TCTAP 2017
Seoul, Korea, April 25-27, 2017

TAVR for Low Risk and Younger Patients

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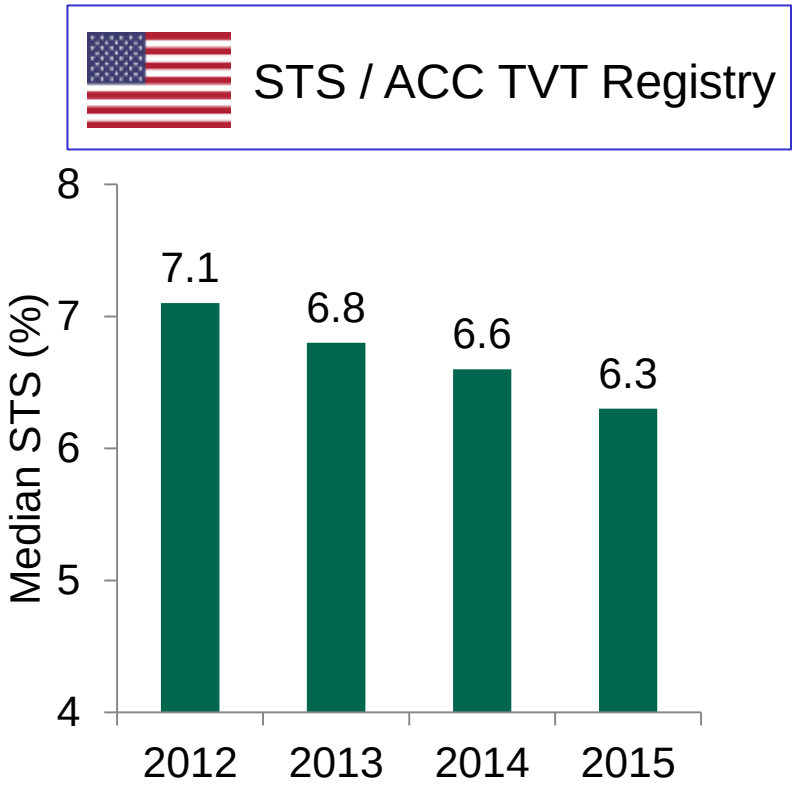
Disclosures

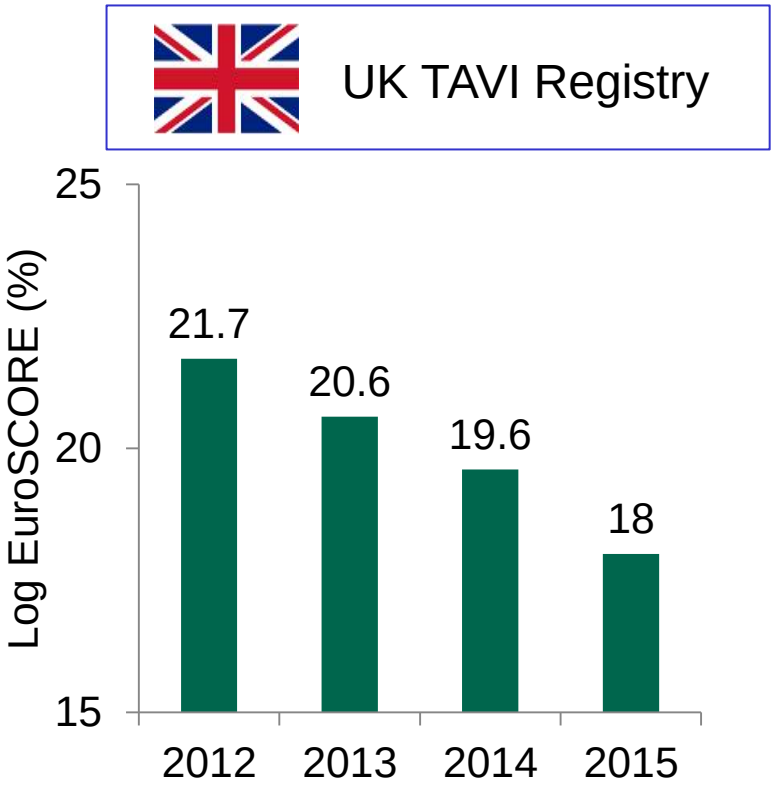
Physician name	Company	Relationship
Horst Sievert	Abbott, Ablative Solutions, Acoredis, Atrium, Biosense Webster, Bioventrix, Boston Scientific, Carag, Cardiac Dimensions, CardioKinetix, Celonova, Cibiem, CGuard, Coherex, Comed B.V., Contego, CSI, CVRx, ev3, FlowCardia, Gardia, Gore, GTIMD Medical, Guided Delivery Systems, Hemoteq, InspireMD, Kona Medical, Lumen Biomedical, Lifetech, Medtronic, Occlutech, pfm Medical, Recor, SentreHeart, Svelte Medical Systems, Terumo, Trivascular, Valtech, Vascular Dynamics, Venus Medical, Veryan	Consulting fees, Travel expenses, Study honoraria
	Cardiokinetix, Access Closure, Coherex, SMT	Stock options

Over the last 15 years

- TAVI has become a routine procedure in more than 65 countries around the world
- > 300,000 patients worldwide
- > 100,000 per year
- Annual growth rate > 20%
- In some countries more TAVIs are performed than surgical valve replacements
- Without approval and reimbursement problems TAVI would grow even faster

Trend towards lower surgical risk patients





[1]Grover, et al., *J Am Coll Cardiol* 2016; epub; [2]Moat, et al., presented at TCT 2016

What is "low risk"?

- According to "intermediate risk" trials:
  - PARTNER 2A: STS <4
  - PARTNER S3i: STS <4
  - CoreValve US Pivotal: STS <4
  - SURTAVI: STS <3

What is a "younger patient"?

- Any patient who is younger than you
- This is obviously irrespective of your age

Low Risk and Younger Patients

- High risk and old
  - Typical PARTNER I patient
- Low risk and old
  - 85 y/o, male, no comorbidities
    - Euroscore 2.7%
- High risk and young
  - 50 y/o, prior CABG, CKD, PAH, COPD, EF poor, PAD
    - Euroscore 40%
- Low risk and young
  - 50 y/o, no comorbidities
    - Euroscore 1%

What was the 30 day TAVR mortality in the "intermediate risk studies"?

