

TCT-AP2017
Seoul, April 25-28, 2017

TAVI Perspective 2017

Current Situation – Controversy - Prospect

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Eberhard Grube, MD

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

G – Grant and or Research Support E – Equity Interests S – Salary, AB – Advisory Board
C – Consulting fees, Honoraria R – Royalty Income I – Intellectual Property Rights
SB – Speaker's Bureau O – Ownership OF – Other Financial Benefits

The State of TAVR in 2017

The tremendous momentum behind transcatheter valve therapies continued to build through the last year with many major accomplishments, including:

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

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

The goal of this presentation is to provide an overview of the current state of TAVR, as well as some thoughts on where the field is headed.

TAVR Journey - 2017

- **The Beginning...**

With global aging, there was an important unmet clinical need in the treatment of aortic stenosis

- open surgery is and was problematic in frail elderly patients with multiple co-morbidities

The early days of TAVR were tumultuous – crude devices, inexperienced operators, and unstable procedures = frequent complications

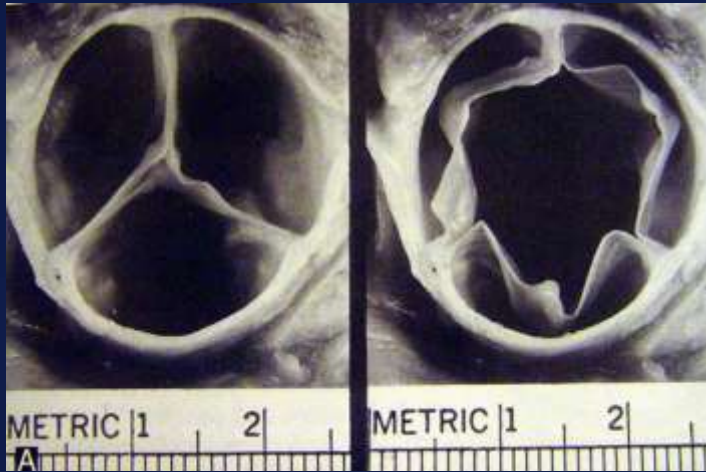
The severe AS-TAVR Po

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



But still enjoying life !

The *Standard* for critical AS Rx was Surgical AVR



Normal



Degenerative
calcific

Bicuspid



Mechanical



Tissue



Stentless

SURGEONS view of the Aortic Stenosis Population



Optimal therapy for valve disease ...



It doesn't take a genius to realize that we need better therapy solutions particularly for elderly patients with end-stage valve disease!!!

Some patients just don't do well with the gold standard...

Rules of Engagement ... ?

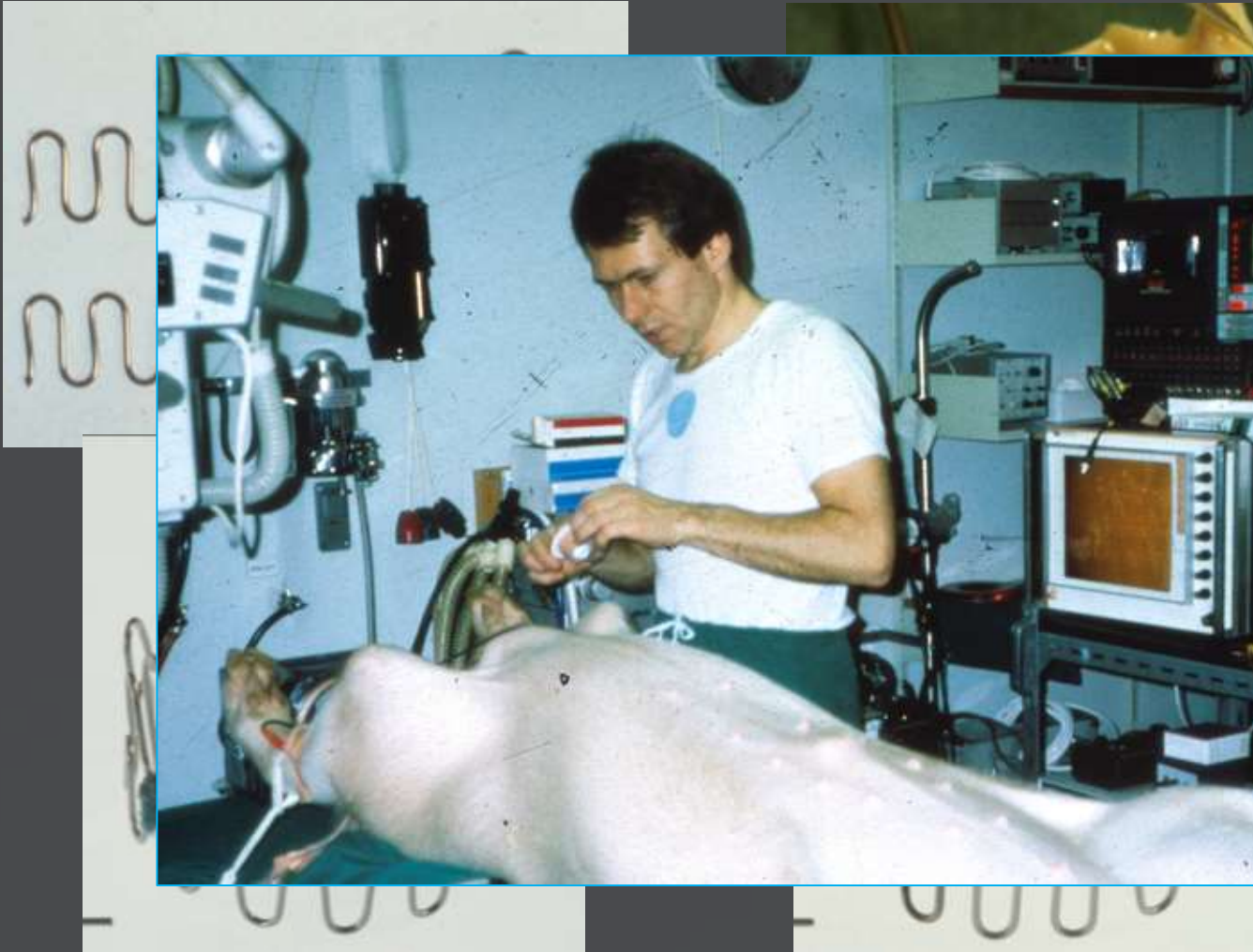
Time of early impact!



CV Surgeon

Interventional
Cardiologist

The Andersen Stent-Valve (1989)



First Sapien and Core Valve Implants



April 16, 2002



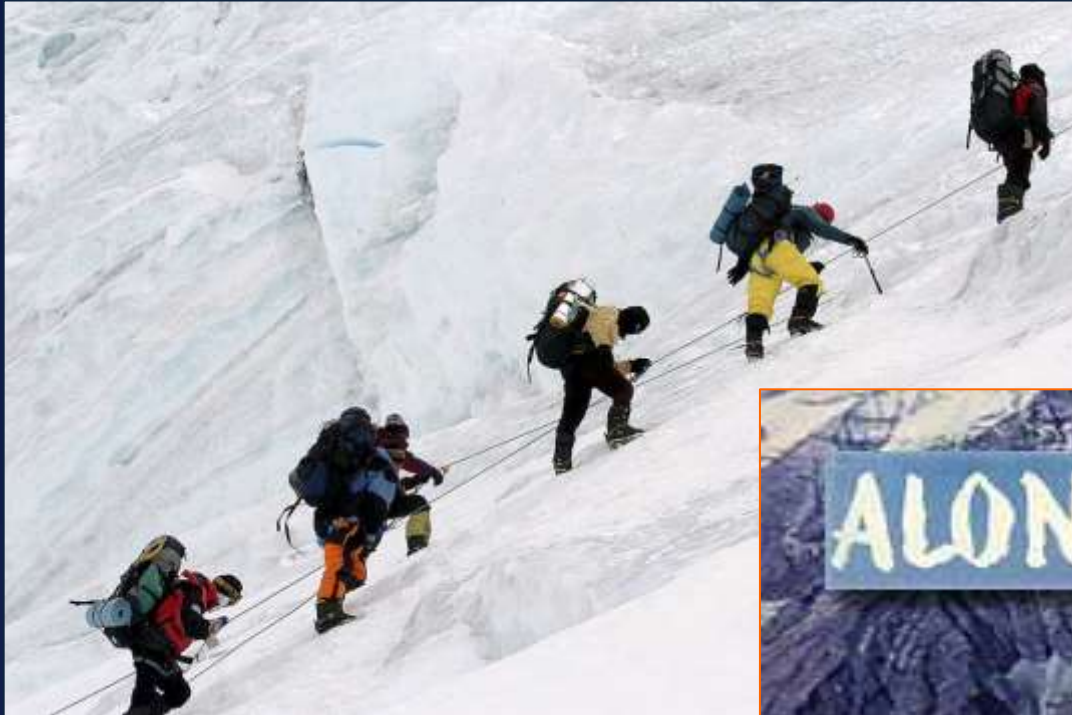
July 12, 2004

TAVR Journey – The early Skeptics

- *Stroke*
- *Aortic Rupture*
- *Coronary Occlusion*
- *Mitral Valve Injury*
- *Valve instability – embolisation*
- *Para Valvular Regurgitation*
- *Valve Durability*
- *Technical challenges will be insurmountable*

This is a crazy project that will fail

When you climb a mountain, you can choose a...



Full team plenty of equipment

Self guided tour with a backpack



The Heart Team - A Deal with the Devil?



Leipzig 2004

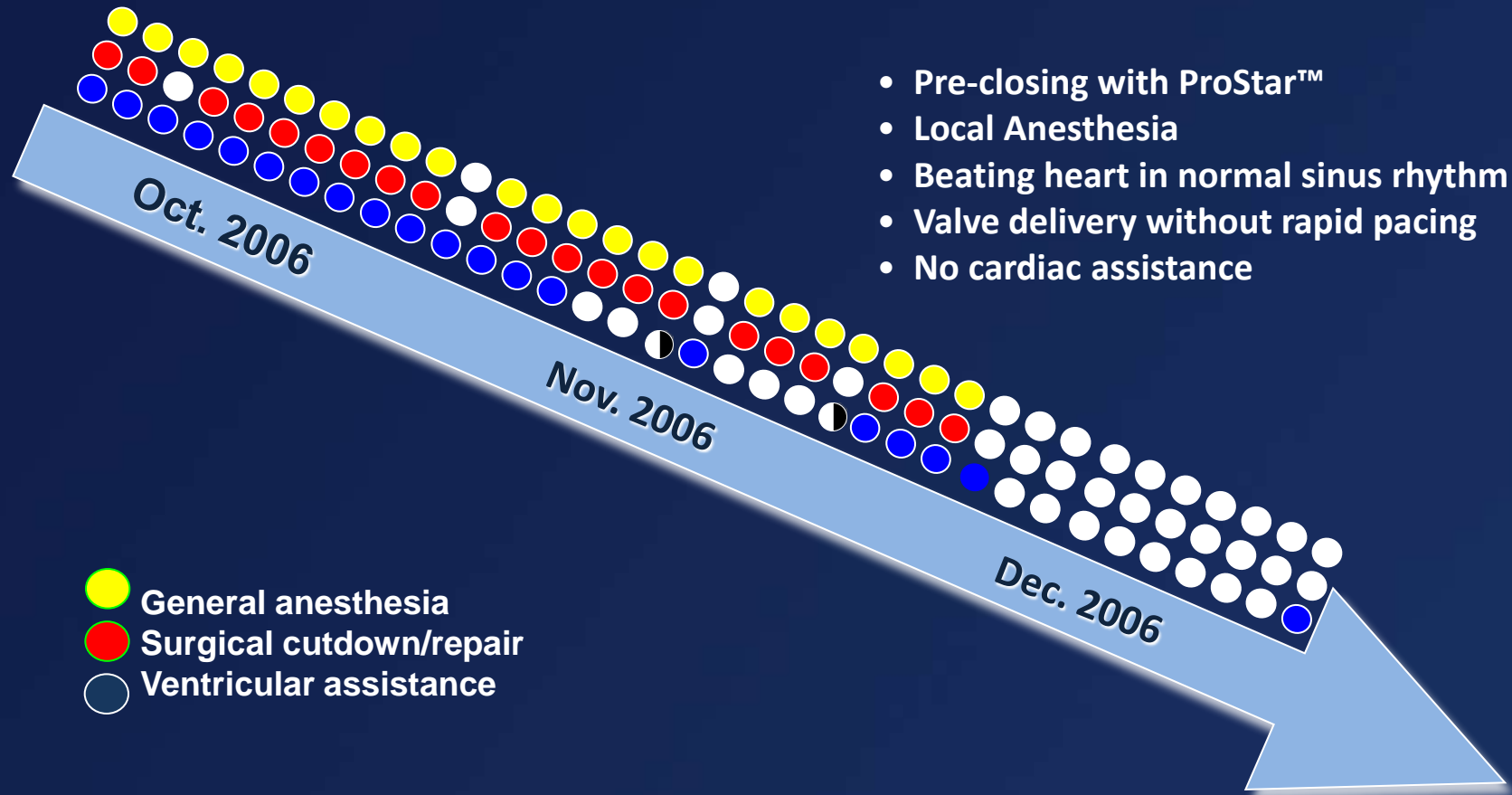
M. Mack

F. Mohr

18 French Procedural Progress

Evolution to « true percutaneous cath lab procedure »

within first 40 patients of 18F study =



Percutaneous Valve Therapy: The Grand Debate....



Interventional
Cardiologist

CV Surgeon

The “Grand” Debate is over!



The Heart Team Bonn

Heart Valve Team

Surgeon

- Cath lab/OR staff
- Nurses, NPs, PAs
- Research staff
- Social work, PT
- Geriatricians
- Coordinators
- Hospital administrators

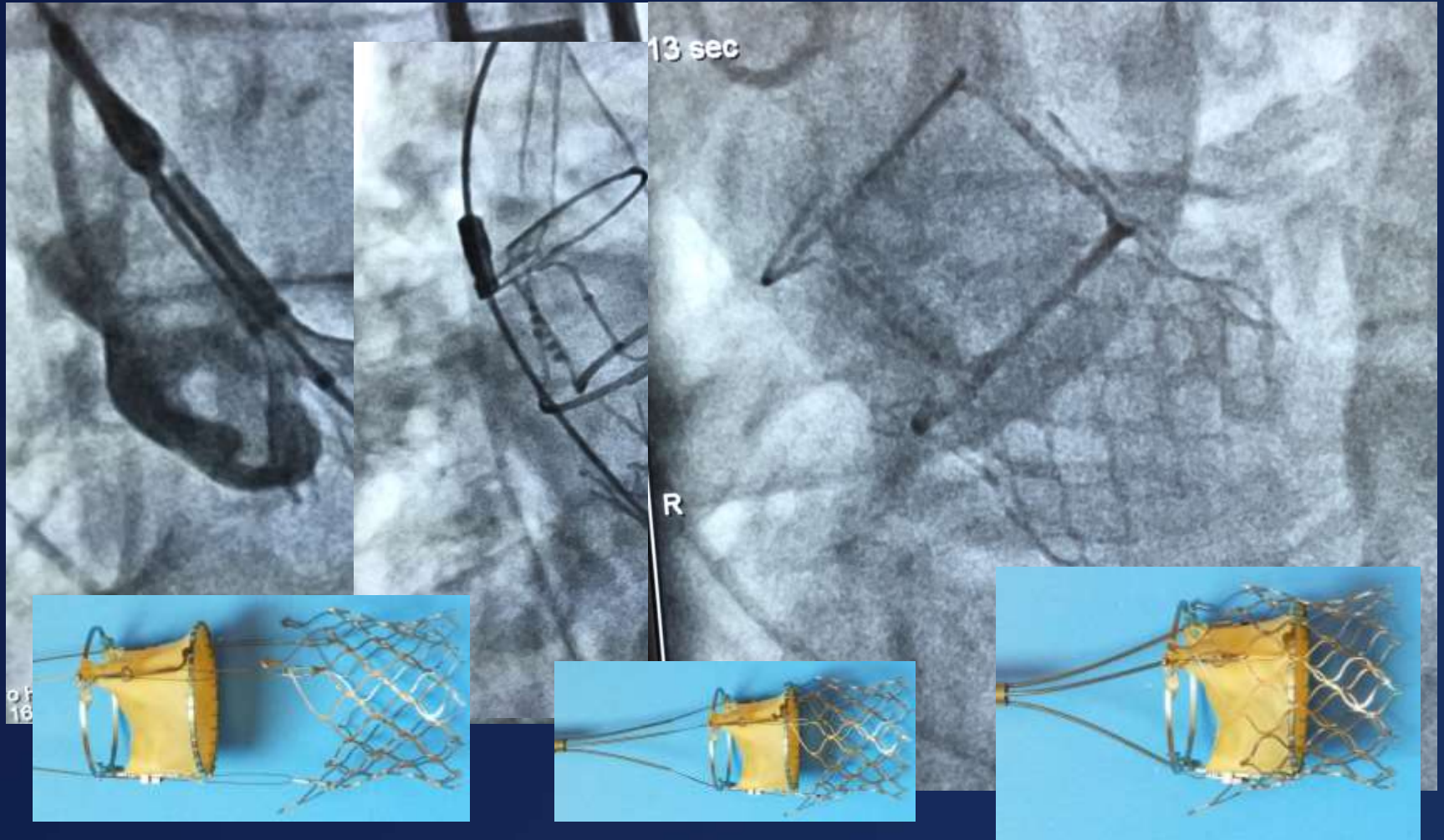
tier

- Valve clinic
- Case selection
- Multi-modality imaging (access site, valve size)
- TAVR procedure (cath lab/OR)
- Post-op care and FU

