TAVR in Low Risk Patients

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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.

Affiliation/Financial Relationship	Company
• Grant/Research Support	• Edwards Lifesciences, Abbott
• Scientific Advisory Board	• Medtronic, Abbott
• Executive Physician Council	• Boston Scientific Corp

Provocative Questions to Address

Who Are These Patients?

- Will these patients be healthy 80 year olds or younger patients who wish to avoid surgery?
- How many patients enrolled will have asymptomatic aortic stenosis (e.g., high gradients or reduced LVEF)
- How will the STS PROM compare to the Heart Team Assessment of surgical risk? How many patients with an STS > 3% will be deemed low risk for surgery by experienced Heart Teams
- How will patients respond to randomization to surgery – will there be drops out similar to earlier Intermediate Risk and High Risk Trials or will healthier patients accept surgery?

Evolut R Low Risk: Study Overview

Primary Objective	To demonstrate that the safety and effectiveness of the Evolut-R TAVR bioprosthesis is non-inferior to SAVR in patients with severe AS at low risk for SAVR
Patients	Subjects with severe AS and an MDT predicted risk of 30-day mortality < 3%
Study Design	• International, prospective, multicenter • 1:1 randomization to either TAVR or SAVR

Evolut R Low Risk: Study Overview

Devices	Investigational TAVR Arm • Evolut R 23, 26, and 29 TAV, 31 mm CV • Transitioned to Evolut PRO and 34 EvolutR Control Arm • Any commercially available bioprosthesis
Number of Subjects	1300+ subjects, inclusive of nearly 400 subjects in LTI sub-study
Scope	US and OUS Clinical Sites

Evolut R Low Risk Patient Selection

Heart Team Evaluation
Two Cardiac Surgeons and One Interventional Cardiologist
Low Surgical Risk (predicted mortality risk <3%)

National Screening Committee
One Cardiac Surgeons and One Interventional Cardiologist
Confirm Low Risk for TAVR and SAVR

1:1 Randomization

TAVR

SAVR

Leaflet sub-study N=200

4D CT for LTI

Leaflet sub-study N=200

Provocative Questions to Address

How did the Screening Committee Contribute?

- Primary goal was to maintain protocol adherence by the clinical sites – every clinical document and all TTE/CT images reviewed by Screening Committee -- incredible oversight
- Controversial areas requiring consistency
  - Low gradients (< 25 mmHg)
  - Bicuspid aortic valve disease
  - Anatomy not suitable for TAVR

Evolut R Low Risk: Clinical Endpoints

Primary Endpoint	• All-cause mortality or disabling stroke at 2 years
Secondary Safety Endpoints	• Composite of death, disabling stroke, life-threatening bleed, major vascular events, or AKI (II or III) at 30 days • New permanent pacemaker implantation at 30 days • Prosthetic valve endocarditis at one year • Prosthetic valve thrombosis at one year • All stroke (disabling and non-disabling) at one year • Life-threatening bleeding at one year • Valve-related dysfunction -> repeat procedure at one year

Provocative Questions to Address

Secondary endpoints will drive the analysis

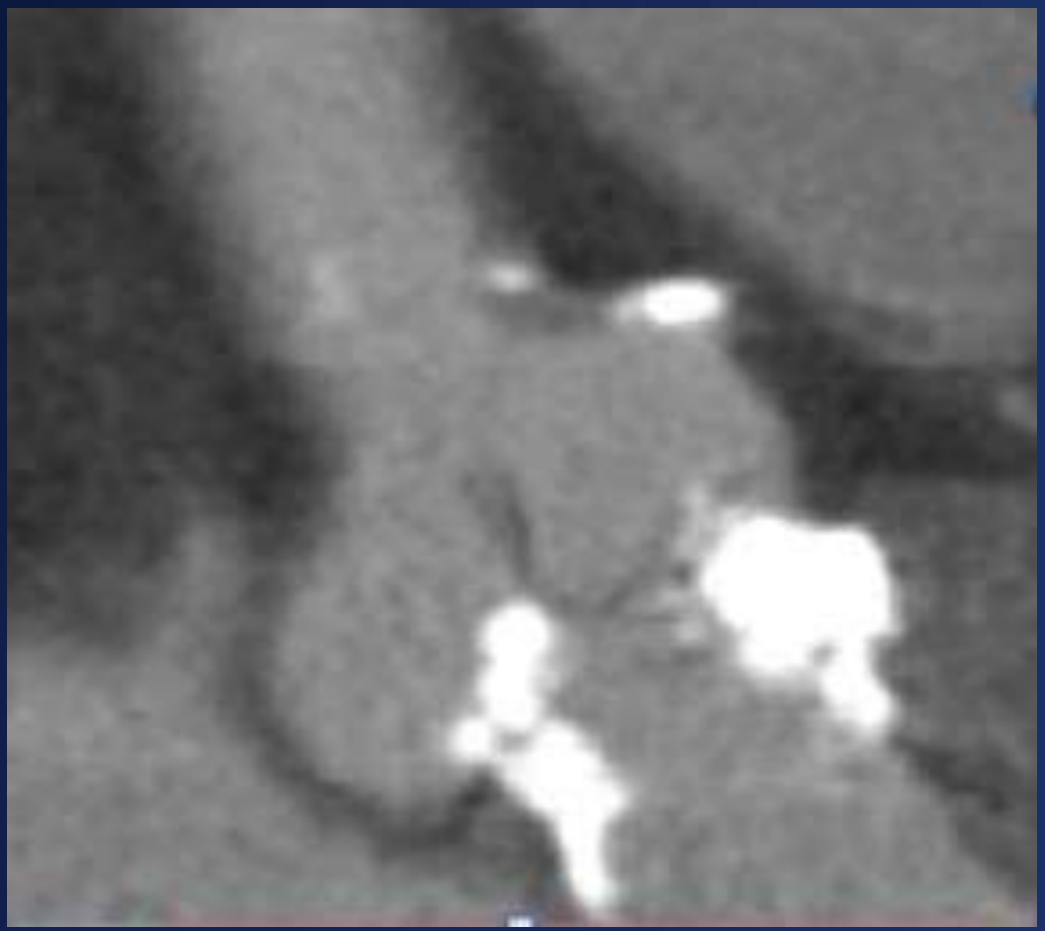
- A very detailed look at surgical valve performance (surgical valve sizing, residual gradients, TTE criteria for SVD at 10 years)
- How will functional status be affected by TAVR v. SAVR in healthier patients without frailties that delay surgical recovery?
- How frequent is leaflet thrombus immobility in both TAVR and SAVR patients – what are its implications?

