Penn Medicine

The SMART Trial

(SMall Annuli Randomized To evolut or sapien)

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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:

Institutional Grant/Research Support

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Cardiovasc Res Found
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Medtronic
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Univ. Laval
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Stock Shareholder/Equity

Microinterventional Devices
Holistick Medical

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

OUTLINE

- Adverse effects of TAVR with suboptimal hemodynamics
  - Lessons from surgery
  - Lessons from TAVR
- Incidence of small annuli in patients undergoing TAVR
- Comparative hemodynamics of TAVR prostheses
- Rationale and design of the SMART trial

Lessons from surgery

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

ibarot[3],

Severe PPM associated with almost 2-fold increase in all-cause mortality and >6-fold increase in cardiac mortality

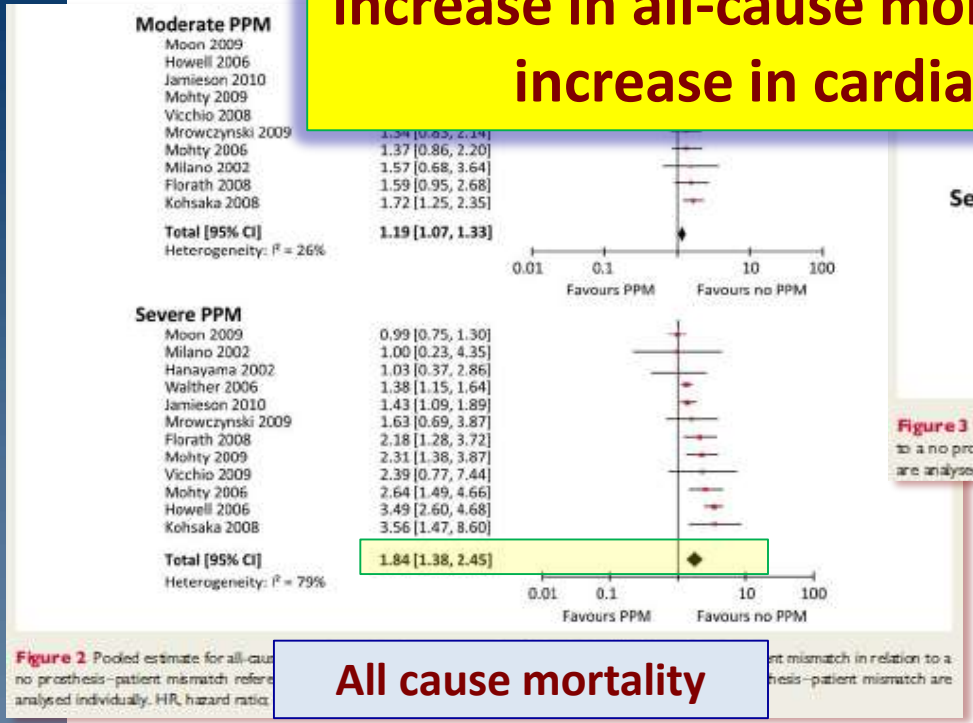


Figure 2 Pooled estimate for all-cau… …nt mismatch in relation to a no prosthesis–patient mismatch refere… …hesis–patient mismatch are analysed individually. HR, hazard ratio

All cause mortality

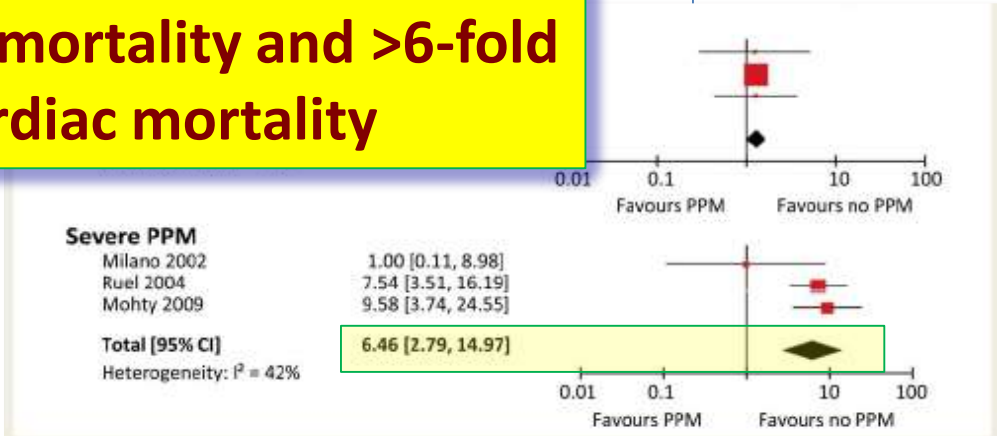


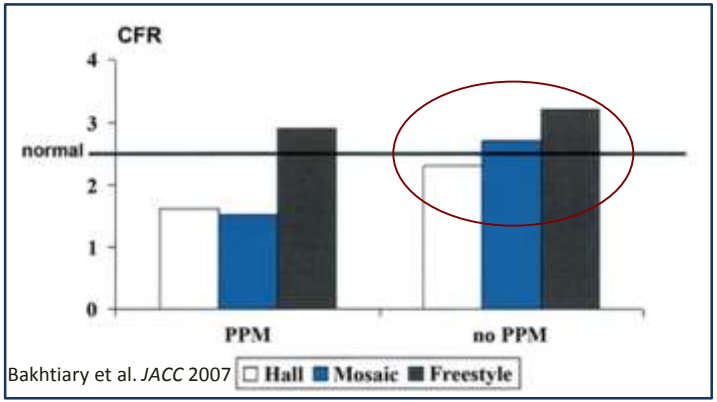
Figure 3 Pooled estimate for cardiac-related mortality ratios demonstrate the additional hazard with prosthesis–patient mismatch in relation to a no prosthesis–patient mismatch reference group. Studies that stratified results according to the severity of prosthesis–patient mismatch are analysed individually. HR, hazar…

