

**TAVR 2015:**  
*A Breakthrough Technology*  
**GOES VIRAL!**  
*Issues and Controversies*

**Martin B. Leon, MD**

**Columbia University Medical Center**  
**Cardiovascular Research Foundation**  
**New York City**

# Disclosure Statement of Financial Interest

## *TVT 2015, Chicago, IL; June 4-6, 2015*

### **Martin B. Leon, MD**

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**

- Grant / Research Support
- Consulting Fees / Honoraria
- Shareholder / Equity

#### **Company**

- Abbott, Boston Scientific, Edwards Lifescience, Medtronic
- Meril Lifescience
- Claret, GDS, Mitralign, Valve Medical

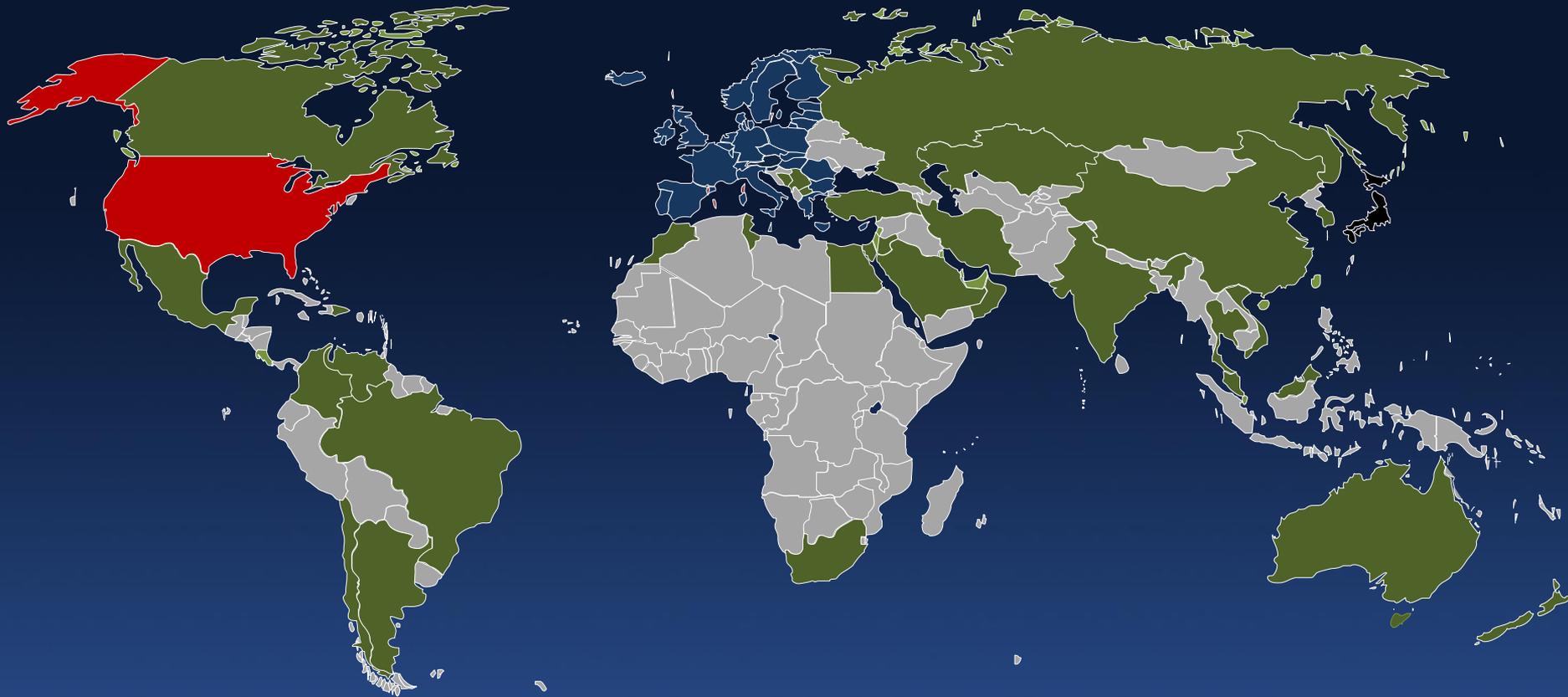
# *What is a Breakthrough Technology?*

- Addresses an unmet clinical need or an important area of clinical medicine not well served by current therapies
- Innovative concept and/or novel device, drug, or diagnostic technology
- Must be validated by rigorous evidence-based medicine clinical research
- Must be “generalizable” to the practicing medical community (sufficiently user-friendly)
- *Rarely, elevates beyond subspecialty medicine and resonates as a significant socio-medical cultural advance (the “X” factor)*

# TAVR in 2015

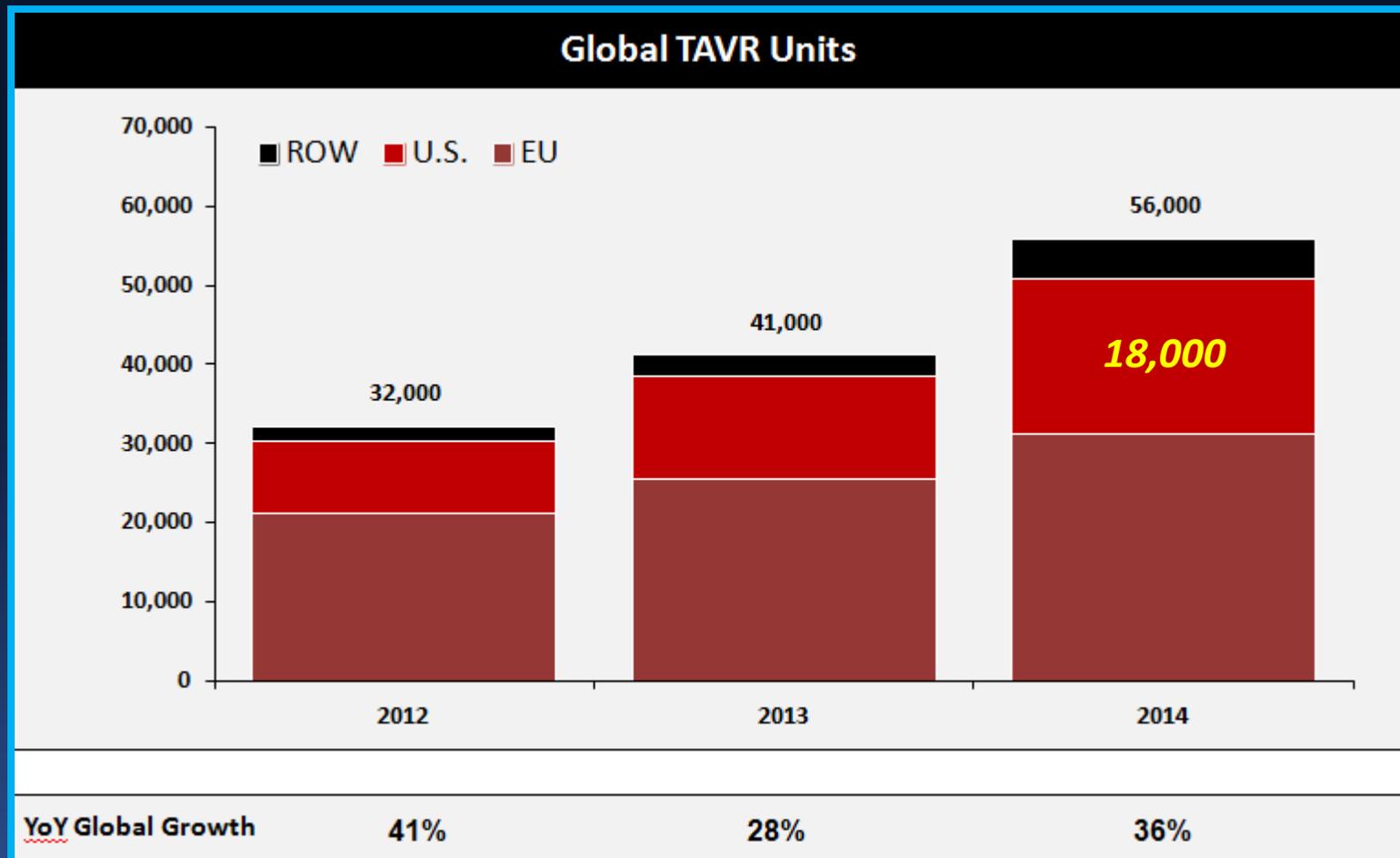
## Demographics & Projections

# TAVR is Available in More Than 65 Countries Around the World



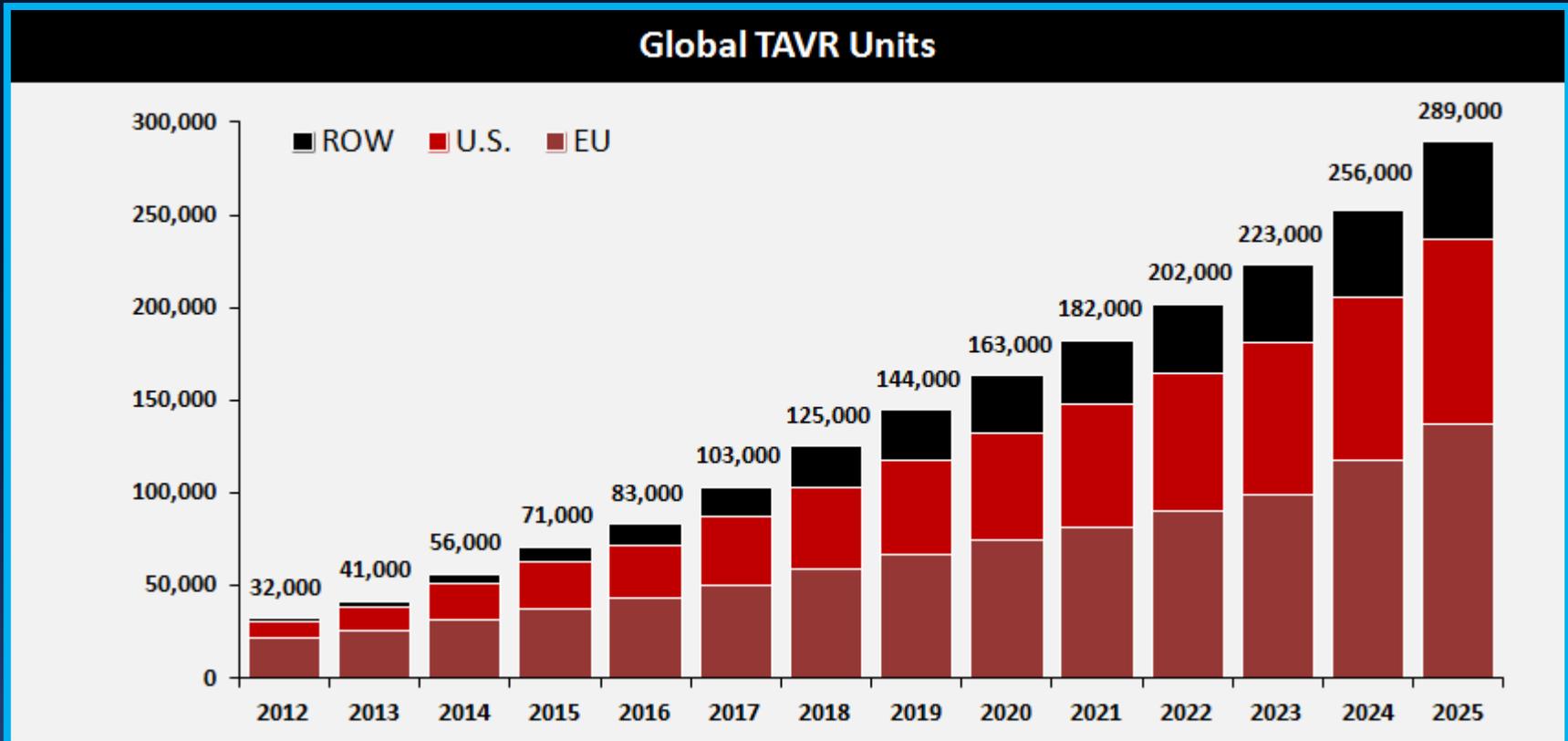
**>200,000 total implants to date**

# Estimated Global TAVR Procedures



SOURCE: Credit Suisse TAVI Comment –January 8, 2015. Revenue split assumption in 2025 is 45% U.S., 35% EU, 10% Japan, 10% ROW

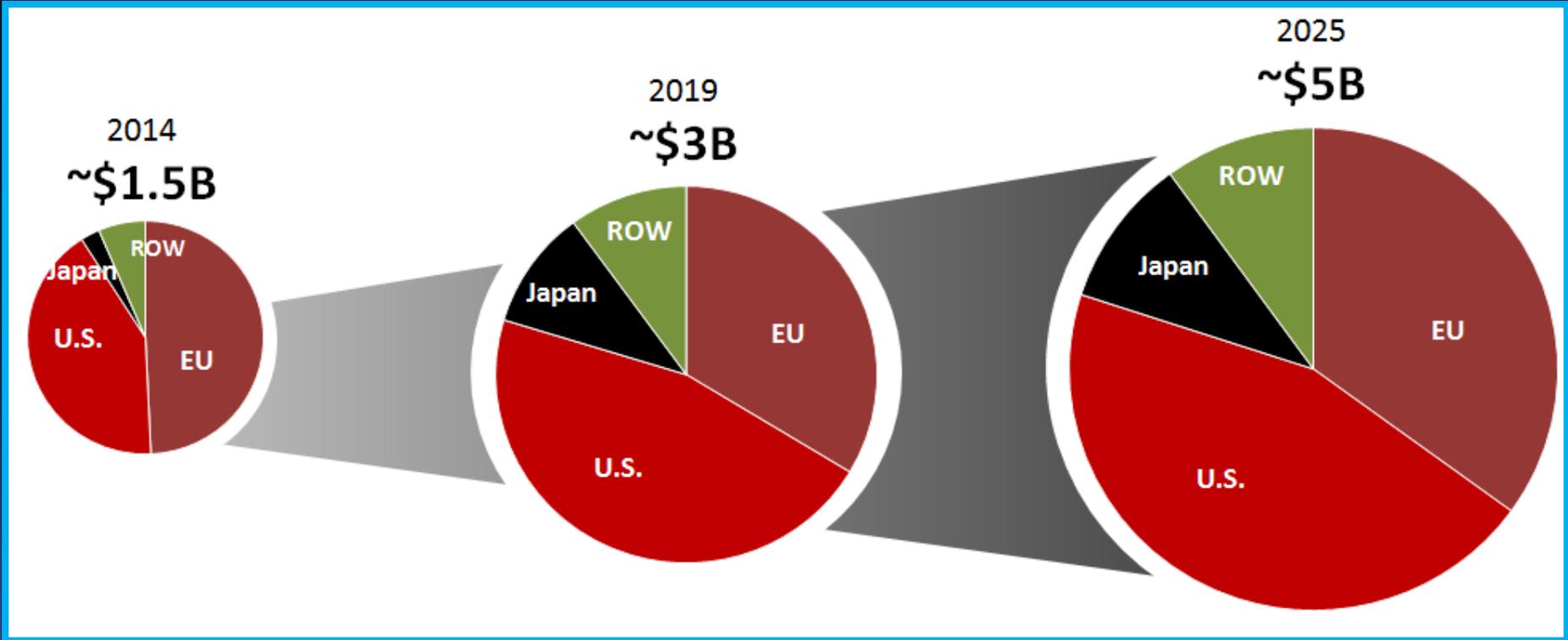
# Estimated Global TAVR Growth



SOURCE: Credit Suisse TAVI Comment –January 8, 2015. ASP assumption for 2024 and 2025 based on analyst model. Revenue split assumption in 2025 is 45% U.S., 35% EU, 10% Japan, 10% ROW

***In the next 10 years, TAVR growth will increase X4!***

# Global \$ TAVR Market Potential (*\$5B by 2025*)



SOURCE: Edwards Lifesciences Investor Conference – Dec 11, 2013; Credit Suisse TAVI Comment –January 8, 2015

