Portico™ Transcatheter Aortic Valve Implantation System

Portico™ Transcatheter Aortic Valve
FlexNav™ Delivery System
FlexNav™ Loading System

REF

PRT-23, PRT-25, PRT-27, PRT-29
FNAV-DS-SM, FNAV-DS-LG
FNAV-LS-SM, FNAV-LS-LG

Instructions for Use

Please verify you have latest version of the IFU prior to using the device by visiting: medical.abbott/manuals.

CAUTION: Federal (USA) law restricts these devices to sale by or on the order of a physician.

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Portico™ Transcatheter Aortic Valve Implantation System

Instructions for Use

CAUTION: The Portico™ Transcatheter Aortic Valve Implantation System should only be used by physicians who have undergone training on use of this system.

Description

Portico™ Transcatheter Aortic Valve Implantation System

The Portico™ Transcatheter Aortic Valve Implantation System (hereafter described as the Implantation system) consists of the Portico™ transcatheter aortic valve, the FlexNav™ delivery system, and the FlexNav™ loading system, as described below.

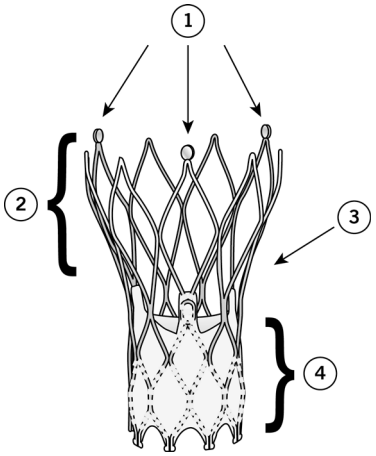
Table 1. Portico™ Implantation System Components

Portico™ Valve Catalog Numbers	FlexNav™ Delivery System Catalog Number	FlexNav™ Loading System Catalog Number
PRT-23 (23 mm) or PRT-25 (25 mm)	FNAV-DS-SM	FNAV-LS-SM
PRT-27 (27 mm) or PRT-29 (29 mm)	FNAV-DS-LG	FNAV-LS-LG

Portico™ Valve

The Portico™ valve is designed to be implanted in the native aortic heart valve without open heart surgery and without concomitant surgical removal of the failed native valve.

Figure 1. Portico™ valve



1. Retainer tabs
2. Aortic end of valve
3. Stent
4. Annulus end of valve

The valve is comprised of three main components: stent, cuff, and leaflets. The stent is made from nitinol, a nickel-titanium alloy that has self-expanding properties and is radiopaque. The cuff consists of porcine pericardium, and the leaflets are made from bovine pericardium which are sutured together into a tri-leaflet configuration on the stent frame.

The cuff and leaflet pericardial tissue is preserved and crosslinked in glutaraldehyde. Glutaraldehyde, formaldehyde and ethanol are used in the valve sterilization process.

The valve leaflets and valve cuff are processed using Linx™ anticalcification technology. The valve is supplied sterile and non-pyrogenic.

Evaluate the patient's cardiac anatomy for the characteristics described in the following table.

Patient Anatomical Criteria

Table 2. Patient Anatomical Specifications

Catalog Number	Valve Size	Annulus Diameter	Ascending Aorta Diameter	Area[1]	Perimeter[1]
PRT-23	23mm	19 - 21 mm	26 - 36 mm	277-346 mm^2	60-66 mm
PRT-25	25mm	21 - 23 mm	28 - 38 mm	338-415 mm^2	66-73 mm
PRT-27	27mm	23 - 25 mm	30 - 40 mm	405-491 mm^2	72-79 mm
PRT-29	29mm	25 - 27 mm	32 - 42 mm	479-573 mm^2	79-85 mm

FlexNav™ Delivery System

The FlexNav™ delivery system facilitates Portico™ valve implantation using transfemoral, subclavian/axillary, or transaortic access methods. The over-the-wire delivery system may be inserted into the vessel with or without an arterial introducer sheath.

The delivery system design facilitates gradual, controlled deployment of the valve. The valve is deployed annulus end first from the distal end of the delivery system. If needed, the valve may be re-sheathed and repositioned up to two times, provided the valve has not been fully deployed.

Table 3. FlexNav™ Delivery System Specifications

Delivery System Catalog Number	Equivalent Integrated Sheath Diameter	Valve Capsule Outer Diameter	Integrated Sheath Working Length	Delivery System Working Length	Minimum Vessel Diameter Requirement	Compatible Guidewire
FNAV-DS-SM	14F	6.0 mm	30 cm	107 cm	≥ 5.0 mm	0.035" (0.89 mm)
FNAV-DS-LG	15F	6.3 mm	30 cm	107 cm	≥ 5.5 mm	0.035" (0.89 mm)

The delivery system is compatible with 18F (FNAV-DS-SM) and 19F (FNAV-DS-LG) introducer sheaths.

Distal end features (Figure 2):

A **valve capsule** covers and maintains the valve in the collapsed position within the delivery system. The valve capsule may be advanced or retracted to facilitate valve loading and deployment. The valve capsule features a radiopaque **valve capsule marker band** that provides a reference point used to determine the extent of the valve deployment. When the valve capsule is retracted the **inner shaft** is exposed.

The valve is loaded onto the **inner shaft**. Retainer tabs on the valve lock into a **retainer receptacle** that is mounted on the inner shaft. A radiopaque **inner shaft marker band** provides a reference point used to initially align the valve in the native annulus.

An atraumatic **radiopaque tip** is used to guide the delivery system and facilitate visualization.

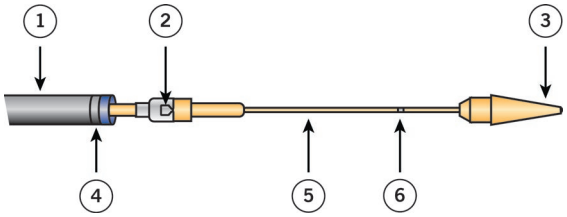
This device is coated with a hydrophilic coating in the following locations:

- The radiopaque tip and valve capsule are coated over their entire surfaces
- The integrated sheath is coated from the distal end to within 5 cm of the integrated sheath hub

Please refer to “Loading the Valve on the Delivery System” for further information on how to prepare and use this device to ensure it performs as intended. Failure to abide by the warnings in this labeling might result in damage to the device coating, which may necessitate intervention or result in serious adverse events.

[1] Area and perimeter specifications are for reference only.

Figure 2. Distal end of the delivery system

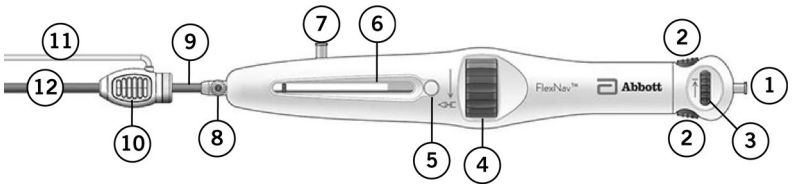


1. Valve capsule
2. Retainer receptacle
3. Radiopaque tip
4. Valve capsule marker band
5. Inner shaft
6. Inner shaft marker band

Proximal end features (Figure 3):

- Two **macro slide buttons** facilitate opening and closure of the distal end of the delivery system.
- A **deployment/re-sheath wheel** is used to adjust the position of the valve capsule during valve loading and deployment.
- A **micro adjustment wheel** is used to close gaps between the valve capsule and the radiopaque tip.
- A **deployment indicator** provides visualization of the extent of valve deployment.
- A **deployment lock button** prevents full valve deployment before valve position is optimized. The deployment lock button will engage when the deployment indicator reaches the gray zone.
- **Flush ports** facilitate de-airing of the system
- An **integrated sheath** facilitates vascular access, minimizing access site size to the capsule diameter.
- A s**tability layer** facilitates stable delivery system retraction by allowing the distal end of the delivery system to move freely within the integrated sheath.

Figure 3. Proximal end of the delivery system

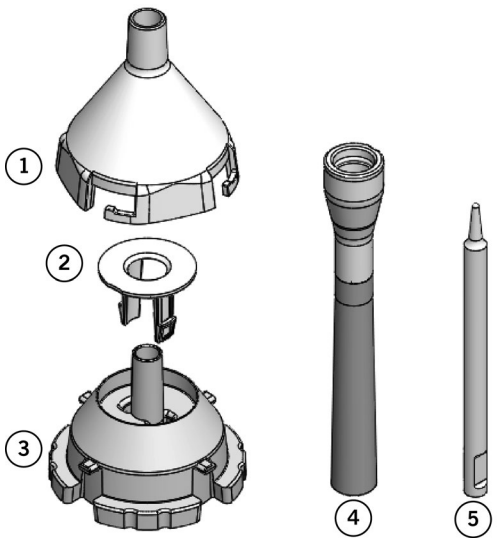


1. Guidewire lumen flush port
2. Macro slide buttons
3. Micro adjustment wheel
4. Deployment/re-sheath wheel
5. Deployment lock button
6. Deployment indicator
7. Valve capsule flush port
8. Stability layer flush port
9. Stability layer
10. Integrated sheath hub
11. Integrated sheath layer flush port
12. Integrated sheath

FlexNav™ Loading System

The FlexNav™ loading system facilitates valve preparation/loading onto the FlexNav™ delivery system. The loading system includes a loading funnel, loading base, base insert, loading tube, and a leaflet tester.

Figure 4. Loading system



1. Loading funnel
2. Base insert
3. Loading base
4. Loading tube
5. Leaflet tester

Indications

The Portico Transcatheter Aortic Valve Implantation 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 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 comorbidities unmeasured by the STS risk calculator).

Contraindications

The valve is contraindicated for patients with inability to tolerate antiplatelet/anticoagulant therapy, nitinol alloy (nickel and titanium), or who have active infections, including endocarditis.

Warnings

Carefully read all warnings, precautions, and instructions for use for all components of the system before use. Failure to read and follow all instructions or failure to observe all stated warnings could cause serious injury or death to the patient

- Perform Portico™ valve implantation in a facility where emergency aortic valve surgery is available.
- Verify that the patient's anatomy is consistent with the specifications set forth in the anatomical specifications tables 2 & 3.
- For single use only. Do not reuse, reprocess, or resterilize the valve, delivery system, or the loading system. Reuse, reprocessing, and/or resterilization creates a risk of contamination of the devices and/or device failure, which could cause patient injury, illness or death.
- Do not manipulate or handle the valve with sharp or pointed objects.
- Rinse the valve as directed before loading the valve onto the delivery system.
- Do not use the valve, the delivery system, or the loading system if the "USE BY" date has elapsed.
- Exercise care to prevent kinking of the delivery system when removing it from the packaging.
- This device contains nitinol, an alloy of nickel and titanium. Persons with allergic reactions to these metals may suffer an allergic reaction to this implant. Prior to implantation, patients should be counseled on the materials contained in the device, as well as potential for allergy/hypersensitivity to these materials.
- Accelerated deterioration of the valve due to calcific degeneration may occur in children, adolescents, young adults, or patients with altered calcium metabolism.

Precautions

Pre-Implantation Precautions

- The safety, effectiveness, and durability of a Portico™ valve implanted within a surgical or transcatheter bioprosthesis have not been demonstrated.
- Long-term durability has not been established for the Portico valve. Regular medical follow-up is advised to evaluate valve performance.
- For transaortic access, ensure the access site and trajectory are free of internal patent right internal mammary artery (RIMA) or pre-existing patent RIMA graft.
- For subclavian/axillary access, use caution in patients with mammary artery grafts.

- Balloon aortic valvuloplasty (BAV) of the native aortic valve is recommended prior to delivery system insertion. The balloon size chosen should be appropriate, not exceeding the minimum diameter of the native aortic annulus as assessed by CT imaging to minimize risk of annular rupture, and not undersized to minimize risk of stent under-expansion which could lead to paravalvular leak (PVL) or device migration.
- Do not use the valve if the shipping temperature indicator on the product package has turned red, or if the valve has been improperly stored in temperature conditions outside of the 5°C–25°C (41°F–77°F) range.
- Do not use the valve if the tamper-evident container seal is damaged, broken, or missing, or if fluid is leaking from the packaging.
- Do not advance the delivery system without the guidewire extending from the tip.
- Do not use the valve without thoroughly rinsing as directed.
- Do not use the delivery system without thoroughly flushing as described in the "Directions for Use" section.
- The safety and effectiveness of the Portico™ valve and FlexNav™ delivery system have not been evaluated in the following patient populations:
    - Congenital unicuspid or bicuspid valve, or any leaflet configuration other than tricuspid
    - Severe ventricular dysfunction with left ventricular ejection fraction <20%
    - Non-calcific aortic annulus
    - Echocardiographic evidence of intracardiac mass, thrombus or vegetation
    - Patients at low or intermediate surgical risk
    - Patients who are pregnant or breastfeeding
    - Pediatric patients (less than 21 years of age)
    - Patients with a pre-existing prosthetic heart valve or prosthetic ring in any position
    - Mixed aortic valve disease (aortic stenosis and aortic regurgitation with predominant aortic regurgitation > 3+)
    - Patients with severe circumferential mitral annular calcification (MAC) which is continuous with calcium in the LVOT, severe (greater than 3+) mitral insufficiency, or severe mitral stenosis with pulmonary compromise
    - Blood dyscrasias as defined: leukopenia (WBC<3000 mm^3), acute anemia (Hb < 9 g/dL), thrombocytopenia (platelet count <50,000 cells/mm^3)
    - Patients with untreated clinically significant coronary artery disease requiring revascularization
    - Patients with bulky calcified aortic valve leaflets in close proximity to coronary ostia
    - Hypertrophic cardiomyopathy with or without obstruction (HOCM)
    - Renal insufficiency (creatinine > 3.0 mg/dL) and/or end stage renal disease requiring chronic dialysis
    - Hemodynamic instability requiring inotropic support or mechanical heart assistance
    - Significant aortic disease, including abdominal aortic or thoracic aneurysm defined as maximal luminal diameter 5cm 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
    - Patients with known hypersensitivity or contraindication to aspirin, heparin, ticlopidine (Ticlid), or clopidogrel (Plavix), or sensitivity to contrast media which cannot be adequately premedicated
    - Patients with access characteristics that would preclude safe placement of the introducer sheath, when necessary, such as severe obstructive calcification, or severe tortuosity

Implantation Precautions

- To minimize risk of guidewire perforations in the left ventricle, a manufacturer pre-shaped guidewire should be used during the procedure and during valve deployment.
- Do not deploy the valve if excessive resistance to deployment is encountered. If the valve does not deploy easily, re-sheath the valve, remove it from the patient, and use a different valve and delivery system.
- Follow the procedure in “Implanting the Valve” to reposition the valve or to remove the valve from the patient.
- Do not attempt to reposition the valve by advancing it distally unless the valve has been fully re-sheathed within the delivery system.
- Do not re-sheath the valve more than two times prior to final valve release. Additional re-sheath attempts may compromise product performance.
- To minimize likelihood of permanent pacemaker implantation (PPI): a) maintain implant depth of 3mm, and b) limit manipulations across the LVOT.

Post-Implantation Precautions

- In the event that a post-implant balloon dilatation is performed to address paravalvular leak (PVL), valve size, patient anatomy, and implant depth must be considered when selecting the size of the balloon for dilatation. The balloon size chosen should not exceed the mean diameter of the native aortic annulus. Moderate or Severe PVL should be addressed at the time of TAVR procedure.
- Exercise care when removing the delivery system from the patient.
- Exercise care when crossing the valve with adjunctive devices.
- Once the valve is fully deployed, repositioning and retrieval of the valve is not possible. Attempted retrieval (e.g., use of a guidewire, snare, or forceps) may cause aortic root, coronary artery, and/or myocardial damage.

- Valve recipients should be maintained on antiplatelet and/or anticoagulant therapy post procedure, per institutional standards and established guidelines, except when contraindicated, using individualized treatment as determined by their physician.
- Post-implant monitoring and/or possible electrophysiology evaluation may be considered in patients with transient high degree or complete AV block or other conduction disturbances during or following implantation of the valve. This may include continuous ECG monitoring after hospital discharge.

Magnetic Resonance (MR) Safety Information

MRI Safety Information

A person with the Portico™ Transcatheter Aortic Valve may be safely scanned under the following conditions. Failure to follow these conditions may result in injury.

Device Name	Portico™ Transcatheter Aortic Valve
Static Magnetic Field Strength (B_0)	1.5T or 3.0T
Maximum Spatial Field Gradient	≤ 30 T/m (3000 gauss/cm)
RF Excitation	Circularly Polarized (CP)
RF Transmit Coil Type	Body coil
Operating Mode	Normal Operating Mode
Maximum Whole Body SAR	2W/kg (Normal Operating Mode)
Maximum Head SAR	NA
Scan Duration	2 W/kg whole body average SAR for 15 minutes of continuous scanning
MR Image Artifact	The presence of this implant may produce an image artifact

Potential Adverse Events

Adverse events potentially associated with the use of transcatheter bioprosthetic heart valves include but are not limited to:

- access site complications (e.g., pain, bleeding, infection, hematoma, pseudoaneurysm, etc.)
- acute coronary obstruction
- acute myocardial infarction
- allergic reaction to antiplatelet agents, contrast medium, or valve components
- aortic rupture
- ascending aorta trauma
- atrio-ventricular node block
- cardiac arrhythmias
- conduction system injury
- dissection
- embolism
- endocarditis
- heart failure
- hemodynamic compromise
- hemolysis
- hemolytic anemia
- hemorrhage
- hypotension or hypertension

- infection
- myocardial ischemia
- mitral valve insufficiency
- multi-organ failure
- non-structural dysfunction (i.e., entrapment by pannus, paravalvular leak, inappropriate sizing or positioning)
- pericardial effusion
- perforation of the myocardium, ventricle, or a blood vessel
- pannus
- regurgitation
- renal insufficiency or renal failure
- respiratory failure
- sepsis
- stroke
- structural deterioration (i.e., calcification, leaflet tear)
- thrombosis
- tamponade
- valve embolization or migration
- vessel dissection or spasm.
- transfusion
- conversion to open surgical procedure
- reoperation
- emergent balloon valvuloplasty
- emergent percutaneous coronary intervention (PCI)
- emergent surgery (i.e., coronary artery bypass, heart valve replacement)
- explantation
- permanent disability
- death
- permanent pacemaker implantation

Materials and Equipment

The following materials and equipment are required for implantation of the Portico™ valve:

- standard cardiac catheterization lab equipment
- fluoroscopy equipment appropriate for use in percutaneous coronary interventions
- transesophageal or transthoracic echocardiographic equipment
- sterile isotonic saline
- 20 cc luer-lock syringe
- balloon catheter
- exchange length 0.035” (0.89 mm) x 260 cm manufacturer pre-shaped super stiff or equivalent manufacturer pre-shaped guidewire
- three sterile 500 mL basins
- sterile gauze pads
- compatible introducer for transaortic procedures (refer to product labels for sizing information)

Packaging and Storage

Valve

The valve is supplied in a jar containing formaldehyde storage solution. The jar has a screw cap closure and tamper-evident seal. The valve is supplied on a disposable holder. The contents of the jar are sterile and must be handled aseptically to prevent contamination. Store the valve in the upright position.