Cardiac mortality

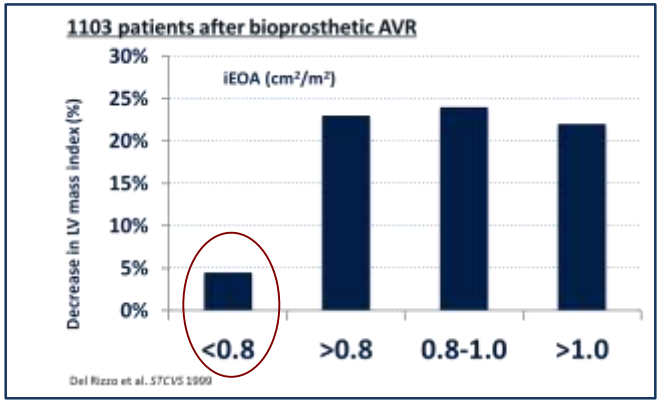
Additional Lessons from Surgery

Less PPM is associated with:

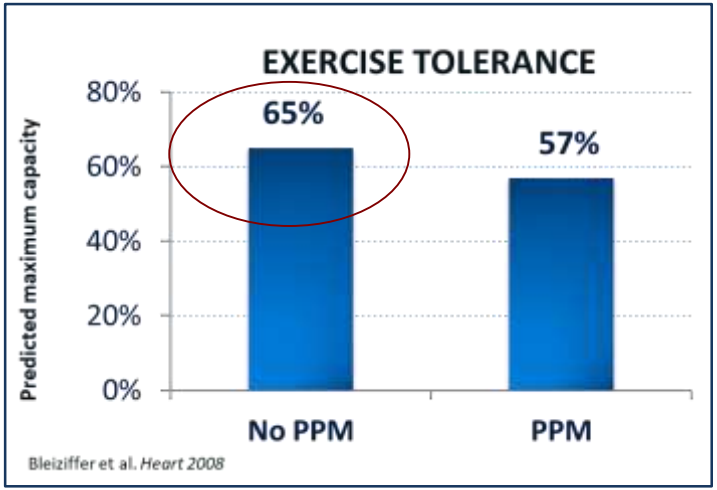
- **Better coronary flow reserve**
- **More LV mass regression**
- **Better exercise tolerance**
- **Improved QOL**



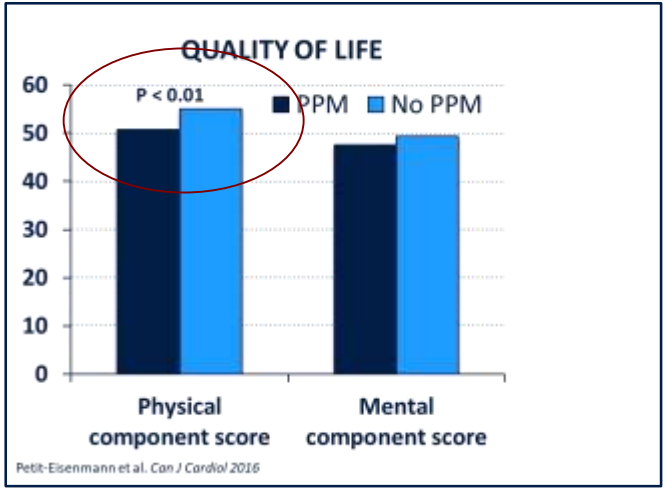
Bakhtiary et al. *JACC* 2007



Del Rizzo et al. *STCVS* 1999



Bleiziffer et al. *Heart 2008*



Petit-Eisenmann et al. *Can J Cardiol 2016*

Prosthesis-Patient Mismatch Predicts Structural Valve Degeneration in Bioprosthetic Heart Valves

Willem Flameng, MD, PhD; Marie-Christine Herregods, MD, PhD; Monique Vercalsteren; Paul Herijgers, MD, PhD; Kris Bogaerts, PhD; Bart Meuris, MD, PhD

Circulation 2010;121:2123-29

- 564 SAVR followed >6 yrs
- Structural valve deterioration (SVD) occurred in 7%
- **PPM independent predictor (HR 2.29) of structural valve degeneration**

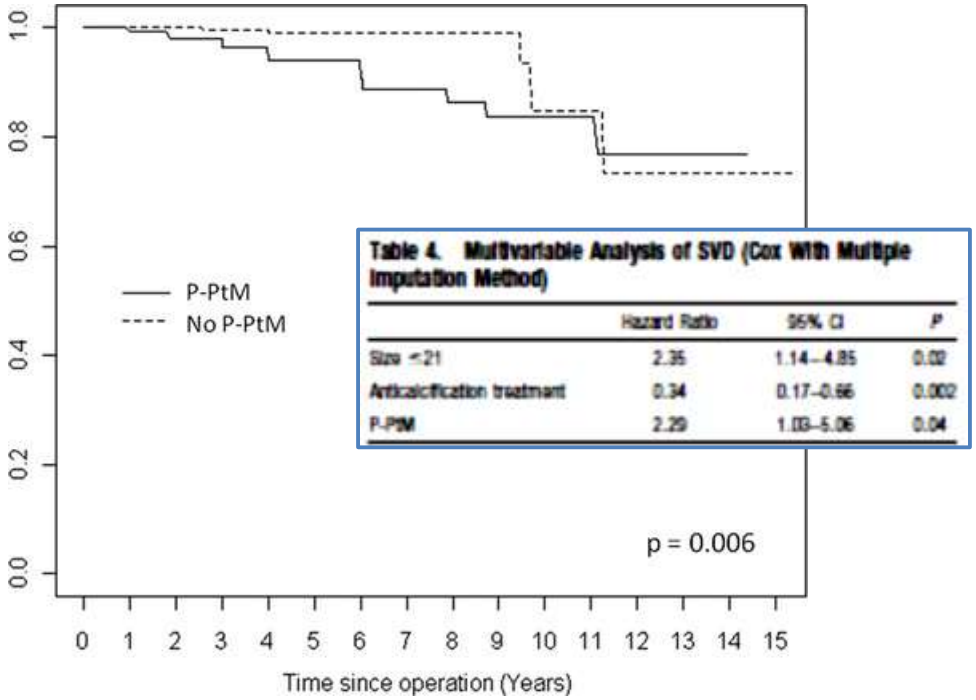


Table 4. Multivariable Analysis of SVD (Cox With Multiple Imputation Method)

