

Implications of Patient Prosthesis Mismatch

- *What Truly Matters?* -

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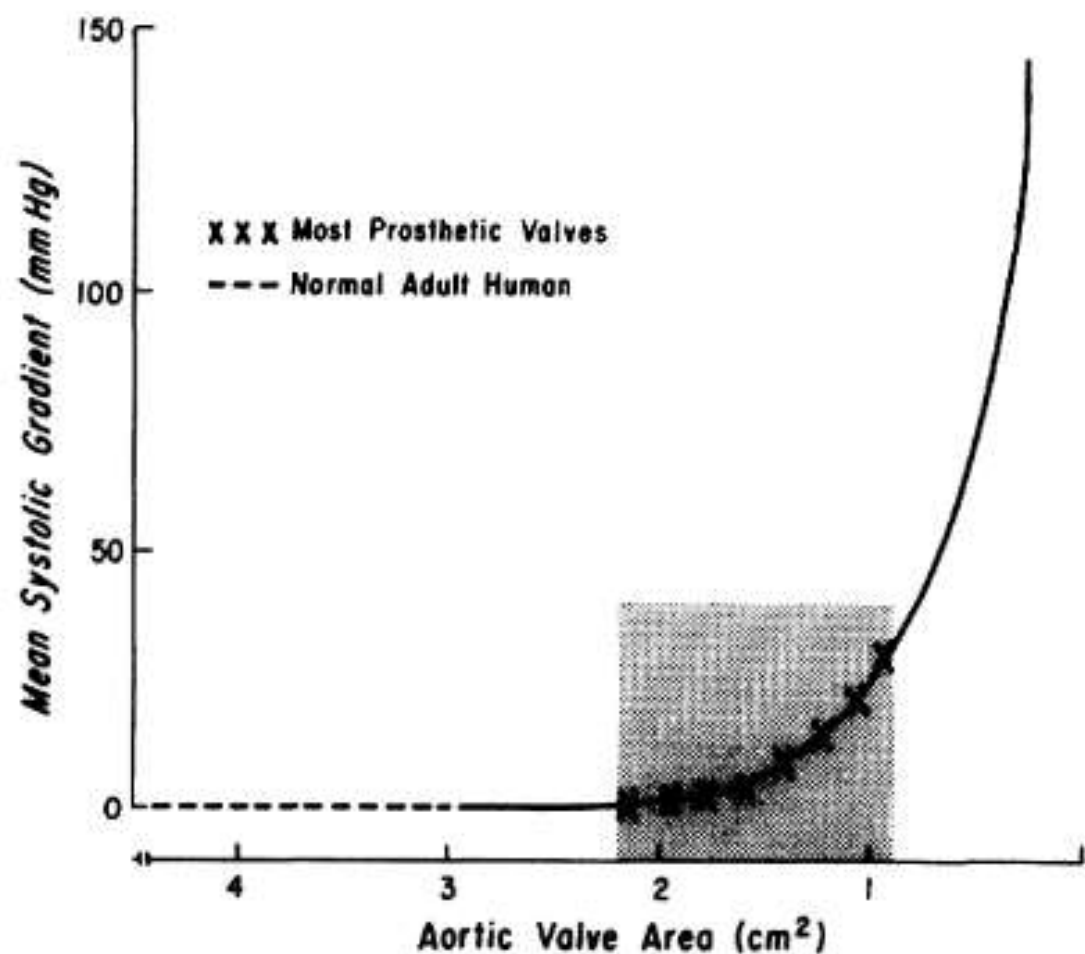
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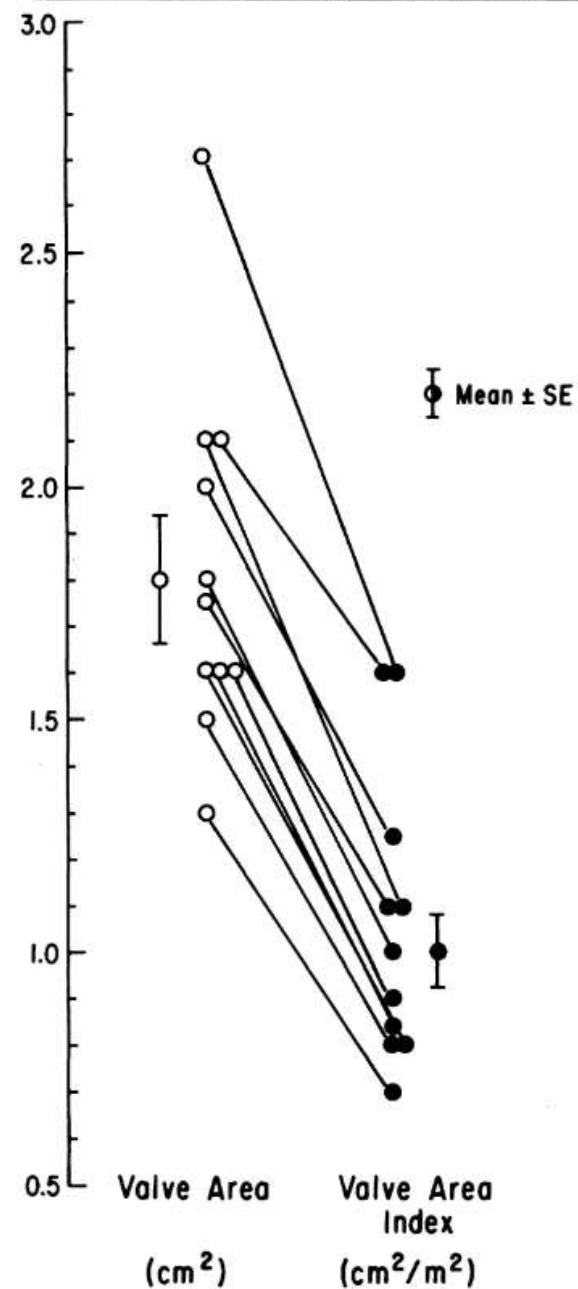
The Problem of Valve Prosthesis-Patient Mismatch

SHAHBUDIN H. RAHIMTOOLA, M.D.

Received January 17, 1978; revision accepted February 23, 1978.



Prosthetic Valve Areas (cm², cm²/m²) Following Aortic Valve Replacement For Isolated Aortic Incompetence

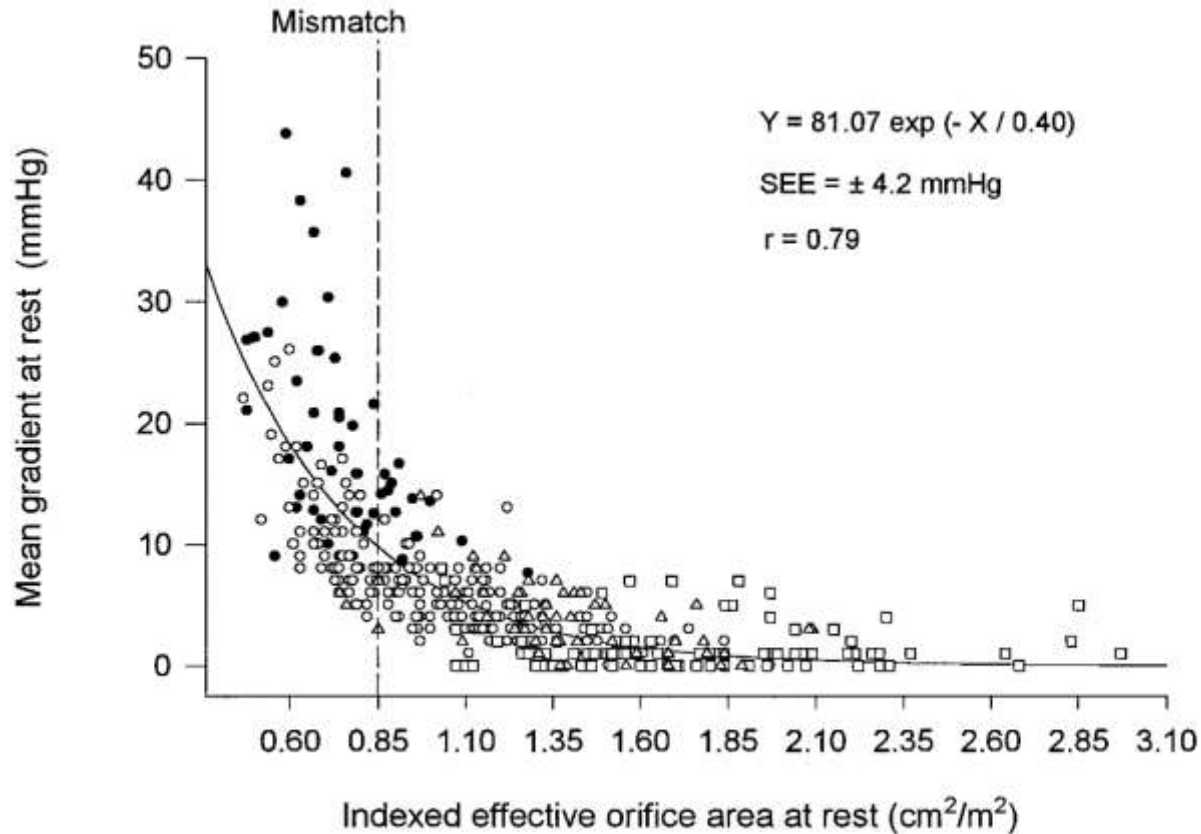


Hemodynamic and Clinical Impact of Prosthesis–Patient Mismatch in the Aortic Valve Position and Its Prevention

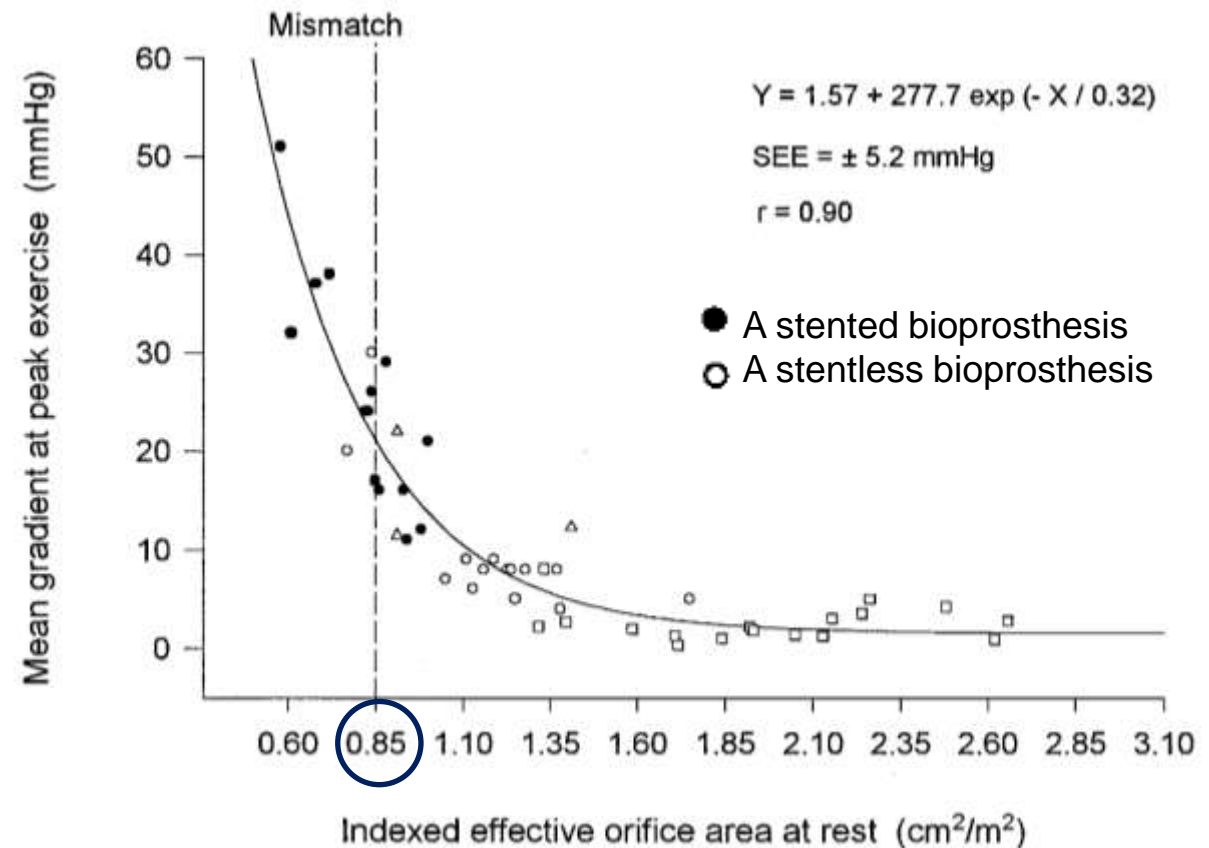
(J Am Coll Cardiol 2000;36:1131–41)

$$\text{indexed EOA} = \frac{\text{EOA of the prosthesis}}{\text{Patient's body surface area}}$$

At rest

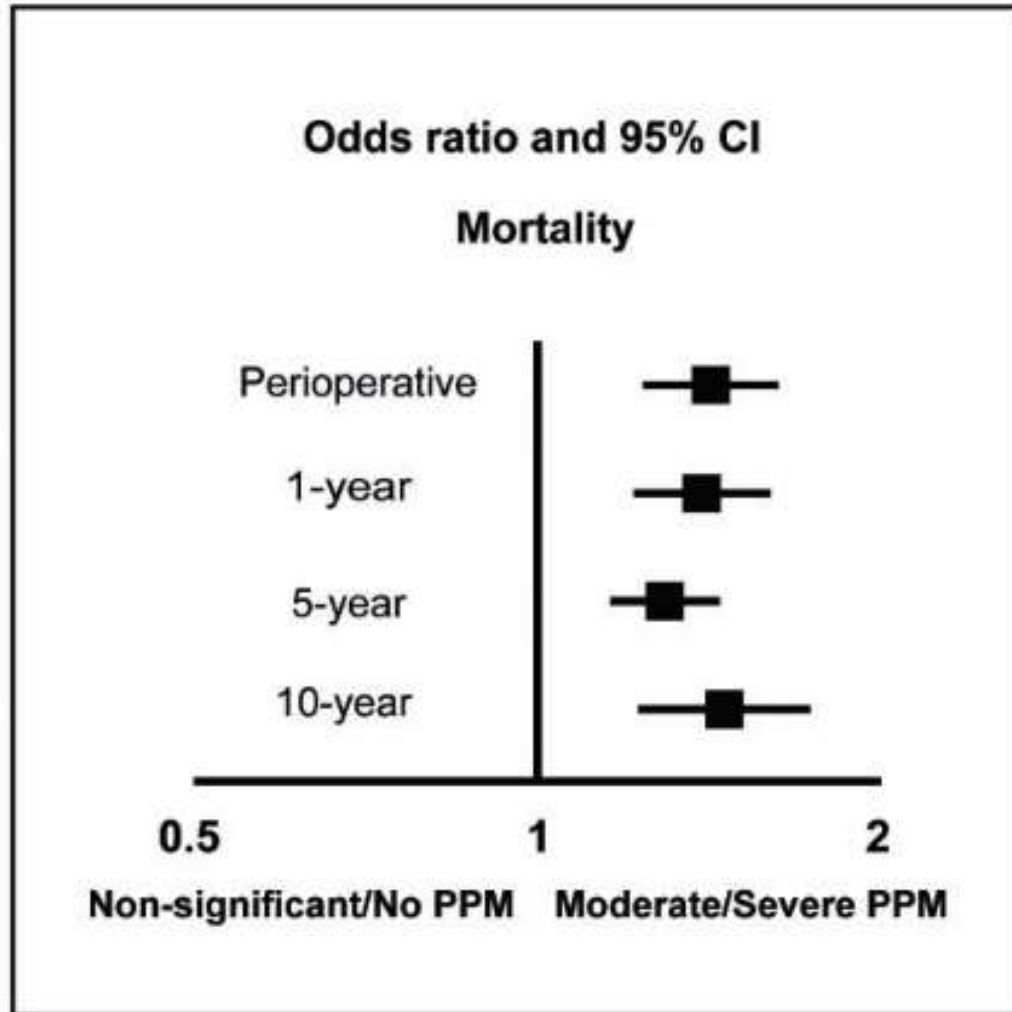


During maximal exercise



Surgical aortic valve replacement and patient-prosthesis mismatch: a meta-analysis of 108 182 patients

All-cause mortality



The impact of prosthesis–patient mismatch on long-term survival after aortic valve replacement: a systematic review and meta-analysis of 34 observational studies comprising 27 186 patients with 133 141 patient-years

