AP Valve
Seoul, August 9, 2018

TAVI Will Be a New Standard Even for Low-Risk Patients

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Financial Disclosures

Physician Name	Company/Relationship
Speaker Bureau/Advisory Board:	Medtronic: C, SB, AB, OF LivaNova: C, SB, AB Highlife: AB, SB Boston Scientific: C, SB, AB Millipede: SB, C Pipeline: SB,C
Equity Interest:	InSeal Medical: E, AB, Valtech: E, SB, Claret: E, AB Shockwave: E, AB Valve Medical: E, AB Mitra/Trialign E, AB, SB

Key

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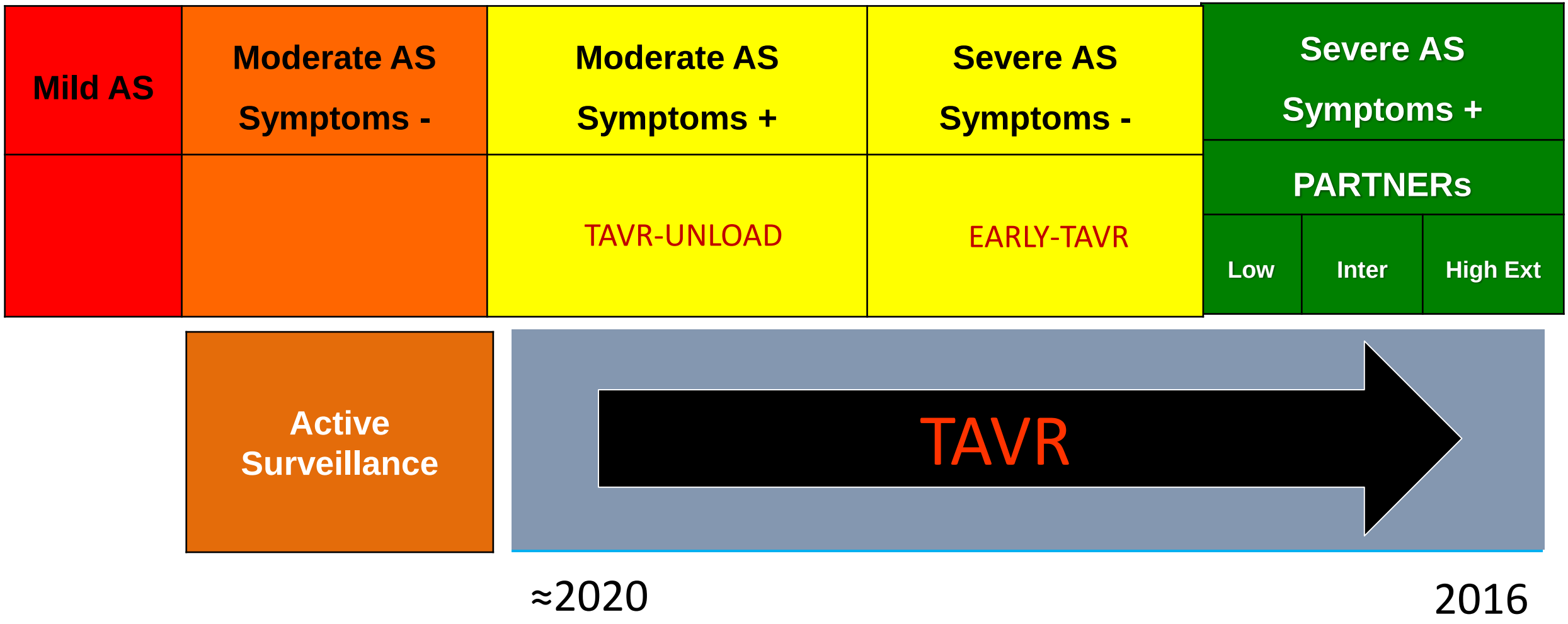
Aortic Stenosis Redefined:
Functional Classification



All things being equal, less-invasive therapies will always reign supreme!

If TAVR = Surgery,
TAVR will become the
"accepted" therapy for AS!

Where Are We Today

The tremendous momentum behind transcatheter valve therapies continues to build, with many major accomplishments in the past few years

- Regulatory approval and guideline changes for intermediate risk patients in Europe and the US
- Initiation of multiple randomized trials for the continued expansion of TAVI indications
- Regulatory approval for iterative device designs (Lotus Edge, 34 mm Evolut R, Evolut PRO)
- Publication of new randomized data on cerebral embolic protection (SENTINEL)

TAVI is clearly reaching new patient populations, and as this happens, both technology and technique continue to iterate and improve.

Presentation Overview

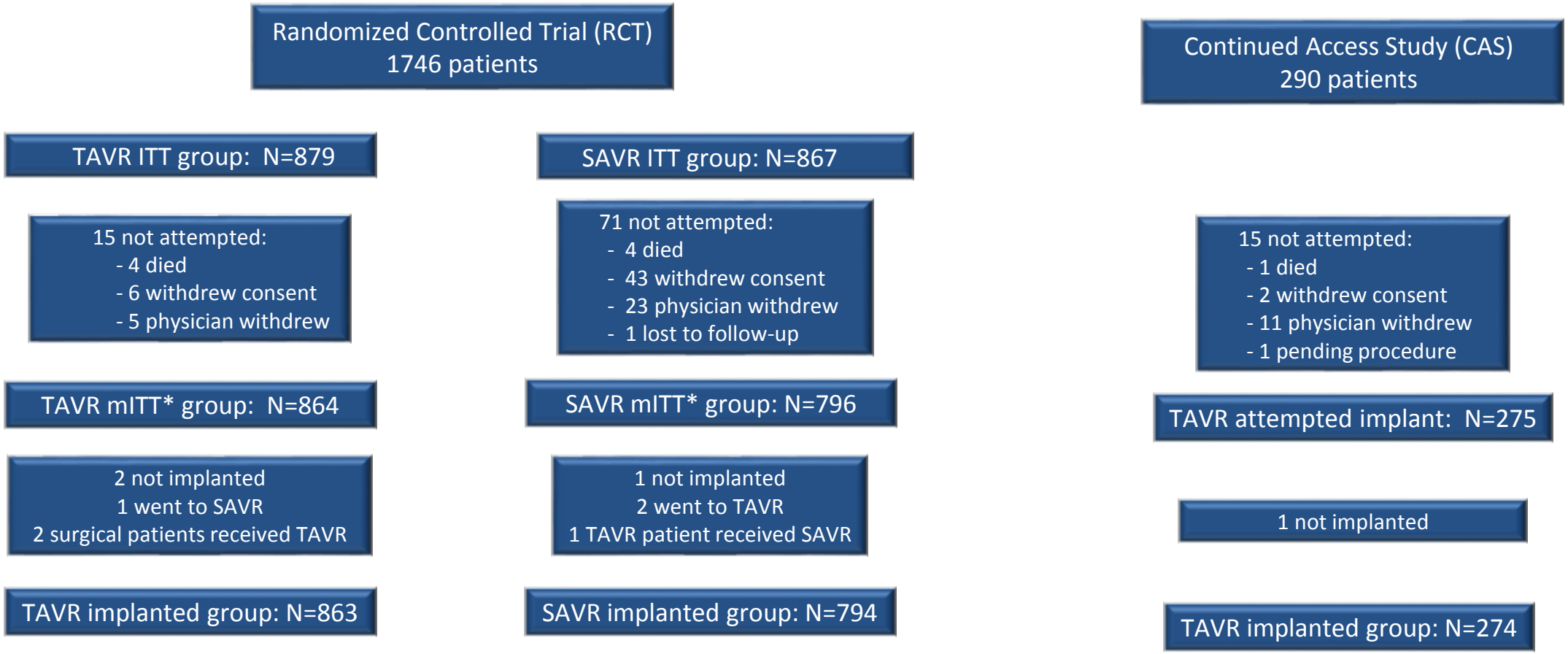
This presentation will demonstrate how TAVI will likely overtake SAVR as the new standard, even for low risk patients

- Contemporary data suggests that TAVI is at least as safe and effective, if not better than SAVR
- There are few remaining questions that will become increasingly important as TAVI is introduced into lower risk patients
- Initiation of randomized low risk trials are justified, with first results expected in early 2019