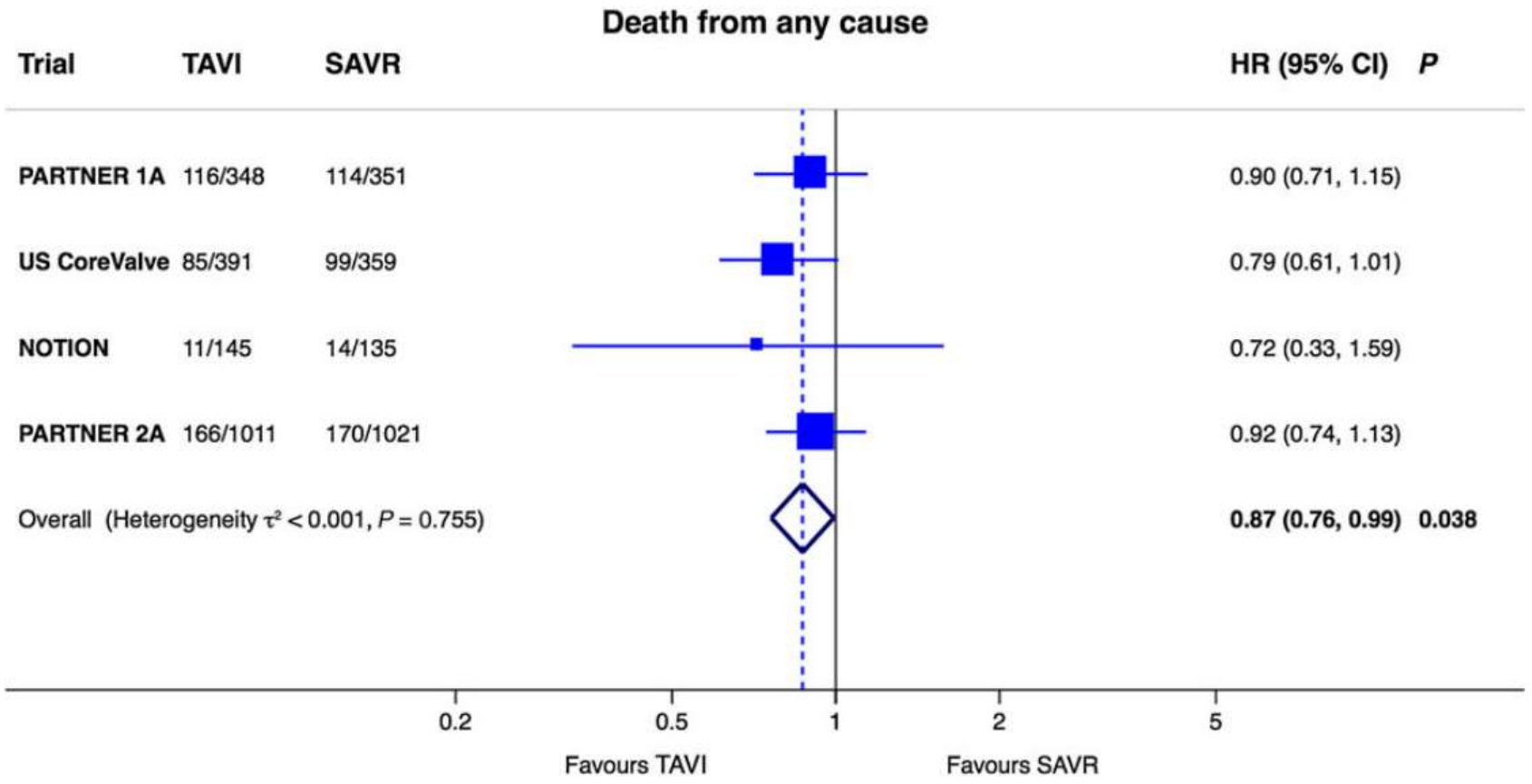
Predicted mortality ≥3 or ≥ 4

- PARTNER 2A: 3.9 %
- PARTNER S3i: 1.1 %
- CoreValve US Pivotal: 3.3 %
- SURTAVI: 2.2 %

The observed TAVR mortality in intermediate surgical risk patients was lower than the predicted surgical mortality

TAVR vs. SAVR
Meta-Analysis

- *TAVR provides a statistically significant, 13% relative risk reduction of death from any cause*
- *This is a class effect, independent of valve type*

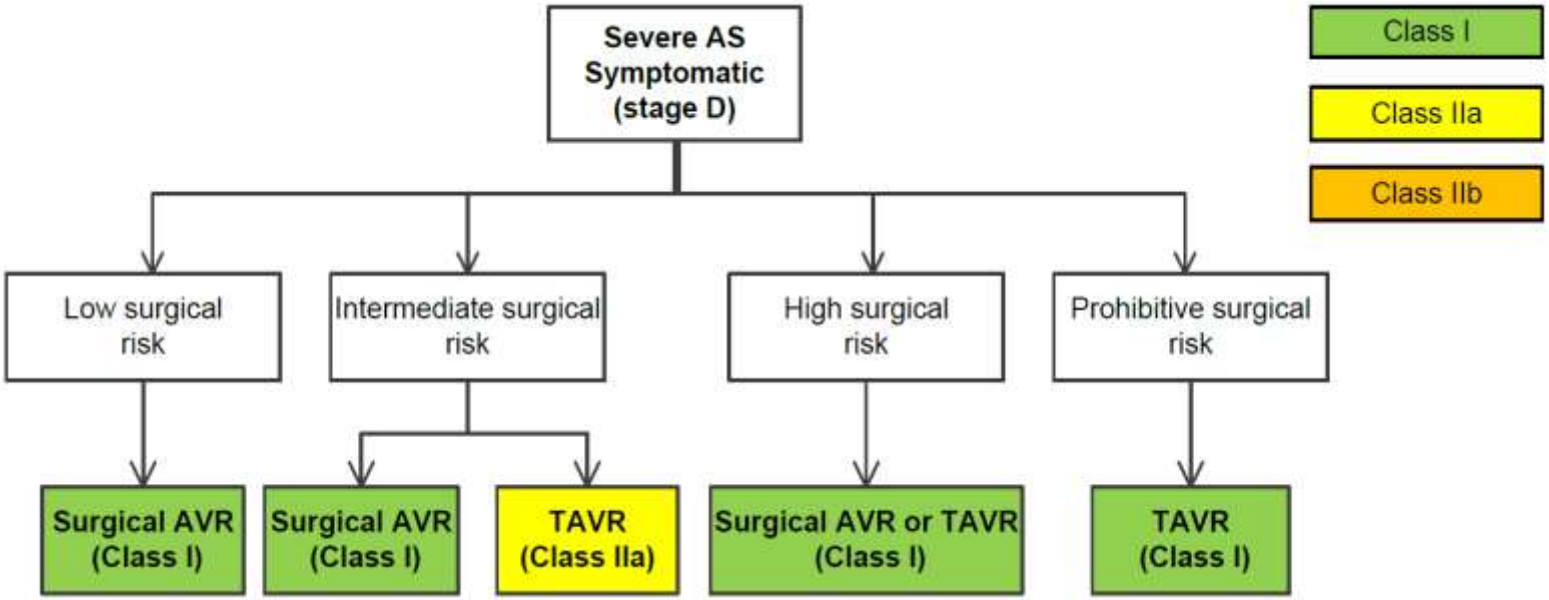


[1]Siontis, et al., *Eur Hear J* 2016; doi:10.1093/eurheartj/ehw225

Current ACC / AHA Guidelines 2017 clearly recommend surgery in low risk patients

2017 AHA/ACC Focused Update of the 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease

A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines



[1]Nishimura, et al., *J Am Coll Cardiol* 2017 Mar 10. pii: S0735-1097(17)36019-9. doi: 10.1016/j.jacc.2017.03.011

Are there trials in very low surgical risk patients? STS < 4

Nordic Aortic Valve Intervention Trial

The NOTION Trial

Objective:	Compare TAVR vs. SAVR in patients ≥70 years eligible for surgery (all-comers population)
Primary outcome:	Composite rate of death from any cause, stroke or myocardial infarction at 1 year (VARC II-defined)
Secondary outcomes:	Safety and efficacy (NYHA), echocardiographic outcomes (VARC II-defined)
Design:	Prospective, multicenter, non-blinded, randomized trial
Enrollment period:	December 2009 - April 2013

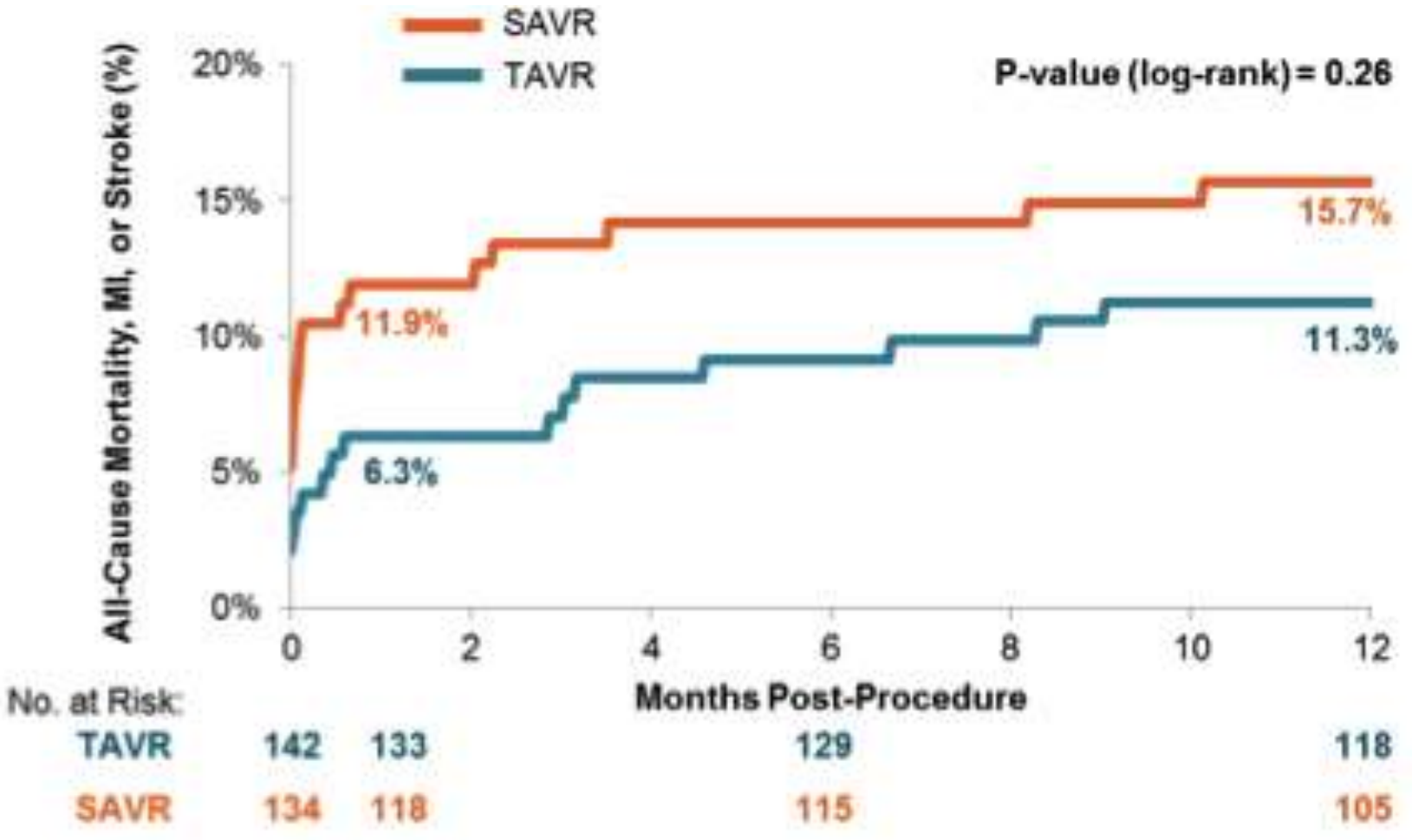
NOTION Trial: TAVI vs Surgery in all-comers
Baseline
Very low surgical risk scores

