Edwards SAPIEN 3 Transcatheter Pulmonary Valve System
Edwards SAPIEN 3 Transcatheter Heart Valve
Edwards SAPIEN 3 Transcatheter Pulmonic Valve Delivery System

Instructions for Use - Pulmonic

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 valvuloplasty.

Please verify that you have the latest version of the instructions for use prior to using the device by visiting http://eifu.edwards.com/ or by calling 1.888.570.4016.

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

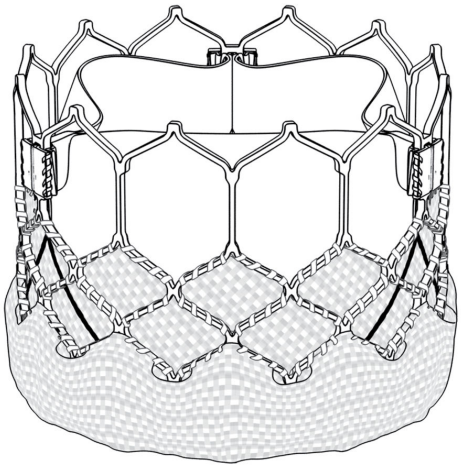
1.0 Device Description

Edwards SAPIEN 3 Transcatheter Pulmonary Valve (TPV) System

The Edwards SAPIEN 3 transcatheter pulmonary valve system consists of the Edwards SAPIEN 3 transcatheter heart valve (THV), the Edwards SAPIEN 3 transcatheter pulmonic valve delivery system (PDS), and accessories.

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

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.



9600TFX

Figure 1: Edwards SAPIEN 3 Transcatheter Heart Valve

Table 1

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

Sizing recommendations for the Edwards SAPIEN 3 transcatheter heart valve in non-compliant right ventricular outflow tract (RVOT) conduits using balloon sizing are shown in the table below:

Table 2: Valve Sizing in RVOT Conduit

Landing Zone Diameter	THV Size
16.5 - 20.0 mm	20 mm
20.0 - 23.0 mm	23 mm
23.0 - 26.0 mm	26 mm
26.0 - 29.0 mm	29 mm

Note: For a failing stentless bioprosthesis, consider sizing recommendations for a non-compliant right ventricular outflow tract (RVOT) conduit landing zone.

Sizing recommendations for implanting the Edwards SAPIEN 3 transcatheter heart valve for THV-in-surgical valve procedures for bioprosthesis based on a True Inner Diameter (True ID) are shown in the table below:

Table 3: Valve Sizing in Failed Bioprosthesis

Surgical Valve True ID	SAPIEN 3 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: The dimensions of the failed bioprosthesis should be determined so that the appropriate valve size can be implanted; and is best determined by using balloon sizing and/or computed tomography to perform the necessary measurements. Surgical valve True ID may be smaller than the labeled valve size.

Note: Exact volume required to deploy the valve may vary depending on the bioprosthesis 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 bioprosthesis to a size smaller than the True ID. These factors should be considered and assessed in order to determine the most appropriate valve size to achieve nominal valve deployment and sufficient anchoring. Do not exceed the rated burst pressure. See Table 4 for inflation parameters.

- **Edwards SAPIEN 3 Transcatheter Pulmonic Valve Delivery System (Figures 2, 3, 4, 5)**

The Edwards SAPIEN 3 Transcatheter Pulmonic Valve Delivery System (PDS)(Figure 2) facilitates the placement of the bioprosthesis. The S3 PDS consists of an inline sheath, balloon catheter for deployment of the Edwards SAPIEN 3 transcatheter heart valve, radiopaque markers on the balloon catheter, and an outer shaft and valve capsule to cover the transcatheter heart valve during insertion and tracking to the intended deployment location. The delivery system includes a tapered tip to facilitate crossing of right heart structures. The valve capsule and tapered tip have a hydrophilic coating. A visual balloon shaft marker is provided to assist with balloon recapture. A stylet is included within the guidewire lumen of the delivery system. The dilator (packaged with the delivery system) has hydrophilic coating and is used to predilate the vessel, if necessary, prior to insertion of the delivery system (Figure 3). The inflation parameters for the valve deployment are shown in the Table 4:

Table 4

Model	Nominal Balloon Diameter	Nominal Inflation Volume	Rated Burst Pressure (RBP)
9631PL20	21 mm	10 ml	9 atm (912 kPa)
9631PL23	24 mm	15 ml	9 atm (912 kPa)

Model	Nominal Balloon Diameter	Nominal Inflation Volume	Rated Burst Pressure (RBP)
9631PL26	27 mm	21 ml	9 atm (912 kPa)
9631PL29	30 mm	29 ml	9 atm (912 kPa)

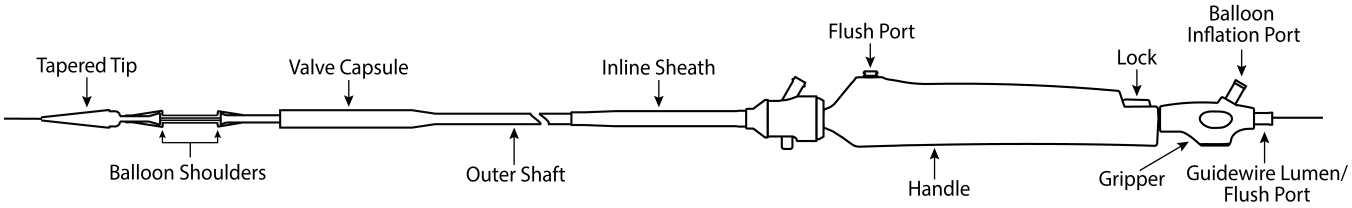


Figure 2: Edwards SAPIEN 3 Transcatheter Pulmonic Valve Delivery System

Additional Accessories

- **Dilator**

The hydrophilic coated dilator (packaged with the delivery system (Table 5)) is used to predilate the vessel, if necessary, prior to insertion of the delivery system (Figure 3).

Figure 3

Table 5

Model	Provided Dilator Size
9631PL20	25 F (8.3 mm)
9631PL23	27 F (9.0 mm)
9631PL26	27 F (9.0 mm)
9631PL29	28 F (9.3 mm)

- **Qualcrimp Crimping Accessory**

The Qualcrimp crimping accessory (packaged with the delivery system) is used during THV crimping (Figure 4).

