Supplemental Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.

eMethods 1. Study End Points

Additional study endpoints used to assess structural valve deterioration (SVD) and changes in valve function included:

VARC-3 SVD: Moderate SVD was defined as hemodynamic valve deterioration (HVD) showing an increase in mean aortic gradient ≥ 10 mmHg from discharge/30-day echo to last available echo with a final mean gradient ≥ 20 mmHg and with a concomitant decrease in EOA ≥ 0.3 cm^2 or ≥ 25% and/or decrease in DVI ≥ 0.1 or ≥ 20% from discharge/30-day echo to last available echo, OR new occurrence or increase of ≥ 1 grade of intraprosthetic aortic regurgitation (AR) resulting in ≥ moderate regurgitation. Severe SVD was defined as HVD showing an increase in mean gradient ≥ 20 mmHg from discharge/30-day echo to last available echo with a final mean gradient ≥ 30 mmHg and with a concomitant decrease in EOA ≥ 0.6 cm^2 or ≥ 50% and/or decrease in DVI ≥ 0.2 or ≥ 40% from discharge/30-day echo to last available echo, OR new occurrence or increase of ≥ 2 grades of intraprosthetic AR resulting in severe regurgitation [1].

HVD: Related to bioprosthetic stenosis and defined as an increase in mean aortic gradient ≥10 mmHg from discharge/30-day echo to last available echo, OR aortic valve reintervention for stenosis > 30 days post-procedure [2,3].

eMethods 2. Statistical Analysis

Interval censored competing risks analyses were carried out using the MICCD R package.[4,5] Analyses included assessment of univariate baseline predictors of SVD via Fine-Gray, and estimated TAVI/Surgery treatment effects as well as associated cumulative incidence plots. Specifically, Fine-Gray P values were computed using multiple imputation via the "MIICD.crreg" function with 25 asymptotic normal outer multiple imputations [6]. Ten sub-imputations were used within each outer imputation. Simulations showed these values, larger than default values, produced repeatability to several decimal places with different random number generator seeds.

The cumulative incidence of SVD was calculated using the "MI.ci" function with 25 imputations and 10 sub-imputations. The analyses included all events with the analysis cutoff of 1900 days; subjects who died without a SVD event were censored at the time of death, if death occurred before 1900 days. The assessment of SVD as a time-dependent predictor was carried out in SAS software's PROC PHREG, Version 9.4 of the SAS System for Windows. Copyright © 2022 SAS Institute, Inc.

Multivariate models were selected via backward elimination using the "finegray_sel" SAS software macro for right-censored data [7]; resulting models were refitted in MIICD to appropriately handle interval-censoring. Parameter estimates and associated P values changed slightly when refitting, indicating that there were only minor differences in the two approaches for hypothesis testing. However, cumulative incidence plots do appreciably change due to the correct handling of interval-censored data with the imputation approach.

eTable 1. Type and Size of Surgical Valves in Randomized Patients

	Surgery RCT (n=971)
Bioprosthetic valve type	
Perimount	392 (40.4)
MitroFlow	35 (3.6)
Trifecta	241 (24.8)
Mosaic	173 (17.8)
Hancock	36 (3.7)
Epic	25 (2.6)
Freestyle	48 (4.9)
3F	6 (0.6)
Solo Smart	3 (0.3)
Other	12 (1.2)
Bioprosthetic valve size *	
17/19 mm	63 (6.5)
21 mm	283 (29.1)
23 mm	347 (35.7)
25 mm	215 (22.1)
27 mm	53 (5.5)
29 mm	9 (0.9)

Data presented as no. of patients (percentage). * One patient with valve size not reported. RCT denotes randomized clinical trial.

