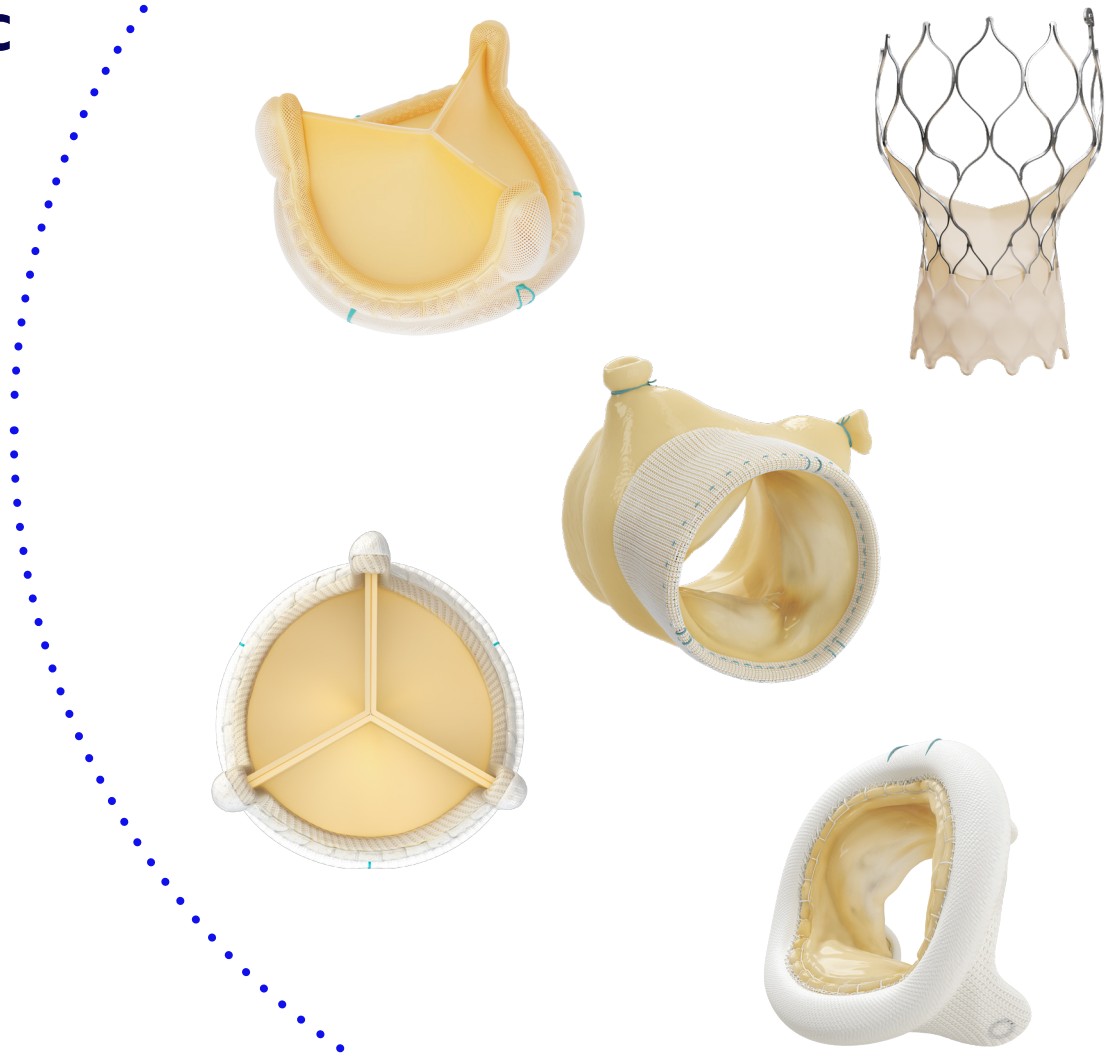
Medtronic



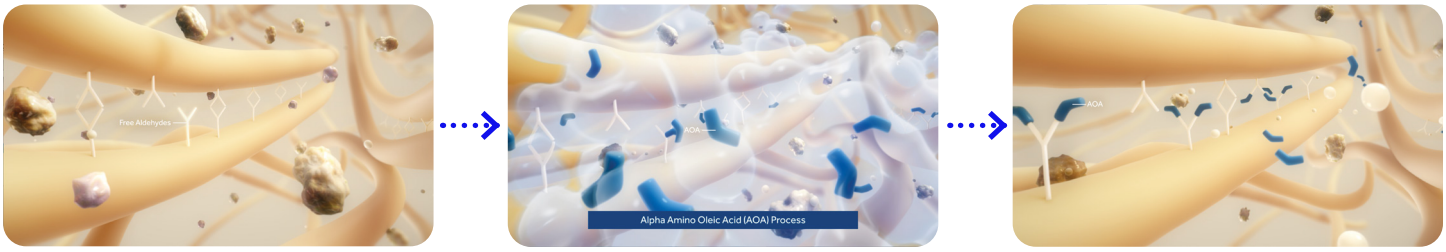
AOA™ tissue treatment

Empowering patient outcomes with enduring reliability

Medtronic anti-calcification tissue treatments are rooted in a deep history of innovation. The Hancock™ II bioprosthesis, with its T-6 treatment, was the first commercially available valve to offer anti-calcification. With our next generation of valves came our second-generation tissue treatment – amino oleic acid (AOA). Medtronic has been using AOA treatment across a suite of surgical and transcatheter valves continuously for more than 30 years. Due to its proven effectiveness to reduce calcification,† the AOA treatment is now used on our most advanced SAVR valve – Avalus Ultra™ bioprosthesis – and our valves within the Evolut™ TAVR platform.

Engineered for longevity

The Medtronic AOA treatment is a biochemical approach to mitigating calcification in the wall and leaflets of tissue valves. AOA was the first tissue treatment with interaction and covalent bonding with the free aldehydes of glutaraldehyde, which makes it an excellent choice to support lifetime patient management.†



After fixation
- Free aldehydes are present

AOA treatment
- AOA covalently bonds with free aldehydes.
- Lipids are washed away.
- Subsequent storage in glutaraldehyde allows any remaining free aldehydes to crosslink.

After treatment
- Large AOA molecule slows diffusion of calcium into tissue matrix.

Examining the clinical data

Edwards Lifesciences launched RESILIA™* tissue treatment with its new INSPIRIS™* valve in 2017. The Medtronic AOA treatment has been in use for over 30 years.

Medtronic AOA tissue treatment

AOA is an innovative tissue treatment used across a suite of Medtronic devices to help drive durable valve replacements and patient lifetime management. Clinical use with these devices encompasses **over half a million patients** for over 30 years.

- Avalus™ valve showed 99% freedom from reintervention for SVD and SHD and stable hemodynamics at 7 years in over 1100 patients in the PERIGON trial.[1]