TAVR vs SAVR Data

TAVI VS SAVR Data
SURTAVI

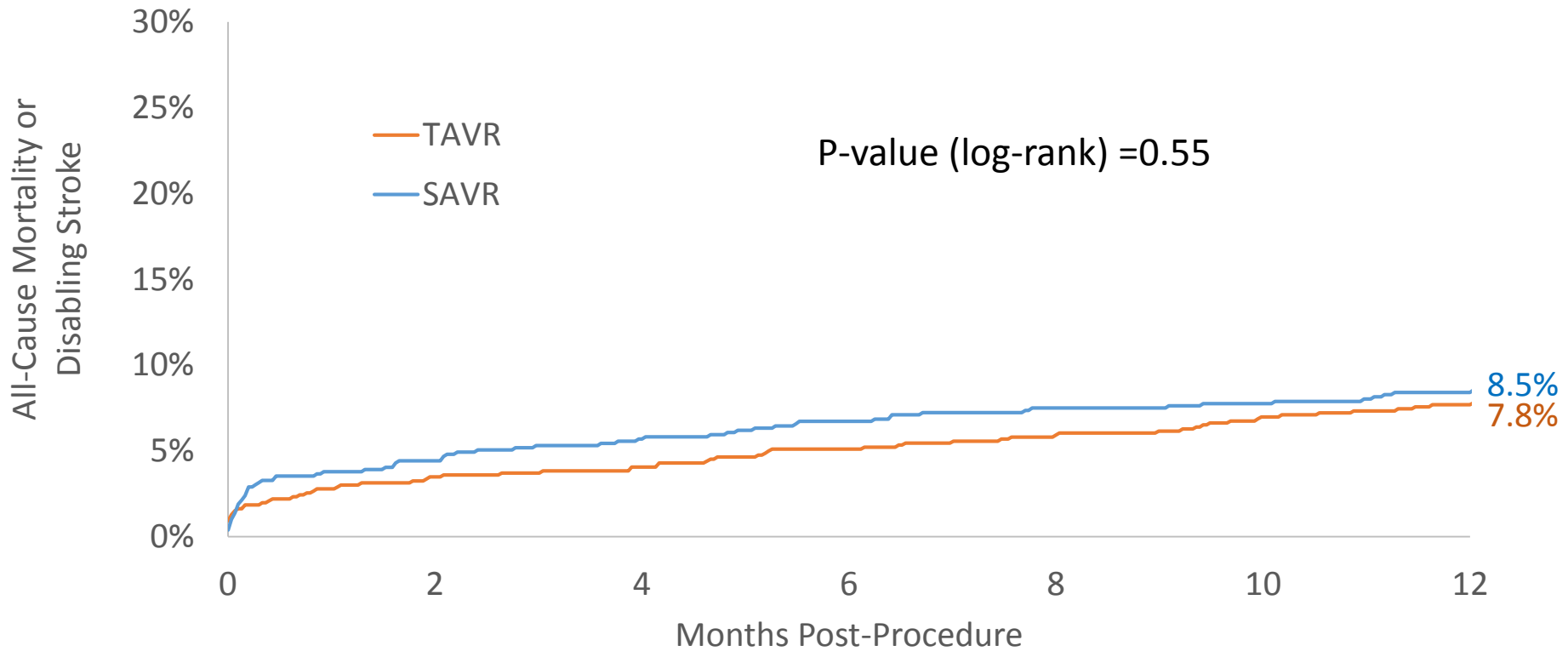
- *The SURTAVI trial randomized 1,660 intermediate risk patients to SAVR or TAVI with CoreValve or Evolut R*
- *The non-randomized continued access study (SURTAVI CAS) added an additional 275 mostly Evolut R patient*



[1]Van Meighem et al., presented at TCT 2017

TAVI VS SAVR Data
SURTAVI

- ***Despite excellent SAVR results, the SURTAVI demonstrated that TAVI with the self-expanding Evolut R or CoreValve has similar outcomes compared to SAVR in patients at intermediate surgical risk***