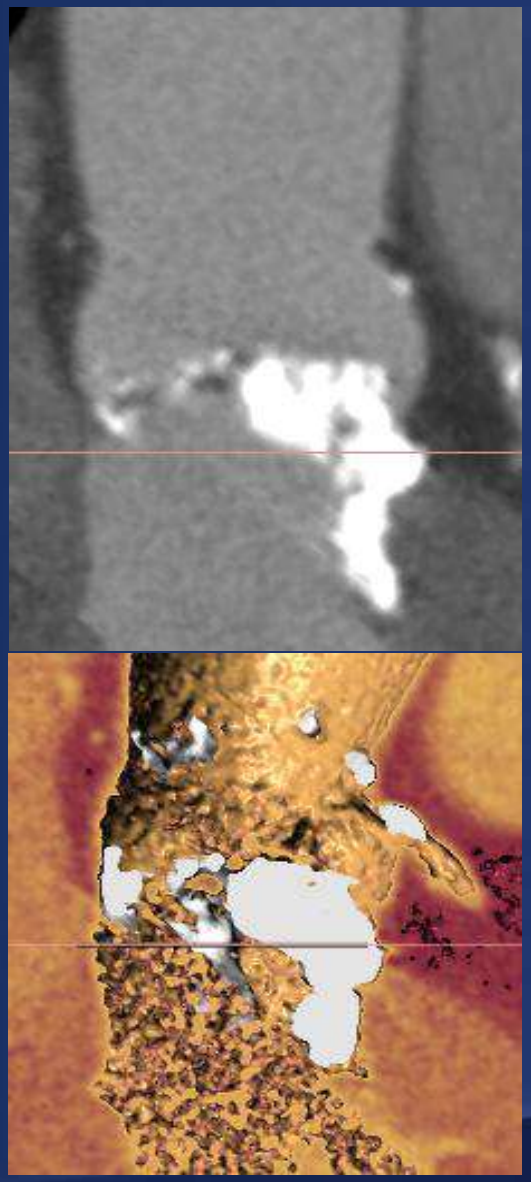
What We Excluded . . .

- Bicuspid aortic valve
- Multivessel CAD with Syntax score >22 and/or unprotected left main
- Acute MI ≤ 30 days prior to the procedure
- Severe MR or TR amenable to surgery
- Moderate or severe mitral stenosis
- Aortic annulus < 18 mm or > 30 mm
- Prohibitive LVOT calcification

Low Risk Exclusion Criteria: What's New?

