Prosthesis-Patient Mismatch and TAVR: Rationale for the SMART Trial

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Disclosure Statement of Financial Interest

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

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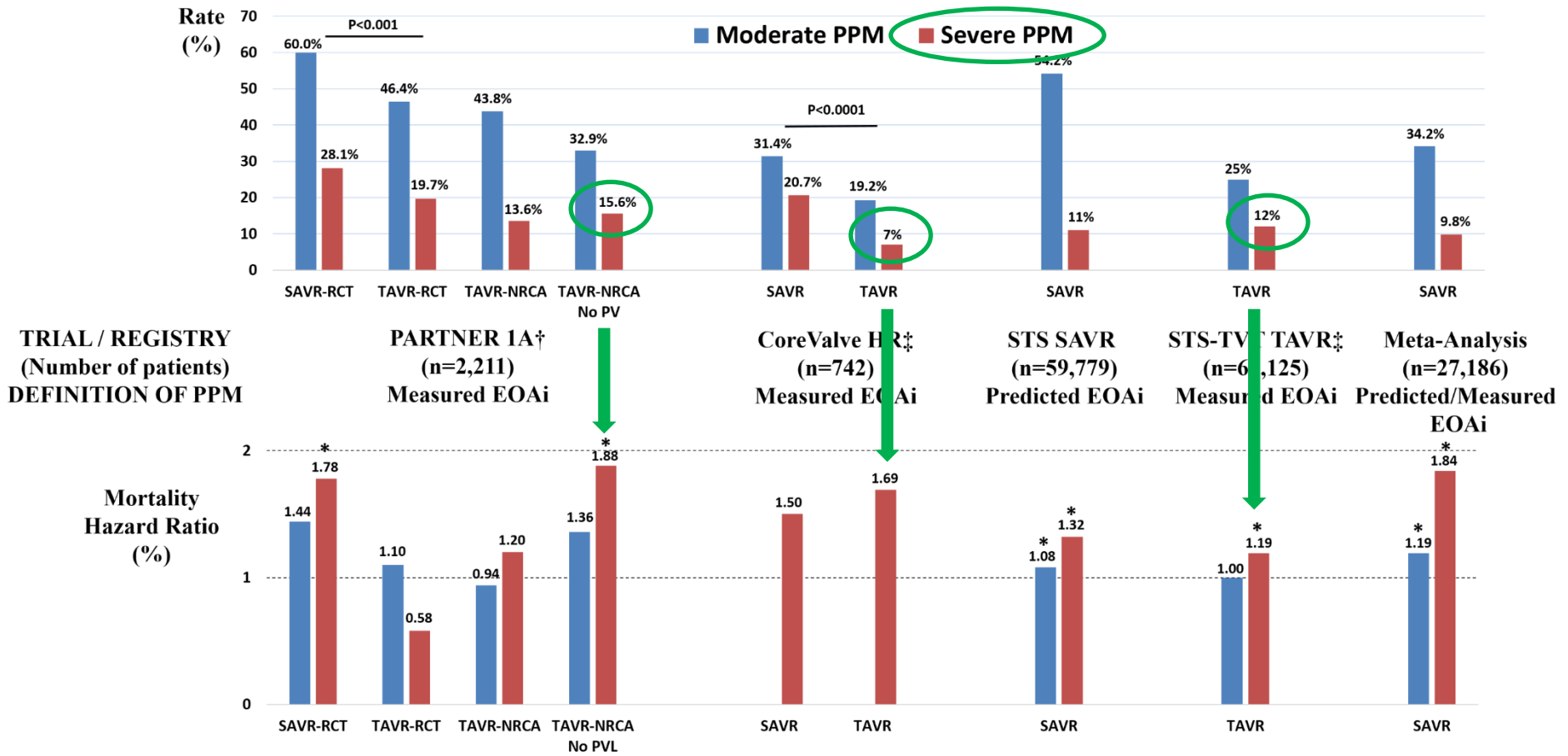
- ***Discussion may include unapproved and off-label devices, procedures, and indications***

Background

- Severe PPM after SAVR is associated with increased all-cause and cardiac mortality, as well as decreased CFR, impaired exercise tolerance, less improvement in QOL, and less LV mass regression
- TAVR valves have larger EOI and a reduced incidence of severe PPM relative to surgery
- Does severe PPM occur after TAVR?
    - If so, how often?
    - Why is there controversy?
    - Does it matter?
    - If so, in whom?

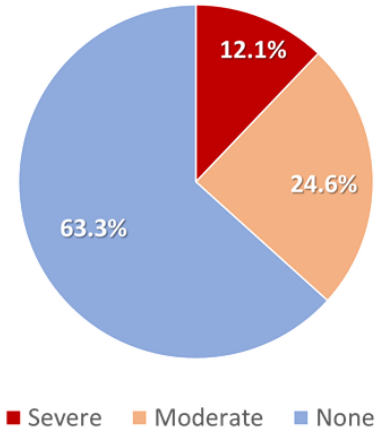
INCIDENCE OF PROSTHESIS-PATIENT MISMATCH



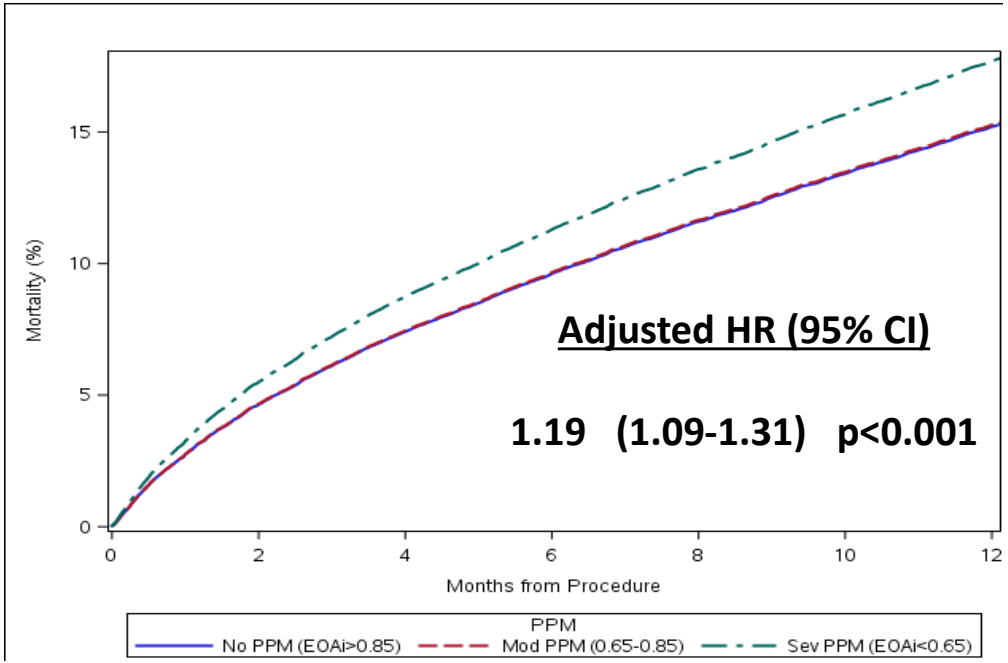
IMPACT OF PROSTHESIS-PATIENT MISMATCH ON MORTALITY

TAVR in STS/ACC TVT Registry™ All TAVR Devices (N=63,393)

TAVRs (2014-2017)



Mortality (%)