# TAVR Procedures and \$ Market

## TAVR Procedures

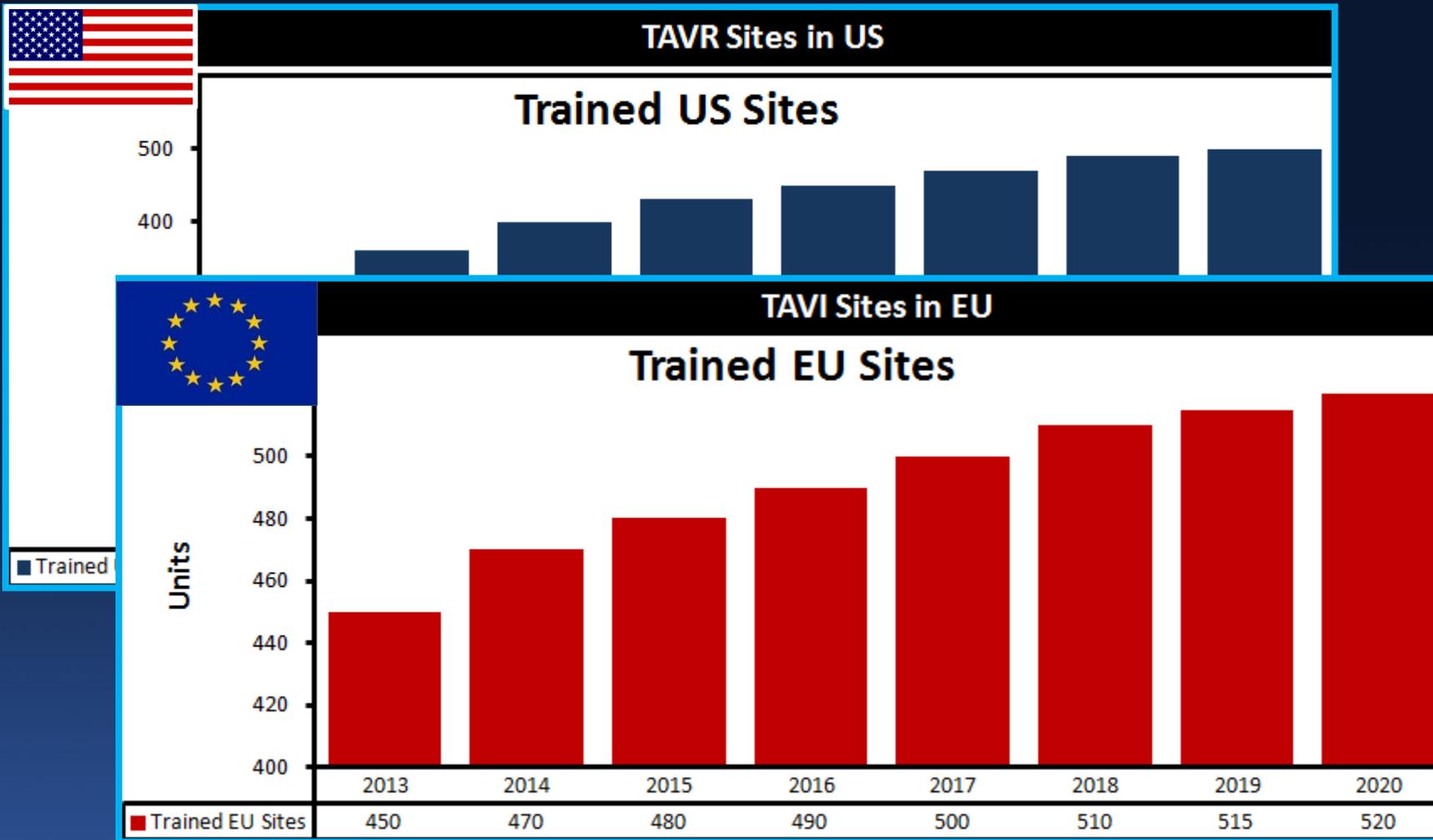


## TAVR \$ Market

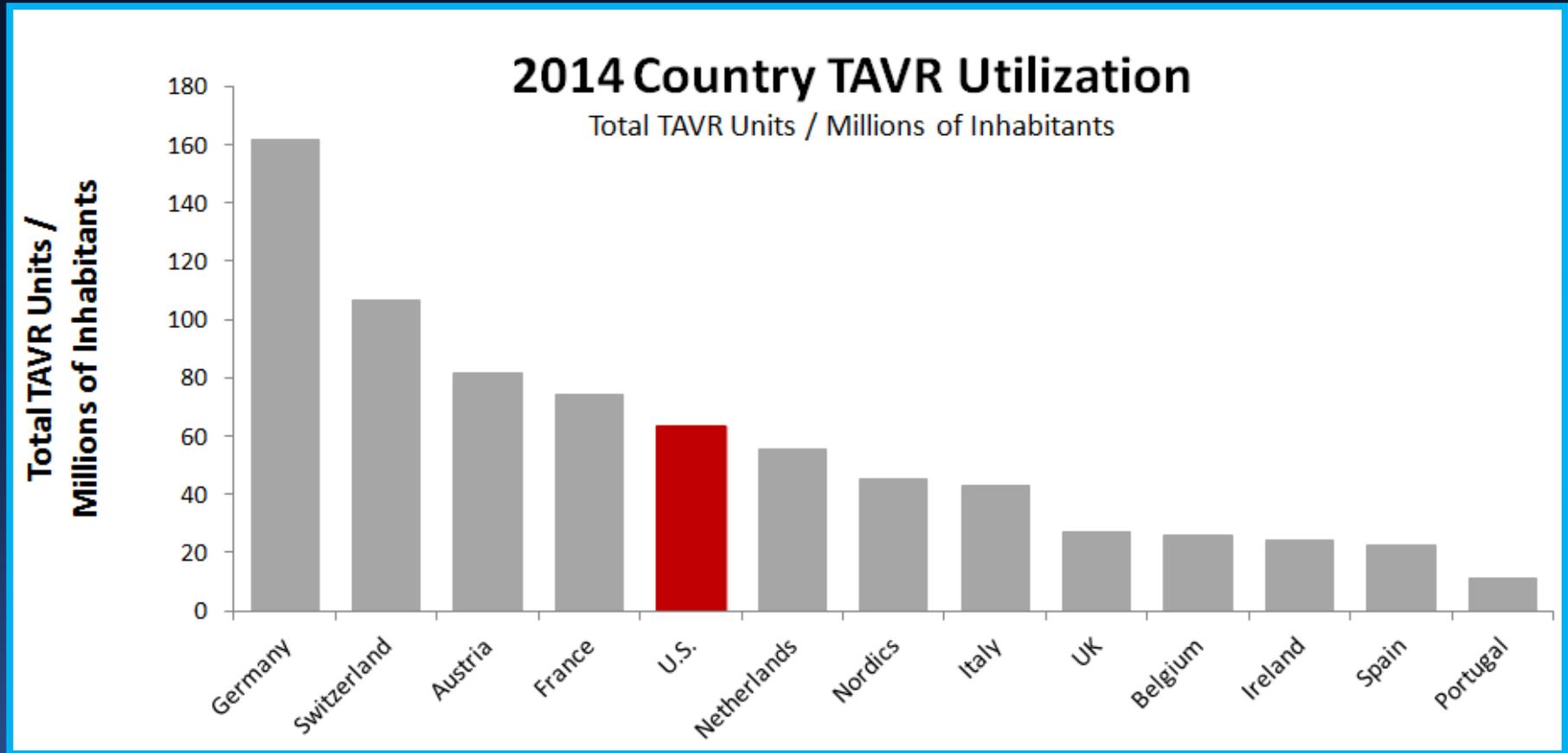


Source: Wall Street Analyst Reports, Company estimates

# Estimated US and EU TAVR Sites

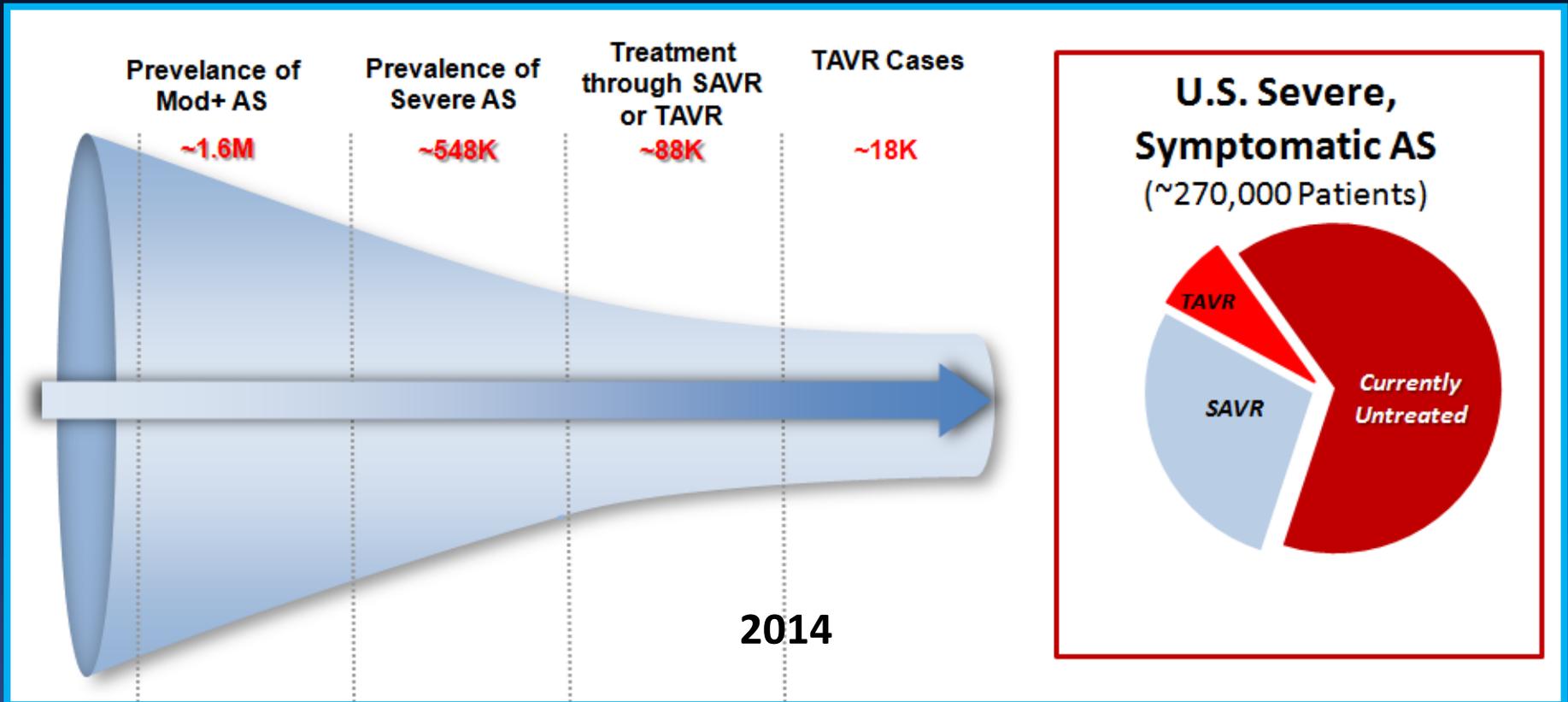


# TAVR “Underutilization” is Largely Driven by Variation in Health Policy and Reimbursement



SOURCE: Eurostat, U.S. Census Bureau, Industry estimates

# The Majority of US Patients with Severe AS Remain “Untreated” (no SAVR/TAVR)



SOURCE: Nkomo 2006, Iivanainen 1996, Aronow 1991, Bach 2007, Freed 2010, Lung 2007, Pellikka 2005; Bach, D. Prevalence and Characteristics of Unoperated Patients with Severe Aortic Stenosis. J Heart Valve Dis. May 2011. (n=406); Industry estimates

# TAVR in 2015

## Achievements

# TAVR in 2015: *Achievements*

- ***Alternative in High-Risk AS Patients*** - The original goal of TAVR, to provide a meaningful less-invasive alternative for high-risk AS patients, has been achieved!

# The severe AS-T

- Old...very old...
- Frail...very frail
- Lots of co-morbidities
  - Prior CABG (poor L
  - CKD
  - Severe COPD
  - PVD
  - Chronic AF
  - Cancer in remission

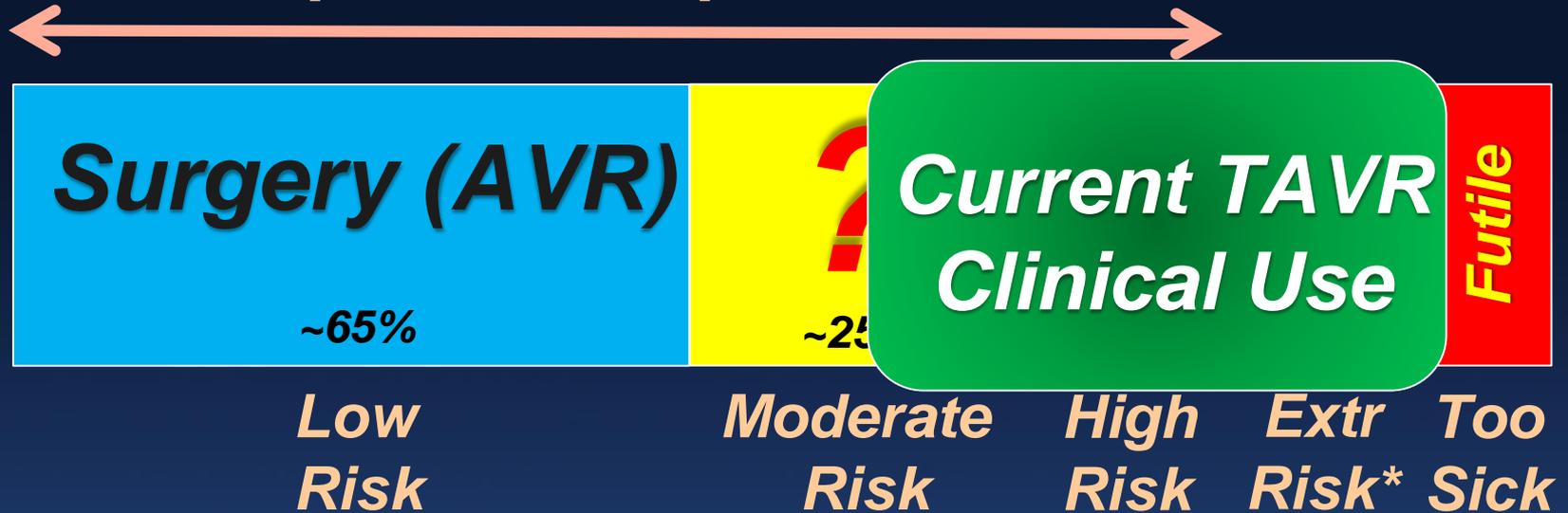


But still enjoying life !