CAUTION: Do not use the valve without thoroughly rinsing as directed.

CAUTION: Do not use the valve if the shipping temperature indicator on the product package has turned red, or if the valve has been improperly stored in temperature conditions outside of the 5°C–25°C (41°F–77°F) range.

Delivery System/Loading System

The delivery system and loading system are sterilized with ethylene oxide gas. The delivery system is supplied in a tray within an outer pouch.

The loading system is supplied in a double-barrier tray. The inner delivery system/loading system trays are supplied sterile provided the outer pouch/tray packaging is not opened or damaged.

Directions for Use

Use standard imaging techniques (including computed tomography [CT] and/or echocardiography) to determine aortic annulus diameter.

Pre-Implant Handling

Do not open the valve package until implantation and sizing are certain.

Warnings:

- **Do not use the valve, delivery system, or loading system if the "USE BY" date has elapsed or if the integrity of the sterile packaging has been compromised.**
- **Do not use the valve if fluid is leaking from the packaging.**
- **Do not resterilize the valve, delivery system, or loading system by any method.**
- **Do not use the valve, the delivery system, or the loading system if it has been dropped, damaged or mishandled in any way.**
- **Avoid wiping the FlexNav device with dry gauze as this may damage the device coating.**
- **Avoid excessive wiping of the coated device.**
- **Avoid using alcohol, antiseptic solutions, or other solvents to pre-treat the device because this may cause unpredictable changes in the coating which could affect the device safety and performance.**
- **Avoid pre-soaking devices for longer than instructed, as this may impact the coating performance.**

Removing the Valve from the Packaging

PRECAUTIONS:

- **Do not place the non-sterile exterior of the valve container in the sterile field.**
- **Do not expose the valve to solutions other than the formaldehyde solution in which it was shipped, the sterile isotonic saline solution used during the rinsing procedure, or the sterile isotonic saline used to irrigate the valve.**
- **Do not add antibiotics to either the formaldehyde storage solution or the rinse solution.**
- **Do not apply antibiotics to the valve.**

1. Once the valve container has been removed from the outer packaging, examine the container for evidence of damage.

   CAUTION: Do not use the valve if the tamper-evident jar seal is damaged, broken, or missing, or if fluid is leaking from the packaging.

   WARNING: Do not use the valve if it is not completely covered by formaldehyde storage solution.

2. Prior to use, verify the valve size and "USE BY" date on the packaging label and the jar label.
3. To remove the valve from the jar, break the seal and remove the screw-top closure.

   CAUTION: Avoid prolonged contact with the formaldehyde storage solution. Immediately after contact, thoroughly flush any skin exposed to the solution with water. In case of contact with eyes, flush with water and seek appropriate medical care.

4. Using sterile forceps or gloved hands, carefully grasp the valve holder and remove the valve from the jar. Drain the valve completely.

   CAUTION: Do not handle the valve or leaflet tissue with unprotected forceps or sharp instruments.

5. Remove the valve from the valve holder by carefully compressing the aortic end of the valve stent circumferentially. Take care not to touch the valve tissue.
6. Inspect the valve for damage. Do not use the valve if there is any sign of damage or deterioration.

Rinsing the Valve

CAUTION: Do not use the valve without thoroughly rinsing as directed.

CAUTION: Do not allow the tissue to dry. Place the valve in sterile isotonic saline rinse solution immediately upon removal from the formaldehyde storage solution.

1. Within the sterile field, prepare three sterile basins with a minimum of 500 mL of sterile isotonic saline in **each** basin. Saline in the first two basins will be used for valve rinsing. Saline in the third basin will be used for delivery system preparation.

   CAUTION: Do not use saline from the first or second basins for delivery system preparation.

   NOTE: Chilled saline is not required.

2. Fully immerse the valve in the sterile isotonic saline solution in the first basin.
3. Continually rinse the valve for 10 seconds, using a gentle back-and-forth motion.
4. Repeat steps 2 and 3 in the second basin.
5. After rinsing, leave the valve fully immersed in the second basin until it is ready to be loaded.

Compressing the Valve in the Loading System

CAUTION: Do not place the non-sterile packaging of the loading system in the sterile field.

Perform the following steps in the sterile field, at room temperature:

1. Confirm the Portico™ valve size to be implanted. If implanting a 23 mm or 27 mm valve, press the base insert into the loading base. If implanting a 25 mm or 29 mm valve, use the loading base without the base insert. To remove the base insert from the loading base, compress the two tabs on the underside of the loading base.
2. Place the annulus end of the valve in the loading base.
3. Wet the loading funnel in sterile isotonic saline.

4. Place the wide end of the loading funnel directly over the aortic end of the valve.
5. Gently push straight down on the loading funnel to compress the valve. Align the loading funnel slots with the tabs on the loading base. Rotate the loading funnel slightly clockwise until it locks into the loading base. The aortic end of the valve will protrude out of the loading system assembly.

Loading the Valve on the Delivery System

Load the valve on the delivery system in the sterile field, at room temperature, under direct visualization.

CAUTION: Do not use the delivery system if it is kinked or damaged.

CAUTION: Do not place the non-sterile packaging of the delivery system in the sterile field.

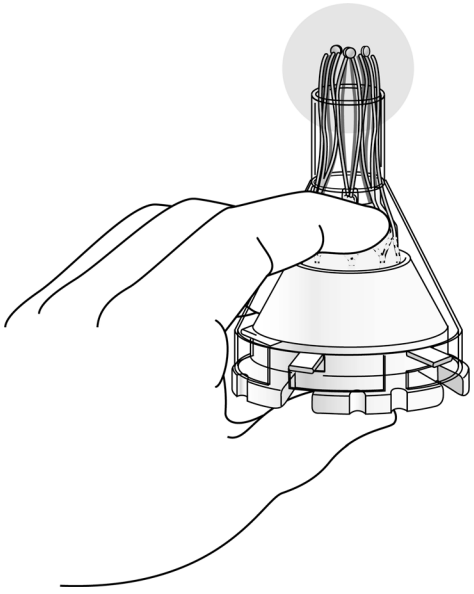
NOTE: The valve must be loaded onto the delivery system by trained personnel.

1. Wet a sterile gauze pad with sterile isotonic saline and wipe the shaft of the delivery system.
2. Wet the loading tube in sterile isotonic saline.
3. Slide the loading tube over the valve capsule of the delivery system. Position the distal end of the loading tube below the distal tip of the valve capsule.
4. Open the delivery system by closing the macro slide. Ensure the slide is locked in the closed position.
5. Fill a 20-cc syringe with sterile isotonic saline.

   NOTE: Use of a syringe size greater than 20 cc may result in inadequate de-airing.
6. Holding the distal tip of the delivery system upright, de-air the system by injecting a minimum of 15-20 cc saline into the valve capsule flush port. Tap the loading tube to dislodge any air bubbles while completing the flush.

   NOTE: Keep the distal end of the delivery system upright until the valve is completely encased in the valve capsule.
7. Remove the syringe.
8. To facilitate passage of the valve over the radiopaque tip of the delivery system, compress the loading funnel and loading base to slightly open the aortic end of the valve, as shown.

Figure 5. Slightly open the aortic end of the valve

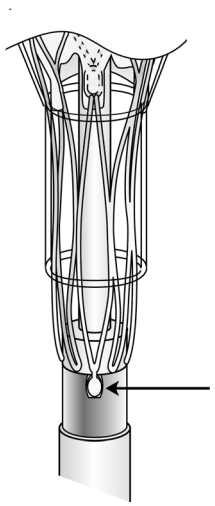


9. Carefully thread the radiopaque tip of the delivery system through the loading funnel and loading base assembly. When the radiopaque tip is just past the stent retainer tabs, slightly release the compression of the loading funnel while continuing to advance the radiopaque tip as it passes through the narrow end of the loading funnel. Guide the three (valve) retainer tabs into the (delivery system) retainer receptacles.

   CAUTION: Carefully insert the radiopaque tip of the delivery system through the center of the loading base to avoid damage to the delivery system.

10. Engage the three retainer tabs with the retainer receptacle by slightly opening the aortic end of the valve (see step 8 of this section). Visually confirm that all three retainer tabs are engaged and that no stent struts are overlapping. The ends of the stent struts without retainer tabs should be aligned with, but not overlapping, the proximal end of the retainer receptacle, as shown.

Figure 6. Retainer tab in the retainer receptacle

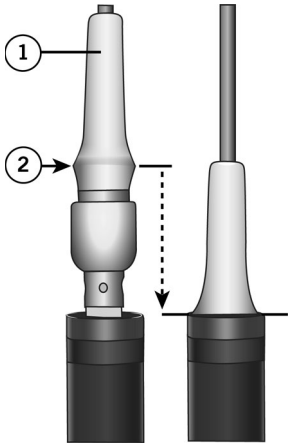


CAUTION: Do not use the valve if the retainer tabs are bent or deformed. Ensure no stent struts are crossed or misaligned.

11. Slowly encapsulate the retainer tabs in the valve capsule, by turning the deployment/re-sheath wheel opposite the direction of the arrow on the handle until the maximum outer diameter (OD) of the strain relief is aligned with the distal end of the valve capsule, as shown below.

    Caution: Ensure the retainer tabs remain engaged in the retainer receptacles and ensure the valve does not tilt or lean during advancement of the valve capsule.

Figure 7. Encapsulate the retainer tabs (shown without valve for clarity)



1. Strain relief
2. Maximum outer diameter

12. Advance the loading tube to meet the narrow end of the loading funnel. Align the black indicator line on the loading tube with the distal end of the valve capsule.

13. Turn the deployment/re-sheath wheel opposite the direction of the arrow on the handle until the funnel is fully seated in the loading tube.
14. Unlock and remove the loading base from the loading funnel.
15. Pour sufficient saline into the loading funnel to cover the valve.
16. Tap the radiopaque tip of the delivery system to remove any air bubbles from the inner shaft.
17. Remove any remaining air bubbles by gently sliding the leaflet tester from the top to the bottom of each leaflet.

    CAUTION: Exercise care to avoid damaging the leaflets with the leaflet tester.
18. Inspect the valve to ensure that no leaflet tissue is trapped between the stent struts. If leaflet tissue is trapped between the stent struts, use the narrow end of the leaflet tester to move the leaflets inside of the stent.
19. Grasp the shaft of the delivery system just below the loading tube while encapsulating the valve. Turn the deployment/re-sheath wheel opposite the direction of the arrow on the handle until the valve is fully encased in the valve capsule.

    NOTE: Ensure the distal end of the valve capsule remains below the black indicator line on the loading tube.

    CAUTION: Do not use the device if excess force is required to turn the deployment/re-sheath wheel during encapsulation.

    CAUTION: Do not re-sheath the valve more than two times prior to final valve release. Additional re-sheath attempts may compromise product performance.
20. If necessary, turn the micro adjustment wheel in the direction of the arrow to close any gaps between the valve capsule and the radiopaque tip. Once the gap is closed, turn the micro adjustment wheel opposite the direction arrow, until the wheel stops.
21. Pour the saline out of the loading funnel.
22. Slide the loading funnel and loading tube off the distal end of the delivery system.

    CAUTION: Inspect the valve capsule to ensure loading was successful. The surface should be smooth and free from ridges or creases. If a device is found to be incorrectly loaded, replace the valve and delivery system with new components.
23. Fill the syringe with sterile isotonic saline, and complete system de-airing as described below:
    a. Flush the stability layer.
    b. Slide the integrated sheath tip off the stability layer.
    c. Flush the integrated sheath.
    d. Close the stopcock on the integrated sheath.
    e. Slide the integrated sheath up to the valve capsule.
    f. Engage the integrated sheath tip onto the valve capsule.
    g. Flush the guidewire lumen.

Implanting the Valve

1. Prepare the access site according to standard practice.

   NOTE: For transaortic procedures, use a separate introducer sheath. Maintain the FlexNav™ integrated sheath at the proximal end of the delivery system throughout the procedure.

   CAUTION: For transaortic procedures, the distance between the annular plane and the aortic access site must be ≥7 cm (2.8").

   CAUTION: For transaortic procedures, the distance between the annular plane and the separate introducer sheath distal tip must be ≥6 cm (2.4").

   CAUTION: If performing transcatheter valve implantation without an arterial introducer sheath, use a minimum 14F introducer sheath for balloon aortic valvuloplasty.

   CAUTION: For subclavian/axillary procedures, the distance between the annular plane and the integrated sheath distal tip must be ≥17 cm (6.7") to allow the valve capsule to retract completely during valve deployment.
2. Predilate the native aortic valve with an appropriate diameter valvuloplasty balloon.

Deploying the Valve

1. Backload the FlexNav™ delivery system onto an 0.035" (0.89 mm)-compatible manufacturer pre-shaped guidewire while maintaining position across the aortic valve.

   NOTE: Wipe the radiopaque tip, valve capsule, and integrated sheath with a wet gauze pad to activate the hydrophilic coating.
2. For transfemoral procedures, advance the distal end of the delivery system through the access site until the integrated sheath hub meets the access site. If using the integrated sheath, be sure to hold on to both the integrated sheath and the delivery system shaft, keeping them joined together upon insertion.
3. Position the delivery system so that the inner shaft marker band is aligned with the native aortic valve annulus plane.
4. Begin deploying the valve by turning the deployment/re-sheath wheel in the direction of the arrow on the handle. Maintain valve position during deployment to ensure accuracy of implant depth during deployment.

   NOTE: Position the leading inflow edge of the valve 3 mm (0.12") below the native aortic annulus.

5. Prior to release, position the fluoro source to ensure the struts at the ventricular end of the nitinol stent are aligned and confirm the depth of the implant is approximately 3mm.

   NOTE: The deployment/re-sheath wheel will make a clicking sound when it has reached the partial deployment lock. The deployment mechanism will not re-engage until the deployment lock button is depressed.

   CAUTION: Do not depress the deployment lock button until you are ready to fully deploy the valve.

6. If the valve must be re-positioned, proceed to instructions for re-sheathing the valve.
7. If proper placement is confirmed, complete valve deployment by pressing the deployment lock button, then turning the deployment/re-sheath wheel in the direction of the arrow on the handle until the valve capsule is fully retracted.

   NOTE: The deployment/re-sheath wheel will make a clicking sound when the valve capsule is fully retracted.

8. Once the valve is fully deployed, confirm (under fluoroscopy, using orthogonal views) that the retainer tabs have detached from the delivery system retainer receptacle.

Re-Sheathing the Valve (Optional)

If repositioning is required, fully re-sheath the valve by turning the deployment/re-sheath wheel opposite the direction of the arrow on the handle. Return to step 3 of "Deploying the Valve."

CAUTION: To prevent potential tissue trauma, close any gap between the valve capsule and the radiopaque tip. If necessary, turn the micro adjustment wheel in the direction of the arrow to close gaps between the valve capsule and the radiopaque tip. Once the gap is closed, turn the micro adjustment wheel opposite the direction of the arrow until the wheel stops.

CAUTION: Do not re-sheath the valve more than two times. If additional positioning attempts are needed, completely re-sheath the valve and remove the valve from the patient. Use a new valve and delivery system to complete the procedure.

Post-Deployment

1. While maintaining the guidewire position, close the delivery system following the instructions below.

   CAUTION: Use care to minimize contact between the valve and the radiopaque tip of the delivery system.

   a. For transfemoral procedures, withdraw the radiopaque tip of the open delivery system through the valve, into the descending aorta. Depress the macro slide buttons and pull back on the proximal end of the handle to close the system. Withdraw the delivery system until the valve capsule reaches the integrated sheath.
   b. For transaortic procedures or subclavian/axillary procedures with a separate introducer sheath, begin to withdraw the open delivery system into the introducer. Stop when the radiopaque valve capsule marker band is aligned with the radiopaque band on the introducer. Maintaining the alignment of the introducer and the valve capsule, depress the macro slide buttons and pull back on the proximal end of the handle to close the system.
   c. For subclavian/axillary procedures with a separate introducer sheath, begin to withdraw the open delivery system into the introducer. Stop when the radiopaque valve capsule marker band is aligned with the radiopaque band on the introducer. Maintaining the alignment of the introducer and the valve capsule, depress the macro slide buttons and pull back on the proximal end of the handle to close the system.
   d. For subclavian/axillary procedures using the integrated sheath, withdraw the radiopaque tip of the open delivery system through the valve until the valve capsule reaches the integrated sheath. Depress the macro slide buttons and pull back on the proximal end of the handle to close the system.

   NOTE: Confirm that the proximal end of the handle is fully retracted before withdrawing the delivery system.

2. Remove the delivery system and leave the guidewire in the vasculature.

   NOTE: Keep integrated sheath and valve capsule together when withdrawing the delivery system.

3. Use fluoroscopy to ensure full expansion of the nitinol valve-frame. Perform an aortogram to assess the degree of PVL, coronary patency, and valve position. Assess hemodynamic function by echo and/or pressure recordings. Greater than mild PVL should be addressed during the index procedure if present.
4. Close the access site according to standard practice.

   NOTE: Patient monitoring for conduction disturbances is recommended.

Patient Registration

A medical device registration form and return envelope are included with each device. Complete the temporary identification card attached to the medical device registration form and provide it to the patient. After implantation, please complete all requested information and return the original form to Abbott Medical. A permanent implant card from Abbott will be mailed to the patient, encourage the patient to carry this card with them as much as possible.

Tracking by manufacturers is mandatory in some countries. Please disregard any request for patient information if this contradicts your local legal or regulatory requirements regarding patient privacy.