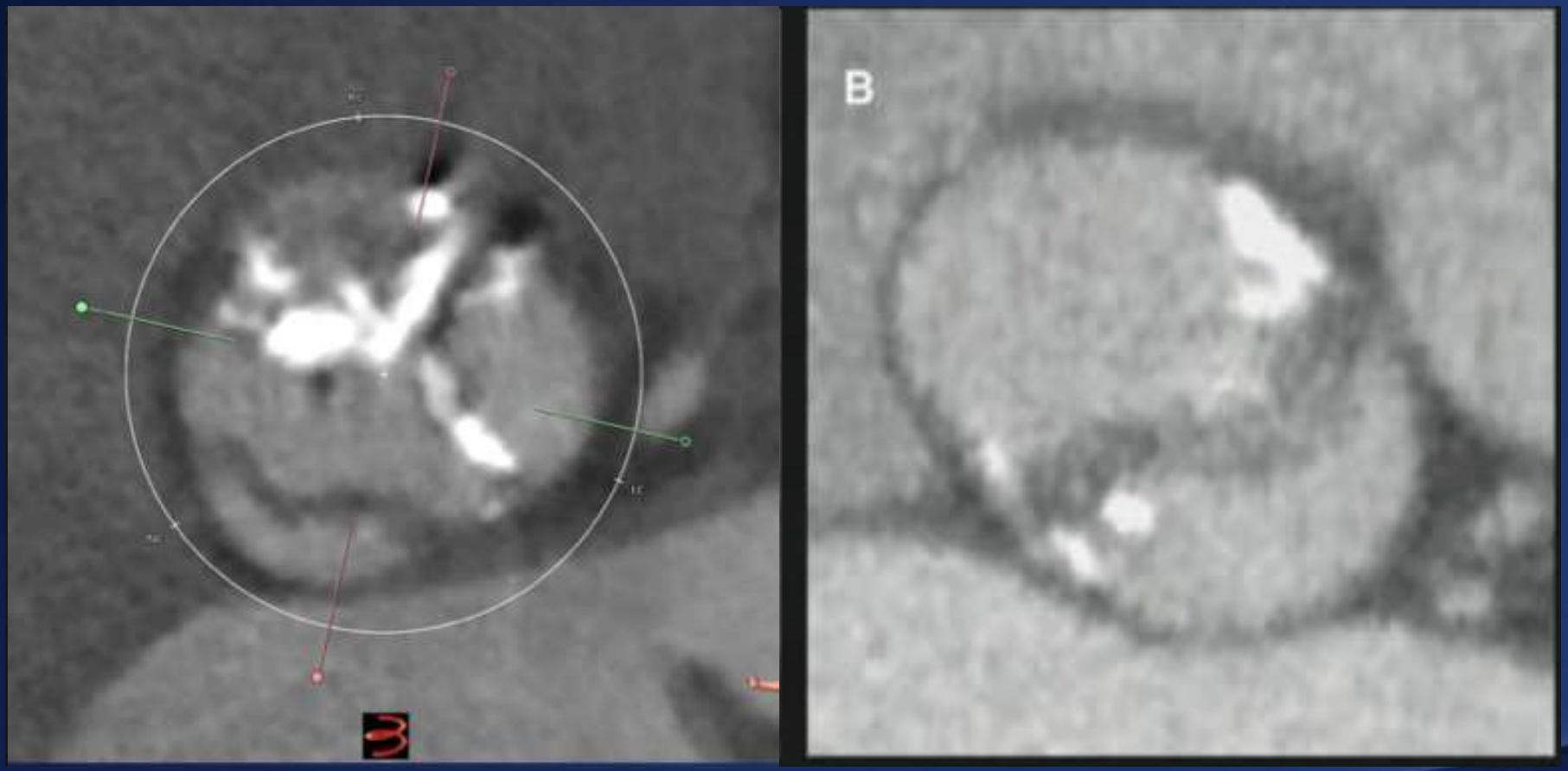
"Prohibitive" LVOT Calcification
No Clinical Equipose with SAVR





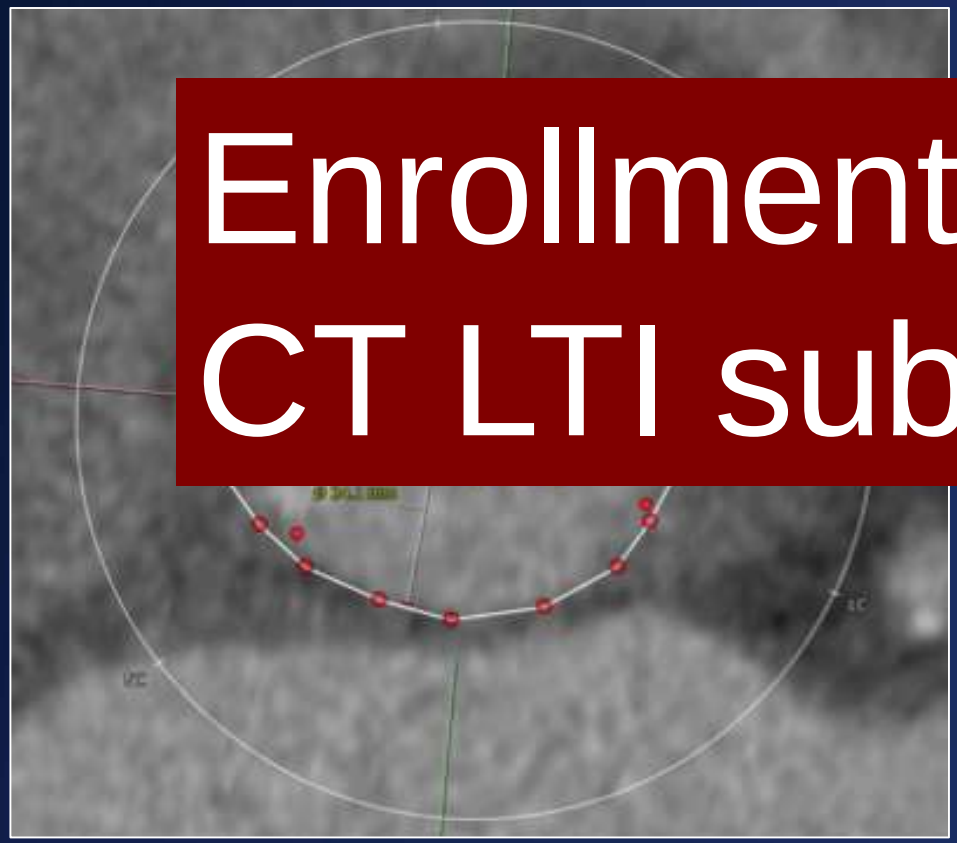
Low Risk Exclusion Criteria: What's New?