- Freestyle™ valve – proven durability in aortic valve replacement, showing excellent results out to 15+ years[2-4] and multiple reports in patient populations 60 and younger.[2,5-6]
- Mosaic™ valve demonstrates industry-leading, unsurpassed durability in mitral valve replacement with reports out to 17 years.[7,8]
- The CoreValve™/Evolut supra-annular valve is the first and only transcatheter bioprosthesis to demonstrate lower rates of SVD compared with surgery in randomized clinical trials.[‡,9]
- Harmony™ valve demonstrated the use of AOA in pulmonic valve replacement.[10]

Edwards RESILIA tissue treatment

RESILIA, another contemporary tissue treatment, has shown promising results in initial reports.

- The COMMENCE study showed 99% freedom from SVD using **Magna Ease™* with RESILIA** tissue treatment in nearly 200 patients out to 7 years.[11]
- The EU RESILIA feasibility study using Magna Ease with RESILIA also showed 0 SVD at 5 years in 133 patients from 2 sites in Poland.[12]
- Limited, short-term data exists with the MITRIS™* RESILIA, KONECT™* RESILIA, INSPIRIS RESILIA, and SAPIEN™* X4 devices also using RESILIA tissue treatment.
- A recent, multicenter registry including nearly 500 INSPIRIS patients reported 5-year freedom from SVD stages 1, 2, and 3, were 95.7%, 98.6%, and 99.3%. This is the longest follow up of the INSPIRIS valve to date.[§]

Universal tissue compatibility

Importantly, AOA has demonstrated efficacy in various tissue types. Native porcine valves and pericardium are both composed primarily of type I collagen and elastin,[13–15] which are cross-linked in phosphate buffered 0.2% glutaraldehyde. Since AOA is binding to the free aldehydes, the binding mechanism is the same for pericardium (porcine and bovine) and porcine aortic valves.

Demonstrated effectiveness in rat testing

AOA is associated with a comparable degree of efficacy in preventing calcification in porcine leaflet and bovine pericardium.

