5-Year Incidence of Bioprosthetic Valve Dysfunction in Patients Randomized to Surgery or TAVR: *Insights from the CoreValve US Pivotal and SURTAVI Trials*

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For the CoreValve – Evolut Clinical Investigators

CRT23

CoreValve-Evolut Pooled Analysis

Disclosures

CoreValve™ Evolut™ Clinical Program

Research support from Boston Scientific and Medtronic.

Honoraria from Boston Scientific and Medtronic outside the submitted work.

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Background

CoreValve™ Evolut™ Clinical Program

Long-term bioprosthetic valve performance is a critical consideration when evaluating the durability of transcatheter aortic valve replacement (TAVR), particularly in younger, low risk patients with longer life expectancies.

The VARC-3 and EAPCI consensus documents recognize four components of valve performance, evaluated as bioprosthetic valve dysfunction (BVD) [1,2]:

- ✓ Structural valve deterioration (SVD)
- ✓ Non-structural valve dysfunction (NSVD)
- ✓ Valve thrombosis
- ✓ Endocarditis

[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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Background

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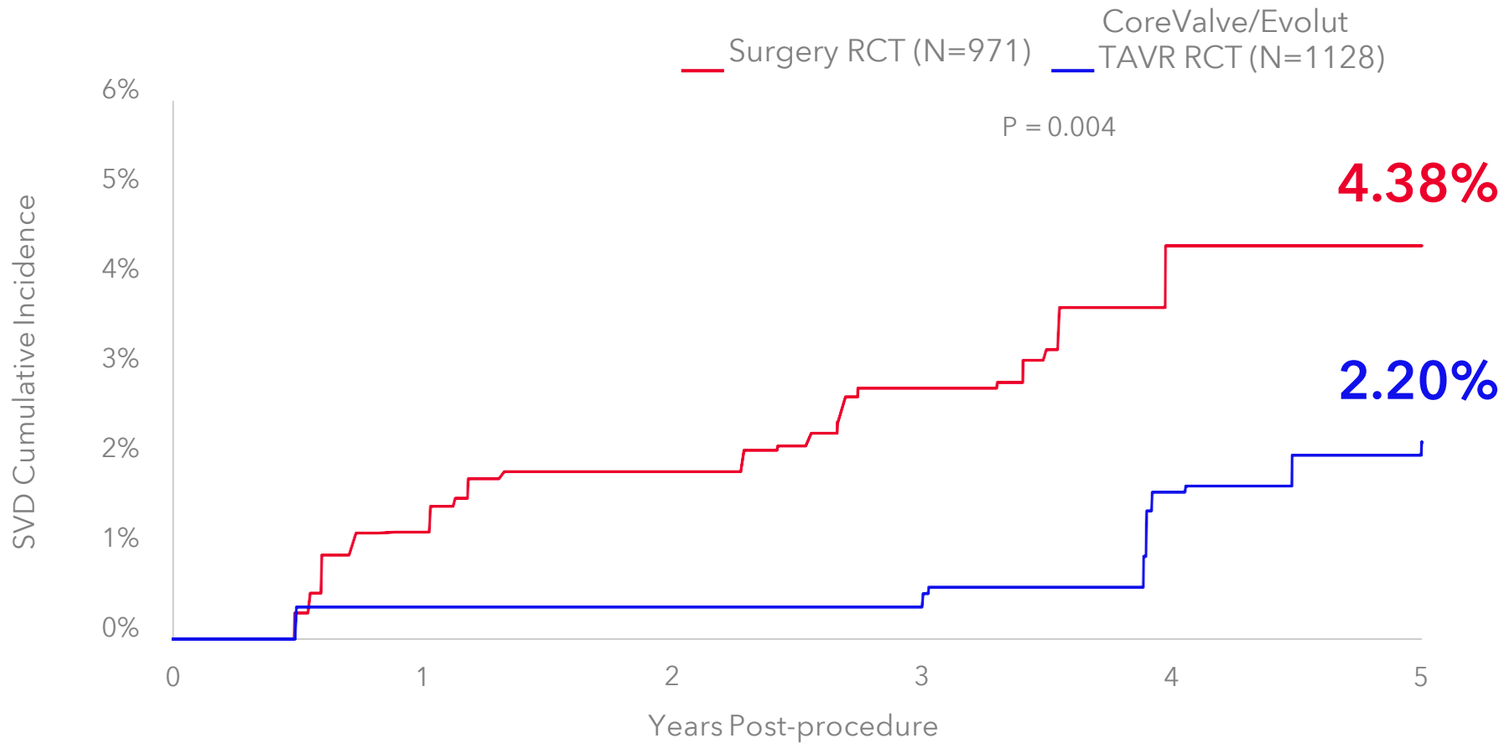
A recent analysis with supra-annular, self-expanding TAVR bioprostheses demonstrated a significantly lower 5-year rate of SVD* with TAVR vs. Surgery and reported an association between SVD and worse clinical outcomes.[1]



