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

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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Background

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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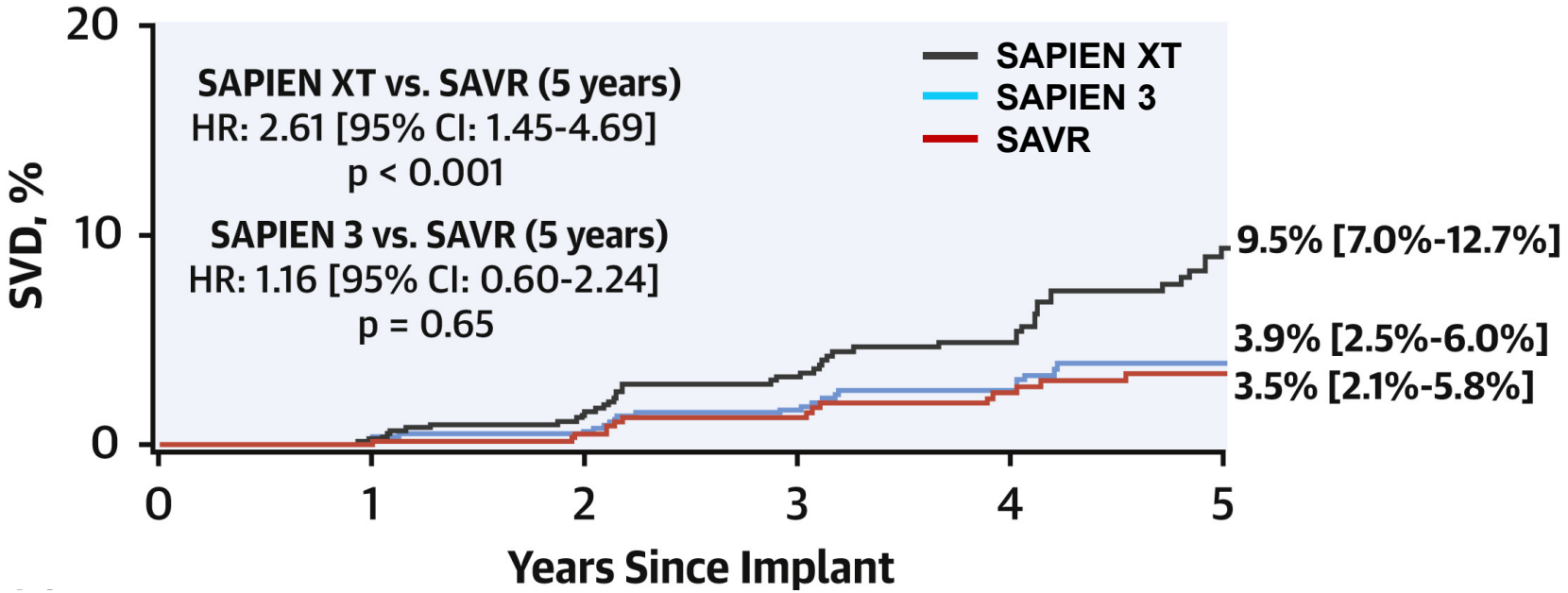