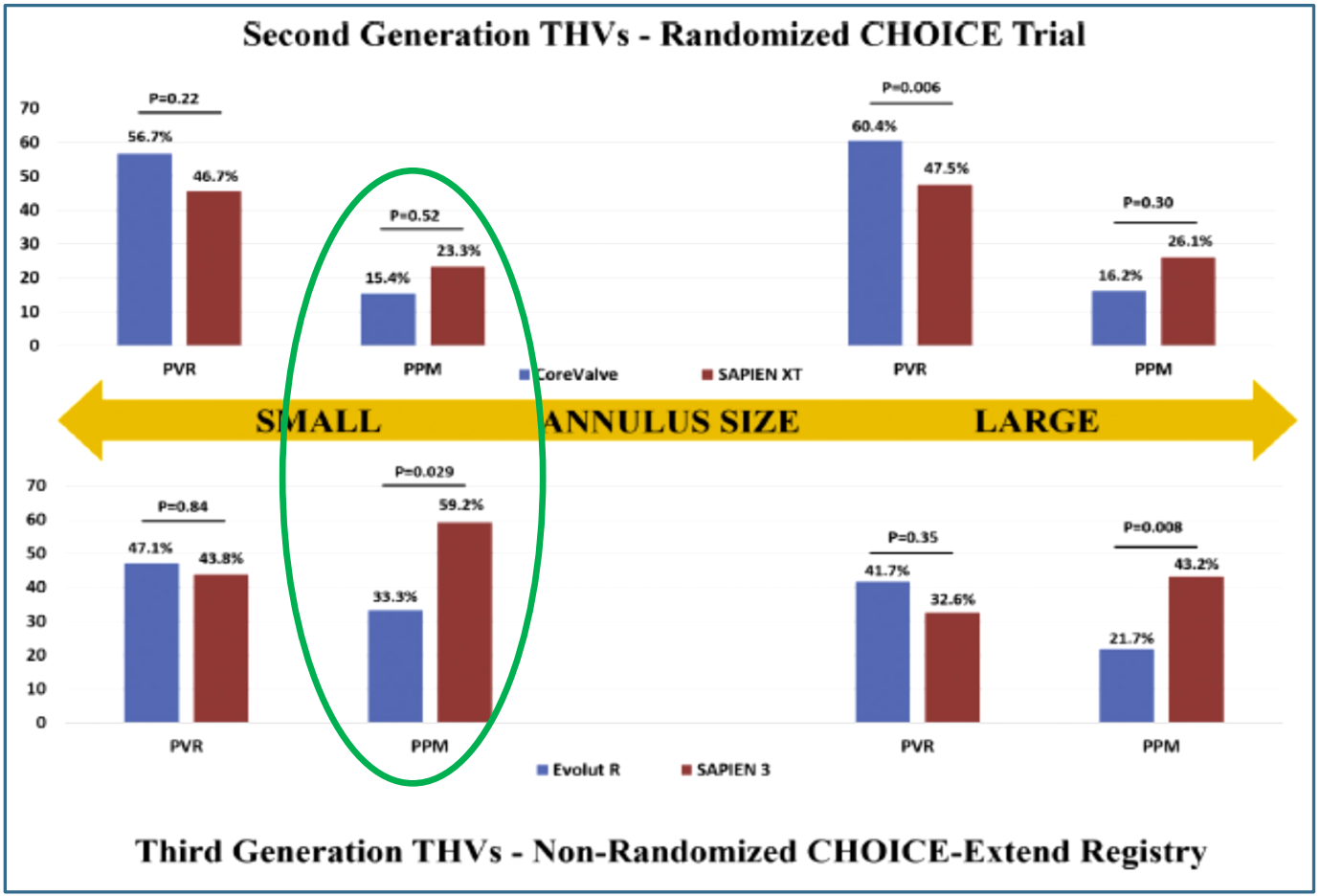
17.2% Severe

15.8% Moderate/None

Number at Risk Adjusting for baseline covariates:

	Day 0	Month 4	Month 8	Month 12
No PPM	23635	21080	16734	13136
Mod PPM	8983	7995	6277	4831
Sev PPM	4152	3626	2976	2130

J Am Coll Cardiol 2018;72:2701–11



Abdelghani M, et al, Insights From the CHOICE Trial, JACC Cardiol Intv 2018

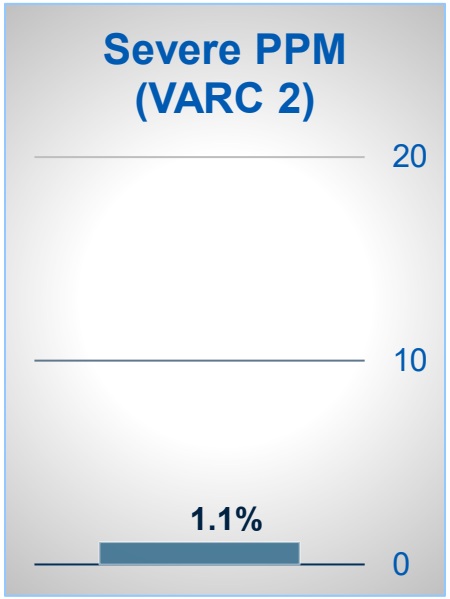
Pibarot P, Editorial, JACC Cardiol Intv 2018

Outcomes of Prosthesis-Patient Mismatch Following Supra-annular TAVR from the STS/ACC TVT Registry

Patients	Severe PPM	mGrad (1 yr)
42,174 native	5.3%	10.2 mmHg
5446 VIV	27.0%	17.1 mmHg

Tang et al, JACC CV Intv 2021;14:964

TAVR with a SE valve in low risk patients

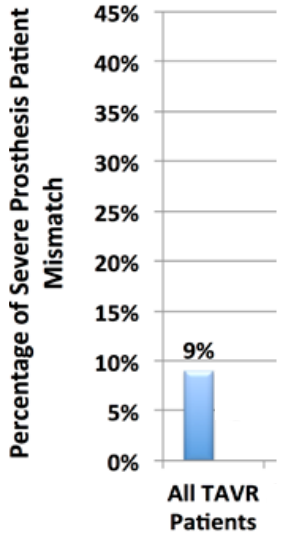


Popma et al, NEJM 2019;380:1706

Impact of Flow on Prosthesis-Patient Mismatch Following Transcatheter and Surgical Aortic Valve Replacement

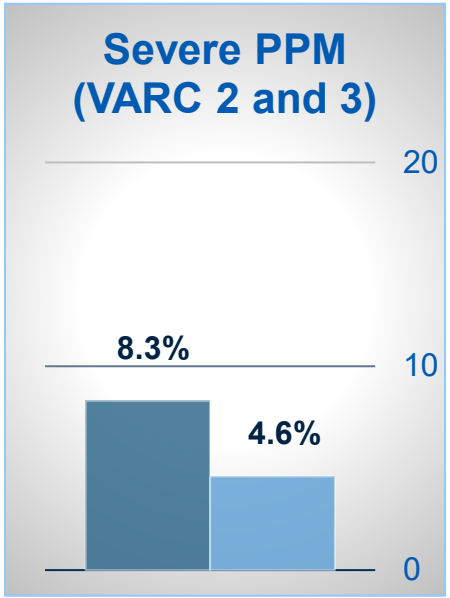
Amr E. Abbas, MD; Julien Ternacle, MD; Philippe Pibarot, PhD, DVM; Ke Xu, PhD; Maria Alu, MS; Erin Rogers, MEng; Rebecca T. Hahn, MD; Martin Leon, MD; Vinod H. Thourani, MD

Circ CV Imaging 2021



954 TAVR patients from Partner 2A and S3i registries

TAVR with a BE valve in low risk patients



Mack et al, NEJM 2019;380:1695

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Definitions for Prosthesis-Patient Mismatch (cm^2/m^2):