Cardiac mortality

Moderate PPM

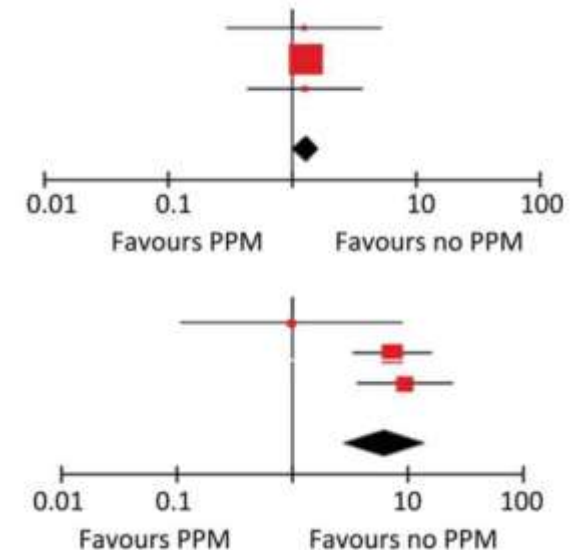
Milano 2002	1.27 [0.30, 5.31]
Mohty 2009	1.32 [1.01, 1.74]
Ruel 2004	1.28 [0.45, 3.70]

Total [95% CI] **1.32 [1.02, 1.71]**
 Heterogeneity: $I^2 = 0\%$

Severe PPM

Milano 2002	1.00 [0.11, 8.98]
Ruel 2004	7.54 [3.51, 16.19]
Mohty 2009	9.58 [3.74, 24.55]

Total [95% CI] **6.46 [2.79, 14.97]**
 Heterogeneity: $I^2 = 42\%$



Size of Surgical Valve Prostheses

Thourani et al, Ann Thorac Surg 2015;99:55

STS 2002-2010: 141,000 patients

≤ 22 mm diam = 40%
23-24 mm = +31%

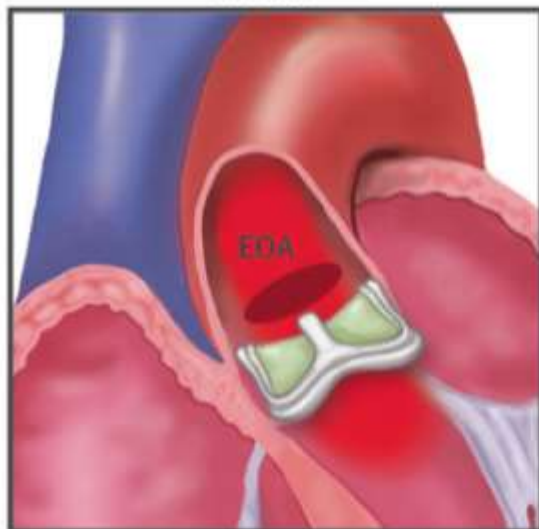
Zorn et al, JThCS 2016;151:1014

Corevalve pivotal trial

≤ 21 mm = 40%
 ≤ 23 mm = +30%

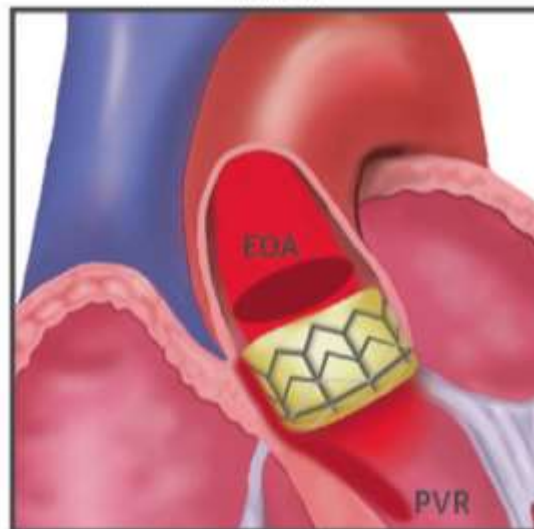
70% !

SAVR



Severe PPM

TAVR



Severe PPM
Moderate -Severe PVR

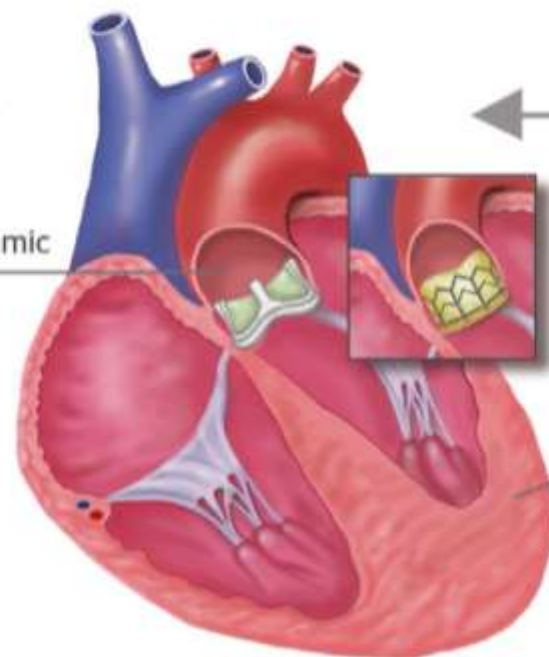
Postprocedural Outcomes

Residual hemodynamic load

Persistent/recurrent symptoms

Persistent LV hypertrophy

↑ Mortality



Prosthesis–Patient Mismatch After Transcatheter Aortic Valve Implantation

Overall, moderate, and severe PPM prevalence after TAVI was 35%, 27%, and 8%, respectively, which may be less than that after SAVR.

Severe PPM

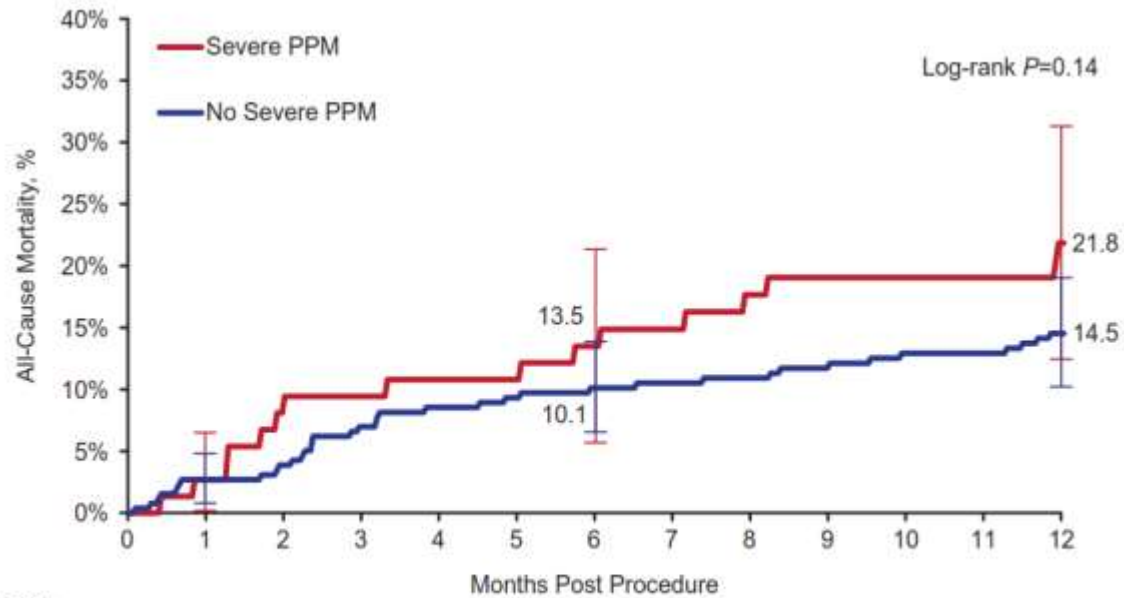
Study	Adjustment	TAVI	SAVR	Diagnosis Timing	Threshold (cm ² /m ²)	TAVI (%)	SAVR (%)	Univariate (OR [95% CI]) ^b
Clavel 2009 [8]	Matching ^a	50	100	At discharge	NR 0.65	10.0	26.0	0.32 [0.11, 0.88] ^b
Finkelstein 2013 [10]	Unadjusted	86	49	Before discharge	0.85 0.65	5.8	26.5	0.17 [0.06, 0.52] ^b
Giannini 2011 [12]	Matching ^c	58	58	At discharge	0.85 0.65	8.6	29.3	0.23 [0.08, 0.67] ^b
Kamperidis 2015 [16] ^d	Propensity-score ^e matching	39	40	At discharge	0.85 0.65	10.3	22.5	0.39 [0.11, 1.41] ^b
Pibarot (PARTNER) 2014 [21]	Unnecessary because of randomization	304	270	At 7 days	0.85 0.65	19.7	28.1	0.63 [0.43, 0.92] ^b
Sherif 2010 [22]	Unadjusted	56	36	At 30 days	0.9 0.6	0	0	Unavailable

Prosthesis–patient mismatch in high-risk patients with severe aortic stenosis: A randomized trial of a self-expanding prosthesis

(J Thorac Cardiovasc Surg 2016;151:1014-23)

Cumulative incidence of all-cause mortality at 1 year

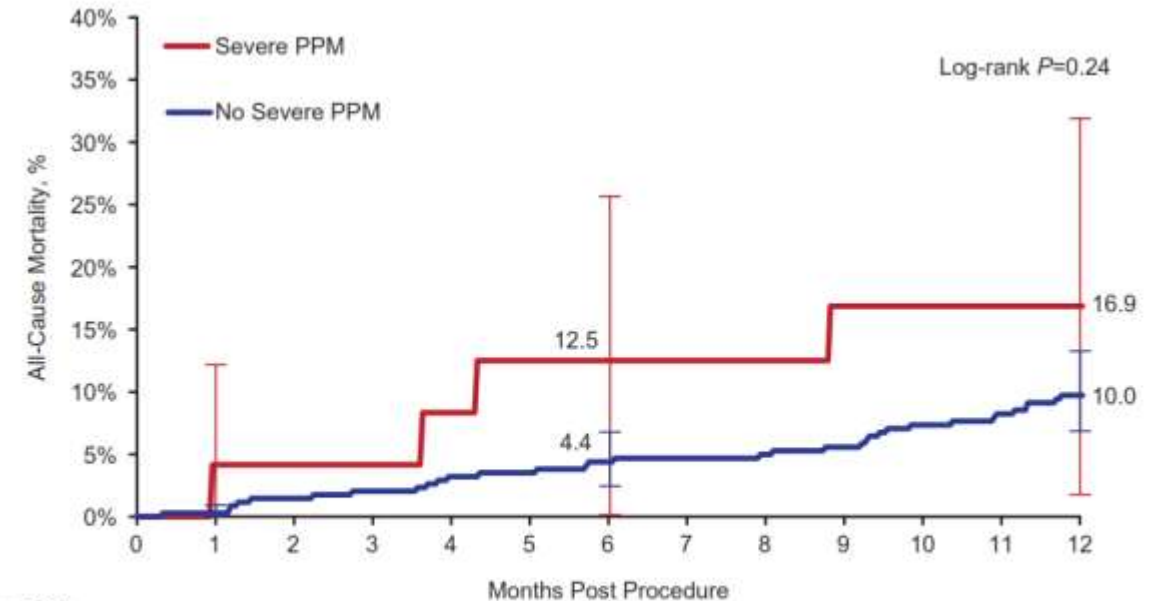
SAVR



A

No. at Risk				
Severe PPM	75	72	63	56
No Severe PPM	259	252	227	212

TAVR



B

No. at Risk				
Severe PPM	24	23	21	19
No Severe PPM	343	342	326	304

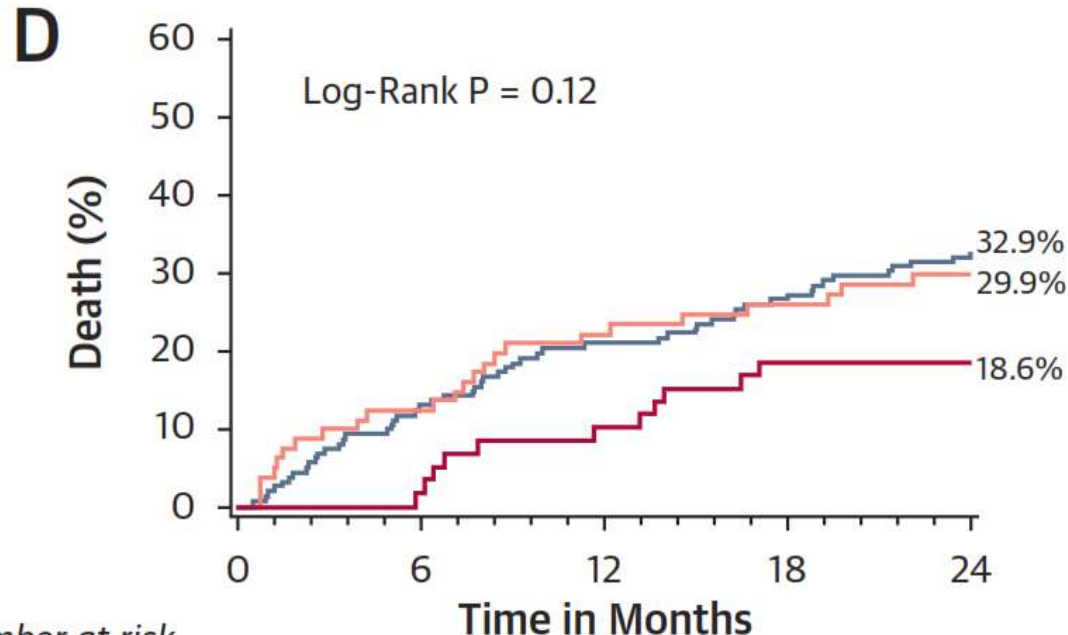
Incidence and Sequelae of Prosthesis-Patient Mismatch in Transcatheter Versus Surgical Valve Replacement in High-Risk Patients With Severe Aortic Stenosis

A PARTNER Trial Cohort-A Analysis

(J Am Coll Cardiol 2014;64:1323-34)

Severe PPM independently predicted mortality at 2 years (HR 1.88, p = 0.02)

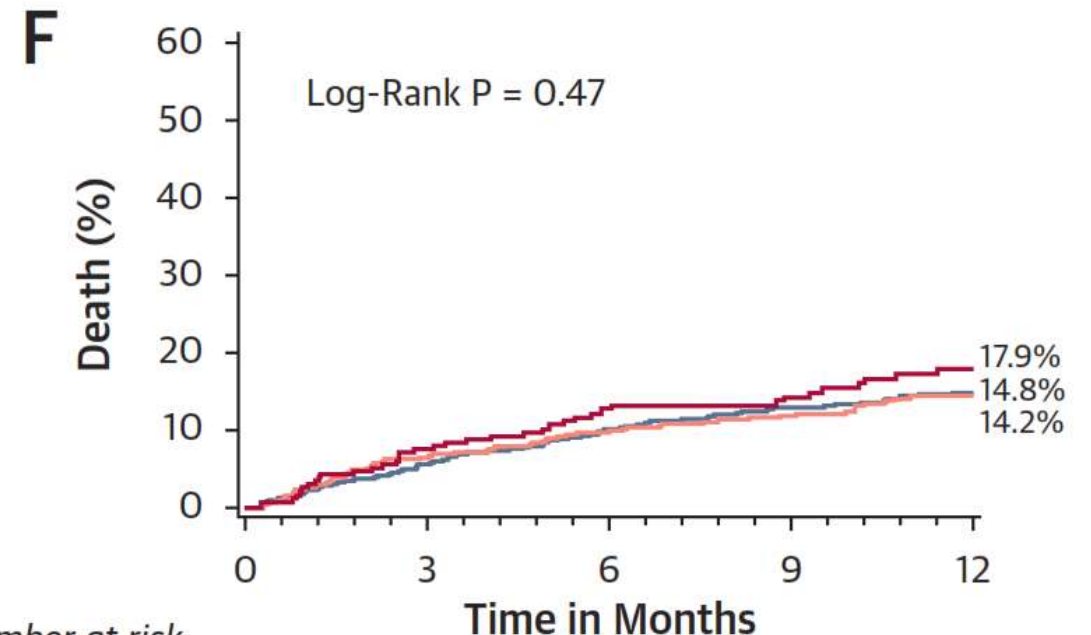
TAVR-RCT



Number at risk

	0	6	12	18	24
No PPM	163	141	128	118	103
Moderate PPM	81	71	63	58	53
Severe PPM	60	59	53	48	47