# TAVR Categories

*(risk is a continuum)*

*Operable AS patients*



**TAVR in 2015**

*irresponsible, reckless*      *“equipoise”*      *OK preferred*      *No*

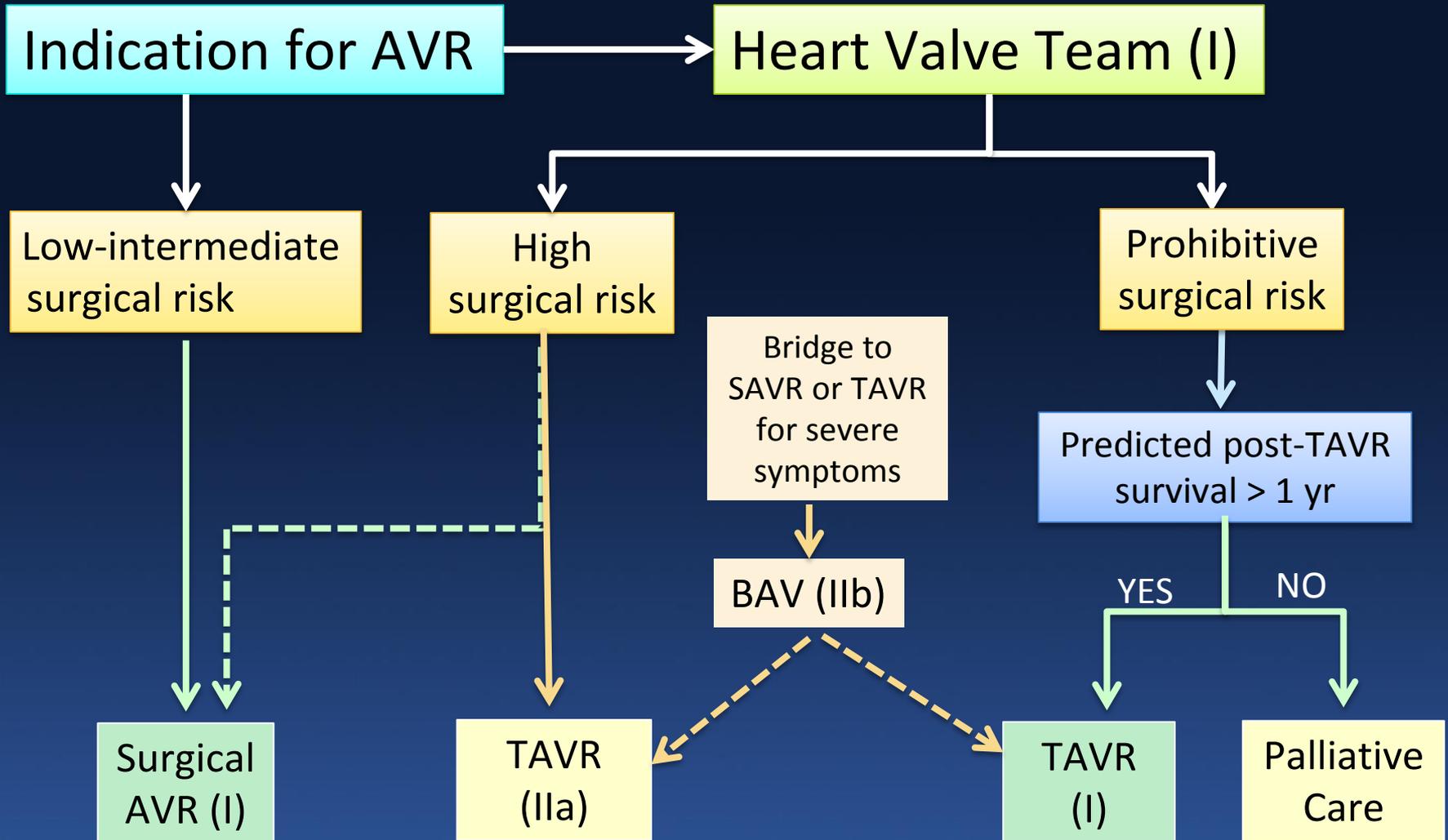
*\* Extreme (prohibitive) risk = “inoperable”*

# TAVR in 2015: *Achievements*

- ***Alternative in High-Risk AS Patients*** - The original goal of TAVR, to provide a meaningful less-invasive alternative for high-risk AS patients, has been achieved!
- ***Heart Valve Team Concept*** - Now embraced as fundamental to TAVR success (optimal clinical outcomes and accepted in the clinical community); but may be challenged and will evolve in the future.

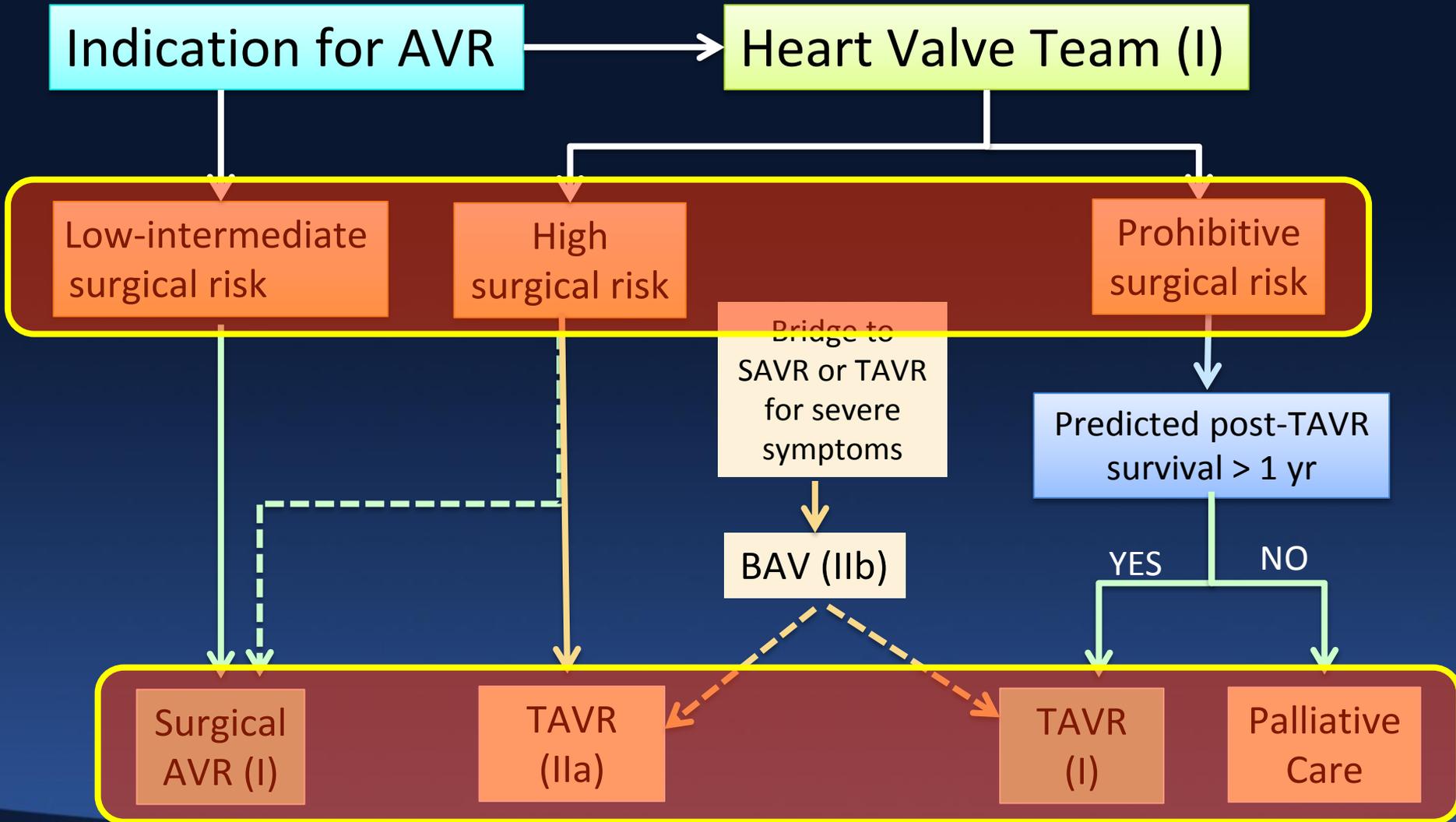
# 2014 ACC/AHA Valve Guidelines

## CHOICE of Intervention for AS



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## CHOICE of Intervention for AS



# TAVR in 2015: *Achievements*

- ***Alternative in High-Risk AS Patients*** - The original goal of TAVR, to provide a meaningful less-invasive alternative for high-risk AS patients, has been achieved!
- ***Heart Valve Team Concept*** - Now embraced as fundamental to TAVR success (optimal clinical outcomes and accepted in the clinical community); but may be challenged and will evolve in the future.
- ***An Evidence-Based Journey*** - Rigorous clinical research methods and numerous studies have validated clinical indications.

# VARC - 1 and 2 Consensus Reports



European Heart Journal (2011) 32, 205–217  
doi:10.1093/eurheartj/ehq406

CLINICAL RESEARCH

Valvular medicine

Standardized  
transcatheter  
trials  
Acad

Martin B.  
Donald  
Roxana M.  
Johanna  
John G.

EXPEDITED REVIEW

Update  
for Tra

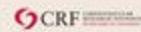
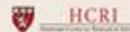
The Valv

A. Pieter K.  
Eugene H.  
Rebecca T.  
Roxana M.

Patrick W. Serruys, Martin B. Leon

*Rotterdam, the Netherlands*

## VARC – 3



Heart Valve Disease

ment†

s M. van Mieghem,  
Gerrit-Anne van Es,  
el J. Mack,  
Windecker,

Leon MB, et al. *J Am Coll Cardiol* 2011;57:253-69

Kappetein AP, et al. *J Am Coll Cardiol* 2012;60:1438-54

# The PARTNER Publications Office (PPO)



## *Current Status:*

- Total # of published or accepted for publication manuscripts = 57
- Total # of presented (or scheduled to be presented ) abstracts = 81
- 60 different first authors/presenters from 24 institutions;  
20 different journals

***Total number of published or presented  
manuscripts and abstracts = 138  
(from PARTNER 1 and 2)***



# TAVR in 2015: *Achievements*

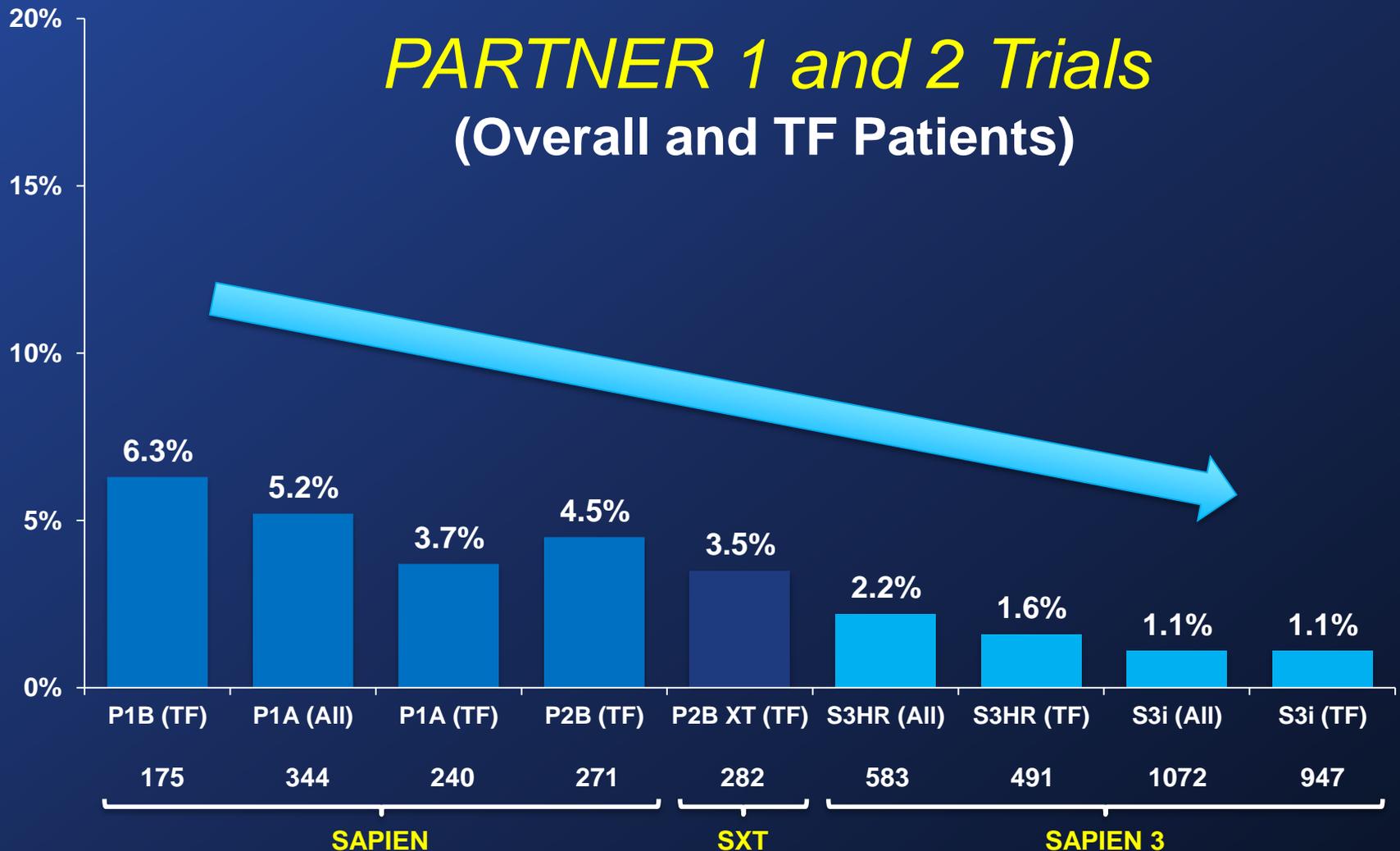
- ***Improved Clinical Outcomes*** - Due to better patient selection, increased operator experience, routine use of 3D adjunctive imaging (esp. CTA), new generation TAVR systems, and strategic post-operative care plans – reduced peri-procedural complications.

# All-Cause Mortality at 30 Days

## Edwards SAPIEN Valves (As Treated)



*PARTNER 1 and 2 Trials*  
(Overall and TF Patients)

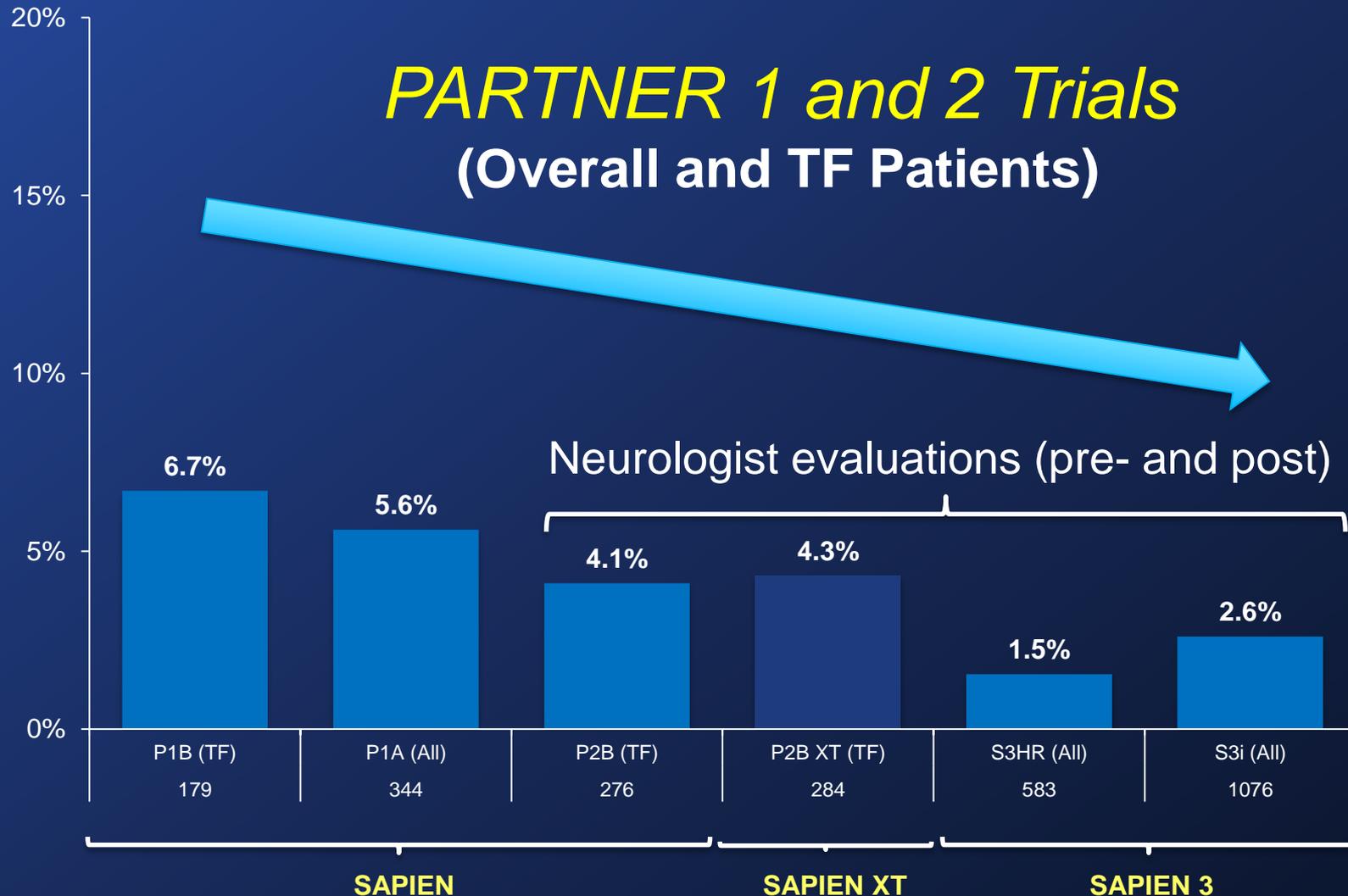


# Strokes (All) at 30 Days

## Edwards SAPIEN Valves



*PARTNER 1 and 2 Trials*  
(Overall and TF Patients)