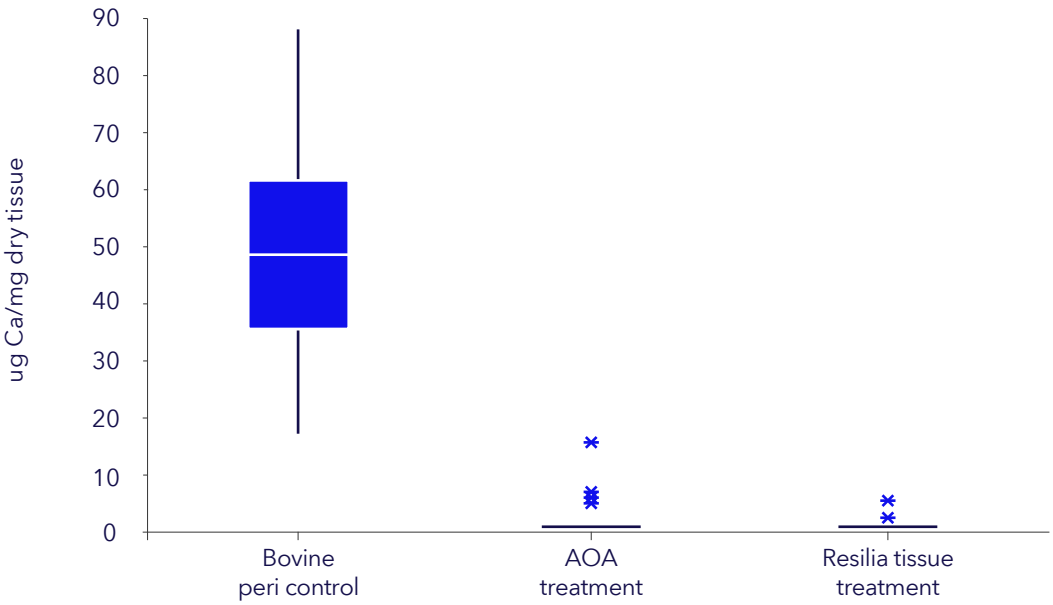
	Mean calcium content	
	Test AOA treated tissue	Control
Porcine leaflet◊	5.12 ± 5.99	44.88 ± 77.56
Porcine pericardium‡	1.73 ± 0.63	38.82 ± 73.92
Bovine pericardium¶	0.96 ± 0.34	71.21 ± 75.9

◊ Nine 3-week-old rats. Control = Base OA = solution without AOA molecule. Inductively coupled plasma spectroscopy after 8 weeks of subcutaneous implant in the back.[16]
¶ Twelve 3-week-old rats. Control = Base OA = solution without AOA molecule. Inductively coupled plasma spectroscopy after 8 weeks of subcutaneous implant in the back.[17]

Positive results in rabbit studies

AOA-treated bovine pericardial tissue demonstrated similar calcification levels as Resilia bovine pericardial treated tissue.

Boxplot of bovine peri control: AOA versus Resilia



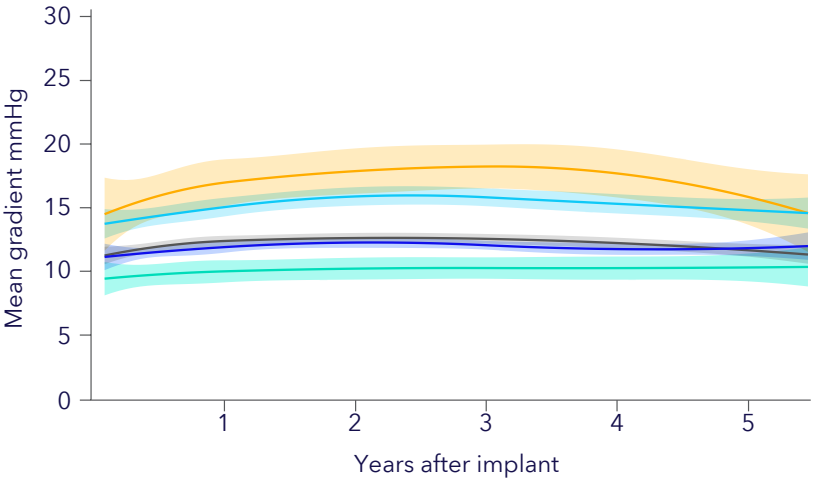
	Bovine peri control	AOA treatment	Resilia tissue treatment
N =	**27**	**27**	**27**
Median (interquartile range)	**48.30 (35.80, 61.80)**	**1.070 (0.793, 1.460)**	**0.894 (0.640, 1.270)**

Intramuscular dorsal implants in 27 rabbits. Each tissue type was implanted in each rabbit. Sacrification at 60 days. Inductively coupled plasma mass spectrometry.[18]

Hemodynamic performance of contemporary surgical valves using AOA and Resilia

Temporal trend

PERIGON Clinical Study (Avalus valve)

