



**Medtronic**

**CoreValve™ System**

**Transcatheter Aortic Valve**

**Delivery Catheter System**

**Compression Loading System**

**CAUTION:** Implantation of the Medtronic CoreValve™ system should be performed only by physicians who have received Medtronic CoreValve™ training.

These devices are supplied sterile for single use only. After use, dispose of the delivery catheter system and the compression loading system in accordance with local regulations and hospital procedures. Do not resterilize.

Instructions for Use

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

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Trademarks may be registered and are the property of their respective owners.

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## Explanation of symbols on package labeling

	Use By
	Consult Instructions for Use at this Website
	Do Not Reuse
	Do Not Resterilize
	Size
	Serial Number
	Sterile LC: Device has been sterilized using Liquid Chemical Sterilants according to EN/ISO 14160.
	Reorder Number
	Lower Limit of Temperature
	Quantity
	Lot Number
	Sterilized Using Ethylene Oxide
	Manufactured In
	Nonpyrogenic
	MR Conditional
	Do Not Use if Package is Damaged
	Manufacturer
	Date of Manufacture
	For US Audiences Only
	Model

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## 1.0 DEVICE DESCRIPTION

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The Medtronic CoreValve™ system consists of 3 components: the transcatheter aortic valve (bioprosthesis)<sup>1</sup>, the delivery catheter system (catheter), and the compression loading system (CLS).

### 1.1 Transcatheter Aortic Valve (Bioprosthesis)



Figure 1

The bioprosthesis is manufactured by suturing 3 valve leaflets and a skirt, made from a single layer of porcine pericardium, onto a self-expanding, multi-level, radiopaque frame made of Nitinol. It is designed to replace the native aortic heart valve without open heart surgery and without concomitant surgical removal of the failed native valve. The bioprosthesis is processed with alpha-amino oleic acid (AOA™), which is an antimineralization treatment derived from oleic acid, a naturally occurring long-chain fatty acid.

The bioprosthesis is available for a range of aortic annulus and ascending aorta diameters as shown in Table 1.

Table 1: Patient Anatomical Diameters

Bioprosthesis Model	Size	Aortic Annulus Diameter	Ascending Aorta Diameter
<b>CoreValve™ Evolut™ Bioprosthesis</b>			
MCS-P4-23-AOA-US	23 mm	18 mm–20 mm	≤34 mm
<b>CoreValve™ Bioprosthesis</b>			
MCS-P3-26-AOA-US	26 mm	20 mm–23 mm	≤40 mm
MCS-P3-29-AOA-US	29 mm	23 mm–26 mm	≤43 mm
MCS-P3-31-AOA-US	31 mm	26 mm–29 mm	≤43 mm

### 1.2 Delivery Catheter System (Catheter)

The catheter with AccuTrak™ stability layer is compatible with a 0.035-in (0.889-mm) guidewire. The distal (deployment) end of the system features an atraumatic, radiopaque tip and a capsule that covers and maintains the bioprosthesis in a crimped position. The handle is located on the proximal end of the catheter and is used to load and deploy the bioprosthesis.

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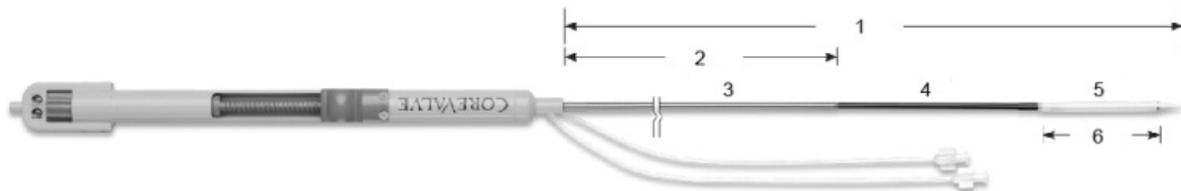
<sup>1</sup> The terms “bioprosthesis” and “transcatheter aortic valve” are synonymous terms and are used interchangeably throughout the document to refer to the CoreValve™ device.

The handle includes a macro slider to open and close the capsule and micro knob to facilitate precise bioprosthesis placement. The micro knob is turned counterclockwise to load the bioprosthesis and clockwise to deploy the bioprosthesis.

The AccuTrak™ stability layer is fixed at the handle and extends down the outside of the catheter shaft approximately 91 cm. It provides a barrier between the retractable delivery catheter system, introducer sheath, and vessel walls, thus enabling the catheter to retract freely and providing a more stable platform for deployment. The outer diameter of the catheter is 15 Fr (AccuTrak™ stability layer) and 12 Fr, and the outer diameter of the valve capsule is 18 Fr (Figure 2). The catheter can be used for femoral, subclavian/axillary, or ascending aortic (direct aortic) access sites. The catheter is available in 2 different models (Table 2).

**Table 2: Catheter Models and System Compatibility**

Catheter Model	Corresponding CLS Model	Corresponding Bioprosthesis Model(s)
DCS-C4-18F-23US	CLS-3000-18F-US	MCS-P4-23-AOA-US
DCS-C4-18F-US	CLS-3000-18F-US	MCS-P3-26-AOA-US, MCS-P3-29-AOA-US, MCS-P3-31-AOA-US



**Figure 2**

1. 112.5 cm
2. 90.9 cm
3. 15 Fr
4. 12 Fr
5. 18 Fr
6. 7.3 cm (Model DCS-C4-18F-US); 6.9 cm (Model DCS-C4-18F-23US)

### 1.3 Compression Loading System (CLS)

The CLS compresses the bioprosthesis into the catheter. The CLS comprises the following:



**Figure 3**

1. Inflow tube (straight tube)
2. Outflow cone
3. Outflow cap
4. Outflow tube (tube with flared ends)
5. Inflow cone

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## 2.0 INDICATIONS

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The Medtronic CoreValve™ system is indicated for relief of aortic stenosis in patients with symptomatic heart disease due to severe native calcific aortic stenosis (aortic valve area  $\leq 1.0 \text{ cm}^2$  or aortic valve area index  $\leq 0.6 \text{ cm}^2/\text{m}^2$ , a mean aortic valve gradient of  $\geq 40 \text{ mm Hg}$ , or a peak aortic-jet velocity of  $\geq 4.0 \text{ m/s}$ ) and with native anatomy appropriate for the 23, 26, 29, or 31 mm valve system who are judged by a heart team, including a cardiac surgeon, to be at high or greater risk for open surgical therapy (i.e., Society of Thoracic Surgeons operative risk score  $\geq 8\%$  or at a  $\geq 15\%$  risk of mortality at 30 days).

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## **3.0 CONTRAINDICATIONS**

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The CoreValve™ system is contraindicated for patients presenting with any of the following conditions:

- known hypersensitivity or contraindication to aspirin, heparin (HIT/HITTS) and bivalirudin, ticlopidine, clopidogrel, Nitinol (Titanium or Nickel), or sensitivity to contrast media, which cannot be adequately premedicated
- ongoing sepsis, including active endocarditis
- preexisting mechanical heart valve in aortic position

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## **4.0 WARNINGS AND PRECAUTIONS**

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### **4.1 Warnings**

#### **4.1.1 General**

- Implantation of the Medtronic CoreValve™ system should be performed only by physicians who have received Medtronic CoreValve™ training.
- The transcatheter aortic valve is to be used only in conjunction with the delivery catheter system and the compression loading system.
- This procedure should only be performed where emergency aortic valve surgery can be performed promptly.
- DO NOT use any of the Medtronic CoreValve™ system components if any of the following has occurred:
  - it has been dropped, damaged, or mishandled in any way
  - the Use By date has elapsed
- Mechanical failure of the delivery catheter system and/or accessories may result in patient complications.

#### **4.1.2 Transcatheter Aortic Valve (Bioprosthesis)**

- DO NOT use the bioprosthesis if any of the following conditions is observed:
  - there is any damage to the container (e.g., cracked jar or lid, leakage, broken or missing seals)
  - the serial number tag does not match the container label
  - the freeze indicator in the secondary package has activated
  - the storage solution does not completely cover the bioprosthesis
- Accelerated deterioration of the bioprosthesis may occur in patients presenting with an altered calcium metabolism.

### **4.2 Precautions**

#### **4.2.1 General**

- DO NOT contact any of the Medtronic CoreValve™ system components with cotton or cotton swabs.
- DO NOT expose any of the Medtronic CoreValve™ system components to organic solvents, such as alcohol.
- DO NOT introduce air into the catheter.

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- The safety and effectiveness of the Medtronic CoreValve™ system have not been evaluated in the pediatric population.
  - The safety and effectiveness of the bioprosthesis for aortic valve replacement have not been evaluated in the following patient populations:
    - without Aortic Stenosis (AS)
    - who are at moderate or low surgical risk (predicted perioperative mortality risk of <15%)
    - with untreated, clinically significant coronary artery disease requiring revascularization
    - with a preexisting prosthetic heart valve in any position
    - with cardiogenic shock manifested by low cardiac output, vasopressor dependence, or mechanical hemodynamic support
  - The safety and effectiveness of a CoreValve™ bioprosthesis implanted within a failed preexisting transcatheter or surgical bioprosthesis have not been demonstrated.
  - The safety and effectiveness of the bioprosthesis for aortic valve replacement have not been evaluated in patient populations presenting with the following:
    - blood dyscrasias as defined: leukopenia (WBC <1000 cells/mm<sup>3</sup>), thrombocytopenia (platelet count <50,000 cells/mm<sup>3</sup>), history of bleeding diathesis or coagulopathy, or hypercoagulable states
    - congenital bicuspid or unicuspid valve verified by echocardiography
    - mixed aortic valve disease (aortic stenosis and aortic regurgitation with predominant aortic regurgitation [3-4+])
    - moderate to severe (3-4+) or severe (4+) mitral or severe (4+) tricuspid regurgitation
    - hypertrophic obstructive cardiomyopathy
    - new or untreated echocardiographic evidence of intracardiac mass, thrombus, or vegetation
    - native aortic annulus size <18 mm or >29 mm per the baseline diagnostic imaging
    - transarterial access not able to accommodate an 18-Fr sheath
    - sinus of valsalva anatomy that would prevent adequate coronary perfusion
    - moderate to severe mitral stenosis
    - severe ventricular dysfunction with left ventricular ejection fraction (LVEF) <20% as measured by resting echocardiogram
    - end-stage renal disease requiring chronic dialysis or creatinine clearance <20 cc/min
    - symptomatic carotid or vertebral artery disease

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- severe basal septal hypertrophy with an outflow gradient
  - DO NOT expose the bioprosthesis to solutions other than the storage and rinse solutions.
  - DO NOT add antibiotics or any other substance to either the storage or rinse solutions. DO NOT apply antibiotics or any other substance to the bioprosthesis.
  - DO NOT allow the bioprosthesis to dry. Maintain tissue moisture with irrigation or immersion.
  - DO NOT attempt to repair a damaged bioprosthesis.
  - DO NOT handle or use forceps to manipulate the bioprosthesis leaflet tissue.
  - DO NOT deform the bioprosthesis in excess of what is experienced during crimping, loading, and implantation.

#### **4.2.2 Prior to Use**

- Exposure to glutaraldehyde may cause irritation of the skin, eyes, nose, and throat. Avoid prolonged or repeated exposure to the vapors. Use only with adequate ventilation. If skin contact occurs, immediately flush the affected area with water (minimum of 15 minutes). In the event of eye contact, flush with water for a minimum of 15 minutes and seek medical attention immediately.
- The bioprosthesis and the glutaraldehyde storage solution are **STERILE**. The outside of the bioprosthesis container is **NONSTERILE** and must not be placed in the sterile field.
- Damage may result from forceful handling of the catheter. Prevent kinking of the catheter when removing it from the packaging.
- This device was designed for single patient use only. Do not reuse, reprocess, or resterilize this product. Reuse, reprocessing, or resterilization may compromise the structural integrity of the device and/or create a risk of contamination of the device, which could result in patient injury, illness, or death.
- The bioprosthesis size must be appropriate to fit the patient's anatomy. Proper sizing of the device is the responsibility of the physician. Refer to Table 1 for available sizes. Failure to implant a device within the sizing matrix could lead to adverse effects such as those listed in Section 5.0.
- Patients must present with femoral or subclavian/axillary access vessel diameters of  $\geq 6$  mm or an ascending aortic (direct aortic) access site  $\geq 60$  mm from the basal plane.
- Implantation of the bioprosthesis should be avoided in patients with aortic root angulation (angle between plane of aortic valve annulus and horizontal plane/vertebrae) of  $>30^\circ$  for right subclavian/axillary access or  $>70^\circ$  for femoral and left subclavian/axillary access.
- Use caution when using the subclavian/axillary approach in patients with a patent Left Internal Mammary Artery (LIMA) graft (for left subclavian/axillary approach only) or patent Right Internal Mammary Artery (RIMA) graft (for right subclavian/axillary approach only).

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### 4.2.3 During Use

- Adequate rinsing of the bioprosthesis with sterile saline, as described in the Instructions for Use, is mandatory before implantation. No other solutions, drugs, chemicals, or antibiotics should ever be added to the glutaraldehyde or rinse solutions as irreparable damage to the leaflet tissue, which may not be apparent under visual inspection, may result.
- During rinsing, do not touch the leaflets or squeeze the bioprosthesis.
- With the exception of attaching the bioprosthesis frame loops to the catheter tabs, do not touch the capsule or the transition between the capsule and the catheter shaft. To protect the capsule, handle the catheter using the catheter shaft or, during loading, the loading tools.
- If a capsule becomes damaged during loading or the capsule fails to close, replace the entire system (bioprosthesis, catheter, and CLS). Do not use a catheter with a damaged capsule.
- Prevent contamination of the bioprosthesis, its storage solution, the catheter, and the CLS with glove powder.
- After a bioprosthesis has been inserted into a patient, do not attempt to reload that bioprosthesis on the same or any other catheter.
- During implantation, if resistance to deployment is encountered (e.g., the micro knob starts clicking or is tight or stuck), apply upward pressure to the macro slider while turning the micro knob. If the bioprosthesis still does not deploy, remove it from the patient and use another system.
- While the catheter is in the patient, ensure the guidewire is extending from the tip. Do not remove the guidewire from the catheter while the catheter is inserted in the patient.
- Once deployment is initiated, retrieval of the bioprosthesis from the patient (e.g., use of the catheter) is not recommended. Retrieval of a partially deployed valve using the catheter may cause mechanical failure of the delivery catheter system, aortic root damage, coronary artery damage, myocardial damage, vascular complications, prosthetic valve dysfunction (including device malposition), embolization, stroke, and/or emergent surgery.
- During deployment, the bioprosthesis can be advanced or withdrawn as long as annular contact has not been made. Once annular contact is made, the bioprosthesis cannot be advanced in the retrograde direction; if necessary, and the frame has only been deployed  $\leq 2/3$  of its length, the bioprosthesis can be withdrawn (repositioned) in the antegrade direction. However, use caution when moving the bioprosthesis in the antegrade direction.
- Use the handle of the delivery system to reposition the bioprosthesis. Do not use the outer catheter sheath.
- Once deployment is complete, repositioning of the bioprosthesis (e.g., use of a snare and/or forceps) is not recommended. Repositioning of a deployed valve may cause aortic root damage, coronary artery damage, myocardial damage, vascular complications,

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prosthetic valve dysfunction (including device malposition), embolization, stroke, and/or emergent surgery.

- Do not attempt to retrieve a bioprosthesis if any one of the outflow struts is protruding from the capsule. If any one of the outflow struts has deployed from the capsule, the bioprosthesis must be released from the catheter before the catheter can be withdrawn.
- Ensure the capsule is closed before catheter removal. If increased resistance is encountered when removing the catheter through the introducer sheath, do not force passage. Increased resistance may indicate a problem and forced passage may result in damage to the device and/or harm to the patient. If the cause of resistance cannot be determined or corrected, remove the catheter and introducer sheath as a single unit over the guidewire, and inspect the catheter and confirm that it is complete.
- Clinical long-term durability has not been established for the bioprosthesis. Evaluate bioprosthesis performance as needed during patient follow-up.
- Postprocedure, administer appropriate antibiotic prophylaxis as needed for patients at risk for prosthetic valve infection and endocarditis.
- Postprocedure, administer anticoagulation and/or antiplatelet therapy per hospital protocol.
- Excessive contrast media may cause renal failure. Preprocedure, measure the patient's creatinine level. During the procedure, monitor contrast media usage.
- Conduct the procedure under fluoroscopy. Fluoroscopic procedures are associated with the risk of radiation damage to the skin, which may be painful, disfiguring, and long-term.
- The safety and efficacy of implanting a second CoreValve™ bioprosthesis within the initial CoreValve™ bioprosthesis have not been demonstrated. However, in the event that a second CoreValve™ bioprosthesis must be implanted within the initial CoreValve™ bioprosthesis to improve valve function, valve size and patient anatomy must be considered before implantation of the second CoreValve™ bioprosthesis to ensure patient safety (e.g., to avoid coronary obstruction).
- In the event that valve function or sealing is impaired due to excessive calcification or incomplete expansion, a postimplant balloon dilatation of the bioprosthesis may improve valve function and sealing. To ensure patient safety, valve size and patient anatomy must be considered when selecting the size of the balloon used for dilatation. The balloon size chosen for dilatation should not exceed the diameter of the native aortic annulus. Refer to the specific balloon catheter manufacturer's labeling for proper instruction on the use of balloon catheter devices. Note: Bench testing has only been conducted to confirm compatibility with NuMED Z-MED II™ Balloon Aortic Valvuloplasty catheters where CoreValve™ bioprosthesis device performance was maintained after dilatation. Data on file.

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### **4.3 Magnetic Resonance Imaging (MRI)**

MRI may be used on the bioprosthesis only under specific conditions. See Section 6.2 MRI Safety Information for more information.

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## 5.0 POTENTIAL ADVERSE EVENTS

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Potential risks associated with the implantation of the Medtronic CoreValve™ transcatheter aortic valve may include, but are not limited to, the following:

- death
- cardiac arrest
- coronary occlusion, obstruction, or vessel spasm (including acute coronary closure)
- emergent surgery (e.g., coronary artery bypass, heart valve replacement, valve explant)
- multi-organ failure
- heart failure
- myocardial infarction
- cardiogenic shock
- respiratory insufficiency or respiratory failure
- cardiovascular injury (including rupture, perforation, or dissection of vessels, ventricle, myocardium, or valvular structures that may require intervention)
- ascending aorta trauma
- cardiac tamponade
- cardiac failure or low cardiac output
- prosthetic valve dysfunction including, but not limited to, fracture; bending (out-of-round configuration) of the valve frame; under-expansion of the valve frame; calcification; pannus; leaflet wear, tear, prolapse, or retraction; poor valve coaptation; suture breaks or disruption; leaks; mal-sizing (prosthesis-patient mismatch); malposition (either too high or too low)/malplacement; regurgitation; stenosis
- thrombosis/embolus (including valve thrombosis)
- valve migration/valve embolization
- ancillary device embolization
- emergent percutaneous coronary intervention (PCI)
- emergent balloon valvuloplasty
- major or minor bleeding that may or may not require transfusion or intervention (including life-threatening or disabling bleeding)
- allergic reaction to antiplatelet agents, contrast medium, or anesthesia
- infection (including septicemia and endocarditis)
- stroke, transient ischemic attack (TIA), or other neurological deficits
- permanent disability

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- renal insufficiency or renal failure (including acute kidney injury)
  - mitral valve regurgitation or injury
  - tissue erosion
  - vascular access related complications (e.g., dissection, perforation, pain, bleeding, hematoma, pseudoaneurysm, irreversible nerve injury, compartment syndrome, arteriovenous fistula, stenosis)
  - conduction system disturbances (e.g., atrioventricular node block, left-bundle branch block, asystole), which may require a permanent pacemaker
  - cardiac arrhythmias
  - encephalopathy
  - pulmonary edema
  - pericardial effusion
  - pleural effusion
  - myocardial ischemia
  - peripheral ischemia
  - bowel ischemia
  - heart murmur
  - hemolysis
  - cerebral infarction-asymptomatic
  - non-emergent reoperation
  - inflammation
  - fever
  - hypotension or hypertension
  - syncope
  - dyspnea
  - anemia
  - angina
  - abnormal lab values (including electrolyte imbalance)

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## 6.0 PATIENT INFORMATION

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### 6.1 Registration Information

A patient registration form is included in each bioprosthesis package. After implantation, please complete all requested information. The serial number is located on both the package and the identification tag attached to the bioprosthesis. Return the original form to the Medtronic address indicated on the form and provide the temporary identification card to the patient prior to discharge.

Medtronic will provide an Implanted Device Identification Card to the patient. The card contains the name and telephone number of the patient's physician as well as information that medical personnel would require in the event of an emergency. Patients should be encouraged to carry this card with them at all times.

### 6.2 MRI Safety Information

Nonclinical testing and modeling has demonstrated that the Medtronic CoreValve™ bioprosthesis is MR Conditional. A patient with this device can be safely scanned in an MR system meeting the following conditions:

- Static magnetic field of 1.5 T and 3 T
- Maximum spatial gradient magnetic field of 2500 gauss/cm (25 T/m)
- Maximum MR system reported, whole body averaged specific absorption rate (SAR) of  $\leq 2.0$  W/kg (Normal Operating Mode)

Based on nonclinical testing and modeling, under the scan conditions defined above, the Medtronic CoreValve™ bioprosthesis is expected to produce a maximum in vivo temperature rise of less than 3.6°C after 15 minutes of continuous scanning. Based on nonclinical data, the image artifact caused by the device will extend no greater than 7 mm from the Medtronic CoreValve™ bioprosthesis when imaged with a gradient echo pulse sequence and a 3.0 T MRI system.