Anesthesia

Imaging
Specialist

First Successful 12 French Valve Medical TAVR Modular Implant



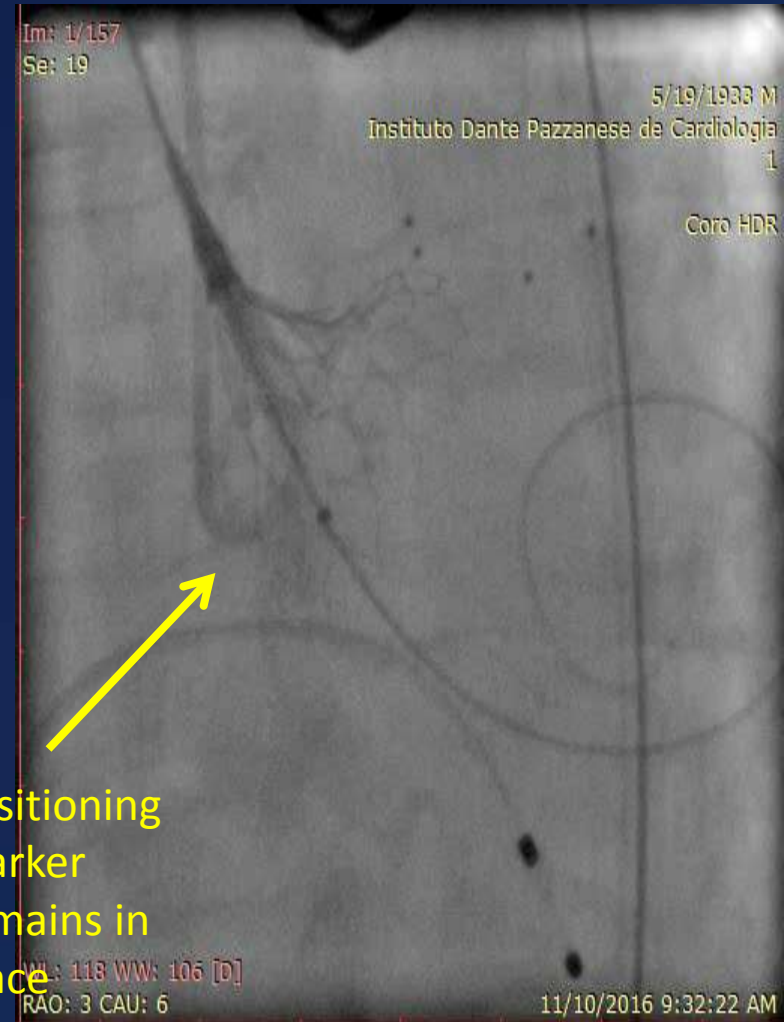
August 4, 2016, Instituto Dante Pazzanese São Paulo
Grube E, Abizaid A, Leon MBL

Deployment of frame module II

Frame Deployment 3

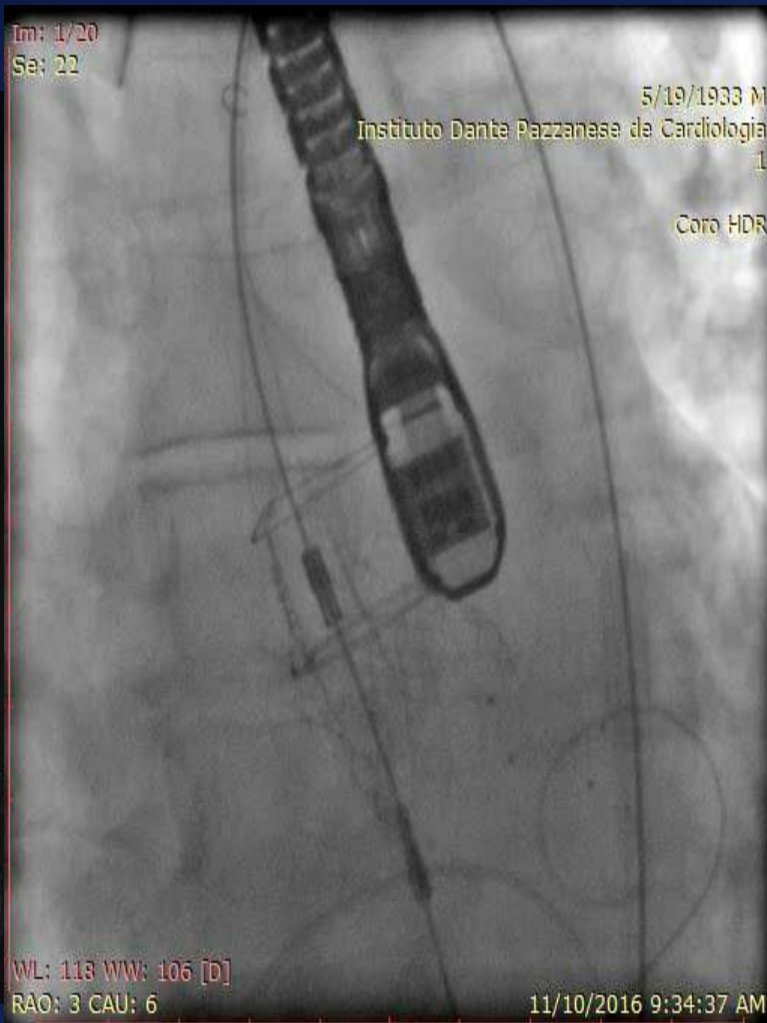


Frame Deployment 4



Docking of Two Modules

Docking



Fully Assembled Valve

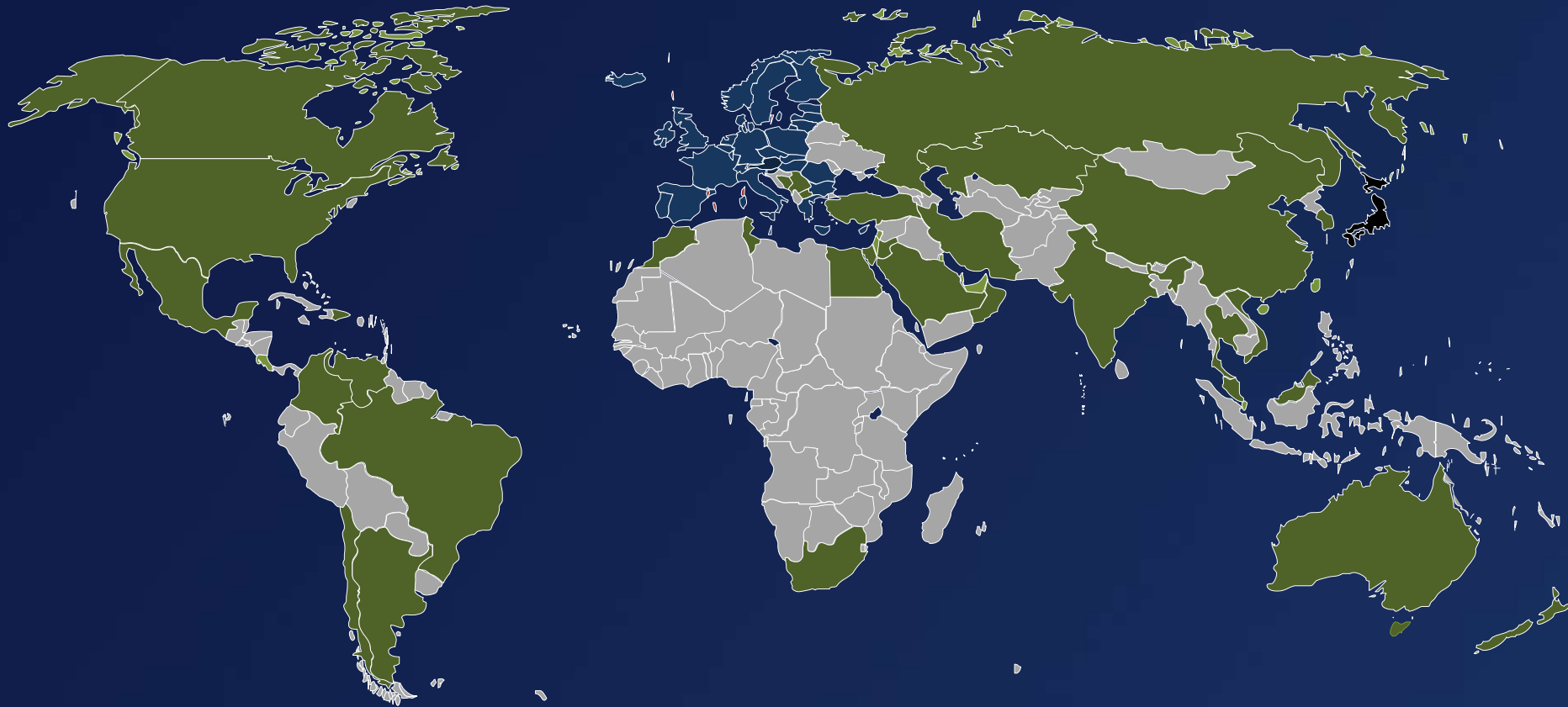


Docked Position



Treatment Trends

TAVR is Available in More Than 65 Countries Around the World



> 300,000 total implants to date

TAVR Journey - 2017

- **Global Demographics and Economics**

Over the next decade 4X growth in TAVR procedures predicted, associated with...

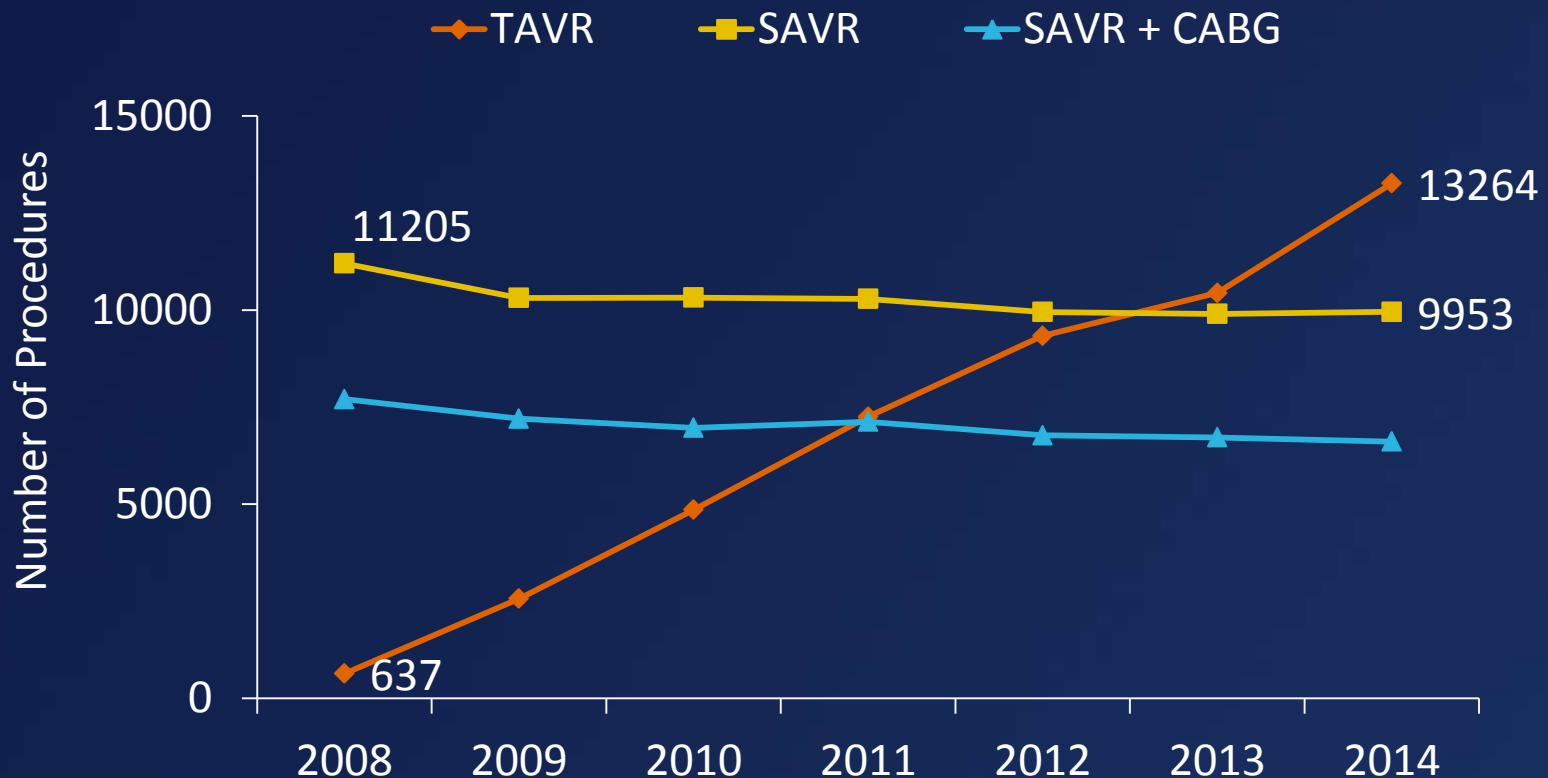
- faster growth in the US, Japan, and ROW
- marked regional growth heterogeneity due to differing reimbursement patterns
- stabilization of trained operator sites
- continued under-diagnosis and under-treatment of severe Aortic Stenosis

Treatment Trends

Germany 2008 - 2014



- In Germany, the number of SAVRs performed between 2008 and 2014 decreased slightly by 11%, whereas the number of TAVRs increased by 2000%
- In current practice, TAVR is performed more often than SAVR

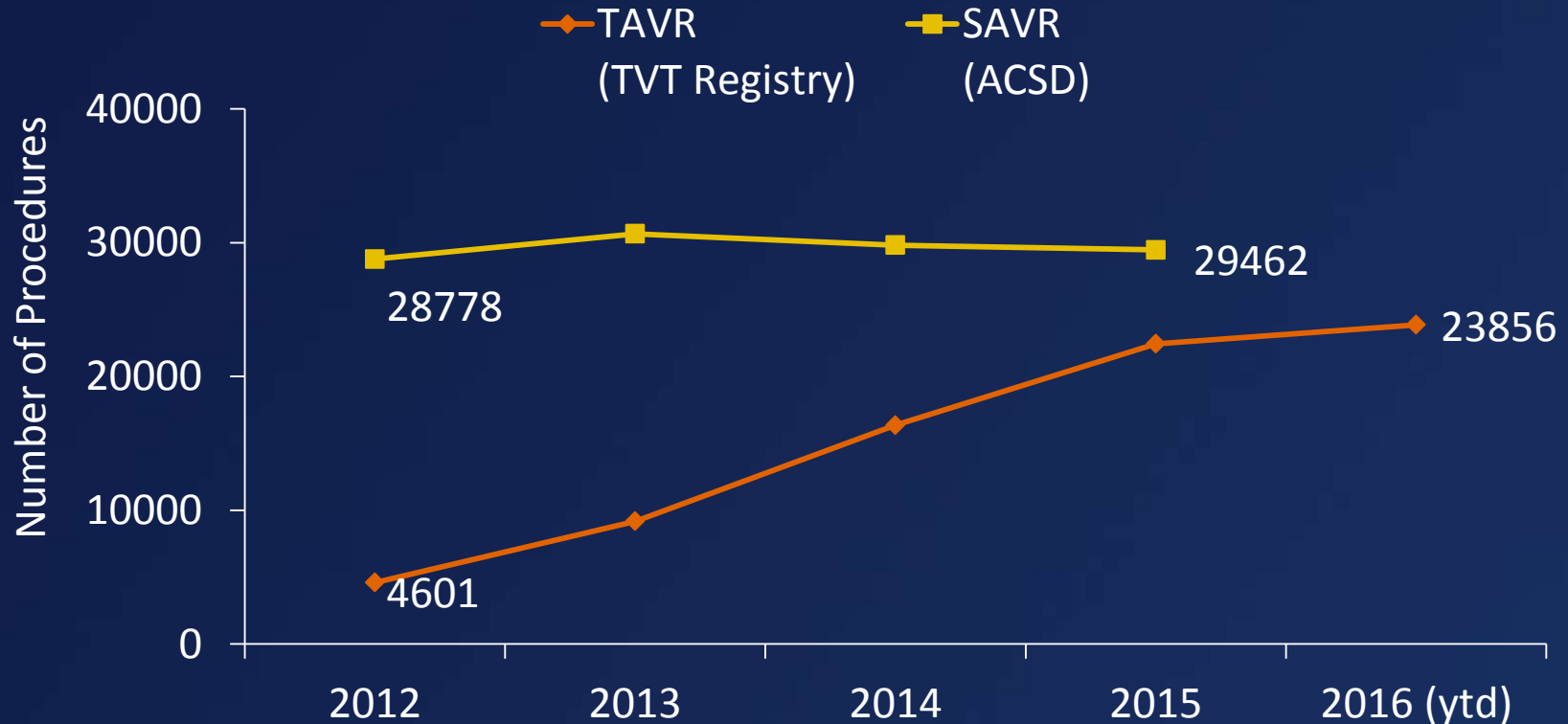


Treatment Trends



United States 2012-2016

- A similar trend is happening in the United States.
- The number of surgical procedures recorded in the Adult Cardiac Surgery Database remained stable at ~29,000 per year between 2012 and 2015, whereas the number of TAVRs recorded in the STS/ACC TVT registry increased by 400% over the same timeframe



