

INDICATIONS

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 $\leq 0.8 \text{ cm}^2$, a mean aortic valve gradient of $>40 \text{ mm Hg}$, or a peak aortic velocity of $>4.0 \text{ m/s}$) and with native aortic annulus diameters between 18 and 29 mm who are judged by a heart team, in consultation with a cardiac surgeon, to be at extreme risk or inoperable for open surgical therapy (predicted risk of operative mortality and/or serious irreversible morbidity $\geq 50\%$ at 30 days).

CONTRAINDICATIONS

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/Nickel), or sensitivity to contrast media, which cannot be adequately premedicated
- ongoing sepsis, including active endocarditis
- preexisting mechanical heart valve in aortic position

WARNINGS

General

- Implantation of the Medtronic CoreValve system should be performed only by physicians who have received Medtronic CoreValve training.
- This procedure should only be performed where emergency aortic valve surgery can be performed promptly.
- Mechanical failure of the delivery catheter system and/or accessories may result in patient complications.

Transcatheter Aortic Valve (Bioprosthesis)

- Accelerated deterioration of the bioprosthesis may occur in patients presenting with an altered calcium metabolism.

Precautions

General

- 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 high, moderate, or low surgical risk (predicted perioperative mortality risk of $<50\%$)
 - 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 ($\text{WBC} < 1000 \text{ cells/mm}^3$), thrombocytopenia (platelet count $< 50,000 \text{ cells/mm}^3$), or 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

NORRED EXHIBIT 2228
Medtronic Inc., Medtronic Valve
Inc. & Medtronic Corevalve
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Case IPR2014-00110/00111

DOCKET
ALARM

Prior to Use

- Exposure to glutaraldehyde may cause irritation of the skin, eyes, nose, and throat. Avoid prolonged or repeated exposure to the vapors.
- 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 Instructions for Use 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 ≥ 6 mm or an ascending aortic (direct aortic) access site ≥ 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 LIMA graft or patent RIMA graft.

During Use

- Adequate rinsing of the bioprosthesis with sterile saline, as described in the Instructions for Use, is mandatory before implantation. During rinsing, do not touch the leaflets or squeeze the bioprosthesis.
- 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.
- 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 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, 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 been 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.

POTENTIAL ADVERSE EVENTS

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)
- perforation of the myocardium or a vessel
- 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; leaflet 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, TIA, or other neurological deficits
- permanent disability
- 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.

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