The Relentless Journey of TAVR to Lower-Risk Patients: Are We There Yet?

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10 mins

Disclosure Statement of Financial Interest

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Within the past 12 months, I or my spouse/partner have had a financial interest/arrangement or affiliation with the organization(s) listed below.

Affiliation / Financial Relationship	Company
• Grant / Research Support / SAB	• Abbott, Boston Scientific, Edwards Lifescience, Medtronic
• Consulting Fees / Honoraria	• None
• Shareholder / Equity	• Claret, GDS, Mitralign, Valve Medical

TAVR Journey - 2016

- Global Demographics and Economics
- The Low-Risk Journey
- Proposing New Guidelines
- The Durability Controversy
- Mission Central = Next Steps to Further Enhance TAVR Value

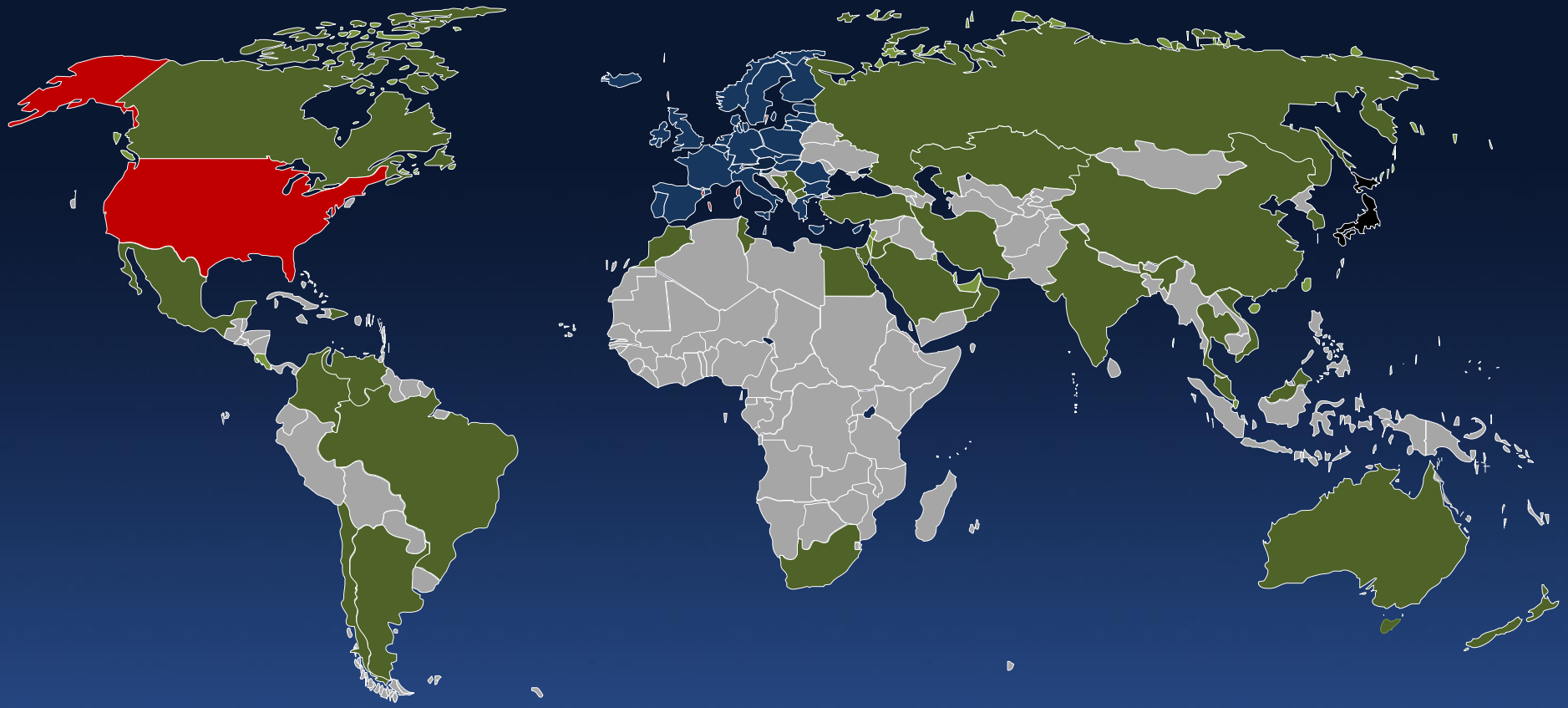
TAVR Journey - 2016

- **Global Demographics and Economics**

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

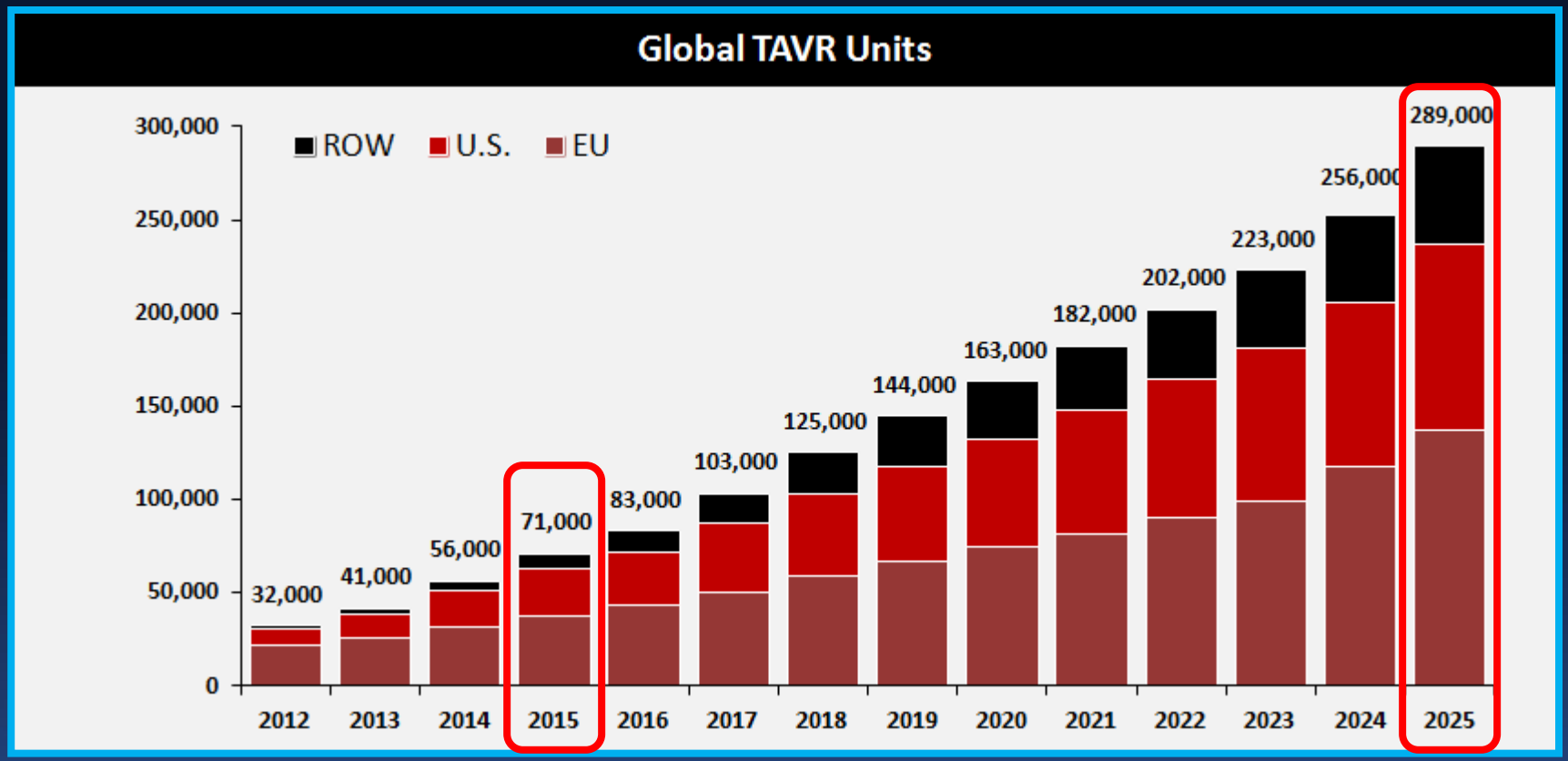
- faster growth in the US, Japan, and ROW
- marked regional growth heterogeneity due to differing reimbursement patterns
- stabilization of trained operator sites
- continued under-diagnosis and under-treatment of AS

