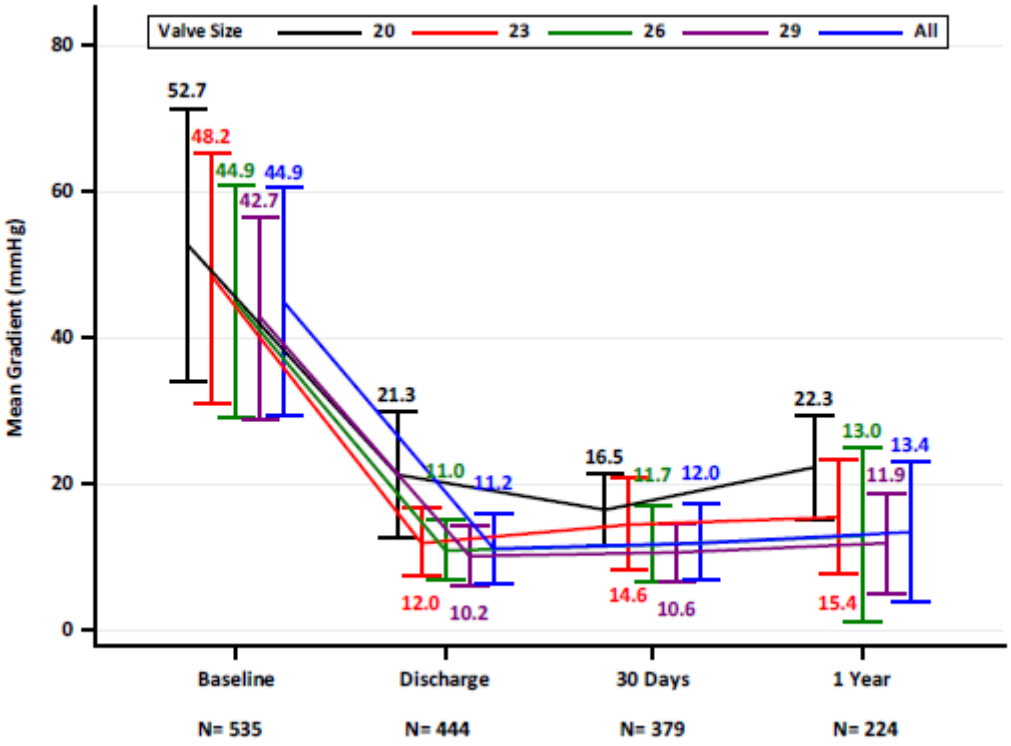


Figure 80: Aortic Mean Gradient - Bicuspid Population (Valve Implant Population)

Note: Line plot with mean and standard deviation. The total number of patients at each time point only counted the patients with valid values.

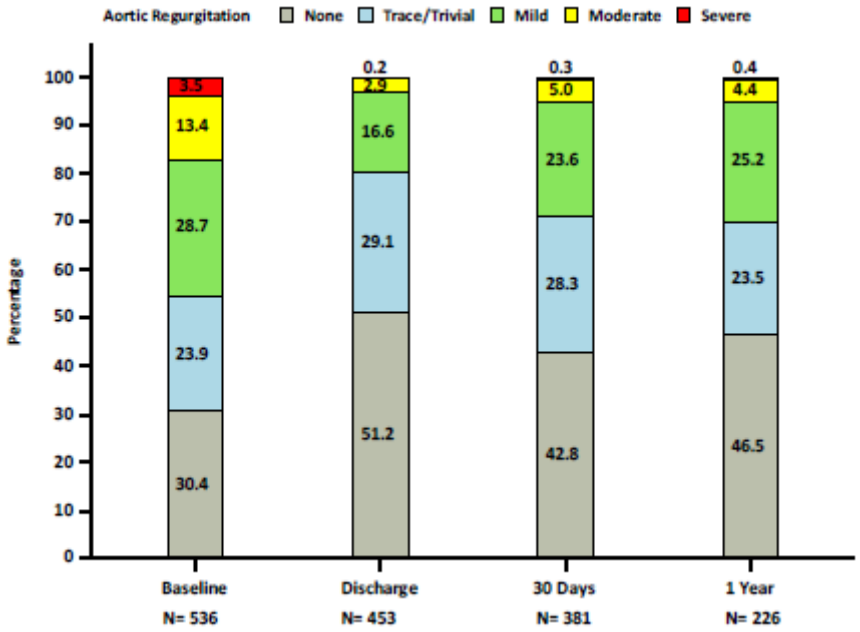


Figure 81: Aortic Regurgitation - Bicuspid Population (Valve Implant Population)

Note: The total number of patients at each time point only counted the patients with valid values.

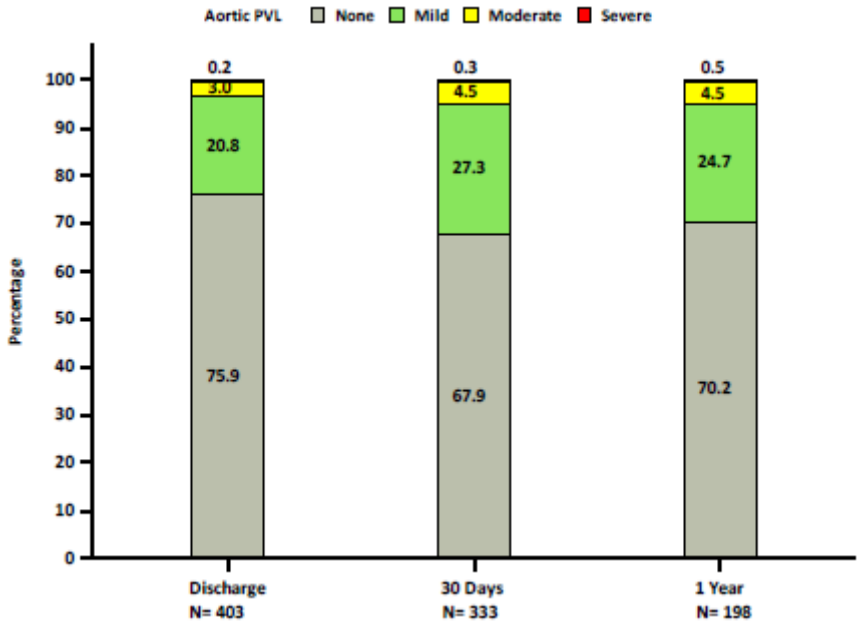


Figure 82: Aortic Paravalvular Leak - Bicuspid Population (Valve Implant Population)

Note: The total number of patients at each time point only counted the patients with valid values.

New York Heart Association Class

The NYHA class distributions at baseline, 30-day visit and one-year visit and the NYHA class changes from baseline to the 30-day visit and to one-year visit are shown in Figure 83 and Table 69, respectively. The majority (84.0% and 82.5%) of the patients had an improved NYHA class at the 30-day visit and one year visit, respectively.

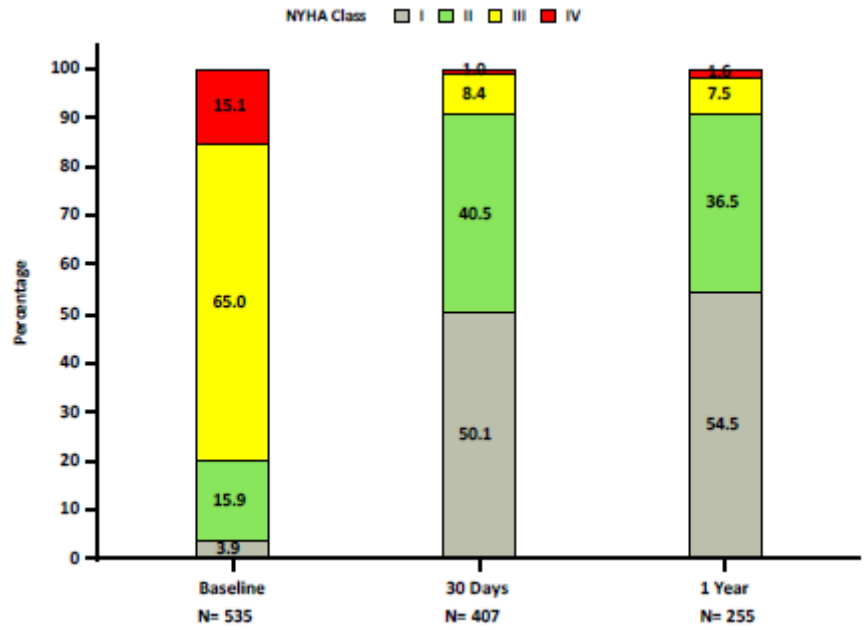


Figure 83: NYHA Functional Class - Bicuspid Population (Valve Implant Population)

Note: The total number of patients at each time point only counted the patients with valid values.

Table 69: NYHA Changes - Bicuspid Population (Valve Implant Population)

	NYHA Class Change*		
	Improved	**Same**	**Worsened**
Baseline to 30-day visit	340/405 (84.0%)	54/405 (13.3%)	11/405 (2.7%)

	NYHA Class Change*		
	Improved	Same	Worsened
Baseline to 1-year visit	208/252 (82.5%)	32/252 (12.7%)	12/252 (4.8%)
*n/Total no. (%); the total no. only counted the patients with valid values.			

Five Meter Walk Test

The results of the five-meter walk test are summarized in Table 70.

Table 70: Five-Meter Walk Test - Bicuspid Population (Valve Implant Population)

Visit	Five Meter Walk Time (seconds)*
Baseline	8.0 ± 4.8 (411)
30-day visit	6.7 ± 2.8 (119)
Change from baseline to 30-day visit	-1.2 ± 3.5 (101)
1-year visit	6.2 ± 2.4 (43)
Change from baseline to 1-year visit	-1.6 ± 3.6 (35)
*Mean ± SD (Total no.). The total number of patients at each time point only counted the patients with valid values.	

Length of Stay

The mean index hospitalization stay was 4.7 days, which included an average of 1.6 days in the intensive care unit (ICU), as summarized in Table 71.

Table 71: Index Hospitalization Stay - Bicuspid Population (Attempted Implant Population)

	Length (days)*
Index hospitalization duration (day)	4.7 ± 3.8 (545)
Intensive care stay (day)	1.6 ± 2.6 (537)
*Mean ± SD (Total no.).	

Quality of Life (QoL)

The QoL at baseline, 30 days and one year as measured by the KCCQ overall summary score, is shown in Figure 84. The mean KCCQ summary score improved from 44.0 at baseline to 77.7 at one year.

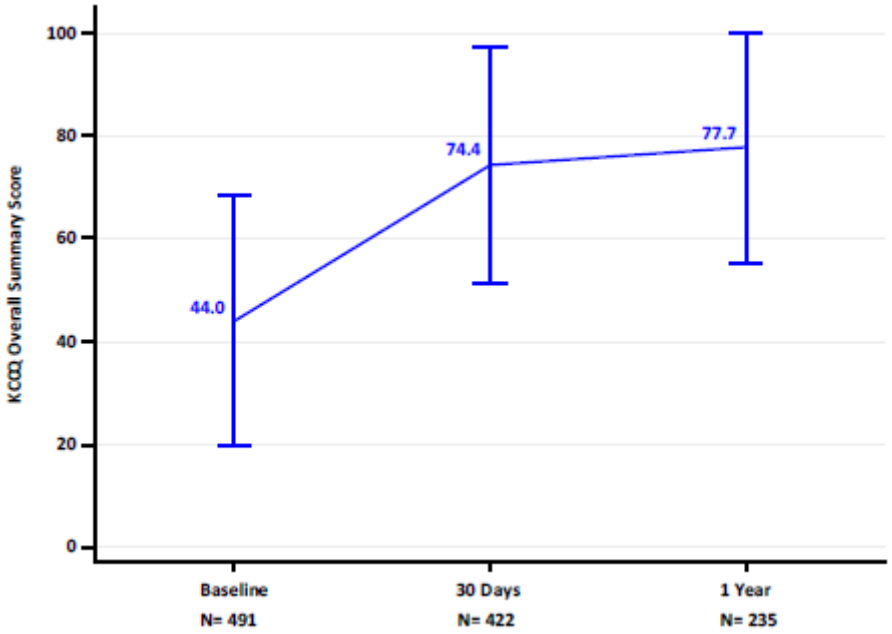


Figure 84: KCCQ Overall Summary - Bicuspid Population (Valve Implant Population)

Note: Line plot with mean and standard deviation. The total number of patients at each time point only counted the patients with valid values.

Procedural Information

The procedure information is presented in Table 72. The most common delivery approach for the bicuspid population was the transfemoral approach, which was used in 94.7% (516/545) of cases, followed by the transapical and transaortic in 1.3% (7/545) and 1.3% (7/545) of cases, respectively, and other alternative approaches (subclavian, transcarotid, and other) in 2.8% (15/545). The device was successfully implanted in 539/544 (99.1%) of patients; five patients were converted to open heart surgery 0.9% (5/545) due to ventricular rupture (1 patient), annulus rupture (1 patient), coronary occlusion (1 patient) and other (2 patients). There were no cases of valve embolization. Device implant success is defined as correct positioning of a single prosthetic heart valve in the proper anatomical location.

Table 72: Procedural Data Summary - Bicuspid Population (Attempted Implant Population)

	Summary Statistics*
Operator reason for procedure	
Inoperable/Extreme risk	115/545 (21.1%)
High risk	394/545 (72.3%)
Intermediate risk	24/545 (4.4%)
Low risk	12/545 (2.2%)
Implant approach	
Transfemoral	516/545 (94.7%)
Transapical	7/545 (1.3%)
Transaortic	7/545 (1.3%)
Subclavian/axillary	9/545 (1.7%)
Transcarotid	3/545 (0.6%)
Other	3/545 (0.6%)
Procedure status	
Elective	497/545 (91.2%)

	Summary Statistics*
Urgent	47/545 (8.6%)
Emergency	1/545 (0.2%)
Valve size	
20 mm	16/545 (2.9%)
23 mm	95/545 (17.4%)
26 mm	220/545 (40.4%)
29 mm	214/545 (39.3%)
Primary procedure indication	
Aortic stenosis (Primary)	535/545 (98.2%)
Aortic insufficiency (Primary)	1/545 (0.2%)
Mixed aortic stenosis/aortic insufficiency	9/545 (1.7%)
Cardiopulmonary bypass (CPB)	5/545 (0.9%)
CPB status	
Elective	2/5 (40.0%)
Emergent	3/5 (60.0%)
CPB time (min)	52.2 ± 24.2 (5)
Type of anesthesia	
General anesthesia	389/545 (71.4%)
Moderate sedation	151/545 (27.7%)
Epidural	1/545 (0.2%)
Combination	4/545 (0.7%)
Total procedure time (min)	109.3 ± 49.5 (545)
Fluoroscopy time (min)	19.9 ± 10.4 (528)
Device implanted successfully	539/544 (99.1%)
Procedure aborted	0/545 (0.0%)
Conversion to open heart surgery	5/545 (0.9%)
Ventricular rupture	1/5 (20.0%)
Annulus rupture	1/5 (20.0%)
Coronary occlusion	1/5 (20.0%)
Other	2/5 (40.0%)
Mechanical assist device in place at start of procedure	5/545 (0.9%)
Intra-aortic balloon pump (IABP)	3/5 (60.0%)
Catheter based assist device	2/5 (40.0%)

*Categorical measures – no./Total no. (%); continuous measures - mean ± SD (Total no.). The total no. only counted the patients with valid values at the time point.

13.10 SAPIEN 3 THV IN BICUSPID AORTIC VALVE FOR PATIENTS AT LOW SURGICAL RISK – PARTNER 3 BICUSPID REGISTRY ANALYSIS

A. Patient Accountability

At the time of the database lock, a total of 75 patients were enrolled in the registry.

There were three different analysis populations reflective of the single-arm study design: All Enrolled, Attempted Implant(AI), and Valve Implant (VI), which are defined in Table 73.

Table 73: Analysis Populations

Analysis Population	Definition	Number of Patients
All Enrolled	All patients who were approved by the Case Review Board and enrolled in the study.	75
Attempted Implant (AI)	All enrolled patients in whom the index procedure had begun, whether or not the procedure was completed.	71
Valve Implant (VI)	All AI patients who received and retained the study valve during the index procedure.	71

The overall follow-up compliance of the registry is summarized in Table 74.

Table 74: Bicuspid Registry Study Compliance (AI Population)

Patient Disposition and Visit Status	30-Day Visit	1-Year Visit
Total patients	71	71
Ineligible*	0	1
Death	0	1
Withdrawn	0	0
Lost to follow-up	0	0
Exit with other reason	0	0
Eligible†	71	70
Follow-up visit completed	71 (100.0%)	69 (97.2%)
*Ineligible includes patients who exited the study prior to the visit or had a pending visit status †Eligible patients = analysis population N – ineligible patients.		

B. Study Population Demographics and Baseline Characteristics

The demographics and baseline characteristics of the study population are typical for a TAVR study performed in the U.S., as shown in Table 75.

Table 75: Patient Demographics and Baseline Characteristics (AI Population)

Demographics and Baseline Characteristics	Summary Statistics* (N = 71)
Age (years)	68.5 ± 6.6
Gender	
Male	69.0% (49/71)
Female	31.0% (22/71)
Society of Thoracic Surgeons (STS) score (%)	1.4 ± 0.59
New York Heart Association (NYHA) class	

Demographics and Baseline Characteristics	Summary Statistics* (N = 71)
I/II	76.1% (54/71)
III/IV	23.9% (17/71)
Previous myocardial infarction	7.0% (5/71)
Previous intervention	
Coronary artery bypass grafting (CABG)	0.0% (0/71)
Percutaneous coronary intervention (PCI)	7.0% (5/71)
Stroke or cerebrovascular accident (CVA)	2.8% (2/71)
Peripheral vascular disease (PVD)	5.6% (4/71)
Atrial fibrillation	4.2% (3/71)
Permanent pacemaker or defibrillator	1.4% (1/71)
Hostile chest	0.0% (0/71)
Echocardiographic findings	
Valve area (cm^2)	0.7 ± 0.2 (65)
Mean gradient (mmHg)	56.1 ± 15.5 (71)
Mean left ventricular ejection fraction (LVEF), %	64.0 ± 11.1 (66)
Moderate or severe aortic regurgitation	5.6% (4/71)
Moderate or severe mitral regurgitation	1.4% (1/70)
Morphology	
Bicuspid Sievers Type 0	14.1% (10/71)
Bicuspid Sievers Type 1	84.5% (60/71)
Bicuspid Sievers Type 2	1.4% (1/71)
*Continuous measures - mean ± SD (Total no.); Categorical measures - % (no./Total no.)	

C. Safety and Effectiveness Results

1. Primary Endpoint

The primary endpoint results are presented in Table 76 and Figure 85. The rate of all-cause death, all stroke, and rehospitalization (valve-related or procedure-related and including heart failure) at 1 year was 8.5%.

Table 76: Primary Endpoint Analysis (AI Population)

Endpoint	Kaplan-Meier Rate* (N = 71)
All-cause death, all stroke, or rehospitalization	8.5% (7, 6)
All-cause death	1.4% (1, 1)
All stroke	2.8% (2, 2)
Rehospitalization	5.6% (4, 4)
*Kaplan-Meier rate (no. of events, no. of patients with the event).	

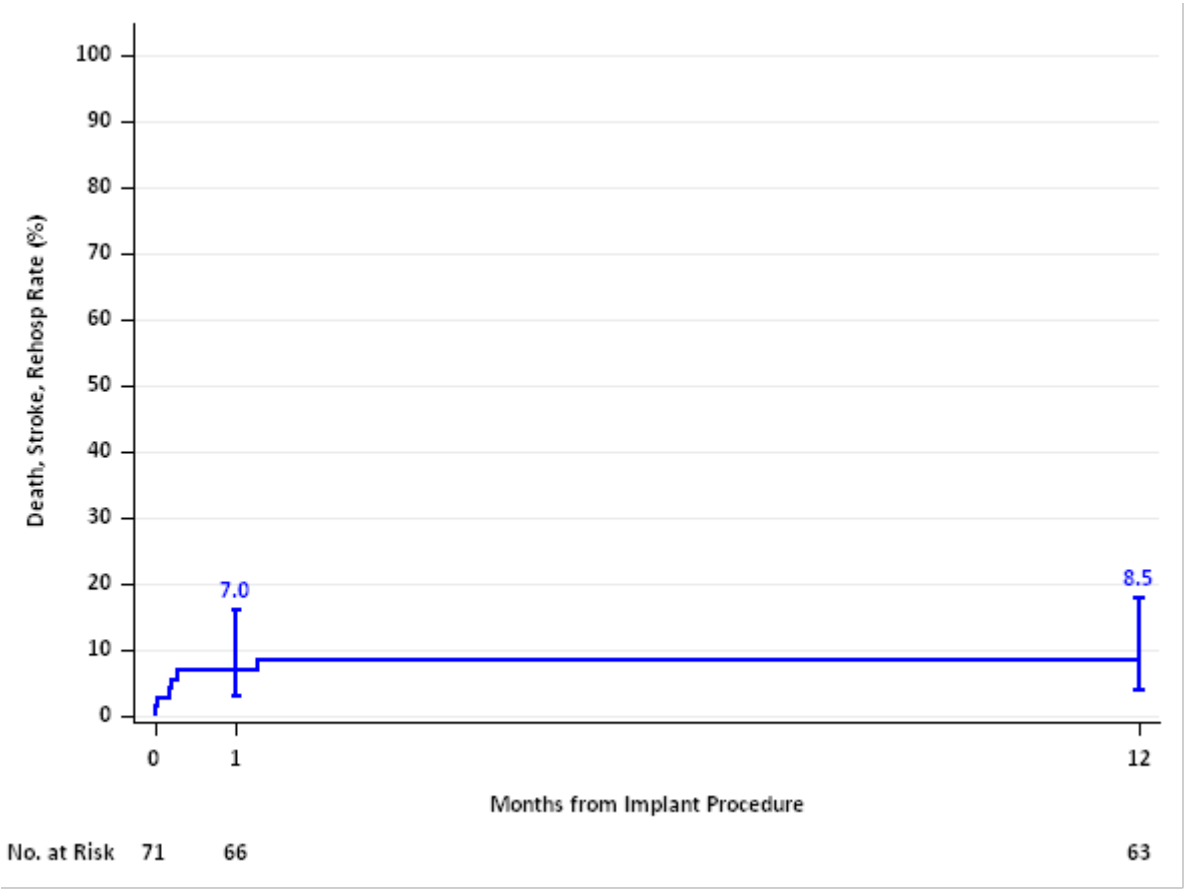


Figure 85: All-Cause Death, All Stroke, and Rehospitalization through 1 Year (AI Population)

Note: Vertical bar represents 95% confidence interval. 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.

2. Secondary Endpoints

A summary of the secondary endpoints is shown in Table 77. No formal statistical tests were performed.

Table 77: Secondary Endpoints Analysis (AI Population)

No.	Endpoint	Summary Statistics*
1	New onset atrial fibrillation at 30 days	4.2% (3/71)
2	Length of index hospitalization (days)	2.6 ± 0.1 (71)
3	Death, KCCQ < 45 or KCCQ decrease from baseline ≥ 10 points at 30 days	1.4% (1/71)
4	Death or all stroke at 30 days	2.8% (2/71)
5	All stroke at 30 days	2.8% (2/71)

*Continuous measures - mean ± SE (Total no.); Categorical measures – observed rate, % (no./Total no.)

Valve Performance

The increase in EOA and decrease in gradient were sustained through 1 year. The proportion of patients with total AR ≥ moderate was 1.4% at 30 days and 1.5% at 1 year. The proportion of patients with paravalvular regurgitation ≥ moderate was 1.4% at 30 days and 0.0% at 1 year. Prothesis patient mismatch (PPM) was measured per VARC-2. The percentages of patients with moderate and severe PPM were 21.5% and 9.2%, respectively. However, no deaths were reported in these patients at 1 year. It should be noted that there are limitations in echocardiogram measurement of PPM in TAVR patients, such as errors in stroke volume calculation, inherent limitations in the Bernoulli equation for deriving post-implant gradients, which will overstate the degree of PPM. Relying on the echocardiogram-derived iEOA alone to estimate PPM without taking into consideration the aortic valve velocity and gradient will lead to conflicting PPM assessment and outcomes post-TAVR[4]. Accounting for pressure recovery, using predicted versus measured iEOA, and using more accurate CT-LVOT area measurement may be required in the assessment of PPM and prosthetic valve function. Thus, interpretation of the PPM rate should take into consideration the current methodological limitations in PPM measurement and the totality of the clinical outcomes data of the device.

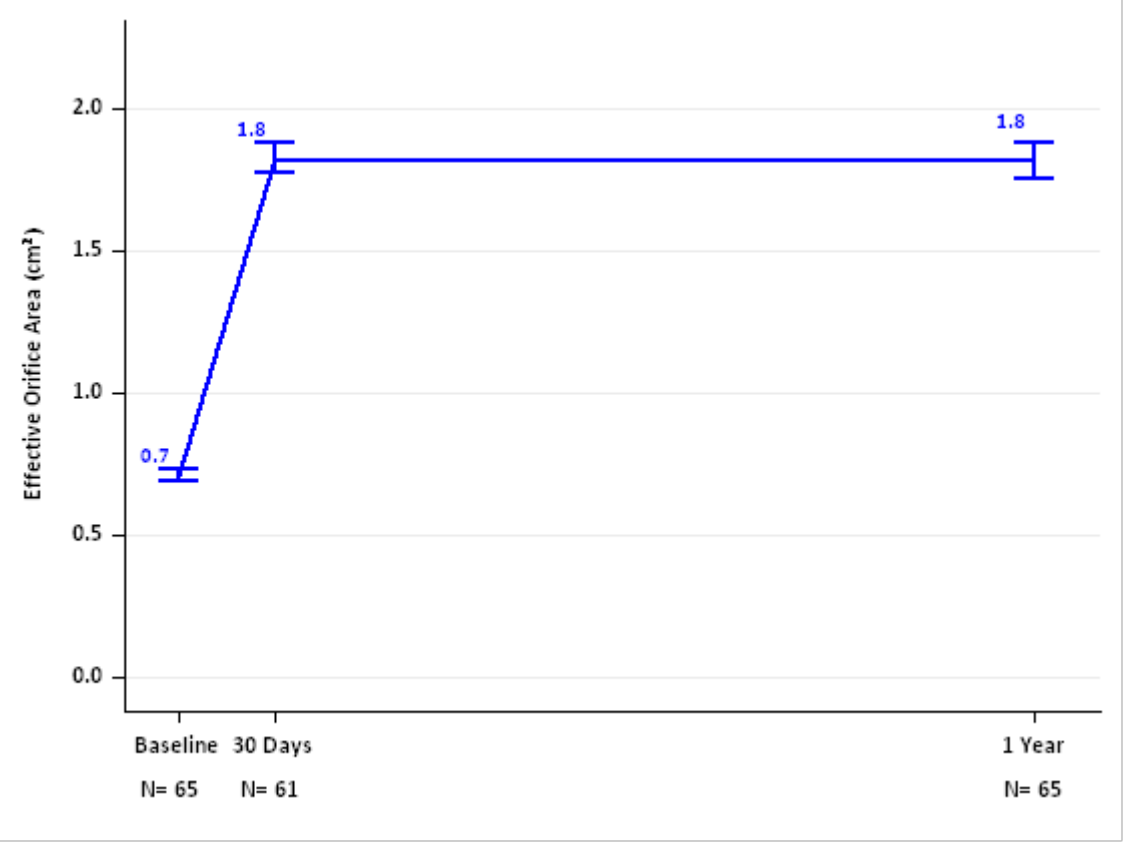


Figure 86: Effective Orifice Area (VI Population)

Note: Line plot with mean and standard error. The total number of patients at each visit time point only counted the patients with valid values.

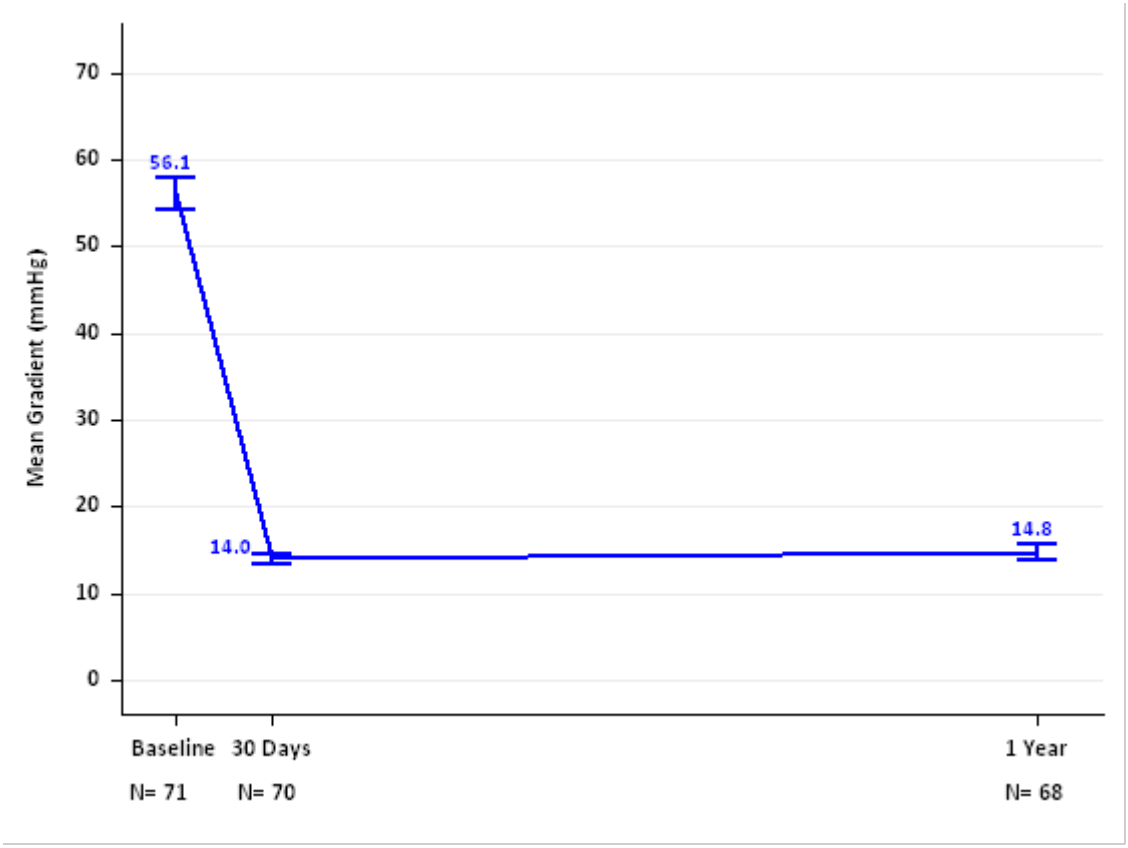


Figure 87: Mean Aortic Gradient (VI Population)

Note: Line plot with mean and standard error. The total number of patients at each visit time point only counted the patients with valid values.

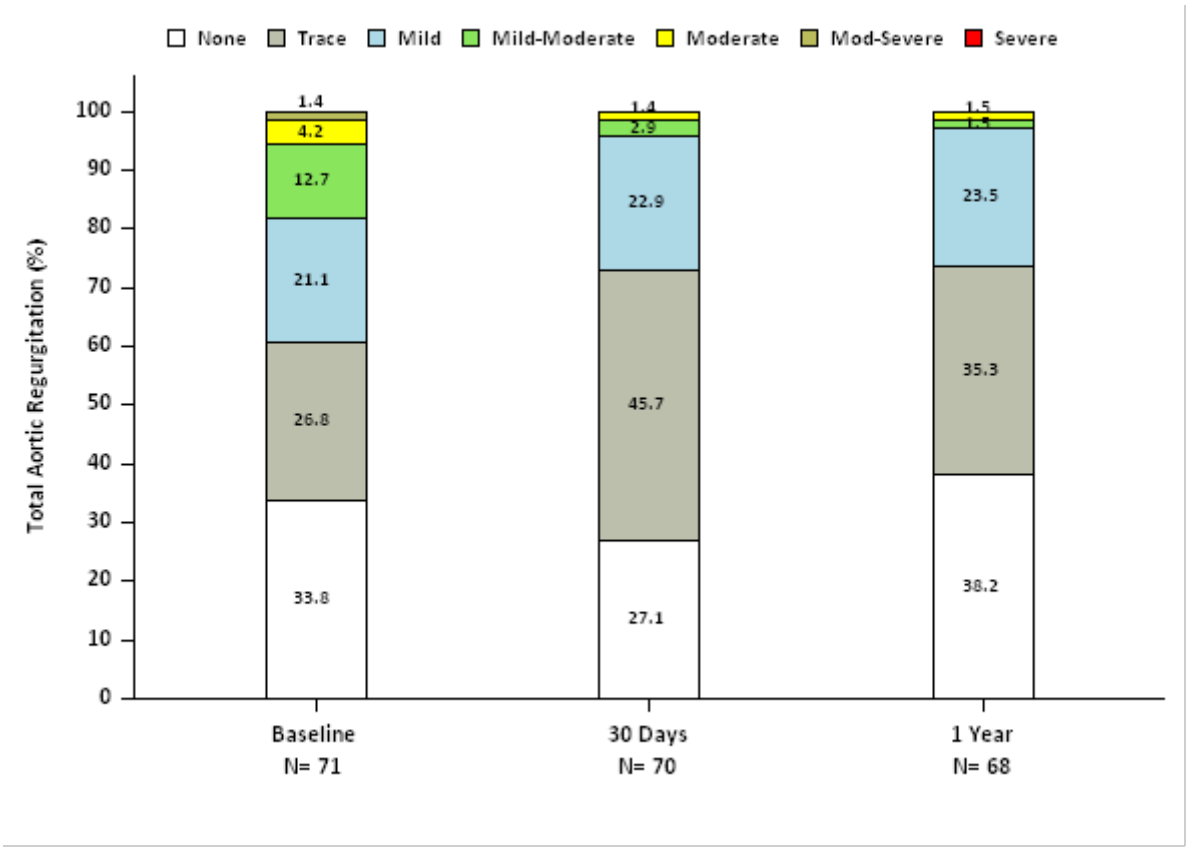


Figure 88: Total Aortic Regurgitation (VI Population)

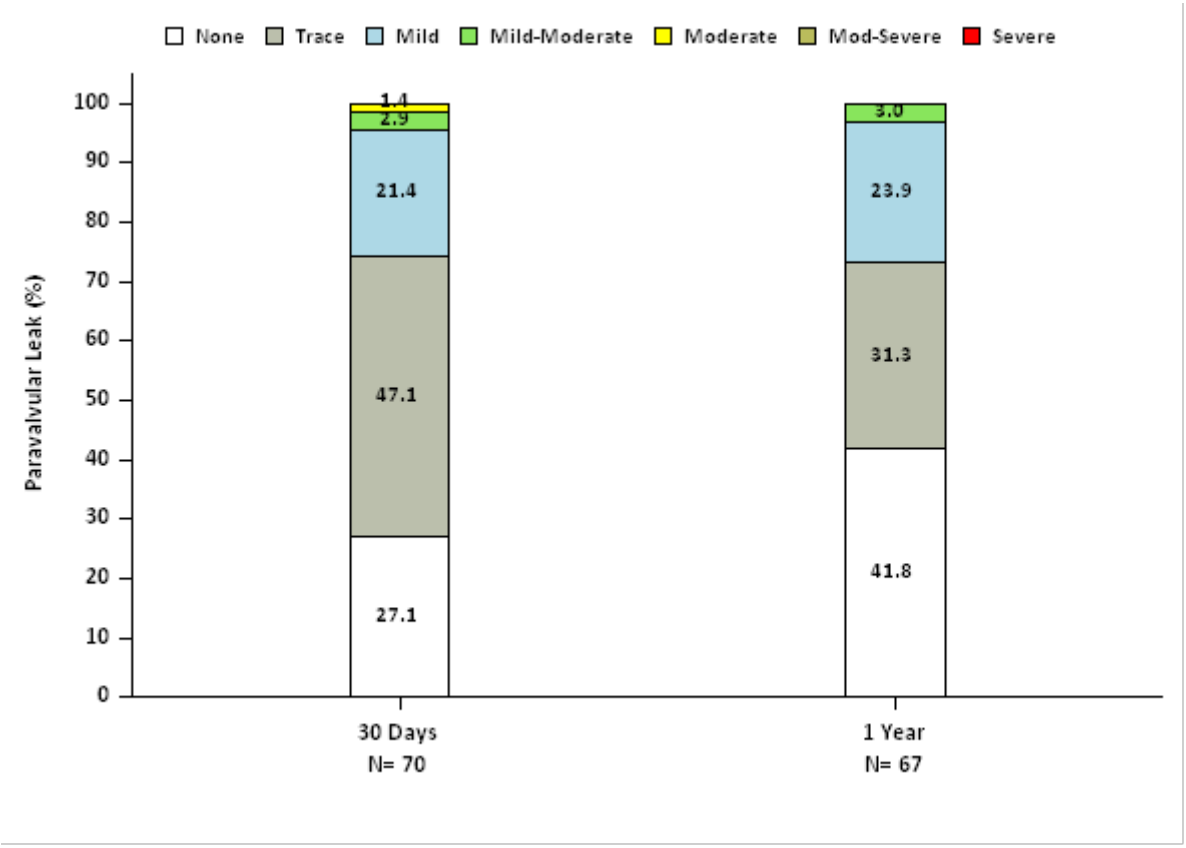


Figure 89: Paravalvular Regurgitation (VI Population)

New York Heart Association (NYHA) Class

The NYHA classifications by visit are presented in Figure 90. At baseline, 23.9% of patients were in NYHA class III/IV. At 1 year, all patients (100.0%) were in NYHA class I/II.

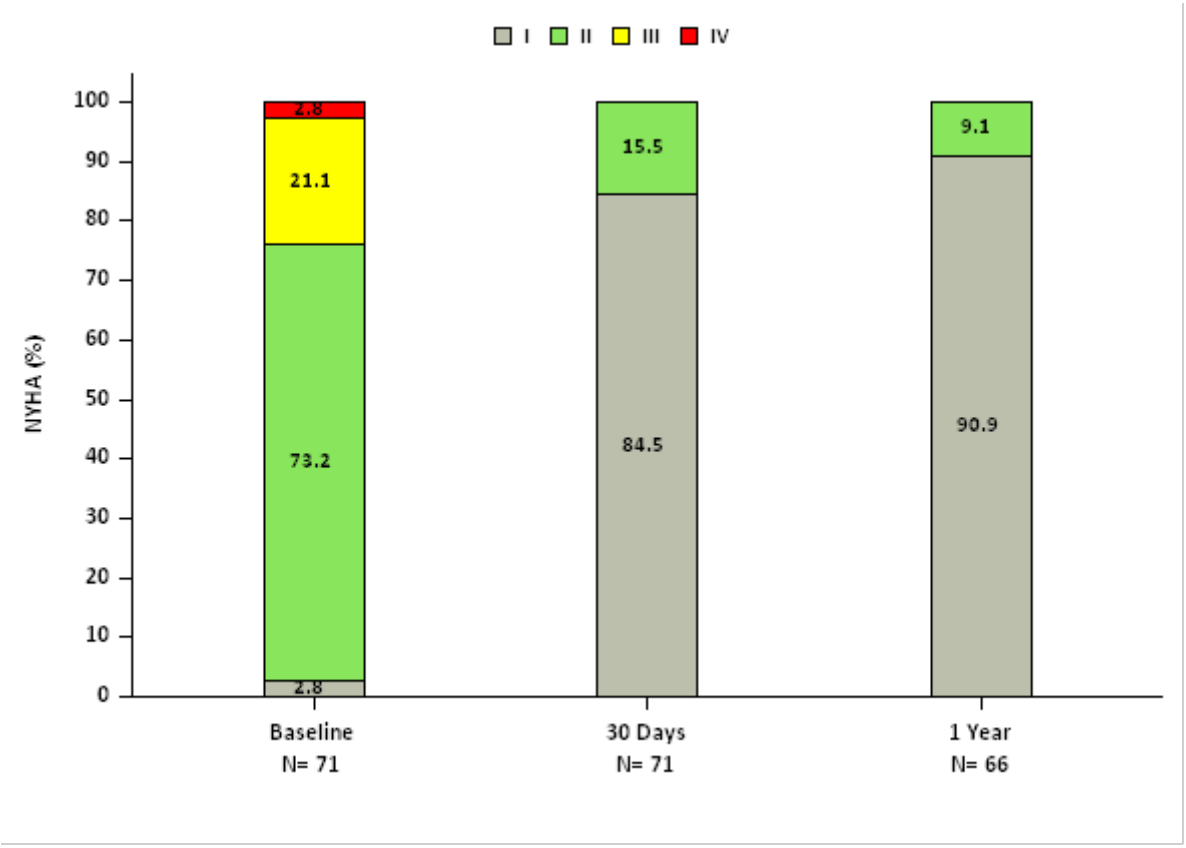


Figure 90: NYHA Class by Visit (VI Population)

Six-Minute Walk Test (6MWT)

The results for the 6MWT are presented in Figure 91. The patients showed an increase in mean 6MWT distance from 361.6 meters at baseline to 376.4 meters at 30 days and 422.4 meters at 1 year.