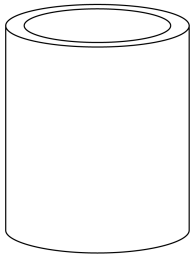


Figure 4

- **Crimp Stopper**

A 2-piece Crimp Stopper (packaged with the delivery system) is used to crimp the THV to its intended diameter (Figure 5).

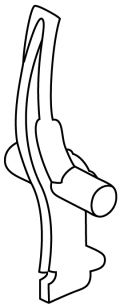


Figure 5

- **Edwards Crimper**

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

2.0 Indications

The Edwards SAPIEN 3 transcatheter heart valve system with Edwards SAPIEN 3 pulmonic valve delivery system is indicated for use in the management of pediatric and adult patients who have a clinical indication for intervention on a dysfunctional right ventricular outflow tract (RVOT) conduit or surgical bioprosthetic valve in the pulmonic position with ≥ moderate regurgitation and/or a mean RVOT gradient of ≥ 35 mmHg.

3.0 Contraindications

The Edwards SAPIEN 3 transcatheter heart valve with use of the Edwards SAPIEN 3 pulmonic valve delivery system is contraindicated in patients who cannot tolerate an anticoagulation/antiplatelet regimen or who have active bacterial endocarditis or other active infections.

4.0 Warnings

- 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.
- Correct sizing of the valve into the non-compliant RVOT conduit or failing bioprosthesis (landing zone) is essential to minimize risks. Too small of a valve may result in paravalvular leak, migration, or valve embolization; whereas too large of a valve may result in residual gradient (patient-prosthesis mismatch) or RVOT rupture.
- Accelerated deterioration of the valve may occur in patients with an altered calcium metabolism.
- Assessment for coronary compression risk prior to valve implantation is essential to prevent the risk of severe patient harm.
- The physician must verify correct orientation of the valve prior to its implantation; the inflow (outer skirt end) of the valve should be oriented towards the proximal end (handle) of the delivery system to prevent the risk of severe patient harm.
- 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.
- Do not use the valve if the tamper evident seal is broken, the storage solution does not completely cover the valve, the temperature indicator has been activated, the valve is damaged, or the expiration date has elapsed.
- Do not mishandle the 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.
- Do not add or apply antibiotics to the storage solution, rinse solutions or to the valve.
- 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 antiplatelet therapy.
- It is recommended that all prosthetic heart valve recipients be prophylactically treated for endocarditis to minimize the possibility of prosthetic valve infection.
- Care should be exercised in patients with hypersensitivities to cobalt, nickel, chromium, molybdenum, titanium, manganese, silicon, and/or polymeric materials.

5.0 Precautions

- Long-term durability has not been established for the valve. Regular medical follow-up is advised to evaluate valve performance.
- Patient venous anatomy should be evaluated to prevent the risk of access that would preclude the delivery and deployment of the device.
- 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.
- Fluoroscopically guided procedures are associated with a risk of radiation injury to the skin. Patient radiation dose should be monitored during the procedure.
- 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.
- Patient should be heparinized to maintain the ACT at ≥ 250 sec prior to introduction of the delivery system in order to prevent thrombosis.
- To maintain proper valve leaflet coaptation, do not overinflate the deployment balloon.

- Safety and effectiveness have not been established for patients with the following characteristics/comorbidities:
  - Blood dyscrasias defined as: leukopenia, acute anemia, thrombocytopenia, or history of bleeding diathesis or coagulopathy
  - A known hypersensitivity or contraindication to heparin, antiplatelets, or sensitivity to contrast media, which cannot be adequately premedicated
  - Positive urine or serum pregnancy test in female patients of child-bearing potential
- Residual mean gradient may be higher in a "THV-in-failing bioprosthesis" configuration than that observed following implantation of the valve inside a native 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 bioprosthetic valve be determined, so that the appropriate valve can be implanted and a prosthesis-patient mismatch be avoided. Additionally, pre-procedure imaging modalities must be employed to make as accurate a determination of the inner diameter as possible.

6.0 Potential Adverse Events

Potential risks associated with the anesthesia, interventional procedure and imaging include but are not limited to:

- Death
- Stroke/transient ischemic attack
- Respiratory insufficiency or respiratory failure
- Cardiovascular or vascular injury, such as perforation or damage (dissection) of vessels, myocardium or valvular structures including rupture of the RVOT that may require intervention
- Pericardial effusion/cardiac tamponade
- Cardiac failure
- Embolic event: air, calcific material, thrombus, device fragments
- Infection including incisional site infection, septicemia and endocarditis
- Myocardial infarction
- Renal insufficiency or renal failure
- Conduction system injury
- Arrhythmia
- Deep vein thrombosis
- Arteriovenous (AV) fistula
- Systemic or peripheral nerve injury
- Systemic or peripheral ischemia
- Pulmonary edema
- Pneumothorax
- Pleural effusion
- Dyspnea
- Atelectasis
- Dislodgement of previously implanted devices (i.e., pacing lead)
- Blood loss requiring transfusion
- Anemia
- Radiation injury
- Electrolyte imbalance
- Hypertension or hypotension
- Allergic reaction to anesthesia, contrast media, antithrombotic therapy, device materials
- Hematoma or ecchymosis
- Syncope
- Pain
- Exercise intolerance or weakness
- Inflammation
- Angina
- Fever

Potential risks that may or may not require intervention associated with the valve, delivery system and/or accessories include, but may not be limited to, the following:

- Cardiac arrest
- Cardiogenic shock
- Coronary flow obstruction/transvalvular flow disturbance
- Device thrombosis
- Injury to tricuspid valve
- Device embolization
- Device acute migration or malposition
- Endocarditis
- Chest pain/discomfort
- Hemolysis / hemolytic anemia
- Device dysfunction (regurgitation and/or stenosis)
- Aortic root distortion
- Embolic event: device fragments
- Mechanical failure of delivery system, and/or accessories
- Emergent and non-emergent re-intervention

See Section 12 for adverse events that occurred in the clinical study.

7.0 Directions for Use

7.1 System Compatibility

Table 6

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 SAPIEN 3 Transcatheter Pulmonic Valve Delivery System	9631PL20	9631PL23	9631PL26	9631PL29
Dilator, Inflation device, Qualcrimp crimping accessory, and crimp stopper provided by Edwards Lifesciences				
Edwards Crimper	9600CR			

Additional Equipment:

- Balloon tip catheter
- Sizing balloons
- 20 cc syringe or larger (x2)
- 50 cc syringe or larger
- High-pressure 3-way stopcock
- Standard cardiac catheterization lab equipment
- Fluoroscopy (appropriate for use in percutaneous coronary interventions)
- Exchange length 0.035 inch (0.89 mm) stiff guidewire
- Sterile rinsing basins; physiological saline, heparinized saline, and 15% diluted radiopaque contrast medium
- Sterile table for valve and device preparation

7.2 Valve Handling and Preparation

Follow sterile technique during device preparation and implantation.