TAVR is Available in More Than 65 Countries Around the World



>250,000 total implants to date

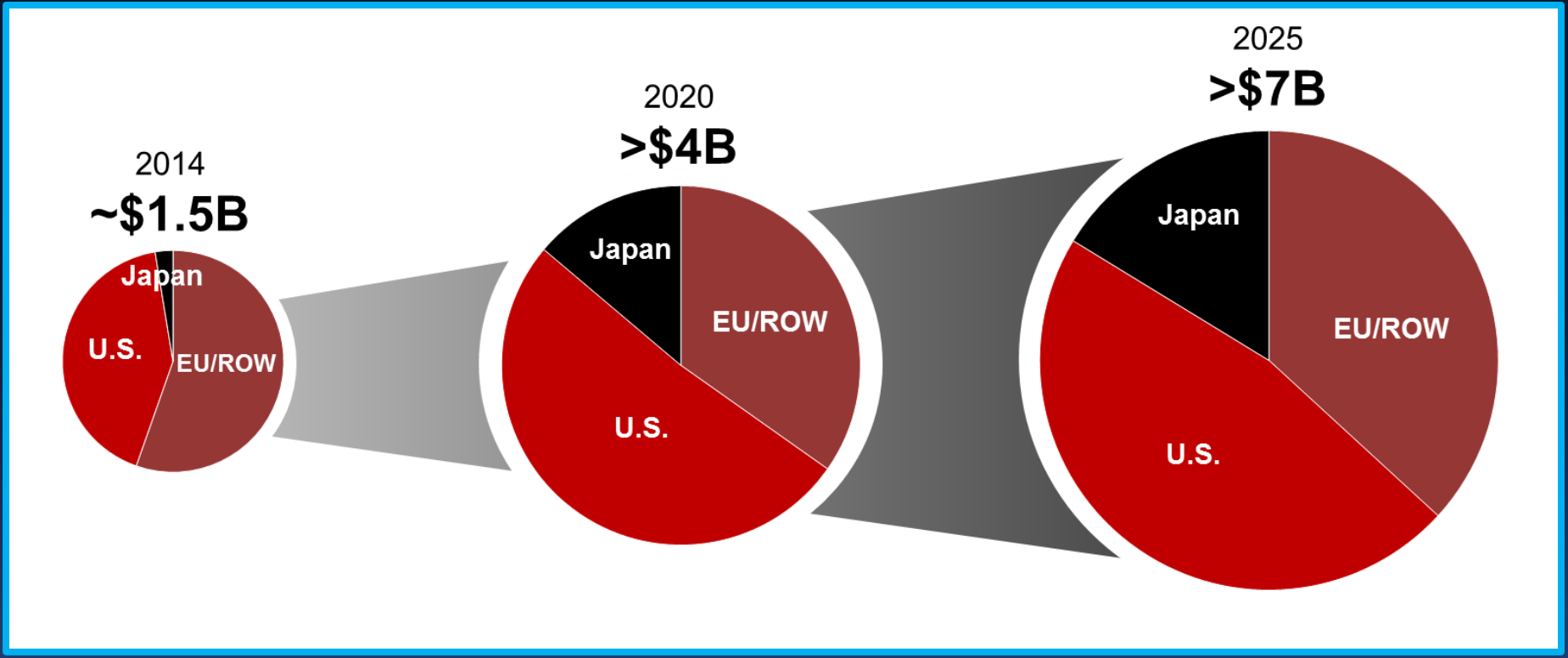
Estimated Global TAVR Procedure Growth



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!

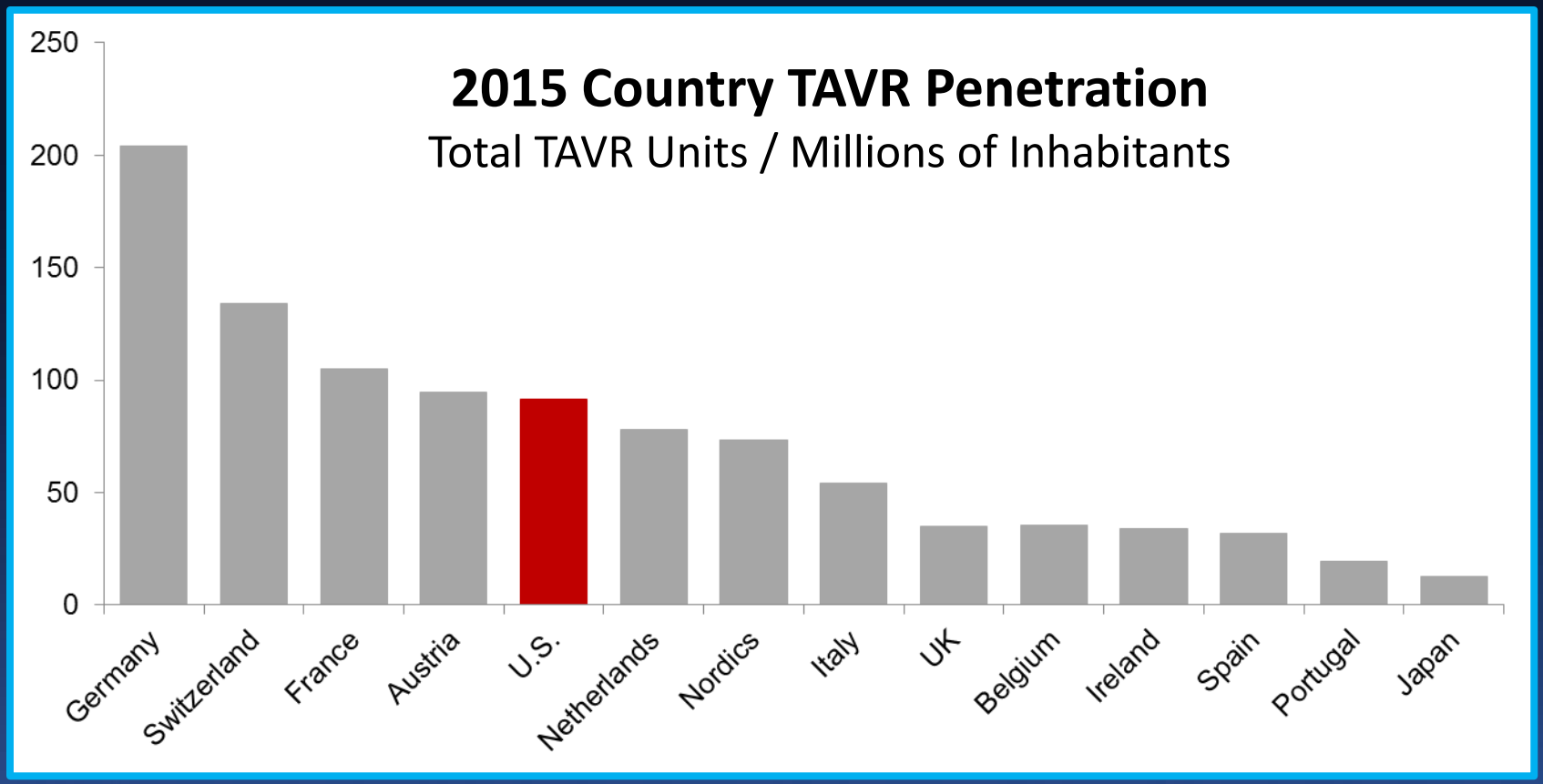
Estimated Global TAVR Economic Growth



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; Morgan Stanley Comment July 6,2015

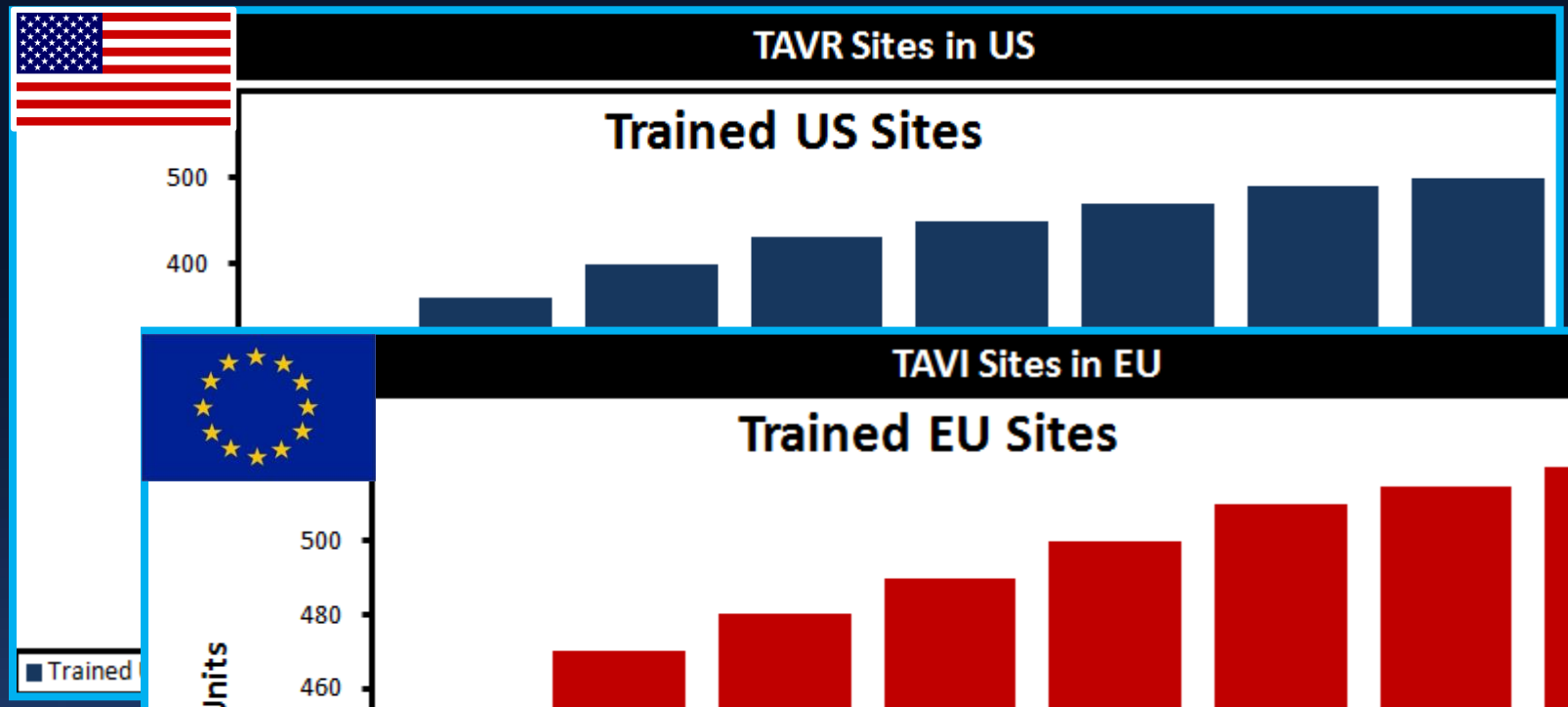
In the next 10 years, TAVR economics will increase X4!

