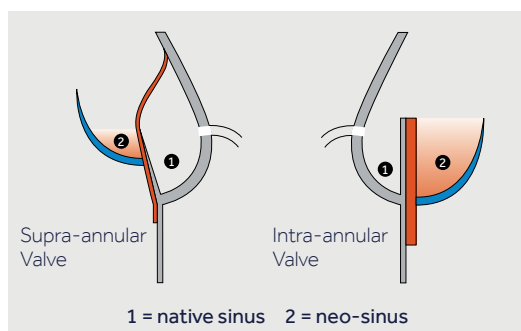


# DESIGNED FOR DURABILITY IMPACTING THROMBOSIS RISK

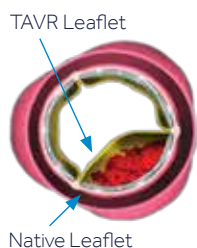
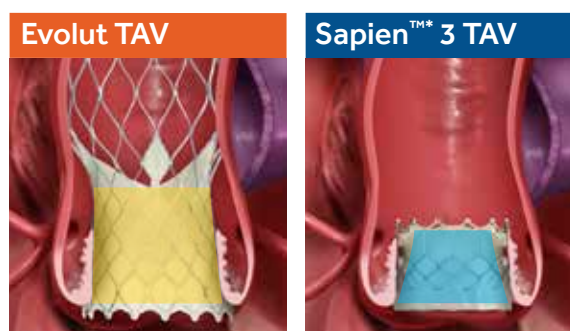
## Evolut™ TAVR Platform

### 1 INTRA-ANNULARITY IS A RISK FACTOR FOR THROMBOSIS FORMATION.<sup>1,2</sup> Evolut TAVR system employs a supra-annular design.

Design elements that produce points of stasis could increase risk of thrombosis, resulting in sub-optimal clinical results.<sup>1</sup>



The Evolut TAVR supra-annular design decreases the likelihood of a neo-sinus — allowing adequate washing behind the native leaflets.<sup>3</sup>



Intra-annularity creates a diminished native sinus where blood movement is reduced and results in stasis. The design creates a neo-sinus, a region between the native and transcatheter aortic valve leaflets where thrombus generally forms.

### 2 Recent data suggest that SUPRA-ANNULAR VALVES MAY HAVE LOWER RATES OF THROMBOSIS.<sup>3</sup>

Prevalence of leaflet thrombosis rates observed in a recently published meta-analysis.<sup>4</sup>

Device	Thrombosis Rate
Portico™ valve	35.2%
Lotus Edge™ valve	14.5%
Sapien™ valve	10.2%
<b>CoreValve™/Evolut™ R valve</b>	<b>6.2%</b>

### 3 IMPACT ON PATIENT OUTCOMES

The presence of reduced leaflet motion (RLM) is associated with increased risk of stroke or transient ischemic attack (TIA).<sup>5</sup>

All Events	Normal leaflet motion (n = 784)		Reduced leaflet motion (n = 106)		p value
	Number of patients	Rate per 100 person-years	Number of patients	Rate per 100 person-years	
<b>Stroke or TIA</b>	<b>27 (3%)</b>	<b>2.36</b>	<b>11 (10%)</b>	<b>7.85</b>	<b>0.001</b>
All stroke <sup>†</sup>	22 (3%)	1.92	6 (6%)	4.12	0.10
Ischemic stroke	21 (3%)	1.83	6 (6%)	4.12	0.08
TIA	7 (1%)	0.60	6 (6%)	4.18	0.0005

<sup>†</sup>Includes hemorrhagic and ischemic strokes.

Source: Chakravarty T, Søndergaard L, Friedman J, et al. Subclinical leaflet thrombosis in surgical and transcatheter aortic valves: an observational study. *Lancet*. June 17, 2017; 389(10087):2383-2392.