7.2.1 Valve Rinsing Procedure

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

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

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 physiological saline and gently agitate for at least one more minute. Ensure the rinse solution in the first bowl is not used. The valve should be left in the final rinse solution until needed to prevent the tissue from drying.

   CAUTION: Do not allow the valve to come into contact with the bottom or sides of the rinse bowl during agitation or swirling in the rinse solution. Direct contact between the identification tag and valve is also to be avoided during the rinse procedure. No other objects should be placed in the rinse bowls. The valve should be kept hydrated to prevent the tissue from drying.

7.2.2 Prepare the System

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

1. Visually inspect all the components for damage. Ensure the handle is fully retracted to the gripper.

   Note: The delivery system is packaged with a balloon cover placed over the balloon and should not be removed until instructed to do so.

2. Attach a 3-way stopcock to the balloon inflation port. Ensure stopcock is tightened securely. Fill a 50 cc or larger syringe with 15-20 ml of diluted contrast medium and attach to the 3-way stopcock.
3. Fill the inflation device provided by Edwards Lifesciences with excess volume of diluted contrast medium relative to the indicated inflation volume. Lock and attach to the 3-way stopcock.
4. Close stopcock to the inflation device. De-air the system using the 50 cc or larger syringe. Slowly release the plunger and return to neutral pressure.

   Note: Do not remove the balloon cover during de-airing.

   Note: May take multiple negative pulls to de-air the balloon catheter.

5. Close stopcock to the delivery system and de-air the inflation device. By rotating the knob of the inflation device, transfer the contrast medium into the syringe to achieve the appropriate volume required to deploy the valve per the inflation parameters.
6. Verify that the inflation volume in the inflation device is correct. Close the stopcock to the 50 cc or larger syringe. Lock the inflation device and remove the syringe. Verify stopcock is securely attached to the balloon inflation port.

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

7.2.3 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 crimper from packaging. Rotate the crimper handle until the aperture is fully open. Attach the 2-piece crimp stopper to the base of the crimper and click into place.
4. Carefully remove the balloon cover from the delivery system. Visually inspect the balloon for damage. Ensure that the stylet is inserted into the guidewire lumen.
5. Remove the valve from the holder and remove the ID tag.
6. With the crimper in the open position, gently place the valve into the crimper aperture. Partially crimp the valve until it fits into the Qualcrimp crimping accessory.
7. Place the Qualcrimp crimping accessory over the valve making sure the edge of the Qualcrimp crimping accessory is parallel to the inflow of the valve.
8. Place the valve and Qualcrimp crimping accessory in crimper aperture. Insert the delivery system coaxially within the valve with the orientation of the valve on the delivery system with the inflow (outer sealing skirt) of the valve towards the handle.

   Note: Verify correct valve orientation with the inflow (outer sealing skirt) oriented towards the handle.

9. Crimp the valve between the shoulders until it reaches the Qualcrimp stop located on the 2-piece crimp stopper.
10. Gently remove the Qualcrimp crimping accessory from the valve. Remove the Qualcrimp stop from the crimp stopper, leaving the final stop in place.

11. Confirm valve is positioned between the shoulders. Center the valve within the crimper aperture. Fully crimp the valve until it reaches the final stop and hold for 5 seconds. Repeat this crimp step three (3) more times for a total of 4 crimps.

    Note: Ensure the valve is coaxial within the crimper aperture and remains between the two internal shoulders of the delivery system.

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

12. Flush the outer shaft with heparinized saline through the flush port on the handle.
13. Cover the crimped valve with the valve capsule by retracting the balloon catheter into the outer shaft. Ensure that the distal edge of the valve capsule meets the tapered tip of the delivery system.

    CAUTION: Keep valve hydrated until ready for implantation.

14. Lock the delivery system.
15. Remove the stylet and flush the guidewire lumen of the delivery system.
16. Flush the inline sheath with heparinized saline. Immediately advance the inline sheath until the sheath tip is against the proximal end of the valve capsule.

    Note: Do not force the inline sheath over the valve capsule.

17. Hydrate the tapered tip and valve capsule of delivery system with heparinized saline.
18. Flush and hydrate the dilator.

7.3 Landing Zone Predilation and Valve Delivery

Landing zone predilation prior to implantation is optional as deemed appropriate by physician.

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

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.

7.3.1 Valve Delivery

1. Gain vascular access using standard catheterization techniques.
2. Ensure tapered tip and valve capsule of delivery system are hydrated, and the delivery system is locked.
3. Insert and advance the guidewire into the intended landing zone per standard technique.
4. If necessary, remove existing sheath.
5. Predilate the vessel with the provided dilator to prepare the vasculature for insertion and advancement of the delivery system and inline sheath.
6. Introduce the delivery system and inline sheath, until the inline sheath is fully inserted into the vasculature.
7. Continue to advance the delivery system while maintaining inline sheath position and advance the valve into the intended landing zone.
8. Verify the correct position of the valve within the intended landing zone, unlock the delivery system. Unsheathe the valve by retracting the outer shaft while maintaining balloon, valve, and inline sheath position. The valve is fully uncovered when the handle meets the gripper. Lock the delivery system.
9. Verify final position and begin valve deployment:
    a) Unlock the inflation device provided by Edwards Lifesciences.
    b) Using slow controlled inflation, deploy the valve with the entire volume in the inflation device, hold for 3 seconds and confirm that the barrel of the inflation device is empty to ensure complete inflation of the balloon.
    c) Deflate the balloon.

7.4 System Removal

1. Once the balloon is fully deflated, ensure the handle is in the locked position, and retract the delivery system into the vena cava.
2. Unlock the delivery system, retract the balloon into the valve capsule.

    CAUTION: Completely cover the balloon prior to removal to minimize the risk of vascular injury.

3. Lock the delivery system.
4. Continue to remove the delivery system until the valve capsule meets the inline sheath tip.

    Remove the inline sheath and the delivery system together.

    Note: A sheath or other device may need to be inserted per standard of care.

5. Remove all devices when the ACT level is appropriate.

Close the access site.