TAVR "Underutilization" is Largely Driven by Variation in Health Policy and Reimbursement

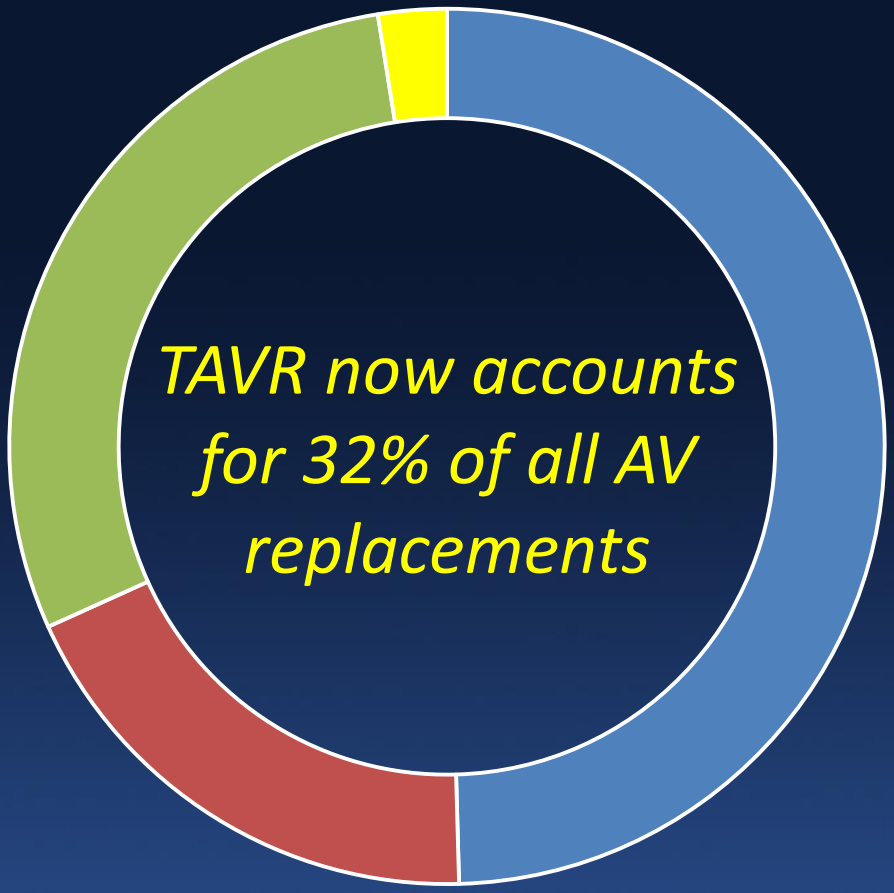


SOURCE: Eurostat, U.S. Census Bureau, Industry estimates

Estimated US and EU TAVR Sites



Medicare AV Cases in 2015



SOURCE: FY2015 MedPAR, all cases on file regardless of IPPS status

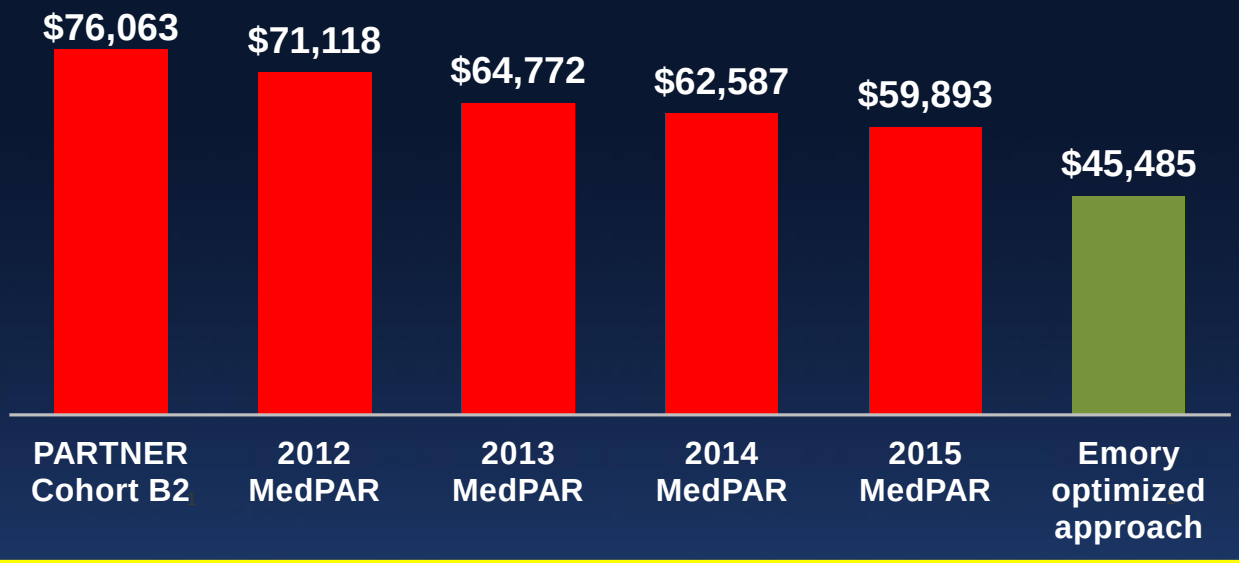
TAVR Journey - 2016

- **Global Demographics and Economics**

  Economic concerns due to high procedure costs have influenced TAVR growth and utilization cw surgery. Improved efficiencies of clinical care pathways after TAVR have reduced the differences and narrowed the gap.

Procedural efficiencies are reducing TAVR costs in the US

Total index hospitalization cost* (TF TAVR)



Length of stay (TF TAVR)

10.1 days	8.1 days	7.9 days	7.1 days	6.4 days	3.0 days

*Index hospitalization cost adjusted to reflect commercial device price

Reynolds et al.,Cost Effectiveness of Transcatheter Aortic Valve Replacement Compared with Standard Care. Circulation. 2012;125:1102-1109
Babaliaros et al., Comparison of a Minimalist Approach Transfemoral TAVR with Standard Approach Transfemoral TAVR. J Am Coll Cardiol. 2014;63(12_S)

TAVR Journey - 2016

- **The Low-Risk Journey**

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

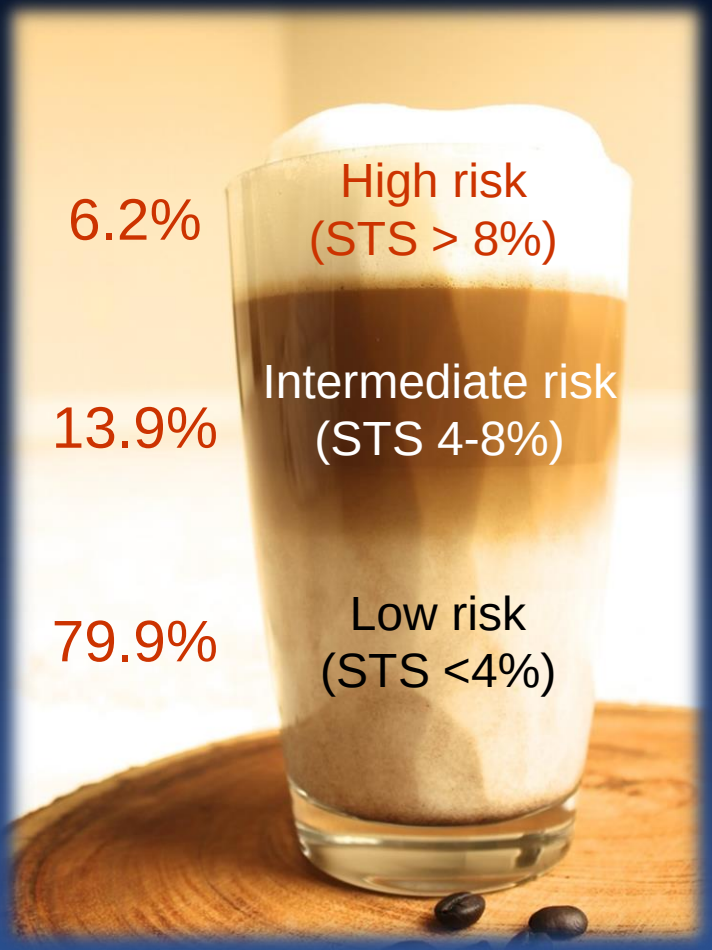
  - the multi-disciplinary heart team
  - commitment to evidence-based medicine
  - rapid technology enhancement
  - simplification of the procedure
  - striking reduction in complications

The Low-Risk Journey

My Favorite Drink = Double-shot Mocha Latte

The Low-Risk Journey

STS database 2002-2010 (141,905 pts)