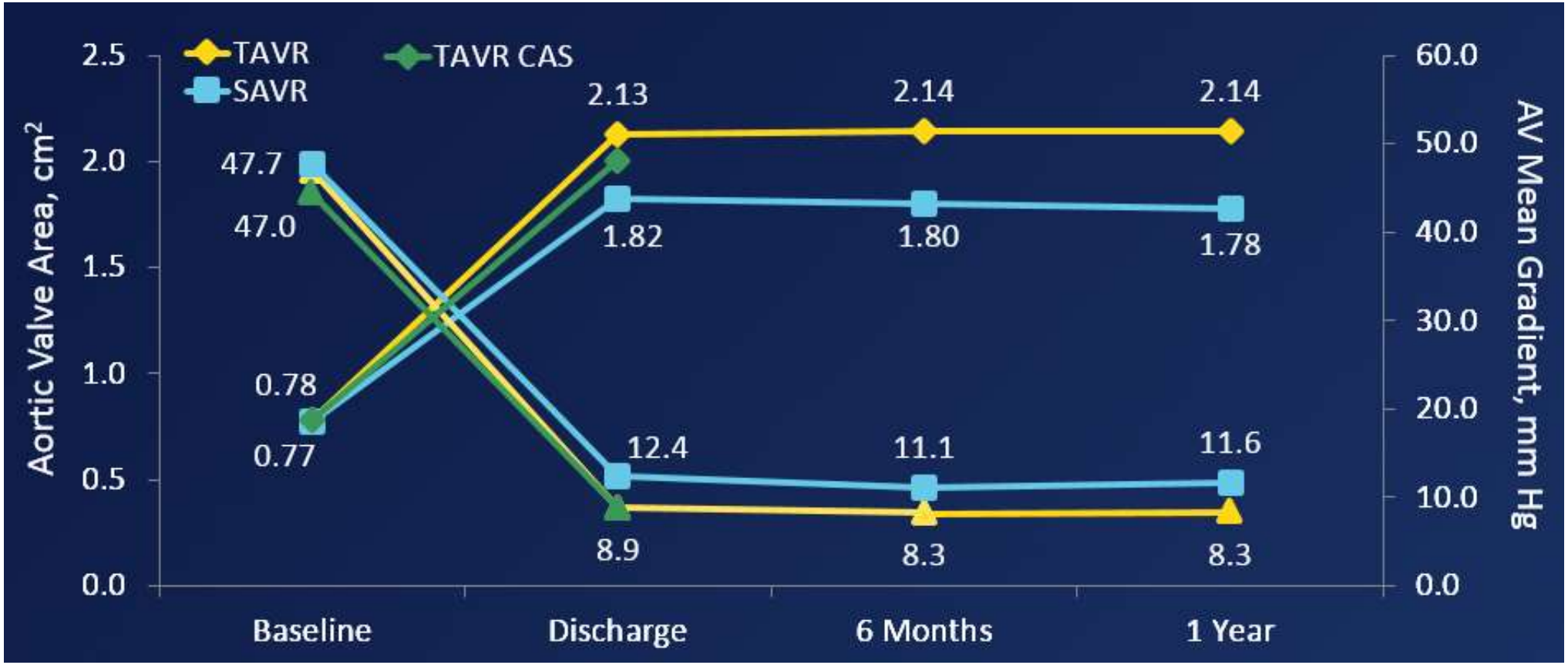


[1]Van Meighem et al., presented at TCT 2017

TAVI VS SAVR Data

SURTAVI

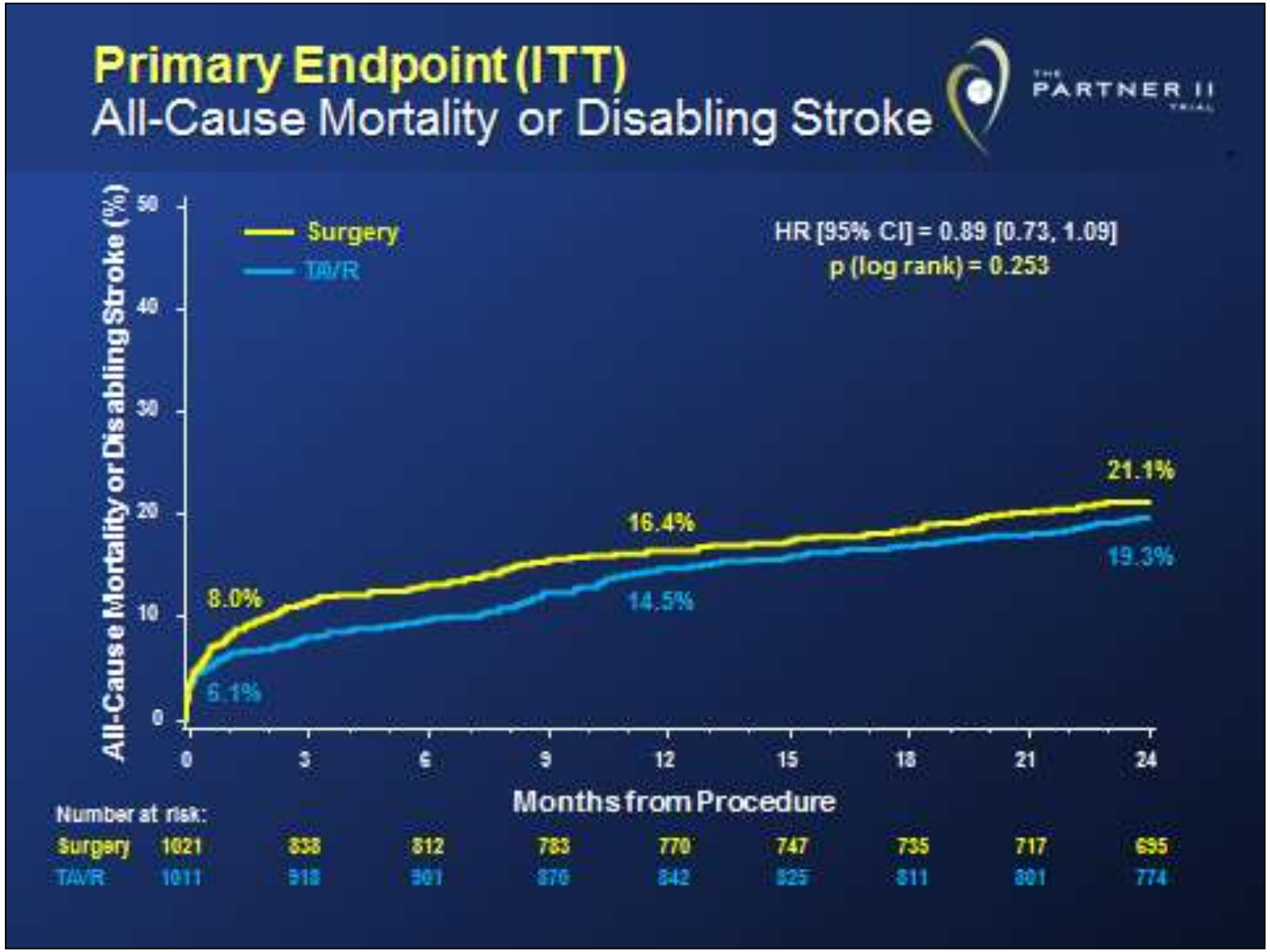
- ***Additionally, the SURTAVI trial found that TAVI with CoreValve or Evolut R has superior hemodynamic outcomes across all follow up visits out to 1 year (P<0.001)***
- ***The SURTAVI CAS study also demonstrated excellent hemodynamic outcomes***



[1]Van Meighem et al., presented at TCT 2017

TAVI VS SAVR Data
PARTNER 2A

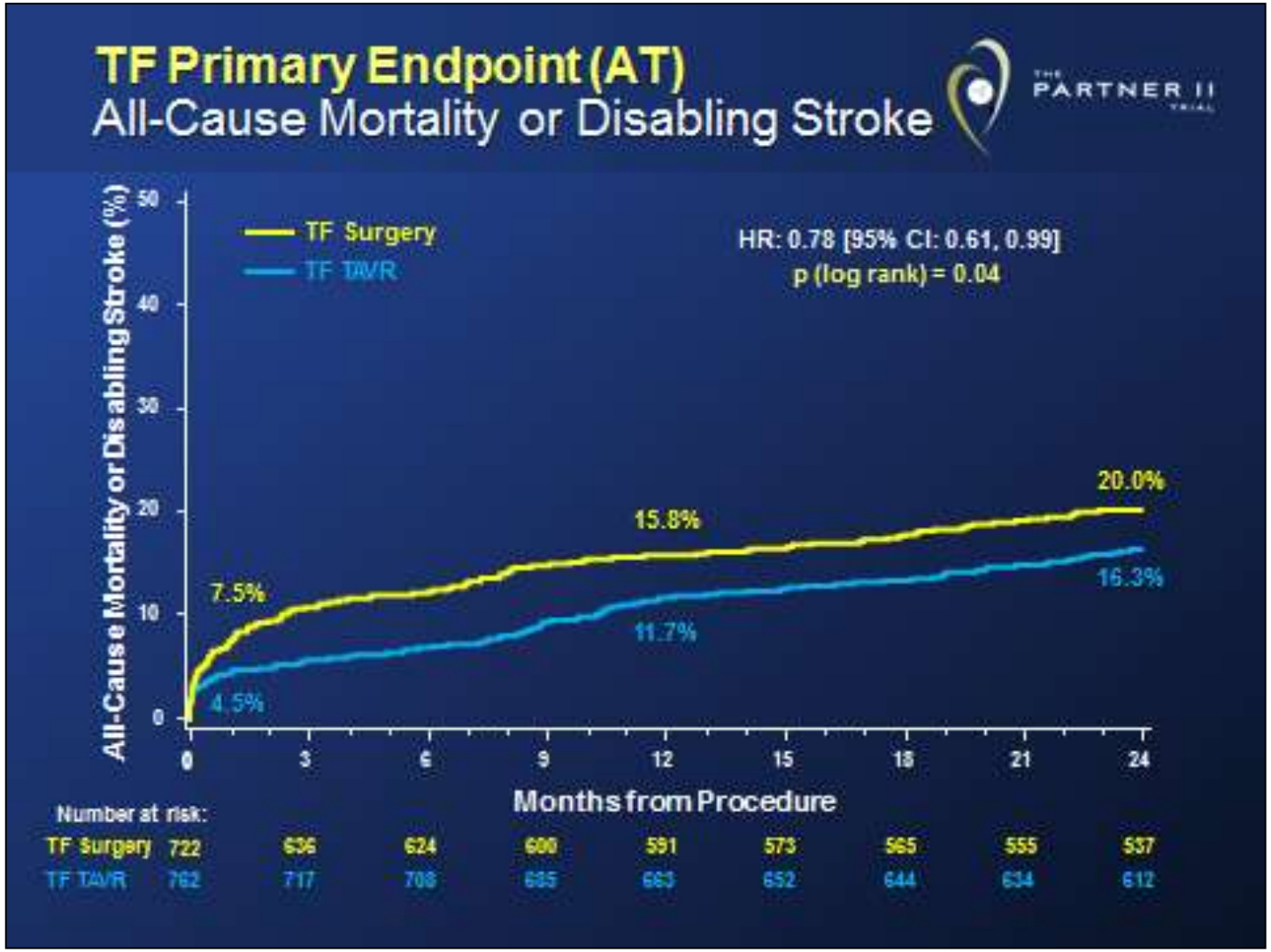
- ***The PARTNER 2A trial results showed that TAVI with Sapien XT was non-inferior to SAVR for the primary endpoint of all-cause mortality or disabling stroke at 2 years***



[1]Smith et al., presented at ACC 2016

TAVI VS SAVR Data
PARTNER 2A

- ***This study also generated convincing evidence that transfemoral TAVR provides an outcome advantage compared to SAVR to intermediate risk patients***
- ***In the as-treated population, TF TAVR significantly reduced all-cause mortality or disabling stroke vs. surgery (p = 0.04)***



[1]Smith et al., presented at ACC 2016

TAVI VS SAVR Data
PARTNER S3i

- *The PARTNER 2 S3i study matched TAVI with Sapien 3 in a non-randomized approach to the SAVR arm from the PARTNER 2 trial*
- *Although concerns exist with the comparison methods, TAVI with Sapien 3 performed well compared to SAVR*

Events (%)	30 Days		1 Year	
	TAVR	Surgery	TAVR	Surgery
Death				
All-cause	1.1	4.0	7.4	13.0
Cardiovascular	0.9	3.1	4.5	8.1
Neurological Events				
Disabling Stroke	1.0	4.4	2.3	5.9
All Stroke	2.7	6.1	4.6	8.2
All-cause Death and Disabling Stroke	2.0	8.0	8.4	16.6

*Unadjusted results

[1]Smith et al., presented at ACC 2016

TAVI VS SAVR Data
NOTION

- ***The NOTION trial was the first to randomize lower risk patients to either TAVI or SAVR***
- ***Patients receiving TAVI with CoreValve (N=145) were compared to SAVR (N=135) and six year results have recently been reported***