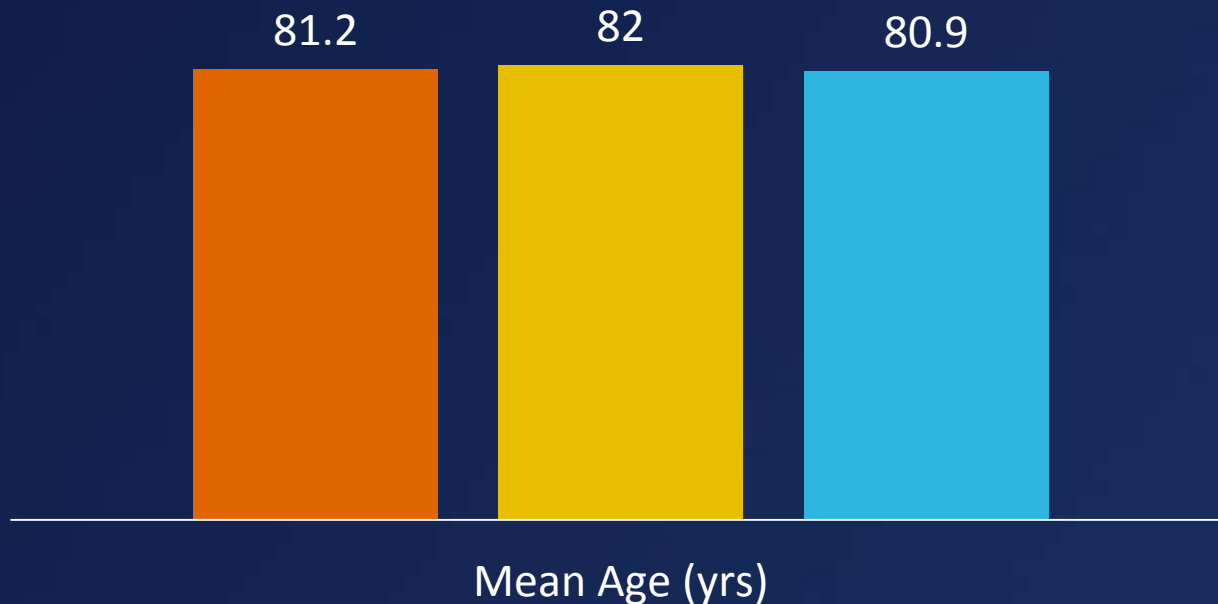
Treatment Trends

Age

As TAVR is applied to more and more patients, we see that they are usually in their 80's, with little evidence of "age creep" into a younger population

Patients Undergoing TAVR in 2014

■ UK Registry ■ STS/ACC TVT Registry ■ Germany



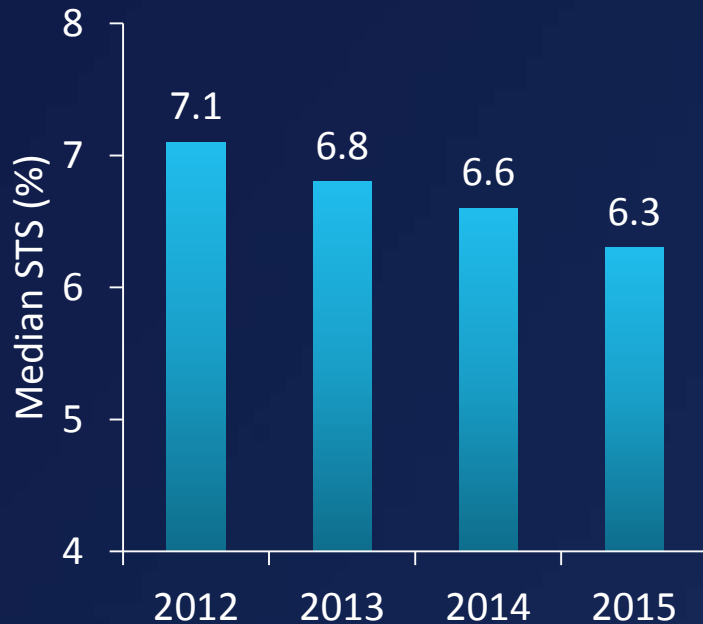
Treatment Trends

United States and UK 2012-2015

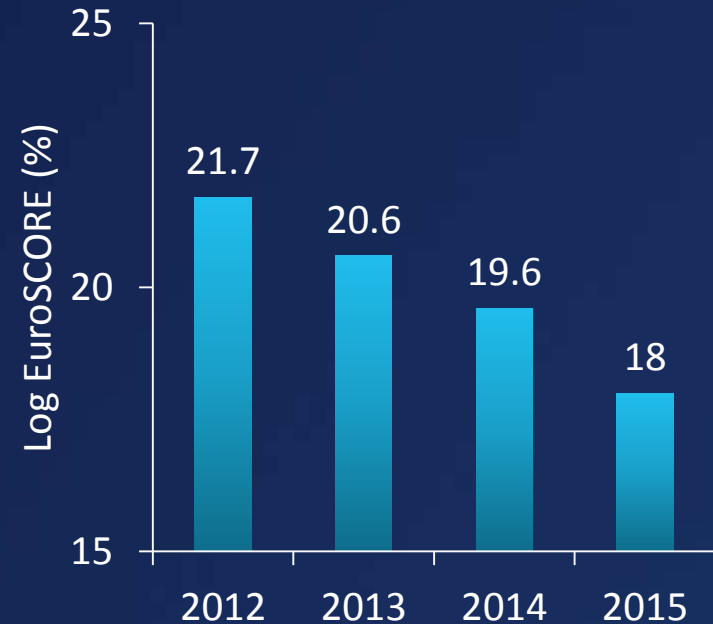
Similar trends can be seen in the US and UK, with a downshift in surgical risk scores over time



STS / ACC TVT Registry



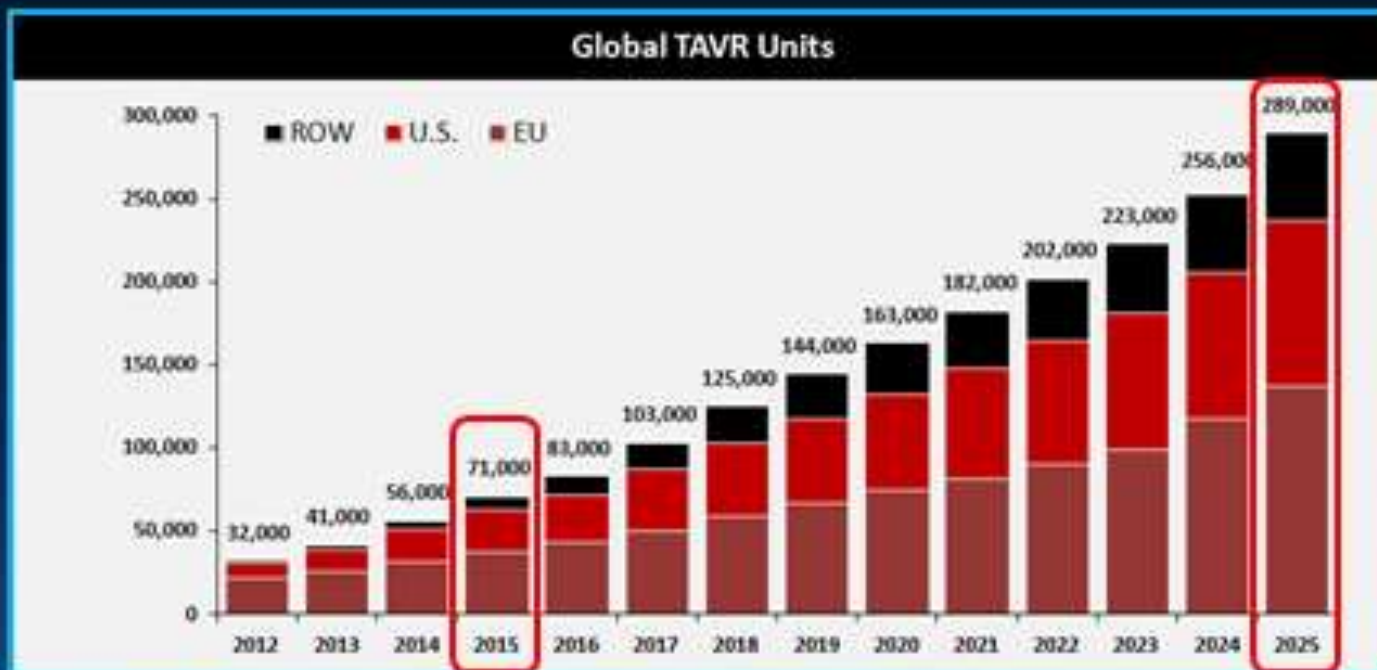
UK TAVI Registry



Treatment Trends

Future TAVR Growth

Estimated Global TAVR Procedure Growth



SOURCE: Credit Suisse TAV Common January 8, 2015. ASP assumption for 2024 and 2025 based on analyst model. Revenue split assumption in 2025 is 45% U.S., 35% EU, 20% Japan, 20% ROW

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

TAVR Journey - 2017



The
Low-Intermediate Risk
Journey

TAVR Journey - 2017

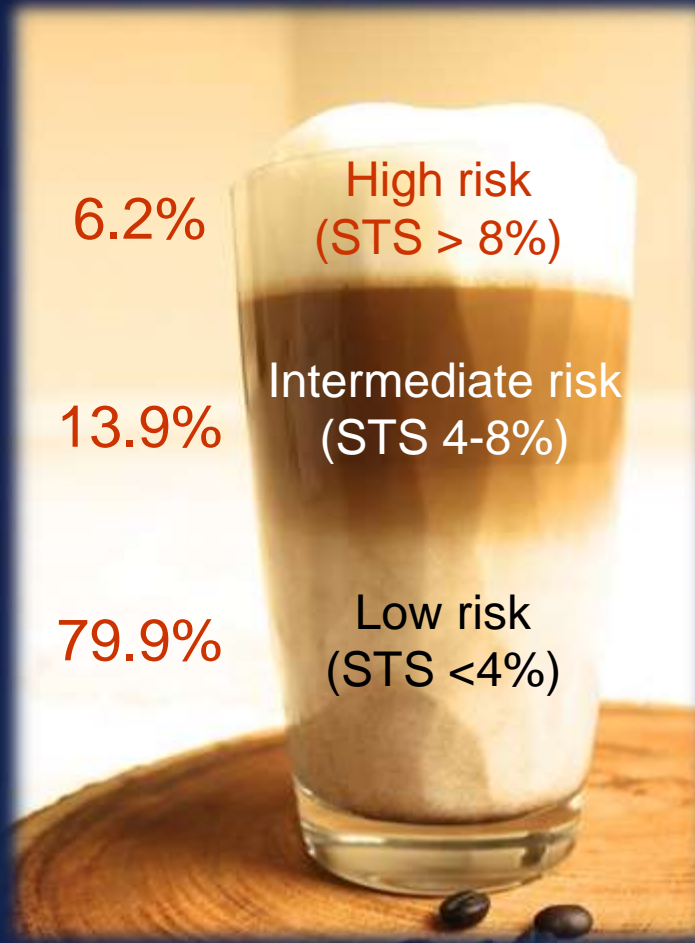
- **The Low-Risk Journey**

The relentless evolution of TAVR's clinical growth has been driven by:

- the multi-disciplinary heart team
- commitment to evidence-based medicine
- rapid technology enhancement
- simplification of the procedure
- striking reduction in complications

The Low-Risk Journey

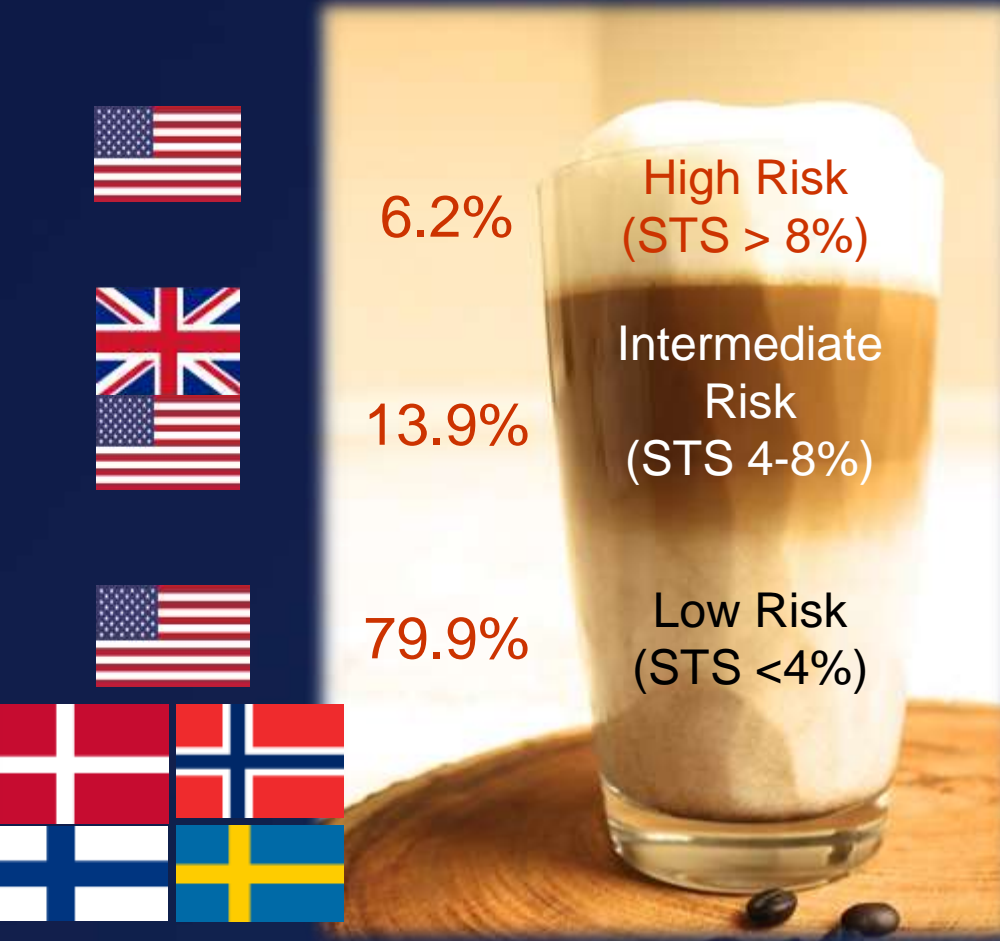
STS database 2002-2010 (141,905 pts)



Since 2007, in the U.S.,
>15,000 patients
have been enrolled
in FDA studies
(including 6 RCTs) with
multiple generations of
two TAVR systems!

The Low Risk Journey

STS Datenbank 2002-2010 (141.905 Pat.)