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- Previous work demonstrated early generation intra-annular, balloon-expandable bioprostheses have significantly higher 5-year rates of SVD compared to surgery, whereas newer generation annular valves have similar SVD rates. [1]
- Our prior analysis 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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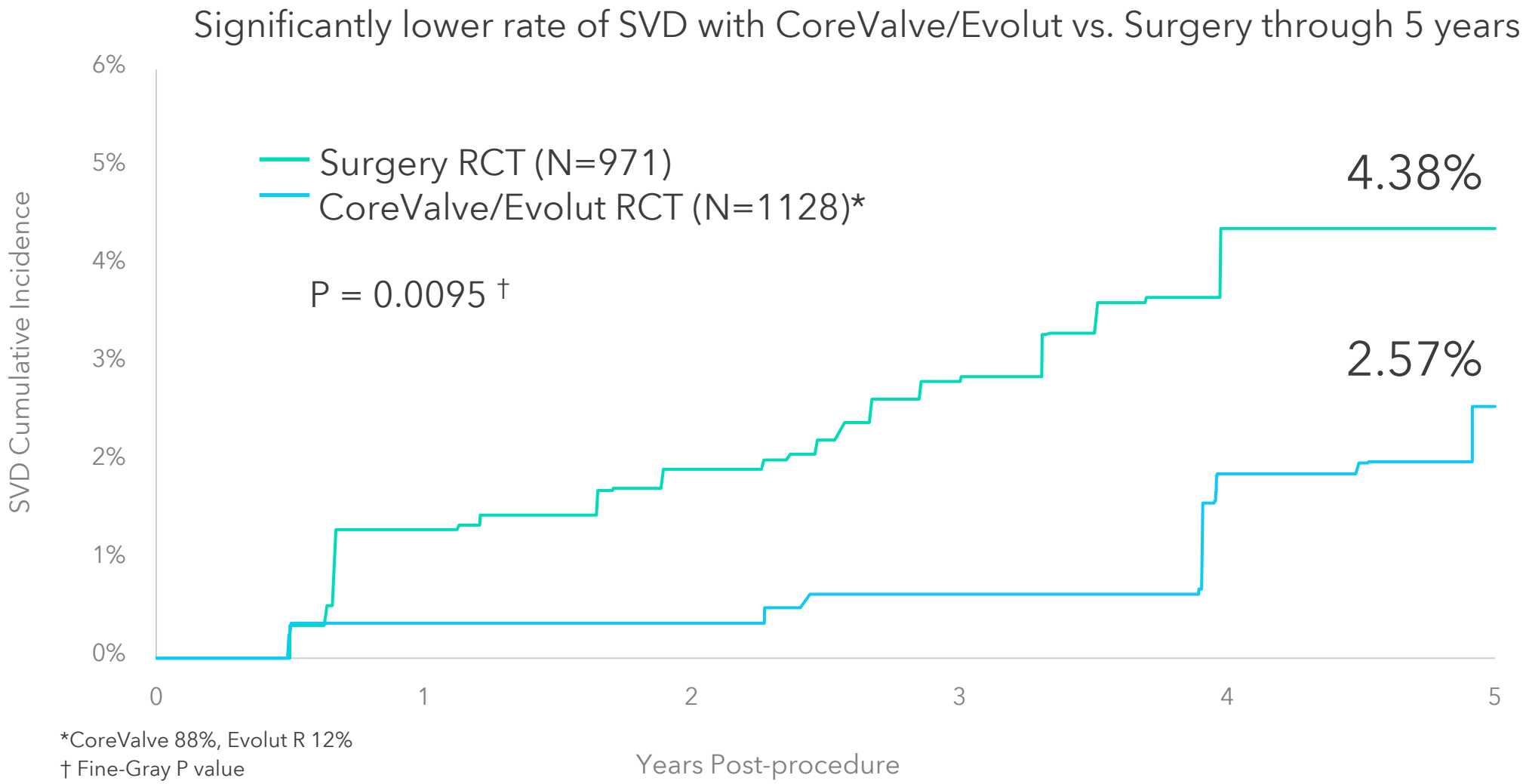
5-Year SVD Adjusted For Competing Risk of Mortality