eTable 2. Echocardiographic Findings Before and After Aortic Valve Replacement

	Surgery RCT (n=971)	TAVI RCT (n=1128)	TAVI Non-RCT * (n=2663)
Baseline TTE			
EOA, cm^2	0.8 ± 0.2 (919)	0.8 ± 0.2 (1061)	0.7 ± 0.3 (2599)
Mean gradient, mmHg	47.6 ± 13.6 (966)	47.3 ± 13.9 (1122)	47.8 ± 13.2 (2660)
LVEF, %	59.8 ± 11.3 (968)	60.4 ± 10.2 (1127)	54.0 ± 13.7 (2655)
Discharge/30-Day TTE			
EOA index, cm^2/m^2	0.9 ± 0.3 (705)	1.1 ± 0.3 (951) †	1.0 ± 0.3 (2437)
Mean gradient, mmHg	12.3 ± 5.8 (872)	8.8 ± 3.9 (1026) †	8.3 ± 3.9 (2633)
Severe PPM (VARC-3), %	83/705 (11.8)	35/951 (3.7) †	192/2437 (7.9)
DVI	0.5 ± 0.1 (815)	0.6 ± 0.1 (989) †	0.6 ± 0.1 (2575)
Severe PVL, %	0/824 (0.0)	7/1012 (0.7)	7/2578 (0.27)

Data presented as mean ± standard deviation (no. of patients) or no. of patients / total no. of patients (percentage). RCT denotes randomized clinical trial, TAVI transcatheter aortic valve implantation, TTE transthoracic echocardiography, LVEF left ventricular ejection fraction, PPM prothesis-patient mismatch, EOA effective orifice area, DVI Doppler velocity index, and VARC-3 Valve Academic Research Consortium 3. There were no significant differences between the RCT cohorts in baseline TTE parameters. *The TAVI non-RCT cohort comprises the pooled CoreValve US Extreme Risk and the CoreValve CAS populations. † P<.001 vs. Surgery RCT.

eTable 3. Echocardiographic Findings in Patients With Structural Valve Deterioration

Last TTE demonstrating SVD	Surgery RCT (n=37)	TAVI RCT (n=21)	TAVI Non-RCT * (n=37)
Patients meeting AS criteria	(n=35)	(n=19)	(n=25)
EOA index, cm^2/m^2	0.6 ± 0.2 (26)	0.6 ± 0.2 (15)	0.7 ± 0.3 (21)
Mean gradient, mmHg	29.0 ± 7.2 (35)	26.3 ± 3.9 (19)	26.5 ± 7.8 (25)
Severe PPM (VARC-3), %	16/35 (45.7)	5/19 (26.3)	6/25 (24.0)
DVI	0.3 ± 0.1 (32)	0.3 ± 0.1 (17)	0.4 ± 0.2 (23)
Patients meeting AR criteria	(n=2)	(n=2)	(n=12)
Moderate intraprosthetic AR	1 (50.0)	2 (100.0)	12 (100.0)
Severe intraprosthetic AR	1 (50.0)	0 (0.0)	0 (0.0)

Data presented as mean ± standard deviation (no. of patients), no. of patients / total no. of patients (percentage) or no. of patients (percentage). RCT denotes randomized clinical trial, TAVI transcatheter aortic valve implantation, TTE transthoracic echocardiography, AS aortic stenosis, AR aortic regurgitation, PPM prothesis-patient mismatch, EOA effective orifice area, DVI Doppler velocity index, and VARC-3 Valve Academic Research Consortium 3. There were no significant differences between the RCT cohorts in TTE parameters. *The TAVI non-RCT cohort comprises the pooled CoreValve US Extreme Risk and the CoreValve CAS populations.