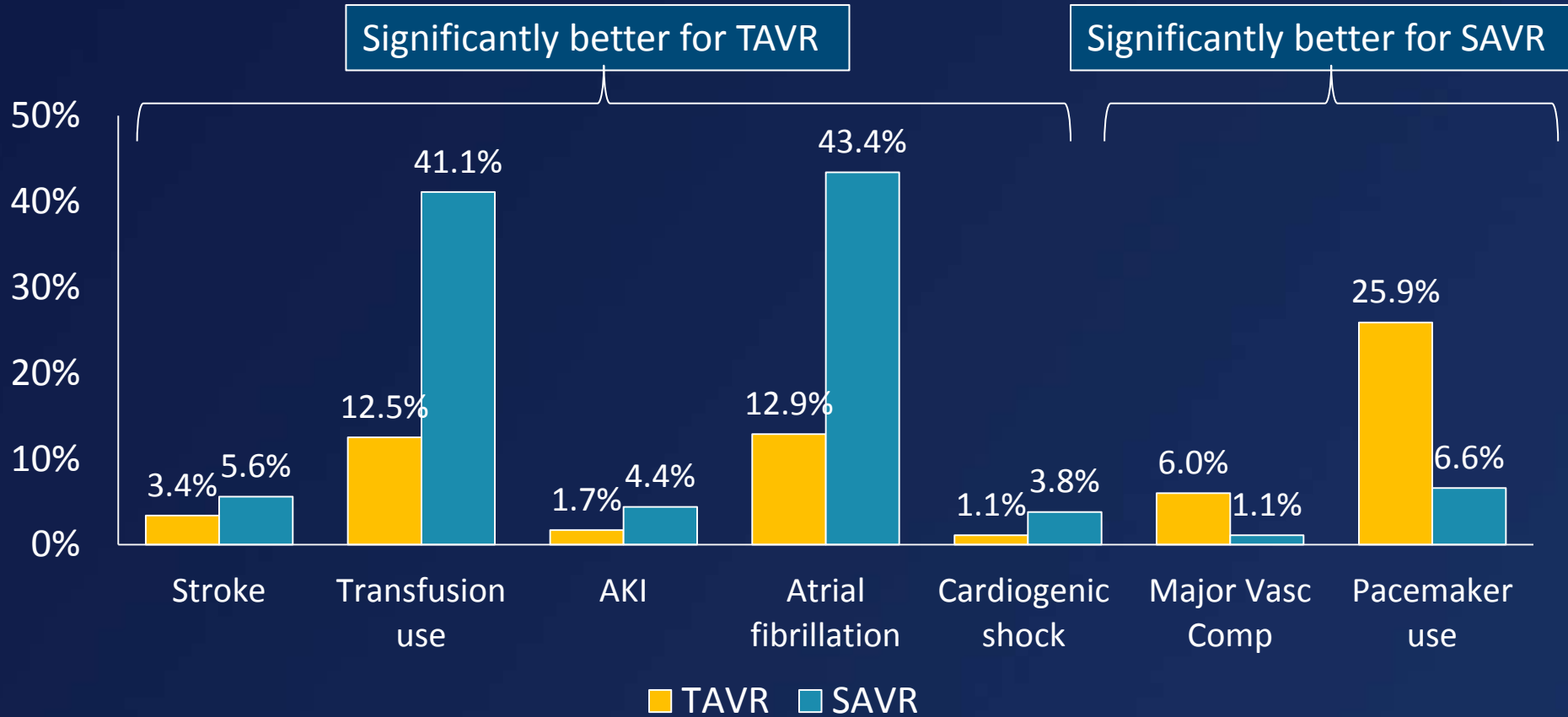
- PARTNER 1A, 1B
- CoreValve Extreme/High Risk

- PARTNER 2A, S3i
- SURTAVI, UK TAVI

- NOTION All Comers
- PARTNER 4 LR, Core Valve LR

Intermediate Risk

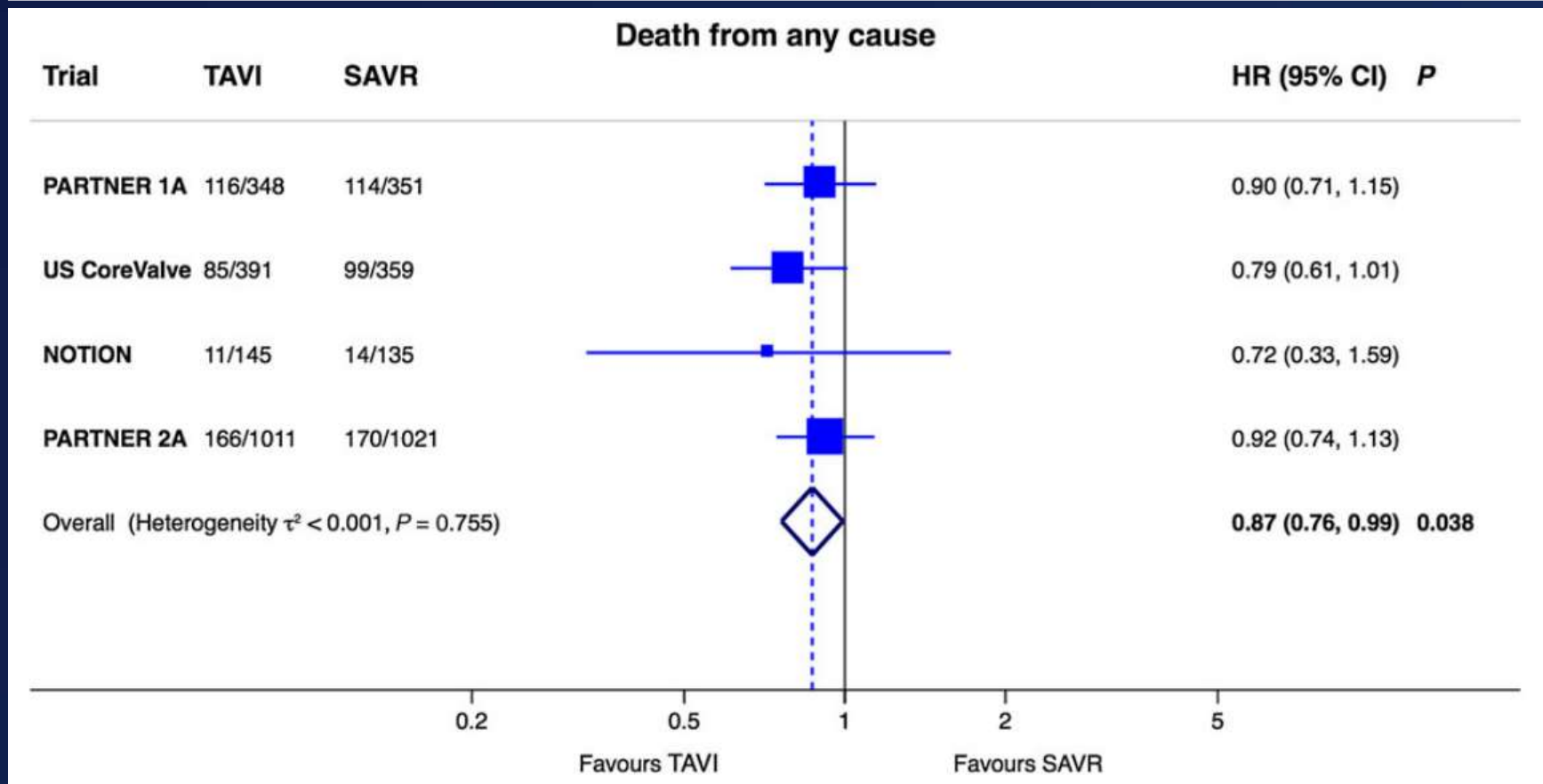
SURTAVI | 30-Day Safety Outcomes



TAVR vs. SAVR

Meta-Analysis

- Putting it all together in a meta-analysis, TAVR when compared to SAVR provides a statistically significant, 13% relative risk reduction of death from any cause
- This is a class effect, independent of valve type



Intermediate Risk

Regulatory Approvals

These data provided the basis for regulatory approval of TAVR in intermediate risk patients in both Europe and the United States

2016



August



Evolut R

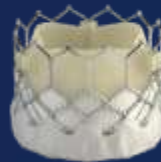
September



SAPIEN 3



August



SAPIEN 3



SAPIEN XT

ACC / AHA Guidelines

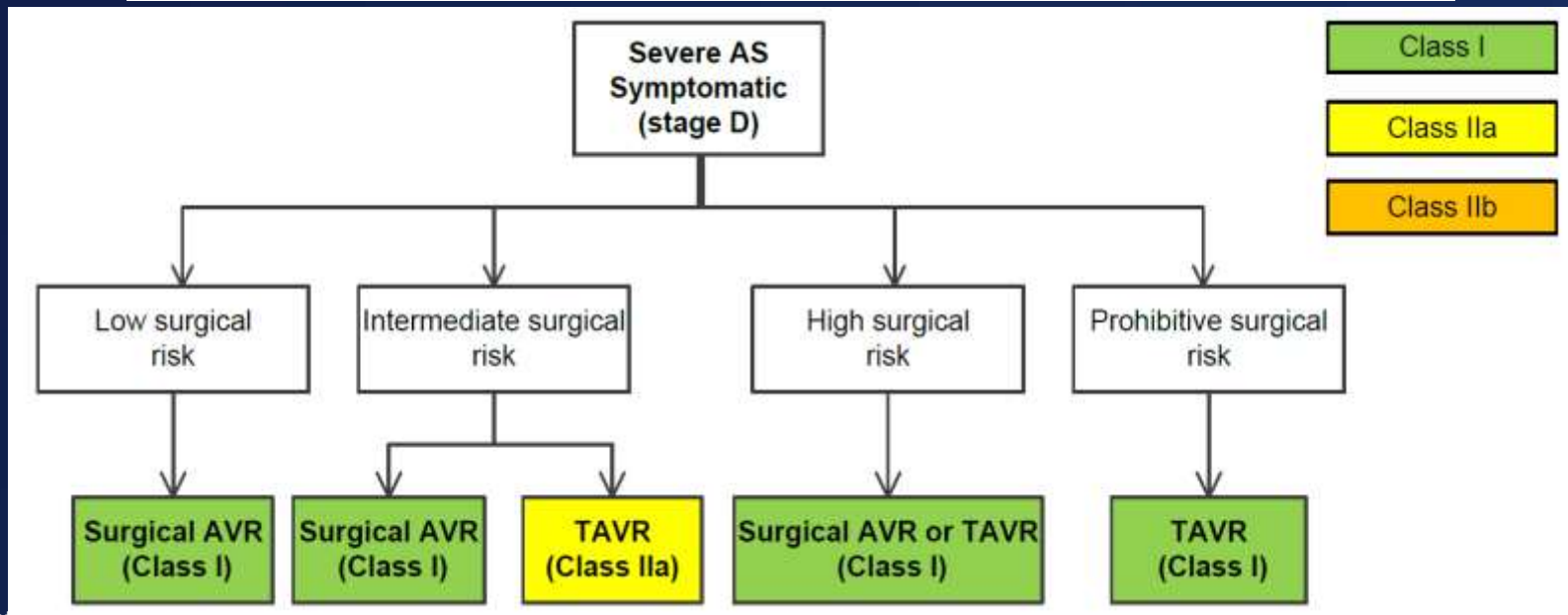
2017 Update

The AHA/ACC Guideline for the Management of Patients with Valvular Heart Disease was recently updated:

- TAVR is now a Class I indication for high risk patients, and a reasonable alternative to surgical AVR in patients at intermediate surgical risk.

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

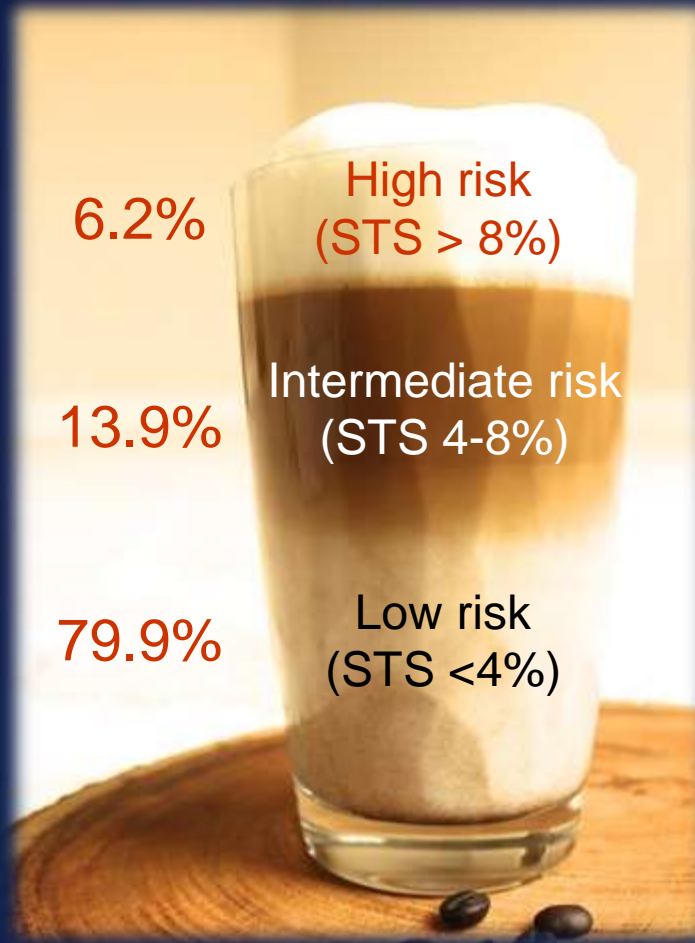


The State of TAVR in 2017

- TAVR has become the gold-standard treatment for patients with severe, symptomatic aortic stenosis at extreme surgical risk, reducing the risk of mortality by at least 30% relative to standard medical therapy.
- For patients at high risk, PARTNER showed that TAVR was non-inferior to surgery, while the CoreValve US Pivotal trial showed that TAVR may provide a durable survival advantage over surgery.
- Recent data from rigorous, randomized trials in intermediate risk patients have confirmed that TAVR is at least non-inferior to SAVR in terms of survival, and it facilitates a faster recovery to an improved quality of life.

The Low-Risk Journey

STS database 2002-2010 (141,905 pts)



The Evidence
for TAVR is
Definitive,
Progressive &
Unprecedented!

TAVR Journey - 2017

- **The Low-Risk Journey**

Risk stratification for TAVR, especially based upon surgical risk scores, is however imprecise, heavily biased, and mainly served a regulatory purpose to control clinical expansion of TAVR and to encourage a disciplined commitment to evidence-based risk-cohort studies!

Concerns About Complications

TAVR Systems

Global Inventory (#25)

- Sapien 3
- Evolut R
- Symetis

*Current
Leaders!*

Centera

- Venus A Valve

- Shanghai Valve
- Trinity
- Colibri
- Inova
- T

*Future
Contenders?*

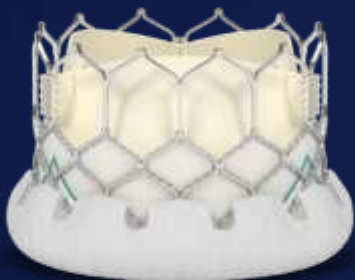
- NVT (Nautilus)
- J - Valve
- Xeltis
- Zurich TEHV

So Many Choices



So many TAVR choices...How do we optimize outcomes with each? And which device is Best for which patient?