		Severe	Moderate
Am Soc Echo/US Guidelines[1]		<0.65	0.65-0.85
VARC-2/European Guidelines[2]		<0.65	0.65-0.85
	BMI ≥30 kg/cm^2	<0.60	0.60-0.90
EACVI (European Assoc CV Imaging)[3]		<0.65	0.65-0.85
VARC 3[4]	BMI ≥30 kg/cm^2	<0.55	0.55-0.70

[1] Zoghbi et al, J AM Soc Echo 2009;22975-1014
[2] Kappetein et al, J Thorac Cardiovasc Surg 2013;145:6-23
[3] Lancellotti et al, Eur Heart J 2012;33:2403-2418
[4] Genereux et al, Eur Heart J 2021;42:1825

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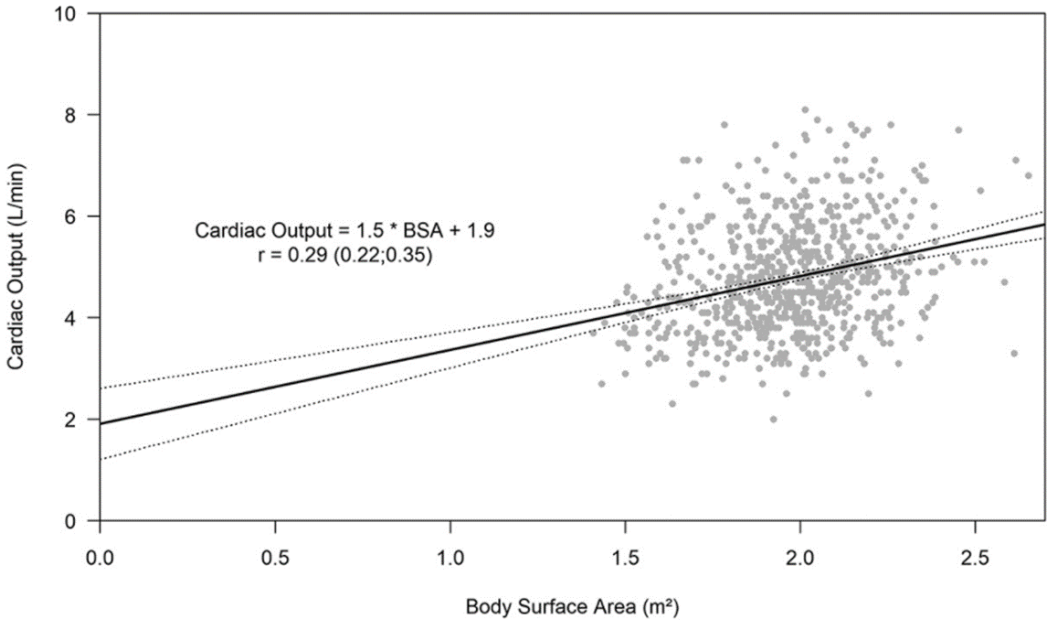
- Why adjust PPM cut-offs for BMI?
  - Rationale: CO requirements may be greater in large patients, though they may exercise less.
  - However, CO requirements do not increase linearly with BMI, and may differ by age and ratio of fat-free muscle mass to fat mass



Vriesendorp et al, Structural Heart 2021
doi.org/10.1080/24748706.2021.1968089

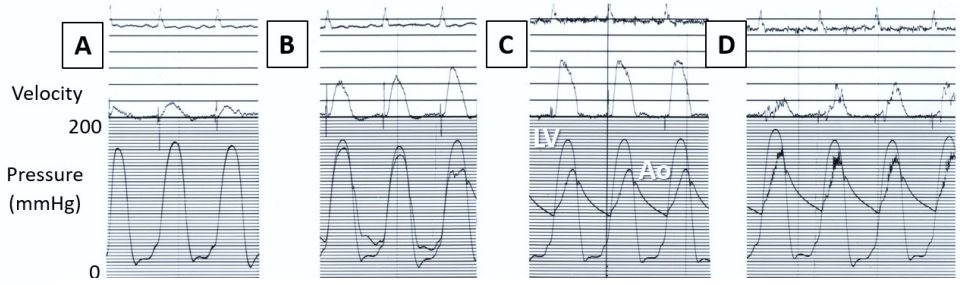
- Why not adjust PPM cut-offs for BMI?
  - Rationale: CO requirements may be greater in large patients, though they may exercise less.
  - However, CO requirements do not increase linearly with BMI, and may differ by age and ratio of fat-free muscle mass to fat mass
  - Surgical studies have differed on effects of severe PPM based on BMI
    - Mohty et al (JACC): increased effect of severe PPM on mortality with *lower* BMI
    - Fallon et al (JTCVS): increased effect of severe PPM on mortality with *higher* BMI
    - Bridges et al (JTCVS): lower operative mort with increasing BSA when EOA constant
  - TVT registry study in TAVR did not find an interaction with BMI:

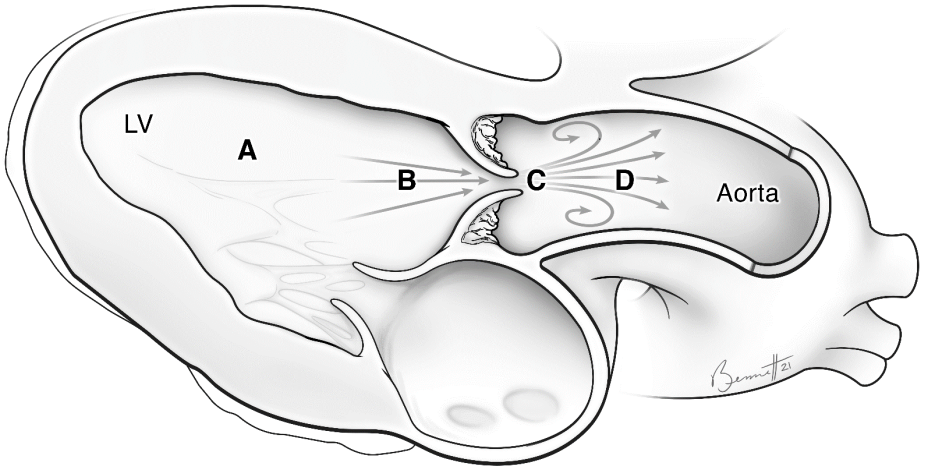
TABLE 3 Subgroup Analyses (Adjusted Models) of Association of Severe PPM and All-Cause Mortality at 1 Year

	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)	

Effect of Pressure Loss Recovery (PLR) on Measured EOAi

- Hydrodynamic phenomenon
- Linear velocity of blood flow increases along a tapering flow field as it approaches the LVOT with a minimum dimension mm beyond the narrowed AV (the vena contracta, VC).
- The increase in velocity is accompanied by a decrease in static pressure, as required by conservation of energy (pressure energy converted to kinetic energy).
- Distal to the VC, velocity is lost, turbulence is apparent, and “recovery” of pressure occurs as kinetic energy is converted back to pressure and disorganized streamlines reattach to the central flow.





Herrmann and Laskey, Cath Cardiovasc Intv 2021: https://doi.org/10.1002/ccd.29729

Factors Affecting Pressure Loss Recovery

The degree of PLR, and overestimation of gradient by echo Doppler, become clinically relevant when:

- Volumetric flow rates are high
- Stenosis/narrowing is at least moderate
- Aorta is small (<3 cm diam)
- Jet is highly eccentric (eg., BAV)

Niederberger J, Schima H, Maurer, et al. Importance of pressure recovery for the assessment of aortic stenosis by Doppler ultrasound. Role of aortic size, aortic valve area, and direction of the stenotic jet in vitro. Circulation 1996;94:1934-40.