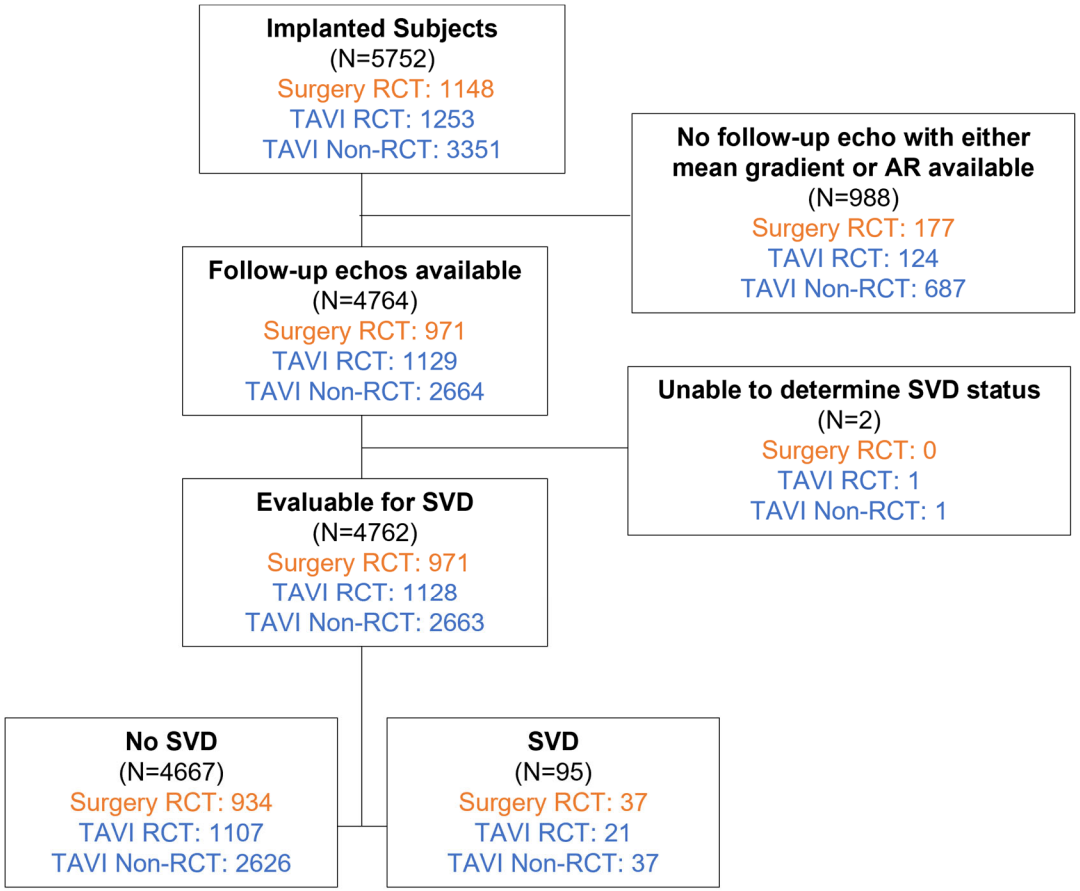
eTable 4. Baseline Clinical Characteristics and Univariate Predictors of Structural Valve Deterioration