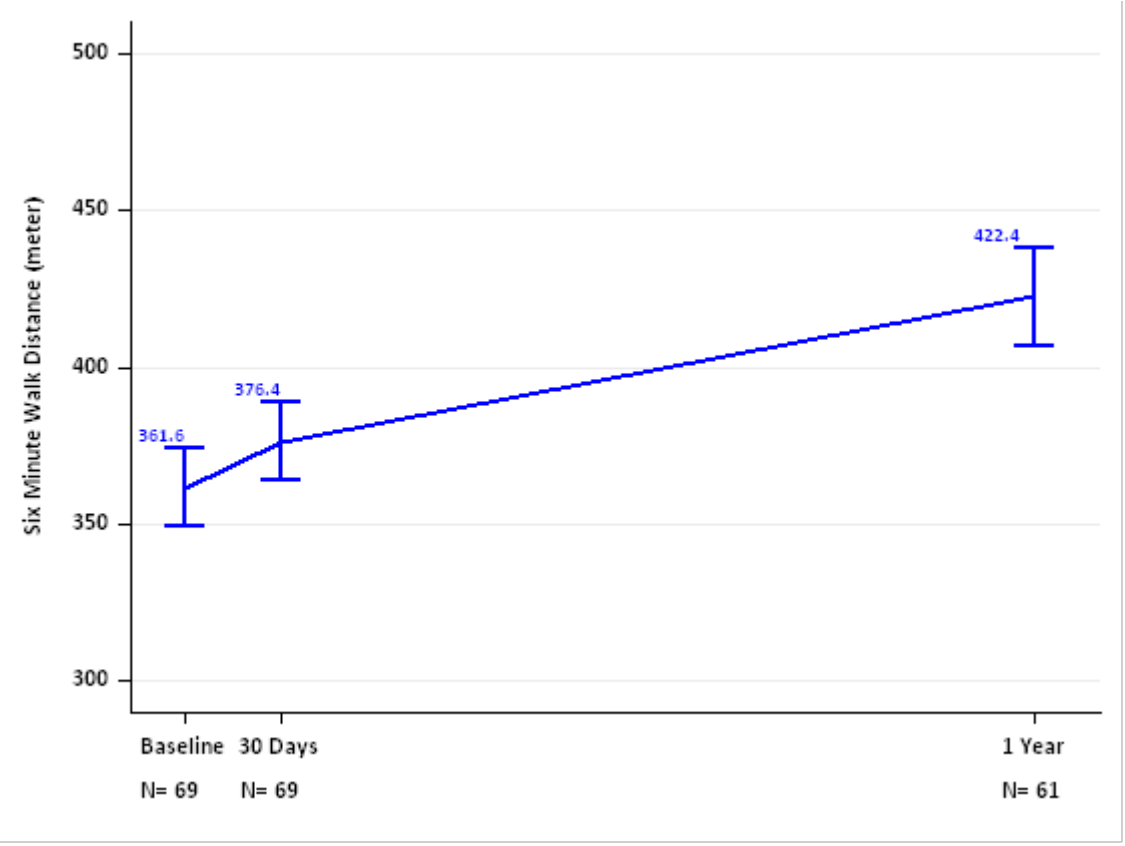


Figure 91: 6MWT Distance (VI Population)

Note: Line plot with mean and standard error. The total number of patients at each visit time point only counted the patients with valid values.

Quality of Life

KCCQ

The results for the KCCQ overall summary score are presented in Figure 92. The mean score increased from 71.0 at baseline to 91.8 at 30 days and 90.8 at 1 year.

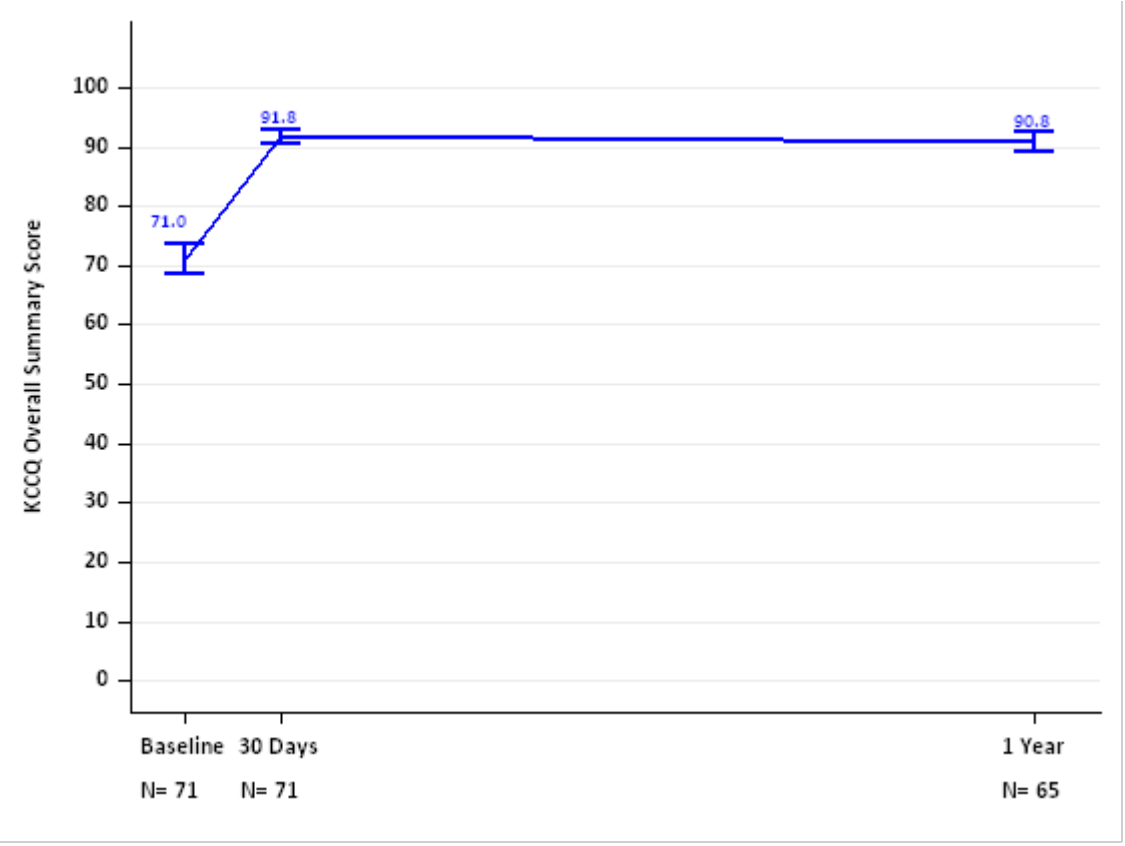


Figure 92: KCCQ Overall Summary Score (VI Population)

Note: Line plot with mean and standard error. The total number of patients at each visit time point only counted the patients with valid values.

EuroQol (EQ-5D)

The results for the EQ-5D visual analog score (VAS) are presented in Figure 93. The mean score was 78.3 at baseline, 87.7 at 30 days, and 86.1 at 1 year.

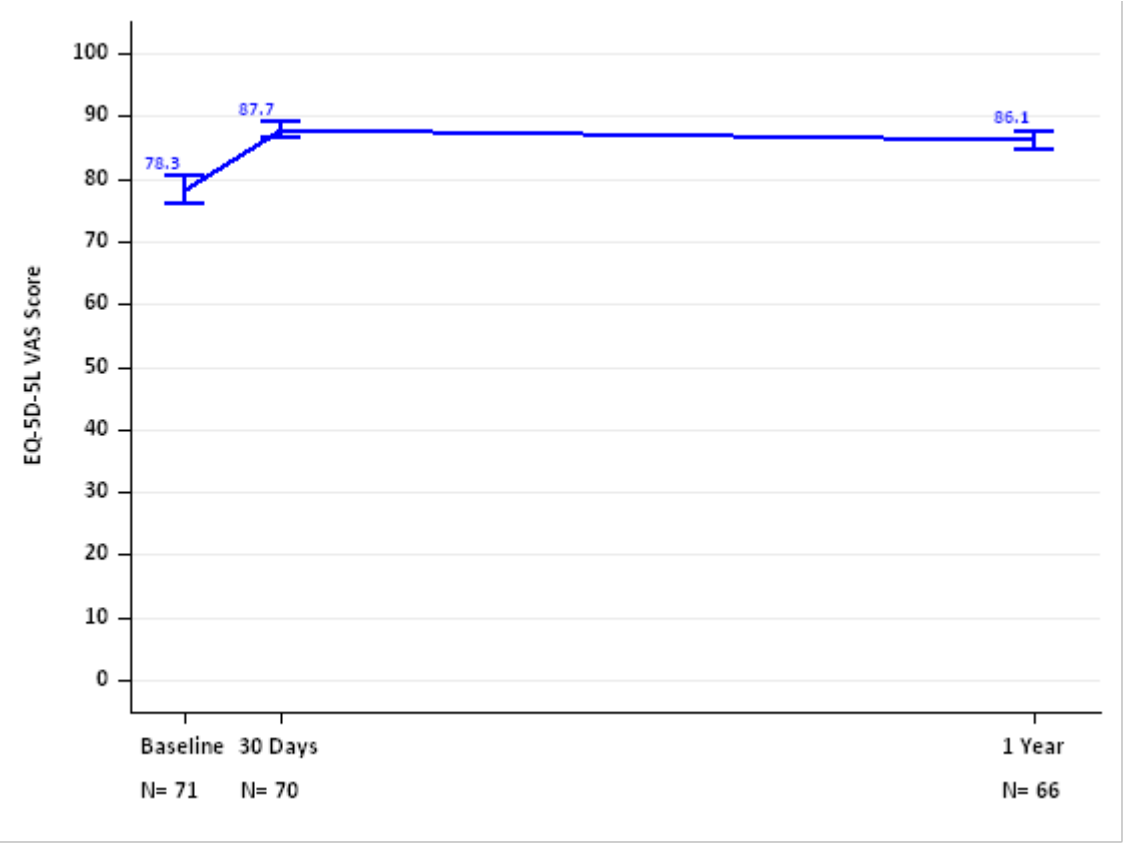


Figure 93: EQ-5D Visual Analog Score (VI Population)

Note: Line plot with mean and standard error. The total number of patients at each visit time point only counted the patients with valid values.

Short Form (SF)-36

The results for the SF-36 physical component summary score and mental component summary score are presented in Figure 94 and Figure 95, respectively.

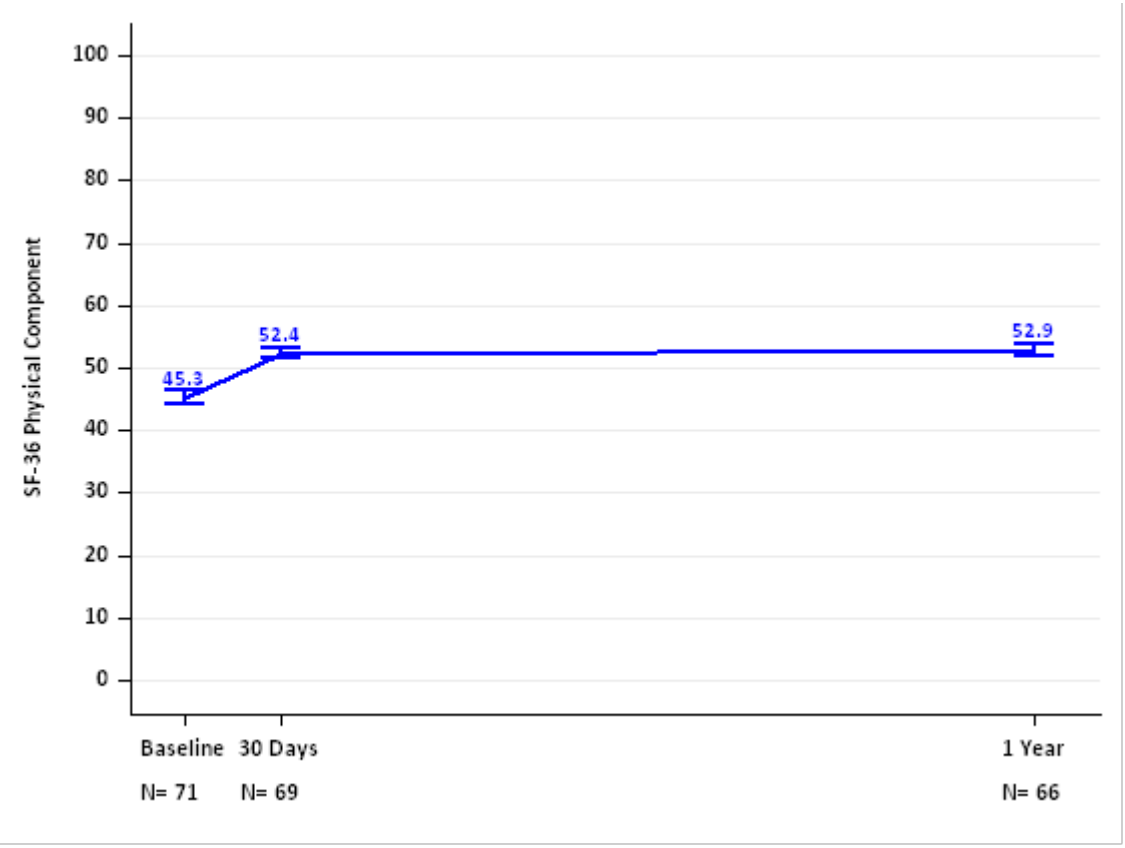


Figure 94: SF-36 Physical Component Summary Score (VI Population)

Note: Line plot with mean and standard error. The total number of patients at each visit time point only counted the patients with valid values.

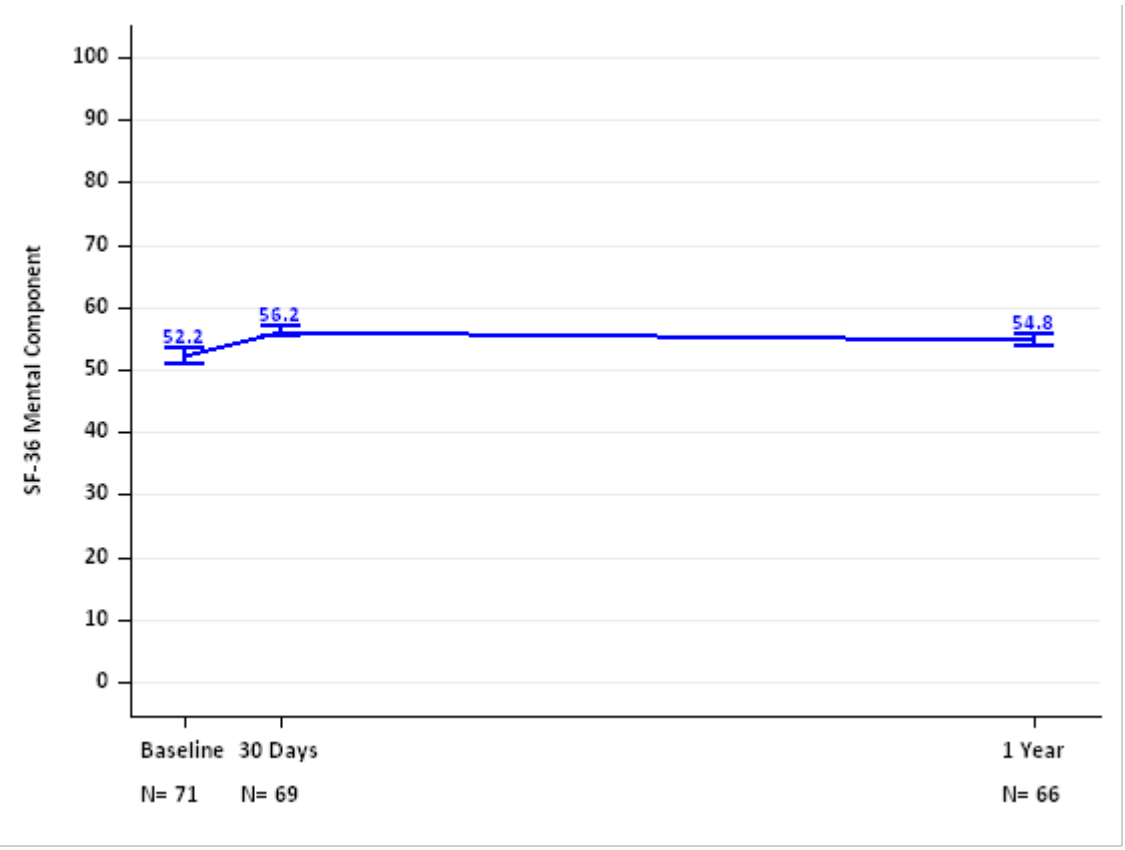


Figure 95: SF-36 Mental Component Summary Score (VI Population)

Note: Line plot with mean and standard error. The total number of patients at each visit time point only counted the patients with valid values.

3. Adverse Events

The Kaplan-Meier estimates of the CEC-adjudicated adverse events through 1 year are shown in Table 78.

Table 78: CEC-Adjudicated Adverse Events through 1 Year (AI Population)

Event	Kaplan-Meier Rate*	
	30 Days	1 Year
All-cause death	0.0% (0, 0)	1.4% (1, 1)
Cardiovascular death	0.0% (0, 0)	1.4% (1, 1)
All stroke	2.8% (2, 2)	2.8% (2, 2)
Disabling stroke	0.0% (0, 0)	0.0% (0, 0)
Non-disabling stroke	2.8% (2, 2)	2.8% (2, 2)
Death or stroke	2.8% (2, 2)	2.8% (3, 2)
Death or disabling stroke	0.0% (0, 0)	1.4% (1, 1)
Major vascular complications	0.0% (0, 0)	0.0% (0, 0)
Life-threatening / disabling, or major bleeding	1.4% (1, 1)	1.4% (1, 1)
Life-threatening /disabling bleeding	0.0% (0, 0)	0.0% (0, 0)
Major bleeding	1.4% (1, 1)	1.4% (1, 1)
Myocardial infarction	0.0% (0, 0)	0.0% (0, 0)
Requirement for renal replacement†	0.0% (0, 0)	0.0% (0, 0)
New permanent pacemaker implantation resulting from new or worsened conduction disturbances‡	9.9% (7, 7)	11.3% (8, 8)
Coronary obstruction requiring intervention	0.0% (0, 0)	0.0% (0, 0)
New onset atrial fibrillation	2.9% (2, 2)	4.4% (3, 3)
Rehospitalization§	4.2% (3, 3)	5.6% (4, 4)

*Kaplan-Meier rate (no. of events, no. of patients with the event).
†Requirement for renal replacement was based on the site-reported event. All the other events were based on the CEC-adjudicated results.
‡Patients with pacemaker or ICD at baseline were not counted as new events.
§Rehospitalization (valve-related or procedure-related and including heart failure).

4. Other Study Observations

Procedural Information

The procedural data are summarized in Table 79. The mean procedure time was 57.5 minutes. Conscious sedation was used in the majority of patients (62.0%).

Table 79: Procedure (AI Population)

Variable	Summary Statistics* (N = 71)
Procedure time (min)	57.5 ± 29.4 (71)
Anesthesia type	
General	36.6% (26/71)

Variable	Summary Statistics* (N = 71)
Conscious sedation	62.0% (44/71)
Conversion from conscious sedation to general anesthesia during the procedure	1.4% (1/71)
Anesthesia time (min)	140.8 ± 47.0 (71)
Concomitant Procedures	12.7% (9/71)
Procedure aborted	0.0% (0/71)
Conversion from TAVR to SAVR	0.0% (0/71)
Valve size	
20 mm	0.0% (0/71)
23 mm	28.2% (20/71)
26 mm	43.7% (31/71)
29 mm	28.2% (20/71)
Successful access, delivery and retrieval of the device delivery system	100.0% (71/71)
Specify arterial access	
Left percutaneous	17.4% (12/69)
Right percutaneous	82.6% (57/69)
Total fluoroscopy time (min)	17.0 ± 11.2 (71)
BAV performed	54.9% (39/71)
Post dilatation performed	19.7% (14/71)
Number of post dilatations	
1	92.9% (13/14)
2	7.1% (1/14)
3	0.0% (0/14)
More than one SAPIEN 3 THV implanted	0.0% (0/71)
*Continuous measures - mean ± SD (n); Categorical measures - % (no./Total no.).	

13.11 SAPIEN 3 THV VALVE-IN-VALVE – STS/ACC TRANSCATHETER VALVE THERAPY REGISTRY (TVTR) ANALYSIS

Patient Accountability

At the time of database extract, of the 314 patients in the aortic valve-in-valve cohort, 299 patients were eligible for the 30-day visit, and 252 (84.3%) patients paid a visit within the 30-day follow-up window defined as the period between the discharge + 1 day or 21 days post-procedure (whichever occurred first) and 75 days post-procedure; of the 311 patients (SAPIEN XT and SAPIEN 3 valve patients combined) in the mitral valve-in-valve cohort, 290 patients were eligible for the 30-day visit, and 244 (84.1%) patients paid a visit within the 30-day follow-up window. A detailed summary of the patient accountability at 30 days for the two cohorts is shown in Table 80.

Table 80: Patient Accountability at 30-Day Follow-Up Visit

	Aortic Valve-in-Valve	Mitral Valve-in-Valve		
		SAPIEN XT	SAPIEN 3	All
Total patients	314	241	70	311
Non-eligible	15	15	6	21
-Death	11	15	4	19

	Aortic Valve-in-Valve	Mitral Valve-in-Valve		
		SAPIEN XT	SAPIEN 3	All
-Withdrawal	0	0	0	0
-Lost to follow-up	1	0	2	2
-Visit not yet due	3	0	0	0
Eligible	299	226	64	290
-Follow-up visit completed	252 (84.3%)	196 (86.7%)	48 (75.0%)	244 (84.1%)
-Missed Visit	47 (15.7%)	30 (13.3%)	16 (25.0%)	46 (15.9%)

The "Attempted Implant" population consisted of all patients for whom the first vascular access was attempted. The "Valve Implant" population consisted of those patients for whom the valve implant procedure has started and a "No" was indicated for both "procedure aborted" and "conversion to open heart surgery." The number of patients in each analysis population of the aortic valve-in-valve and mitral valve-in-valve cohorts is shown in Table 81.

Table 81: Analysis Populations

Analysis Population	Aortic Valve-in-Valve	Mitral Valve-in-Valve		
		SAPIEN XT	SAPIEN 3	All
All Enrolled population	314	241	70	311
Attempted Implant population	314	241	70	311
Valve Implant population	314	236	69	305

Study Population Demographics and Baseline Characteristics

The demographics and baseline characteristics of both the aortic and mitral valve-in-valve patients, as shown in Table 82 and Table 83, present an elderly, multimorbid cohort of patients, consistent with the high operative risk of the populations.

Table 82: Patient Demographics and Baseline Characteristics - Aortic Valve-in-Valve (Attempted Implant Population)

Demographics and Baseline Characteristics	Summary Statistics*
Age – years	74.3 ± 12.10 (313)
Male sex	188/314
Society of Thoracic Surgeons (STS) score	9.0 ± 8.0 (304)
New York Heart Association (NYHA) class	
I/II	45/312 (14.4%)
III/IV	267/312 (85.6%)
Previous myocardial infarction	62/313 (19.8%)
Previous intervention	
Coronary artery bypass grafting (CABG)	119/314 (37.9%)
Percutaneous coronary intervention (PCI)	56/314 (17.8%)
Prior aortic valvuloplasty	10/306 (3.3%)
Cerebrovascular accident (CVA)	46/313 (14.7%)
Peripheral vascular disease	79/314 (25.2%)
Atrial fibrillation	126/314 (40.1%)
Permanent pacemaker	53/314 (16.9%)
Porcelain aorta	19/314 (6.1%)

Demographics and Baseline Characteristics	Summary Statistics*
Hostile chest	58/314 (18.5%)
Echocardiographic findings (Valve Implant Population)	
Valve area - cm^2	0.8 ± 0.4 (230)
Mean aortic-valve gradient – mmHg	39.3 ± 15.8 (251)
Mean left ventricular ejection fraction (LVEF)%	52.2 ± 13.1 (308)
Moderate or severe aortic regurgitation	168/310 (54.2%)
Moderate or severe mitral regurgitation	126/261 (48.3%)
*Continuous measures - Mean ± SD (Total no.); Categorical measures - n. / Total no. (%)	

Table 83: Patient Demographics and Baseline Characteristics - Mitral Valve-in-Valve (Attempted Implant Population)

Demographics and Baseline Characteristics	Summary Statistics*		
	SAPIEN XT	SAPIEN 3	All
Age - years	73.9 ± 12.4 (241)	71.5 ± 15.0 (70)	73.4 ± 13.1 (311)
Male sex	88/241 (36.5%)	32/70 (45.7%)	120/311 (38.6%)
Society of Thoracic Surgeons (STS) score	13.2 ± 9.1 (237)	12.2 ± 8.7 (65)	13.0 ± 8.98 (302)
New York Heart Association (NYHA) class			
I/II	30/238 (12.6%)	3/70 (4.3%)	33/308 (10.7%)
III/IV	208/238 (87.4%)	67/70 (95.7%)	275/308 (89.3%)
Previous myocardial infarction	47/239 (19.7%)	18/70 (25.7%)	65/309 (21.0%)
Previous intervention			
Coronary artery bypass grafting (CABG)	93/236 (39.4%)	28/69 (40.6%)	121/305 (39.7%)
Percutaneous coronary intervention (PCI)	32/238 (13.4%)	9/69 (13.0%)	41/307 (13.4%)
Cerebrovascular accident (CVA)	45/241 (18.7%)	15/70 (21.4%)	60/311 (19.3%)
Peripheral vascular disease	42/239 (17.6%)	6/70 (8.6%)	48/309 (15.5%)
Atrial fibrillation/flutter	155/241 (64.3%)	50/70 (71.4%)	205/311 (65.9%)
Permanent pacemaker	74/240 (30.8%)	20/69 (29.0%)	94/309 (30.4%)
Porcelain aorta	6/240 (2.5%)	1/69 (1.4%)	7/309 (2.3%)
Hostile chest	41/241 (17.0%)	6/70 (8.6%)	47/311 (15.1%)
Echocardiographic findings (Valve Implant Population)			
Mitral valve area - cm^2	1.5 ± 0.9 (153)	1.4 ± 1.0 (46)	1.5 ± 0.88 (199)
Mean mitral-valve gradient - mmHg	12.7 ± 5.5 (215)	13.7 ± 6.2 (65)	12.9 ± 5.65 (280)
Mean left ventricular ejection fraction (LVEF), %	54.4 ± 11.7 (230)	53.8 ± 13.9 (67)	54.3 ± 12.2 (297)
Moderate or severe aortic regurgitation	35/231 (15.2%)	7/67 (10.5%)	42/298 (14.1%)
Moderate or severe mitral regurgitation	149/233 (63.9%)	39/68 (57.4%)	188/301 (62.5%)
*Continuous measures - Mean ± SD (Total no.); categorical measures - n. / Total no. (%). The total no. only counted the patients with valid values.			

Safety and Effectiveness Results

Aortic Valve-in-Valve

Safety Endpoints

The mortality rates at discharge and 30 days and the Kaplan-Meier curve for all-cause mortality for the aortic valve-in-valve cohort are shown in Table 84 and Figure 102, respectively. There were a total of 12 deaths reported at 30 days.

Table 84: Death Rate - Aortic Valve-in-Valve (Attempted Implant Population)

	Discharge*	30 Days†
All-cause death	2.5% (8)	4.5% (12)
Cardiac death	1.3% (4)	2.2% (6)

*Observed rate - % (n)
†Kaplan-Meier estimate - % (n)

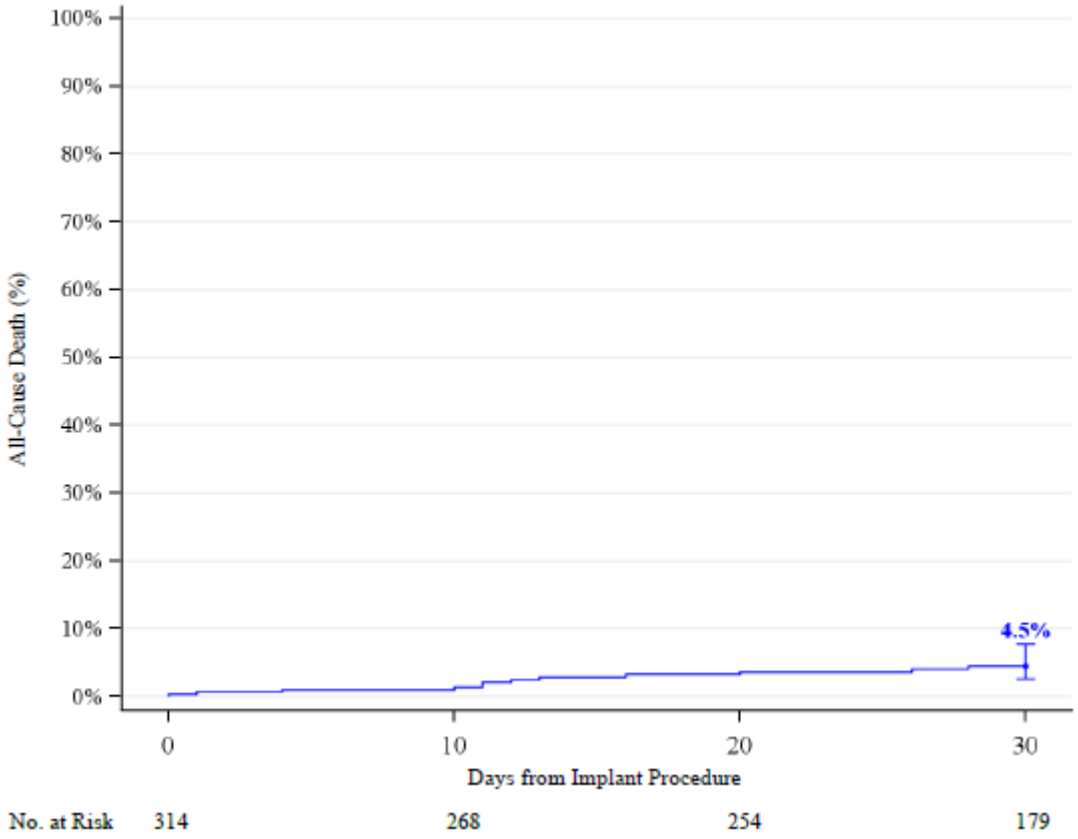


Figure 96: All-Cause Death Rate - Aortic Valve-in-Valve (Attempted Implant Population)

The DCRI adjudicated events, including all strokes/TIAs and aortic valve reinterventions at discharge and 30 days for the aortic valve-in-valve cohort, are shown in Table 85.

Table 85: Duke Clinical Research Institute Adjudicated Events - Aortic Valve-in-Valve (Attempted Implant Population)

Events	Discharge*	30 Days†
All stroke	1.0% (3, 3)	1.0% (3, 3)
Ischemic stroke	1.0% (3, 3)	1.0% (3, 3)
Hemorrhagic stroke	0.0% (0, 0)	0.0% (0, 0)
Transient ischemic attack (TIA)	0.0% (0, 0)	0.0% (0, 0)

Events	Discharge*	30 Days†
Aortic valve reintervention	0.3% (1, 1)	0.3% (1, 1)

*Observed rate - % (no. of events, no. of subjects with the event)
†Kaplan-Meier estimate - % (no. of events, no. of subjects with the event)

Site Reported Adverse Events

The site reported adverse events at discharge and 30 days for the aortic valve-in-valve cohort are shown in Table 86.

Table 86: Site Reported Adverse Events - Aortic Valve-in-Valve (Attempted Implant Population)

Events	Discharge*	30 Days†
Non-valve related readmission	N/A	5.9% (15, 15)
Minor vascular complication	3.8% (12, 12)	4.3% (13, 13)
Conduction/native pacer disturbance requiring pacer	2.9% (9, 9)	3.0% (9, 9)
Hematoma at access site	2.9% (9, 9)	2.9% (9, 9)
Atrial fibrillation	2.5% (8, 8)	2.6% (8, 8)
Bleeding at access site	2.5% (8, 8)	2.5% (8, 8)
Cardiac arrest	2.5% (8, 8)	2.5% (8, 8)
Unplanned vascular surgery or intervention	1.6% (5, 5)	2.0% (7, 6)
Percutaneous coronary intervention (PCI)	1.3% (4, 4)	1.7% (5, 5)
Other bleed	1.3% (4, 4)	1.3% (4, 4)
Coronary compression or obstruction	1.0% (3, 3)	1.0% (3, 3)
Hemorrhagic stroke	0.6% (2, 2)	1.1% (3, 3)
Life threatening bleeding	N/A	1.1% (3, 3)
Unplanned other cardiac surgery or intervention	1.0% (3, 3)	1.0% (3, 3)
Major bleeding event	N/A	0.8% (2, 2)
Major vascular complication	0.6% (2, 2)	0.6% (3, 2)
Myocardial infarction	0.3% (1, 1)	0.7% (2, 2)
New requirement for dialysis	0.6% (2, 2)	0.8% (2, 2)
Other device related event	0.6% (2, 2)	0.6% (2, 2)
Aortic valve re-intervention	0.0% (0, 0)	0.4% (1, 1)
Conduction/native pacer disturbance requiring implantable cardioverter defibrillator (ICD)	0.3% (1, 1)	0.3% (1, 1)
Device migration	0.3% (1, 1)	0.3% (1, 1)
Gastrointestinal bleeding (GI) bleed	0.3% (1, 1)	0.3% (1, 1)
Transapical related event	0.3% (1, 1)	0.3% (1, 1)
Valve related readmission	N/A	0.4% (1, 1)
Device thrombosis	0.0% (0, 0)	0.0% (0, 0)

*Observed rate - % (no. of events, no. of subjects with the event)
†Kaplan-Meier estimate - % (no. of events, no. of subjects with the event)

Effectiveness Endpoints

Valve Performance

The aortic valve-in-valve echocardiographic performance data are summarized in Figure 97 to Figure 99. The mean gradients improved from 39.3 ± 15.8 mmHg at baseline to 21.5 ± 11.3 mmHg at 30 days. Moderate/severe aortic regurgitation was observed in 54.2% of the patients at baseline, which decreased to 1.5% of the patients at 30 days.

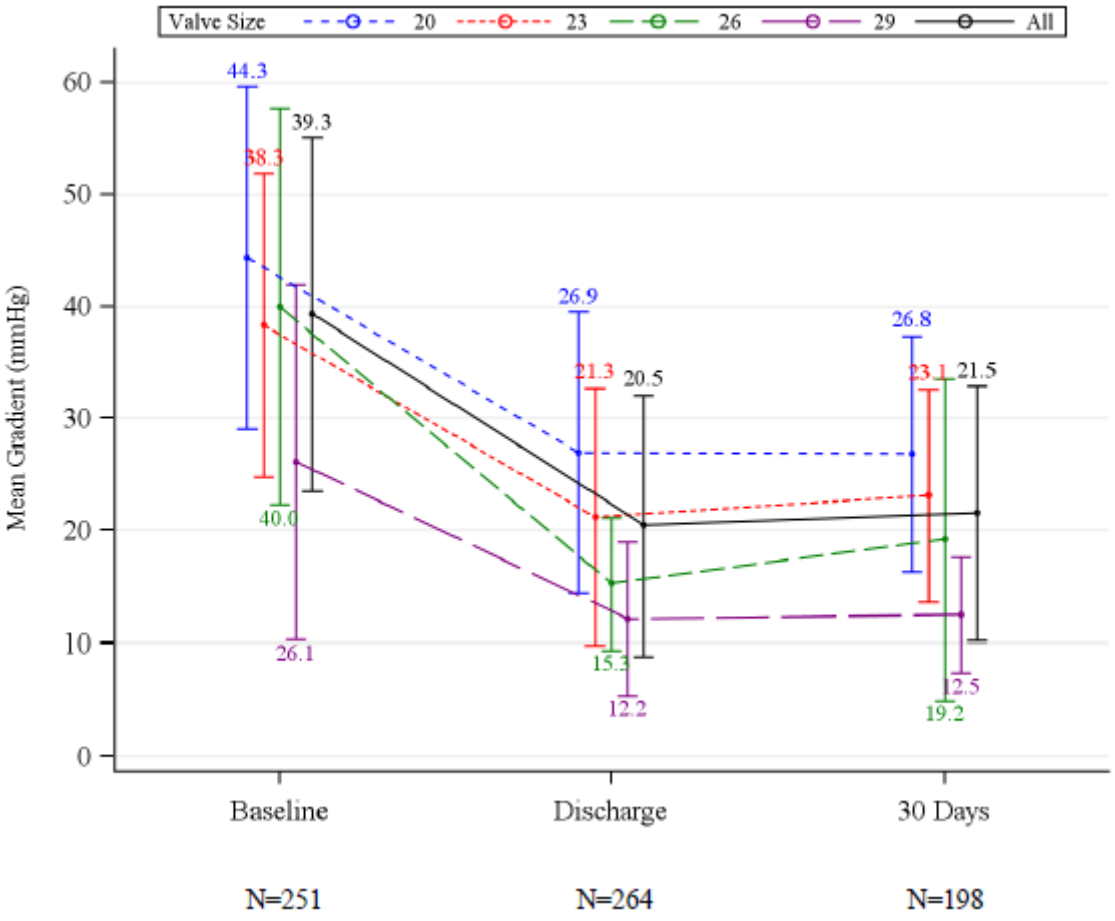


Figure 97: Mean Gradient by Visit - Aortic Valve-in-Valve (Valve Implant Population)

Note: Line plot with mean and standard deviation. The total number of patients at each time point only counted the patients with valid values.

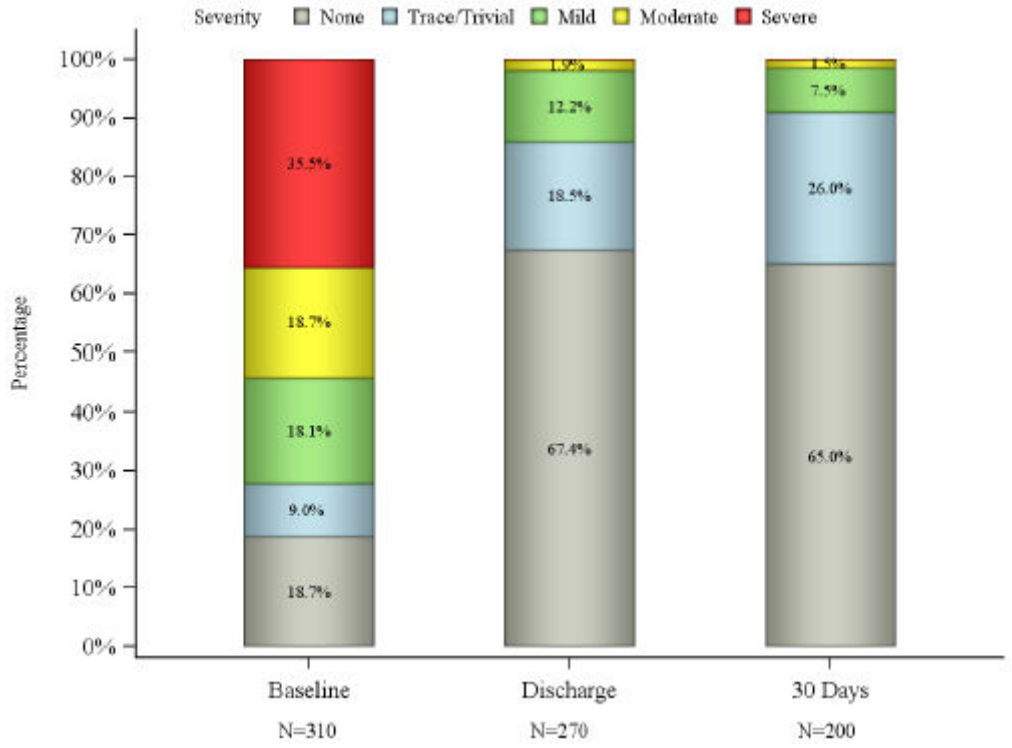


Figure 98: Aortic Regurgitation by Visit - Aortic Valve-in-Valve (Valve Implant Population)

Note: Line plot with mean and standard deviation. The total number of patients at each time point only counted the patients with valid values.

Note: The total number of patients at each time point only counted the patients with valid values.

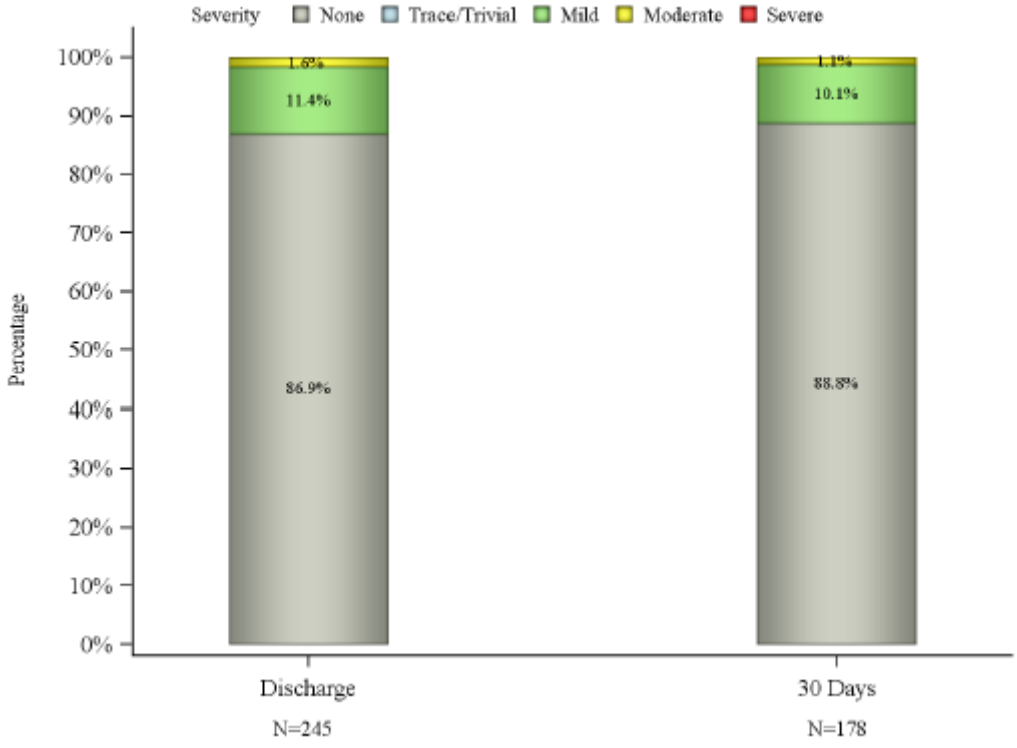


Figure 99: Paravalvular Regurgitation by Visit - Aortic Valve-in-Valve (Valve Implant Population)

Note: The total number of patients at each time point only counted the patients with valid values.

New York Heart Association Class

The NYHA class distributions at baseline and the 30-day visit and the NYHA class changes from baseline to the 30-day visit are shown in Figure 100 and Table 87, respectively. The majority (85.4%) of the patients had an improved NYHA class at the 30-day visit.