## REFERENCES

- 1 Midha PA, Raghav V, Sharma R, et al. The Fluid Mechanics of Transcatheter Heart Valve Leaflet Thrombosis in the Neosinus. *Circulation*. October 24, 2017;136(17):1598-1609.
- 2 Gunning PS, Saikrishnan N, Yoganathan AP, McNamara LM. Total ellipse of the heart valve: the impact of eccentric stent distortion on the regional dynamic deformation of pericardial tissue leaflets of a transcatheter aortic valve replacement. *JR Soc Interface*. December 6, 2015;12(113): 20150737.
- 3 Vahidkhal K, Barakat M, Abbasi M, et al. Valve thrombosis following transcatheter aortic valve replacement: significance of blood stasis on the leaflets. *Eur J Cardiothorac Surg*. May 1, 2017;51(5):927-935.

**INDICATIONS** The Medtronic CoreValve™ Evolut™ R and CoreValve™ Evolut™ PRO systems are indicated for relief of aortic stenosis in patients with symptomatic heart disease due to severe native calcific aortic stenosis who are judged by a heart team, including a cardiac surgeon, to be at intermediate or greater risk for open surgical therapy (e.g., predicted risk of surgical mortality  $\geq 3\%$  at 30 days, based on the Society of Thoracic Surgeons [STS] risk score and other clinical comorbidities unmeasured by the STS risk calculator).

The Medtronic CoreValve Evolut R and CoreValve Evolut PRO systems are indicated for use in patients with symptomatic heart disease due to failure (stenosed, insufficient, or combined) of a surgical bioprosthetic aortic valve who are judged by a heart team, including a cardiac surgeon, to be at high or greater risk for open surgical therapy (e.g., STS predicted risk of operative mortality score  $\geq 8\%$  or at a  $\geq 15\%$  risk of mortality at 30 days).

**CONTRAINDICATIONS** The CoreValve Evolut R and PRO systems are 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 pre-medicated; ongoing sepsis, including active endocarditis; and pre-existing mechanical heart valve in the aortic position.

**WARNINGS** General Implantation of the CoreValve Evolut R and PRO systems should be performed only by physicians who have received Medtronic CoreValve Evolut R or PRO 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. Accelerated deterioration of the bioprosthesis may occur in patients presenting with an altered calcium metabolism.

**PRECAUTIONS** General The safety and effectiveness of the CoreValve Evolut R and PRO systems 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: Patients who do not meet the criteria for symptomatic severe native aortic stenosis as defined: (1) symptomatic severe high-gradient aortic stenosis — aortic valve area  $\leq 1.0$  cm<sup>2</sup> or aortic valve area index  $\leq 0.6$  cm<sup>2</sup>/m<sup>2</sup>, a mean aortic valve gradient  $\geq 40$  mm Hg, or a peak aortic-jet velocity  $\geq 4.0$  m/s; (2) symptomatic severe low-flow, low-gradient aortic stenosis — aortic valve area  $\leq 1.0$  cm<sup>2</sup> or aortic valve area index  $\leq 0.6$  cm<sup>2</sup>/m<sup>2</sup>, a mean aortic valve gradient  $< 40$  mm Hg, and a peak aortic-jet velocity  $< 4.0$  m/s; who are at low surgical risk (predicted perioperative mortality risk  $< 3\%$ ); with untreated, clinically significant coronary artery disease requiring revascularization; with a pre-existing prosthetic heart valve with a rigid support structure in either the mitral or pulmonary position if either the pre-existing prosthetic heart valve could affect the implantation or function of the bioprosthesis or the implantation of the bioprosthesis could affect the function of the pre-existing prosthetic heart valve; with cardiogenic shock manifested by low cardiac output, vasopressor dependence, or mechanical hemodynamic support. The safety and effectiveness of a CoreValve Evolut R and PRO bioprosthesis implanted within a failed pre-existing transcatheter bioprosthesis has not been demonstrated. Implanting a CoreValve Evolut R or PRO bioprosthesis in a degenerated surgical bioprosthesis (transcatheter aortic valve in surgical aortic valve [TAV in SAV]) should be avoided in the following conditions: The degenerated surgical bioprosthesis presents with: A significant concomitant paravalvular leak (between the prosthesis and the native annulus) that is not securely fixed in the native annulus, or is not structurally intact (e.g., wire form frame fracture); partially detached leaflet that in the aortic position may obstruct a coronary ostium; stent frame with a manufacturer's labeled inner diameter  $< 17$  mm. 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 as leukopenia (WBC  $< 1,000$  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 unicuspid valve; 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  $> 30$  mm for CoreValve Evolut R and  $< 18$  mm or  $> 26$  mm for CoreValve Evolut PRO per the baseline diagnostic imaging or surgical bioprosthetic aortic annulus size  $< 17$  mm or  $> 30$  mm for CoreValve Evolut R and  $< 17$  mm or  $> 26$  mm for CoreValve Evolut PRO; transarterial access unable to accommodate an 18 Fr sheath or the 14 Fr equivalent EnVeo InLine™ sheath when using Model ENVEOR-US/ENVPRO-14-US or transarterial access unable to accommodate a 20 Fr introducer sheath or the 16 Fr equivalent EnVeo InLine sheath when using Model ENVEOR-N-US/ENVPRO-16-US; sinus of Valsalva anatomy that would prevent adequate coronary perfusion; moderate to severe mitral stenosis; severe ventricular dysfunction with left ventricular ejection fraction (LVEF)  $< 20\%$ ; symptomatic carotid or vertebral artery disease; and severe basal septal hypertrophy with an outflow gradient.