			Univariate Model	
Pooled Surgery RCT and All TAVI * (n=4762)	Patients with SVD (n=95)	Patients without SVD (n=4667)	HR (95% CI)	P value
Age, years	79.4 ± 8.8	82.1 ± 7.4	0.96 (0.94, 0.98)	<0.001
Male	47 (49.5)	2558 (54.8)	0.79 (0.53, 1.17)	0.24
Body surface area, m^2	1.9 ± 0.3	1.9 ± 0.2	1.21 (1.01, 1.45) †	0.04
STS-PROM ‡, %	6.0 ± 4.1	7.2 ± 4.2	0.92 (0.85, 0.99)	0.03
New York Heart Association class III/IV	67 (70.5)	3617 (77.5)	0.71 (0.46, 1.10)	0.13
Coronary artery disease	67 (70.5)	3450 (73.9)	0.80 (0.52, 1.25)	0.33
Prior coronary artery bypass surgery	22 (23.2)	1393 (29.8)	0.70 (0.43, 1.12)	0.14
Prior percutaneous coronary intervention	22 (23.2)	1563 (33.5)	0.59 (0.37, 0.9)	0.03
Cerebrovascular disease	18 (18.9)	1032 (22.3)	0.82 (0.49, 1.37)	0.45
Peripheral vascular disease	33 (35.5)	1847 (39.7)	0.84 (0.55, 1.29)	0.43
Diabetes mellitus	41 (43.2)	1708 (36.6)	1.29 (0.86, 1.94)	0.21
Hypertension	83 (87.4)	4320 (92.6)	0.56 (0.31, 1.03)	0.06
Chronic lung disease/COPD	41 (43.2)	2173 (46.6)	0.85 (0.57, 1.28)	0.44
Creatinine clearance <30 ml/min	8 (8.4)	405 (8.7)	0.96 (0.47, 1.98)	0.92
Prior atrial fibrillation/flutter	24 (25.3)	1761 (37.8)	0.55 (0.35, 0.87)	0.01
CT-measured aortic annulus ≤23 mm	24 (25.3)	1035 (22.3)	1.19 (0.75, 1.88)	0.47
Body mass index, kg/m^2	30.3 ± 8.0	28.5 ± 6.2	1.04 (1.01, 1.07)	0.01
Baseline anticoagulation therapy	16 (16.8)	1014 (21.7)	0.72 (0.42, 1.23)	0.22
Baseline antiplatelet therapy	28 (29.5)	1695 (36.3)	0.72 (0.46, 1.11)	0.14
Baseline LVEF, %	56.7 ± 12.9	56.7 ± 12.8	1.00 (0.99, 1.02)	0.89
Baseline mean gradient, mmHg	48.2 ± 13.5	47.7 ± 13.5	1.00 (0.99, 1.02)	0.58
Baseline EOA, cm^2	0.7 ± 0.3	0.7 ± 0.3	1.20 (0.66, 2.21)	0.55

Data presented as mean ± standard deviation or no. of patients (percentage). SVD denotes structural valve deterioration, RCT randomized clinical trial, TAVI transcatheter aortic valve implantation, COPD denotes chronic obstructive pulmonary disease, LVEF left ventricular ejection fraction, EOA effective orifice area, HR Hazard ratio, and CI confidence interval. * The All TAVI cohort comprises the pooled RCT and non-RCT populations. † HR units = 0.2. ‡ The Society of Thoracic Surgeons Predicted Risk of Mortality (STS-PROM) provides an estimate of the risk of death at 30 days among patients undergoing surgical aortic valve replacement based on several demographic and procedural variables.

eFigure 1. Patient Flowchart

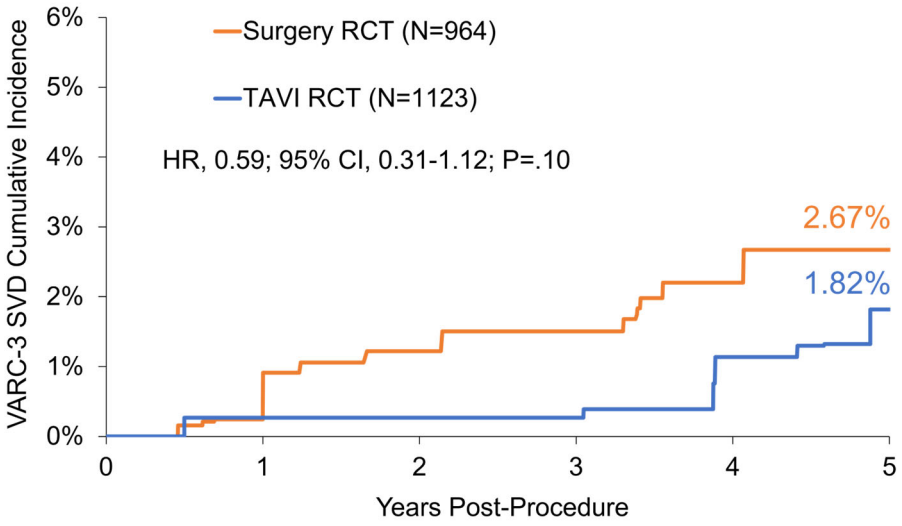
SVD-assessed populations. SVD denotes structural valve deterioration, RCT randomized clinical trial, TAVI transcatheter aortic valve implantation, echo echocardiography, and AR aortic regurgitation.