Characteristic, % or mean ± SD	TAVR n=145	SAVR 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 Surgeons (STS) Score	2.9 ± 1.6	3.1 ± 1.7	0.30
STS Score < 4%	83.4	80.0	0.46
Logistic EuroSCORE I	8.4 ± 4.0	8.9 ± 5.5	0.38
NYHA class III or IV	48.6	45.5	0.61

Thyregod et al, ACC 2015

NOTION Trial: TAVI vs Surgery in all-comers

Very strong trend towards better outcome with TAVI regarding the **primary endpoint death, stroke, myocardial infarction**



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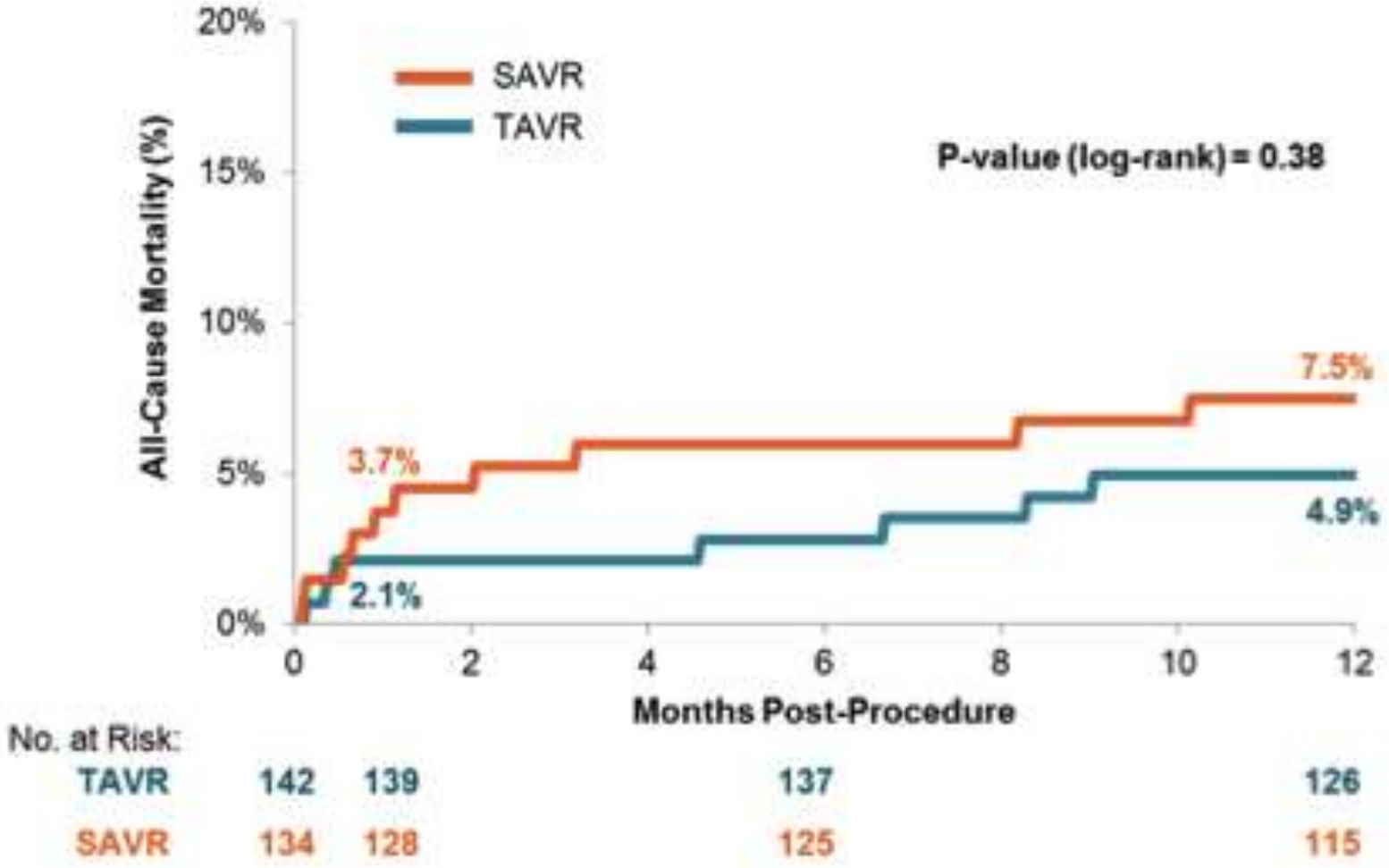


Thyregod et al, ACC 2015

NOTION Trial: TAVI vs Surgery in all-comers

Significant better outcome with TAVI regarding most parameters at 30 days

Outcome, %	TAVR n=142	SAVR n=134	p-value
Death, any cause	2.1	3.7	0.43
Death, cardiovascular	2.1	3.7	0.43
Bleeding, life-threatening+major	11.3	20.9	0.03
Cardiogenic shock	4.2	10.4	0.05
Vascular lesion, major	5.6	1.5	0.10
Acute kidney injury (stage II+III)	0.7	6.7	0.01
Stroke	1.4	3.0	0.37
TIA	1.4	0	0.17
Myocardial infarction	2.8	6.0	0.20
Atrial fibrillation	16.9	57.8	<0.001
Pacemaker	34.1	1.6	<0.001