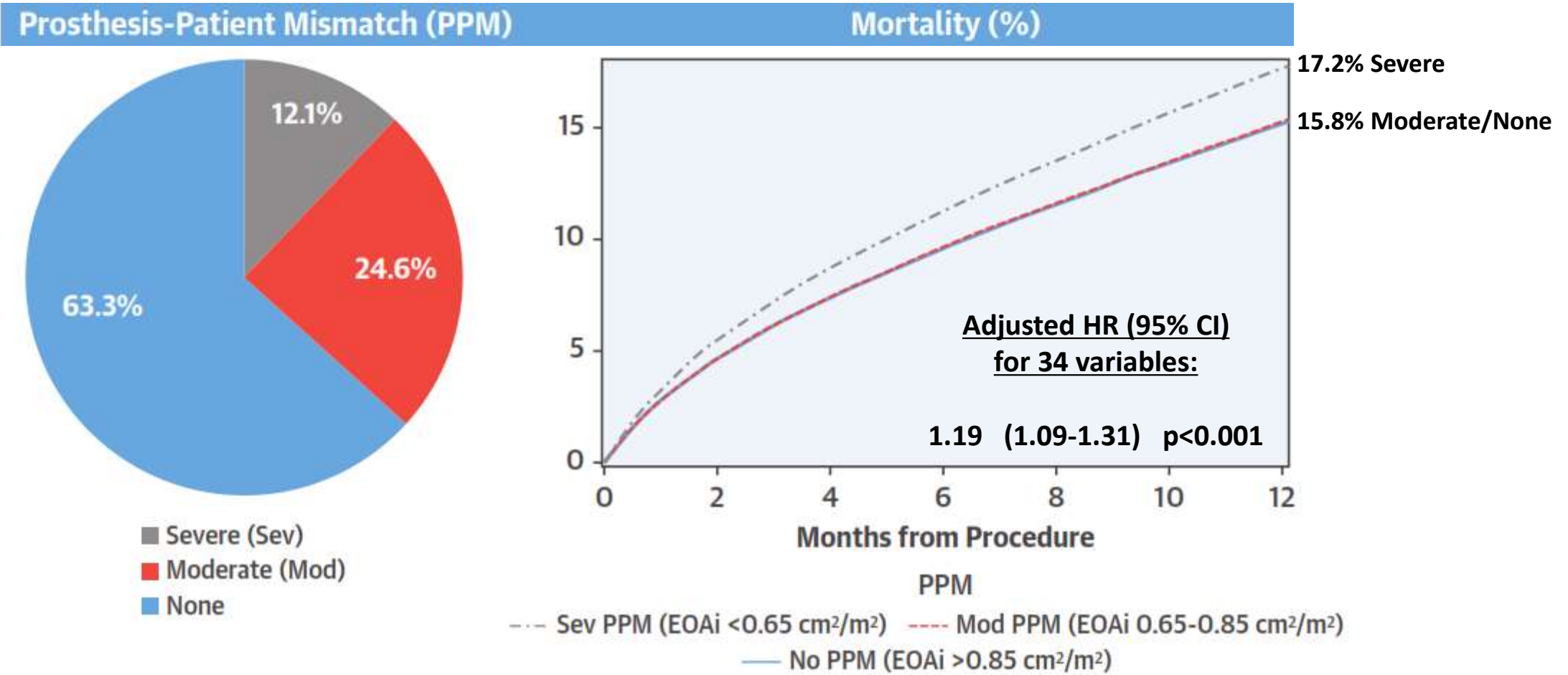
TAVR-NRCA



Number at risk

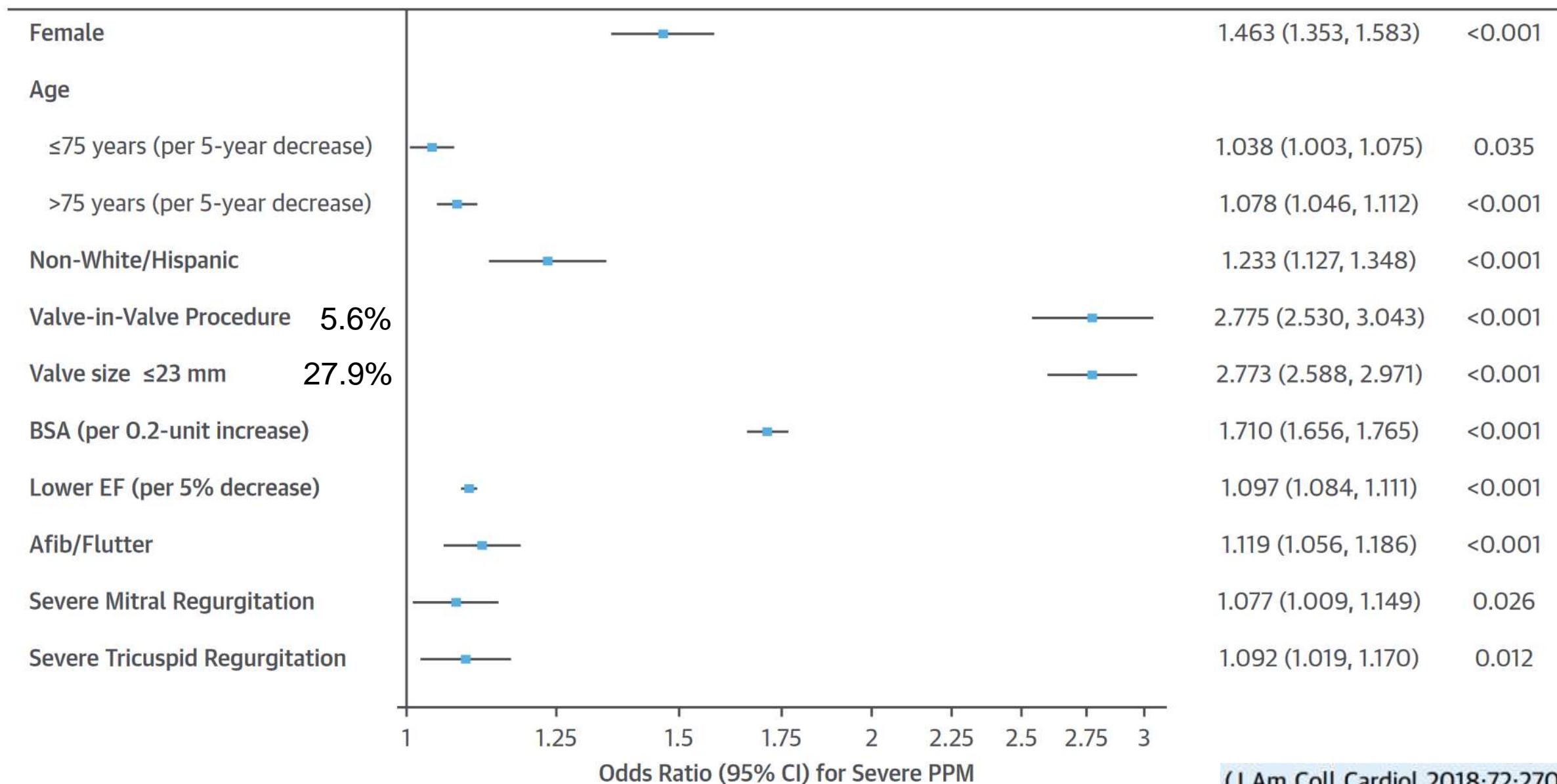
	0	3	6	9	12
No PPM	920	853	736	651	433
Moderate PPM	495	452	403	351	256
Severe PPM	222	203	168	146	91

— No PPM — Moderate PPM — Severe PPM



Number at Risk Adjusting for Baseline Covariates:

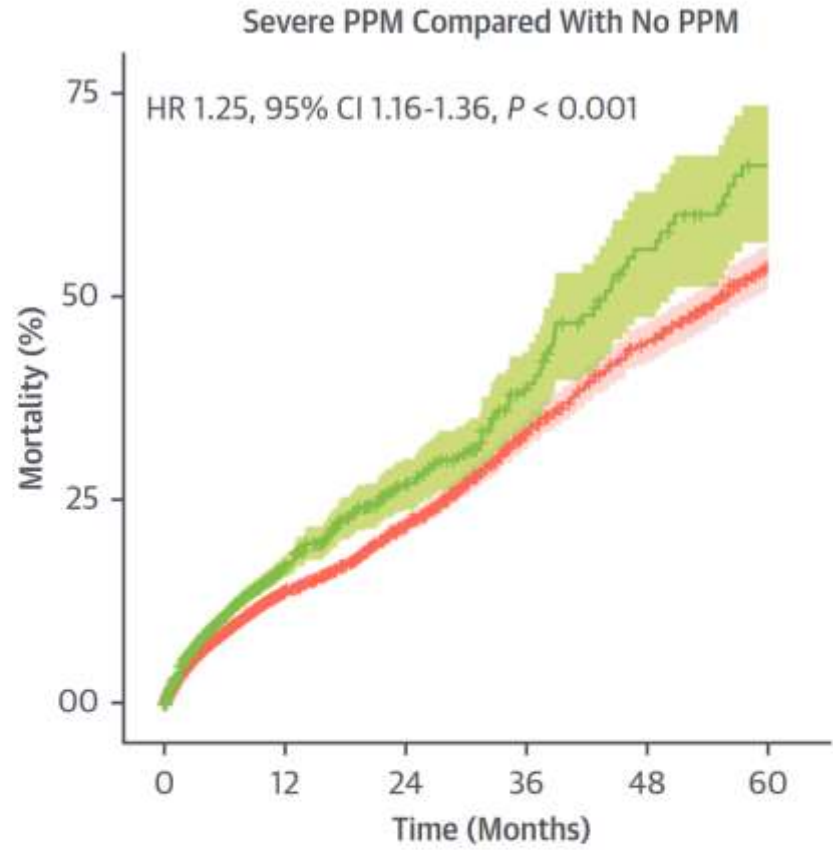
	Day 0	Month 4	Month 8	Month 12
No PPM	23,635	21,080	16,734	13,136
Mod PPM	8,983	7,995	6,277	4,831
Sev PPM	4,152	3,626	2,976	2,130

FIGURE 2 Forest Plot of Predictors of Severe PPM

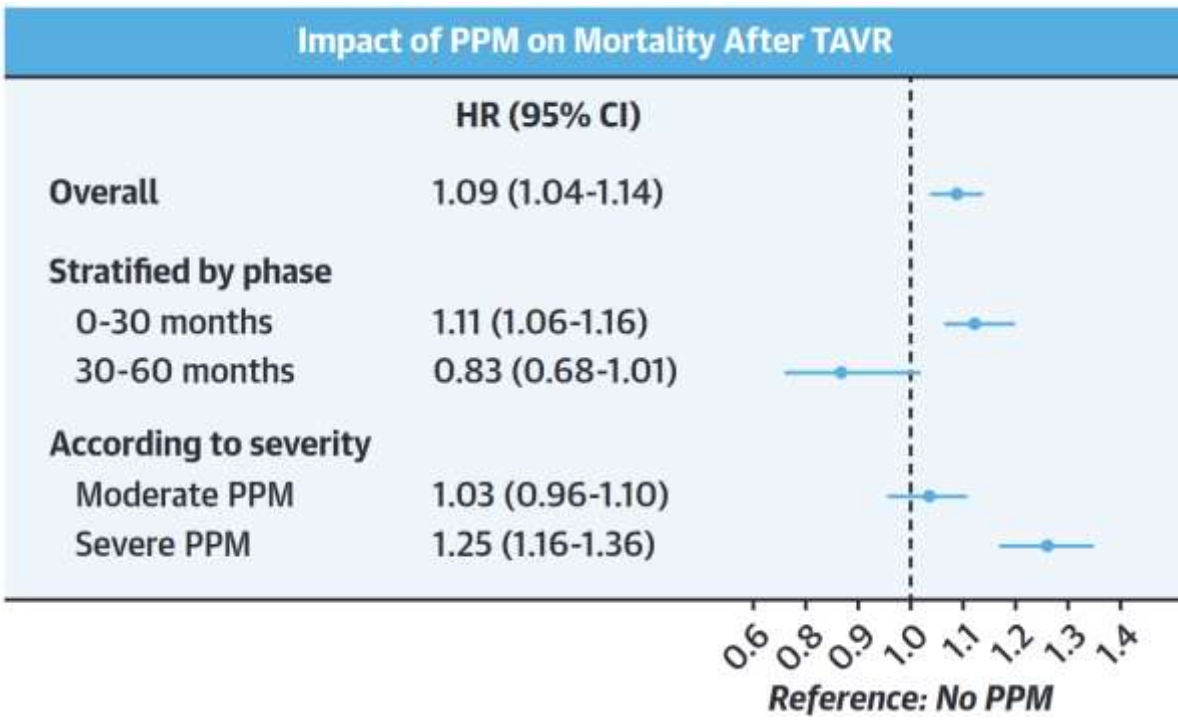
Impact of Prosthesis-Patient Mismatch After Transcatheter Aortic Valve Replacement

Meta-Analysis of Kaplan-Meier-Derived Individual Patient Data

N = 81,969 patients, from 23 studies



		Number at risk					
Group		0	12	24	36	48	60
+	No PPM	29,275	3,426	1,715	713	538	47
+	Severe PPM	4,944	545	223	68	42	4



Bioprosthetic Aortic Valve Hemodynamics: Definitions, Outcomes, and Evidence Gaps

JACC State-of-the-Art Review

(J Am Coll Cardiol 2022;80:527-544)

TABLE 3 Definitions for Prosthesis-Patient Mismatch

	Severe, cm ² /m ²	Moderate, cm ² /m ²
ASE guidelines ²⁶	<0.65	0.65-0.85
VARC-2 ¹⁰⁵	<0.65	0.65-0.85
BMI ≥30 kg/m ²	<0.60	0.60-0.70
EACVI recommendations ⁸⁰	<0.65	0.65-0.85
BMI ≥30 kg/m ²	<0.55	0.55-0.70
VARC 3 ⁶	≤0.65	0.66-0.85
BMI ≥30 kg/m ²	<0.55	0.55-0.70

ASE = American Society of Echocardiography; BMI = body mass index; EACVI = European Association of Cardiovascular Imaging; VARC = Valve Academic Research Consortium.

TABLE 4 Summary of Reasons for Discrepancy in Effects of Severe PPM on Outcomes

Reasons why the reported incidence of PPM varies after AVR
Method of EOA calculation (measured vs predicted)
Correction or not for obesity
Timing of measurement (immediate vs later)
Effect of underlying flow state
Method of gradient determination (echocardiographic vs hemodynamic)
Reasons why the effects of severe PPM on outcomes are conflicting
Measurements and calculations differ as above
Incomplete correction for confounding and competing outcome variables
Paravalvular aortic regurgitation
Low flow state
Older patients or other survival limitations
Underpowered analyses
Limited follow-up (1 year may not be sufficient)

AVR = aortic valve replacement; EOA = effective orifice area; PPM = prosthesis-patient mismatch.