[1] O'Hair, D., et al. JAMA Cardiology (2022) doi:10.1001/jamacardio.2022.4627

*Mean gradient increase ≥10 mmHg from discharge/30-day to last echo AND ≥20 mmHg at last echo OR new onset/increase of ≥ moderate intraprosthetic aortic regurgitation

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Background

CoreValve™ Evolut™ Clinical Program

- A recent analysis with supra-annular, self-expanding TAVR bioprostheses demonstrated a significantly lower 5-year rate of SVD with TAVR vs. Surgery and reported an association between SVD and worse clinical outcomes.[1]

- Limited data exist on the incidence and clinical importance of all components of valve performance after TAVR and surgery from large-scale, multicenter and randomized clinical trials.

[1] O'Hair, D., et al. JAMA Cardiology (2022) doi:10.1001/jamacardio.2022.4627

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Study Objective

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To evaluate the incidence, outcomes and predictors of long-term valve performance, as assessed by 5-year BVD, in patients undergoing supra-annular, self-expanding TAVR or surgery

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Study Population and Definitions

Datasets: CoreValve US high risk pivotal and SURTAVI intermediate risk randomized clinical trials

Analysis 1: Cumulative incidence rate of valve performance (BVD)

Analysis 2: Association of valve performance (BVD) with clinical outcomes

Analysis 3: Pre-procedure predictors of valve performance (BVD)

BVD definition[1,2]	
SVD [3]	Mean gradient increase ≥10 mmHg from discharge/30-day to last echo AND ≥20 mmHg at last echo OR new onset/increase of ≥ moderate intraprosthetic aortic regurgitation*
NSVD	Severe prosthesis-patient mismatch PPM (VARC-3) at 30-day/discharge[1] OR severe paravalvular regurgitation (PVL) through 5 years *
Thrombosis†	Clinical valve thrombosis
Endocarditis†	Modified Duke criteria

*Core lab if available, otherwise site-reported

†CEC adjudicated

[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
[3] Adapted from VARC-3 Writing Committee, et al. & Capodanno D., et al.

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Study Demographics

CoreValve US Pivotal and SURTAVI trials (N=2099)	Surgery (N=971)	CoreValve/Evolut TAVR (N=1128)
Age, years	80.6 ± 6.3	80.9 ± 6.5
Male	527 (54.3)	632 (56.0)
Body surface area, m^2	1.9 ± 0.2	1.9 ± 0.2
STS-PROM, %	5.3 ± 2.5	5.2 ± 2.4
NYHA III/IV	639 (65.8)	757 (67.1)
Diabetes mellitus	374 (38.5)	390 (34.6)
Hypertension	889 (91.6)	1056 (93.6)
Cerebrovascular disease	184 (19.0)	218 (19.4)
Coronary artery bypass surgery	213 (21.9)	229 (20.3)
Atrial fibrillation/flutter	305 (31.4)	348 (30.9)
Prior percutaneous coronary intervention	253 (26.1)	280 (24.8)
6-minute walk, m	241.1 ± 119.9	236.8 ± 118.0
Creatinine clearance < 30 ml/min	42 (4.3)	57 (5.1)
Prior antiplatelet therapy	182 (18.7)	387 (34.3)
Prior anticoagulation therapy	236 (24.3)	236 (20.9)