Thyregod et al, ACC 2015

Notion: TAVI in all-comers

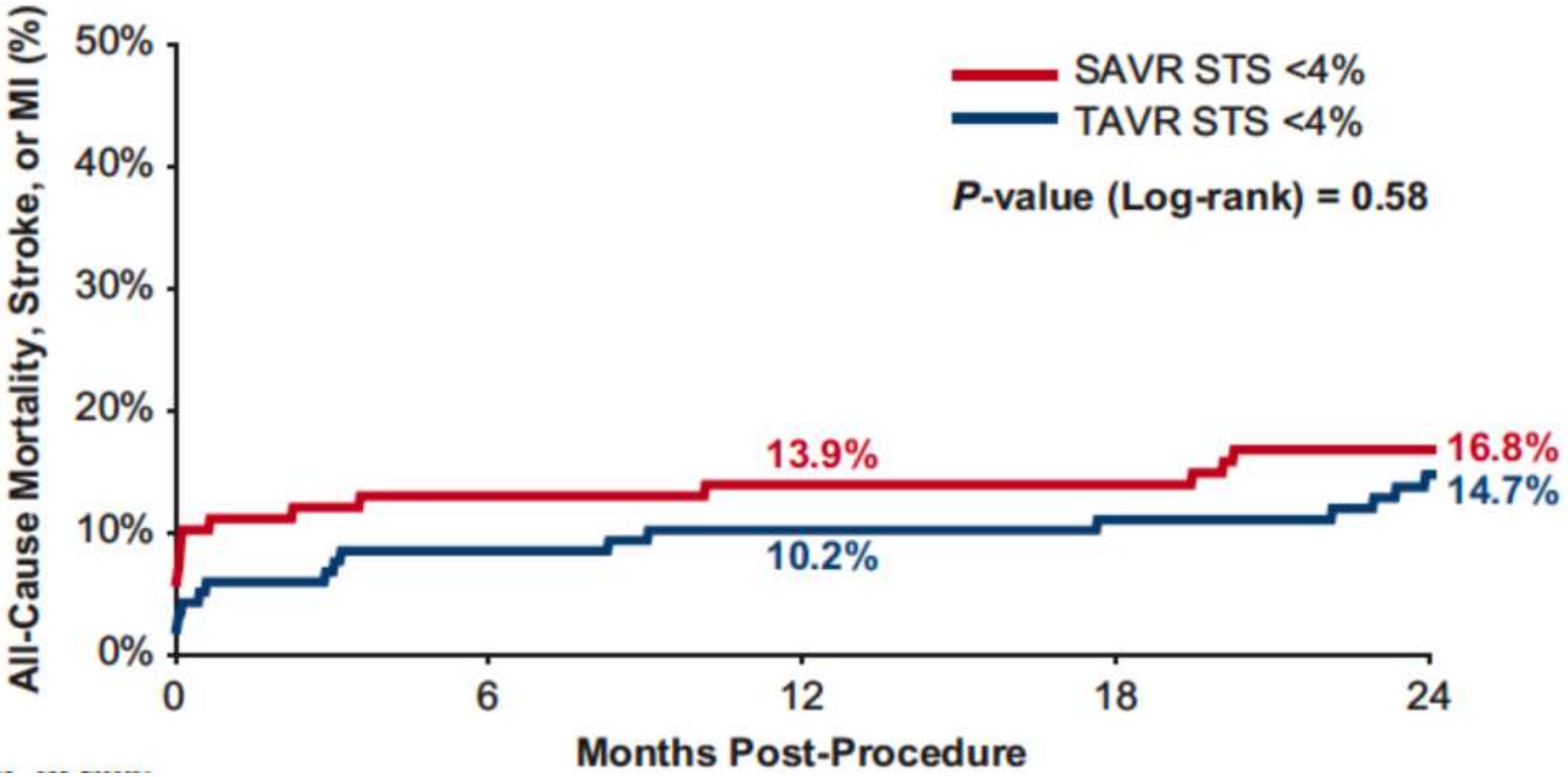
- >80% of the patients had been at low surgical risk
- The trial was underpowered to show a significant difference in death/stroke/MI after 1 year (primary endpoint)
- However, there was a strong trend in favor of TAVI
- 30 day results showed superiority of TAVI regarding most parameters

In the Notion trial all-comers had been randomized

Similar results in low surgical risk patients?

Subgroup analysis of Notion

All-cause mortality, stroke or MI
Patients with STS <4%



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What has changed since 2009-2013?

No relevant change in surgical techniques or outcomes over the last 5-10 years

However, there have been major improvements in TAVI

- Increased operator experience
- The procedure has become much simpler and easier
- New valves, new technologies
  - Vascular closure devices, embolic protection, ….

The randomized trials in high and intermediate surgical risk patients are already outdated

New valves

Evolut R

Lotus

SAPIEN 3

Portico

ACURATE neo

	Nitinol	Nitinol	Cobalt Chromium	Nitinol	Nitinol
PVL Managment	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

Improvements in TAVI

- Feasibility?
- Stroke?
- Need for permanent pacemakers?
- Vascular complications?
- Paravalvular leaks?
- Long-term durability?

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There is no question that with newer valves TAVI has become a much more feasible procedure

- Every single step has been standardized
- 1 hour procedure
- Technical success rate >98%
- "as easy as PCI – at least!"

Improvements in TAVI

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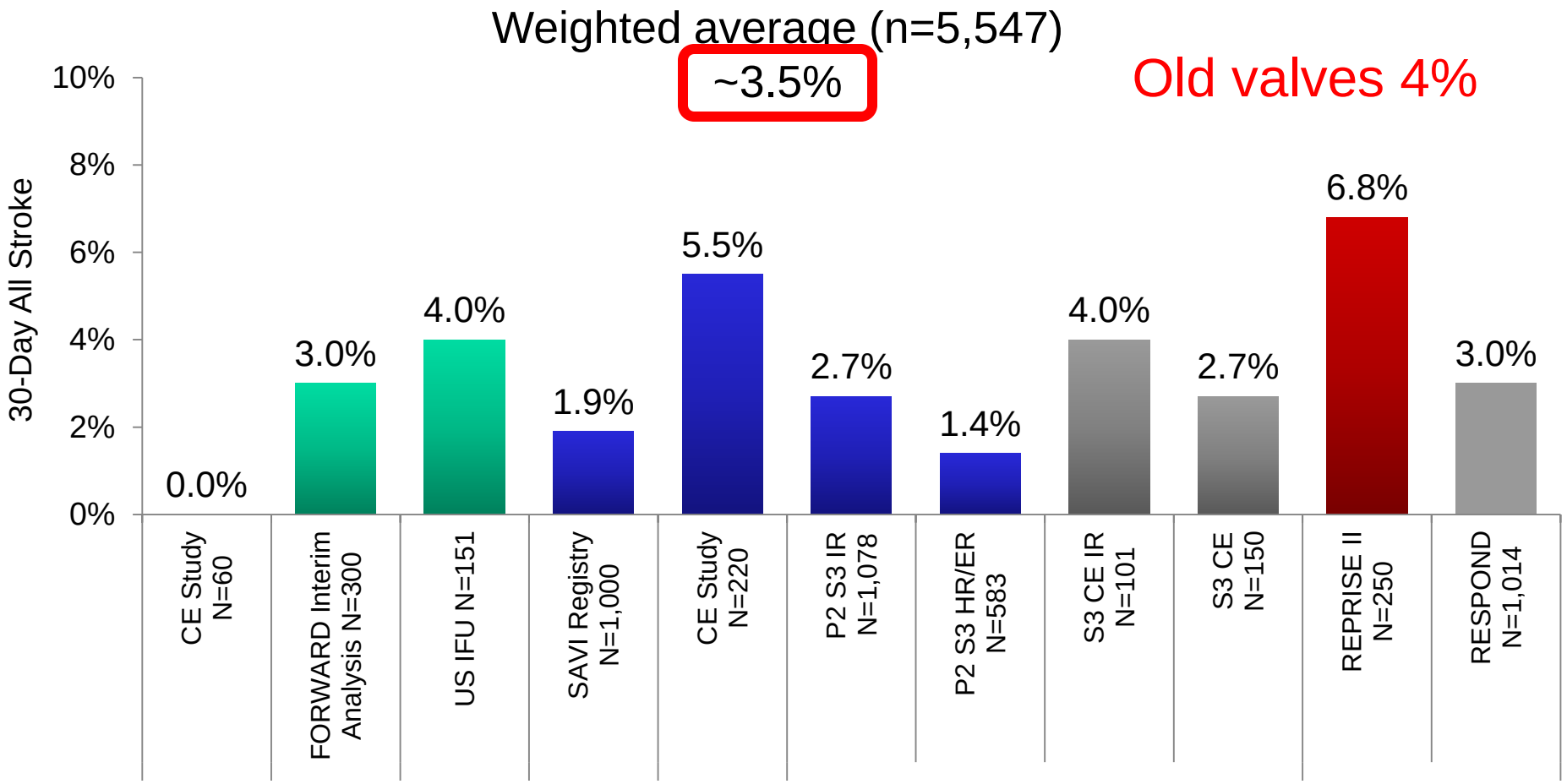
Stroke – Newer Valves