eFigure 2. Comparison of VARC-3 Structural Valve Deterioration and Hemodynamic Valve Deterioration in Patients Randomized to Surgery or TAVI

A) The 5-year cumulative incidence rate of VARC-3 SVD, and B) The 5-year cumulative incidence rate of HVD. SVD denotes structural valve deterioration, HVD hemodynamic valve deterioration, VARC-3 Valve Academic Research Consortium 3, and TAVI transcatheter aortic valve implantation. Hazard ratio (HR) and 95% confidence intervals (CI) are reported. Fine-Gray P value.

A



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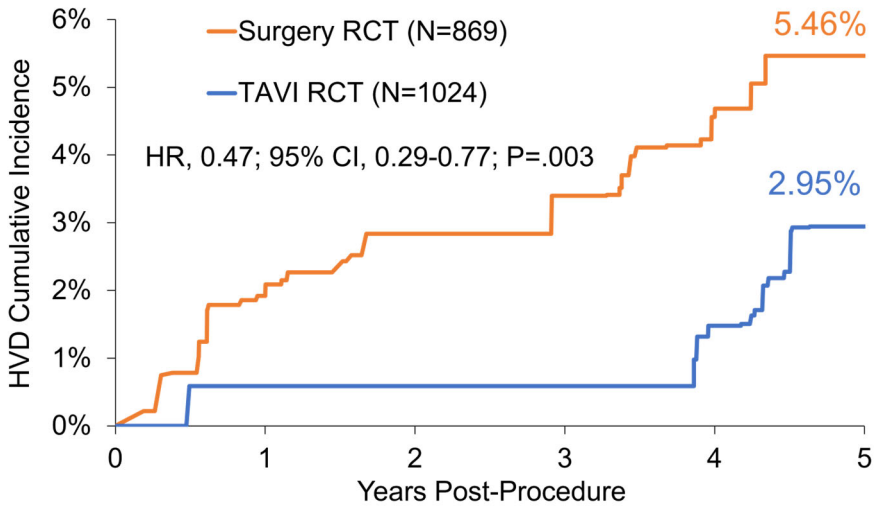
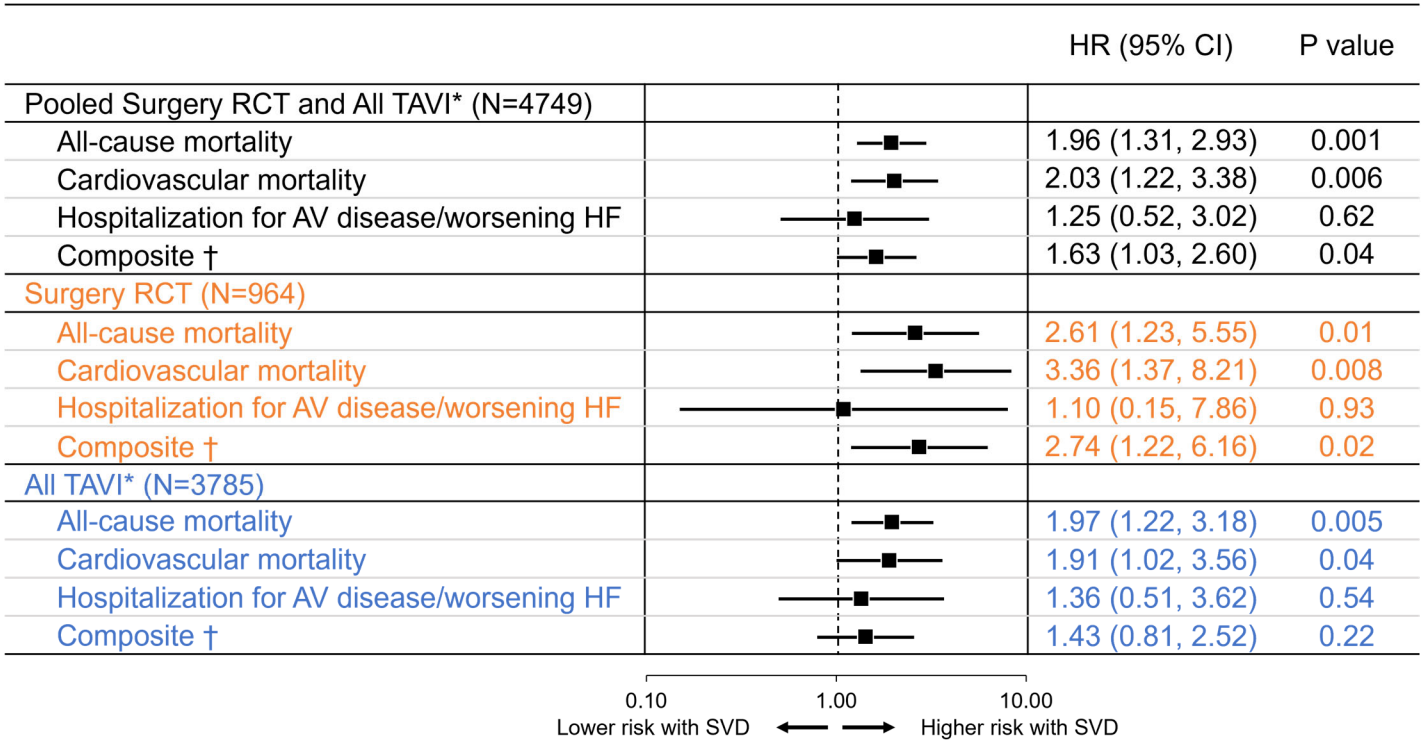


