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:

### Institutional Grant/Research Support

<table>
<thead>
<tr>
<th>Abbott Vascular</th>
<th>WL Gore</th>
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<tr>
<td>Bayer</td>
<td>Highlife</td>
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<tr>
<td>Boston Scientific</td>
<td>Shockwave</td>
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<tr>
<td>CRF</td>
<td>St. Jude Medical</td>
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<td>Corvia</td>
<td>Medtronic</td>
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<td>Edwards Lifesciences</td>
<td>Univ Laval</td>
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### Consulting Fees/Honoraria

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<tr>
<th>Edwards Lifesciences</th>
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<td>Medtronic</td>
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<td>Wells Fargo</td>
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<td>Cowan</td>
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### Editorial

<table>
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<th>Mass Medical Society</th>
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### Major Stock Shareholder/Equity

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<tr>
<th>Microinterventional Devices</th>
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<td>Holistick</td>
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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

TRIAL / REGISTRY
(Number of patients)

DEFINITION OF PPM

PARTNER IA‡
(n=2,211)

Measured EOAi

CoreValve HR‡
(n=742)

Measured EOAi

STS SAVR

(n=59,779)

Predicted EOAi

STS-TAVR‡

(n=611,125)

Measured EOAi

Meta-Analysis

(n=27,186)

Predicted/Measured
EOAi

IMPACT OF PROSTHESIS-PATIENT MISMATCH ON MORTALITY
TAVR in STS/ACC TVT Registry™ All TAVR Devices (N=63,393)

Mortality (%)

17.2% Severe
15.8% Moderate/None

Adjusted HR (95% CI)

1.19 (1.09-1.31) p<0.001
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

<table>
<thead>
<tr>
<th>Patients</th>
<th>Severe PPM</th>
<th>mGrad (1 yr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>42,174 native</td>
<td>5.3%</td>
<td>10.2 mmHg</td>
</tr>
<tr>
<td>5446 VIV</td>
<td>27.0%</td>
<td>17.1 mmHg</td>
</tr>
</tbody>
</table>

TAVR with a SE valve in low risk patients

Severe PPM (VARC 2)

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

Popma et al, NEJM 2019;380:1706
Impact of Flow on Prosthesis-Patient Mismatch Following Transcatheter and Surgical Aortic Valve Replacement

Amr E. Abbasi, MD; Julien Tremblay, MD; Philippe Pibarot, PhD; DVM; Ke Xu, PhD; Maria Aue, MS; Erin Rogers, MEng; Rebecca T. Hahn, MD; Martin Leon, MD; Vnood H. Thourani, MD

Circ CV Imaging 2021

954 TAVR patients from Partner 2A and S3i registries

Mack et al, NEJM 2019;380:1695

TAVR with a BE valve in low risk patients

Severe PPM (VARC 2 and 3)

Percentage of Severe Prosthesis Patient Mismatch

45%

40%

35%

30%

25%

20%

15%

10%

5%

0%

All TAVR Patients

4.6%
### Definitions for Prosthesis-Patient Mismatch (cm²/m²):

<table>
<thead>
<tr>
<th>Source</th>
<th>Severe</th>
<th>Moderate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Am Soc Echo/US Guidelines¹</td>
<td>&lt;0.65</td>
<td>0.65-0.85</td>
</tr>
<tr>
<td>VARC-2/European Guidelines²</td>
<td>&lt;0.65</td>
<td>0.65-0.85</td>
</tr>
<tr>
<td>BMI ≥30 kg/cm²</td>
<td>&lt;0.60</td>
<td>0.60-0.90</td>
</tr>
<tr>
<td>EACVI (European Assoc CV Imaging)³</td>
<td>&lt;0.65</td>
<td>0.65-0.85</td>
</tr>
<tr>
<td>VARC 3⁴</td>
<td>BMI ≥30 kg/cm²</td>
<td>&lt;0.55</td>
</tr>
</tbody>
</table>

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¹ Zoghbi et al, J AM Soc Echo 2009;22975-1014
³ Lancellotti et al, Eur Heart J 2012;33:2403-2418
⁴ Genereux et al, Eur Heart J 2021;42:1825
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.

\[ \text{Cardiac Output} = 1.5 \times \text{BSA} + 1.9 \]

\[ r = 0.29 \ (0.22;0.35) \]
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:

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<table>
<thead>
<tr>
<th>BMI</th>
<th>Mortality Effect</th>
<th>Interaction P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;30 kg/m²</td>
<td>1.149 (1.031–1.281)</td>
<td>0.204</td>
</tr>
<tr>
<td>≥30 kg/m²</td>
<td>1.277 (1.115–1.464)</td>
<td></td>
</tr>
</tbody>
</table>
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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)


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

Stanova V et al, Cath Cardiovasc Intv 2021 (in press)
EOA = LVOT area * \( \frac{LV\ VTI}{Ao\ VTI} \)