# TAVR in 2015

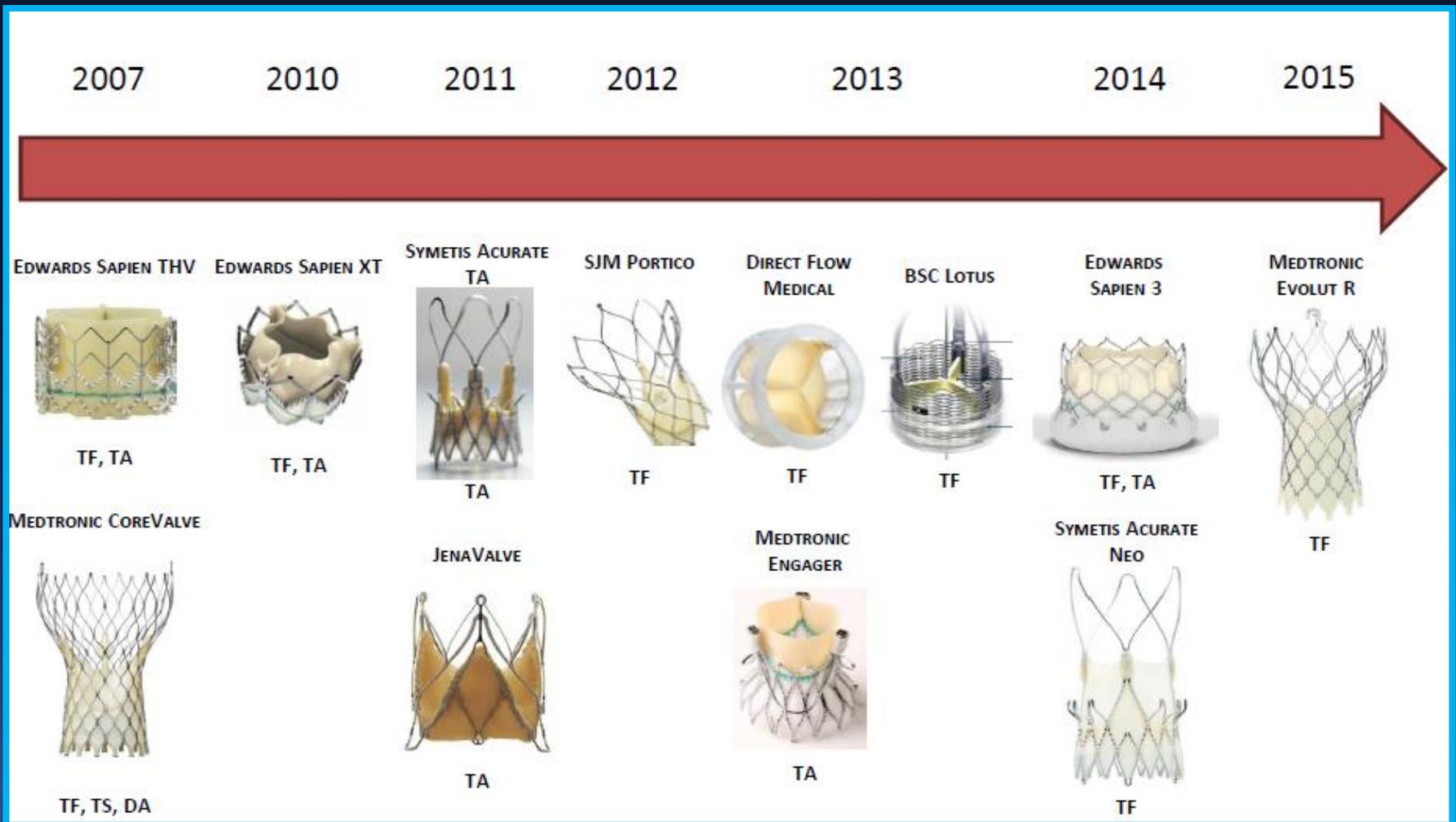
## *New performance benchmarks for high-risk AS patients (@ 30 days)*

- All-cause mortality < 3%
- Major (disabling) strokes < 2%
- Major vascular complications < 5%
- New permanent pacemakers < 10%
- Mod-severe para-valvular regurgitation < 5%

# TAVR in 2015: *Achievements*

- ***Improved Clinical Outcomes*** - Due to better patient selection, increased operator experience, routine use of 3D adjunctive imaging (esp. CTA), new generation TAVR systems, and strategic post-operative care plans – reduced peri-procedural complications.
- ***Dramatic Technology Enhancements*** - Striking response from the medical device industry to address shortcomings of early TAVR systems, coupled with advanced imaging systems and new accessory devices (sheaths/wires/emb prot, etc).

# TAVR Systems with CE-Approval (2007-15)



# TAVR in 2015

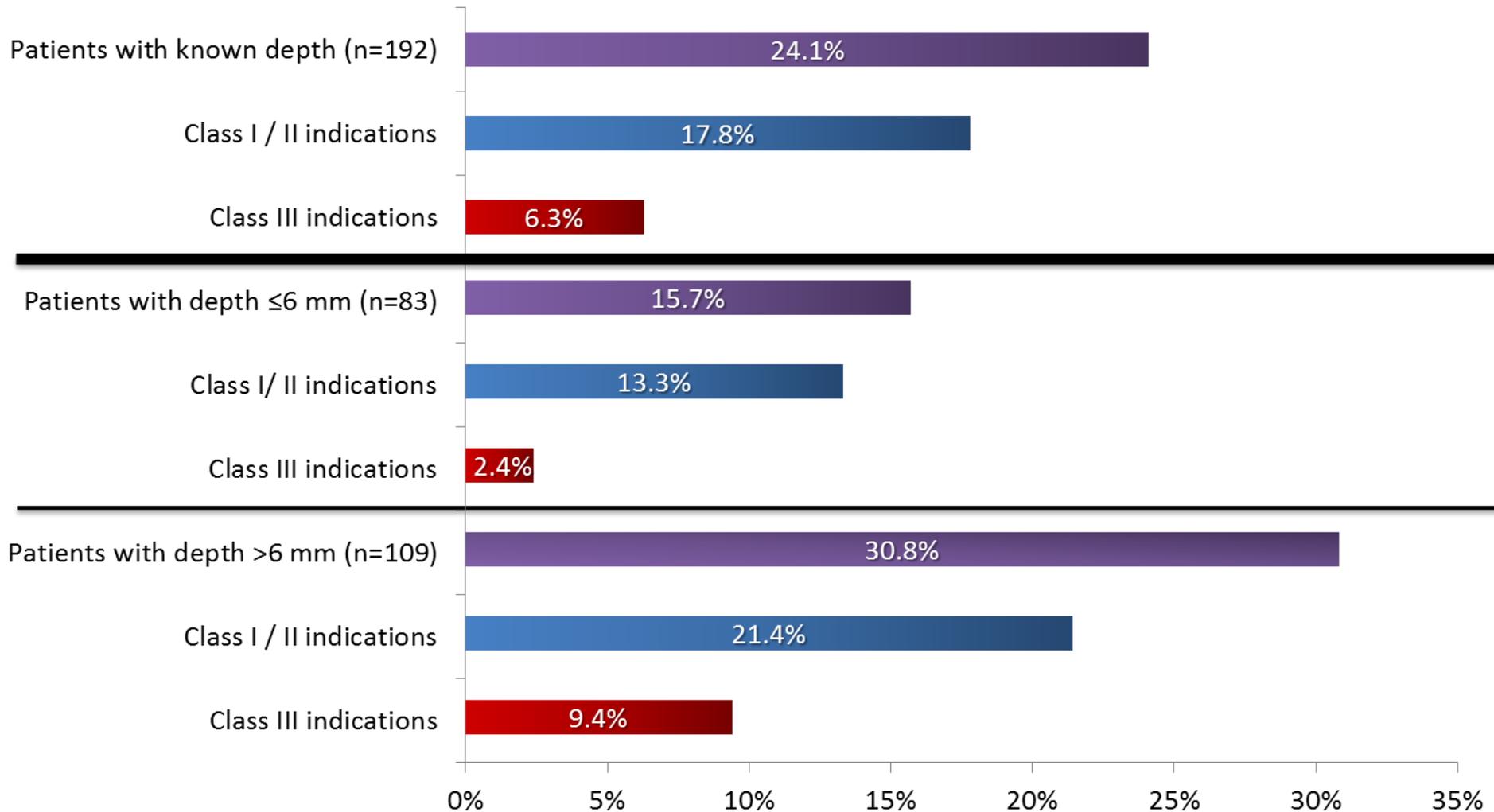
## Issues

# TAVR in 2015: *Issues*

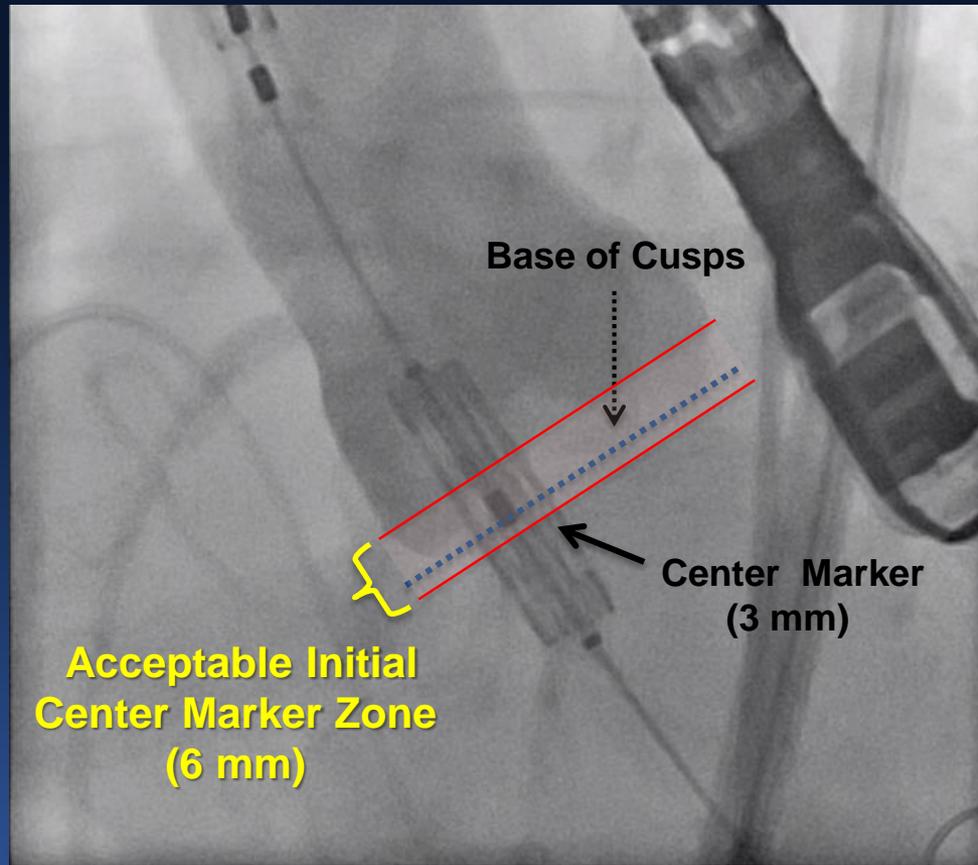
- ***Valve Sizing and Positioning*** – Remains problematic; complex interplay between the valve, the anatomy, imaging systems, and the operator's ability to precisely implant at the desired location; affects PVL, annulus rupture, and PPM rates.

# ADVANCE II

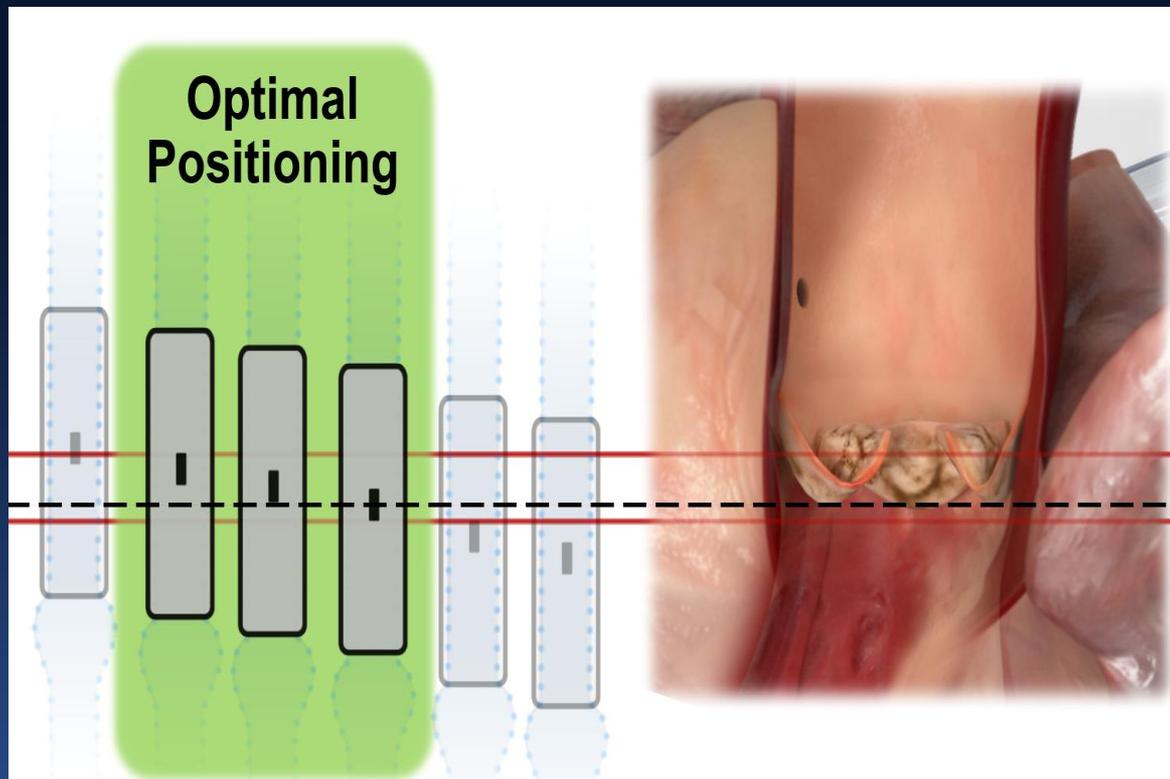
## *New Permanent Pacemaker Rate at 30 Days*