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## **7.0 HOW SUPPLIED**

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### **7.1 Packaging**

The bioprosthesis is supplied STERILE and NONPYROGENIC in a sealed container made of glass and a screw cap with a liner. The outside of the container is NONSTERILE and must not be placed in the sterile field. A freeze indicator is placed inside the labeled carton. If the freeze indicator has been activated, do not use the bioprosthesis.

The catheter is packaged in a double-pouch configuration and sterilized with ethylene oxide gas. The catheter is sterile if the pouches are undamaged and unopened. The outer surfaces of the outer pouch are NONSTERILE and must not be placed in the sterile field.

The CLS is packaged in a double-pouch configuration. The CLS is sterile if the pouches are undamaged and unopened. The outer surfaces of the outer pouch are NONSTERILE and must not be placed in the sterile field. The CLS is sterilized with ethylene oxide gas.

### **7.2 Storage**

Store the bioprosthesis at room temperature. Avoid exposing to extreme fluctuations of temperature. Avoid freezing. Appropriate inventory control should be maintained so that bioprostheses with earlier Use By dates are implanted preferentially. Store the catheter and CLS in a cool, dry environment.

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## 8.0 ADDITIONAL EQUIPMENT

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**Note:** While extensive, this equipment list is not meant to cover all possible scenarios.

### **Transesophageal echocardiogram (TEE) or transthoracic echocardiography (TTE) on standby**

#### **Temporary pacer insertion**

- temporary pacemaker catheter (4 Fr or 5 Fr), per hospital protocol
- sterile sleeve for pacemaker catheter
- hemostatic vessel introducer sheath
- temporary pacemaker generator
- sterile temporary pacemaker-to-generator cable

#### **If indicated, pulmonary artery catheter insertion**

- standard pulmonary artery catheter
- hemostatic vessel introducer sheath
- saline flush line connected to pressure transducer

#### **Baseline aortography via radial, brachial, or femoral approach**

- 5-Fr or 6-Fr pigtail angiographic catheter
- 6-Fr hemostatic vessel introducer sheath
- 2-port manifold with saline flush line and pressure tubing or transducer
- power injector syringe
- contrast media
- high-pressure power injector tubing

#### **Predilatation of implant site**

- 2-port manifold with saline flush and transducer
- 9-Fr and 18-Fr hemostatic vessel introducer sheaths
- standard length 0.035-in (0.889-mm) straight guidewire
- appropriate suture-mediated closure system, if applicable
- angiographic catheter
- 0.035-in (0.889-mm) x 260-cm standard high-support guidewire to be shaped with a pigtail loop
- balloon valvuloplasty catheters,  $\leq 4$  cm length x 18 mm, 20 mm, 22 mm or 23 mm, and 25 mm diameters
- inflation device or syringe and diluted 1:5 contrast media

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**Bioprosthesis implantation**

- 18-Fr hemostatic vessel introducer sheath

**Standby supplies (must be available in the room)**

- pericardiocentesis tray
- 35-mm x 120-cm single loop snare
- standard percutaneous coronary intervention (PCI) equipment
- 14-Fr and 16-Fr hemostatic vessel introducer sheaths
- standard cardiac catheterization lab equipment
- intra-aortic balloon pump (IABP)

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## 9.0 INSTRUCTIONS FOR USE

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Figure 4

1. Catheter tip
2. Capsule
3. Catheter shaft
4. Tube flush port
5. AccuTrak™ stability layer
6. Macro slider
7. Micro knob
8. Luer-lock connection flush port

### 9.1 Inspection and Bioprosthesis Loading Procedure

**Caution:** Once the bioprosthesis is removed from its container and the catheter and CLS are removed from their packaging, ensure all subsequent procedures are performed in a sterile field.

#### 9.1.1 Inspection Prior to Use

1. Before removing the bioprosthesis, catheter, or CLS from its primary packaging, carefully inspect the packaging for any evidence of damage that could compromise the sterility or integrity of the device (e.g., cracked jar or lid, leakage, broken or missing seals, torn or punctured pouch).

**Caution:** Do not use the product if there is evidence of damage.

2. Inspect the temperature indicator located within the packaging for the bioprosthesis to ensure it has not been activated.

**Caution:** Do not use the bioprosthesis if the temperature indicator has been activated.

#### 9.1.2 Preparation of the Catheter

3. Wipe the length of the catheter with a moist (saline) gauze.
4. Use the micro knob and macro slider on the handle to open and close the catheter (Figure 4).

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5. Attach a stopcock to the first flush port. Attach a 10-mL syringe filled with saline to the stopcock on the first flush port and flush. Repeat step for the second flush port on the catheter (Figure 5).



**Figure 5**

6. Verify no catheter leakage is observed during any of the flushing steps. If leakage is observed, use a new system.
7. Attach a 10-mL syringe filled with saline to the third flush port on the handle on the catheter (Figure 6) and flush.



**Figure 6**

8. Fill a loading bath with cold, sterile saline (0°C to 8°C [32°F to 46°F]), and place the CLS components in the bath.

### **9.1.3 Bioprosthesis Rinsing Procedure**

9. Fill each of 3 rinsing bowls with approximately 500 mL of fresh, sterile saline at ambient temperature between 15°C to 25°C (59°F to 77°F).
10. Confirm the integrity of the primary bioprosthesis container. Open the container and remove the bioprosthesis by carefully grasping one of the frame loops. Let any remaining solution drain from the bioprosthesis completely.

**Caution:** The bioprosthesis should not be handled or manipulated with sharp or pointed objects. Use atraumatic blunt-tipped forceps only. DO NOT use the forceps to grasp the tissue portion of the bioprosthesis.

**Note:** Retain the container with the original solution. **It may be needed to store and return a rejected bioprosthesis.**

11. Compare the serial number on the container with the serial number on the tag attached to the bioprosthesis.

**Caution:** If the serial numbers do not match, DO NOT use the bioprosthesis.

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12. Carefully remove the serial number tag from the bioprosthesis and retain the tag. Ensure that the suture that was used to secure the serial number tag to the bioprosthesis is completely removed from the bioprosthesis.
  13. Immerse the entire bioprosthesis in a sterile rinsing bowl.
  14. Gently agitate the bioprosthesis by hand for 2 minutes to remove the glutaraldehyde from the bioprosthesis.
  15. Repeat steps 13 and 14 in each of the 2 remaining rinsing bowls to ensure complete removal of glutaraldehyde from the bioprosthesis.
  16. Leave the bioprosthesis submerged in sterile saline until it is ready to be loaded.

### 9.1.4 Bioprosthesis Loading Procedure

**Caution:** Rapid capsule advancement can contribute to difficulties with loading the valve. Slowly advancing the capsule helps facilitate successful loading.

**Caution:** With the exception of attaching the bioprosthesis frame loops to the catheter tabs, do not touch the capsule or the transition between the capsule and the catheter shaft. To protect the capsule, handle the catheter using the catheter shaft or, during loading, the loading tools.

**Note:** If a capsule becomes damaged during loading or the capsule fails to close, replace the entire system (bioprosthesis, catheter, and CLS). Do not use a catheter with a damaged capsule.

Perform the bioprosthesis loading procedure while the bioprosthesis, CLS, capsule, and catheter tip are immersed in cold, sterile saline (0°C to 8°C [32°F to 46°F]).

17. To open the capsule, activate the macro slider and slide back.
18. Submerge and cool the bioprosthesis in a bath filled with cold, sterile saline.
19. Advance the outflow tube (tube with flared ends) over the catheter shaft toward the handle (Figure 7).



**Figure 7**

20. Gently squeeze the outflow part of the cold bioprosthesis frame and insert it into the outflow cone (Figure 8).

**Note:** As applicable, all subsequent bioprosthesis loading steps should be performed under chilled (0°C to 8°C [32°F to 46°F]) saline.



**Figure 8**

21. Slowly continue to insert the frame into the outflow cone.
22. Once the bioprosthesis is fully inserted, secure the outflow cap onto the outflow cone (Figure 9).



**Figure 9**

23. Carefully insert the inflow tube (straight tube) into the outflow cap (Figure 10).



**Figure 10**

24. Gently continue to advance the inflow tube until the bioprosthesis frame loops begin to separate.
25. Insert the distal catheter tip into the inflow tube (Figure 11).



**Figure 11**

26. Carefully withdraw the inflow tube and attach the exposed frame loops to the catheter tabs (Figure 12).



**Figure 12**

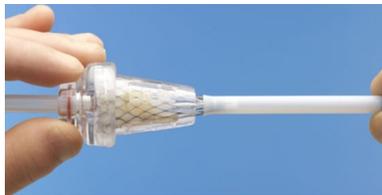
27. Rotate the micro knob to advance the capsule to cover the bioprosthesis frame loops and the top of the outflow struts (Figure 13).

**Note:** Ensure that the capsule has covered all of the outflow struts and the bioprosthesis frame loops are securely attached to the catheter tabs.



**Figure 13**

28. Advance the outflow tube over the radiopaque marker band of the capsule prior to advancing the capsule further (Figure 14).



**Figure 14**

29. Remove the outflow cap and inflow tube from the outflow cone (Figure 15).



**Figure 15**

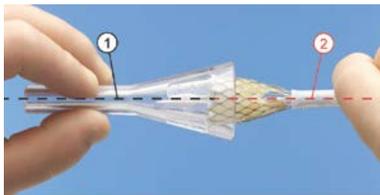
30. Move the outflow cone away from the bioprosthesis over the catheter toward the handle.

31. Advance the inflow cone over the bioprosthesis using the outflow tube (Figure 16).



**Figure 16**

**Note:** Ensure the bioprosthesis frame axis is visually aligned (coaxial) with the inflow cone axis during the insertion of the bioprosthesis into the inflow cone (Figure 17). Complete the insertion of the bioprosthesis into the inflow cone in one uninterrupted movement.



**Figure 17**

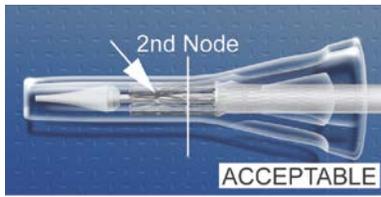
1. Inflow cone axis
  2. Bioprosthesis frame axis
32. Continue to advance the bioprosthesis into the inflow cone until the outflow tube contacts the inside of the inflow cone (Figure 18).



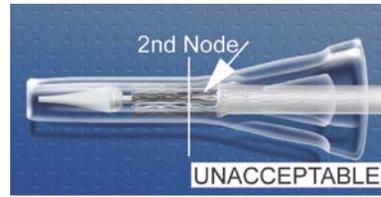
**Figure 18**

33. Visually inspect the bioprosthesis within the inflow cone to verify there is no crease or infold in the frame beyond the second node from the inflow end. Ensure inspection is performed circumferentially around the entire bioprosthesis.

**Caution:** If a crease or infold greater than 2 nodes long is noticed, do not use the bioprosthesis or catheter. Prepare a new bioprosthesis to load into a new catheter.



**Figure 19**



**Figure 20**

34. Hold the inflow cone against the outflow tube while slowly advancing the capsule over the bioprosthesis until the capsule comes within approximately 5 mm of the catheter tip (Figure 21). If the micro knob clicks, apply upward pressure to the macro slider and continue turning the micro knob (Figure 22).



**Figure 21**



**Figure 22**

35. With the catheter tip submerged in cold saline, flush both tube flush ports with saline.
36. Slowly advance the capsule over the bioprosthesis until the capsule contacts the catheter tip.
37. If the micro knob has fully advanced the capsule and a small gap remains between the end of the capsule and the catheter tip, stabilize the handle with one hand; position the other hand on the blue catheter shaft and gently advance the capsule manually to close the gap between the capsule and the catheter tip (Figure 23).



**Figure 23**

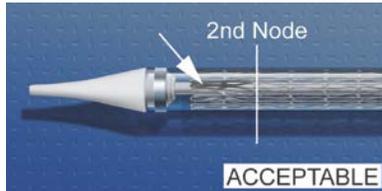
38. Remove the outflow cone and outflow tube from the catheter (Figure 24).



**Figure 24**

- 
39. Conduct a final visual inspection of the loaded bioprosthesis to make sure the frame is free of creases or infolds beyond the second node from the inflow end. Ensure inspection is performed circumferentially around the entire bioprosthesis.

**Caution:** If a crease or infold greater than 2 nodes long is noticed, do not use the bioprosthesis or catheter. Prepare a new bioprosthesis to load into a new catheter.



**Figure 25**



**Figure 26**

40. Leave the loaded bioprosthesis submerged in cold saline until implantation.

## 9.2 Bioprosthesis Implantation

### 9.2.1 Vascular Access

**Note:** Vascular access should be achieved per hospital protocol (either percutaneously or via surgical cutdown).

**Note:** The primary access artery will be used to introduce the CoreValve™ system and the balloon catheter; the secondary access artery will be used to introduce the reference pigtail.

1. Establish a central venous line. Insert a 4-Fr or 5-Fr temporary pacemaker catheter via the right internal jugular vein (or other appropriate access vessel) per hospital protocol.
2. Insert a 6-Fr introducer sheath into the secondary access artery.
3. Insert an 18-Fr introducer sheath into the primary access artery.
4. Administer anticoagulant according to hospital protocol. If heparin is administered as an anticoagulant, check the activated clotting time (ACT) after initial bolus of heparin and recheck every 30 minutes thereafter. Maintain ACT  $\geq$ 250 seconds.

**Note:** Anticoagulant may be administered at any time prior to this point, but avoid delaying beyond this point.

### 9.2.2 Crossing the Native Valve

5. Advance the graduated pigtail catheter to the ascending aorta and position the distal tip in the noncoronary cusp of the native aortic valve.
6. Identify the ideal annular viewing plane using contrast injections at various angiographic angles.

**Note:** It is recommended that a dedicated individual prepare and operate the contrast injector.

- 
7. Insert an angiographic catheter over a standard J-tip guidewire into the primary access sheath and advance to the ascending aorta.
  8. Exchange the J-tip guidewire for a 0.035-in (0.889-mm) straight-tip guidewire. Advance the straight-tip guidewire across the native aortic valve into the left ventricle (LV).
  9. After crossing the native aortic valve with the guidewire, advance the angiographic catheter into the LV.
  10. Exchange the straight-tip guidewire for an exchange-length J-tip guidewire.
  11. Exchange the angiographic catheter for a 6-Fr pigtail catheter.
  12. Remove the guidewire and connect the catheter to the transducer. Using both catheters, record the aortic pressure gradient.
  13. Using a right anterior oblique (RAO) projection, advance the previously pigtail-shaped, 0.035-in (0.889-mm) high-support guidewire through the pigtail catheter and position in the apex of the LV.
  14. Remove the pigtail catheter while maintaining guidewire position in the LV.

### **9.2.3 Predilatation of the Implant Site**

15. Insert the valvuloplasty balloon through the 18-Fr introducer sheath and advance it to the ascending aorta.
16. Reposition the angiographic equipment to the ideal viewing plane. Position the valvuloplasty balloon across the native valve, while maintaining strict fluoroscopic surveillance of the distal tip of the guidewire in the LV.
17. Perform balloon valvuloplasty per hospital protocol and remove the valvuloplasty balloon while maintaining guidewire position across the native aortic valve.

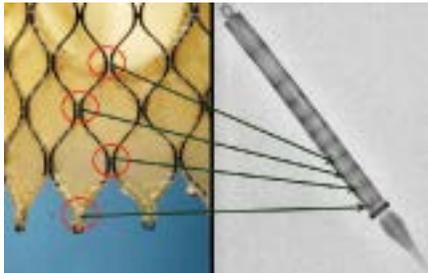
### **9.2.4 Deployment**

18. Insert the device over the 0.035-in (0.889-mm) guidewire and into the introducer sheath with the macro slider facing upward. Advance the device while maintaining strict fluoroscopic surveillance of the guidewire in the LV.
19. When crossing the aortic arch, it is critical that the guidewire is controlled to prevent it from moving forward. Without proper management of the distal tip of the guidewire, the guidewire could move forward and cause trauma to the LV.
20. Advance the device through the native valve. Perform an angiogram to confirm that the pigtail catheter is in position within the noncoronary cusp of the aortic root. Fluoroscopically identify the appropriate landmarks.

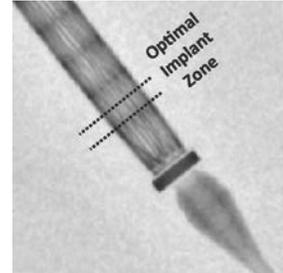


**Figure 27**

21. Note the radiopaque bands (Figure 28). Follow the diagrams in Figure 29 and Figure 32 for the optimal placement of the bioprosthesis. The bioprosthesis should be placed so that the skirt is within the aortic annulus (approximately 4 mm to 6 mm below the annulus). The annulus is defined as the angiographic floor of the aortic root.



**Figure 28**



**Figure 29**

22. After attaining optimal catheter position, slowly turn the micro knob and begin to deploy the bioprosthesis. As the inflow aspect of the bioprosthesis starts to flare outward, monitor bioprosthesis position under fluoroscopy.

**Caution:** During implantation, if resistance to deployment is encountered (e.g., the micro knob starts clicking or is tight or stuck), apply mild upward pressure to the macro slider while turning the micro knob (Figure 22). If the bioprosthesis still does not deploy, remove it from the patient and use another system.



**Figure 30**

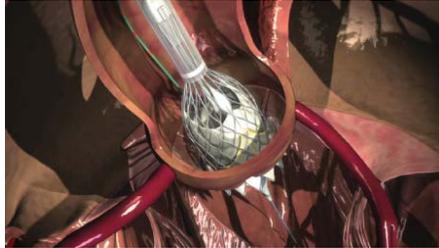
23. Perform an angiogram. Once annular contact is made, the bioprosthesis should not be advanced into a lower position.

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**Note:** The force required to move the bioprosthesis into a higher position becomes noticeably greater once annular contact is made.

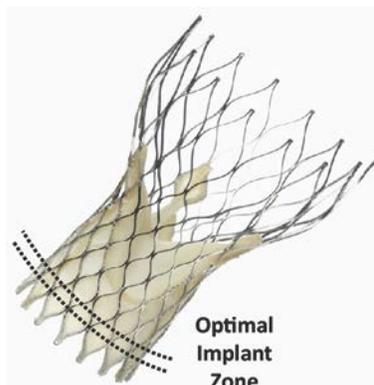
24. Continue deploying rapidly to the 2/3 deployment point; stop turning the micro knob.

**Note:** Shortly after annular contact, the blood pressure will be reduced until the 2/3 deployment point, when the bioprosthesis leaflets are exposed and are functioning.



**Figure 31**

25. Perform an angiogram to assess the location of the bioprosthesis. Refer to Figure 29 and Figure 32 for the optimal placement of the bioprosthesis skirt within the aortic annulus (approximately 4 mm to 6 mm below the annulus).



**Figure 32**

26. If the bioprosthesis is positioned low, slight repositioning of a partially deployed bioprosthesis ( $\leq 2/3$  of the bioprosthesis length) can be achieved by carefully withdrawing the catheter.
27. When satisfactory position is achieved, withdraw the reference pigtail catheter to the ascending aorta. Continue to turn the micro knob until both frame loops disengage. Use orthogonal views under fluoroscopy to confirm that the frame loops have detached from the catheter tabs. If a frame loop is still attached to a catheter tab, do not pull on the catheter. Under fluoroscopy, advance the catheter slightly and, if necessary, gently rotate the handle clockwise ( $<180^\circ$ ) and then counterclockwise ( $<180^\circ$ ) to disengage the loop from the catheter tab.

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### 9.2.5 Postdeployment

28. Under fluoroscopic guidance, confirm that the catheter tip is coaxial with the inflow portion of the bioprosthesis.

29. Withdraw the catheter to the aorta, while maintaining guidewire position.

**Note:** For transfemoral access, withdraw the catheter until the catheter tip is positioned in the descending aorta. For direct aortic access and subclavian access, withdraw the catheter until the catheter tip is close to the distal tip of the introducer sheath.

30. Close the capsule and remove the catheter through the 18-Fr introducer sheath.

**Note:** If the capsule does not close properly, gently rotate the catheter clockwise (<180°) and then counterclockwise (<180°) until the capsule closes.

**Caution:** Ensure the capsule is closed before catheter removal. If increased resistance is encountered when removing the catheter through the introducer sheath, do not force passage. Increased resistance may indicate a problem and forced passage may result in damage to the device and/or harm to the patient. If the cause of resistance cannot be determined or corrected, remove the catheter and introducer sheath as a single unit over the guidewire, and inspect the catheter and confirm that it is complete.

31. Dispose of the device in accordance with local regulations and hospital procedures.

32. Advance a 6-Fr pigtail catheter over the guidewire into the LV.

33. Remove the guidewire and connect the pigtail catheter to the transducer.

34. Using both pigtail catheters, record aortic pressure gradient.

35. Remove the 6-Fr pigtail over a standard, J-tip guidewire.

36. Perform a postimplant aortogram with the reference pigtail to ensure coronary patency and assess aortic regurgitations.

**Note:** In the event that valve function or sealing is impaired due to excessive calcification or incomplete expansion, a postimplant balloon dilatation of the bioprosthesis may improve valve function and sealing. To ensure patient safety, valve size and patient anatomy must be considered when selecting the size of the balloon used for dilatation. The balloon size chosen for dilatation should not exceed the diameter of the native aortic annulus. Refer to the specific balloon catheter manufacturer's labeling for proper instruction on the use of balloon catheter devices. Note: Bench testing has only been conducted to confirm compatibility with NuMED Z-MED II™ Balloon Aortic Valvuloplasty catheters where CoreValve™ bioprosthesis device performance was maintained after dilatation. Data on file.