Mean ± SD or no. (%)
No significant differences between randomized cohorts except for prior antiplatelet therapy

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5-Year Valve Performance

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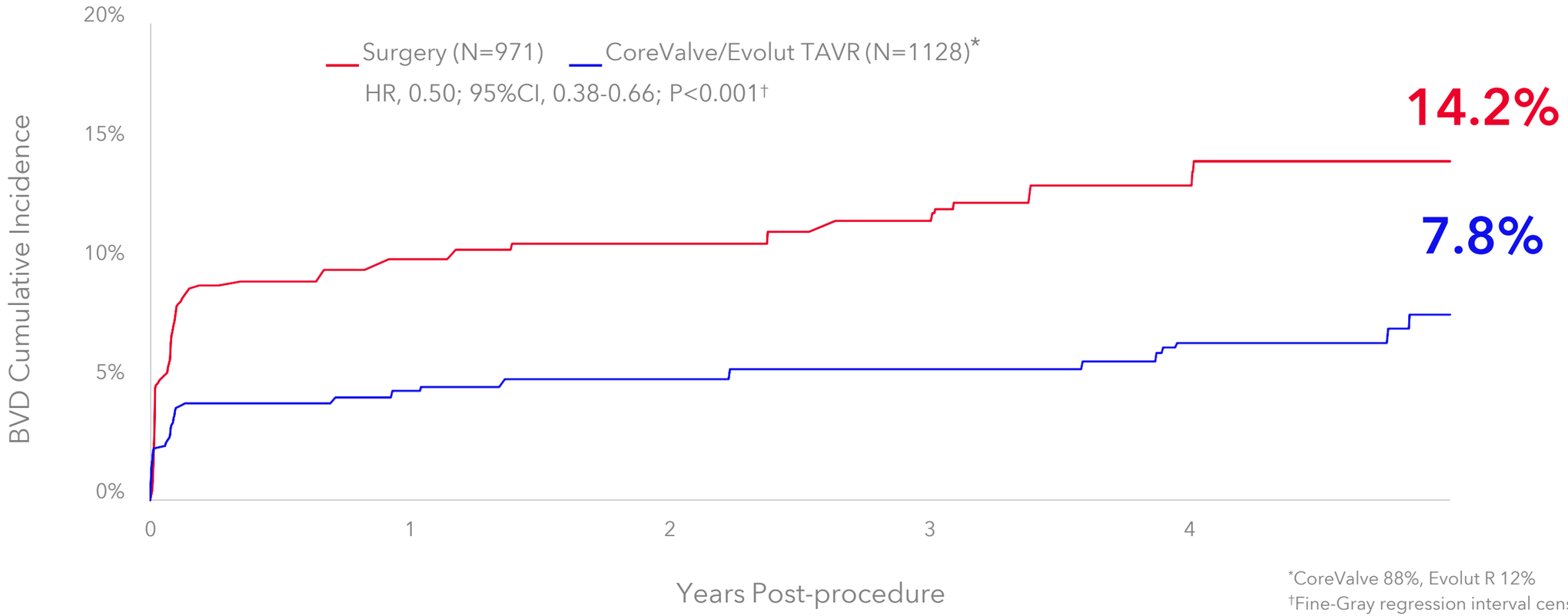
Significantly lower rate of BVD with CoreValve/Evolut TAVR vs. Surgery through 5 years



*CoreValve 88%, Evolut R 12%
†Fine-Gray regression interval censoring and treating death as a competing risk

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Components of 5-Year Valve Performance

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2x lower SVD and **3x** lower severe PPM with CoreValve/Evolut TAVR vs. Surgery