The Low-Risk Journey

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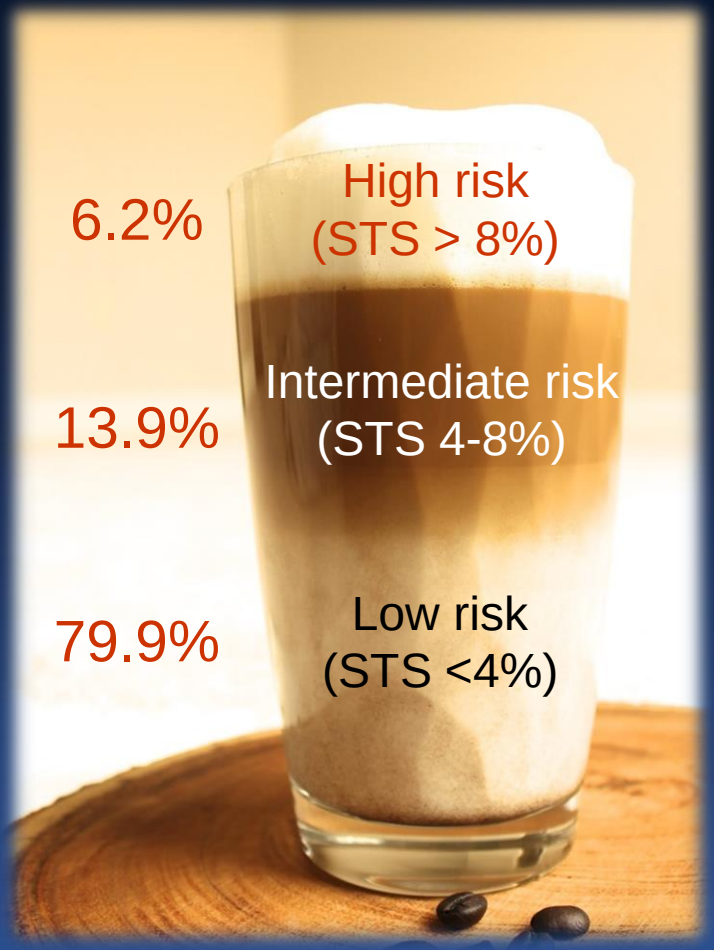
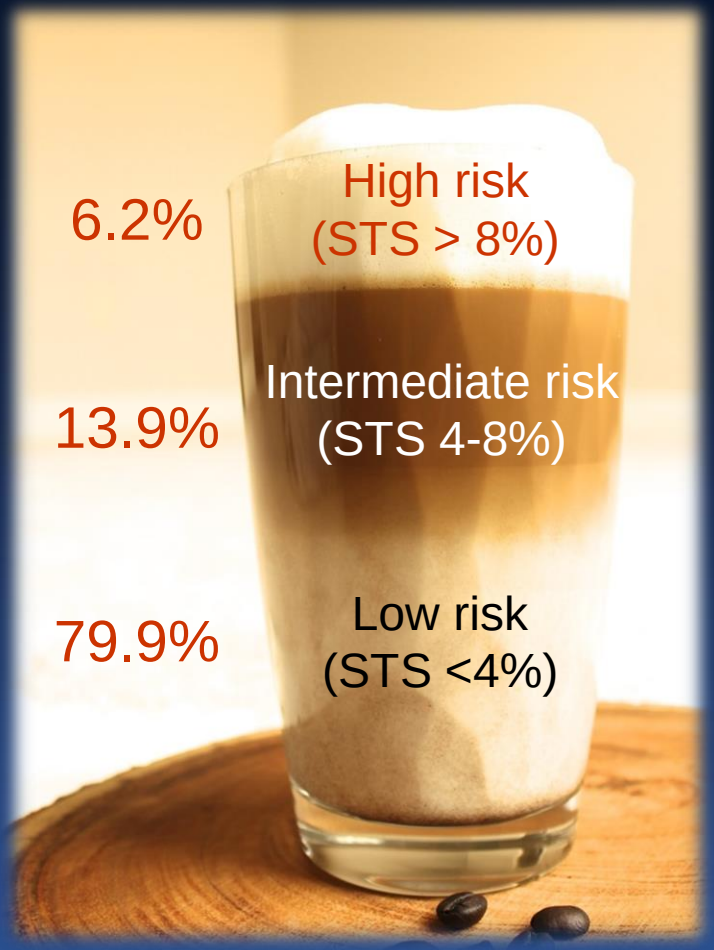


Since 2007, in the U.S., >15,000 patients have been enrolled in FDA studies (including 6 RCTs) with multiple generations of two TAVR systems!

The Low-Risk Journey

STS database 2002-2010 (141,905 pts)



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

PARTNER Manuscripts in NEJM (October, 2010 – May, 2012)

THE PARTNER TRIAL

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 OCTOBER 21, 2010 VOL. 363 NO. 17

Transcatheter Aortic-Valve Implantation for Aortic Stenosis in Patients Who Cannot Undergo Surgery

Martin B. Leon, M.D., Craig R. Smith, M.D., Michael Mack, M.D., D. Craig Miller, M.D., Jeffrey W. Moses, M.D., Lars G. Svensson, M.D., Ph.D., E. Murat Tuzcu, M.D., John G. Webb, M.D., Gregory P. Fontana, M.D., Raj R. Makkar, M.D., David L. Brown, M.D., Peter C. Block, M.D., Robert A. Guyton, M.D., Augusto D. Pichard, M.D., Joseph E. Bavaria, M.D., Howard C. Herrmann, M.D., Pamela S. Douglas, M.D., John L. Petersen, M.D., Jodi J. Akin, M.S., William N. Anderson, Ph.D., Duolao Wang, Ph.D., and Stuart Pocock, Ph.D., for the PARTNER Trial Investigators*

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 9, 2011 VOL. 364 NO. 23

Transcatheter and Surgical Aortic-Valve Replacement in High-Risk Patients

Craig R. Smith, M.D., Martin B. Leon, M.D., Michael J. Mack, M.D., D. Craig Miller, M.D., Jeffrey W. Moses, M.D., Lars G. Svensson, M.D., Ph.D., E. Murat Tuzcu, M.D., John G. Webb, M.D., Gregory P. Fontana, M.D., Raj R. Makkar, M.D., Mathew Williams, M.D., Todd Dewey, M.D., Samir Kapadia, M.D., Vasilis Babaliaros, M.D., Vinod H. Thourani, M.D., Paul Corso, M.D., Augusto D. Pichard, M.D., Joseph E. Bavaria, M.D., Howard C. Herrmann, M.D., Jodi J. Akin, M.S., William N. Anderson, Ph.D., Duolao Wang, Ph.D., and Stuart J. Pocock, Ph.D., for the PARTNER Trial Investigators*

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Transcatheter Aortic-Valve Replacement for Inoperable Severe Aortic Stenosis

Raj R. Makkar, M.D., Gregory P. Fontana, M.D., Hasan Jilaihawi, M.D., Samir Kapadia, M.D., Augusto D. Pichard, M.D., Pamela S. Douglas, M.D., Vinod H. Thourani, M.D., Vasilis C. Babaliaros, M.D., John G. Webb, M.D., Howard C. Herrmann, M.D., Joseph E. Bavaria, M.D., Susheel Kodali, M.D., David L. Brown, M.D., Bruce Bowers, M.D., Todd M. Dewey, M.D., Lars G. Svensson, M.D., Ph.D., Murat Tuzcu, M.D., Jeffrey W. Moses, M.D., Matthew R. Williams, M.D., Robert J. Siegel, M.D., Jodi J. Akin, M.S., William N. Anderson, Ph.D., Stuart Pocock, Ph.D., Craig R. Smith, M.D., and Martin B. Leon, M.D., for the PARTNER Trial Investigators*

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Two-Year Outcomes after Transcatheter or Surgical Aortic-Valve Replacement

Susheel K. Kodali, M.D., Mathew R. Williams, M.D., Craig R. Smith, M.D., Lars G. Svensson, M.D., Ph.D., John G. Webb, M.D., Raj R. Makkar, M.D., Gregory P. Fontana, M.D., Todd M. Dewey, M.D., Vinod H. Thourani, M.D., Augusto D. Pichard, M.D., Michael Fischbein, M.D., Wilson Y. Szeto, M.D., Scott Lim, M.D., Kevin L. Greason, M.D., Paul S. Teirstein, M.D., S. Chris Malaisrie, M.D., Pamela S. Douglas, M.D., Rebecca T. Hahn, M.D., Brian Whisenant, M.D., Alan Zajarias, M.D., Duolao Wang, Ph.D., Jodi J. Akin, M.S., William N. Anderson, Ph.D., and Martin B. Leon, M.D., for the PARTNER Trial Investigators*

CoreValve High-Risk U.S. Pivotal Trial (1 and 2-Yr Follow-up)

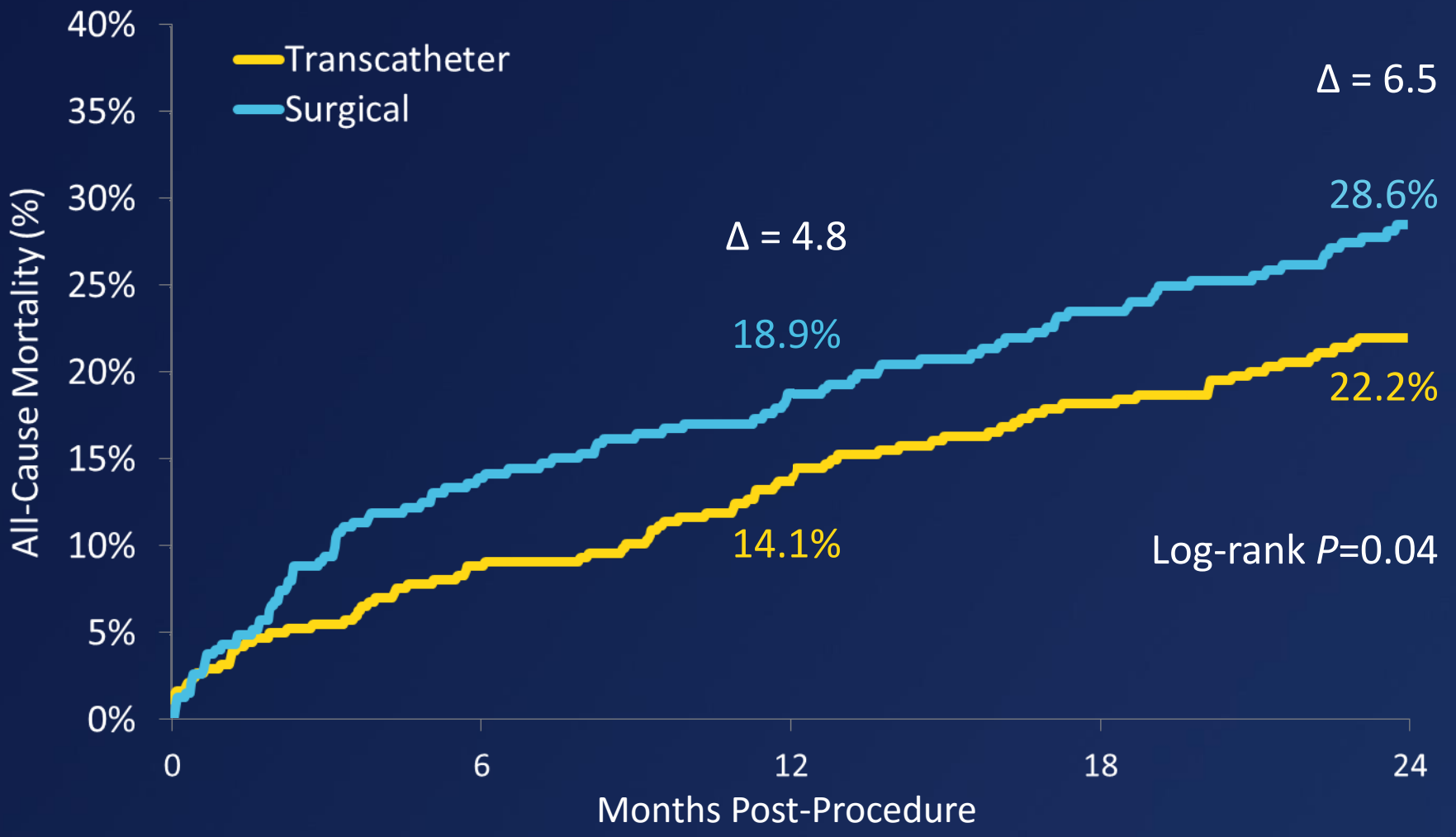
JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY VOL. ■, NO. ■, 2015