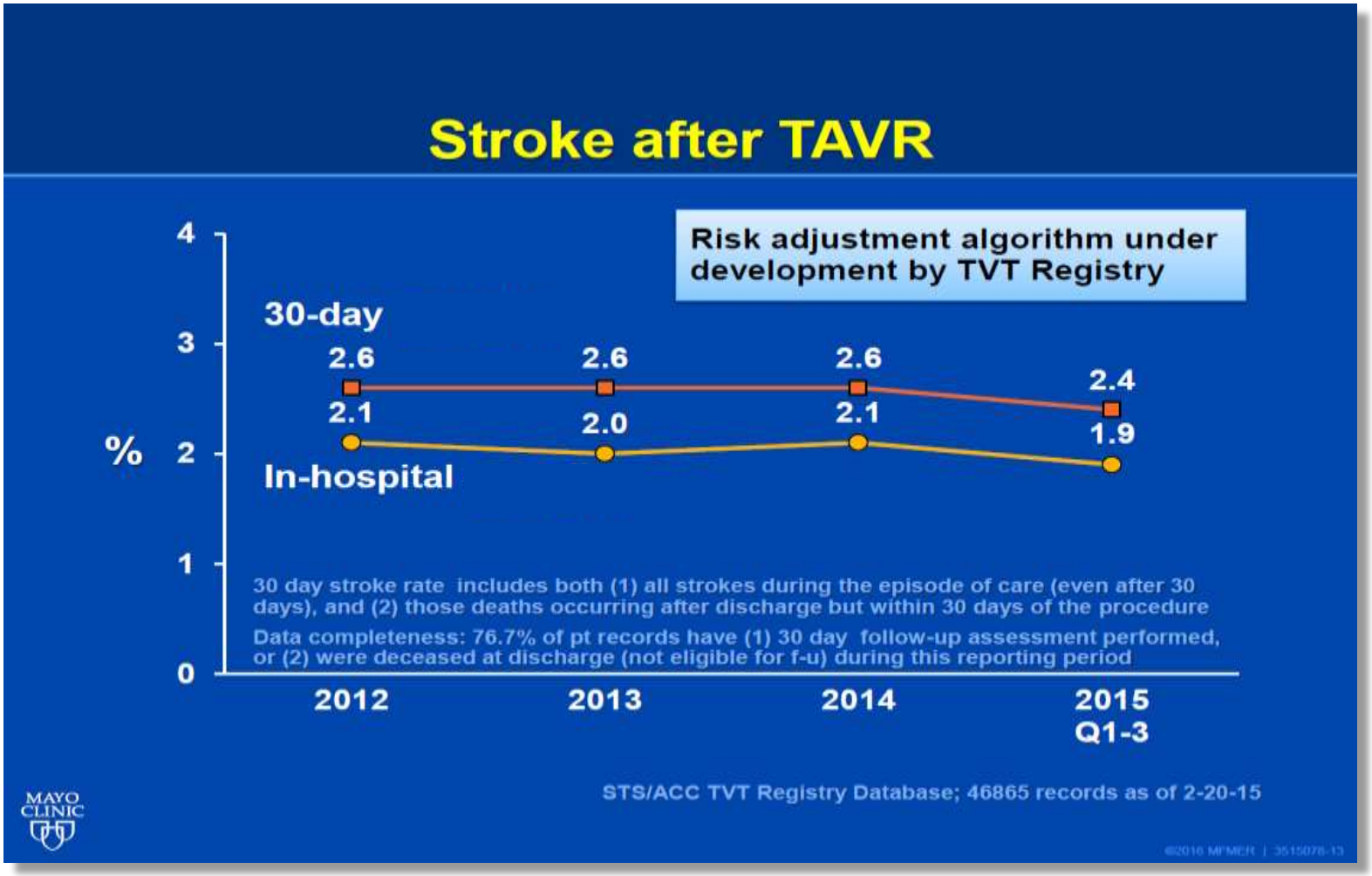
Stroke rate did not decrease significantly yet



[1]Manoharan, et al., *J Am Coll Cardiol Intv* 2015; 8: 1359-67; [2]Moellman, et al., presented at PCR London Valves 2015; [3]Linke, et al., presented at PCR London Valves 2015; [4]Kodali, et al., *Eur Heart J* 2016; doi:10.1093/eurheartj/ehw112; [5]Vahanian, et al., presented at EuroPCR 2015; [6]Webb, et. al. *J Am Coll Cardiol Intv* 2015; 8: 1797-806; [7]DeMarco, et al, presented at TCT 2015; [8]Meredith, et al., presented at PCR London Valves 2015; [10]Falk, et al., presented at EuroPCR 2016