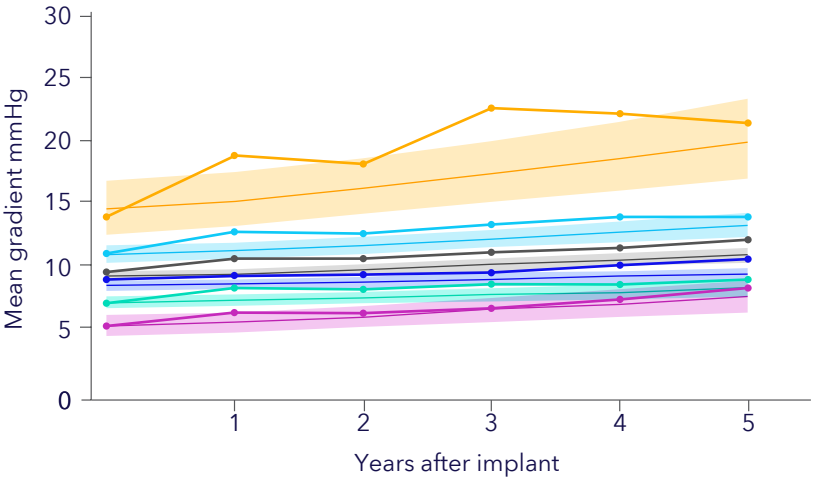


The PERIGON Pivotal Trial was designed to evaluate the safety and effectiveness of the Model 400 (Avalus) bovine pericardial stented aortic bioprosthesis in a patient population undergoing surgical aortic valve replacement. Patients were from Canada (268), Europe (475), and the United States (375). A total of 1118 patients were implanted with the Avalus valve.[19]

- Predicted mean 19 mm — Band
- Predicted mean 21 mm — Band
- Predicted mean 23 mm — Band
- Predicted mean 25 mm — Band
- Predicted mean 27 mm — Band

Results after 30 days post-procedure to predict mean gradient for each patient at each time point.

COMMENCE (Magna Ease valve with Resilia)



The COMMENCE trial was conducted to evaluate the safety and effectiveness of aortic valve replacement using Magna Ease with Resilia tissue (Edwards Lifesciences). A total of 689 patients were included in the study.[20]

Valve size

- 19 mm
- 21 mm
- 23 mm
- 25 mm
- 27 mm
- 29 mm

The 0-year time point represents the three-month post-operative baseline. Dots represent the observed means at each follow-up, and the unadjusted model estimated means and confidence bands are illustrated by lighter shaded lines and ribbons for each valve size patient cohort.

If you are located in the United States, please refer to the brief statement(s) below to review applicable indications, safety, and warning information. See the device manual for a full list of information regarding the instructions for use, the implant procedure, indications, contraindications, warnings, precautions, and potential complications/adverse events. For further information, please call Medtronic at 1.763.514.4000 and/or consult the Medtronic website at **medtronic.com**.

If you are located outside the United States, see the device manual for a full list of information regarding instructions for use, the implant procedure, indications, contraindications, warnings, precautions, and potential adverse events. For further information, contact your local Medtronic representative and/or consult the Medtronic website at **medtronic.com** and select your appropriate country/region.

For applicable products, consult instructions for use on **manuals.medtronic.com**. Manuals can be viewed using a current version of any major internet browser. For best results, use Adobe Acrobat® Reader with the browser.