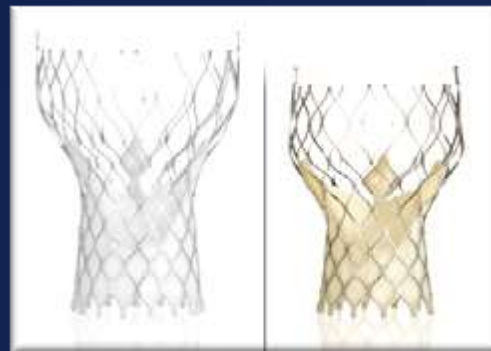
SAPIEN 3
Edwards



CENTERA EVOLUTION
Edwards



CoreValve & EVOLUT-R
Medtronic



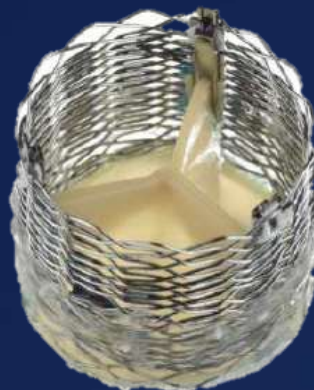
Portico
St. Jude Medical



DirectFlow
DirectFlow Medical



Lotus Valve
Boston Scientific



Symetis Accurate
Valve



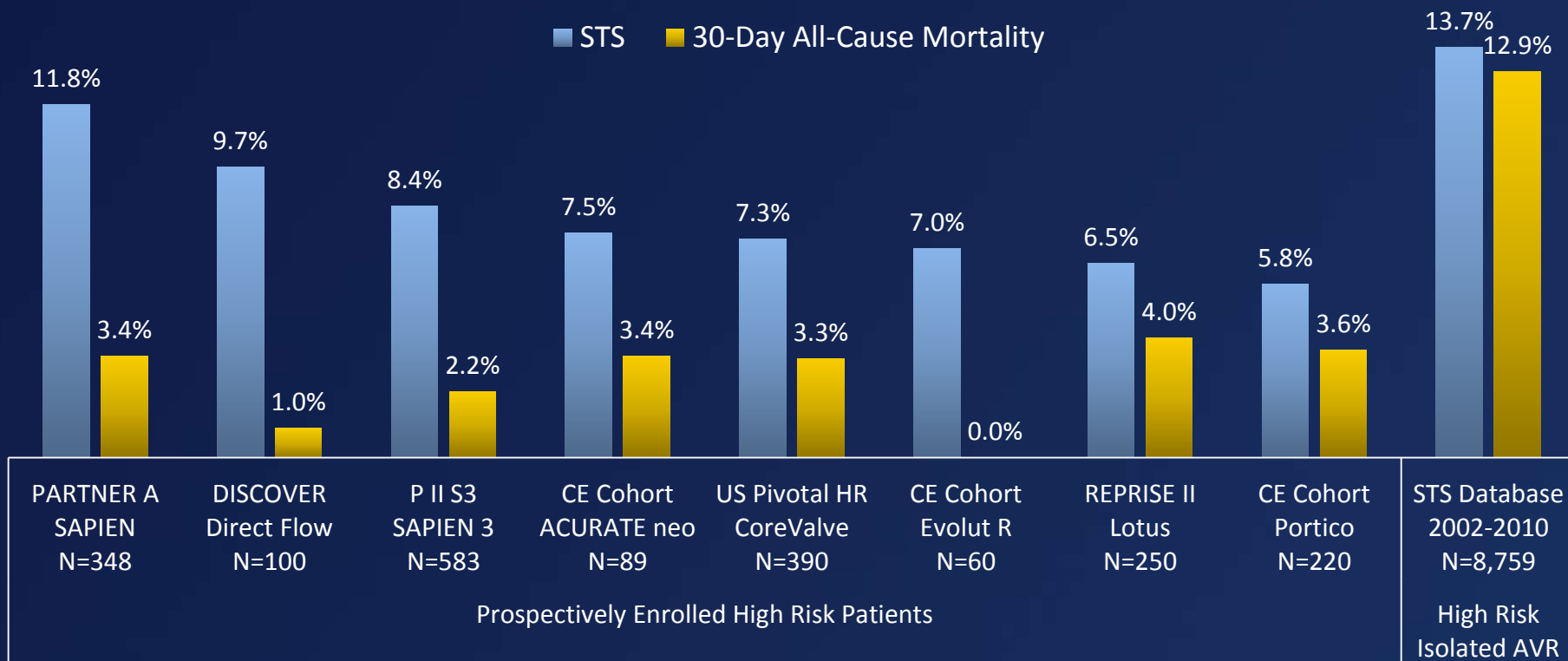
Jena Valve



All-Cause Mortality

30-Day Mortality Compared to STS Score

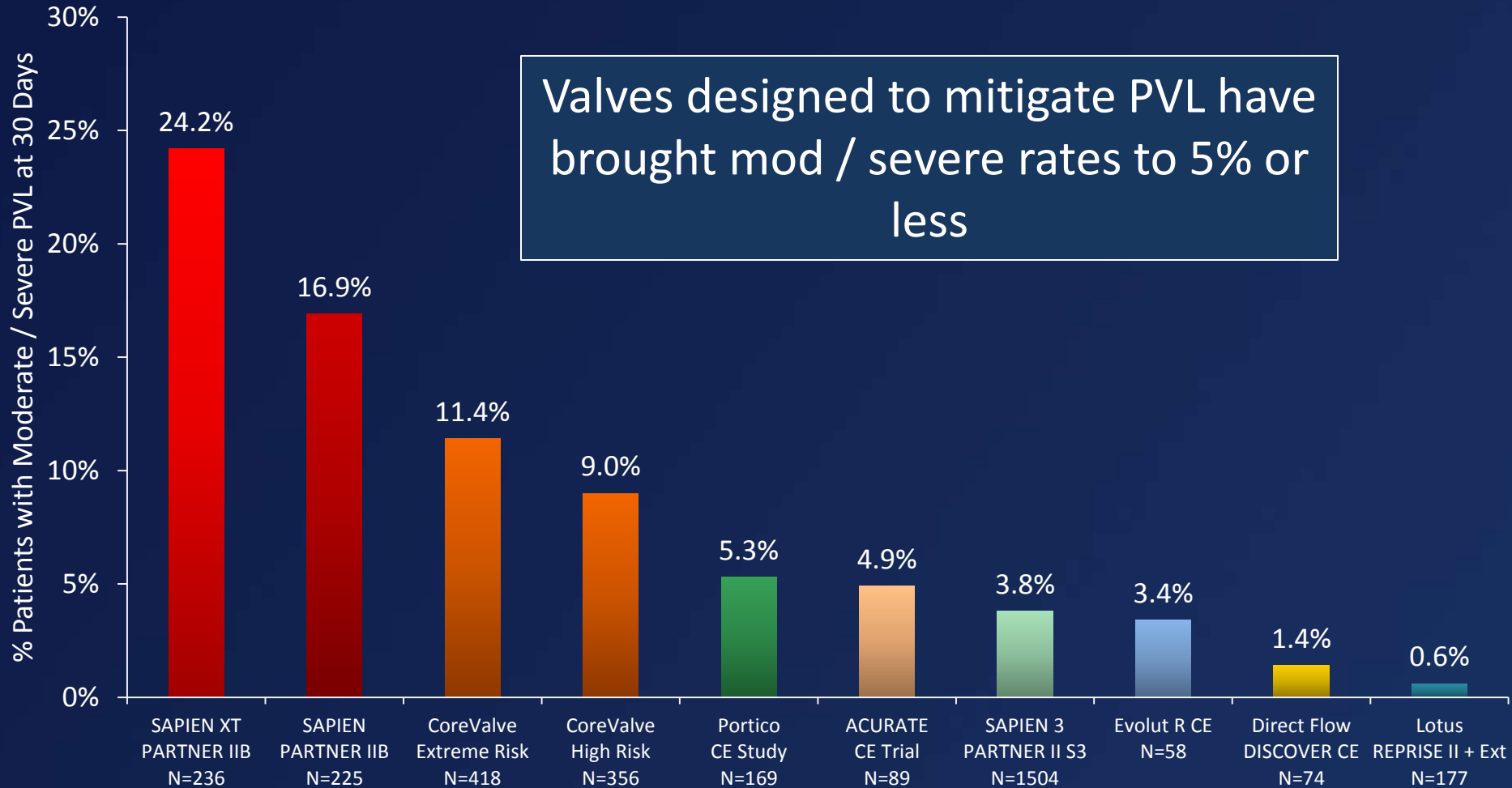
Despite wide-ranging predicted risk, TAVI has consistently produced all-cause mortality rates under 5% (both old and new platforms)



¹Smith, et al., *N Engl J Med* 2011; 364: 2187-98; ²Schofer, et al., *J Am Coll Cardiol* 2014; 63: 763-8; ³Kodali, et al., presented at ACC 2015; ⁴Abizaid, et al., presented at CRT 2015; ⁵Adams, et al., *N Engl J Med* 2014; 370: 1790-8; ⁶Manoharan, et al., presented at TCT 2015; ⁷Meredith, et al, presented at PCR London Valves 2014; ⁸Linke, et. al. presented at PCR London Valves 2015; ⁹Thourani, et al., *Ann Thorac Surg* 2015; 99: 55-61

Paravalvular Leak

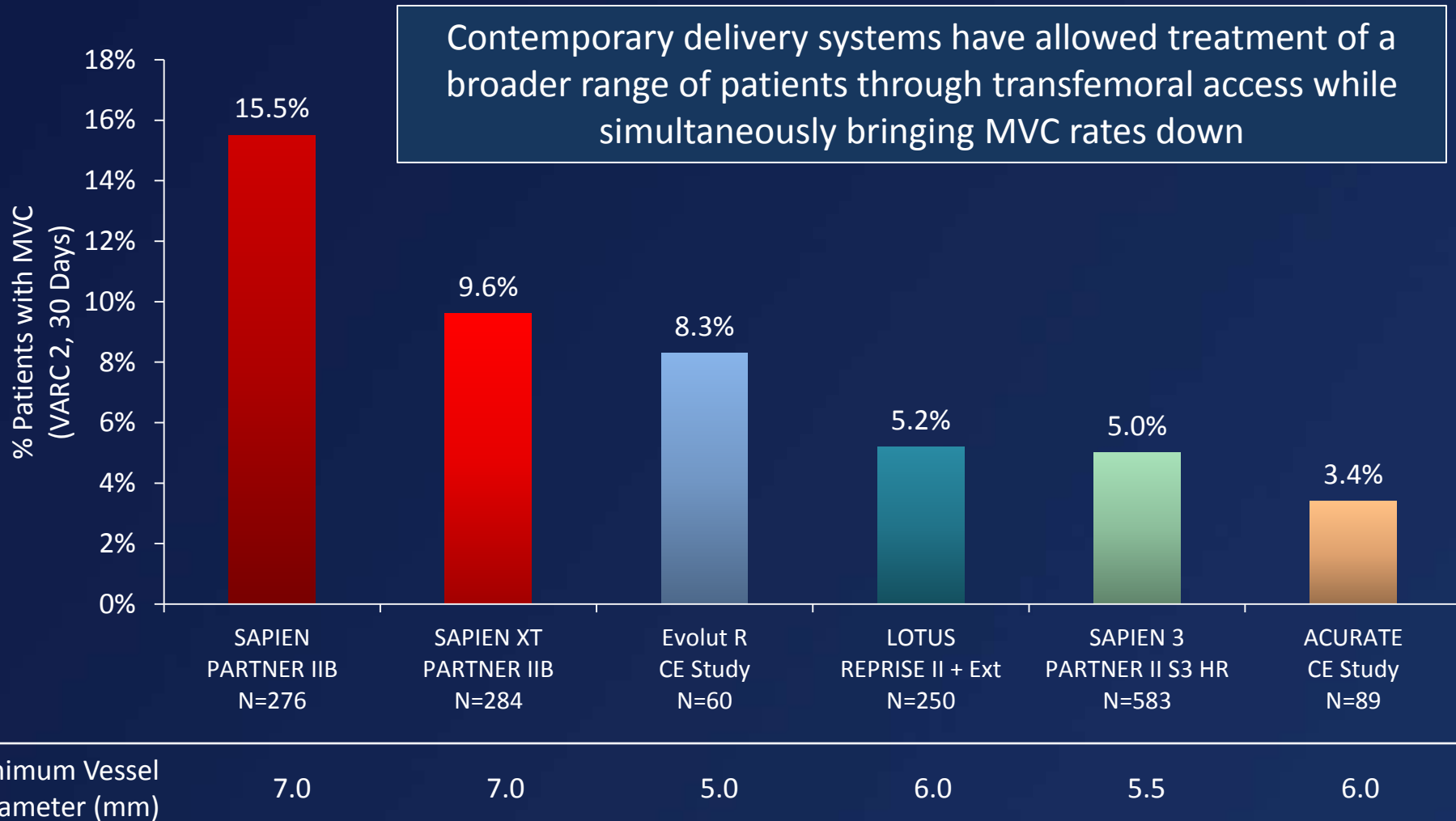
Moderate / Severe at 30 Days



¹Leon, et. al. presented at ACC 2013; ²Popma, et al., *J Am Coll Cardiol* 2014; 63: 1972-81; ³Adams, et al., *N Engl J Med* 2014; 370: 1790-8; ⁴Linke, et. al. presented at PCR London Valves 2015; ⁵Abizaid, et al., presented at CRT 2015; ⁶Kodali, et al., presented at ACC 2015; ⁷Manoharan, et al., presented at TCT 2015; ⁸Naber, et al., presented at EuroPCR 2015; ⁹Vahanian, et al., presented at EuroPCR 2015; ¹⁰Schofer, et al., *J Am Coll Cardiol* 2014; 63: 763-8; ¹¹Meredith, et al., presented at PCR London Valves 2014

Major Vascular Complications

Rates According to VARC 2



Take Home Messages

New valve designs, procedural improvements, operator experience, and better patient selection have combined to lead to excellent outcomes with the new systems:

- 30-day all-cause mortality is under 4% across platforms in both clinical trial and real-world settings.
- 30-day PVL rates are consistently under 5% across platforms, and under 1% for Lotus.
- There may have been a tradeoff of increased pacemaker rates with some valves with 30-day rates approaching 30%.
- Smaller indicated vessel sizes allows treatment of ~90% of patients with the transfemoral approach, with rates of major vascular complications consistently under 10%.

Contemporary technology and practices have led to extremely good outcomes for patients!

Lifetime Management

Strokes after TAVR

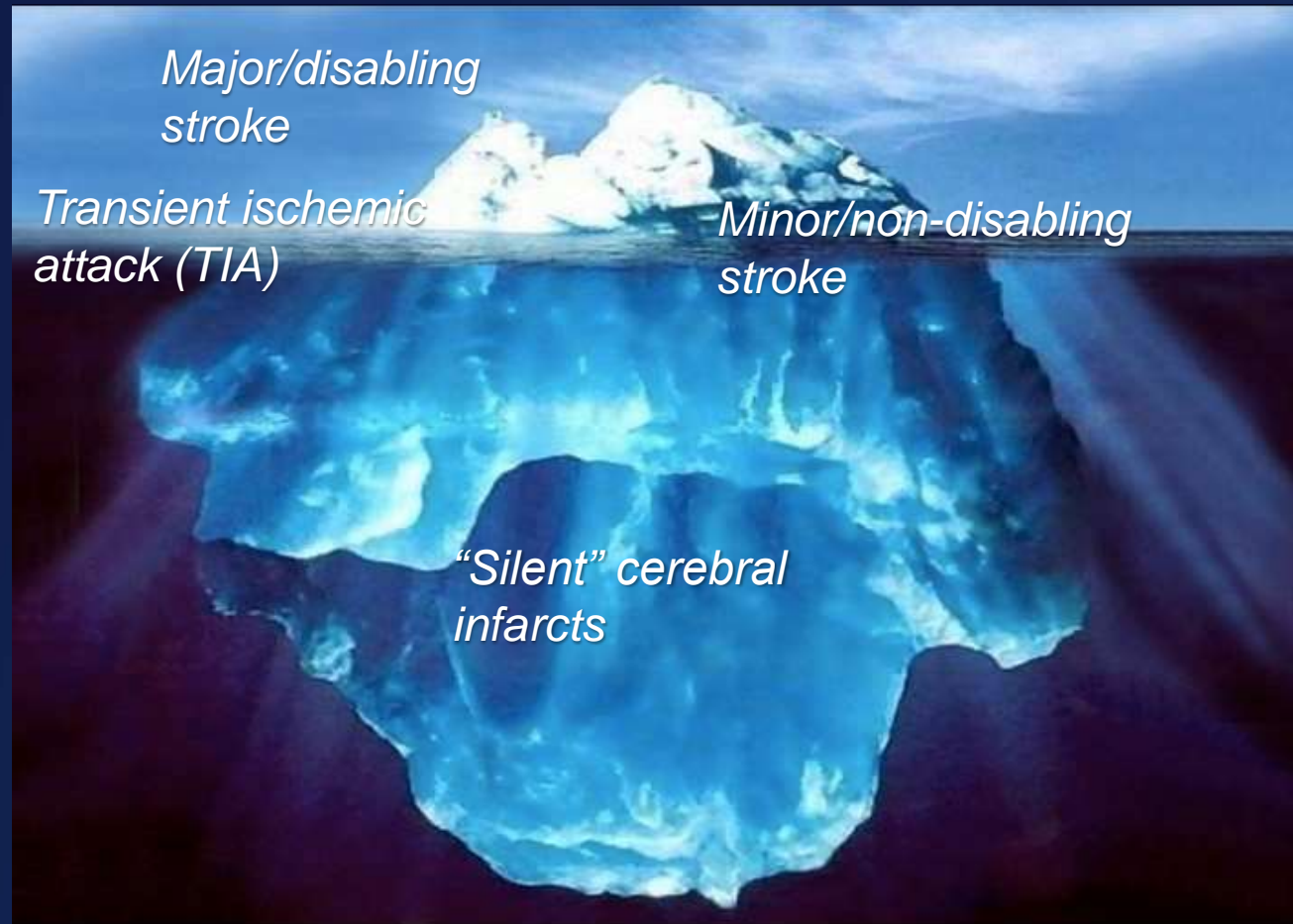


Most damage is unseen

Clinically
apparent

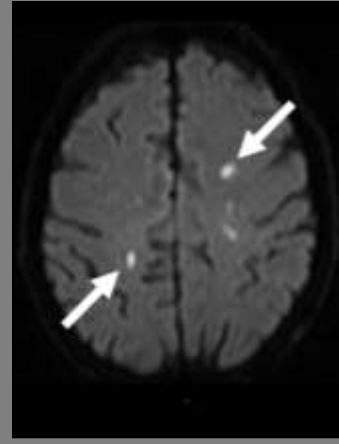
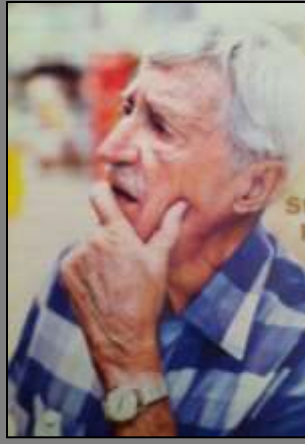
Subtle and
often
undetected