Patient Counseling Information

The risks and benefits of long-term antiplatelet therapy or anticoagulant therapy should be considered. Long-term anticoagulation therapy, unless contraindicated, is recommended for all patients with bioprosthetic heart valves who have risk factors for thromboembolism.

Prophylaxis against infective endocarditis is recommended for patients with prosthetic heart valves and patients with a history of infective endocarditis. Patients with bioprostheses who undergo dental procedures that involve manipulation of gingival tissue or the periapical region of the teeth, or perforation of the oral mucosa should receive endocarditis prophylactic antibiotic therapy.

Abbott Medical publishes a patient brochure. Copies of this booklet are available through your Abbott Medical sales representative.

SUMMARY OF PRIMARY CLINICAL STUDIES

The applicant performed a clinical study, the PORTICO randomized controlled trial (RCT), to establish a reasonable assurance of safety and effectiveness of transcatheter aortic valve implantation with the Portico Transcatheter Aortic Valve Implantation System in patients with symptomatic severe native aortic stenosis who are considered high or greater surgical risk in the United States and Australia under IDE # G120263.

The FlexNav Delivery System represents a design modification to the first-generation Portico Delivery System to improve the ease of use, reduce the occurrence of major vascular complications, and improve procedural safety outcomes observed in the RCT. The FlexNav Delivery System was evaluated in a non-randomized FlexNav DS Study arm added to the PORTICO study following completion of enrollment in the RCT cohort. The PORTICO FlexNav DS Study and a parallel study being conducted outside the U.S. (OUS) under a similar protocol, called the FlexNav EU CE Mark Study (NCT03724812), were combined to make two cohorts to supplement PORTICO RCT for the PMA approval decision: FlexNav PMA Analysis Cohort and FlexNav Global Cohort.

The FlexNav PMA Analysis Cohort was a prospective study group consisting of a subset of subjects from the PORTICO FlexNav DS Study and the FlexNav EU CE Mark Study. This cohort excludes roll-in subjects, continued access enrollees, and those enrolled after submission of the marketing application to FDA.

The Global FlexNav Cohort consists of all patients in the FlexNav DS Study and the FlexNav EU CE Mark Study, including patients in the FlexNav PMA Analysis Cohort plus those enrolled after submission of the marketing application to FDA. The results of the Global FlexNav Cohort represent the totality of pre-market evidence on the FlexNav DS while the FlexNav PMA Analysis Cohort represents a subset of this evidence.

Table 4 captures the major characteristics of the primary RCT and supplemental studies. Figure 8 illustrates the relationship of the FlexNav DS studies and the composition of the supplemental FlexNav cohorts.

Table 4: Summary of Clinical Studies

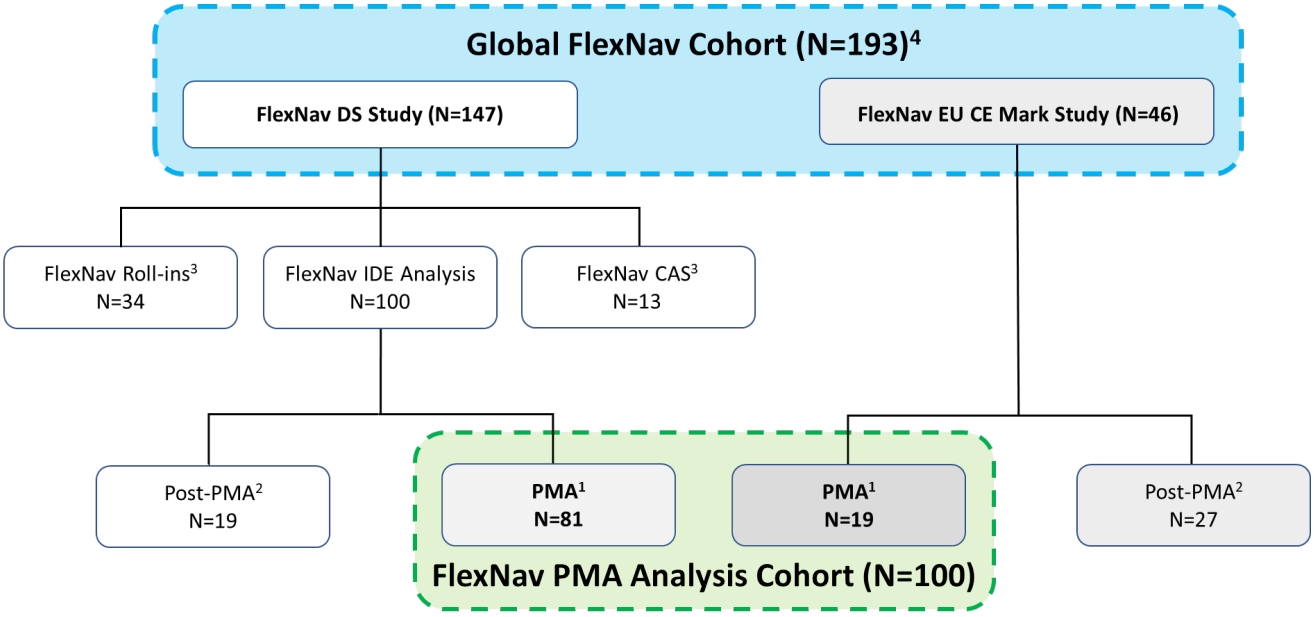
Study/Cohort	N	Device	Geographies	Design and Endpoints
PORTICO RCT (ITT) • Portico Arm (n=381) • Control Arm (n=369)	750	Portico Valve vs. CAV Portico 1st Generation DS	US, AUS	Prospective Randomized (1:1) **Primary Safety:** Non-inferiority of a 5-component composite[2] at 30 days. **Primary Effectiveness:** Non-inferiority of a 2-component composite[3] at 1 year.
FlexNav PMA Analysis Cohort • PORTICO FlexNav DS Analysis Cohort (n=81) • FlexNav EU CE Mark Study (n=19)	100	Portico Valve FlexNav DS/LS	US, AUS, EU	Prospective Single Arm **Primary Safety:** Major vascular complication rate at 30 days.
Global FlexNav Cohort[1] • FlexNav Roll-ins (n=34) • PORTICO FlexNav DS Analysis Cohort (n=100) • FlexNav Continued Access Study (n=13) • FlexNav EU CE Mark Study (n=46)	193	Portico Valve FlexNav DS/LS	US, AUS, EU	Observational Single Arm There were no prespecified primary endpoints for this aggregate Global FlexNav cohort, however key PORTICO RCT and FlexNav Study endpoints were summarized descriptively.

[1] The Global FlexNav Cohort is inclusive of the patients in the FlexNav PMA Analysis Cohort, including 81 patients in the FlexNav IDE Analysis cohort and 19 patients in the FlexNav EU CE Mark Study

[2] The 5 components of the safety composite endpoint were all-cause mortality, disabling stroke, Acute Kidney Injury stage 3 requiring dialysis, life-threatening bleed requiring a transfusion and major vascular complications at 30 days.

[3] The 2 components of the effectiveness composite endpoint were all-cause mortality and disabling stroke at 1 year.

Figure 8: Supplemental FlexNav Studies & Cohorts



1. Subjects enrolled prior to submission of marketing application to FDA were included in the FlexNav PMA Analysis Cohort
2. Subjects enrolled after submission of the marketing application to FDA were not included in the FlexNav PMA Analysis Cohort
3. FlexNav Roll-In and Continued Access Study (CAS) subjects were not included in the FlexNav IDE or PMA Analysis Cohorts
4. The Global FlexNav Cohort included all subjects from FlexNav DS Study and FlexNav EU CE Mark Study, including the FlexNav PMA Analysis Cohort.

A summary of the primary clinical study, PORTICO RCT, is presented below. Summaries of the supplemental clinical cohorts to evaluate the safety and performance of the FlexNav Delivery System design iteration (i.e., FlexNav PMA Analysis Cohort and Global FlexNav Cohort) are presented in **Section XI**. Data from the PORTICO RCT, in conjunction with supplemental data from the FlexNav PMA Analysis Cohort and Global FlexNav Cohort, were the basis for the PMA approval decision.

Study Design

PORTICO RCT Study

Patients were enrolled between May 30, 2014 and October 10, 2017. The database for this PMA reflected data collected through July 31, 2019 and included 750 randomized patients enrolled at 52 investigational sites in the United States and Australia.

The PORTICO study was a prospective, multicenter, randomized controlled, open label non-inferiority trial designed to evaluate the safety and effectiveness of the Portico Transcatheter Aortic Valve System for transcatheter aortic valve implantation (TAVI) via transfemoral, subclavian/axillary, or transaortic delivery for treatment of patients with symptomatic severe native aortic stenosis who are considered high or extreme surgical risk. All Portico valve implants in the PORTICO RCT were delivered with the Portico first-generation delivery system.

The control group was any FDA-approved and commercially available TAVI System for the treatment of severe symptomatic aortic stenosis in a high or extreme surgical risk patient population. The following commercially available TAVI Systems were used in the control group, referred to hereafter as "CAV" (Commercially Available Valves): SAPIEN, SAPIEN XT, SAPIEN 3, CoreValve, CoreValve Evolut R, and CoreValve Evolut PRO.

All patients were reviewed by an independent Subject Selection Committee (SSC) to confirm study eligibility and access route suitability. An independent Clinical Events Committee (CEC) adjudicated all primary endpoint clinical events according to Valve Academic Research Consortium (VARC)-2 criteria. Independent core laboratories assessed all echocardiographic and CT imaging data.

Patients were randomized in a 1:1 ratio to receive a Portico valve or CAV. Permuted block randomization was used and stratified by: (1) clinical investigational site, (2) surgical risk cohort (high vs extreme; as determined by the subject selection committee

(SSC)), and (3) vascular access method (transfemoral or alternative access). Treatment assignment was not masked to the investigational site, implanting physician or study participant.

The analysis plan to demonstrate non-inferiority of the Portico Transcatheter Aortic Valve System compared to CAV in the safety and effectiveness endpoints was based on Kaplan-Meier estimates at the analysis timepoint and standard errors. Assuming 80% high risk and 20% extreme risk patients, and estimated event rates (in both Portico valve and CAV groups) of 30.81% for the primary safety endpoint at 30 days and 25.0% for the primary effectiveness endpoint at 1 year, 750 randomized patients were required to demonstrate non-inferiority with margins of 8.5% and 8.0% respectively.

A subset of consecutive randomized patients was enrolled in a computed tomography (CT) sub-study to investigate the prevalence of reduced leaflet motion (RLM). For these patients with interpretable 4D-CT, leaflet motion and Hypoattenuated Leaflet Thickening (HALT) were assessed by a CT core laboratory.

Clinical Inclusion and Exclusion Criteria

Enrollment in the PORTICO RCT was limited to patients who met the following inclusion criteria:

Inclusion Criteria

- Patients must have co-morbidities such that the surgeon and cardiologist Co-Investigators concur that the predicted risk of operative mortality is ≥15% or a minimum STS score of 8%. A candidate who does not meet the STS score criteria of ≥ 8% can be included in the study if a peer review by at least two surgeons concludes and documents that the patient's predicted risk of operative mortality is ≥15%. The surgeon's assessment of operative comorbidities not captured by the STS score must be documented in the study case report form as well as in the patient medical record.
- Subject is 21 years of age or older at the time of consent.
    - Subject has senile degenerative aortic valve stenosis with echocardiographically derived criteria: mean gradient >40 mmHg or jet velocity greater than 4.0 m/s or Doppler Velocity Index <0.25 and an initial aortic valve area (AVA) of ≤ 1.0 cm^2 (indexed EOA ≤ 0.6 cm^2/m^2). (Qualifying AVA baseline measurement must be within 60 days prior to informed consent).
    - Subject has symptomatic aortic stenosis as demonstrated by NYHA Functional Classification of II, III, or IV.
    - The subject has been informed of the nature of the study, agrees to its provisions and has provided written informed consent as approved by the Institutional Review Board (IRB) of the respective clinical site.
    - The subject and the treating physician agree that the subject will return for all required post-procedure follow-up visits.
    - Subject's aortic annulus is 19-27mm diameter as measured by CT conducted within 12 months prior to informed consent. Note: if CT is contraindicated and/or not possible to be obtained for certain patients, a 3D echo and non-contrast CT of chest and abdomen/pelvis may be accepted if approved by the subject selection committee.

For a subject to be considered an Extreme Risk candidate they must meet # 2, 3, 4, 5, 6, 7 of the above criteria, and:

- The subject, after formal consults by a cardiologist and two cardiovascular surgeons agree that medical factors preclude operation, based on a conclusion that the probability of death or serious, irreversible morbidity exceeds the probability of meaningful improvement. Specifically, the probability of death or serious, irreversible morbidity should exceed 50%. The surgeons' consult notes shall specify the medical or anatomic factors leading to that conclusion and include a printout of the calculation of the STS score to additionally identify the risks in these patients.

Patients were <u>not</u> permitted to enroll in the PORTICO study if they met any of the following exclusion criteria:

Exclusion Criteria

- Evidence of an acute myocardial infarction (defined as: ST Segment Elevation as evidenced on 12 Lead ECG) within 30 days prior to index procedure.
- Aortic valve is a congenital unicuspid or congenital bicuspid valve or is non-calcified as verified by echocardiography.
- Mixed aortic valve disease (aortic stenosis and aortic regurgitation with predominant aortic regurgitation 3-4+).
- Any percutaneous coronary or peripheral interventional procedure performed within 30 days prior to index procedure.
- Pre-existing prosthetic heart valve or other implant in any valve position, prosthetic ring, severe circumferential mitral annular calcification (MAC) which is continuous with calcium in the LVOT, severe (greater than 3+) mitral insufficiency, or severe mitral stenosis with pulmonary compromise. Patients with pre-existing surgical bioprosthetic aortic heart valve should be considered for the Valve-in-Valve registry.

- Blood dyscrasias as defined: leukopenia (WBC<3000 mm^3), acute anemia (Hb < 9 g/dL), thrombocytopenia (platelet count <50,000 cells/mm^3).
- History of bleeding diathesis or coagulopathy.
- Cardiogenic shock manifested by low cardiac output, vasopressor dependence, or mechanical hemodynamic support.
- Untreated clinically significant coronary artery disease requiring revascularization.
- Hemodynamic instability requiring inotropic support or mechanical heart assistance.
- Need for emergency surgery for any reason.
- Hypertrophic cardiomyopathy with or without obstruction (HOCM).
- Severe ventricular dysfunction with LVEF <20% as measured by resting echocardiogram.
- Echocardiographic evidence of intracardiac mass, thrombus or vegetation.
- Active peptic ulcer or upper GI bleeding within 3 months prior to index procedure.
- A known hypersensitivity or contraindication to aspirin, heparin, ticlopidine (Ticlid), or clopidogrel (Plavix), or sensitivity to contrast media which cannot be adequately premedicated.
- Recent (within 6 months prior to index procedure date) cerebrovascular accident (CVA) or a transient ischemic attack (TIA).
- Renal insufficiency (creatinine > 3.0 mg/dL) and/or end stage renal disease requiring chronic dialysis.
- Life expectancy < 12 months from the time of informed consent due to non-cardiac co-morbid conditions.
- Significant aortic disease, including abdominal aortic or thoracic aneurysm defined as maximal luminal diameter 5cm 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 (applicable for transfemoral patients only).
- Native aortic annulus size < 19 mm or > 27 mm per the baseline diagnostic imaging.
- Aortic root angulation > 70° (applicable for transfemoral patients only).
- Currently participating in an investigational drug or device study.
- Active bacterial endocarditis within 6 months prior to the index procedure.
- Bulky calcified aortic valve leaflets in close proximity to coronary ostia.
- Non-calcified aortic annulus
- Iliofemoral vessel characteristics that would preclude safe placement of the introducer sheath such as severe obstructive calcification, or severe tortuosity (applicable for transfemoral patients only).

Additional Exclusion Criteria (Transcatheter Access-Related)

For selection of an appropriate alternative access delivery method, patients were screened using the following transaortic access specific exclusion criteria:

- Subject has pre-existing patent right internal mammary arterial (RIMA) graft that would preclude access.
- Subject has a hostile chest or other condition that complicates transaortic access.
- Subject has a porcelain aorta, defined as an extensive circumferential calcification of the ascending aorta that would complicate transaortic access.

Subclavian/Axillary Subject Cohort Specific Exclusion Criteria

- Subject's access vessel (subclavian/axillary) diameter will not allow for introduction of the applicable 18 Fr or 19 Fr delivery system.
- Subject's subclavian/axillary arteries have severe calcification and/or tortuosity.
- Subject's aortic root angulation is:
    - Left Subclavian/Left Axillary: >70°
    - Right Subclavian/Right Axillary: >30°
- Subject has a history of patent LIMA/RIMA graft that would preclude access

Follow-up Schedule

All patients were scheduled to return for follow-up examinations at discharge, 30 days, 6 months, 12 months, and then annually for 5 years post-procedure. For patients who were unable to attend an in-person follow-up visit at 12 months, a vital status phone call to determine survival and any new adverse events within 12 months was permitted. RCT patients who did not receive a study valve were followed for 12 months and then allowed to withdraw.

Preoperatively, patients were screened by a local Heart team to confirm they met study eligibility criteria including CT and echocardiographic imaging assessments to assess severity of aortic stenosis and confirm transcatheter vascular access route

suitability. Baseline assessments included laboratory tests, quality of life surveys, functional and cognitive tests, and neurological assessments.

Postoperatively, the objective parameters measured during the study included New York Heart Association (NYHA) functional classification, neurological assessments, transthoracic echocardiogram (TTE) evaluation and quality of life surveys. Adverse events and complications were recorded at all visits.

The key timepoints are shown below in the tables summarizing safety and effectiveness.

Clinical Endpoints

Primary Safety Endpoint:
The primary safety endpoint was a non-hierarchical composite of all-cause mortality, disabling stroke, life threatening bleeding requiring blood transfusion, acute kidney injury requiring dialysis, or major vascular complications at 30 days. The primary hypothesis was as follows:

$$H_0: \lambda_{test} \geq \lambda_{control} + \Delta_{p1}$$
$$H_a: \lambda_{test} < \lambda_{control} + \Delta_{p1}$$

where λ_{test} is the probability of a subject experiencing a primary safety endpoint event by 30 days in the Portico valve (test) group, $\lambda_{control}$ is the probability of a subject experiencing a primary safety endpoint event in the CAV (control) group, and Δ_{p1} is the non-inferiority margin for the primary safety endpoint pre-defined as 8.5%.