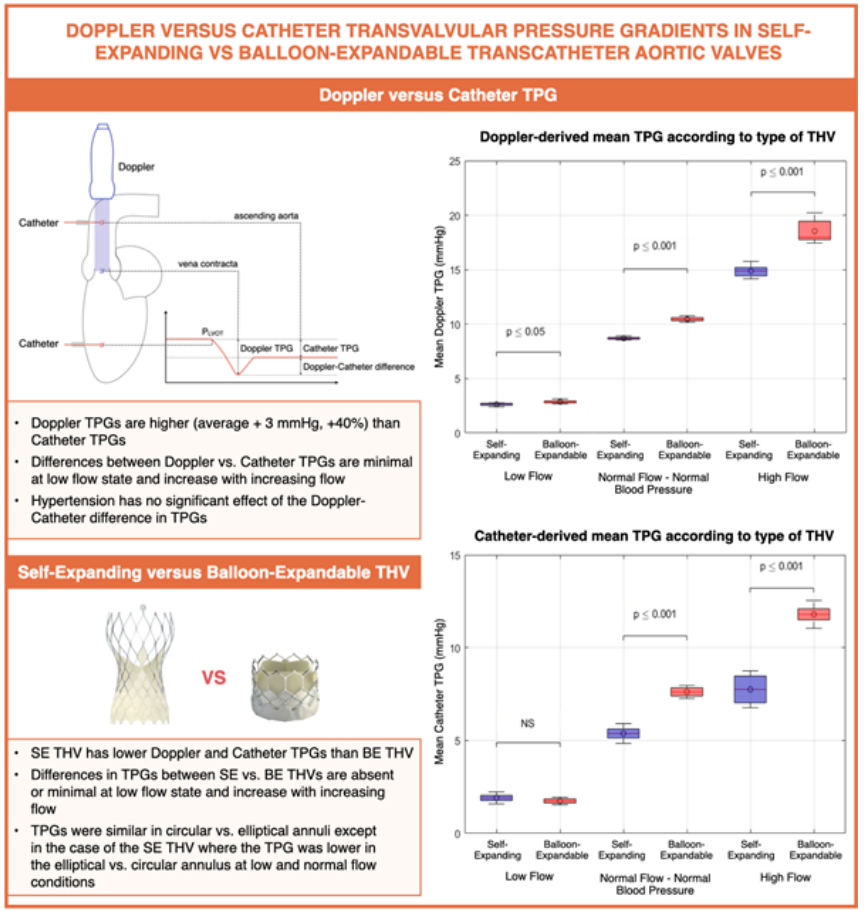
Garcia D, Dumesnil JG, Durand L-G, et al. Discrepancy between catheter and Doppler estimates of valve effective orifice area can be predicted from the pressure recovery phenomenon: practical implications with regards to quantification of aortic stenosis severity. J Am Coll Cardiol 2003;41:435-42.

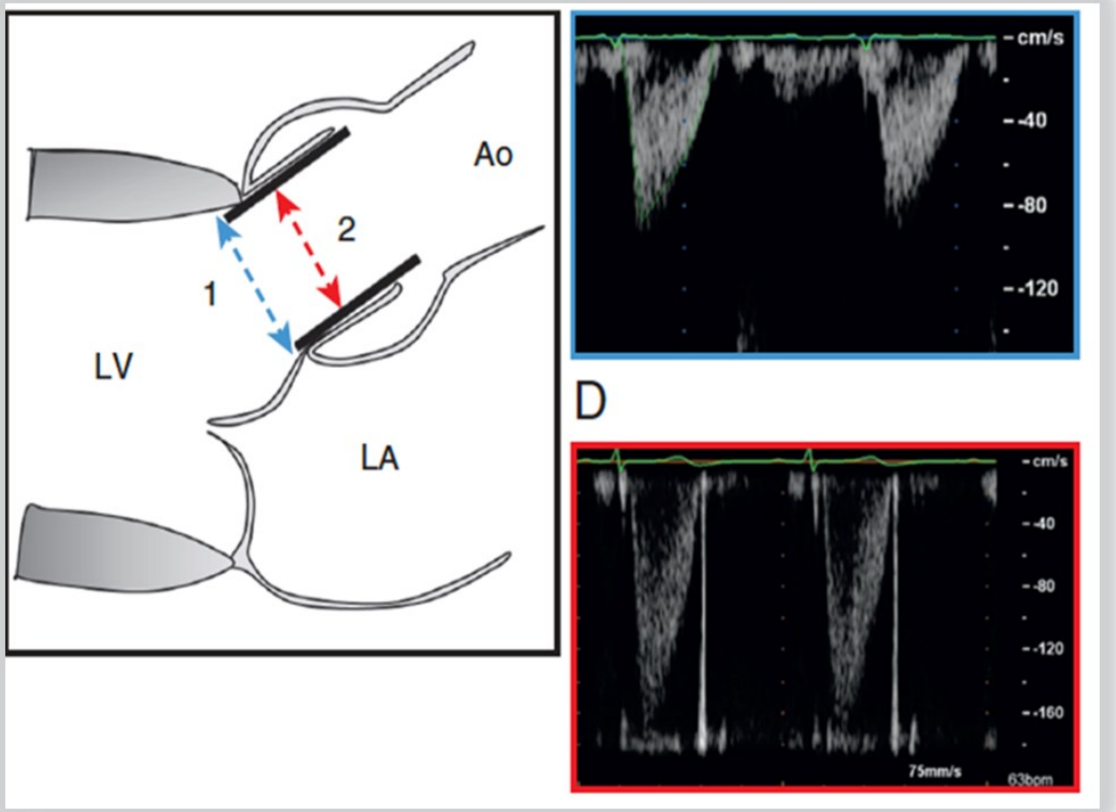
PERFORMANCE OF 26 MM SELF EXPANDING THV V 23 MM BALLOON EXPANDABLE VALVES USING CW DOPPLER AND MICROTIP CATHETER GRADIENTS (IN VITRO)

- Cath gradients lower than Doppler *and* lower in low flow conditions
- Contribution of pressure loss recovery to post TAVR gradient is small (2-4 mmHg)
- Similar contributions of "pressure loss recovery" to S3 and EV

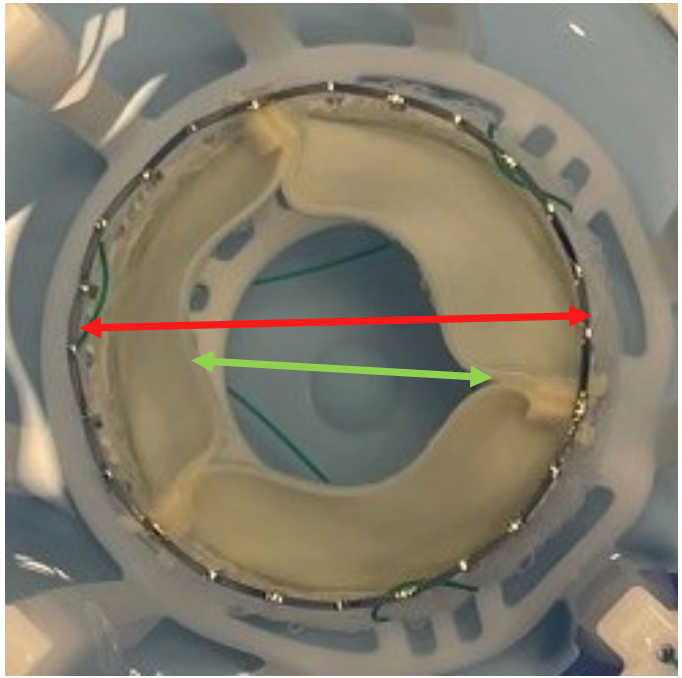
Configurations	CoreValve Evolut PRO		SAPIEN 3	
	Pressure recovery		Pressure recovery	
	(mmHg)	%	(mmHg)	%
Low flow	0.72	31.72	1.13	49.02
Normal conditions	3.32	47.16	2.84	31.42
High flow	7.12	62.95	6.95	45.53
Mean ± SD	3.7±1.9	47±9	3.6±1.7	42±5