E. Grube, CRT 2017

TVT Registry



- > 53,000 patients
- No decline in stroke rate over time
- But low rate anyway

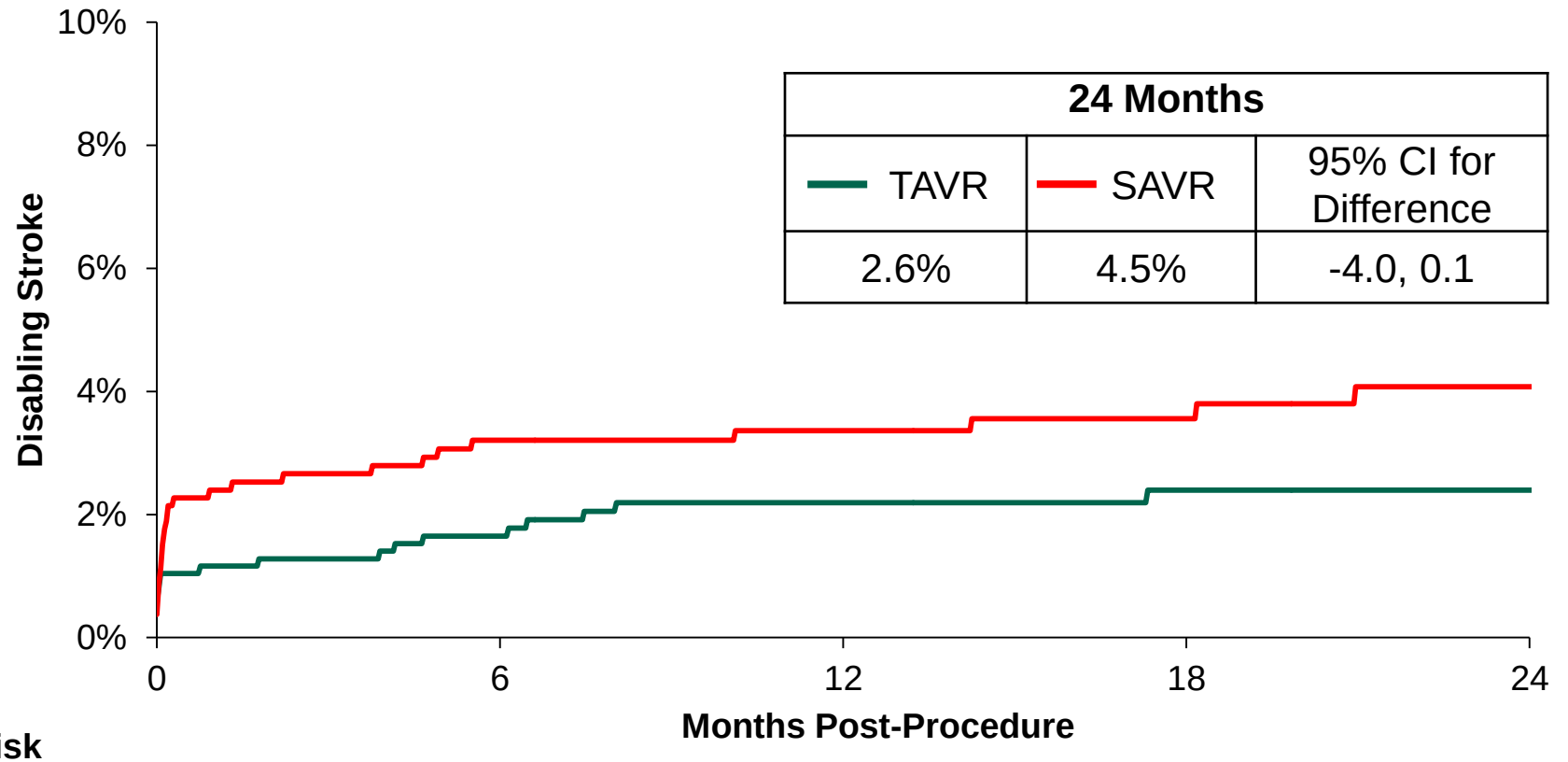
Holmes D, et al. ACC 2016

Surgical arm of PARTNER II compared with the Sapien 3 Trial

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

Corevalve SURTAVI: Disabling Stroke

STS Score ≥3% and <15%



24 Months		
TAVR	SAVR	95% CI for Difference
2.6%	4.5%	-4.0, 0.1

No. at Risk					
SAVR	796	674	555	407	241
TAVR	864	755	612	456	272

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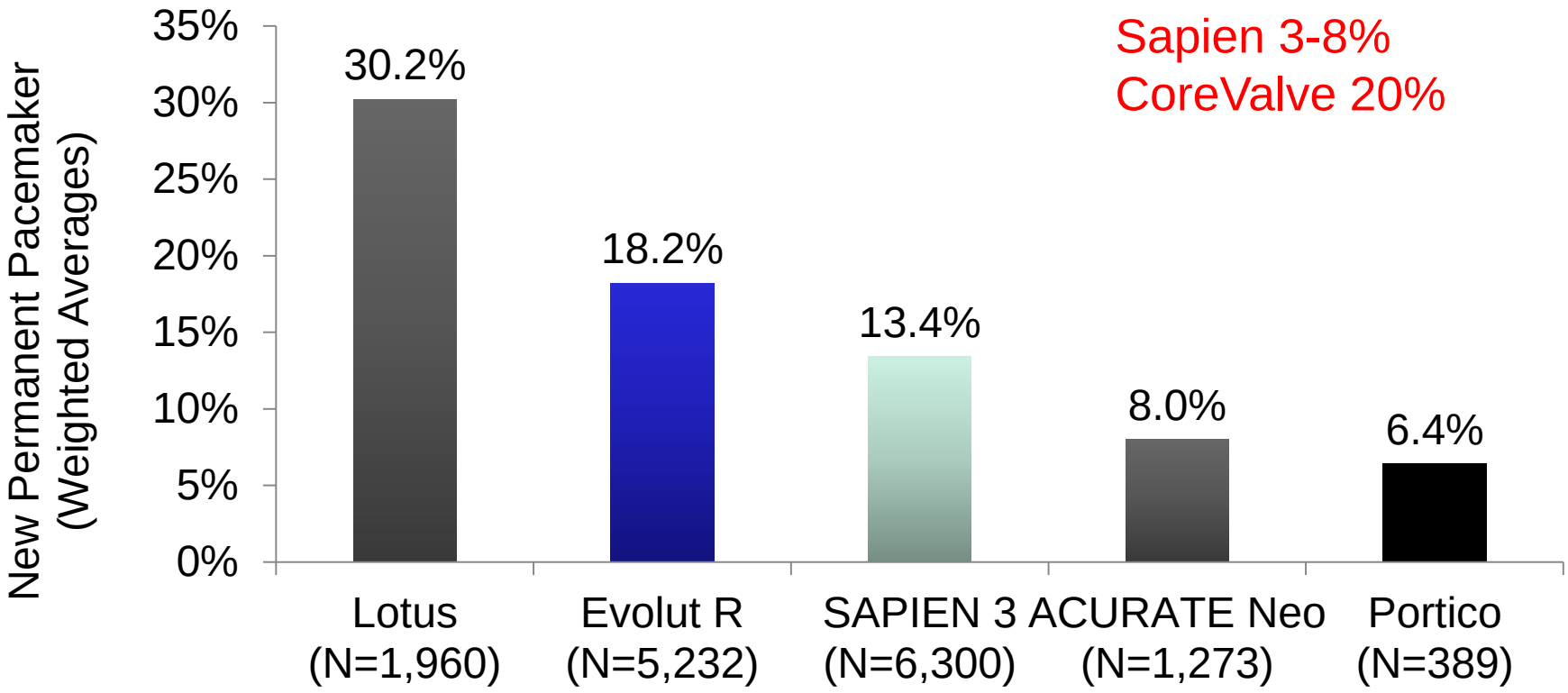
New Permanent Pacemakers – Newer Valves

- The rate of new permanent pacemakers depends upon valve type
- The rates are highest with the Lotus valve followed by Evolut R and SAPIEN 3

Old valves 11.3%
Sapien 3-8%
CoreValve 20%



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Improvements in TAVI

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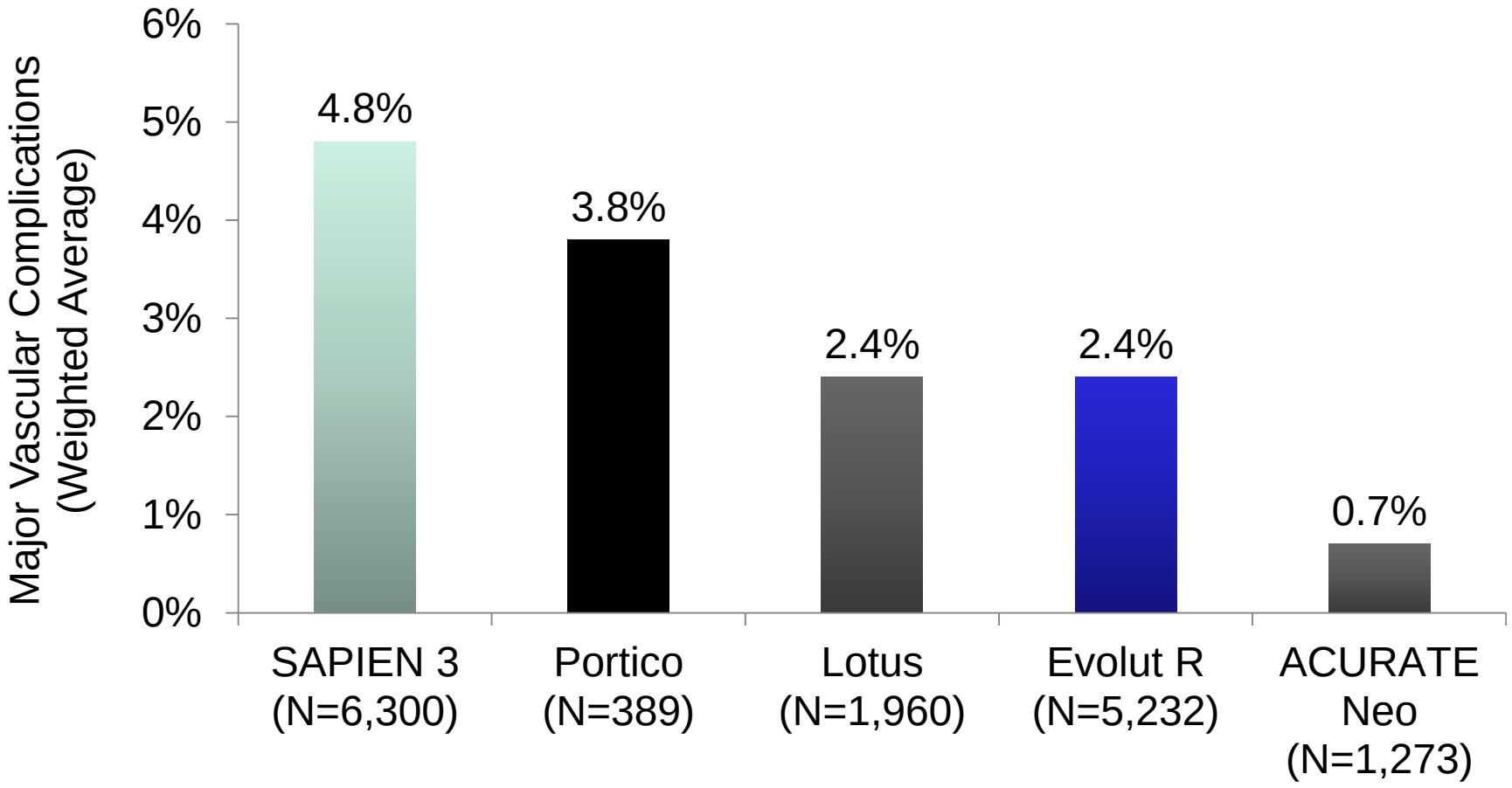
Major Vascular Complications – Newer Valves