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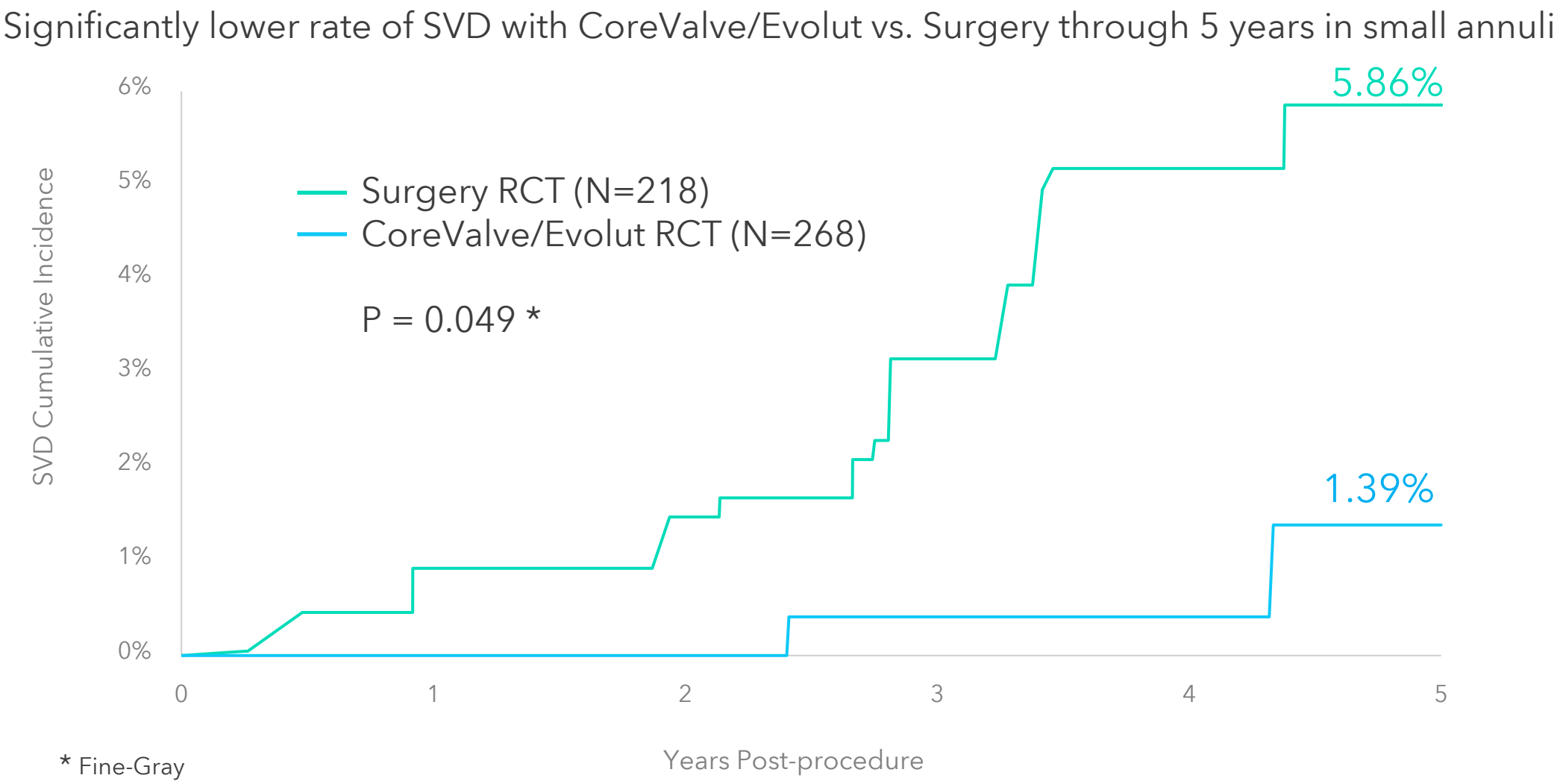
5-Year SVD in Smaller (≤23mm) Annular Diameter



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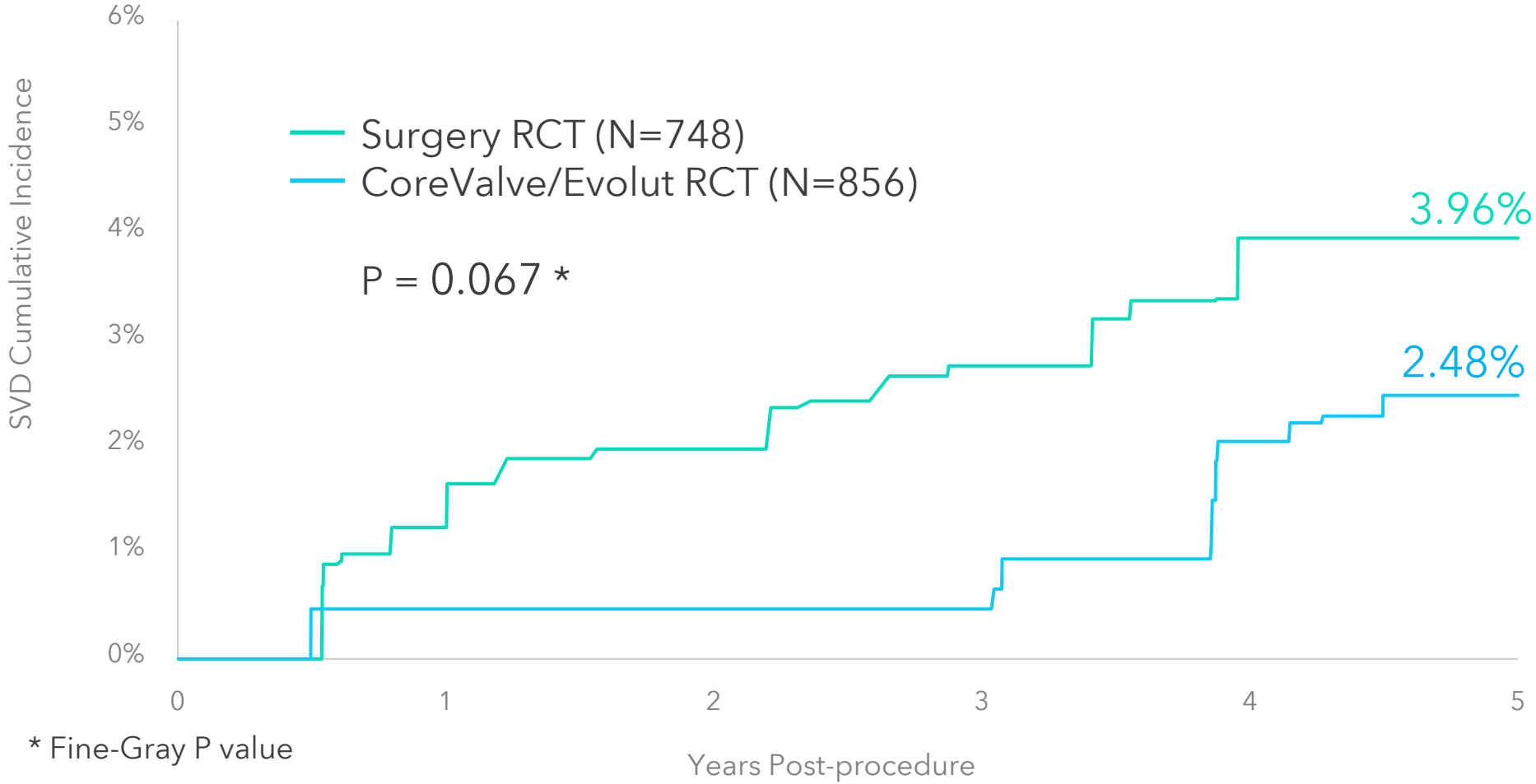
5-Year SVD in Larger (≥23mmm) Annular Diameter