8.0 How Supplied

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

8.1 Storage

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

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

9.0 Magnetic Resonance (MR) Safety Information

MR Conditional

A person with the SAPIEN 3 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
Static Magnetic Field Strength (B0)	1.5 tesla (T) or 3.0 tesla (T)
Maximum Spatial Field Gradient	3000 gauss/cm (30 T/m)
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	2.0 W/kg
Scan Duration	2.0 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.	

10.0 Patient Information

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

11.0 Recovered Valve and Device Disposal

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

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

12.0 Clinical Studies

SUMMARY OF CLINICAL STUDY

The COMPASSION S3 Trial Overview, SAPIEN 3 Valve

Patients were enrolled between July 2016 and July 2018. The database for this PMA reflected data collected through November 4, 2019. The patients received an Edwards SAPIEN 3 transcatheter heart valve placed with a Commander delivery system.

The COMPASSION S3 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 study. An independent echocardiographic core laboratory was used for standardized assessment of echocardiograms.

Clinical Inclusion and Exclusion Criteria

Patients receiving an Edwards SAPIEN 3 transcatheter heart valve in the clinical study included those with a dysfunctional RVOT conduit or previously implanted valve in the pulmonic position with a clinical indication for intervention.

Clinical Endpoints

The endpoints analyzed in this application included: valve performance based on echocardiographic data, RVOT reintervention, adjudicated adverse events (coronary artery compression requiring intervention, major vascular complications, life-threatening or disabling bleeding, device-related endocarditis and death), THV frame fracture, site reported adverse events, and New York Heart Association (NYHA) classification. The analyses in the application focused on the 30-day and one-year time points.

A. Accountability of the PMA Main Cohort

At the time of database lock, a total of 58 subjects were enrolled in the study, including 38 with a dysfunctional RVOT and 20 with a dysfunctional bioprosthetic valve in the pulmonic position.

There were three different analysis populations defined in the protocol: All Treated (AT), Attempted Implant (AI), and Valve Implant (VI), as summarized in Table 7.

Table 7: Analysis Populations

Analysis Population	Definition	Number of Patients
All Treated	All subjects who signed informed consent, passed screening and for whom the procedure was begun (defined as the time of vascular access - incision or puncture)	58
Attempted Implant	All AT subjects who had an attempted implant of the study valve (introducer sheath for vascular delivery of the Edwards SAPIEN 3 THV was inserted into the subject).	56
Valve Implant	All AI patients who received and retained the intended valve upon leaving the catheterization laboratory/hybrid suite.	56

Study visit compliance is summarized in Table 8. Three subjects have exited the study.

Table 8: Study Visit Compliance

	AT Population (N=58)		
	30 Days	**6 Months**	**1 Year**
Ineligible*	2	2	2
Eligible	56	56	56
Visit performed	55 (98.2%)	54 (96.4%)	52 (92.9%)

*Ineligible subjects included those who exited the study prior to the visit

B. Study Population Demographics and Baseline Characteristics

The demographics and baseline characteristics of the study population are typical for a transcatheter pulmonary valve study performed in the U.S., as shown in Table 9.

Table 9: Demographics and Baseline Characteristics (AT Population)

Variable	Summary Statistics* (N=58)
Age (years)	31.8 ± 13.2 (58)
<12 years (child)	8.6% (5/58)
12-21 years (adolescent)	13.8% (8/58)
≥22 years (adult)	77.6% (45/58)

Variable	Summary Statistics* (N=58)
Gender	
Male	69.0% (40/58)
Weight (kg)	74.1 ± 21.2 (58)
NYHA class	
Class I	15.8% (9/57)
Class II	73.7% (42/57)
Class III	10.5% (6/57)
Class IV	0.0% (0/57)
NYHA class grouped	
Class I/II	89.5% (51/57)
Class III/IV	10.5% (6/57)
Primary indication	
Pulmonary stenosis only	12.3% (7/57)
Pulmonary regurgitation only	19.3% (11/57)
Both	68.4% (39/57)
Original CHD diagnosis	
Aortic valve disease resulting in Ross procedure	21.1% (12/57)
Atrial septal defect	17.2% (10/58)
Coarctation of the aorta	1.7% (1/58)
Double outlet right ventricle	5.2% (3/58)
Pulmonary atresia	17.2% (10/58)
Pulmonary valve stenosis	50.0% (29/58)
Tetralogy of Fallot	55.2% (32/58)
Transposition of the great arteries	6.9% (4/58)
Truncus arteriosus	5.2% (3/58)
Ventricular septal defect	34.5% (20/58)
Other	32.8% (19/58)
Most recent RVOT/PV repair/replacement	
Homograft	50.0% (29/58)
Biological valved conduit	13.8% (8/58)
Synthetic valved conduit	1.7% (1/58)
Surgical heart valve	34.5% (20/58)

*Continuous measures - Mean ± SD (Total no.); categorical measures - % (no./Total no.)

The distribution of prior cardiac interventions in the AT population stratified by patient age is shown in Table 10. The minimum and maximum diameters of the landing zone stratified by prior cardiac intervention and patient age are provided in Table 11.

Table 10: Prior Cardiac Interventions by Age Group (AT Population)

Endpoint	Summary Statistics*		
	<12 Years (N=5)	12-21 Years (N=8)	≥22 Years (N=45)
Most recent RVOT/PV repair/replacement			
Homograft	60.0% (3/5)	37.5% (3/8)	51.1% (23/45)
Biological valved conduit	20.0% (1/5)	50.0% (4/8)	6.7% (3/45)
Synthetic valved conduit	0.0% (0/5)	0.0% (0/8)	2.2% (1/45)

Endpoint	Summary Statistics*		
	<12 Years (N=5)	12-21 Years (N=8)	≥22 Years (N=45)
Surgical heart valve	20.0% (1/5)	12.5% (1/8)	40.0% (18/45)

*Categorical measures - % (No. / Total no.).