Major improvements - Less than 5%



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Improvements in TAVI

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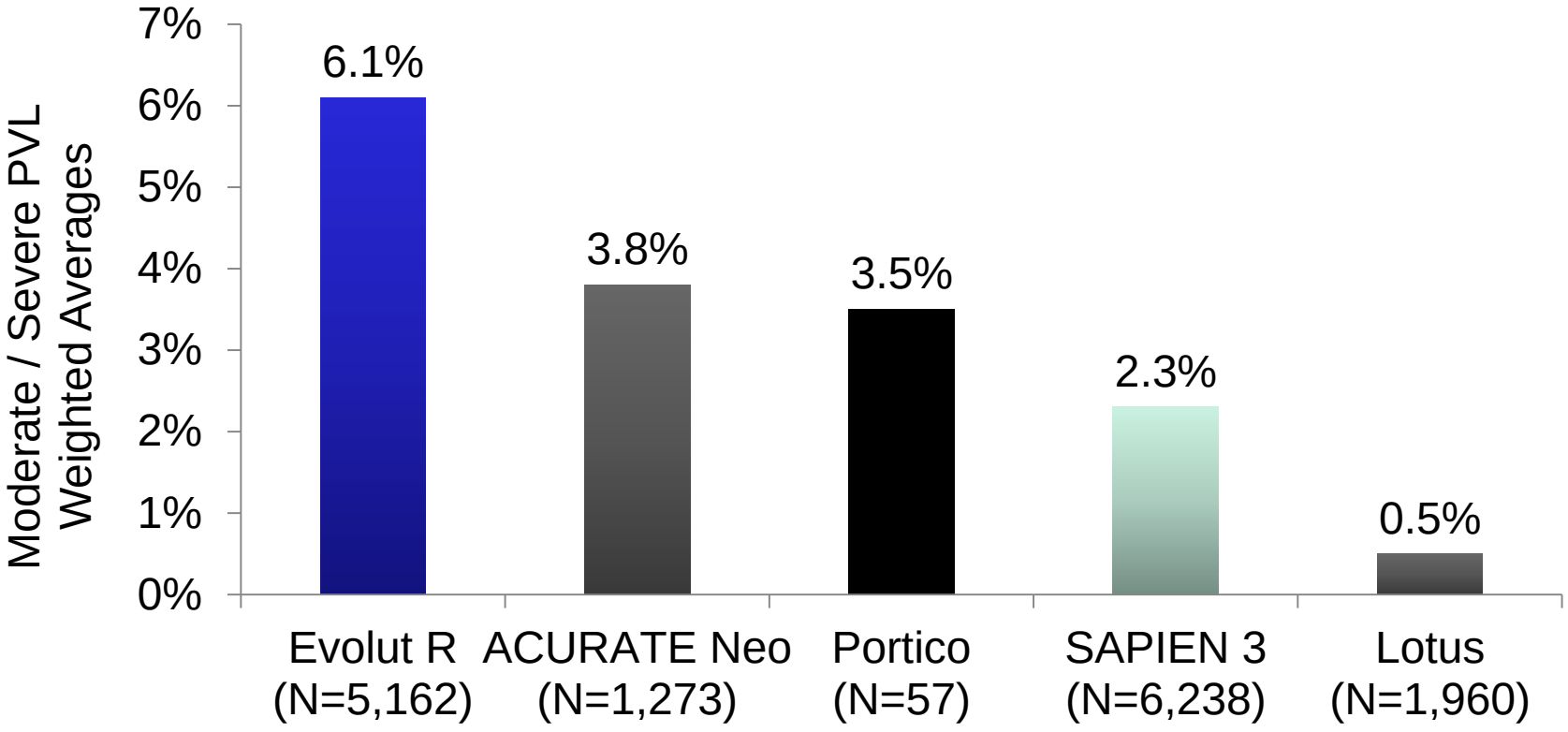
Moderate / Severe Paravalvular Leak – Newer Valves

Lower rate compared to old valves

Old valves >10%



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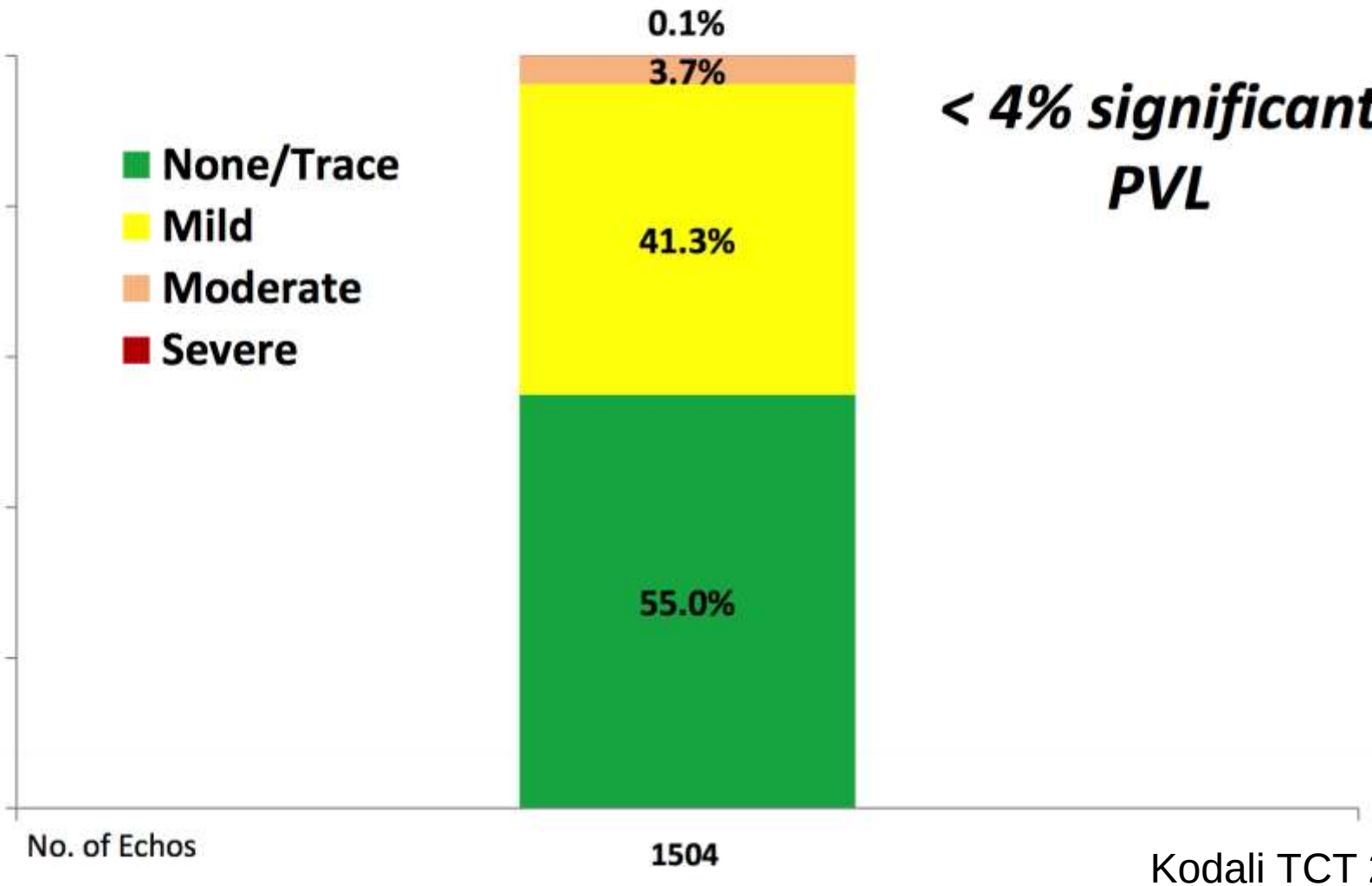
Low Rates of PVL at 30 Days