	CoreValve/ Evolut TAVR (N=1128)	Surgery (N=971)	HR (95% CI)	P value
BVD, %	**7.8**	**14.2**	**0.50 (0.38, 0.66)**	**<0.001**
SVD	2.2	4.4	0.46 (0.27, 0.78)	0.004
NSVD*	4.3	8.8	0.48 (0.33, 0.68)	<0.001
Severe PPM – VARC3 (30-day/discharge)	3.7	11.8	0.29 (0.19, 0.43) †	<0.001
Severe PVL	1.2	0.2	5.51 (1.24,24.41)	0.02
Thrombosis	0.3	0.2	1.26 (0.21, 7.62)	0.80
Endocarditis	1.1	1.3	0.85 (0.38, 1.88)	0.68

BVD, SVD, NSVD, and severe PVL were calculated using Fine-Gray regression interval censoring and treating death as a competing risk.[1] Rate of severe PPM was estimated as a proportion (n/N). Thrombosis and endocarditis rates were estimated using proportional sub-distribution hazard regression for right-censored data.

*The survival method used to estimate the rate of NSVD considered all patients in the analysis. However, the proportion rate of severe PPM excluded subjects without 30-day/discharge echo from the denominator. Therefore, due to the smaller denominator the rate of severe PPM may be higher than the overall rate of NSVD.

†OR (95% CI)

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

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5-Year Valve Performance in Smaller (≤ 23 mm) Annular Diameters

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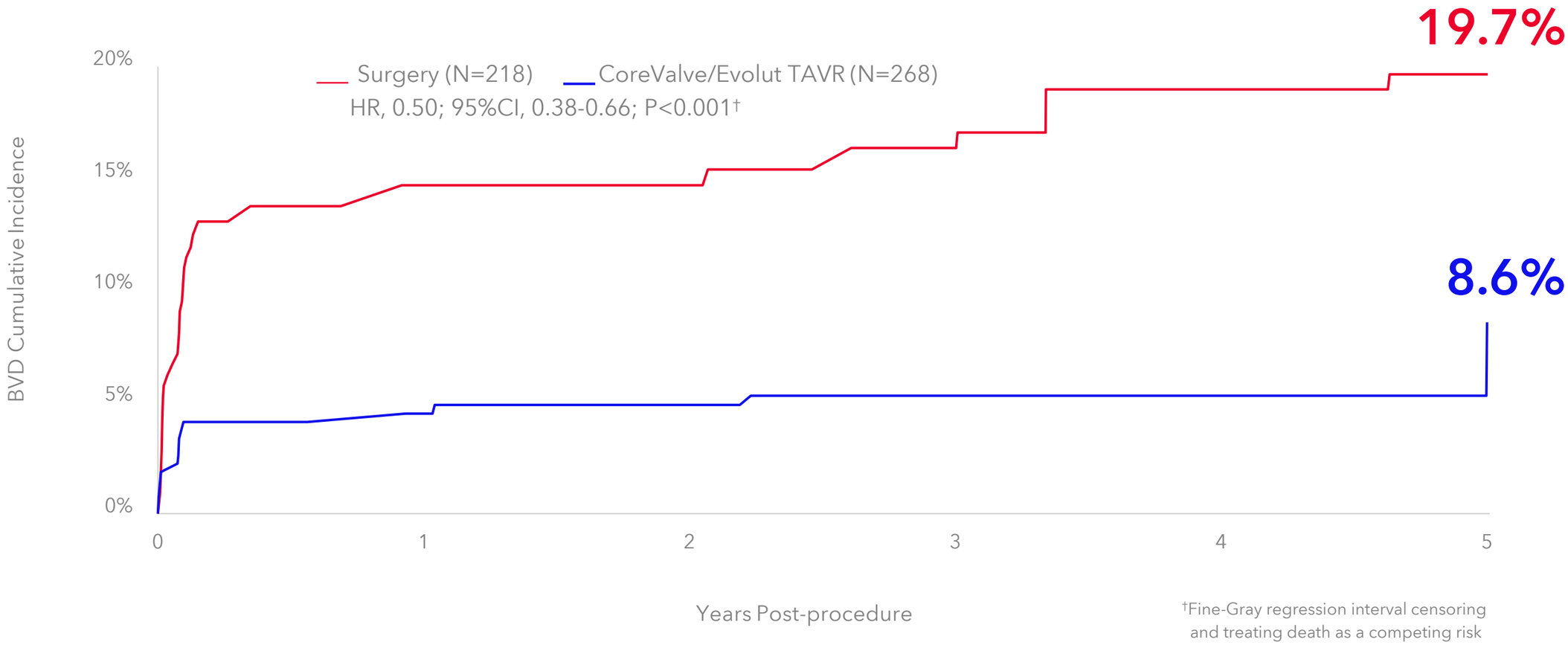
Significantly lower rate of BVD with CoreValve/Evolut TAVR vs. Surgery through 5 years in small annuli