Stanova V et al, Cath Cardiovasc Intv 2021 (in press)





$$\text{EOA} = \text{LVOT area} * \frac{\text{LV VTI}}{\text{Ao VTI}}$$



Hahn et al, JACC CV Imaging 2019;12:25

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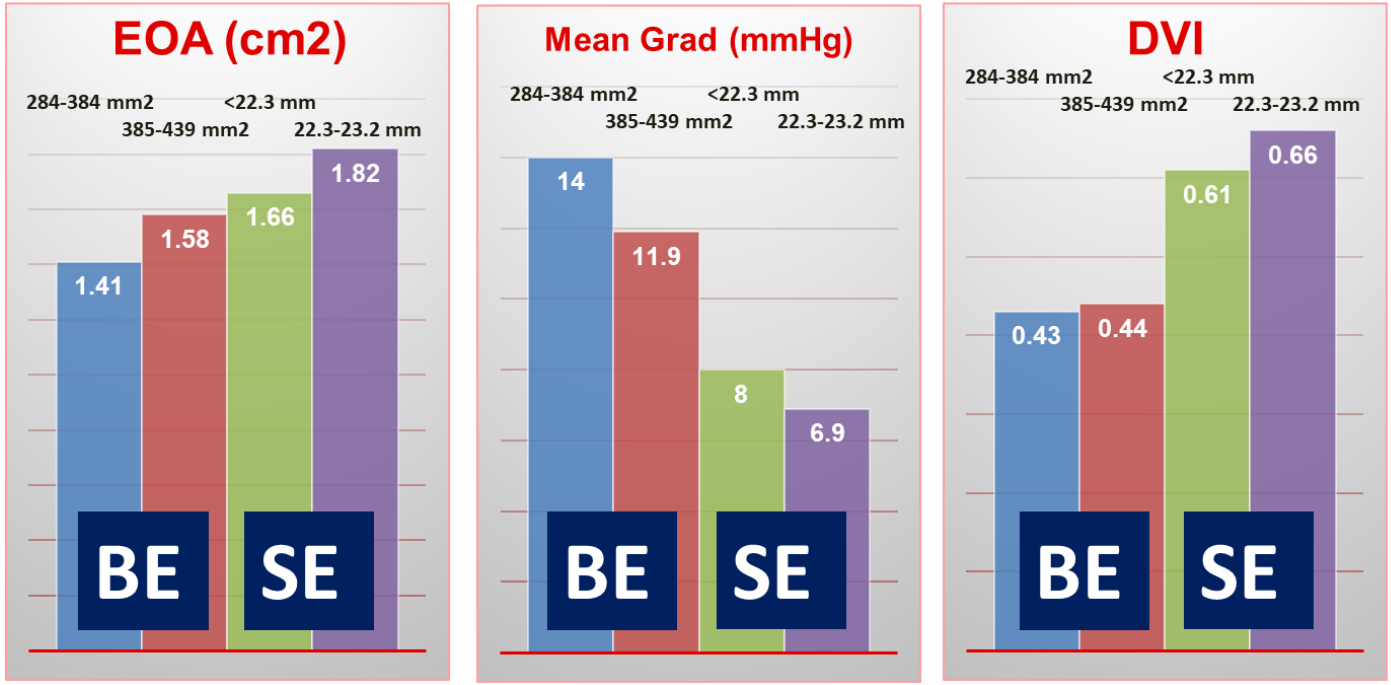
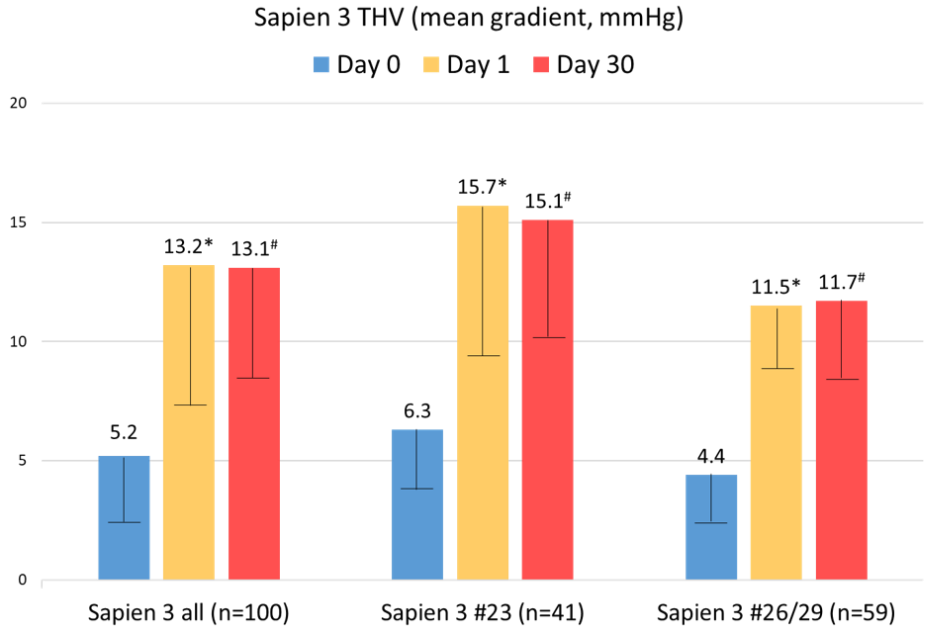
Echo core lab (n=3) analysis at 30 days

Small Annulus (lowest 2 quintiles)

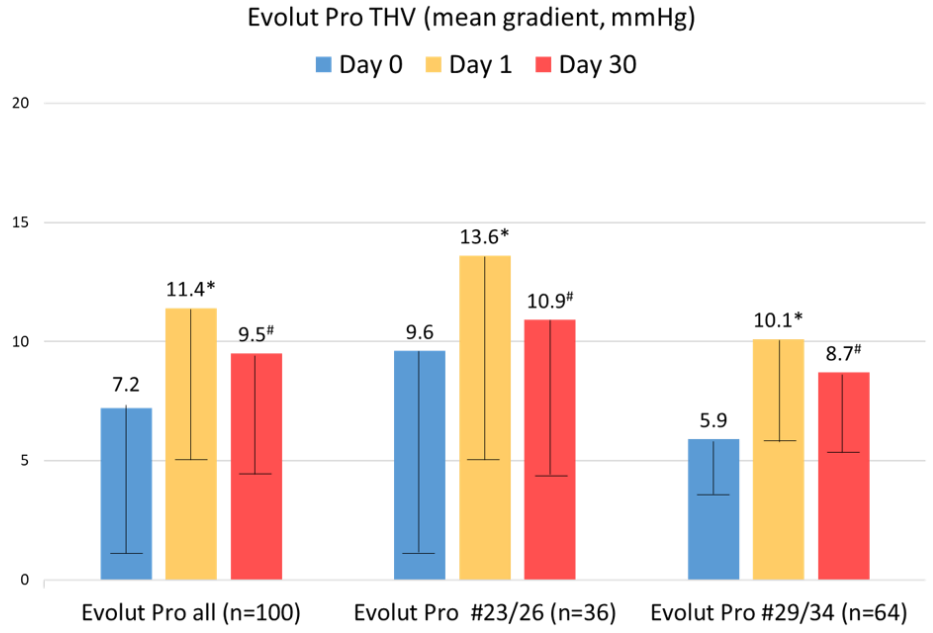


Hahn et al, JACC CV Imaging 2019;12:25

Impact of time of measurement on gradient determination



	LV VTI	Ao VTI	DVI
Day 0	20.8	33.5	0.62
Day 1	22.8*	45.6*	0.50*



	LV VTI	Ao VTI	DVI
Day 0	25.3	37.8	0.67
Day 1	27.4*	44.2*	0.62*

Naidu and Herrmann, JACC CV Intv 2021 (in press)

