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:

<table>
<thead>
<tr>
<th>Institutional Grant/Research Support</th>
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<td>Abbott Vascular</td>
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<td>Ancora</td>
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<td>Bayer</td>
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**Editorial**

Mass. Medical Society

➢ 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
Severe PPM associated with almost 2-fold increase in all-cause mortality and >6-fold increase in cardiac mortality
Additional Lessons from Surgery

Less PPM is associated with:

• Better coronary flow reserve

• More LV mass regression

• Better exercise tolerance

• Improved QOL
• 564 SAVR followed >6 yrs

• Structural valve deterioration (SVD) occurred in 7%

• PPM independent predictor (HR 2.29) of structural valve degeneration
INCIDENCE OF PROSTHESIS-PATIENT MISMATCH

TRIAL / REGISTRY
(Number of patients)
DEFINITION OF PPM

PARTNER IA†
(n=2,211)
Measured EOAi

CoreValve HR‡
(n=742)
Predicted EOAi

STS SAVR
(n=59,779)
Measured EOAi

STS-TVT TAVR‡
(n=62,125)
Predicted/Measured EOAi

Meta-Analysis
(n=27,186)

Mortality Hazard Ratio (%)

IMPACT OF PROSTHESIS-PATIENT MISMATCH ON MORTALITY
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
US TAVR – All Cause Readmission

HF Rehospitalization (%)

HR 95% CI (severe vs not severe PPM): 1.12 (1.02-1.24) p=0.017
**Odds Ratios (95% CI) for Multivariate Model Predictors of Severe PPM**

- **Female**: 1.463 (1.353, 1.583) < .001
- **Age**
  - ≤75 yr (per 5 yr decrease): 1.038 (1.003, 1.075) 0.035
  - >75 yr (per 5 yr decrease): 1.078 (1.046, 1.112) < .001
- **Non-White/Hispanic**: 1.233 (1.127, 1.348) < .001
- **Valve-in-Valve Procedure**: 2.775 (2.530, 3.043) < .001
- **Valve size ≤23 mm**: 2.773 (2.588, 2.971) < .001
- **BSA (per 0.2 unit increase)**: 1.710 (1.656, 1.765) < .001
- **Lower EF (per 5% decrease)**: 1.097 (1.084, 1.111) < .001
- **Afib/Flutter**: 1.119 (1.056, 1.186) < .001
- **Severe MR**: 1.077 (1.009, 1.149) 0.026
- **Severe TR**: 1.092 (1.019, 1.170) 0.012
• **Small Annuli Are Common:**

SAVR prostheses \( \leq 21 \text{ mm} \) \(^1\) = **22-44%**

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

<table>
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<th></th>
<th>Area ( \leq 430 \text{ mm}^2 ) (IFU 20/23 mm BE)</th>
<th>Perimeter-derived diam ( \leq 23.4 \text{ mm} ) (IFU 23/26 SE)</th>
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<tr>
<td>Intermediate Risk Trials (^2,3)</td>
<td>36%</td>
<td>22%</td>
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<tr>
<td>Low Risk Trials (^4,5)</td>
<td>31%</td>
<td>21%</td>
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• **Higher in Southern Europe and Asia** \(^1\)

• **TAV in SAV = 70-80%** \(^6,7\)

• **Several fold higher in women who make up \( \sim 90\% \) of small annulus population** \(^1\)

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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
Randomized TAVR Trials (all annulus sizes at 1 year)

**EOA (cm²)**

- **CHOICE**
- **REPRISE 3**
- **PORTICO**
- **SCOPE 1**
- **SCOPE 2**

Mean Gradient (mmHg)

- **CHOICE**
- **REPRISE 3**
- **PORTICO**
- **SCOPE 1**
- **SCOPE 2**

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

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)

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

Randomization
1:1 Stratified by Sex

Prospective, multi-center, international, randomized controlled,
post-market study to be conducted in approximately 700 randomized
subjects at 90 sites in Canada, EMEA and the United States

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)
**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 ≥20 mmHg
- **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 cm²/m²

**For subjects with BMI ≥ 30 kg/cm**

**Severe PPM:** EOAI = ≤ 0.55