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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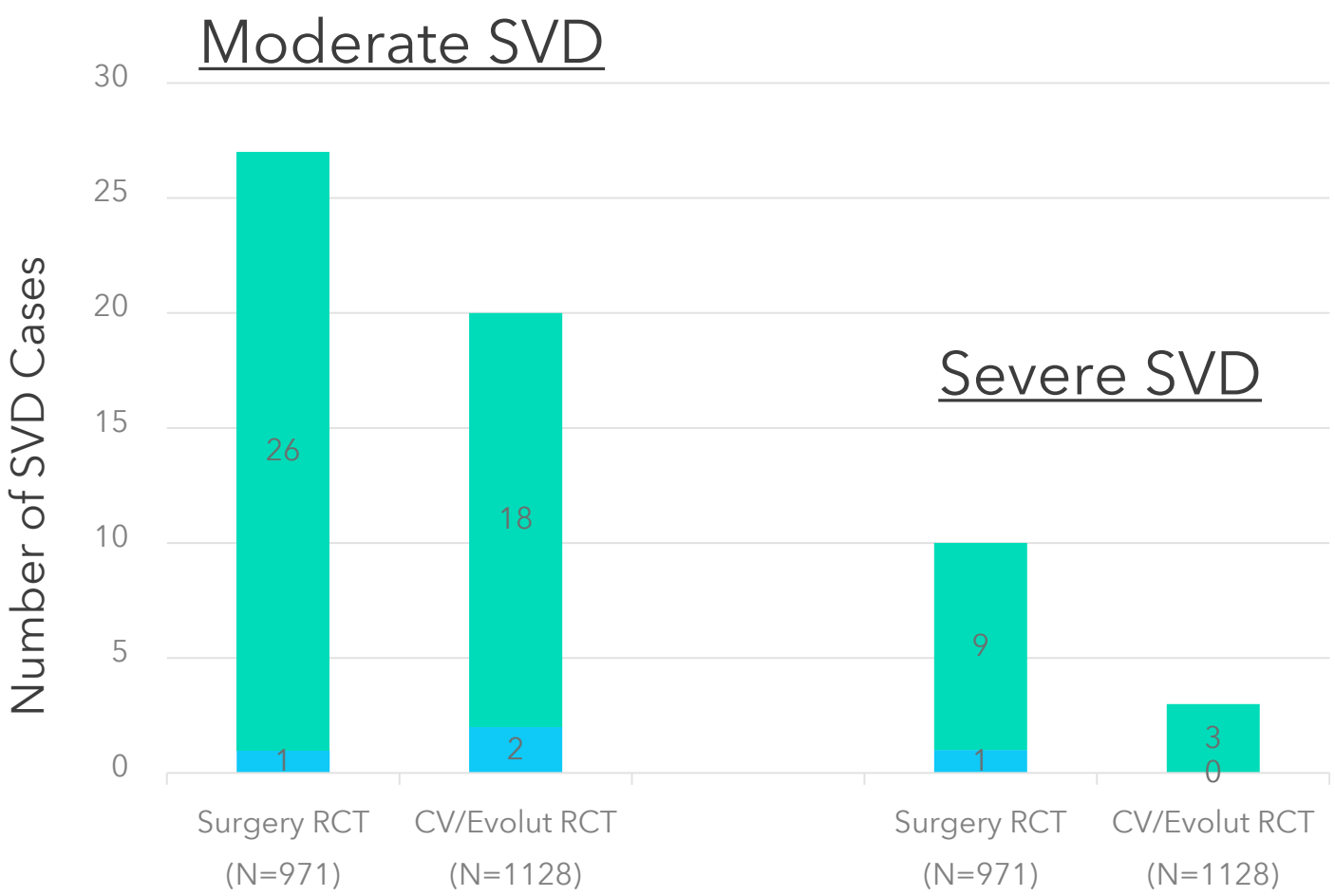
TAVR Reductions with Both Moderate and Severe SVD