ISSN 0735-1097/$36.00
PUBLISHED BY ELSEVIER INC. http://dx.doi.org/10.1016/j.jacc.2015.05.017

2-Year Outcomes in Patients Undergoing Surgical or Self-Expanding Transcatheter Aortic Valve Replacement

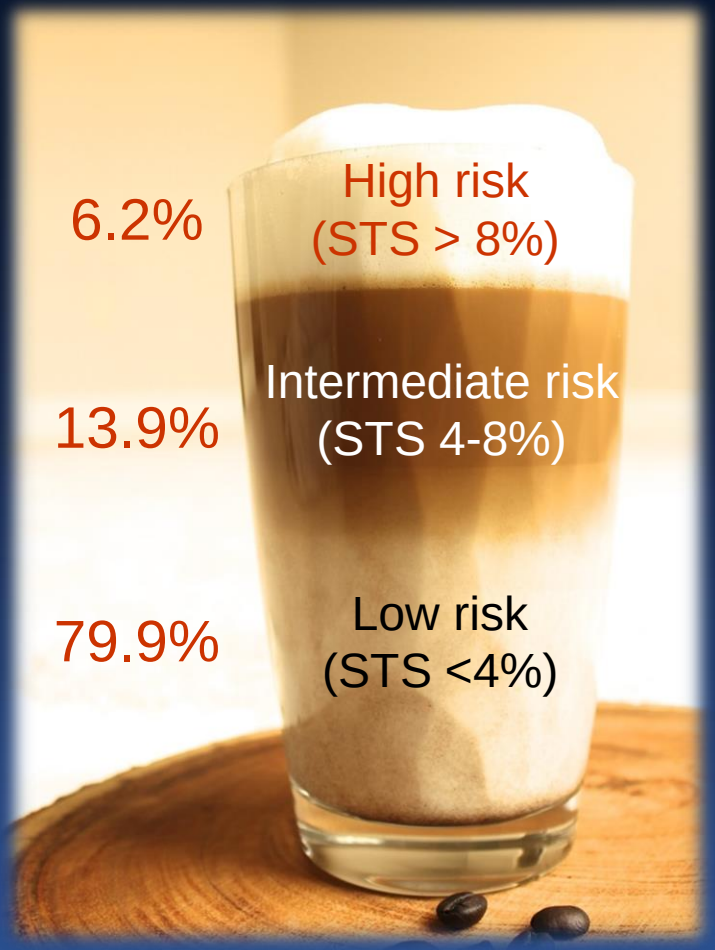
Michael J. Reardon, MD,* David H. Adams, MD,† Neal S. Kleiman, MD,* Steven J. Yakubov, MD,‡
Joseph S. Coselli, MD,§ G. Michael Deeb, MD,‖ Thomas G. Gleason, MD,¶ Joon Sup Lee, MD,¶
James B. Hermiller, Jr, MD,# Stan Chetcuti, MD,‖ John Heiser, MD,** William Merhi, MD,** George L. Zorn III, MD,††
Peter Tadros, MD,†† Newell Robinson, MD,‡‡ George Petrossian, MD,‡‡ G. Chad Hughes, MD,§§
J. Kevin Harrison, MD,§§ Brijeshwar Maini, MD,‖‖ Mubashir Mumtaz, MD,‖‖ John V. Conte, MD,¶¶
Jon R. Resar, MD,¶¶ Vicken Aharonian, MD,## Thomas Pfeffer, MD,## Jae K. Oh, MD,*** Hongyan Qiao, PhD,†††
Jeffrey J. Popma, MD‡‡‡

All-Cause Mortality



The Low-Risk Journey

STS database 2002-2010 (141,905 pts)



PARTNER 2A, S3i
SURTAVI, UK TAVI

The PARTNER 2A and S3i Trial
The NEJM and Lancet On-line

THE PARTNER II TRIAL

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Transcatheter aortic valve replacement versus surgical valve replacement in intermediate-risk patients: a propensity score analysis

Vinod H Thourani, Susheel Kodali, Raj R Makkar, Howard C Herrmann, Mathew Williams, Vasilis Babaliaros, Richard Smalling, Scott Lim, S Chris Malaisrie, Samir Kapadia, Wilson Y Szeto, Kevin L Greason, Dean Kereiakes, Gorav Ailawadi, Brian K Whisenant, Chandan Devireddy, Jonathon Leipsic, Rebecca T Hahn, Philippe Pibarot, Neil J Weissman, Wael A Jaber, David J Cohen, Rakesh Suri, E Murat Tuzcu, Lars G Svensson, John G Webb, Jeffrey W Moses, Michael J Mack, D Craig Miller, Craig R Smith, Maria C Alu, Rupa Parvataneni, Ralph B D'Agostino Jr, Martin B Leon

Brian K. Whisenant, M.D., Robert W. Hodson, M.D., Jeffrey W. Moses, M.D., Alfredo Trento, M.D., David L. Brown, M.D., William F. Fearon, M.D., Philippe Pibarot, D.V.M., Ph.D., Rebecca T. Hahn, M.D., Wael A. Jaber, M.D., William N. Anderson, Ph.D., Maria C. Alu, M.M., and John G. Webb, M.D., for the PARTNER 2 Investigators*

The Low-Risk Journey

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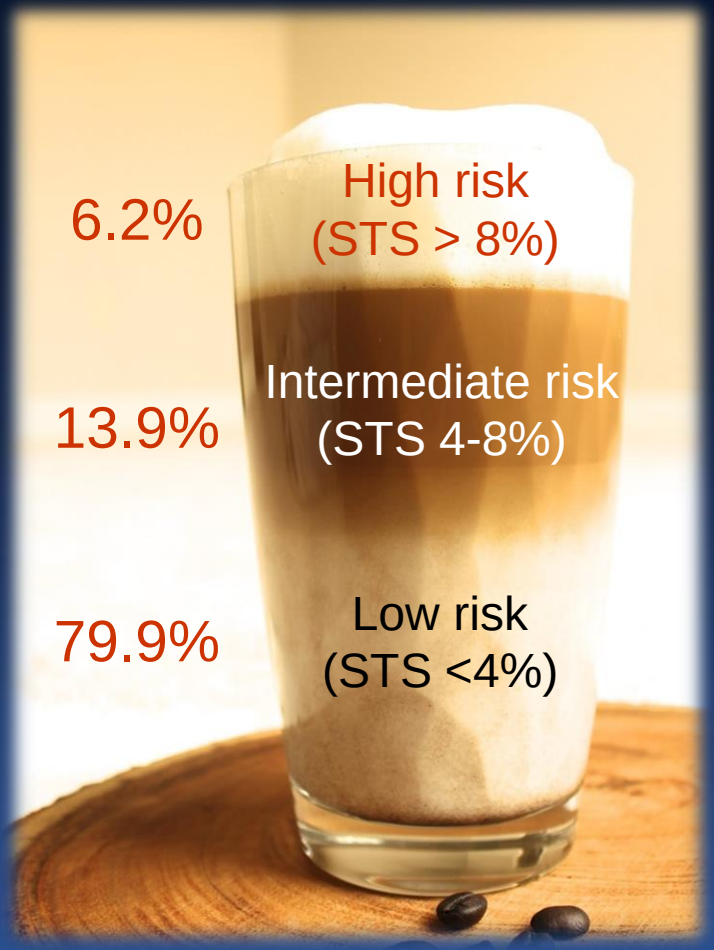
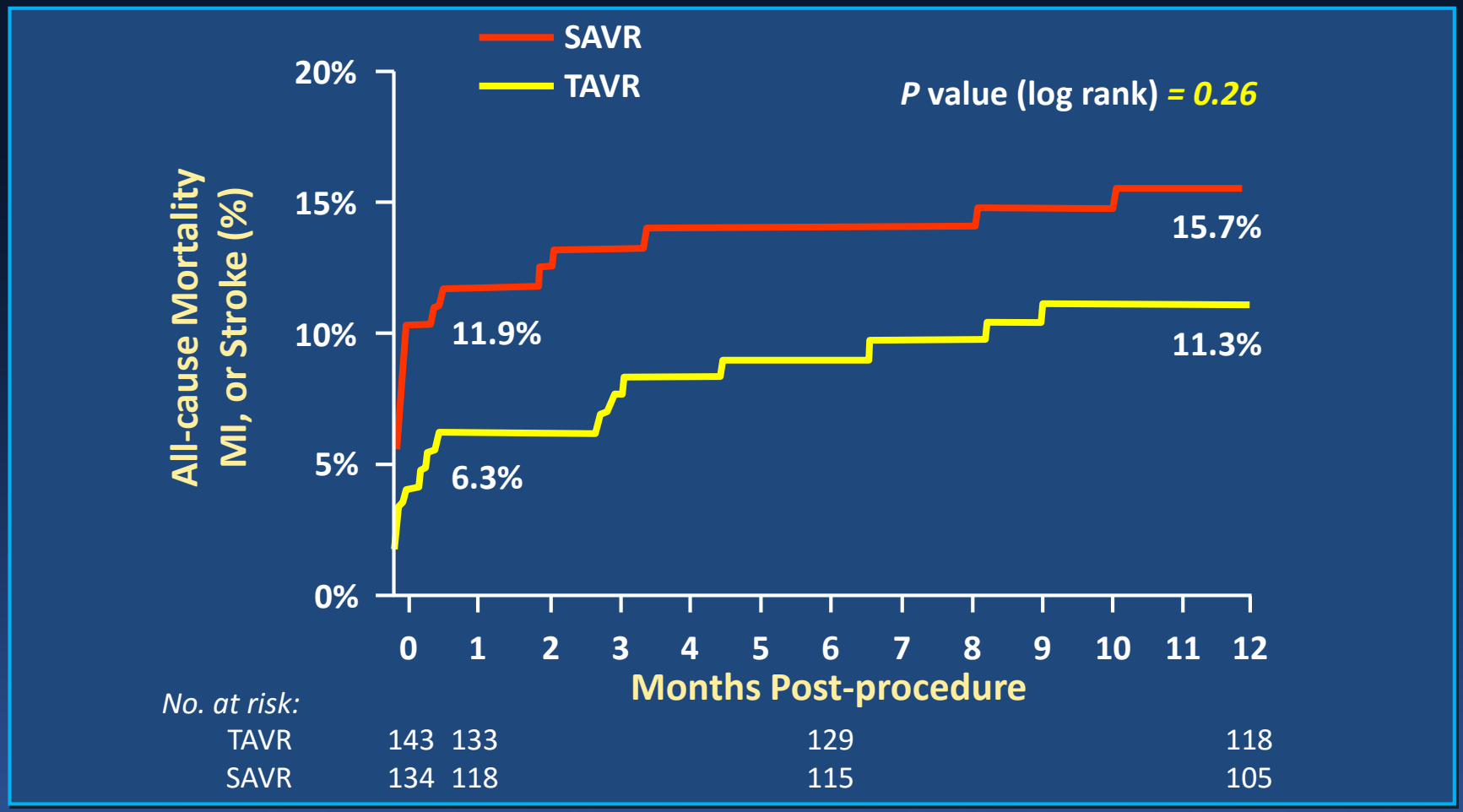