37. Remove the 18-Fr introducer sheath and complete the puncture site closure per hospital protocol.

38. Perform contrast angiography to verify the absence of any vascular complications.

39. Remove the reference pigtail catheter over a standard guidewire. Remove the 6-Fr introducer and close the access site per hospital protocol.

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40. Administer anticoagulation and/or antiplatelet therapy as required according to hospital protocol.

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## **10.0 RETURN OF EXPLANTED BIOPROSTHESES**

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Medtronic is interested in obtaining recovered bioprostheses. Specific pathological studies of the explanted bioprosthesis will be conducted under the direction of a consulting pathologist. A written summary of the findings will be returned to the physician. To obtain a product return kit, contact a Medtronic distribution center or a Medtronic Representative. If a kit is not available, place the explanted bioprosthesis in a container of glutaraldehyde or 10% buffered formalin immediately after excision. For further instructions on the return of an explanted device, contact a Medtronic Representative.

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## 11.0 SUMMARY OF CLINICAL STUDY

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The Medtronic CoreValve™ U.S. Pivotal Trial was designed and executed to evaluate the safety and effectiveness of the CoreValve™ system to treat symptomatic severe aortic stenosis in subjects necessitating aortic valve replacement. The trial was divided into 2 cohorts—patients who were determined by a heart team to be at high risk for surgery (predicted operative mortality of  $\geq 15\%$  [and predicted operative mortality or serious, irreversible morbidity risk of  $< 50\%$ ]) or those who were determined to be at extreme risk for surgery (irreversible morbidity risk of  $\geq 50\%$  at 30 days). Section 11.1 presents the results of the High Risk cohort, and Section 11.2 presents the results of the Extreme Risk cohort.

### 11.1 High Risk Cohort

The CoreValve™ U.S. Pivotal Trial High Risk cohort was a prospective, randomized, unblinded, multi-center investigational study. Patients were stratified by intended access site (iliofemoral or non-iliofemoral) prior to randomization to ensure patients were allocated to each comparison group proportionately. Prior to randomization, patients were first evaluated for iliofemoral access. If patients were not eligible for iliofemoral access due to their inadequate vasculature or peripheral vascular disease, they were then considered for non-iliofemoral access. Patients were then individually evaluated for subclavian or direct aortic access.

The purpose of the study was to evaluate the safety and effectiveness of the Medtronic CoreValve™ system in the treatment of symptomatic severe aortic stenosis in subjects necessitating aortic valve replacement, with predicted operative mortality of  $\geq 15\%$  (and predicted operative mortality or serious, irreversible morbidity risk of  $< 50\%$ ) at 30 days (High Risk).

The High Risk cohort enrolled a total of 795 subjects with symptomatic severe aortic stenosis (394 subjects were randomized to transcatheter aortic valve replacement [TAVR] and 401 subjects were randomized to surgical aortic valve replacement [SAVR]) at 45 activated centers in the United States. Severe aortic stenosis was defined as an aortic valve area of  $\leq 0.8 \text{ cm}^2$  or aortic valve area index  $\leq 0.5 \text{ cm}^2$ , a mean aortic valve gradient of  $> 40 \text{ mm Hg}$  or jet velocity  $> 4 \text{ m/sec}$ . The primary endpoint of the study was to demonstrate that the safety and effectiveness of the Medtronic CoreValve™ system (TAVR), as measured by all-cause death at 12 months, is non-inferior to surgical aortic valve replacement (SAVR) in the treatment of symptomatic severe aortic stenosis in subjects who have a predicted high risk for aortic valve surgery.

Of the 394 subjects randomized to TAVR, 390 received an attempted implant and comprise the as treated (AT) TAVR population while 357 of the 401 subjects randomized to SAVR received an attempted implant and comprise the AT SAVR population.

The following data summarize the results from the High Risk cohort (TAVR iliofemoral and TAVR non-iliofemoral vs. SAVR iliofemoral eligible and SAVR non-iliofemoral eligible).

### 11.1.1 Patient Population

The demographics of the study population were typical for an aortic stenosis valve replacement study performed in the U.S., as shown in Table 3. A high proportion of the patients had significant co-morbidities, frailties, or disabilities, and these risk factors were generally well balanced between the study arms. The mean age for patients participating in the trial was approximately 83 years old, and slightly greater than 50% of patients were male. The mean STS score was approximately 7. In addition, approximately 85% of all patients were in NYHA classes III or IV.

**Table 3: High Risk Baseline Characteristics and Echocardiographic Findings (ITT)**

Demographic	Iliofemoral		Non-Iliofemoral		Pooled		P-Values
	TAVR N=330	SAVR N=333	TAVR N=64	SAVR N=68	TAVR N=394	SAVR N=401	
Age (years)	83.4 ± 6.8	83.6 ± 6.3	81.8 ± 8.0	82.9 ± 6.5	83.2 ± 7.1	83.5 ± 6.3	0.5102
Gender (Male)	53.9% (178/330)	53.8% (179/333)	51.6% (33/64)	48.5% (33/68)	53.6% (211/394)	52.9% (212/401)	0.8464
NYHA Classification							
II	13.0% (43/330)	12.0% (40/333)	20.3% (13/64)	19.1% (13/68)	14.2% (56/394)	13.2% (53/401)	0.6723
III	65.2% (215/330)	69.7% (232/333)	67.2% (43/64)	66.2% (45/68)	65.5% (258/394)	69.1% (277/401)	
IV	21.8% (72/330)	18.3% (61/333)	12.5% (8/64)	14.7% (10/68)	20.3% (80/394)	17.7% (71/401)	
STS Score (Risk of Mortality, %)	7.3 ± 3.1	7.5 ± 3.1	7.2 ± 2.6	7.6 ± 3.9	7.3 ± 3.0	7.5 ± 3.2	0.2680
Coronary Artery Disease	75.5% (249/330)	74.2% (247/333)	75.0% (48/64)	86.8% (59/68)	75.4% (297/394)	76.3% (306/401)	0.7597
Previous MI	23.3% (77/330)	23.4% (78/333)	37.5% (24/64)	29.4% (20/68)	25.6% (101/394)	24.4% (98/401)	0.6972
Previous Interventions							
Coronary Artery Bypass Surgery	31.2% (103/330)	29.1% (97/333)	21.9% (14/64)	35.3% (24/68)	29.7% (117/394)	30.2% (121/401)	0.8828
Percutaneous Coronary Intervention	32.1% (106/330)	37.8% (126/333)	42.2% (27/64)	38.2% (26/68)	33.8% (133/394)	37.9% (152/401)	0.2226
Balloon Valvuloplasty	4.5% (15/330)	6.3% (21/333)	12.5% (8/64)	7.4% (5/68)	5.8% (23/394)	6.5% (26/401)	0.7048
Cerebral Vascular Disease	24.7% (81/328)	23.2% (77/332)	29.0% (18/62)	35.9% (23/64)	25.4% (99/390)	25.3% (100/396)	0.9660
Prior Stroke	13.6% (45/330)	12.6% (42/333)	9.4% (6/64)	16.4% (11/67)	12.9% (51/394)	13.3% (53/400)	0.8984
Peripheral Vascular Disease	37.6% (123/327)	37.2% (123/331)	62.5% (40/64)	68.7% (46/67)	41.7% (163/391)	42.5% (169/398)	0.8257
Chronic Lung Disease/COPD	44.5% (147/330)	46.2% (154/333)	45.3% (29/64)	38.2% (26/68)	44.7% (176/394)	44.9% (180/401)	0.9508

Demographic	Iliofemoral		Non-Iliofemoral		Pooled		P-Values
	TAVR N=330	SAVR N=333	TAVR N=64	SAVR N=68	TAVR N=394	SAVR N=401	
Home Oxygen	13.4% (44/329)	12.3% (41/333)	9.4% (6/64)	10.3% (7/68)	12.7% (50/393)	12.0% (48/401)	0.7472
Creatinine Level >2 mg/dl	3.3% (11/330)	4.5% (15/333)	3.1% (2/64)	5.9% (4/68)	3.3% (13/394)	4.7% (19/401)	0.3021
Atrial Fibrillation/Atrial Flutter	40.6% (134/330)	48.8% (162/332)	42.9% (27/63)	41.2% (28/68)	41.0% (161/393)	47.5% (190/400)	0.0640
Pre-Existing Permanent Pacemaker Placement/ICD	24.8% (82/330)	21.6% (72/333)	15.6% (10/64)	16.2% (11/68)	23.4% (92/394)	20.7% (83/401)	0.3669
Aorta Calcification <sup>1</sup>							
Severe	10.6% (35/330)	10.5% (35/333)	19.0% (12/63)	16.2% (11/68)	12.0% (47/393)	11.5% (46/401)	0.8307
Porcelain	0.0% (0/330)	0.0% (0/333)	1.6% (1/63)	0.0% (0/68)	0.3% (1/393)	0.0% (0/401)	0.4950
Chest Wall Deformity	1.8% (6/330)	0.3% (1/333)	4.7% (3/64)	0.0% (0/68)	2.3% (9/394)	0.2% (1/401)	0.0106
Hostile Mediastinum	3.9% (13/330)	0.9% (3/331)	3.1% (2/64)	2.9% (2/68)	3.8% (15/394)	1.3% (5/399)	0.0218
Cirrhosis of the Liver	2.4% (8/330)	1.8% (6/333)	3.1% (2/64)	1.5% (1/68)	2.5% (10/394)	1.7% (7/401)	0.4400
Wheelchair Bound	4.8% (16/330)	7.5% (25/333)	0.0% (0/64)	7.4% (5/68)	4.1% (16/394)	7.5% (30/401)	0.0389
Echocardiographic Findings							
Ejection Fraction (visual estimate, %)	58.1 ± 10.9	57.5 ± 11.8	57.4 ± 13.4	58.3 ± 12.4	58.0 ± 11.3	57.7 ± 11.9	0.7110
Aortic Valve Area (cm <sup>2</sup> )	0.72 ± 0.23	0.73 ± 0.24	0.70 ± 0.18	0.71 ± 0.22	0.72 ± 0.23	0.73 ± 0.23	0.5801
Mean Gradient Across Aortic Valve (MGV <sub>2</sub> , mmHg)	48.36 ± 15.09	47.69 ± 14.39	47.38 ± 16.74	48.08 ± 12.51	48.20 ± 15.35	47.75 ± 14.07	0.6725
Mitral Regurgitation: Moderate/Severe	10.2% (33/325)	10.5% (34/324)	8.1% (5/62)	9.0% (6/67)	9.8% (38/387)	10.2% (40/391)	0.8486

1. Aorta Calcification is measured on screening CT Angiogram  
Plus-minus values present the mean ± standard deviation.

The STS score predicted a 30-day mortality of 7.5% for the average surgeon at the average hospital. The Kaplan-Meier (K-M) 30-day mortality for the As Treated SAVR arm was 4.5%. Therefore, the observed/expected ratio was 0.60 in this trial, indicating better than average care in the SAVR arm.

### 11.1.2 Procedure Data

As recommended in the protocol, the procedure was to occur within 30 days of randomization. As such, time to procedure was calculated between the randomization date and the date of the first attempted procedure. It was  $13.1 \pm 10.9$  days for TAVR patients and  $18.1 \pm 14.3$  days for SAVR patients.

Table 4 provides a summary of the procedure data for the TAVR cohort. The overall device success rate was 86.9% for the iliofemoral cohort and 87.3% for the non-iliofemoral cohort. Procedure success was defined as device success and absence of in-hospital MACCE and procedure success rates were 81.5% and 82.8% for the iliofemoral and non-iliofemoral cohorts, respectively.

**Table 4: High Risk TAVR Procedure Data - As Treated Population**

	<b>TAVR IF N=323</b>	<b>TAVR NIF N=67</b>	<b>TAVR Pooled N=390</b>
Number of Index Procedures <sup>1</sup>	323	66	389
Total Time in Cath Lab or OR (min)	209.6 ± 58.6 (323)	249.1 ± 63.4 (66)	216.3 ± 61.2 (389)
Total Procedure Time (min) (skin to skin)	61.4 ± 33.9 (321)	55.6 ± 41.7 (65)	60.4 ± 35.3 (386)
General Anesthesia	93.8% (303/323)	98.5% (65/66)	94.6% (368/389)
Valve-in-Valve Procedure	4.3% (14/323)	0.0% (0/66)	3.6% (14/389)
Converted to surgical AVR	0.3% (1/323)	1.5% (1/66)	0.5% (2/389)
Number of Valves Used			
0 <sup>2</sup>	0.0% (0/323)	1.5% (1/67)	0.3% (1/390)
1	91.3% (295/323)	92.5% (62/67)	91.5% (357/390)
2	8.4% (27/323)	6.0% (4/67)	7.9% (31/390)
3	0.3% (1/323)	0.0% (0/67)	0.3% (1/390)
Number of Valves Implanted			
0	0.0% (0/323)	1.5% (1/67)	0.3% (1/390)
1	95.0% (307/323)	98.5% (66/67)	95.6% (373/390)
2	5.0% (16/323)	0.0% (0/67)	4.1% (16/390)
3	0.0% (0/323)	0.0% (0/67)	0.0% (0/390)
Valve Size Implanted			
23 mm	1.5% (5/323)	1.5% (1/66)	1.5% (6/389)
26 mm	29.4% (95/323)	40.9% (27/66)	31.4% (122/389)
29 mm	49.5% (160/323)	48.5% (32/66)	49.4% (192/389)
31 mm	19.5% (63/323)	9.1% (6/66)	17.7% (69/389)
Device Success <sup>3</sup>	86.9% (273/314)	87.3% (55/63)	87.0% (328/377)
Procedure Success <sup>4</sup>	81.5% (260/319)	82.8% (53/64)	81.7% (313/383)

<sup>1</sup> The table includes patients with the index procedure. Index procedure (TAVR): the first procedure that the Medtronic CoreValve™ system catheter is introduced.

<sup>2</sup> A single patient had no valves used or implanted during the procedure as the patient became hypotensive after the TEE probe was placed and the patient was converted to SAVR.

<sup>3</sup> Device success is defined as deployment, only 1 valve implanted, only 1 valve in correct anatomic location, EOA >1.2 cm<sup>2</sup> for 26, 29, and 31mm and ≥0.9 cm<sup>2</sup> for 23 mm, mean gradient <20 mm Hg, and aortic regurgitation < moderate.

<sup>4</sup> Procedure success is defined as device success and absence of in-hospital MACCE.

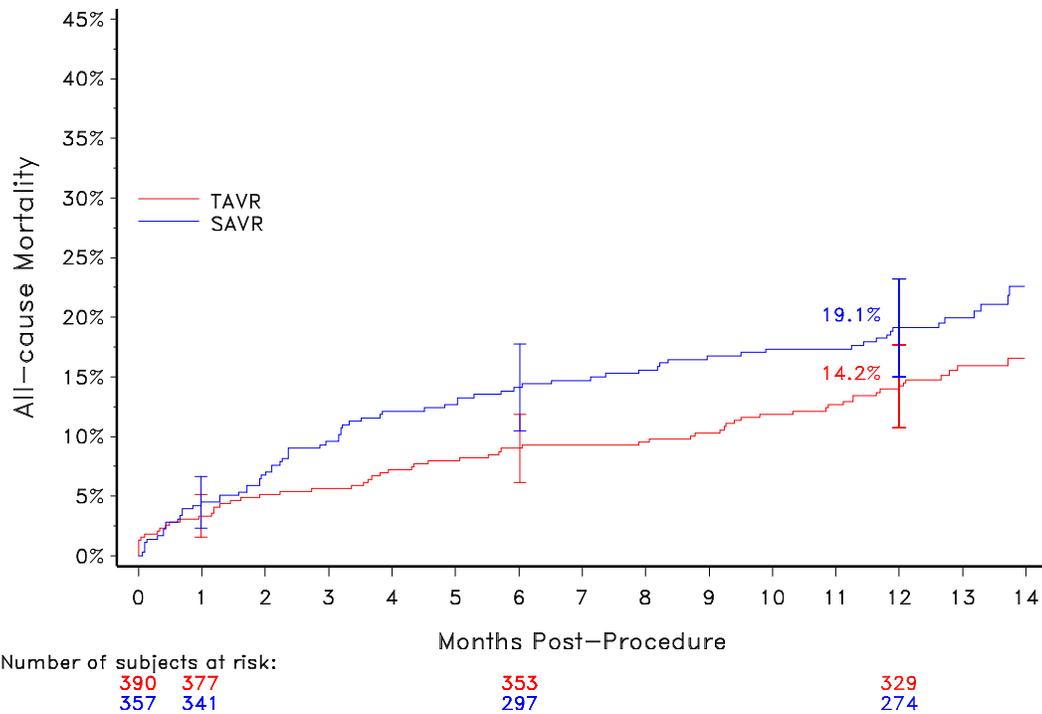
### 11.1.3 Safety and Effectiveness Results

#### 11.1.3.1 Primary Safety and Effectiveness Endpoint

The primary endpoint of all-cause mortality at 12 months included all deaths (cardiovascular and non-cardiovascular) from any cause after a valve intervention. Figure 33 shows the Kaplan-Meier (K-M) rates of all-cause mortality in the AT population for both treatment arms up to 12 months follow-up. The K-M rate of all-cause mortality at 12 months was 14.22% for TAVR and 19.12% for SAVR with a difference of -4.89% (TAVR-SAVR) and an upper 1-sided 95% confidence interval of -0.37%, which was statistically less than the pre-specified non-inferiority margin of 7.5% ( $p < 0.0001$ ). Therefore, the null hypothesis that TAVR was inferior to SAVR for the primary endpoint of all-cause mortality at 12 months was rejected and the alternative hypothesis that TAVR was non-inferior to SAVR within a non-inferiority margin of 7.5% was accepted. Subsequently, a pre-specified test for superiority of TAVR over SAVR was also conducted, which demonstrated that the rate of all-cause mortality at 12 months for TAVR was significantly less than that for SAVR at the one-sided 0.05 level ( $p = 0.0377$ ).

**Table 5: Primary Endpoint: All-Cause Mortality at 12 Months – As Treated Population**

	TAVR N=390	SAVR N=357
Total # of Patients	390	357
# of Patients Died within 1 Year	55	67
# of Patients Censored prior to 1 Year	7	16
# of Patients Alive at 1 Year	328	274
Mortality Rate at 1 Year (K-M)	14.22%	19.12%
Standard Error at 1 Year	1.78%	2.10%
Mortality Difference (TAVR-SAVR)	-4.89%	
Standard Error of Difference	2.75%	
95% 1-sided UCB for Difference	-0.37%	
Primary Objective – Non-Inferiority		
Non-inferiority Margin	7.50%	
Z-Score	-4.5019	
P-Value	<0.0001	
Non-Inferiority Test	Passed	
Primary Objective – Superiority		
Z-Score	-1.7776	
P-Value	0.0377	
Superiority Test	Passed	



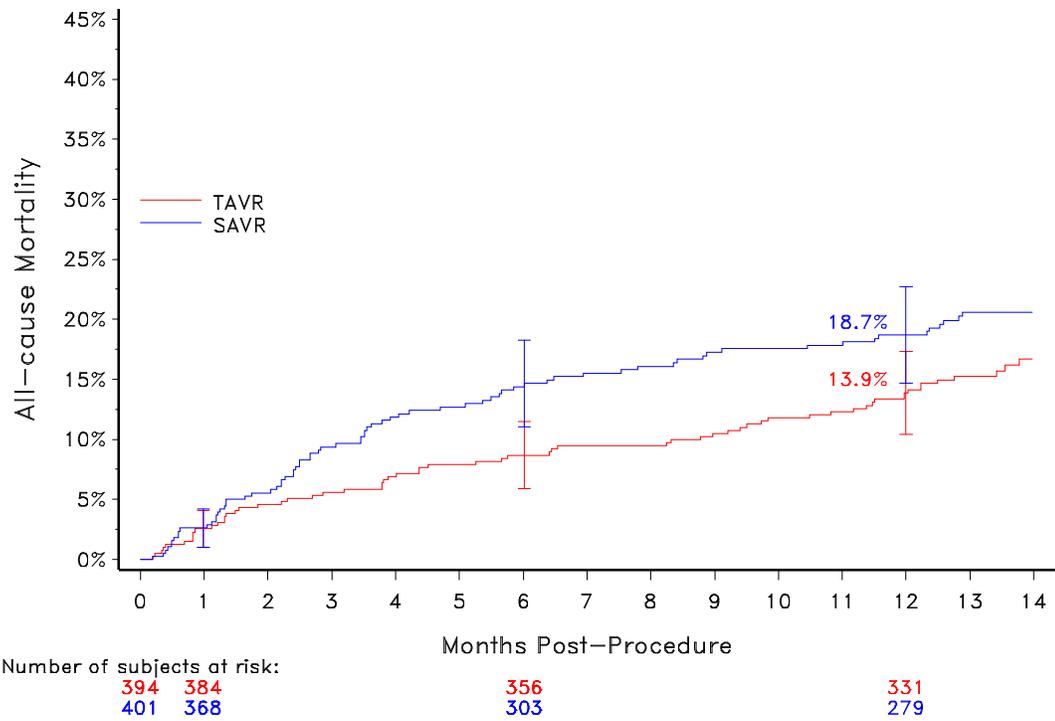
**Figure 33: High Risk All-Cause Mortality Kaplan-Meier Event Rate – As Treated Population**

The primary endpoint hypothesis testing was also pre-specified for the intent-to-treat (ITT), Implanted, and Per Protocol populations, as presented in Table 6 and Figure 34 - Figure 36. The ITT population consisted of all randomized patients. The Implanted population consisted of all AT patients who were actually implanted with either a CoreValve device or a surgical valve. The Per Protocol population consisted of all implanted subjects who: (1) were implanted according to their randomization and access site stratification; (2) had at least 12 months (365 days) of follow-up or had experienced the primary endpoint (death) prior to 12 months; (3) did not cross to a different type of procedure from their first attempted procedure types (TAVR or SAVR) before their 12 month visit; and (4) had satisfied all inclusion/exclusion criteria. Non-inferiority of TAVR compared to SAVR was concluded for all analysis populations ( $p < 0.0001$  for all). Subsequent superiority null hypothesis was rejected at one-sided 0.05 level for the ITT ( $p = 0.0365$ ) and Implanted ( $p = 0.042$ ) populations, but not for the Per Protocol population ( $p = 0.07$ ).

