



**Heart & Vascular  
Institute**

Westchester Medical Center Health Network

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# Conflicts of Interest

## Advisory Boards:

- MyoKardia (modest, < \$10,000)
- Abbott Vascular (modest, < \$10,000)

## SCAI:

- SCAI has no conflicts to disclose

## Question 2

“How confident are we that surrogate and intermediate endpoints are predictive of standalone, meaningful primary health outcomes in clinical research studies of heart failure treatment technologies for:

- a) Heart failure with preserved EF
- b) Heart failure secondary to MR where the focus is MV repair / replacement
- c) Heart failure with reduced EF”

# Discussion Points

- If greater than or equal to intermediate confidence, please identify the specific surrogate or intermediate endpoints and associated disease or therapy which you believe are sufficiently predictive of meaningful health outcomes
- Please discuss how these intermediate and surrogate endpoints meaningfully contribute towards the evidence base for heart failure treatment technologies
- Please discuss important factors to consider when assessing utility of surrogate and intermediate endpoints

# SCAI Interventional Heart Failure Working Group, 2011 - present

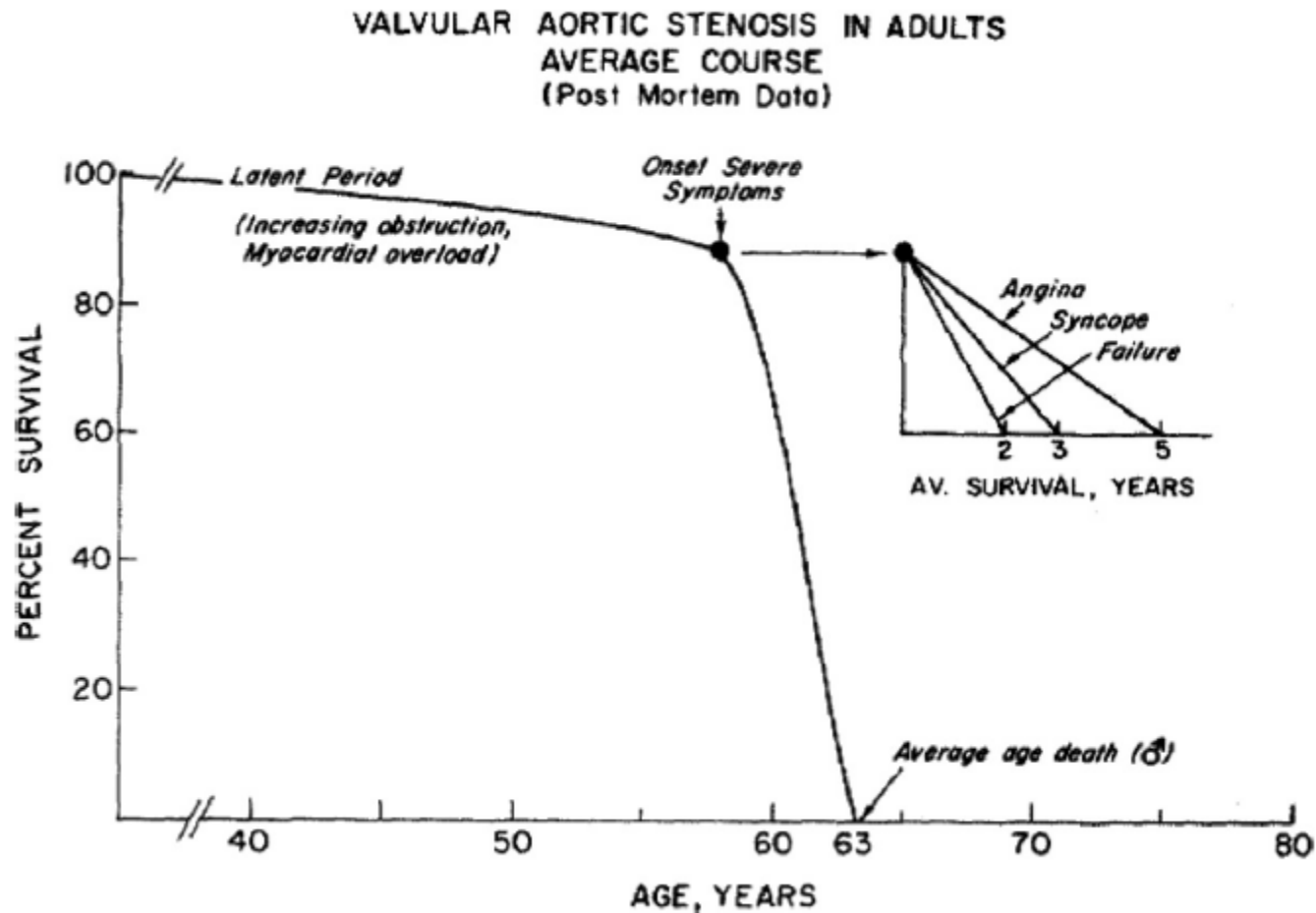
To address the growing epidemic of heart failure through promotion of interventional therapies.