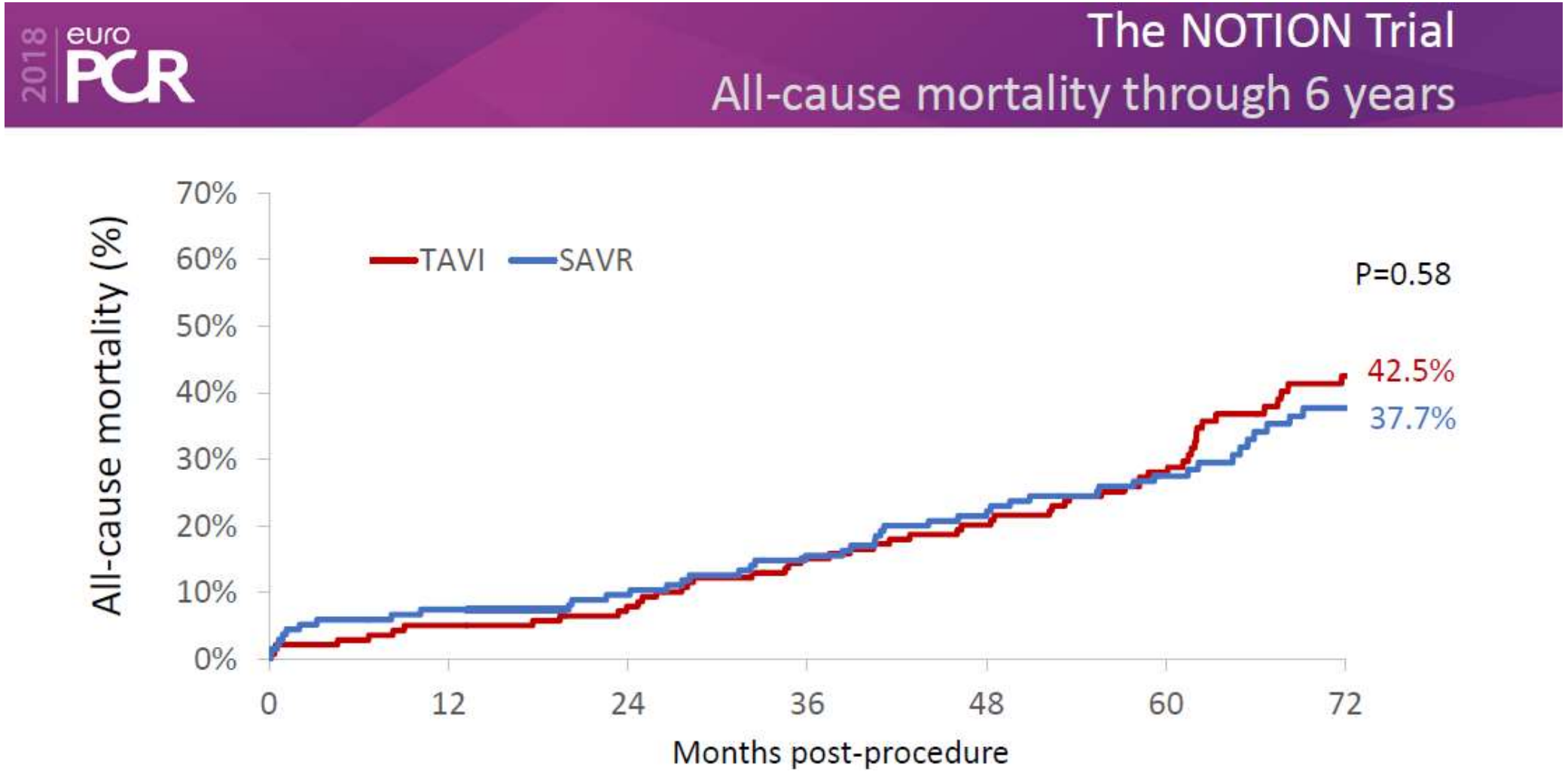
Objective:	To compare TAVI vs. SAVR in lower risk patients ≥70 years
Primary outcome:	Composite rate of all-cause mortality, stroke or myocardial infarction at 1 year (VARC II-defined)
Secondary outcomes:	Safety, efficacy, and echocardiographic outcomes (VARC II-defined)
Design:	Prospective, multi-centre,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

[1]Sondergaard et al., presented at EuroPCR 2018

TAVI VS SAVR Data

NOTION

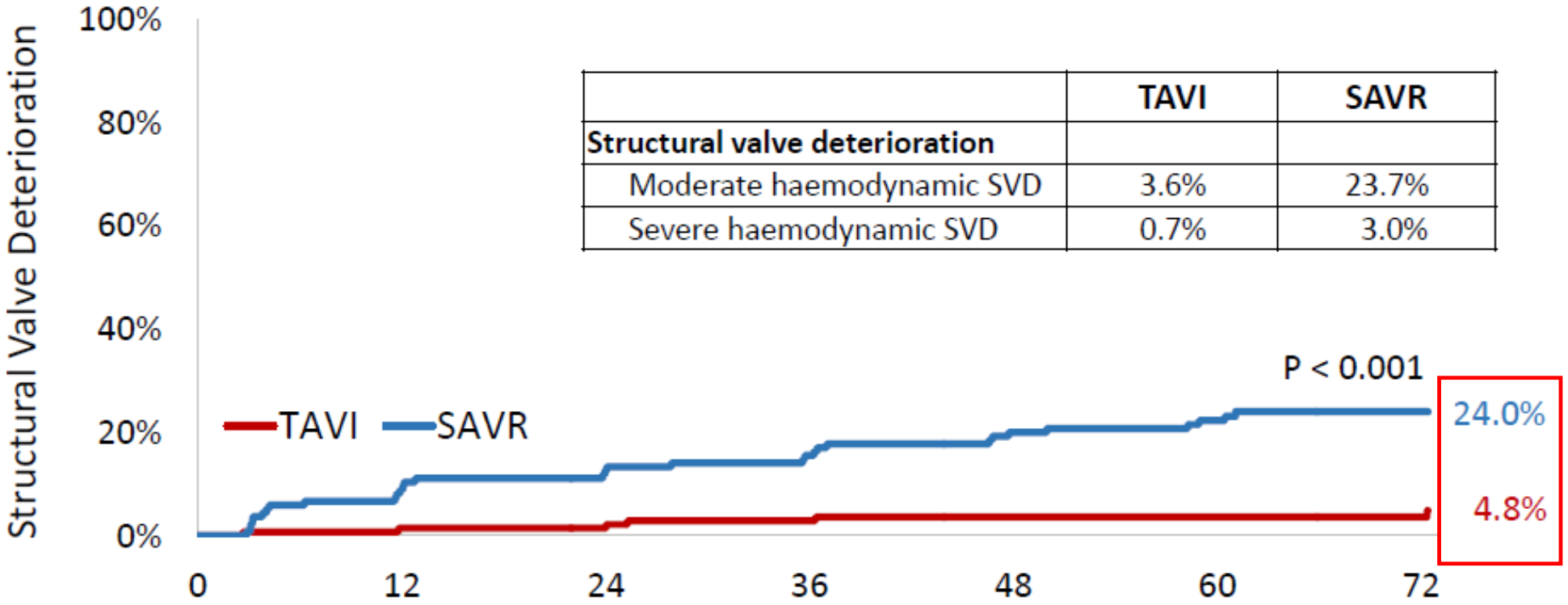
- ***The six year results demonstrated similar rates of mortality between TAVI and SAVR in the lower risk population***



[1]Sondergaard et al., presented at EuroPCR 2018

TAVI VS SAVR Data
NOTION

- ***Additionally, when using the NOTION data to focus on important long-term outcomes, TAVI performed exceptionally well***
- ***TAVI with CoreValve had significantly better hemodynamic outcomes at all follow-ups and which lead to less structural valve deterioratio***