# Optimal SAPIEN 3 Positioning Based on Current Analysis



# Optimal SAPIEN 3 Positioning Based on Current Analysis



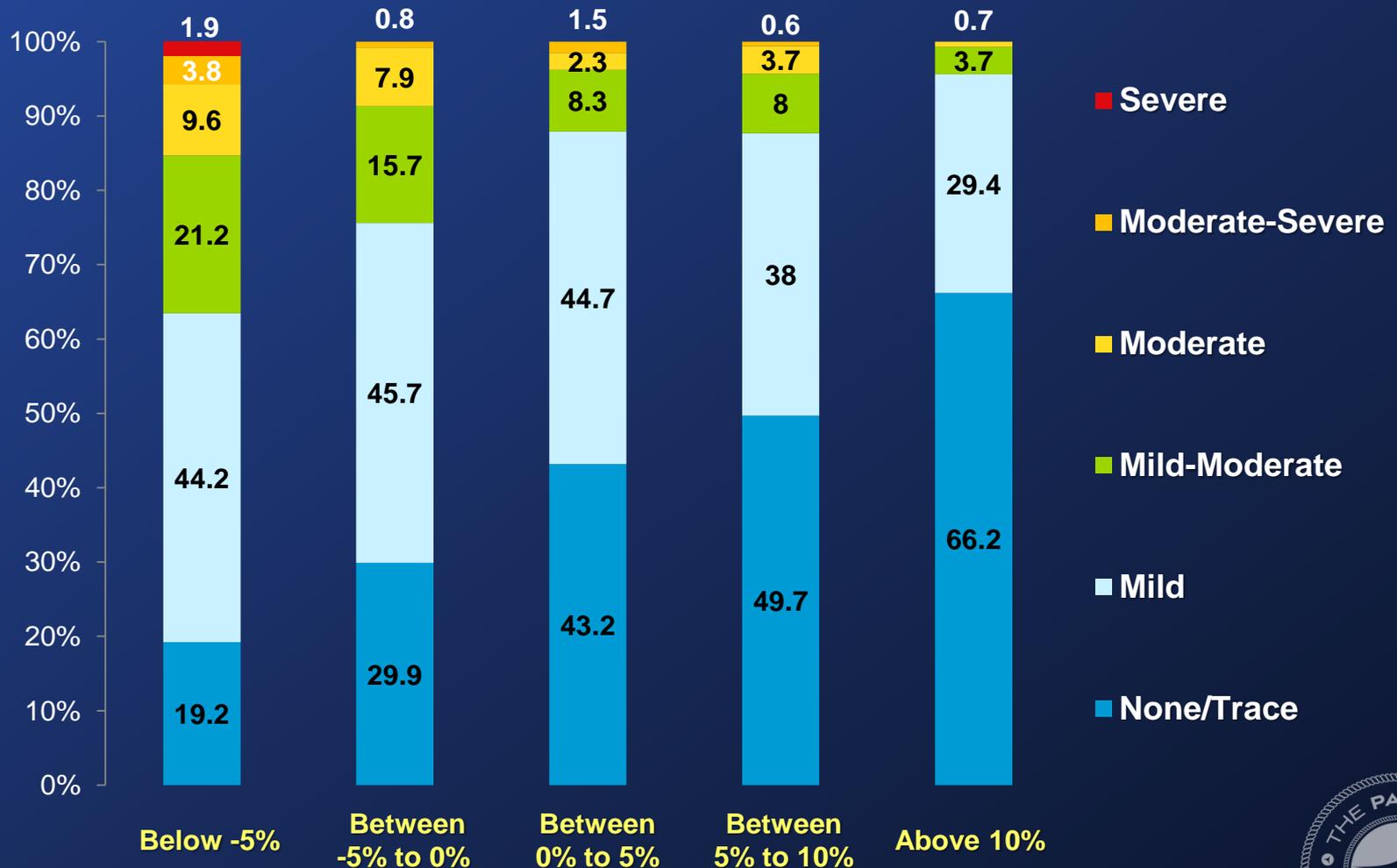
**Optimal S3 Study (D. Dvir et al)**

# Clinical Outcomes

	<b>Optimal Position (n=66)</b>	<b>Non-Optimal Position (n=82)</b>	<b>P-value</b>
S3 size (mm)	25.9 ± 2.2	25.9 ± 2	0.86
S3 crimped height (mm)	27.3 ± 2.3	27.3 ± 2.1	0.90
Non-transfemoral approach	19.7%	23.2%	0.88
Post inflation	0%	7.1%	0.04
Coronary obstruction (%)	0%	0%	NA
PM implant (%)	6.7%	18.2%	0.04
Major stroke (%)	0%	1.9%	0.31
Death (%)	0%	4.9%	0.07
PVL ≥ moderate (%)	1.5%	2.4%	0.87
PVL ≥ mild (%)	13.6%	25.6%	0.05

# SAPIEN 3 CTA Sizing Study

## PAR Stratified by % Oversizing by Area



(P. Blanke; PCR 2015)

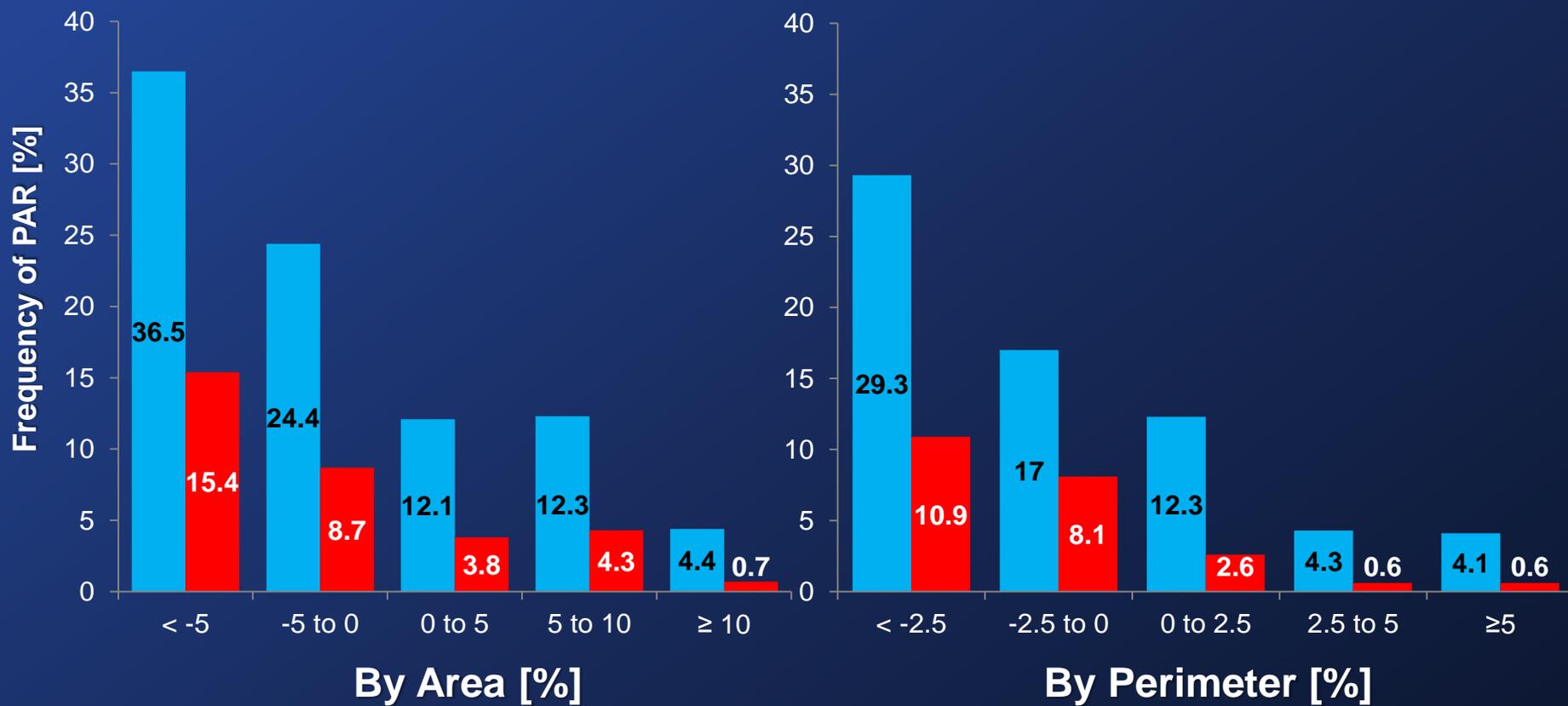
*No annulus rupture!*



# SAPIEN 3 CTA Sizing Study



≥ Mild-to-Moderate and ≥ Moderate PAR stratified by Oversizing



Undersizing/Oversizing



# TAVR in 2015: *Issues*

- **Valve Sizing and Positioning** - Remains problematic; complex interplay between the valve, the anatomy, imaging systems, and the operator's ability to precisely implant at the desired location; affects PVL, annulus rupture, and PPM rates.
- **Minimalist Strategy** – Includes percutaneous TF access, reduced # operators in the room, no GA, no TEE, no pre-dilatation (and very limited post-dilatation), no hybrid cath lab/OR, and early discharge programs; ? equivalent clinical outcomes and carry-over to lower risk patients.

# ***I Strongly Favor Selective/Frequent TEE for Most TAVR Procedures!!!***

- I don't want to disengage (dismantle) the Heart Team from routine TAVR
- GA – TEE is generally safe and well tolerated (95% patients extubated in the cath lab)
- I prefer advanced imaging for procedural planning and guidance
- ***I need advanced imaging (3D-TEE) for accurate diagnosis and management of complications – esp. important in lower risk patients!***

Parachute use to prevent death and major trauma related to gravitational challenge: systematic review of randomised controlled trials

Gordon C S Smith, Jill P Pell



***When the BP suddenly and unexpectedly drops to 50 mmHg during a TAVR...***

***Call...***

***1-800 RTHOMG***

# TAVR in 2015: *Issues*

- ***Device vs. Device Conundrums*** - Significant technology differences among devices, and currently, 3 TAVR device vs. device RCTs in the U.S.; thusfar, no major mortality/stroke differences between Sapien vs. CV; choice determined by secondary outcomes and anatomic considerations.

# The Ideal Transcatheter Aortic Valve

**Durable**

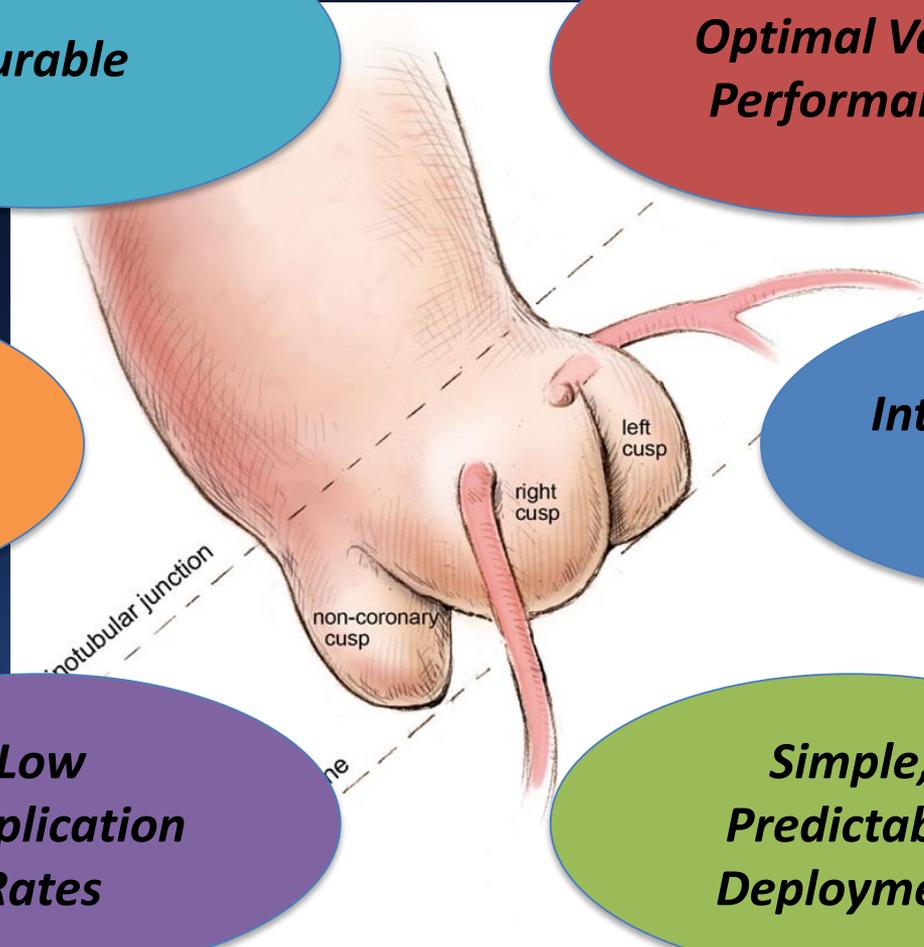
**Optimal Valve Performance**

**Low Profile for Transfemoral Delivery**

**Minimal Interference with Surrounding Structures**

**Low Complication Rates**

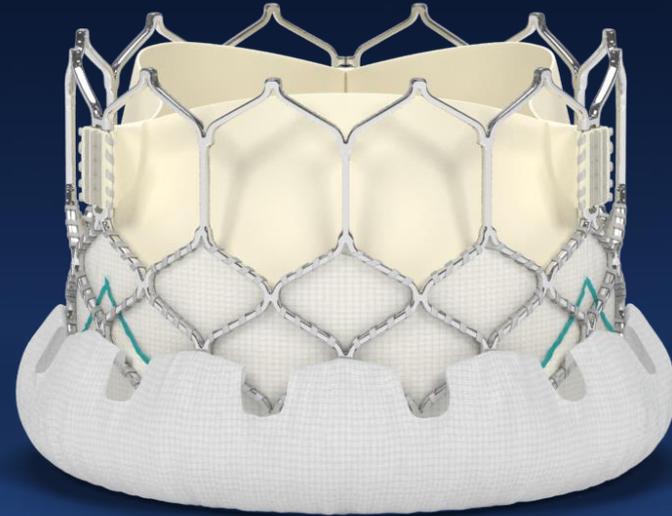
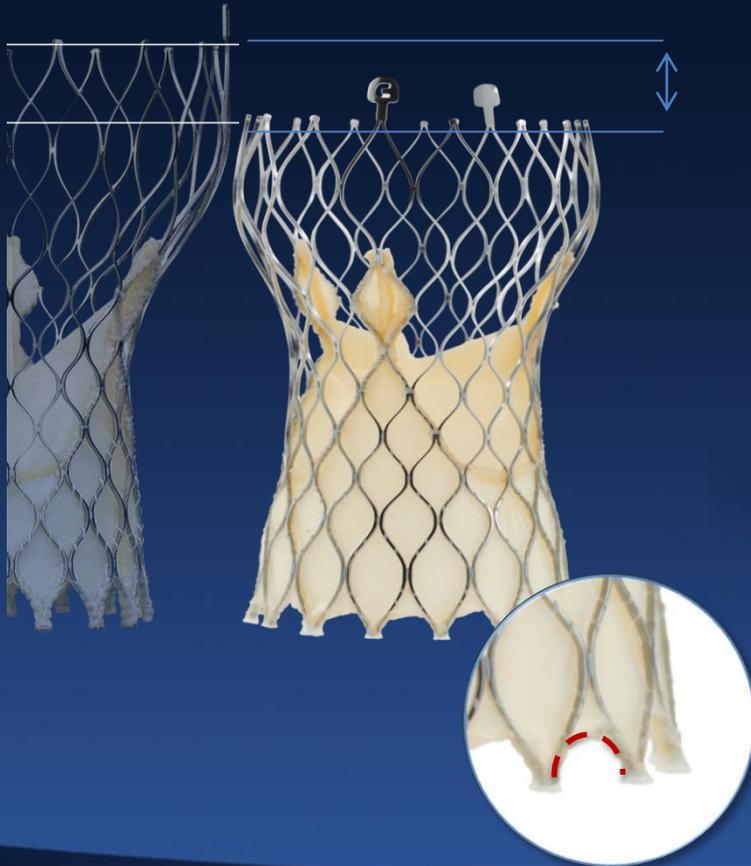
**Simple, Predictable Deployment**