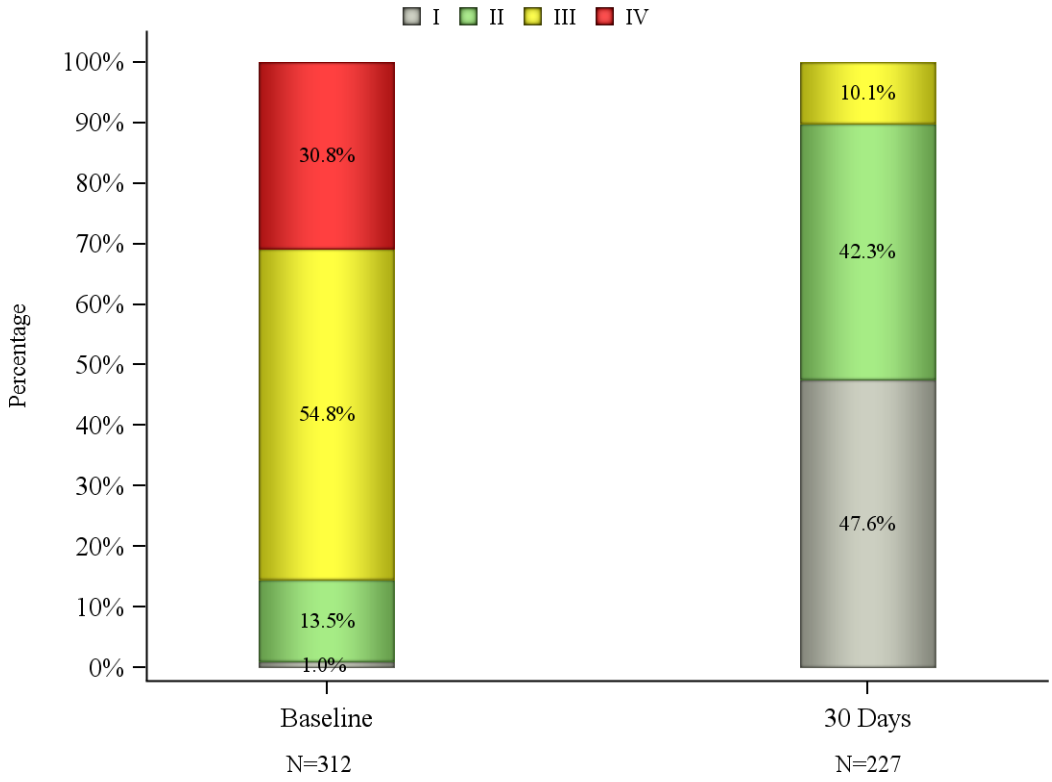


Figure 100: NYHA Functional Class - Aortic Valve-in-Valve (Valve Implant Population)

Note: The total number of patients at each time point only counted the patients with valid values.

Table 87: NYHA Class Change - Aortic Valve-in-Valve (Valve Implant Population)

	NYHA Class Change*		
	Improved	**Same**	**Worsened**
Baseline to 30-day visit	193/226 (85.4%)	31/226 (13.7%)	2/226 (0.9%)
*n/Total no. (%); the total no. only counted the patients with valid values.			

Five-Meter Walk Test

The results of the five-meter walk test are summarized in Table 88.

Table 88: Five-Meter Walk Test - Aortic Valve-in-Valve (Valve Implant Population)

Visit*	Five Meter Walk Time (seconds)†
Baseline	7.6 ± 3.9 (209)
30-day visit	5.9 ± 2.4 (68)
Change from baseline to 30-day visit	-1.4 ± 2.9 (51)
*There were up to 3 five-meter walk tests for each patient at each visit, and the results were averaged. †Mean ± SD (Total no.). The total number of patients at each time point only counted the patients with valid values.	

Length of Stay

The mean index hospitalization stay was 4.9 days, which included an average of 1.8 days in the intensive care unit (ICU), as summarized in Table 89.

Table 89: Index Hospitalization Stay - Aortic Valve-in-Valve (Attempted Implant Population)

	Length (days)*
Index Hospitalization Stay	4.9 ± 3.9 (314)
Intensive Care Stay	1.8 ± 2.6 (311)
*Mean ± SD (Total no.).	

Quality of Life (QoL)

The QoL at baseline and 30 days as measured by the KCCQ clinical summary score is shown in Figure 101. The mean KCCQ summary score improved from 39.4 at baseline to 75.3 at 30 days.

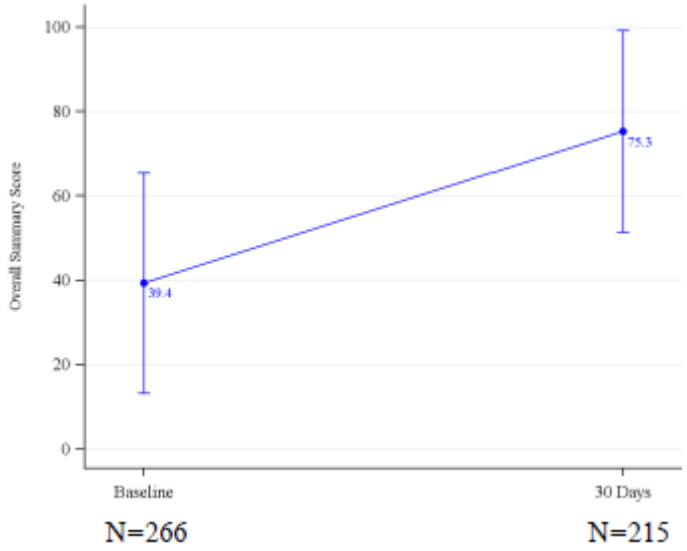


Figure 101: KCCQ Overall Summary Score - Aortic Valve-in-Valve (Valve Implant Population)

Note: Line plot with mean and standard deviation. The total number of patients at each time point only counted the patients with valid values.

Procedural Information

The procedure information is presented in Table 90. The most common delivery approach for the aortic valve-in-valve implantation was the transfemoral approach, which was used in 93.0% (292/314) of cases, followed by the transapical approach in 4.1% (13/314) of cases, and other alternative approaches (transaortic, subclavian, and other) in 2.9% (9/314) of cases. There were no aborted procedures or conversions to open heart surgery. The overall device success rate was 88.9% (272/306), which was defined as the following:

- Successful vascular access, delivery, and deployment of the device and successful retrieval of the delivery system, and
- Correct position of the device in the proper anatomical location, and
- Intended performance of the prosthetic heart valve (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 regurgitation), and
- Only one valve implanted in the proper anatomical location.

Table 90: Procedural Data Summary - Aortic Valve-in-Valve (Attempted Implant Population)

Procedural Data	Summary Statistics*
Operator Reason for Procedure	

Procedural Data	Summary Statistics*
Inoperable/extreme risk	80/313 (25.6%)
High risk	219/313 (70.0%)
Intermediate risk	10/313 (3.2%)
Low risk	4/313 (1.3%)
Implant Approach	
Transfemoral	292/314 (93.0%)
Transapical	13/314 (4.1%)
Transaortic	1/314 (0.3%)
Subclavian/axillary	6/314 (1.9%)
Other†	2/314 (0.6%)
Prior Valve Type	
Bioprosthetic stented	159/308 (51.6%)
Bioprosthetic stentless	79/308 (25.6%)
Procedure Status	
Elective	231/314 (73.6%)
Urgent	74/314 (23.6%)
Emergency	8/314 (2.5%)
Salvage	1/314 (0.3%)
Valve Size	
20 mm	83/314 (26.4%)
23 mm	130/314 (41.4%)
26 mm	57/314 (18.2%)
29 mm	44/314 (14.0%)
Primary Procedure Indication	
Aortic stenosis (Primary)	95/313 (30.4%)
Aortic insufficiency (Primary)	19/313 (6.1%)
Mixed aortic stenosis/aortic insufficiency	10/313 (3.2%)
Failed bioprosthetic valve	189/313 (60.4%)
Cardiopulmonary Bypass (CPB)	5/314 (1.6%)
CPB status	
Elective	4/5 (80.0%)
Emergent	1/5 (20.0%)
CPB time (min)	90.5 ± 140.9 (4)
Type of Anesthesia	
General anesthesia	240/314 (76.4%)
Moderate sedation	72/314 (22.9%)
Epidural	0/314 (0.0%)
Combination	2/314 (0.6%)

Procedural Data	Summary Statistics*
Total procedure time (min)	110.7 ± 63.0 (314)
Fluoroscopy time (min)	21.2 ± 16.1 (304)
Device success	272/306 (88.9%)
Procedure aborted	0/314 (0.0%)
Conversion to open heart surgery	0/314 (0.0%)
Mechanical assist device in place at start of procedure	5/313 (1.6%)
Intra-aortic balloon pump (IABP)	2/5 (40.0%)
Catheter based assist device	3/5 (60.0%)

*Categorical measures – no./Total no. (%); continuous measures - mean ± SD (Total no.). The total no. only counted the patients with valid values at the time point.
†The data collection form was changed in February 2013 to specify non-transfemoral (non-TF), non-transapical (non-TA) approaches rather than "other"; hence, "other" likely included the non-TF and non-TA approaches.

Mitral Valve-in-Valve

Safety Endpoints

The mortality rates at discharge and 30 days and the Kaplan-Meier curve for all-cause mortality for the mitral valve-in-valve cohort are shown in Table 91 and Figure 102, respectively. There were 16 reported deaths in the SAPIEN XT valve patients and 4 in the SAPIEN 3 valve patients at 30 days.

Table 91: Death Rate - Mitral Valve-in-Valve (Attempted Implant Population)

Event	Discharge*			30 Days†		
	SAPIEN XT	SAPIEN 3	All	SAPIEN XT	SAPIEN 3	All
All-cause death	5.0% (12)	5.7% (4)	5.1% (16)	6.9% (16)	6.6% (4)	6.8% (20)
Cardiac death	3.7% (9)	4.3% (3)	3.9% (12)	4.2% (10)	4.9% (3)	4.3% (13)

*Observed rate - % (n)

†Kaplan-Meier estimate - % (n)

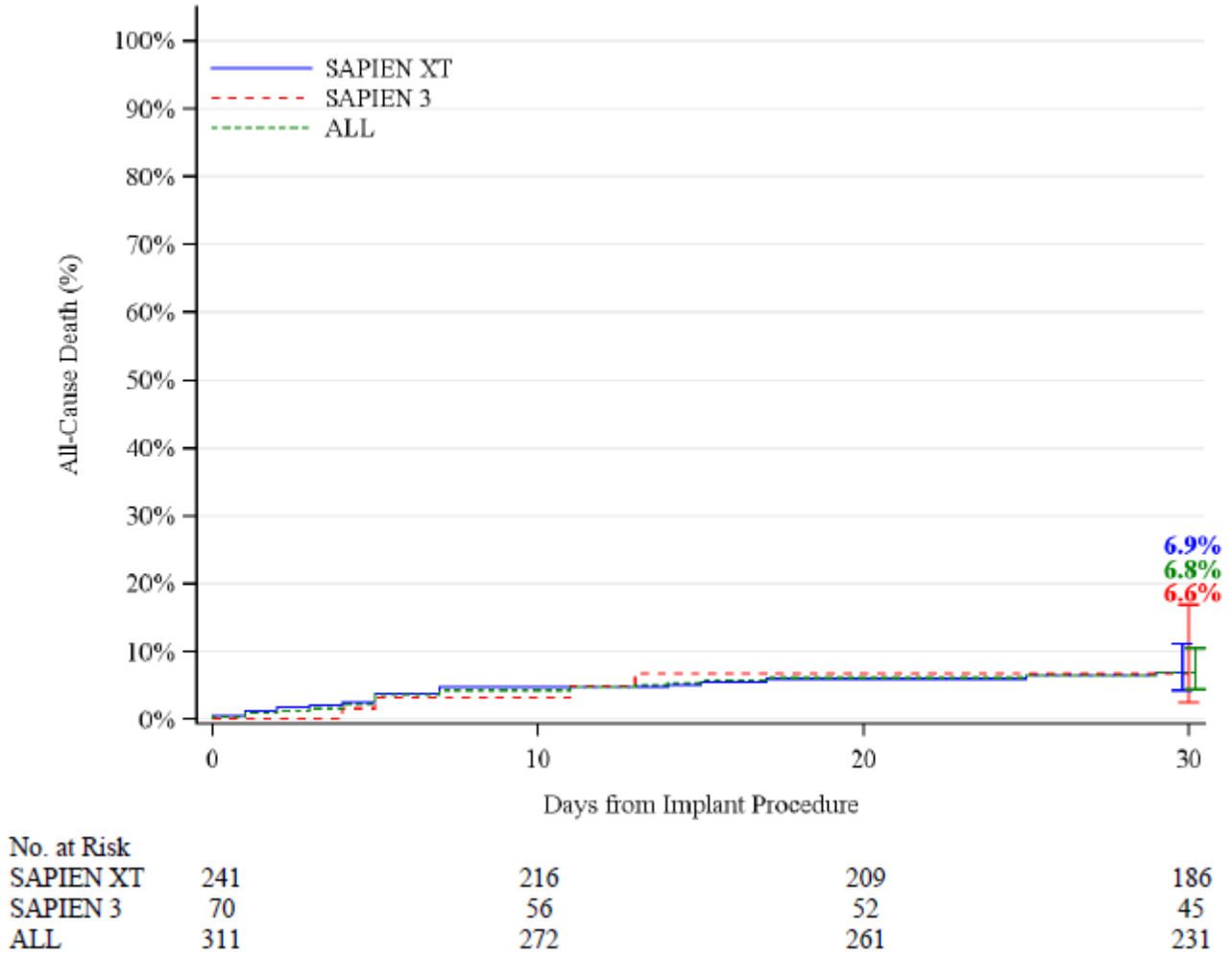


Figure 102: All-Cause Death Rate - Mitral Valve-in-Valve (Attempted Implant Population)

The DCRI-adjudicated events, including all strokes/TIAs, heart failure readmissions, and mitral valve reinterventions at discharge and 30 days, for the mitral valve-in-valve cohort are shown in Table 92.

Table 92: Duke Clinical Research Institute Adjudicated Events - Mitral Valve-in-Valve (Attempted Implant Population)

Events	Discharge*			30 Days†		
	SAPIEN XT	SAPIEN 3	All	SAPIEN XT	SAPIEN 3	All
All stroke	0.4% (1, 1)	1.4% (1, 1)	0.6% (2, 2)	0.4% (1, 1)	1.5% (1, 1)	0.7% (2, 2)
Ischemic stroke	0.4% (1, 1)	1.4% (1, 1)	0.6% (2, 2)	0.4% (1, 1)	1.5% (1, 1)	0.7% (2, 2)
Hemorrhagic stroke	0.0% (0, 0)	0.0% (0, 0)	0.0% (0, 0)	0.0% (0, 0)	0.0% (0, 0)	0.0% (0, 0)
Transient ischemic attack (TIA)	0.0% (0, 0)	0.0% (0, 0)	0.0% (0, 0)	0.0% (0, 0)	0.0% (0, 0)	0.0% (0, 0)
Readmission - heart failure	N/A	N/A	N/A	1.0% (2, 2)	0.0% (0, 0)	0.8% (2, 2)
Mitral valve reintervention	0.0% (0, 0)	0.0% (0, 0)	0.0% (0, 0)	0.5% (1, 1)	0.0% (0, 0)	0.4% (1, 1)

*Observed rate - % (no. of events, no. of subjects with the event)
†Kaplan-Meier estimate - % (no. of events, no. of subjects with the event)

Site Reported Adverse Events

The site reported adverse events at discharge and 30 days for the mitral valve-in-valve cohort are shown in Table 93.

Table 93: Site Reported Adverse Events - Mitral Valve-in-Valve (Attempted Implant Population)

Events	Discharge*			30 Days†		
	SAPIEN XT	SAPIEN 3	All	SAPIEN XT	SAPIEN 3	All
Other bleed	5.4% (13, 13)	4.3% (3, 3)	5.1% (16, 16)	6.1% (14, 14)	4.4% (3, 3)	5.8% (17, 17)
Readmission - not cardiac	N/A	N/A	N/A	5.8% (12, 12)	0.0% (0, 0)	4.6% (12, 12)
Atrial septal defect closure following transseptal catheterization	4.6% (11, 11)	5.7% (4, 4)	4.8% (15, 15)	4.6% (11, 11)	5.7% (4, 4)	4.9% (15, 15)
Cardiac arrest	4.1% (10, 10)	2.9% (2, 2)	3.9% (12, 12)	4.2% (10, 10)	3.2% (2, 2)	4.0% (12, 12)
Unplanned other cardiac surgery or intervention	3.3% (8, 8)	0.0% (0, 0)	2.6% (8, 8)	3.8% (9, 9)	0.0% (0, 0)	3.0% (9, 9)
Atrial fibrillation	3.3% (8, 8)	1.4% (1, 1)	2.9% (9, 9)	3.4% (8, 8)	1.5% (1, 1)	2.9% (9, 9)
New requirement for dialysis	2.9% (7, 7)	1.4% (1, 1)	2.6% (8, 8)	3.0% (7, 7)	1.6% (1, 1)	2.7% (8, 8)
Bleeding at access site	2.5% (6, 6)	1.4% (1, 1)	2.3% (7, 7)	2.5% (6, 6)	1.4% (1, 1)	2.3% (7, 7)
Unplanned vascular surgery or intervention	2.5% (6, 6)	2.9% (2, 2)	2.6% (8, 8)	2.5% (6, 6)	3.2% (2, 2)	2.6% (8, 8)
Perforation with or w/o tamponade	2.1% (5, 5)	0.0% (0, 0)	1.6% (5, 5)	2.1% (5, 5)	0.0% (0, 0)	1.6% (5, 5)
Hematoma at access site	1.2% (3, 3)	0.0% (0, 0)	1.0% (3, 3)	1.3% (3, 3)	0.0% (0, 0)	1.0% (3, 3)
Minor vascular complication	1.2% (3, 3)	1.4% (1, 1)	1.3% (4, 4)	1.2% (3, 3)	1.7% (1, 1)	1.3% (4, 4)
Transapical related event	1.2% (3, 3)	0.0% (0, 0)	1.0% (3, 3)	1.2% (3, 3)	0.0% (0, 0)	1.0% (3, 3)
Transseptal related event	1.2% (3, 3)	0.0% (0, 0)	1.0% (3, 3)	1.2% (3, 3)	0.0% (0, 0)	1.0% (3, 3)
Gastrointestinal bleed	0.8% (2, 2)	1.4% (1, 1)	1.0% (3, 3)	0.9% (2, 2)	1.4% (1, 1)	1.1% (3, 3)
Major vascular complication	0.8% (2, 2)	0.0% (0, 0)	0.6% (2, 2)	0.8% (2, 2)	0.0% (0, 0)	0.6% (2, 2)
Readmission - cardiac	N/A	N/A	N/A	0.9% (2, 2)	0.0% (0, 0)	0.8% (2, 2)
Device embolization	0.0% (0, 0)	0.0% (0, 0)	0.0% (0, 0)	0.5% (1, 1)	0.0% (0, 0)	0.4% (1, 1)
Device migration	0.0% (0, 0)	1.4% (1, 1)	0.3% (1, 1)	0.5% (1, 1)	1.4% (1, 1)	0.7% (2, 2)
Device recapture or retrieval	0.0% (0, 0)	1.4% (1, 1)	0.3% (1, 1)	0.5% (1, 1)	1.4% (1, 1)	0.7% (2, 2)
Genitourinary bleed	0.4% (1, 1)	0.0% (0, 0)	0.3% (1, 1)	0.4% (1, 1)	0.0% (0, 0)	0.3% (1, 1)
Major bleeding event	N/A	N/A	N/A	0.5% (1, 1)	0.0% (0, 0)	0.4% (1, 1)

Events	Discharge*			30 Days†		
	SAPIEN XT	SAPIEN 3	All	SAPIEN XT	SAPIEN 3	All
Non-valve related readmission	N/A	N/A	N/A	0.5% (1, 1)	0.0% (0, 0)	0.4% (1, 1)
Conduction/native pacer disturbance requiring pacer	0.0% (0, 0)	1.4% (1, 1)	0.3% (1, 1)	0.0% (0, 0)	1.5% (1, 1)	0.3% (1, 1)
Device thrombosis	0.0% (0, 0)	0.0% (0, 0)	0.0% (0, 0)	0.0% (0, 0)	0.0% (0, 0)	0.0% (0, 0)
Endocarditis	0.0% (0, 0)	0.0% (0, 0)	0.0% (0, 0)	0.0% (0, 0)	0.0% (0, 0)	0.0% (0, 0)
Life threatening bleeding	N/A	N/A	N/A	0.0% (0, 0)	0.0% (0, 0)	0.0% (0, 0)
Myocardial infarction	0.0% (0, 0)	1.4% (1, 1)	0.3% (1, 1)	0.0% (0, 0)	1.4% (1, 1)	0.3% (1, 1)
Other device related event	0.0% (0, 0)	1.4% (1, 1)	0.3% (1, 1)	0.0% (0, 0)	1.4% (1, 1)	0.3% (1, 1)
Transient ischemic attack	0.4% (1, 1)	0.0% (0, 0)	0.3% (1, 1)	0.4% (1, 1)	0.0% (0, 0)	0.3% (1, 1)
Ischemic stroke	0.4% (1, 1)	1.4% (1, 1)	0.6% (2, 2)	0.4% (1, 1)	1.5% (1, 1)	0.7% (2, 2)
Readmission - heart failure	N/A	N/A	N/A	1.0% (2, 2)	3.8% (2, 2)	1.6% (4, 4)

*Observed rate, % (no. of events, no. of subjects with the event).
†Kaplan-Meier estimate, % (no. of events, no. of subjects with the event).

Effectiveness Endpoints

Valve Performance

The mitral valve-in-valve echocardiographic performance data are summarized in Figure 103 to Figure 105. The mean gradients improved from 12.9 mmHg at baseline to 7.1 mmHg at 30 days. Moderate/severe mitral regurgitation was observed in 62.5% of the patients at baseline, which decreased to 2.2% of the patients at 30 days.

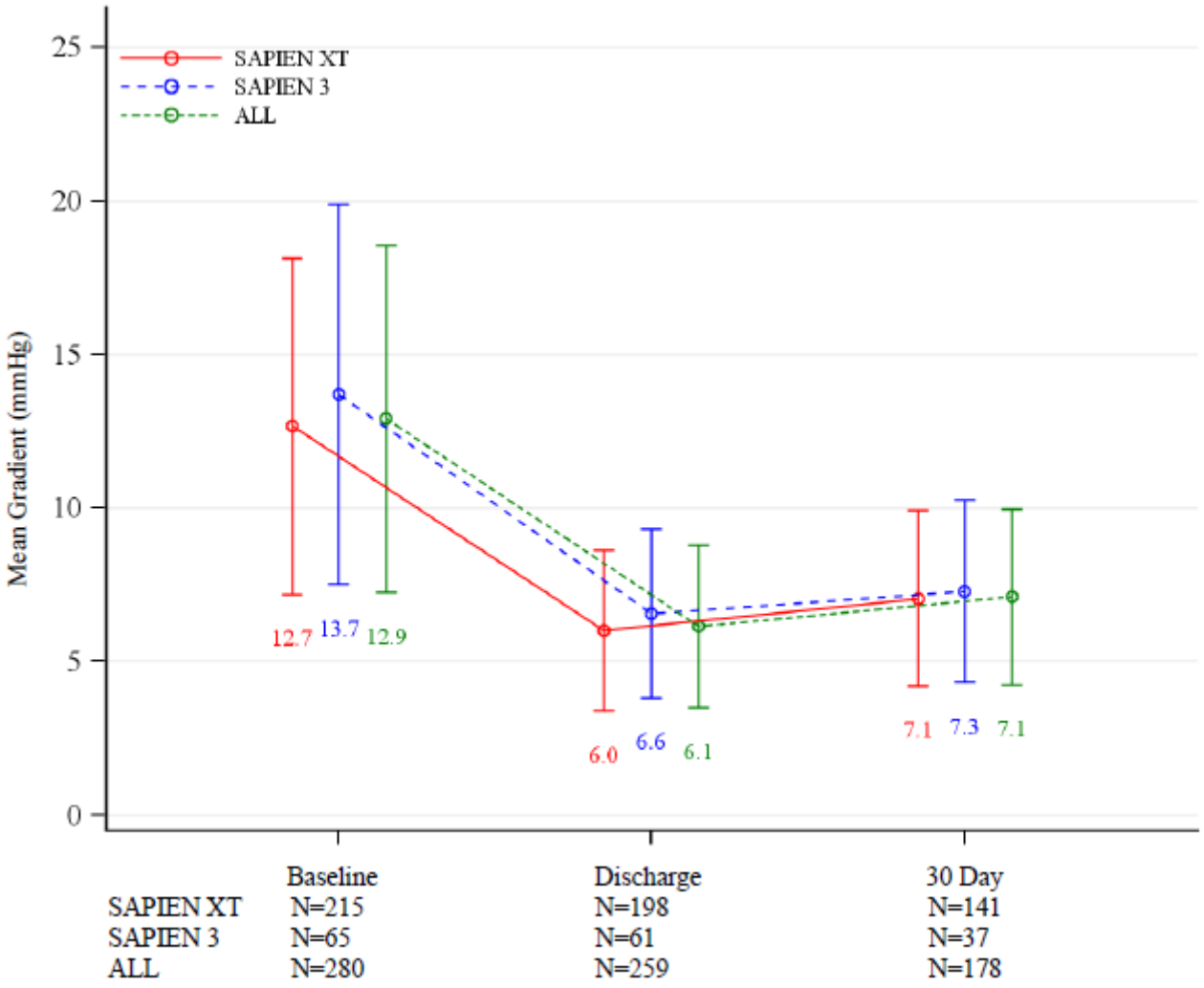


Figure 103: Mean Gradient by Visit - Mitral Valve-in-Valve (Valve Implant Population)

Note: Line plot with mean and standard deviation. The total number of patients at each time point only counted the patients with valid values.

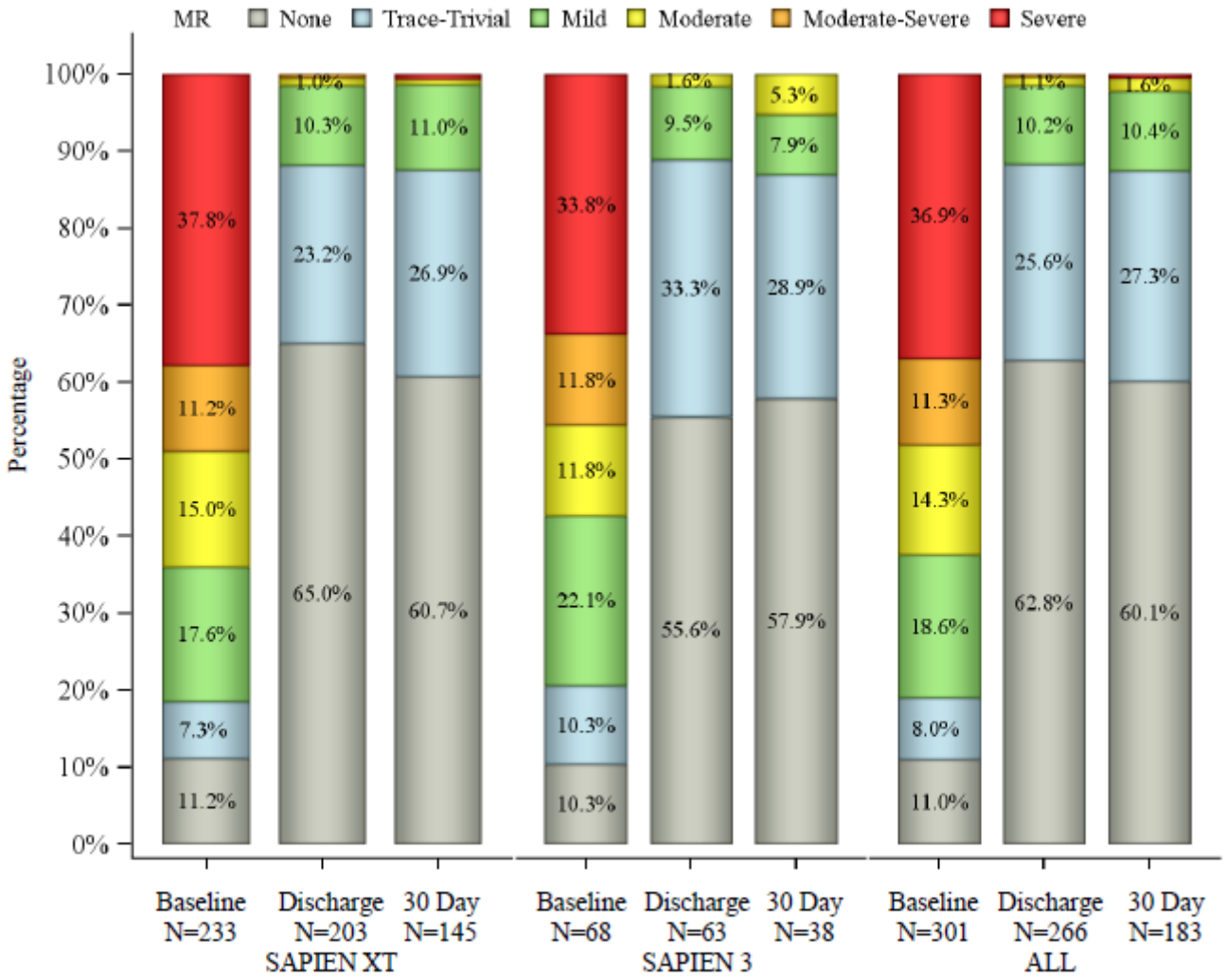


Figure 104: Mitral Regurgitation by Visit - Mitral Valve-in-Valve (Valve Implant Population)

Note: Values that are < 1.0% are not labeled in the bar chart. The total number of patients at each time point only counted the patients with valid values.

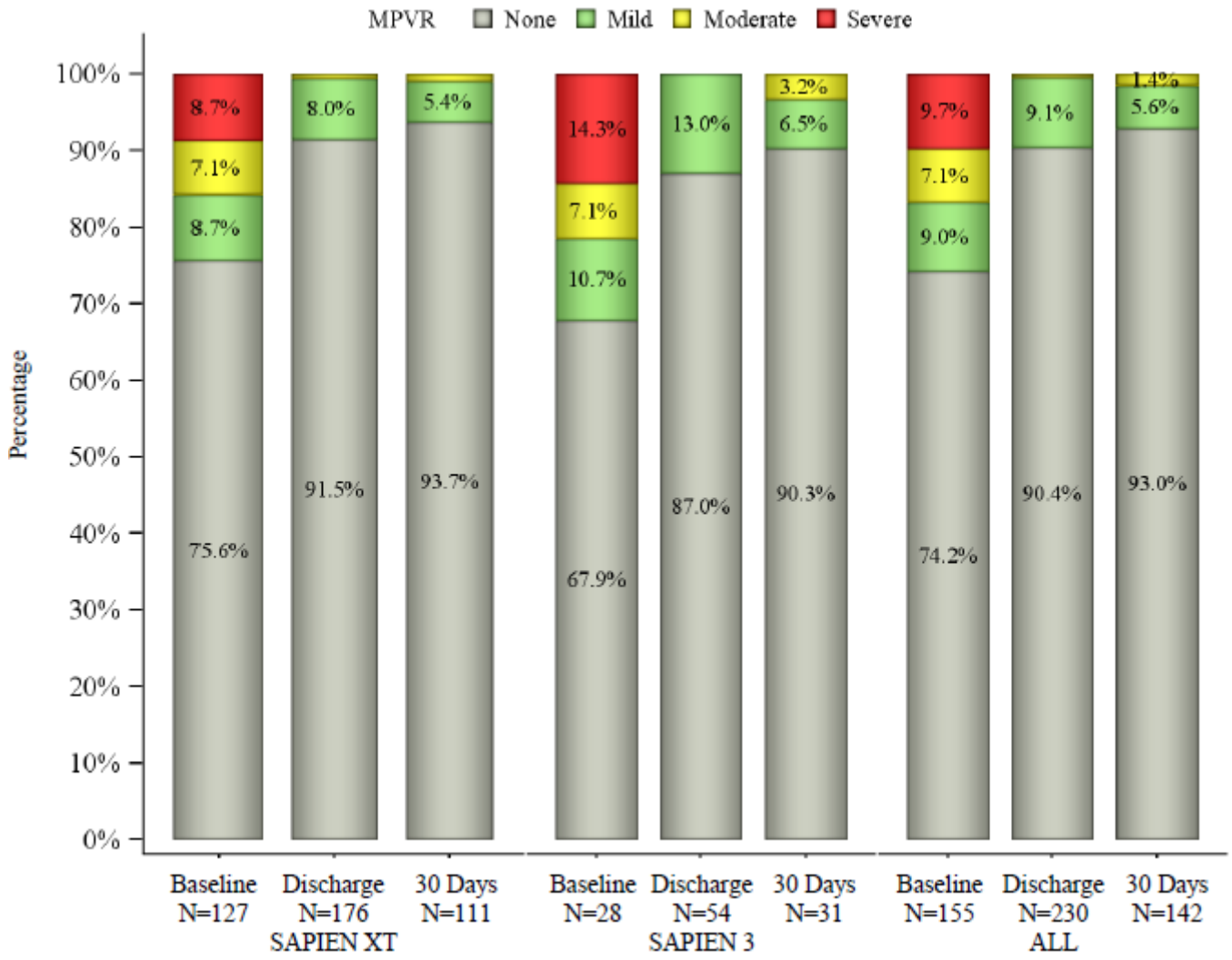


Figure 105: Paravalvular Regurgitation by Visit - Mitral Valve-in-Valve (Valve Implant Population)

Note: Values that are < 1.0% are not labeled in the bar chart. The total number of patients at each time point only counted the patients with valid values.

New York Heart Association Class

The NYHA class distributions at baseline and the 30-day visit and the NYHA class changes from baseline to the 30-day visit are shown in Figure 106 and Table 94, respectively. The majority (85.6%) of the patients had an improved NYHA class at the 30-day visit.

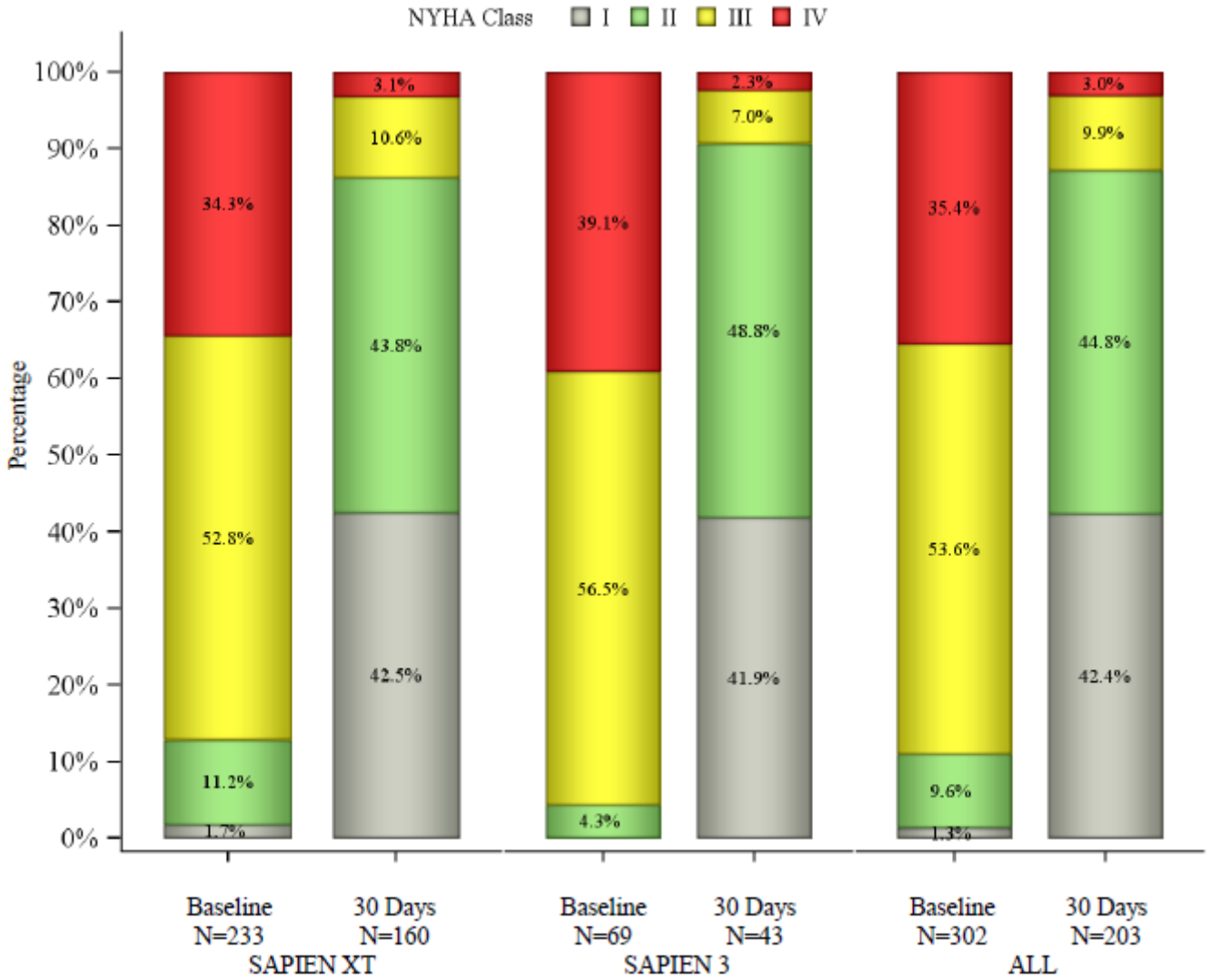


Figure 106: NYHA Functional Class - Mitral Valve-in-Valve (Valve Implant Population)

Note: The total number of patients at each time point only counted the patients with valid values.

Table 94: NYHA Class Change - Mitral Valve-in-Valve (Valve Implant Population)

		NYHA Class Change*		
		Improved	**Same**	**Worsened**
Baseline to 30-day visit	SAPIEN XT	133/159 (83.6%)	24/159 (15.1%)	2/159 (1.3%)
	SAPIEN 3	40/43 (93.0%)	3/43 (7.0%)	0/43 (0.0%)
	All	173/202 (85.6%)	27/202 (13.4%)	2/202 (1.0%)

*n/Total no. (%); the total no. only counted the patients with valid values.

Six-Minute Walk Test (6MWT)

The results of the 6MWT are summarized in Table 95.

Table 95: Six-Minute Walk Test - Mitral Valve-in-Valve (Valve Implant Population)

Visit	6-Minute Walk Distance (feet)*		
	SAPIEN XT	SAPIEN 3	All
Baseline	240.5 ± 366.2 (77)	375.6 ± 370.4 (32)	280.2 ± 370.9 (109)
30-day visit	768.7 ± 480.6 (34)	977.5 ± 597.4 (8)	808.5 ± 503.7 (42)
Change from baseline to 30 days	479.0 ± 471.3 (20)	457.6 ± 348.1 (5)	474.7 ± 442.9 (25)

*Mean ± SD (Total no.). The total number of patients at each time point only counted the patients with valid values. The 6-minute walk distance was counted as 0 for the 6-minute walk tests not performed due to cardiac reasons.

Length of Stay

The mean index hospitalization stay was 8.5 days, which included an average of 3.4 days in the intensive care unit (ICU), as summarized in Table 96.

Table 96: Index Hospitalization Stay - Mitral Valve-in-Valve (Attempted Implant Population)

	Length (days)		
	SAPIEN XT	SAPIEN 3	All
Index hospitalization stay	8.8 ± 7.1 (241)	7.6 ± 7.4 (70)	8.5 ± 7.1 (311)
Intensive care stay	3.3 ± 4.8 (234)	3.7 ± 7.1 (63)	3.4 ± 5.3 (297)

*Mean ± SD (Total no.).

Quality of Life (QoL)

The KCCQ clinical summary scores at baseline and 30 days are shown in Figure 107. The mean KCCQ summary score improved from 31.6 at baseline to 68.2 at 30 days.

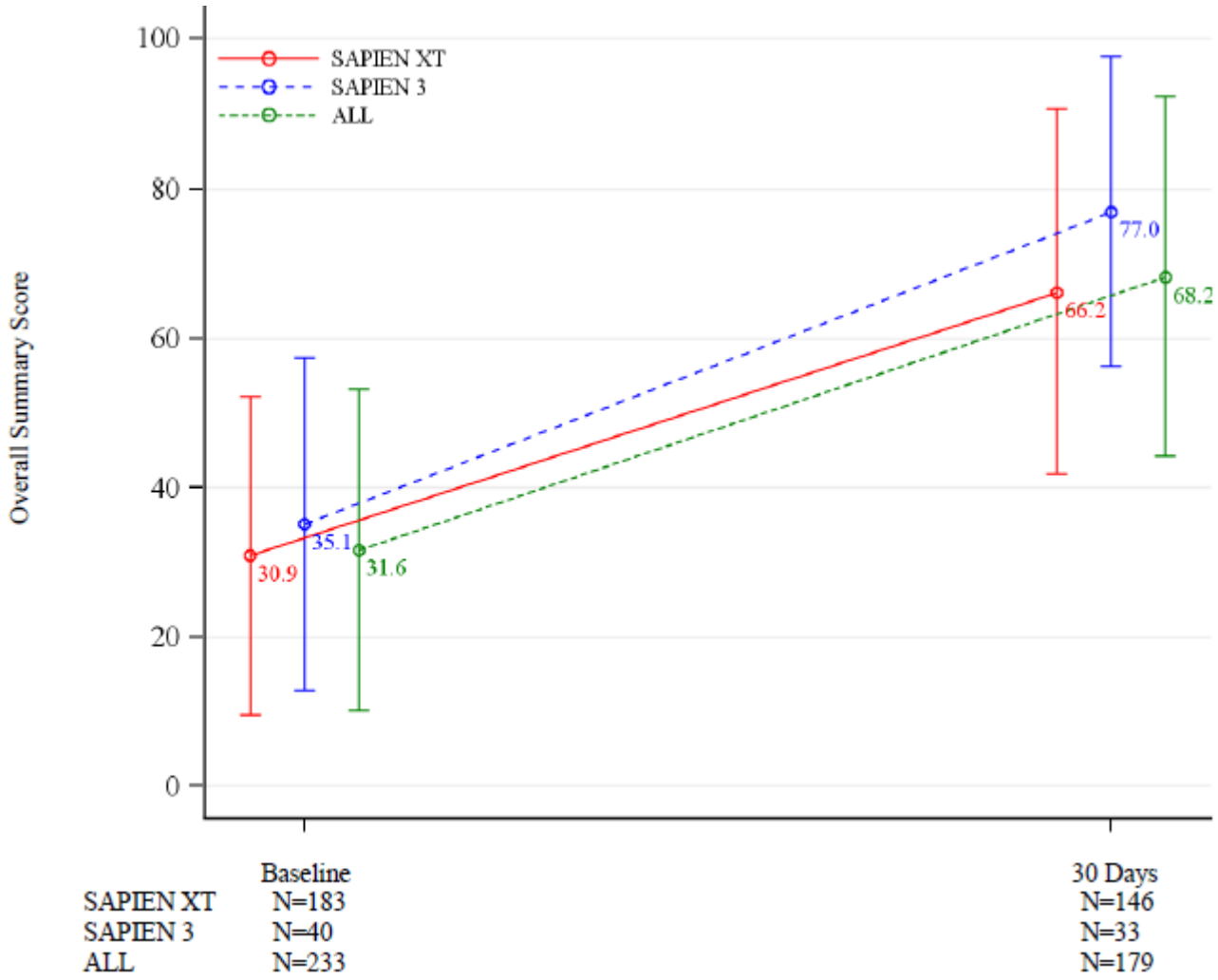


Figure 107: KCCQ Overall Summary Score - Mitral Valve-in-Valve (Valve Implant Population)

Note: Line plot with mean and standard deviation. The total number of patients at each time point only counted the patients with valid values.