PARTNER II – Sapien 3



< 4% significant PVL

Kodali TCT 2016

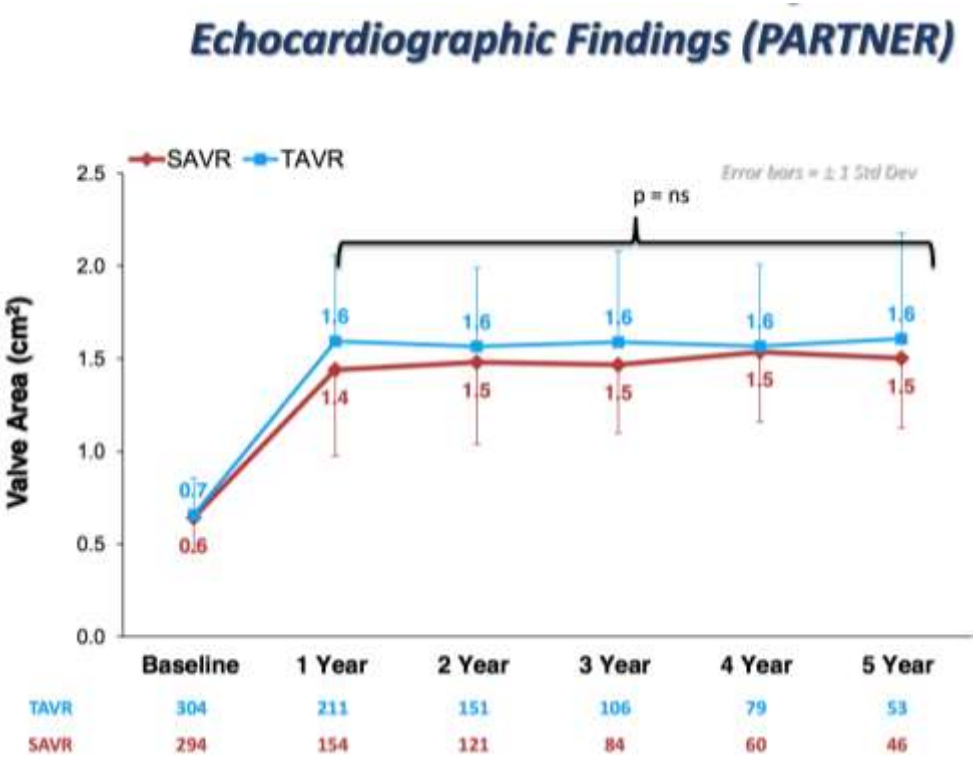
Improvements in TAVI

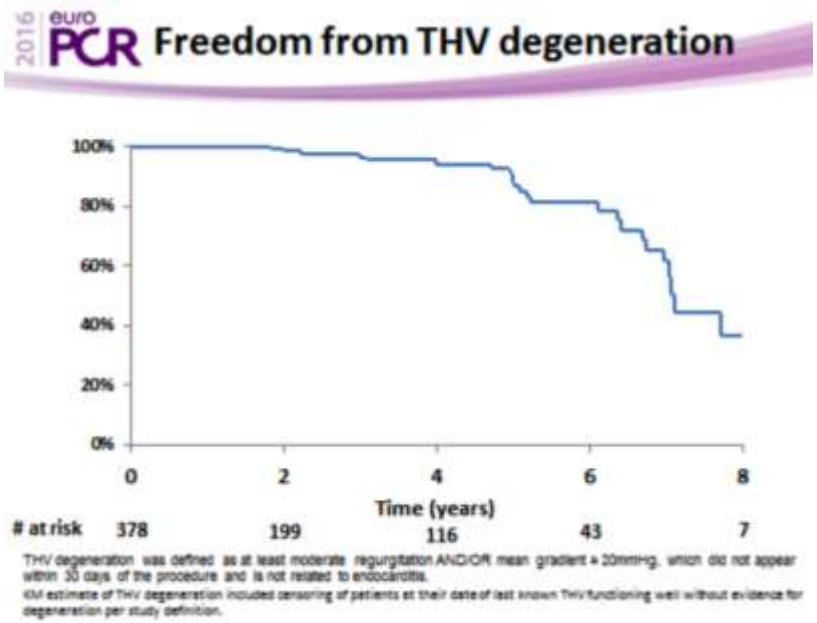
- Feasibility?
- Stroke?
- Need for perm
- Vascular complications?
- Paravalvular leaks?
- Long-term durability?

The key factor for younger patients!!!

Long-term durability still unknown

Conflicting observations





- However, we have to keep in mind that in case of leaflet degeneration we have the option of valve in valve

In any case, all restrictions like …

- "Euroscore has to be > 20"
- "STS score has to be > 10"
- "Age has to be > 80"
- "A heart team decision is required"

- … have no scientific background
- … are not validated
- … are driven by economical and "political" considerations

With the currently available data ….

- … should we consider TAVI in a patient with low surgical risk?
  - Yes!
    - In a free and rich country with no reimbursement issues, we should discuss the pro and cons individually with the patient
  - No!
    - In all the less free countries with reimbursement, approval, regulatory, guideline and other issues

Low Surgical Risk

Active Trials Randomizing TAVR to SAVR

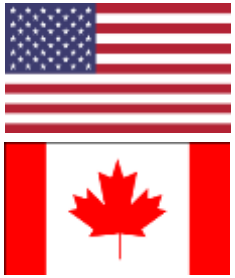
Medtronic Low Risk[1]

N = ~1200

Up to 80 centers
Evolut R, all routes

Industry-sponsored
10-year follow-up

PARTNER 3[2]



N = 1228

Up to 64 centers
SAPIEN 3,
transfemoral

Industry-sponsored
10-year follow-up

UK TAVI[3]

N = 808

All UK TAVI centers
All valves, all routes

Publically funded
5-year follow-up

NOTION-2[4]

N = 992

All Nordic countries
All valves,
transfemoral

Physician and
industry-sponsored
5-year follow-up

[1]Popma, et al., TCT 2016; [2]Mack, et al., TCT 2016; [3]Moat, et al., TCT 2016; [4]Sondergaard, et al., TCT 2016

What could be the outcome of these trials?

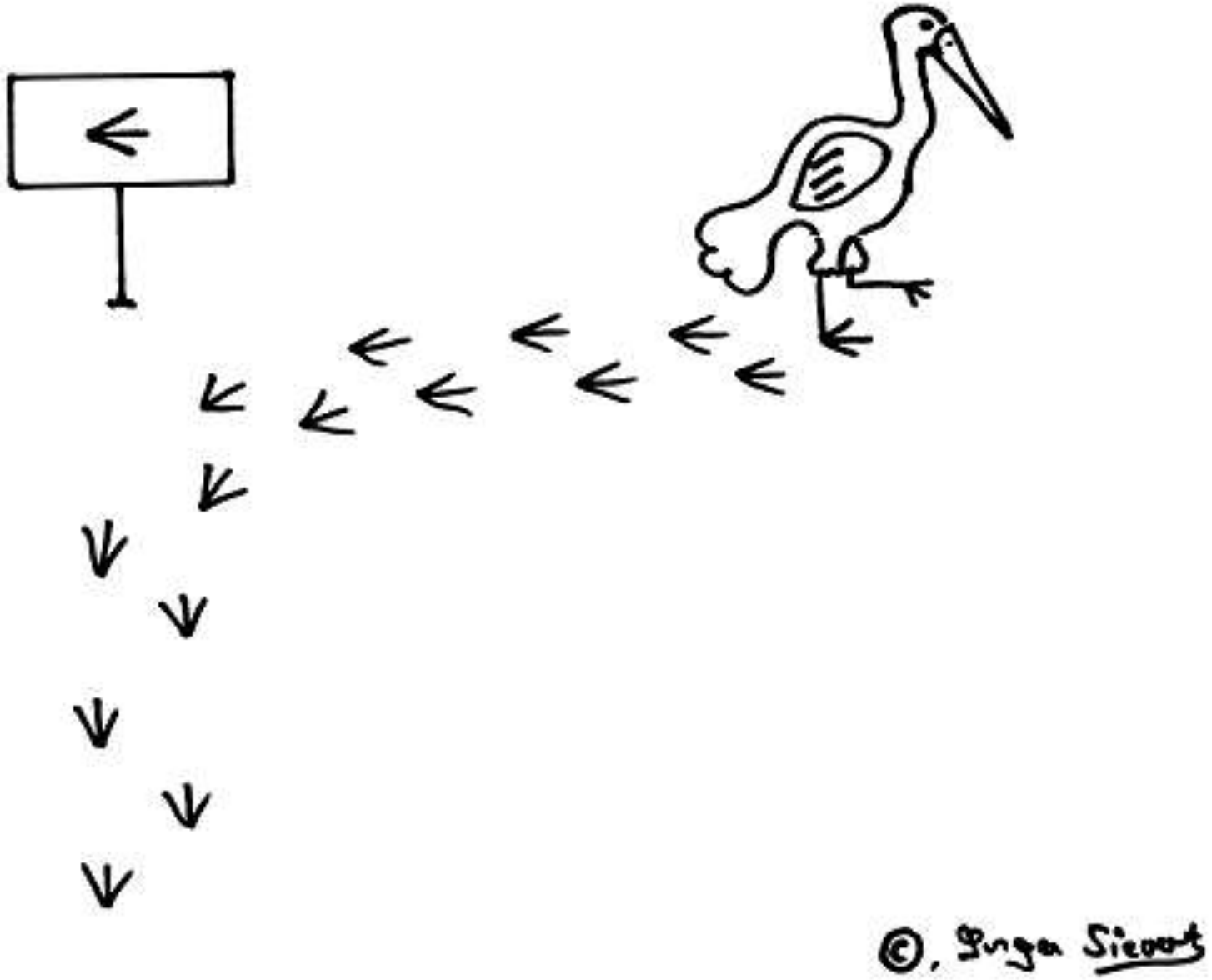
For example:

Mortality Treatment A: 1.5%

Mortality Treatment B: 0.9%

This could be statistically highly significant …

… but may be clinically not very relevant



A study result which looks like a clear signal for scientists, doctors, regulators and payers ….

…. may look completely different in the view of the patient

Summary and Conclusions

- TAVI is accepted as standard of therapy in patients who can not be operated
- It is also accepted as alternative to surgery in
  - high and
  - intermediate surgical risk patients
- TAVI is on a rise with new valves and new technologies every year
- Patients always prefer less invasive treatment options
- It is only a question of time until TAVI will become an alternative also in low surgical risk patients

Thank you!

LIVE CASES

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