5-Year Incidence, Outcomes and Predictors of Structural Valve Deterioration of Transcatheter and Surgical Aortic Bioprostheses: *Insights from the CoreValve US Pivotal and SURTAVI Trials*

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Corevalve Evolut Pooled Analysis

Disclosures

Within the past 12 months, I have had a financial interest/arrangement or affiliation with the organization(s) listed below

Financial Relationship:	**Company:**
Research grants	Boston Scientific, Medtronic

Medtronic personnel performed all statistical analyses and assisted with the graphical display of the data presented

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Background

- Transcatheter aortic valve replacement (TAVR) is an established treatment for severe aortic stenosis (AS) in patients of all risk levels.
- Younger, low risk patients with increasingly long expected survivals are being offered TAVR.
- The lifetime management of these patients requires an understanding of bioprosthetic valve durability and failure.
- The VARC-3 and EAPCI consensus documents define four modes of bioprosthetic valve dysfunction: Structural valve deterioration (SVD), non-structural valve dysfunction, thrombosis and endocarditis. [1,2]

[1] VARC-3 Writing Committee, et al. European Heart Journal 42.19 (2021): 1825-1857
[2] Capodanno D., et al. European Heart Journal 38.45 (2017): 3382-3390

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Limited data exist on the incidence and factors associated with SVD after TAVR and surgery from large-scale, multicenter and randomized clinical trials

- Previous work demonstrated early generation intra-annular, balloon-expandable bioprostheses have significantly higher 5-year rates of SVD compared to surgery, whereas newer generation annular valves have similar SVD rates. [1]

[1] Pibarot P., et al. Journal of the American College of Cardiology 76.16 (2020): 1830-1843

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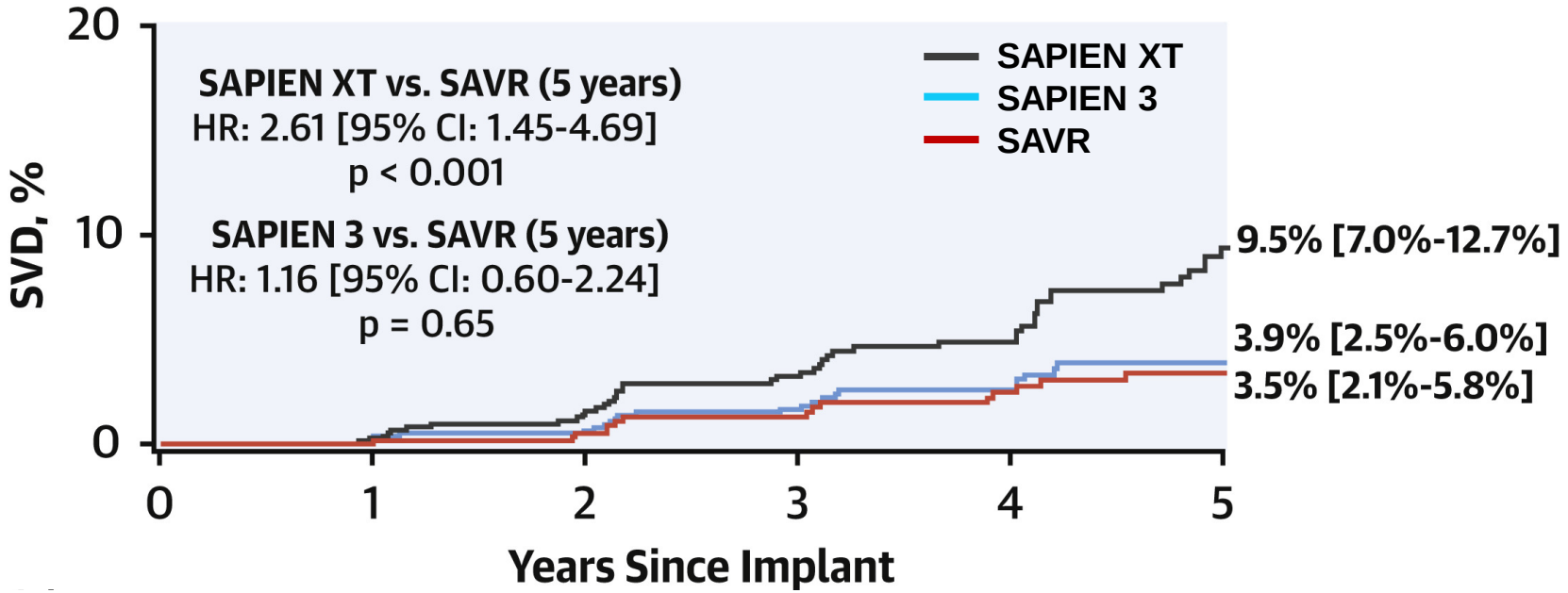