Bicuspid Aortic Valve Excluded



What is the Same with the US IDE Trials?

Best Practices



Enrollment Ended in CT LTI substudy

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  - Aortography
- Post dilation for AR
- Early Discharge

Summary

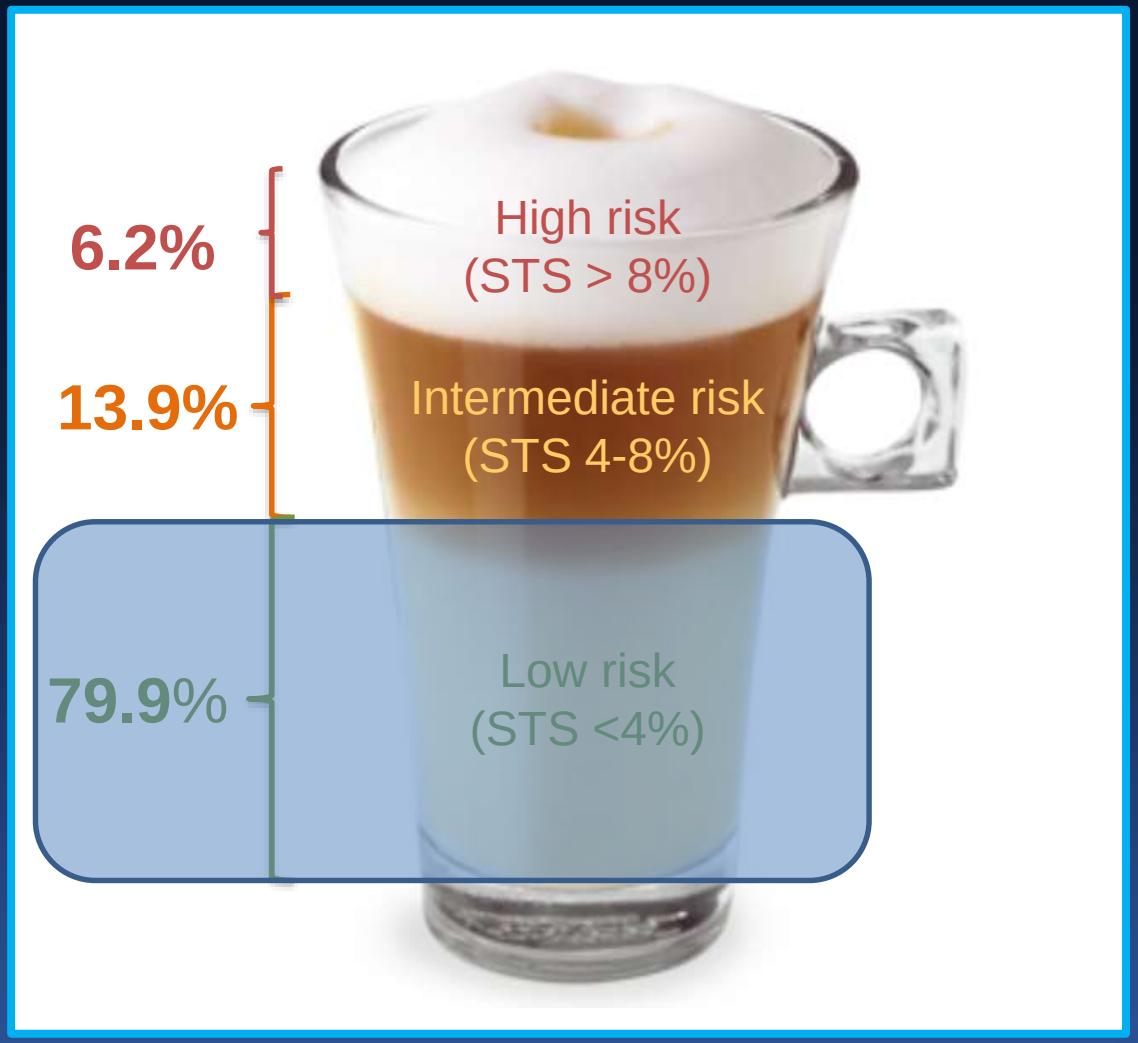
- Arguably, this will be the last RCT with surgery in the TAVR portfolio for aortic stenosis patients – and will likely have the most profound implications for clinical care
- Communications within the Heart Team remains essential due to the simple fact that not all patients are optimal patients for TAVR (e.g., calcium, complex bicuspid, coronary artery disease and location)
- There is simply no room for error in Low Risk TAVR patients – meticulous care planning and anticipation of complications