Clinically
unrecognized



....but can have far-reaching effects

Cerebral Injury



obvious - apparent - quiet - subtle - silent - subclinical

2-4%

3-10%

15-20%

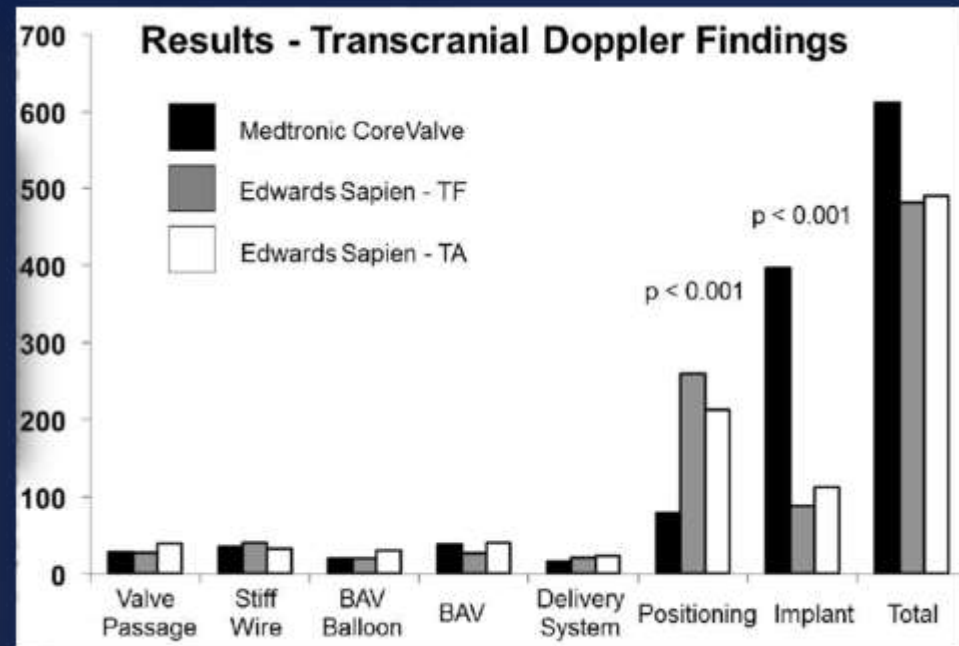
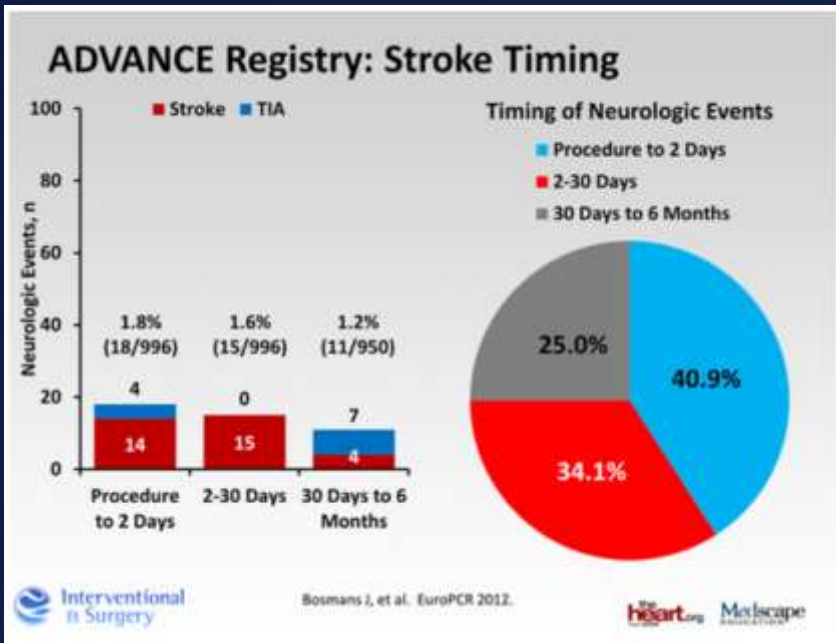
68-84%

?%

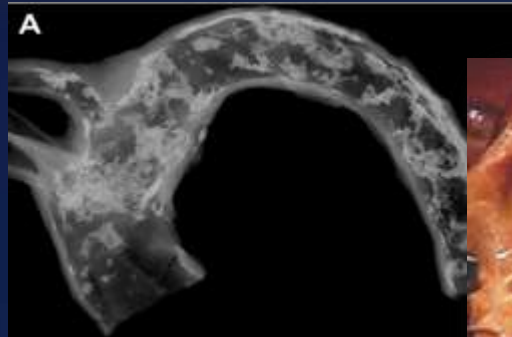
Known consequences of cerebral injury:

Increased risk of: later CVA, cognitive impairment, vascular dementia

Majority of Strokes Occur Periprocedurally



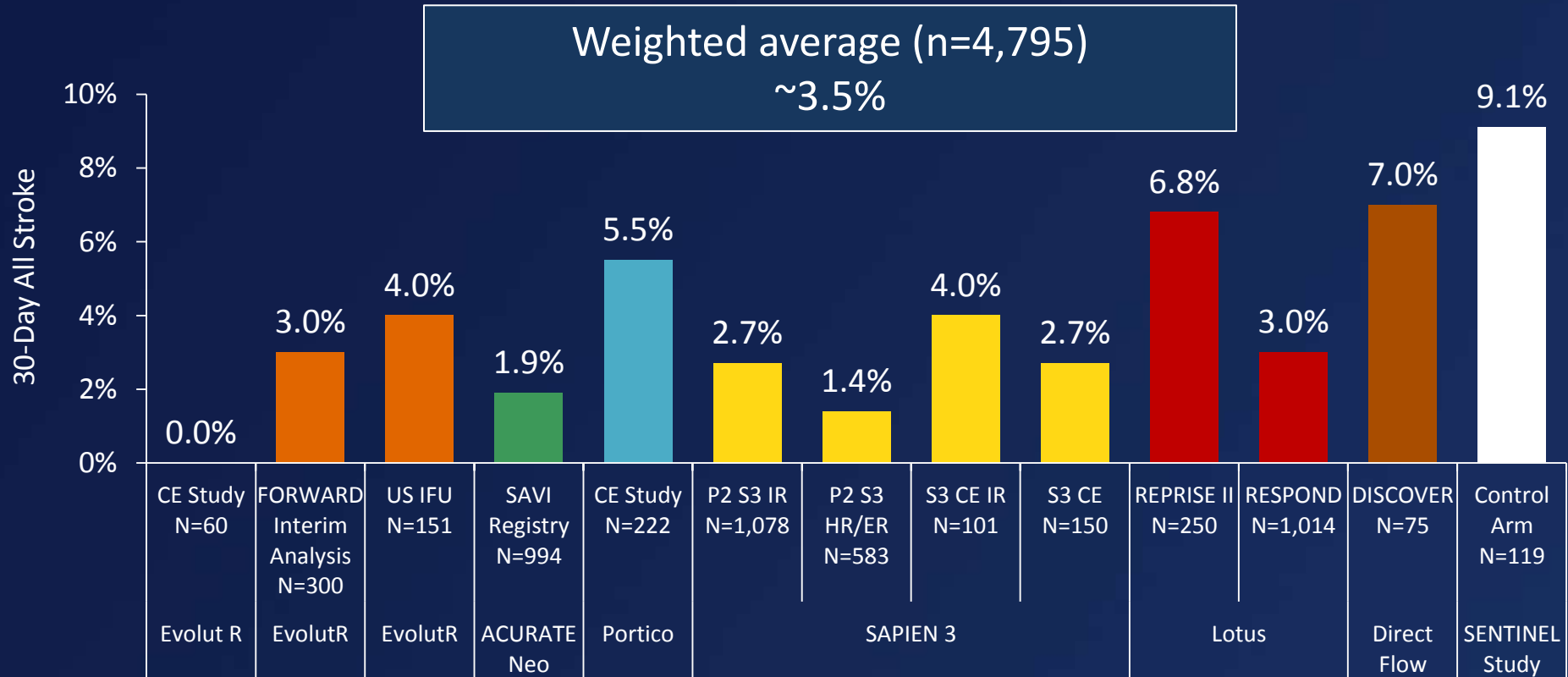
P. Kahlert et al, Circulation 2012;126:1245-1255



TAVR Stroke

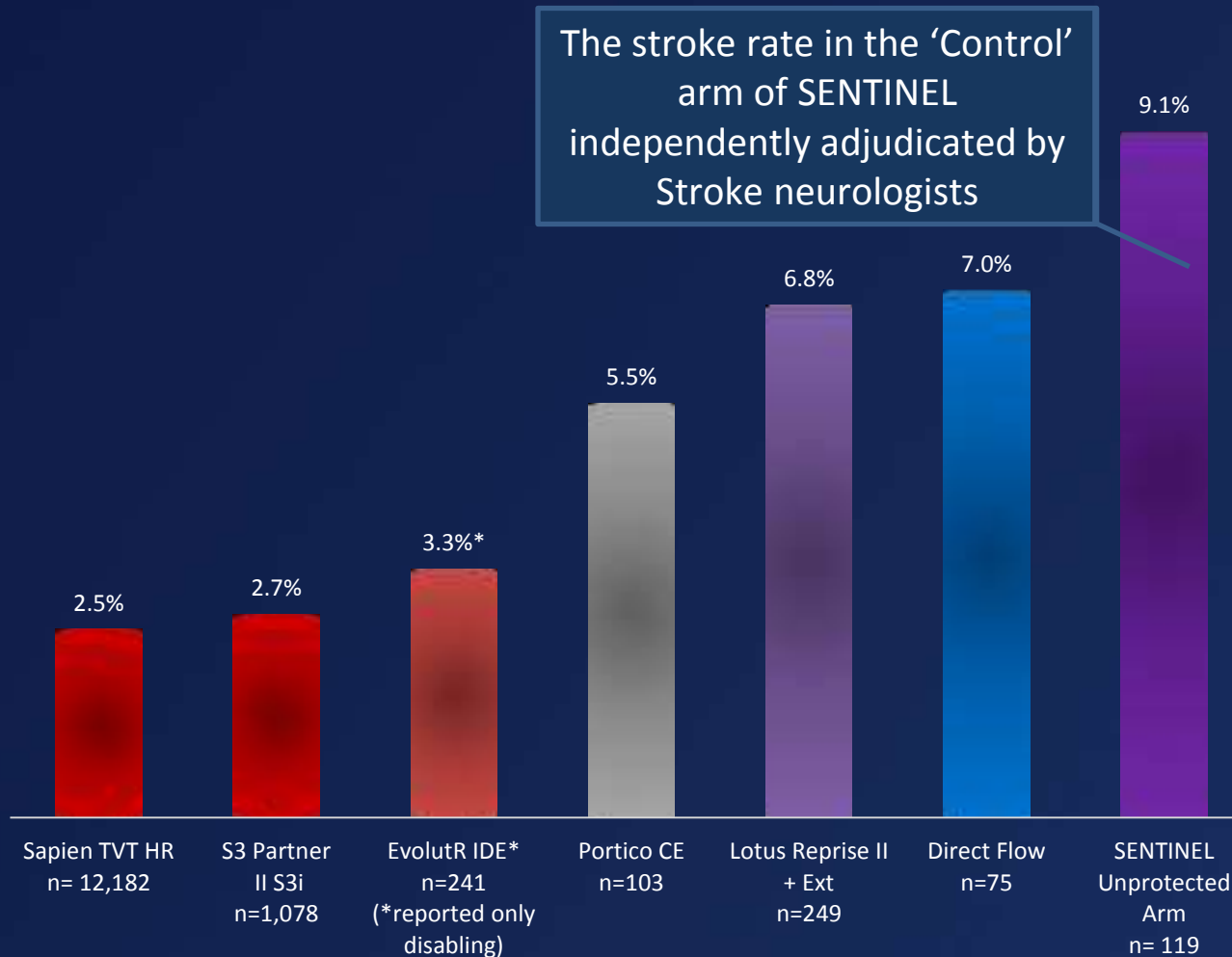
Rates with Contemporary Devices

- In contemporary practice, the overall stroke rate remains around 3%



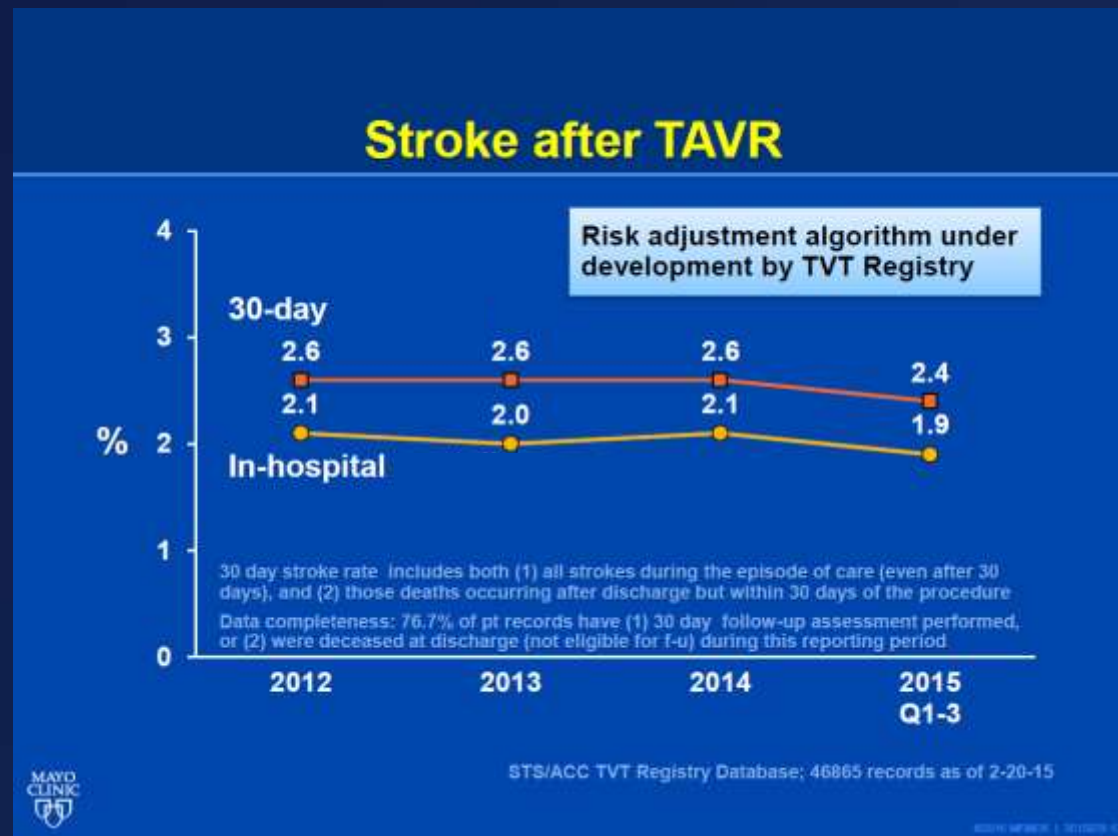
¹Manoharan, et al., *J Am Coll Cardiol Interv* 2015; 8: 1359-67; ²Moellman, et al., presented at PCR London Valves 2015; ³Linke, et al., presented at PCR London Valves 2015; ⁴Kodali, et al., *Eur Heart J* 2016; doi:10.1093/eurheartj/ehw112; ⁵Vahanian, et al., presented at EuroPCR 2015; ⁶Webb, et al. *J Am Coll Cardiol Interv* 2015; 8: 1797-806; ⁷DeMarco, et al, presented at TCT 2015; ⁸Meredith, et al., presented at PCR London Valves 2015; ¹⁰Falk, et al., presented at EuroPCR 2016; ¹¹Kodali, presented at TCT 2016

Stroke in TAVR is likely more frequent than thought



The true incidence of stroke is most likely UNDER-reported in many trials!!