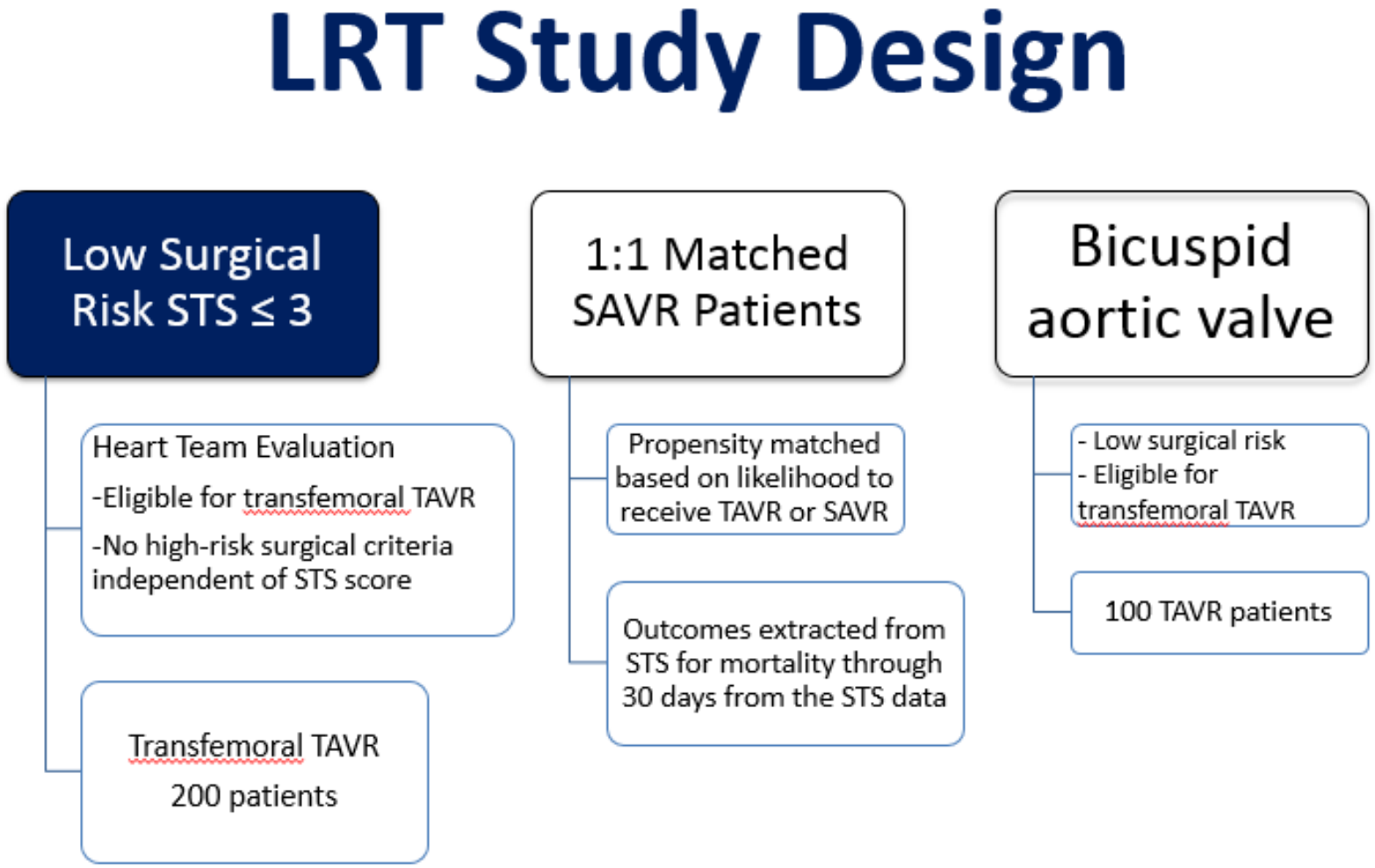


	TAVI	SAVR
Structural valve deterioration		
Moderate haemodynamic SVD	3.6%	23.7%
Severe haemodynamic SVD	0.7%	3.0%

[1]Sondergaard et al., presented at EuroPCR 2018

TAVI VS SAVR Data
LRT Clinical trial

- ***The Low Risk TAVR (LRT) trial was designed to assess the safety and feasibility of TAVI in patients with an STS score ≤3%***
- ***The study will include a propensity matched analysis to isolated SAVR patients from the STS database as well as a bicuspid aortic valve analysis***



[1]Waksmen et al., presented at CRT 2018

TAVI VS SAVR Data
LRT Clinical trial

- ***Currently, the LRT has only reported results from the TAVI arm. However, results have been promising when comparing with TAVI results from other lower risk studies***

	LRT	NOTION	SAPIEN 3 IR
Type of transcatheter valve	Edwards Sapien 3, Medtronic Evolut R or Evolut PRO	Medtronic CoreValve	Edwards Sapien 3
	N=125	N=145	N=1077
Age (years)	74.6 ± 5.7	79.2 ± 4.9	81.9 ± 6.6
STS score (%)	1.9 ± 0.5	2.9 ± 1.6	5.2 (4.3–6.3)
All-cause mortality	0.0%	2.1%	1.1%
Disabling stroke	0.0%	1.4%	1.0%
Paravalvular leak (≥ moderate)	0.0%	15.3%‡	3.8%
Major vascular complications	4.0%	5.6%	6.1%
Major and life-threatening bleeding	4.0%	11.3%	4.6%
New PPM implantation	4.8%	34.1%	10.2%

[1]Waksmen et al., presented at CRT 2018; [2]Popma et al., presented at ACC 2018

What Questions Remain with Contemporary Valves to Become the New Standard?

In the Beginning … Two Workhorse Valves with Different "Footprints" – Balloon Expandable and Self-Expanding

Edwards Lifesciences
Sapien

Medtronic
CoreValve

TAVI Technologies

Today, valve designs vary drastically and the selection process can be complicated. Not all TAVI devices are created equal, valve design will be essential in optimizing outcomes and improving lifetime management in tomorrow's patients.

Next Steps

To be the new standard, TAVI will have to treat patients who are younger, healthier, and have longer life expectancies. Reducing complications such as PVL, ppm rates, strokes, and MVC with be increasingly important.

PVL

Advanced sealing

Adaptive sizing

Frame advancements

Pacemaker Rates

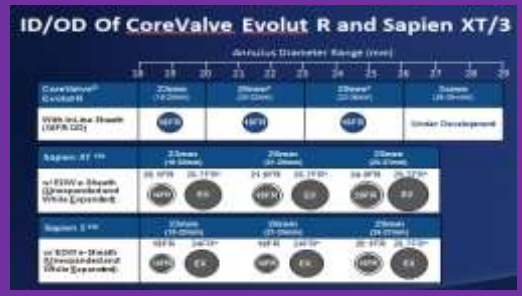
Frame advancements

Optimal Positioning through Repositionability

Stroke

Embolic Protection

Vascular Complications



Reduce Profile

Iterative Device Design

Contemporary devices have been designed to mitigate complications, simplify the procedure, and improve upon current anatomic exclusions to enable the treatment of more patients

Evolut R

Lotus

SAPIEN 3

Portico

ACURATE neo

Frame	Nitinol	Nitinol	Cobalt Chromium	Nitinol	Nitinol
PVL Management	Extended Skirt	Adaptive Seal	PET Fabric Skirt	Pericardial cuff	Pericardial skirt
Annular Range	18-30 mm	20-27 mm	16-28 mm	19-27 mm	21-27 mm
Positioning	Recapturable	Recapturable	--	Recapturable	--
Caliber	14 Fr/16 Fr equiv.	18 Fr	14 Fr / 16 Fr	18 Fr / 19 Fr	18 Fr

Next Generation Iterations

Device modifications for improved outcomes continue to roll out

Evolut PRO

Pericardial tissue wrap to enhance sealing

1 Year Results Presented at ACC 2018

SAPIEN 3 Ultra Delivery System

On-balloon design removes valve alignment step

Pusher is eliminated, reducing steps required during deployment

Lotus Edge

Depth guard to limit implant depth

Better flexibility

First results at CRT 2017

Lifetime Management:
PCI After TAVI and Valve Thrombosis/Anticoagulation

PCI After TAVR
Real World Experience

- ***In current practice, post-TAVI PCI remains an uncommon (but feasible) procedure***
- ***The option to perform post-TAVI PCI will become increasingly important in lower risk patients with longer life expectancies***

	Kerckhoff-Klinik	Segeberg Registry	UK Registry	TAVR-LM Registry
Incidence	**35 / 1,000 (3.5%)**	**17 / 296 (5.7%)**	**18 / 2,588 (0.7%)**	**9 / 6,405 (0.1%)**
ACS Indication	11.4%	37.5%	65%	78%
Time to Intervention Post-TAVR	233 ± 158 days	17.7 months (range: 1-72)	136 days (range: 1-1092)	368 days (IQR: 204-534)
Type of TAV Implanted			Not Reported	
CoreValve	29%	100%		44%
SAPIEN XT	54%			55%
JenaValve	3%			
Symetis	11%			
Portico	3%			
Procedural Success	74%	95.8%	Not Reported	100%

[1]Blumenstein, et al., *Clin Res Cardiol* 2015; 104:632-39; [2]Allali, et al., *Cardiovasc Revasc Med* 2016; epub ahead of print; [3]Snow, et al., *Int J Cardiol* 2015; 199:253-60; [4]Chakravarty, et al., *J Am Coll Cardiol* 2016; 67:951-60

Lifetime Management

Anticoagulation | Valve Thrombosis

Valve thrombosis has come to the forefront with studies reporting

- *Reduced leaflet motion in 22 of 55 (40%) patients analyzed from the PORTICO IDE Cohort (16 of 37 (40%) Portico patients, 6 of 14 (43%) Sapien XT patients, and 0 of 4 (0%) CoreValve patients).*
- ***In the pooled RESOLVE and SAVORY registry patients, reduced leaflet motion was found in 14% of patients and 7% of SAVR patients***