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Limited data exist on the incidence and factors associated with SVD after TAVR and surgery from large-scale, multicenter and randomized clinical trials

- Previous work demonstrated early generation intra-annular, balloon-expandable bioprostheses have significantly higher 5-year rates of SVD compared to surgery, whereas newer generation annular valves have similar SVD rates. [1]
- Our prior analysis with supra-annular, self-expanding bioprostheses found significantly lower 5-year rates of hemodynamic valve deterioration (HVD) or reintervention due to stenosis with TAVR vs. Surgery, and reported an association between HVD and clinical outcomes. [2]

[1] Pibarot P., et al. Journal of the American College of Cardiology 76.16 (2020): 1830-1843
[2] O'Hair, D., et al. Journal of the American College of Cardiology, 77(18_Supplement_1), 904-904

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Study Objective

To evaluate the 5-year incidence, outcomes and predictors of hemodynamic structural valve deterioration (SVD) in patients undergoing supra-annular, self-expanding TAVR and surgery from the CoreValve US Pivotal and SURTAVI trials

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Study Population and Definitions

Comparison of SVD rates between TAVR and Surgery:

- CoreValve US High Risk Pivotal Trial
- SURTAVI Intermediate Risk Trial

} Randomized Clinical Trials (RCTs)

Association with clinical outcomes and predictors of SVD:

- CoreValve US Extreme Risk Pivotal Trial
- CoreValve Continued Access Study (CAS)

} Addition of Non-RCTs

SVD was defined as ≥ moderate hemodynamic valve deterioration (HVD): [1]

- Increase in mean gradient ≥10 mm Hg from discharge/30-day echo to last available echo AND mean gradient ≥20 mm Hg at last available echo.
- OR new onset/increase of intra-prosthetic aortic regurgitation (AR) ≥ moderate

Independent Core laboratory assessed TTEs were used (if not available, site-reported readings).

[1] Adapted from VARC-3 Writing Committee, et al. European Heart Journal 42.19 (2021): 1825-1857 and Capodanno D., et al. European Heart Journal 38.45 (2017): 3382-3390 1825-1857

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Study Methods

- The 5-year cumulative incidence of SVD was calculated for the RCT cohorts using Fine-Gray regression interval censoring and treating death as competing risk. [1]

- Univariate Cox proportional hazard models examined the association of SVD (time dependent covariate) with clinical outcomes: all-cause mortality, cardiovascular mortality and hospitalization for AV disease or worsening heart failure.

- Baseline characteristics associated with SVD were identified using univariate and multivariate Fine-Gray regression for interval censoring analysis and treating death as competing risk.

[1] Delord M. and Genin E., Journal of Statistical Computation and Simulation 86.11 (2016): 2217-2228

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Study Demographics

	Surgery RCT (N=971)	CoreValve/Evolut RCT (N=1128)	CoreValve/Evolut Non-RCT (N=2663)
Age, years	80.6 ± 6.3	80.9 ± 6.5	83.1 ± 8.0*
Male	527 (54.3)	632 (56.0)	1446 (54.3)
Body surface area, m^2	1.9 ± 0.2	1.9 ± 0.2	1.9 ± 0.3*
STS-PROM, %	5.3 ± 2.5	5.2 ± 2.4	8.7 ± 4.6*
NYHA III/IV	639 (65.8)	757 (67.1)	2288 (85.9)*
Prior percutaneous coronary intervention	253 (26.1)	280 (24.8)	1052 (39.5)*
Prior coronary artery bypass surgery	213 (21.9)	229 (20.3)	973 (36.5)*
Hypertension	889 (91.6)	1056 (93.6)	2458 (92.3)
Creatinine > 2.0 mg/dL	24 (2.5)	24 (2.1)	121 (4.5)*
Prior atrial fibrillation/flutter	305 (31.4)	348 (30.9)	1132 (42.6)*
Baseline anticoagulation therapy	236 (24.3)	236 (20.9)	558 (21.0)