Spring 2019

- Anticipated first data presentation ACC2019 by Dr. Michael Reardon

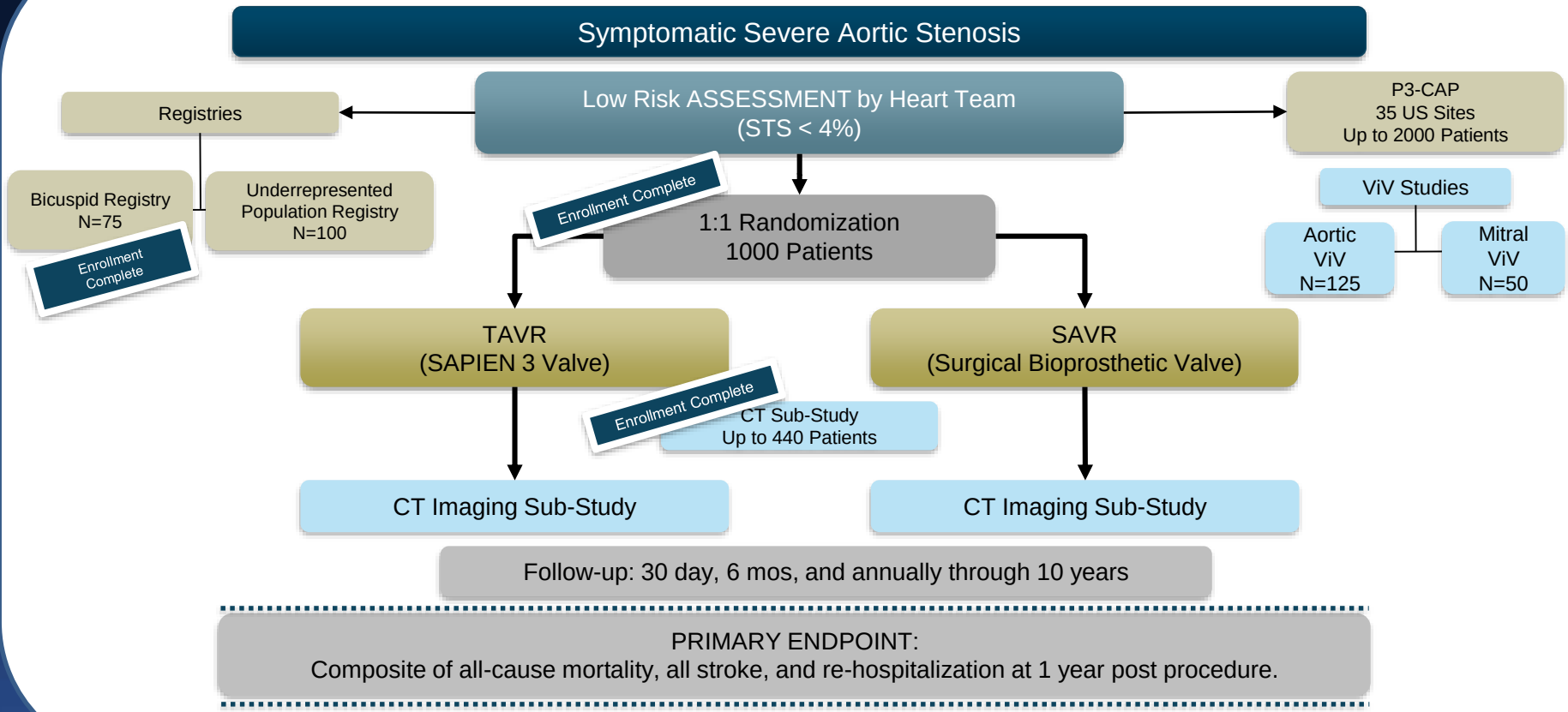
STS database 2002-2010

(141,905 pts)