†Fine-Gray regression interval censoring and treating death as a competing risk

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5-Year Valve Performance in Larger (> 23 mm) Annular Diameters

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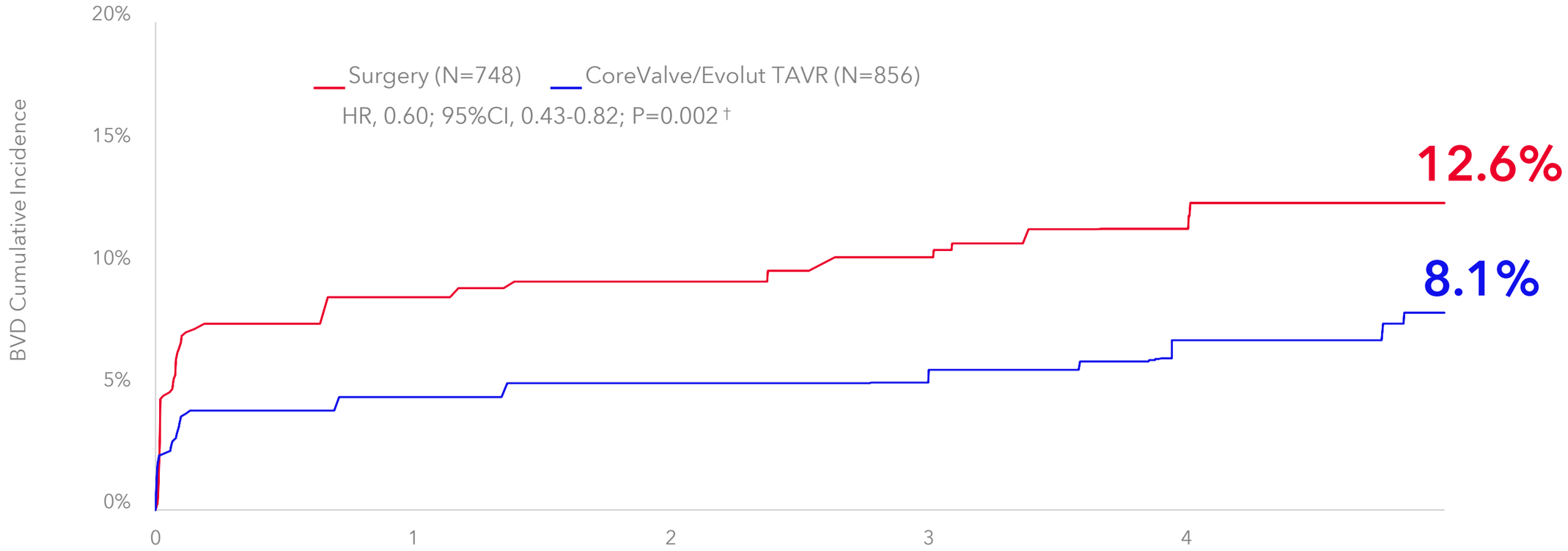
Significantly lower rate of BVD with CoreValve/Evolut TAVR vs. Surgery through 5 years in a large annuli



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Worsened Clinical Outcomes in Patients who developed BVD