Table 11: Landing Zone Diameters by Prior Cardiac Interventions and Patient Age (AT Population)

Most Recent RVOT Repair / Replacement	Summary Statistics*					
	<12 Years (N=5)		12-21 Years (N=8)		≥22 Years (N=45)	
	Landing Zone Minimum Diameter (mm)	Landing Zone Maximum Diameter (mm)	Landing Zone Minimum Diameter (mm)	Landing Zone Maximum Diameter (mm)	Landing Zone Minimum Diameter (mm)	Landing Zone Maximum Diameter (mm)
All Subjects	17.8±1.8 (5/5)	19.3±0.8 (5/5)	21.9±4.7 (6/8)	24.3±0.9 (6/8)	20.4±3.1 (40/45)	23.0±4.3 (41/45)
Homograft	17.4±2.4 (3/5)	19.2±1.0 (3/5)	18.4±7.9 (2/8)	24.2±0.2 (3/8)	20.1±3.5 (22/45)	23.0±5.4 (23/45)
Biological valved conduit	19.0±NA (1/5)	20.0±NA (1/5)	22.8±1.8 (3/8)	23.5±0.2 (2/8)	18.0±2.6 (3/45)	21.0±1.0 (3/45)
Synthetic valved conduit	NA	NA	NA	NA	18.7±NA (1/45)	19.7±NA (1/45)
Surgical heart valve	18.0±NA (1/5)	19.0±NA (1/5)	25.9±NA (1/8)	25.9±NA (1/8)	21.6±2.0 (14/45)	23.7±2.3 (14/45)

*Continuous measures - Mean ± SD (No./Total no.)

C. Safety and Effectiveness Results

1. Primary Endpoint

The primary endpoint results are presented in Table 12. THV dysfunction at 1 year was 4.3% (CI: 0.5% to 14.5%). Since the upper limit of the 95% confidence interval for the primary endpoint event rate was < 25%, the endpoint was met.

Table 12: Primary Endpoint: THV Dysfunction at 1 Year (VI Population)

Variable	Summary Statistics* (N=56)	95% Confidence Interval	Less than the pre-specified performance goal (25%)?
THV dysfunction	4.3% (2/47)	(0.5%, 14.5%)	Yes
RVOT reintervention†	0.0% (0/56)	(0.0%, 6.4%)	
Moderate or greater PR	2.1% (1/47)	(0.1%, 11.3%)	
Mean RVOT gradient > 40 mmHg	2.1% (1/48)	(0.1%, 11.1%)	

*Summary statistics: Categorical measures - % (no./Total no.)

†Includes reintervention for both RVOT conduit and THV

2. Secondary Safety Endpoints

The results of the secondary safety endpoints as adjudicated by the CEC are summarized in Table 13.

Table 13: Summary of Secondary Safety Endpoint Results (AT Population)

Freedom from Adverse Events	Summary Statistics*
30-day endpoints (at risk† =57)	
Coronary artery compression requiring intervention post-implantation	100.0% (0, 0)
Major vascular complications	100.0% (0, 0)
Life threatening or disabling bleeding	100.0% (0, 0)
6-month endpoint (at risk =55)	

Freedom from Adverse Events	Summary Statistics*
THV frame fracture (site-reported)	100.0% (0, 0)
1-year endpoints (at risk =51)	
All-cause death	100.0% (0, 0)
Procedure- or device-related death	100.0% (0, 0)
Device related endocarditis	100.0% (0, 0)

*Kaplan-Meier estimate (No. events, No. patients with event)

†At risk numbers reflect the number of subjects on study at the end of the interval.

3. Secondary Effectiveness Endpoints

Device Success

Device success was achieved in 98.1% of the subjects, as shown in Table 14.

Table 14: Device Success (AI Population)

Endpoint	Summary Statistics* (N=56)
Device success	98.1% (53/54)
Single THV implanted in the desired location	98.2% (55/56)
RV-PA peak-to-peak gradient < 35 mmHg post implantation	100.0% (56/56)
Less than moderate PR by discharge TTE (or earliest evaluable TTE)	100.0% (54/54)
Free of explant at 24 hours post implantation	100.0% (56/56)

*Categorical measures - % (no./Total no.)

RVOT Reintervention

No subject had RVOT intervention within 1 year of the valve implant procedure.

THV Hemodynamic Function

The mean RVOT gradient, peak RVOT gradient, peak RVOT gradient stratified by landing zone type, total PR and paravalvular regurgitation results at 1 year are shown in Figure 6 through Figure 10, respectively. The decrease in gradient was sustained through 1 year. The proportion of patients with total PR ≥ moderate was 0.0% at 30 days and 2.1% at 1 year. The proportion of patients with paravalvular regurgitation ≥ moderate was 0.0% at 30 days and 1 year.

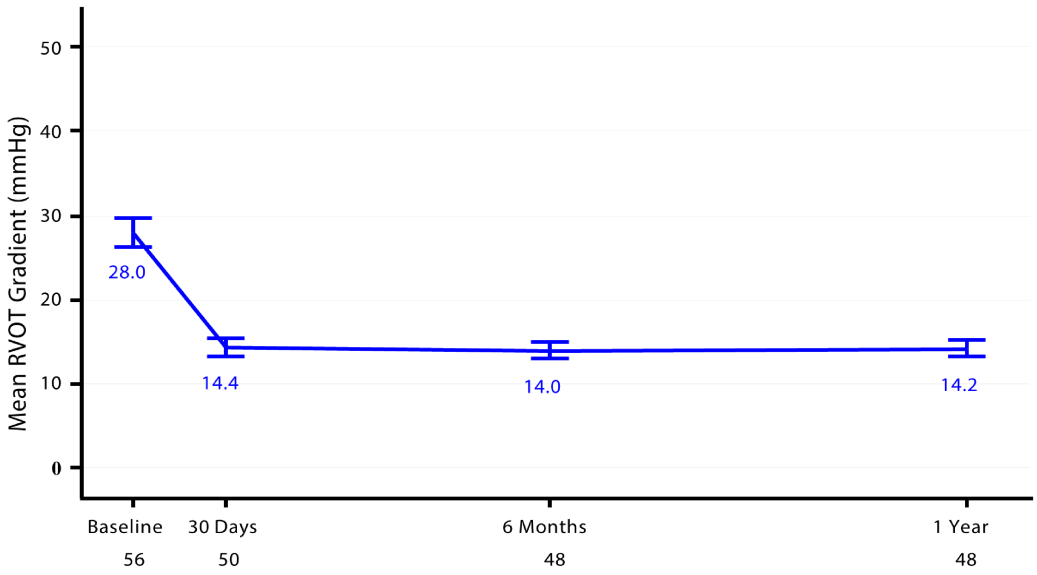


Figure 6: Mean RVOT Gradient (VI Population)