Reasons why the reported incidence of PPM varies after TAVR:

- Method of gradient determination (echo vs cath)
- Method of EOA calculation (measured vs predicted)
- Timing of measurement (immediate vs later)
- Correction or not for obesity

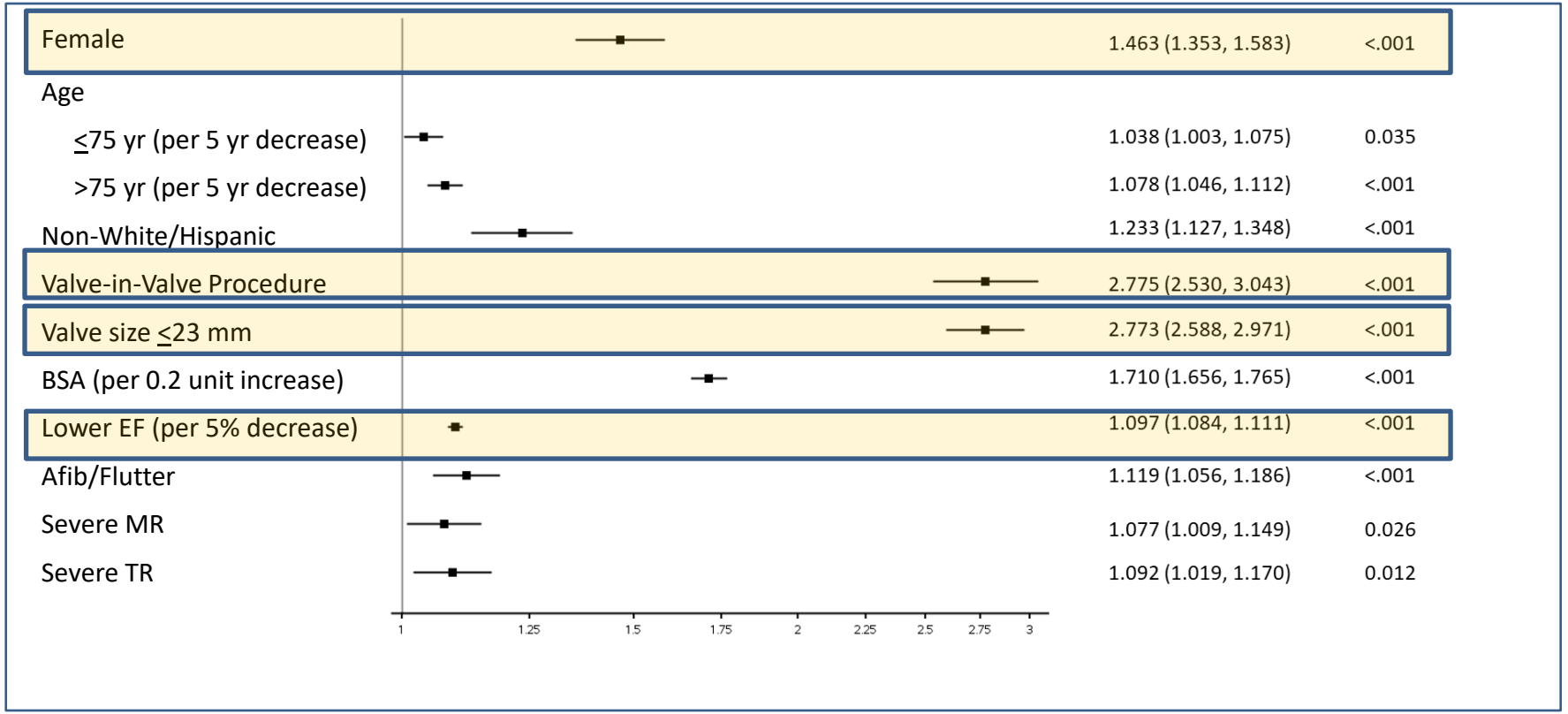
Reasons why the effects of severe PPM on outcomes are conflicting:

- Measurements and calculations differ as above
- Incomplete correction for confounding variables (eg., PVL)
- Under-powered analyses
  - <12% of patients have severe PPM
  - Limited follow-up (1 year may not be sufficient)

Where does it matter the most?

- Small annulus (women, VIV)
- Young, active (exercise)
- Low flow and low EF

Odds Ratios (95% CI) for Multivariate Model Predictors of Severe PPM



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Using data to drive quality

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NATIONAL CARDIOVASCULAR DATA REGISTRY

J Am Coll Cardiol 2018;72:2701–11

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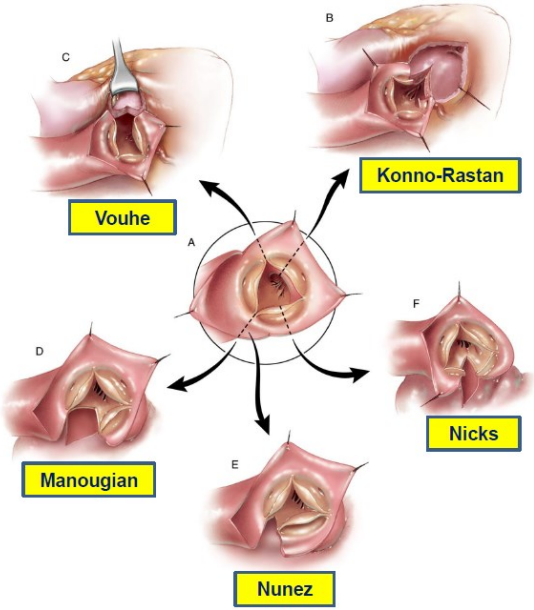
- *Small Annuli Are Common:*

  SAVR prostheses ≤ 21 mm [1] = **22-44%**

- *Use of small TAVR prostheses:*

	Area ≤ 430 mm2 (IFU 20/23 mm BE)
Intermediate Risk Trials [2,3]	**36%**
Low Risk Trials [4,5]	**31%**