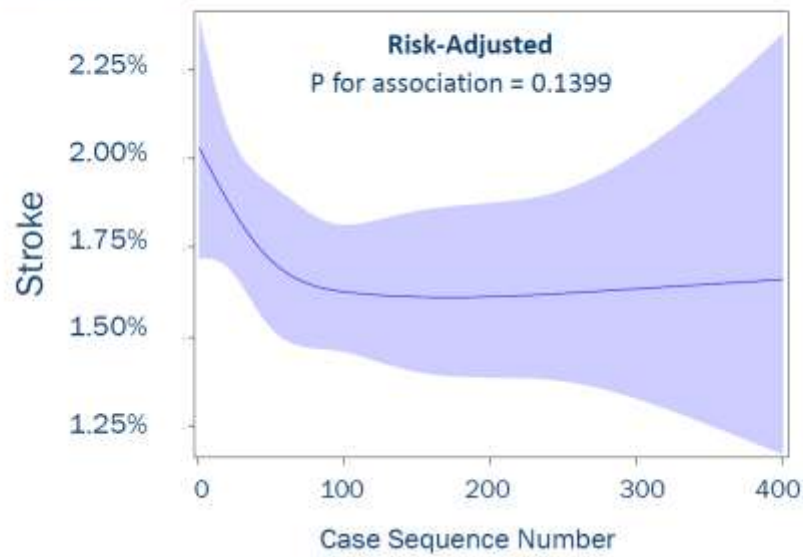
TVT Registry shows no significant decline in stroke rate over time



- Over 53,000 US TAVR patients
- No significant decline in stroke rate over time

TVT Registry shows stroke risk is independent of experience

Stroke Complication



Relationship Between Procedure Volume and Outcome for Transcatheter Aortic Valve Replacement in U.S. Clinical Practice:

Insights from the STS/ACC TVT Registry

Sunday, April 3, 2016, 11:45 am

John D. Carroll, Sreekanth Vemulapalli, Dadi (David) De, Roland Matsouka, Eugene Blackstone, Fred Edwards, Frederick Masoudi, Michael Mack, Eric Peterson, David Holmes, John Rumsfeld, E. Mural Tiattu, Frederick Grover

STS/ACC TVT Registry

University of Colorado, Aurora, CO, USA,
Duke University, Durham, NC, USA



- Over 53,000 US TAVR patients from >350 US centers
- No significant decline in stroke rate as centers gain experience
- Self-reported rates without prospective neurologist exams pre and post-procedure likely underestimate true rates

TAVI and SAVR in-hospital stroke rates are similar across the surgical risk spectrum

Complete dataset of TAVI and SAVR patients treated in 2013 in Germany (n=20,340 patients)

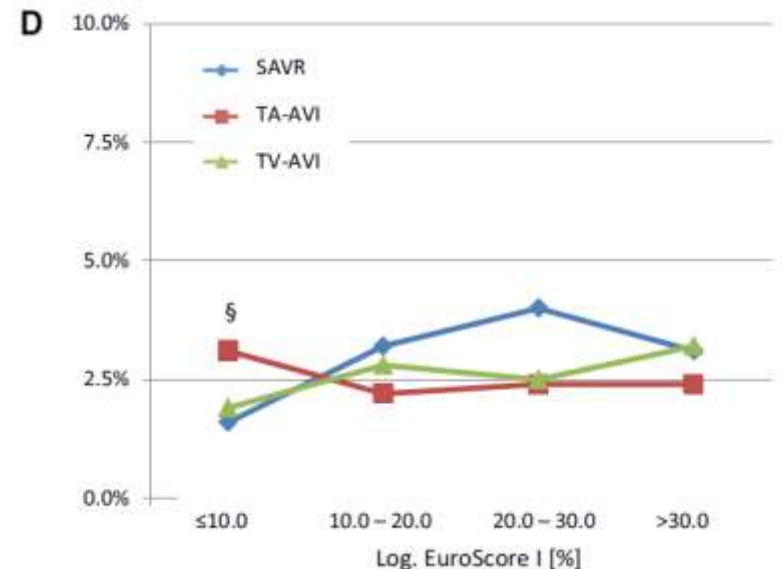
Clin Res Cardiol
DOI 10.1007/s00392-016-0962-4



ORIGINAL PAPER

In-hospital outcome of transcatheter vs. surgical aortic valve replacement in patients with aortic valve stenosis: complete dataset of patients treated in 2013 in Germany

Helge Möllmann¹ · Kurt Bestehorn¹ · Maike Bestehorn¹ · Konstantinos Papoutsis¹ · Eckart Fleck¹ · Georg Ertl¹ · Karl-Heinz Kuck¹ · Christian Hamm¹



- Overall in-hospital stroke rate of 2.3%
- Stroke occurred more frequently in low-risk patients treated with trans-apical TAVI (TA-AVI)
- There were no statistically significant differences in stroke rates for all other comparisons

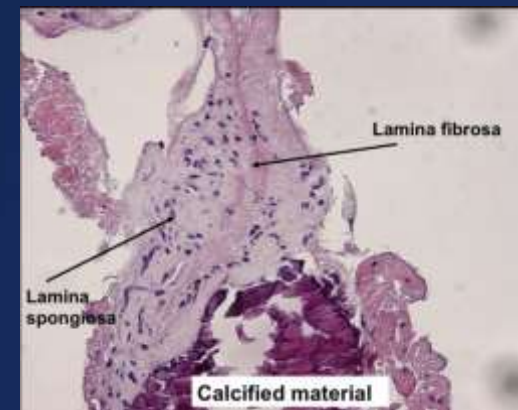
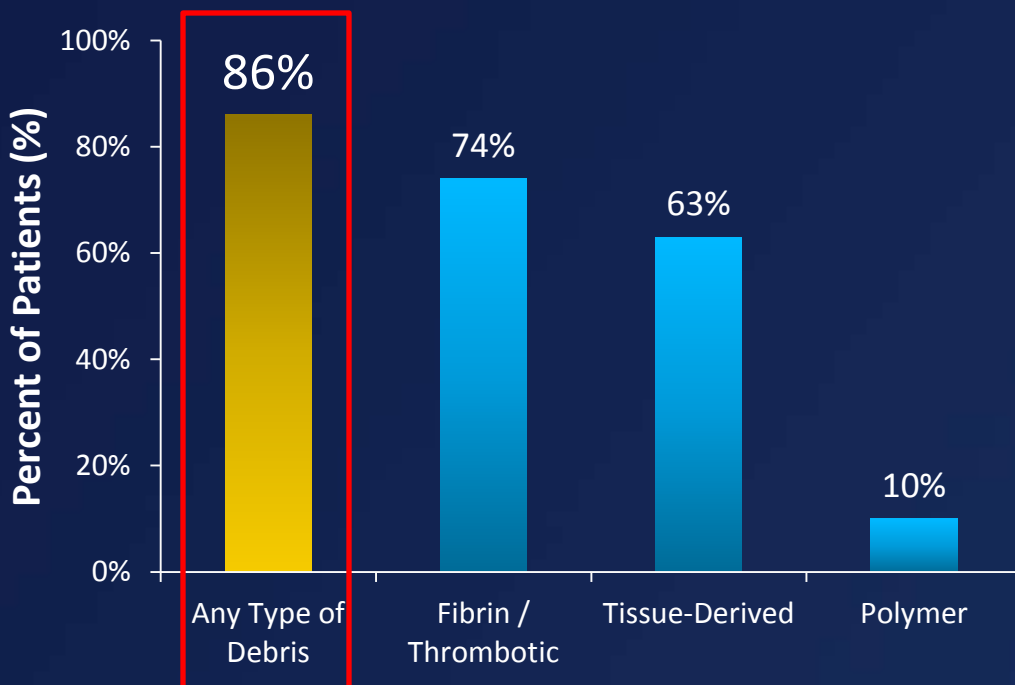
Neurologic Injury

How Does it Happen?

Van Mieghem, et al., placed Claret Montage filters into the brachiocephalic and left common carotid arteries during TAVR, and examined the contents after the procedure.

The key findings:

- Macroscopic debris was released into the circulation in ~90% of procedures
- The debris was composed of thrombotic material, fragments of valve leaflet, calcified particles, myocardial tissue, and plastic fragments from interventional tools

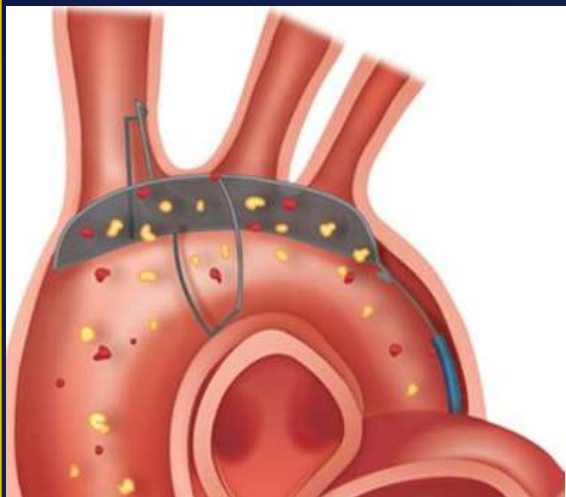


Debris and Fragments of aortic valve leaflet

Neurologic Injury

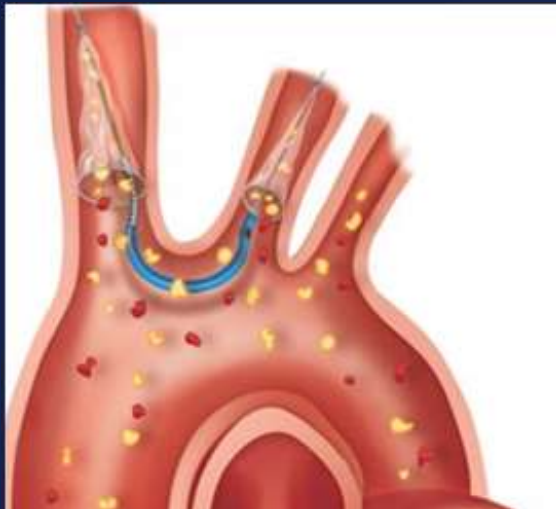
Embolic protection devices provide a key therapeutic strategy to mitigate complications caused by procedural embolic debris

TriGuard Embolic Deflection Device (Keystone Heart)¹



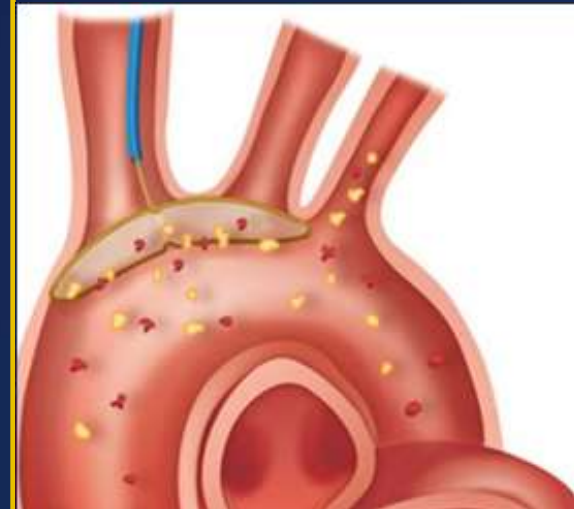
- ✓ Pore Size: 130 μm
- ✓ Delivery Sheath: 9F
- ✓ Access: Transfemoral
- ✓ Coverage: Brachiocephalic, left common carotid, left subclavian

Sentinel Cerebral Protection System (Claret Medical)²



- ✓ Pore Size: 140 μm
- ✓ Delivery Sheath: 6F
- ✓ Access: Brachial or radial
- ✓ Coverage: Brachiocephalic, left common carotid

Embrella Embolic Deflector System (Edwards Lifesciences)³



- ✓ Pore Size: 100 μm
- ✓ Delivery Sheath: 6F
- ✓ Access: Brachial
- ✓ Coverage: Brachiocephalic, left common carotid

TAVR Journey - 2017



The Durability Controversy

TAVR Journey - 2017

- **The Durability Controversy**

Given the sensitivity of these long-term FU data, it's the responsibility of all TAVR investigators to carefully examine their late FU patients according to agreed-upon principles and definitions, including FDA studies like PARTNER and Core Valve, which will now extend clinical and echo FU to 10 years!

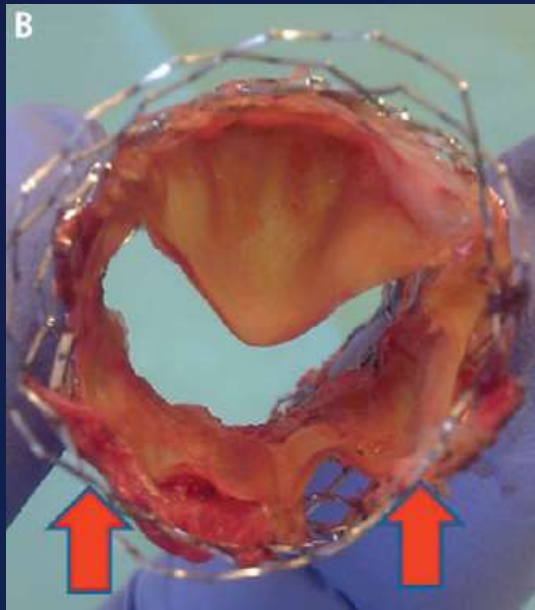
Lifetime Management

Key Concerns

As TAVR is applied to younger patients, new strategies will be needed to manage inevitable clinical realities later in their lives

Failed TAVs

Redo TAVR or surgical revision will be required for a subset of patients



SAPIEN XT at explant (1 year)²

Coronary Artery Disease

Strategies to manage CAD post TAVR will be needed



Hypothetical reasons for reduced THV durability*

Device characteristics

- Lack of advanced anti calcification treatment
- Lack of multiple iterative design enhancements d/t limited years of clinical practice
- Leaflet morphology and design

Device deployment

- Valve crimping
- Valve damage during small sheath delivery / balloon inflation / unsheathing

Device-anatomy interaction

- Lack of native leaflet decalcification
- Device under expansion
- Paravalvular regurgitation
- Asymmetric expansion
- Lack of stent tip deflection

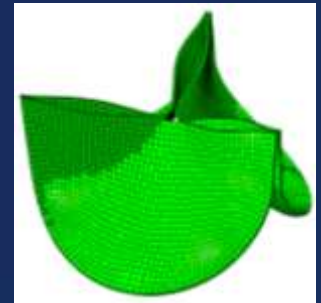
Li and Sun. *Ann Biomed Eng.* 2010

Sun, Li and Sirois. *J Biomech.* 2010

Martin C and Sun W, *J Biomech.* 2015

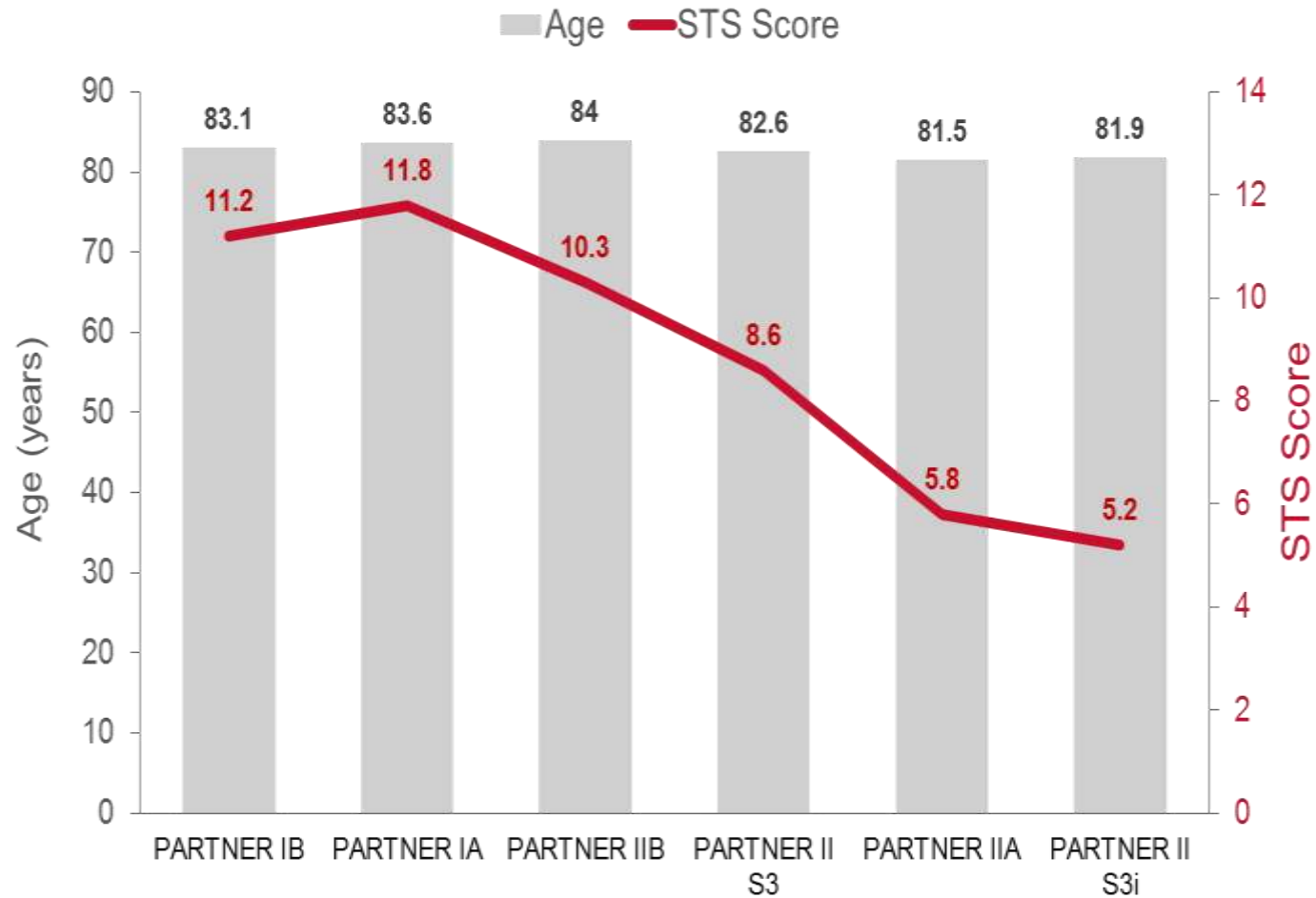
Kiefer P. *Ann Thorac Surg.* 2011

* May apply for specific THV devices only



Lower risk does not necessarily equals younger patients!