Mean ± SD or no. (%)
No significant differences between RCT cohorts
*P<0.01 vs. TAVR RCT

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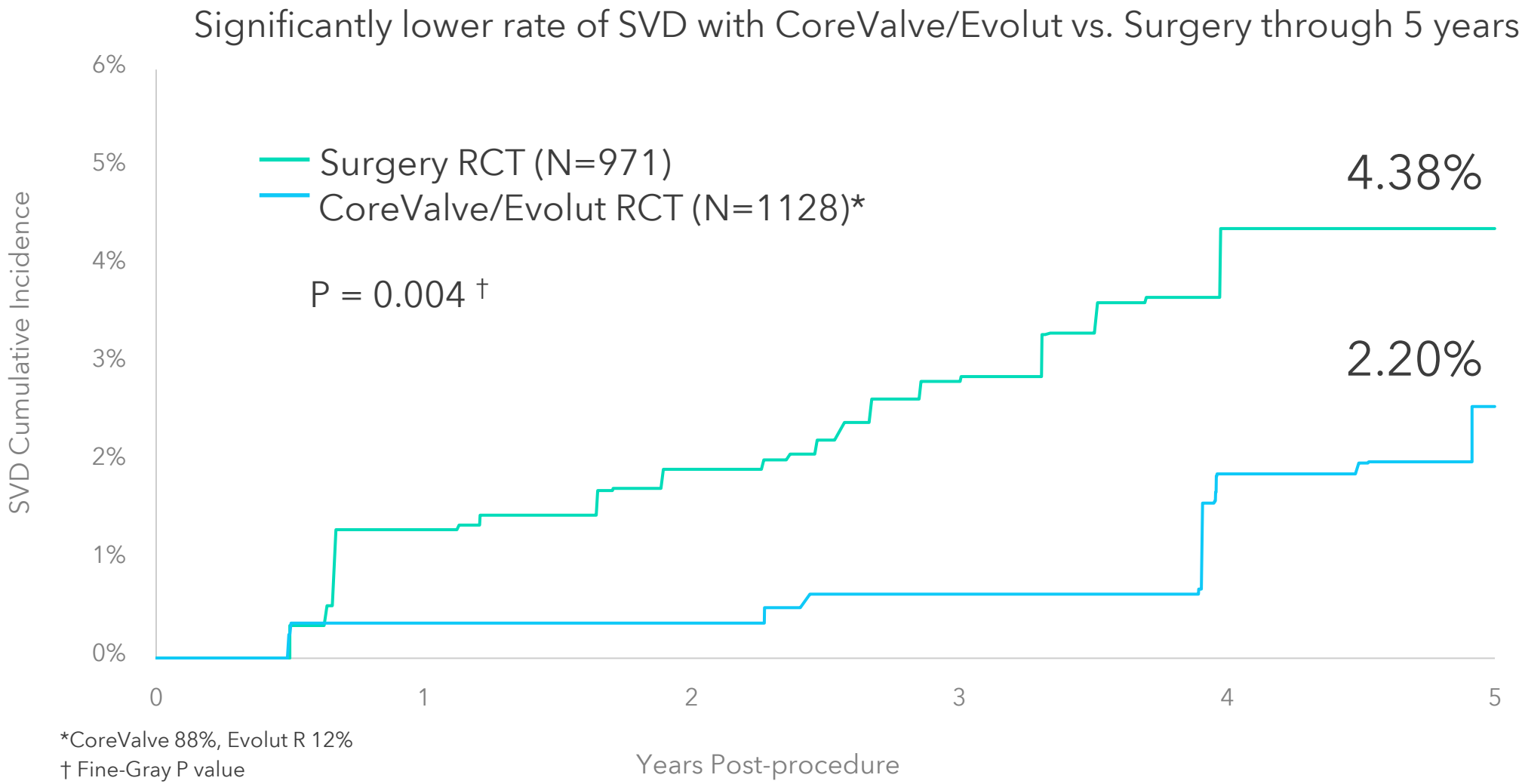
5-Year SVD Adjusted For Competing Risk of Mortality