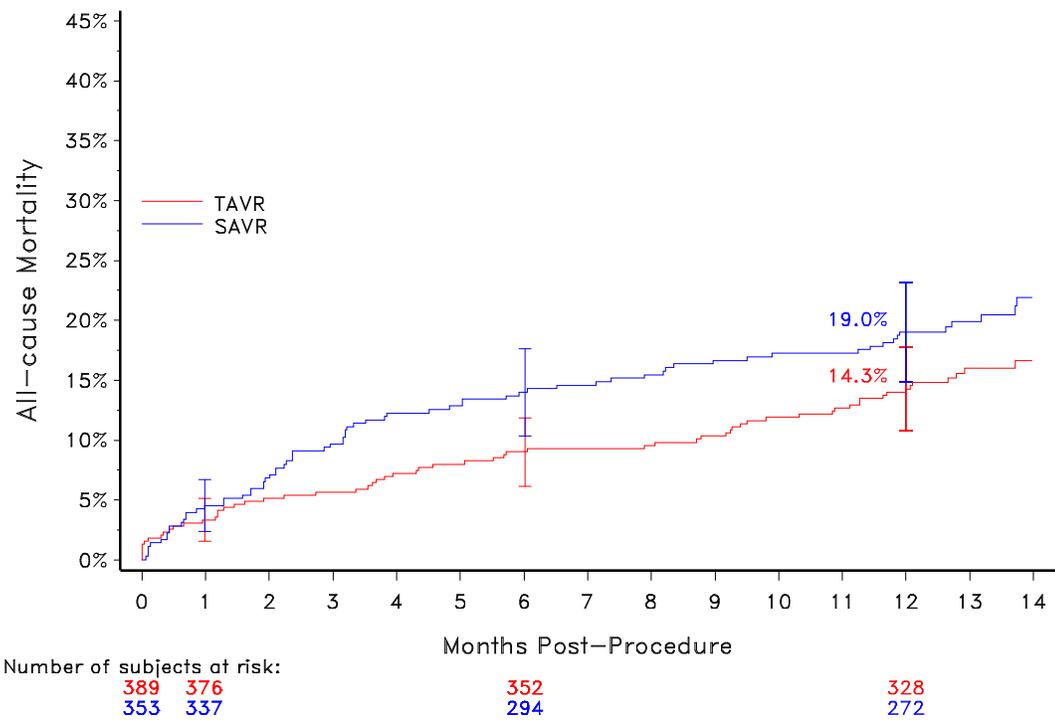
**Table 6: Primary Endpoint: All-Cause Mortality at 12 Months – Pre-specified Additional Populations**

	Intent-to-Treat		Implanted		Per Protocol	
	TAVR N=394	SAVR N=401	TAVR N=389	SAVR N=353	TAVR N=365	SAVR N=326
Total # of Patients	394	401	389	353	365	326
# of Patients Died within 1 Year	54	68	55	66	53	61
# of Patients Censored prior to 1 Year	9	54	7	15	0	0
# of Patients Alive at 1 Year	331	279	327	272	312	265
Mortality Rate at 1 Year (K-M)	13.87%	18.70%	14.26%	19.03%	14.52%	18.71%
Standard Error at 1 Year	1.75%	2.05%	1.78%	2.11%	1.84%	2.16%
Mortality Difference (TAVR-SAVR)	-4.83%		-4.77%		-4.19%	
Standard Error of Difference	2.70%		2.76%		2.84%	
95% 1-sided UCB for Difference	-0.40%		-0.23%		0.48%	
Primary Objective – Non-Inferiority						
Non-inferiority Margin	7.50%		7.50%		7.50%	
Z-Score	-4.5734		-4.4443		-4.1164	
P-Value	<0.0001		<0.0001		<0.0001	
Non-Inferiority Test	Passed		Passed		Passed	
Primary Objective – Superiority						
Z-Score	-1.7926		-1.7283		-1.4757	
P-Value	0.0365		0.0420		0.0700	
Superiority Test	Passed		Passed		Failed	

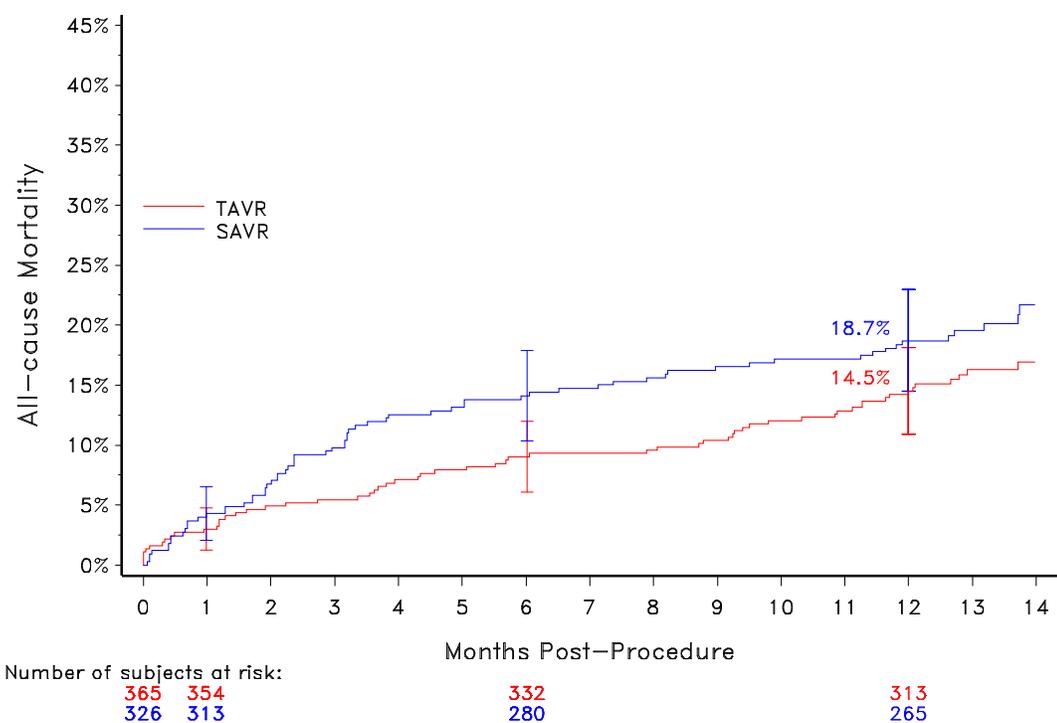
It is worth noting that although the study primary endpoint passed the pre-specified superiority test after it passed the non-inferiority test in the As-Treated primary analysis population, the statistical robustness of the superiority test across different analysis populations should be interpreted based on the specific statistical parameters used.



**Figure 34: All-Cause Mortality Kaplan-Meier Event Rate – Intent-to-Treat Population**



**Figure 35: All-Cause Mortality Kaplan-Meier Event Rate – Implanted Population**



**Figure 36: All-Cause Mortality Kaplan-Meier Event Rate – Per Protocol Population**

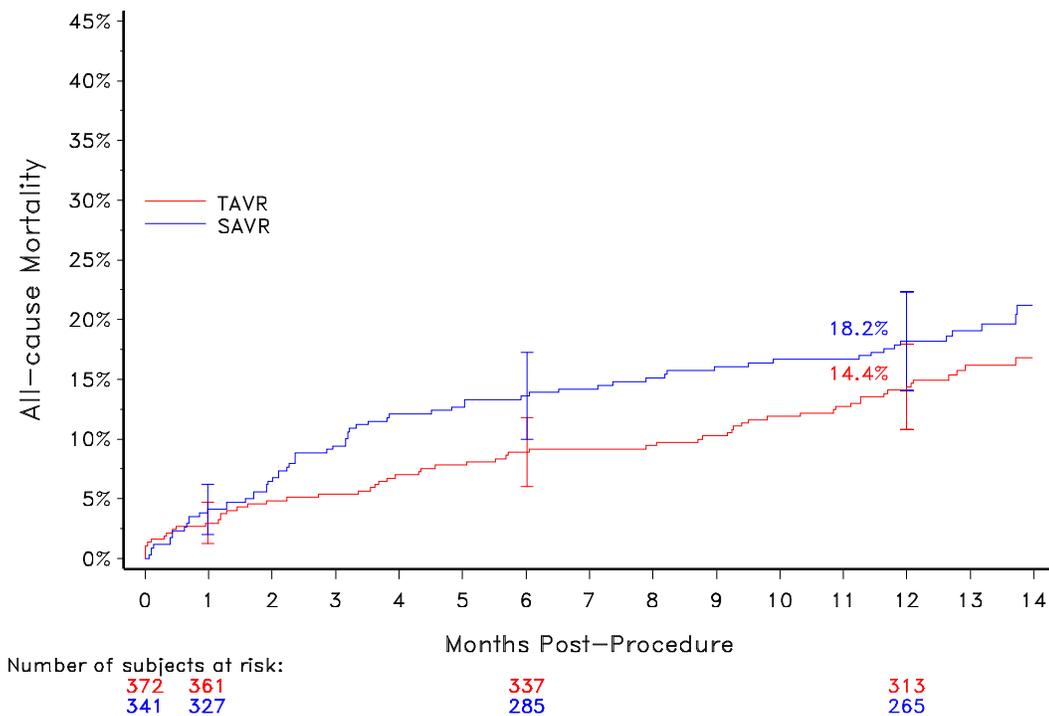
A post hoc analysis was also performed on the primary endpoint hypothesis testing for the Modified Per Protocol population. The Modified Per Protocol population included 22 additional subjects (7 TAVR, 15 SAVR) who were censored prior to 1 year as compared with the Per Protocol population. In addition, a post hoc analysis was conducted on the worst-case Modified Per Protocol population, which assumed all 7 censored TAVR subjects had died at the censoring time and all 15 censored SAVR subjects were alive at 1 year). In both analyses, non-inferiority was demonstrated. The results are presented in Table 7, Figure 37 and Figure 38.

**Table 7: Primary Endpoint: All-Cause Mortality at 12 Months – Ad-Hoc Additional Populations**

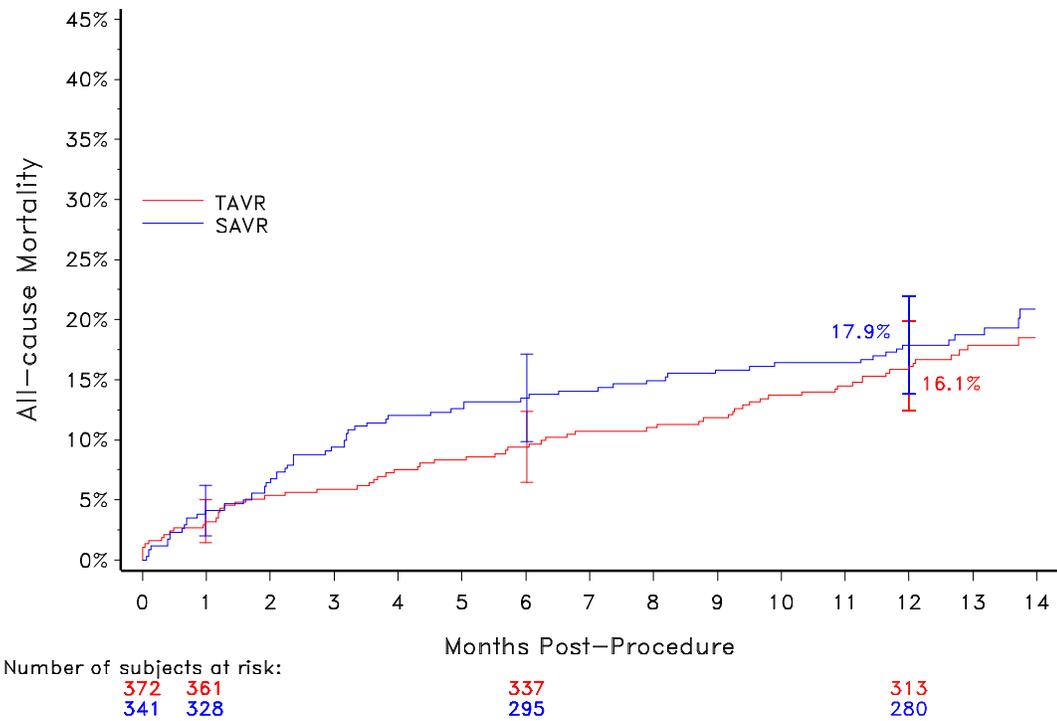
	Modified Per Protocol		Modified Per Protocol Worst Case Scenario	
	TAVR N=372	SAVR N=341	TAVR N=372	SAVR N=341
Total # of Patients	372	341	372	341
# of Patients Died within 1 Year	53	61	60	61
# of Patients Censored prior to 1 Year	7	15	0	0
# of Patients Alive at 1 Year	312	265	312	280
Mortality Rate at 1 Year (K-M)	14.38%	18.21%	16.13%	17.89%
Standard Error at 1 Year	1.83%	2.11%	1.91%	2.08%
Mortality Difference (TAVR-SAVR)	-3.83%		-1.76%	

	Modified Per Protocol		Modified Per Protocol Worst Case Scenario	
	TAVR N=372	SAVR N=341	TAVR N=372	SAVR N=341
Standard Error of Difference	2.79%		2.82%	
95% 1-sided UCB for Difference	0.76%		2.88%	
Primary Objective – Non-Inferiority				
Non-inferiority Margin	7.50%		7.50%	
Z-Score	-4.0572		-3.2853	
P-Value	< 0.0001		0.0005	
Non-Inferiority Test	Passed		Passed	

Subjects (7 TAVR, 15 SAVR) censored before 1 year were included in the modified per protocol.  
For worst case scenario the following assumptions were made for the censored subjects: the 7 TAVR subjects were assumed to have died on date of censoring and the 15 SAVR subjects were assumed to be alive at 1 year.



**Figure 37: All-Cause Mortality Kaplan-Meier Event Rate – Modified Per Protocol Population**



**Figure 38: All-Cause Mortality Kaplan-Meier Event Rate – Modified Per Protocol Population – Worst Case Scenario**

### 11.1.3.2 Key Secondary Safety and Effectiveness Endpoint

#### Hierarchical Testing of Secondary Endpoints

Hypothesis testing was performed on six pre-specified secondary endpoints using a hierarchical test procedure, as shown in Table 8. TAVR was found to be statistically non-inferior to SAVR within the pre-specified non-inferiority margins in terms of changes in mean gradient and EOA as well as in NYHA functional classification and Kansas City Cardiomyopathy Questionnaire (KCCQ) from baseline to 12 months. However, TAVR was not found to be statistically superior to SAVR with respect to the MACCE rate ( $p=0.1033$ ), which was a powered secondary endpoint, as discussed in more detail later. In other words, the powered secondary endpoint of MACCE rate was not met. As a result, no hypothesis testing was conducted on SF-12 per the pre-specified hierarchical testing protocol.

**Table 8: High Risk Secondary Endpoints: Hierarchical Testing**

Secondary Objective	TAVR	SAVR	Difference (TAVR-SAVR)	Confidence Limit of the Difference	p-value	Test Result
<b>Implanted Population</b>						
#9 / Mean gradient change (12 Month – Baseline; mmHg) Ha: TAVR > SAVR-15 95% Lower CI	39.04 ± 13.63 (n=290)	35.42 ± 15.42 (n=222)	3.62	1.49	<0.0001	Passed
#9 / EOA change (12 Month – Baseline; cm <sup>2</sup> ) Ha: TAVR > SAVR-0.375 95% Lower CI	1.20 ± 0.53 (n=253)	0.81 ± 0.50 (n=182)	0.39	0.31	<0.0001	Passed
<b>AT Population</b>						
#5 / NYHA change (12 Month – Baseline) Ha: TAVR > SAVR-0.375 95% Lower CI	1.46 ± 0.76 (n=305)	1.46 ± 0.81 (n=232)	-0.001	-0.11	<0.0001	Passed
#8 / KCCQ change (12 Month – Baseline) Ha: TAVR > SAVR-5 95% Lower CI	23.20 ± 25.56 (n=243)	21.88 ± 26.57 (n=189)	1.32	-2.84	0.0063	Passed
Powered Secondary #1 / MACCE event rate at 1 Month (K-M) Ha: TAVR < SAVR 97.5% Upper CI	8.21% (n=390)	10.93% (n=357)	-2.73%	1.51%	0.1033	Failed
#8 / SF-12 change (1 Month – Baseline) Ha: TAVR ≠ SAVR 95% two-sided CI	4.91 ± 10.26 (n=215)	-0.12 ± 10.04 (n=158)	5.03	(2.94, 7.13)	NA	Not Tested

**Powered Secondary Hypothesis**

For the AT population, the MACCE rate was 8.21% for TAVR and 10.93% for SAVR (p = 0.1033). The null hypothesis that TAVR was equal to SAVR in the MACCE rate could not be rejected. Of note is that the MACCE rate observed in the trial for SAVR was considerably lower than that assumed in the power calculation (20% vs. 12.1%), which resulted in the pre-specified sample size being too small to detect a difference between the two study arms even if a difference exists. Therefore, this particular secondary endpoint was underpowered for the specified hypothesis testing.

### 11.1.3.3 Additional Safety Data

#### Adverse Events that Occurred in the PMA Clinical Study

Table 9, Table 10, and Table 11 provide a summary of the adverse events (AEs) that occurred in this study for the pooled, iliofemoral and non-iliofemoral High Risk cohorts. AEs for the AT population are summarized and K-M rates are provided.

The primary endpoint of all-cause mortality at 12 months includes all deaths (cardiovascular and non-cardiovascular) from any cause after or during a valve intervention. The rates of all-cause mortality at 12 months in the pooled AT population for both the TAVR and SAVR treatment were 14.2% and 19.1% respectively.

Generally the rates of complications for the iliofemoral subjects were similar to the overall rates of the pooled population since they comprised a significant majority of the overall study cohort (323 of 390 subjects for TAVR and 300 of 357 subjects for SAVR).

Additionally, the rates of complications for the non-iliofemoral subjects were higher than the rates for iliofemoral subjects for both TAVR and SAVR treatment arms.