Harmony Transcatheter Pulmonary Valve System

Indications: The Harmony™ transcatheter pulmonary valve (TPV) system is indicated for use in the management of pediatric and adult patients with severe pulmonary regurgitation (i.e., severe pulmonary regurgitation as determined by echocardiography and/or pulmonary regurgitant fraction ≥ 30% as determined by cardiac magnetic resonance imaging) who have a native or surgically-repaired right ventricular outflow tract and are clinically indicated for surgical pulmonary valve replacement. **Contraindications:** The following are contraindications for the use of this device: active bacterial endocarditis or other active infections, known intolerance to Nitinol (titanium or nickel), or an anticoagulation/antiplatelet regimen. **Warnings:** General: Implantation of the Harmony TPV system should be performed only by physicians who have received Harmony TPV system training. The transcatheter pulmonary valve (TPV) is to be used only in conjunction with the Harmony delivery catheter system (DCS). This procedure should only be performed where emergency pulmonary valve surgery can be performed promptly. Do not use any of the Harmony TPV system components if any of the following has occurred: it has been dropped, damaged, or mishandled in any way, or if the use-by date has elapsed. Transcatheter pulmonary valve (TPV): This device was designed for single use only. Do not reuse, reprocess, or resterilize the TPV. 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. Do not resterilize the TPV by any method. Exposure of the device and container to irradiation, steam, ethylene oxide, or other chemical sterilants renders the device unfit for use. The device is packaged with a temperature sensor. Do not freeze the device. Do not expose the device to extreme temperatures. Do not use the device if the arrow on the sensor points to the symbol that indicates that the temperature limit has been exceeded. Do not use the device if any of the following have occurred: the tamper-evident seal is broken, the serial number tag does not match the container label, the arrow on the sensor points to the symbol that indicates that the temperature limit has been exceeded, or the device is not completely covered by the storage solution. Do not contact any of the Harmony TPV system components with cotton or cotton swabs. Do not expose any of the Harmony TPV system components to organic solvents, such as alcohol. Do not introduce air into the catheter. Do not expose the device to solutions other than the storage and rinse solutions. Do not add or apply antibiotics to the device, the storage solution, or the rinse solution. Do not allow the device to dry. Maintain tissue moisture with irrigation or immersion. Do not attempt to repair a damaged device. Do not handle the valve leaflet tissue or use forceps to manipulate the valve leaflet tissue. Do not attempt to recapture the device once deployment has begun. Do not attempt to retrieve the TPV if any one of the outflow TPV struts is protruding from the capsule. If any one of the outflow TPV struts has deployed from the capsule, the TPV must be released from the catheter before the catheter can be withdrawn. Do not attempt post-implant balloon dilatation (PID) of the TPV during the procedure, which may cause damage to or failure of the TPV leading to injury to the patient resulting in reintervention. Delivery catheter system (DCS): This device was designed for single use only. Do not reuse, reprocess, or resterilize the DCS. 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. Do not reuse or resterilize the DCS. If resistance is met, do not advance the guidewire, DCS, or any other component without first determining the cause and taking remedial action. Do not remove the guidewire from the DCS at any time during the procedure. **Precautions:** General: Clinical long-term durability has not been established for the Harmony TPV. Evaluate the TPV performance as needed during patient follow-up. The safety and effectiveness of Harmony TPV implantation in patients with pre-existing prosthetic heart valve or prosthetic ring in any position has not been demonstrated. The Harmony TPV system has not been studied in female patients of child-bearing potential with positive pregnancy. Before use: Exposure to glutaraldehyde may cause irritation of the skin, eyes, nose, and throat. Avoid prolonged or repeated exposure to the chemical vapor. Use only with adequate ventilation. If skin contact occurs, immediately flush the affected area with water (for a minimum of 15 minutes) and seek medical attention immediately. The TPV and the glutaraldehyde storage solution are sterile. The outside of the TPV container is nonsterile and must not be placed in the sterile field. The TPV and DCS should be used only in a sterile catheterization laboratory (cath lab) environment. Ensure that sterile technique is used at all times. Strictly follow the TPV rinsing procedure. For TPV 25: Ensure that all green sutures have been removed from the attachment suture loops on the TPV before loading onto the DCS. Prevent contamination of the TPV, its storage solution, and the DCS with glove powder. Verify the orientation of the TPV before loading it onto the DCS. The inflow end of the TPV with attachment suture loops must be loaded first. Do not place excessive pressure on the TPV during loading. Inspect the sealed DCS packaging before opening. If the seal is broken or the packaging has been damaged, sterility cannot be assured. Proper functioning of the DCS depends on its integrity. Use caution when handling the DCS. Damage may result from kinking, stretching, or forceful wiping of the DCS. This DCS is not recommended to be used for pressure measurement or delivery of fluids. Carefully flush the DCS and maintain tight DCS connections to avoid the introduction of air bubbles. During use: The TPV segment is rigid and may make navigation through vessels difficult. Do not advance any portion of the DCS under resistance. Identify the cause of resistance using fluoroscopy and take appropriate action to remedy the problem before continuing to advance the DCS. Careful management of the guidewire is recommended to avoid dislodgement of the TPV during DCS removal. Once deployment is initiated, retrieval of the TPV from the patient is not recommended. Retrieval of a partially deployed valve may cause mechanical failure of the delivery catheter system or may cause injury to the patient. Refer to the section below for a list of potential adverse events associated with Harmony TPV implantation. During deployment, the DCS can be advanced or withdrawn prior to the outflow struts protruding from the capsule. Once the TPV struts contact the anatomy during deployment, it is not recommended to reposition the device. Advancing the catheter forward once the TPV struts make contact with the anatomy may lead to an undesired deployment or may cause damage to or failure of the TPV and injury to the patient. Refer to the section below for a list of potential adverse events associated with the Harmony TPV implantation. Physicians should use judgment when considering repositioning of the TPV (for example, using a snare or forceps) once deployment is complete. Repositioning the bioprosthesis is not recommended, except in cases where imminent serious harm or death is possible (for example, occlusion of the main, left, or right pulmonary artery). Repositioning of a deployed valve may cause damage to or failure of the TPV and injury to the patient. Refer to the section below for a list of potential adverse events associated with the Harmony TPV implantation. Ensure the capsule is closed before DCS removal. If increased resistance is encountered when removing the DCS 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 harm to the patient. If the cause of resistance cannot be determined or corrected, remove the DCS and introducer sheath as a single unit over the guidewire, and inspect the DCS and confirm that it is complete. If there is a risk of coronary artery compression, assess the risk and take the necessary precautions. Endocarditis is a potential adverse event associated with all bioprosthetic valves. Patients should make their healthcare providers aware that they have a bioprosthetic valve before any procedure. Post-procedure, administer appropriate antibiotic prophylaxis as needed for patients at risk for prosthetic valve infection and endocarditis. Prophylactic antibiotic therapy is recommended for patients receiving a TPV before undergoing dental procedures. Post-procedure, administer anticoagulation and/or antiplatelet therapy per physician/clinical judgment and/or institutional 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. **Potential Adverse Events:** Potential risks associated with the implantation of the Harmony TPV may include, but are not limited to, the following: • death • valve dysfunction • tissue deterioration • hematoma • heart failure • cerebrovascular incident • perforation • rupture of the right ventricular outflow tract (RVOT) • compression of the aortic root • compression of the coronary arteries • sepsis • pseudoaneurysm • erosion • stent fracture • arrhythmias • device embolization or migration • pulmonary embolism • occlusion of a pulmonary artery • laceration or rupture of blood vessels • device misorientation or misplacement • valve deterioration • regurgitation through an incompetent valve • physical or chemical implant deterioration • paravalvular leak • valve dysfunction leading to hemodynamic compromise • residual or increasing transvalvular gradients n progressive stenosis and obstruction of the implant • hemorrhage • endocarditis • thromboembolism • thrombosis • thrombus • intrinsic and extrinsic calcification • bleeding • bleeding diathesis due to anticoagulant use • fever • pain at the catheterization site • allergic reaction to contrast agents • infection • progressive pulmonary hypertension • progressive neointimal thickening and peeling • leaflet thickening • hemolysis. General surgical risks applicable to transcatheter pulmonary valve implantation: • abnormal lab values (including electrolyte imbalance and elevated creatinine) • allergic reaction to antiplatelet agents, contrast medium, or anesthesia • exposure to