*CoreValve 88%, Evolut R 12%

† Fine-Gray P value

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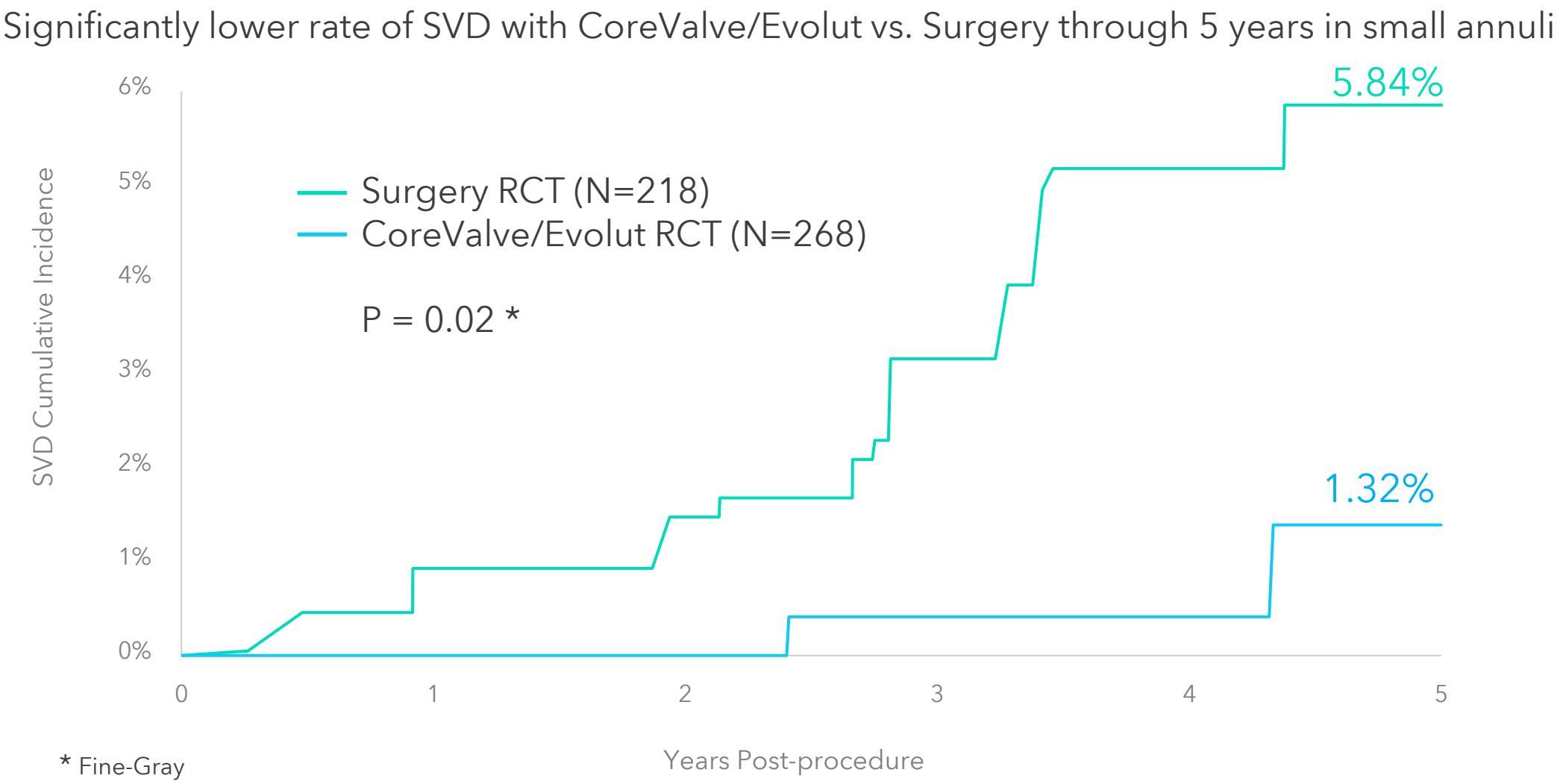
5-Year SVD in Smaller (≤23mm) Annular Diameter