**Table 9: High Risk Adverse Event Summary – As Treated Population**

Event	0-30 Days				0-12 Months			
	TAVR N=390		SAVR N=357		TAVR N=390		SAVR N=357	
	# Pts (#Event)	K-M Rate (%)						
All-Cause Mortality	13 (13)	3.3%	16 (16)	4.5%	55 (55)	14.2%	67 (67)	19.1%
Cardiovascular	12 (12)	3.1%	16 (16)	4.5%	40 (40)	10.4%	44 (44)	12.8%
Valve-Related <sup>1</sup>	9 (9)	2.3%	2 (2)	0.6%	21 (21)	5.6%	7 (7)	2.2%
Non-Cardiovascular	1 (1)	0.3%	0 (0)	0.0%	15 (15)	4.2%	23 (23)	7.3%
Reintervention	3 (3)	0.8%	0 (0)	0.0%	7 (7)	1.9%	0 (0)	0.0%
Surgical	2 (2)	0.5%	0 (0)	0.0%	3 (3)	0.8%	0 (0)	0.0%
Percutaneous	1 (1)	0.3%	0 (0)	0.0%	4 (4)	1.1%	0 (0)	0.0%
All Stroke	19 (20)	4.9%	22 (23)	6.2%	33 (34)	8.8%	42 (45)	12.6%
Major Stroke	15 (16)	3.9%	11 (11)	3.1%	22 (23)	5.8%	23 (23)	7.0%
Minor Stroke	4 (4)	1.0%	12 (12)	3.4%	11 (11)	3.0%	20 (22)	6.0%
All-Cause Mortality or Major Stroke	23 (29)	5.9%	24 (27)	6.7%	63 (78)	16.3%	79 (90)	22.5%
CEC Adjudicated Bleed <sup>2, 6</sup>	150 (161)	38.5%	NA	NA	160 (186)	41.2%	NA	NA
Life Threatening or Disabling	48 (53)	12.3%	NA	NA	59 (65)	15.3%	NA	NA
Major Bleed	106 (108)	27.3%	NA	NA	110 (121)	28.4%	NA	NA
Re-Classified Bleed <sup>3</sup>	157 (170)	40.3%	243 (258)	68.1%	167 (195)	43.0%	252 (290)	70.8%

Event	0-30 Days				0-12 Months			
	TAVR N=390		SAVR N=357		TAVR N=390		SAVR N=357	
	# Pts (#Event)	K-M Rate (%)						
“Life Threatening or Disabling”	53 (58)	13.6%	125 (130)	35.0%	64 (70)	16.6%	136 (150)	38.4%
“Major Bleed”	109 (112)	28.1%	123 (128)	34.5%	114 (125)	29.5%	130 (140)	36.7%
Major Vascular Complication	23 (23)	5.9%	6 (6)	1.7%	24 (24)	6.2%	7 (7)	2.0%
Acute Kidney Injury	23 (23)	6.0%	54 (54)	15.1%	23 (23)	6.0%	54 (54)	15.1%
MI	3 (3)	0.8%	3 (3)	0.8%	7 (7)	1.9%	5 (5)	1.5%
Peri-Procedural	3 (3)	0.8%	2 (2)	0.6%	3 (3)	0.8%	2 (2)	0.6%
Spontaneous	0 (0)	0.0%	1 (1)	0.3%	4 (4)	1.1%	3 (3)	0.9%
Cardiac Perforation	5 (5)	1.3%	0 (0)	0.0%	5 (5)	1.3%	0 (0)	0.0%
Cardiogenic Shock	9 (9)	2.3%	11 (11)	3.1%	9 (9)	2.3%	11 (11)	3.1%
Cardiac Tamponade	6 (6)	1.5%	4 (4)	1.1%	7 (7)	1.8%	5 (5)	1.4%
Valve Endocarditis	0 (0)	0.0%	0 (0)	0.0%	2 (2)	0.6%	4 (4)	1.4%
Valve Thrombosis	0 (0)	0.0%	0 (0)	0.0%	0 (0)	0.0%	0 (0)	0.0%
Valve Embolism/Device Migration	0 (0)	0.0%	0 (0)	0.0%	0 (0)	0.0%	0 (0)	0.0%
MACCE <sup>4</sup>	30 (39)	7.7%	37 (42)	10.4%	79 (103)	20.4%	96 (117)	27.3%
MAE <sup>5,6</sup>	200 (311)	51.3%	NA	NA	229 (417)	58.8%	NA	NA
Aortic Valve Hospitalization	15 (15)	3.9%	18 (19)	5.2%	59 (85)	16.1%	43 (59)	13.5%
New Permanent Pacemaker Implant <sup>7</sup>	76 (77)	25.7%	24 (24)	8.6%	84 (86)	28.6%	36 (36)	13.5%
Permanent Pacemaker Implant <sup>8</sup>	76 (77)	19.8%	25 (25)	7.1%	85 (87)	22.3%	38 (38)	11.3%

Event	0-30 Days				0-12 Months			
	TAVR N=390		SAVR N=357		TAVR N=390		SAVR N=357	
	# Pts (#Event)	K-M Rate (%)						
<sup>1</sup> Valve-related death is any death caused by prosthetic valve dysfunction, valve thrombosis, embolism, bleeding event, or implanted valve endocarditis or related to reintervention on the operated valve. <sup>2</sup> For TAVR, periprocedural transfusions meeting VARC I major and life-threatening bleeding criteria were adjudicated as events by the CEC irrespective of whether an overt bleeding complication had occurred. Since peri-procedural transfusions meeting VARC I criteria may be considered standard of care for SAVR procedures depending on the clinical circumstances, the same criteria were not applied and evidence of an overt bleeding complication (in addition to units transfused) were required to adjudicate an event for SAVR only. This makes a direct comparison of the CEC adjudicated bleeding rates in the trial inappropriate. For this reason, CEC adjudicated bleeding complications are shown for TAVR only. <sup>3</sup> For the transfusion-based reclassification of bleeding events, units transfused were summed during the procedure, on the day of the procedure and the day following the procedure. Patients who received 2-3 units of packed red blood cells or homologous whole blood were considered to have had a “major bleeding complication” and patients receiving ≥4 units were considered to have had a “life-threatening or disabling bleeding complication” for both TAVR and SAVR. The nomenclature of the original adjudication was applied for consistency with this transfusion based re-classification. <sup>4</sup> MACCE includes all-cause death, myocardial infarction (MI), all stroke, and reintervention. <sup>5</sup> MAE includes all death, MI, all stroke, reintervention, cardiac perforation, cardiac tamponade, cardiogenic shock, valve embolism/device migration, prosthetic valve dysfunction, acute kidney injury, major vascular complication, life threatening of disabling bleed, major bleed, valve endocarditis VARC I Definitions. <sup>6</sup> Bleeding complications and MAE rate cells have been intentionally left blank for SAVR in this table because of differing definitions employed for bleeding complications have made comparison of the rates to TAVR inappropriate. <sup>7</sup> Patients with pacemaker or ICD at baseline are excluded from the numerator and denominator. Note one (1) TAVR patient and two (2) SAVR patients with baseline pacemaker/ICD, received new pacemaker/ICD between 30–365 days. <sup>8</sup> Patients with pacemaker or ICD at baseline are included in the denominator.								

**Table 10: High Risk Adverse Event Summary – Iliofemoral As Treated Population**

Event	0-30 Days				0-12 Months			
	TAVR N=323		SAVR N=300		TAVR N=323		SAVR N=300	
	# Pts (#Event)	K-M Rate (%)						
All-Cause Mortality	11 (11)	3.4%	13 (13)	4.3%	43 (43)	13.4%	52 (52)	17.6%
Cardiovascular	10 (10)	3.1%	13 (13)	4.3%	32 (32)	10.1%	35 (35)	12.0%
Valve-Related <sup>1</sup>	8 (8)	2.5%	1 (1)	0.3%	18 (18)	5.7%	4 (4)	1.5%
Non-Cardiovascular	1 (1)	0.3%	0 (0)	0.0%	11 (11)	3.7%	17 (17)	6.3%
Reintervention	2 (2)	0.6%	0 (0)	0.0%	6 (6)	2.0%	0 (0)	0.0%
Surgical	1 (1)	0.3%	0 (0)	0.0%	2 (2)	0.7%	0 (0)	0.0%
Percutaneous	1 (1)	0.3%	0 (0)	0.0%	4 (4)	1.3%	0 (0)	0.0%
All Stroke	16 (17)	5.0%	15 (15)	5.0%	28 (29)	9.0%	30 (32)	10.8%
Major Stroke	12 (13)	3.7%	6 (6)	2.0%	18 (19)	5.8%	13 (13)	4.7%
Minor Stroke	4 (4)	1.3%	9 (9)	3.0%	10 (10)	3.3%	17 (19)	6.2%
CEC Adjudicated Bleed <sup>2,6</sup>	107 (112)	33.1%	NA	NA	117 (136)	36.4%	NA	NA

Event	0-30 Days				0-12 Months			
	TAVR N=323		SAVR N=300		TAVR N=323		SAVR N=300	
	# Pts (#Event)	K-M Rate (%)						
Life Threatening or Disabling	32 (34)	9.9%	NA	NA	42 (45)	13.2%	NA	NA
Major Bleed	76 (78)	23.6%	NA	NA	80 (91)	25.0%	NA	NA
Re-Classified Bleed <sup>3</sup>	113 (119)	35.0%	204 (218)	68.0%	123 (143)	38.3%	210 (238)	70.2%
“Life Threatening or Disabling”	35 (37)	10.8%	105 (110)	35.0%	45 (48)	14.1%	113 (121)	38.0%
“Major Bleed”	80 (82)	24.9%	103 (108)	34.4%	85 (95)	26.6%	108 (117)	36.2%
Major Vascular Complication	21 (21)	6.5%	5 (5)	1.7%	22 (22)	6.8%	6 (6)	2.0%
Acute Kidney Injury	16 (16)	5.0%	43 (43)	14.3%	16 (16)	5.0%	43 (43)	14.3%
MI	3 (3)	0.9%	2 (2)	0.7%	7 (7)	2.3%	4 (4)	1.4%
Peri-Procedural	3 (3)	0.9%	2 (2)	0.7%	3 (3)	0.9%	2 (2)	0.7%
Spontaneous	0 (0)	0.0%	0 (0)	0.0%	4 (4)	1.4%	2 (2)	0.8%
Cardiac Perforation	4 (4)	1.2%	0 (0)	0.0%	4 (4)	1.2%	0 (0)	0.0%
Cardiogenic Shock	6 (6)	1.9%	8 (8)	2.7%	6 (6)	1.9%	8 (8)	2.7%
Cardiac Tamponade	5 (5)	1.5%	3 (3)	1.0%	6(6)	1.9%	4 (4)	1.3%
Valve Endocarditis	0 (0)	0.0%	0 (0)	0.0%	2 (2)	0.7%	3 (3)	1.2%
Valve Thrombosis	0 (0)	0.0%	0 (0)	0.0%	0 (0)	0.0%	0 (0)	0.0%
Valve Embolism/Device Migration	0 (0)	0.0%	0 (0)	0.0%	0 (0)	0.0%	0 (0)	0.0%
MACCE <sup>4</sup>	26 (33)	8.0%	29 (30)	9.7%	65 (85)	20.2%	76 (88)	25.6%
MAE <sup>5,6</sup>	151 (239)	46.7%	NA	NA	177 (331)	54.8%	NA	NA
Aortic Valve Hospitalization	8 (8)	2.5%	11 (12)	3.8%	44 (68)	14.5%	30 (43)	11.3%
New Permanent Pacemaker Implant <sup>7</sup>	64 (65)	26.5%	21 (21)	9.0%	70 (72)	29.1%	33 (33)	14.9%
Permanent Pacemaker Implant <sup>8</sup>	64 (65)	20.1%	21 (21)	7.1%	71 (73)	22.4%	34 (24)	12.1%

Event	0-30 Days				0-12 Months			
	TAVR N=323		SAVR N=300		TAVR N=323		SAVR N=300	
	# Pts (#Event)	K-M Rate (%)						
<p><sup>1</sup> Valve-related death is any death caused by prosthetic valve dysfunction, valve thrombosis, embolism, bleeding event, or implanted valve endocarditis or related to reintervention on the operated valve.</p> <p><sup>2</sup> For TAVR, periprocedural transfusions meeting VARC I major and life-threatening bleeding criteria were adjudicated as events by the CEC irrespective of whether an overt bleeding complication had occurred. Since peri-procedural transfusions meeting VARC I criteria may be considered standard of care for SAVR procedures depending on the clinical circumstances, the same criteria were not applied and evidence of an overt bleeding complication (in addition to units transfused) were required to adjudicate an event for SAVR only. This makes a direct comparison of the CEC adjudicated bleeding rates in the trial inappropriate. For this reason, CEC adjudicated bleeding complications are shown for TAVR only.</p> <p><sup>3</sup> For the transfusion-based reclassification of bleeding events, units transfused were summed during the procedure, on the day of the procedure and the day following the procedure. Patients who received 2-3 units of packed red blood cells or homologous whole blood were considered to have had a “major bleeding complication” and patients receiving ≥4 units were considered to have had a “life-threatening or disabling bleeding complication” for both TAVR and SAVR. The nomenclature of the original adjudication was applied for consistency with this transfusion based re-classification.</p> <p><sup>4</sup> MACCE includes all-cause death, MI, all stroke, reintervention, cardiac perforation, cardiac tamponade, cardiogenic shock, valve embolism/device migration, prosthetic valve dysfunction, acute kidney injury, major vascular complication, life threatening of disabling bleed, major bleed, valve endocarditis VARC I Definitions.</p> <p><sup>5</sup> MAE includes all death, MI, all stroke, reintervention, cardiac perforation, cardiac tamponade, cardiogenic shock, valve embolism/device migration, prosthetic valve dysfunction, acute kidney injury, major vascular complication, life threatening of disabling bleed, major bleed, valve endocarditis VARC I Definitions.</p> <p><sup>6</sup> Bleeding complications and MAE rate cells have been intentionally left blank for SAVR in this table due to differing definitions employed for bleeding complications have made comparison of the rates to TAVR inappropriate.</p> <p><sup>7</sup> Patients with pacemaker or ICD at baseline are not included.</p> <p><sup>8</sup> Patients with pacemaker or ICD at baseline are included.</p>								

**Table 11: High Risk Adverse Event Summary – Non-Iliofemoral As Treated Population**

Event	0-30 Days				0-12 Months			
	TAVR N=67		SAVR N=57		TAVR N=67		SAVR N=57	
	# Pts (#Event)	K-M Rate (%)						
All-Cause Mortality	2 (2)	3.0%	3 (3)	5.3%	12 (12)	18.1%	15 (15)	27.3%
Cardiovascular	2 (2)	3.0%	3 (3)	5.3%	8 (8)	12.4%	9 (9)	16.8%
Valve-Related <sup>1</sup>	1 (1)	1.5%	1 (1)	1.8%	3 (3)	4.8%	3 (3)	6.0%
Non-Cardiovascular	0 (0)	0.0%	0 (0)	0.0%	4 (4)	6.6%	6 (6)	12.6%
Reintervention	1 (1)	1.5%	0 (0)	0.0%	1 (1)	1.5%	0 (0)	0.0%
Surgical	1 (1)	1.5%	0 (0)	0.0%	1 (1)	1.5%	0 (0)	0.0%
Percutaneous	0 (0)	0.0%	0 (0)	0.0%	0 (0)	0.0%	0 (0)	0.0%
All Stroke	3 (3)	4.5%	7 (8)	12.3%	5 (5)	7.7%	12 (13)	22.3%
Major Stroke	3 (3)	4.5%	5 (5)	8.8%	4 (4)	6.1%	10 (10)	18.7%
Minor Stroke	0 (0)	0.0%	3 (3)	5.3%	1 (1)	1.6%	3 (3)	5.3%
CEC Adjudicated Bleed <sup>2, 6</sup>	43 (49)	64.2%	NA	NA	43 (50)	64.2%	NA	NA

Event	0-30 Days				0-12 Months			
	TAVR N=67		SAVR N=57		TAVR N=67		SAVR N=57	
	# Pts (#Event)	K-M Rate (%)						
Life Threatening or Disabling	16 (19)	23.9%	NA	NA	17 (20)	25.5%	NA	NA
Major Bleed	30 (30)	45.1%	NA	NA	30 (30)	45.1%	NA	NA
Re-Classified Bleed <sup>3</sup>	44 (51)	65.7%	39 (40)	68.4%	44 (52)	65.7%	42 (52)	74.3%
“Life Threatening or Disabling”	18 (21)	26.9%	20 (20)	35.1%	19 (22)	28.5%	23 (29)	40.5%
“Major Bleed”	29 (30)	43.6%	20 (20)	35.1%	29 (30)	43.6%	22 (23)	39.8%
Major Vascular Complication	2 (2)	3.0%	1 (1)	1.8%	2 (2)	3.0%	1 (1)	1.8%
Acute Kidney Injury	7 (7)	10.6%	11 (11)	19.3%	7 (7)	10.6%	11 (11)	19.3%
MI	0 (0)	0.0%	1 (1)	1.8%	0 (0)	0.0%	1 (1)	1.8%
Peri-Procedural	0 (0)	0.0%	0 (0)	0.0%	0 (0)	0.0%	0 (0)	0.0%
Spontaneous	0 (0)	0.0%	1 (1)	1.8%	0 (0)	0.0%	1 (1)	1.8%
Cardiac Perforation	1 (1)	1.5%	0 (0)	0.0%	1 (1)	1.5%	0 (0)	0.0%
Cardiogenic Shock	3 (3)	4.5%	3 (3)	5.3%	3 (3)	4.5%	3 (3)	5.3%
Cardiac Tamponade	1 (1)	1.5%	1 (1)	1.9%	1 (1)	1.5%	1 (1)	1.9%
Valve Endocarditis	0 (0)	0.0%	0 (0)	0.0%	0 (0)	0.0%	1 (1)	2.3%
Valve Thrombosis	0 (0)	0.0%	0 (0)	0.0%	0 (0)	0.0%	0 (0)	0.0%
Valve Embolism/Device Migration	0 (0)	0.0%	0 (0)	0.0%	0 (0)	0.0%	0 (0)	0.0%
MACCE <sup>4</sup>	4 (6)	6.1%	8 (12)	14.0%	14 (18)	21.4%	20 (29)	36.1%
MAE <sup>5, 6</sup>	49 (72)	73.1%	NA	NA	52 (86)	77.6%	NA	NA
Aortic Valve Hospitalization	7 (7)	10.7%	7 (7)	12.9%	15 (17)	23.8%	13 (16)	25.2%
New Permanent Pacemaker Implant <sup>7</sup>	12 (12)	22.2%	3 (3)	6.3%	14 (14)	26.3%	3 (3)	6.3%
Permanent Pacemaker Implant <sup>8</sup>	12 (12)	18.2%	4 (4)	7.1%	14 (14)	21.7%	4 (4)	7.1%

<sup>1</sup> Valve-related death is any death caused by prosthetic valve dysfunction, valve thrombosis, embolism, bleeding event, or implanted valve endocarditis or related to reintervention on the operated valve.

<sup>2</sup> For TAVR, periprocedural transfusions meeting VARC I major and life-threatening bleeding criteria were adjudicated as events by the CEC irrespective of whether an overt bleeding complication had occurred. Since peri-procedural transfusions meeting VARC I criteria may be considered standard of care for SAVR procedures depending on the clinical circumstances, the same criteria were not applied and evidence of an overt bleeding complication (in addition to units transfused) were required to adjudicate an event for SAVR only. This makes a direct comparison of the CEC adjudicated bleeding rates in the trial inappropriate. For this reason, CEC adjudicated bleeding complications are shown for TAVR only.

<sup>3</sup> For the transfusion-based reclassification of bleeding events, units transfused were summed during the procedure, on the day of the procedure and the day following the procedure. Patients who received 2-3 units of packed red blood cells or homologous whole blood were considered to have had a “major bleeding complication” and patients receiving ≥4 units were considered to

Event	0-30 Days				0-12 Months			
	TAVR N=67		SAVR N=57		TAVR N=67		SAVR N=57	
	# Pts (#Event)	K-M Rate (%)						

have had a “life-threatening or disabling bleeding complication” for both TAVR and SAVR. The nomenclature of the original adjudication was applied for consistency with this transfusion based re-classification.

<sup>4</sup> MACCE includes all-cause death, myocardial infarction (MI), all stroke, and reintervention.

<sup>5</sup> MAE includes all death, MI, all stroke, reintervention, cardiac perforation, cardiac tamponade, cardiogenic shock, valve embolism/device migration, prosthetic valve dysfunction, acute kidney injury, major vascular complication, life threatening of disabling bleed, major bleed, valve endocarditis VARC I Definitions.

<sup>6</sup> Bleeding complications and MAE rate cells have been intentionally left blank for SAVR in this table due to differing definitions employed for bleeding complications have made comparison of the rates to TAVR inappropriate.

<sup>7</sup> Patients with pacemaker or ICD at baseline are not included.

<sup>8</sup> Patients with pacemaker or ICD at baseline are included.

### 11.1.3.4 Additional Effectiveness Data

Improvement in NYHA functional classification was evaluated for As Treated TAVR and SAVR patients. An evaluation of cardiac symptom severity based on NYHA classification was conducted at several evaluation time points through the first year of follow-up (Figure 45). Change from baseline to 12 months was evaluated for measures of forward flow hemodynamic performance (EOA and mean gradient) for TAVR and SAVR patients (Figure 46).

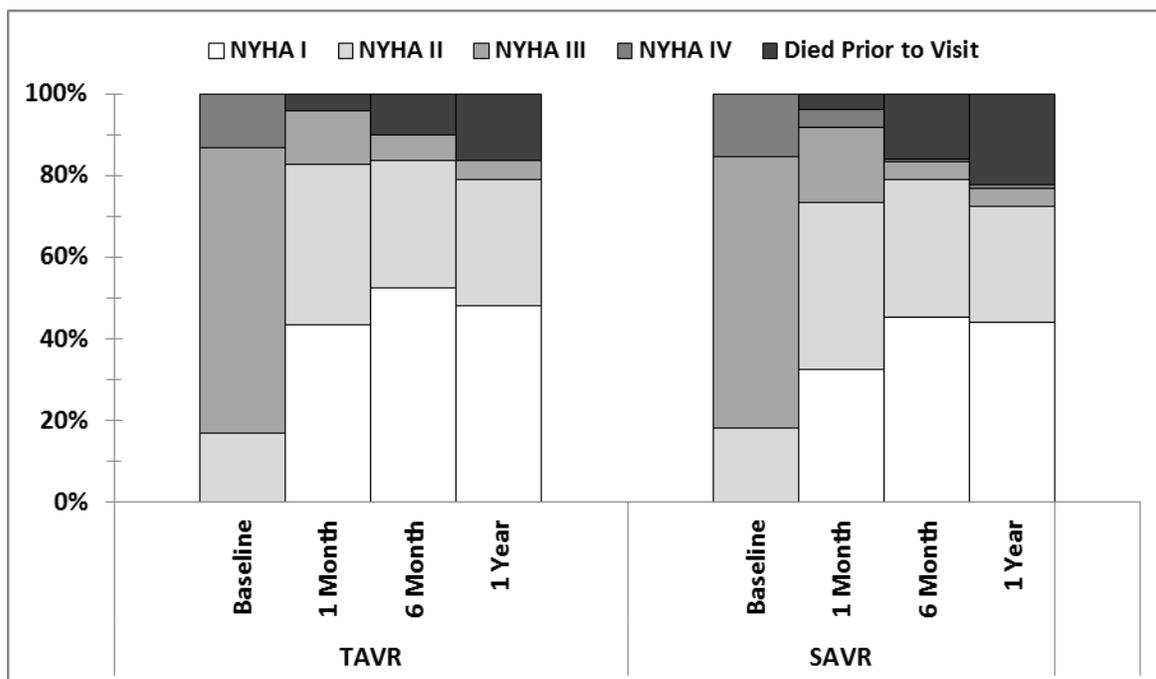
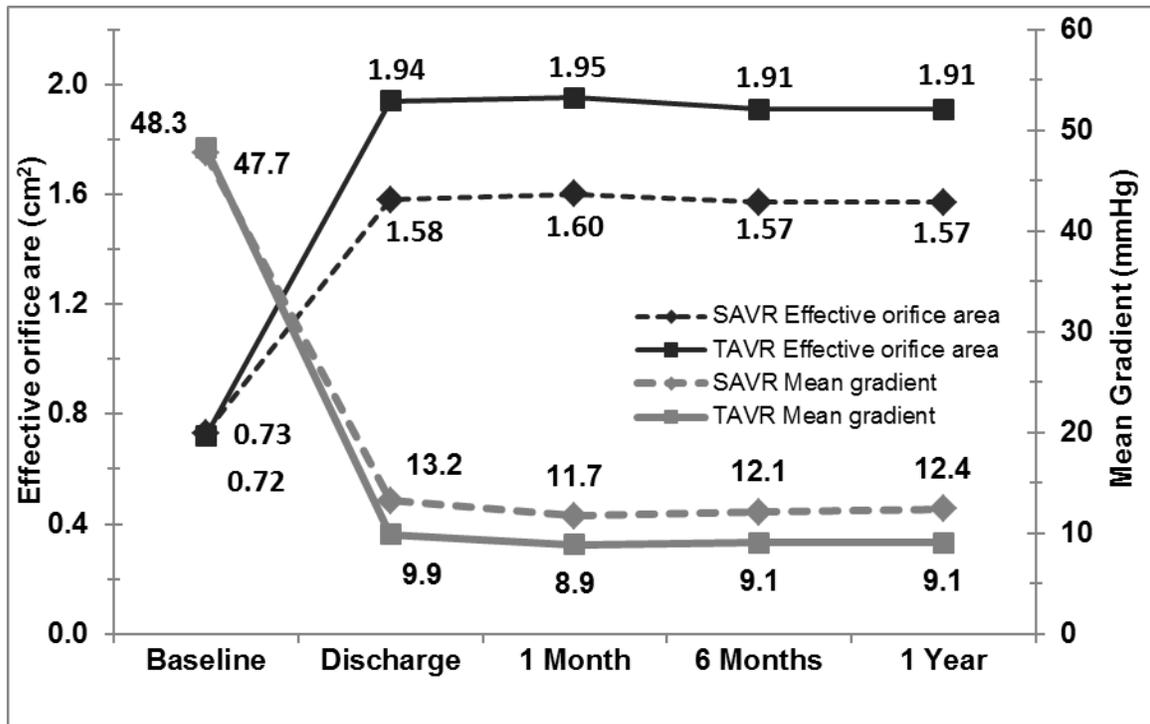


Figure 39: High Risk NYHA Classification By Visit –As Treated Population



**Figure 40: High Risk EOA and Mean Gradient by Visit –HR Cohort Implanted TAVR & SAVR population**

Figure 47 shows total aortic regurgitation (AR) severity over time in the Implanted TAVR and SAVR arms. These data are presented per valve size as well as for all sizes combined for both arms of the High Risk cohort.