**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. These devices were designed for single-patient use only. Do not reuse, reprocess, or re-sterilize these products. Reuse, reprocessing, or re-sterilization may compromise the structural integrity of the devices and/or create a risk of contamination of the devices, 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 devices is the responsibility of the physician. Refer to the Instructions for Use for available sizes. Failure to implant a device within the sizing matrix could lead to adverse effects such as those listed below. Patients must present with transarterial access vessel diameters of  $\geq 5$  mm when using Model ENVEOR-US/ENVPRO-14-US or  $\geq 5.5$  mm when using Model ENVEOR-N-US/ENVPRO-16-US, or patients must present with an ascending aortic (direct aortic) access site  $\geq 60$  mm from the basal plane for both systems. 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. For direct aortic access, ensure the access site and trajectory are free of patent RIMA or a pre-existing patent RIMA graft. For use in patients presenting with a bicuspid aortic valve, the heart team should consider the patient's age and the need for ascending aorta intervention when determining the appropriate treatment option for the patient.

**During Use** For direct aortic and subclavian access procedures, care must be exercised when using the tip-retrieval mechanism to ensure adequate clearance to avoid advancement of the catheter tip through the bioprosthesis leaflets during device closure. For direct aortic access procedures, use a separate introducer sheath; do not use the EnVeo InLine sheath. 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 misload is detected, unsheath the bioprosthesis and examine the bioprosthesis for damage (e.g., permanent frame deformation, frayed sutures, or valve damage). Do not attempt to reload a damaged bioprosthesis. Do not load the bioprosthesis onto the catheter more than