- a) Most therapies that have improved mortality have resulted in more patients living with heart failure
- b) Current and future therapies must focus not only on mortality but perhaps even more on heart failure and related outcomes
- c) Patients and physicians value quality of life as much as or more than quantity of life, especially as patients age; emergence of heart failure readmission and surrogate endpoints
- d) Teamwork with our heart failure, surgical and other colleagues will be required to achieve improved outcomes in heart failure
- e) Advocacy, education and further research are necessary to help foster technological advancements to reduce the burden of heart failure, including health care costs

# The Search For Meaningful Endpoints

- When death occurs with high frequency, especially in the short-term, improvement in mortality is an ideal primary target
- Many of our therapies have markedly reduced mortality (e.g. ICDs), however, leaving the patient with ongoing and progressive heart failure
- Clinical events related to the heart failure state have emerged as accepted secondary targets

# Aortic Stenosis



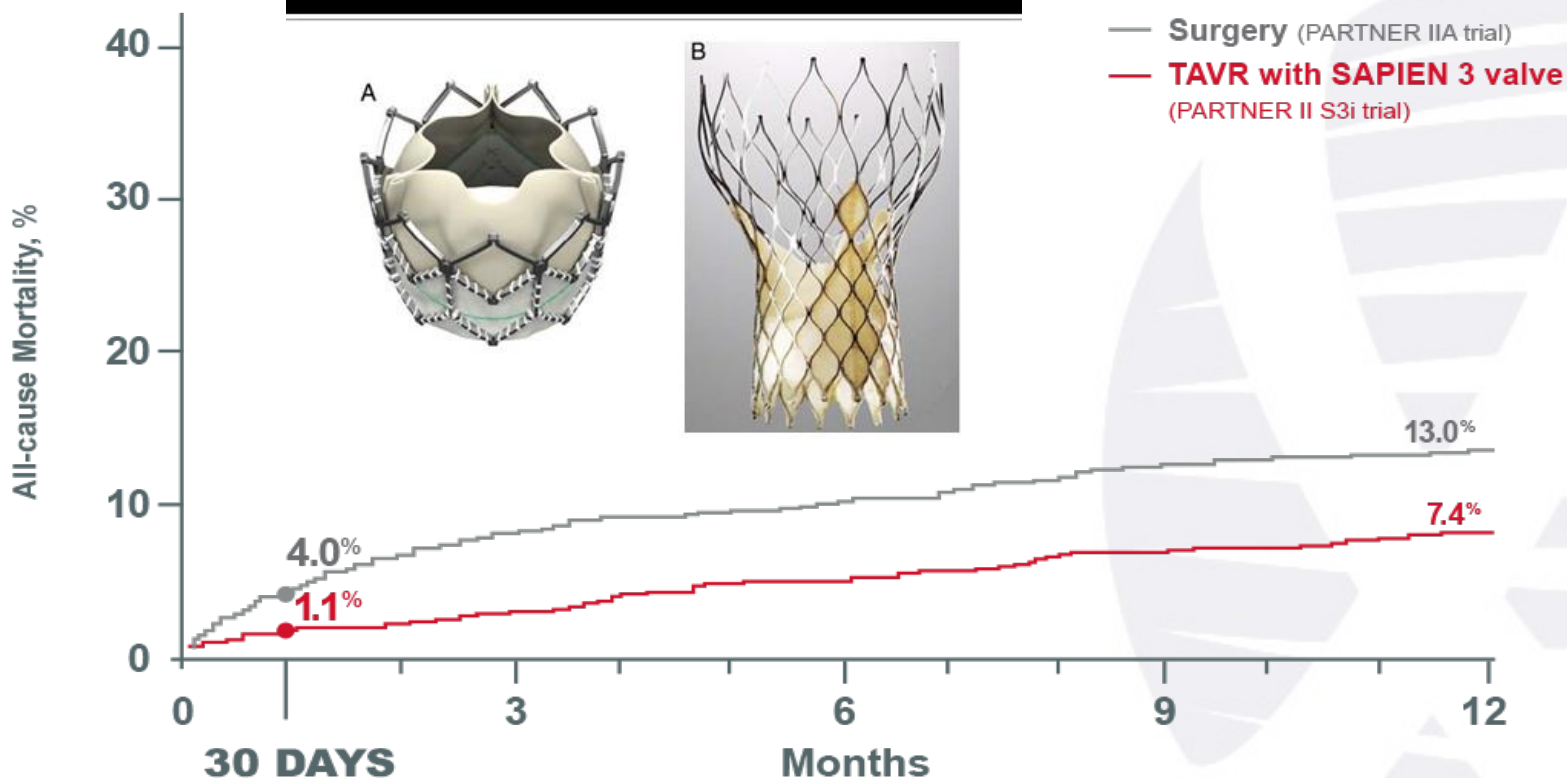
# The TAVR Story: Mortality

- Untreated Symptomatic AS will lead to death in relatively short order
- Surgical treatment of AS has a defined risk / mortality
- Catheter valve replacement in high risk individuals appears as safe or safer, and the only option in the non-operable
- Mortality risk so high that it can be used in clinical trials over a short time course to prove meaningful benefits