Imaging criteria or the identification and quantitation of prosthesis-patient mismatch

Mild or not clinically significant

Moderate

Severe

Aortic prosthetic valves

Indexed EOA (projected or measured)

BMI < 30 kg/m²

> 0.85

0.85–0.66

≤ 0.65

BMI ≥ 30 kg/m²

> 0.70

0.70–0.56

≤ 0.55

European Heart Journal – Cardiovascular Imaging
doi:10.1093/ehjci/jew025

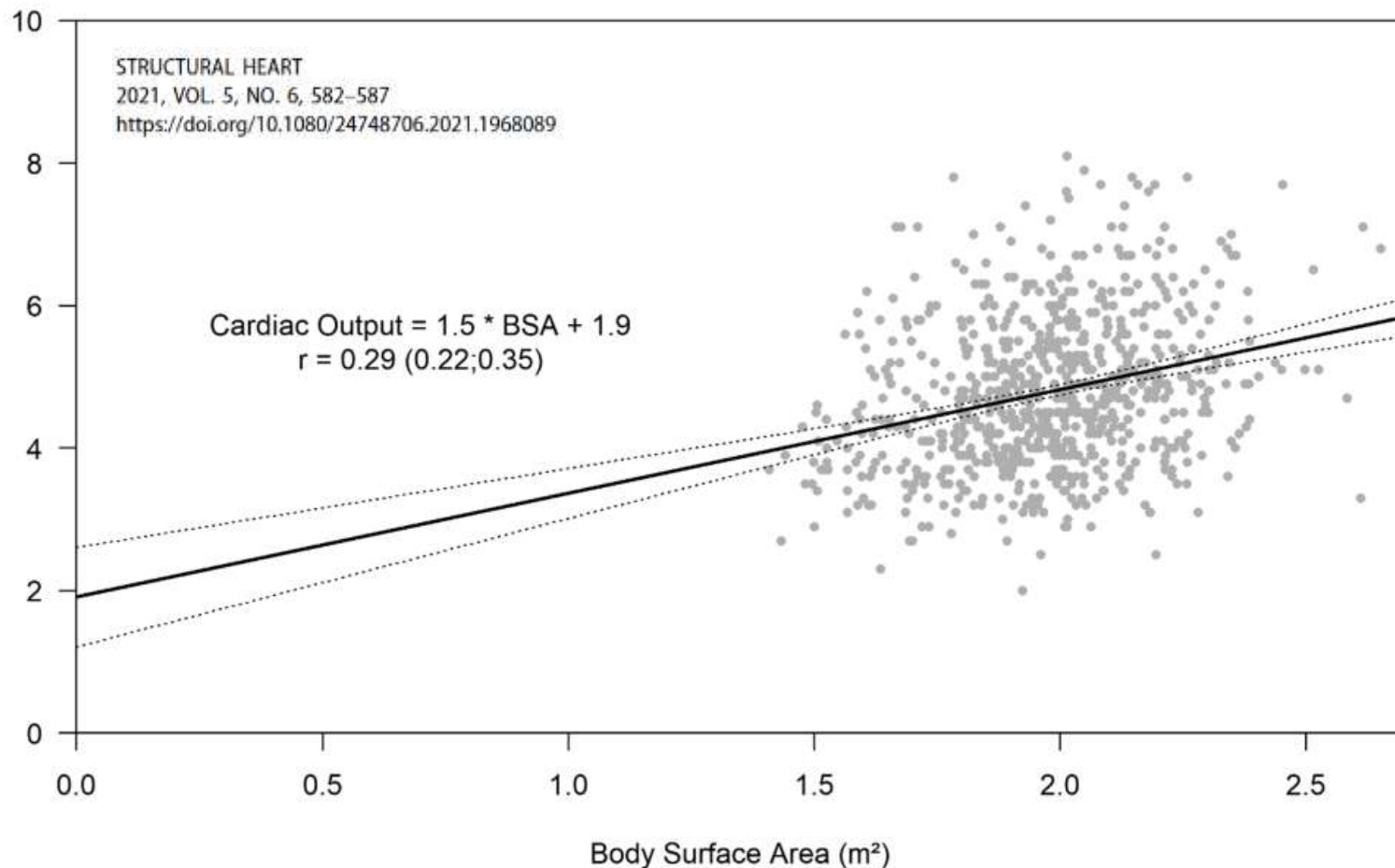


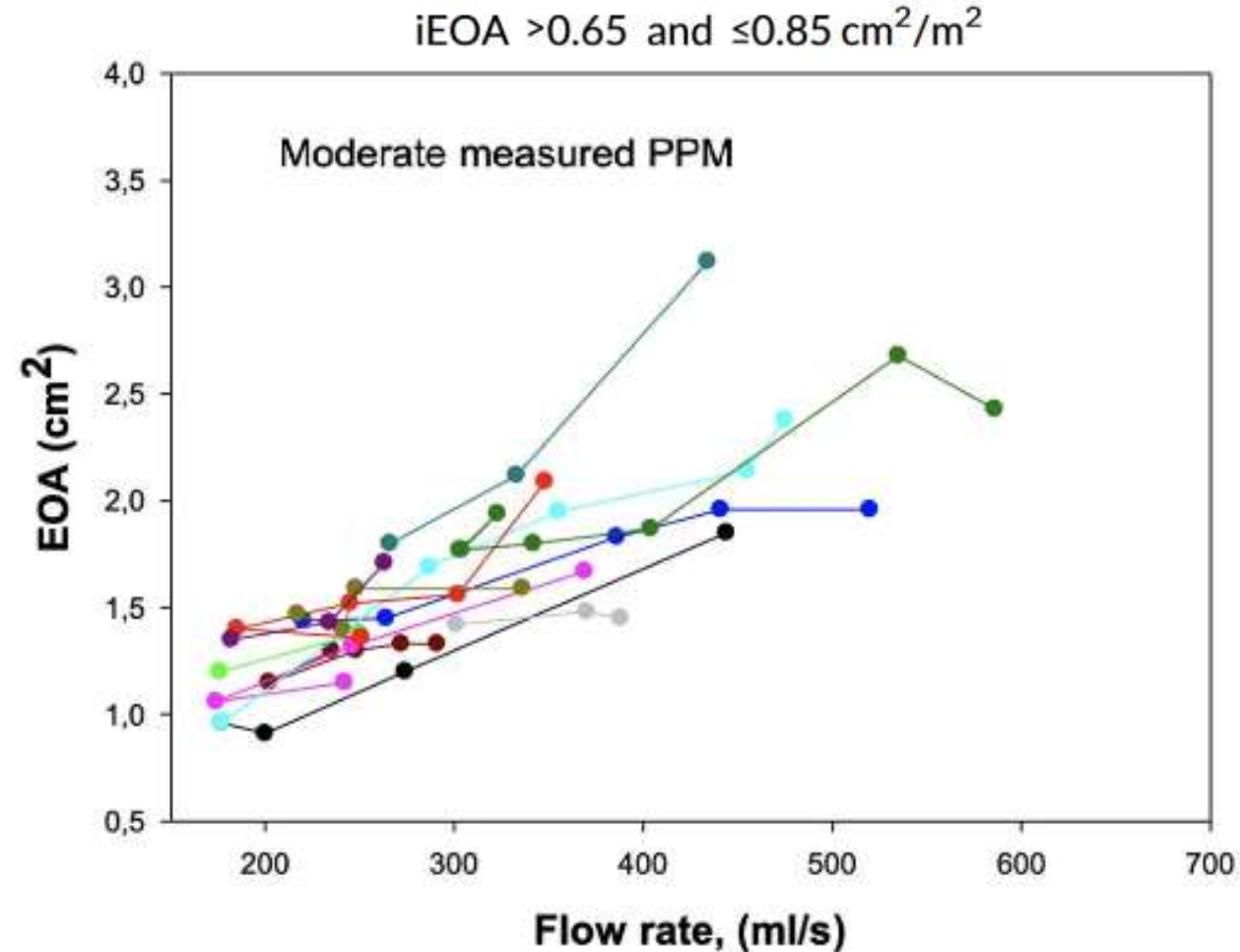
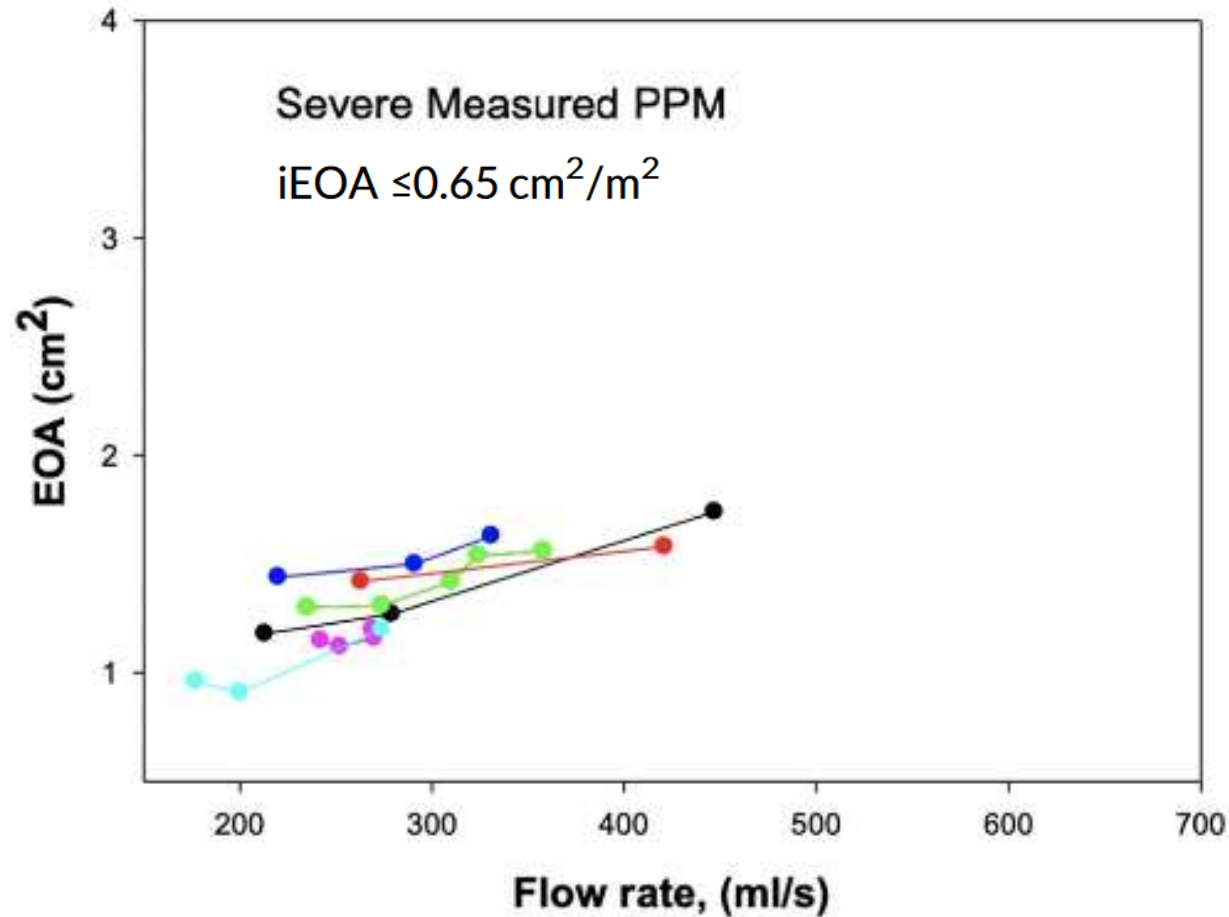
TABLE 3 Subgroup Analyses (Adjusted Models) of Association of Severe PPM and All-Cause Mortality at 1 Year

	Mortality Effect Estimate (95% CI)	Interaction p Value
BMI		0.204
<30 kg/m ²	1.149 (1.031–1.281)	
≥30 kg/m ²	1.277 (1.115–1.464)	

(J Am Coll Cardiol 2018;72:2701–11)

Stress exercise haemodynamic performance and opening reserve of a stented bovine pericardial aortic valve bioprosthesis

N = 148 patients, SAVR with the Avalor valve



Stress exercise haemodynamic performance and opening reserve of a stented bovine pericardial aortic valve bioprosthesis

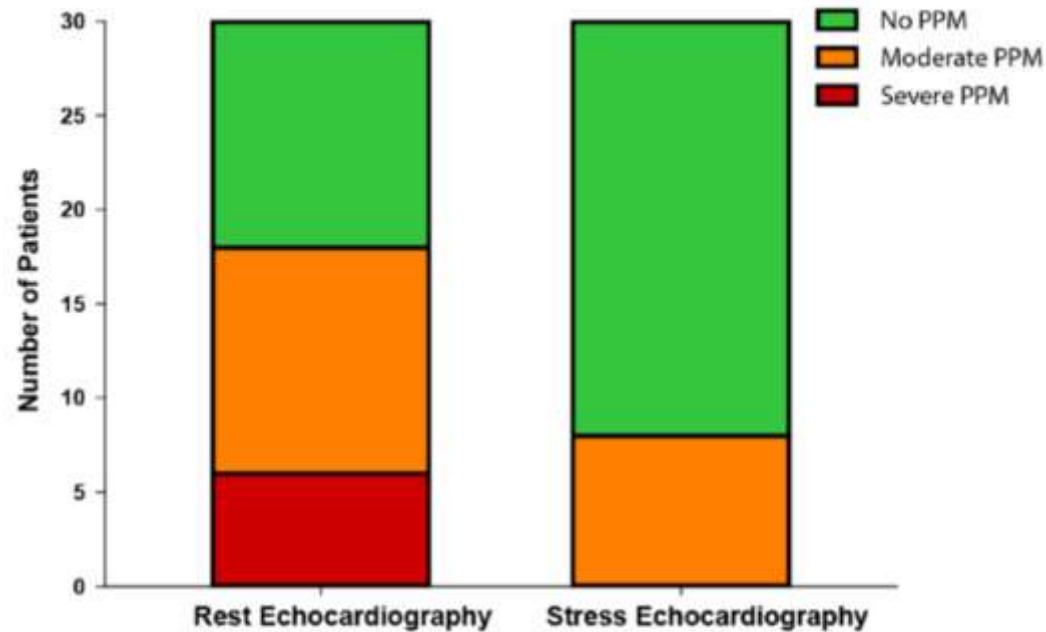
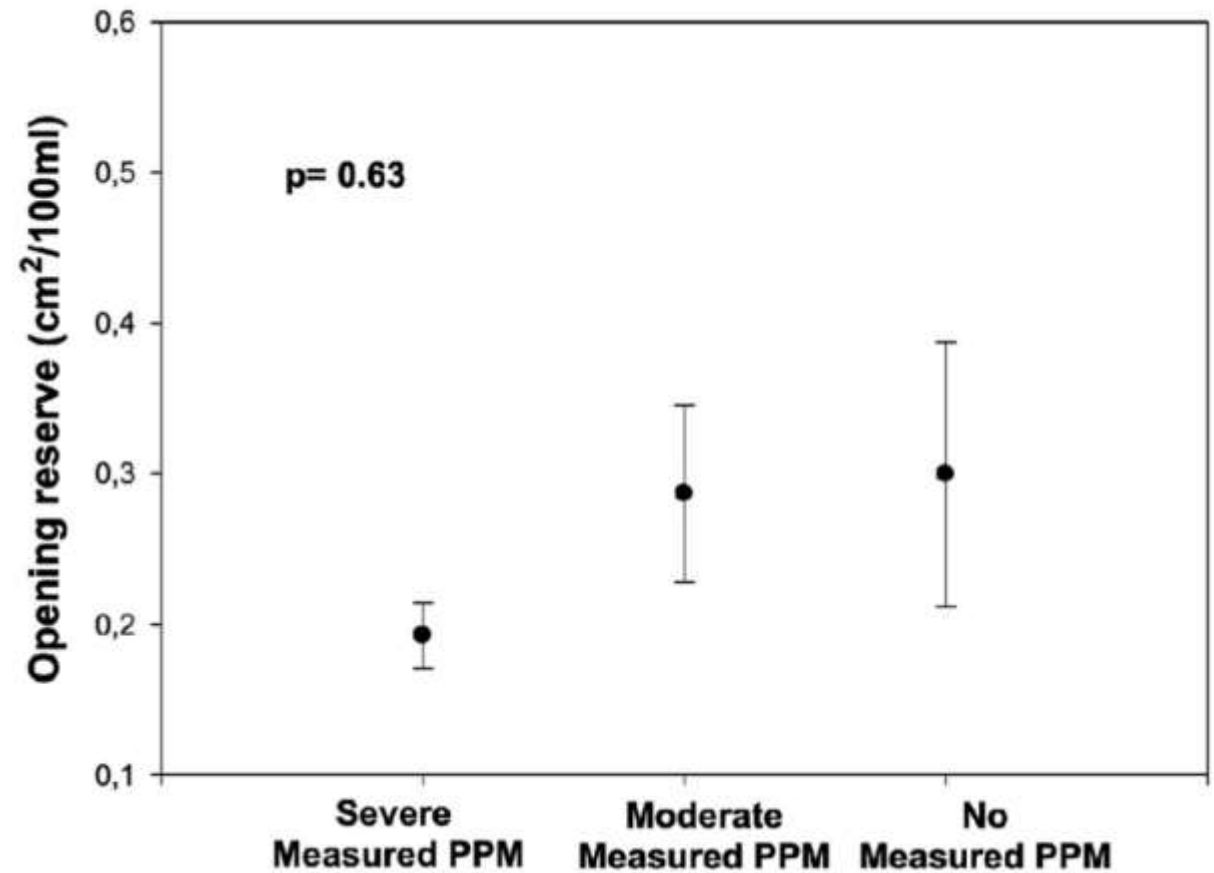


FIGURE 2 Evolution of measured PPM status from rest to peak exercise. From rest to peak exercise, the increase in measured iEOA at stress supported reclassification of the patient's PPM status, leading to 73% of the patients within the whole cohort without PPM and none with severe PPM. iEOA, indexed effective orifice area; PPM, patient-prosthesis mismatch



Reclassification of prosthesis–patient mismatch after transcatheter aortic valve replacement using predicted vs. measured indexed effective orifice area

European Heart Journal - Cardiovascular Imaging (2021) 22, 11–20

- i. Measured EOA_i: The EOA was measured at discharge transthoracic echocardiogram using the continuity equation.^{19,20} The diameter of
- ii. Predicted EOA_i: The predicted EOA was obtained from the published normal reference values of EOA for each model and size of transcatheter valve (Supplementary data online, Table S1).²¹ The predicted EOA was then indexed to BSA.