Procedural Information

The procedure information is presented in Table 97. The most common delivery approach for the mitral valve-in-valve implantation was the transapical approach, which was used in 65.3% (203 of 311) of cases, followed by the transseptal approach in 27.0% (84 of 311) of cases, the transfemoral approach in 6.1% (19/311) of cases, and other alternative approaches in 1.6% (5 of 311) of cases. The procedures were considered elective in 71.0% (220/310) of cases, urgent in 27.7% (86/310) of cases, and emergent or salvage in 1.3% (4/310) of cases. Two (2) cases were aborted and 5 were converted to open heart surgery. Overall, the device was implanted successfully in 97.4% (303/311) of the cases, which was defined as correct positioning of a single prosthetic heart valve in the proper anatomical location.

Table 97: Procedural Data Summary - Mitral Valve-in-Valve (Attempted Implant Population)

Procedural Data	Summary Statistics*		
	SAPIEN XT	SAPIEN 3	All
Operator reason for procedure			
Inoperable/extreme risk	96/241 (39.8%)	11/69 (15.9%)	107/310 (34.5%)
High risk	141/241 (58.5%)	52/69 (75.4%)	193/310 (62.3%)
Intermediate risk	4/241 (1.7%)	5/69 (7.2%)	9/310 (2.9%)

Procedural Data	Summary Statistics*		
	SAPIEN XT	SAPIEN 3	All
Low risk	0/241 (0.0%)	1/69 (1.4%)	1/310 (0.3%)
Implant approach			
Transapical	192/241 (79.7%)	11/70 (15.7%)	203/311 (65.3%)
Transseptal	43/241 (17.8%)	41/70 (58.6%)	84/311 (27.0%)
Femoral artery	4/241 (1.7%)	15/70 (21.4%)	19/311 (6.1%)
Other	2/241 (0.8%)	3/70 (4.3%)	5/311 (1.6%)
Prior valve type			
Bioprosthetic stented	143/180 (79.4%)	35/41 (85.4%)	178/221 (80.5%)
Bioprosthetic stentless	37/180 (20.6%)	6/41 (14.6%)	43/221 (19.5%)
Procedure status			
Elective	173/241 (71.8%)	47/69 (68.1%)	220/310 (71.0%)
Urgent	64/241 (26.6%)	22/69 (31.9%)	86/310 (27.7%)
Emergency	2/241 (0.8%)	0/69 (0.0%)	2/310 (0.6%)
Salvage	2/241 (0.8%)	0/69 (0.0%)	2/310 (0.6%)
Valve size			
23 mm	22/241 (9.1%)	5/70 (7.1%)	27/311 (8.7%)
26 mm	93/241 (38.6%)	24/70 (34.3%)	117/311 (37.6%)
29 mm	126/241 (52.3%)	41/70 (58.6%)	167/311 (53.7%)
Cardiopulmonary bypass	25/241 (10.4%)	2/69 (2.9%)	27/310 (8.7%)
Status of CP Bypass			
Elective	20/25 (80.0%)	0/2 (0.0%)	20/27 (74.1%)
Emergent	5/25 (20.0%)	2/2 (100.0%)	7/27 (25.9%)
CP Bypass Time (min)	38.3 ± 51.2 (24)	148.0 ± 157.0 (2)	46.7 ± 65.4 (26)
Type of anesthesia			
General anesthesia	240/241 (99.6%)	68/69 (98.6%)	308/310 (99.4%)
Moderate sedation	0/241 (0.0%)	1/69 (1.4%)	1/310 (0.3%)
Epidural	0/241 (0.0%)	0/69 (0.0%)	0/310 (0.0%)
Combination	1/241 (0.4%)	0/69 (0.0%)	1/310 (0.3%)
Total procedure time (min)	143.6 ± 60.4 (240)	157.7 ± 107.2 (69)	146.7 ± 73.5 (309)
Fluoroscopy time (min)	23.9 ± 20.7 (223)	36.9 ± 27.3 (63)	26.8 ± 22.9 (286)
Device implanted successfully	234/241 (97.1%)	69/70 (98.6%)	303/311 (97.4%)
Procedure aborted	1/241 (0.4%)	1/70 (1.4%)	2/311 (0.6%)
Procedure aborted reason			
Navigation issue after successful access	1/1 (100.0%)	0/1 (0.0%)	1/2 (50.0%)
Other	0/1 (0.0%)	1/1 (100.0%)	1/2 (50.0%)
Procedure aborted action			
Conversion to open heart surgery	0/1 (0.0%)	1/1 (100.0%)	1/2 (50.0%)

Procedural Data	Summary Statistics*		
	SAPIEN XT	SAPIEN 3	All
Other	1/1 (100.0%)	0/1 (0.0%)	1/2 (50.0%)
Conversion to open heart surgery	4/241 (1.7%)	1/70 (1.4%)	5/311 (1.6%)
Tamponade/bleeding in the heart	4/4 (100.0%)	0/1 (0.0%)	4/5 (80.0%)
Other	0/4 (0.0%)	1/1 (100.0%)	1/5 (20.0%)
Mechanical assist device in place at start of procedure	9/241 (3.7%)	4/70 (5.7%)	13/311 (4.2%)
IABP	7/9 (77.8%)	3/4 (75.0%)	10/13 (76.9%)
Catheter-based assist device	2/9 (22.2%)	1/4 (25.0%)	3/13 (23.1%)

*Categorical measures – no./Total no. (%); continuous measures - mean ± SD (Total no.). The total no. only counted the patients with valid values at the time point.

13.12 SAPIEN 3 AND SAPIEN 3 ULTRA THV THV-IN-THV - STS/ACC TRANSCATHETER VALVE THERAPY REGISTRY (TVTR) ANALYSIS

Accountability of PMA Cohorts

At the time of database extract, 242 of the 263 patients were eligible for the 30-day visit and 216 (89.3%) completed the visit within the 30-day follow-up window, defined as the period between 21 days post-procedure and 75 days post-procedure. At 1 year, 200 patients were eligible for the 1-year visit and 136 (68.0%) completed the visit within the follow-up window, defined as the period between 305 days post-procedure and 425 days post-procedure. A detailed summary of the patient accountability at 30 days and 1 year is shown in Table 98.

Table 98: Patient Visit Accountability (AI Population)

	30-day Visit	1-year Visit
Total patients	263	263
Non-eligible	21	63
Death	19	47
Lost to follow-up	1	13
Eligible	242	200
Follow-up visit completed	89.3% (216)	68.0% (136)
Missed visit	10.7% (26)	32.0% (64)

The "Attempted Implant "population consisted of all patients for whom the first vascular access was attempted. The "Valve Implant" population consisted of those patients for whom the valve implant procedure has started and a "No" was indicated for both "procedure aborted" and "conversion to open heart surgery". The number of patients in the analysis population is shown in Table 99.

Table 99: Analysis Populations

Analysis Population	Number of Patients
Attempted Implant Population	263
Valve Implant Population	261

Study Population Demographics and Baseline Characteristics

The demographics and baseline characteristics of the patients, as shown in Table 100 present an elderly, multimorbid cohort of patients, consistent with the high operative risk of the populations.

Table 100: Patient Demographics and Baseline Characteristics (AI Population)

Demographics and Baseline Characteristics	Summary Statistics* (N = 263)
Age - years	78.9 ± 10.5
Male sex	55.1% (145/263)
Society of Thoracic Surgeons (STS) score	10.2 ± 8.6 (242)
New York Heart Association (NYHA) class	
I/II	12.3% (32/261)
III/IV	87.7% (229/261)
Previous myocardial infarction	26.6% (70/263)
Previous intervention	
Coronary artery bypass grafting (CABG)	28.1% (74/263)
Percutaneous coronary intervention (PCI)	34.0% (89/262)
Prior aortic valvuloplasty	13.7% (36/263)
Stroke or Cerebrovascular accident (CVA)	18.3% (48/263)
Peripheral vascular disease (PVD)	32.1% (84/262)
Atrial fibrillation/flutter	48.7% (128/263)
Permanent pacemaker	32.2% (84/261)
Porcelain aorta	8.0% (21/262)
Hostile chest	8.7% (23/263)
Echocardiographic findings (Valve Implant Population)	
Valve area (cm^2)	1.0 ± 0.5 (115)
Mean gradient (mmHg)	29.4 ± 19.0 (135)
Mean left ventricular ejection fraction (LVEF), %	49.3 ± 15.1 (257)
Moderate or severe aortic regurgitation	79.3% (207/261)
Moderate or severe mitral regurgitation	42.1% (98/233)
*Continuous measures - Mean ± SD (Total no.); Categorical measures - % (no./Total no.)	

Safety and Effectiveness Results

Safety Endpoints

The Kaplan-Meier estimates of site-reported adverse events through 1 year are presented in Table 101. The Kaplan-Meier curve for all-cause mortality is shown in Figure 108. The all-cause mortality rate was 5.8% at 30 days and 18.2% at 1 year, including a cardiovascular death rate of 2.7% at 30 days and 5.4% at 1 year. Other relatively more frequent adverse events included conduction/native pacer disturbance requiring pacer (8.2% at 30 days and 10.6% at 1 year) and valve-related readmission (4.3% at 30 days and 8.6% at 1 year).

Table 101: Site Reported Adverse Events (AI Population)

Adverse Event	Kaplan-Meier Rate*	
	30 Days (N = 263)	1 Year (N = 263)
All-cause death	5.8% (15, 15)	18.2% (45, 45)
Cardiovascular death	2.7% (7, 7)	5.4% (13, 13)
All stroke	2.3% (6, 6)	2.8% (7, 7)

Adverse Event	Kaplan-Meier Rate*	
	30 Days (N = 263)	1 Year (N = 263)
Ischemic stroke	1.9% (5, 5)	2.4% (6, 6)
Undetermined stroke	0.4% (1, 1)	0.4% (1, 1)
Transient ischemic attack (TIA)	0.8% (2, 2)	1.9% (4, 4)
Major vascular complication	0.4% (1, 1)	1.0% (2, 2)
Major bleeding	1.2% (3, 3)	2.5% (7, 5)
Myocardial infarction	0.8% (3, 2)	3.1% (6, 5)
New requirement for dialysis	0.4% (1, 1)	1.6% (3, 3)
Conduction/native pacer disturbance requiring pacer	8.2% (21, 21)	10.6% (25, 25)
Conduction/native pacer disturbance requiring implantable cardioverter defibrillator (ICD)	0.4% (1, 1)	2.2% (4, 4)
Aortic valve re-intervention	0.4% (1, 1)	1.2% (2, 2)
Unplanned other cardiac surgery or intervention	2.4% (6, 6)	4.5% (9, 9)
Unplanned vascular surgery or intervention	1.5% (4, 4)	2.6% (6, 6)
Device thrombosis	0.4% (1, 1)	1.0% (2, 2)
Valve-related readmission	4.3% (11, 11)	8.6% (22, 18)

*Kaplan-Meier rate - (no. of events, no. of patients with the event).

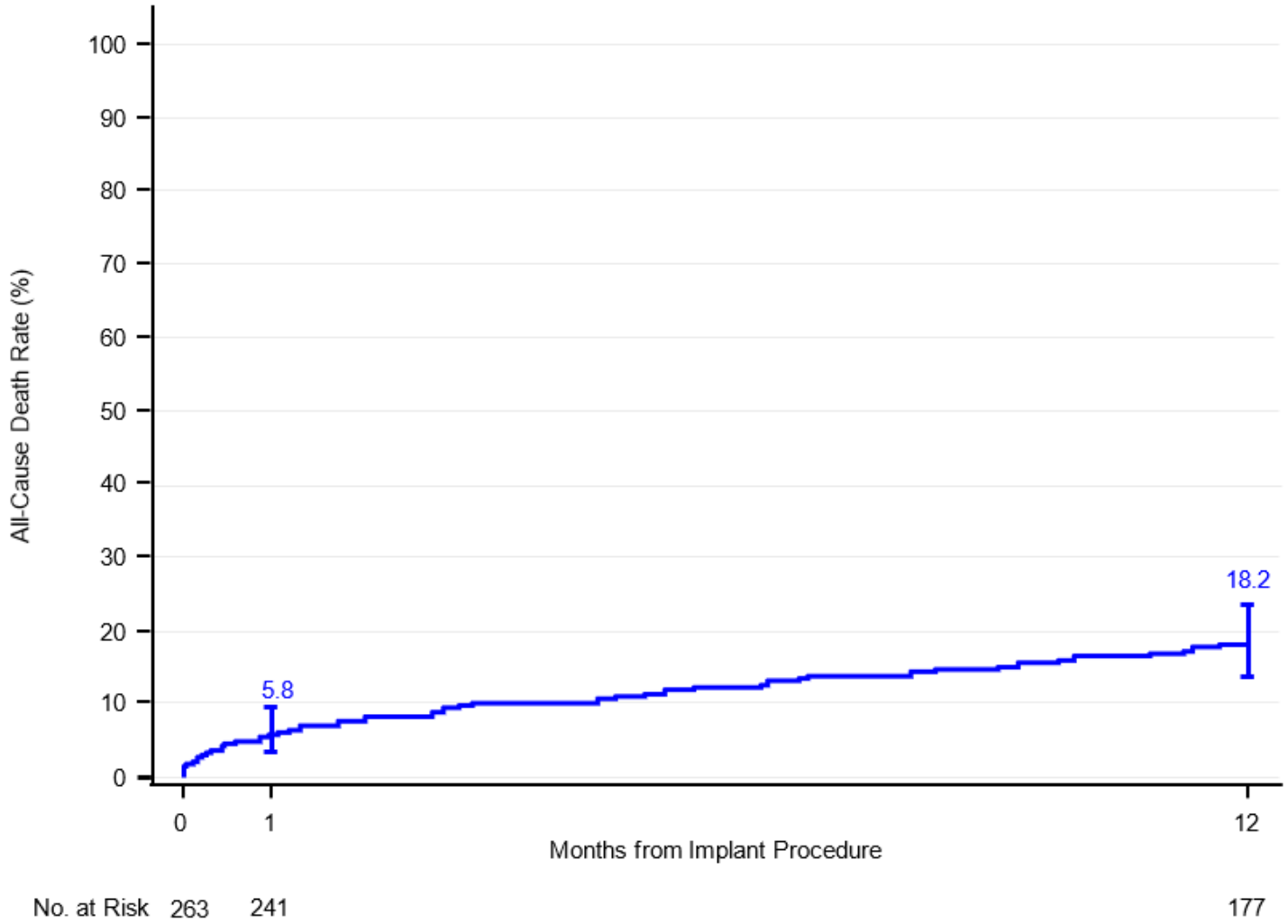


Figure 108: All-Cause Mortality through 1 Year (AI Population)

Note: The 95% 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.

Effectiveness Endpoints

Valve Performance

The echocardiographic valve performance results are shown in Figure 109 to Figure 111. The decrease in gradients were sustained through 1 year. The mean aortic gradient decreased from 29.4 mmHg at baseline to 14.4 mmHg at 30 days, which was maintained through 1 year (13.3 mmHg). Moderate or severe total aortic regurgitation was observed in 79.3% of the patients at baseline, which decreased to 4.6% at 30 days and 3.4% at 1 year. The proportion of patients with ≥ moderate paravalvular regurgitation was 4.5% at 30 days and 2.6% at 1 year.

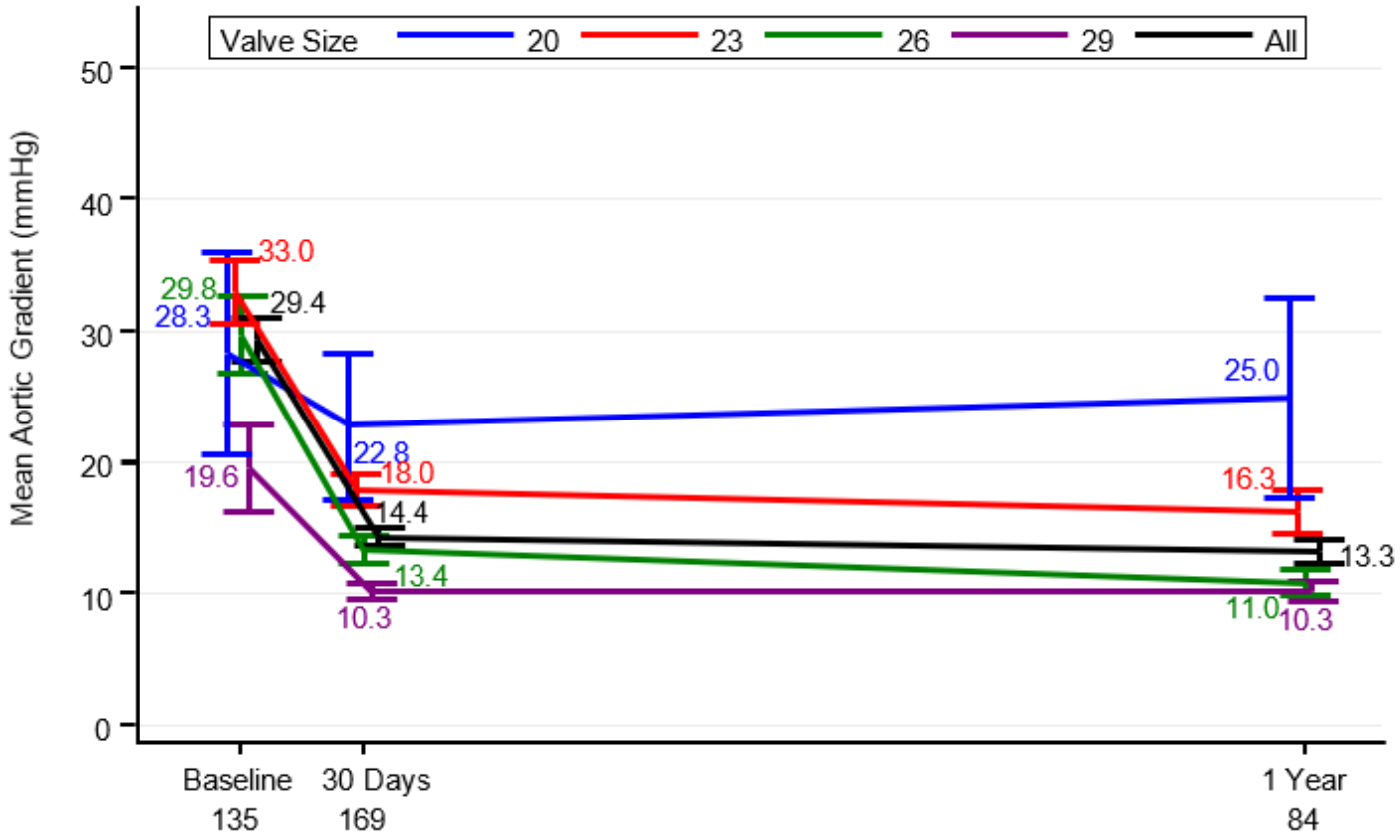


Figure 109: Mean Aortic Gradient (VI Population)

Note: Line plot with mean and standard error. The total number of patients at each visit time point only counted the patients with valid values.

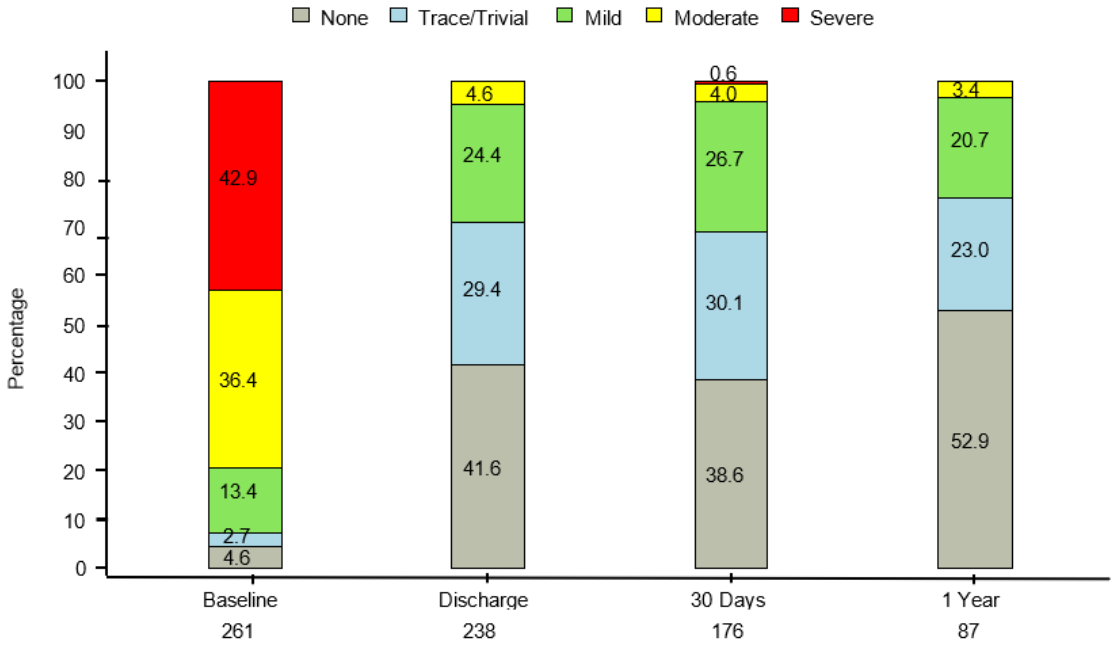


Figure 110: Total Aortic Regurgitation (VI Population)

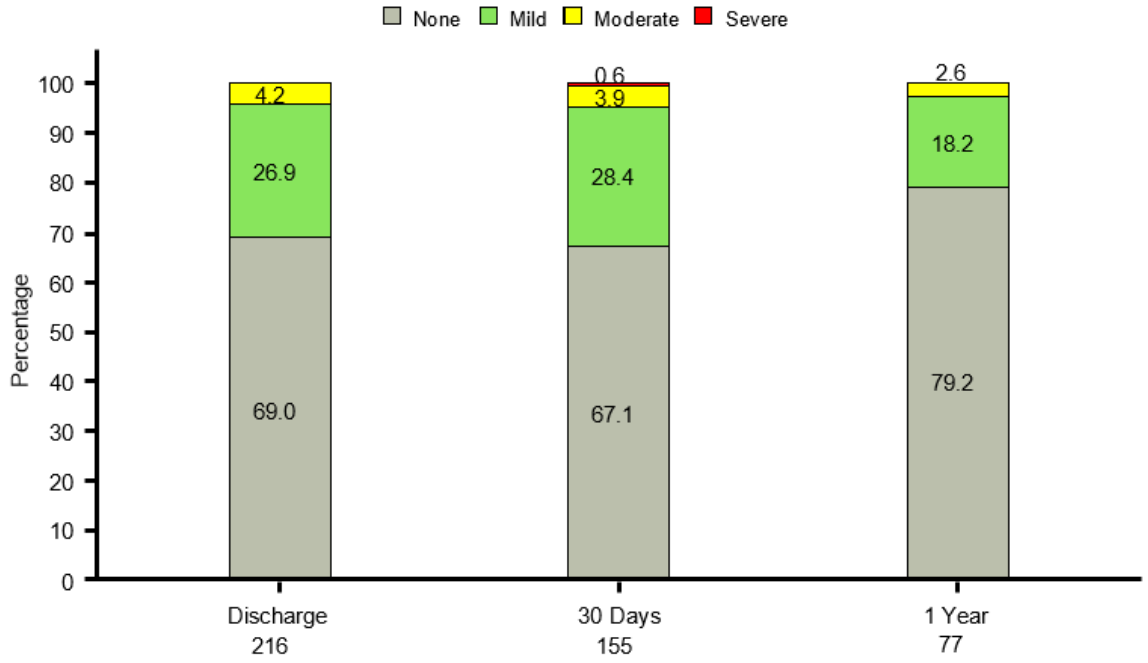


Figure 111: Paravalvular Regurgitation (VI Population)

New York Heart Association Functional Class

The NYHA functional class distributions by visit are presented in Figure 112. At baseline, 87.7% of patients were in NYHA III/IV. At 1 year, the majority (88.4%) of patients were in NYHA I/II.

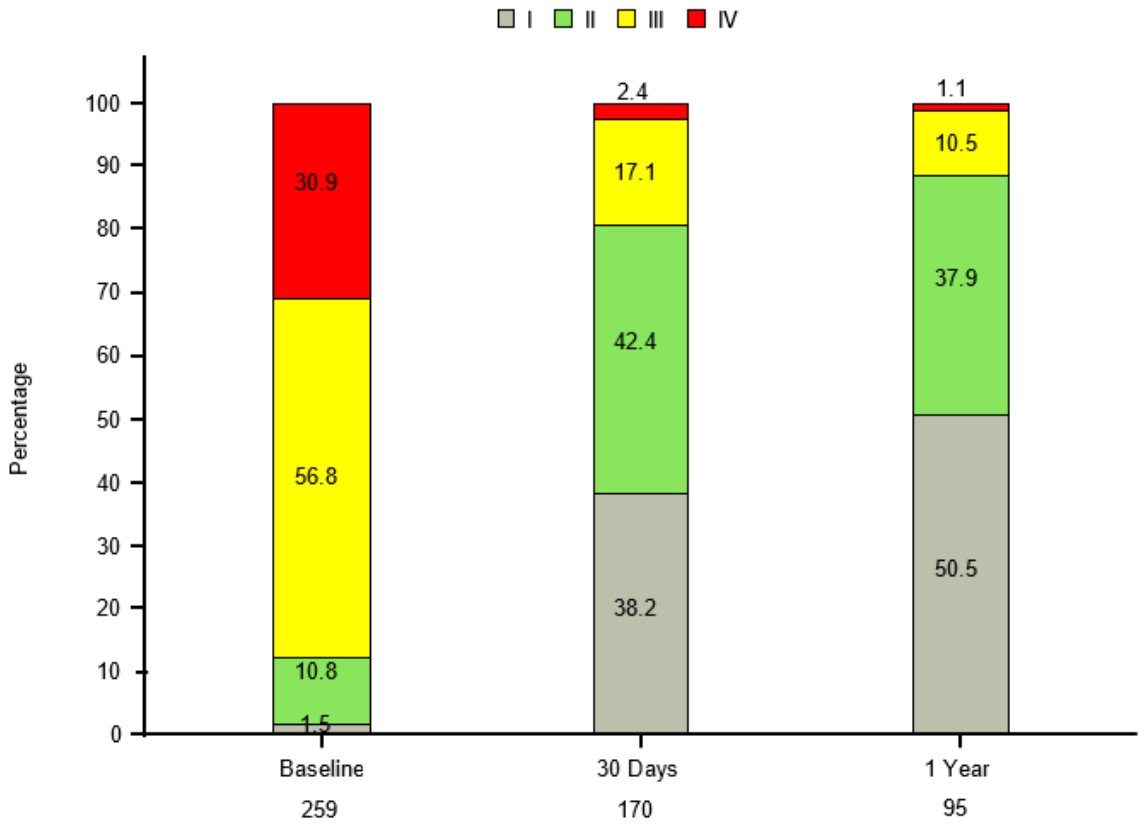


Figure 112: NYHA Class by Visit (VI Population)

Length of Stay

The mean index hospitalization stay was 4.9 days, which included an average of 1.7 days in the intensive care unit (ICU), as summarized in Table 102.

Table 102: Index Hospitalization (AI Population)

	Length of Stay (days)*
Index hospitalization duration	4.9 ± 0.3 (263)
Intensive care stay	1.7 ± 0.2 (255)
*Mean ± SE (Total no.)	

Quality of Life

The results for the KCCQ overall summary score are presented in Figure 113. The mean score increased from 38.7 at baseline to 65.3 and 73.7 at 30 days and 1 year, respectively.

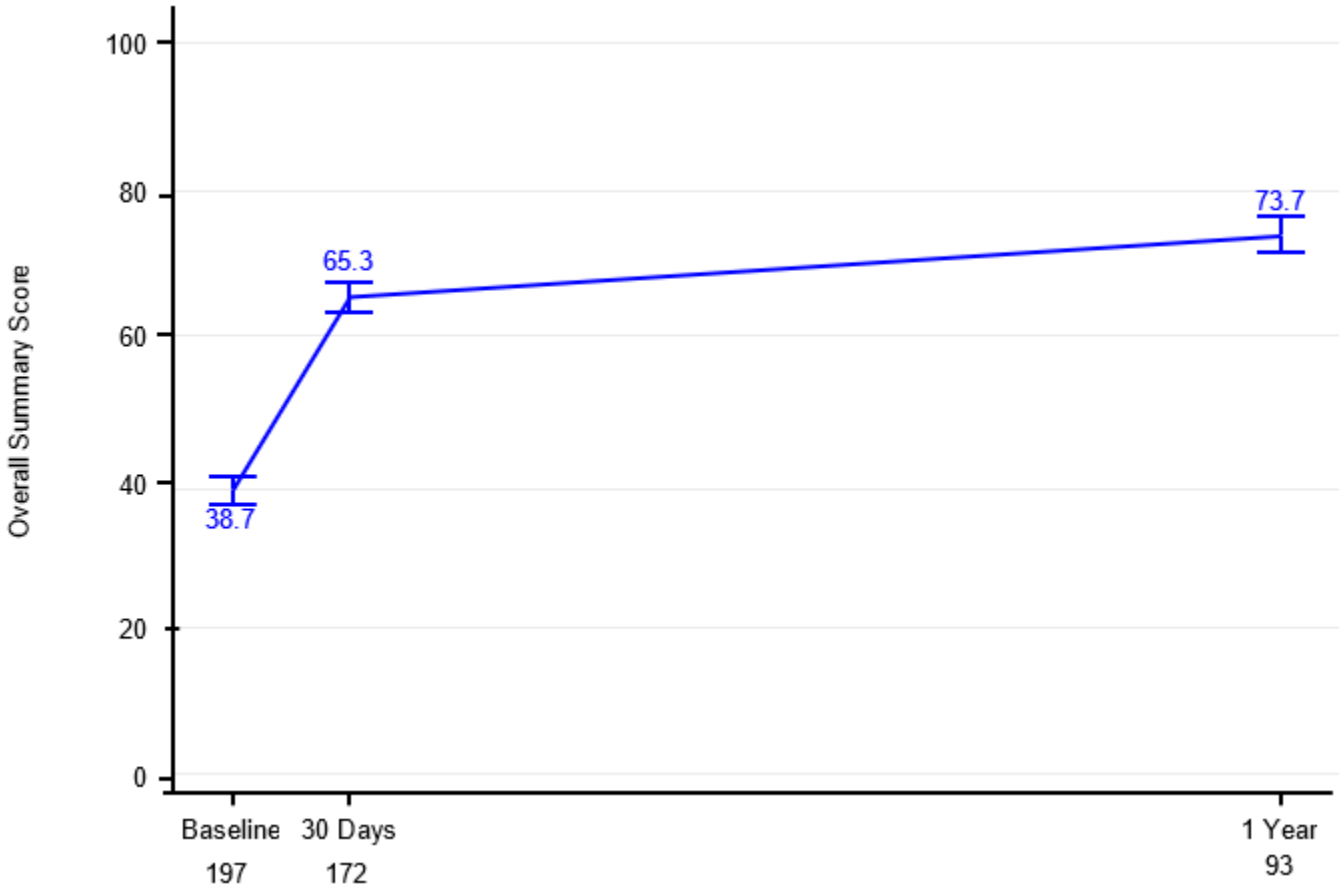


Figure 113: KCCQ Overall Summary Score (VI Population)

Note: Line plot with mean and standard error. The total number of patients at each time point only counted patients with valid values.

Other Study Observations

Procedural Information

The procedural information is summarized in Table 103. General anesthesia was used in the majority (70%) of patients. Conversion to open heart surgery occurred in two patients due to ventricular rupture and annulus rupture, respectively.

Table 103: Procedural Data Summary (AI Population)

Procedural Data	Summary Statistics*
Operator reason for procedure	
Inoperable/extreme risk	20.8% (54/259)
High risk	69.1% (179/259)
Intermediate risk	9.7% (25/259)
Low risk	0.4% (1/259)
Implant approach	
Transfemoral	95.8% (252/263)
Transapical	1.1% (3/263)
Transaortic	0.8% (2/263)
Subclavian/axillary	0.8% (2/263)
Transseptal	0.4% (1/263)
Transcarotid	1.1% (3/263)
Valve size	
20 mm	2.3% (6/263)
23 mm	35.0% (92/263)
26 mm	30.8% (81/263)
29 mm	31.9% (84/263)
Cardiopulmonary bypass	0.4% (1/263)
Cardiopulmonary bypass status	
Emergent	100.0% (1/1)
Cardiopulmonary bypass time, minutes	254.0 ± NA (1)
Type of anesthesia	
General anesthesia	70.0% (184/263)
Moderate sedation	29.7% (78/263)
Combination	0.4% (1/263)
Total procedure time, minutes	108.5 ± 4.3 (263)
Device implanted successfully	98.9% (260/263)
Procedure aborted	0.0% (0/263)
Conversion to open heart surgery	0.8% (2/263)
Ventricular rupture	1
Annulus rupture	1
Mechanical assist device in place at start of procedure	0.4% (1/263)
Catheter-based assist device	100.0% (1/1)

*Continuous measures - mean ± SE (n); categorical measures - % (no./Total no.)

13.13 SAPIEN 3 VALVE IN RING - STS/ACC TRANSCATHETER VALVE THERAPY REGISTRY (TVTR) & MITRAL IMPLANTATION OF TRANSCATHETER VALVES (MITRAL) STUDY ANALYSIS

Patient Accountability

At the time of database extract, 205 of the 236 patients were eligible for the 30-day visit and 178 (86.8%) completed the visit within the 30-day follow-up window, defined as the period between 21 days post-procedure and 75 days post-procedure. At 1 year, 152 patients were eligible for the 1-year visit and 103 (67.8%) completed the visit within the follow-up window, defined as the period between 305 days post-procedure and 425 days post-procedure. A detailed summary of the patient accountability at 30 days and 1 year is shown in Table 104.

Table 104: Patient Visit Accountability

	30-day Visit	1-year Visit
Total patients	236	236
Non-eligible	31	84
Death	24	54
Withdrawal	3	5
Lost to follow-up	4	13
Visit not yet due	0	12
Eligible	205	152
Follow-up visit completed	86.8% (178)	67.8% (103)
Missed visit	13.2% (27)	32.2% (49)

The "Attempted Implant (AI) "population consisted of all patients in the dataset. The "Valve Implant (VI)" population consisted of those patients for whom the valve implant procedure has started and a "No" was indicated for both "procedure aborted" and "conversion to open heart surgery" in the case report form of the TVT Registry (no patients in the MITRAL study had an aborted procedure). The numbers of patients in these two analysis populations are shown in Table 105.

Table 105: Analysis Populations

Analysis Population	Number of Patients
Attempted implant population	236
Valve implant population	232

Study Population Demographics and Baseline Characteristics

Patient demographics and baseline characteristics, as shown in Table 106, present an elderly, multimorbid cohort of patients, consistent with the high operative risk of the populations.

Table 106: Patient Demographics and Baseline Characteristics (AI Population)

Demographics and Baseline Characteristics	Summary Statistics*		
	TVT Registry (N = 206)	MITRAL Study (N = 30)	Overall (N = 236)
Age - years	72.1 ± 10.3 (206)	71.7 ± 8.9 (30)	72.1 ± 10.1 (236)
Male sex	47.6% (98/206)	63.3% (19/30)	49.6% (117/236)
Society of Thoracic Surgeons (STS) score	9.4 ± 6.4 (196)	8.7 ± 4.7 (30)	9.3 ± 6.2 (226)
New York Heart Association (NYHA) class			
I/II	18.7% (38/203)	23.3% (7/30)	19.3% (45/233)
III/IV	81.3% (165/203)	76.7% (23/30)	80.7% (188/233)

Demographics and Baseline Characteristics	Summary Statistics*		
	TVT Registry (N = 206)	MITRAL Study (N = 30)	Overall (N = 236)
Previous myocardial infarction	30.2% (62/205)	22.2% (6/27)	29.3% (68/232)
Stroke	15.0% (31/206)	13.8% (4/29)	14.9% (35/235)
Transient Ischemic Attack	8.8% (18/205)	7.1% (2/28)	8.6% (20/233)
Diabetes	31.1% (64/206)	30.0% (9/30)	30.9% (73/236)
Hypertension	88.3% (182/206)	90.0% (27/30)	88.6% (209/236)
Previous intervention			
Coronary artery bypass grafting (CABG)	46.1% (95/206)	63.3% (19/30)	48.3% (114/236)
Percutaneous coronary Intervention (PCI)	25.2% (52/206)	31.0% (9/29)	26.0% (61/235)
Atrial fibrillation/flutter	66.0% (136/206)	70.0% (21/30)	66.5% (157/236)
Permanent pacemaker	23.3% (48/206)	36.7% (11/30)	25.0% (59/236)
Porcelain aorta	1.9% (4/206)	0.0% (0/30)	1.7% (4/236)
Previous implantable cardioverter defibrillator (ICD)	23.3% (48/206)	23.3% (7/30)	23.3% (55/236)
Echocardiographic findings (Valve Implant Population)			
Mitral valve area (cm^2)	1.9 ± 0.9 (115)	2.7 ± 0.8 (30)	2.1 ± 0.9 (145)
Mitral valve mean gradient (mmHg)	8.0 ± 4.6 (171)	7.5 ± 4.8 (30)	7.9 ± 4.6 (201)
Left ventricular ejection fraction (LVEF)	47.0 ± 14.5 (201)	46.3 ± 14.0 (30)	46.9 ± 14.4% (231)
≥ Moderate mitral regurgitation	80.1% (161/201)	66.7% (20/30)	78.4% (181/231)
Annuloplasty ring type			
Partial ring	16.5% (34/206)	26.7% (8/30)	17.8% (42/236)
Circumferential ring	83.5% (172/206)	73.3% (22/30)	82.2% (194/236)
*Continuous measures - Mean ± SD (Total no.); Categorical measures - % (no./Total no.)			

Safety and Effectiveness Results

Safety Endpoints

The Kaplan-Meier estimates of site-reported adverse events through 1 year are presented in Table 107. The Kaplan-Meier curves for all-cause mortality and cardiovascular mortality are shown in Figure 114. The all-cause mortality rate was 10.9% at 30 days and 28.6% at 1 year, including a cardiovascular mortality rate of 5.6% at 30 days and 9.5% at 1 year. Other relatively more frequent adverse events included new requirement for dialysis (6.8% at both 30 days and 1 year), left ventricular outflow tract (LVOT) obstruction (6.6% at 30 days and 7.2% at 1 year), readmission due to heart failure (6.2% at 30 days and 22.4% at 1 year), and non-cardiac readmission (8.9% at 30 days and 32.6% at 1 year).

Table 107: Site-Reported Adverse Events (AI Population)

	Kaplan-Meier Rate*	
Adverse Event	30 Days (N = 236)	1 Year (N = 236)
All-cause death	10.9% (24, 24)	28.6% (53, 53)
Cardiovascular death	5.6% (12, 12)	9.5% (18, 18)

	Kaplan-Meier Rate*	
Adverse Event	**30 Days (N = 236)**	**1 Year (N = 236)**
All stroke	1.3% (3, 3)	1.3% (3, 3)
Ischemic stroke	0.9% (2, 2)	0.9% (2, 2)
Hemorrhagic stroke	0.4% (1, 1)	0.4% (1, 1)
Transient Ischemic Attack	0.4% (1, 1)	1.4% (2, 2)
Major vascular complication	2.2% (5, 5)	2.2% (5, 5)
Life threatening/Major bleeding	1.4% (3, 3)	4.8% (8, 7)
Myocardial infarction	0.8% (2, 2)	1.5% (4, 3)
New onset atrial fibrillation	2.9% (6, 6)	6.6% (11, 11)
Conduction/native pacer disturbance requiring pacer	0.9% (2, 2)	3.0% (5, 5)
New requirement for dialysis	6.8% (15, 15)	6.8% (15, 15)
Mitral valve reintervention	4.7% (12, 10)	11.4% (22, 19)
Device thrombosis	1.0% (2, 2)	1.0% (2, 2)
Device embolization	0.8% (2, 2)	0.8% (2, 2)
Device migration	0.5% (1, 1)	0.5% (1, 1)
LVOT Obstruction	6.6% (15, 15)	7.2% (16, 16)
Other device related event	4.9% (12, 11)	5.7% (13, 12)
Endocarditis	0.0% (0, 0)	0.8% (1, 1)
Readmission - heart failure	6.2% (13, 12)	22.4% (48, 34)
Readmission - cardiac	3.1% (6, 6)	14.5% (33, 22)
Readmission - non-cardiac	8.9% (18, 18)	32.6% (62, 49)
Unplanned other cardiac surgery or intervention	10.1% (23, 23)	11.7% (25, 25)

*Kaplan-Meier rate - % (no. of events, no. of patients with the event)

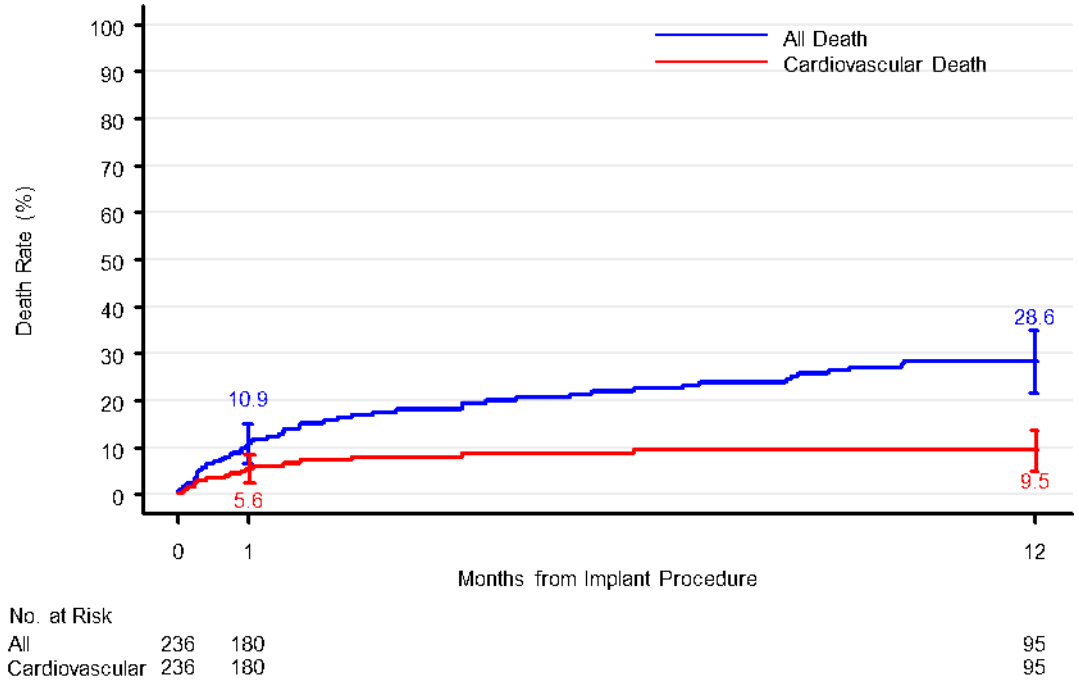


Figure 114: Mortality through 1 Year (AI Population)

Note: The 95% 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.