two times or after it has been inserted into a patient. Use the deployment knob to deploy and recapture the bioprosthesis. Do not use the trigger for deploying or recapturing because it could cause inaccurate placement of the bioprosthesis. Once the radiopaque capsule marker band reaches the distal end of the radiopaque paddle attachment (point of no recapture), retrieval of the bioprosthesis from the patient is not recommended. Retrieval after the point of no recapture 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; recapture until the bioprosthesis is free from annular contact, and then reposition in the retrograde direction. If necessary, and the radiopaque capsule marker band has not yet reached the distal end of the radiopaque paddle attachment, the bioprosthesis can be withdrawn (repositioned) in the antegrade direction. However, use caution when moving the bioprosthesis in the antegrade direction. 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. Use the handle of the delivery system to reposition the bioprosthesis. Do not use the outer catheter sheath. There will be some resistance when the catheter is advanced through the vasculature. If there is a significant increase in resistance, stop advancement and investigate the cause of the resistance (e.g., magnify the area of resistance) before proceeding. Do not force passage. Forcing passage could increase the risk of vascular complications (e.g., vessel dissection or rupture). Persistent force on the catheter can cause the catheter to kink, which could increase the risk of vascular complications (e.g., vessel dissection or rupture). Once deployment is complete, repositioning of the bioprosthesis 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 or to recapture 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. When using a separate introducer sheath, 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. After the procedure, administer appropriate antibiotic prophylaxis as needed for patients at risk for prosthetic valve infection and endocarditis. After the procedure, administer anticoagulation and/or antiplatelet therapy per physician/clinical judgment. Excessive contrast media may cause renal failure. Prior to the procedure, measure the patient's creatinine level. During the procedure, monitor contrast media usage. Conduct the procedure under fluoroscopy. The safety and efficacy of a CoreValve Evolut R or CoreValve Evolut PRO bioprosthesis implanted within a transcatheter bioprosthesis have not been demonstrated. However, in the event that a CoreValve Evolut R or CoreValve Evolut PRO bioprosthesis must be implanted within a transcatheter bioprosthesis to improve valve function, valve size and patient anatomy must be considered before implantation of the CoreValve Evolut R or CoreValve Evolut PRO bioprosthesis to ensure patient safety (e.g., to avoid coronary obstruction). In the event that valve function or sealings is impaired due to excessive calcification or incomplete expansion, a post-implant 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 or, for surgical bioprosthetic valves, the manufacturer's labeled inner diameter. Refer to the specific balloon catheter manufacturer's compliance chart to ensure that the applied inflation pressure does not result in a balloon diameter that exceeds the indicated annulus range for the bioprosthesis. 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™\* and Z-MED II™\* balloon aortic valvuloplasty catheters where CoreValve Evolut R and CoreValve Evolut PRO bioprosthesis device performance was maintained after dilation. Data on file.

**POTENTIAL ADVERSE EVENTS** Potential risks associated with the implantation of the CoreValve Evolut R or CoreValve Evolut PRO transcatheter aortic valve may include, but are not limited to, the following:

- Death
- myocardial infarction, cardiac arrest, cardiogenic shock, cardiac tamponade
- coronary occlusion, obstruction, or vessel spasm (including acute coronary closure)
- cardiovascular injury (including rupture, perforation, tissue erosion, or dissection of vessels, ascending aorta trauma, ventricle, myocardium, or valvular structures that may require intervention)
- emergent surgical or transcatheter intervention (e.g., coronary artery bypass, heart valve replacement, valve explant, percutaneous coronary intervention (PCI), balloon valvuloplasty)
- prosthetic valve dysfunction (regurgitation or stenosis) due to fracture; bending (out-of-round configuration) of the valve frame; underexpansion 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)
- prosthetic valve migration/embolization
- prosthetic valve endocarditis
- prosthetic valve thrombosis
- delivery catheter system malfunction resulting in the need for additional re-crossing of the aortic valve and prolonged procedural time
- delivery catheter system component migration/embolization
- stroke (ischemic or hemorrhagic), transient ischemic attack (TIA), or other neurological deficits
- heart failure
- cardiac failure or low cardiac output
- ancillary device embolization
- individual organ (e.g., cardiac, respiratory, renal [including acute kidney failure]) or multi-organ insufficiency or failure
- major or minor bleeding that may require transfusion or intervention (including life-threatening or disabling bleeding)
- vascular access-related complications (e.g., dissection, perforation, pain, bleeding, hematoma, pseudoaneurysm, irreversible nerve injury, compartment syndrome, arteriovenous fistula, stenosis)
- mitral valve regurgitation or injury
- conduction system disturbances (for example, atrioventricular node block, left-bundle branch block, asystole), which may require a permanent pacemaker
- infection (including septicemia)
- hypotension or hypertension
- hemolysis
- peripheral ischemia
- bowel ischemia
- abnormal lab values (including electrolyte imbalance)
- allergic reaction to antiplatelet agents, contrast medium, or anesthesia
- exposure to radiation through fluoroscopy and angiograph
- permanent disability.

Please reference the CoreValve Evolut R and CoreValve Evolut PRO Instructions for Use for more information regarding indications, warnings, precautions, and potential adverse events.

**Caution:** Federal Law (USA) restricts these devices to the sale by or on the order of a physician.

The commercial name of the Evolut™ PRO device is Medtronic CoreValve™ Evolut™ PRO System.

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