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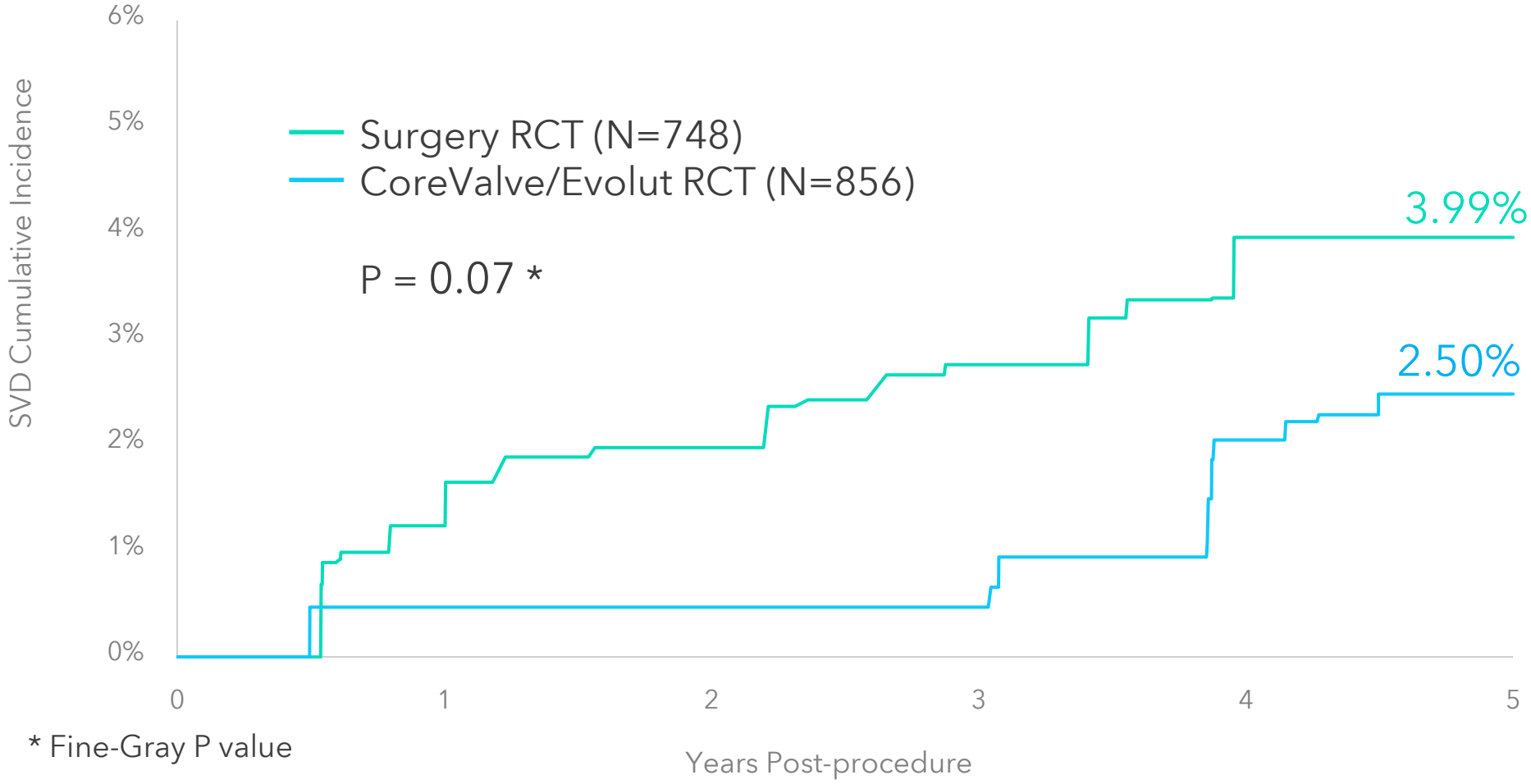
5-Year SVD in Larger (≥23mmm) Annular Diameter

Trend towards a lower rate of SVD with CoreValve/Evolut vs. Surgery through 5 years in larger annuli