Hahn et al, JACC CV Imaging 2019;12:25
Echo core lab (n=3) analysis at 30 days

Small Annulus (lowest 2 quintiles)

EOA (cm²)

Mean Grad (mmHg)

DVI

Hahn et al, JACC CV Imaging 2019;12:25
Impact of time of measurement on gradient determination

**Sapien 3 THV (mean gradient, mmHg)**
- Day 0: 13.2* (n=100)
- Day 1: 15.1* (n=41)
- Day 0: 15.7* (n=59)

**Evolut Pro THV (mean gradient, mmHg)**
- Day 0: 13.6* (n=100)
- Day 1: 10.9* (n=36)
- Day 1: 10.1* (n=64)

<table>
<thead>
<tr>
<th></th>
<th>LV VTI</th>
<th>Ao VTI</th>
<th>DVI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sapien 3 all</strong></td>
<td>Day 0</td>
<td>20.8</td>
<td>0.62</td>
</tr>
<tr>
<td></td>
<td>Day 1</td>
<td>22.8*</td>
<td>0.50*</td>
</tr>
<tr>
<td><strong>Sapien 3 #23</strong></td>
<td>Day 0</td>
<td>6.3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Day 1</td>
<td>11.4*</td>
<td></td>
</tr>
<tr>
<td><strong>Sapien 3 #26/29</strong></td>
<td>Day 0</td>
<td>4.4</td>
<td>11.5*</td>
</tr>
<tr>
<td></td>
<td>Day 1</td>
<td>11.7*</td>
<td>0.79</td>
</tr>
</tbody>
</table>

**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

Herrmann HC, Small Annulus Hemodynamics and TAVR, JACC CV Intv 2021;14(11):1229-1230
<table>
<thead>
<tr>
<th>Predictor</th>
<th>Odds Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>1.463 (1.353, 1.583)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;75 yr (per 5 yr decrease)</td>
<td>1.038 (1.003, 1.075)</td>
<td>0.035</td>
</tr>
<tr>
<td>&gt;75 yr (per 5 yr decrease)</td>
<td>1.078 (1.046, 1.112)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Non-White/Hispanic</td>
<td>1.233 (1.127, 1.348)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Valve-in-Valve Procedure</td>
<td>2.775 (2.530, 3.043)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Valve size ≤23 mm</td>
<td>2.773 (2.588, 2.971)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>BSA (per 0.2 unit increase)</td>
<td>1.710 (1.656, 1.765)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Lower EF (per 5% decrease)</td>
<td>1.097 (1.084, 1.111)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Afib/Flutter</td>
<td>1.119 (1.056, 1.186)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Severe MR</td>
<td>1.077 (1.009, 1.149)</td>
<td>0.026</td>
</tr>
<tr>
<td>Severe TR</td>
<td>1.092 (1.019, 1.170)</td>
<td>0.012</td>
</tr>
</tbody>
</table>
- **Small Annuli Are Common:**
  SAVR prostheses ≤ 21 mm = 22-44%

- **Use of small TAVR prostheses:**

<table>
<thead>
<tr>
<th></th>
<th>Area ≤ 430 mm² (IFU 20/23 mm BE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intermediate Risk Trials</td>
<td>36%</td>
</tr>
<tr>
<td>Low Risk Trials</td>
<td>31%</td>
</tr>
</tbody>
</table>

- **Higher in Southern Europe and Asia**

- **TAV in SAV = 70-80%**

- **Several fold higher in women who make up ~90% of small annulus population**

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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 mm$^2$ 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)
Outcomes with Severe PPM in Men

Severe v. None HR=0.27
Log rank P = 0.3705

Outcomes with Severe PPM in Women

Severe v. None HR=3.67
Log rank P = 0.0115

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

SAVR, 81%  TAVR, 19%

Age/Sex Adjusted 1-Year Mortality

Mean Gradient (mmHg)

20–40  >40

29.0%  33.6%

>22.5 mmHg

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)

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

CORRELATION WITH HVD AND 5 YEAR MORTALITY

<table>
<thead>
<tr>
<th>Time-dependent covariate: HVD</th>
<th>HR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All TAVR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>3.224 (2.188, 4.751)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cardiovascular mortality</td>
<td>3.182 (1.941, 5.216)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>AV-related hospitalization</td>
<td>3.834 (2.112, 6.960)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Composite</td>
<td>3.227 (2.190, 4.755)</td>
<td>&lt;0.001</td>
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O'Hair D, et al. Presented at ACC 2021
SMART TRIAL DESIGN (SMall Annuli Randomized To evolut or sapien)

Severe native aortic valve stenosis with a small annulus (≤ 430 mm² by MDCT)

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

Co-primary endpoints at 12 mos:
1. Death, disabling stroke, re-hosp HF
2. Bioprosthetic valve dysfunction

Medtronic Evolut PRO/PRO+

Edwards SAPIEN 3/ SAPIEN 3 Ultra

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)