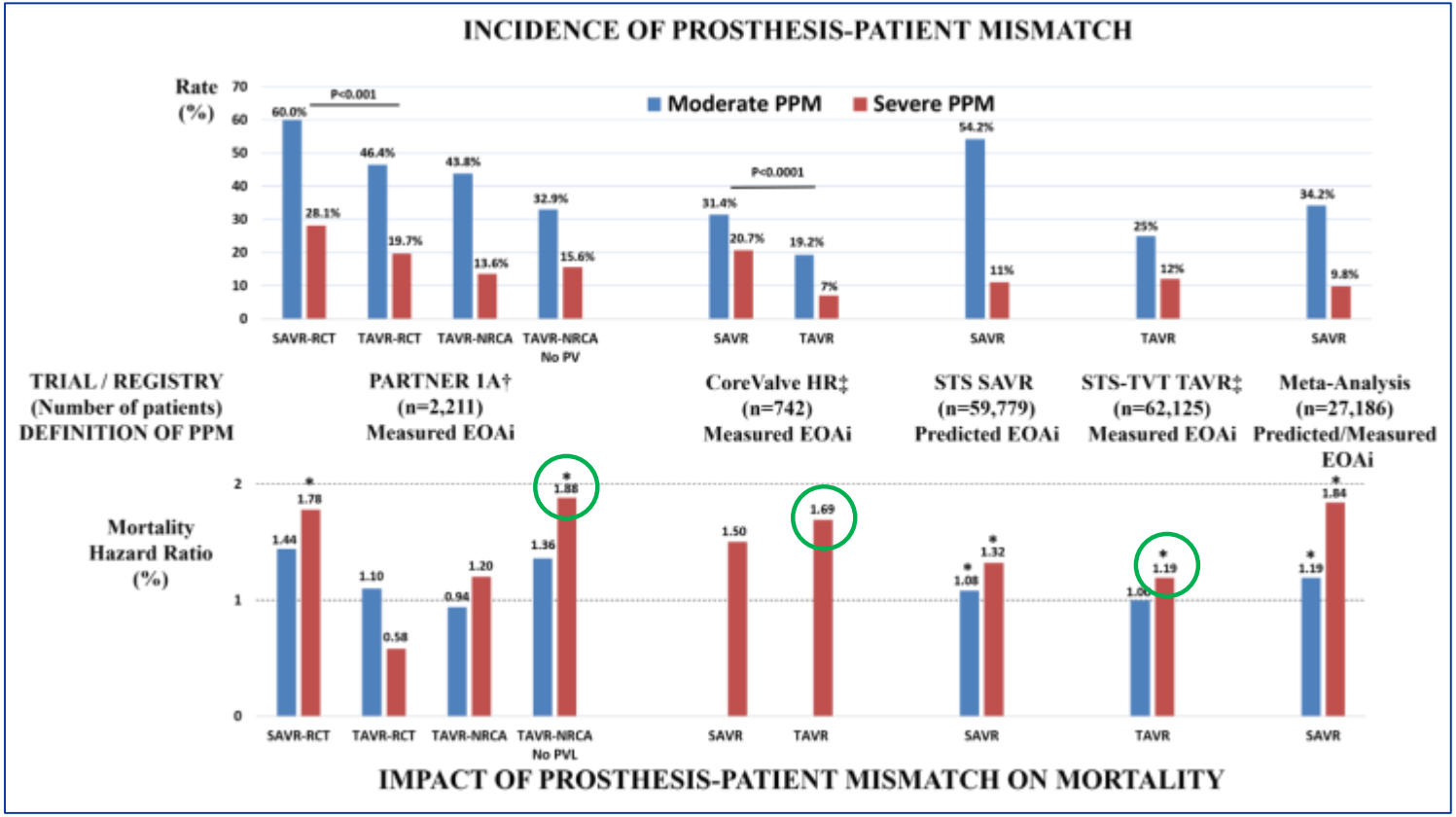
	Hazard Ratio	95% CI	P
Size <21	2.35	1.14–4.85	0.02
Anticalcification treatment	0.34	0.17–0.66	0.002
P-PtM	2.29	1.03–5.06	0.04

Prosthesis-Patient Mismatch After Transcatheter Aortic Valve Replacement

It Is Neither Rare Nor Benign*

Philippe Pibarot, DVM, PhD, Marie-Annick Clavel, DVM, PhD

JACC 2018;72:2712



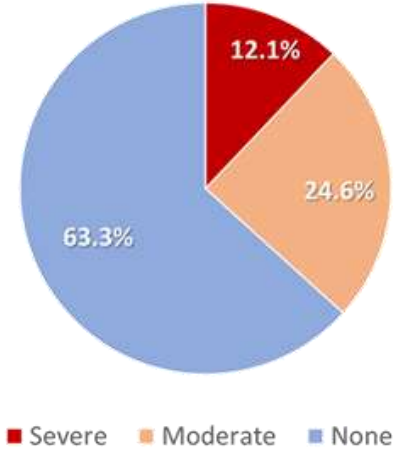
Prosthesis-Patient Mismatch in Patients Undergoing Transcatheter Aortic Valve Replacement