# All-cause Mortality<sup>‡</sup>

## Sapien XT and Corevalve



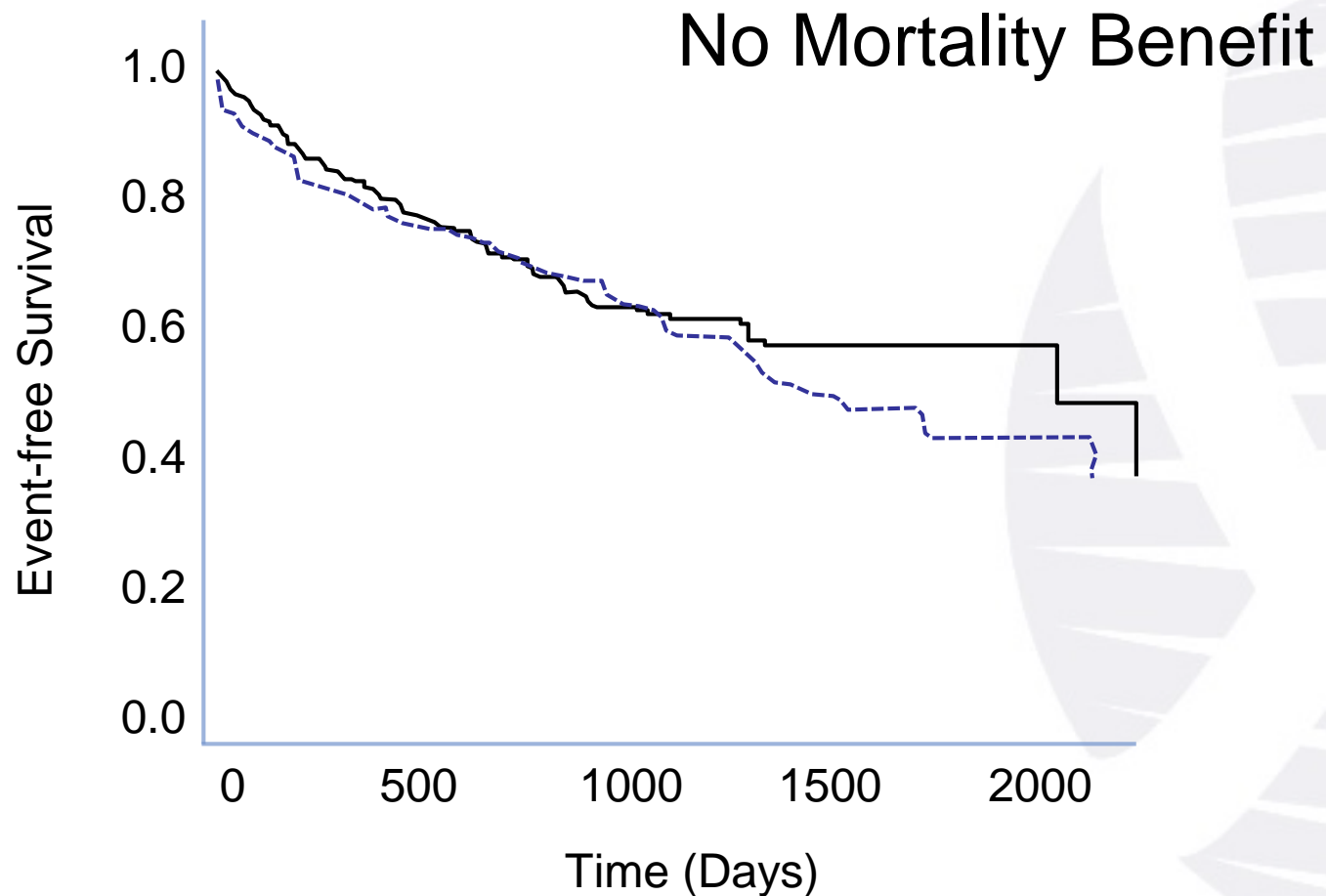
No. at risk:

Surgery	944	859	836	808	795
SAPIEN 3 TAVR	1,077	1,043	1,017	991	963

# What About Mitral Disease

- More gradual clinical trajectory of untreated mitral regurgitation, with mortality affected over the long-term but not short- or intermediate-term
- The physiologic impact of mitral regurgitation is congestion and often heart failure hospitalization, which markedly increases morbidity
- Surgical approaches have not improved survival over the short- or intermediate-term, unlike aortic disease
- Heart failure endpoints show meaningful improvement