Effectiveness Endpoints

Valve Performance

The echocardiographic valve performance results are shown in Figure 115 to Figure 117. The mean mitral gradient was 7.9 mmHg at baseline, which was maintained at 30 days (7.9 mmHg) and through 1 year (8.1 mmHg). Moderate or greater total mitral regurgitation was observed in 78.4% of the patients at baseline, which decreased to 5.3% at 30 days and 5.5% at 1 year. The proportion of patients with moderate or greater paravalvular regurgitation was 3.3% at 30 days and 0.0% at 1 year.

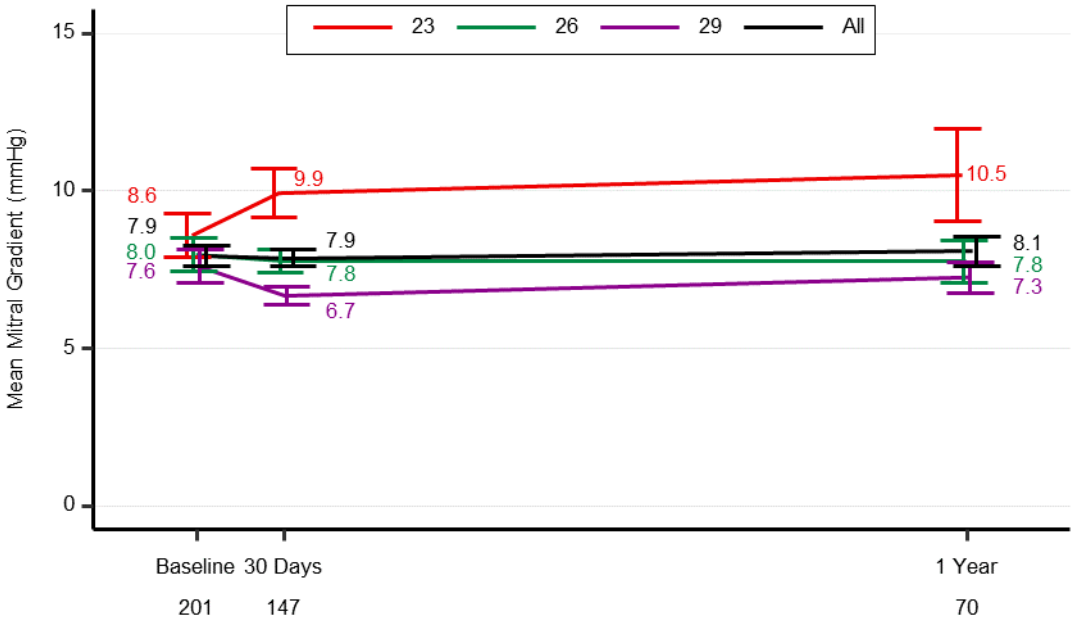


Figure 115: Mean Mitral Gradient (VI Population)

Note: Line plot with mean and standard error. The total number of patients at each time point only counted the patients with valid values.

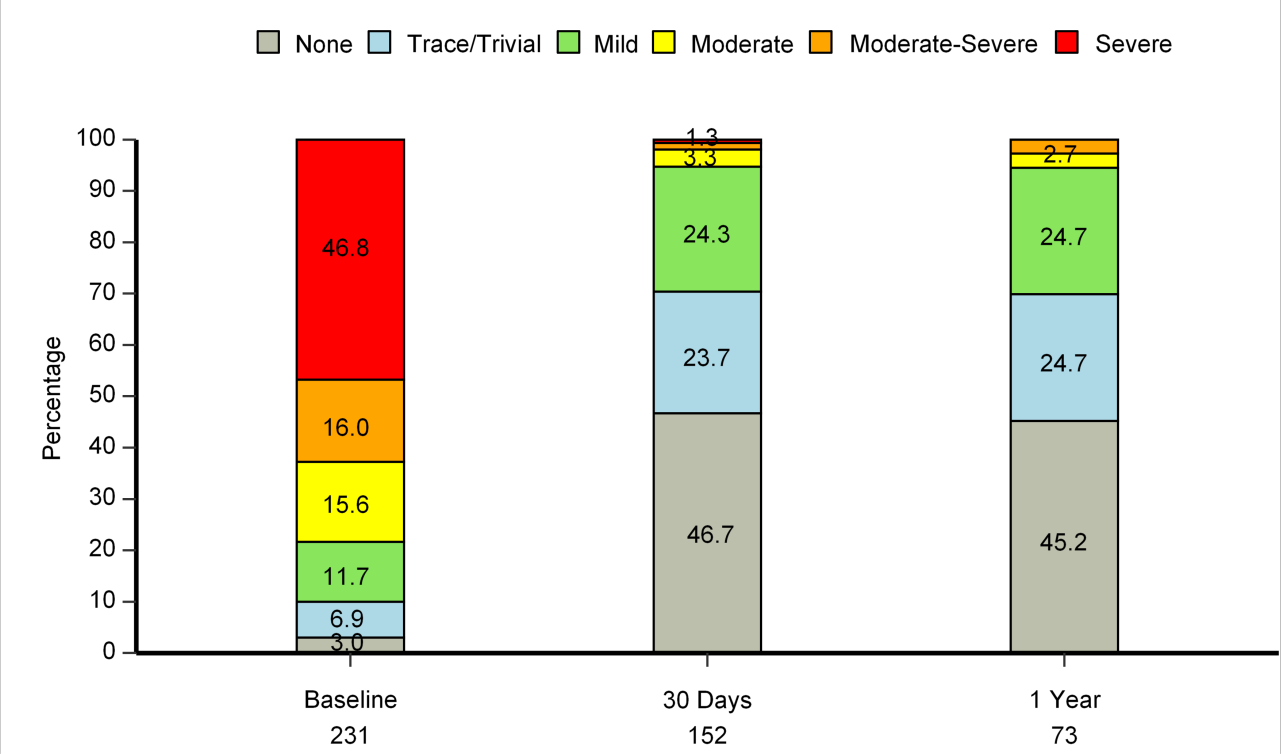


Figure 116: Total Mitral Regurgitation (VI Population)

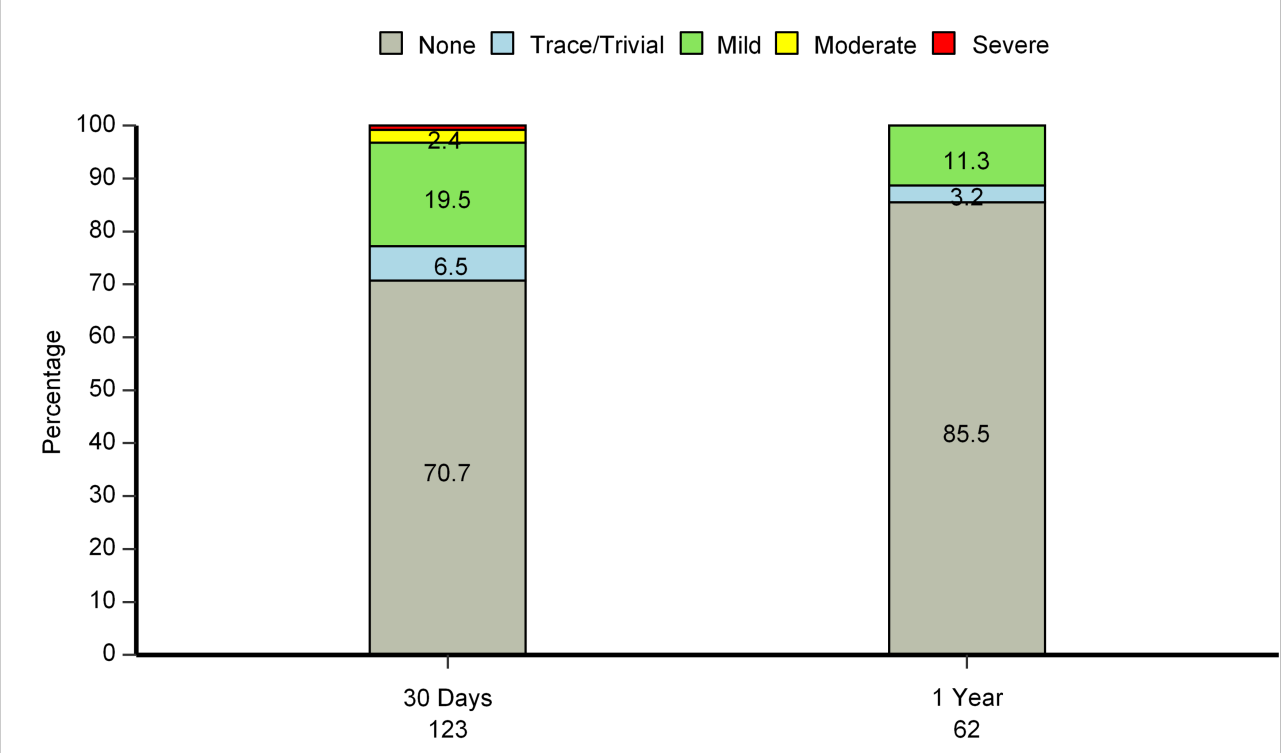


Figure 117: Paravalvular Regurgitation (VI Population)

New York Heart Association Functional Class

The NYHA functional class distributions by visit are presented in Figure 118. At baseline, 80.4% of patients were in NYHA III/IV. At 1 year, the majority (76.3%) of patients were in NYHA I/II.

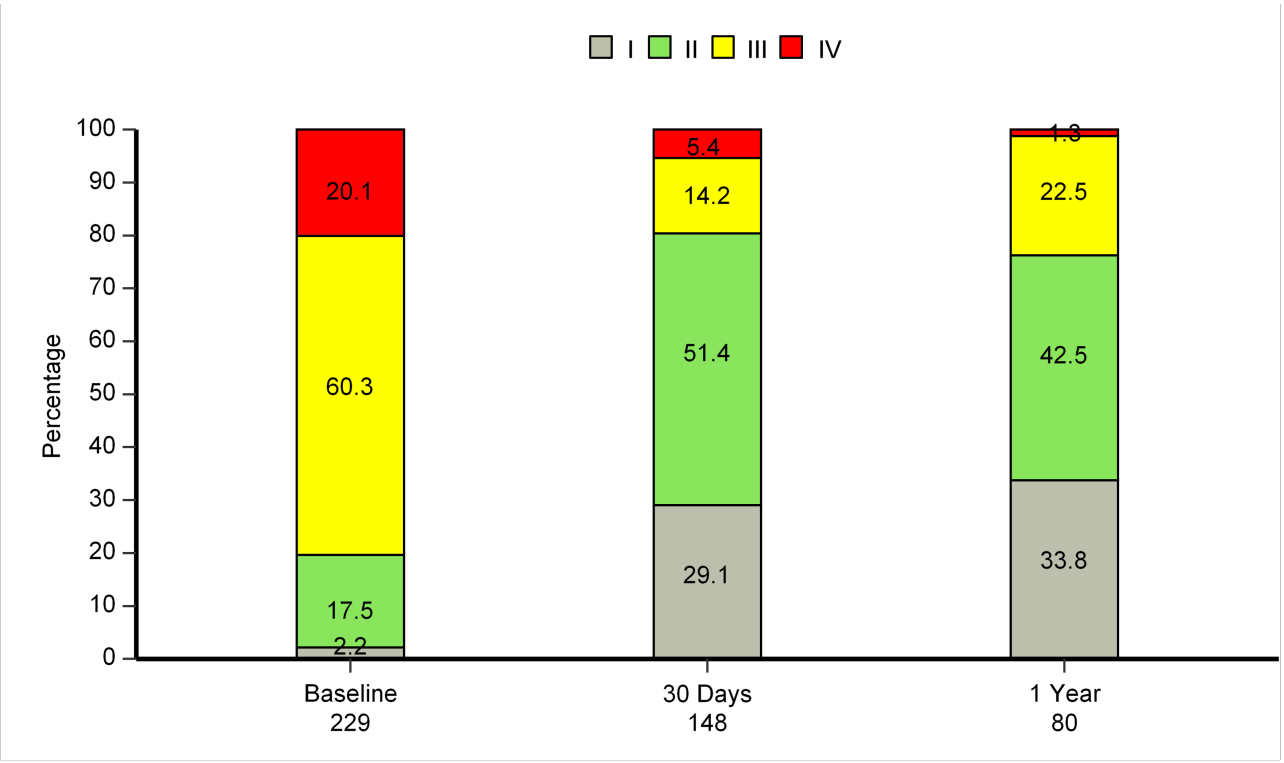


Figure 118: NYHA Class by Visit (VI Population)

Length of Stay

The mean index hospitalization stay was 7.4 days, which included an average of 2.8 days in the intensive care unit (ICU), as summarized in Table 108.

Table 108: Index Hospitalization (AI Population)

Index hospitalization	Length in days*
Index hospitalization duration	7.4 ± 0.55 (236)
Intensive care stay	2.8 ± 0.31 (233)
*Mean ± SE (Total no.).	

Quality of Life

The results for the KCCQ overall summary score are presented in Figure 119. The mean score increased from 40.3 at baseline to 58.1 and 65.6 at 30 days and 1 year, respectively.

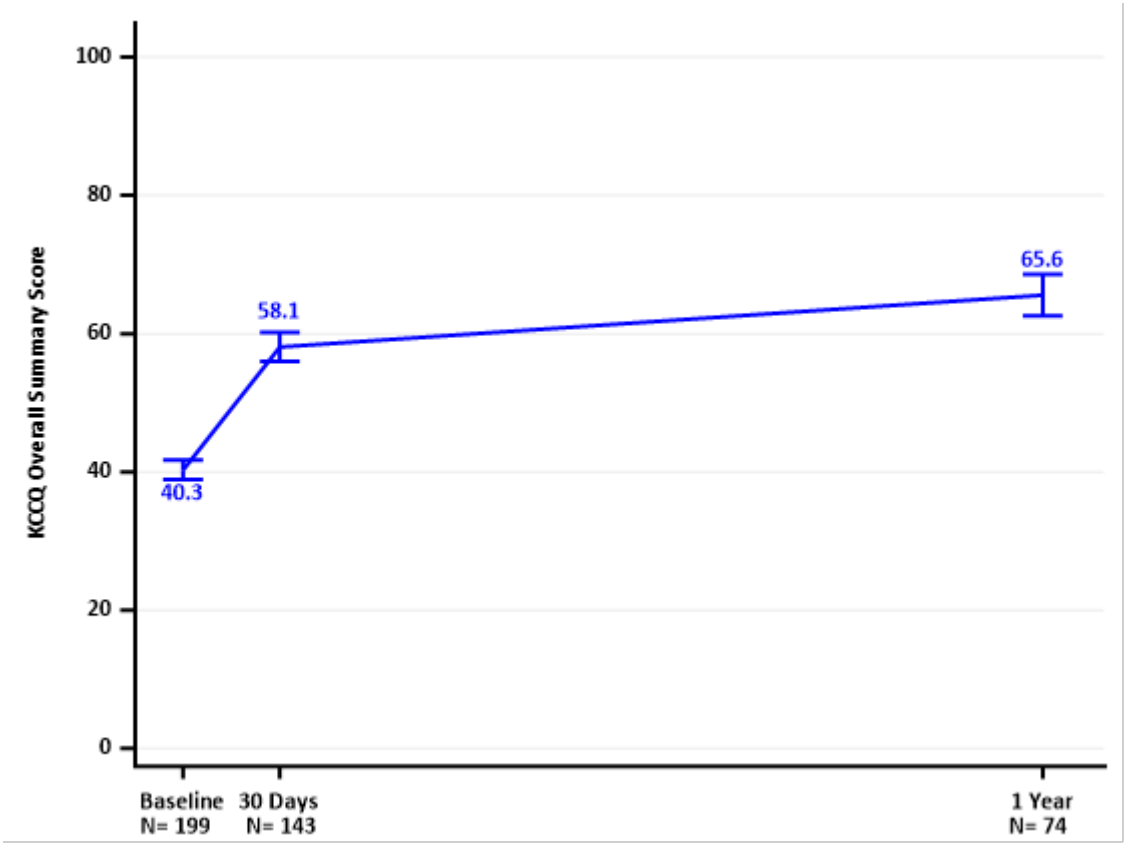


Figure 119: KCCQ Overall Summary Score (VI Population)

Note: Line plot with mean and standard error. The total number of patients at each time point only counted the patients with valid values.

Other Study Observations

Procedural Information

The procedural information is summarized in Table 109. General anesthesia was used in the majority (97.9%) of patients. Conversion to open heart surgery occurred in two patients due to access related problem/injury and device embolization, respectively.

Table 109: Procedural Data Summary (AI Population)

Procedural Data	Summary Statistics* (N = 236)
Operator reason for procedure	
Inoperable/high risk	87.7% (207/236)
Intermediate risk	12.3% (29/236)
Implant approach	
Transseptal	81.8% (193/236)
Transapical	8.5% (20/236)
Femoral artery	8.9% (21/236)
Direct left atrium	0.4% (1/236)
Other	0.4% (1/236)
Valve size	
20 mm	0.4% (1/236)

Procedural Data	Summary Statistics* (N = 236)
23 mm	19.9% (47/236)
26 mm	44.5% (105/236)
29 mm	35.2% (83/236)
Type of anesthesia	
General anesthesia	97.9% (231/236)
Moderate sedation	2.1% (5/236)
Total procedure time (minute)	151.2 ± 82.9 (235)
Device implanted successfully	92.4% (218/236)
Procedure aborted	0.8% (2/236)
Access related	50.0% (1/2)
System issue	50.0% (1/2)
Conversion to open heart surgery	0.8% (2/236)
Access related problem/injury	50.0% (1/2)
Device embolization	50.0% (1/2)
*Continuous measures - mean ± SD (n); categorical measures - % (no./Total no.)	

Subgroup analysis

The Kaplan-Meier curves for all-cause mortality and cardiovascular mortality are shown in Figure 120 and Figure 121 for patients with a partial and circumferential annuloplasty ring, respectively. In patients with a partial annuloplasty ring, the 1-year all-cause and cardiovascular mortality rates were 25.1% and 10.9%, respectively, as compared to the corresponding rates of 29.4% and 9.2% for those with a circumferential annuloplasty ring.

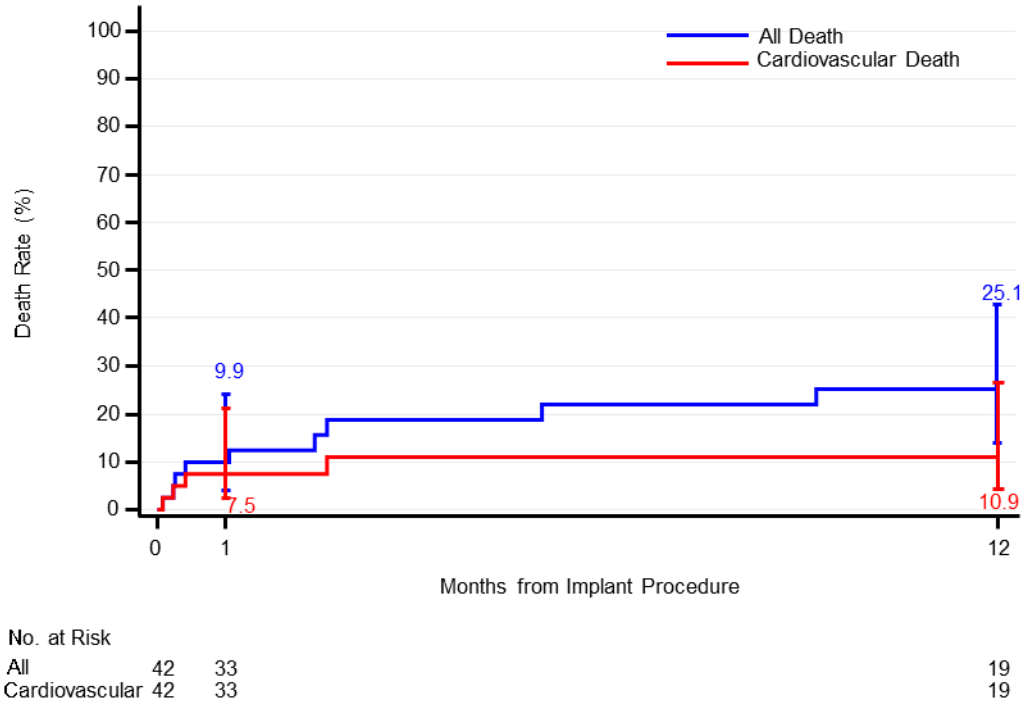


Figure 120: Mortality Through 1 Year (Partial Ring Patients)

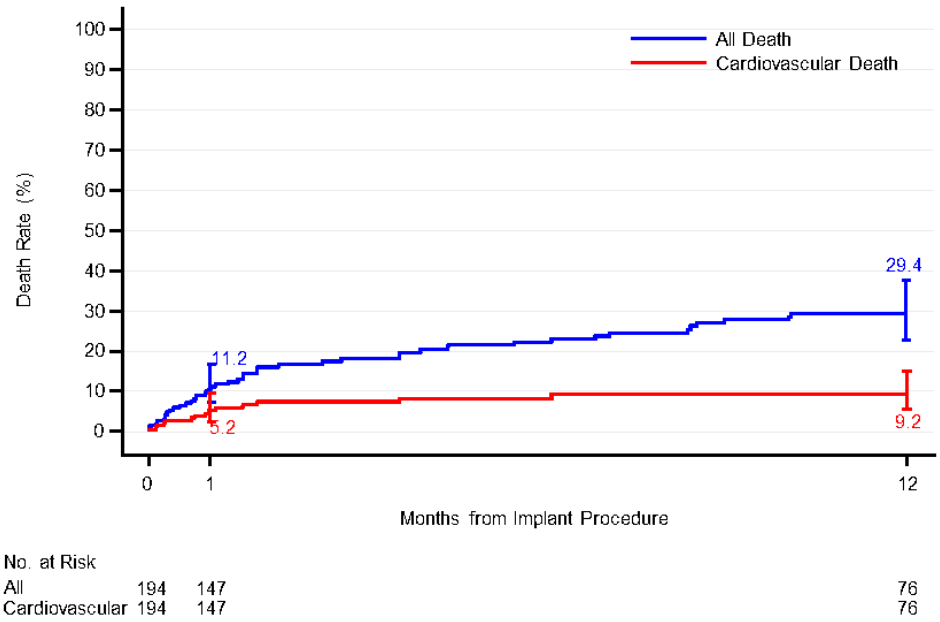


Figure 121: Mortality Through 1 Year (Circumferential Ring Patients)

13.14 SAPIEN 3 ULTRA SYSTEM

Patient Accountability

At the time of the database extract, all 40 patients enrolled were implanted, discharged and completed 30-day follow-up.

Patient Demographics and Baseline Characteristics

The demographics and baseline characteristics are shown in Table 110.

Table 110: Patient Demographics and Baseline Characteristics

Demographics and Baseline Characteristic	Summary Statistics
Age - years	83.4 ± 5.13 (40)
Male sex	24/40 (60.0%)
Society of Thoracic Surgeons (STS) score	3.4 ± 1.27 (40)
New York Heart Association (NYHA) class	
I/II	20/40 (50.0%)
III/IV	20/40 (50.0%)
Previous myocardial infarction	1/40 (2.5%)
Previous intervention	9/40 (22.5%)
Coronary artery bypass grafting (CABG)	3/40 (7.5%)
Percutaneous bypass intervention (PCI)	8/40 (20.0%)
Prior aortic valvuloplasty	0/40 (0.0%)
Cerebrovascular accident (CVA)	1/40 (2.5%)
Peripheral vascular disease	4/40 (10.0%)
Atrial fibrillation	19/40 (47.5%)
Prior pacemaker	5/40 (12.5%)
Porcelain aorta	0/40 (0.0%)

Demographics and Baseline Characteristic	Summary Statistics
Echocardiographic findings	
Valve area - cm^2	0.7 ± 0.16 (40)
Mean aortic-valve gradient -mmHg	51.0 ± 13.17 (40)
Mean left ventricular ejection fraction (LVEF) %	60.6 ± 7.06 (40)
Moderate or severe aortic regurgitation	1/39 (2.6%)
*Continuous measures—Mean ± SD (Total no.); Categorical measures—n./Total no. (%)	

Safety and Effectiveness Results

Primary Endpoint

The primary endpoint was procedural success, defined as freedom from mortality, conversion to surgery, and moderate or severe PVR at exit from the procedure room which was achieved in all subjects as outlined in Table 111.

Table 111: Primary Endpoint Analysis

Primary Endpoint	Results
Overall procedural success	40/40 (100.0%)
Freedom from mortality at exit from procedure room	40/40 (100.0%)
Freedom from conversion to surgery at exit from procedure room	40/40 (100.0%)
Freedom from moderate or severe paravalvular regurgitation at exit from procedure room	40/40 (100.0%)

Secondary Endpoints

There were no major vascular complications, valve migrations, or embolizations through discharge.

Adverse Events

There were no deaths or strokes through 30 days. The selected adverse events for the treated population are presented in Table 112.

Table 112: Selected Adverse Events

Adverse Event	Discharge*	30 Days†
Major vascular complications	0.0% (0, 0)	0.0% (0, 0)
Acute kidney injury (Stage III)	0.0% (0, 0)	0.0% (0, 0)
Life threatening bleeding	0.0% (0, 0)	0.0% (0, 0)
Major bleeding	5.0% (2,2)	5.0% (2,2)
Hematoma	5.0% (2,2)	5.0% (2,2)
Bleeding at access site	15.0% (6,6)	15.0% (6,6)
Dissection	2.5% (1,1)	2.5% (1,1)
Pseudoaneurysm	2.5% (1,1)	2.5% (1,1)
Aortic-valve reintervention	0.0% (0, 0)	0.0% (0, 0)
Endocarditis	0.0% (0, 0)	0.0% (0, 0)
Device thrombosis	0.0% (0, 0)	0.0% (0, 0)
*Observed rate,% (no. of events, no. of subjects with the event) †Kaplan-Meier estimate,% (no. of events, no. of subjects with the event)		

The new conduction abnormalities requiring permanent pacemaker implantation through 30 days for the first 20 subjects and the last 20 subjects are presented in Table 113.

Table 113: New Conduction Abnormalities Requiring Permanent Pacemaker Implantation

	First 20 Subjects		Last 20 Subjects	
Adverse Event	**Discharge***	**30 Days†**	**Discharge***	**30 Days†**
Conduction disturbance requiring permanent pacemaker‡	29.4% (5,5)	29.4% (5,5)	5.6% (1,1)	5.6% (1,1)

‡5 Subjects (3 from First 20 subject cohort and 2 from Last 20 subject cohort) with baseline pacemaker were excluded from the analysis.
*Observed rate,% (no. of events, no. of subjects with the event)
†Kaplan-Meier estimate,% (no. of events, no. of subjects with the event)

Other Results

Procedural Information

Overall, the mean procedure time was 56.5 ± 26.8 minutes. Conscious sedation was utilized in 95% of the patients with one patient converted to general anesthesia. The valve was placed in the intended position in all cases, there were no aborted implantation procedures or conversion to open heart surgery. Successful access, delivery and retrieval of the device and delivery system occurred in all cases. The average length of stay was 4.1 ± 2.4 days.

Valve Performance

The measurements of effective orifice area, mean gradient, total aortic regurgitation, aortic paravalvular regurgitation (PVL) are presented in Figure 122 to Figure 125. Mean EOA increased and gradients decreased. PVL was trace or none in 85% of the patients.

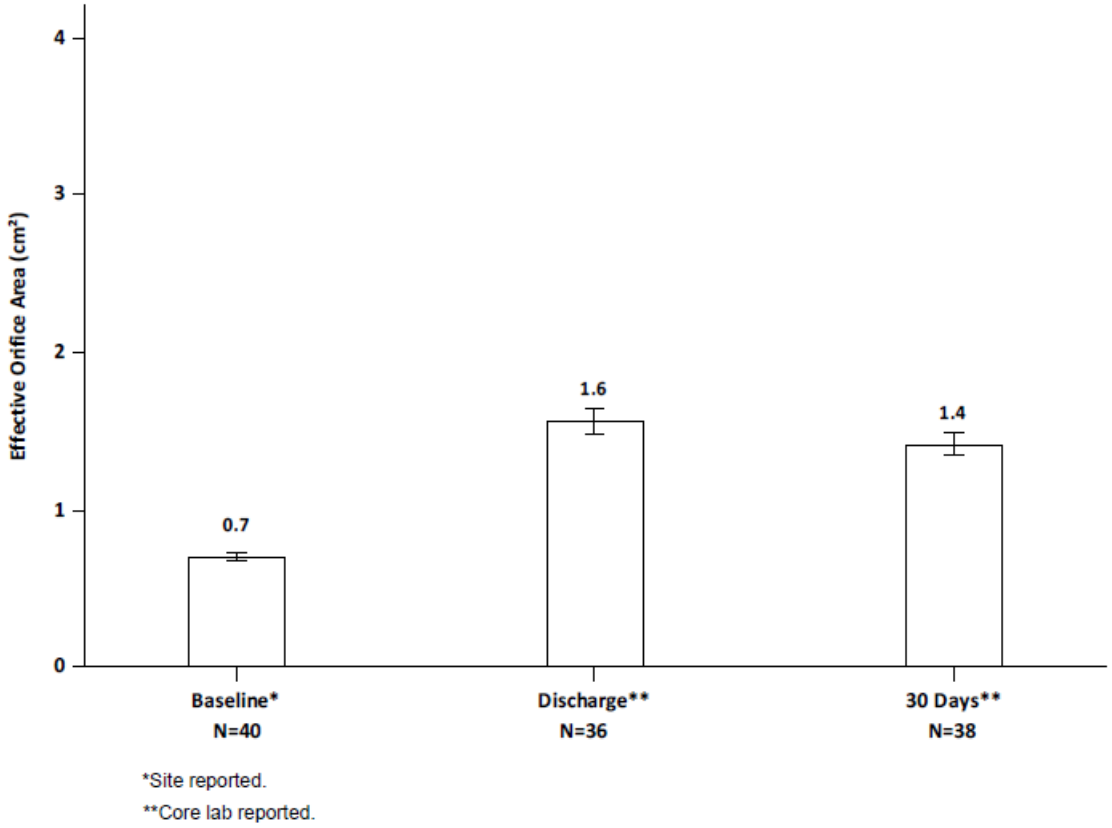


Figure 122: Effective Orifice Area

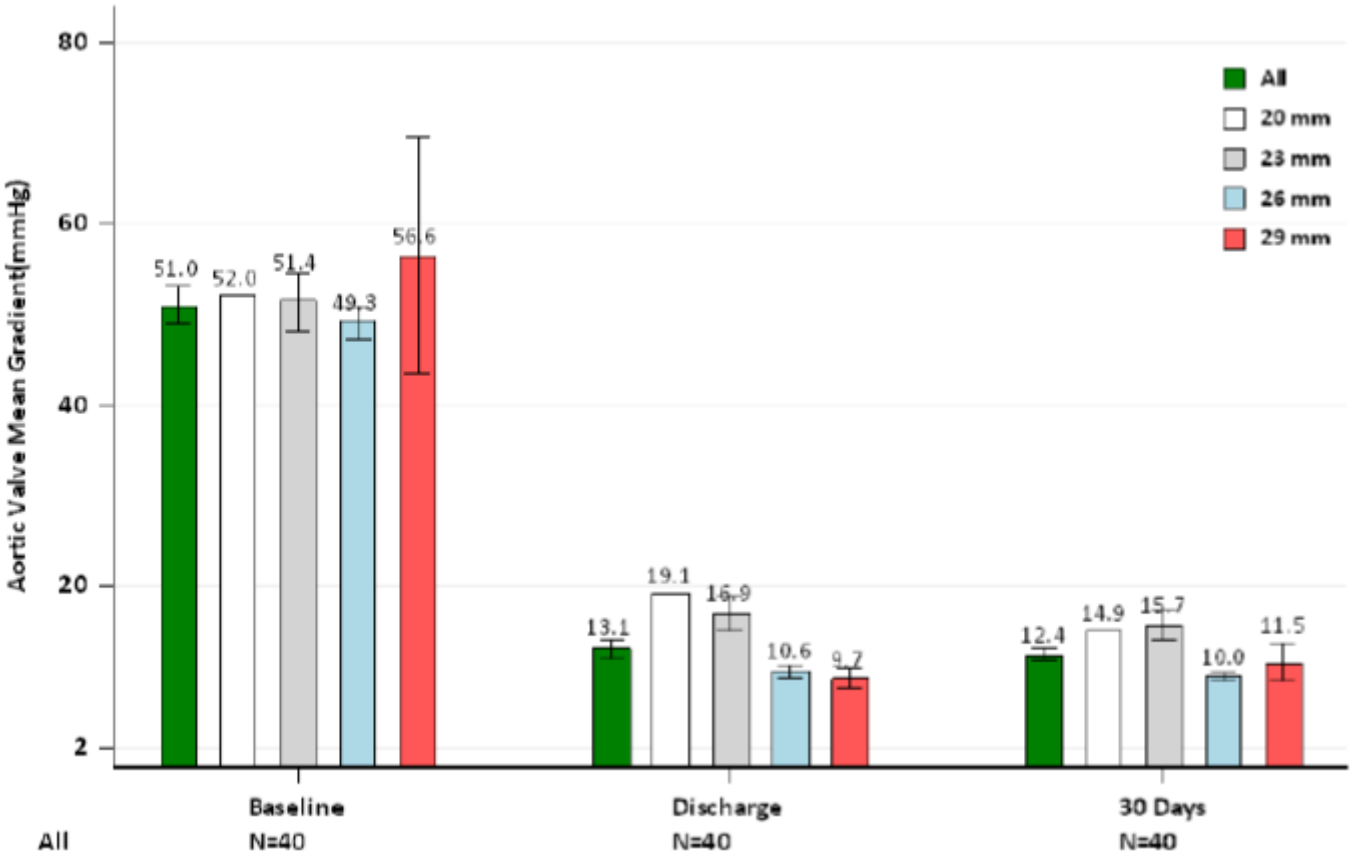


Figure 123: Mean Gradient by Valve Size

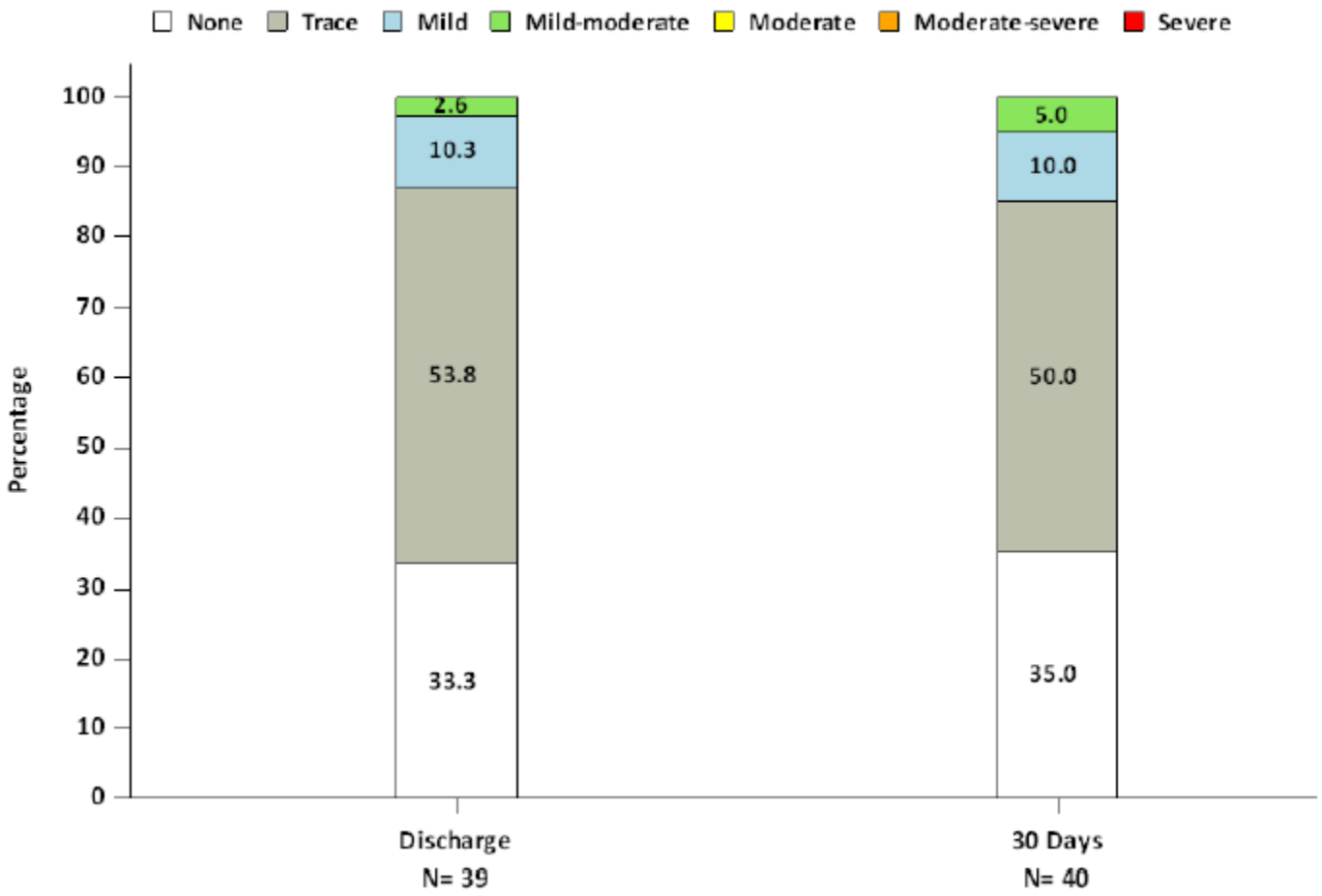


Figure 124: Total Aortic Regurgitation

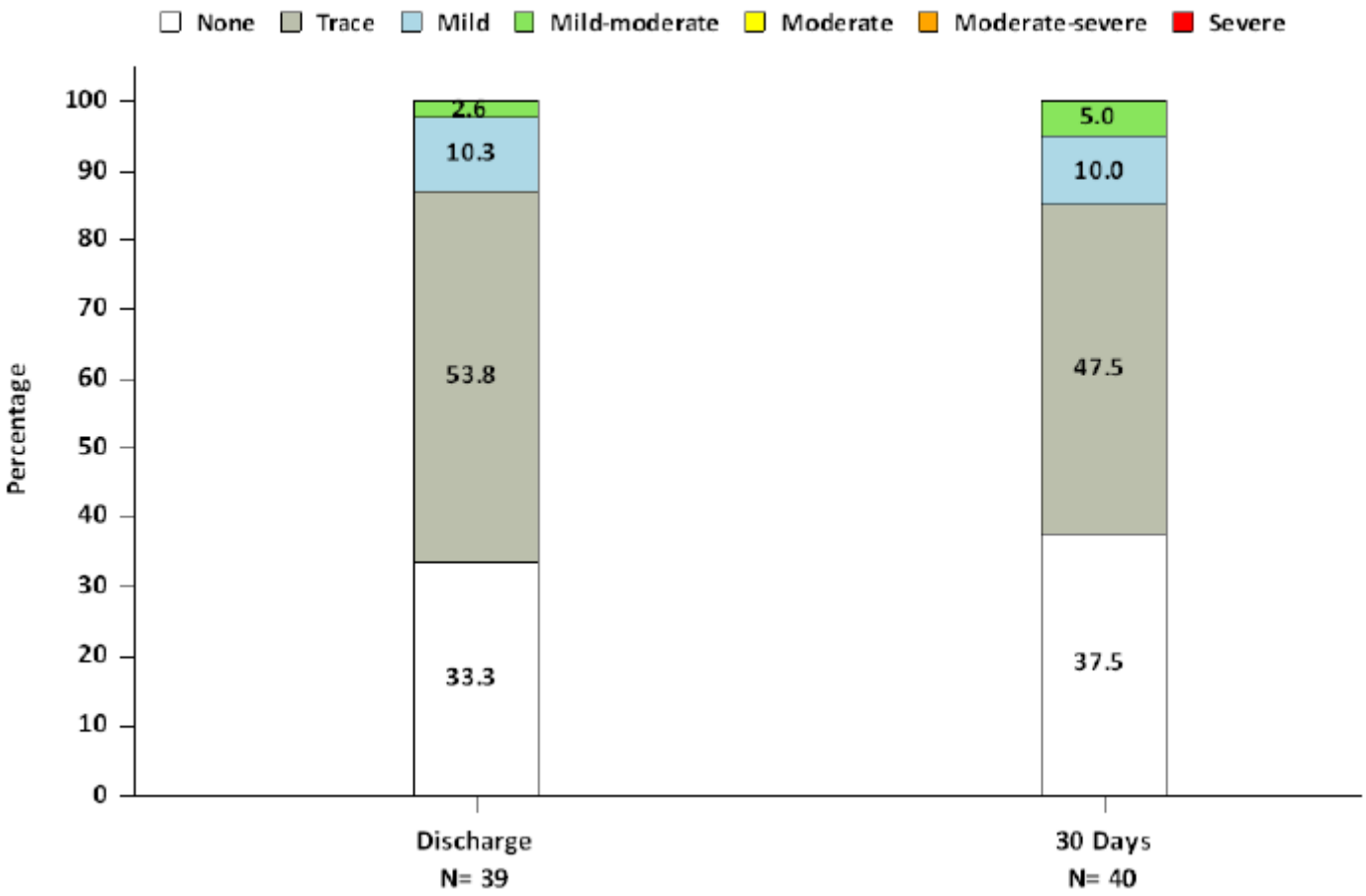


Figure 125: Aortic Paravalvular Regurgitation

New York Heart Association

The NYHA Functional Class summary is shown in Figure 126. At 30-day follow-up, 80.0% of subjects experienced improvement in NYHA Class and all subjects were in Class I/II.