# *The Ideal Transcatheter Aortic Valve*

## MDT Evolut R

## Edwards Sapien 3

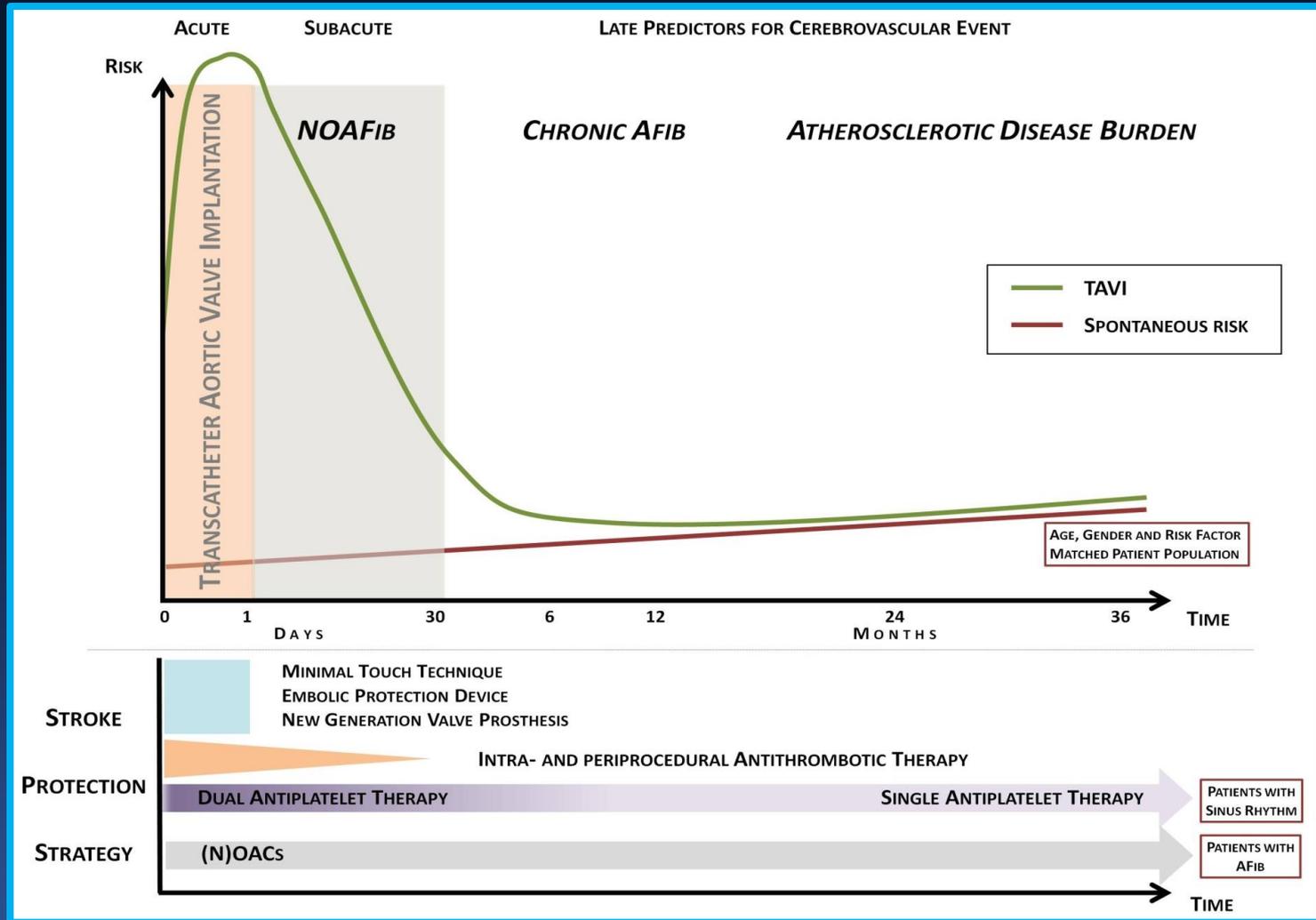


# TAVR in 2015: *Issues*

- **Device vs. Device Conundrums** - Significant technology differences among devices, and currently, 3 TAVR device vs. device RCTs in the U.S.; thusfar, no major mortality/stroke differences between Sapien vs. CV; choice determined by secondary outcomes and anatomic considerations.
- **Adjunctive Pharmacology** - An emerging area of major importance; poorly standardized, few meaningful studies and will likely affect patient outcomes, including strokes (esp. AF patients), ? valve thrombosis, and bleeding concerns.

# TAVI AND CEREBROVASCULAR EVENTS

**STORTECKY, WINDECKER. CIRCULATION 2012;126:2921-4**



# TAVR Adjunct Pharmacology

## *Customized Patient-Based Therapy*

BEFORE-	DURING	AFTER
Acetylsalicylic acid (ASA)	<b>UNFRACTIONATED HEPARIN:</b> target ACT $\geq 300''$	<b>ASA + CLOPIDOGREL</b> 
	<b>Bivalirudin:</b> 	<b>Acetylsalicylic acid (ASA)</b> ARTE trial
	 <small>Bivalirudin and Aortic Valve Intervention Outcomes</small>	<u>Non anti-VKA Oral Anticoagulant</u> <u>± ASA:</u>
	<u>Low Molecular Weight Heparin</u> 	 
		

# New TAVR Pharmacology Trial



## Trial design

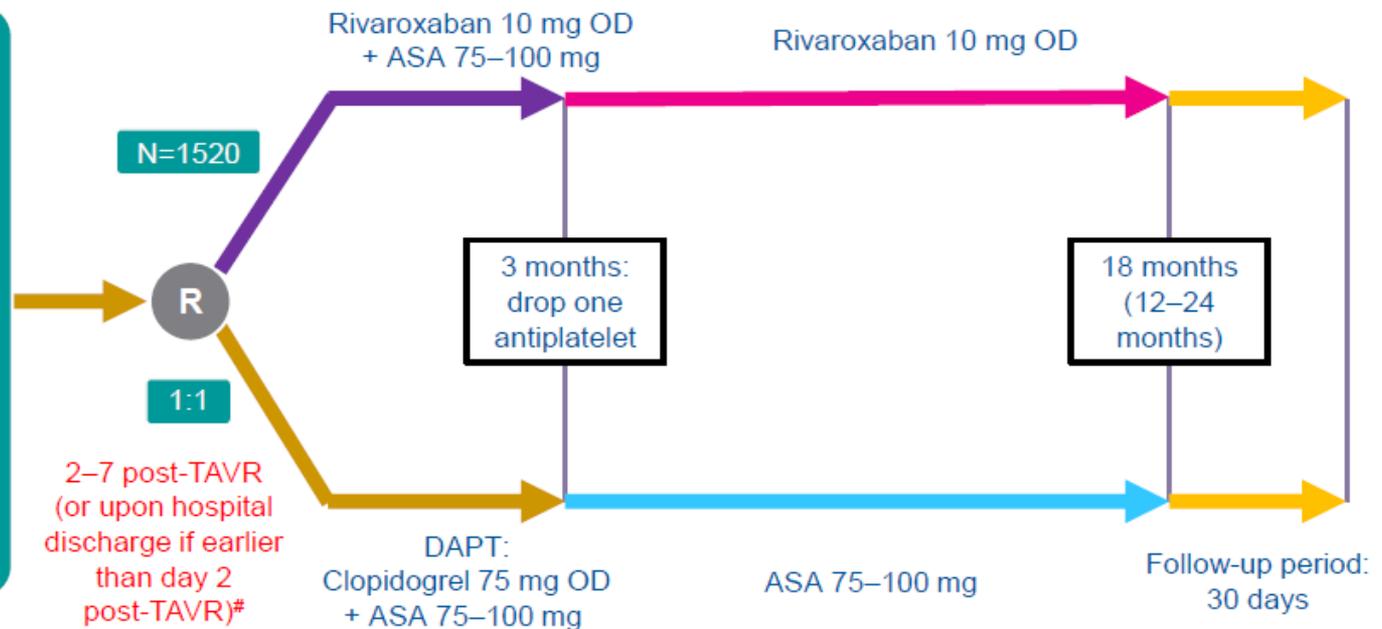
Prospective, randomized, open-label with blinded endpoint evaluation (PROBE), parallel-group, active-controlled, multicenter international study

### Study population:

Patients with successful TAVR\*

### Key excl. criteria:

Ongoing indication for DAPT or anticoagulation, previous ischemic stroke, active peptic ulcer or upper GI bleeding, previous ICH, or severe renal insufficiency



\*~110 sites in Europe & North America (15 countries)

# Majority of patients will be on DAPT after TAVR  
Gastric protection recommended throughout study

PIs: Dangas, G.  
Windecker, S.

# PARTNER 1A and 1B

## Stroke and Bleeding over Time

Cohort-Risk	30d	1 Year	2 Years	3 Years	5 Years
Inoperable (B)	1.7%	11.0%	13.6%	15.7%	14.6%
High Risk (A)	1.7%	11.0%	13.6%	15.7%	10.4%
Inoperable (B)	16.5%	16.5%	32.0%	32.0%	33.5%
High Risk (A)	9.3%	15.7%	19.0%	20.8%	26.6%

**Major Bleeding 2.5x  
more Frequent than  
Stroke**

Leon NEJM 2010; Smith NEJM 2010; Kodali NEJM 2012; Makkar NEJM 2012;  
Kapadia Circulation 2014; Kapadia Lancet 2015.; Mack Lancet 2015

Généreux P. AHA 2014, Chicago

# 2,401 Patient Survivors post-TAVR

6% Major Bleeding between 30dys -1yr

8.6% if Atrial Fibrillation

(median time of occurrence: 132 [71, 230] days)



Major Bleeding between 30dys -1yr:

Adjusted Mortality: HR 3.83 (2.62-5.61) p<0.0001

Généreux P. et al. JACC 2014;64; 2605-15

# TAVR in 2015

## Controversies

# TAVR in 2015: *Controversies*

- ***Crossroads: Expanded Clinical Indications*** -  
Are we poised for a MAJOR expansion in TAVR indications, including moderate and low-risk patients, bioprosthetic valve failure, asymptomatic severe AS, and other scenarios; have we passed the durability “sniff test” for THV? Will regulatory agencies or reimbursement delays blunt progress?

# Expanded Clinical Indications

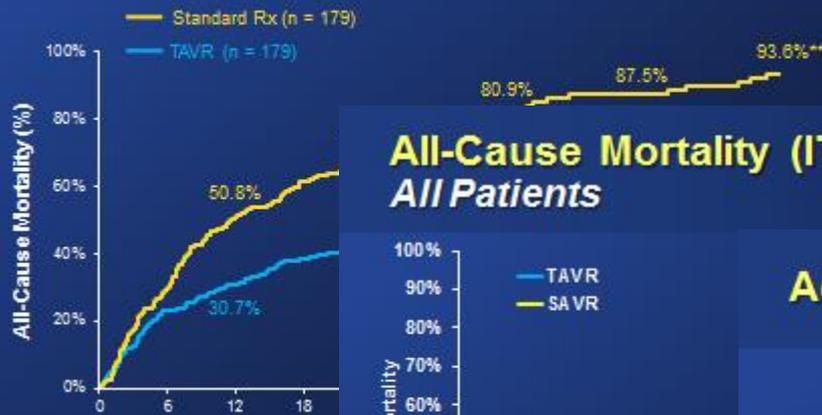
## *A TAVR Crossroads?*



# PARTNER 5-year FU in Lancet (March, 2015)

## All-Cause Mortality (ITT)

Crossover Patients Censored at Crossover



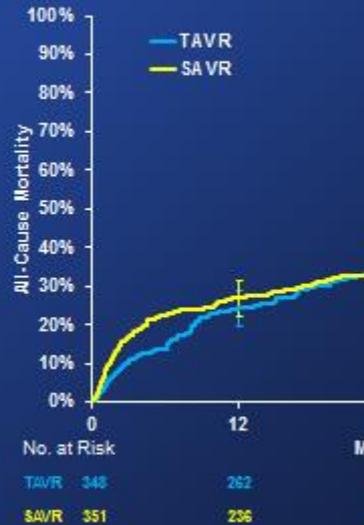
\* In an age and gender matched cohort, the mortality at 5 years is 41%  
 \*\* Only 1 standard Rx patient crossed over to TAVR or had SAVR (out of 179)

surgical aortic valve replacement  
 with aortic stenosis

Michael J Mack, Martin B Leon, William N Anderson, Eugene H Blackstone, Vinod H Thourani, Vasilis Babaliaros, Augusto Pichard, Howard C Gersh, Lars G Svensson, for the PARTNER 1 trial investigators

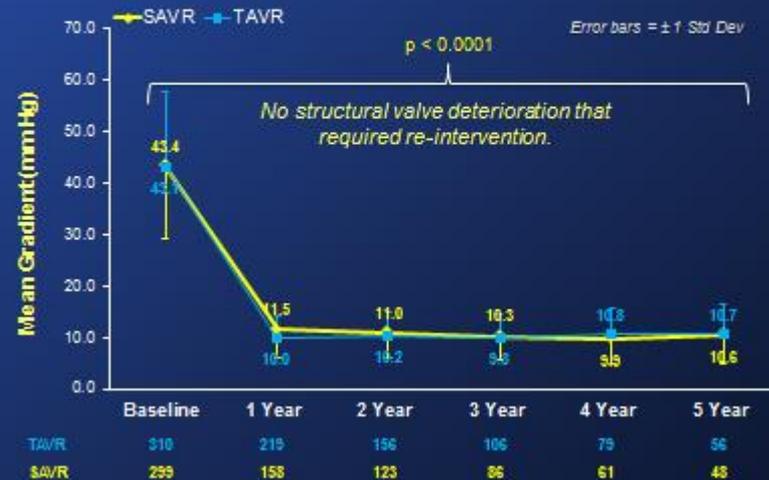
for aortic valve replacement  
 ent for patients with  
 NER 1): a randomised

## All-Cause Mortality (ITT) All Patients



No. at Risk	TAVR	SAVR
0	348	351
12	262	236

## Aortic Valve Mean Gradient



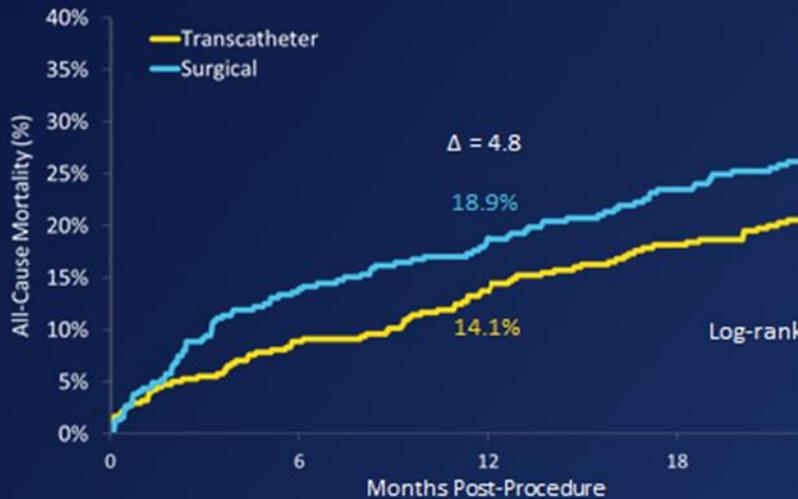
	Baseline	1 Year	2 Year	3 Year	4 Year	5 Year
TAVR	310	219	156	106	79	56
SAVR	299	158	123	86	61	48

# Transcatheter Aortic-Valve Replacement with a Self-Expanding Prosthesis

CoreValve US Clinical Trials  
ACC 2015

M.D., Michael J. Reardon, M.D.,  
M.D., G. Michael Deeb, M.D.,  
er, M.D., James Hermiller, Jr., M.D.,  
n Heiser, M.D., William Merhi, D.O.,  
D., Newell Robinson, M.D.,  
M.D., Kevin Harrison, M.D.