# Surgery for Secondary MR



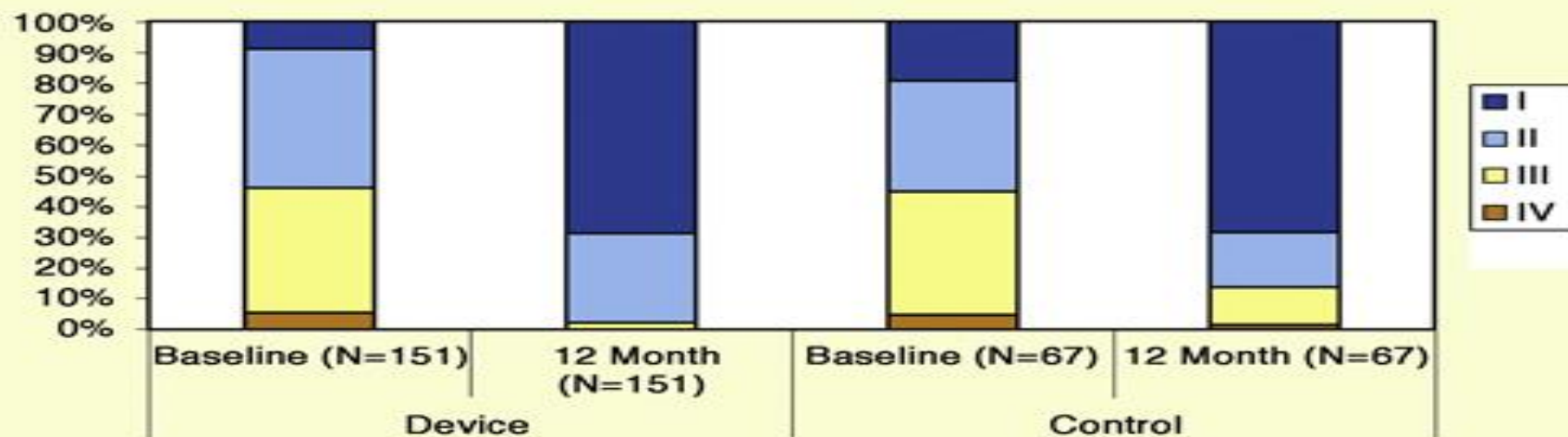
# EVEREST 4 Year Results: Percutaneous Therapies for MR

	<b>Percutaneous (n = 161)</b>	<b>Surgical (n = 73)</b>	<b>P Value</b>
<b>Composite Efficacy Endpoint</b>	39.8%	53.4%	0.070
<b>Death</b>	17.4%	17.8%	0.914