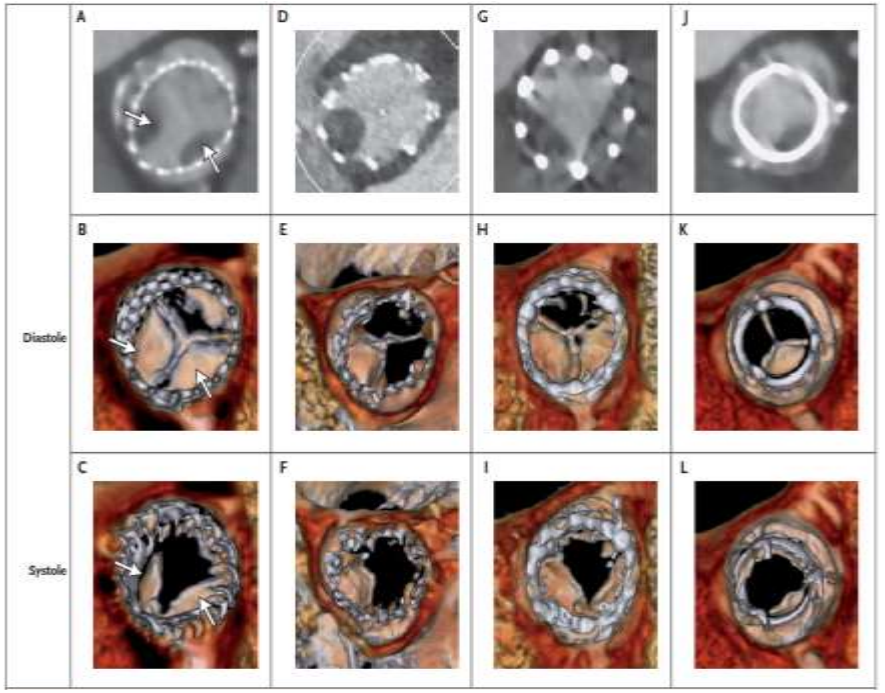
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Possible Subclinical Leaflet Thrombosis in Bioprosthetic Aortic Valves

R.R. Makkar, G. Fontana, H. Jilaihawi, T. Chakravarty, K.F. Kofoed, O. De Backer, F.M. Asch, C.E. Ruiz, N.T. Olsen, A. Trento, J. Friedman, D. Berman, W. Cheng, M. Kashif, V. Jelnin, C.A. Kliger, H. Guo, A.D. Pichard, N.J. Weissman, S. Kapadia, E. Manasse, D.L. Bhatt, M.B. Leon, and L. Søndergaard

ABSTRACT



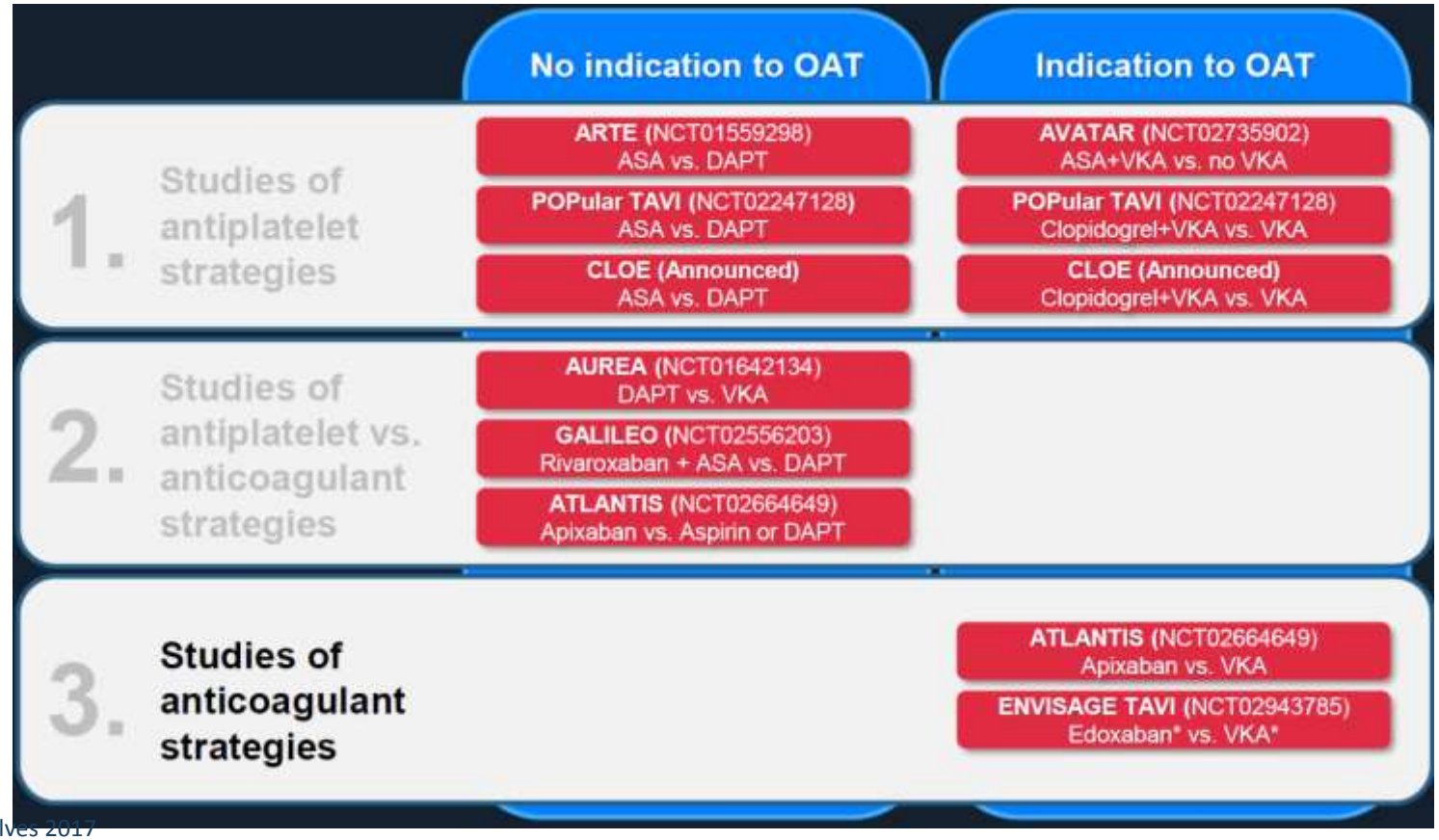
[1]Makkar, et al., *N Engl J Med.* 2015 Nov 19;373(21):2015-24

Lifetime Management

Anticoagulation

Current clinical antithrombotic therapy post-TAVR is mostly empirical and practice variation is quite high. Clinical trials are currently underway and will bring clarity and guidance on this important topic.

I predict the post TAVR Implant strategy will change and Anticoagulation will be recommended



[1]Capodanno, et al., presented at London Valves 2017

Lifetime Management: Durability

Durability
Definitions

- *In the past year there were much needed advances in providing standard definitions of valve failure and valve surveillance. As TAVR is introduced into healthier patients with longer life expectancies, the durability of the valves will become increasingly important*
- *The ESC/EATCS/EAPCI provided a consensus statement aiming to level the playing field between TAVI and SAVR which will allow a better understanding of both TAVI and SAVR durability*

Standardized definitions of structural deterioration and valve failure in assessing long-term durability of transcatheter and surgical aortic bioprosthetic valves: a consensus statement from the European Association of Percutaneous Cardiovascular Interventions (EAPCI) endorsed by the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS)