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

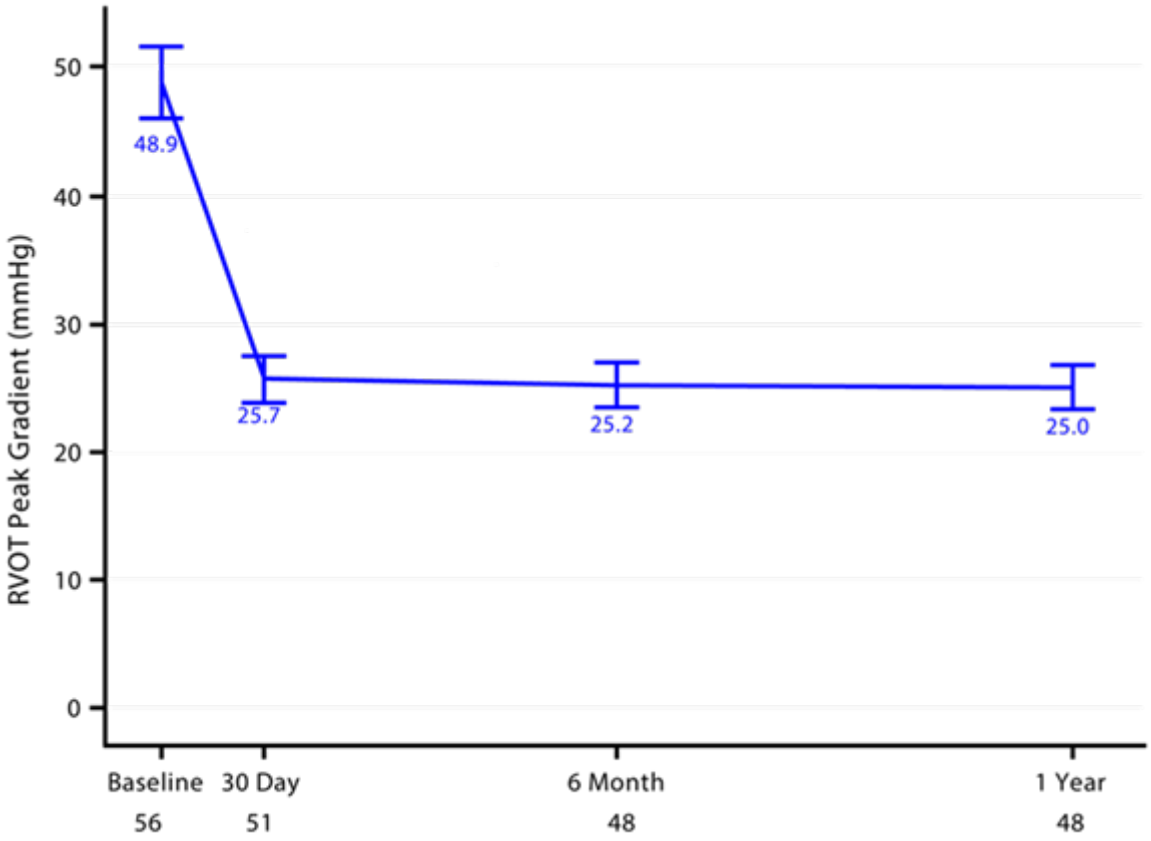


Figure 7: Peak RVOT Gradient (VI Population)

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

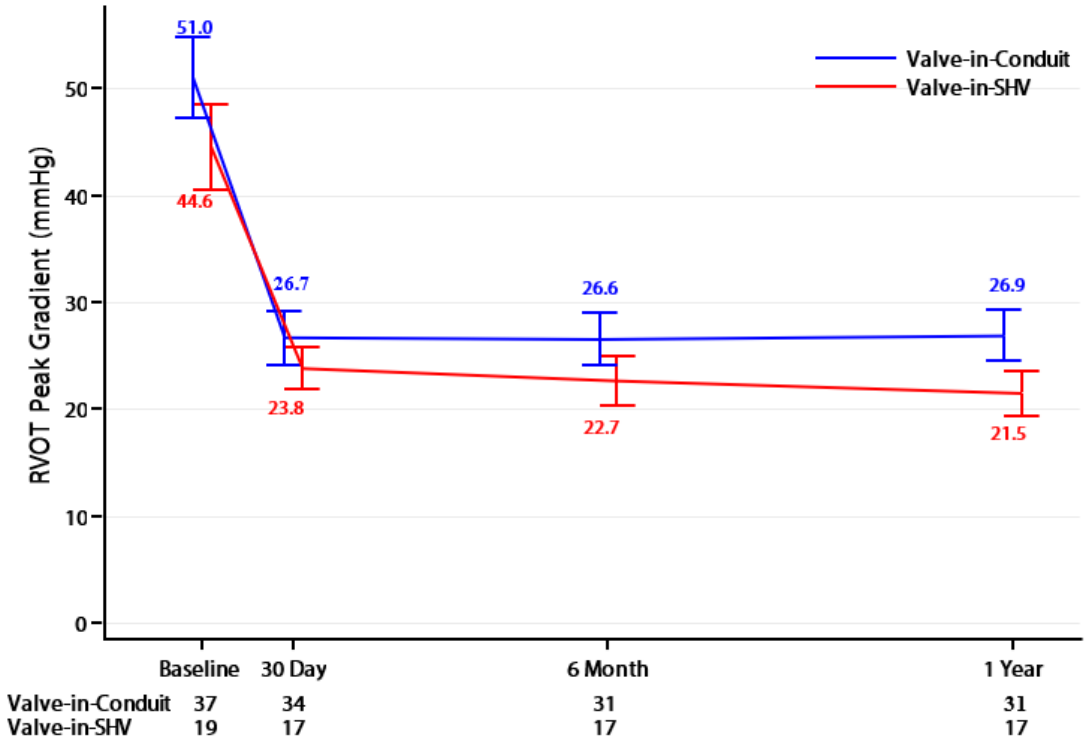


Figure 8: RVOT Peak Gradient by Landing Zone Type (VI Population)