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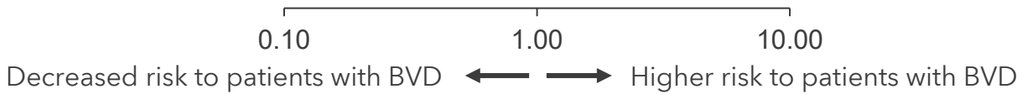
	HR (95% CI)	P value
Pooled Surgery and TAVR (N=2099)		
All-cause mortality	1.46 (1.13, 1.88)	0.004
Cardiovascular mortality	1.84 (1.34, 2.51)	<0.001
Hospitalization for valve disease/worsening HF	1.67 (1.23, 2.26)	0.001
Composite†	1.46 (1.16, 1.83)	0.001
Surgery (N=971)		
All-cause mortality	1.58 (1.15, 2.19)	0.005
Cardiovascular mortality	2.14 (1.44, 3.18)	<0.001
Hospitalization for valve disease/worsening HF	1.67 (1.11, 2.51)	0.01
Composite†	1.51 (1.12, 2.02)	0.007
CoreValve/Evolut TAVR (N=1128)		
All-cause mortality	1.34 (0.88, 2.04)	0.18
Cardiovascular mortality	1.51 (0.87, 2.60)	0.14
Hospitalization for valve disease/worsening HF	1.82 (1.14, 2.91)	0.01
Composite†	1.49 (1.04, 2.15)	0.03

† All-cause mortality or hospitalization for valve disease or worsening heart failure (HF)



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Baseline Characteristics of Patients with and without BVD

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Pooled Surgery and CoreValve/Evolut TAVR (N=2099)	Patients with BVD (N=210)	Patients without BVD (N=1889)
Age, years	79.5 ± 7.0	80.9 ± 6.3†
Male	101 (48.1)	1058 (56.0)†
Body surface area, m^2	1.9 ± 0.2	1.9 ± 0.2
STS-PROM, %	5.3 ± 2.8	5.2 ± 2.4
NYHA III/IV	141 (67.1)	1255 (66.4)
Diabetes mellitus	86 (41.0)	678 (35.9)
Hypertension	189 (90.0)	1756 (93.0)
Cerebrovascular disease	33 (15.7)	369 (19.6)
6-minute walk, m	216.9 ± 131.1	241.1 ± 117.2†
Creatinine clearance < 30 ml/min	18 (8.6)	81 (4.3)†
Baseline LVEF, % *	57.5 ± 12.5	60.4 ± 10.5†
Baseline AVA, cm^2 *	0.7 ± 0.2	0.8 ± 0.2†
Baseline mean gradient, mmHg *	50.0 ± 14.4	47.2 ± 13.7†

Mean ± SD or no. (%)
*Core lab if available, otherwise site-reported
† P<0.05 vs. Patients with BVD

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Pre-procedure Predictors of 5-Year BVD

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	Univariable Model		Multivariable Model§	
Pooled Surgery and CoreValve/Evolut TAVR (N=2099)	**HR (95% CI)**	**P value**	**HR (95% CI)**	**P value**
Age, years	0.97 (0.95, 0.99)	0.004	0.98 (0.96, 1.00)	0.02
Male	0.73 (0.56, 0.96)	0.03	0.61 (0.44, 0.86)	0.004
Body surface area (BSA), m^2*	1.10 (0.98, 1.23)	0.12	1.22 (1.06, 1.40)	0.005
Diabetes mellitus	1.20 (0.92, 1.58)	0.18		
Hypertension	0.70 (0.44, 1.09)	0.12		
Cerebrovascular disease	0.77 (0.53, 1.11)	0.17		
6-minute walk, m	1.00 (1.00, 1.00)	0.02		
Creatinine clearance < 30 ml/min	1.99 (1.24, 3.20)	0.005	1.96 (1.21, 3.17)	0.006
CT-measured aortic annulus ≤ 23 mm	1.28 (0.94, 1.73)	0.11		
Baseline LVEF, %†	0.98 (0.97, 0.99)	<0.001	0.98 (0.97, 0.99)	<0.001
Baseline AVA, cm^2†	0.22 (0.10, 0.48)	<0.001	0.29 (0.12, 0.73)	0.008
Baseline mean gradient, mmHg†	1.01 (1.00, 1.02)	0.002	1.01 (1.00, 1.02)	0.07

Lower risk in older patients, men, and those with a higher baseline LVEF and AVA

Higher risk in patients with a higher body surface area and worse renal impairment

*HR per 0.2 m^2 increase in BSA

†Core lab if available, otherwise site-reported

§Backwards elimination multivariable modeling with stay criteria of P=0.1.