From the STS/ACC TVT Registry

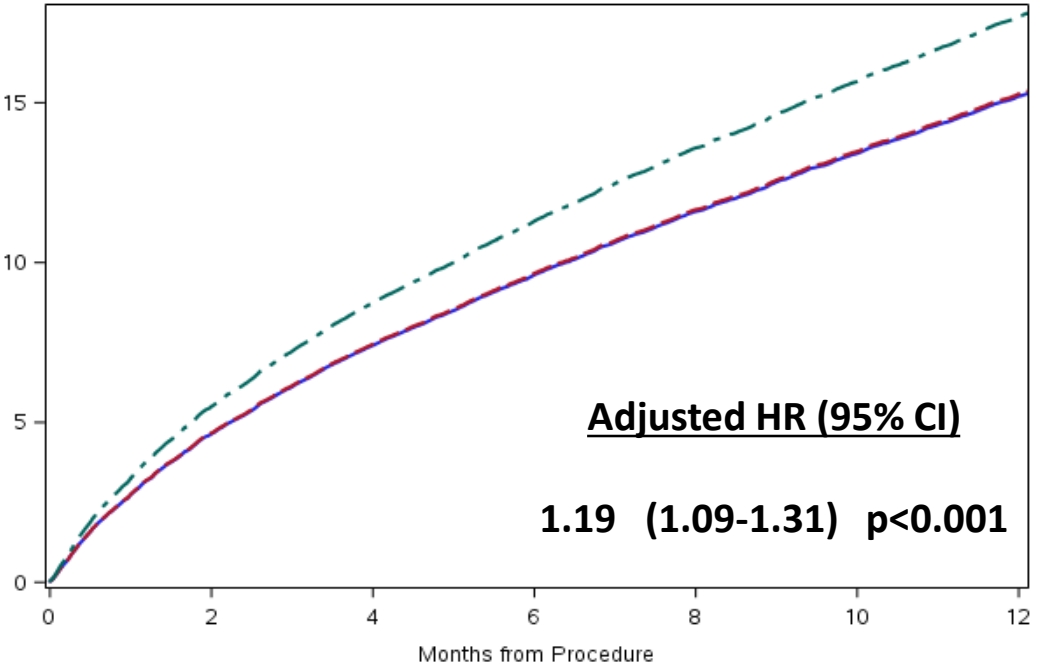
Howard C. Herrmann, MD,[1] Samuel A. Dawdowar, MD,[1] Gregg C. Fonarow, MD,[2] Amanda Shel
Seshadri Vemulapalli, MD,[1] Nimesh D. Desai, MD,[3] David J. Malenka, MD,[4] Vinod H. Thouran
Jennifer Rymer, MD,[1] Andrzej S. Kosinski, PhD[1]

J Am Coll Cardiol 2018;72:2701–11

62,125 commercial TAVR
2014-2017



Mortality (%)



17.2% Severe

15.8% Moderate/None

Adjusted HR (95% CI)

1.19 (1.09-1.31) p<0.001

PPM
No PPM (EOAi>0.85) — Mod PPM (0.65-0.85) — Sev PPM (EOAi<0.65)

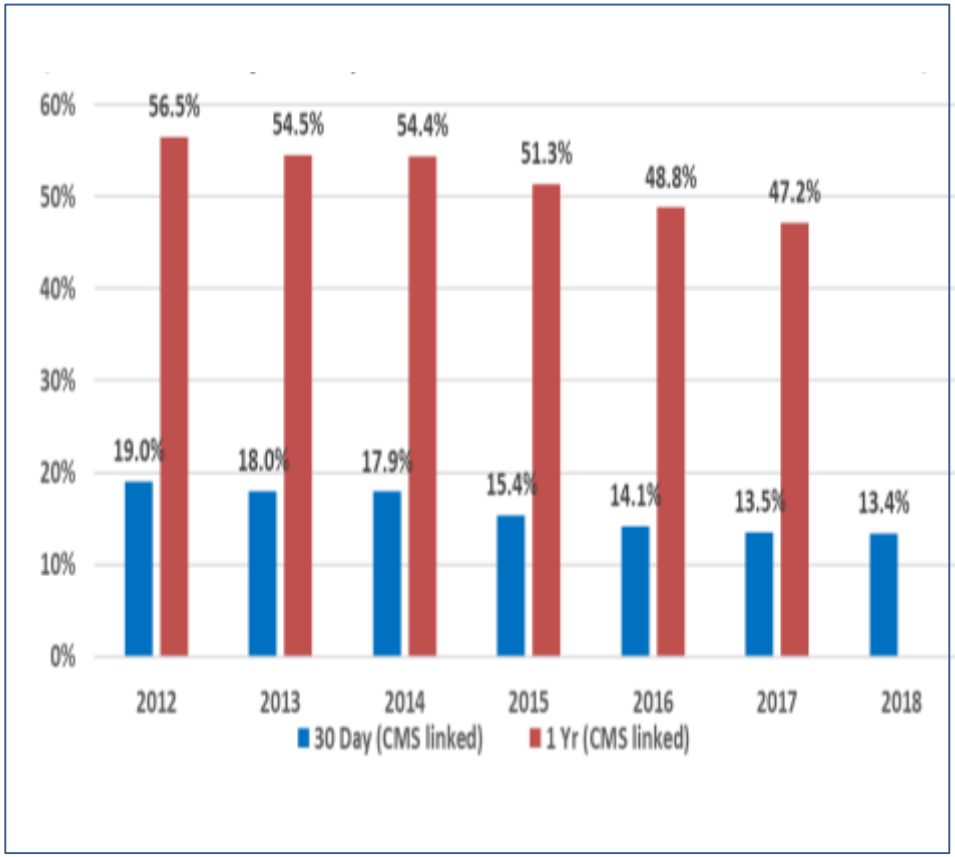
Number at Risk Adjusting for baseline covariates:

	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

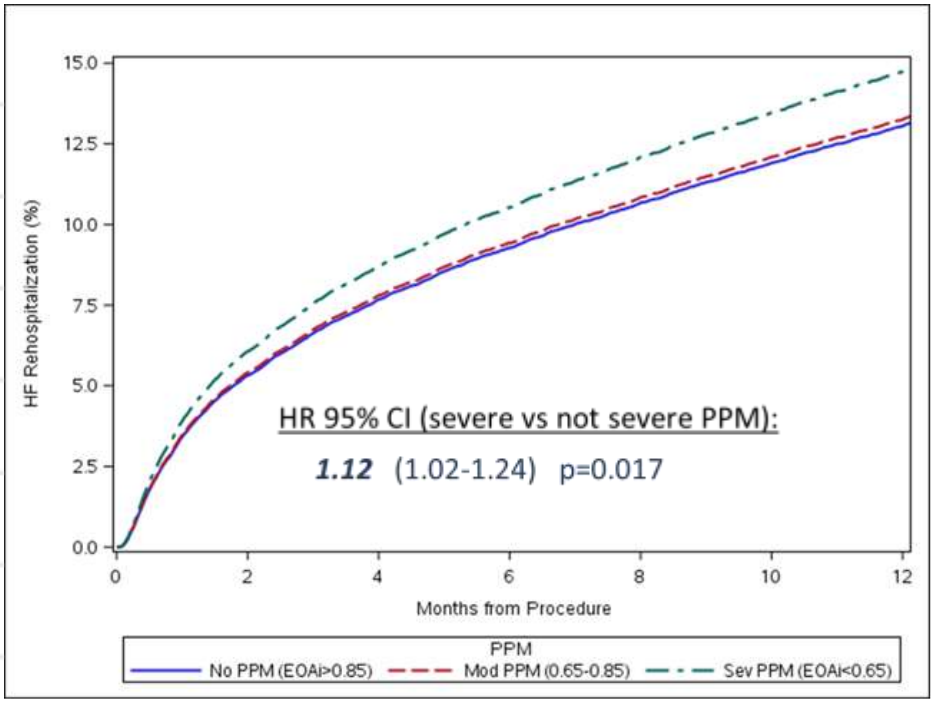
STS National Database™
Using data to drive quality

NCDR®
NATIONAL CARDIOVASCULAR DATA REGISTRY

US TAVR – All Cause Readmission



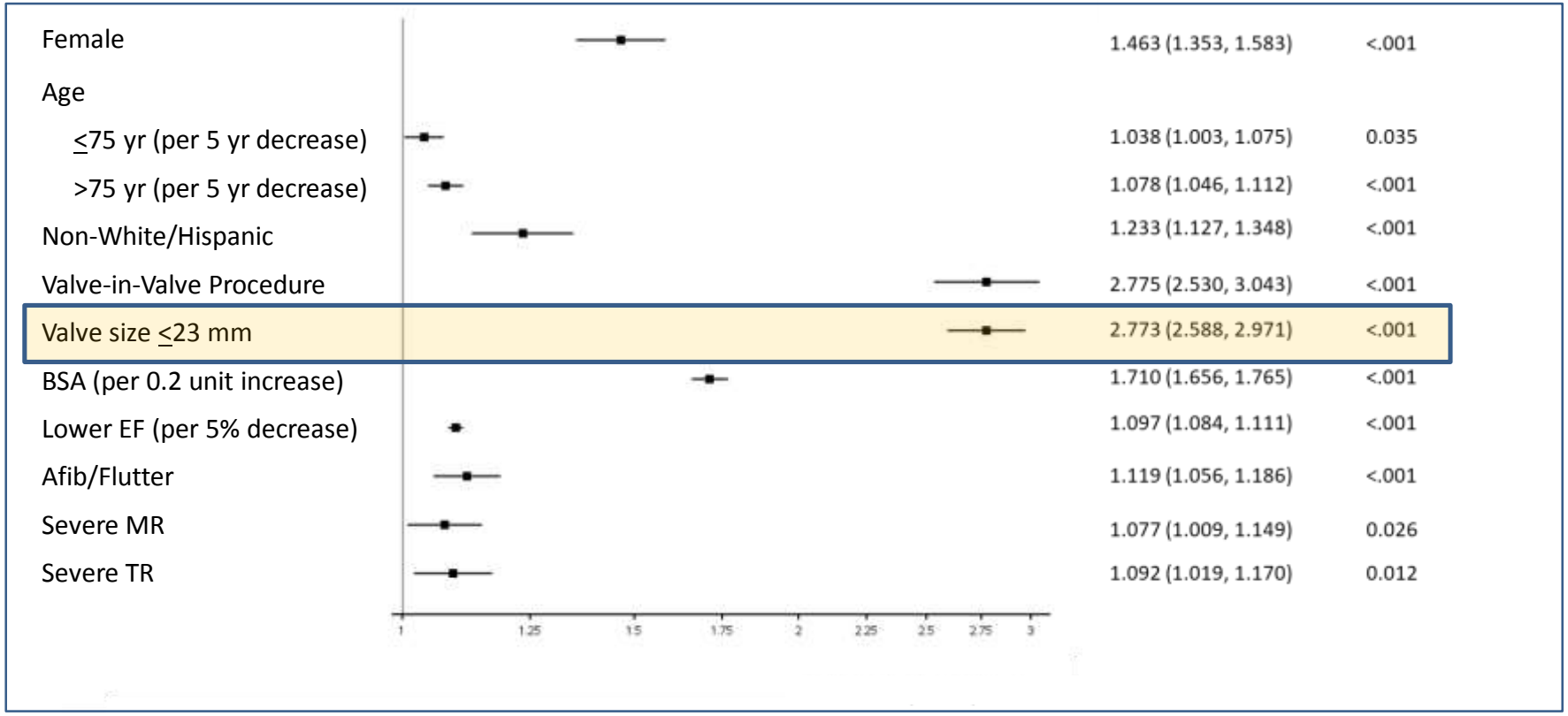
HF Rehospitalization (%)