Table 1 Incidence of PPM at discharge using measured vs. predicted EOA for definition of PPM

Parameters	Measured PPM (n = 1088)	Predicted PPM (n = 1088)	P value
EOA (cm ²)	1.54 ± 0.5	1.72 ± 0.2	<0.001
EOA _i (cm ² /m ²)	0.87 ± 0.3	0.96 ± 0.2	<0.001
Any PPM, N (%)	561 (51)	222 (20)	<0.001
Any PPM adjusted for obesity ^a , N (%)	482 (44)	115 (11)	<0.001
Moderate PPM, N (%)	330 (30)	201 (18)	<0.001
Moderate PPM adjusted for obesity ^a , N (%)	297 (27)	104 (10)	<0.001
Severe PPM, N (%)	231 (21)	21 (2)	<0.001
Severe PPM adjusted for obesity ^a , N (%)	185 (17)	11 (1)	<0.001

EOA, effective orifice area; EOA_i, effective orifice area indexed to body surface area; PPM, prosthesis–patient mismatch.

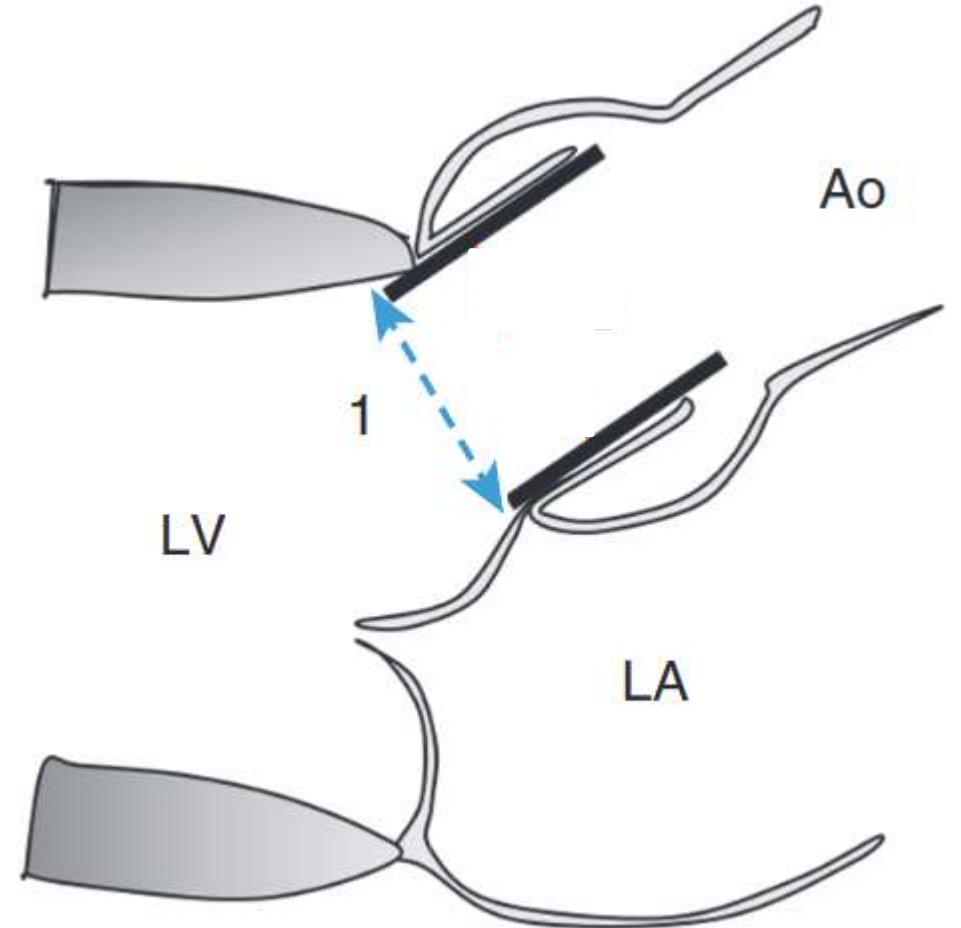
^aAny and moderate PPM defined by an EOA_i ≤0.70 cm²/m², and severe PPM defined by an EOA_i ≤0.55 cm²/m² in patients with a body mass index ≥30 kg/m².

Echocardiographic Measurements

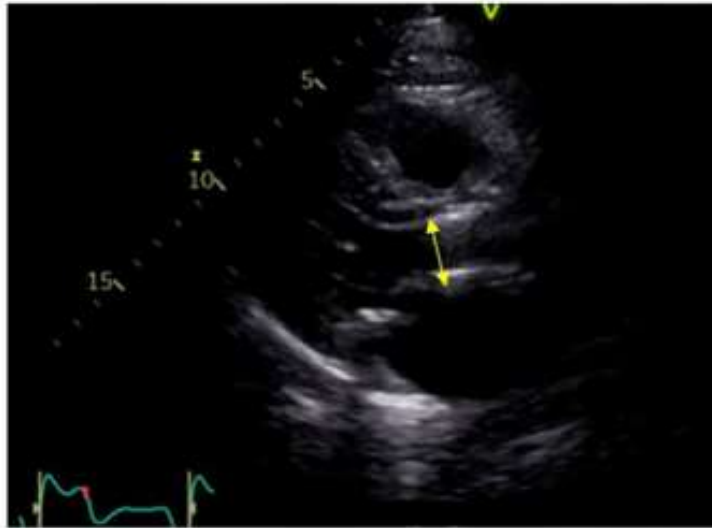
$$\begin{aligned} \text{EOA} &= \text{CSA} \times \text{VTI}_{\text{LVOT}} / \text{VTI}_{\text{PrV}} \\ &= 0.785 \times (\underline{D_{\text{LVOT}}})^2 \times \text{VTI}_{\text{LVOT}} / \text{VTI}_{\text{PrV}} \end{aligned}$$

$$\text{EOA} = \frac{\text{Stroke volume}}{\text{VTI}_{\text{PrV}}}$$

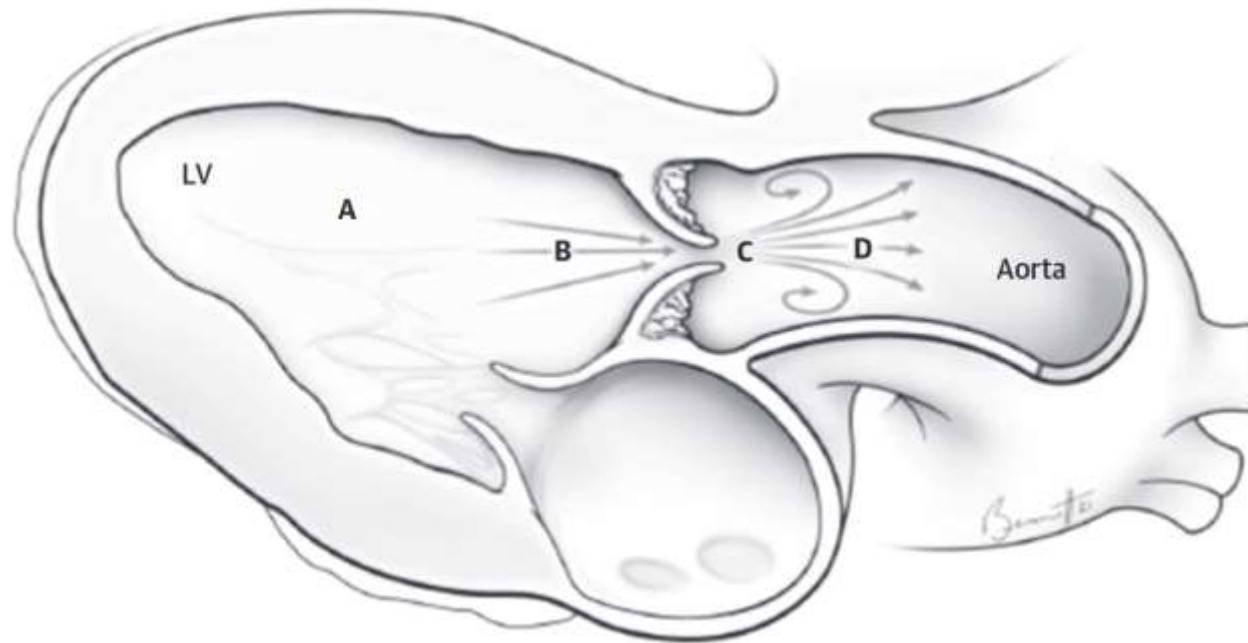
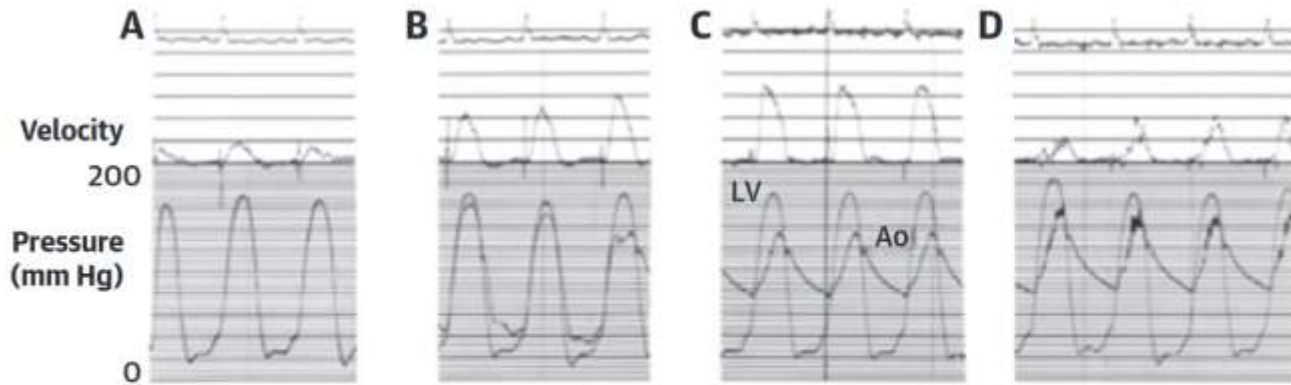
At the inferior edge of the THV stent



from outer-edge to outer-edge

A**B****C**

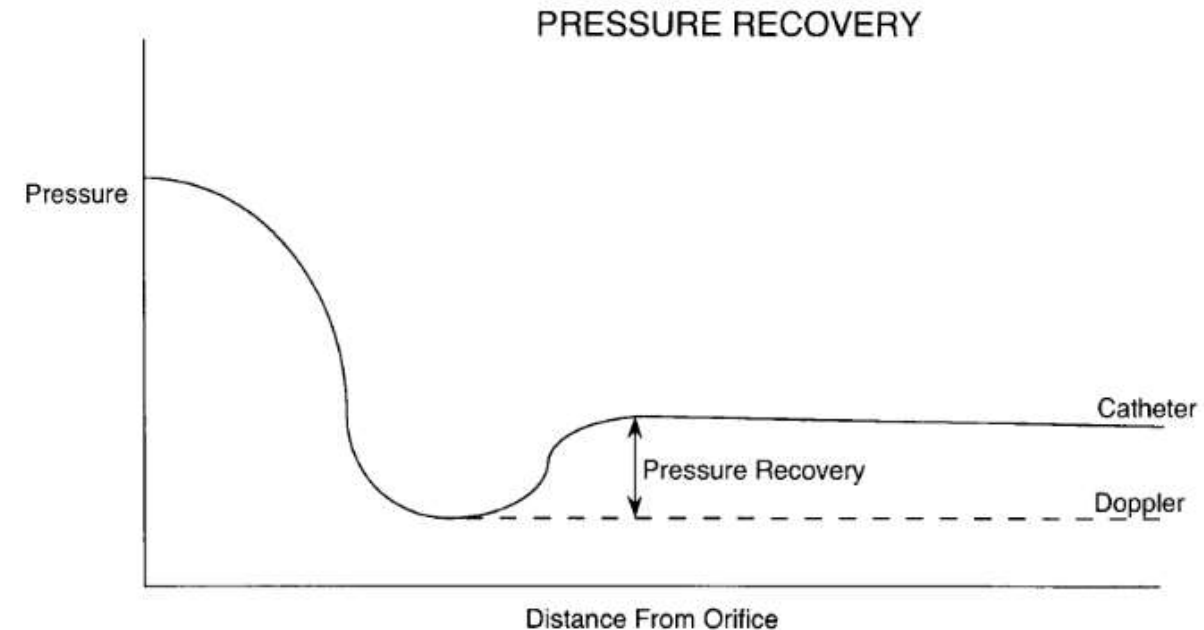
Pressure Loss Recovery in Aortic Stenosis



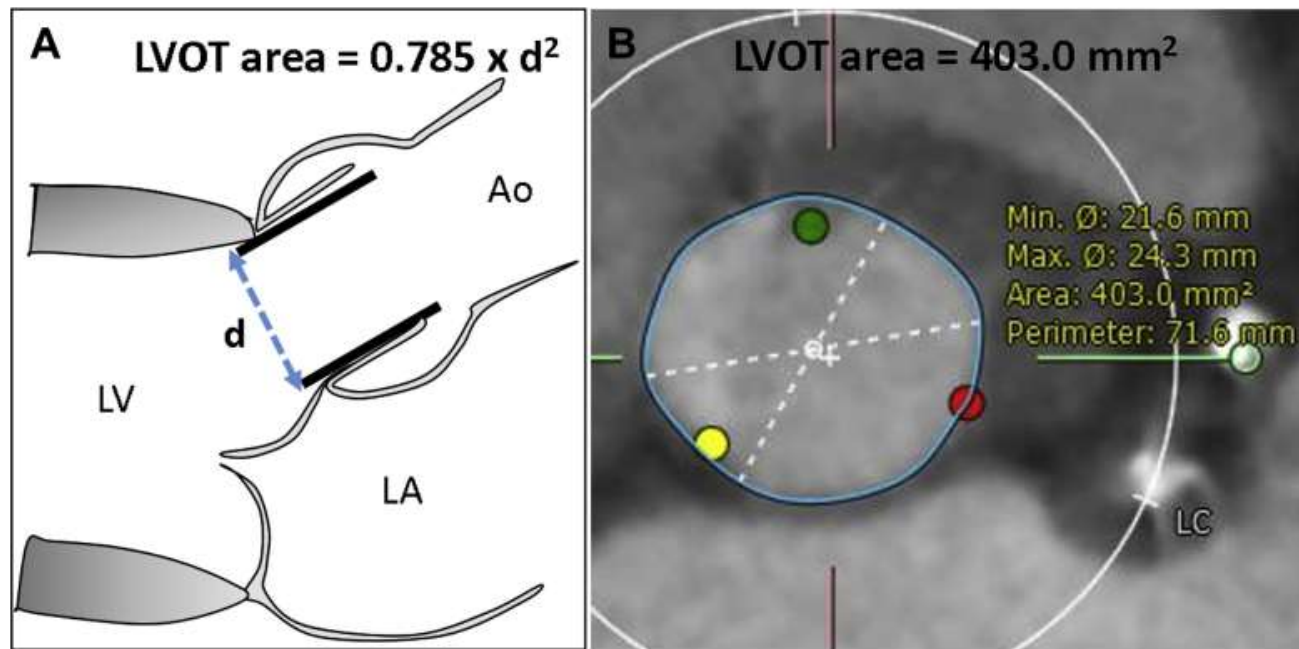
Modified-Bernoulli

$$\Delta P = [(4V_2^2 - 4V_1^2) + \text{Flow Acceleration} + \text{Viscous Forces}] - \text{Pressure Recovery}$$

(ΔP = change in pressure/gradient; V_2 = aortic velocity; V_1 = left ventricular velocity)