NOTION All Comers,
PARTNER 3 LR, CoreValve LR

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



TAVR Journey - 2016

- **The Low-Risk Journey**

  Risk stratification for TAVR, especially based upon surgical risk scores, is 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!

ACC/AHA 2014 Risk Assessment (with MHT*)

Combining STS Risk Estimate, Frailty, Major Organ System Dysfunction, and Procedure-Specific Impediments

	Low Risk (ALL criteria)	Intermediate Risk (any 1)	High Risk (any 1 criteria)	Prohibitive Risk (any 1 criteria)
STS PROM*	<4% **AND**	4% to 8% **OR**	>8% **OR**	Predicted risk with surgery of death or major morbidity (all-cause) >50% at 1 y **OR**
Frailty	**None** **AND**	1 index (mild) **OR**	2 or more indices (moderate-severe) **OR**	
Major organ system compromise not to be improved postop	None **AND**	1 organ system **OR**	No more than 2 organ systems **OR**	3 or more organ systems **OR**
Procedure-specific impediment	None	Possible procedure-specific impediment	Possible procedure-specific impediment	Severe procedure-specific impediment

** Multi-disciplinary Heart Team*

The Low-Risk Journey

Imagery of TAVR Risk Strata

AS Patient Population Requiring Treatment

The Low-Risk Journey

Imagery of TAVR Risk Strata

AS Patient Population Requiring Treatment

The Low-Risk Journey

Imagery of TAVR Risk Strata

AS Patient Population Requiring Treatment

TAVR Risk Model from TVT Registry

Original Investigation

Development and Validation of a Risk Prediction Model for In-Hospital Mortality After Transcatheter Aortic Valve Replacement

Fred H. Edwards, MD; David J. Cohen, MD; Sean M. O'Brien, PhD; Eric D. Peterson, MD, MPH; Michael J. Mack, MD; David M. Shahian, MD; Frederick L. Grover, MD; E. Murat Tuzcu, MD; Vinod H. Thourani, MD; John Carroll, MD; J. Matthew Brennan, MD, MPH; Ralph G. Brindis, MD, MPH; John Rumsfeld, MD, PhD; David R. Holmes Jr, MD; for the Steering Committee of the Society of Thoracic Surgeons/American College of Cardiology Transcatheter Valve Therapy Registry

- Development sample = 13,718 consecutive U.S. patients from 265 centers in the STS/ACC TVT registry undergoing TAVR from Nov 1, 2011 to Feb 28, 2014. Validation cohort 6,868 consecutive patients from March 1 to Oct 8, 2014
- Covariates selected based on expert opinion and statistical analysis; relationship between in-hospital mortality and baseline covariates estimated by logistic egression; final predictors selected via stepwise variable selection

JAMA Cardiol; March 9, 2016

TAVR Risk Model from TVT Registry

Model Coefficients

Covariate	Coefficient	OR (95% CI)[a]
Age per 5-y increments	0.12185	1.13 (1.06-1.20)
Glomerular filtration rate per 5-U increments	−0.06933	0.93 (0.91-0.95)
Dialysis vs no dialysis	1.17932	3.25 (2.42-4.37)
NYHA class IV	0.22304	1.25 (1.03-1.52)
Severe chronic lung disease	0.51084	1.67 (1.35-2.05)
Nonfemoral access site	0.67347	1.96 (1.65-2.33)
Acuity category[b]		
2	0.45070	1.57 (1.20-2.05)
3	0.99269	2.70 (2.05-3.55)
4	1.20737	3.34 (1.59-7.02)

- Development sample: mean age 82.1 yrs, 51.1% women and in-hospital mortality = 5.3%
- C statistic for discrimination = 0.67 (95% CI 0.65-0.69)

JAMA Cardiol; March 9, 2016

TAVR Journey - 2016

- **The Low-Risk Journey**

  Realization of TAVR (society guidelines and reimbursement) for essentially ALL patients (including low-risk) with AS requiring treatment, will still require…

  - completion of the low-risk RCTs
  - meaningful TAVR risk scores
  - management of valve durability issues

The PARTNER 3 Trial
Study Design

Symptomatic Severe Calcific Aortic Stenosis

Low Risk ASSESSMENT by Heart Team
(STS < 4%, TF only)

1:1 Randomization
(n=1228)

TF - TAVR (SAPIEN 3)	Surgery (Bioprosthetic Valve)
CT Imaging Sub-Study (n=200)	CT Imaging Sub-Study (n=200)
Actigraphy/QoL Sub-Study (n=100)	Actigraphy/QoL Sub-Study (n=100)

PARTNER 3 Registries

- Alternative Access (n=100) (TA/TAo/Subclavian)
- Bicuspid Valves (n=100)
- ViV (AV and MV) (n=100)

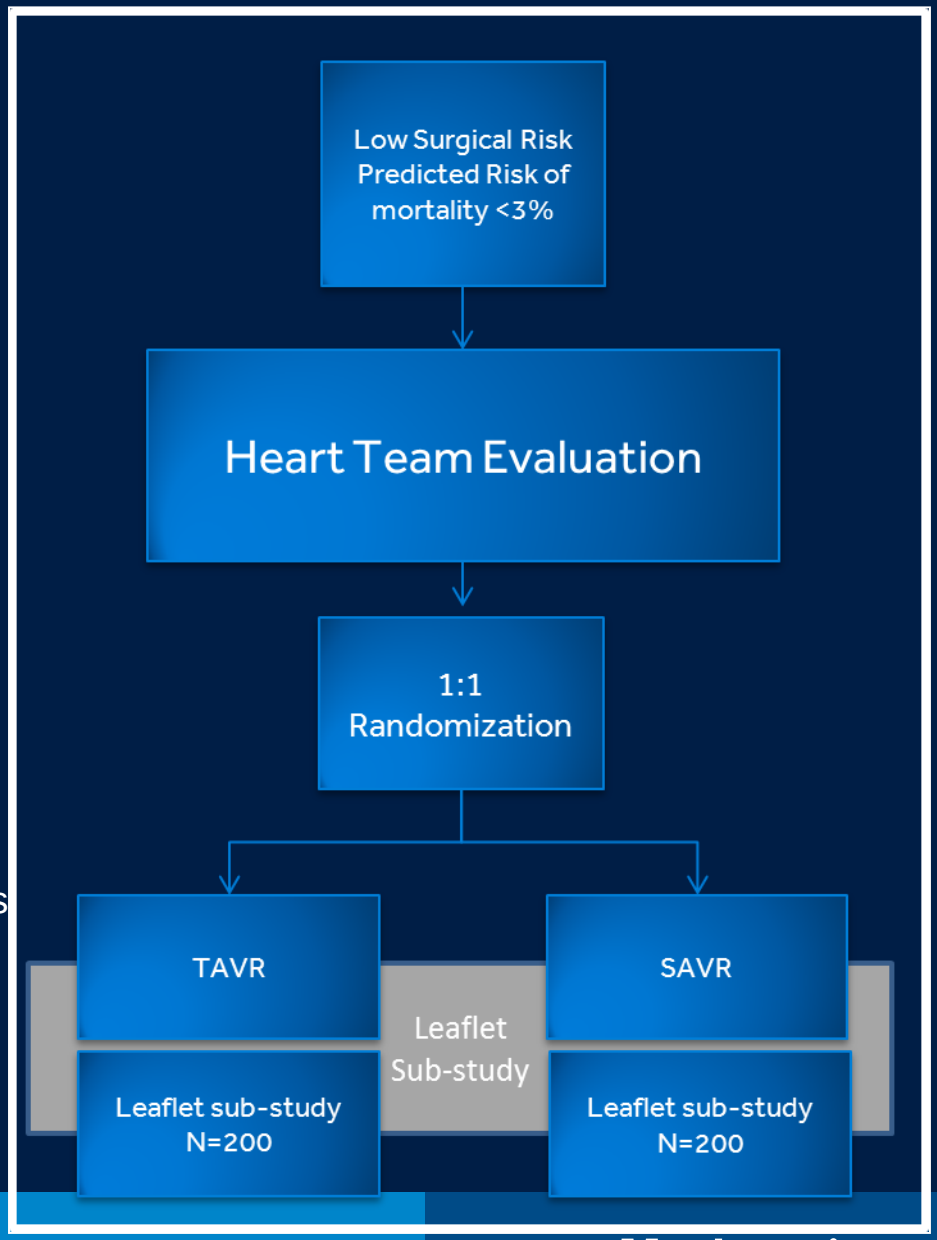
PRIMARY ENDPOINT:
Composite of all-cause mortality, all strokes, or re-hospitalization at 1 year post-procedure