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

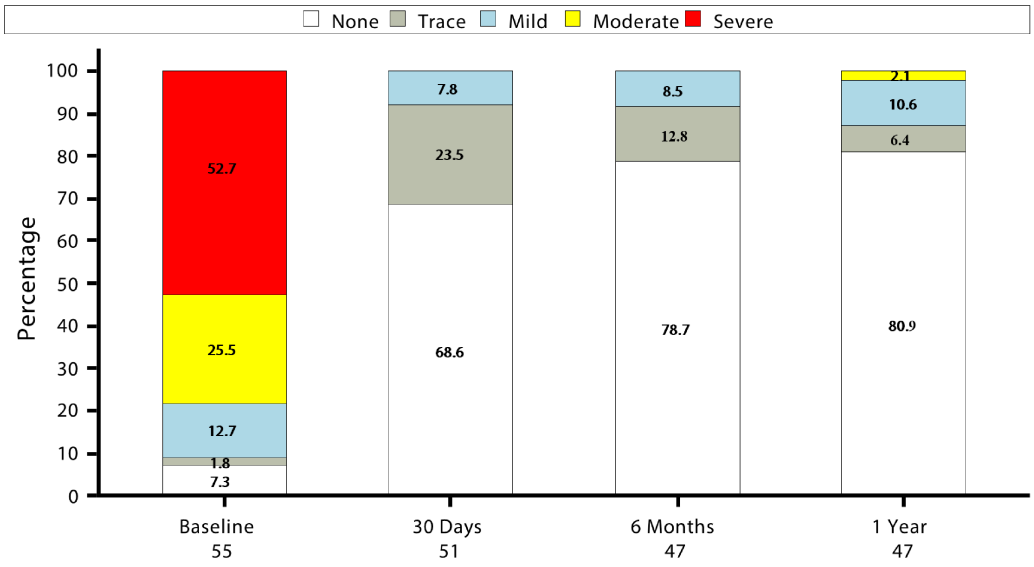


Figure 9: Total Pulmonary Regurgitation (VI Population)

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

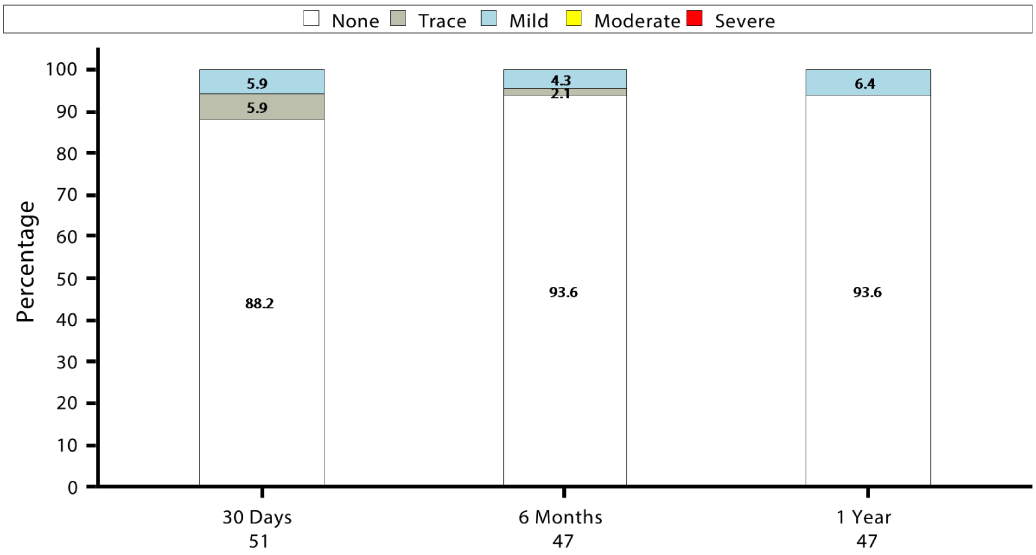


Figure 10: Paravalvular Regurgitation (VI Population)

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

NYHA Functional Class

NYHA classifications by visit are presented in Figure 11. At baseline, 89.1% of subjects were in NYHA Class I/II. At 1 year, all subjects were in NYHA Class I/II.

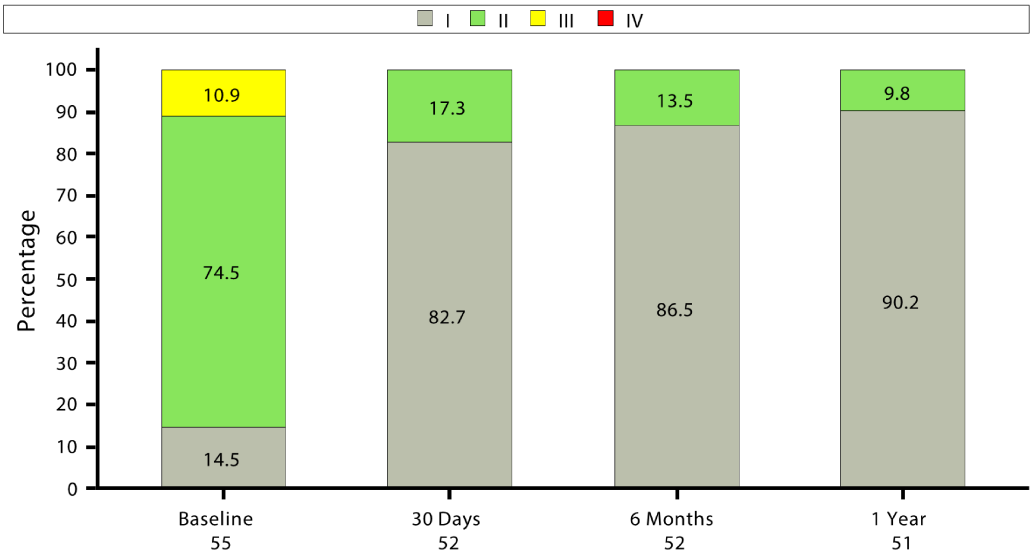


Figure 11: NYHA Class by Visit (VI Population)

4. Adverse Events

The Kaplan-Meier estimates of the CEC-adjudicated adverse events through 1 year are presented in Table 15.