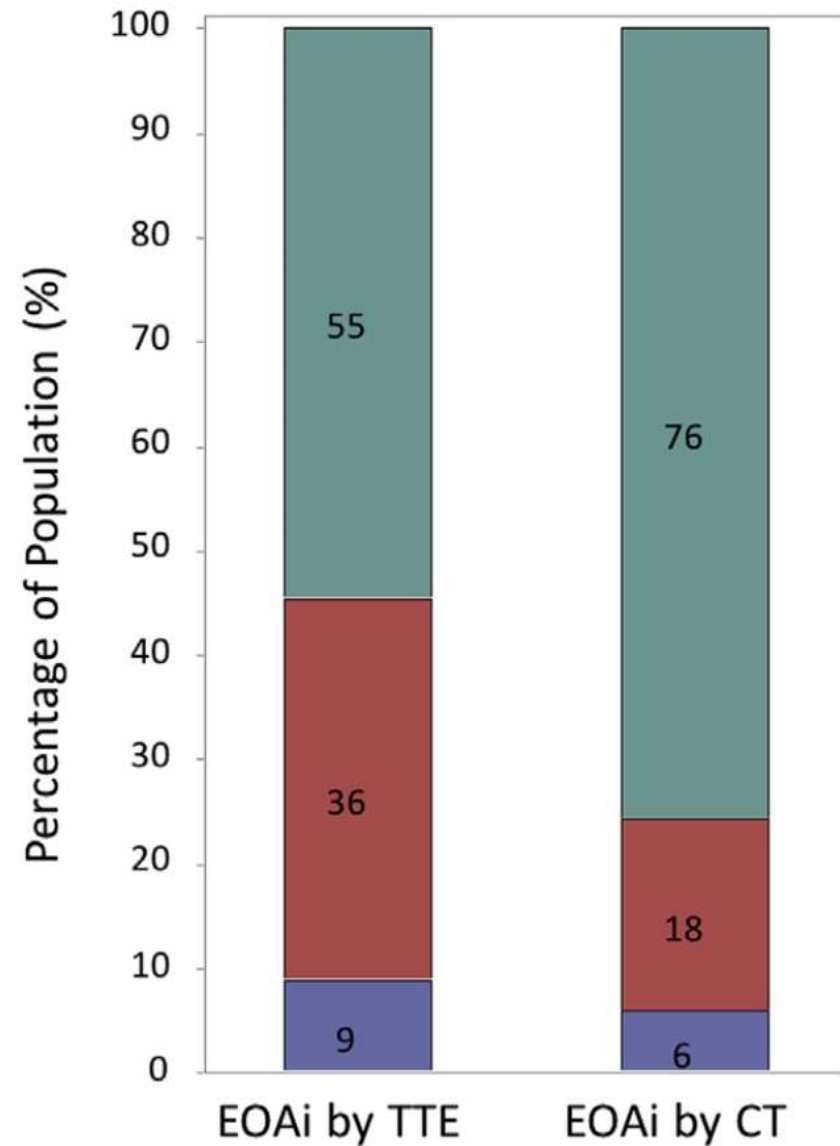


CT-Defined Prosthesis-Patient Mismatch Downgrades Frequency and Severity, and Demonstrates No Association With Adverse Outcomes After Transcatheter Aortic Valve Replacement



$$EOA_{TTE} = \pi \times (LVOT_{TTE}/2)^2 \times VTI_{LVOT}/VTI_{AO}$$

$$EOA_{CT} = A \times VTI_{LVOT}/VTI_{AO}$$



— No PPM

— Moderate PPM

— Severe PPM

Prosthesis-patient mismatch defined by cardiac computed tomography versus echocardiography after transcatheter aortic valve replacement

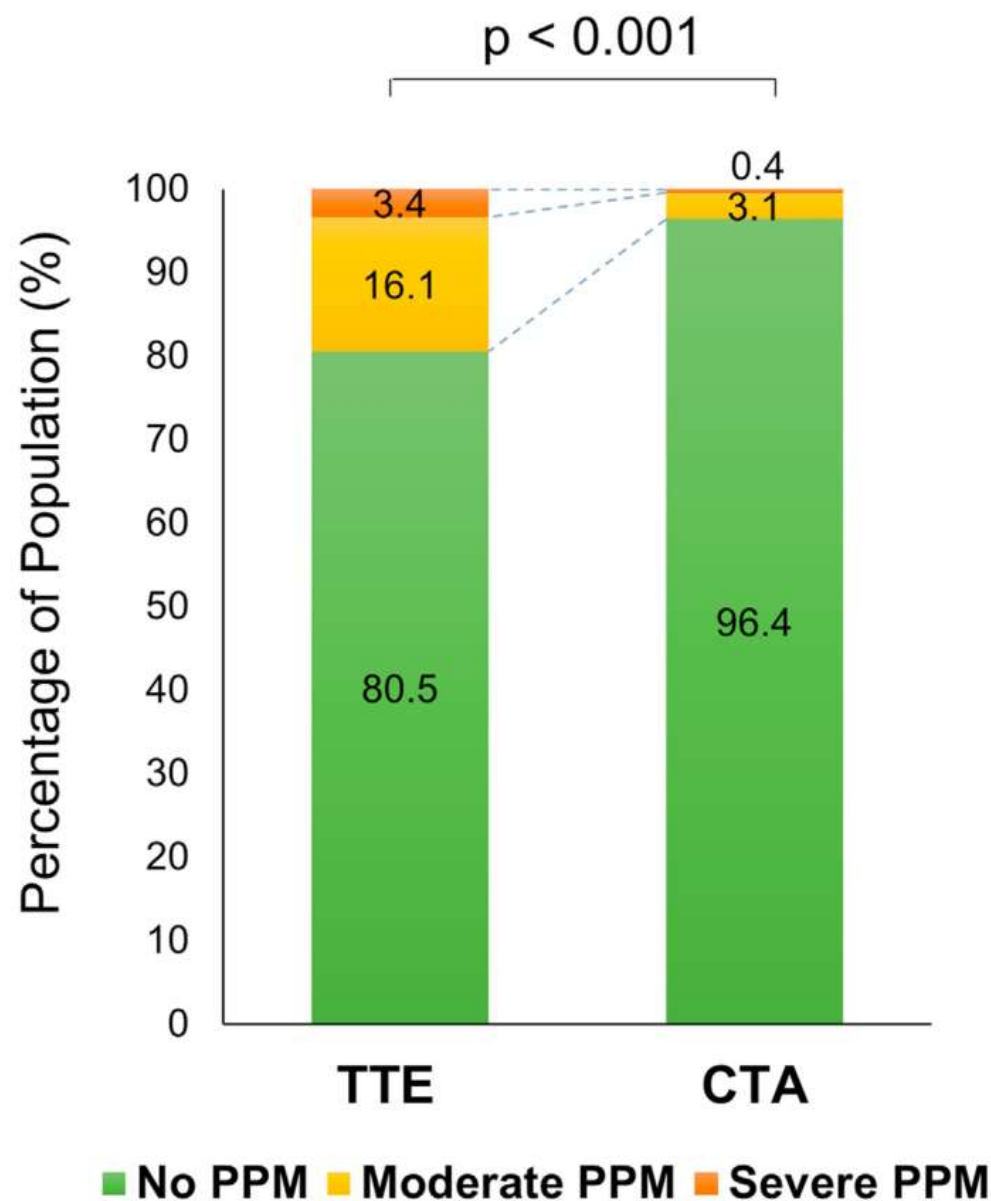
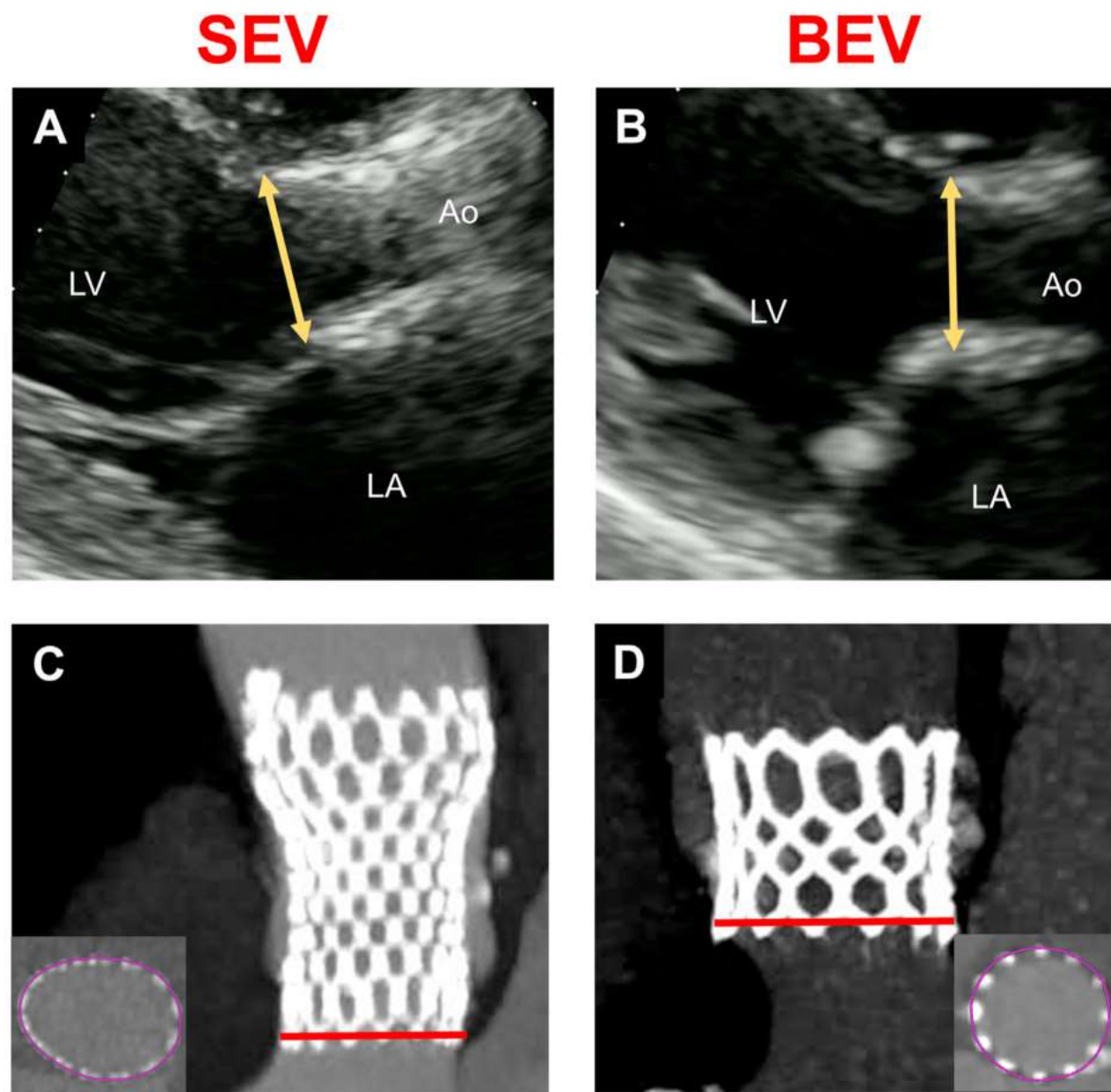
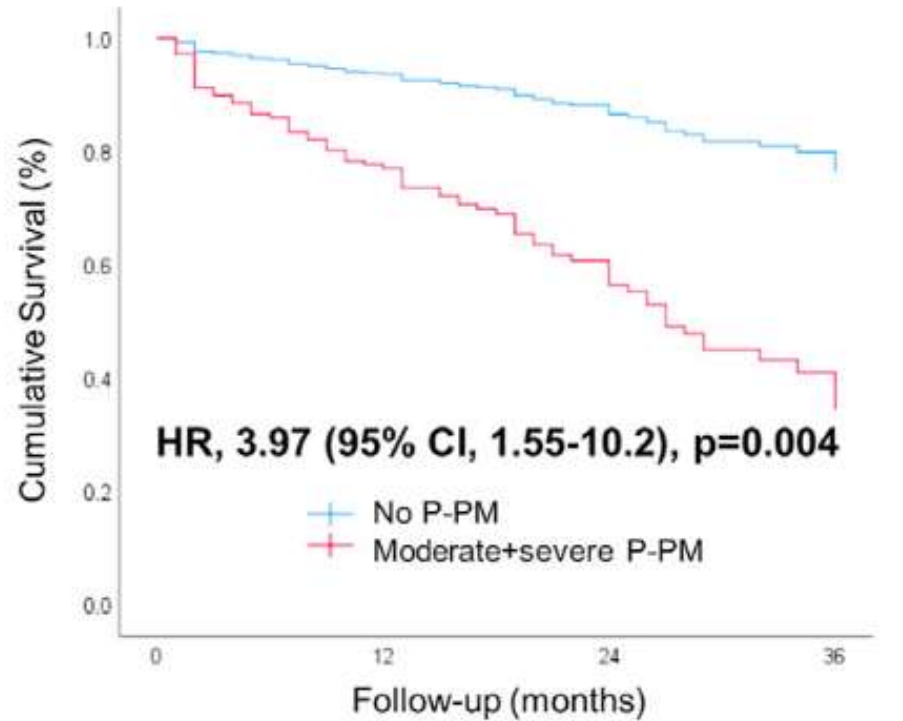


Fig. 2. Prevalence of P-PM according to TTE and CTA Classification of prosthesis-patient mismatch (P-PM) severity by TTE and CTA (n = 447)CTA, computed tomography angiography; TTE, transthoracic echocardiography.