* Fine-Gray P value

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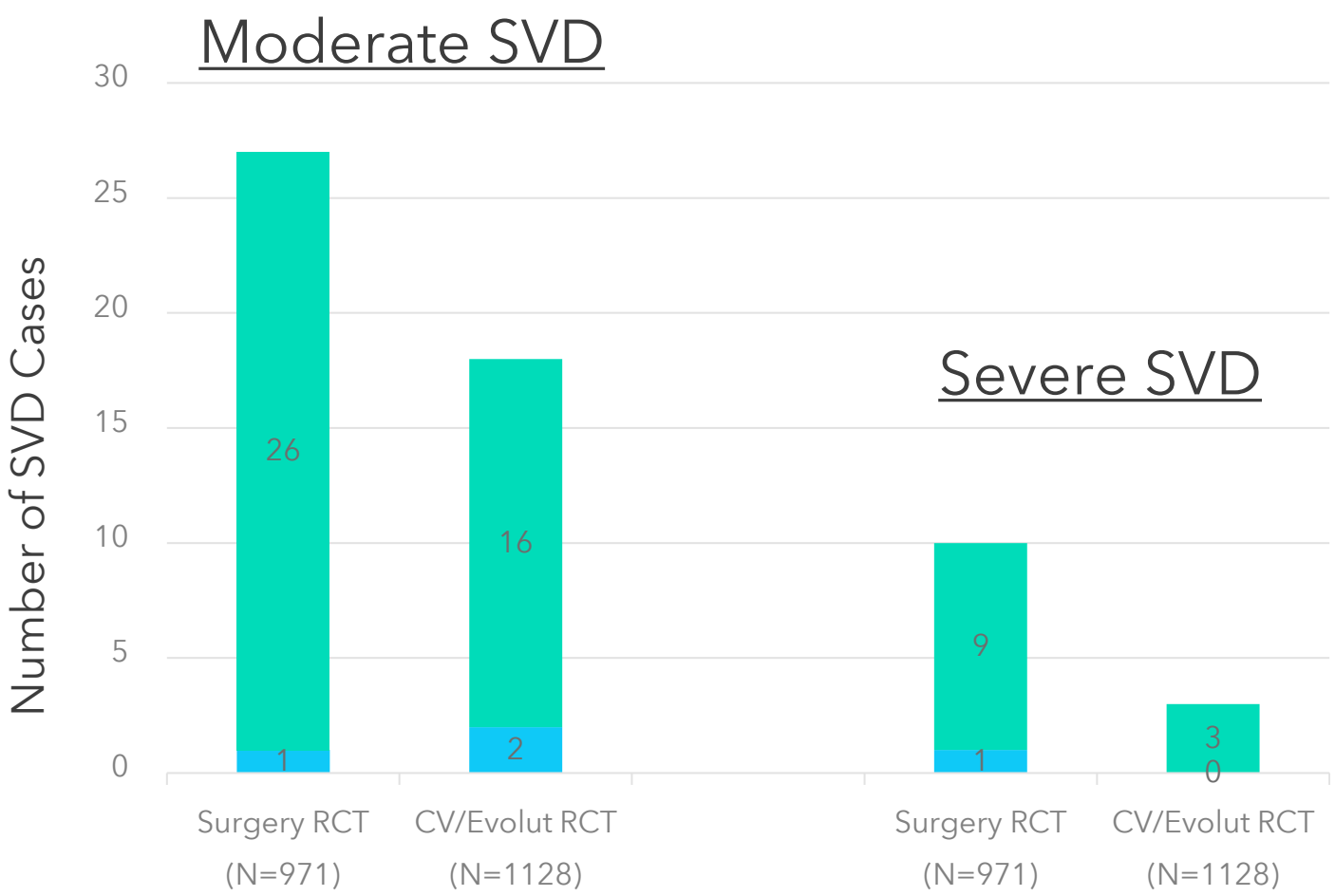
TAVR Reductions with Both Moderate and Severe SVD



Stenosis

Moderate AS: Increase in mean gradient ≥10 mm Hg from discharge/30-day echo to last available echo AND mean gradient ≥20 mm Hg at last available echo

Severe AS: Increase in mean gradient ≥20 mm Hg from discharge/30-day echo to last available echo AND mean gradient ≥30 mm Hg at last available echo

Regurgitation

Moderate AR: New onset or increase of intra-prosthetic AR resulting in ≥ moderate

Severe AR: New onset or increase of ≥ 2 grades of intra-prosthetic AR resulting in severe

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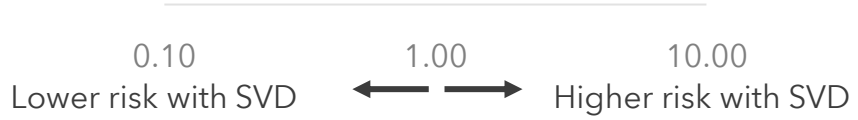
Worsened Clinical Outcomes in Patients Who Develop SVD