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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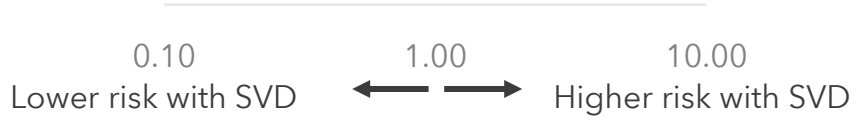
Worsened Clinical Outcomes in Patients Who Develop SVD

	HR (95% CI)	P value
Pooled Surgery RCT and All CoreValve/Evolut* (N=4762)		
All-cause mortality	1.98 (1.42, 2.76)	<0.001
Cardiovascular mortality	1.82 (1.17, 2.84)	0.008
Aortic valve-related hospitalization	2.11 (1.19, 3.74)	0.010
Composite †	1.96 (1.38, 2.80)	<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)	0.027
Aortic valve-related hospitalization	2.20 (0.81, 5.98)	0.121
Composite †	2.73 (1.53, 4.88)	<0.001
All CoreValve/Evolut TAVR* (N=3791)		
All-cause mortality	2.24 (1.48, 3.38)	<0.001
Cardiovascular mortality	2.07 (1.20, 3.59)	0.009
Aortic valve-related hospitalization	2.34 (1.16, 4.71)	0.017
Composite †	1.93 (1.23, 3.03)	0.005



*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	79.3 ± 8.7	82.1 ± 7.4 †
Male	47 (48.5)	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	69 (71.1)	3615 (77.5)
Prior percutaneous coronary intervention	22 (22.7)	1563 (33.5) †
Prior coronary artery bypass surgery	22 (22.7)	1393 (29.9)
Hypertension	85 (87.6)	4318 (92.6)
Creatinine > 2.0 mg/dL	3 (3.1)	166 (3.6)
Prior atrial fibrillation/flutter	24 (24.7)	1761 (37.8) †
Prior anticoagulation therapy	16 (16.5)	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)	0.038
Male	0.75 (0.51, 1.12)	0.165	0.60 (0.38, 0.94)	0.027
Body surface area (BSA), m^2 †	1.21 (1.01, 1.44)	0.040	1.28 (1.06, 1.55)	0.011
STS-PROM, %	0.92 (0.85, 0.99)	0.025		
NYHA III/IV	0.73 (0.47, 1.13)	0.160		
Prior coronary artery bypass grafting	0.68 (0.42, 1.09)	0.106		
Prior percutaneous coronary intervention	0.57 (0.36, 0.92)	0.021	0.60 (0.37, 0.98)	0.040
Diabetes mellitus	1.30 (0.87, 1.94)	0.199		
Hypertension	0.58 (0.32, 1.05)	0.071	0.56 (0.31, 1.02)	0.059
Prior atrial fibrillation/flutter	0.54 (0.34, 0.85)	0.008	0.55 (0.34, 0.89)	0.015
CT-measured aortic annulus ≤23 mm	1.28 (0.82, 2.01)	0.272		
Body mass index, kg/m^2	1.04 (1.01, 1.07)	0.005		
Baseline anticoagulation therapy	0.70 (0.41, 1.19)	0.189		
Baseline antiplatelet therapy	0.70 (0.45, 1.08)	0.104		

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 2.57% in patients undergoing CoreValve/Evolut TAVR (P=0.0095)
- This difference in SVD was more profound in patients with smaller (≤23 mm) annuli (5.86% surgery vs 1.39% TAVR; P=0.049), but a trend was also found in patients with larger (>23 mm) annuli (3.96% surgery vs 2.48% TAVR; P=0.067).
- 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=0.01) 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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