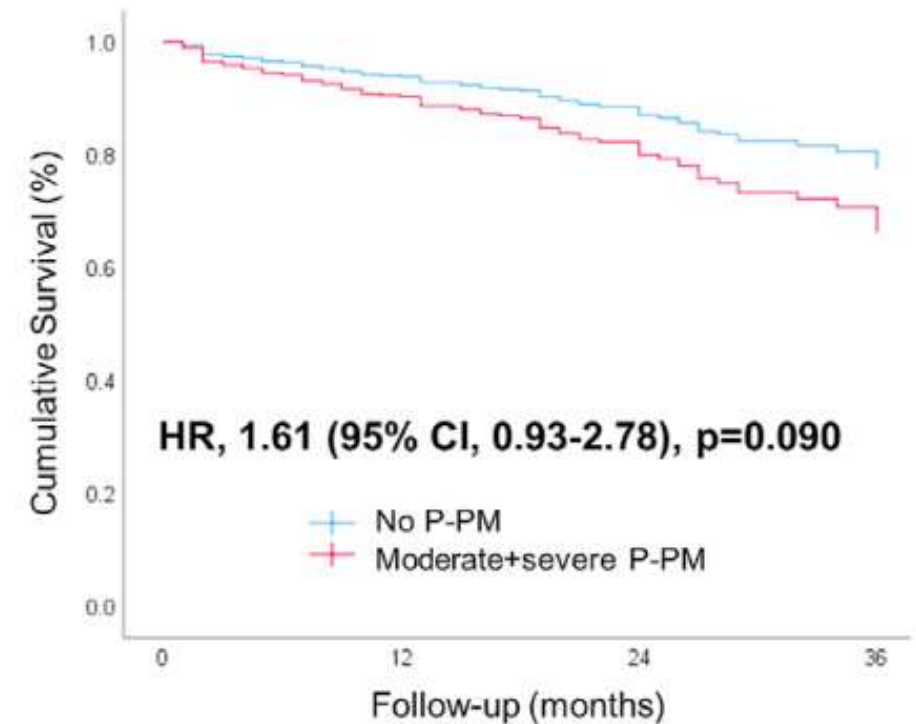
All-cause mortality at 3 year

CTA defined PPM

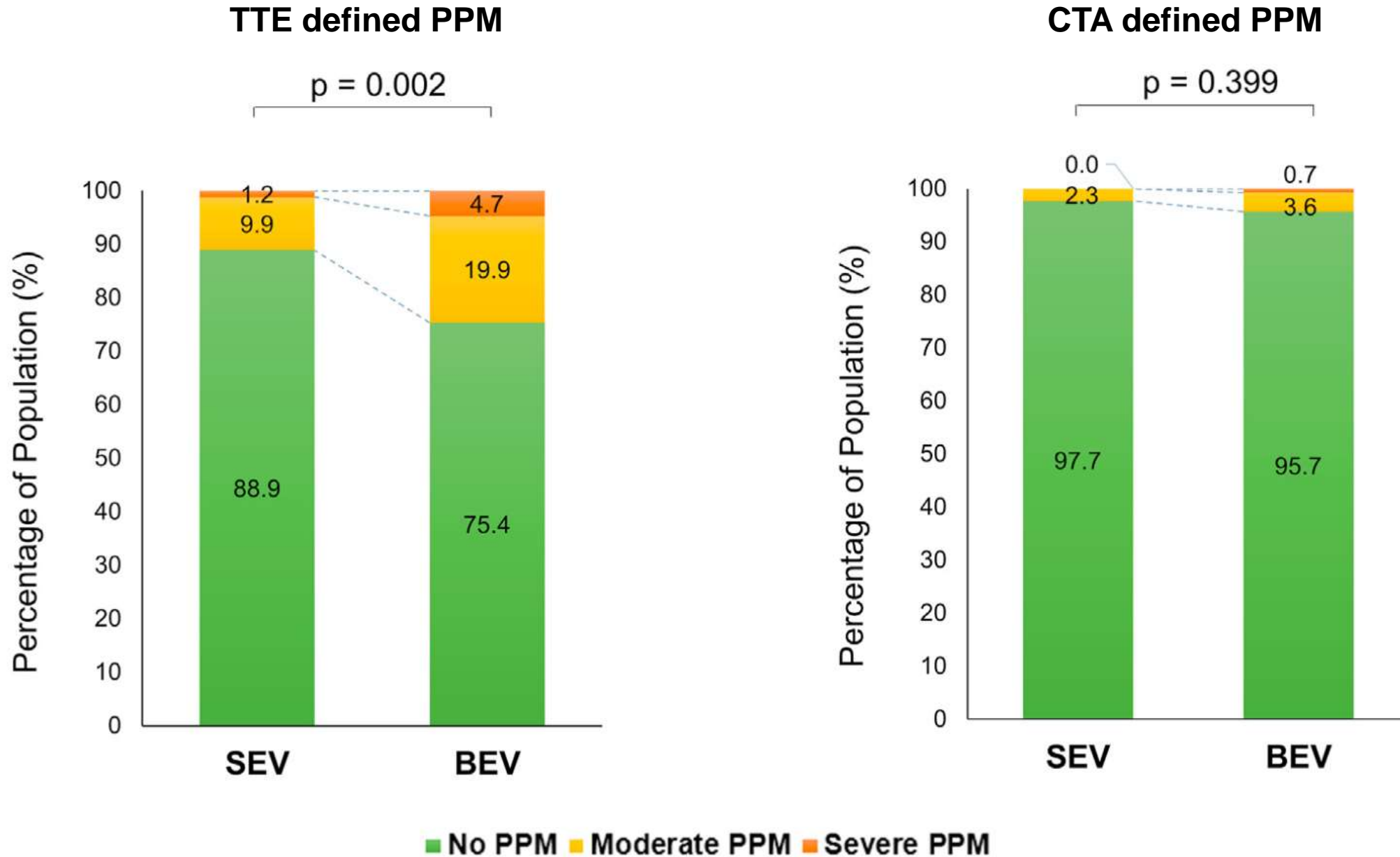


None	431	371	188	47
Moderate/severe	16	11	6	2

TTE defined PPM



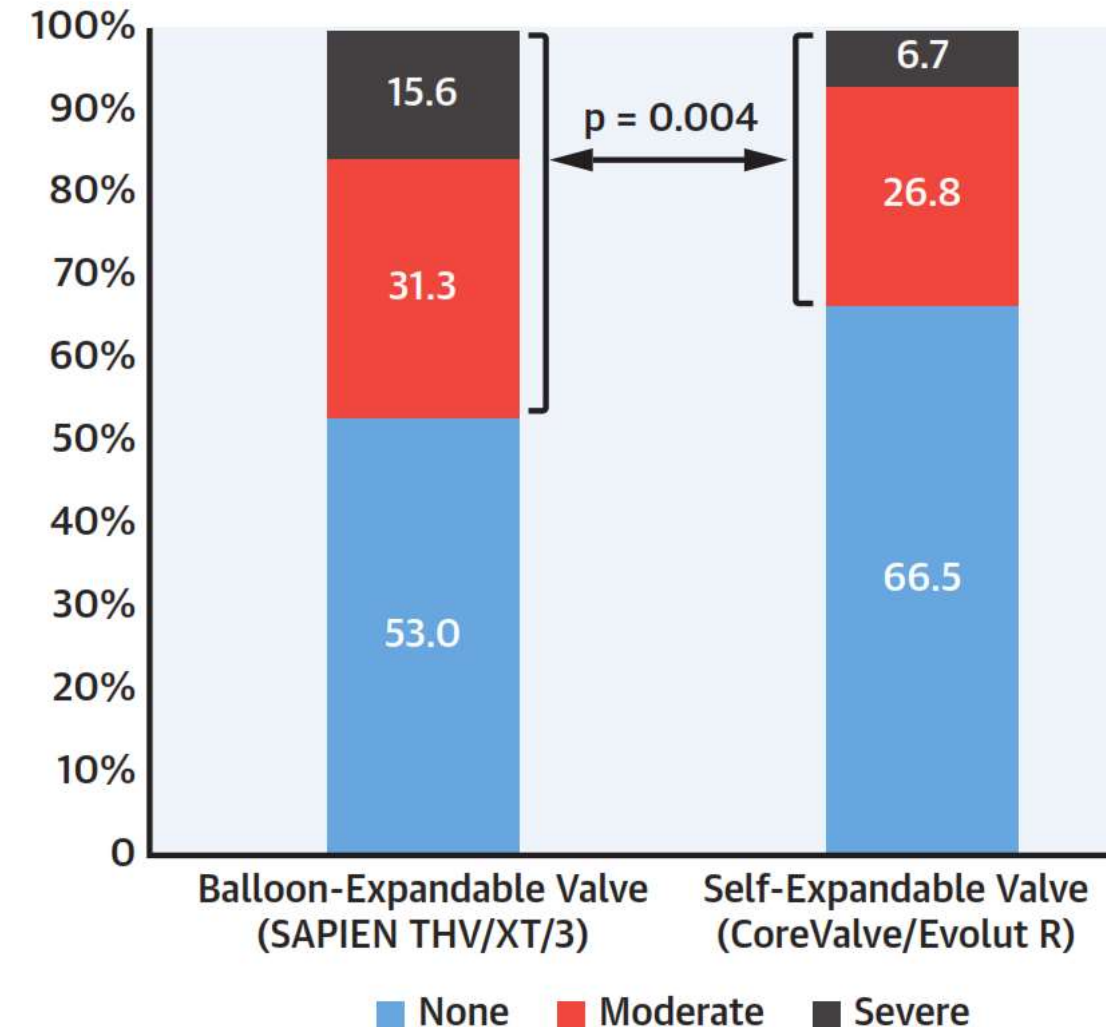
None	360	310	156	38
Moderate/severe	87	72	38	11



Prosthesis-Patient Mismatch Following Transcatheter Aortic Valve Replacement With Supra-Annular and Intra-Annular Prostheses

Prosthesis-Patient Mismatch

N = 757 patients, The Bern TAVI registry, between August 2007 and June 2017

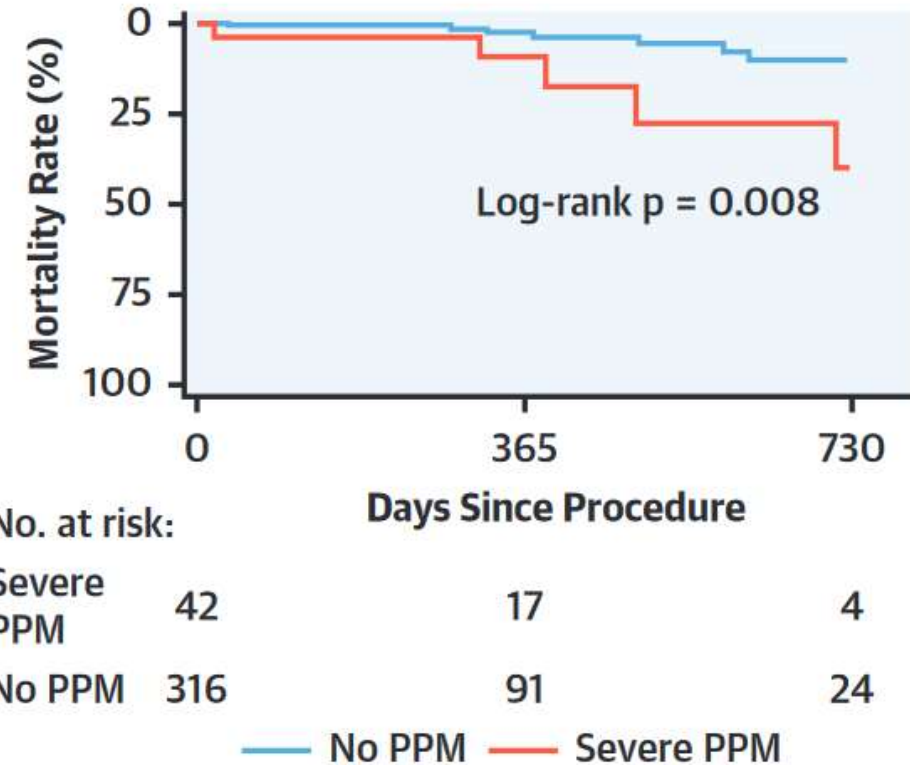
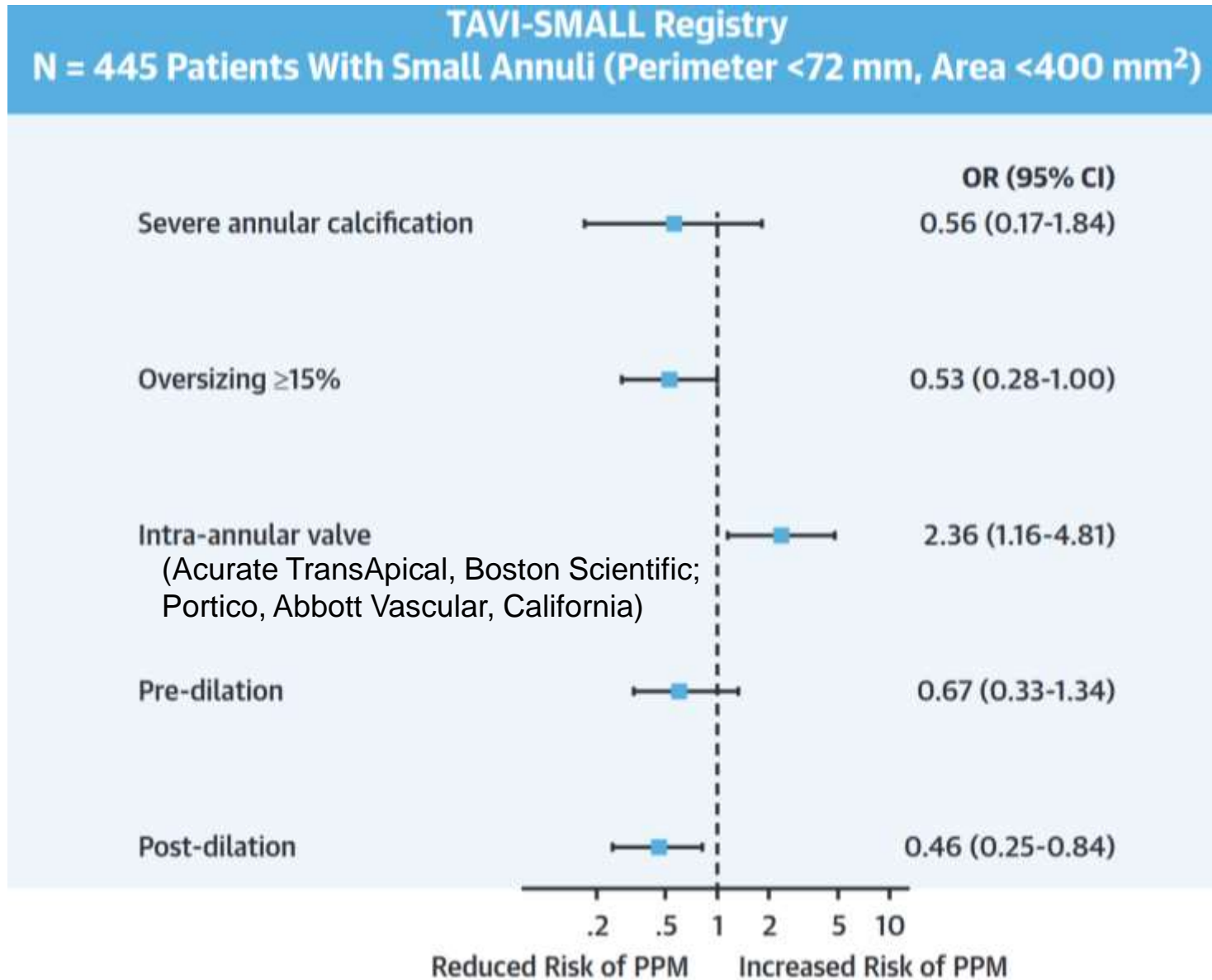


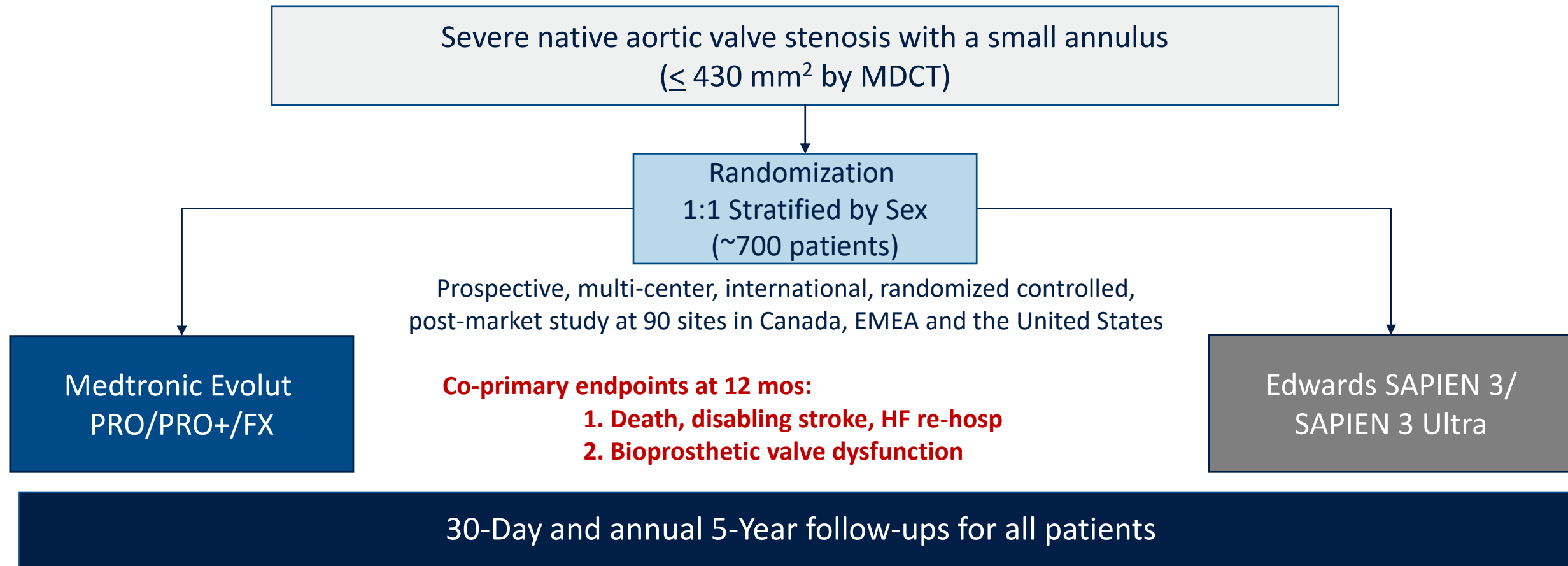
	Intra-Annular Valves (SAPIEN THV/XT/3) (n = 224)	Supra-Annular Valves (CoreValve, Evolut R) (n = 224)	p Value
EOA, cm ²	1.68 ± 0.52	1.80 ± 0.46	0.010
Indexed EOA, cm ² /m ²	0.93 ± 0.31	0.99 ± 0.27	0.021
Transvalvular mean gradient, mm Hg	10.7 ± 4.7	8.3 ± 3.9	<0.001
LVEF, %	56.5 ± 11.5	56.5 ± 10.8	0.959

Prosthesis-Patient Mismatch Following Transcatheter Aortic Valve Replacement With Supra-Annular and Intra-Annular Prostheses

Group	Balloon-Expandable Valve (SAPIEN THV/XT/3) Mismatch/Total (%)	Self-Expandable Valve (CoreValve, Evolut R) Mismatch/Total (%)	SEV vs. BEV Odds Ratio (95% CI)	Odds Ratio (95% CI)					p Value	
				0.05	0.10	0.25	0.50	1.0		2.0
All patients										
PPM	105/224 (46.9%)	75/224 (33.5%)	0.57 (0.39-0.84)							0.004
Severe PPM	35/224 (15.6%)	15/224 (6.7%)	0.39 (0.21-0.73)							0.003
Annulus area										
<430 mm²										
PPM	45/88 (51.1%)	27/93 (29.0%)	0.39 (0.21-0.72)							0.003
Severe PPM	12/88 (13.6%)	8/93 (8.6%)	0.60 (0.23-1.54)							0.284
≥430 mm²										
PPM	60/136 (44.1%)	48/131 (36.6%)	0.73 (0.45-1.20)							0.214
Severe PPM	23/136 (16.9%)	7/131 (5.3%)	0.28 (0.11-0.67)							0.004

Predictors and Clinical Impact of Prosthesis-Patient Mismatch After Self-Expandable TAVR in Small Annuli