The hypothesis test was a non-inferiority test performed in the Intention-to-Treat (ITT) population by calculating a 95% one-sided upper confidence limit for the difference of (λ_{test} - $\lambda_{control}$), using Kaplan-Meier estimates for the event rates and standard errors. If the upper confidence limit for the difference was less than 8.5%, the Portico valve group was determined to be non-inferior to the CAV group. The endpoint was also analyzed for the As-Treated (AT) and Per Protocol (PP) populations.

Primary Effectiveness Endpoint:
The primary effectiveness endpoint was a composite of all-cause mortality or disabling stroke assessed at 1 year. The primary hypothesis was as follows:

$$H_o: p_{test} \geq p_{control} + \Delta_{p2}$$
$$H_a: p_{test} < p_{control} + \Delta_{p2}$$

where p_{test} is the probability of a subject experiencing a primary effectiveness endpoint event by 1 year in the Portico valve (test) group, $p_{control}$ is the probability of a subject experiencing a primary effectiveness endpoint event by 1 year in the CAV (control) group, and Δ_{p2} is the non-inferiority margin for the primary effectiveness endpoint pre-defined as 8.0%.

The hypothesis test was a non-inferiority test performed in the ITT population by calculating the 95% one-sided upper confidence limit for the difference of (p_{test} - $p_{control}$), using Kaplan-Meier estimates for the event rates and standard errors. If the upper confidence limit for the difference was less than 8.0%, the Portico valve group was determined to be non-inferior to the CAV group. The endpoint was also analyzed for the AT and PP populations.

Secondary Endpoints:
Four pre-specified secondary endpoints were tested in a hierarchical testing scheme (as shown in Table 5 below). Non-inferiority tests were performed in the ITT population for each secondary endpoint. To claim non-inferiority, both secondary endpoints tested per group must be within the pre-specified non-inferiority margins.

Table 5: Secondary Endpoints

Group	Secondary Endpoint	Alternative Hypothesis Test	Non-inferiority Margin
1	Severe aortic regurgitation (AR) at 1 year[1]	Ha: $\theta test_{,1} < \theta control_{,1} + 0.04$	4%
1	KCCQ Overall Score at 1 year[2]	Ha: $\theta test_{,2} > \theta control_{,2} - 10$	10 points
2	Moderate or severe aortic regurgitation at 1 year[1]	Ha: $\theta test_{,3} < \theta control_{,3} + 0.06$	6%

2	6-minute walk at 1 year[2]	Ha: $\theta test_{,4} > \theta control_{,4} - 36$	36m
[1] based on the Farrington-Manning method [2] based on a two-sample t-test			

Descriptive Endpoints:
Descriptive endpoints including acute device success, quality of life, NYHA functional classification, valve hemodynamics, and clinical outcomes were assessed at 30 days, 6 months, and 12 months post index procedure, unless otherwise specified. All descriptive endpoints were summarized using descriptive statistics.

- Acute device success defined as:
  - Absence of procedural mortality AND
  - Correct positioning of a single prosthetic heart valve into the proper anatomical location AND
  - Intended performance of the prosthetic heart valve (mean aortic valve gradient <20 mmHg or peak velocity <3 m/s, no moderate or severe prosthetic valve regurgitation) AND
  - Successful access was obtained as intended by group assignment
- Kansas City Cardiomyopathy Questionnaire (KCCQ) at 1 year
- Major vascular complications at 30 days
- NYHA functional classification at 30 days, 6 months, and 1 year
- Six-minute walk test at 30 days, 6 months, and 1 year
- Paravalvular Leak (PVL) at 30 days, 6 months, and 1 year
- Aortic insufficiency greater than trace at 30 days, 6 months, 1 year, and 2 years
- Reintervention to treat aortic insufficiency at 1 year and 2 years
- Permanent pacemaker insertion at 30 days
- Major bleeding at 30 days
- Acute kidney injury at 30 days
- Individual components of the primary effectiveness endpoint
  - All-cause mortality at 30 days, 6 months, 1 year and 2 years
  - Disabling stroke at 30 days, 6 months, 1year and 2 years
- Non-disabling Stroke and Transient Ischemic Attack (TIA) at 30 days, 6 months, 1 year, and 2 years
- Atrial fibrillation at 1 year and 2 years
- Quality of Life (QOL) from baseline to 30 days, 6 months and 1 year

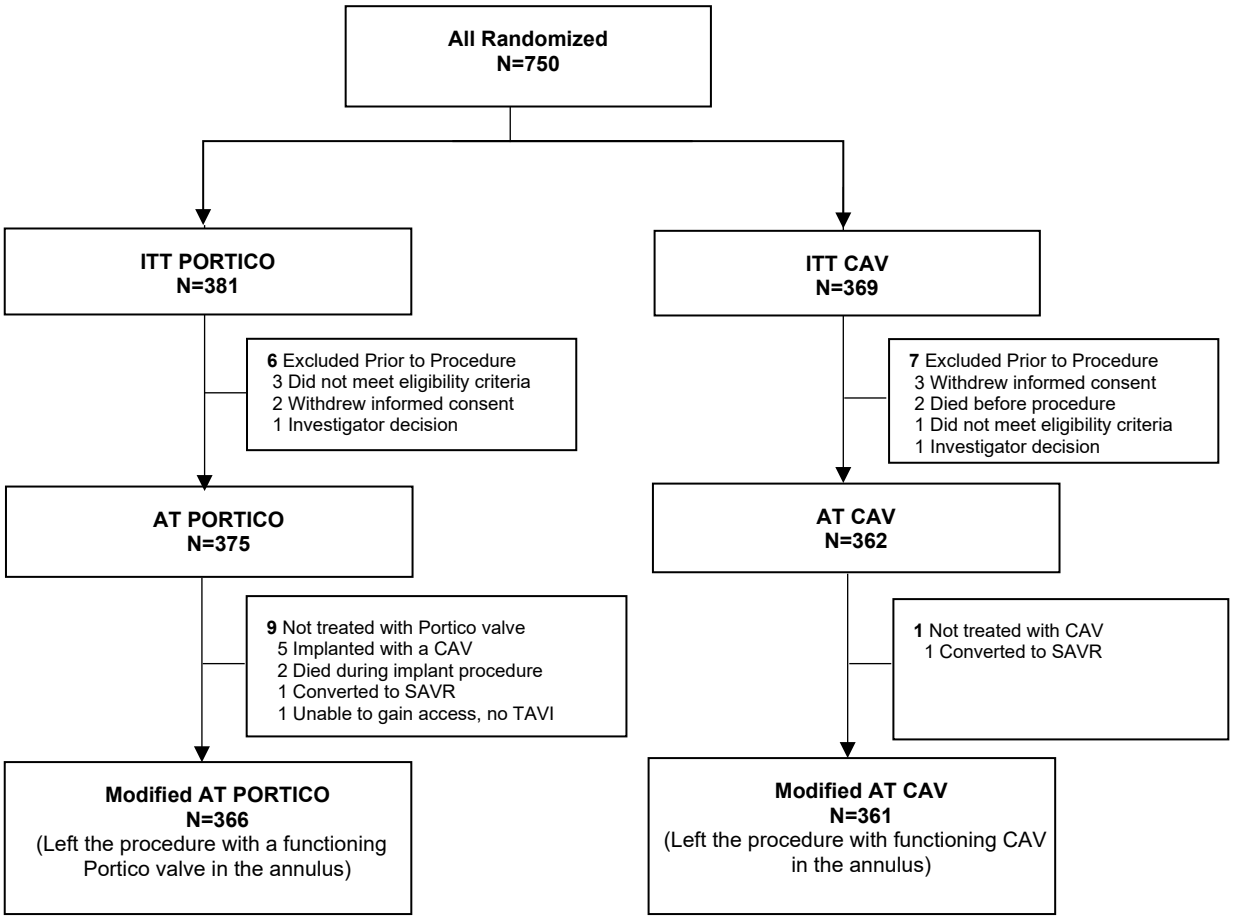
Accountability of PORTICO RCT Cohort

At the time of database lock, a total of 750 patients were randomized in the study, including 381 Portico valve patients and 369 CAV patients.

There were four different analysis populations defined in the protocol: Intention-to-treat (ITT), As-Treated (AT), Modified As-Treated (mod AT), and Per Protocol (PP), as summarized in Table 6 and Figure 9 below. The primary analysis was based on the ITT population, with the date of randomization considered Day 0.

Table 6: Summary of Analysis Populations and Patient Accountability			
Analysis Populations	**Definition**	**Cohort**	
		Portico valve (N)	**CAV (N)**
Intention-to-Treat (ITT; *primary*)	All randomized patients, with the date of randomization considered Day 0	**381**	**369**
As-Treated (AT)	All randomized patients in whom treatment was initiated (defined as entering the procedure room), with date of the index procedure considered Day 0.	**375**	**362**
Per protocol (PP)	All randomized patients who were successfully treated with the assigned valve implant and had no deviation for inclusion/exclusion in the study, with date of the index procedure considered Day 0	**350**	**348**
Modified As-Treated (mod AT)	All randomized patients who were implanted with one or more valves per the assigned treatment (Portico valve or CAV) at the time of the index procedure. Patients that died during procedure, were converted to surgery or received a valve different than assigned were excluded. Date of the index procedure considered Day 0	**366**	**361**

Figure 9: Population Flowchart



Of the 750 randomized patients, 82.3% were alive and available for follow-up (i.e. not withdrawn) at the 12-month post-operative visit. The overall disposition of the patients and compliance for each follow-up visit is presented by group in Table 7.

Table 7: Overall Disposition and Study Compliance

Group	Visit Interval	Completed Visits	Expected Visits[1]	Missed Visits	Study Exits		Follow-up Compliance %
					Death	Withdrawal[2]	
Portico Valve (Intention-to-Treat)	Baseline	381	381	0	N/A	N/A	100.0%
	Procedure	375	375	0	0	6	100.0%
	Discharge	368	369	1	6	0	99.7%
	30 Days	346	356	10	13	1	97.2%
	6 Months	307	330	23	19	7	93.0%
	12 Months[3]	302	308	6	18	4	98.1%
CAV (Intention-to-Treat)	Baseline	369	369	N/A	N/A	N/A	100.0%
	Procedure	362	362	0	2	5	100.0%
	Discharge	360	360	0	2	0	100.0%
	30 Days	347	356	9	4	0	97.5%
	6 Months	314	334	20	19	3	94.0%
	12 Months[3]	301	309	8	18	7	97.4%

[1] Expected = Completed + Missed
[2] Withdrawals include subject withdrawals, investigator withdrawals and lost to follow-up.
[3] 12 Month visits include visits completed by phone.

Study Population Demographics and Baseline Parameters

The baseline demographics of the study population are typical for a TAVI study performed in the United States and are summarized in Table 8. The treatment cohorts were generally well balanced with respect to age, gender, baseline NYHA classification, and STS risk score.

Table 8: **Study Population Demographics and Baseline Parameters (ITT population)**

	Portico valve (N=381)	**CAV (N=369)**
Demographics		
Age, mean (SD), y	83.0 (7.6)	83.7 (7.0)
Female	198 (52.0%)	197 (53.4%)
NYHA functional class		
NYHA II	109 (28.6%)	100 (27.1%)
NYHA III	229 (60.1%)	234 (63.4%)
NYHA IV	43 (11.3%)	35 (9.5%)
STS PROM Score[1], %		
Mean (SD)	6.4 (3.4)	6.6 (3.4)
STS <4%	102 (26.8%)	88 (23.8%)
STS 4-7.9%	182 (47.8%)	173 (46.9%)
STS ≥8%	97 (25.5%)	108 (29.3%)
EuroSCORE II, %	6.8 (7.6)	6.6 (5.8)
Extreme risk	70 (18.4%)	63 (17.1%)
High risk	311 (81.6%)	306 (82.9%)
Comorbidities		
Hypertension	358 (94.0%)	331 (89.7%)
Diabetes mellitus	143 (37.5%)	142 (38.5%)
Oral controlled	73/143 (51.0%)	71/142 (50.0%)
Kidney disease	96 (25.2%)	94 (25.5%)
Atrial fibrillation	125 (32.8%)	145 (39.3%)
Permanent pacemaker	57 (15.0%)	63 (17.1%)
Pre-existing RBBB	56 (14.7%)	43 (11.7%)
Prior stroke	29 (7.6%)	49 (13.3%)
Prior transient ischemic attack	33 (8.7%)	25 (6.8%)
Carotid artery disease	93/380 (24.5%)	82 (22.2%)
Coronary artery disease	266 (69.8%)	256 (69.4%)
Prior coronary stenting	108 (28.3%)	107 (29.0%)
Prior bypass graft surgery	88 (23.1%)	76 (20.6%)
Prior myocardial infarction	55 (14.4%)	43 (11.7%)
Peripheral vascular disease	72 (18.9%)	65 (17.6%)
Chronic lung disease	158 (41.5%)	148 (40.1%)
Hostile chest/Prohibitive chest deformity	11 (2.9%)	19 (5.1%)
Porcelain aorta	11 (2.9%)	10 (2.7%)
Severe liver disease	4 (1.0%)	3 (0.8%)
Pulmonary hypertension	131 (34.4%)	126 (34.1%)

Table 8: **Study Population Demographics and Baseline Parameters (ITT population)**		
	Portico valve (N=381)	**CAV (N=369)**
Total frailty score (out of 4), mean (SD)	1.8 (0.9)	1.9 (0.8)
Katz index of activities of daily living, ≤4	40 (10.5%)	41 (11.1%)
Grip strength, <BMI and height-based cut-off	298/379 (78.6%)	302 (81.8%)
15-foot (5m) walk test ≥Height and sex-based cut-off	268/359 (74.7%)	256/342 (74.9%)
Albumin < 3.5g/dl	87/380 (22.9%)	93/366 (25.4%)
KCCQ-OS score, mean (SD)	55.0 (23.2) (375)	53.9 (23.7) (358)
EQ-5D Index score, mean (SD)	0.73 (0.19) (373)	0.74 (0.19) (359)
Six-minute walk distance, mean (SD), m	207.5 (116.5) (320)	208.9 (110.2) (306)
Echocardiographic parameters[2]		
Aortic valve area, mean (SD), cm^2	0.68 (0.17)	0.67 (0.16) (367)
Mean gradient, mean (SD), mm Hg	46.2 (11.2) (379)	45.9 (11.9) (368)
Ejection fraction, mean (SD), %	57.3 (11.5) (377)	57.4 (11.1) (367)
Mitral insufficiency (moderate/severe)	78/380 (20.5%)	83/367 (22.6%)
Tricuspid insufficiency (moderate/severe)	70/380 (18.4%)	67/367 (18.3%)

Data are presented as n (%), mean (SD), n/N (%) or mean (SD) (n).

KCCQ-OS= Kansas City Cardiomyopathy Questionnaire Overall Summary. NYHA= New York Heart Association. STS PROM= Society of Thoracic Surgeons predicted risk of mortality. EuroSCORE= European System for Cardiac Operative Risk Evaluation. EQ-5D= EuroQol- 5 Dimension. RBBB= Right Bundle Branch Block.

[1] Patients screened after November 15, 2018 were evaluated using risk models developed using STS data from 2011 to 2014 and validated using 2014 to 2016 data.

[2] Site-reported echo data

Safety and Effectiveness Results

Primary Safety Endpoint

The composite rate of all-cause mortality, disabling stroke, life threatening bleeding requiring blood transfusion, acute kidney injury requiring dialysis, or major vascular complications at 30 days for the Intention-to-Treat (ITT) and As-Treated (AT) populations are shown in Table 9.

The primary analysis was prespecified for the ITT population, for which Kaplan-Meier analysis shows the composite rate at 30 days was 13.8% in the Portico valve group and 9.6% in the CAV group. The 95% upper confidence limit of the difference was 8.1% for the ITT population, which falls within the pre-specified non-inferiority margin of 8.5%, indicating the study's primary safety endpoint was met for the primary analysis population. A confirmatory analysis was also pre-specified using the AT population; however, the 95% upper confidence limit of the difference for the AT population was 8.9%, which was not within the pre-specified non-inferiority margin. Thus, non-inferiority of the Portico valve for the primary safety endpoint was not confirmed by the AT population.

Table 9: Primary Safety Endpoint Analysis (30 Days)					
Analysis Set	**Kaplan-Meier Estimate (SE) of Event Rate**		**Difference in event rate between groups**	**Upper limit of the one-sided 95% confidence interval of event rate difference[1]**	**P-value**
	Portico valve	**CAV**			
Intention-to-Treat (N=750)	13.8% (1.8%) (N=381)	9.6% (1.5%) (N=369)	4.2%	8.1%	0.03
As-Treated (N=737)	14.4% (1.8%) (N=375)	9.4% (1.5%) (N=362)	5.0%	8.9%	0.07

[1] Kaplan-Meier method was used to estimate the event rate (SE). If the upper limit of the one-sided 95% confidence interval for the difference of event rate (Portico – CAV) is < 8.5%, then non-inferiority is demonstrated.
Note: Endpoint is measured from Day of Randomization for ITT and from Day of Procedure for AT.

Event rates for individual components of the composite primary safety endpoint for the ITT and AT analysis populations are shown in Table 10, along with 95% confidence intervals. Event rates for all-cause mortality and major vascular complications are numerically higher in the Portico group (ITT: 3.5% and 9.6%, respectively) than in the CAV group (ITT: 1.9% and 6.3%, respectively). Comparison of the component event rate differences between Portico and CAV groups across the ITT population, which included all randomized subjects with follow-up beginning at randomization, and the AT population, which included all treated subjects with follow-up beginning at the index procedure, identified that the individual component event rate differences were consistent across two populations, except for all-cause mortality. In the AT population, there were 2 fewer patient deaths in the CAV group (occurred before index procedure) and 4 more patient deaths in the Portico group (occurred after 30 days from randomization but within 30 days of index procedure). As a result, the all-cause mortality rate difference increased 1.5% from the ITT to AT population (+1.6% vs. +3.1%, respectively) in favor of the CAV group.