<b>Surgery or Re-operation for Mitral Valve Dysfunction</b>	24.8%	5.5%	< 0.001
<b>MR 3+ or 4+</b>	21.7%	24.7%	0.745

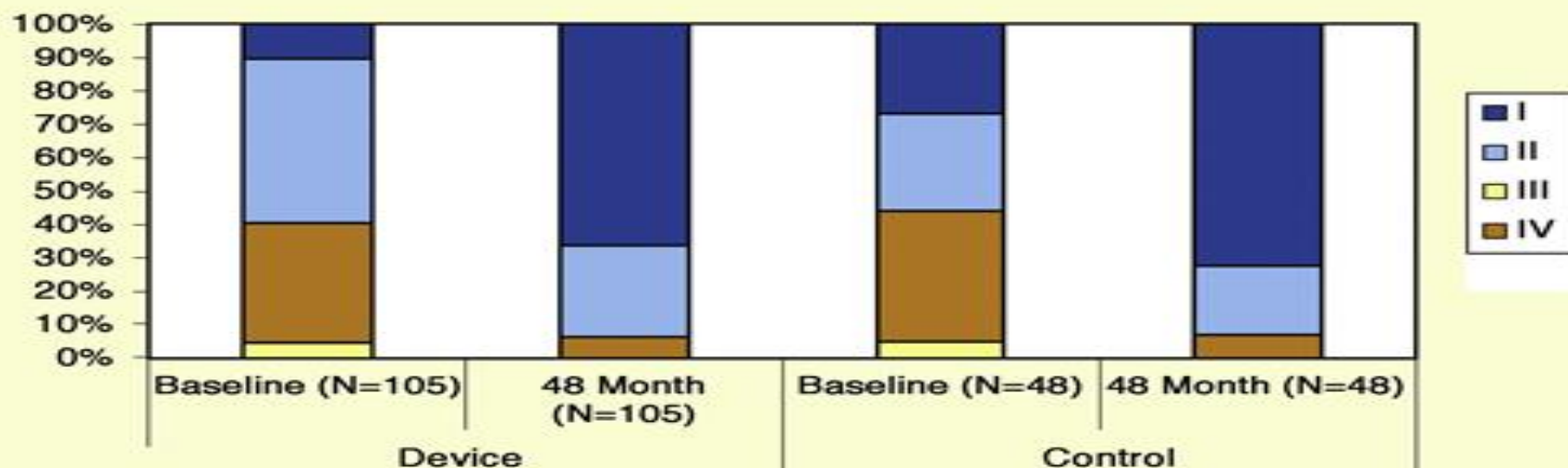
- NS difference in mortality and similar improvement in MR
- Differences emerge in secondary endpoints