Number at Risk Adjusting for baseline covariates:

	Day 0	Month 4	Month 8	Month 12
No PPM	23642	19561	15086	11502
Mod PPM	8986	7386	5581	4183
Sev PPM	4153	3328	2475	1819

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



STS National Database
Using data to drive quality

NCDR
NATIONAL CARDIOVASCULAR DATA REGISTRY

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- *Small Annuli Are Common:*

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

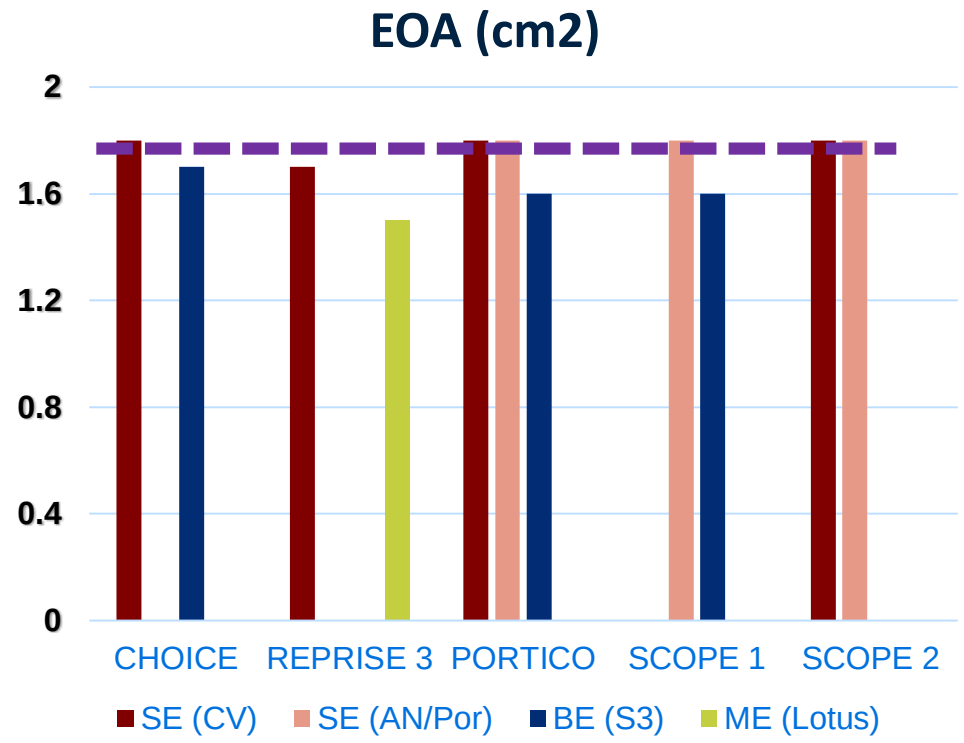
- *Use of small TAVR prostheses in randomized trials:*

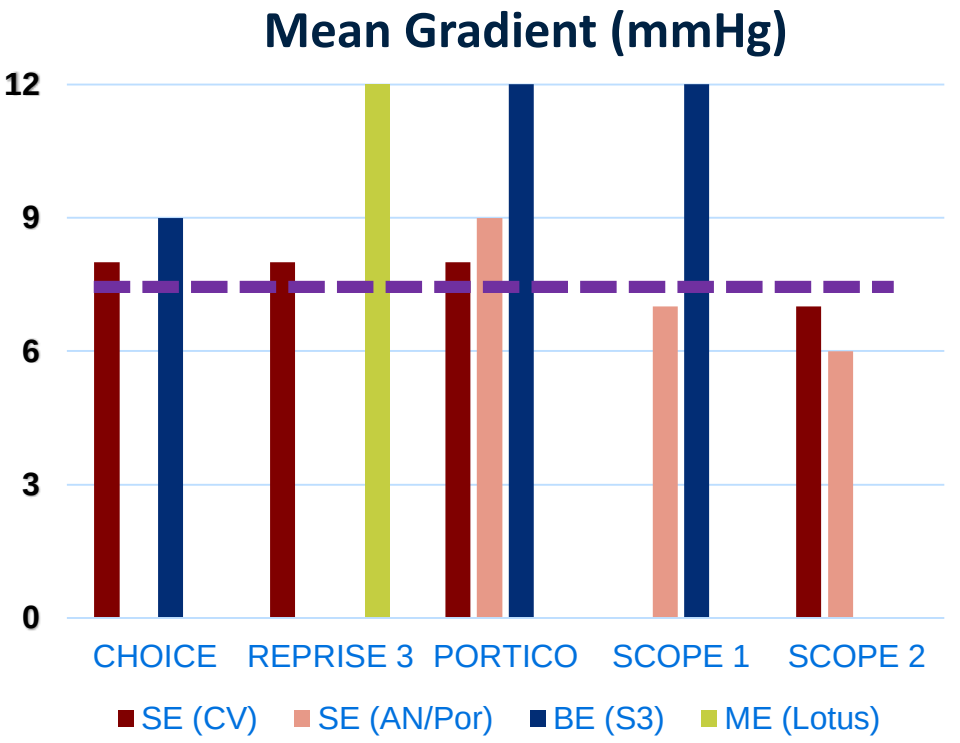
	Area ≤ 430 mm2 (IFU 20/23 mm BE)	Perimeter-derived diam ≤ 23.4 mm (IFU 23/26 SE)
Intermediate Risk Trials [2,3]	**36%**	**22%**
Low Risk Trials [4,5]	**31%**	**21%**

- *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

Randomized TAVR Trials (all annulus sizes at 1 year)





JACC 2015;66:791
JAMA 2018;319:27
Lancet 2019;396:669
Lancet 2019;394:1619
Circulation Oct 15, 2020