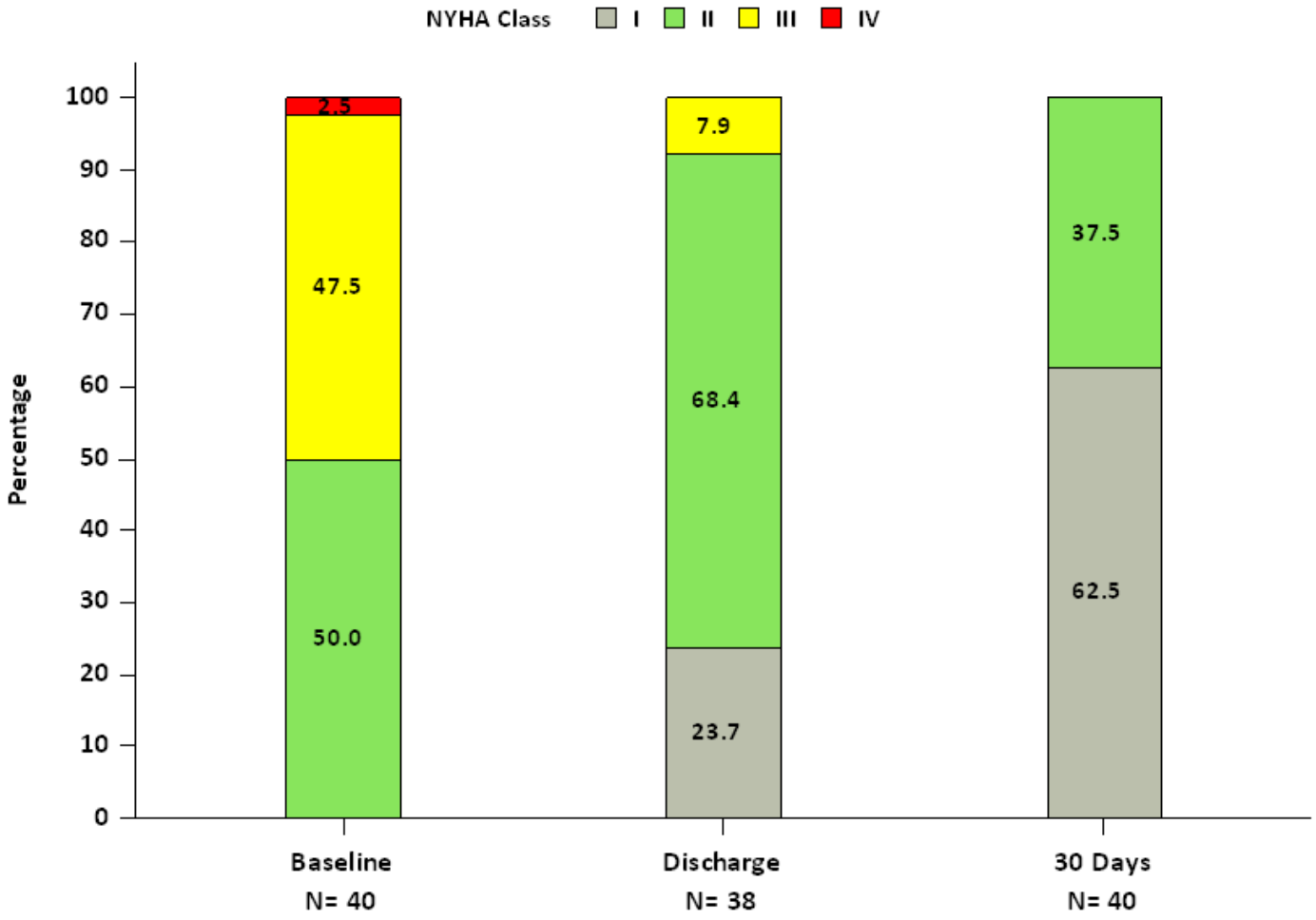


Figure 126: NYHA Class by Visit

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3. Imbens G. W. (2004) Nonparametric Estimation of Average Treatment Effects under Exogeneity: A Review. The Review of Economics and Statistics, February 2004, 86(1): 4–29.
4. Abbas AE, et al. (2020) Hemodynamic principles of prosthetic aortic valve evaluation in the transcatheter aortic valve replacement era. Echocardiography, 2020;37:738-757.

13.15 SAPIEN 3 VALVE IN VALVE INTERMEDIATE RISK - STS/ACC TRANSCATHETER VALVE THERAPY REGISTRY (TVTR) & PARTNER 3 MITRAL VALVE IN VALVE (P3 MVIV) STUDY ANALYSIS

Patient Accountability

At the time of database extract, 483 of the 502 patients were eligible for the 30-day visit and 425 (88.0%) completed the visit within the 30-day follow-up window, defined as the period between 21 days post-procedure and 75 days post-procedure. At 1 year, 439 patients were eligible for the 1-year visit and 308 (70.2%) completed the visit within the follow-up window, defined as the period between 305 days post-procedure and 425 days post-procedure. A detailed summary of the patient accountability at 30 days and 1 year is shown in Table 114.

Table 114: Patient Visit Accountability

	30-day Visit	1-year Visit
Total patients	502	502
Non-eligible	19	63
Death	9	28
Withdrawal	37	28
Lost to follow-up	10	35
Visit not yet due	0	0
Eligible	483	439
Follow-up visit completed	88.0% (425)	70.2% (308)
Missed visit	12.0% (58)	29.8% (131)

The "Attempted Implant (AI)" population consisted of subjects from the P3 MVIV STUDY for whom the index procedure had begun and the patients entered into the TVTR mitral module with prior surgical mitral valve replacement procedure who underwent a procedure to implant SAPIEN 3 or S3U. The "Valve Implant (VI)" population consisted of those patients for whom the valve implant procedure has started and a "No" was indicated for both "procedure aborted" and "conversion to open heart surgery" in the TVT Registry. The numbers of patients in these two analysis populations are shown in Table 115.

Table 115: Analysis Population

Analysis Population	Number of Patients
Attempted implant population	502
Valve implant population	499

Study Population Demographics and Baseline Characteristics

The demographics and baseline characteristics of the patients, as shown in Table 116, present an elderly cohort of patients, with comorbidities consistent with the intermediate operative risk of the populations. A majority of patients were white and the study appears to underrepresent other racial and ethnic subpopulations.

Table 116: Demographics and Baseline Physical Characteristics (Pooled Cohort) Attempted Implant Population (N=502)

Demographics and Baseline Characteristics	Summary Statistics
Age (year)	71.7 ± 10.10 (502) 73.0 (66.0, 78.0) [59.0, 83.0]
Gender	
Male	43.2% (217/502)
Female	56.8% (285/502)
Hispanic or Latino Ethnicity	6.7% (33/494)
Race	
White	82.3% (413/502)
Black/African American	9.6% (48/502)
Asian	1.8% (9/502)
American Indian/Alaskan Native	0.8% (4/502)
Native Hawaiian/Pacific Islander	0.2% (1/502)

Demographics and Baseline Characteristics	Summary Statistics
Multiple	0.8% (4/502)
Unknown	3.2% (16/502)
Other	1.4% (7/502)
Society of Thoracic Surgeons (STS) score	5.0 ± 2.21 (479) 4.9 (3.7, 6.1) [2.6, 7.4]
New York Heart Association (NYHA) class	
I/II	29.2% (143/490)
III/IV	70.8% (347/490)
Previous myocardial infarction	13.0% (65/501)
Previous intervention	
Coronary artery bypass grafting (CABG)	26.3% (132/502)
Percutaneous coronary intervention (PCI)	13.7% (69/502)
Cerebrovascular accident (CVA)	16.3% (82/502)
Peripheral vascular disease	12.2% (61/502)
Atrial fibrillation/flutter	63.9% (321/502)
Permanent pacemaker	23.7% (119/502)
Hostile chest	12.5% (63/502)
Echocardiographic findings	
Mitral valve area (cm^2)	1.3 ± 0.73 (358) 1.1 (0.8, 1.7) [0.6, 2.3]
Mean mitral-valve gradient (mmHg)	12.5 ± 5.80 (478) 12.0 (9.0, 15.0) [6.0, 19.0]
Left ventricular ejection fraction (LVEF) (%)	56.6 ± 10.82 (492) 59.8 (52.0, 63.0) [41.0, 68.0]
≥Moderate mitral regurgitation	53.5% (264/493)
≥Moderate aortic regurgitation	8.3% (41/494)
≥Moderate tricuspid regurgitation	42.0% (210/500)
Continuous measures - Mean ± SD (Total no), median (Q1, Q3), [10%tile, 90%tile]; Categorical measures - % (n/Total no.); The total no. only counted the patients with valid values.	

Safety and Effectiveness Results

Co-Primary Endpoints

The co-primary endpoints are presented in Table 117 and in Kaplan-Meier curves in Figure 127 and Figure 128. The composite rate of death and stroke at 30 days was 2.5% which was less than the prespecified performance goal of 10.4%. Thus the first co-primary endpoint was met. The rate of death at 1 year was 6.9% which was less than the prespecified performance goal of 19.6%. Thus, the second co-primary endpoint was also met.

Table 117: Co-primary Endpoints (Pooled Cohort) Attempted Implant Population (N=502)

Primary Endpoint	Summary Statistics	95% Confidence Interval	Performance Goal	Pass/Fail*
All-cause death or all stroke at 30 day	2.5% (13, 12), 442	[1.41, 4.32]	10.4%	Pass
All-cause death at 1 year	6.9% (28, 28), 260	[4.81, 9.90]	19.6%	Pass

Kaplan-Meier estimate - % (no. of events, no. of subjects with the event), no. at risk. 95% CI is calculated based on normal distribution with KM estimated mean rate and Greenwood formula calculated standard error.

*Tests are performed sequentially. Test for 1 year death is performed only if the composite endpoint of all-cause death or all stroke at 30 day has passed performance goal.

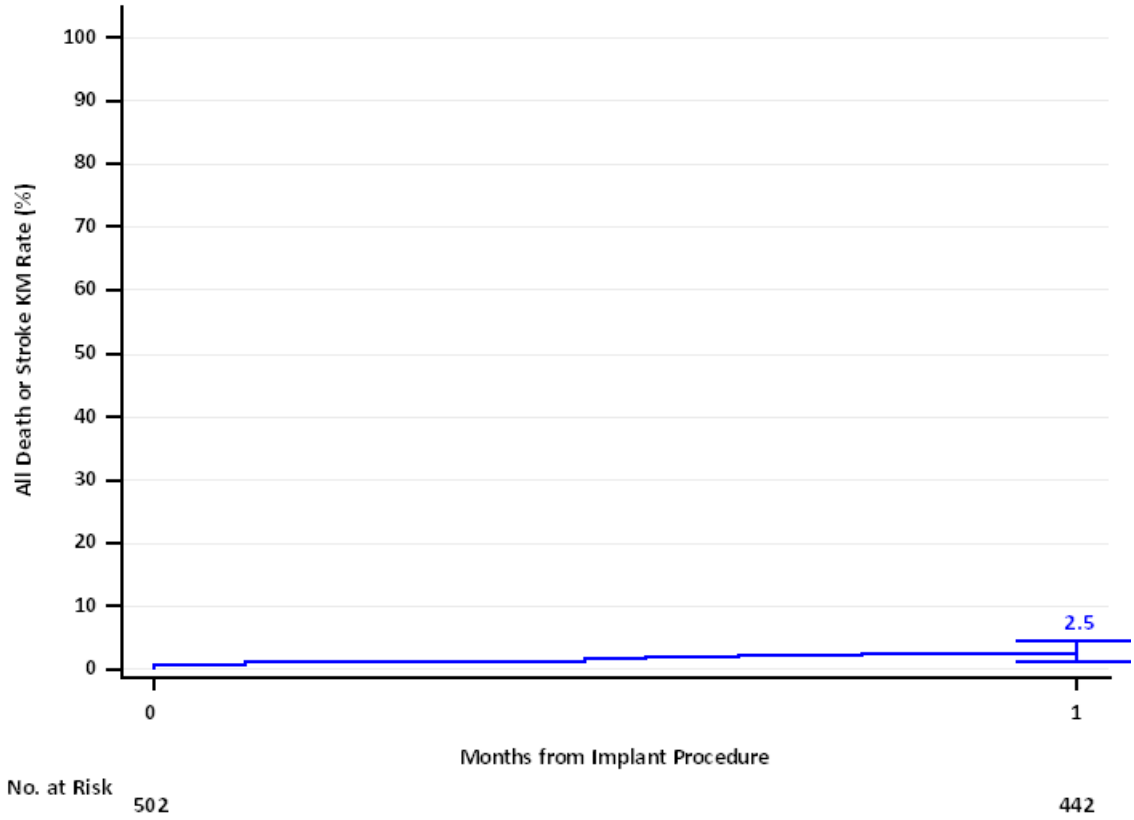


Figure 127: All-Cause Death or All Stroke at 30 days (AI Population)

Note: The 95% 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.

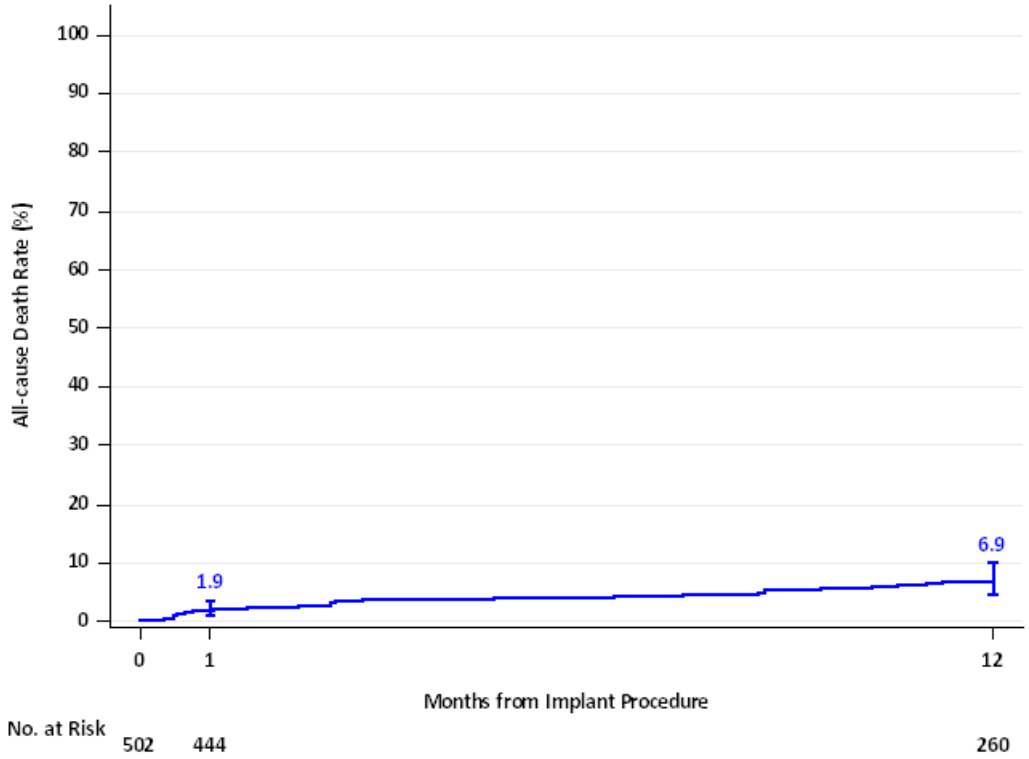


Figure 128: All-Cause Death at 1 year (AI Population)

Note: The 95% 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.

Additional Data Extract

As noted above, study compliance was 88% at 30 days and 70.2% at 1 year as of data submission. Edwards completed an updated analyses as of January 2024 and twenty additional patients had 1-year endpoint data. The updated co-primary endpoints with the twenty additional patients are presented in the table below.

Table 118: Co-primary Endpoints (Jan 2024) Attempted Implant Population (N=502)

Primary Endpoint	Summary Statistics	95% Confidence Interval	Performance Goal	Pass/Fail*
All-cause death or all stroke at 30 day	2.5% (13, 12), 448	[1.41, 4.31]	10.4%	Pass
All-cause death at 1 year	7.2% (30, 30), 278	[5.07, 10.16]	19.6%	Pass

Kaplan-Meier estimate - % (no. of events, no. of subjects with the event), no. at risk. 95% CI is calculated based on normal distribution with KM estimated mean rate and Greenwood formula calculated standard error.

*Tests are performed sequentially. Test for 1 year death is performed only if the composite endpoint of all-cause death or all stroke at 30 day has passed performance goal.

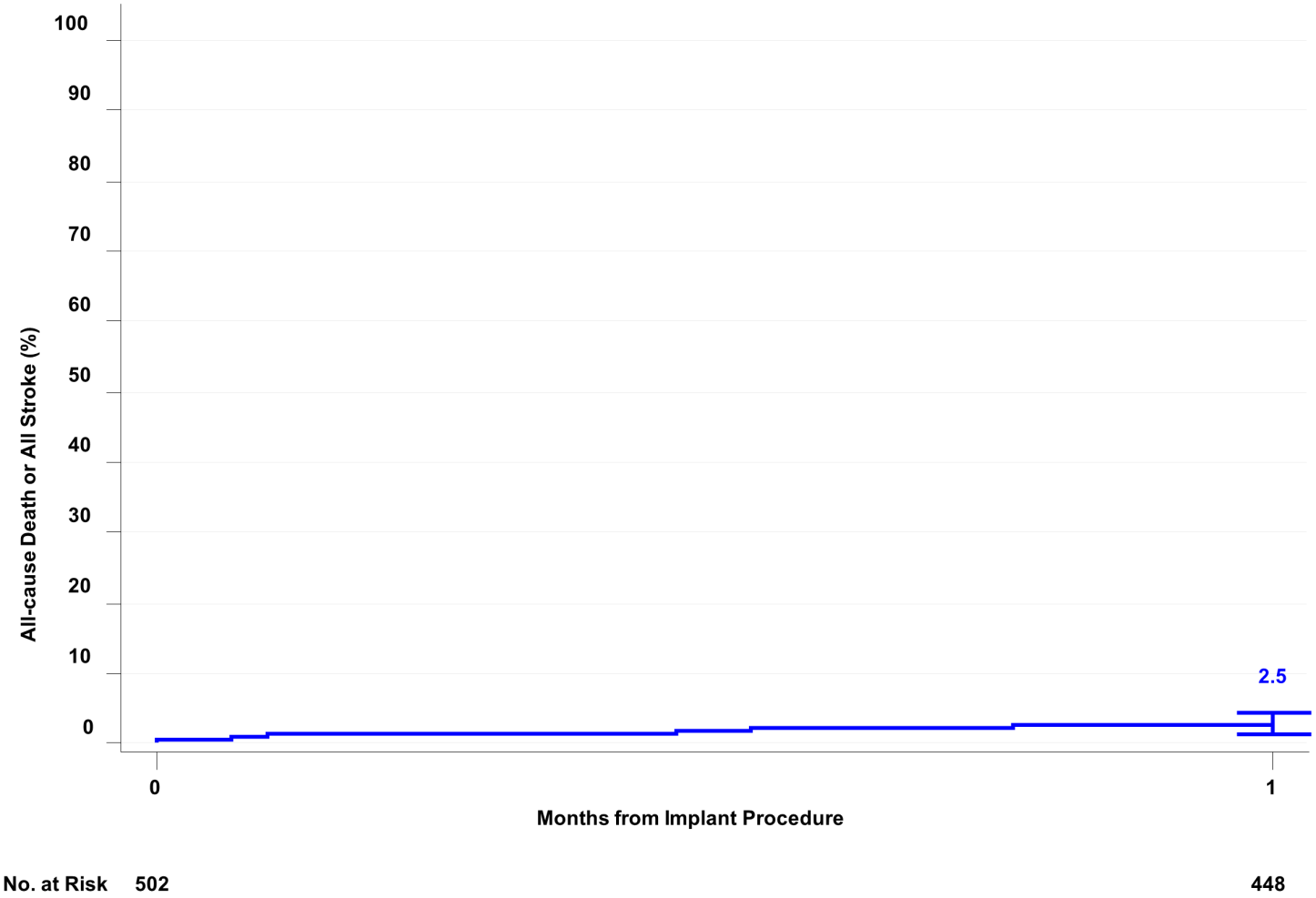


Figure 129: All-Cause Death or All Stroke at 30 days (Jan 2024) (AI Population)

Note: The 95% 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.

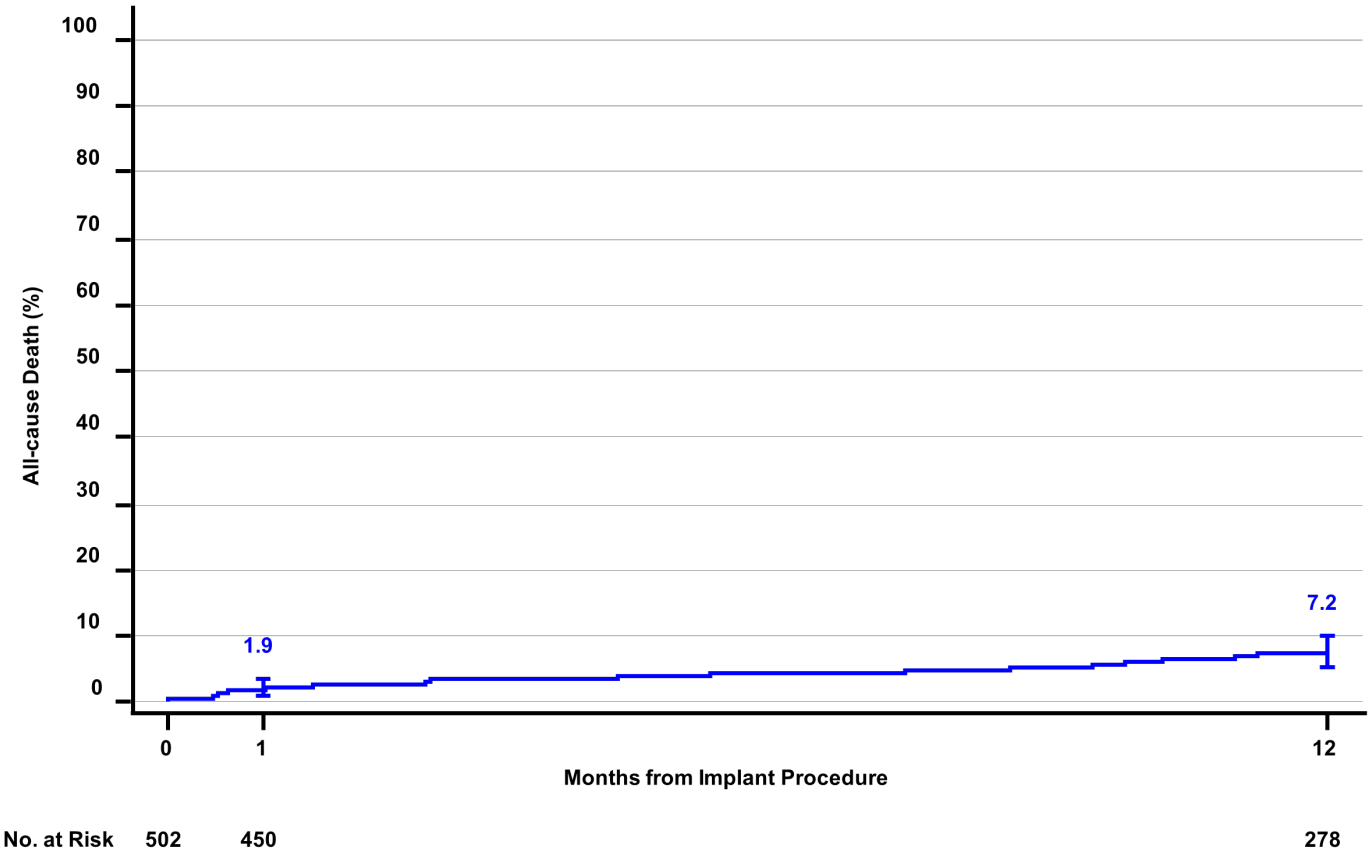


Figure 130: All-Cause Death (Jan 2024) (AI Population)

Note: The 95% 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.

In order to determine the impact of missing data on study outcomes, Edwards performed a tipping point analysis by imputing the number of events in subjects with missing data across multiple scenarios ranging from worst-case to best-case scenarios. To exceed the performance threshold for death, deaths at 1 year among the 195 patients with missing data at 1 year would have had to occur in 52 or more patients (26.7 percent), which would correspond to a risk in subjects with missing data that is 3.7 times the risk of death observed in those without missing data (7.2%). The tipping point analysis demonstrated that it is highly unlikely that the primary endpoints would have failed under a reasonable scenario if the data for these subjects were available. Therefore, the sensitivity analyses to address missing data issues are supportive of the primary analysis findings.

Safety Endpoints

The Kaplan-Meier estimates of site-reported adverse events through 1 year are presented in Table 119. The Kaplan-Meier curves for all-cause death or stroke at 30 days, all-cause death, and cardiac death are shown in Figure 131, Figure 132, and Figure 133, respectively. The all-cause mortality rate was 1.9% at 30 days and 6.9% at 1 year, including a cardiovascular mortality rate of 0.6% at 30 days and 2.5% at 1 year. Other relatively more frequent adverse events included major vascular complication (1.6% at 30 days and 1.9% at 1 year), major bleeding (1.3% at 30 days and 2.4% at 1 year), readmission due to heart failure (1.1% at 30 days and 5.7% at 1 year), and non-cardiac readmission (1.1% at 30 days and 6.1% at 1 year).

Table 119: Site-Reported Adverse Events (AI Population)

Adverse Event	Kaplan-Meier Rate*	
	30 Days (N = 502)	1 Year (N = 502)
Death or Stroke	2.5% (13, 12)	8.8% (38, 36)
All-cause death	1.9% (9, 9)	6.9% (28, 28)
All stroke	0.8% (4, 4)	2.2% (10, 9)
Cardiac Death	0.6% (3, 3)	2.5% (10, 10)
Mitral valve reintervention	0.0% (0, 0)	0.8% (4, 3)
Major vascular complication	1.6% (8, 8)	1.9% (10, 9)
Life threatening/Major bleeding**	1.5% (7, 7)	3.7% (17, 15)
Life threatening bleeding*	0.2% (1, 1)	1.3% (7, 5)
Major bleeding*	1.3% (6, 6)	2.4% (10, 10)
Myocardial infarction	0.4% (2, 2)	1.2% (5, 5)
New onset atrial fibrillation†	0.8% (3, 3)	2.7% (8, 8)
New permanent pacemaker†	0.8% (3, 3)	1.9% (6, 6)
Readmission - cardiac	2.1% (10, 10)	11.1% (53, 43)
Heart failure	1.1% (5, 5)	5.7% (29, 22)
Non-heart failure	1.1% (5, 5)	6.1% (24, 23)

*Kaplan-Meier rate - % (no. of events, no. of patients with the event)

**In TVTR data, in-hospital bleeding is not captured as life-threatening or major, therefore rates only include bleeding reported after index hospitalization.

†Subjects with baseline condition are excluded.

Effectiveness Endpoints

Mitral Regurgitation

Mitral regurgitation is shown in Figure 131. Moderate or greater total mitral regurgitation was observed in 53.5% of the patients at baseline, which decreased to 0.8% at 30 days and 1.0% at 1 year.

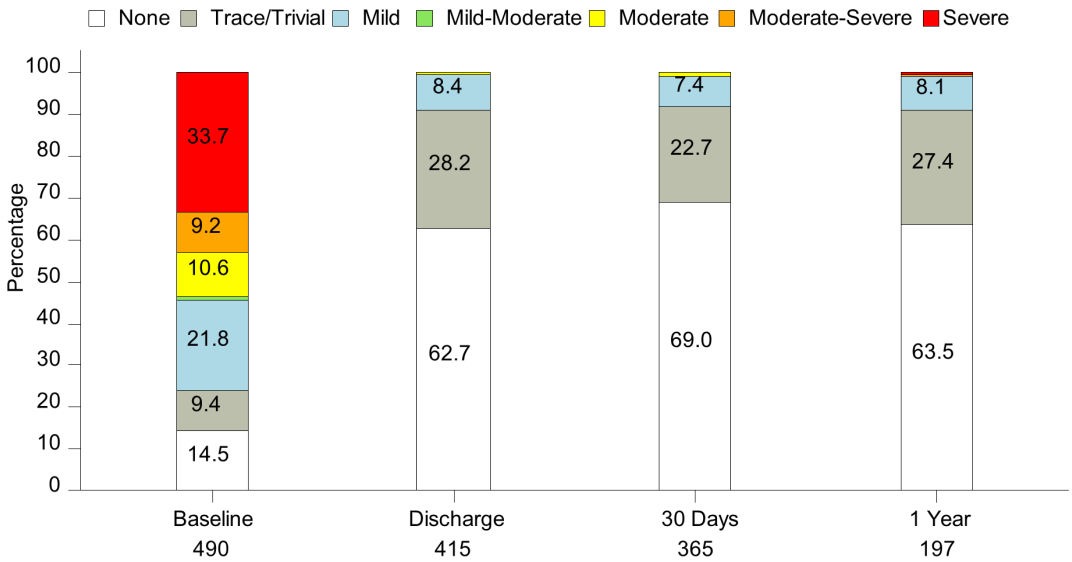


Figure 131: Mitral Regurgitation (VI Population)

Note: The total number of subjects at each visit time point only counted the subjects with valid values.

Paravalvular Leak

Paravalvular leak (PVL) is shown in Figure 132. Moderate or greater PVL was observed in 9.9% of the patients at baseline, which decreased to 0.3% at 30 days and 1.2% at 1 year.

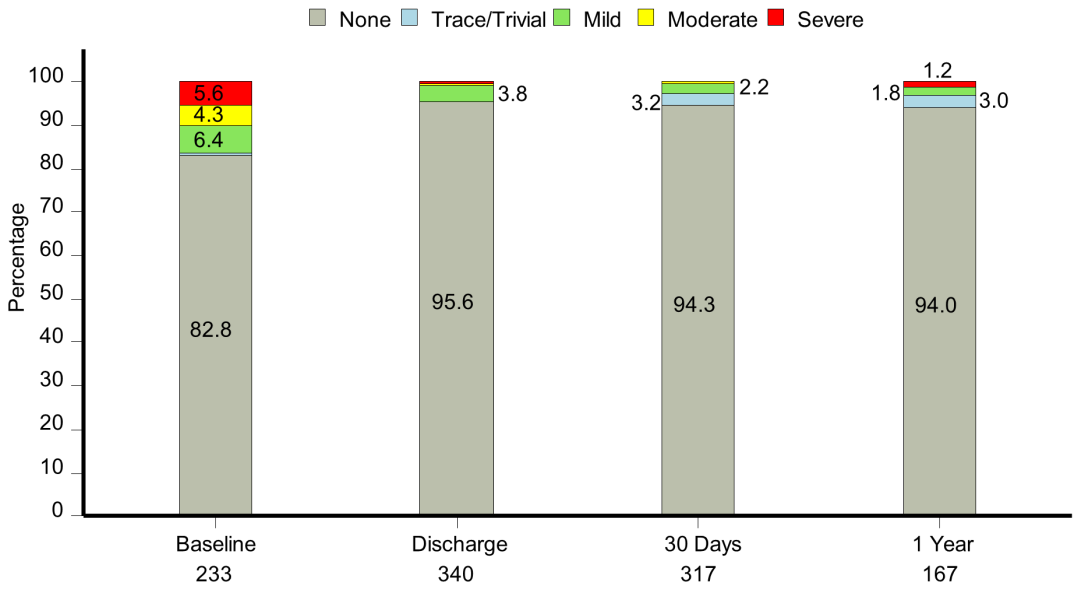


Figure 132: Paravalvular Leak (VI Population)

Note: The total number of subjects at each visit time point only counted the subjects with valid values.

Mean Mitral Gradient

Mean mitral gradient is shown in Figure 133. At baseline, mean mitral gradient was 12.5 mmHg. At 30 days, the mean gradient decreased to 7.6 mmHg at 30 days and 7.5 mmHg at 1 year.

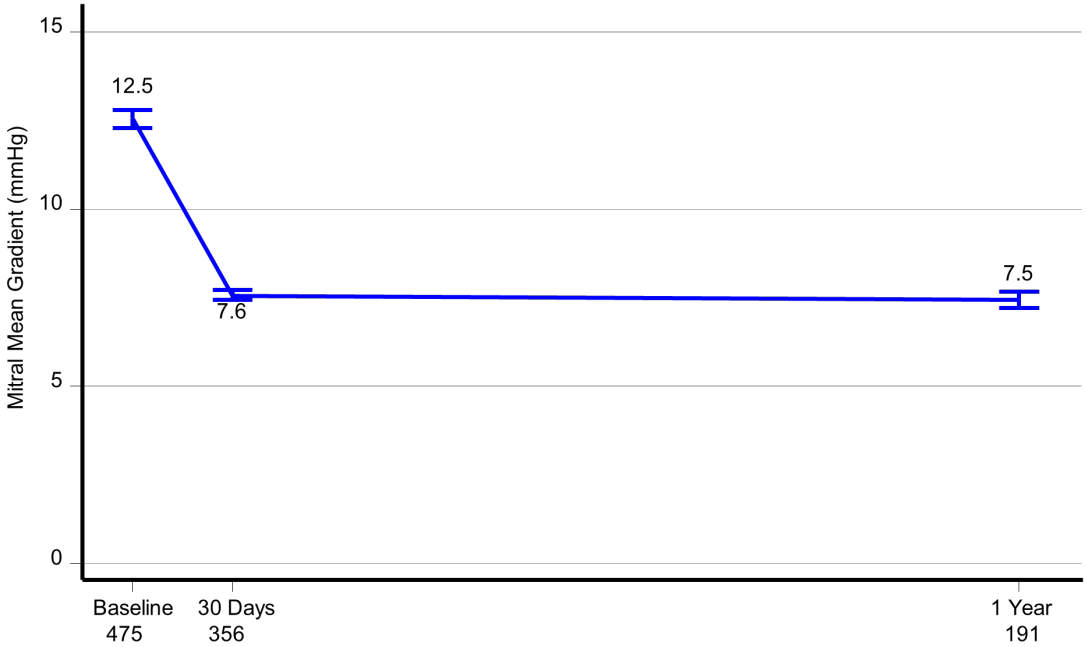


Figure 133: Mean Mitral Gradient (VI Population)

Mitral Valve Area

At baseline, mean mitral valve area was 1.31 cm^2. At 30 days, the mean mitral valve area increased to 1.72 cm^2 and 1.69 cm^2 at 1 year.

Table 120: Mitral Valve Area (Pooled Cohort) Valve Implant Population (N=499)

	Baseline	30-day visit	1-year visit
Mitral valve area (cm^2)	1.31 ± 0.039 (356) 1.08 (0.80, 1.68) [0.60, 2.30]	1.72 ± 0.052 (240) 1.54 (1.20, 2.00) [0.96, 2.71]	1.69 ± 0.075 (122) 1.50 (1.23, 1.88) [1.10, 2.30]

Continuous measures - Mean ± SE (Total no), median (Q1, Q3), [10%tile, 90%tile]. The total no. only counted the patients with valid values. The echo data from IDE cohort are from echo core lab and TVT echo data are from site-reported.

Left Ventricular Ejection Fraction (LVEF)

At baseline, LVEF was 56.5%. At 30 days, LVEF was 55.4% and 55.3% at 1 year.

Table 121: Left Ventricular Ejection Fraction (LVEF) (Pooled Cohort) Valve Implant Population (N=499)

	Baseline	30-day visit	1-year visit
LVEF (%)	56.5 ± 0.49 (489) 59.0 (52.0, 63.0) [41.0, 68.0]	55.4 ± 0.58 (360) 57.0 (50.0, 63.0) [40.0, 68.5]	55.3 ± 0.80 (203) 57.0 (50.0, 63.0) [42.0, 68.0]

Continuous measures - Mean ± SE (Total no), median (Q1, Q3), [10%tile, 90%tile]. The total no. only counted the patients with valid values. The echo data from IDE cohort are from echo core lab and TVT echo data are from site-reported.

Six-Minute Walk Test

At baseline, the six-minute walk test distance was 221.5 meters. At 30 days, the six-minute walk test distance was 332.9 meters and 331.5 meters at 1 year.

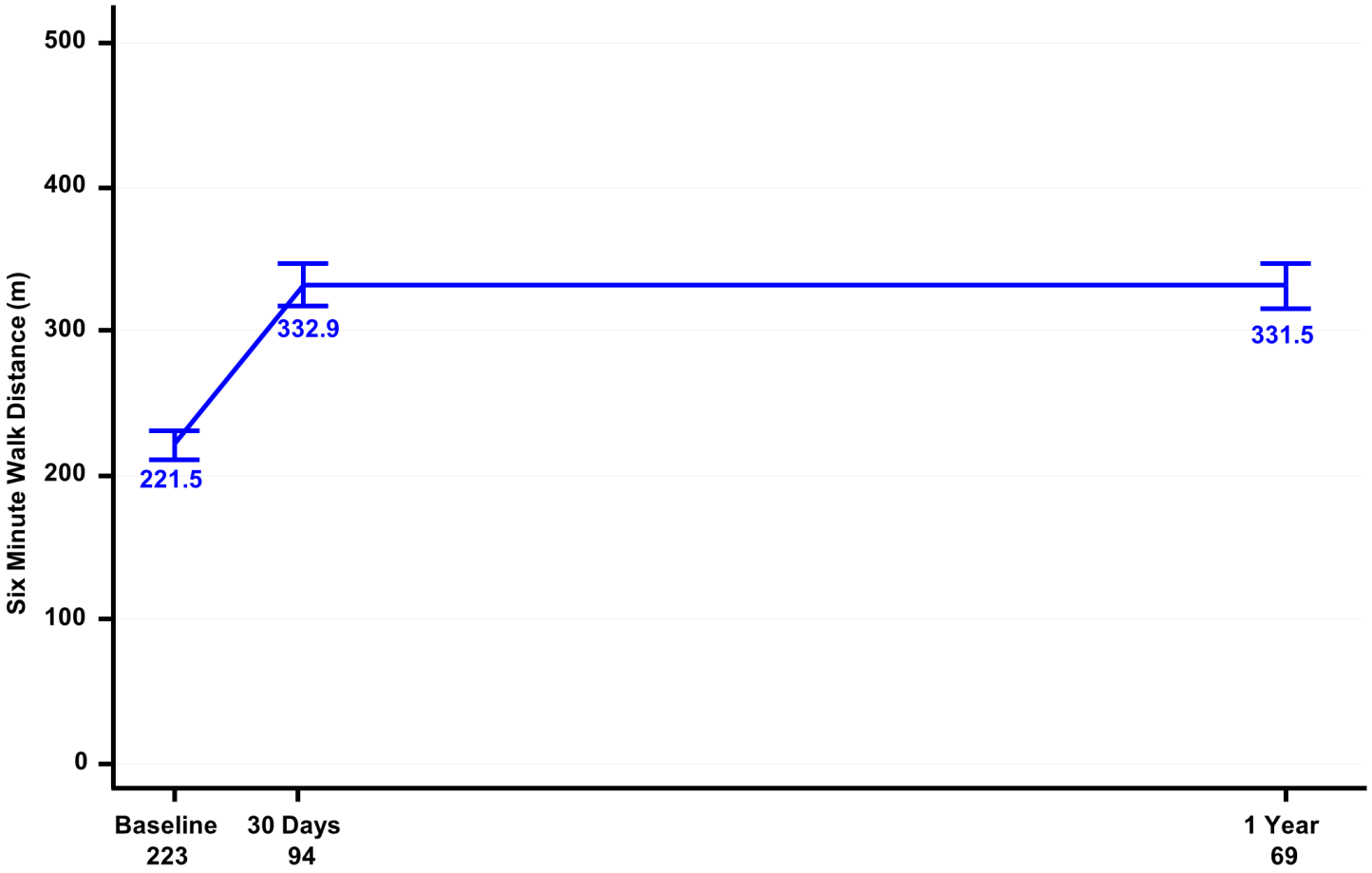


Figure 134: Six-Minute Walk Test (Meter) (Pooled Cohort) Valve Implant Population (N=499)

Note: The total number of subjects at each visit time point only counted the subjects with valid values.

New York Heart Association Functional Class

The NYHA functional class distributions by visit are presented in Figure 135. At baseline, 70.6% of patients were in NYHA Class III/IV. At 1 year, the majority (89.3%) of patients were in NYHA Class I/II.

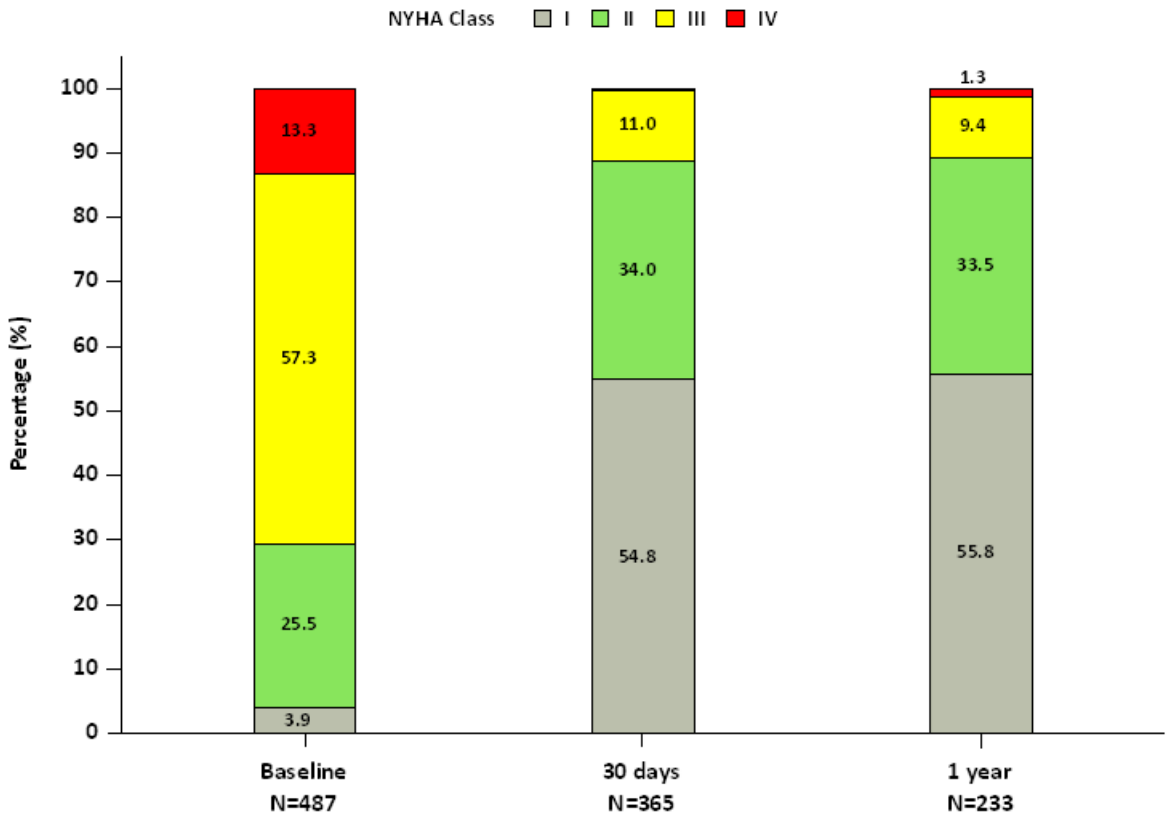


Figure 135: NYHA Class by Visit (VI Population)

Length of Stay

The mean index hospitalization stay was 2.4 days as summarized in Table 122.