radiation through fluoroscopy and angiography • permanent disability. Please reference the Harmony TPV system 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.

Hancock II™ and Hancock II Ultra™ Bioprostheses

Indications: The Hancock II bioprostheses are indicated for patients who require replacement of their native or prosthetic aortic and/or mitral valves. **Contraindications:** None known. **Warnings/Precautions/Adverse Events:** Accelerated deterioration due to calcific degeneration of bioprosthesis may occur in children, adolescents, young adults, and patients with altered calcium metabolism (e.g., chronic renal failure, hyperparathyroidism). Adverse events can include: angina, cardiac dysrhythmias, death, endocarditis, heart failure, hemolysis, hemolytic anemia, anticoagulant/antiplatelet-related hemorrhage, transvalvular or paravalvular leak, myocardial infarction, nonstructural dysfunction (obstructive pannus ingrowth, suture dehiscence, inappropriate sizing, other), stroke, structural deterioration (calcification, leaflet tear, stenosis, other), thromboembolism, valve thrombosis, and infection other than endocarditis. It is possible that these complications could lead to reoperation, explantation, permanent disability, or death. **Caution:** Federal law (USA) restricts these devices to sale by or on the order of a physician. For a listing of indications, contraindications, precautions, warnings, and potential adverse events, please refer to the Instructions for Use (IFU). If applicable, consult electronic IFUs (eIFUs) at www.medtronic.com/manuals. Note: eIFUs can be viewed using a current version of any major internet browser.

Avalus™ Bioprosthesis

Indications: The Avalus bioprosthesis is indicated for the replacement of diseased, damaged, or malfunctioning native or prosthetic aortic valves. **Contraindications:** None known. **Warnings/Precautions/Adverse Events:** Only physicians who have received proper training in valve replacement should use this device. Accelerated structural deterioration due to calcific degeneration of bioprosthesis may occur in children, adolescents, young adults, and patients with altered calcium metabolism (e.g., chronic renal failure, or hyperparathyroidism). Adverse events can include: angina, cardiac dysrhythmias, endocarditis, heart failure, hemolysis, hemolytic anemia, hemorrhage, infection other than endocarditis, transvalvular or paravalvular leak, myocardial infarction, nonstructural valve dysfunction (leaflet entrapment/impingement, obstructive pannus ingrowth, suture dehiscence, inappropriate sizing or positioning, or other), pericardial effusion or tamponade, prosthesis regurgitation, prosthesis stenosis, prosthesis thrombosis, stroke, structural valve deterioration (calcification, leaflet tear or perforation, or other), thromboembolism, tissue dehiscence, and transient ischemic attack. These complications could lead to reoperation, explant of the bioprosthesis, permanent disability, or death.

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

For a listing of indications, contraindications, precautions, warnings, and potential adverse events, please refer to the Instructions for Use (IFU). If applicable, consult electronic IFUs (eIFUs) at www.medtronic.com/manuals. Note: eIFUs can be viewed using a current version of any major internet browser.

Freestyle™ Aortic Root Bioprosthesis

Indications: The Freestyle bioprosthesis is indicated for the replacement of malfunctioning native or prosthetic aortic valves with the option, for Model 995 only, of aortic root replacement. **Contraindications:** None known. **Warnings/Precautions/Adverse Events:** Accelerated deterioration due to calcific degeneration of bioprosthesis may occur in children, adolescents, young adults, and patients with altered calcium metabolism (e.g., chronic renal failure, hyperparathyroidism). Adverse events can include: cardiac dysrhythmias, death, endocarditis, hemolysis, anticoagulant/antiplatelet-related hemorrhage, transvalvular or paravalvular leak, nonstructural dysfunction (pannus, suture, inappropriate sizing, or other), structural deterioration (calcification, leaflet tear, intracuspal hematoma, pseudoaneurysm (Model 995), or other), thromboembolism, valve thrombosis, root dilatation (Model 995), angina, infection other than endocarditis, heart failure, hemolytic anemia, myocardial infarction, acute kidney injury, or renal failure. It is possible that these complications could lead to reoperation, explantation, permanent disability, or death.