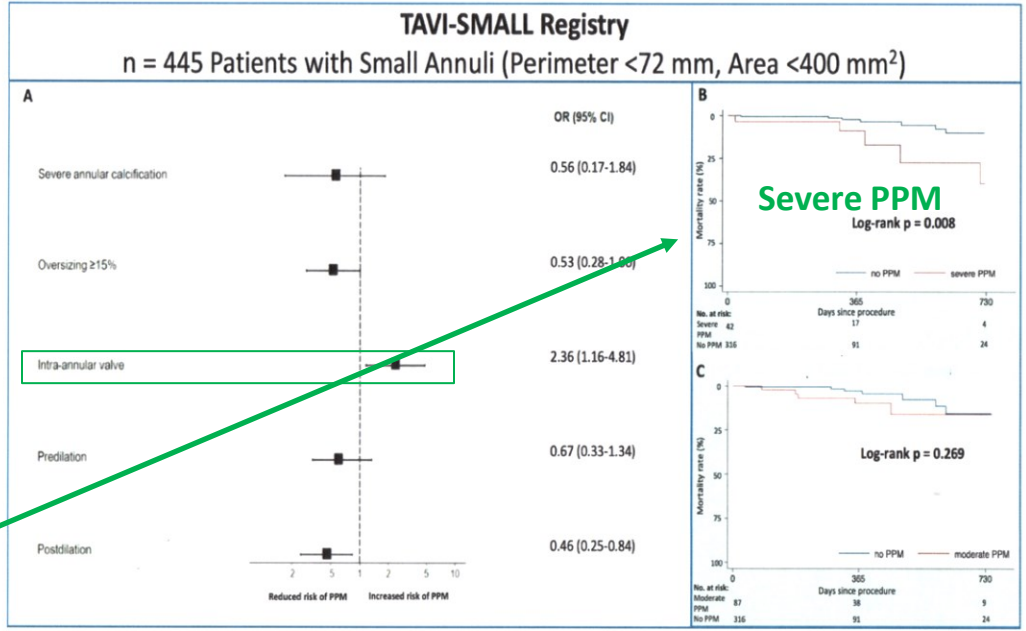


- *Higher in Southern Europe and Asia* [1]
- *TAV in SAV = **70-80%*** [6,7]
- *Several fold higher in women who make up ~**90%*** of small annulus population [1]

1 Freitas-Ferraz et al, Circ 2017;139:2685
2 Reardon et al, NEJM 2017;376:1321
3 Kodali et al, European Heart J 2016;37:2252
4 Popma et al, NEJM 2019;380:1706
5 Mack et al, NEJM 2019;380:1695
6 Dvir et al, JAMA 2014;312:162
7 Webb et al, JACC 2017;69:2253

Predictors and clinical impact of prosthesis-patient mismatch after self-expandable TAVI in small annuli

- International multi-center registry of 445 patients with small annulus (area <400 mm2 or perimeter <72 mm); *90% women*
- Supra-annular (80% Evolut, 20% Accurate Neo) compared to Intra-annular (70% Portico, 30% Accurate TA)
- Severe PPM in 9%
  - IA prosthesis predictor of severe PPM (adjusted OR 2.36)
  - Higher adjusted all-cause 1-year mortality (adjusted HR 4.27)



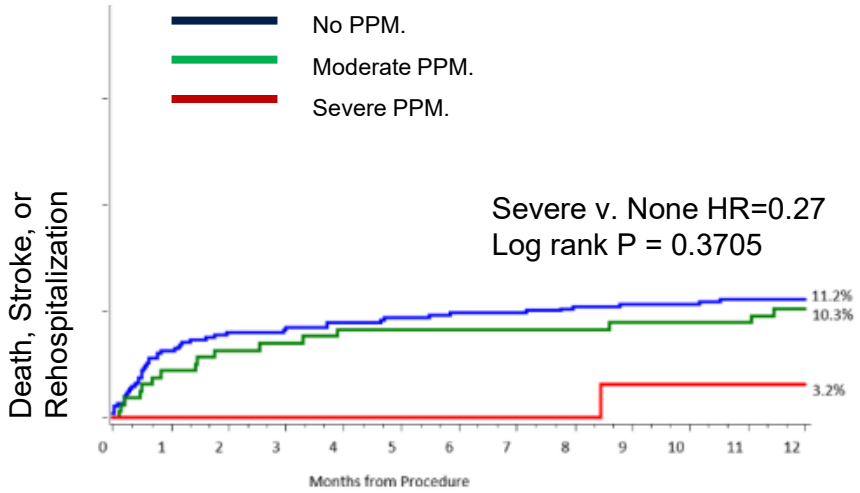
Central illustration.

Chiarito M, ESC presentation 2020
Leone, Regazzoili, et al,, JACC CV Intv 2021 (in press)

PROSTHESIS PATIENT MISMATCH IN PARTNER III LOW RISK PARTNER

CLINICAL OUTCOME IN WOMEN WITH SEVERE PPM AFTER SAPIEN 3 TAVR

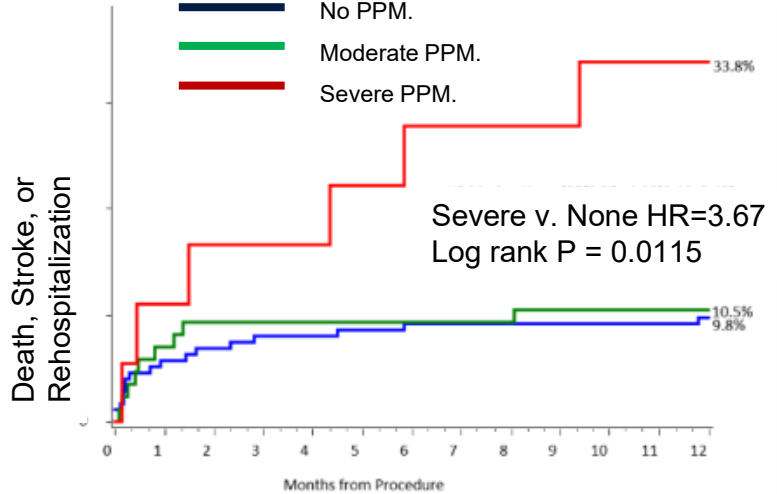
Outcomes with Severe PPM in Men



Number at risk:

None	446	418			393
Moderate	157	149			136
Severe	31	31			30

Outcomes with Severe PPM in Women



Number at risk:

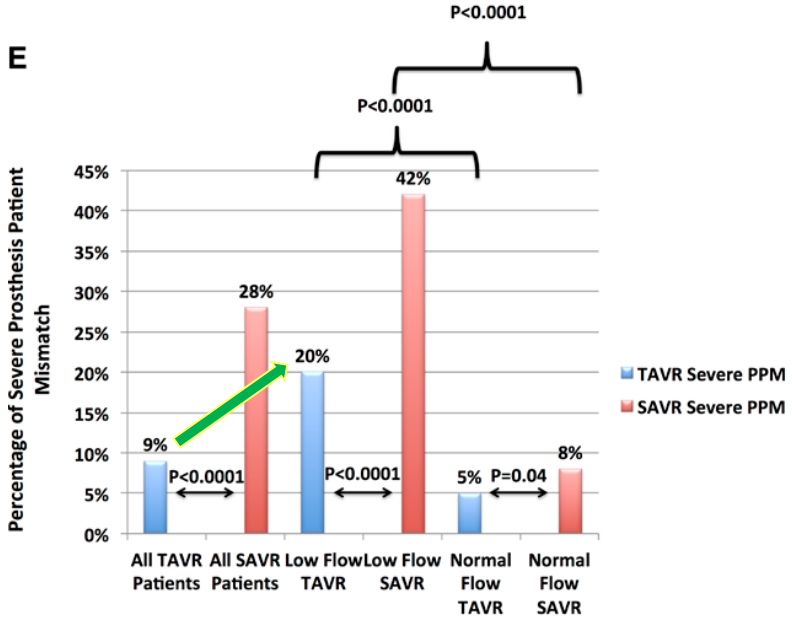
None	174	163			155
Moderate	86	79			76
Severe	18	16			11

Source: Pibarot P, et al. *Circulation*. 2020;141:1527-1537.