Table 10: Components of Primary Safety Endpoint (30 Days)

Component	PORTICO RCT (Intention-to-Treat)		PORTICO RCT (As-Treated)	
	Portico valve (N=381)	CAV (N=369)	Portico valve (N=375)	CAV (N=362)
All-Cause Mortality[1]	3.5% (13/375)	1.9% (7/364)	4.5% (17/374)	1.4% (5/362)
[95% Confidence interval][2]	[1.86%, 5.86%]	[0.78%, 3.92%]	[2.67%, 7.18%]	[0.45%, 3.19%]
Disabling Stroke[1]	1.6% (6/375)	1.1% (4/364)	1.6% (6/374)	0.8% (3/362)
[95% Confidence interval][2]	[0.59%, 3.45%]	[0.30%, 2.79%]	[0.59%, 3.46%]	[0.17%, 2.40%]
Life Threatening Bleeding Requiring Blood Transfusion[1]	4.5% (17/375)	3.6% (13/364)	4.8% (18/374)	3.6% (13/362)
[95% Confidence interval][2]	[2.66%, 7.16%]	[1.92%, 6.03%]	[2.88%, 7.50%]	[1.93%, 6.06%]
Acute Kidney Injury Requiring Dialysis[1]	1.1% (4/375)	0.8% (3/364)	1.1% (4/374)	0.8% (3/362)
[95% Confidence interval][2]	[0.29%, 2.71%]	[0.17%, 2.39%]	[0.29%, 2.72%]	[0.17%, 2.40%]
Major Vascular Complications[1]	9.6% (36/375)[3]	6.3% (23/364)[4]	9.6% (36/374)	6.6% (24/362)
[95% Confidence interval][2]	[6.81%, 13.04%]	[4.05%, 9.33%]	[6.83%, 13.08%]	[4.29%, 9.70%]

[1] The proportion of patients who experienced each event was calculated. The numerator for the 30-day rate is the number of patients who experienced an event by 30 days (post randomization for ITT and post index procedure for AT). The denominator for each event type is the number of analysis patients excluding patients that have withdrawn before 30 days without an event.

[2] By Clopper-Pearson exact confidence interval.

[3] Of the 36 major vascular complications in the Portico ITT group, 19 (5.1%) occurred at an access site (3.2% TAVI, 1.9% non-TAVI access site), 16 (4.3%) did not occur at an access site, and 1 subject (0.3%) had multiple events (1 at the access site and 1 non-access site).

[4] Of the 23 major vascular complications in the CAV ITT group, 16 (4.4%) occurred at an access site (3.0% TAVI, 1.4% non-TAVI access site), 6 (1.6%) did not occur at an access site, and 1 subject (0.3%) had multiple events (1 at the access site and 1 non-access site).

Primary Effectiveness Endpoint

The composite rate of all-cause mortality or disabling stroke at 1 year for the Intention-to-Treat (ITT) and As-Treated (AT) populations are shown in Table 11.

The primary analysis was pre-specified for ITT population, for which Kaplan-Meier analysis shows the composite rate was 14.9% in the Portico valve group and 13.4% in the CAV group. A confirmatory analysis was also pre-specified using the AT population. The 95% upper confidence limit for the difference was 5.7% in the ITT population and 6.2% in the AT population, which both fall within the pre-specified non-inferiority margin of 8.0%, indicating the study's primary effectiveness endpoint was met.

Table 11: Primary Effectiveness Endpoint Analysis (1 Year)					
Analysis Set	**Kaplan-Meier Estimate (SE) of Event Rate**		**Difference in event rate between groups**	**Upper limit of the one-sided 95% confidence interval of event rate difference[1]**	**P-value**
	Portico valve (N=381)	**CAV (N=369)**			
Intention-to-Treat (N=750)[2]	14.9% (1.8%) (N=381)	13.4% (1.8%) (N=369)	1.5%	5.7%	0.006
As-Treated (N=737)[3]	15.2% (1.9%) (N=375)	13.2% (1.8%) (N=362)	2.0%	6.2%	0.010
[1] Kaplan-Meier method was used to estimate the event rate (SE). If the upper limit of the one-sided 95% confidence interval for the difference of event rate (Portico – CAV) is < 8.0%, non-inferiority is demonstrated. [2] Endpoint is measured from Day of Randomization [3] Endpoint is measured from Day of Procedure					

Event rates for individual components of the composite primary effectiveness endpoint for the ITT and AT analysis populations are shown in Table 12 along with 95% confidence intervals. The individual component event rates of Portico and CAV groups were consistent across ITT and AT populations. While the mortality rate numerically favored the CAV group at 30-days and 1-year, the difference of all-cause mortality between Portico and CAV groups at 1-year was similar to the difference at 30 days (Table 17), suggesting the post-procedural mortality risk (beyond 30-days) is consistent between the Portico and CAV groups. Although the rate of disabling stroke at 30 days favored CAV (1.6% vs. 1.1%) (Table 17), the disabling stroke rate at 1 year numerically favored the Portico valve (1.6% vs. 2.9%).

Table 12: Components of Primary Effectiveness Endpoint (1 Year)				
Component	**PORTICO RCT (Intention-to-Treat)**		**PORTICO RCT (As-Treated)**	
	Portico valve (N=381)	**CAV (N=369)**	**Portico valve (N=375)**	**CAV (N=362)**
All-Cause Mortality[1] [95% Confidence interval][2]	14.4% (1.8%) [11.17%, 18.38%]	12.0% (1.7%) [9.05%, 15.85%]	14.7% (1.8%) [11.43%, 18.71%]	11.8% (1.7%) [8.86%, 15.63%]
Disabling Stroke[1] [95% Confidence interval][2]	1.6% (0.7%) [0.73%, 3.58%]	2.9% (0.9%) [1.56%%, 5.29%]	1.6% (0.7%) [0.73%, 3.54%]	2.6% (0.9%) [1.36%, 4.94%]
[1] Kaplan-Meier method was used to estimate the event rate (SE). [2] The 95% confidence interval was estimated using KM method with Greenwood standard error.				

Secondary Endpoints

The analysis of predefined secondary endpoints in the RCT was based on the ITT analysis population of 750 randomized patients that had available data at 1 year.

As shown in Table 13, the Portico valve group was found to be non-inferior to CAV within the pre-specified non-inferiority margins for proportion of severe aortic regurgitation and overall KCCQ score at 1 year. However, the Portico valve group was found to be inferior to CAV with respect to proportion of moderate or severe aortic regurgitation at 1 year. The remaining secondary endpoint (6-minute walk) in the hierarchy test was not tested.

Table 13: Non-Inferiority Testing of Secondary Endpoints (ITT population)					
Secondary Endpoints at 1 year	**Portico valve (N=381)**	**CAV (N=369)**	**Difference (Portico-CAV)**	**95% Upper or Lower Confidence Limit**	**P-value**
Severe aortic regurgitation	0.4% (1/269)	0.0% (0/269)	0.4%	2.34%[1]	0.0012[5]
Kansas City Cardiomyopathy Questionnaire (KCCQ) Overall Score	75.4 (274)	75.9 (283)	-0.5	-3.50[2]	<0.0001[6]

Moderate or severe aortic regurgitation	7.8% (21/269)	1.5% (4/269)	6.3%	9.24%[3]	0.5714[5]
6-minute walk distance (m)	235.0 (227)	231.5 (225)	3.5	-15.36[4]	No test[6]

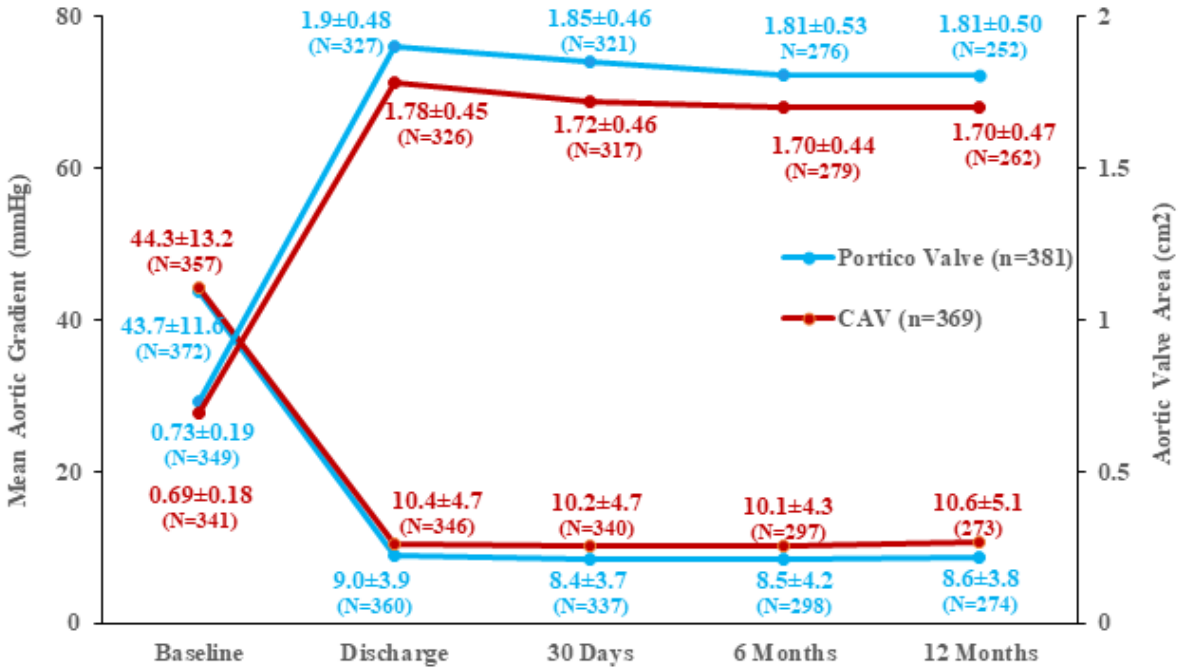
Note: all available data for randomized patients
[1] If the one-sided 95% upper confidence limit for the difference of proportions (Portico – CAV) is < 4%, then non-inferiority is demonstrated.
[2] If the one-sided 95% lower confidence limit for the difference of score (Portico – CAV) is > -10, then non-inferiority is demonstrated.
[3] If the one-sided 95% upper confidence limit for the difference of proportions (Portico – CAV is < 6%, then non-inferiority is demonstrated.
[4] If the one-sided 95% lower confidence limit for the difference of score (Portico – CAV) is > -36m, then non-inferiority is demonstrated.
[5] Farrington-Manning test
[6] Hypothesis testing was stopped after non-inferiority was not met for moderate or severe aortic regurgitation non-inferiority.

Additional Effectiveness Results

Valve Hemodynamics

Figure 10 presents mean aortic gradients and aortic valve areas at baseline through follow-up in the PORTICO RCT. Improvements in mean aortic gradients and valve areas from baseline to discharge were maintained through 30 days and through 1 year in both the Portico and CAV groups. The randomized Portico valve group reported numerically larger valve areas and smaller mean gradients compared to the randomized CAV group at 1 year.

Figure 10: Valve Hemodynamics Through 1 Year (ITT population)

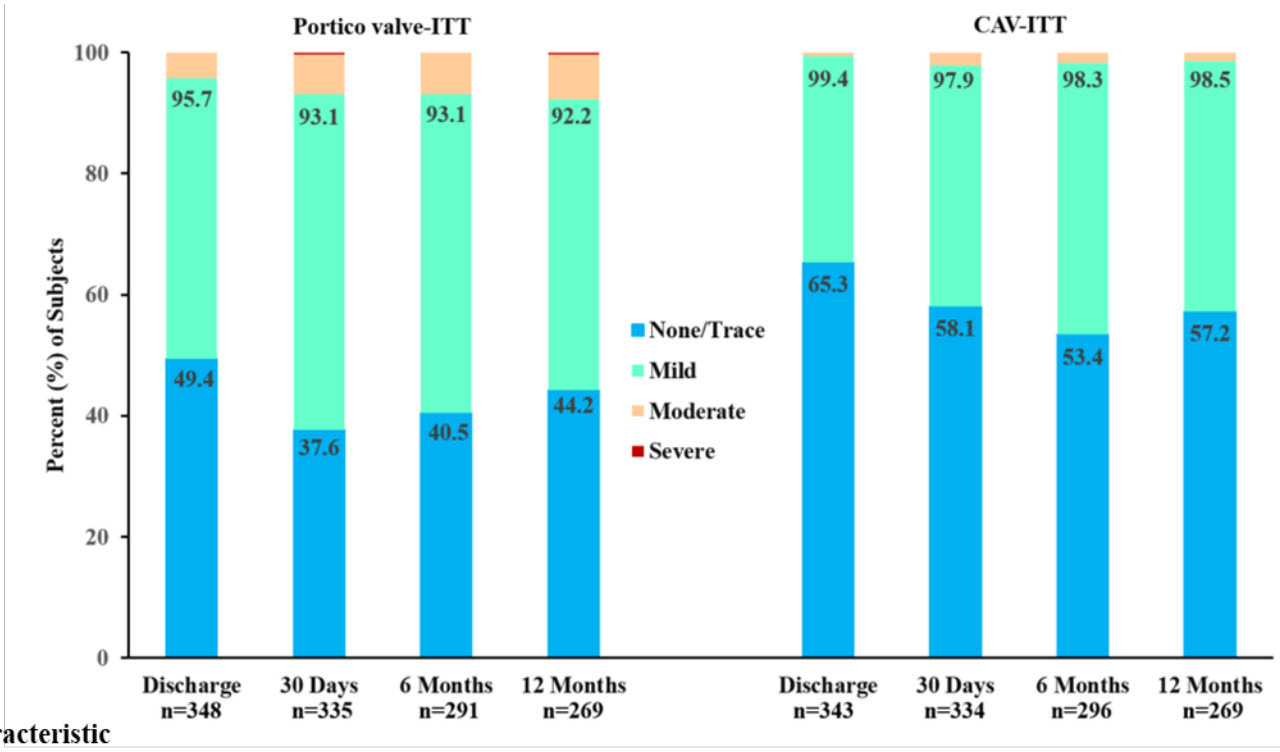


Total Aortic Regurgitation & Paravalvular Aortic Regurgitation

Figure 11 and Figure 12 present core laboratory observed rates of total aortic regurgitation and paravalvular aortic regurgitation at discharge through follow-up in the PORTICO RCT, respectively. As determined in the secondary endpoint analysis, clinically significant total aortic regurgitation after 1 year was lower in the CAV group (1.5%) than in the Portico group (7.8%). In the Portico group, all reported moderate or severe total aortic regurgitation was attributable to paravalvular regurgitation. Patients

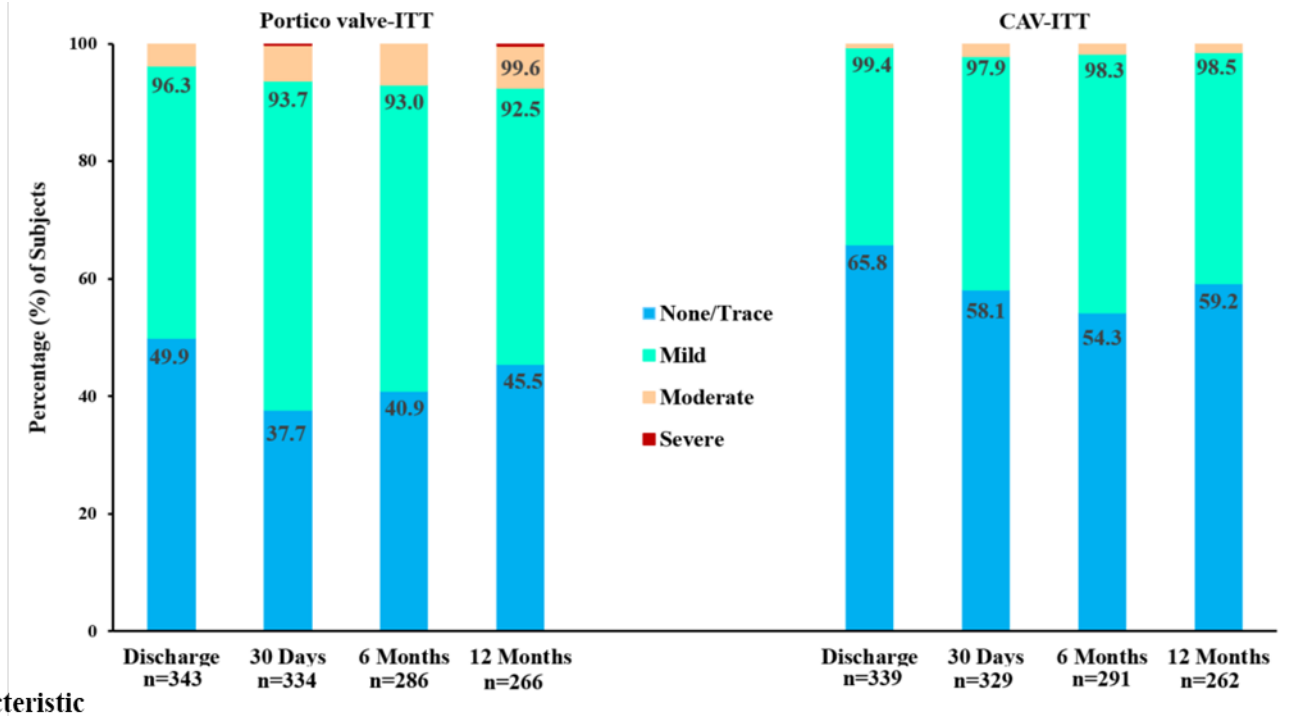
treated with the Portico valve reported a three-times higher rate of clinically significant paravalvular regurgitation (6.3%) compared to the patients in the CAV group (2.1%) at 30 days, which persisted through 1 year (7.5% vs. 1.5%, respectively).