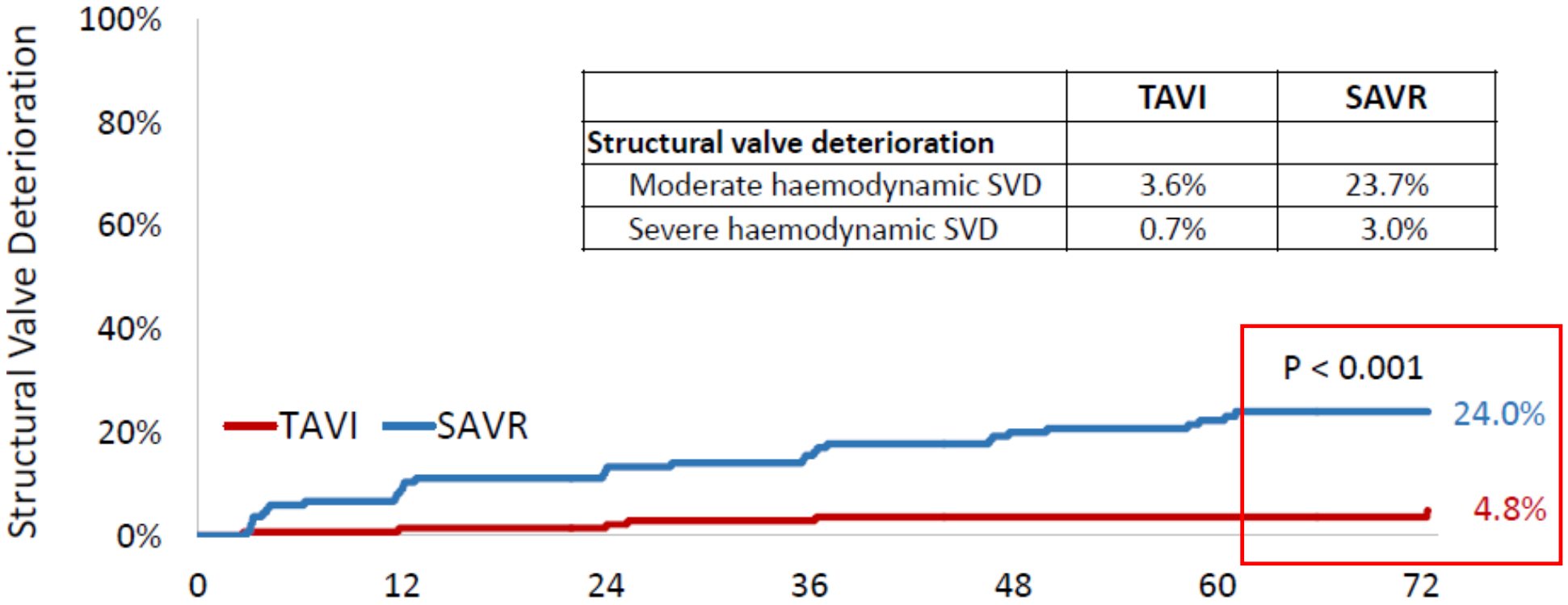
Davide Capodanno[1*†], Anna S. Petronio[2†], Bernard Prendergast[3], Helene Eltchaninoff[4], Alec Vahanian[5], Thomas Modine[6], Patrizio Lancellotti[7], Lars Sondergaard[8], Peter F. Ludman[9], Corrado Tamburino[1], Nicolò Piazza[10], Jane Hancock[3], Julinda Mehilli[11], Robert A. Byrne[12], Andreas Baumbach[13], Arie Pieter Kappetein[14], Stephan Windecker[15], Jeroen Bax[16], and Michael Haude[17]

Capodanno et al., Eur J CardioThoracSurg. 2017; 52 408-417

Durability
Long-term TAVI data

- ***Long-term clinical TAVR data is limited, however initial reports have been promising. Both the NOTION 6 year and CoreValve Extreme Risk 5 year data presented in the last year supported excellent long-term outcomes with CoreValve compared to SAVR***

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

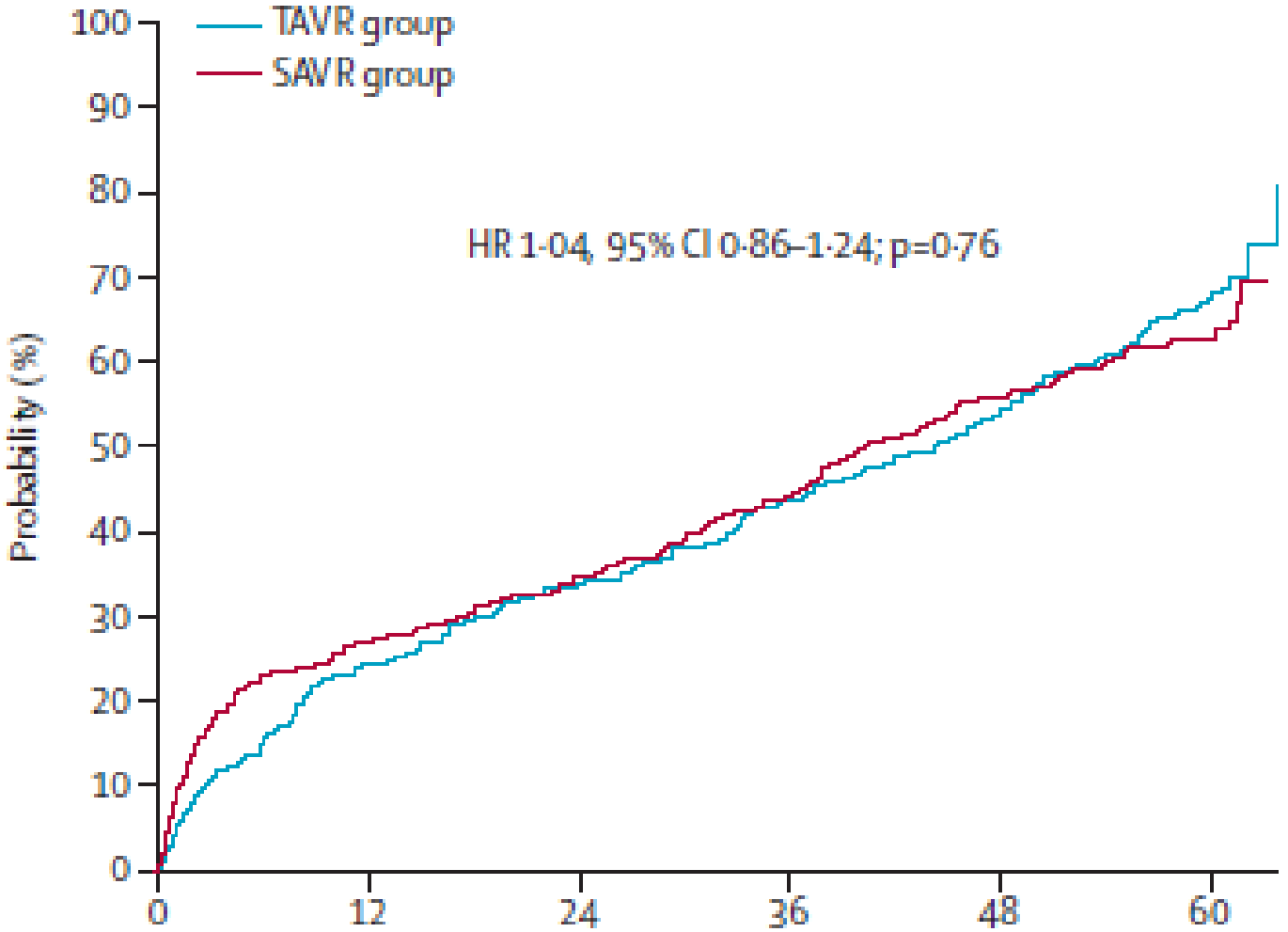


[1]Sondergaard et all., presented at EuroPCR 2018; [2]Petrossian et al., presented at ACC 2018

Durability
Long-term TAVI data

- ***The PARTNER 1 trial randomizing high risk patients to TAVI with Sapien or SAVR also showed encouraging long-term results***

Kaplan-Meier Analysis of All-Cause Mortality



[1]Sondergaard et all., presented at EuroPCR 2018; [2]Petrossian et al., presented at ACC 2018

Ongoing Low-Risk Randomized Trials

Low Risk

Ongoing Trials

Low-risk trials are currently underway and results of the Medtronic and PARTNER trials are expected in early 2019. ***I predict results will show TAVR is non-inferior or superior to SAVR.***