## All-Cause Mortality



$\Delta = 6.5$

## Echocardiographic Findings

CoreValve US Clinical Trials  
ACC 2015

TAVR had significantly better valve performance over SAVR at all follow-up visits ( $P < 0.001$ )





ACC.15

TCT@ACC-15 | innovation in intervention

64<sup>th</sup> Annual Scientific Session & Expo

# An All-comers Randomized Clinical Trial Comparing Transcatheter with Surgical Aortic Valve Replacement in Patients with Aortic Valve Stenosis

## *Nordic Aortic Valve Intervention Trial (NOTION)*

Hans Gustav Hørsted Thyregod, MD

Dep. of Cardiothoracic Surgery, Copenhagen University Hospital, Denmark



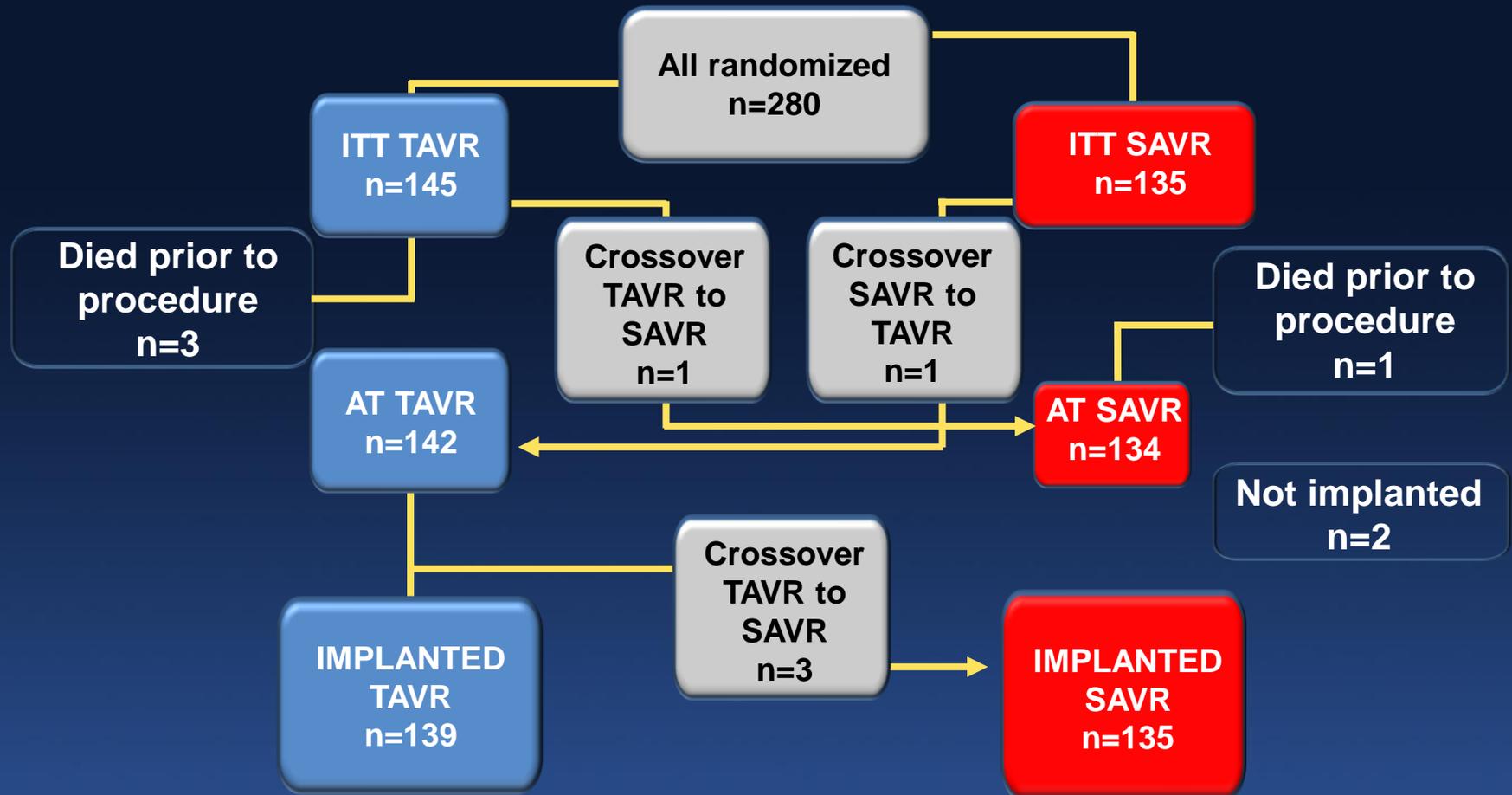
TVT CHICAGO

Transcatheter Valve Therapies (TVT)  
A Multidisciplinary Heart Team Approach



CARDIOVASCULAR  
RESEARCH FOUNDATION  
At the heart of innovation

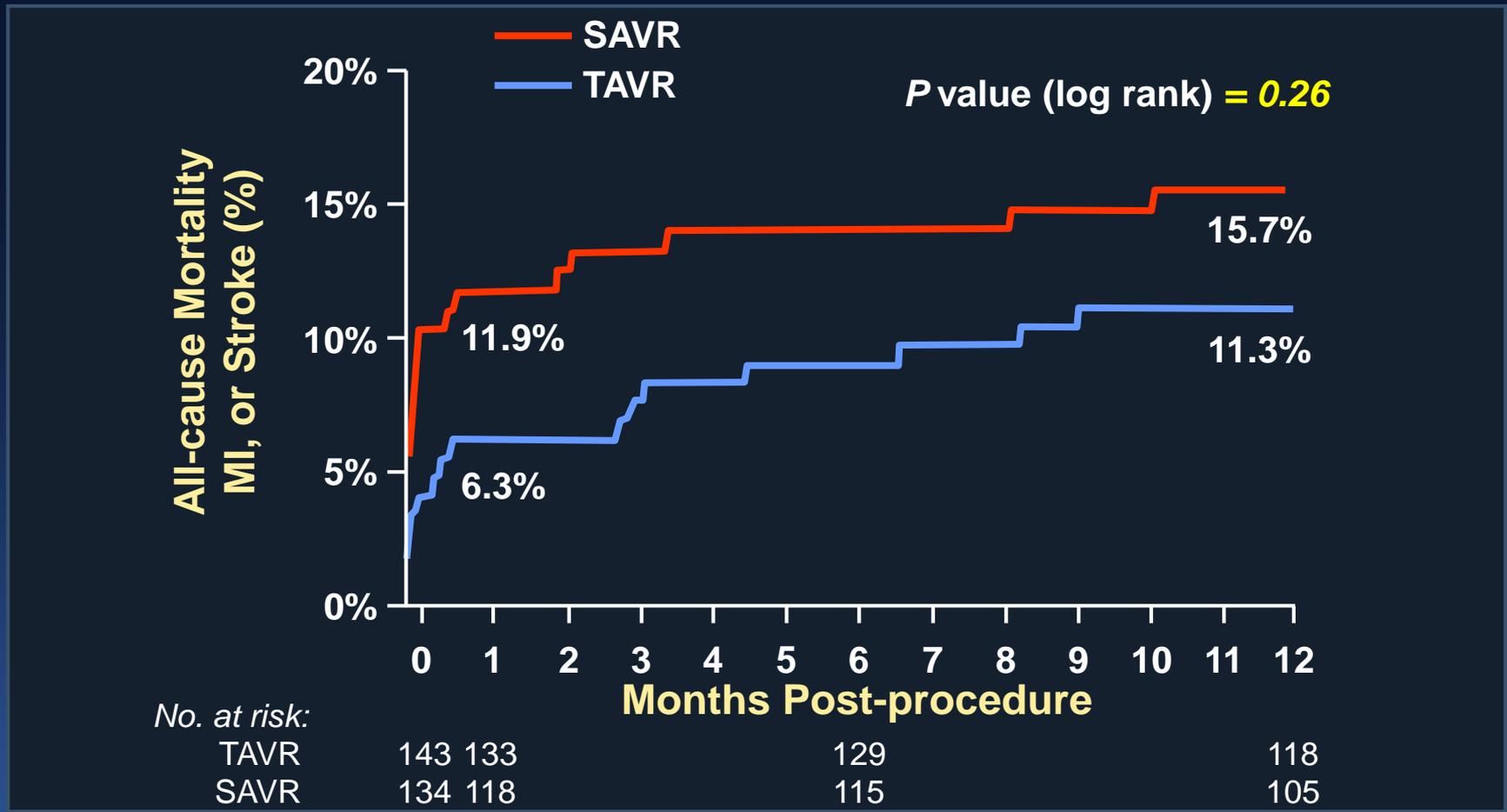
# NOTION: Study Flow



# NOTION: Baseline Characteristics

Characteristic, % or mean $\pm$ SD	TAVR n=145	SAVR n=135	P value
Age (yrs)	79.2 $\pm$ 4.9	79.0 $\pm$ 4.7	0.71
Male	53.8	52.6	0.84
Society of Thoracic Surgeons (STS) Score	2.9 $\pm$ 1.6	3.1 $\pm$ 1.7	0.30
STS Score < 4%	83.4	80.0	0.46
Logistic EuroSCORE I	8.4 $\pm$ 4.0	8.9 $\pm$ 5.5	0.38
NYHA class III or IV	48.6	45.5	0.61

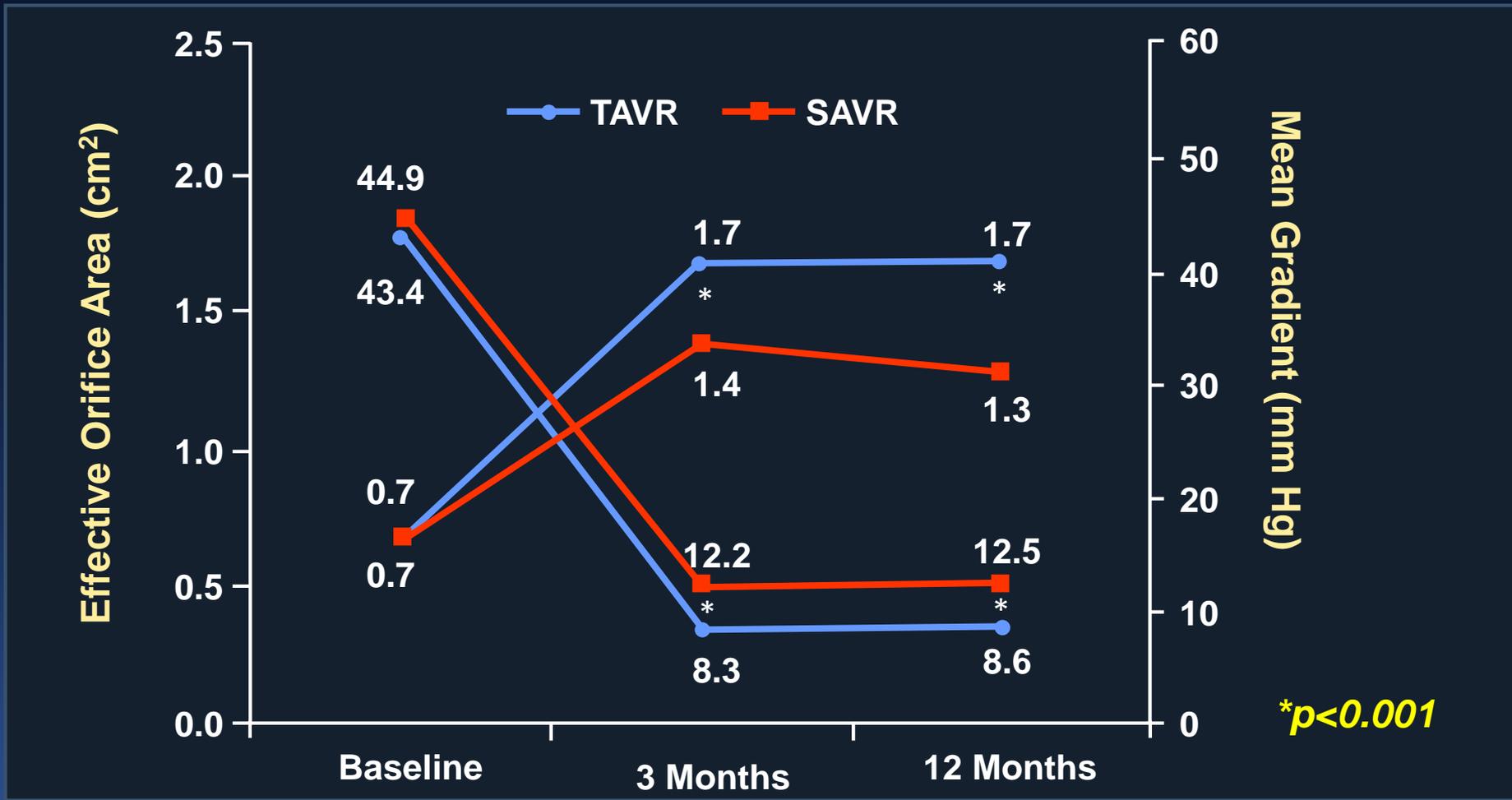
# NOTION: Death (all-cause), Stroke or MI at 1 Year (as-treated)

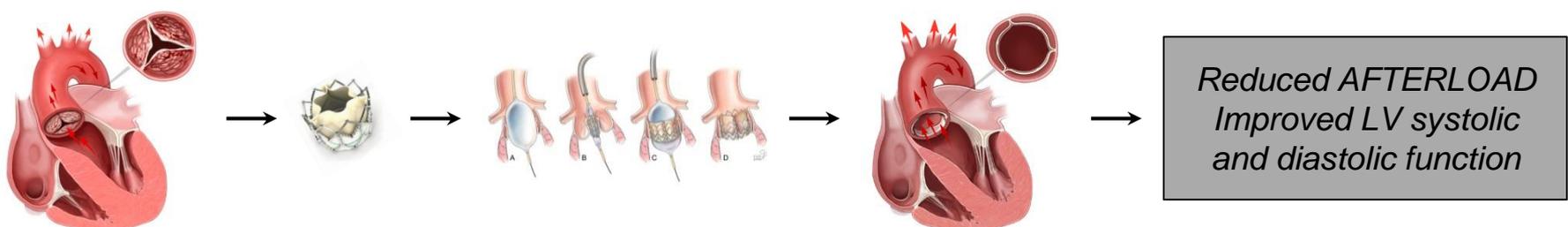
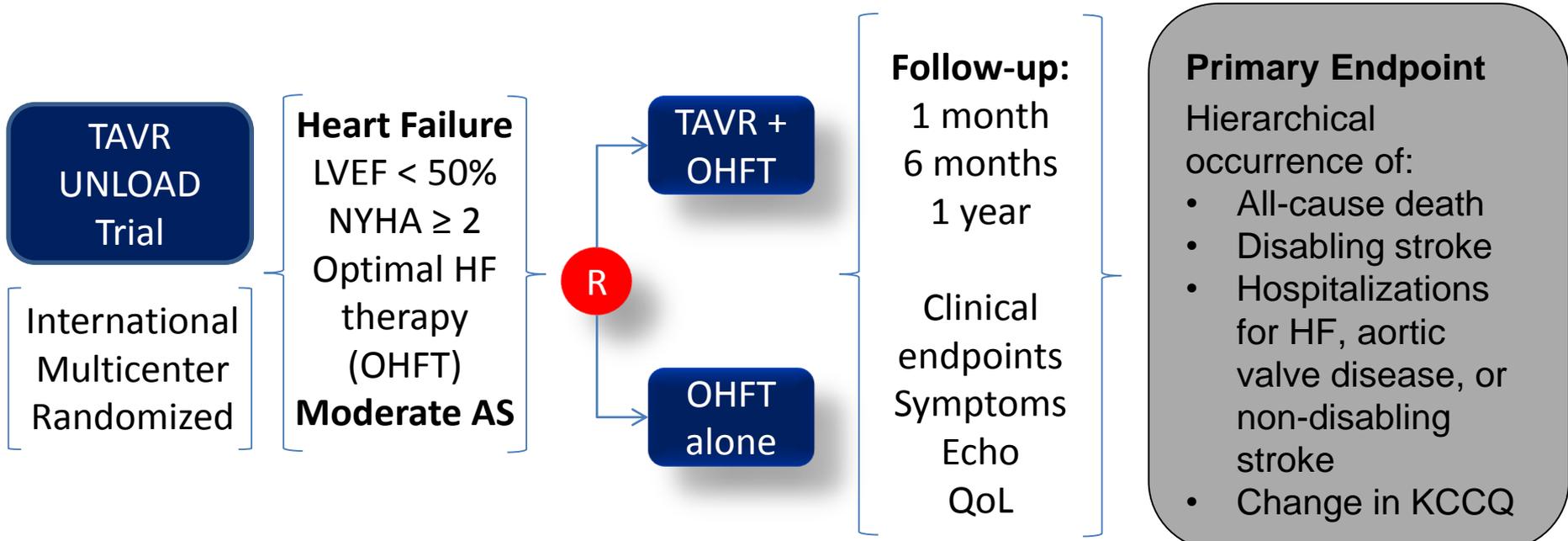