**A**

## NYHA Functional Class at Baseline and 12 Months

**B**

## NYHA Functional Class at Baseline and 48 Months



# Path Forward: Concepts

- Novel “hard” endpoints are required
  - ✓ Days alive and out of the hospital, or HF rehospitalizations, or total hospitalizations (efficacy)
    - Has value to all parties, patient, doctor, family and health care system which covers costs of care
  - ✓ Surrogate Endpoints (effectiveness)
    - Device and disease-specific
    - Measure of how well the therapy does what it is supposed to do (eg., reduction in MR in mitral repair)
- Not every treatment saves lives
  - ✓ Or the magnitude of effect is too small to measure without an unrealistic “mega-trial”

# EXAMPLES where mortality benefit would not be realistic targets

- PA monitoring through temporary or permanent catheters / devices
  - ✓ ESCAPE trial
  - ✓ CardioMEMS
- Appropriate targets are surrogate endpoints of heart failure, which would be reasonable predictors of improved quality or quantity of life over the longer-term

**What would be meaningful surrogates in heart failure trials where mortality is not the driver of short- or intermediate-term outcomes?**



# Combined Surrogate Endpoints

- Heart failure with preserved ejection fraction
  - ✓ 6MWT, biomarkers (NT pro-BNP)
  - ✓ Escalation of Medical Therapy
- Heart failure secondary to MR
  - ✓ Reduction to trace, 1-2+ MR
  - ✓ 6MWT, biomarkers (NT pro-BNP)
  - ✓ LV remodeling (volumes)
  - ✓ Escalation of Medical Therapy
- Heart failure with reduced ejection fraction
  - ✓ 6MWT, biomarkers (NT pro-BNP)
  - ✓ LV remodeling (volumes)
  - ✓ Escalation of Medical Therapy

Surrogate endpoints should ideally be part of combined endpoints and are generally not sufficient as standalone variables

- demonstrate congruence between hard endpoints and surrogates
- confirm safety

# Further Discussion

- It is important to note that the aforementioned surrogates in general have been proven in large population-based studies of heart failure, and not prospectively as part of device-related heart failure trials
- We would encourage in randomized trials hypotheses that validate these potential surrogate endpoints

# Summary

- Except for heart failure etiologies with high mortality (i.e. AS), most others affect quality of life primarily and this is an important target
- Hard endpoints will need to include novel endpoints such as re-hospitalization or “days alive and out of hospital”
- Additional surrogate endpoints (as part of combined endpoints) will be necessary to prove improvements in the heart failure syndrome that are technology and disease-specific
- There is no “one size fits all” and a tailored approach to selecting surrogates will be required, understanding that devices should maintain low procedural risk
- Effects on mortality should be tracked as registries over the longer term, understanding that the goal of “days alive and out of hospital” may not always relate to reduced mortality

# Concluding Remarks

- SCAI applauds MEDCAC/CMS for looking beyond mortality as a meaningful endpoint
  - ✓ To address the main clinical outcomes in heart failure, i.e. morbidity
  - ✓ To prioritize quality of life as much as, and perhaps more than, quantity of life, consistent with palliative care principles
  - ✓ To facilitate advances in technology to treat the epidemic of heart failure