Figure 11: Total Aortic Regurgitation Through 1 Year (ITT population)



Characteristic								
None/Trace	49.4%	37.6%	40.5%	44.2%	65.3%	58.1%	53.4%	57.2%
Mild	46.3%	55.5%	52.6%	48.0%	34.1%	44.9%	44.9%	41.3%
Moderate	4.3%	6.6%	6.9%	7.4%	0.6%	1.7%	1.7%	1.5%
Severe	0.0%	0.3%	0.0%	0.4%	0.0%	0.0%	0.0%	0.0%

Figure 12: Paravalvular Aortic Regurgitation Through 1 Year (ITT population)



Characteristic								
None/Trace	49.9%	37.7%	40.9%	45.5%	65.8%	58.1%	54.3%	59.2%
Mild	46.4%	56.0%	52.1%	47.0%	33.6%	39.8%	44.0%	39.3%
Moderate	3.8%	6.0%	7.0%	7.1%	0.6%	2.1%	1.7%	1.5%
Severe	0.0%	0.3%	0.0%	0.4%	0.0%	0.0%	0.0%	0.0%

Reintervention to Treat Aortic Regurgitation

Table 14 presents the results for reintervention to treat aortic regurgitation (defined as moderate or greater paravalvular aortic regurgitation or transvalvular aortic insufficiency) among subjects after the TAVI procedure (N=732).

A total of 9 subjects (8 Portico, 1 CAV) required reintervention to treat moderate or greater paravalvular aortic regurgitation within 365 days post-index procedure; no subjects reported transvalvular aortic insufficiency. Of the 8 Portico subjects that required reintervention to treat aortic regurgitation, 7 underwent a TAV-in-TAV procedure with a commercially available valve and 1 was implanted with an Amplatzer Vascular Plug. The CAV subject that required reintervention to treat aortic regurgitation underwent a balloon aortic valvuloplasty procedure.

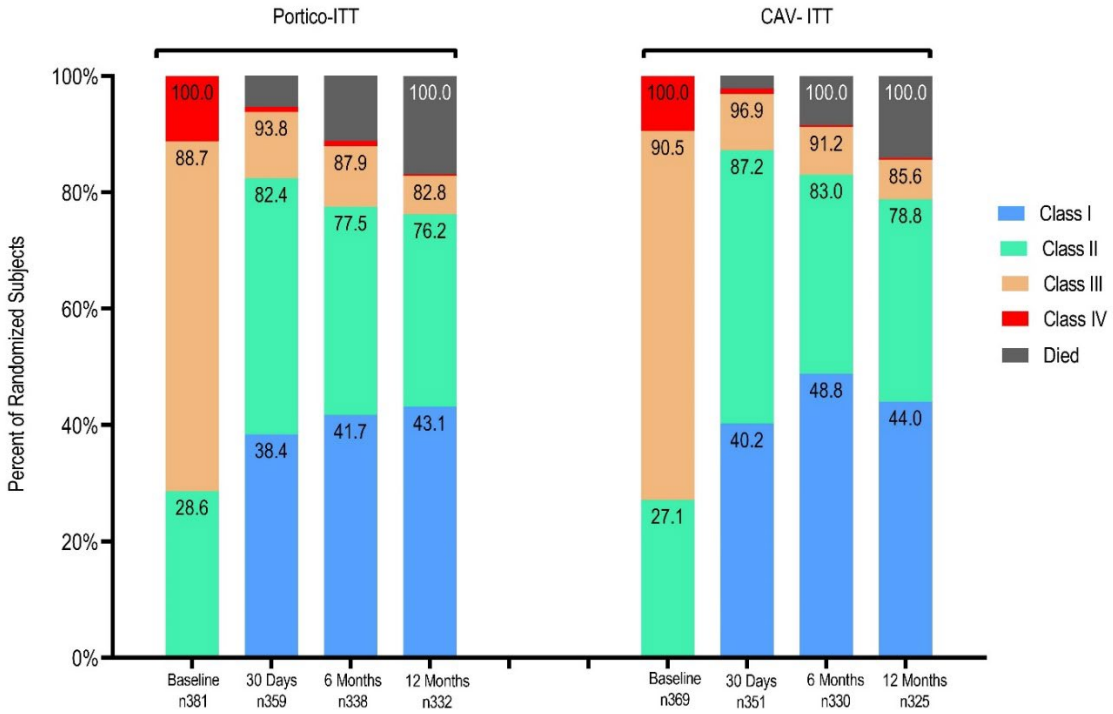
Table 14: Reintervention to Treat Aortic Regurgitation at 1 Year

Characteristic	Implanted Population	
	Portico (N=371)	CAV (N=361)
Reintervention for Aortic Regurgitation	2.2% (8/371)	0.3% (1/361)

NYHA Functional Classification

Figure 13: New York Heart Association (NYHA) Functional Class Through 1 Year (ITT population) presents NYHA functional class of patients at baseline through 1 year. The presentation of severe cardiac symptoms (NYHA class III or IV) was reduced from 71.4% at baseline to 8.4% at 1 year in the Portico patients and from 72.9% at baseline to 8.3% at 1 year in the CAV patients, which represents a similar improvement of clinically significant heart failure classification in both treatment groups.

Figure 13: New York Heart Association (NYHA) Functional Class Through 1 Year (ITT population)



Quality of Life

Table 15 summarizes self-reported quality of life over time as measured by KCCQ Overall Summary Score in the PORTICO RCT. KCCQ scores improved by approximately 20 points in both cohorts at 1 year.

Table 15: KCCQ Quality of Life Scores Through 1 Year (ITT population)

Characteristic	Portico valve (N=381)	CAV (N=369)
KCCQ score at Baseline	54.99 ± 23.17 (375)	53.93 ± 23.71 (358)
KCCQ score at 30 days	69.59 ± 22.98 (335)	72.05 ± 22.22 (340)
KCCQ score at 6 months	73.49 ± 22.70 (297)	75.66 ± 21.16 (302)
KCCQ score at 1 year	75.43 ± 22.18 (274)	75.94 ± 20.48 (283)

Adverse Events

Table 16 presents VARC-2 defined endpoints in the PORTICO RCT at 30 days and 1 year.

Table 16: VARC-2 Clinical Events (ITT population)				
Outcomes	**At 30 Days[1]**		**At 1 Year[2]**	
	Portico valve (N=381)	**CAV (N=369)**	**Portico valve (N=381)**	**CAV (N=369)**
All-cause mortality	13 (3.5%)	7 (1.9%)	53 (14.3%)	43 (12.0%)
Cardiovascular	12 (3.2%)	6 (1.6%)	32 (8.8%)	28 (8.0%)
Non-cardiovascular	1 (0.3%)	1 (0.3%)	21 (6.0%)	15 (4.4%)
All stroke	10 (2.7%)	9 (2.5%)	16 (4.5%)	19 (5.4%)
Disabling stroke	6 (1.6%)	4 (1.1%)	6 (1.6%)	10 (2.9%)
Non-disabling stroke	4 (1.1%)	5 (1.4%)	10 (2.9%)	10 (2.9%)
Transient ischemic attack	4 (1.1%)	1 (0.3%)	7 (2.0%)	6 (1.8%)
All Bleeding	40 (10.6%)	30 (8.2%)	NR	NR
Life threatening or disabling bleeding	22 (5.9%)	14 (3.8%)	NR	NR
Life threatening or disabling bleeding requiring transfusion	17 (4.5%)	13 (3.6%)	NR	NR
Major bleeding	19 (5.1%)	16 (4.4%)	NR	NR
Minor bleeding	33 (8.8%)	34 (9.3%)	NR	NR
Major vascular complications	36 (9.6%)	23 (6.3%)	NR	NR
Minor vascular complications	35 (9.3%)	32 (8.8%)	NR	NR
Acute kidney injury	22 (5.9%)	26 (7.1%)	NR	NR
Stage 1	10 (2.7%)	19 (5.2%)	NR	NR
Stage 2	5 (1.3%)	3 (0.8%)	NR	NR
Stage 3	7 (1.9%)	4 (1.1%)	NR	NR
Acute kidney injury requiring dialysis	4 (1.1%)	3 (0.8%)	NR	NR
Atrial fibrillation	15 (4.0%)	17 (4.7%)	27 (7.5%)	25 (7.0%)
New permanent pacemaker[3]	88 (27.7%)	35 (11.6%)	98 (31.1%)	41 (13.7%)
Myocardial infarction[4]	NR	NR	7 (1.8%)	6 (1.6%)
Endocarditis[4]	NR	NR	1 (0.3%)	1 (0.3%)
Valve intervention due to prosthetic valve thrombosis[4]	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Valve intervention due to endocarditis[4]	0 (0%)	0 (0%)	0 (0%)	0 (0%)

Data are presented as n (binomial proportion %) at 30 days and as n (Kaplan-Meier probability %) at 1 year

[1] The numerator for the 30-day rate is the number of patients who experienced an event by 30 days post randomization. The denominator for each event type is the number of patients excluding patients that have withdrawn (e.g. due to subject preference or lost to follow-up) before 30 days without an event.

[2] Kaplan-Meier method was used to estimate the event rate at 1 year

[3] New pacemaker implant events were CEC adjudicated through 30 days and site reported at 1 year.

[4] Site reported, data not adjudicated by CEC. Data are presented as n (binomial proportion %).

NOTE: Event rates are from day of randomization for ITT analysis Population.

NR: Data Not Adjudicated at 1 Year

Other Results

Procedural Outcomes and Implant Characteristics

Table 17 shows the procedural outcomes and implant characteristics of the 737 PORTICO RCT patients that attended the index procedure (As-Treated population).

Table 17: Procedural Outcomes and Implant Characteristics (AT population)		
Outcome	**Portico valve (N=375)**	**CAV (N=362)**
Procedural outcomes (final disposition)		
Procedural success[1]	359 (95.7%)	356 (98.3%)
Procedural mortality	2 (0.5%)	0 (0%)
Conversion to open heart surgery	1 (0.3%)	1 (0.3%)
Need for second valve (TAV-in-TAV)	10 (2.7%)	5 (1.4%)
Unable to implant assigned valve type	2 (0.5%)	0 (0%)
Unable to gain vascular access, no TAVI implant	1 (0.3%)	0 (0%)
Implant characteristics		
Conscious sedation anesthesia	112 (29.9%)	116 (32.0%)
Implantation time[2], min	13.3 (13.8)	6.8 (13.7)
Pre-balloon valvuloplasty[3]	322/373 (86.3%)	200/361 (55.4%)
Resheathing performed	144 (38.4%)	NR
Post-implantation balloon valvuloplasty	186 (49.6%)	74 (20.4%)
Final TAVI Access route		
Transfemoral	347/371 (93.5%)	343/361 (95.0%)
Subclavian/Axillary	8/371 (2.2%)	5/361 (1.4%)
Transaortic	16/371 (4.3%)	12/361 (3.3%)
Transapical	0/371 (0%)	1/361 (0.3%)
Implanted prosthesis size[4]		
20 mm	..	7/361 (1.9%)
23 mm	14/371 (3.8%)	97/361 (26.9%)
25 mm	77/371 (20.8%)	..
26 mm	..	151/361 (41.8%)
27 mm	135/371 (36.4%)	..
29 mm	145/371 (39.1%)	87/361 (24.1%)
31 mm	..	7/361 (1.9%)
34 mm	..	12/361 (3.3%)

Data presented as n/N (%) or mean (SD)

[1] Procedural success is defined as: absence of procedural mortality and successful delivery of a single TAVI valve placed in the desired location

[2] Total implant time: Implant Start Time is defined as delivery system from first attempted valve inserted into the body; Implant End Time is defined as the time of last attempted valve fully deployed

3 Denominator is number of patients with implant attempted

4 Device size based on last implanted (functioning) valve; note that some device sizes are not available across all valve brands

Computed Tomography (CT) Sub-study

A subset of RCT patients were enrolled in a CT sub-study to investigate the prevalence of Hypoattenuated Leaflet Thickening (HALT) and reduced leaflet motion (RLM). Per protocol, a minimum of 200 consecutive RCT patients implanted with either a Portico valve or CAV with an adequate multi-slice 4D CT scan (or TEE, if the CT scan is medically or technically contraindicated) for leaflet mobility assessment at both 30 days and 6 months were required. The sub-study's primary outcome measure was the prevalence of RLM in all sub-study patients, defined as moderate or severely reduced motion or immobility of at least one valve leaflet.

There were 313 randomized patients (165 Portico valve and 148 CAV) with an interpretable 30-day CT/TEE, and 202 patients (111 Portico valve and 91 CAV) with a corresponding interpretable 6-month CT/TEE. Presence of HALT and RLM imaging findings are summarized in **Table 18** along with the associated mean aortic pressure gradients.

Table 18: Leaflet Mobility Findings and Mean Gradients

Findings	At 30 Days		At 6 Months	
	Portico valve (N=165)	CAV (N=148)	Portico valve (N=111)	CAV (N=91)
Oral Anticoagulant Use				
Proportion of patients on oral anticoagulants (OAC)* at the time of scan	13.3% (22/165)	12.8% (19/148)	9.9% (11/111)	19.8% (18/91)
HALT[1]				
Any Leaflets with Thickening (yes)	34.5% (57/165)	15.5% (23/148)	38.7% (43/11)	18.7% (17/91)
Mean Gradient (mmHg)	8.2 ± 2.5 (57)	12.9 ± 6.0 (23)	8.3 ± 3.9 (43)	11.0 ± 5.1 (17)
0 leaflet[2]	65.5% (108/165)	84.5% (125/148)	61.3% (68/111)	81.3% (74/91)
Mean Gradient (mmHg)	8.2 ± 3.5 (107)	9.7 ± 3.8 (124)	7.7 ± 3.2 (67)	9.9 ± 3.6 (73)
1 leaflet	27.3% (45/165)	10.1% (15/148)	27.0% (30/111)	9.9% (9/91)
Mean Gradient (mmHg)	8.0 ± 2.4 (45)	12.5 ± 6.1 (15)	8.3 ± 4.4 (30)	12.5 ± 6.2 (9)
2 leaflets	6.1% (10/165)	5.4% (8/148)	9.9% (11/111)	6.6% (6/91)
Mean gradient (mmHg)	9.5 ± 2.9 (10)	13.8 ± 6.2 (8)	8.3 ± 2.7 (11)	9.4 ± 3.5 (6)
3 leaflets	1.2% (2/165)	0%	1.8% (2/111)	2.2% (2/91)
Mean Gradient (mmHg)	6.2 ± 0.7 (2)	NA	8.5 ± 0.1 (2)	8.5 ± 1.9 (2)
Number of Leaflets with Reduced Motion (moderate or severe reduction in excursion, or immobile)				
0 leaflet[2]	74.5% (123/165)	93.2% (138/148)	79.3% (88/111)	89.0% (81/91)
1 leaflet	21.2% (35/165)	4.7% (7/148)	19.8% (22/111)	7.7% (7/91)
2 leaflets	4.2% (7/165)	2.0% (3/148)	0.9% (1/111)	3.3% (3/91)
3 leaflets	0% (0/165)	0% (0/148)	0% (0/111)	0% (0/91)
Degree of Leaflet Motion (5 categories)[3]				
Mobile- all leaflets	63.6% (105/165)	83.8% (124/148)	62.2% (69/111)	80.2% (73/91)
Mean Gradient (mmHg)	8.2 ± 3.5 (104)	9.7 ± 3.8 (123)	7.5 ± 3.0 (68)	9.9 ± 3.6 (72)
Mildly reduced in ≥1leaflet	10.9% (18/165)	9.5% (14/148)	17.1% (19/111)	8.8% (8/91)
Mean Gradient (mmHg)	8.6 ± 2.6 (18)	10.5 ± 4.9 (14)	7.6 ± 3.5 (19)	10.5 ± 4.8 (8)
Moderately reduced in ≥1leaflet	8.5% (14/165)	4.7% (7/148)	11.7% (13/111)	4.4% (4/91)
Mean Gradient (mmHg)	7.4 ± 1.9 (14)	15.2 ± 6.6 (7)	10.2 ± 5.2 (13)	9.6 ± 3.6 (4)
Severely reduced in ≥1leaflet	9.1% (15/165)	0.7% (1/148)	3.6% (4/111)	3.3% (3/91)

Mean Gradient (mmHg)	8.4 ± 2.7 (15)	21.4 (1)	8.9 ± 2.2 (4)	10.7 ± 4.3 (3)
Immobile in ≥1 leaflet	7.9% (13/165)	1.4% (2/148)	5.4% (6/111)	3.3% (3/91)
Mean Gradient (mmHg)	8.5 ± 2.8 (13)	16.7 ± 3.8 (2)	7.7 ± 3.8 (6)	14.5 ± 8.3 (3)

The analysis population included all patients enrolled in the CT sub-study that had an adequate CT for assessment of leaflet thickening or RLM 30 days.

* OACs include warfarin/coumadin, Heparin, or Enoxaparin/Levenox/Clexane, with or without anti-platelet therapy

[1] HALT is a dichotomous measure (Yes vs No), with the presence of any hypo-attenuation in a leaflet defined as HALT (yes).

[2] At 30 days, 11 patients had an adequate CT for assessment of 2 leaflets only. Both leaflets had no evidence of RLM, therefore these patients are included in the "no leaflet thickening" and "no RLM" category at 30 days

[3] Reduced Leaflet Motion Severity: Mildly reduced is <50% reduction in leaflet opening, Moderately reduced is 50-70% reduction in leaflet opening, Severely reduced is >70% reduction in leaflet opening; For patients with 2 leaflets with motion abnormalities, the degree of leaflet motion assigned is based on the most conservative reduced leaflet excursion assignment

Table 19 and **Table 20** present mean aortic gradient at 6 months for Portico valve and CAV patients by leaflet thickening and leaflet mobility status at 30 days follow-up, respectively.

Table 19: Mean Aortic Gradient at 6 Months Stratified by Any Leaflet Thickening at 30 Days

Findings	Summary Statistics			
	No Leaflet Thickening at 30 Days		Any Leaflet Thickening at 30 Days	
	Portico valve (N=108)	CAV (N=125)	Portico valve (N=57)	CAV (N=23)
Mean Gradient (mmHg) at 6 months	8.1 ± 3.8 (91)	9.8 ± 3.9 (108)	7.2 ± 2.4 (51)	10.2 ± 4.2 (23)

Data presented as mean ± SD (n patients).

The analysis population included all patients enrolled in the CT sub-study that had an adequate CT for assessment of presence of leaflet thickening or RLM at 30 days.