Follow-up: 30 days, 6 mos, 1 year and annually through 10 years

MEDTRONIC TAVR IN LOW RISK PATIENTS

TRIAL DESIGN & LEAFLET SUB-STUDY

- **Patient Population: Low Risk Cohort**
  - Determined by Heart Team to be low surgical risk
- **Primary Endpoint:**
  - Safety: Death, all stroke, life-threatening bleeding, major vascular complications, or AKI at 30 days
  - Efficacy: Death or major stroke at 2 years
- **Sample Size: ~1200 Subjects**
- **Follow-up Evaluations:**
  - 30-days, 6-month , 18-month, and 1 Through 5 years
- **Number of Sites: Up to 80 sites**



Medtronic

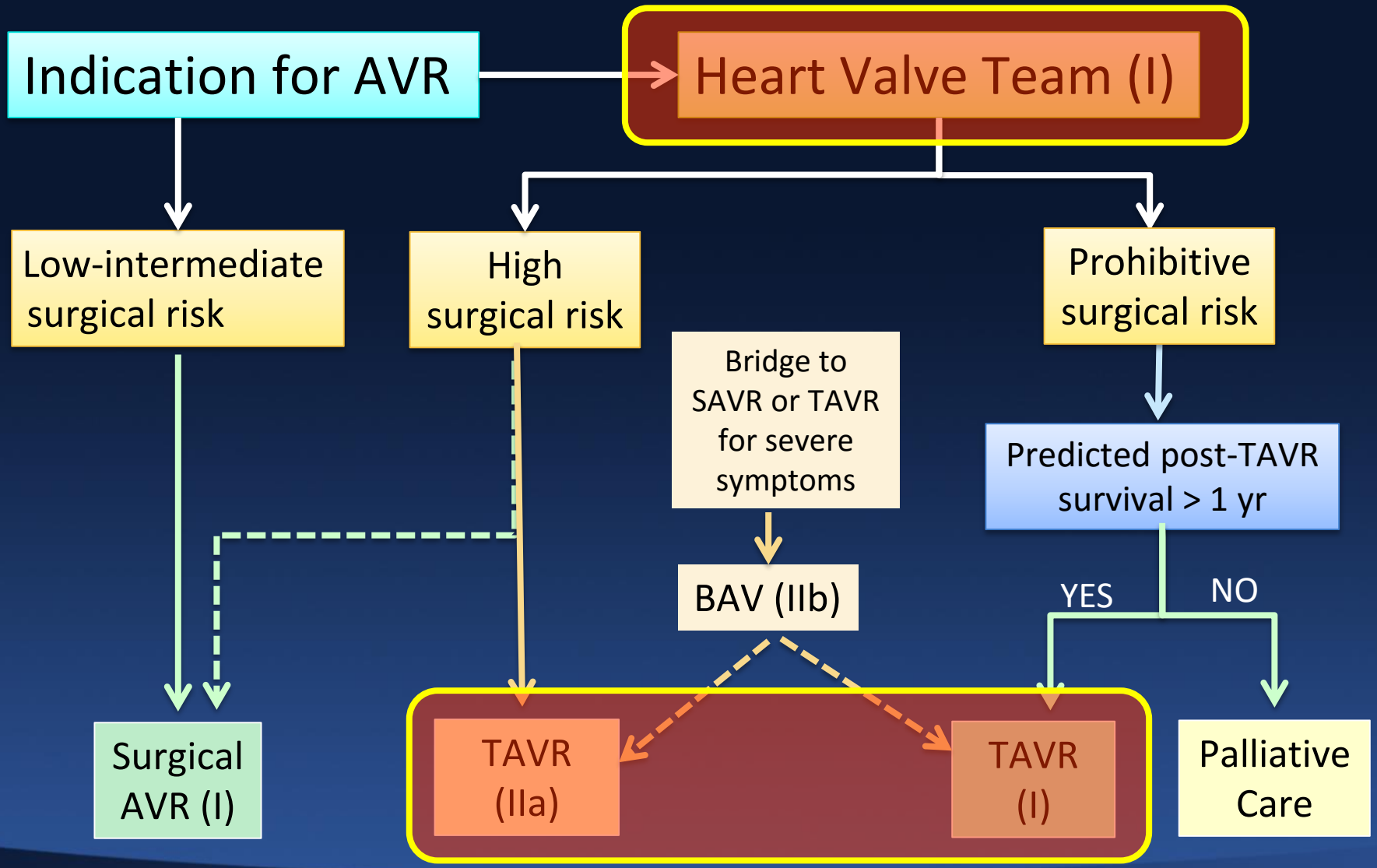
TAVR Journey - 2016

- **Proposing New Guidelines**

  The current TAVR guidelines (ESC and AHA/ACC) are already anachronistic and don't reflect clinical practice!

2014 ACC/AHA Valve Guidelines

CHOICE of Intervention for AS



TAVR Journey - 2016

- **Proposing New Guidelines**

  Therefore, until the guidelines are updated, we should consider introducing "clinical" guidelines to help the practicing TAVR community, based upon…

  - ALL available clinical trial evidence
  - global trends and accepted clinical practices
  - important "secondary" endpoints which better indicate the impact/value of TAVR

2014 ACC/AHA Valve Guidelines

CLASSIFICATION of Recommendations

ESTIMATE OF CERTAINTY (PRECISION) OF TREATMENT EFFECT	SIZE OF TREATMENT EFFECT			
	CLASS I *Benefit >>> Risk* Procedure/Treatment **SHOULD** be performed/ administered	**CLASS IIa** *Benefit >> Risk* *Additional studies with focused objectives needed* **IT IS REASONABLE** to perform procedure/administer treatment	**CLASS IIb** *Benefit ≥ Risk* *Additional studies with broad objectives needed; additional registry data would be helpful* Procedure/Treatment **MAY BE CONSIDERED**	**CLASS III** *No Benefit* or **CLASS III** *Harm* Procedure/ Test / Treatment COR III: No benefit — Not Helpful — No Proven Benefit COR III: Harm — Excess Cost w/o Benefit or Harmful — Harmful to Patients
LEVEL A Multiple populations evaluated* Data derived from multiple randomized clinical trials or meta-analyses	■ Recommendation that procedure or treatment is useful/effective ■ Sufficient evidence from multiple randomized trials or meta-analyses	■ Recommendation in favor of treatment or procedure being useful/effective ■ Some conflicting evidence from multiple randomized trials or meta-analyses	■ Recommendation's usefulness/efficacy less well established ■ Greater conflicting evidence from multiple randomized trials or meta-analyses	■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Sufficient evidence from multiple randomized trials or meta-analyses
LEVEL B Limited populations evaluated* Data derived from a single randomized trial or nonrandomized studies	■ Recommendation that procedure or treatment is useful/effective ■ Evidence from single randomized trial or nonrandomized studies	■ Recommendation in favor of treatment or procedure being useful/effective ■ Some conflicting evidence from single randomized trial or nonrandomized studies	■ Recommendation's usefulness/efficacy less well established ■ Greater conflicting evidence from single randomized trial or nonrandomized studies	■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Evidence from single randomized trial or nonrandomized studies
LEVEL C Very limited populations evaluated* Only consensus opinion of experts, case studies, or standard of care	■ Recommendation that procedure or treatment is useful/effective ■ Only expert opinion, case studies, or standard of care	■ Recommendation in favor of treatment or procedure being useful/effective ■ Only diverging expert opinion, case studies, or standard of care	■ Recommendation's usefulness/efficacy less well established ■ Only diverging expert opinion, case studies, or standard of care	■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Only expert opinion, case studies, or standard of care

TAVR Clinical Use in 2016
(evidence + common sense)

CLASS I

Benefit >>> Risk

SHOULD be performed

Class Ia (of course!)

- Cannot have surgery (= inoperable, extreme risk, prohibitive risk)
  - ✓ esp. technical reasons (e.g. hostile chest, chest RT, etc.)
  - ✓ beware futility (e.g. wheelchair-bound, ultra-frail, extreme co-morbidities)
- "Very" high-risk for surgery
  - ✓ e.g. severe COPD, chronic liver disease, dementia, severe PH

TAVR Clinical Use in 2016
(evidence + common sense)

CLASS I

Benefit >>> Risk

SHOULD be performed

Class Ib (enough already!)