PARTNER 3 Low-Risk Trial

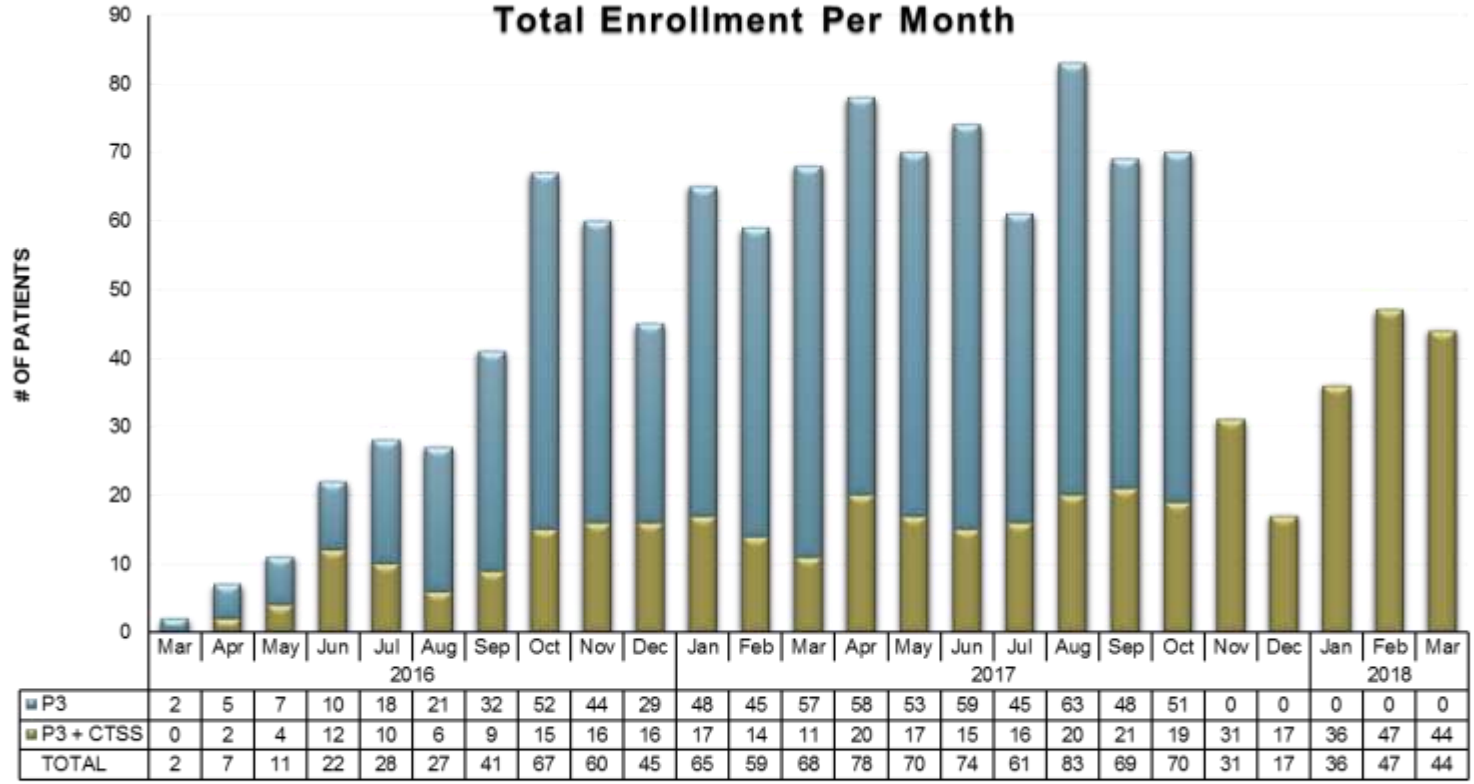
Study Design



Co - PIs: Martin B. Leon, MD and Michael J. Mack, MD

PARTNER 3 Low-Risk Trial

Enrollment Cadence



	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec	Jan	Feb	Mar
	2016										2017												2018		
P3	2	5	7	10	18	21	32	52	44	29	48	45	57	58	53	59	45	63	48	51	0	0	0	0	0
P3 + CTSS	0	2	4	12	10	6	9	15	16	16	17	14	11	20	17	15	16	20	21	19	31	17	36	47	44
TOTAL	2	7	11	22	28	27	41	67	60	45	65	59	68	78	70	74	61	83	69	70	31	17	36	47	44

Primary Analysis: 1000 Patients enrolled March 25, 2016 – October 26, 2017

CT Imaging Sub-study: 435 Patients enrolled April 20, 2016 – March 16, 2018

PARTNER 3 Low-Risk Trial

Inclusion Criteria

Severe, Calcific Aortic Stenosis:

- AVA ≤ 1.0 cm^2 or AVA index ≤ 0.6 cm^2/m^2
- Jet velocity ≥ 4.0 m/s or mean gradient ≥ 40 mmHg **AND**
  - NYHA Functional Class ≥ 2 **OR**
  - Positive ETT **OR**
  - Asymptomatic with LVEF < 50%

Low Risk:

- Determined by multi-disciplinary Heart Team
- STS < 4%

Concomitant Procedures

- Same day or staged concomitant PCI allowed if approved and planned during case review

PARTNER 3 Low-Risk Trial

Primary Endpoint (safety and effectiveness)

At 1 year, composite of:

- All-cause mortality
- All stroke
- Rehospitalization

Non-inferiority trial design:

- 90% power (N=1000)
- NI margin = 6%

PARTNER 3 Low-Risk Trial
Key Secondary Endpoints

- Acute kidney injury
- Bleeding
- New-onset AF
- New Permanent pacemakers
- 6-minute walk distance
- QOL assessments (KCCQ)
- Cost-effectiveness (economic substudy)
- Hemodynamic changes and PVL (echo core lab)
- LOS (ICU and hospitalization)

PARTNER 3 Low-Risk Trial

Final Thoughts

- "Real World" low-risk AS study population – few exclusions
- Rigorous trial design with meaningful 1^{ry} endpoint and numerous important 2^{ry} endpoints (including QoL and health economics)
- Your
- 10-y
- Important sub-studies and registries – serial CTAs (valve leaflet thickening/motion), bicuspid valve disease, under-represented populations, and aortic/mitral ViV

THE FINAL FRONTIER!