# NOTION: 2<sup>ry</sup> Outcomes at 30 Days

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

# NOTION: Aortic Valve Performance



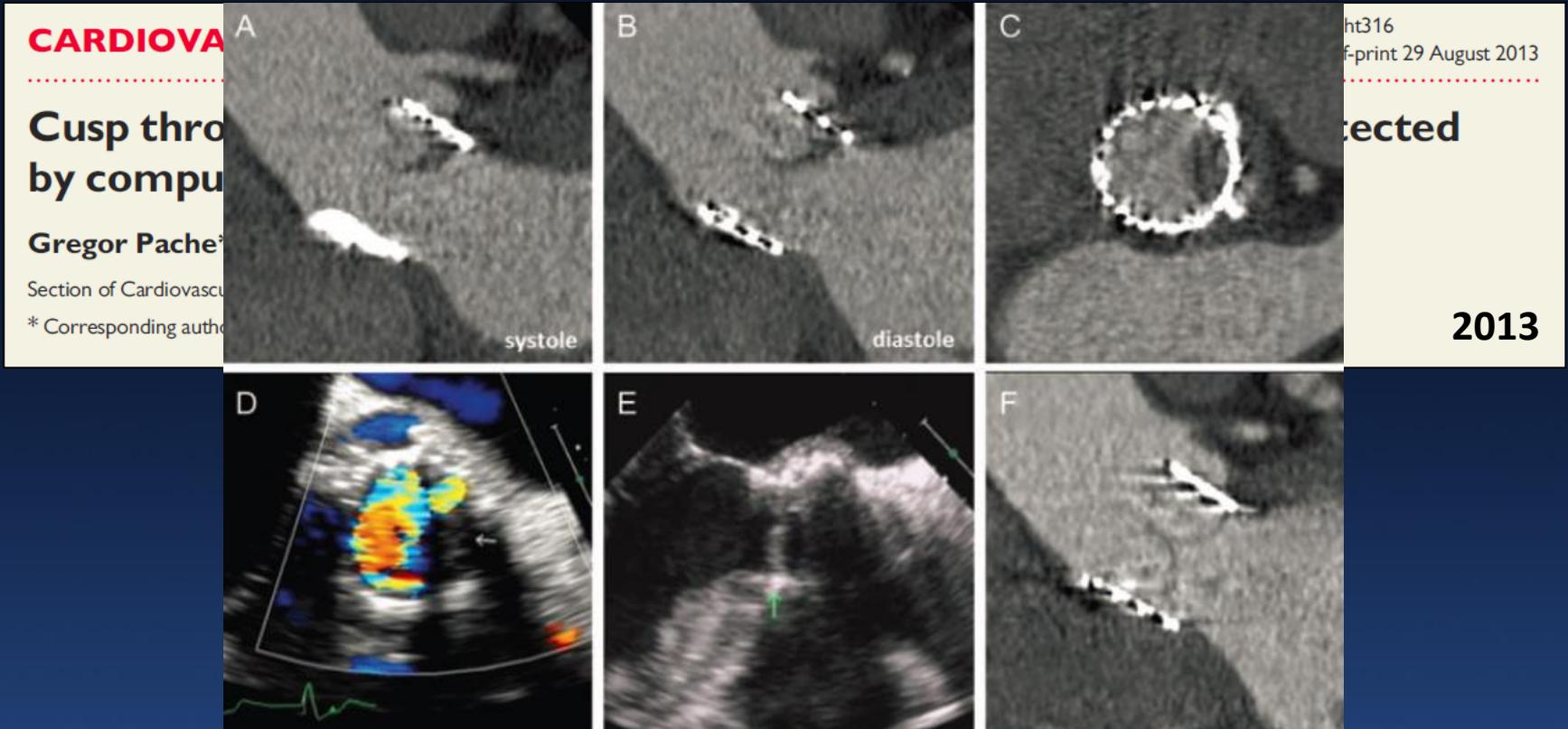




# TAVR in 2015: *Controversies*

- ***Crossroads: Expanded Clinical Indications*** - Are we poised for a MAJOR expansion in TAVR indications, including moderate and low-risk patients, bioprosthetic valve failure, asymptomatic severe AS, and other scenarios; have we passed the durability “sniff test” for THV? Will regulatory agencies or reimbursement delays blunt progress?
- ***“Fatal” Flaws*** - Early or late structural valve failure which may limit TAVR expansion; Is the recent 4D-CT valve leaflet abnormality controversy just a hiccup or a troubling sign?

# Valve Leaflet Abnormalities



- 7 days after Edwards Sapien XT 29mm TAVR, leaflet thickening on 4D-cine CT
- No symptoms and mean AVG 9 mmHg
- Warfarin for 10 wks: complete disappearance of CT and TEE abnormalities

# Valve Leaflet Abnormalities

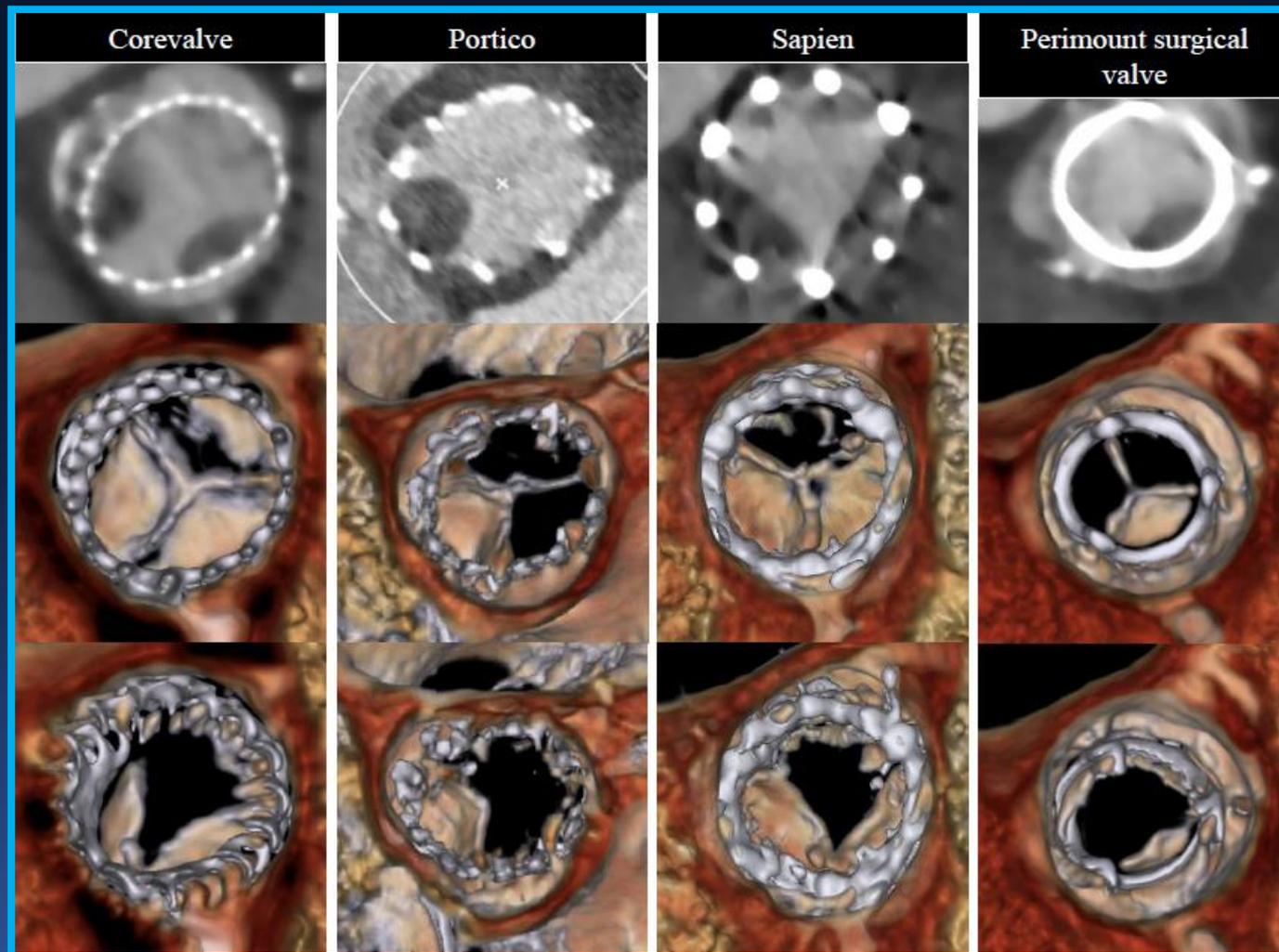
## Treatment and Clinical Outcomes of Transcatheter Heart Valve Thrombosis

Azeem Latib, MD\*; Toru Naganuma, MD\*; Mohamed Abdel-Wahab, MD; Haim Danenberg, MD; Linda Cota, MD; Marco Barbanti, MD; Helmut Baumgartner, MD; Ariel Finkelstein, MD; Victor Legrand, MD; José Suárez de Lezo, MD; Joelle Kefer, MD; David Messika-Zeitoun, MD; Gert Richardt, MD; Eugenio Stabile, MD; Gerrit Kaleschke, MD; Alec Vahanian, MD; Jean-Claude Laborde, MD; Martin B. Leon, MD; John G. Webb, MD; Vasileios F. Panoulas, MD; Francesco Maisano, MD; Ottavio Alfieri, MD; Antonio Colombo, MD

- From Jan 2008 to Sept 2013, among 4266 TAVR cases, 26 patients with THV thrombosis (0.61%); 20 Edwards Sapien/Sapien XT , 6 MDT CoreValve
- Median time from TAVR to imaging findings 181 days
- Most common Sx was DOE (65%) and 31% were without Sx
- Echo (TTE usually): mean AV gradient 40.5 mmHG, thickened leaflets 77% and thrombotic mass 23%
- Warfarin for 2 mos: 23 (88%) reduced symptoms and improved gradients

**Latib A et al. Circ Cardiovasc Interv 2015 Apr 8**

# Valve Leaflet Abnormalities



**Diastole**

**Systole**

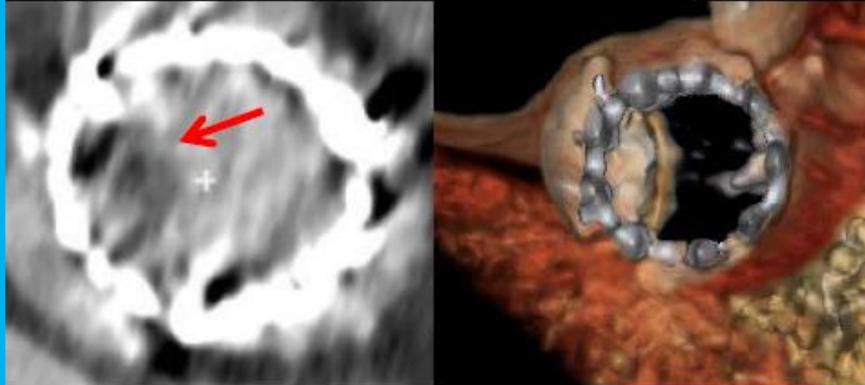
# Valve Leaflet Abnormalities

## Knowledge

- *Frequency:*
  - Neumann 16/156 = 10.2%
  - Sondegaard (SAVORY) 10/62 = 15%
  - Makkar : Portico IDE 22/52 = 40% and RESOLVE 7/70 = 10%
  - **TOTAL 55/340 = 16.2%**
- *Subclinical:* no evidence of increased gradients, symptoms, or clinical events (not seen on TTE)
- *Anticoagulation:* suggestive case series indicating improvement in imaging abnormalities after systemic anticoagulation

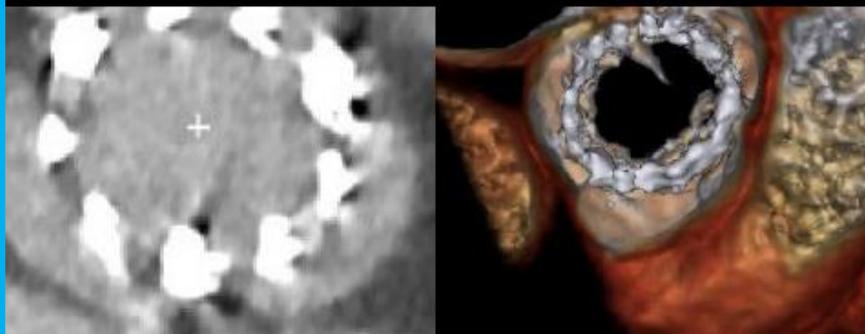
# Valve Leaflet Abnormalities

Reduced leaflet motion on 30-day CT



**Patient was started on Warfarin**

Resolution of thrombus and restoration of leaflet motion on 7 month follow-up CT



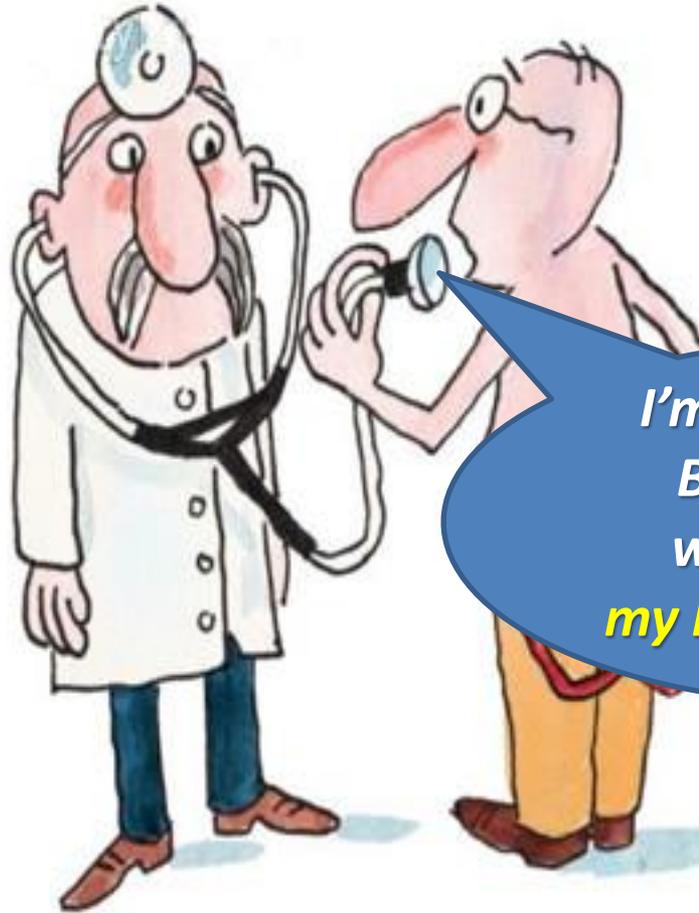
# Valve Leaflet Abnormalities

## Gaps

- *Imaging observations and pathobiology*
  - Ultra-sensitive imaging tool documenting adaptive biocompatibility responses, OR
  - Forme fruste of accelerated valve dysfunction with future clinical consequences
- *Treatment thresholds (anticoagulation)*
  - High vs. low; selective vs. universal
  - Will require large RCTs to sort out
- *Risk + resource consumption vs. benefit*
  - Imaging costs and bleeding risks of anticoagulation

# Doctor patient relationship!

## Routine 4D CT after TAVI



*I'm doing great!!  
But I'm really  
worried about  
my leaflet thickness*

# *Valve Leaflet Abnormalities*

## Next Steps



# April 16, 2002; FIM-TAVI; Rouen, FR



# TAVI: 10-Year Anniversary



# “Outpatient” Same-Day TAVR

*Sacre-Coeur Hospital; Montreal, CN*



Philippe  
Genereux

Philippe  
Demers

Donald  
Palisaitis