	HR (95% CI)	P value
Pooled Surgery RCT and All CoreValve/Evolut* (N=4762)		
All-cause mortality	2.03 (1.46, 2.82)	<0.001
Cardiovascular mortality	1.86 (1.20, 2.90)	0.006
Aortic valve-related hospitalization	2.17 (1.23, 3.84)	0.008
Composite †	2.02 (1.42, 2.88)	<0.001
Surgery RCT (N=971)		
All-cause mortality	2.45 (1.40, 4.30)	0.002
Cardiovascular mortality	2.37 (1.10, 5.08)	0.03
Aortic valve-related hospitalization	2.20 (0.81, 5.98)	0.12
Composite †	2.73 (1.53, 4.88)	<0.001
All CoreValve/Evolut TAVR* (N=3791)		
All-cause mortality	2.34 (1.55, 3.53)	<0.001
Cardiovascular mortality	2.17 (1.26, 3.76)	0.006
Aortic valve-related hospitalization	2.45 (1.22, 4.93)	0.01
Composite †	2.03 (1.29, 3.19)	0.002



*RCT and Non-RCT cohorts
CoreValve 97%, Evolut R 3%
† All-cause mortality or aortic valve-related hospitalization

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Baseline Characteristics of Patients With and Without SVD

	Patients with SVD* (N=97)	Patients without SVD* (N=4665)
Age, years	79.4 ± 8.8	82.1 ± 7.4 †
Male	47 (49.5)	2558 (54.8)
Body surface area, m^2	1.9 ± 0.3	1.9 ± 0.2 †
STS-PROM, %	6.0 ± 4.1	7.2 ± 4.2 †
NYHA III/IV	67 (70.5)	3617 (77.5)
Prior percutaneous coronary intervention	22 (23.2)	1563 (33.5) †
Prior coronary artery bypass surgery	22 (23.2)	1393 (29.8)
Hypertension	85 (87.4)	4320 (92.6)
Creatinine > 2.0 mg/dL	3 (3.2)	166 (3.6)
Prior atrial fibrillation/flutter	24 (25.3)	1761 (37.8) †
Prior anticoagulation therapy	16 (16.8)	1014 (21.7)

Mean ± SD or no. (%)

* RCT and Non-RCT cohorts

† P<0.05 vs. Patients with SVD

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Univariate and Multivariate Predictors of 5-year SVD

	Univariate Model		Multivariate Model	
Pooled Surgery RCT and All CoreValve/Evolut TAVR* (N=4762)	HR (95% CI)	P value	HR (95% CI)	P value
Age, years	0.96 (0.94, 0.98)	<0.001	0.97 (0.95, 1.00)	0.05
Male	0.79 (0.53, 1.17)	0.24	0.62 (0.39, 0.99)	0.04
Body surface area (BSA), m^2 †	1.21 (1.01, 1.45)	0.04	1.28 (1.05, 1.55)	0.01
STS-PROM, %	0.92 (0.85, 0.99)	0.03		
NYHA III/IV	0.71 (0.46, 1.10)	0.13		
Prior coronary artery bypass grafting	0.70 (0.43, 1.12)	0.14		
Prior percutaneous coronary intervention	0.59 (0.37, 0.95)	0.03	0.62 (0.38, 1.00)	0.05
Diabetes mellitus	1.29 (0.86, 1.94)	0.21		
Hypertension	0.56 (0.31, 1.03)	0.06	0.55 (0.30, 0.99)	0.05
Prior atrial fibrillation/flutter	0.55 (0.35, 0.87)	0.01	0.57 (0.35, 0.91)	0.02
CT-measured aortic annulus ≤23 mm	1.19 (0.75, 1.88)	0.47		
Body mass index, kg/m^2	1.04 (1.01, 1.07)	0.01		
Baseline anticoagulation therapy	0.72 (0.42, 1.23)	0.22		
Baseline antiplatelet therapy	0.72 (0.46, 1.11)	0.14		

Higher risk of developing SVD in patients with a higher body surface area

* RCT and Non-RCT cohorts; † HR units = 0.2

Backwards elimination multivariate modeling with stay criteria of P=0.1

Univariate analysis was also performed for additional covariates resulting in P>0.3 and included: Coronary artery disease, cerebrovascular disease, peripheral vascular disease, chronic lung disease/COPD, creatinine clearance <30 ml/min, baseline LVEF, baseline mean gradient, baseline EOA

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Limitations

- Current follow-up is limited to 5 years. Ten-year follow-up is ongoing for the SURTAVI and Low Risk RCTs.
- Contemporary criteria for SVD require prospective collection of comprehensive echocardiographic parameters. In the current studies, there was incomplete collection of changes in EOA and DVI, and this analysis was restricted to changes in gradients and AR severity.
- Correlates with invasive gradients were not collected in this study, although changes in Doppler TTE gradients were highly predictive of 5-year outcomes.
- The competing risk of mortality limited the number of subjects with SVD, similar to prior surgical trials.