The valve sizes had a relatively similar distribution of total AR during follow-up, although at each evaluation a greater percentage of subjects with a 26 mm valve had no AR and a smaller percentage had moderate or greater AR than for the 29 and 31 mm valves. All valve sizes pooled are shown for the SAVR treatment arm. A notably smaller percentage of subjects in the TAVR treatment arm had no AR than in the SAVR treatment arm (28.6% vs. 68.2% at 12 months) and a greater percentage of subjects in the TAVR treatment arm had moderate or greater AR (7.1% vs. 1.3% at 12 months).

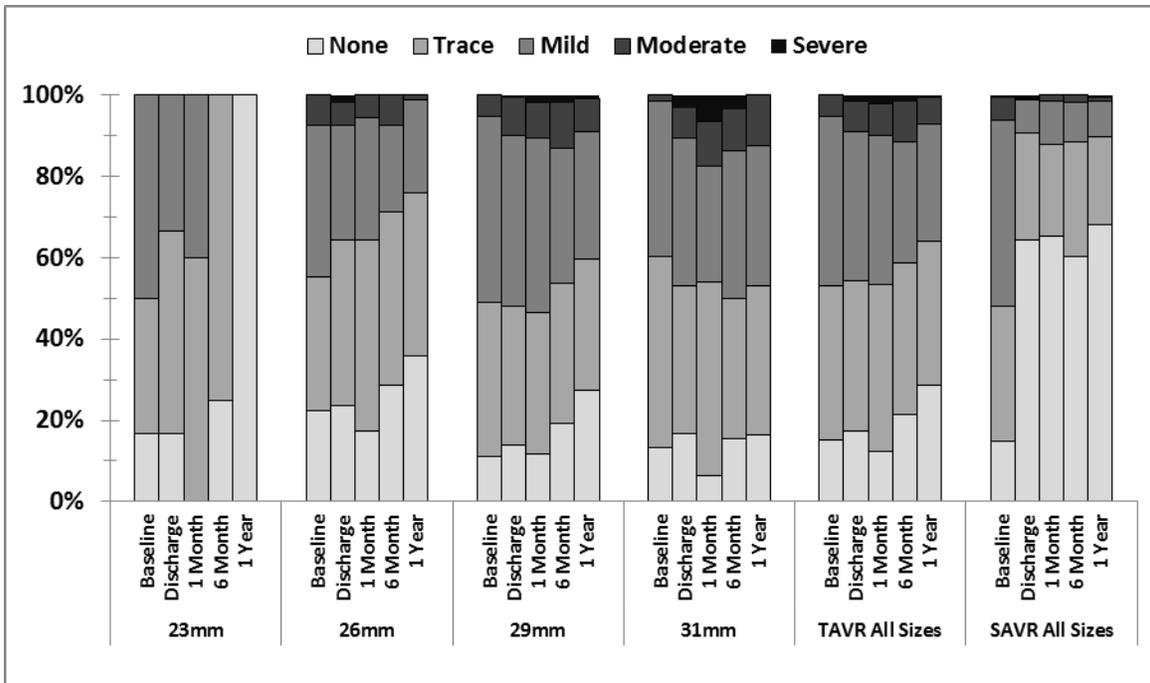
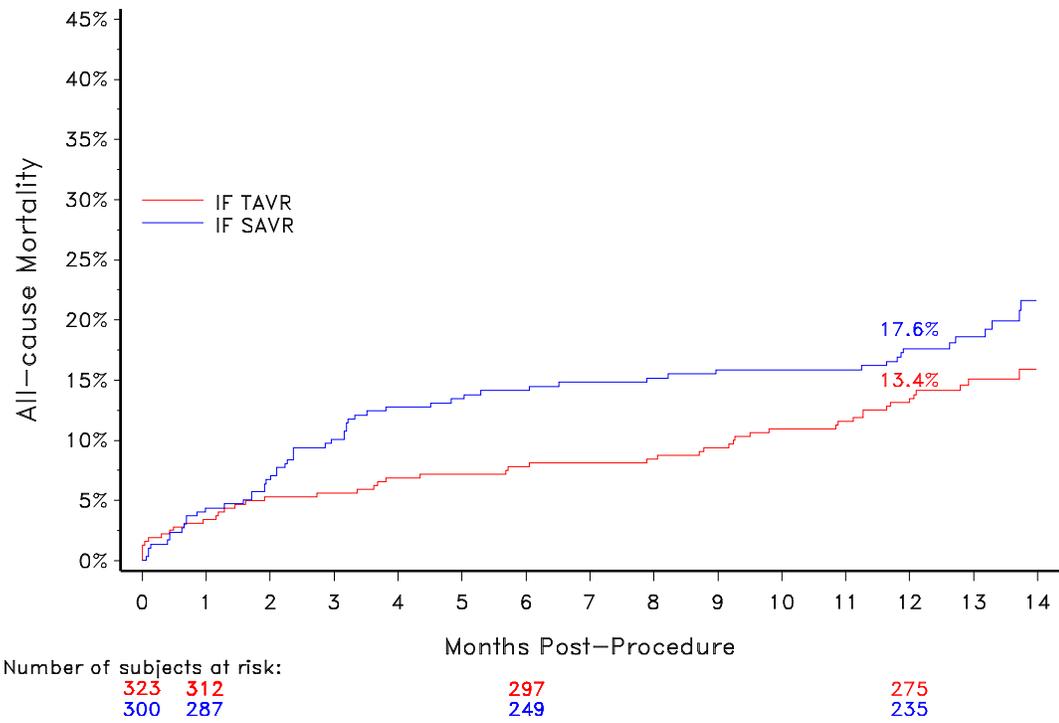


Figure 41: High Risk Total Aortic Regurgitation By Visit (Core Lab) – Implanted Population

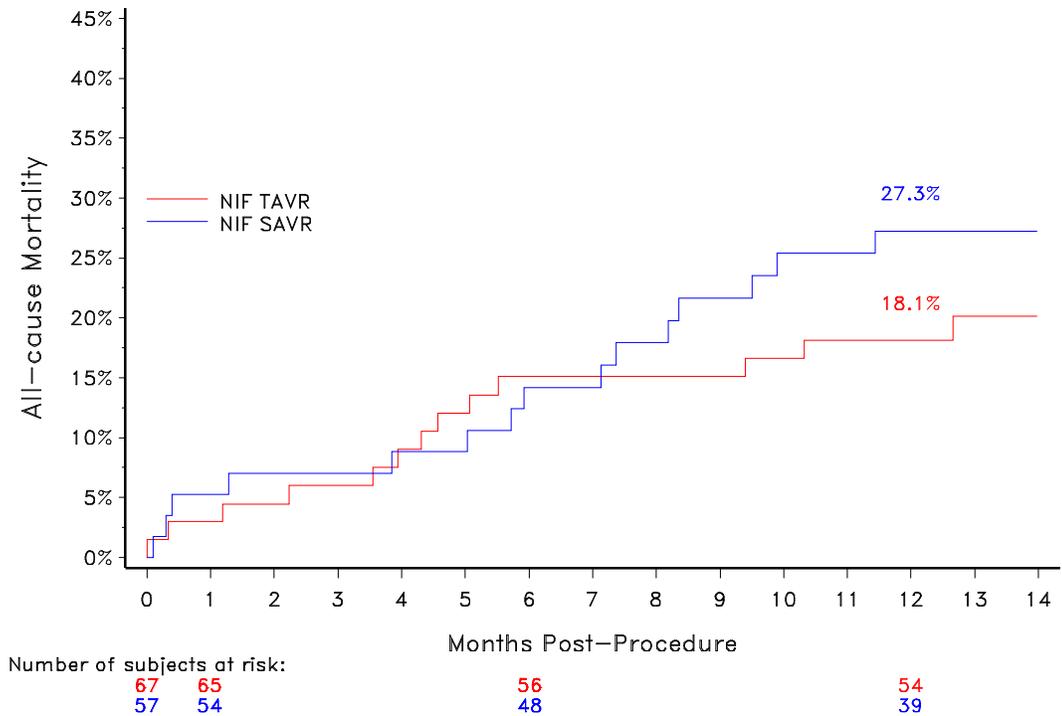
#### 11.1.4 Additional Study Observations

##### Primary Endpoint Stratified by Access Route

The study was powered to demonstrate non-inferiority of TAVR compared to SAVR for the primary endpoint for all patients (iliofemoral and non-iliofemoral) pooled. It was pre-specified that the primary endpoint would be assessed for different access route subgroups independently, but this assessment was not powered and would not be the basis for assessing success or failure of the primary endpoint. The all-cause mortality rates are shown in Figure 39 for the iliofemoral subgroup and Figure 40 for the non-iliofemoral subgroup.



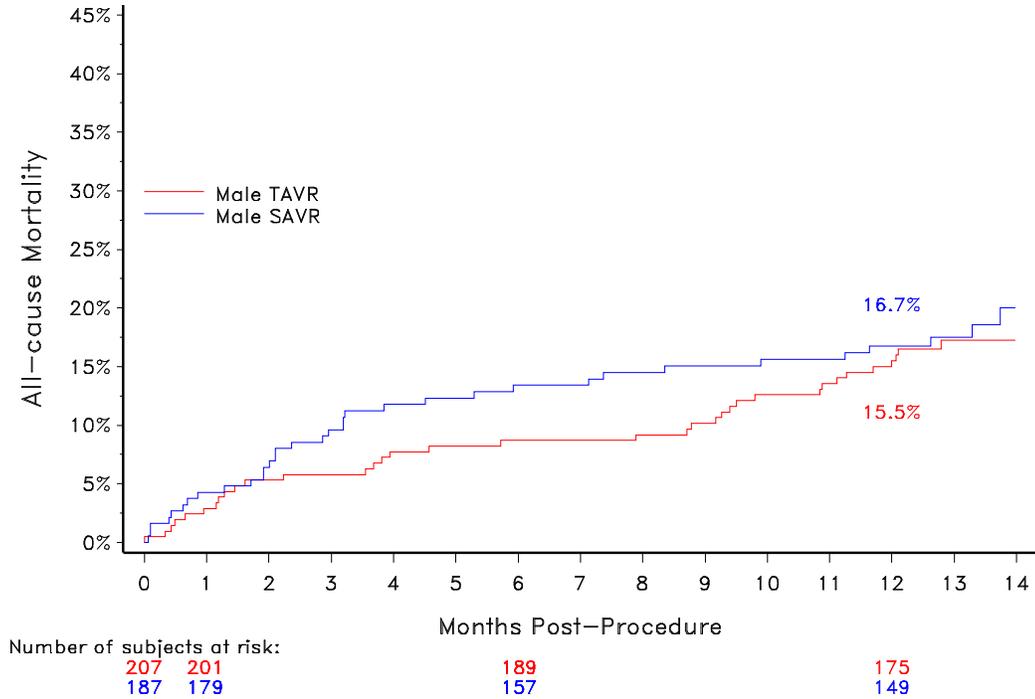
**Figure 42: All-Cause Mortality – Iliofemoral As Treated Population**



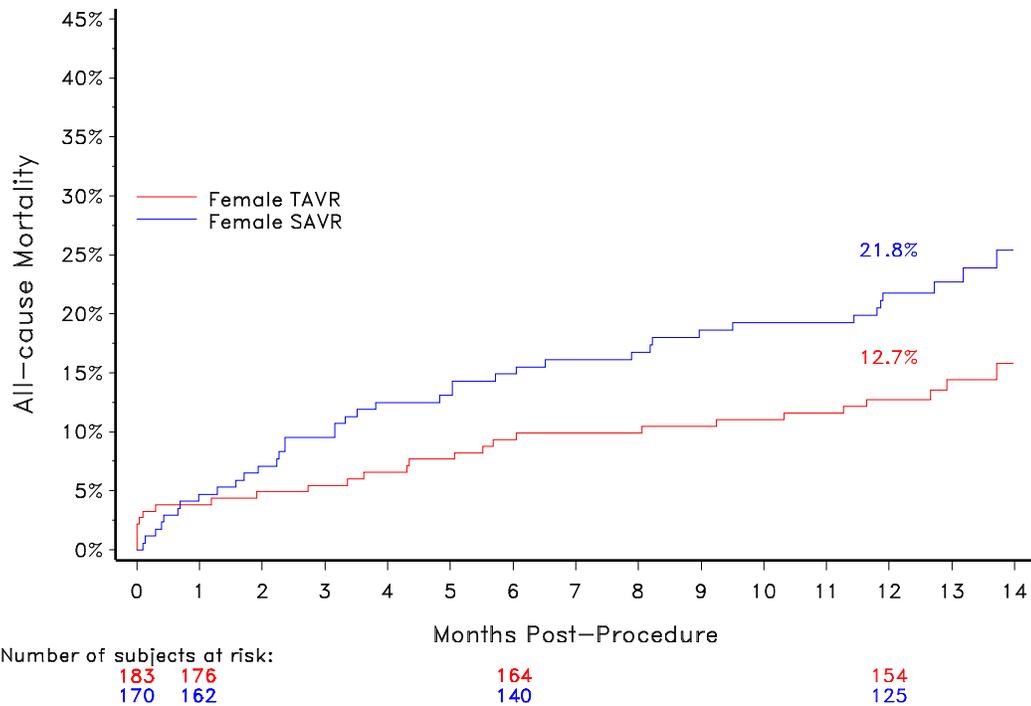
**Figure 43: All-Cause Mortality – Non-Iliofemoral As Treated Population**

## Gender Analysis

The primary endpoint and the powered secondary endpoint of MACCE rate were examined for gender differences as shown in Figure 41 and Figure 42.



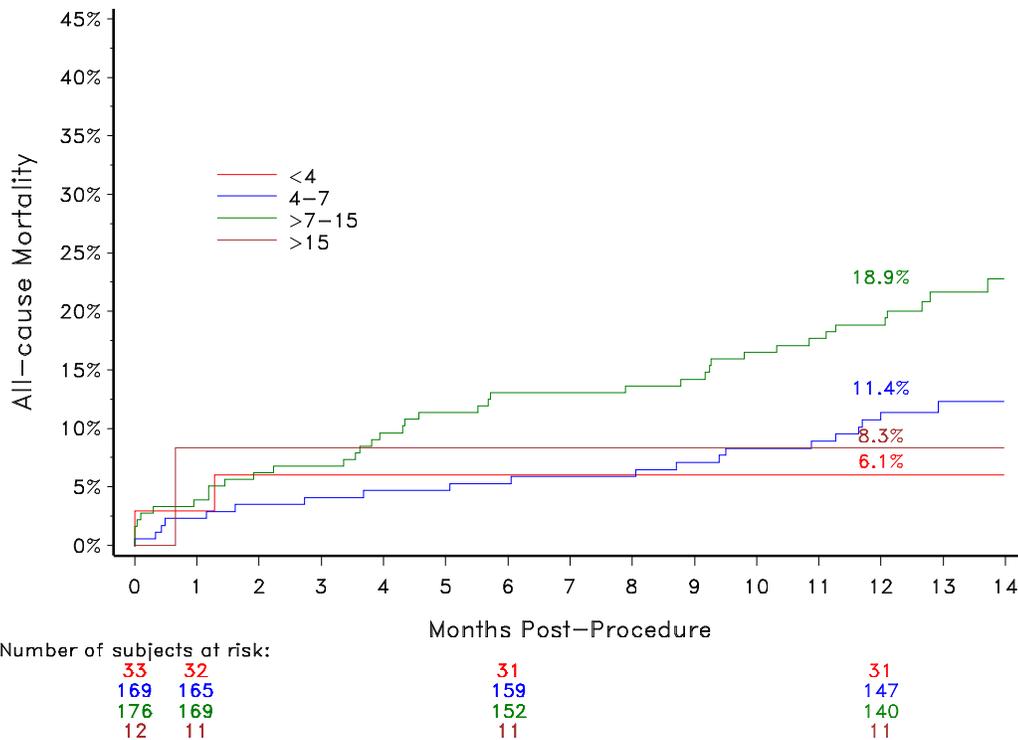
**Figure 44: All-Cause Mortality at 12 Months for Male Patients – As Treated Population**



**Figure 45: All-Cause Mortality at 12 Months for Female Patients – As Treated Population**

### Mortality Stratified by STS Score

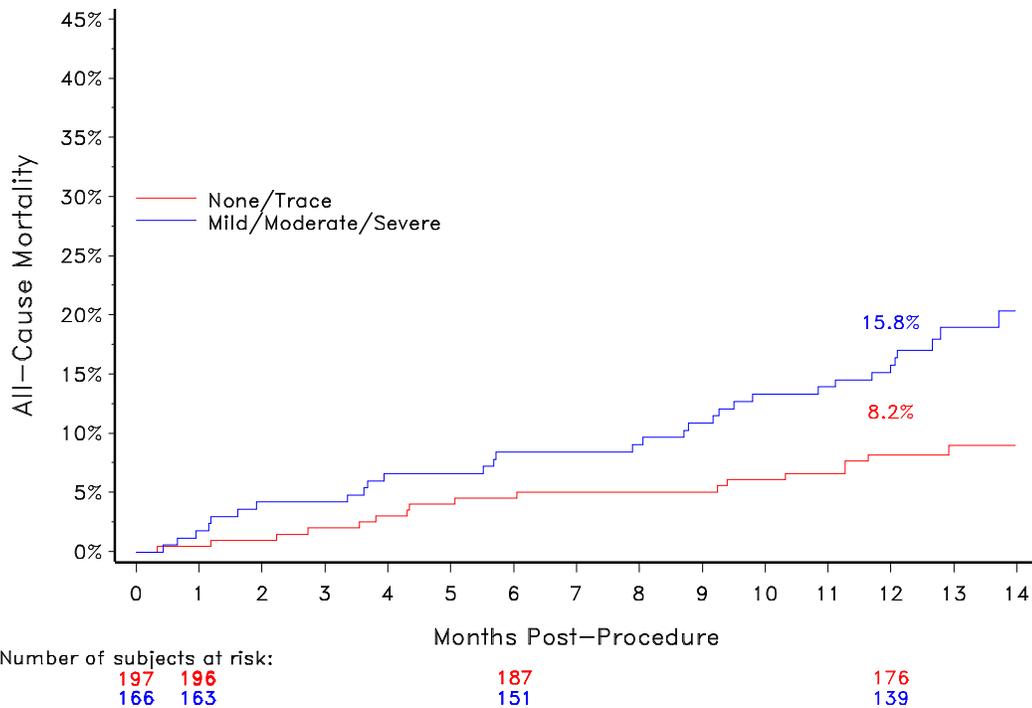
An analysis was performed for TAVR patients to examine the relationship between all-cause mortality and STS predicted risk of mortality at baseline (Figure 43). Patients were stratified by STS score with the subgroups being STS <4, STS 4–7, STS >7–15, and STS >15.