Note: At 30 days, 11 patients had an adequate CT for assessment of 2 leaflets only. Both leaflets had no evidence of RLM, therefore these patients are included in the "no leaflet thickening" category at 30 days

Table 20: Mean Aortic Gradient at 6 Months Stratified by Leaflet Mobility at 30 Days

Findings	Summary Statistics			
	No RLM at 30 Days		RLM at 30 Days	
	Portico valve (N=123)	CAV (N=138)	Portico valve (N=42)	CAV (N=10)
Mean Gradient (mmHg) at 6 months	8.0 ± 3.7 (105)	9.8 ± 4.0 (121)	7.1 ± 2.2 (37)	10.7 ± 3.5 (10)

Data presented as mean ± SD (n patients).

The analysis population included all patients enrolled in the CT sub-study that had an adequate CT for assessment of RLM at 30 days.

Note: At 30 days, 11 patients had an adequate CT for assessment of 2 leaflets only. Both leaflets had no evidence of RLM, therefore these patients are included in the "no leaflet thickening" and "no RLM" category at 30 days

Table 21 and **Table 22** summarize the rate of all-cause mortality, all stroke and transient ischemic attack (TIA) at 6 months from index procedure for Portico valve and CAV patients stratified by any leaflet thickening and leaflet mobility at 30 days follow-up, respectively.

Table 21: All-Cause Mortality, Stroke and TIA at 6 Months by Leaflet Thickening Status at 30 Days				
Outcomes at 6 Months	**Kaplan-Meier Rate**			
	No Leaflet Thickening at 30 Days		**Any Leaflet Thickening at 30 Days**	
	Portico valve (N=108)	**CAV (N=125)**	**Portico valve (N=57)**	**CAV (N=23)**
All-cause mortality	5.6% (6)	4.8% (6)	5.3% (3)	0.0% (0)
All stroke	1.9% (2)	3.2% (4)	1.8% (1)	4.3% (1)
TIA	1.9% (2)	0.8% (1)	1.8% (1)	4.3% (1)
Composite of mortality, stroke and TIA	8.4% (9)	7.3% (9)	8.8% (5)	4.3% (1)
Adverse events adjudicated by an independent Clinical Events Committee				

Table 22: All-Cause Mortality, Stroke and TIA at 6 Months by Leaflet Mobility Status at 30 Days				
Outcomes at 6 Months	**Kaplan-Meier Rate**			
	No RLM at 30 Days		**RLM at 30 Days**	
	Portico valve (N=123)	**CAV (N=138)**	**Portico valve (N=42)**	**CAV (N=10)**
All-cause mortality	5.7% (7)	4.4% (6)	4.8% (2)	0.0% (0)
All stroke	2.5% (3)	3.6% (5)	0.0% (0)	0.0% (0)
TIA	1.7% (2)	1.5% (2)	2.4% (1)	0.0% (0)
Composite of mortality, stroke and TIA	9.0% (11)	7.3% (10)	7.1% (3)	0.0% (0)
Adverse events adjudicated by an independent Clinical Events Committee				

The CT sub-study demonstrated that 34.5% and 38.7% of subjects receiving a Portico valve exhibited some degree of leaflet thickening at 30 days and 6 months, respectively, as compared to 15.5% and 18.7% of CAV subjects. In addition, 25.5% and 20.7% of Portico subjects experienced some degree of reduced leaflet mobility at 30-days and 6 months, respectively, as compared to 6.8% and 11.0% of CAV subjects. Regardless, mean aortic valve pressure gradients were clinically comparable in Portico valve and CAV subjects, independent of RLM and leaflet thickening. In addition, the data did not suggest that the presence of RLM or thickening result in worse mortality or neurological safety outcomes in Portico valve subjects. However, the CT sub-study was not designed to assess the severity of HALT, powered to compare the relative incidence of RLM between the treatment cohorts, or determine whether late clinical outcomes were affected by the presence of HALT or reduced leaflet mobility.

Subgroup Analyses

The protocol pre-specified subgroup analyses of the primary safety and effectiveness endpoints based on gender (male vs. female), surgical risk status (high vs. extreme risk) and access route (transfemoral vs. alternative). As shown in Table 23 – Table 25, predefined subgroup analyses revealed no significant treatment by subgroup interaction effect on the primary safety and effectiveness endpoints.

Table 23: Analyses of Primary Safety and Effectiveness Endpoints by Gender (ITT population)				
Subgroup / Outcomes	**Primary Safety Endpoint (30 Days)**		**Primary Effectiveness Endpoint (1 Year)**	
	Portico valve (N=381)	**CAV (N=369)**	**Portico valve (N=381)**	**CAV (N=369)**
Male				

KM Estimate (SE) of Event Rate (%)	12.1% (2.4%) (N=183)	5.9% (1.8%) (N=172)	16.1% (2.7%) (N=183)	14.4% (2.7%) (N=172)
Female				
KM Estimate (SE) of Event Rate (%)	15.4% (2.6%) (N=198)	12.9% (2.4%) (N=197)	13.6% (2.5%) (N=198)	12.5% (2.4%) (N=197)
Treatment*Gender interaction p-value (Cox model)	0.248		0.995	
Note: Endpoint is measured from day of randomization for ITT				

Table 24: Analyses of Primary Safety and Effectiveness Endpoints by Surgical Risk (ITT population)

Subgroup / Outcomes	Primary Safety Endpoint (30 Days)		Primary Effectiveness Endpoint (1 Year)	
	Portico valve (N=381)	CAV (N=369)	Portico valve (N=381)	CAV (N=369)
High Risk				
KM Estimate (SE) of Event Rate (%)	13.6% (2.0%) (N=311)	8.9% (1.6%) (N=306)	12.2% (1.9%) (N=311)	11.8% (1.9%) (N=306)
Extreme Risk				
KM Estimate (SE) of Event Rate (%)	14.6% (4.3%) (N=70)	12.9% (4.2%) (N=63)	27.2% (5.5%) (N=70)	21.0% (5.2%) (N=63)
Treatment*Risk interaction p-value (Cox model)	0.5401		0.5259	
Note: Endpoint is measured from day of randomization for ITT				

Table 25: Analyses of Primary Safety and Effectiveness Endpoints by Access Site (As-Treated population)

Subgroup / Outcomes	Primary Safety Endpoint (30 Days)		Primary Effectiveness Endpoint (1 Year)	
	Portico valve (N=375)	CAV (N=362)	Portico valve (N=375)	CAV (N=362)
Transfemoral Access				
KM Estimate (SE) of Event Rate (%)	13.7% (1.8%) (N=351)	9.0% (1.5%) (N = 343)	14.2% (1.9%) (N=351)	12.2% (1.8%) (N=343)
Alternative Access				
KM Estimate (SE) of Event Rate (%)	25.0% (8.8%) (N=24)	15.8% (8.4%) (N=19)	30.0% (9.5%) (N=24)	31.6% (10.7%) (N=19)
Treatment*Access interaction p-value (Cox model)	0.9078		0.5621	
Note: Endpoint is measured from day of procedure for AT				

Pediatric Extrapolation

In this premarket application, existing clinical data was not leveraged to support approval of a pediatric patient population.

Financial Disclosure

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conducting clinical studies covered by the regulation. The clinical study included 103 primary investigators of which none were full-time or part-time employees of the sponsor and 9 had disclosable financial interests/arrangements as defined in 21 CFR 54.2(a), (b), (c) and (f) and described below:

- Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 1
- Significant payment of other sorts: 7
- Proprietary interest in the product tested held by the investigator: 0
- Significant equity interest held by investigator in sponsor of covered study: 2

The applicant has adequately disclosed the financial interest/arrangements with clinical investigators. Statistical analyses were conducted by FDA to determine whether the financial interests/arrangements had any impact on the clinical study outcome. The information provided does not raise any questions about the reliability of the data.

SUMMARY OF SUPPLEMENTAL CLINICAL INFORMATION

Description of Supplemental Clinical Cohorts

PORTICO FlexNav DS Study / FlexNav PMA Analysis Cohort

The PORTICO FlexNav DS Study was a prospective, multicenter, single-arm investigational study designed to characterize the safety of the FlexNav Delivery System in high or extreme surgical risk patients at 30 days after Portico valve implantation (FlexNav PMA Analysis cohort). Enrollment in the PORTICO FlexNav DS Study arm commenced approximately 12-months after the last patient was enrolled in the PORTICO RCT. Patients in the FlexNav PMA Analysis cohort were enrolled between November 7, 2018 and June 14, 2019 at 23 investigational sites in the United States, Australia, Italy, Demark, United Kingdom and Switzerland. The primary analyses of the PORTICO FlexNav DS Study were based on the FlexNav PMA Analysis cohort, which includes 100 patients that underwent a Portico valve implant attempt with a FlexNav DS (FlexNav IDE Analysis cohort=81 and FlexNav EU CE Mark Study=19).

The primary safety endpoint of the PORTICO FlexNav DS Study (FlexNav PMA Analysis Cohort) was VARC-2 defined major vascular complication rate at 30 days post-index procedure. The primary safety endpoint rate at 30 days was descriptively compared with results of the PORTICO RCT AT population. Descriptive endpoints included a selection of endpoints from the PORTICO RCT that were assessed post index procedure and summarized using descriptive statistics.

Global FlexNav Cohort

The Global FlexNav Cohort was a retrospective, multicenter, single-arm analysis group that included patients at high or greater surgical risk undergoing an attempted Portico valve implant with the FlexNav Delivery System. Patients were enrolled between October 15, 2018 and February 10, 2020 in the Global FlexNav Cohort at 28 investigational sites in the United States, Australia, Italy, Denmark, United Kingdom and Switzerland. The Global FlexNav Cohort included 193 patients, comprised of 147 patients enrolled in the prospective, multicenter PORTICO IDE FlexNav DS Study arm and 46 patients enrolled in the prospective, multi-center FlexNav EU CE Mark Study.

The endpoints for the Global FlexNav Cohort were not prespecified; however, the Global FlexNav Cohort was assessed for key 30-day and 1-year endpoints of the PORTICO IDE study, with the date of the index procedure considered Day 0. Data from this cohort that contributed to the PMA approval decision are listed below:

- All-cause mortality at 30 days and 1 year from the index procedure
- Permanent pacemaker insertion at 30 days and 1 year from the index procedure
- Paravalvular Leak (PVL) at 30 days and 1 year

Clinical Inclusion and Exclusion Criteria of FlexNav Cohorts

Patient selection criteria, assessments, key data collection, and adjudication were consistent across the PORTICO IDE FlexNav DS Study and the FlexNav EU CE Mark study to facilitate aggregate presentation of the FlexNav DS data.

Enrollment for both FlexNav PMA Analysis Cohort and FlexNav Global Cohort followed the same inclusion and exclusion criteria as described in Section X.A, with the following additional exclusion criteria for transaortic and subclavian/axillary access using the FlexNav Delivery System:

Transaortic access

- Subject has a distance between the annular plane and the aortic access site <7 cm (2.8")
- Subject has a distance between the annular plane and the separate introducer sheath distal tip <6 cm (2.4")

Subclavian/axillary access

- Subject's access vessel (subclavian/axillary) has a distance between the annular plane and the integrated sheath distal tip <17 cm (6.7")
- Subject's access vessel requires the delivery system to be advanced through a separate introducer sheath

Follow-up Schedule of FlexNav Cohorts

For both FlexNav cohorts, follow-up began at the date of the index procedure. Patients returned for follow-up examinations according to the schedule described in Section X.A, with the following exceptions: (i) a 6-month visit was not required for FlexNav CAP patients, and (ii) FlexNav EU CE Mark Study patients contributing to the FlexNav PMA Analysis cohort and Global FlexNav Cohort were followed for 1 year.

Accountability of FlexNav Cohorts

Table 26 presents the disposition and follow-up visit compliance of patients in the FlexNav PMA Analysis Cohort up to 30 days after the index procedure and in the Global FlexNav Cohort up to 1 year after the index procedure.

Of the 100 FlexNav PMA Analysis Cohort patients, all were alive and available for follow-up at the 30-day visit. Of the 193 patients enrolled in the Global FlexNav Cohort, 99.0% (191/193) were alive and available for follow-up at the 30-day visit and 93.3% (180/193) were alive and available for follow-up at the 12-month visit.

Table 26: Overall Disposition and Compliance in FlexNav Cohorts

Group	Visit Interval	Completed Visits	Expected Visits[1]	Missed Visits	Study Exits		Follow-up Compliance %
					Death	Withdrawal[2]	
FlexNav PMA Analysis Cohort	Baseline	100	100	0	N/A	N/A	100.0%
	Procedure	100	100	0	0	0	100.0%
	Discharge	100	100	0	0	0	100.0%
	30 Days	99	100	1	0	0	99.0%
Global FlexNav Cohort	Baseline	193	193	0	N/A	N/A	100.0%
	Procedure	193	193	0	0	0	100.0%
	Discharge	193	193	0	0	0	100.0%
	30 Days	189	191	2	2	0	99.0%
	12 Months	179	180	1	8	3	99.4%

[1] Expected = Completed + Missed
[2] Withdrawals include Lost to Follow-up.

Demographics and Baseline Parameters of FlexNav Cohorts

The baseline demographics of patients enrolled in FlexNav PMA Analysis cohort and Global FlexNav Cohort are overall similar to those of the PORTICO RCT population, with a few differences. FlexNav DS cohorts exhibited lower frequency of NYHA Class IV, STS score ≥ 8%, and certain comorbidities in patients compared to PORTICO RCT cohorts. A sub-set of patient demographics highlighting key parameters, as well as similarities and differences from RCT, are presented in **Table 27.**

Table 27: Study Population Demographics and Baseline Parameters				
Characteristic	**PORTICO RCT (As-Treated)**		**FlexNav PMA Analysis Cohort (N=100)**	**Global FlexNav Cohort (N=193)**
	Portico valve (N=375)	**CAV (N=362)**		
Demographics				
Age, mean (SD), y	82.96 (7.6)	83.58 (7.02)	85.2 (5.7)	84.8 (5.7)
Female	193 (51.5%)	193 (53.3%)	60 (60.0%)	115 (59.6%)
NYHA II	108 (28.8%)	98 (27.1%)	35 (35.0%)	77 (39.9%)
NYHA III	225 (60.0%)	230 (63.5%)	61 (61.0%)	109 (56.5%)
NYHA IV	42 (11.2%)	34 (9.4%)	4 (4.0%)	7 (3.6%)
STS PROM Score[1], %, Mean (SD)	6.3 (3.4)	6.6 (3.4)	5.0 (2.4)	5.2 (2.8)
STS <4%	102 (27.2%)	87 (24.0%)	42 (42.0%)	84 (43.5%)
STS ≥8%	93 (24.8%)	103 (28.5%)	12 (12.0%)	31 (16.1%)
EuroSCORE II, %	6.6 (7.2)	6.7 (5.9)	4.8 (3.1)	4.6 (3.5)
Extreme risk	69 (18.4%)	61 (16.9%)	20 (20.0%)	41(21.2%)
High risk	306 (81.6%)	301 (83.1%)	80 (80.0%)	152 (78.8%)
Comorbidities				
Kidney disease	94 (25.1%)	93 (25.7%)	21 (21.0%)	37 (19.2%)
Atrial fibrillation	122 (32.5%)	140 (38.7%)	29 (29.0%)	57 (29.5%)
Permanent pacemaker	55 (14.7%)	60 (16.6%)	11 (11.0%)	18 (9.3%)
Prior stroke	28 (7.5%)	49 (13.5%)	11 (11.0%)	15 (7.8%)
Coronary artery disease	261 (69.6%)	250 (69.1%)	60 (60.0%)	114 (59.1%)
Prior coronary stenting	106 (28.3%)	103 (28.5%)	25 (25.0%)	44 (22.8%)
Prior bypass graft surgery	86 (22.9%)	75 (20.7%)	14 (14.0%)	27 (14.0%)
Prior myocardial infarction	54 (14.4%)	40 (11.0%)	10 (10.0%)	20 (10.4%)
Peripheral vascular disease	18.7% (70/375)	18.0% (65/362)	14 (14.0%)	24 (12.4%)
Chronic lung disease	156 (41.6%)	144 (39.8%)	27 (27.0%)	52 (26.9%)
Porcelain aorta	11 (2.9%)	10 (2.8%)	0 (0%)	1 (0.5%)
Severe liver disease	4 (1.1%)	3 (0.8%)	0 (0%)	0 (0%)
Pulmonary hypertension	128 (34.1%)	124 (34.3%)	40 (40.0%)	60 (31.1%)
Total frailty score (out of 4), mean (SD)	1.8 (0.9)	1.9 (0.8)	1.7 (0.7)	1.7 (0.7)
Echocardiographic parameters[2]				
Aortic valve area, mean (SD), cm^2	0.69 (0.18)	0.67 (0.16)	0.68 (0.18)	0.69 (0.17)
Mean gradient, mean (SD), mmHg	46.2 (11.2)	46.1 (11.8)	45.1 (13.3)	44.1 (12.0)

Data are presented as n (%), mean (SD), n/N (%) or mean (SD) (n).

[1] Patients screened after November 15, 2018 were evaluated using risk models developed using STS data from 2011 to 2014 and validated using 2014 to 2016 data.

[2] Site-reported echo data

Although the FlexNav cohorts used the same enrollment criteria as the PORTICO RCT, the baseline demographics suggest potential differences between the study cohorts, which represents a limitation when comparing between the FlexNav cohorts and PORTICO RCT groups. To mitigate confounding and reduce the uncertainty in the descriptive comparisons of the FlexNav cohorts, post hoc propensity analyses of the primary safety endpoint composite and components, as well as clinically significant paravalvular regurgitation, were conducted and considered in the PMA approval decision. Overall, the post hoc propensity analyses indicated that patient population stratification did not have a significant, consistent effect on estimating the differences of the endpoints between the Global FlexNav and RCT CAV cohorts, which supported assessment of the FlexNav cohort data being presented in **Section XI.D**.

Safety and Effectiveness Results of FlexNav Cohorts

Primary Endpoint

Table 28 reports the major vascular complications for FlexNav PMA Analysis Cohort and Global FlexNav Cohort compared to PORTICO RCT groups.

Portico valve implantation with the FlexNav DS showed an observed rate of 7.0 % for major vascular complications at 30 days. The observed rate was numerically lower than the Portico valve group in the PORTICO RCT (9.6%) and similar to the CAV group (6.6%), owing to a reduction in access-related major vascular complications.