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Conclusions

- In patients with severe AS at intermediate or high surgical risk, the 5-year rate of SVD was 4.38% in patients undergoing surgery and 2.20% in patients undergoing CoreValve/Evolut TAVR (P=0.004)
- This difference in SVD was more profound in patients with smaller (≤23 mm) annuli (5.84% surgery vs 1.32% TAVR; P=0.02), but a trend was also found in patients with larger (>23 mm) annuli (3.99% surgery vs 2.50% TAVR; P=0.07).
- The Doppler-derived SVD imparted a near 2-fold risk for all cause mortality (P< 0.001) and hospitalization for AV disease or worsening heart failure (P=0.008) at 5 years.
- Multivariate predictor analysis found a higher risk of developing SVD in patients with a higher body surface area, and a lower risk of SVD in men, older patients and those with prior PCI and atrial fibrillation.

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Clinical Implications

- The CoreValve / Evolut supra-annular, self-expanding bioprostheses is the first and only transcatheter bioprostheses to demonstrate lower rates of SVD compared with Surgery in RCTs (This pooled analysis; 8-year NOTION[1]).

- Serial Doppler TTE is a valuable tool to monitor patients after TAVR. This is the first analysis to validate clinical criteria for SVD and its association with clinical outcomes, resulting in a near 2-fold increased risk for death and hospitalization for AV disease or worsening heart failure.

- Long term 10-year follow-up is ongoing, valve durability should be an important consideration for the selection of the first bioprosthetic valve in lower risk patients with severe symptomatic AS.

1Jørgensen, Troels Højsgaard, et al. European heart journal 42.30 (2021): 2912-2919

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Indications The Medtronic CoreValve™ Evolut™ R, CoreValve™ Evolut™ PRO, and 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 appropriate for the transcatheter heart valve replacement therapy. The Medtronic CoreValve Evolut R, CoreValve Evolut PRO, and 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 ≥ 8% or at a ≥ 15% risk of mortality at 30 days).
Contraindications The CoreValve Evolut R, CoreValve Evolut PRO, and Evolut PRO+ systems are contraindicated in patients who cannot tolerate Nitinol (titanium or nickel), an anticoagulation/antiplatelet regimen, or who have active bacterial endocarditis or other active infections.
Warnings *General* Implantation of the CoreValve Evolut R, PRO, and PRO+ systems should be performed only by physicians who have received Medtronic CoreValve Evolut R, PRO, 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. *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 CoreValve Evolut R, PRO, 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 ≤ 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 a CoreValve Evolut R, Evolut PRO, or Evolut PRO+ bioprosthesis implanted within a failed preexisting transcatheter bioprosthesis has not been demonstrated. Implanting a CoreValve Evolut R, Evolut PRO, or Evolut PRO+ 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 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^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 for Evolut R/ Evolut PRO+ 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/Evolut PRO+ and < 17 mm or > 26 mm for 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/D-EVPROP2329US 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 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; 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 Model ENVEOR-US/ENVPRO-14-US/D-EVPROP2329US or ≥ 5.5 mm when using Model ENVEOR-N-US/ENVPRO-16-US or ≥ 6 mm when using Model D-EVPROP34US, 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 ENVPRO-14-US/ENVEOR-L-US/D-EVPROP2329US or ≥ 6 mm when using Models ENVPRO-16-US and ENVEOR-N-US or ≥ 6.5 mm when using Model D-EVPROP34US. 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 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 a CoreValve Evolut R, Evolut PRO, or Evolut PRO+ bioprosthesis implanted within a transcatheter bioprosthesis have not been demonstrated.
Potential adverse events Potential risks associated with the implantation of the CoreValve Evolut R, CoreValve Evolut PRO, or Evolut PRO+ 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 CoreValve Evolut R, CoreValve Evolut PRO, and 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™ R device is Medtronic CoreValve™ Evolut™ R System, the commercial name of the Evolut™ PRO device is Medtronic CoreValve™ Evolut™ PRO System, and the commercial name of the Evolut™ PRO+ device is Medtronic Evolut™ PRO+ System.

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UC202216679b EN
06/2022