Univariable analysis was also performed for additional covariates resulting in P>0.3 and included: STS-PROM, NYHA III/IV, chronic lung disease/COPD, peripheral vascular disease, coronary artery disease, coronary artery bypass surgery, atrial fibrillation/flutter, prior percutaneous coronary intervention, prior antiplatelet therapy, and prior anticoagulation therapy.

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Limitations

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- Current follow-up is limited to 5 years. Ten-year follow-up is ongoing for the SURTAVI clinical trial.
- Further analysis in younger patients is warranted.
- The competing risk of mortality and inclusion of only randomized patients limited the number of subjects with BVD.

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Conclusions

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- In patients with symptomatic severe AS undergoing aortic valve replacement, valve performance was superior at 5-years in patients undergoing TAVR compared to surgery (7.8% BVD TAVR vs. 14.2% BVD surgery; P<0.001).
- This difference in valve performance was driven by a 2-fold lower SVD and 3-fold lower severe PPM with TAVR vs. surgery and was more profound in patients with smaller (≤23 mm) annuli (8.6% BVD TAVR vs. 19.7% BVD surgery; P<0.001).
- BVD imparted a ~1.5-fold risk for all-cause mortality (P=0.004), cardiovascular mortality (P<0.001), and hospitalization for valve disease or worsening heart failure (P=0.001) at 5 years.

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Clinical Implications

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- Long-term valve performance should be a key consideration in the selection of the first bioprosthesis, particularly in younger, low risk patients with longer life expectancies.
- The CoreValve / Evolut supra-annular, self-expanding bioprosthesis is the only transcatheter valve to demonstrate superior valve performance at 5 years compared with surgery in randomized clinical trials.
- This is the first analysis to validate clinical criteria for valve performance (BVD) and its association with clinical outcomes, resulting in a near ~1.5-fold increased risk for death and hospitalization for valve disease or worsening heart failure.

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

Warnings
General Implantation of the CoreValve Evolut R, Evolut PRO+, and Evolut FX Systems should be performed only by physicians who have received Medtronic CoreValve Evolut R, Evolut PRO+, 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 CoreValve Evolut R, Evolut PRO+, 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 a CoreValve Evolut R, Evolut PRO+, or Evolut FX bioprosthesis implanted within a failed preexisting transcatheter bioprosthesis have not been demonstrated. Implanting a CoreValve Evolut R, Evolut PRO+, 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 EnVeo InLine™ Sheath when using models ENVEOR-US/D-EVPROP2329US or Evolut FX Delivery Catheter System with InLine™ Sheath when using model D-EVOLUTFX-2329 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 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 ENVEOR-US/D-EVPROP2329US/D-EVOLUTFX-2329 or ≥ 5.5 mm when using model ENVEOR-N-US 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 ENVEOR-L-US/D-EVPROP2329US/D-EVOLUTFX-2329 or ≥ 6 mm when using model ENVEOR-N-US 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 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 FX bioprosthesis implanted within a transcatheter bioprosthesis have not been demonstrated.

Potential adverse events
Potential risks associated with the implantation of the CoreValve Evolut R, Evolut PRO+, 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 CoreValve Evolut R, Evolut PRO+, 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™ R device is Medtronic CoreValve™ Evolut™ R System, the commercial name of the Evolut™ PRO+ device is Medtronic Evolut™ PRO+ System, and the commercial name of the Evolut™ FX device is Medtronic Evolut™ FX System.

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UC2023011899b EN
02/2023

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