Impact of Flow on Prosthesis-Patient Mismatch Following Transcatheter and Surgical Aortic Valve Replacement

Amr E. Abbas, MD; Julien Ternacle, MD; Philippe Pibarot, PhD, DVM; Ke Xu, PhD; Maria Alu, MS; Erin Rogers, MEng; Rebecca T. Hahn, MD; Martin Leon, MD; Vinod H. Thourani, MD

Circ CV Imaging 2021



- **Compared 954 TAVR and 726 SAVR patients from the Partner 2A and S3i registries**
- **Severe PPM in 9% of TAVR pts (n=89) and 20% if low flow (n=49)**
  - **Predicted by SVI and small valve size**
  - **Assoc with rehospitalization in all**
  - **Assoc with cardiac death in LF**

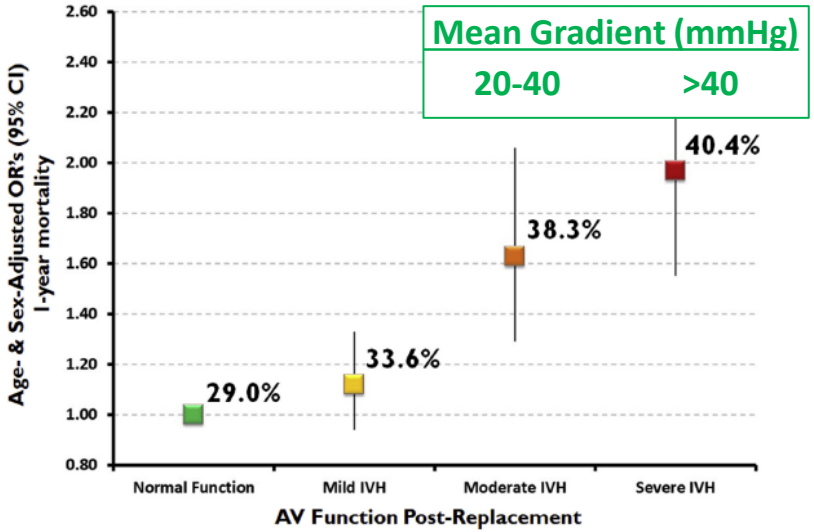
HEMODYNAMIC STRUCTURAL VALVE DYSFUNCTION: RESIDUAL GRADIENTS AFFECT LATE MORTALITY

AUSTRALIAN NATIONAL ECHO REGISTRY

6,050 individuals aged ≥18 years with prior Aortic Valve Replacement
3,943 males (aged 69.3 ± 15.6 years) & 2,107 females (aged 70.9 ± 16.2 years)
Median 770 (IQR 381 – 1,584) days of follow up

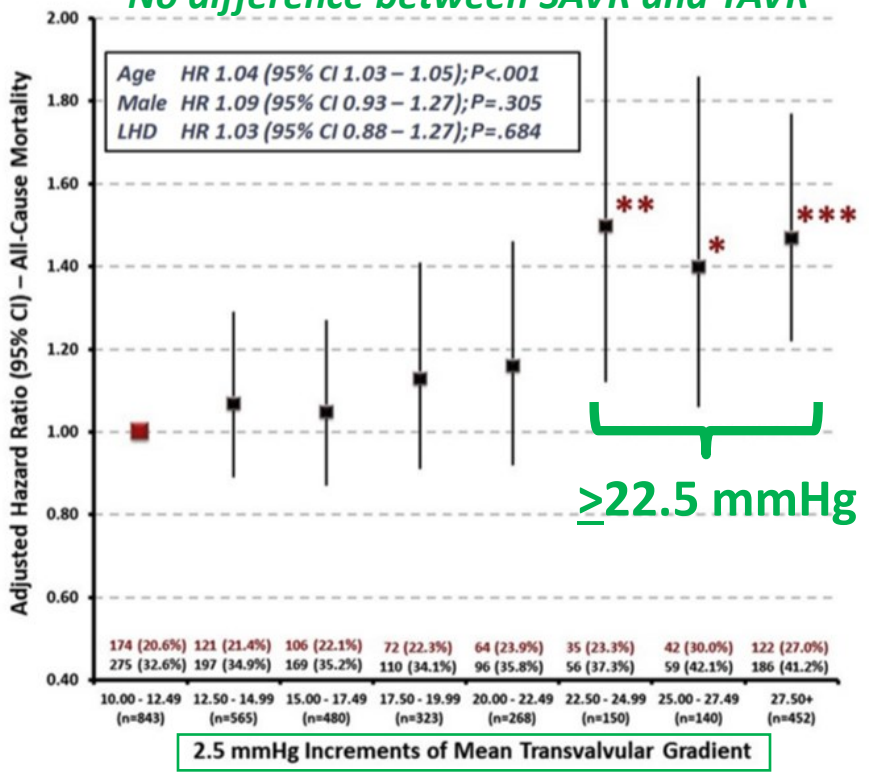
SAVR, 81% TAVR, 19%

Age/Sex Adjusted 1-Year Mortality



All-Cause Mortality at 5 years (Adjusted HR)

No difference between SAVR and TAVR



Playford D et al JASE 2020:33:1077-86

HEMODYNAMIC VALVE DETERIORATION (HVD)

POOLED ANALYSIS OF 4604 SE PATIENTS IN SURTAVI, HIGH RISK RCT, COREVALVE CAS AND EXPANDED USE REGISTRIES
(>10 mmHg from 30 days to last FU - or reintervention)

MULTIVARIABLE PREDICTORS OF HVD - 5 YEARS (TAVR ONLY)

All TAVR	HR (95% CI)	P value
MODEL 1		
Age, years	0.951 (0.921, 0.982)	0.002
Mean Gradient *	**1.107 (1.072, 1.144)**	**<0.001**
MODEL 2		
Age, years	0.941 (0.915, 0.968)	<0.001
History of Hypertension	0.452 (0.199, 1.023)	0.057
DVI *	0.272 (0.018, 4.107)	0.347
MODEL 3		
Age, years	0.945 (0.917, 0.974)	<0.001
Severe PPM (vs not severe) *	**2.873 (1.296, 6.371)**	**0.009**
MODEL 4		
Age, years	0.945 (0.917, 0.972)	<0.001
NYHA class III/IV (Yes vs No)	0.554 (0.285, 1.076)	0.081
EOA *	0.689 (0.349, 1.362)	0.284

CORRELATION WITH HVD AND 5 YEAR MORTALITY

Time-dependent covariate: HVD	HR (95% CI)	P value
All TAVR		
All-cause mortality	3.224 (2.188, 4.751)	<0.001
Cardiovascular mortality	3.182 (1.941, 5.216)	<0.001
AV-related hospitalization	3.834 (2.112, 6.960)	<0.001
Composite	3.227 (2.190, 4.755)	<0.001

O'Hair D, et al. Presented at ACC 2021

SMART TRIAL DESIGN (SMall Annuli Randomized To evolut or sapien)

ClinicalTrials.gov Identifier: NCT04722250
AHJ 2022;243:92-102

Severe native aortic valve stenosis with a small annulus
(≤ 430 mm^2 by MDCT)

Randomization
1:1 Stratified by Sex
(~700 patients)

Prospective, multi-center, international, randomized controlled, post-market study at 90 sites in Canada, EMEA and the United States

Medtronic Evolut PRO/PRO+

Edwards SAPIEN 3/ SAPIEN 3 Ultra

Co-primary endpoints at 12 mos:

1. **Death, disabling stroke, re-hosp HF**
2. **Bioprosthetic valve dysfunction**

30-Day and annual 5-Year follow-ups for all patients

Study Organization	Chair/PI: Howard C. Herrmann, MD Co-PIs: Roxana Mehran, MD and Didier Tchetche MD
Major inclusion/exclusion criteria	• 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)