Table 122: Index Hospitalization (AI Population)

Index hospitalization	Length in days*
Index hospitalization duration	2.4 ± 0.11 (496)
In-hospital death	1.2% (6/502)
Discharge location	
Home	95.6% (474/496)
Skilled nursing facility	1.4% (7/496)
Extended care/TCU/rehab	2.4% (12/496)
Other acute care hospital	0.2% (1/496)
Other discharge location	0.4% (2/496)

*Continuous measures - mean ± SE (Total no.); Categorical measures - % (no./Total no).

Quality of Life

The results for the KCCQ overall summary score are presented in Figure 136. The mean score increased from 42.6 at baseline to 77.3 and 78.6 at 30 days and 1 year, respectively.

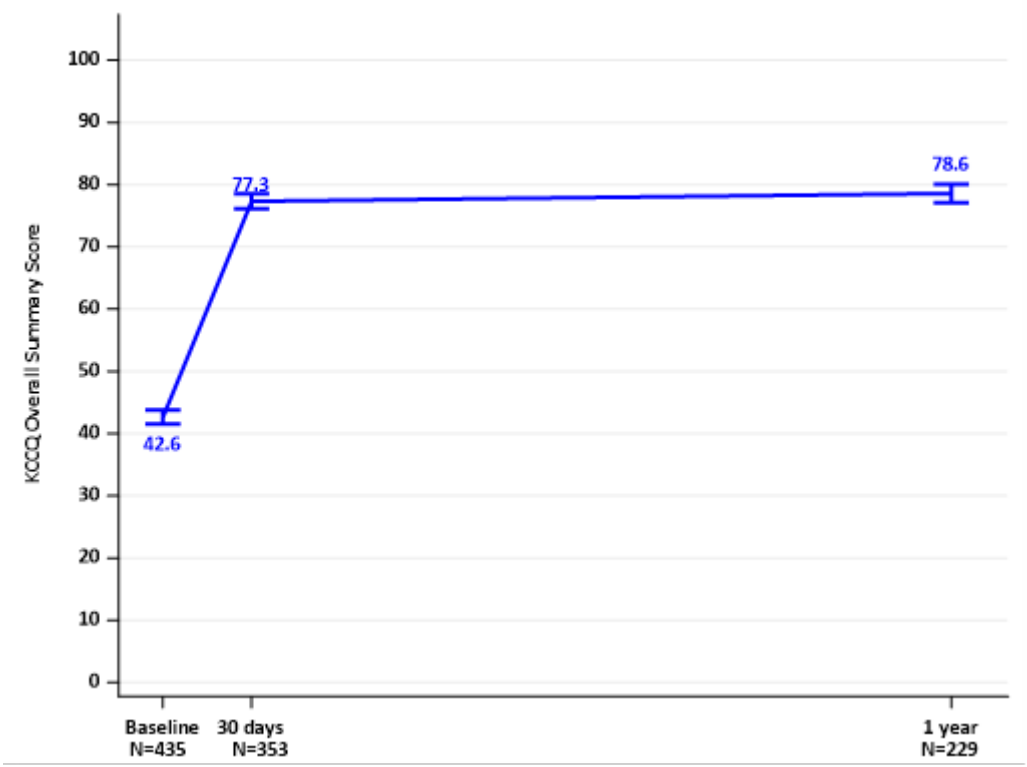


Figure 136: KCCQ Overall Summary Score (VI Population)

Note: Line plot with mean and standard error. The total number of patients at each time point only counted the patients with valid values.

Subgroup Analyses

The following baseline characteristics were evaluated for potential association with safety and effectiveness outcomes: gender, race and ethnicity. The study was not specifically powered for gender, race and ethnicity subgroups. Although race and ethnic groups were under-represented when compared with their representation in the U.S. census population, the results for subgroup analyses of the primary endpoints were consistent with those of the primary analysis.

Table 123: Co-primary Endpoints by Gender Attempted Implant Population (N=502)

	Male (N=217)		Female (N=285)	
Primary Endpoint	**Summary Statistics**	**95% Confidence Interval**	**Summary Statistics**	**95% Confidence Interval**
All-cause death or all stroke at 30 day	1.9% (4, 4), 191	[0.72, 5.01]	2.9% (9, 8), 251	[1.46, 5.71]
All-cause death at 1 year	9.2% (16, 16), 114	[5.74, 14.67]	5.1% (12, 12), 146	[2.92, 8.90]
Kaplan-Meier estimate - % (no. of events, no. of subjects with the event), no. at risk. 95% CI is calculated based on normal distribution with KM estimated mean rate and Greenwood formula calculated standard error.				

Table 124: Co-primary Endpoints by Race Attempted Implant Population (N=502)

	Summary Statistics							
	White (N=413)	Black/ African American (N=48)	Asian (N=9)	American Indian/ Alaskan Native (N=4)	Native Hawaiian/ Pacific Islander* (N=1)	Multiple (N=4)	Unknown (N=16)	Other (N=7)
All-cause death or all stroke at 30 day	(12, 11), 364	(1, 1), 41	(0, 0), 9	(0, 0), 2	(0, 0), .*	(0, 0), 4	(0, 0), 15	(0, 0), 7
All-cause death at 1 year	(24, 24), 212	(2, 2), 21	(0, 0), 5	(0, 0), 2	(0, 0), .*	(0, 0), 4	(2, 2), 9	(0, 0), 7

*The patient exits the study on Day 29.

Kaplan-Meier estimate - % (no. of events, no. of subjects with the event), no. at risk. 95% CI is calculated based on normal distribution with KM estimated mean rate and Greenwood formula calculated standard error.

Table 125: Co-primary Endpoints by Ethnicity Attempted Implant Population (N=502)

	Hispanic (N=33)		Non-Hispanic (N=461)	
Primary Endpoint	Summary Statistics	95% Confidence Interval	Summary Statistics	95% Confidence Interval
All-cause death or all stroke at 30 day	3.0% (1, 1), 31	[0.43, 19.63]	2.5% (12, 11), 405	[1.37, 4.41]
All-cause death at 1 year	14.7% (4, 4), 18	[5.73, 34.71]	6.4% (24, 24), 240	[4.34, 9.49]

Kaplan-Meier estimate - % (no. of events, no. of subjects with the event), no. at risk. 95% CI is calculated based on normal distribution with KM estimated mean rate and Greenwood formula calculated standard error.

Table 126: Site Reported Adverse Events by Gender Attempted Implant Population (N=502)

	Kaplan-Meier Estimate			
	Male (N=217)		Female (N=285)	
	30 Days	1 Year	30 Days	1 Year
Death or stroke	1.9% (4, 4), 191	10.9% (19, 19), 112	2.9% (9, 8), 251	7.2% (19, 17), 142
All-cause death	1.4% (3, 3), 192	9.2% (16, 16), 114	2.2% (6, 6), 252	5.1% (12, 12), 146
All stroke	0.5% (1, 1), 191	1.7% (3, 3), 112	1.1% (3, 3), 251	2.5% (7, 6), 142
Cardiac death	0.0% (0, 0), 192	3.0% (5, 5), 114	1.1% (3, 3), 252	2.1% (5, 5), 146
Mitral valve reintervention	0.0% (0, 0), 192	0.6% (1, 1), 113	0.0% (0, 0), 252	0.9% (3, 2), 146
Major vascular complication	1.9% (4, 4), 189	1.9% (4, 4), 113	1.4% (4, 4), 250	1.9% (6, 5), 145
Life threatening/major bleeding*	1.5% (3, 3), 189	2.7% (5, 5), 112	1.5% (4, 4), 249	4.4% (12, 10), 143
Life threatening bleeding*	0.0% (0, 0), 192	0.6% (1, 1), 114	0.4% (1, 1), 252	1.8% (6, 4), 145
Major bleeding*	1.5% (3, 3), 189	2.1% (4, 4), 112	1.1% (3, 3), 249	2.6% (6, 6), 144
Myocardial infarction	0.0% (0, 0), 192	1.9% (3, 3), 112	0.7% (2, 2), 251	0.7% (2, 2), 146
New onset atrial fibrillation†	0.0% (0, 0), 145	1.0% (1, 1), 82	1.4% (3, 3), 198	4.0% (7, 7), 108
New permanent pacemaker†	1.3% (2, 2), 142	3.0% (4, 4), 87	0.5% (1, 1), 197	1.1% (2, 2), 115
Readmission - cardiac	1.0% (2, 2), 190	11.1% (20, 18), 104	3.0% (8, 8), 245	11.1% (33, 25), 132
Heart failure	1.0% (2, 2), 190	6.1% (12, 10), 110	1.1% (3, 3), 250	5.4% (17, 12), 141

	Kaplan-Meier Estimate			
	Male (N=217)		Female (N=285)	
	30 Days	1 Year	30 Days	1 Year
Non-heart failure	0.0% (0, 0), 192	5.1% (8, 8), 108	1.9% (5, 5), 247	6.8% (16, 15), 136

Kaplan-Meier estimate - % (no. of events, no. of subjects with the event), no. at risk.

*In TVTR data, in-hospital bleeding is not captured as life-threatening or major, therefore rates only include bleeding reported after index hospitalization.

†Subjects with baseline condition are excluded.

Table 127: Site Reported Adverse Events by Race - 30 Days Attempted Implant Population (N=502)

	Kaplan-Meier Estimate			
	White (N=413)	Black/African American (N=48)	Asian (N=9)	American Indian/ Alaskan Native (N=4)
Death or stroke	(12, 11), 364	(1, 1), 41	(0, 0), 9	(0, 0), 2
All-cause death	(8, 8), 366	(1, 1), 41	(0, 0), 9	(0, 0), 2
All stroke	(4, 4), 364	(0, 0), 41	(0, 0), 9	(0, 0), 2
Cardiac death	(3, 3), 366	(0, 0), 41	(0, 0), 9	(0, 0), 2
Mitral valve reintervention	(0, 0), 366	(0, 0), 41	(0, 0), 9	(0, 0), 2
Major vascular complication	(8, 8), 361	(0, 0), 41	(0, 0), 9	(0, 0), 2
Life threatening/major bleeding†	(5, 5), 362	(2, 2), 39	(0, 0), 9	(0, 0), 2
Life threatening bleeding†	(1, 1), 366	(0, 0), 41	(0, 0), 9	(0, 0), 2
Major bleeding†	(4, 4), 362	(2, 2), 39	(0, 0), 9	(0, 0), 2
Myocardial infarction	(2, 2), 365	(0, 0), 41	(0, 0), 9	(0, 0), 2
New onset atrial fibrillation‡	(3, 3), 278	(0, 0), 35	(0, 0), 6	(0, 0), 2
New permanent pacemaker‡	(3, 3), 273	(0, 0), 34	(0, 0), 8	(0, 0), 1
Readmission - cardiac	(6, 6), 361	(1, 1), 40	(0, 0), 9	(1, 1), 1
Heart failure	(2, 2), 365	(1, 1), 40	(0, 0), 9	(1, 1), 1
Non-heart failure	(4, 4), 362	(0, 0), 41	(0, 0), 9	(0, 0), 2

*The patient exits the study on Day 29.

Kaplan-Meier estimate - % (no. of events, no. of subjects with the event), no. at risk.

†In TVTR data, in-hospital bleeding is not captured as life-threatening or major, therefore rates only include bleeding reported after index hospitalization.

‡Subjects with baseline condition are excluded.

Table 128: Site Reported Adverse Events by Race - 30 Days (continued) Attempted Implant Population (N=502)

	Kaplan-Meier Estimate			
	Native Hawaiian/ Pacific Islander (N=1)	Multiple (N=4)	Unknown (N=16)	Other (N=7)
Death or stroke	(0, 0), 0*	(0, 0), 4	(0, 0), 15	(0, 0), 7
All-cause death	(0, 0), 0*	(0, 0), 4	(0, 0), 15	(0, 0), 7

	Kaplan-Meier Estimate			
	Native Hawaiian/ Pacific Islander (N=1)	Multiple (N=4)	Unknown (N=16)	Other (N=7)
All stroke	(0, 0), 0*	(0, 0), 4	(0, 0), 15	(0, 0), 7
Cardiac death	(0, 0), 0*	(0, 0), 4	(0, 0), 15	(0, 0), 7
Mitral valve reintervention	(0, 0), 0*	(0, 0), 4	(0, 0), 15	(0, 0), 7
Major vascular complication	(0, 0), 0*	(0, 0), 4	(0, 0), 15	(0, 0), 7
Life threatening/major bleeding†	(0, 0), 0*	(0, 0), 4	(0, 0), 15	(0, 0), 7
Life threatening bleeding†	(0, 0), 0*	(0, 0), 4	(0, 0), 15	(0, 0), 7
Major bleeding†	(0, 0), 0*	(0, 0), 4	(0, 0), 15	(0, 0), 7
Myocardial infarction	(0, 0), 0*	(0, 0), 4	(0, 0), 15	(0, 0), 7
New onset atrial fibrillation‡	(0, 0), 0*	(0, 0), 3	(0, 0), 13	(0, 0), 6
New permanent pacemaker‡	(0, 0), 0*	(0, 0), 3	(0, 0), 13	(0, 0), 7
Readmission - cardiac	(0, 0), 0*	(0, 0), 4	(0, 0), 14	(1, 1), 6
Heart failure	(0, 0), 0*	(0, 0), 4	(1, 1), 14	(0, 0), 7
Non-heart failure	(0, 0), 0*	(0, 0), 4	(1, 1), 15	(1, 1), 6

*The patient exits the study on Day 29.

Kaplan-Meier estimate - % (no. of events, no. of subjects with the event), no. at risk.

†In TVTR data, in-hospital bleeding is not captured as life-threatening or major, therefore rates only include bleeding reported after index hospitalization.

‡Subjects with baseline condition are excluded.

Table 129: Site Reported Adverse Events by Ethnicity Attempted Implant Population (N=502)

	Kaplan-Meier Estimate			
	Hispanic (N=33)		Non-Hispanic (N=461)	
	30 Days	1 Year	30 Days	1 Year
Death or stroke	3.0% (1, 1), 31	14.7% (4, 4), 18	2.6% (12, 11), 405	8.5% (34, 32), 234
All-cause death	3.0% (1, 1), 31	14.7% (4, 4), 18	1.8% (8, 8), 407	6.4% (24, 24), 240
All stroke	0.0% (0, 0), 31	0.0% (0, 0), 18	0.9% (4, 4), 405	2.4% (10, 9), 234
Cardiac death	3.0% (1, 1), 31	6.9% (2, 2), 18	0.4% (2, 2), 407	2.2% (8, 8), 240
Mitral valve reintervention	0.0% (0, 0), 31	0.0% (0, 0), 18	0.0% (0, 0), 407	0.8% (4, 3), 239
Major vascular complication	3.0% (1, 1), 31	3.0% (1, 1), 18	1.5% (7, 7), 402	1.8% (9, 8), 238
Life threatening/major bleeding*	0.0% (0, 0), 31	0.0% (0, 0), 18	1.6% (7, 7), 401	4.0% (17, 15), 235
Life threatening bleeding*	0.0% (0, 0), 31	0.0% (0, 0), 18	0.2% (1, 1), 407	1.4% (7, 5), 239
Major bleeding*	0.0% (0, 0), 31	0.0% (0, 0), 18	1.4% (6, 6), 401	2.6% (10, 10), 236
Myocardial infarction	0.0% (0, 0), 31	4.3% (1, 1), 17	0.5% (2, 2), 406	1.0% (4, 4), 239
New onset atrial fibrillation†	4.3% (1, 1), 21	4.3% (1, 1), 14	0.6% (2, 2), 316	2.7% (7, 7), 174
New permanent pacemaker†	0.0% (0, 0), 20	0.0% (0, 0), 14	0.9% (3, 3), 314	2.1% (6, 6), 186
Readmission - cardiac	3.1% (1, 1), 30	7.0% (2, 2), 17	1.8% (8, 8), 400	11.3% (50, 40), 218
Heart failure	0.0% (0, 0), 31	4.0% (1, 1), 17	1.2% (5, 5), 403	5.9% (28, 21), 232

	Kaplan-Meier Estimate			
	Hispanic (N=33)		Non-Hispanic (N=461)	
	30 Days	1 Year	30 Days	1 Year
Non-heart failure	3.1% (1, 1), 30	3.1% (1, 1), 18	0.7% (3, 3), 404	6.1% (22, 21), 225

Kaplan-Meier estimate - % (no. of events, no. of subjects with the event), no. at risk.

*In TVTR data, in-hospital bleeding is not captured as life-threatening or major, therefore rates only include bleeding reported after index hospitalization.

†Subjects with baseline condition are excluded.

Table 130: Mitral Regurgitation by Gender Valve Implant Population (N=499)

	Summary Statistics					
	Male (N=217)			Female (N=282)		
	Baseline	30-day Visit	1-year Visit	Baseline	30-day Visit	1-year Visit
Mitral regurgitation						
None	14.2% (30/212)	71.0% (115/162)	67.0% (61/91)	14.7% (41/278)	67.5% (137/203)	60.4% (64/106)
Trace/Trivial	9.9% (21/212)	23.5% (38/162)	27.5% (25/91)	9.0% (25/278)	22.2% (45/203)	27.4% (29/106)
Mild	19.8% (42/212)	5.6% (9/162)	3.3% (3/91)	23.4% (65/278)	8.9% (18/203)	12.3% (13/106)
Mild-Moderate	0.5% (1/212)	0.0% (0/162)	0.0% (0/91)	1.1% (3/278)	0.0% (0/203)	0.0% (0/106)
Moderate	11.8% (25/212)	0.0% (0/162)	0.0% (0/91)	9.7% (27/278)	1.5% (3/203)	0.0% (0/106)
Moderate-Severe	9.9% (21/212)	0.0% (0/162)	1.1% (1/91)	8.6% (24/278)	0.0% (0/203)	0.0% (0/106)
Severe	34.0% (72/212)	0.0% (0/162)	1.1% (1/91)	33.5% (93/278)	0.0% (0/203)	0.0% (0/106)
Grouped mitral regurgitation						
<Moderate	44.3% (94/212)	100.0% (162/162)	97.8% (89/91)	48.2% (134/278)	98.5% (200/203)	100.0% (106/106)
≥Moderate	55.7% (118/212)	0.0% (0/162)	2.2% (2/91)	51.8% (144/278)	1.5% (3/203)	0.0% (0/106)

Continuous measures - Mean ± SE (Total no), median (Q1, Q3), [10%tile, 90%tile]. The total no. only counted the patients with valid values.

Table 131: Mitral Regurgitation by Ethnicity Valve Implant Population (N=499)

	Summary Statistics					
	Hispanic (N=32)			Non-Hispanic (N=459)		
	Baseline	30-day Visit	1-year Visit	Baseline	30-day Visit	1-year Visit
Mitral regurgitation						
None	12.5% (4/32)	79.2% (19/24)	70.0% (7/10)	14.7% (66/450)	68.0% (229/337)	63.0% (116/184)
Trace/Trivial	12.5% (4/32)	16.7% (4/24)	20.0% (2/10)	9.3% (42/450)	23.4% (79/337)	28.3% (52/184)
Mild	15.6% (5/32)	4.2% (1/24)	10.0% (1/10)	22.0% (99/450)	7.7% (26/337)	7.6% (14/184)
Mild-Moderate	3.1% (1/32)	0.0% (0/24)	0.0% (0/10)	0.7% (3/450)	0.0% (0/337)	0.0% (0/184)
Moderate	6.3% (2/32)	0.0% (0/24)	0.0% (0/10)	11.1% (50/450)	0.9% (3/337)	0.0% (0/184)
Moderate-Severe	3.1% (1/32)	0.0% (0/24)	0.0% (0/10)	9.8% (44/450)	0.0% (0/337)	0.5% (1/184)

	Summary Statistics					
	Hispanic (N=32)			Non-Hispanic (N=459)		
	Baseline	30-day Visit	1-year Visit	Baseline	30-day Visit	1-year Visit
Severe	46.9% (15/32)	0.0% (0/24)	0.0% (0/10)	32.4% (146/450)	0.0% (0/337)	0.5% (1/184)
Grouped mitral regurgitation						
<Moderate	43.8% (14/32)	100.0% (24/24)	100.0% (10/10)	46.7% (210/450)	99.1% (334/337)	98.9% (182/184)
≥Moderate	56.3% (18/32)	0.0% (0/24)	0.0% (0/10)	53.5% (240/450)	0.9% (3/337)	1.1% (2/184)
Continuous measures - Mean ± SE (Total no), median (Q1, Q3), [10%tile, 90%tile]. The total no. only counted the patients with valid values.						

Table 132: Mitral Regurgitation by Race Valve Implant Population (N=499)

	Summary Statistics							
	White (N=410)	Black/ African American (N=48)	Asian (N=9)	American Indian/ Alaskan Native (N=4)	Native Hawaiian/ Pacific Islander* (N=1)	Multiple (N=4)	Unknown (N=16)	Other (N=7)
Baseline								
Mitral regurgitation								
None	55	9	0	2	0	1	2	2
Trace/Trivial	39	2	0	0	0	0	4	1
Mild	88	13	3	0	0	1	2	0
Mild-Moderate	4	0	0	0	0	0	0	0
Moderate	43	5	1	1	0	1	1	0
Moderate-Severe	31	6	1	1	0	0	3	3
Severe	143	13	3	0	1	0	4	1
Grouped mitral regurgitation								
<Moderate	186	24	3	2	0	2	8	3
≥Moderate	217	24	5	2	1	1	8	4
30-day Visit								
Mitral regurgitation								
None	211	27	2	0	0	2	8	2
Trace/Trivial	67	4	3	1	0	2	2	4
Mild	20	4	1	0	0	0	1	1
Mild-Moderate	0	0	0	0	0	0	0	0
Moderate	3	0	0	0	0	0	0	0
Moderate-Severe	0	0	0	0	0	0	0	0
Severe	0	0	0	0	0	0	0	0

	Summary Statistics							
	White (N=410)	Black/ African American (N=48)	Asian (N=9)	American Indian/ Alaskan Native (N=4)	Native Hawaiian/ Pacific Islander* (N=1)	Multiple (N=4)	Unknown (N=16)	Other (N=7)
Grouped mitral regurgitation								
<Moderate	298	35	6	1	0	4	11	7
≥Moderate	3	0	0	0	0	0	0	0
1-year Visit								
Mitral regurgitation								
None	109	5	2	0	0	1	4	4
Trace/Trivial	44	4	2	0	0	0	1	3
Mild	13	3	0	0	0	0	0	0
Mild-Moderate	0	0	0	0	0	0	0	0
Moderate	0	0	0	0	0	0	0	0
Moderate-Severe	1	0	0	0	0	0	0	0
Severe	1	0	0	0	0	0	0	0
Grouped mitral regurgitation								
<Moderate	166	12	4	0	0	1	5	7
≥Moderate	2	0	0	0	0	0	0	0
The total no. only counted the patients with valid values.								

Other Study Observations

Procedural Information

The procedural information is summarized in Table 133. General anesthesia was used in the majority (96.8%) of patients. Conversion to open heart surgery occurred in two events due to ventricular rupture and other due to unknown cause, respectively.

Table 133: Procedural Data Summary (AI Population)

Procedural Data	Summary Statistics* (n=502)
Primary procedure indication	
Mitral stenosis	60.6% (114/188)
Mitral regurgitation	34.0% (64/188)
Both regurgitation and stenosis	5.3% (10/188)
Access site	
Transseptal	100.0% (502/502)
Valve type	
SAPIEN 3	83.7% (420/502)
SAPIEN 3 Ultra	16.3% (82/502)
Valve size	
20 mm	0.2% (1/502)

Procedural Data	Summary Statistics* (n=502)
23 mm	4.8% (24/502)
26 mm	42.0% (211/502)
29 mm	53.0% (266/502)
Type of anesthesia	
General anesthesia	96.8% (486/502)
Deep sedation/analgesia	0.2% (1/502)
Moderate sedation/analgesia	3.0% (15/502)
Total procedure time (minutes)	99.0 ± 2.31 (502)
Device implanted successfully	98.6% (495/502)
Procedure aborted	0.0% (0/452)
Conversion to open heart surgery	0.4% (2/452)
Ventricular rupture	1
Other	1
Subjects with more than one valve implanted during procedure	0.8% (4/502)
*Continuous measures - mean ± SE (Total no.); categorical measures - % (no./Total no.)	

13.16 THE EARLY-TAVR TRIAL, SAPIEN 3 and SAPIEN 3 Ultra THV - STUDY ANALYSIS

A. Accountability of the PMA Cohort

At the time of database extract, a total of 901 patients were randomized in the study. The analysis populations included Intention-to-Treat (ITT) and Valve Implant (VI), as defined in Table 134. The primary endpoint analysis was the ITT analysis.

Table 134: Analysis Populations

Analysis Population	Definition	Number of Patients	
		TAVR	CS
Intention-To-Treat (ITT)	All randomized patients.	455	446
Valve Implant (VI)	All patients who received and retained a replacement aortic valve (a study valve or a non-study valve) upon leaving the procedural room.	444	388
TAVR: transcatheter aortic valve replacement; CS: clinical surveillance.			

The VI population that originated from the CS population constitutes the delayed AVR (DAVR) cohort.

The follow-up compliance at 2 years post-randomization is summarized in Table 135.

Table 135: Overall Study Compliance (ITT Population)

Patient Accountability	2-Year Visit*	
	TAVR (N=455)	CS (N=446)
Total patients	455	446
Non-eligible	31	25
Death	17	12
Withdrawal	10	11
Lost to follow-up	0	0

Patient Accountability	2-Year Visit*	
	TAVR (N=455)	CS (N=446)
Termination by investigator	1	2
Exit with other reason	3	0
Visit not yet due	0	0
Eligible	424	421
Follow-up visit completed	98.6% (418)	98.3% (414)
Visit not completed	1.4% (6)	1.7% (7)
*2-year visit is post-procedure for the TAVR cohort and post-randomization for the CS cohort.		

B. Study Population Demographics and Baseline Characteristics

The demographics and baseline characteristics of the study population are typical for a TAVR study performed in the U.S., as shown in Table 136. The study cohorts were generally well balanced.

Table 136: Patient Demographics and Baseline Characteristics (ITT Population)

Demographics and Baseline Characteristics	Summary Statistics*	
	TAVR (N=455)	CS (N=446)
Age - years	76.0 ± 6.03	75.6 ± 5.97
Male sex	71.2% (324/455)	67.0% (299/446)
Hispanic or Latino Ethnicity	2.4% (11/455)	2.0% (9/446)
Race		
American Indian or Alaska Native	0.0% (0/455)	0.0% (0/446)
Asian	1.5% (7/455)	2.0% (9/446)
Black or African American	2.0% (9/455)	2.5% (11/446)
Native Hawaiian or other Pacific Islander	0.0% (0/455)	0.0% (0/446)
White	95.8% (436/455)	94.6% (422/446)
Multiple races	0.4% (2/455)	0.4% (2/446)
Unknown	0.2% (1/455)	0.4% (2/446)
Society of Thoracic Surgeons (STS) score	1.8 ± 1.00 (455)	1.7 ± 0.96 (446)
Able to perform treadmill stress test	90.3% (411/455)	90.8% (405/446)
Biomarker - NT-proBNP (pg/mL)†	275.6 (138.8, 598.9) (414)	296.8 (147.6, 607.7) (384)
New York Heart Association (NYHA) Class I	100.0% (455/455)	100.0% (446/446)
Previous myocardial infarction	5.1% (23/455)	4.0% (18/446)
Previous intervention		
Coronary artery bypass grafting (CABG)	5.9% (27/455)	6.5% (29/446)
Percutaneous coronary intervention (PCI)	18.0% (82/455)	13.9% (62/446)
Stroke	4.2% (19/455)	4.5% (20/446)
Peripheral vascular disease (PVD)	7.3% (33/455)	4.7% (21/446)
Atrial fibrillation	15.6% (71/455)	13.2% (59/446)
Atrial flutter	2.9% (13/455)	3.4% (15/446)
Permanent pacemaker or defibrillator	4.6% (21/455)	2.0% (9/446)

Demographics and Baseline Characteristics	Summary Statistics*	
	TAVR (N=455)	CS (N=446)
Echocardiographic findings		
Aortic valve area (cm^2)	0.9 ± 0.23 (436)	0.8 ± 0.23 (425)
Aortic valve mean gradient (mmHg)	46.5 ± 10.08 (451)	47.3 ± 10.61 (442)
Left ventricular ejection fraction (LVEF) (%)	67.4 ± 6.54 (451)	67.4 ± 6.68 (444)
Moderate or severe aortic regurgitation	2.2% (10/449)	3.2% (14/441)
Moderate or severe mitral regurgitation	1.3% (6/448)	1.8% (8/435)

*Continuous measures - Mean ± SD (Total no.); Categorical measures - % (no./Total no.).
†Continuous measures (NT-proBNP) - Median (Q1, Q3) (Total no.)

C. Safety and Effectiveness Results

1. Primary Endpoint

The primary endpoint results are presented in Table 137 and Figure 137. During a median follow-up of 3.8 years, a primary endpoint event occurred in 122 patients (26.8%) in the TAVR cohort and in 202 patients (45.3%) in the CS cohort, with a p-value of <0.0001. Superiority of the TAVR cohort compared to the CS cohort was achieved, driven primarily by unplanned cardiovascular hospitalization, especially aortic valve intervention within 6 months of randomization in the CS cohort.

Table 137: Primary Endpoint Analysis (ITT Population)

Event	Summary Statistics*		P-value†	Pass/Fail
	TAVR (N=455)	CS (N=446)		
Composite of all-cause death, all stroke, and unplanned cardiovascular hospitalization	122 (26.8%)	202 (45.3%)	<0.0001	Pass
All-cause death	38 (8.4%)	41 (9.2%)	---	---
All stroke	19 (4.2%)	30 (6.7%)	---	---
Unplanned cardiovascular hospitalization	95 (20.9%)	186 (41.7%)	---	---
Admission through an emergency department or same day admission from a clinic	94 (20.7%)	107 (24.0%)	---	---
Aortic valve intervention/ reintervention within 6 months	2 (0.4%)	116 (26.0%)	---	---

*no. of patients with the event (%). Reference start date for ITT population is randomization date.
†P-value is from log-rank test of all available data through 1825 days (i.e., 5 years).

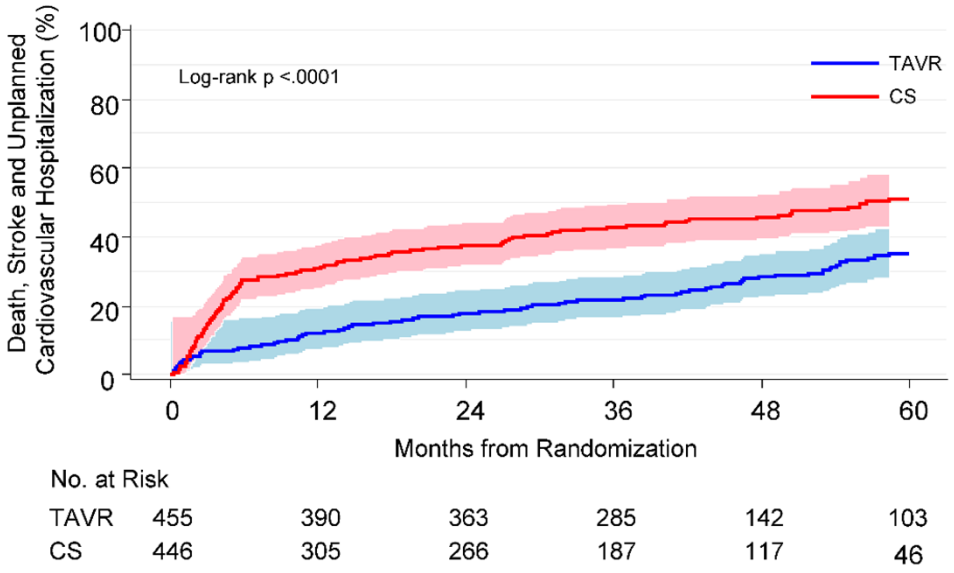


Figure 137: Kaplan-Meier Curves for All-Cause Death, All Stroke, and Unplanned Cardiovascular Hospitalization Through 5 Years (ITT Population)

The times to first event for each of the primary endpoint components are shown in Figure 138 through Figure 140.

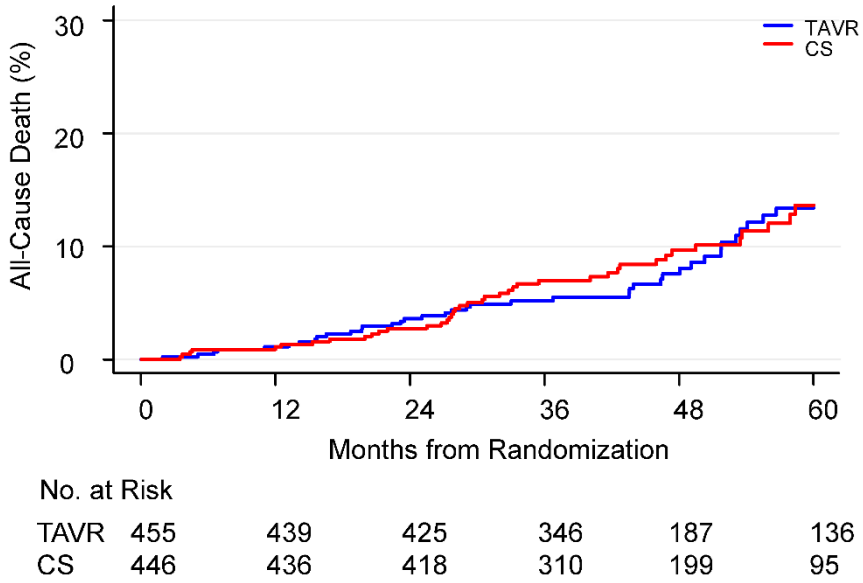


Figure 138: All-Cause Death Through 5 Years (ITT Population)

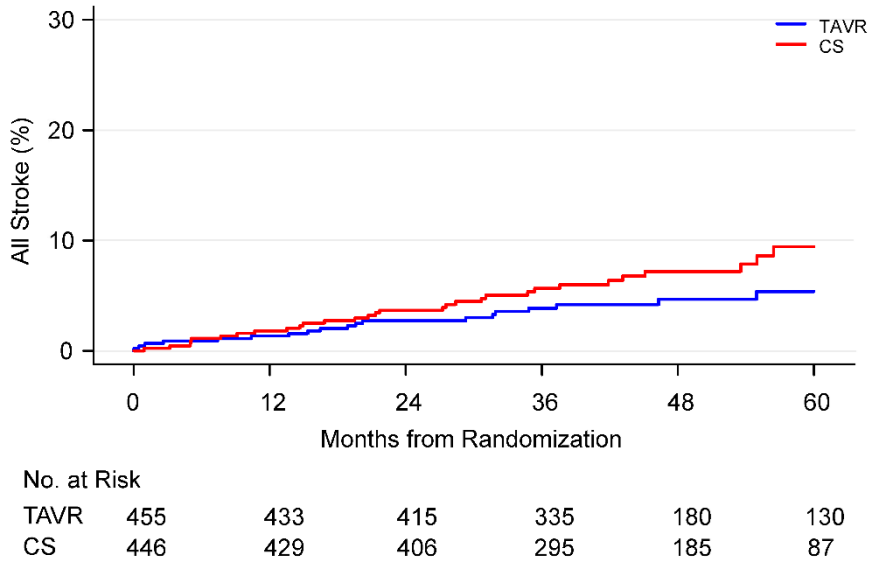


Figure 139: All Stroke Through 5 Years (ITT Population)

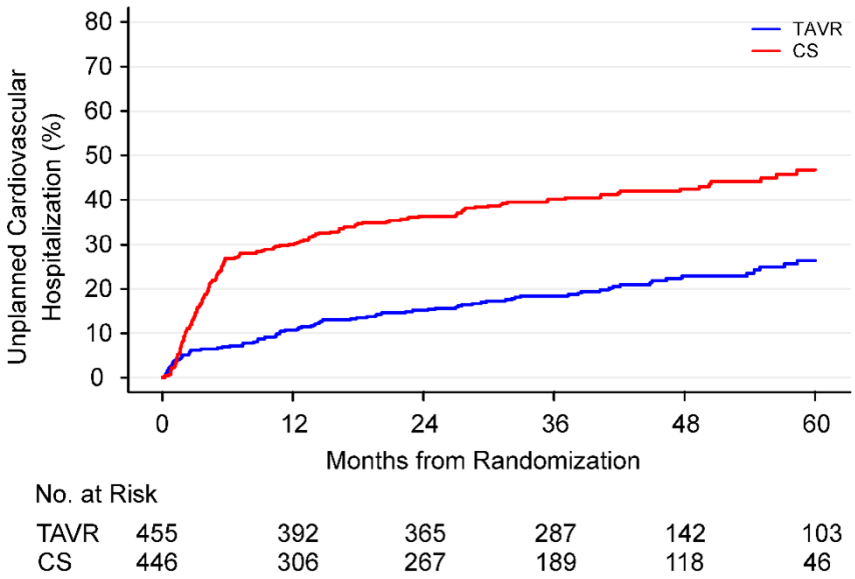


Figure 140: Unplanned Cardiovascular Hospitalization Through 5 Years (ITT Population).

2. Secondary Endpoints

Since the primary endpoint passed superiority testing, prespecified superiority testing was carried out on 5 secondary endpoints sequentially, as summarized in Table 138. The secondary endpoints for the composite of being alive with a favorable KCCQ overall summary score and integrated measure of LV health were met. However, there was no significant difference in the change in LVEF at 2 years between the TAVR and CS cohorts. Thus, hypothesis testing was not performed for the remaining endpoints on the hierarchical list.

Table 138: Superiority Testing of Secondary Endpoints (ITT Population)

No.	Endpoint	Summary Statistics*		P-value	Test Result
		TAVR (N=455)	CS (N=446)		
1	Composite of being alive with a favorable KCCQ overall summary score at 2 years	86.6% (354/409)	68.0% (266/391)	<0.0001	Pass
2	Integrated measure of left heart health at 2 years	48.1% (180/374)	35.9% (121/337)	0.0011	Pass
3	Change in LVEF at 2 years	-1.2 ± 0.40 (393)	-1.3 ± 0.39 (355)	0.6637	Fail
4	New onset atrial fibrillation†	13.0% (50)	12.4% (48)	---	---
5	Death or disabling stroke	9.7% (44)	11.2% (50)	---	---

KCCQ: Kansas City Cardiomyopathy Questionnaire; LVEF: left ventricular ejection fraction.
*Continuous measures – mean ± SE (n); Categorical measures – % (no./Total no.); Time to event measures - % (no. of patients with the event). Reference start date for ITT population is randomization date.
†New onset atrial fibrillation is only estimated among those without atrial fibrillation at baseline.

3. Adverse Events

The Kaplan-Meier estimates of CEC-adjudicated adverse events through 2 years are presented in Table 139.

Table 139: CEC-Adjudicated Adverse Events Through 2 Years (ITT Population)

Event	Kaplan-Meier Estimate*			
	1 Year		2 Years	
	TAVR (N=455)	CS (N=446)	TAVR (N=455)	CS (N=446)
All-cause death	1.1% (5, 5)	1.1% (5, 5)	3.6% (16, 16)	2.7% (12, 12)
Cardiovascular death	0.9% (4, 4)	0.7% (3, 3)	2.7% (12, 12)	1.8% (8, 8)
All stroke	1.3% (6, 6)	1.8% (8, 8)	2.7% (12, 12)	3.7% (17, 16)
Disabling stroke	0.0% (0, 0)	0.7% (3, 3)	0.9% (4, 4)	1.6% (7, 7)
Non-disabling stroke	1.3% (6, 6)	1.1% (5, 5)	1.8% (8, 8)	2.1% (10, 9)
Death or stroke	2.5% (11, 11)	2.9% (13, 13)	5.9% (28, 26)	5.7% (29, 25)
Death or disabling stroke	1.1% (5, 5)	1.8% (8, 8)	4.1% (20, 18)	3.9% (19, 17)
Hospitalization	22.7% (139, 101)	50.5% (301, 223)	33.7% (238, 149)	76.1% (515, 333)
Cardiovascular	11.4% (67, 51)	48.3% (252, 213)	17.0% (103, 75)	73.0% (406, 319)
Non-cardiovascular	12.6% (72, 56)	8.6% (49, 38)	21.8% (135, 96)	17.2% (109, 75)
New permanent pacemaker†	7.2% (31, 31)	3.3% (16, 14)	8.2% (35, 35)	7.3% (33, 31)
Myocardial infarction	1.1% (5, 5)	0.9% (4, 4)	1.8% (9, 8)	1.4% (6, 6)

*Kaplan-Meier Estimate - % (no. of events, no. of patients with the event). Reference start date for ITT population is randomization date.
†New pacemaker was only estimated among those without pacemaker at baseline.

4. Subgroup Analyses

The results of the prespecified subgroup analyses on gender, STS score, ability to perform the treadmill stress test, and aortic valve peak velocity are presented in Figure 141.