Age Has Not Decreased with STS Score

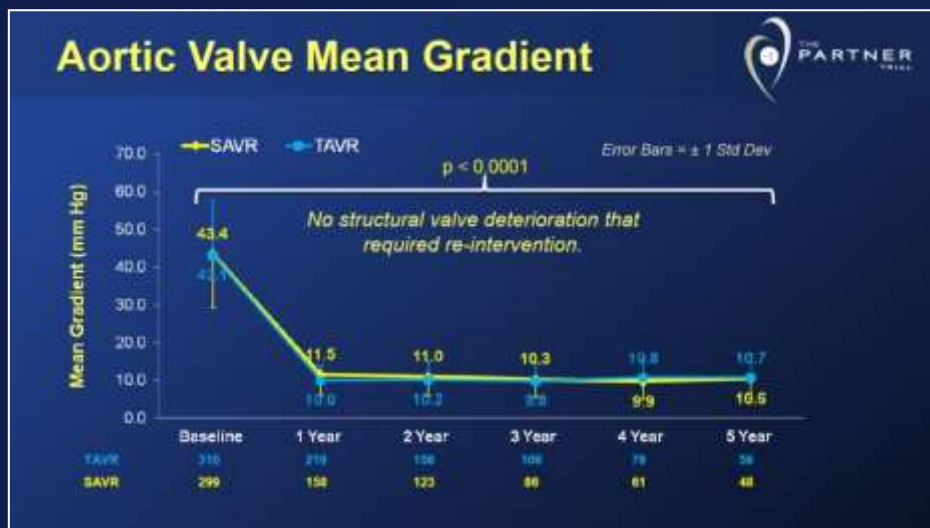


Durability

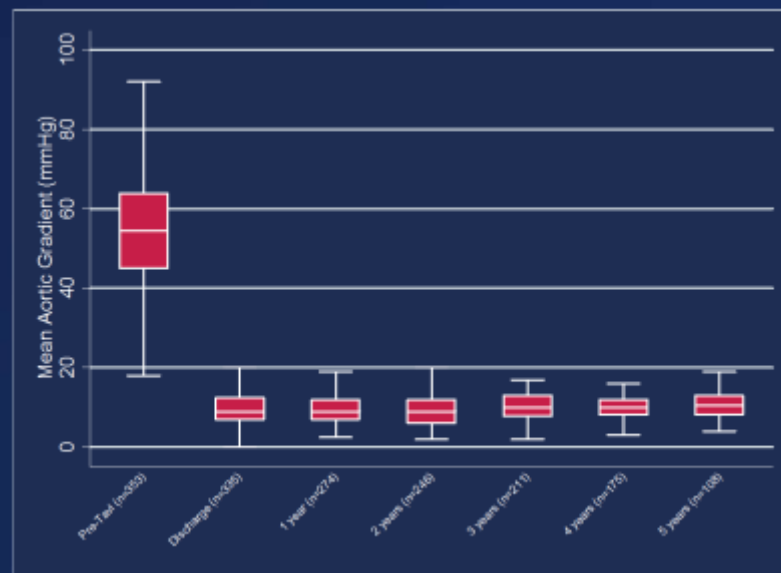
Long-term Follow-up

- Echo analyses have shown that SAPIEN and CoreValve maintain stable hemodynamic performance out to 5 years, however many wonder whether this will continue over the long term
- Also, these population-based analyses may not reflect structural valve degeneration occurring at the patient level

PARTNER A | SAPIEN



Italian Registry | CoreValve



Paradigm Shift?

How *durable* is a device?

VS

How *treatable* is a device
(how safe is it to treat the device if it fails?)

TAVR Journey - 2017

- **The Durability Controversy**

Until there is long-term (>10 years) reliable clinical and echo data on normal-risk patients treated with “modern era” transcatheter bioprosthetic valves, there will always be concerns regarding “durability”!

What lies Ahead?



TAVR Journey - 2017



Enhancing
TAVR Value

Expanding Clinical Indications

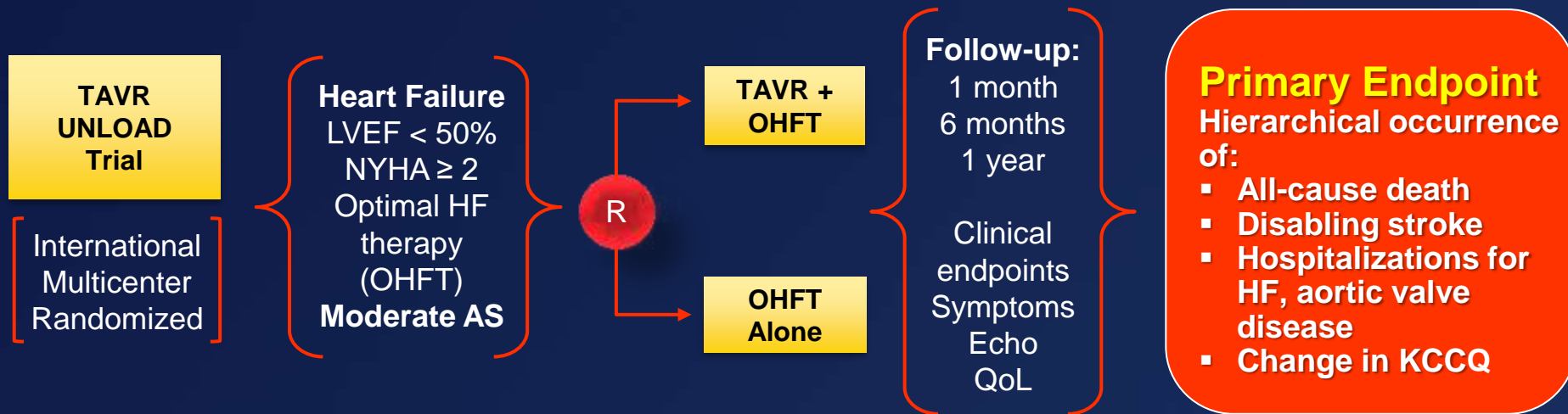
A TAVR Crossroads?

- *Bioprosthetic valve failure (aortic and mitral)*
- *Intermediate and low-risk patients*
- *Low-flow, low-gradient AS*
- *Bicuspid AV disease*
- *AS + concomitant disease (CAD, MR, AF)*
- *Severe asymptomatic AS*
- *Moderate AS + CHF*
- *High-risk AR*

TAVR - UNLOAD Trial Design

Moderate AS + HF

(600 patients, 1:1 randomized)

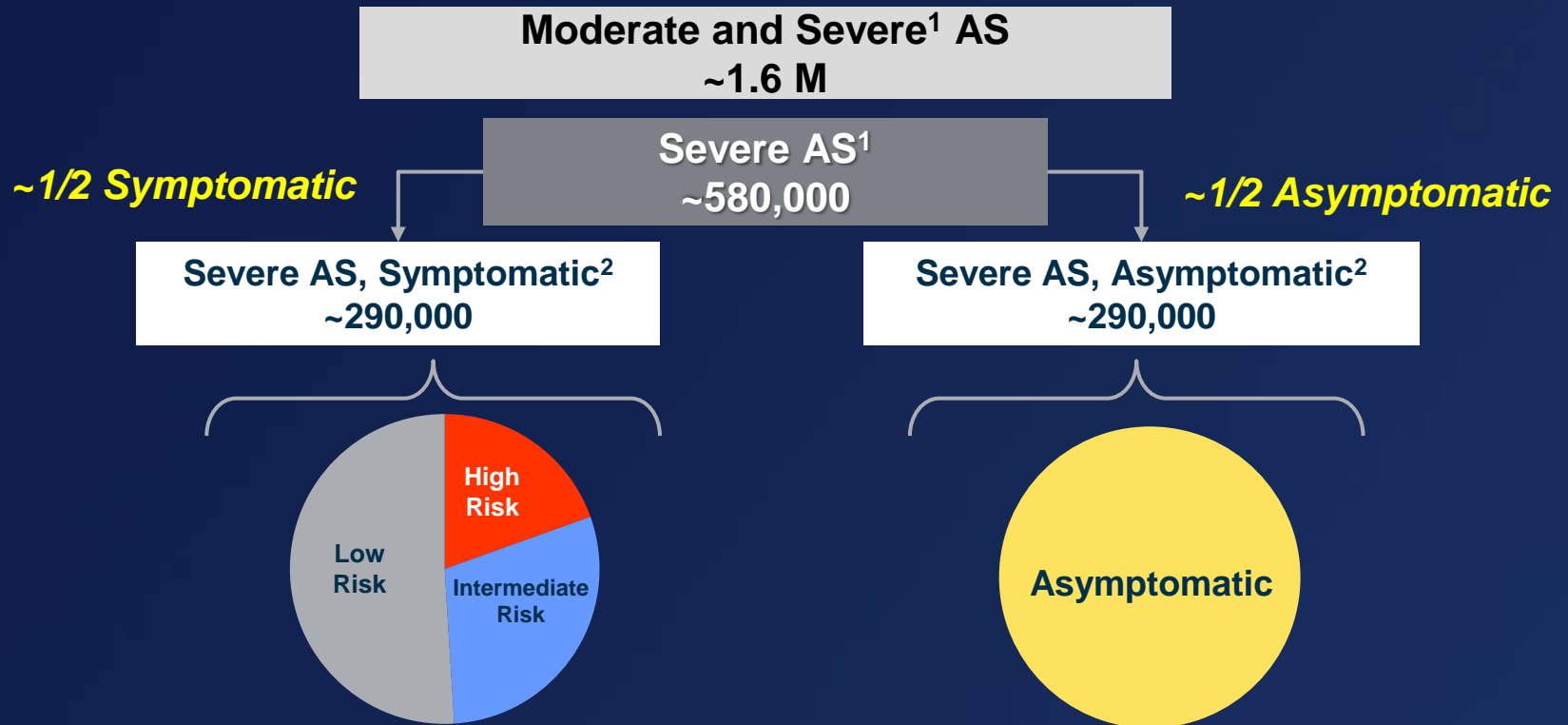


Reduced AFTERLOAD
Improved LV systolic and diastolic function

Severe AS in Asymptomatic Patients

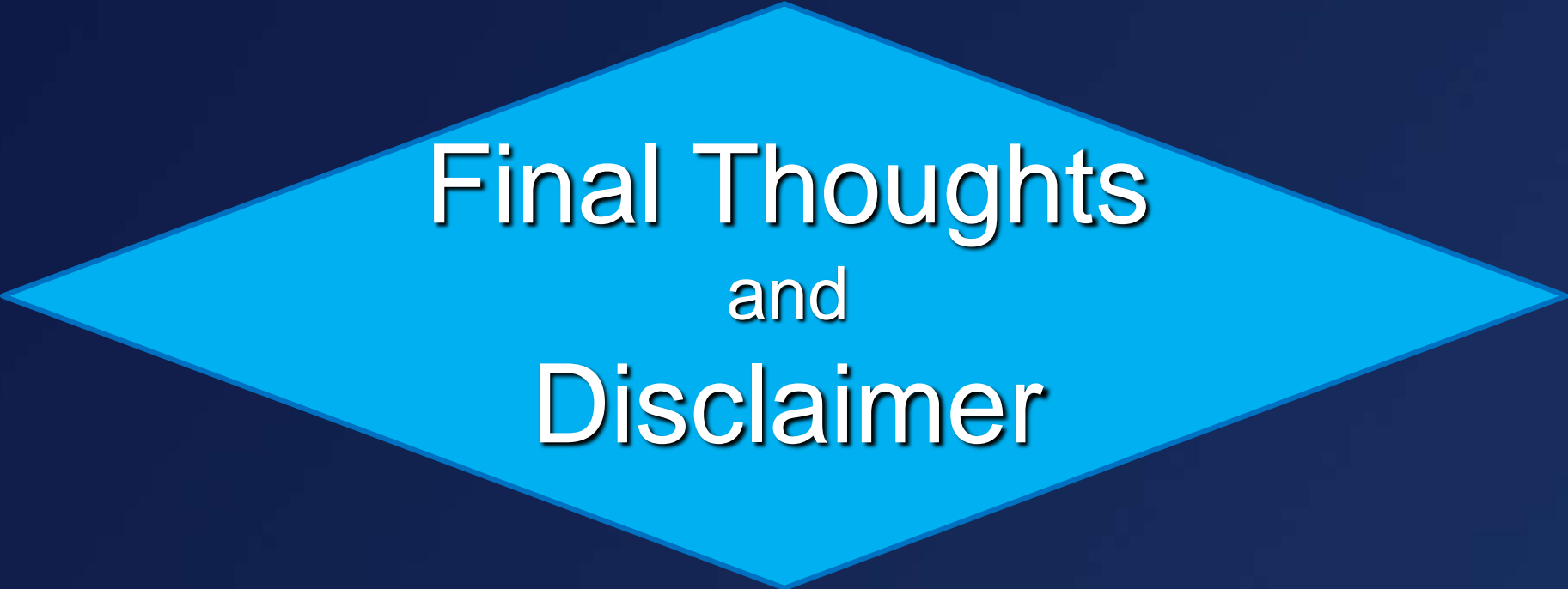
EARLY TAVR Trial

2015 Total U.S. Population



1. Nkomo 2006, Iivainen 1996, Aronow 1991, Bach 2007
2. Freed 2010, Lung 2007, Pellikka 2005; Brown 2008 (n=622)

TAVR Journey - 2017



Final Thoughts
and
Disclaimer

Heritage of Intervention

- *We believe that “less invasive” is better (certainly for patients and also for the healthcare system in general; and less-invasive means catheter-based, non-surgical, whenever possible)*
- *We are technology addicts (esp. new gizmos which can shorten procedures, improve outcomes, and expand treatment indications)*
- *We are passionate about experimental and clinical research and evidence-based medicine (fundamental to every important therapy change and to the interventional device development process)*

Heritage of Intervention

- *We rely heavily on adjunctive imaging - a visual subspecialty (a growing trend...echo/IVUS, MR/CT, “fusion” imaging, and other new invasive imaging modalities)*
- *We are passionate about the interface of clinical medicine and the rapid communication of ideas (educational meetings, physician training, new IT developments, patient care initiatives, and marketing opportunities)*
- *We have a vibrant entrepreneurial spirit, are risk-takers, and rapidly embrace new therapies*
- *We strongly support and promote global and multi-disciplinary collaborations*

Heritage of Intervention

- *We have a cultural identity ... innovation, strong industry partnerships, impatience leading to evolution and forward motion;*
- *We have a need to stimulate change and to continually re-invent ourselves, in pace with advances in bio-medical science and technology!*

TAVR Journey - 2017

Are We There Yet?

The ultimate role of TAVR is yet to be determined.

But we can foresee when the use of TAVR will be an objective risk-benefit assessment based upon clinical, anatomic, and evidence-based factors, ensuring optimal care for all patients with Aortic Valve Stenosis!

The train of TAVR has left the station, and it ain't coming back!