PARTNER 3 Low-Risk Trial

Final Thoughts

- "Real World" low-risk AS study population – few exclusions
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PRIMARY ENDPOINT RESULTS AT ACC 2019!

cuspid valve disease, under-represented populations, and aortic/mitral ViV

2018 euroPCR

Longevity of Transcatheter and Surgical Bioprosthetic Aortic Valves in Patients with Severe Aortic Stenosis and Lower Surgical Risk

Lars Sondergaard, MD, DMSc

Professor of Cardiology

Rigshospitalet, Copenhagen, Denmark

- On behalf of the NOTION trial investigators

EAPCI European Society of Cardiology PCR

Nordic Aortic Valve Intervention Trial
the NOTION trial

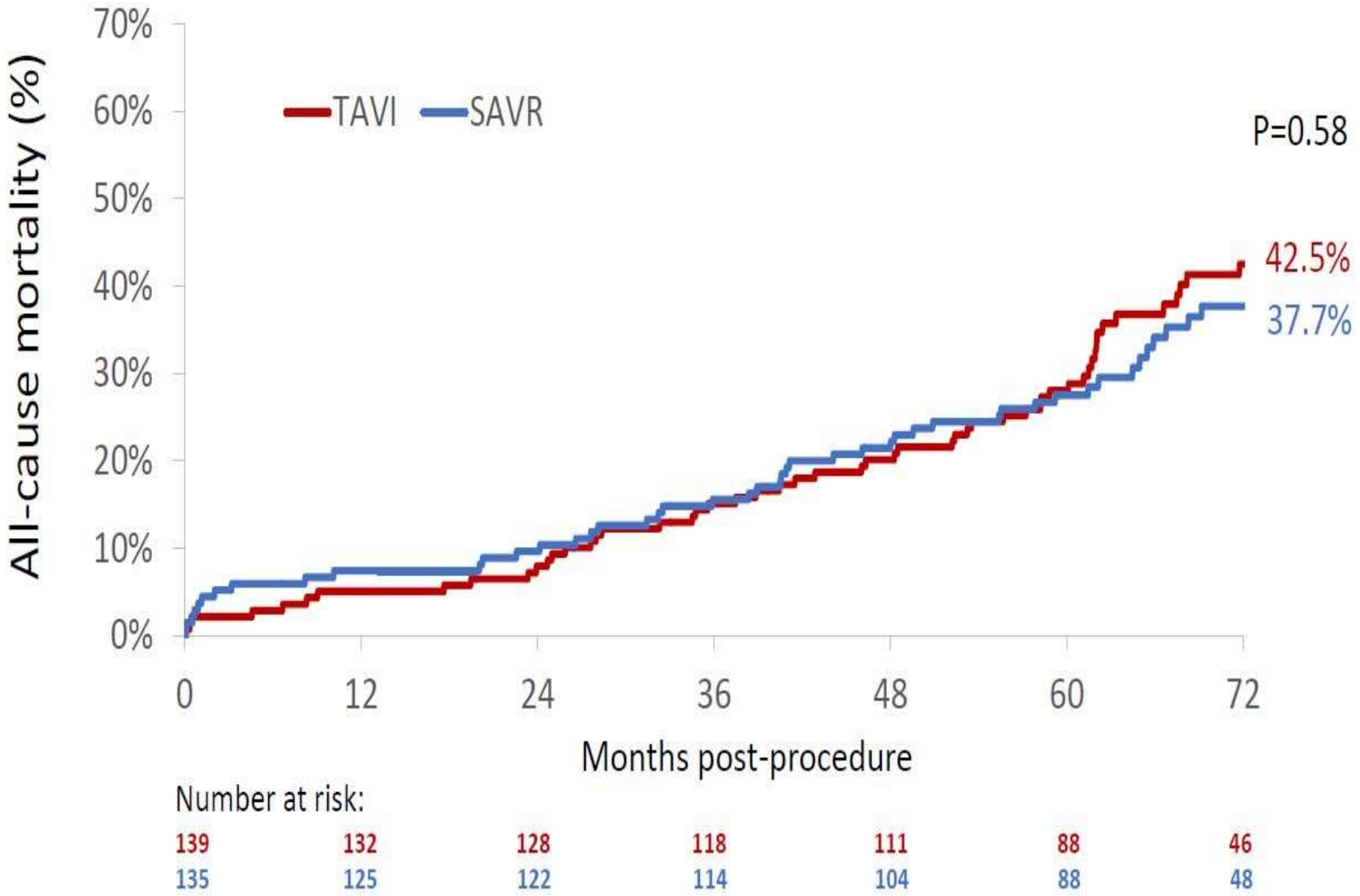
Objective:	To compare TAVI vs. SAVR in lower risk patients ≥70 years
Primary outcome:	Composite rate of all-cause mortality, stroke or myocardial infarction at 1 year (VARC II-defined)
Secondary outcomes:	Safety, efficacy, and echocardiographic outcomes (VARC II-defined)
Design:	Prospective, multi-centre, non-blinded, randomised trial
Enrollment period:	December 2009 - April 2013