Table 15: CEC-Adjudicated Adverse Events Through 1 Year (AT Population)

Event	Summary Statistics*		
	30 Days (N=57)	6 Months (N=55)	1 Year (N=51)
Death	0.0% (0,0)	0.0% (0,0)	0.0% (0,0)
Cardiovascular	0.0% (0,0)	0.0% (0,0)	0.0% (0,0)
Non-Cardiovascular	0.0% (0,0)	0.0% (0,0)	0.0% (0,0)
Reintervention†	0.0% (0,0)	0.0% (0,0)	0.0% (0,0)
Arrhythmia	3.4% (2,2)	7.1% (5,4)	7.1% (5,4)
Permanent Pacemaker	0.0% (0,0)	1.8% (1,1)	1.8% (1,1)
Acute Kidney Injury	0.0% (0,0)	--	--
Bleeding	10.3% (6,6)	--	--
Life Threatening or Disabling	0.0% (0,0)	--	--
Major	0.0% (0,0)	--	--
Minor	10.3% (6,6)	--	--
Coronary Artery Compression	0.0% (0,0)	--	--
Endocarditis	0.0% (0,0)	0.0% (0,0)	0.0% (0,0)
Myocardial Infarction	0.0% (0,0)	--	--
Pulmonary Embolism	0.0% (0,0)	0.0% (0,0)	0.0% (0,0)
Stroke	0.0% (0,0)	0.0% (0,0)	0.0% (0,0)
TIA	0.0% (0,0)	0.0% (0,0)	0.0% (0,0)
Vascular Injury or Access Site Complication	12.1% (7,7)	--	--
Major	0.0% (0,0)	--	--
Minor	12.1% (7,7)	--	--

*Kaplan-Meier estimate (No. events, No. patients with event).

†Includes reintervention for both RVOT conduit and THV

5. Other Study Observations

Procedural Information

Procedural data are summarized in Table 16. General anesthesia was used in the majority of subjects (91.4%). Pre-stenting occurred in 53.4% of the procedures. The most frequent procedural complication was RVOT conduit tear, which occurred in 8.6% of patients. The interventions associated with these procedural complications are summarized in Table 17.

Table 16: Procedural Data (AT Population)

Variable	Summary Statistics* (N=58)
Catheterization laboratory time (min)	238.2 ± 92.5 (58)
Procedure time (min)	120.4 ± 97.8 (57)
Anesthesia time (min)	227.7 ± 93.3 (55)
Type of anesthesia used	
General	91.4% (53/58)
Conscious sedation	8.6% (5/58)
Planned concomitant procedures	6.9% (4/58)

Variable	Summary Statistics* (N=58)
Procedural complications	12.1% (7/58)
RVOT conduit tear	8.6% (5/58)
Difficulty removing delivery system	1.7% (1/58)
Difficulty advancing the delivery system	1.7% (1/58)
Pre-dilatation performed	79.3% (46/58)
Pre-stenting performed	53.4% (31/58)
Any stent placed	53.4% (31/58)
Stent placed during procedure	53.4% (31/58)
Edwards SAPIEN 3 THV implanted	96.6% (56/58)
20 mm	19.6% (11/56)
23 mm	37.5% (21/56)
26 mm	37.5% (21/56)
29 mm	5.4% (3/56)
Post-dilatation performed	26.8% (15/56)
Valve not fully expanded	86.7% (13/15)
Other	13.3% (2/15)
Second SAPIEN 3 THV implanted	1.8% (1/57)

*Continuous measures - Mean ± SD (Total no.); categorical measures - % (no./Total no.)

Table 17: Procedural Complication Interventions

Variable	Summary Statistics* (N=58)
Action taken to resolve complication	
Transcatheter implant of commercial valve	1.7% (1/58)
Placement of covered stent	6.9% (4/58)
Other	3.4% (2/58)
Venotomy to remove ruptured balloon	1.7% (1/58)
Prolonged intubation	1.7% (1/58)

*Categorical measures - % (no./Total no.)

Subgroup Analyses

The pre-specified subgroup analyses by age, gender, valve size, and pre-stenting are summarized in Table 18.

Table 18: THV Dysfunction at 1 Year: Subgroup Analysis (VI Population)

Subgroup	Endpoint	Summary Statistics* (N=56)
By Age Group		
≤ 21 (N=12)	THV Dysfunction	0.0% (0/11)
	RVOT reintervention	0.0% (0/12)
	Moderate or greater PR	0.0% (0/11)
	Mean RVOT gradient >40 mmHg	0.0% (0/11)
≥ 22 (N=44)	THV Dysfunction	5.6% (2/36)
	RVOT reintervention	0.0% (0/44)
	Moderate or greater PR	2.8% (1/36)
	Mean RVOT gradient >40 mmHg	2.7% (1/37)

Subgroup	Endpoint	Summary Statistics* (N=56)
By Gender		
Female (N=18)	THV Dysfunction	0.0% (0/17)
	RVOT reintervention	0.0% (0/18)
	Moderate or greater PR	0.0% (0/17)
	Mean RVOT gradient >40 mmHg	0.0% (0/17)
Male (N=38)	THV Dysfunction	6.7% (2/30)
	RVOT reintervention	0.0% (0/38)
	Moderate or greater PR	3.3% (1/30)
	Mean RVOT gradient >40 mmHg	3.2% (1/31)
By Valve Size		
20mm (N=11)	THV Dysfunction	22.2% (2/9)
	RVOT reintervention	0.0% (0/11)
	Moderate or greater PR	11.1% (1/9)
	Mean RVOT gradient >40 mmHg	11.1% (1/9)
23mm (N=21)	THV Dysfunction	0.0% (0/17)
	RVOT reintervention	0.0% (0/21)
	Moderate or greater PR	0.0% (0/17)
	Mean RVOT gradient >40 mmHg	0.0% (0/17)
26mm (N=21)	THV Dysfunction	0.0% (0/18)
	RVOT reintervention	0.0% (0/21)
	Moderate or greater PR	0.0% (0/18)
	Mean RVOT gradient >40 mmHg	0.0% (0/19)
29mm (N=3)	THV Dysfunction	0.0% (0/3)
	RVOT reintervention	0.0% (0/3)
	Moderate or greater PR	0.0% (0/3)
	Mean RVOT gradient >40 mmHg	0.0% (0/3)
By Pre-stenting		
Pre-stented (N=31)	THV Dysfunction	8.0% (2/25)
	RVOT reintervention	0.0% (0/31)
	Moderate or greater PR	4.0% (1/25)
	Mean RVOT gradient >40 mmHg	4.0% (1/25)
No pre-stent (N=25)	THV Dysfunction*	0.0% (0/22)
	RVOT reintervention	0.0% (0/25)
	Moderate or greater PR	0.0% (0/22)
	Mean RVOT gradient >40 mmHg	0.0% (0/23)

*Categorical measures - % (no./Total no.)

13.0 References

[1] Bapat V, Attia R, Thomas M. Effect of Valve Design on the Stent Internal Diameter of a Bioprosthetic Valve: A Concept of True Internal Diameter and Its Implications for the Valve-in-Valve Procedure. JACC: Cardiovascular Interventions. Vol. 7, No. 2 2014: 115-127.

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