eFigure 3. Association Between Clinical Outcomes and VARC-3 Structural Valve Deterioration / Hemodynamic Valve Deterioration

A) Clinical outcomes and VARC-3 SVD, and B) Clinical outcomes and HVD. SVD denotes structural valve deterioration, VARC-3 Valve Academic Research Consortium 3, HVD hemodynamic valve deterioration, RCT randomized clinical trial, TAVI transcatheter aortic valve implantation, AV aortic valve, and HF heart failure. *The All TAVI cohort comprises the pooled RCT and non-RCT populations. † Composite of all-cause mortality or hospitalization for AV disease or worsening HF. Hazard ratio (HR) and 95% confidence intervals (CI) are reported.

A



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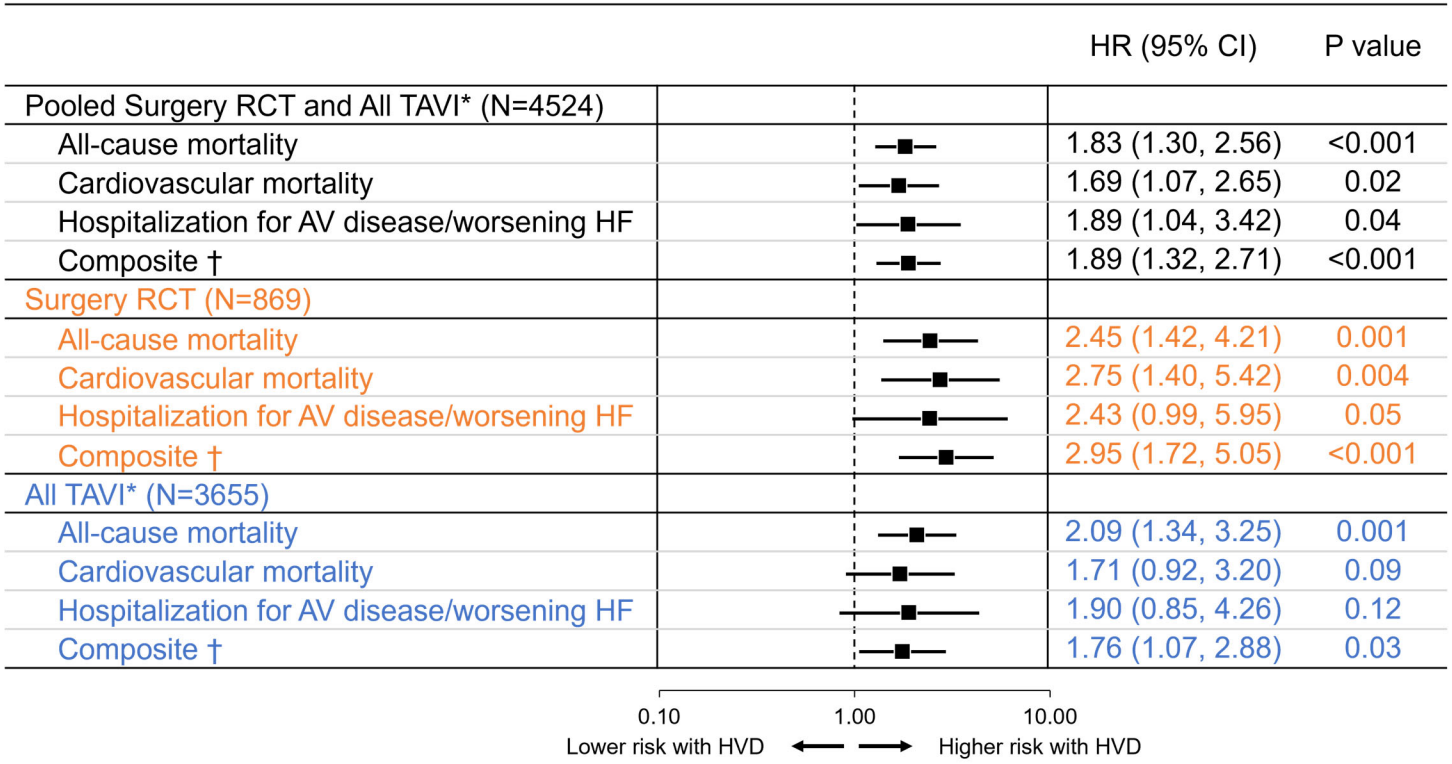

eReferences.

1. Généreux P, Piazza N, Alu MC, et al. Valve Academic Research Consortium 3: updated endpoint definitions for aortic valve clinical research. *Journal of the American College of Cardiology.* 2021.
2. Vemulapalli S, Holmes DR, Jr., Dai D, et al. Valve hemodynamic deterioration and cardiovascular outcomes in TAVR: A report from the STS/ACC TVT Registry. *Am Heart J.* 2018;195:1-13.
3. O'Hair D, Reardon M, Yakubov S, Li S, Deeb GM. Relationship of hemodynamic valve deterioration and late clinical outcomes after TAVR with a self-expanding bioprosthesis and surgery. *Journal of the American College of Cardiology.* 2021;77(18_Supplement_1):904-904.
4. Delord M, Génin E. Multiple imputation for competing risks regression with interval-censored data. *Journal of Statistical Computation and Simulation.* 2016;86(11):2217-2228.
5. Delord M. MIICD: Multiple Imputation for Interval Censored Data. *R package version.* 2017;2.
6. Pan W. A multiple imputation approach to Cox regression with interval-censored data. *Biometrics.* 2000;56(1):199-203.
7. Zhang C, Liu Y, Jia Y. SAS® Macros on Performing Competing Risks Survival Data: CIF Plot, Backward Elimination Fine & Gray's Model and Cause-Specific Hazard Model. 2019.