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

For a listing of indications, contraindications, precautions, warnings, and potential adverse events, please refer to the Instructions for Use (IFU). If applicable, consult electronic IFUs (eIFUs) at www.medtronic.com/manuals. Note: eIFUs can be viewed using a current version of any major internet browser.

Mosaic™ Bioprosthesis

Indications: The Mosaic bioprostheses are indicated for the replacement of malfunctioning native or prosthetic aortic and/or mitral heart valves. **Contraindications:** None known. **Warnings/Precautions/Adverse Events:** Accelerated deterioration due to calcific degeneration of bioprosthesis may occur in children, adolescents, young adults, and patients with altered calcium metabolism (e.g., chronic renal failure, hyperparathyroidism). Adverse events can include: angina, cardiac dysrhythmias, death, endocarditis, heart failure, hemolysis, hemolytic anemia, anticoagulant/antiplatelet-related hemorrhage, infection other than endocarditis, transvalvular or paravalvular leak, myocardial infarction, nonstructural dysfunction (obstructive pannus ingrowth, suture dehiscence, inappropriate sizing, other), stroke, structural deterioration (calcification, leaflet tear, other), thromboembolism, and valve thrombosis. It is possible that these complications could lead to reoperation, explantation, permanent disability, or death. **Caution:** Federal law (USA) restricts these devices to sale by or on the order of a physician. For a listing of indications, contraindications, precautions, warnings, and potential adverse events, please refer to the Instructions for Use (IFU). If applicable, consult electronic IFUs (eIFUs) at www.medtronic.com/manuals. Note: eIFUs can be viewed using a current version of any major internet browser.

Evolut™ Transcatheter aortic valve replacement system

Indications
The Medtronic Evolut™ PRO+, Evolut™ FX, and Evolut™ FX+ 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 appropriate for the transcatheter heart valve replacement therapy.

The Medtronic Evolut PRO+, Evolut FX, and Evolut FX+ 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 ≥ 8% or at a ≥ 15% risk of mortality at 30 days).

Contraindications
The Medtronic Evolut PRO+, Evolut FX, and Evolut FX+ Systems are contraindicated in patients who cannot tolerate Nitinol (titanium or nickel), gold (for Evolut FX and Evolut FX+ Systems alone), an anticoagulation/antiplatelet regimen, or who have active bacterial endocarditis or other active infections.

Warnings
General Implantation of the Evolut PRO+, Evolut FX, and Evolut FX+ Systems should be performed only by physicians who have received Medtronic Evolut PRO+, Evolut FX, or Evolut FX+ 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 due to calcific degeneration of the bioprostheses may occur in: children, adolescents, or young adults; patients with altered calcium metabolism (e.g., chronic renal failure or hyperthyroidism).

Precautions

General Clinical long-term durability has not been established for the bioprosthesis. Evaluate bioprosthesis performance as needed during patient follow-up. The safety and effectiveness of the Evolut PRO+, Evolut FX, and Evolut FX+ Systems have not been evaluated in the pediatric population. The safety and effectiveness of

the bioprostheses 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 ≤ 1.0 cm^2 or aortic valve area index ≤ 0.6 cm^2/m^2, a mean aortic valve gradient ≥ 40 mm Hg, or a peak aortic-jet velocity ≥ 4.0 m/s; (2) symptomatic severe low-flow, low-gradient aortic stenosis – aortic valve area ≤ 1.0 cm^2 or aortic valve area index ≤ 0.6 cm^2/m^2, a mean aortic valve gradient < 40 mm Hg, and a peak aortic-jet velocity < 4.0 m/s; with untreated, clinically significant coronary artery disease requiring revascularization; with a preexisting prosthetic heart valve with a rigid support structure in either the mitral or pulmonic position if either the preexisting prosthetic heart valve could affect the implantation or function of the bioprosthesis or the implantation of the bioprosthesis could affect the function of the preexisting prosthetic heart valve; patients with liver failure (Child-Pugh Class C); with cardiogenic shock manifested by low cardiac output, vasopressor dependence, or mechanical hemodynamic support; patients who are pregnant or breastfeeding. The safety and effectiveness of an Evolut PRO+, Evolut FX, or Evolut FX+ bioprosthesis implanted within a failed preexisting transcatheter bioprosthesis have not been demonstrated. Implanting an Evolut PRO+, Evolut FX, or Evolut FX+ bioprosthesis in a degenerated surgical bioprosthetic valve (transcatheter aortic valve in surgical aortic valve [TAV-in-SAV]) should be avoided in the following conditions: The degenerated surgical bioprosthetic valve presents with: a significant concomitant paravalvular leak (between the prosthesis and the native annulus), 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-labeled inner diameter < 17 mm. The safety and effectiveness of the bioprostheses 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^3), thrombocytopenia (platelet count < 50,000 cells/mm^3), 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 per the baseline diagnostic imaging or surgical bioprosthetic aortic annulus size < 17 mm or > 30 mm; transarterial access unable to accommodate an 18 Fr introducer sheath or the 14 Fr equivalent Evolut PRO+ inline sheath when using model D-EVPROP2329US or Evolut FX Delivery Catheter System with inline sheath when using model D-EVOLUTFX-2329 or transarterial access unable to accommodate a 22 Fr introducer sheath or the 18 Fr equivalent Evolut PRO+ inline sheath when using model D-EVPROP34US or Evolut FX Delivery Catheter System with inline sheath when using model D-EVOLUTFX-34; prohibitive left ventricular outflow tract calcification; sinus of Valsalva anatomy that would prevent adequate coronary perfusion; significant aortopathy requiring ascending aortic replacement; 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.