The NOTION Trial
Baseline demographics*

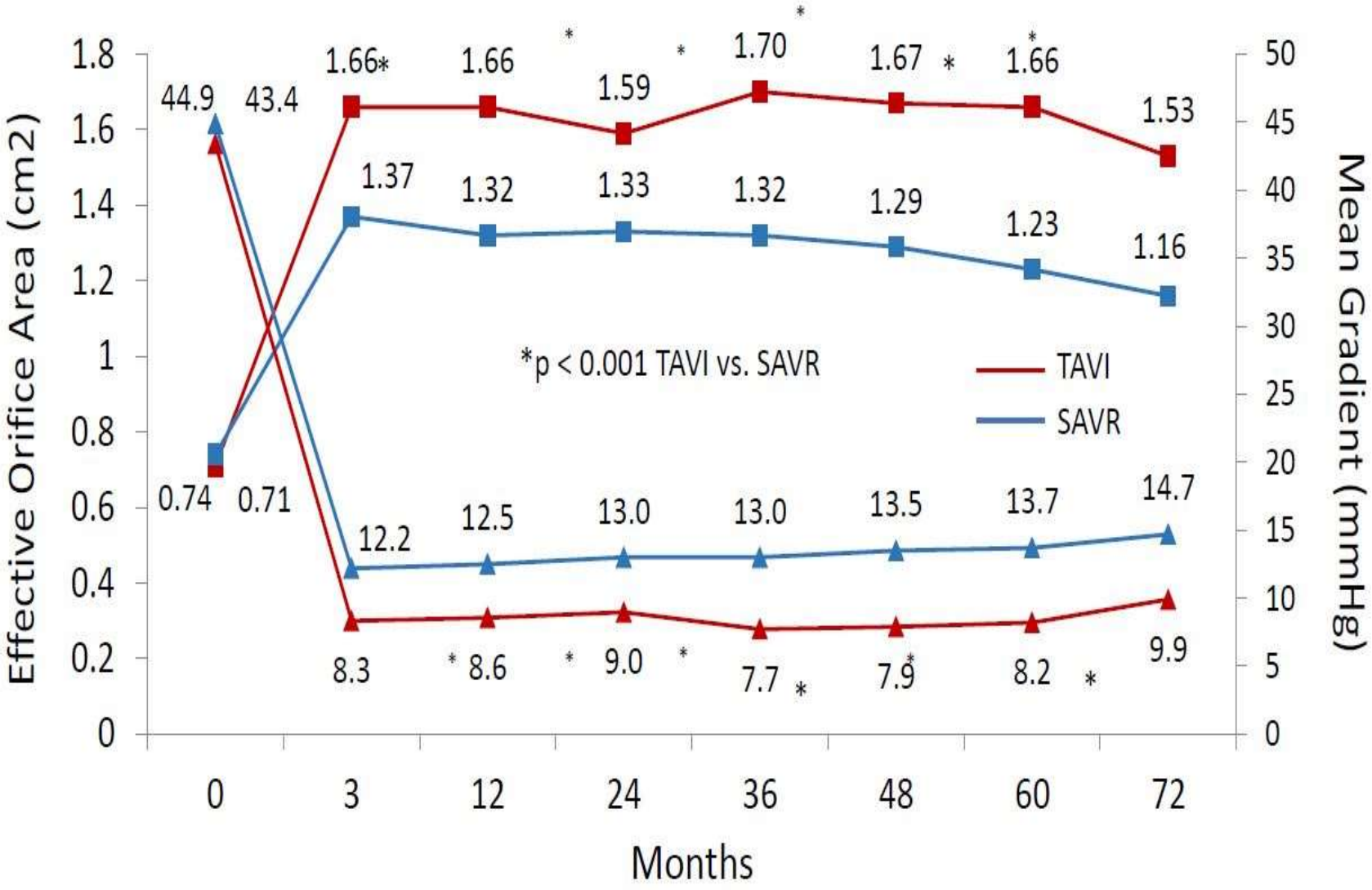
Characteristic, % or mean ± SD	Transcatheter N=145	Surgical N=135	p-value
Age (yrs)	79.2 ± 4.9	79.0 ± 4.7	0.71
Male	53.8	52.6	0.84
Society of thoracic surgeon's score (STS)	2.9 ± 1.6	3.1 ± 1.7	0.30
Logistic EuroSCORE	8.4 ± 4.0	8.9 ± 5.5	0.38
NYHA III or IV	48.6	45.5	0.61
Diabetes	17.9	20.7	0.55
Peripheral vascular disease	4.1	6.7	0.35
Prior stroke	6.2	9.6	0.29
Chronic obstructive pulmonary disease	11.7	11.9	0.97
Creatinine > 2 mg/dl	1.4	0.7	>0.99
Prior myocardial infarction	5.5	4.4	0.68
Prior percutaneous coronary intervention	7.6	8.9	0.69

*Intention-to-treat population

The NOTION Trial
All-cause mortality



The NOTION Trial
Aortic valve performance



The NOTION Trial
Structural valve deterioration

	TAVI	SAVR
Structural valve deterioration		
Moderate haemodynamic SVD	3.6%	23.7%
Severe haemodynamic SVD	0.7%	3.0%