Global FlexNav Cohort demonstrated a 5.7% major vascular complication rate at 30 days. The observed rate was numerically improved from the rates observed in the FlexNav PMA Analysis cohort (7.0%) and lower than the RCT CAV group (6.6%).

Table 28: Primary Endpoint – Major Vascular Complication (30 Days)

Primary Endpoint (pre-defined for PORTICO FlexNav DS Study arm)	**PORTICO RCT (As-Treated)**		**FlexNav PMA Analysis Cohort (N=100)**	**Global FlexNav Cohort (N=193)**
	Portico valve (N=375)	**CAV (N=362)**		
Major Vascular Complications	9.6% (36/375)	6.6% (24/362)	7.0% (7/100)	5.7% (11/193)
Access Site[a]	5.1% (19/375)	4.7% (17/362)	6.0% (6/100)	5.2% (10/193)
TAVI Delivery System Access Site	3.2% (12/375)	3.0% (11/362)	4.0% (4/100)	3.6% (7/193)
Non-TAVI Delivery System Access Site	1.9% (7/375)	1.7% (6/362)	2.0% (2/100)	1.6% (3/193)
Access-Related[b]	4.3% (16/375)	1.7% (6/362)	1.0% (1/100)	0.5% (1/193)
Multiple Events (1 Access Site and 1 Access-Related)	0.3% (1/375)	0.3% (1/362)	0.0% (0/100)	0.0% (0/193)

[a] Access site major vascular complication is defined as vascular injury at an arterial or venous access site used by a guidewire, vascular sheath or delivery catheter.
[b] Access-related major vascular complication is defined as vascular complication or injury that occurs along the arterial (usually) or venous pathway to the aortic root, or rupture of the aortic annulus or perforation of the left ventricle (LV).

Table 29 presents all-cause mortality at 30 days for Global FlexNav Cohort subjects that experienced a major vascular complication (n=11) and those that did not (n=182) compared to PORTICO RCT subjects, suggesting reduced rate and severity of major vascular complications with the FlexNav Delivery System.

Table 29: Impact of Major Vascular Complication on Mortality

All-Cause Mortality	**PORTICO RCT (As-Treated)**		**Global FlexNav Cohort (N=193)**
	Portico valve (N=375)	**CAV (N=362)**	
All Patients	4.5% (17/374)	1.4% (5/362)	1.0% (2/193)
With MVC at 30 days	19.4% (7/36)	8.3% (2/24)	9.1% (1/11)
No MVC at 30 days	2.9% (10/339)	0.9% (3/338)	0.5% (1/182)

PORTICO RCT Safety Endpoint – FlexNav Cohorts

Table 30 shows the primary safety composite results and the components (as defined for the PORTICO RCT) for FlexNav PMA Analysis Cohort and Global FlexNav Cohort compared to PORTICO RCT cohorts (AT population). Results for the composite endpoint and individual components are consistent between the FlexNav PMA Analysis Cohort and Global FlexNav Cohort, which are comparable to the RCT CAV outcomes.

Table 30: Components of PORTICO RCT Primary Safety Endpoint (30 Days)

Primary Endpoint/Component	PORTICO RCT (As-Treated)		FlexNav PMA Analysis Cohort (N=100)[3]	Global FlexNav Cohort (N=193)[4]
	Portico valve (N=375)	CAV (N=362)		
Primary Safety Endpoint (30 days)				
Kaplan-Meier Estimate (SE) of Event Rate	14.4% (1.8%)	9.4% (1.5%)	8.0% (2.7%)	9.8% (2.1%)
Primary Safety Components (30 days)				
All-Cause Mortality[1] [95% Confidence interval][2]	4.5% (17/374) [2.7%, 7.2%]	1.4% (5/362) [0.45%, 3.2%]	0.0% (0/100) [0.0%, 3.6%]	1.0% (2/193) [0.13%, 3.7%]
Disabling Stroke[1] [95% Confidence interval][2]	1.6% (6/374) [0.59%, 3.5%]	0.8% (3/362) [0.17%, 2.4%]	0.0% (0/100) [0.0%, 3.6%]	2.1% (4/193) [0.57%, 5.2%]
Life Threatening Bleeding Requiring Blood Transfusion[1] [95% Confidence interval][2]	4.8% (18/374) [2.9%, 7.5%]	3.6% (13/362) [1.9%, 6.1%]	4.0% (4/100) [1.1%, 9.9%]	4.1% (8/193) [1.8%, 8.0%]
Acute Kidney Injury Requiring Dialysis[1] [95% Confidence interval][2]	1.1% (4/374) [0.29%, 2.7%]	0.8% (3/362) [0.17%, 2.4%]	0.0% (0/100) [0.0%, 3.6%]	0.0% (0/193) [0.0%, 1.9%]
Major Vascular Complications[1] [95% Confidence interval][2]	9.6% (36/374) [6.8%, 13.1%]	6.6% (24/362) [4.3%, 9.7%]	7.0% (7/100)[3] [2.9%, 13.9%]	5.7% (11/193)[3] [2.9%, 10.0%]

[1] The proportion of patients who experienced each event was calculated. The numerator for the 30-day rate is the number of patients who experienced an event by 30 days post index procedure. The denominator for each event type is the number of analysis patients excluding patients that have withdrawn before 30 days without an event.

[2] By Clopper-Pearson exact confidence interval.

[3] Of the 7 major vascular complications in the FlexNav PMA Analysis cohort, 6 (6.0%) occurred at an access site (4.0% TAVI and 2.0% non-TAVI access site), and 1 (1.0%) did not occur at an access site.

[4] Of the 11 major vascular complications in the Global FlexNav DS cohort, 10 (5.2%) occurred at an access site (3.6% TAVI 1.6% non-TAVI access site), and 1 (0.5%) did not occur at an access site.

PORTICO RCT Effectiveness Endpoint – FlexNav Cohorts

Table 31 shows the primary 1-year effectiveness composite results and the components (as defined for the PORTICO RCT) for Global FlexNav Cohort. The rate of all-cause mortality at 1 year in the Global FlexNav Cohort was 4.7%, which is numerically lower than all-cause mortality occurring in RCT Portico group (14.7%) and RCT CAV group (11.8%).

Table 31: Components of PORTICO RCT Primary Effectiveness Endpoint (1 Year)

Primary Endpoint/Component	PORTICO RCT (As-Treated)		Global FlexNav Cohort (N=193)
	Portico valve (N=375)	CAV (N=362)	
Primary Effectiveness Endpoint (1 Year)			
Kaplan-Meier Estimate (SE) of Event Rate[1]	15.2% (1.9%)	13.2% (1.8%)	5.7% (1.7%)
Primary Effectiveness Components (1 Year)			
All-Cause Mortality[1] [95% Confidence interval][2]	14.7% (1.8%) [11.43%, 18.71%]	11.8% (1.7%) [8.86%, 15.63%]	4.7% (1.5%) [2.47%, 8.84%]
Disabling Stroke[1] [95% Confidence interval][2]	1.6% (0.7%) [0.73%, 3.54%]	2.6% (0.9%) [1.36%, 4.94%]	2.1% (1.0%) [0.78%, 5.43%]

[1] Kaplan-Meier method was used to estimate the event rate (SE).
[2] The 95% confidence interval was estimated using KM method with Greenwood standard error.

Other Results

Technical device success using the FlexNav Delivery System was assessed in the Global FlexNav Cohort, which was defined as successful vascular access, delivery and deployment of the Portico valve; retrieval with the delivery system and correct positioning of a single valve in the proper anatomical location. The composite technical device success rate was 96.9%, as shown in **Table 32**.

Table 32: Technical Device Success in the Global FlexNav Cohort

Component of Technical Success	Global FlexNav Cohort (N=193)
1. Successful vascular access, delivery and deployment of the Portico valve	100.0% (193/193)
2. Retrieval with the delivery system	100.0% (193/193)
3. Correct positioning of a single valve in the proper anatomical location	96.9% (187/193)
4. Technical device success	96.9% (187/193)

Table 33 presents the results for CEC adjudicated VARC-2 events at 30 days in the FlexNav PMA Analysis cohort. There were no deaths, disabling strokes, or acute kidney injury events requiring dialysis within 30 days.

Table 33: VARC-2 Clinical Events at 30 Days

Outcomes	PORTICO RCT (As-Treated)		FlexNav PMA Analysis cohort (N=100)
	Portico valve (N=375)	CAV (N=362)	
All-cause mortality	17 (4.5%)	5 (1.4%)	0 (0%)
Cardiovascular	15 (4.0%)	4 (1.1%)	0 (0%)
Non-cardiovascular	2 (0.5%)	1 (0.3%)	0 (0%)

All stroke	11 (2.9%)	8 (2.2%)	3 (3.0%)
Disabling stroke	6 (1.6%)	3 (0.8%)	0 (0%)
Non-disabling stroke	5 (1.3%)	5 (1.4%)	3 (3.0%)
Transient ischemic attack	4 (1.1%)	1 (0.3%)	0 (0%)
All Bleeding	42 (11.2%)	30 (8.3%)	11 (11.0%)
Life threatening or disabling bleeding	24 (6.4%)	14 (3.9%)	4 (4.0%)
Life threatening or disabling bleeding requiring transfusion	18 (4.8%)	13 (3.6%)	4 (4.0%)
Major bleeding	20 (5.3%)	16 (4.4%)	7 (7.0%)
Minor bleeding	32 (8.5%)	33 (9.1%)	10 (10.0%)
Major vascular complications	36 (9.6%)	4 (6.6%)	7 (7.0%)
Minor vascular complications	35 (9.3%)	32 (8.8%)	10 (10.0%)
Acute kidney injury	21 (5.6%)	26 (7.2%)	1 (1.0%)
Stage 1	10 (2.7%)	19 (5.2%)	1 (1.0%)
Stage 2	4 (1.1%)	3 (0.8%)	0 (0%)
Stage 3	7 (1.9%)	4 (1.1%)	0 (0%)
Acute kidney injury requiring dialysis	4 (1.1%)	3 (0.8%)	0 (0%)
Atrial fibrillation	19 (5.1%)	19 (5.2%)	0 (0%)
New permanent pacemaker[2]	89/320 (27.8%)	35/302 (11.6%)	13/89 (14.6%)
Valve intervention due to prosthetic valve thrombosis[3]	0 (0%)	0 (0%)	0 (0%)
Valve intervention due to endocarditis[3]	0 (0%)	0 (0%)	0 (0%)

Data are presented as n (binomial proportion %) at 30 days

[1] The numerator for the 30-day rate is the number of patients who experienced an event by 30 days post procedure. The denominator for each event type is the number of patients excluding patients that have withdrawn (e.g. due to subject preference or lost to follow-up) before 30 days without an event.

[2] New pacemaker implant events were CEC adjudicated through 30 days and site reported at 1 year.

3Site reported, data not adjudicated by CEC.

Table 34 summarizes the paravalvular aortic regurgitation at 30 days and 1 year for the Global FlexNav Cohort and the PORTICO RCT patients with evaluable echocardiograms. The observed rate of clinically significant PVL (moderate or greater) in the Global FlexNav Cohort was 2.8% at 30 days and 0.6% at 1 year, with no subjects demonstrating severe PVL at either timepoint.

Table 34: Paravalvular Aortic Regurgitation Severity at 30 Days and 1 Year

PVL Severity	Paravalvular AR at 30 Days			Paravalvular AR at 1 Year		
	PORTICO RCT (Modified As-Treated)		Global FlexNav Cohort (N=178)	PORTICO RCT (Modified As-Treated)		Global FlexNav Cohort (N=160)
	Portico valve (N=329)	CAV (N=329)		Portico valve (N=262)	CAV (N=262)	
None/Trace	37.4% (123)	58.1% (191)	44.4% (79)	44.7% (117)	59.2% (155)	61.9% (99)
Mild	56.5% (186)	39.8% (131)	52.8% (94)	47.7% (125)	39.3% (103)	37.5% (60)
Moderate	5.8% (19)	2.1% (7)	2.8% (5)	7.3% (19)	1.5% (4)	0.6% (1)
Severe	0.3% (1)	0.0% (0)	0% (0)	0.4% (1)	0.0% (0)	0% (0)

Note: Results presented based on echocardiographic core laboratory assessment at 30 days and 1 year.
AR = aortic regurgitation

The rate of new permanent pacemaker implantation in the FlexNav PMA Analysis Cohort was 14.6% which was reduced from 28.1% in the PORTICO RCT and comparable to the RCT CAV observed rate of 11.6% **(Table 35).** New permanent pacemaker implantation rates in the Global FlexNav Cohort remained durable through 1-year follow-up, with 32 patients (18.4%) requiring new pacemaker implantation by 1 year.

Table 35: New Permanent Pacemaker Rates (30 Days)

New Permanent Pacemaker Implantation	PORTICO RCT (Modified As-Treated)		FlexNav Analysis Cohort (N=100)	Global FlexNav Cohort (N=175)
	Portico valve (N=366)	CAV (N=361)		
Naïve Subjects [a]	87 (28.1%)	35 (11.6%)	13 (14.6%)	27 (15.4%)
Subjects without pre-existing RBBB[b]	58 (21.9%)	25 (9.4%)	10 (12.5%)	15 (9.7%)

Data presented as: Number of Subjects (KM Event Rate, %)
[a] Subjects with a pre-existing pacemaker at baseline are excluded from the numerator and denominator
[b] Subjects with a pre-existing right bundle branch block (RBBB) and a pre-existing pacemaker at baseline are excluded from the numerator and dominator

Disposal & Device Explants

This instructions for use is recyclable. Dispose of all packaging materials as appropriate. Dispose of valves, delivery systems and loading systems per standard solid biohazard waste procedures. Abbott provides explant kits for returning explanted devices to Abbott for analysis, these kits can be obtained from your local Abbott sales representative or from Abbott customer service. If a valve was not used due to a performance issue, the valve can be returned in the original jar/lid packaging filled with a histological fixative solution (formalin or 2.0% glutaraldehyde).

Limited Warranty

This limited warranty is available during the warranty period stated below if the implantation system fails to perform consistent with its labeling due to a material defect at the time of manufacturing. This warranty shall continue for a period of one year from delivery of the system to you, and is in lieu of, AND ABBOTT MEDICAL HEREBY DISCLAIMS AND EXCLUDES, ALL OTHER WARRANTIES, REPRESENTATIONS, OR CONDITIONS, WHETHER EXPRESS OR IMPLIED BY OPERATION OF LAW OR OTHERWISE, INCLUDING, BUT NOT LIMITED TO, ANY IMPLIED WARRANTIES OF MERCHANTABILITY, NON-INFRINGEMENT, COURSE OF DEALING, QUIET ENJOYMENT, OR FITNESS FOR A PARTICULAR PURPOSE. Handing, storage, cleaning, and sterilization of this system as well as factors relating to the patient, diagnosis, treatment, surgical procedures, and other matters beyond Abbott Medical's control directly affect this system and the result obtained from its use, and ABBOTT MEDICAL IS NOT RESPONSIBLE FOR THE FOREGOING OR ANY USE OF THE SYSTEM INCONSISTENT WITH OR CONTRARY TO THE ABOVE INSTRUCTIONS FOR USE ("IFU"). ABBOTT MEDICAL SHALL NOT BE LIABLE FOR ANY INCIDENTAL, INDIRECT, SPECIAL, COVER, PUNITIVE, OR CONSEQUENTIAL LOSS, DAMAGE, OR EXPENSE DIRECTLY OR INDIRECTLY ARISING FROM THE USE OF OR RELATED TO THIS SYSTEM. ABBOTT MEDICAL'S SOLE LIABILITY, AND YOUR SOLE REMEDY, RELATED TO THE SYSTEM IS THE REPAIR OR REPLACEMENT OF ALL OR PART OF IT, OR REFUND OF THE SYSTEM PURCHASE PRICE IF REPAIR OR REPLACEMENT IS NOT FEASIBLE AS DETERMINED BY ABBOTT MEDICAL. IN NO EVENT SHALL ABBOTT MEDICAL BE LIABLE TO YOU OR ANY THIRD PARTY FOR ANY CLAIM OR DAMAGES, HOWEVER ARISING, IN AN AMOUNT THAT EXCEEDS THE SYSTEM PURCHASE PRICE. Abbott Medical neither assumes, nor authorizes any other person to assume for it, any other or additional liability or responsibility in connection with this system.

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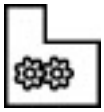
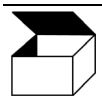
Descriptions of specifications, appearing in Abbott Medical literature, are meant solely to generally describe the system at the time of manufacture and do not constitute any express warranties.

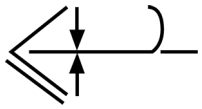
⚠ WARNING: This product can expose you to chemicals including ethylene oxide, which is known to the State of California to cause cancer and birth defects or other reproductive harm. For more information, go to www.P65Warnings.ca.gov.

Symbols

The following symbols may be used in this document and on some of the products and packaging:

Symbol	Description
REF	Catalog Number

Symbol	Description
℞ ONLY	Prescription only
STERILE EO	Sterilized using ethylene oxide
STERILE LC	Sterilized by liquid chemical sterilant
STERILE A	Sterilized using aseptic processing techniques
Transcatheter Heart Valve	Transcatheter heart valve
Storage Solution Formaldehyde	Storage solution – formaldehyde
	Follow instructions for use on this website
	Consult instructions for use
	MR Conditional
	Date of Manufacture
LOT	Lot Number
	Temperature limitations
	Do not reuse
SN	Serial number
	Use by
	Length
	Manufacturing facility
EC REP	Authorized EC Representative in the European Community
RINSE 2 x 500ml x 10 sec	Rinse - 2 x 500 mL x 10 seconds
Loading System	Loading System
Delivery System	Delivery System
PEEL OFF LABELS ON BOTTOM OF TRAY	Peel off labels on bottom of tray
	Manufacturer
	Quantity, package contents

Symbol	Description
	Do not use if package is damaged
	Do not resterilize
	Temperature Indicator: If red, no not use
	Outer diameter
	Inner dimension
equivalent integrated sheath	Equivalent Integrated Sheath
AORTIC	Aortic
CE 2797	Conformité Européenne (European Conformity). Affixed in accordance with European Council Directive 93/42/EEC (NB 2797) and 2011/65/EU. Hereby, Abbott Medical declares that this device is in compliance with the essential requirements and other relevant provisions of this directive.
UDI	Unique Device Identification

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