**Figure 46: High Risk All-Cause Mortality by STS – TAVR As Treated Population**

### Post-Implant Aortic Regurgitation and All-Cause Mortality

A post hoc subgroup analysis was performed for all TAVR patients (iliofemoral and non-iliofemoral) of the Implanted population to investigate the relationship between all-cause mortality and severity of aortic regurgitation at discharge (7 days post procedure or discharge, whichever is first). Two subgroups of iliofemoral patients with none/trace and greater than or equal to mild total aortic regurgitation at discharge were analyzed. The results from the analysis are shown in Figure 44 which show that residual aortic regurgitation at discharge appeared to be associated with long-term mortality in the TAVR patients. However, it was also noted that there were some differences in important baseline clinical characteristics of the patients between the two subgroups, as summarized in Table 12. As a result, it is not clear whether there was a causal relationship between residual aortic regurgitation and mortality. Nevertheless, the incidence of residual aortic regurgitation and its apparent association with late-term mortality will need to be carefully monitored in post-approval follow-up.



**Figure 47: All-Cause Mortality by Severity of Aortic Regurgitation (None/Trace vs Mild/Moderate/Severe) – TAVR Implanted Population**

**Table 12: Patient Demographics and Clinical Characteristics Stratified by AR – TAVR Implanted Population**

	None/Trace AR N=197	Mild/Moderate/Severe AR N=166
<b>DEMOGRAPHICS</b>		
Age (yrs)	82.7 ± 7.4	83.8 ± 6.4
Male	46.7% (92/197)	60.8% (101/166)
<b>NYHA Class</b>		
II	16.2% (32/197)	12.7% (21/166)
III	65.0% (128/197)	66.9% (111/166)
IV	18.8% (37/197)	20.5% (34/166)
STS Score (Risk of Mortality, %)	7.3 ± 3.1	7.2 ± 2.8
Coronary Artery Disease	73.1% (144/197)	77.7% (129/166)
Previous MI	25.4% (50/197)	22.9% (38/166)
<b>Previous Interventions</b>		
Coronary Artery Bypass Surgery	30.5% (60/197)	28.9% (48/166)
Percutaneous Coronary Intervention	35.5% (70/197)	31.9% (53/166)
Balloon Valvuloplasty	5.6% (11/197)	5.4% (9/166)
Cerebrovascular Disease	22.4% (44/196)	25.8% (42/163)
Prior Stroke	10.2% (20/197)	15.1% (25/166)
Peripheral Vascular Disease	44.7% (88/197)	34.1% (56/164)

	<b>None/Trace AR N=197</b>	<b>Mild/Moderate/Severe AR N=166</b>
Chronic Lung Disease/COPD	39.6% (78/197)	50.0% (83/166)
Home Oxygen	10.7% (21/196)	13.9% (23/166)
Creatinine Level >2 mg/dl	2.0% (4/197)	4.8% (8/166)
Atrial Fibrillation/Atrial Flutter	38.1% (75/197)	45.5% (75/165)
Pre-Existing Permanent Pacemaker Placement / ICD	19.3% (38/197)	26.5% (44/166)
Aorta Calcification <sup>1</sup>		
Severe	14.2% (28/197)	9.7% (16/165)
Porcelain	0.5% (1/197)	0.0% (0/165)
Chest Wall Deformity	2.5% (5/197)	2.4% (4/166)
Hostile Mediastinum	4.6% (9/197)	3.6% (6/166)
Wheelchair Bound	3.6% (7/197)	3.6% (6/166)
1. Aorta Calcification is measured on screening CT Angiogram. Plus-minus values present the mean ± standard deviation.		

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## 11.2 Extreme Risk Cohort

The CoreValve™ U.S. Pivotal Trial Extreme Risk cohort was a prospective, non-randomized, unblinded, multi-center investigational study. All enrolled patients were assigned to transcatheter aortic valve replacement (TAVR) with the Medtronic CoreValve™ system. The purpose of this clinical study was to evaluate the safety and effectiveness of the Medtronic CoreValve™ system in the treatment of symptomatic severe aortic stenosis in patients requiring aortic valve replacement with predicted operative mortality or serious, irreversible morbidity risk of  $\geq 50\%$  at 30 days (Extreme Risk).

This Extreme Risk cohort enrolled 656 patients with symptomatic severe aortic stenosis (500 iliofemoral and 156 non-iliofemoral patients) at 41 of the 43 activated centers in the United States with baseline characteristics described in Table 13. Severe aortic stenosis was defined as an aortic valve area of  $\leq 0.8 \text{ cm}^2$  or aortic valve area index  $\leq 0.5 \text{ cm}^2$ , a mean aortic valve gradient of  $>40 \text{ mm Hg}$  or jet velocity  $>4 \text{ m/sec}$ . The primary endpoint was all-cause mortality or major stroke at 12 months. The primary analysis compared the primary endpoint against a pre-specified performance goal.

Patients received the CoreValve™ bioprosthesis either through the iliofemoral access route or through the non-iliofemoral (subclavian and direct aortic) access routes. An attempted implant was performed on 489 patients via iliofemoral access and who embody the Attempted Implant<sup>2</sup> iliofemoral cohort (n=489), which was the basis for assessment of the primary endpoint. Of the 489 attempted implants via iliofemoral access, 486 patients were implanted with the CoreValve™ bioprosthesis and embody the Implanted<sup>3</sup> iliofemoral cohort (n=486), which was the basis for secondary endpoints related to hemodynamic data.

An attempted implant was performed on 150 patients via non-iliofemoral access and these patients embody the Attempted Implant cohort. Of these 150 patients, 148 were implanted with the CoreValve™ bioprosthesis and embody the Implanted non-iliofemoral cohort. Per protocol, non-iliofemoral patients were not included in the primary analysis due to anticipated heterogeneity in patient selection and outcome. Compared with patients enrolled in the iliofemoral cohort, patients in the non-iliofemoral cohort were, generally, at a higher risk with respect to specific critical co-morbidities.

The following data summarize the results from the Extreme Risk cohort (iliofemoral and non-iliofemoral).

### 11.2.1 Patient Population

The patient characteristics analyzed for the iliofemoral and non-iliofemoral enrolled cohorts include demographics, clinical characteristics, medical history, and potentially prohibitive anatomic factors for surgical aortic valve replacement (SAVR) and assessments for co-morbidity, frailty, and disability (Table 13). The ability of a patient to obtain a functional recovery after SAVR is largely based on the presence of significant co-morbidities, frailties, and disabilities, with the combination of the factors having higher weight than the individual

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<sup>2</sup> The Attempted Implant population consisted of all patients with an attempted procedure, defined as when the patient was brought into the procedure room and any of the following had occurred: anesthesia administered, vascular line placed, TEE placed, or any monitoring line placed.

<sup>3</sup> The Implanted population consisted of all Attempted Implant patients who were actually implanted with the CoreValve™ bioprosthesis.

factors alone. As detailed in Table 13, a high proportion of the CoreValve™ Extreme Risk patients had significant co-morbidities, frailties, or disabilities, which established the study population as “Extreme Risk.” The mean age for patients participating in the trial was approximately 83 years old, and slightly less than 50% of patients were male. The mean Society of Thoracic Surgeons (STS) score was approximately 10. Greater than 90% of all patients were in NYHA classes III or IV.

Additionally, coronary artery disease was present in approximately 80% of patients, and greater than 30% of patients had previous MI. Peripheral vascular disease, COPD, and home oxygen use were more prevalent for non-iliofemoral patients.

**Table 13: Extreme Risk Baseline Characteristics and Echocardiographic Findings (All Enrolled)**

Demographic	Iliofemoral N=500	Non-Iliofemoral N=156
Age (years)	83.1 ± 8.6 (500)	81.6 ± 7.7 (156)
Gender (Male)	48.0% (240/500)	44.9% (70/156)
NYHA Classification		
II	8.6% (43/500)	8.3% (13/156)
III	63.6% (318/500)	66.0% (103/156)
IV	27.8% (139/500)	25.6% (40/156)
STS Score (Risk of Mortality, %)	10.3 ± 5.5	10.5 ± 5.7
Coronary Artery Disease	81.8% (409/500)	78.8% (123/156)
Previous MI	31.0% (155/500)	31.4% (49/156)
Previous Interventions		
Coronary Artery Bypass Surgery	39.0% (195/500)	41.0% (64/156)
Percutaneous Coronary Intervention	37.4% (187/500)	30.1% (47/156)
Balloon Valvuloplasty	20.4% (102/500)	22.4% (35/156)
Cerebral Vascular Disease	24.0% (119/496)	28.4% (44/155)
Prior Stroke	13.6% (68/499)	14.2% (22/155)
Peripheral Vascular Disease	36.0% (179/497)	59.0% (92/156)
Chronic Lung Disease/COPD	59.6% (298/500)	69.9% (109/156)
Home Oxygen	30.8% (154/500)	41.7% (65/156)
Creatinine Level >2 mg/dl	4.6% (23/500)	2.6% (4/156)
Atrial Fibrillation/Atrial Flutter	47.4% (236/498)	48.4% (75/155)
Preexisting Permanent Pacemaker Placement/ICD	25.8% (129/500)	24.4% (38/156)
Aorta Calcification <sup>1</sup> : Severe/Porcelain		
Severe	16.6% (83/499)	17.5% (27/154)

Demographic	Iliofemoral N=500	Non-Iliofemoral N=156
Porcelain	5.2% (26/499)	7.8% (12/154)
Chest Wall Deformity	5.6% (28/500)	1.9% (3/156)
Hostile Mediastinum	12.0% (60/499)	9.0% (14/156)
Cirrhosis of the Liver	3.0% (15/500)	1.3% (2/156)
Wheelchair Bound	16.6% (83/500)	12.2% (19/156)
Echocardiographic Findings		
Ejection Fraction (Visual Estimate, %)	53.2 ± 13.6 (498)	54.3 ± 15.3 (156)
Aortic Valve Area (cm <sup>2</sup> )	0.67 ± 0.25 (485)	0.62 ± 0.23 (153)
Mean Gradient across Aortic Valve (MGV <sub>2</sub> , mm Hg)	47.72 ± 13.53 (498)	49.67 ± 16.85 (156)
Mitral Regurgitation: Moderate/Severe	24.2% (120/496)	23.2% (36/155)
1. Aorta Calcification is measured on screening CT Angiogram. Plus-minus values present the mean ± standard deviation.		

### 11.2.2 Procedure Data

Table 14 provides a summary of the transcatheter valve implantation procedures for the iliofemoral and non-iliofemoral cohorts, respectively. Overall device success rate was 84.6% for the iliofemoral cohort and 88.7% for the non-iliofemoral cohort. Procedure success was defined as device success and absence of in-hospital MACCE and procedure success rates were 77.6% and 77.5% for the iliofemoral and non-iliofemoral cohorts, respectively.

**Table 14: Extreme Risk TAVR Procedure Data (Attempted Implant)**

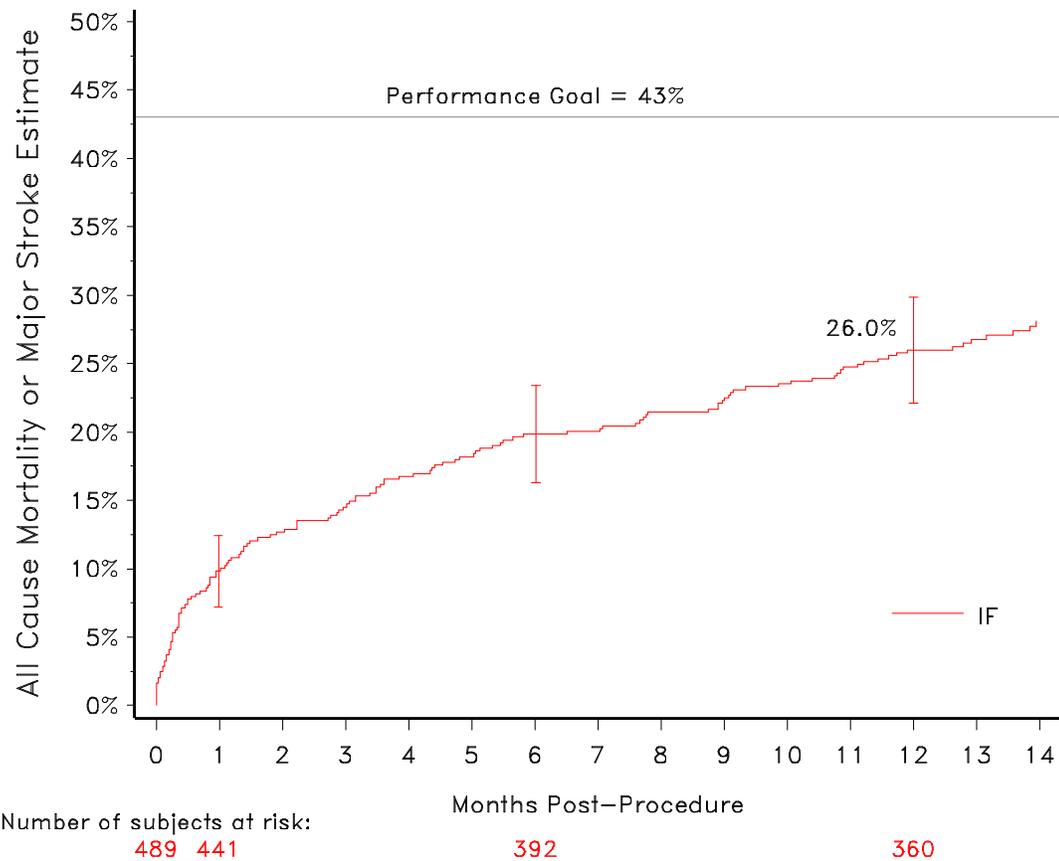
	Iliofemoral N=489	Non-Iliofemoral N=150
Time to Procedure (days)	8.9 ± 12.3 (489)	10.2 ± 15.5 (150)
Total Time in Cath Lab or OR (min)	214.8 ± 64.9 (486)	258.7 ± 72.5 (148)
Total Procedure Time (min) (skin to skin)	66.1 ± 39.0 (484)	60.5 ± 46.5 (145)
General Anesthesia	94.4% (459/486)	99.3% (147/148)
Valve-in-Valve Procedure	2.5% (12/486)	0.7% (1/148)
Emergent Operation Due to Device or Procedure	0.0% (0/486)	0.0% (0/148)
Number of Devices Used		
0	0.6% (3/489)	1.3% (2/150)
1	93.3% (456/489)	94.7% (142/150)
2	6.1% (30/489)	4.0% (6/150)
Valve Size Implanted		
23 mm	2.5% (12/486)	6.1% (9/148)

	<b>Iliofemoral N=489</b>	<b>Non-Iliofemoral N=150</b>
26 mm	35.0% (170/486)	41.2% (61/148)
29 mm	58.4% (284/486)	49.3% (73/148)
31 mm	4.1% (20/486)	3.4% (5/148)
Device Success <sup>1</sup>	84.6% (397/469)	88.7% (125/141)
Procedure Success <sup>2</sup>	77.6% (370/477)	77.5% (110/142)
<p>1. Device success is defined as deployment, only 1 valve implanted, only 1 valve in correct anatomic location, EOA &gt;1.2 cm<sup>2</sup> for 26, 29, and 31 mm and ≥0.9 cm<sup>2</sup> for 23 mm, mean gradient &lt;20mm Hg, and aortic regurgitation &lt; moderate.</p> <p>2. Procedure success is defined as device success and absence of in-hospital MACCE.</p> <p>Plus-minus values present the mean ± standard deviation.</p>		

## 11.2.3 Safety and Effectiveness Results

### 11.2.3.1 Primary Safety and Effectiveness Endpoint

The estimated K-M rate for all-cause mortality or major stroke at 12 months for the Attempted Implant iliofemoral cohort was 26.0% with an upper 2-sided 95% CI of 29.9%. The upper 95% CI was lower than the pre-specified Performance Goal rate of 43% for this primary endpoint (p<0.0001) (Figure 48).



**Figure 48: Extreme Risk Primary Endpoint: All-Cause Mortality or Major Stroke Kaplan-Meier Event Rate — Iliofemoral Attempted Implant**

Table 15 and Table 16 provide a summary of the adverse events (AEs) that occurred in this study for the iliofemoral and non-iliofemoral cohorts. AEs for the Attempted Implant populations are summarized and Kaplan-Meier (K-M) rates are provided.

The rates of all-cause mortality or major stroke (the primary endpoint of the trial) were 26.0% and 39.4% at 1 year for the iliofemoral and non-iliofemoral cohorts, respectively. Mortality was the primary driver of the primary endpoint for both the iliofemoral and non-iliofemoral cohorts and cardiovascular mortality made up the majority of all deaths experienced in both cohorts. The greater event rate of all-cause mortality or major stroke in the non-iliofemoral cohort was expected based on the comorbidities identified in this group of patients.

Several important periprocedural complications including acute kidney injury, myocardial infarction, and major vascular complications generally occurred at similar rates for iliofemoral and non-iliofemoral patients. Bleeding complications were the most frequently observed early adverse events. Early (within 30 days) permanent pacemaker implantation (PPI) occurred in a significant minority of patients in both cohorts.

**Table 15: Extreme Risk Adverse Event Summary – Iliofemoral Attempted Implant**

Event	Iliofemoral N=489					
	0-30 Days			0-12 Months		
	# Events	# Patients	K-M Rate (%)	# Events	# Patients	K-M Rate (%)
All-Cause Mortality or	52	48	9.8%	139	127	26.0%
All-Cause	41	41	8.4%	119	119	24.3%
Cardiovascular	41	41	8.4%	88	88	18.3%
Valve-Related <sup>1</sup>	12	12	2.5%	23	23	5.1%
Neurological Events	80	74	15.5%	141	117	25.3%
All Stroke	20	19	4.0%	34	31	7.0%
Major Stroke	11	11	2.3%	20	19	4.3%
Bleed	191	179	36.7%	236	206	42.8%
Life Threatening	63	62	12.7%	88	83	17.6%
Major Bleed	128	121	24.9%	148	136	28.5%
Major Vascular Complication	44	40	8.2%	45	41	8.4%
Acute Kidney	57	57	11.8%	57	57	11.8%
MI	6	6	1.2%	9	9	2.0%
MACCE <sup>2</sup>	72	60	12.3%	171	143	29.2%
Cardiogenic	13	13	2.7%	13	13	2.7%
Cardiogenic Tamponade	9	9	1.9%	10	10	2.1%
Reintervention	5	5	1.1%	9	8	1.8%
Surgical	0	0	0.0%	0	0	0.0%
Percutaneous	5	5	1.1%	9	8	1.8%
Valve	0	0	0.0%	5	5	1.3%
Valve	0	0	0.0%	0	0	0.0%
Valve Embolism/	0	0	0.0%	1	1	0.2%
New Permanent Pacemaker Implant <sup>3</sup>	105	104	29.4%	125	121	34.9%
Permanent Pacemaker Implant <sup>4</sup>	105	104	21.6%	127	123	26.2%

<sup>1</sup> Valve-related death is any death caused by prosthetic valve dysfunction, valve thrombosis, embolism, bleeding event, or implanted valve endocarditis or related to reintervention on the operated valve.  
<sup>2</sup> MACCE includes all-cause death, myocardial infarction (MI), all stroke, and reintervention.  
<sup>3</sup> Patients with pacemaker or ICD at baseline are not included.  
<sup>4</sup> Patients with pacemaker or ICD at baseline are included.

**Table 16: Extreme Risk Adverse Event Summary – Non-Illofemoral Attempted Implant**

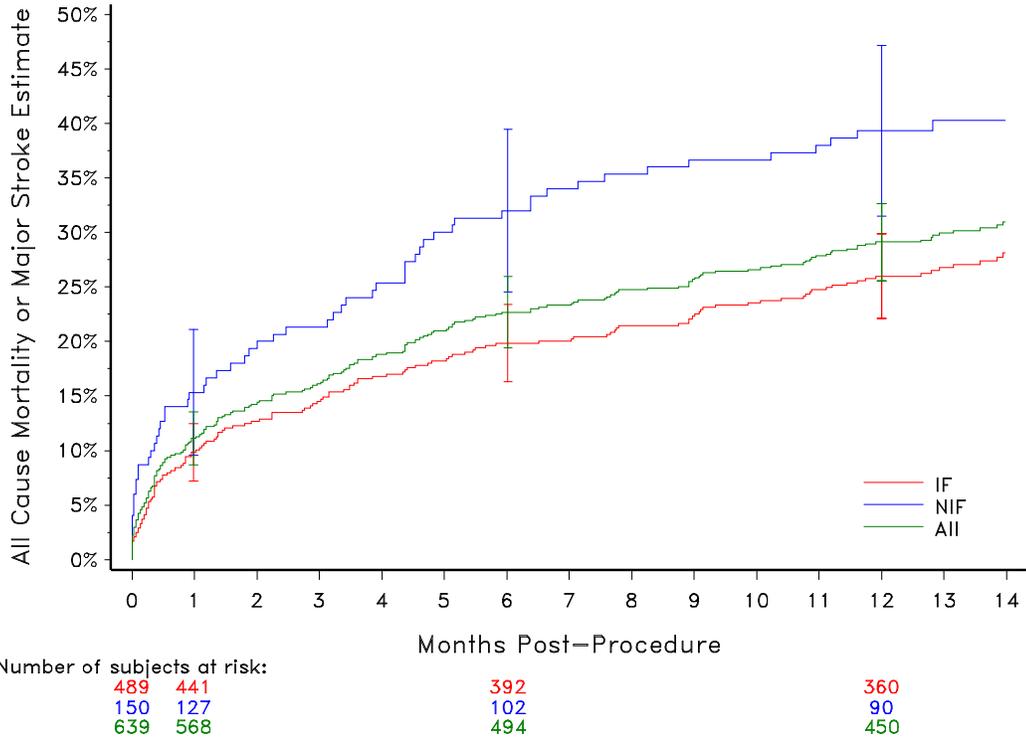
Event	Non-Illofemoral N=150					
	0-30 Days			0-12 Months		
	# Events	# Patients	K-M Rate (%)	# Events	# Patients	K-M Rate (%)
All-Cause Mortality or Major Stroke	28	23	15.3%	67	59	39.4%
All-Cause	17	17	11.3%	54	54	36.0%
Cardiovascular	17	17	11.3%	42	42	28.8%
Valve-Related <sup>1</sup>	4	4	2.8%	7	7	5.4%
Neurological Events	36	32	21.8%	46	40	28.5%
All Stroke	14	13	8.8%	19	18	13.0%
Major Stroke	11	11	7.5%	13	13	9.1%
Bleed	92	87	58.3%	106	96	65.1%
Life Threatening or Major Bleed	36	36	24.2%	43	43	29.4%
Major Bleed	56	55	37.1%	63	60	41.9%
Major Vascular Complication	13	13	8.7%	14	14	9.5%
Acute Kidney	21	21	14.2%	21	21	14.2%
MI	3	3	2.1%	3	3	2.1%
MACCE <sup>2</sup>	34	26	17.3%	77	62	41.4%
Cardiogenic	9	9	6.0%	9	9	6.0%
Cardiogenic Tamponade	2	2	1.3%	2	2	1.3%
Reintervention	0	0	0.0%	1	1	1.0%
Surgical	0	0	0.0%	0	0	0.0%
Percutaneous	0	0	0.0%	1	1	1.0%
Valve	1	1	0.7%	2	2	1.7%
Valve	0	0	0.0%	2	1	0.8%
Valve Embolism/	0	0	0.0%	0	0	0.0%
New Permanent Pacemaker Implant <sup>3</sup>	24	24	22.0%	30	30	28.8%
Permanent Pacemaker Implant <sup>4</sup>	24	24	16.4%	30	30	21.5%

<sup>1</sup> Valve-related death is any death caused by prosthetic valve dysfunction, valve thrombosis, embolism, bleeding event, or implanted valve endocarditis or related to reintervention on the operated valve.  
<sup>2</sup> MACCE includes all-cause death, myocardial infarction (MI), all stroke, and reintervention.  
<sup>3</sup> Patients with pacemaker or ICD at baseline are not included.  
<sup>4</sup> Patients with pacemaker or ICD at baseline are included.