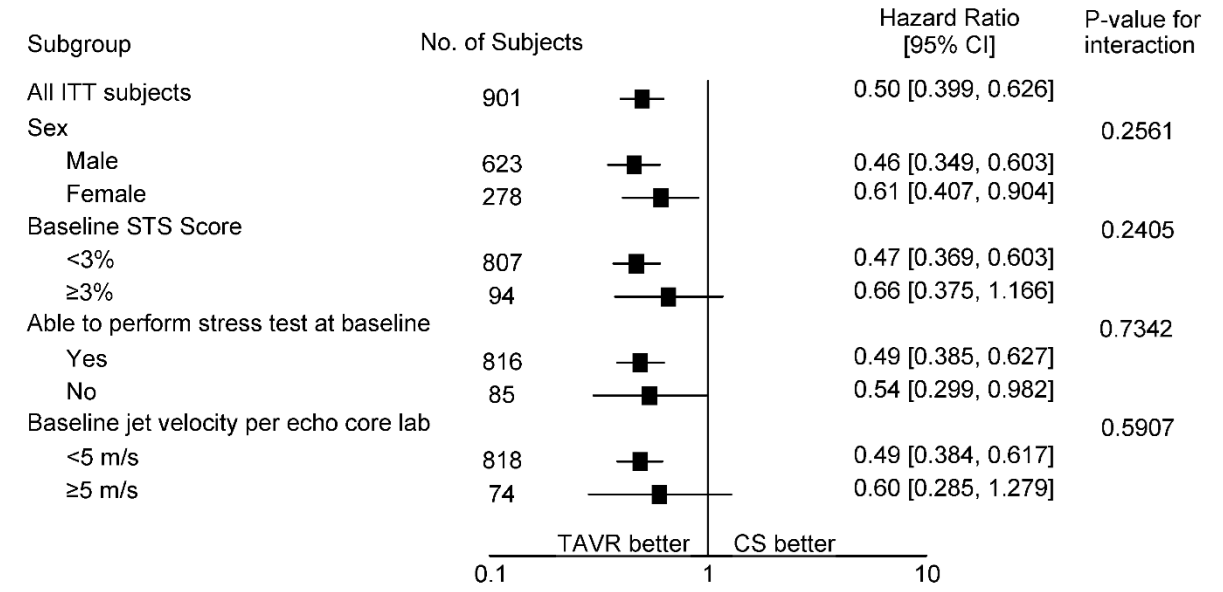


Figure 141: Subgroup Analyses of Primary Endpoint by Sex, STS Score, Ability to Perform Treadmill Stress Test, and Aortic Valve Peak Velocity (ITT Population)

Confidence intervals (CIs) and p-values are provided for information purposes only without multiplicity adjustment. P-values were based on interaction test of subgroup*treatment from Cox proportional hazards model with data up to 5 years.

The majority (83.6%) of patients randomized were deemed to be at low surgical risk as evaluated by the local heart team. The results of a *post hoc* subgroup analysis of the primary endpoint by heart team-determined surgical risk are shown in Figure 142.

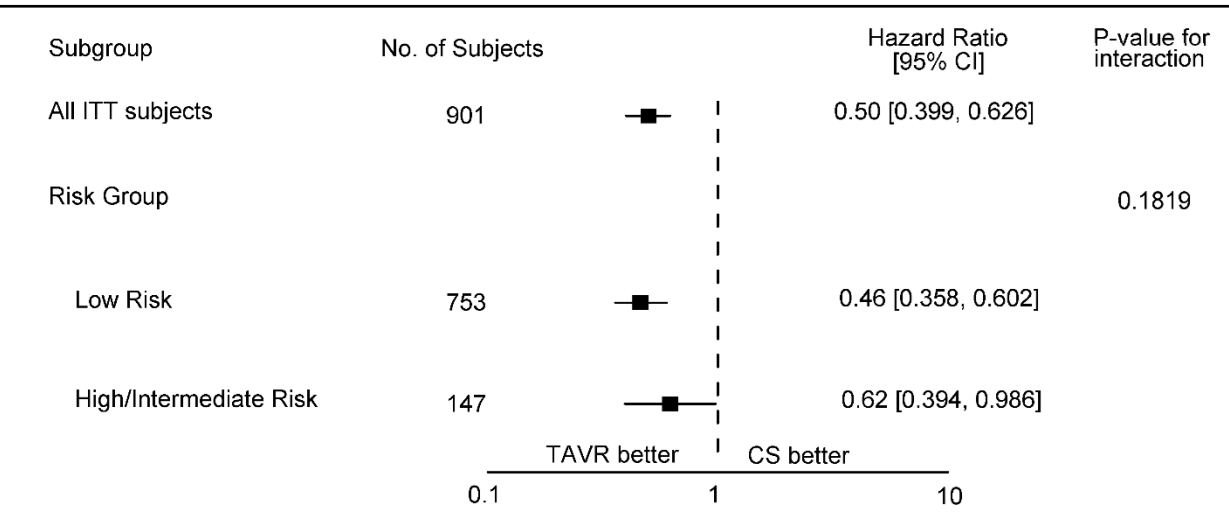


Figure 142: Subgroup Analysis of Primary Endpoint by Heart Team-Determined Surgical Risk (ITT Population)

Confidence intervals (CIs) and p-value are provided for information purposes only without multiplicity adjustment. P-value was based on interaction test of subgroup*treatment from Cox proportional hazards model with data up to 5 years.

The primary endpoint result by race is shown in Table 140.

Table 140: Primary Endpoint Result by Race (ITT Population)

Race	Composite of All-cause Death, All Stroke, and Unplanned Cardiovascular Hospitalization*	
	TAVR	CS
American Indian or Alaska Native	0/0	0/0
Asian	2/7	5/9
Black or African American	2/9	5/11
Native Hawaiian or other Pacific Islander	0/0	0/0
White	116/436	191/422
Multiple	2/2	0/2
Unknown	0/1	1/2
*no. of patients with events/total no. patients in the subgroup.		

VI Population Analyses

Conversion to AVR

The Kaplan-Meier estimates for the incidence of DAVR post randomization in the CS cohort are presented in Figure 143. By 12 months post randomization, 47.2% of the patients in the CS cohort became symptomatic and underwent AVR. The median time to DAVR was 332.5 days.

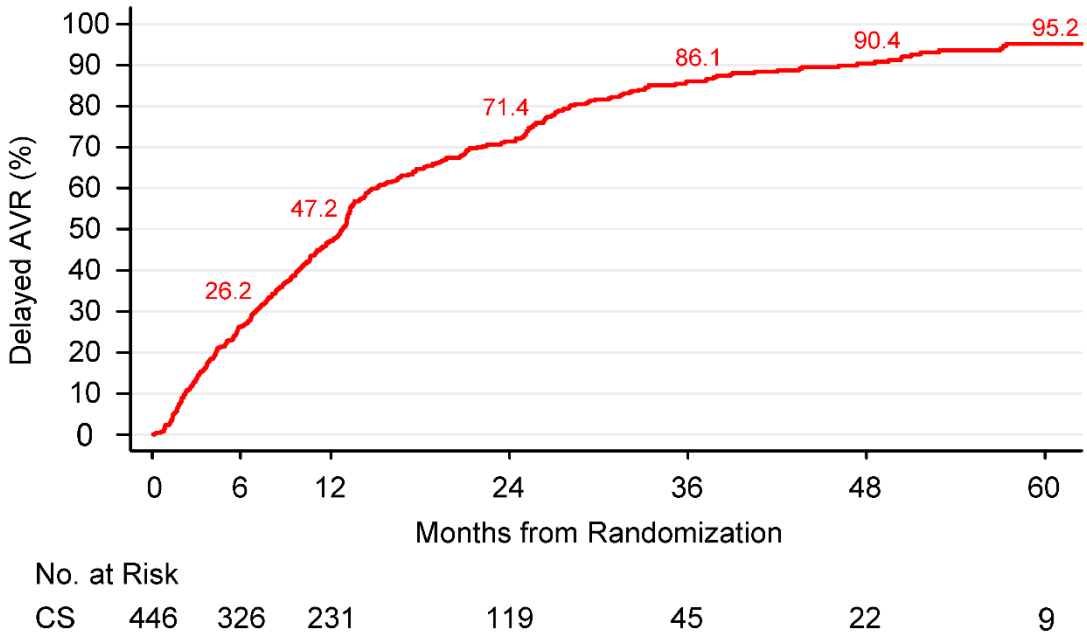


Figure 143: Cumulative Incidence of Delayed Aortic Valve Replacement (CS Cohort)

Valve Performance

The effective orifice area (EOA), mean aortic gradient, total aortic regurgitation (AR), and paravalvular regurgitation values obtained over time for the TAVR cohort and DAVR cohort patients are summarized in Figure 144 through Figure 147, respectively. Hemodynamic results at screening were similar between the two cohorts, remained unchanged (aortic valve area) or declined (aortic valve mean gradient) in the DAVR cohort pre-procedure, and improved similarly in both cohorts post procedure through 2 years.

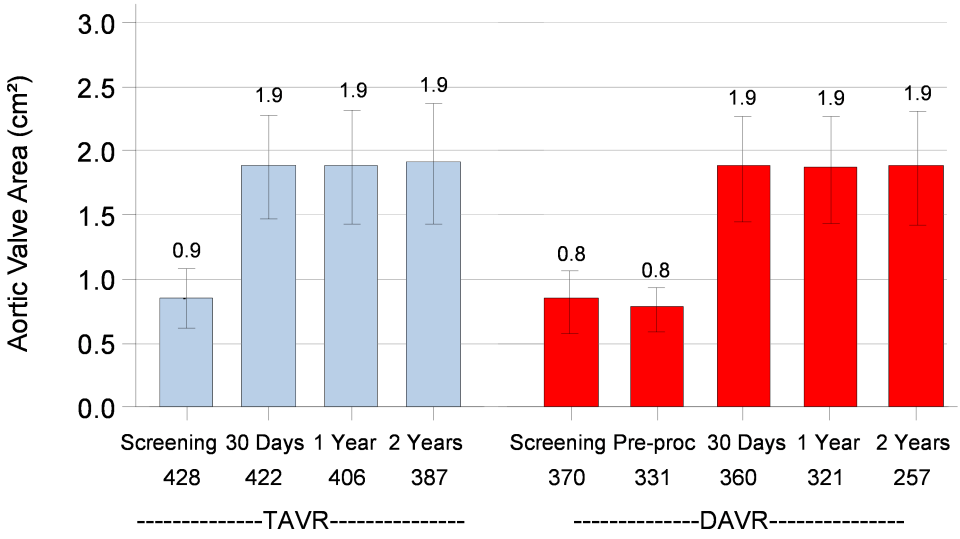


Figure 144: Aortic Valve Area by Visit (VI Population)

The error bars represent standard deviations.

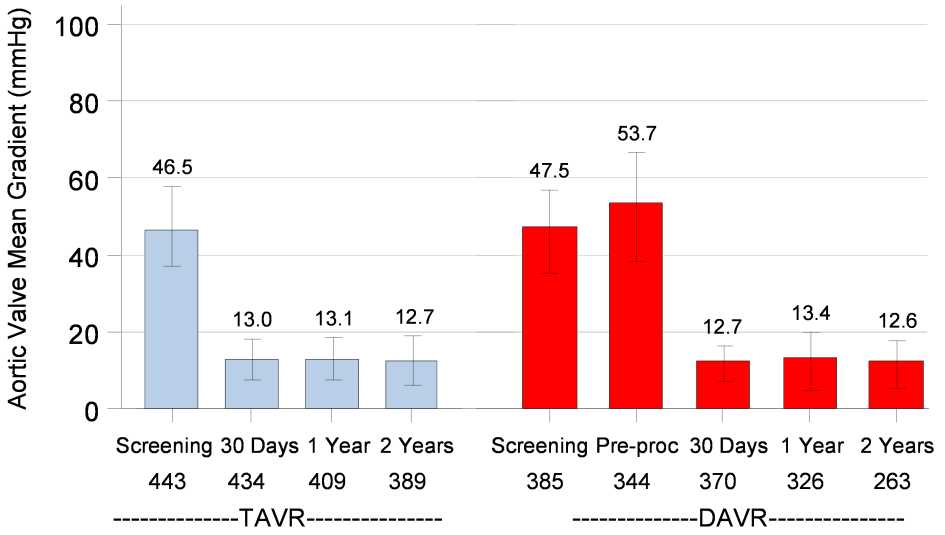


Figure 145: Aortic Valve Mean Gradient by Visit (VI Population)

The error bars represent standard deviations.

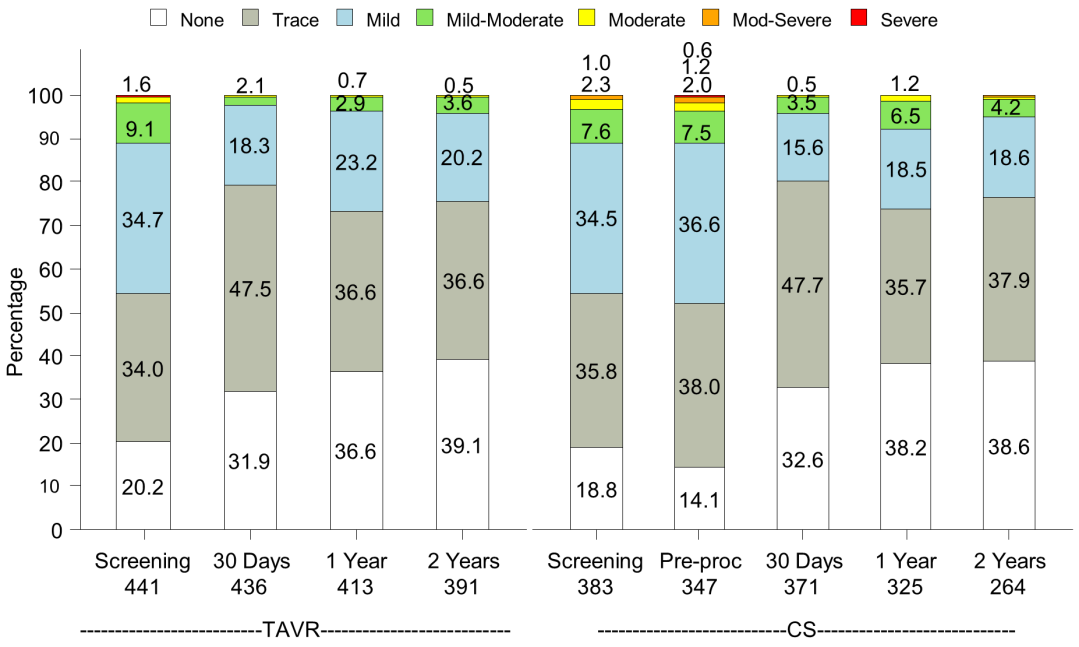


Figure 146: Total Aortic Regurgitation by Visit (VI Population)

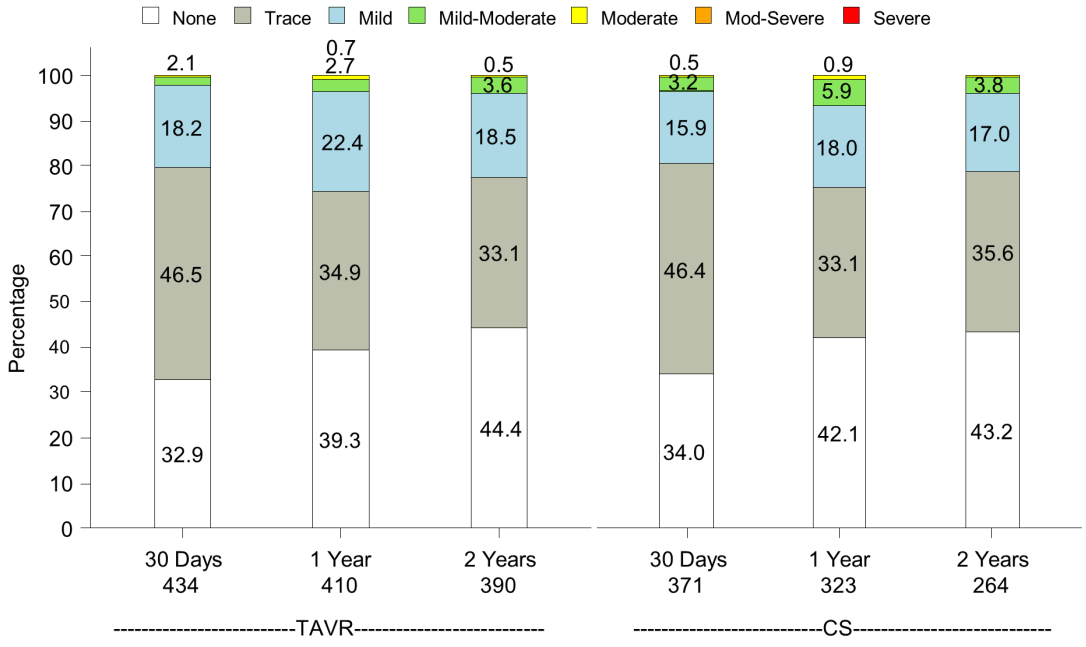


Figure 147: Paravalvular Regurgitation by Visit (VI Population)

Integrated Left Heart Health

The proportions of patients in the two study cohorts with a healthy integrated left heart function are shown in Figure 148. The results were similar at screening between the two cohorts, declined in the CS cohort prior to DAVR, and improved in both cohorts after the procedure, with similar rates seen through 2 years.

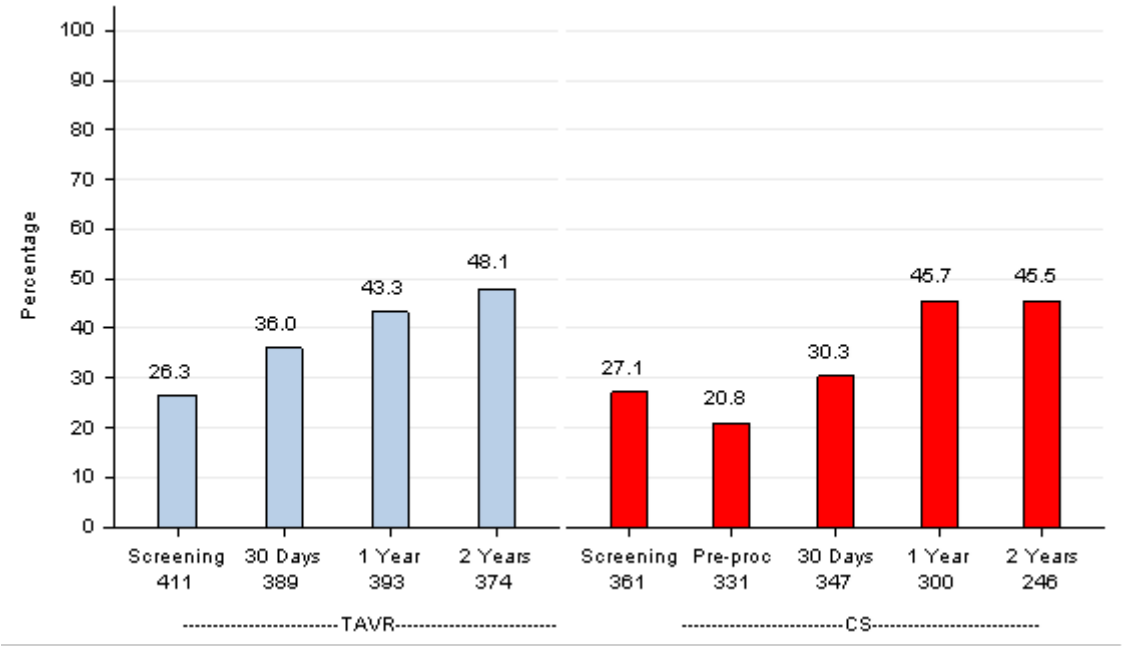


Figure 148: Integrated Left Heart Health by Visit (VI Population)

New York Heart Association Functional Class

The NYHA classifications by visit are presented in Figure 149. The majority of patients (>90%) in the TAVR cohort remained in NYHA class I at all follow-up visits through 2 years. In contrast, in the CS cohort, a decline in NYHA class was seen pre-procedure with the majority of patients (83.6%) becoming symptomatic (NYHA >1). After DAVR, the NYHA class improved and the outcomes at 2 years were similar between the two cohorts.

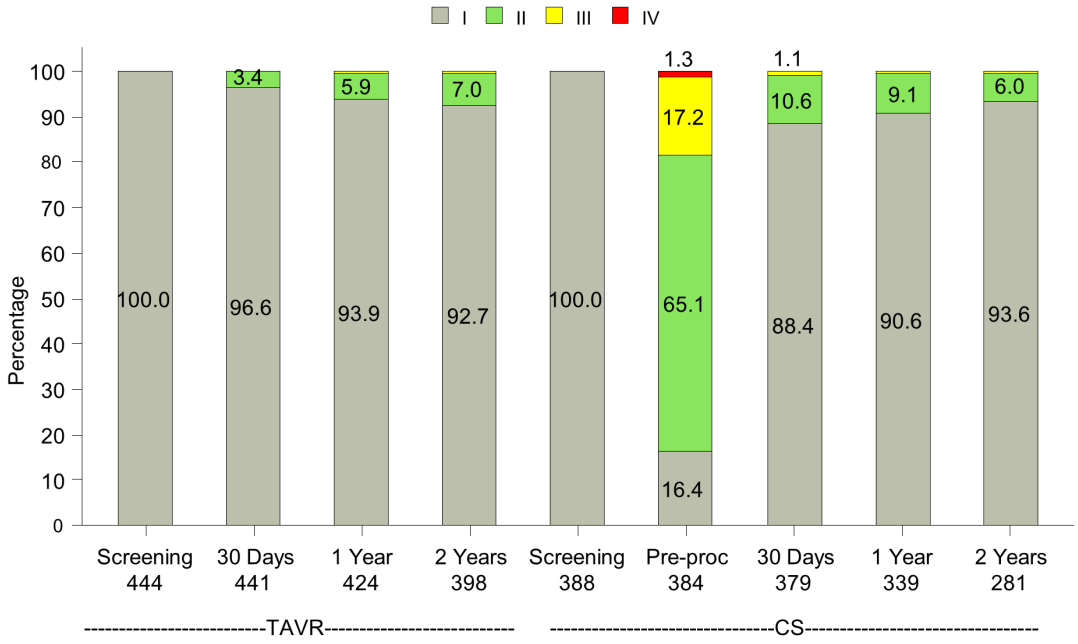


Figure 149: NYHA Functional Class by Visit (VI Population)

6-Minute Walk Test (6MWT)

The results for the 6MWT distance are presented in Figure 150. The mean walk distances at screening were similar between the TAVR cohort and the DAVR cohort. However, the mean walk distance in the DAVR cohort decreased by about 45 meters pre-procedure and improved by about 24 meters post-procedure, with similar distances between the two cohorts at 2 years (355.1 vs. 350.9 meters).

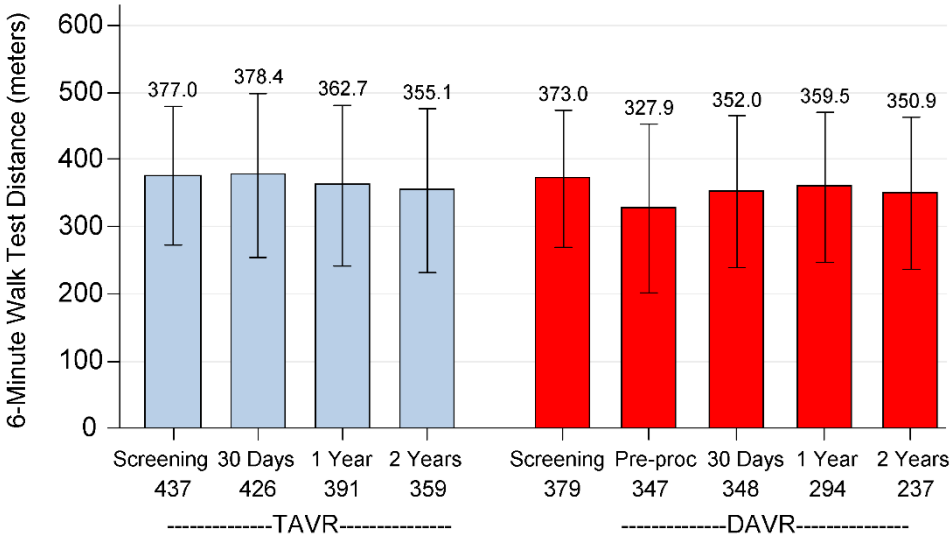


Figure 150: 6-Minute Walk Test Distance by Visit (VI Population)

The error bars represent standard deviations.

Health Status

The results for the KCCQ overall summary score, EQ-5D-5L VAS score, and Short Form (SF)-36 summary scores are shown in Figure 151 through Figure 153, respectively. There is a common trend in the KCCQ overall summary score, EQ-5D-5L VAS score, and SF-36 physical component summary score: These scores were similar between the two cohorts at screening. They remained mostly stable through 2 years in the TAVR cohort while seeing a decline prior to DAVR and then a return to the screening values post DAVR in the CS cohort. For example, the mean KCCQ overall summary scores at screening were similar between the TAVR cohort and the DAVR cohort (92.9 vs. 92.5). Patients in the TAVR cohort maintained the high score through 2 years post-procedure. In contrast, patients in the DAVR cohort first saw a clinically significant decline in the score to 77.7 pre-procedure and then a recovery to 92.5 post-procedure, which remained mostly unchanged through 2 years post-procedure.

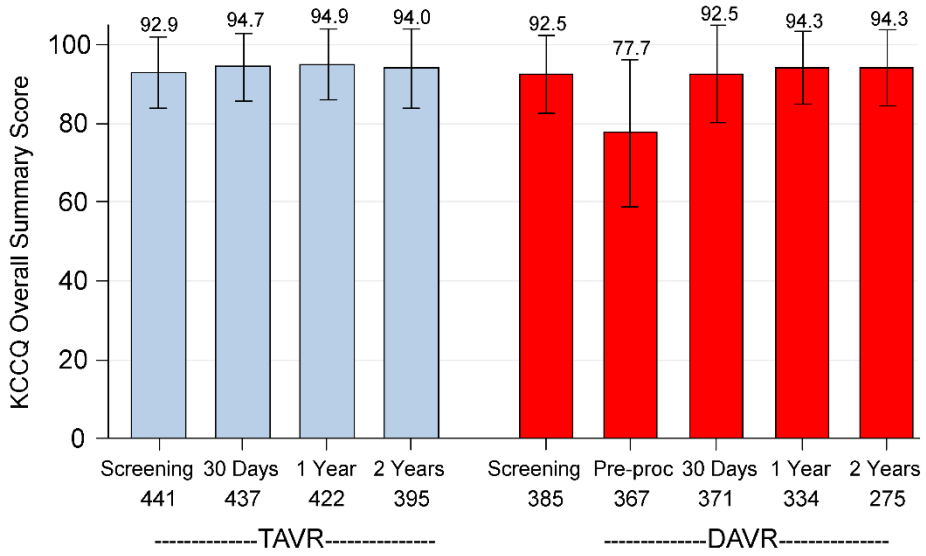


Figure 151: KCCQ Overall Summary Score by Visit (VI Population)

The error bars represent standard deviations.

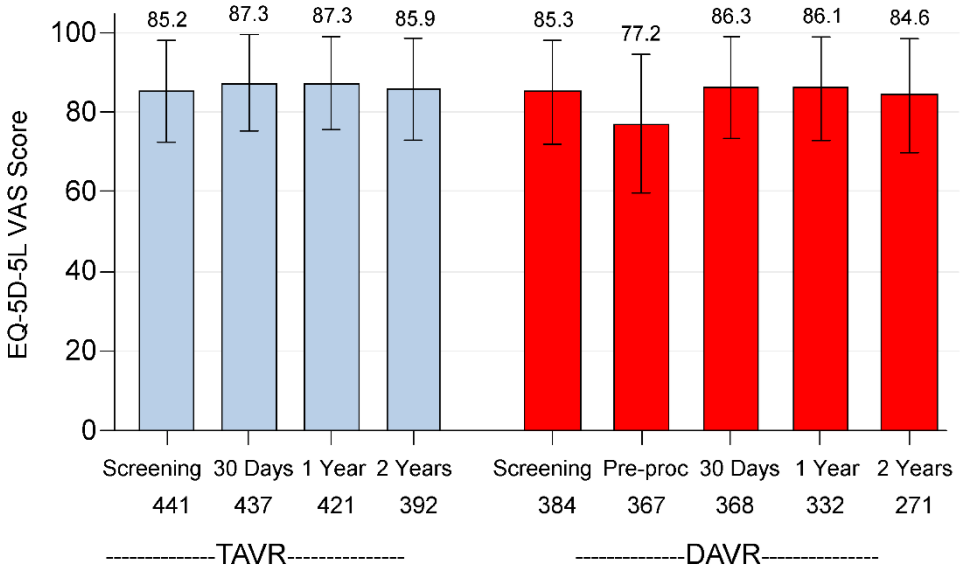
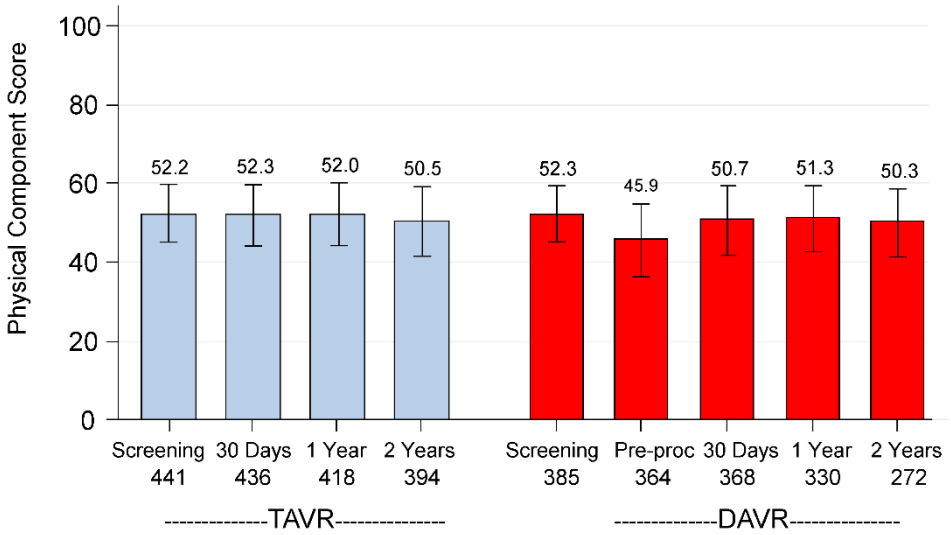


Figure 152: EQ-5D-5L VAS Score by Visit (VI Population)

The error bars represent standard deviations.

A. Physical Component



B. Mental Component

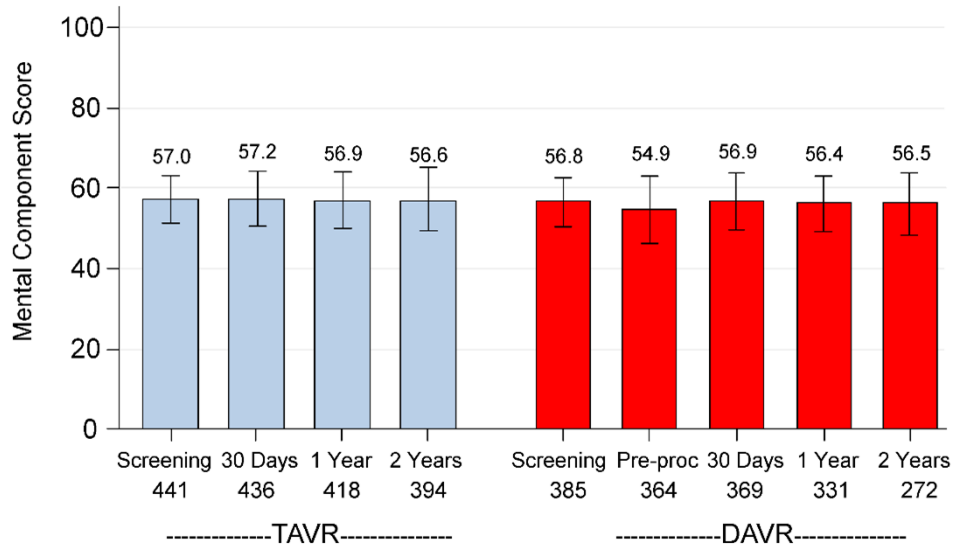


Figure 153: SF-36 Summary Score by Visit (VI Population)

The error bars represent standard deviations.

NT-proBNP Assessment

The NT-proBNP results are shown in Figure 154. Compared to the results at screening, the TAVR cohort saw a slight reduction in median NT-proBNP level from 272.5 pg/mL to 239.8 pg/mL at 30 days post procedure, while the CS cohort saw an increase in median NT-proBNP level from 298.6 pg/mL to 462.2 pg/mL prior to DAVR and then a decrease to a level (247.7 pg/mL) closer to the screening value post procedure.

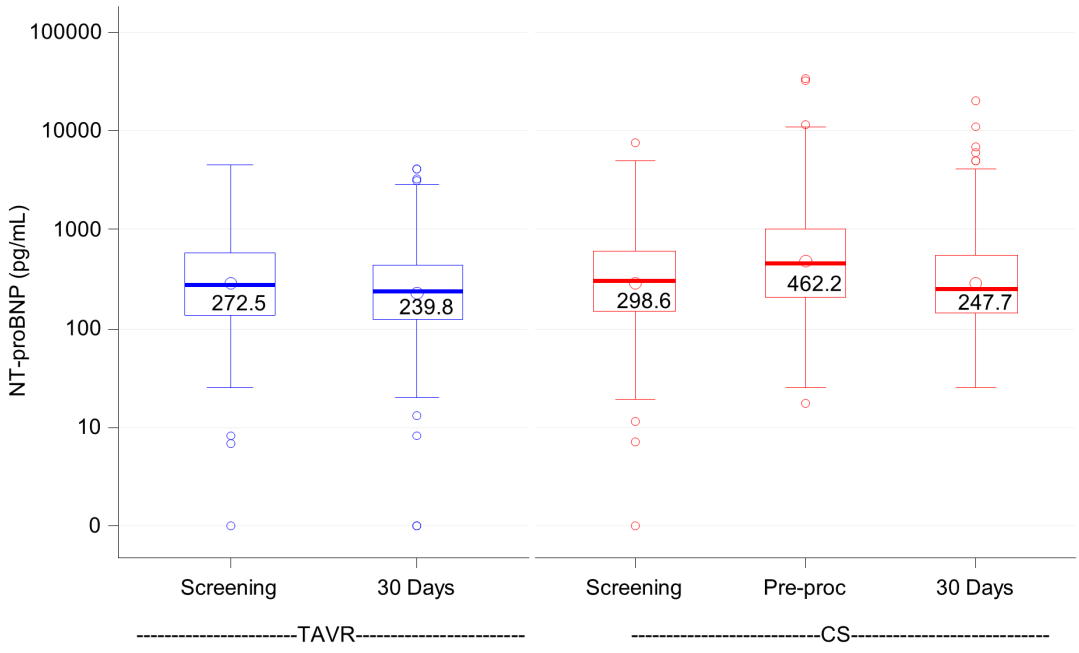


Figure 154: NT-proBNP Values by Visit (VI Population)

Safety Endpoints

The Kaplan-Meier estimates of the CEC-adjudicated safety endpoints for the VI population through 2 years are presented in Table 141.

Table 141: CEC-Adjudicated Safety Endpoints through 2 Years (VI Population)

Event	Kaplan-Meier Estimate*					
	30 Days		1 Year		2 Years	
	TAVR (N=444)	DAVR (N=388)	TAVR (N=444)	DAVR (N=388)	TAVR (N=444)	DAVR (N=388)
All cause death	0.2% (1, 1)	0.0% (0, 0)	1.1% (5, 5)	2.2% (8, 8)	3.8% (17, 17)	5.6% (19, 19)
Cardiovascular death	0.0% (0, 0)	0.0% (0, 0)	0.9% (4, 4)	1.1% (4, 4)	3.0% (13, 13)	3.3% (11, 11)
All stroke	0.9% (4, 4)	1.8% (8, 7)	1.4% (6, 6)	2.6% (11, 10)	2.7% (12, 12)	4.5% (18, 16)
Disabling stroke	0.0% (0, 0)	1.0% (4, 4)	0.0% (0, 0)	1.3% (5, 5)	0.9% (4, 4)	2.2% (8, 8)
Non-disabling stroke	0.9% (4, 4)	0.8% (4, 3)	1.4% (6, 6)	1.3% (6, 5)	1.8% (8, 8)	2.3% (10, 8)
Death or stroke	1.1% (5, 5)	1.8% (8, 7)	2.5% (11, 11)	4.2% (19, 16)	6.1% (29, 27)	8.9% (37, 31)
Death or disabling stroke	0.2% (1, 1)	1.0% (4, 4)	1.1% (5, 5)	3.2% (13, 12)	4.3% (21, 19)	6.9% (27, 24)
Hospitalization	6.1% (27, 27)	8.6% (36, 33)	21.9% (136, 97)	22.8% (114, 85)	33.5% (241, 148)	33.5% (186, 119)
Cardiovascular	4.7% (21, 21)	6.7% (27, 26)	11.1% (65, 49)	12.7% (51, 48)	16.6% (102, 73)	17.5% (73, 63)
Non-cardiovascular	1.4% (6, 6)	2.1% (9, 8)	12.2% (71, 54)	13.8% (63, 51)	22.3% (139, 98)	23.4% (113, 81)
New permanent pacemaker †	5.7% (24, 24)	8.4% (33, 32)	7.1% (30, 30)	9.8% (39, 37)	8.3% (35, 35)	10.4% (41, 39)
Myocardial infarction	0.5% (2, 2)	0.5% (2, 2)	1.1% (5, 5)	0.5% (2, 2)	1.8% (9, 8)	1.1% (4, 4)

Event	Kaplan-Meier Estimate*					
	30 Days		1 Year		2 Years	
	TAVR (N=444)	DAVR (N=388)	TAVR (N=444)	DAVR (N=388)	TAVR (N=444)	DAVR (N=388)
Major vascular complications	1.4% (6, 6)	1.0% (5, 4)	-	-	-	-
Bleeding complications	12.8% (63, 57)	13.7% (58, 53)	-	-	-	-
Acute kidney injury ‡	2.5% (11, 11)	3.4% (13, 13)	-	-	-	-
Coronary obstruction requiring intervention	0.0% (0, 0)	0.0% (0, 0)	---	---	---	---

*Kaplan-Meier estimate - % (no. of events, no. of patients with the event). Reference start date for VI population is procedure date.
†New pacemaker was only estimated among those without pacemaker at baseline (for DAVR patients, "baseline" means pre-procedure visit).
‡Acute kidney injury was from site reported data.

5. Other Study Observations

Procedural Information

The procedural data for the TAVR and DAVR cohorts are summarized in Table 142. The procedural characteristics were generally comparable between the two cohorts with the exception of a higher percentage of SAPIEN 3 Ultra valves implanted in the DAVR cohort due to the commercial approval of this device later in the study.

Table 142: Procedure Data (VI Population)

Variable	Summary Statistics*	
	TAVR (N=444)	DAVR (N=388)
Anesthesia type		
General anesthesia	18.9% (84/444)	18.8% (73/388)
Conscious sedation	80.0% (355/444)	80.2% (311/388)
Conversion from conscious sedation to general anesthesia	1.1% (5/444)	1.0% (4/388)
Anesthesia duration (min)	117.2 ± 2.19 (444)	119.2 ± 2.40 (386)
Procedure duration (min)	40.0 ± 0.84 (443)	45.0 ± 2.02 (380)
Total fluoroscopy time (min)†	12.8 ± 0.31 (442)	13.8 ± 0.35 (374)
Balloon aortic valvuloplasty performed†	28.2% (125/444)	33.6% (128/381)
Final valve type		
SAPIEN 3	81.3% (361/444)	55.4% (215/388)
SAPIEN 3 Ultra	18.7% (83/444)	40.2% (156/388)
Non-study transcatheter heart valve (THV)	-	2.6% (10/388)
Surgical valve	-	1.8% (7/388)
Study valve size		
20 mm	3.2% (14/444)	0.8% (3/371)
23 mm	28.6% (127/444)	34.8% (129/371)

Variable	Summary Statistics*	
	TAVR (N=444)	DAVR (N=388)
26 mm	48.9% (217/444)	45.8% (170/371)
29 mm	19.4% (86/444)	18.6% (69/371)
Post dilatation performed†	14.0% (62/444)	13.7% (52/380)
Cerebral protection device used	21.6% (96/444)	26.8% (102/381)
More than one THV implanted†	0.9% (4/444)	0.5% (2/381)
*Continuous measures – mean ± SE (n); Categorical measures - % (no./total no.). †Only reported among those with TAVR procedure.		

Composite of All-Cause Death, All Stroke, or Heart Failure Hospitalization

A *post hoc* exploratory analysis for the composite of all-cause death, all stroke, or heart failure hospitalization is presented in Table 143 and Figure 155. There appears to be a lower incidence of composite event of all-cause death, all stroke, or heart failure hospitalization through 5 years in the TAVR cohort than in the CS cohort (13.6% vs. 21.3%).

Table 143: All-Cause Death, All Stroke, or Heart Failure Hospitalization Through 5 Years (ITT Population)

Event	Summary Statistics*	
	TAVR (N=455)	CS (N=446)
Composite of all-cause death, all stroke, or heart failure hospitalization	62 (13.6%)	95 (21.3%)
All-cause death	38 (8.4%)	41 (9.2%)
All stroke	19 (4.2%)	30 (6.7%)
Heart failure hospitalization†	15 (3.3%)	44 (9.9%)
* no. of patients with the event (%). Reference start date for ITT population is randomization date. †Heart failure hospitalization was defined as hospitalization for symptoms of congestive heart failure and administration of intravenous diuresis or inotropic therapy, institution of mechanical support, or hemodialysis and was adjudicated by the CEC.		

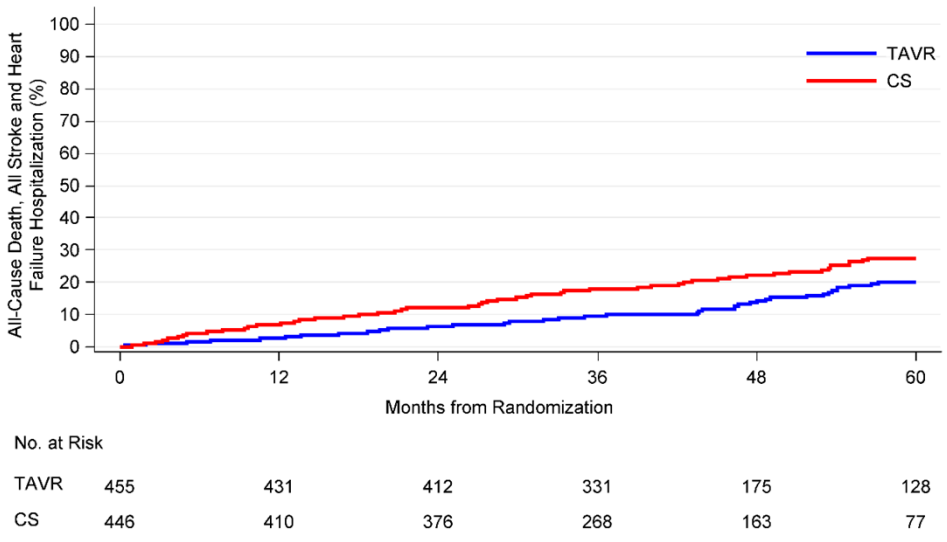


Figure 155: Kaplan-Meier Curves for All-Cause Death, All Stroke, and Heart Failure Hospitalization Through 5 Years (ITT Population)

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