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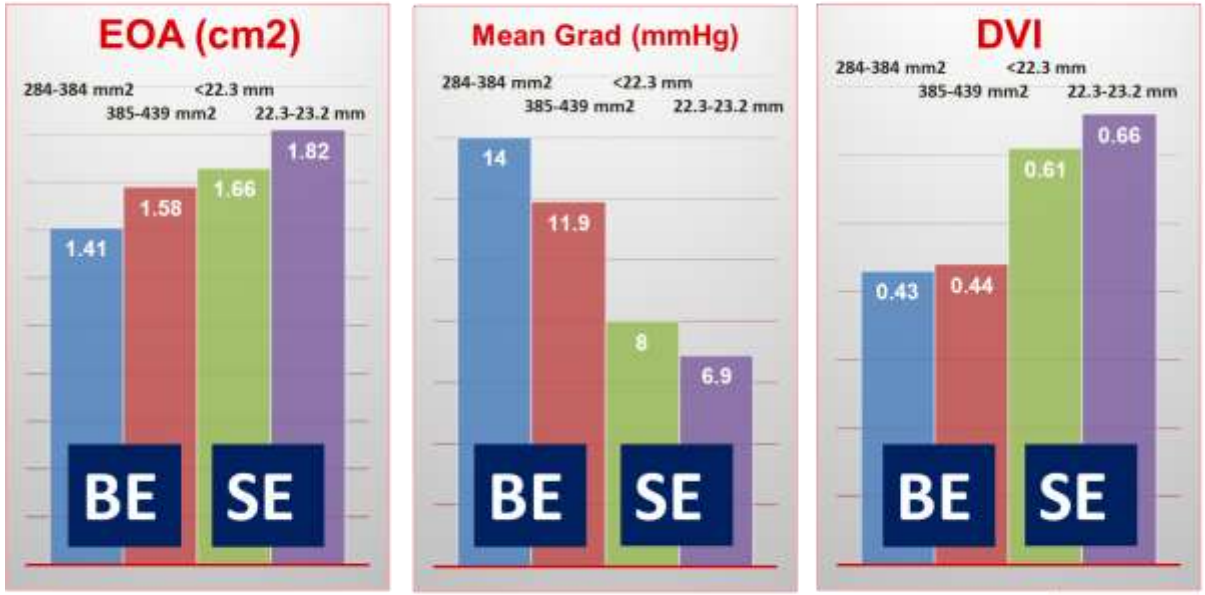
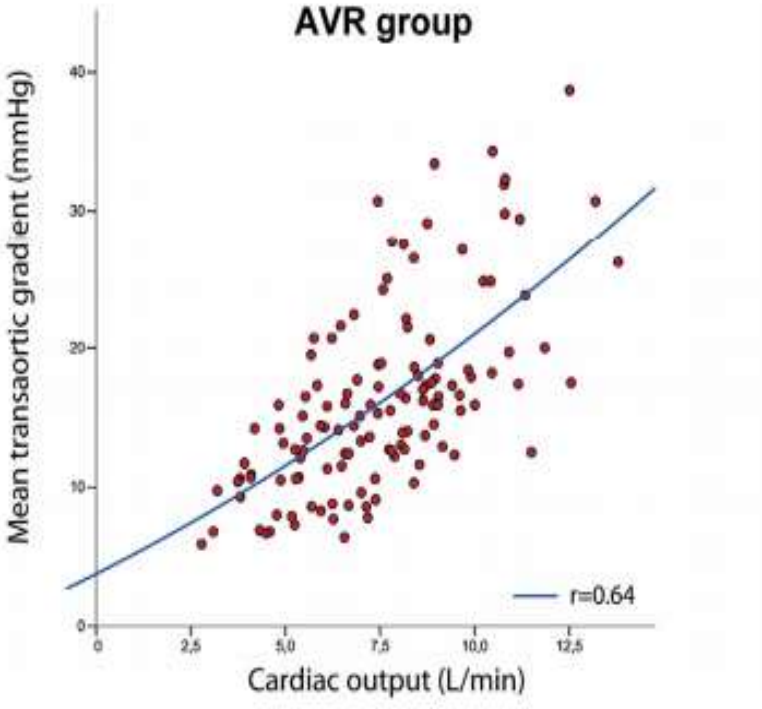
When choosing a TAVR prosthesis, consider the hemodynamic differences on clinical outcomes, durability, and prosthesis-patient mismatch

Echo core lab analysis at 30 days:
small annulus (lowest 2 quintiles)



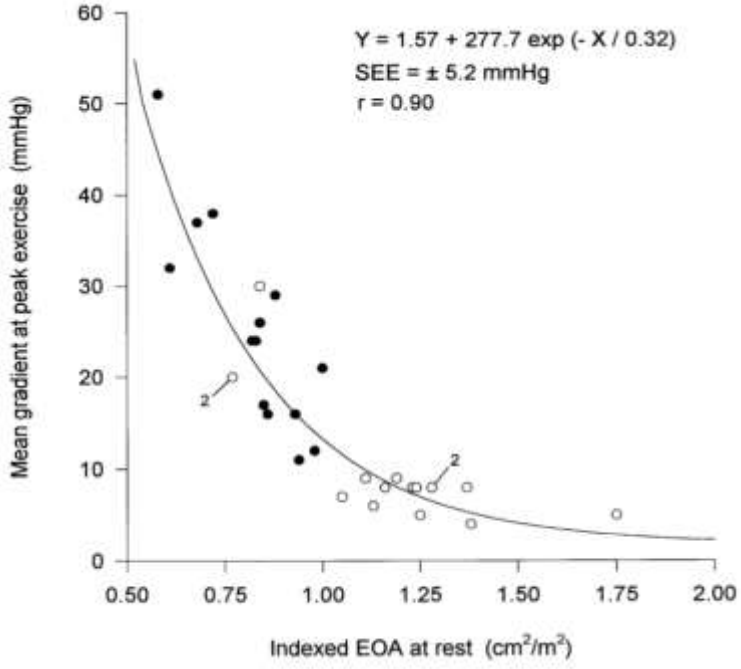
Hahn et al, JACC CV Imaging 2019;12:25

POST AVR GRADIENTS ARE ACCENTUATED WITH EXERCISE (MOST IMPORTANT IN YOUNGER AND MORE ACTIVE PATIENTS)



- Bertrand et al J Am Soc Echocardiogr 2017 **30**(4): 404-413.