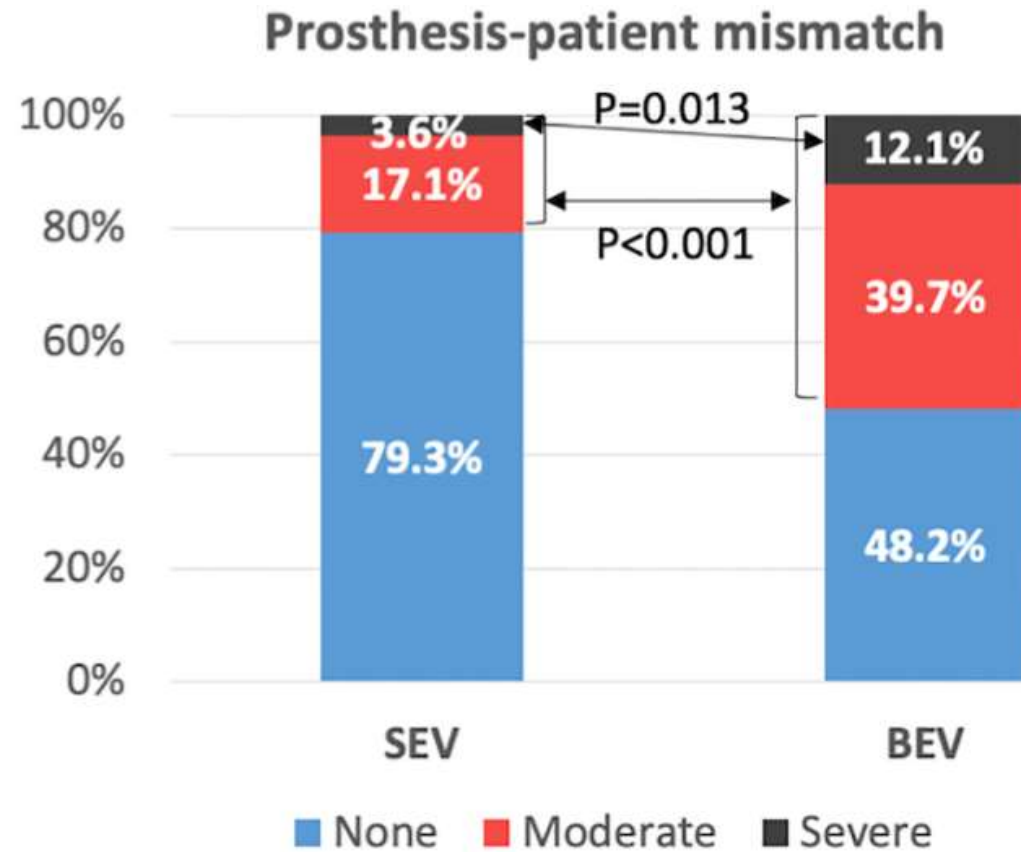
Study Organization	Chair/PI: Howard C. Herrmann, MD Co-PIs: Roxana Mehran, MD and Didier Tchetché MD
Major inclusion/exclusion criteria	<ul style="list-style-type: none"> • Small annulus with all risk groups (low to high) • An “all-comers” trial (including bicuspid valves) • Patient’s anatomy must be suitable for TF TAVR treatment with both devices
External Support (Medtronic)	Echocardiographic Core Laboratory, Clinical Events Committee (CEC), Data Safety Monitoring Board (DSMB), Subject Confirmation of Qualification/Case Planning Committee (screening phase)

5-Year Outcomes With Self-Expanding vs Balloon-Expandable Transcatheter Aortic Valve Replacement in Patients With Small Annuli

N = 723 patients, The Bern TAVI registry with an annulus area <430 mm² between January 2012 and June 2021

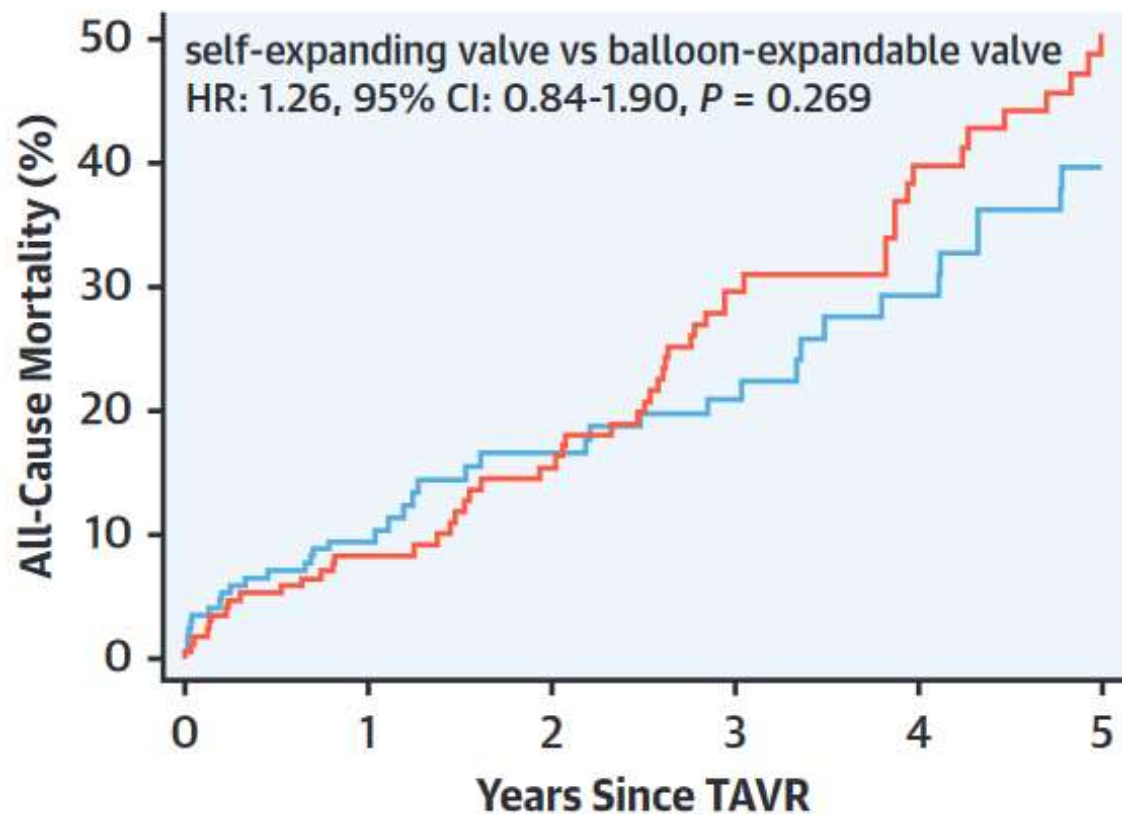
	All Patients (N = 723)	Prematching Cohort				Matched Cohort			
		SEV (n = 389)	BEV (n = 334)	P Value	ASD	SEV (n = 171)	BEV (n = 171)	P Value	ASD
Age, y	82.5 ± 6.2	83.1 ± 6.1	81.7 ± 6.3	0.003	0.222	82.2 ± 6.2	82.7 ± 6.4	0.484	0.076
Male	137 (18.9)	42 (10.8)	95 (28.4)	<0.001	0.455	27 (15.8)	25 (14.6)	0.880	0.032
Body mass index, kg/cm ²	26.4 ± 5.8	25.9 ± 6.0	26.9 ± 5.4	0.026	0.168	26.9 ± 6.1	26.5 ± 5.6	0.513	0.071
STS PROM	4.94 ± 3.43	5.13 ± 3.43	4.71 ± 3.42	0.101	0.123	5.15 ± 3.81	5.34 ± 3.64	0.633	0.052
NYHA functional class III or IV	472 (65.3)	270 (69.4)	202 (60.5)	0.012	0.188	112 (65.5)	119 (69.6)	0.488	0.087
Echocardiographic data									
Aortic valve area, cm ²	0.60 ± 0.23	0.58 ± 0.22	0.63 ± 0.23	0.002	0.230	0.61 ± 0.21	0.61 ± 0.24	0.964	0.005
Aortic valve mean gradient, mm Hg	41.2 ± 17.5	41.5 ± 18.2	40.7 ± 16.5	0.542	0.046	40.1 ± 18.1	39.5 ± 17.8	0.761	0.033
LVEF, %	59.5 ± 11.9	59.5 ± 11.8	59.6 ± 12.1	0.935	0.006	59.5 ± 11.9	58.7 ± 12.8	0.564	0.063
Aortic regurgitation, ≥ moderate	51 (7.1)	27 (6.9)	24 (7.2)	1.000	0.010	13 (7.6)	13 (7.6)	>0.999	0.000
Mitral regurgitation, ≥ moderate	115 (18.2)	77 (22.1)	38 (13.3)	0.005	0.231	19 (11.1)	26 (15.2)	0.337	0.121
Tricuspid regurgitation, ≥ moderate	71 (11.7)	47 (14.1)	24 (8.8)	0.056	0.167	16 (9.9)	18 (11.0)	0.857	0.034

5-Year Outcomes With Self-Expanding vs Balloon-Expandable Transcatheter Aortic Valve Replacement in Patients With Small Annuli



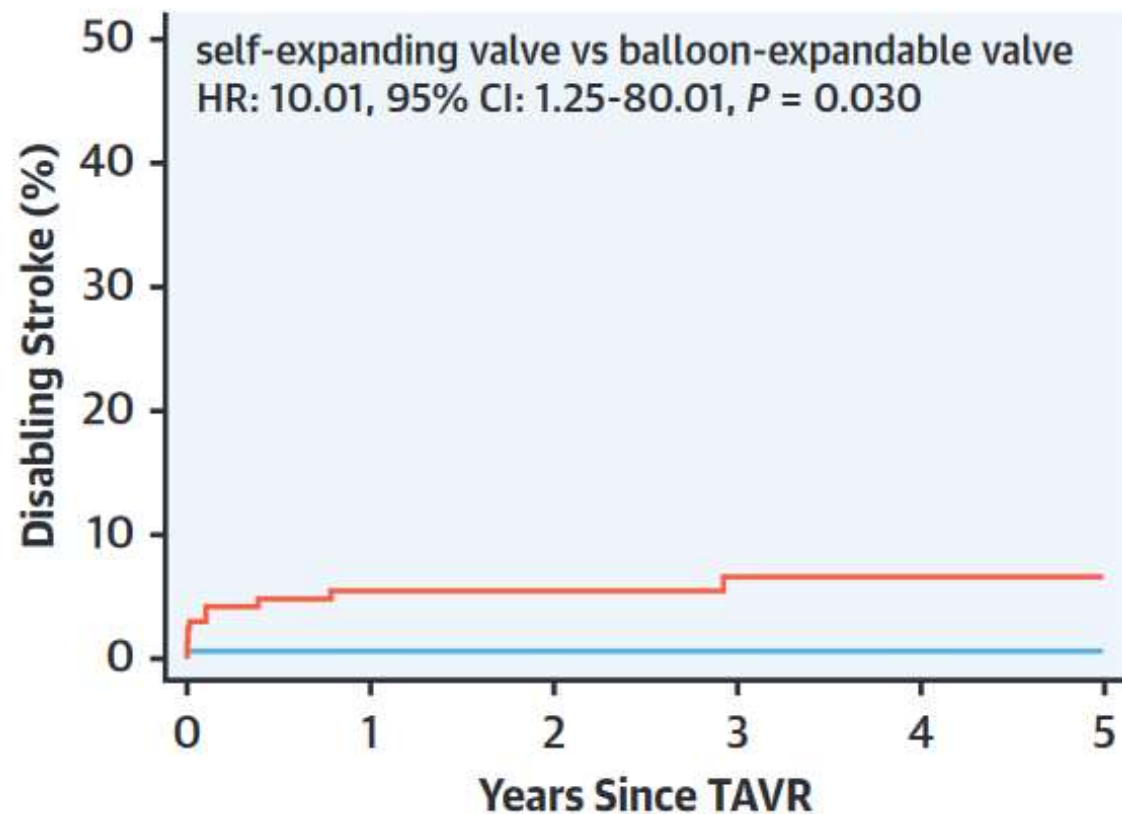
Matched Cohort	SEV (n = 171)	BEV (n = 171)	P Value
Type of valve			Exact matching
Old generation (SAPIEN XT, CoreValve)	11 (6.4)	11 (6.4)	
Newer generation (SAPIEN 3/3Ultra, Evolut R/PRO/PRO ⁺)	160 (93.6)	160 (93.6)	
Echocardiographic assessment (discharge)			
Aortic valve area, mm	1.81 ± 0.46	1.49 ± 0.42	<0.001
Transvalvular mean gradient, mm Hg ^c	8.0 ± 4.8	12.5 ± 4.5	<0.001
Transvalvular mean gradient ≥20, mm Hg ^c	5 (2.9)	12 (7.1)	0.087
Prosthesis-patient mismatch ^c	(n = 140)	(n = 141)	<0.001
Insignificant	111 (79.3)	68 (48.2)	
Moderate	24 (17.1)	56 (39.7)	
Severe	5 (3.6)	17 (12.1)	
"Predicted" prosthesis-patient mismatch ^d	(n = 171)	(n = 170)	<0.001
Insignificant	161 (94.2)	110 (64.7)	
Moderate	10 (5.8)	60 (35.3)	
Severe	0 (0.0)	0 (0.0)	

Severe Aortic Stenosis Patients With Small Annuli Among the Bern TAVI Registry



No. at risk:

	0	1	2	3	4	5
— BEV	171	130	78	68	41	26
— SEV	171	136	95	75	41	27

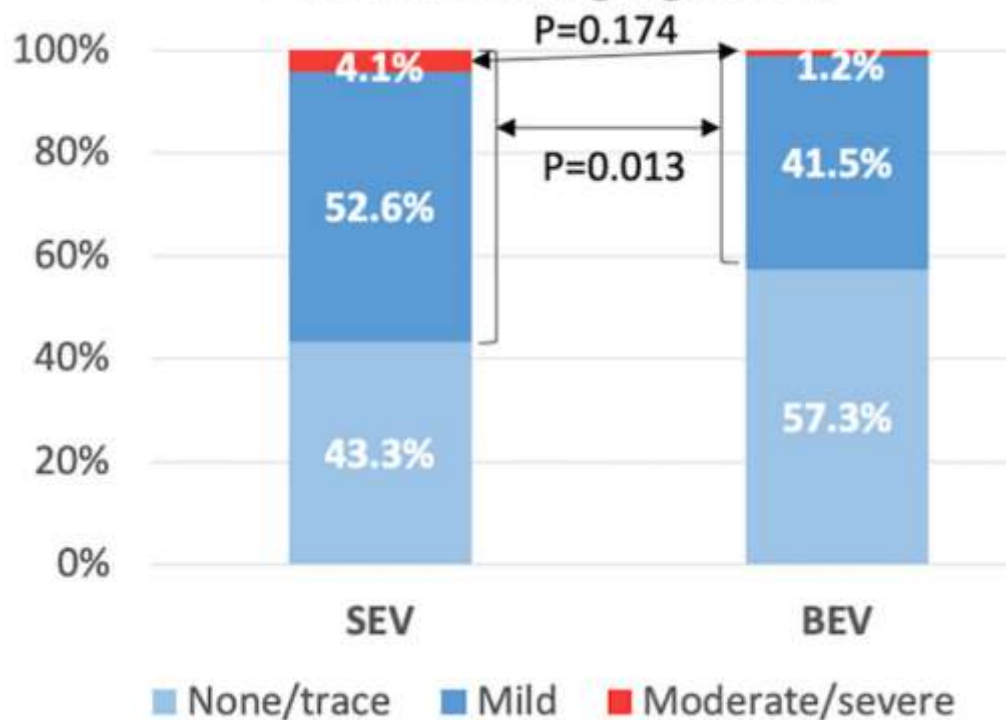


No. at risk:

	0	1	2	3	4	5
— BEV	171	130	78	68	41	26
— SEV	171	129	92	71	38	25

5-Year Outcomes With Self-Expanding vs Balloon-Expandable Transcatheter Aortic Valve Replacement in Patients With Small Annuli

Paravalvular regurgitation



Matched Cohort

	SEV (n = 171)	BEV (n = 171)	P Value
At 5 years			
All-cause mortality	52 (50.4)	38 (39.6)	0.269
Cardiovascular mortality	35 (39.0)	32 (35.0)	0.996
Any stroke (disabling and nondisabling)	18 (12.3)	10 (7.2)	0.114
Disabling stroke	10 (6.6)	1 (0.6)	0.030
Myocardial infarction	1 (0.6)	5 (5.0)	0.143
Life-threatening or major bleeding	33 (22.2)	26 (21.1)	0.336
Structural valve deterioration	2 (1.6)	4 (3.2)	0.367
Repeat aortic valve intervention ^b	3 (2.1)	2 (1.2)	0.689
NYHA functional class III or IV	3/ 27 (11.1)	4/ 34 (11.8)	0.937

Summary

- Previous TAVR studies mainly used “measured” PPM and yielded conflicting results.
- Several methodological pitfalls
 - Obese patients
 - Discordance between echocardiographic and invasive measurement
 - LVOT circular assumption
 - A low-flow state
- Clinically meaningful residual high gradients and PPM might be less frequent even in patients with small annuli treated with an intra-annular THV.
- Awareness and prediction of the risk of severe PPM after TAVR is a key first step.