Before 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. 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 ≥ 5 mm when using models D-EVPROP2329US/D-EVOLUTFX-2329 or ≥ 6 mm when using models D-EVPROP34US/D-EVOLUTFX-34, or patients must present with an ascending aortic (direct aortic) access site ≥ 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° for right subclavian/axillary access or > 70° for femoral and left subclavian/axillary access. For subclavian access, patients with a patent left internal mammary artery (LIMA) graft must present with access vessel diameters that are either ≥ 5.5 mm when using models D-EVPROP2329US/D-EVOLUTFX-2329 or ≥ 6.5 mm when using models D-EVPROP34US/D-EVOLUTFX-34. 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 preexisting patent RIMA graft. For transfemoral access, use caution in patients who present with multiplanar curvature of the aorta, acute angulation of the aortic arch, an ascending aortic aneurysm, or severe calcification in the aorta and/or vasculature. If ≥ 2 of these factors are present, consider an alternative access route to prevent vascular complications. Limited clinical data are available for transcatheter aortic valve replacement in patients with a congenital bicuspid aortic valve who are deemed to be at low surgical risk. Anatomical characteristics should be considered when using the valve in this population. In addition, patient age should be considered as long-term durability of the valve has not been established.

During Use If a misload is detected during fluoroscopic inspection, do not attempt to reload the bioprosthesis. Discard the entire system. Inflow crown overlap that has not ended before the 4th node within the capsule increases the risk of an infold upon deployment in constrained anatomies, particularly with moderate-severe levels of calcification and/or bicuspid condition. Do not attempt to direct load the valve. 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. 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 an Evolut PRO+, Evolut FX, or Evolut FX+ bioprosthesis implanted within a transcatheter bioprosthesis have not been demonstrated.

Potential adverse events
Potential risks associated with the implantation of the Evolut PRO+, Evolut FX, or Evolut FX+ transcatheter aortic valve may include, but are not limited to, the following: • death • myocardial infarction, cardiac arrest, cardiogenic shock, or 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 recrossing 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 • 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, or stenosis) • mitral valve regurgitation or injury • conduction system disturbances (e.g., atrioventricular node block, left bundle-branch block, asystole), which may require a permanent pacemaker • infection (including septicemia) • hypotension or hypertension • hemolysis • peripheral ischemia • General surgical risks applicable to transcatheter aortic valve implantation: • bowel ischemia • abnormal lab values (including electrolyte imbalance) • allergic reaction to antiplatelet agents, contrast medium, or anesthesia • exposure to radiation through fluoroscopy and angiography • permanent disability.

Please reference the Evolut PRO+, Evolut FX, and Evolut FX+ 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 Evolut™ PRO+ System, the commercial name of the Evolut™ FX device is Medtronic Evolut™ FX System, and the commercial name of the Evolut™ FX+ device is Medtronic Evolut™ FX+ System.

† The benefits of AOA tissue treatment have been demonstrated through animal testing. No direct clinical evaluation of the benefits of AOA treatment in humans has been conducted.

‡ Moderate SVD was defined as (1) hemodynamic valve deterioration (HVD) showing an increase in mean aortic gradient of 10 mmHg or greater from discharge or 30-day echocardiography to last available echocardiography with a final mean gradient of 20 mmHg or greater or (2) new occurrence or increase of 1 grade or more of intraprosthetic AR resulting in moderate or severe AR. Severe SVD was defined as (1) HVD showing an increase in mean gradient of 20 mmHg or greater from discharge or 30-day echocardiography to last available echocardiography with a final mean gradient of 30 mmHg or greater or (2) new occurrence or increase of 2 grades or more of intraprosthetic AR resulting in severe AR.

§ Per VARC-3 criteria.

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