Exercise Gradients by EOA



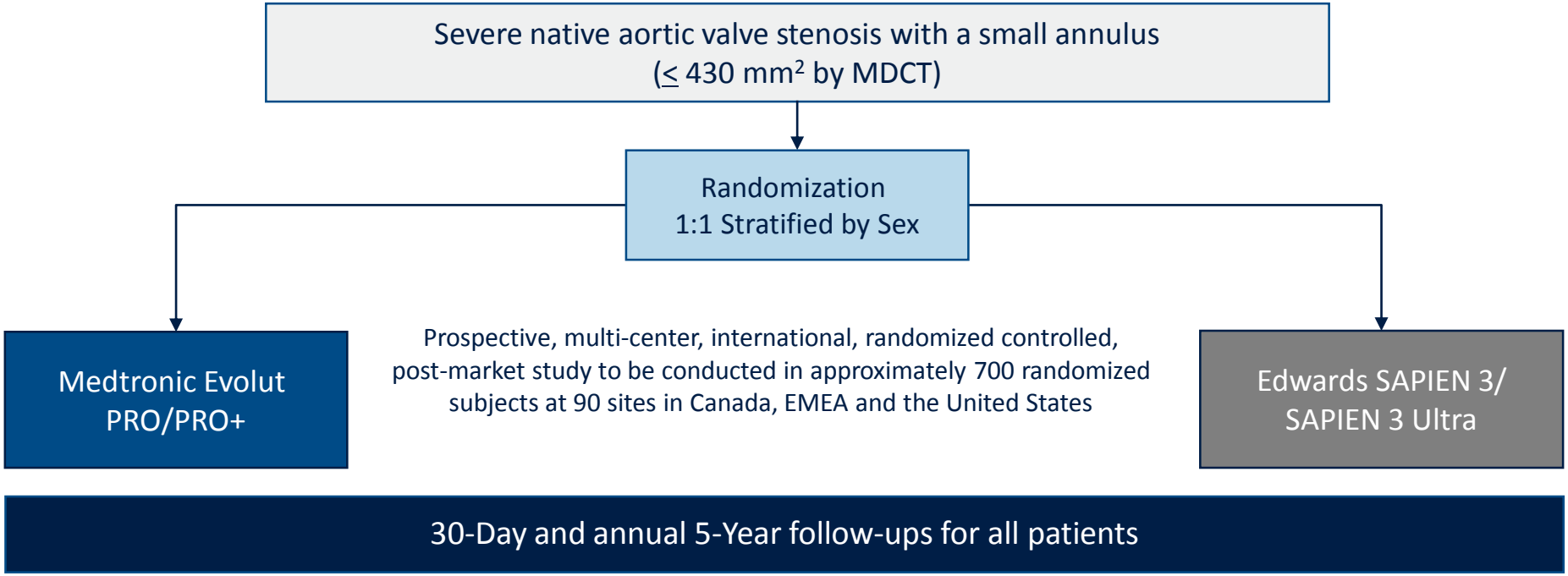
- Pibarot P et al JACC 1999;34(5):1609-1617

Conclusions

- Expansion of TAVR to younger and lower risk patients emphasizes the need for optimal results - both short and long-term
- Awareness of the risks of adverse hemodynamics (severe PPM, low DVI, high gradients) is important
  - These risks include higher mortality, reduced exercise tolerance, less LV mass regression, impaired exercise tolerance, and worse durability
  - The effects of adverse hemodynamics are amplified in patients:
    - Younger
    - More active
    - Those with small annuli (particularly women)

Utilizing the largest prosthesis based on annulus area/perimeter and manufacturer recommendations with the most optimal hemodynamics is key to best outcomes and is the rationale for the SMART Trial

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



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)

STUDY ENDPOINTS (POWERED)

Co-Primary Endpoints	Primary Endpoint #1: mortality, disabling stroke or rehospitalization (valve-related or worsening of heart failure) at 12 months (clinical outcome) Primary Endpoint #2: bioprosthetic valve dysfunction (BVD) at 12 months (valve durability). BVD is defined as a composite of: • Hemodynamic Structural Valve Dysfunction (HSVD): mean gradient ≥20 mmHg • Non-Structural Valve Dysfunction (NSVD): severe PPM, ≥ moderate AR • Thrombosis • Endocarditis • Aortic valve re-operation or re-intervention
Powered Secondary Endpoints	1. BVD in the female subjects at 12 months 2. HSVD in all subjects at 12 months 3. Hemodynamic mean gradient (continuous variable) at 12 months

HSVD and NVSD are based on Echo core lab data, and events thrombosis, endocarditis and aortic valve reintervention are from CEC adjudications.

Bioprosthetic Valve Dysfunction Definition:

HSVD: hemodynamic SVD: mean gradient ≥20mmHg

NSVD: severe PPM, ≥ moderate AR

Thrombosis (VARC-3): clinically apparent leaflet thrombosis (leaflet thrombus formation associated with clinically relevant hemodynamic changes, symptoms, or sequela compatible with valve thrombosis or thromboembolism)

Endocarditis (VARC-3): Duke endocarditis criteria or abscess/pus/vegetation confirmed at reop or autopsy

Aortic valve re-operation or re-intervention

Severe Prosthesis-Patient Mismatch (PPM) Definition

Using the VARC-3 definition with obesity correction

For subjects with BMI < 30 kg/cm
Severe PPM: EOAI = ≤ 0.65 cm^2/m^2

For subjects with BMI ≥ 30 kg/cm
Severe PPM: EOAI = ≤ 0.55