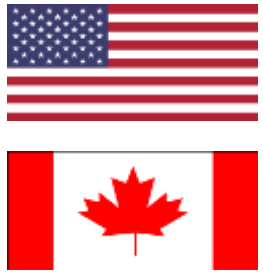
Medtronic Low Risk

N = ~1200

Up to 80 centers
Evolut R, all routes

Industry-sponsored
10-year follow-up

PARTNER 3



N = 1228

Up to 64 centers
SAPIEN 3, transfemoral

Industry-sponsored
10-year follow-up

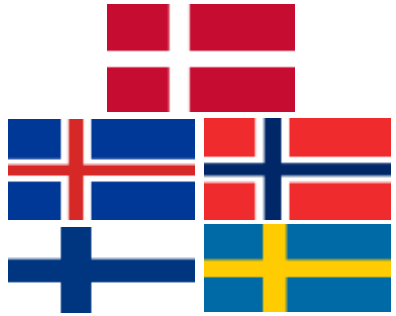
UK TAVR

N = 808

All UK TAVR centers
All valves, all routes

Publically funded
5-year follow-up

NOTION-2



N = 992

All Nordic countries
All valves, transfemoral

Physician and industry-sponsored
5-year follow-up

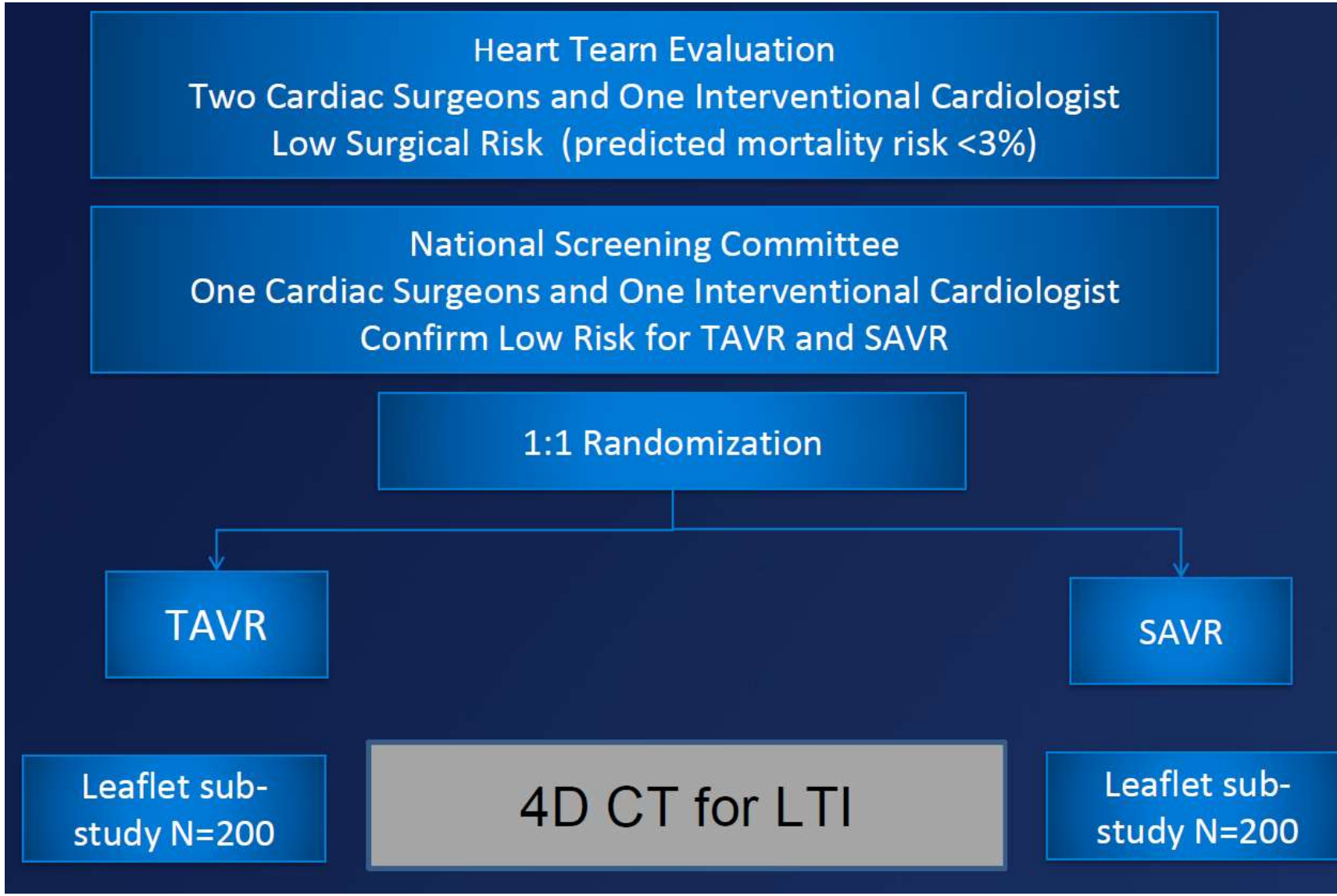
[1]Popma, presented at TCT 2016; [2]Mack, presented at TCT 2016; [3]Moat, presented at TCT 2016; [4]Sondergaard, presented at TCT 2016

Low Risk Randomized Trials

Evolut R Low Risk Randomized Clinical Trial

- ***The Evolut R Low Risk randomized clinical trial's primary objective is to demonstrate that the safety and effectiveness of the Evolut R is non-inferior to SAVR in patients at low risk for SAVR***

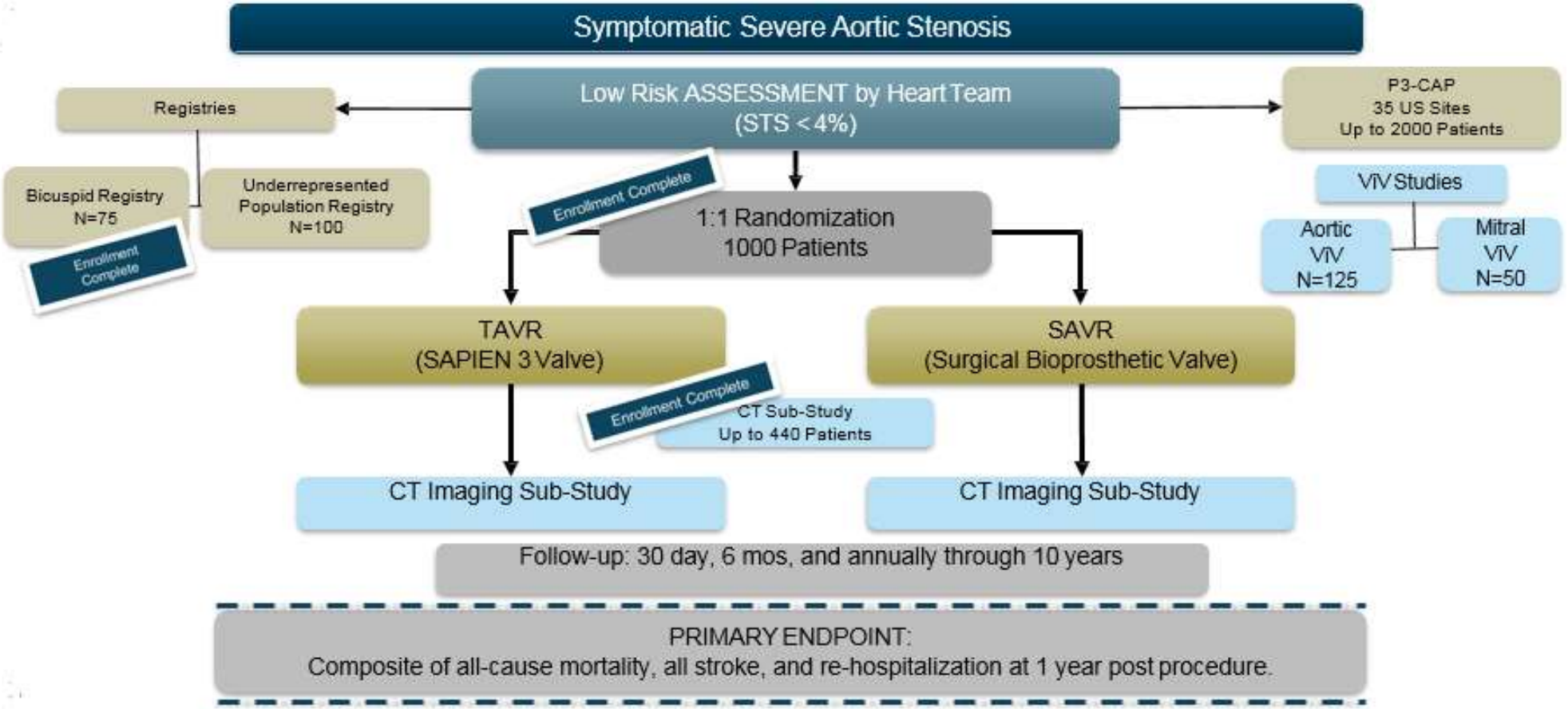
- ***The study will include 1300+ subjects and importantly will include nearly 400 subjects in a leaflet sub-study***



[1]Popma et al., presented at TVT 2018

Low Risk Randomized Trials
Partner 3 Low-Risk

- ***The PARTNER 3 Low Risk trial has a similar design and objective, also including a CT imaging sub study***



[1]Leon et al., presented at TVT 2018

Conclusion

- Contemporary data comparing TAVI and SAVR favors TAVI
- Tomorrow's patients will comprise of many of the same patients treated successfully by TAVI today, but will also likely include younger, healthier, patients with longer life expectancies.
- Avoiding complications such as paravalvular leak and optimizing lifetime management after TAVI will be increasingly important
- Initial experiences with improved techniques and next-generation technologies have demonstrated promising results in mitigating these challenges
- We excitedly await the outcomes of ongoing randomized TAVI and SAVR trials in low-risk patients, but do not be surprised if TAVI wins