Patients with unsuitable iliofemoral anatomy for placement of an 18-Fr sheath are at a higher risk with respect to specific critical co-morbidities including peripheral vascular disease, cerebrovascular disease, and chronic lung disease. While at a higher risk, these non-iliofemoral patients with suitable axillary/subclavian or direct aortic access may be treated with the CoreValve™ device. Given the unavailability of any viable treatment option, the overall performance of the device and the associated benefits of treatment outweigh the risks for this non-iliofemoral Extreme Risk patient population.

The estimated K-M rate of all-cause mortality or major stroke at 12 months for the Attempted Implant non-iliofemoral cohort was 39.4% with an upper 95% CI of 47.2%, which was higher than for the iliofemoral cohort (Figure 49).

Table 17 provides a summary of the K-M estimate of event free rates of key outcomes for both the iliofemoral and non-iliofemoral cohorts. As shown in Table 17, the non-iliofemoral cohort reported higher rates of all-cause death and all-stroke, which resulted in higher MACCE and MAE rates compared to the iliofemoral cohort.



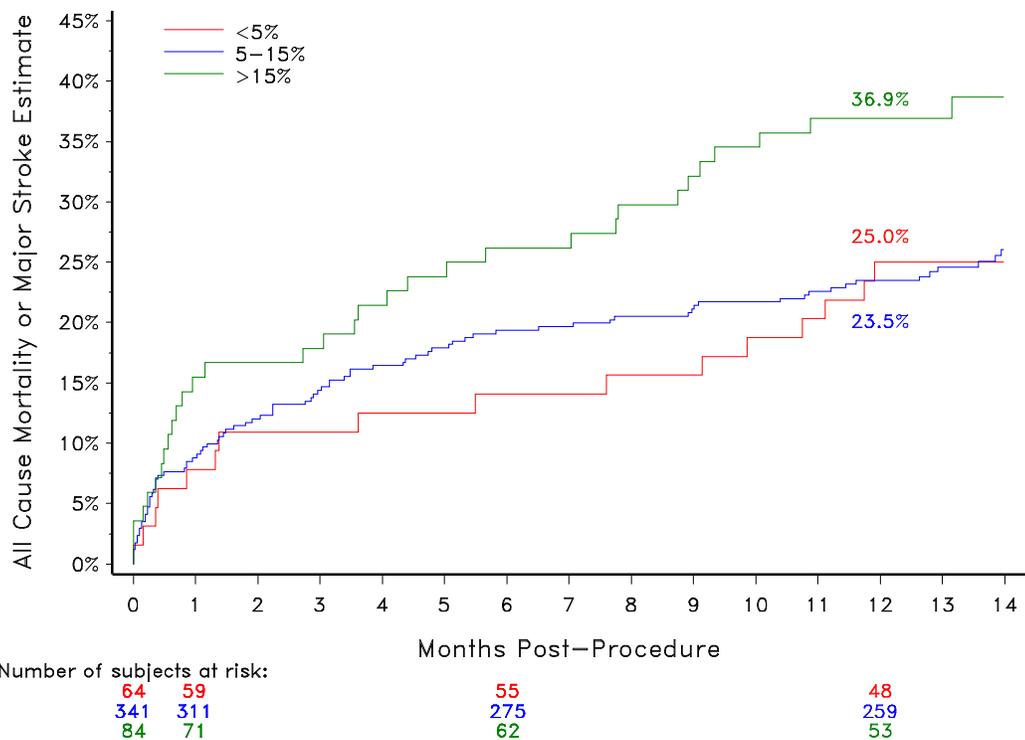
**Figure 49: Extreme Risk All-Cause Mortality or Major Stroke Kaplan-Meier Event Rate Attempted Implant (IF: iliofemoral; NIF: non-iliofemoral)**

**Table 17: Extreme Risk Kaplan-Meier Estimate of Event-Free Rates: Results by IF (N=489) and NIF (N=150) Cohorts**

Event	Access Site	Days post Attempted Implant			p-value*
		30 days	6 months (183 days)	12 months (365 days)	
MACCE	IF	87.7	77.5	70.8	0.004
	NIF	82.7	65.3	58.6	
All-Cause Death	IF	91.6	81.4	75.7	0.004
	NIF	88.7	71.3	64.0	
Myocardial Infarction	IF	98.8	98.5	98.0	0.861
	NIF	97.9	97.9	97.9	
All Stroke	IF	96.0	94.8	93.0	0.015
	NIF	91.2	88.0	87.0	
Reintervention	IF	98.9	98.5	98.2	0.408
	NIF	100.0	100.0	99.0	
MAE	IF	46.2	40.1	37.2	<0.001
	NIF	30.7	24.0	20.0	

\*p-value from Log-Rank test comparing freedom from curves through 365 days

A post hoc analysis was conducted to compare the K-M event rates for all-cause mortality or major stroke at 12 months between Attempted Implant iliofemoral patients in different Society of Thoracic Surgeons (STS) risk score categories (<5%, 5–15%, >15%). The STS risk score calculates the risk of operative mortality and morbidity of adult cardiac surgery on the basis of patient demographic and clinical variables. The Log-rank p-value for the K-M analysis was 0.042, indicating a statistically significant difference in the event rate between different STS score categories (Figure 50).



**Figure 50: Extreme Risk Primary Endpoint: All-Cause Mortality or Major Stroke Stratified by STS Score – Attempted Implant Iliofemoral**

### 11.2.3.2 Additional Effectiveness Data

Improvement in NYHA functional classification was evaluated for Implanted iliofemoral and non-iliofemoral patients. An evaluation of cardiac symptom severity based on NYHA classification was conducted at several evaluation time points through the first year of follow-up (Figure 51). Change from baseline to 12 months was evaluated for measures of forward flow hemodynamic performance (EOA and mean gradient) for iliofemoral and non-iliofemoral patients (Figure 52 and Figure 53).

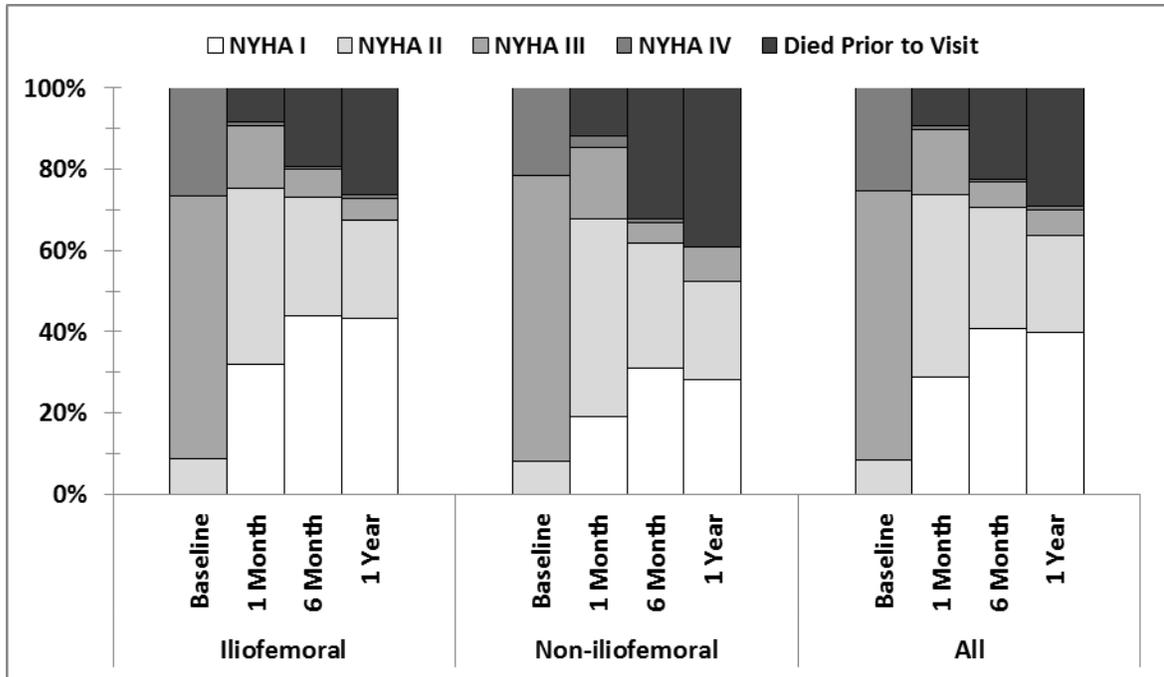


Figure 51: Extreme Risk NYHA Classification by Visit – Attempted Implant

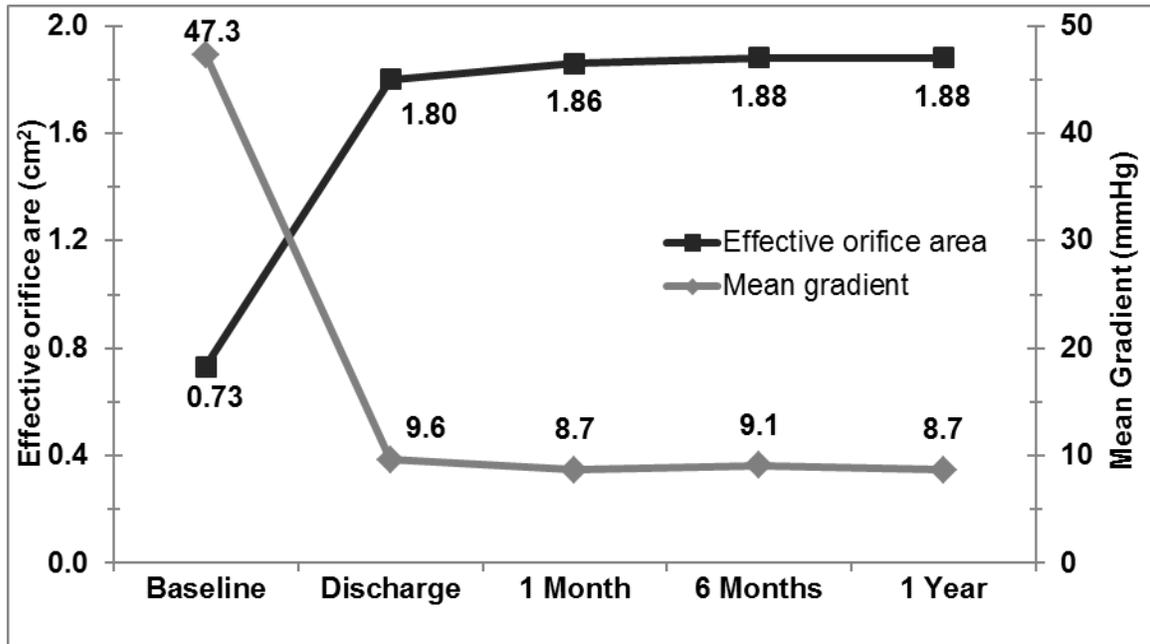


Figure 52: Extreme Risk EOA and Mean Gradient by Visit – Iliofemoral Implanted

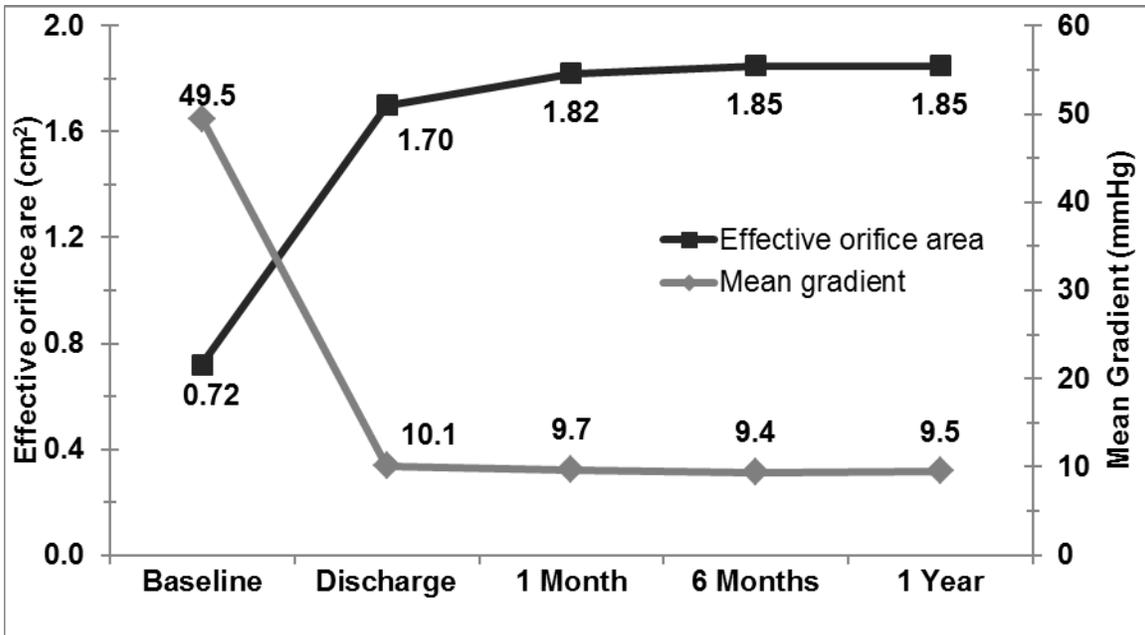


Figure 53: Extreme Risk EOA and Mean Gradient by Visit – Non-Iliofemoral Implanted

Figure 54 shows total aortic regurgitation (AR) severity over time in the Implanted iliofemoral population. These data are presented per valve size as well as for all sizes combined. Considering all valve sizes, the majority of patients presented at 1, 6, and 12 months with AR severity classified as trivial or mild. Over time, the percentage of patients with moderate or severe AR decreased to 0% at 12 months. The number of patients with no AR increased over time to 21.3% at 12 months.

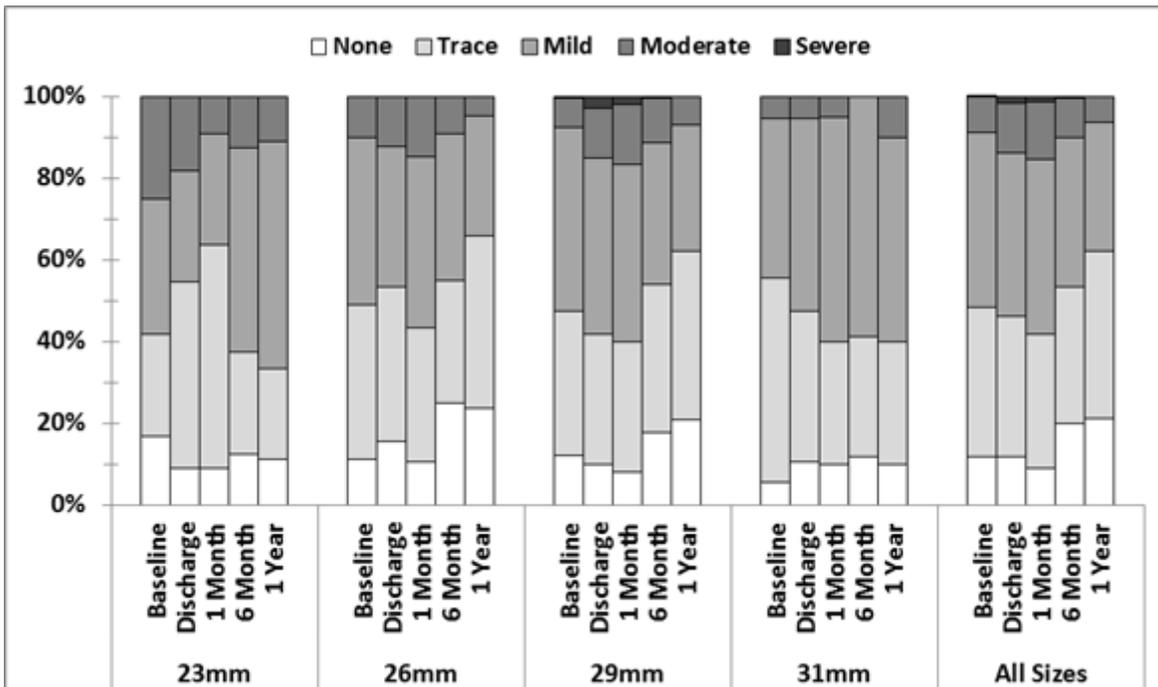


Figure 54: Extreme Risk Total Aortic Regurgitation by Visit – Iliofemoral Implanted

Figure 55 shows total AR severity over time in the Implanted non-iliofemoral population. Considering all valve sizes, the majority of patients presented at 1 month with AR severity classified as mild or less. Over time, the percentage of patients with no AR increased to 39.0% at 12 months.

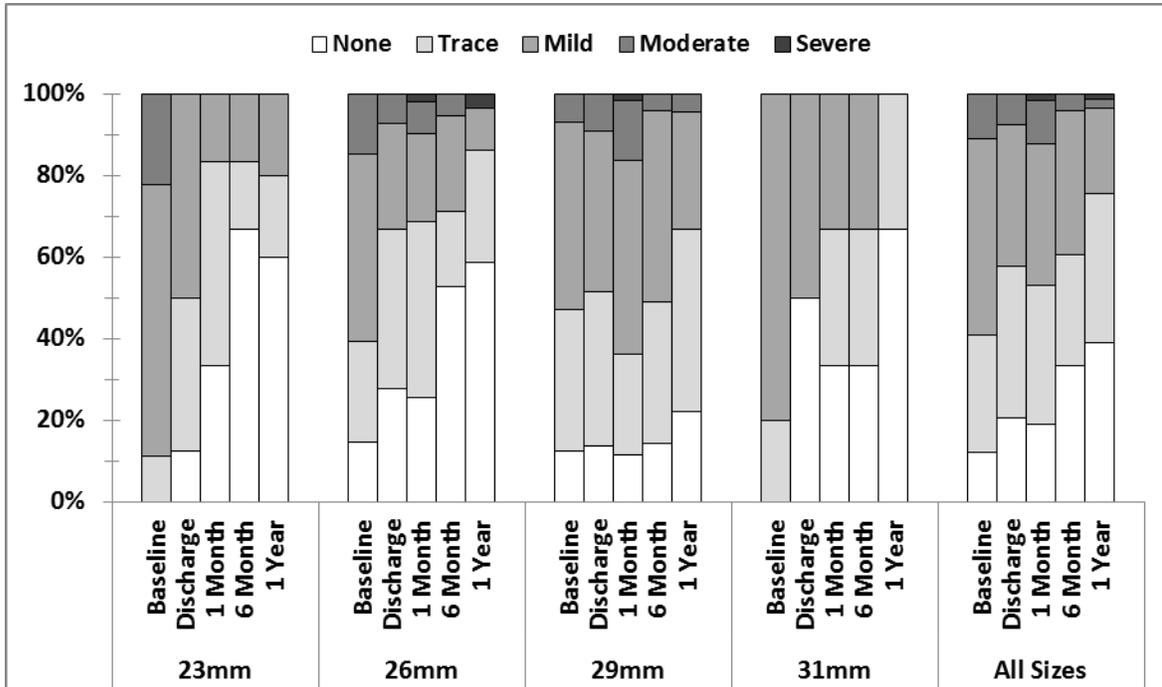


Figure 55: Extreme Risk Total Aortic Regurgitation by Visit – Non-Iliofemoral Implanted

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## 12.0 DISCLAIMER OF WARRANTY

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### DISCLAIMER OF WARRANTY

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