- ≥ 90 years old
- All other high-risk patients
- Aortic valve-in-valve (high-risk)
- Special considerations
  - ✓ low EF (esp. <30%)
  - ✓ CKD on dialysis
  - ✓ small annulus (esp. in women)
  - ✓ low flow-low gradient AS

TAVR Clinical Use in 2016
(evidence + common sense)

CLASS IIa

Benefit >> Risk

IT IS REASONABLE to perform

Class IIa (strong preference!)

- Intermediate-risk patients (esp. TF)
- ≥ 80 years old
- Aortic valve-in-valve (normal risk)
- Severe *asymptomatic* AS (PV > 5 m/s)
- Concomitant disease
  - ✓ previous CABG
  - ✓ CKD not requiring dialysis
  - ✓ CAD – non-complex
  - ✓ RH failure

TAVR Clinical Use in 2016
(evidence + common sense)

CLASS IIb

Benefit ≥ Risk

MAY BE CONSIDERED to perform

Class IIb (on the fence = need more evidence; proceed with caution)

- Low-risk patients (except as above)
  - ✓ ? bicuspid aortic valve disease
  - ✓ < 65 years old (the durability issue)
- High "anatomic" risk for TAVR
  - ✓ extreme calcification (esp. LVOT) and high risk of rupture or CA occlusion
  - ✓ marked horizontal aorta

TAVR Clinical Use in 2016
(evidence + common sense)

CLASS III

No Benefit
OR Harm

SHOULD NOT
be performed

Class III (stay away!)

- Concomitant CV lesions requiring surgery (e.g. aortopathies, complex CAD, other valve lesions)
- Poor candidates for TAVR due to technical or anatomic reasons
  - ✓ annulus size too small/large
  - ✓ LV thrombus or endocarditis

TAVR Journey - 2016

- **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"!

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

THE PARTNER TRIAL

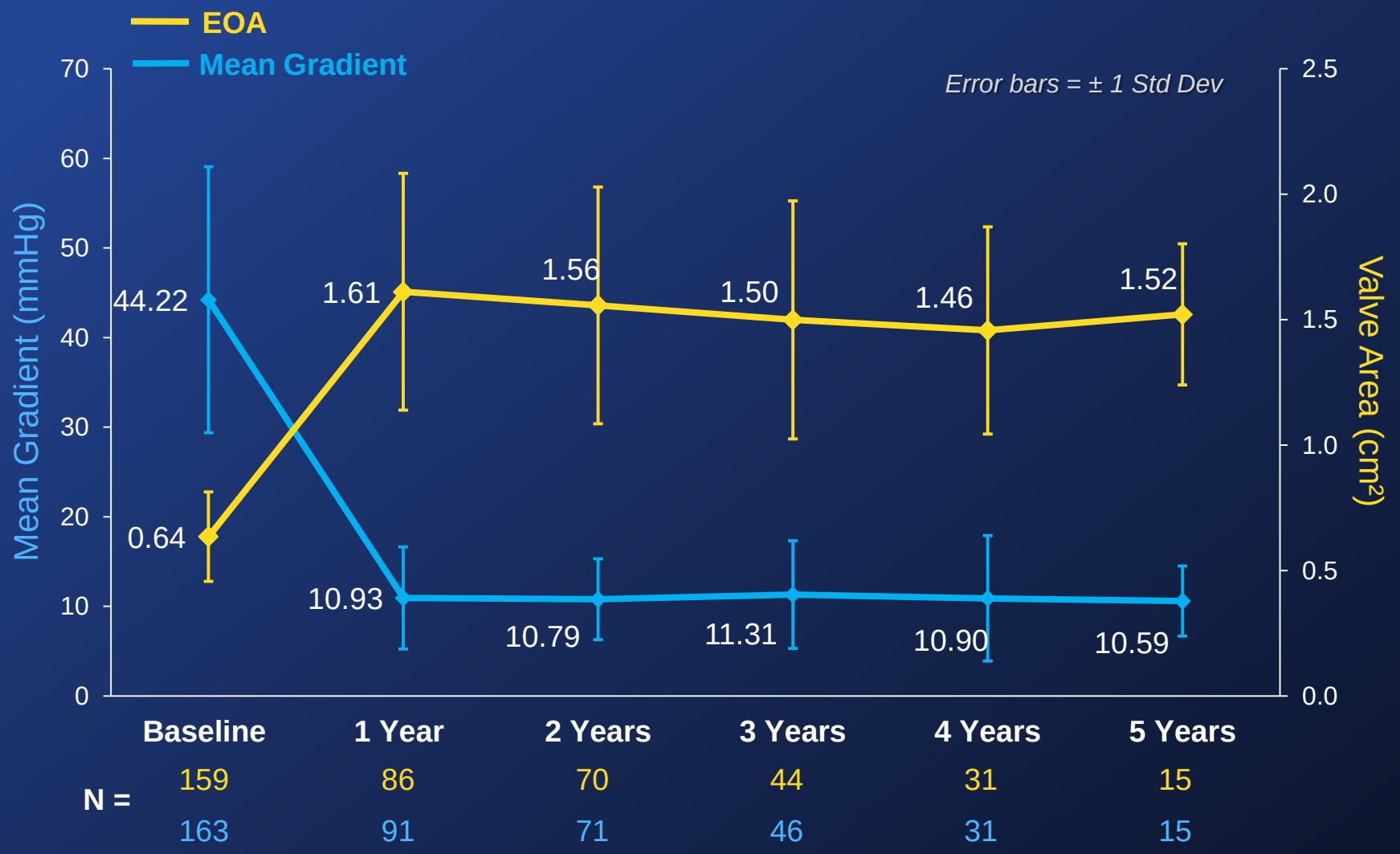
5-year outcomes of transcatheter aortic valve replacement compared with standard treatment for patients with inoperable aortic stenosis (PARTNER 1): a randomised controlled trial

Samir R Kapadia, Martin B Leon, Raj R Makkar, E Murat Tuzcu, Lars G Svensson, Susheel Kodali, John G Webb, Michael J Mack, Pamela S Douglas, Vinod H Thourani, Vasilis C Babaliaros, Howard C Herrmann, Wilson Y Szeto, Augusto D Pichard, Mathew R Williams, Gregory P Fontana, D Craig Miller, William N Anderson, Jodi J Akin, Michael J Davidson†, Craig R Smith, for the PARTNER trial investigators*

5-year outcomes of transcatheter aortic valve replacement or surgical aortic valve replacement for high surgical risk patients with aortic stenosis (PARTNER 1): a randomised controlled trial

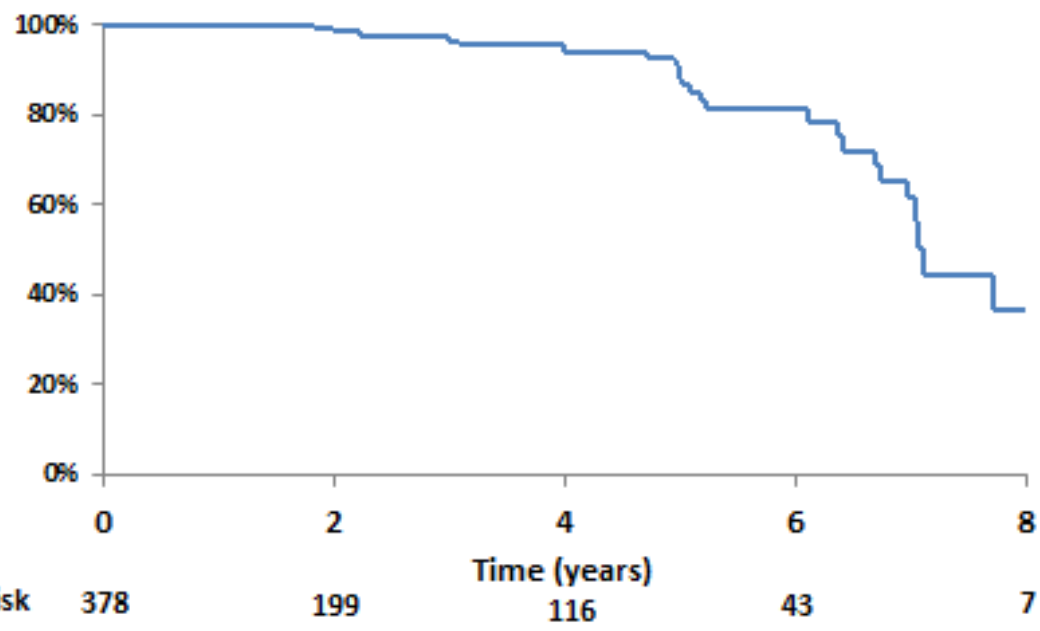
Michael J Mack, Martin B Leon, Craig R Smith, D Craig Miller, Jeffrey W Moses, E Murat Tuzcu, John G Webb, Pamela S Douglas, William N Anderson, Eugene H Blackstone, Susheel K Kodali, Raj R Makkar, Gregory P Fontana, Samir Kapadia, Joseph Bavaria, Rebecca T Hahn, Vinod H Thourani, Vasilis Babaliaros, Augusto Pichard, Howard C Herrmann, David L Brown, Mathew Williams, Jodi Akin, Michael J Davidson†, Lars G Svensson, for the PARTNER 1 trial investigators*

Mean Gradient & Valve Area (AT)
P1B - All Patients



TAVR Durability Issues

Freedom from THV degeneration



THV degeneration was defined as at least moderate regurgitation AND/OR mean gradient ≥ 20mmHg, which did not appear within 30 days of the procedure and is not related to endocarditis.

KM estimate of THV degeneration included censoring of patients at their date of last known THV functioning well without evidence for degeneration per study definition.

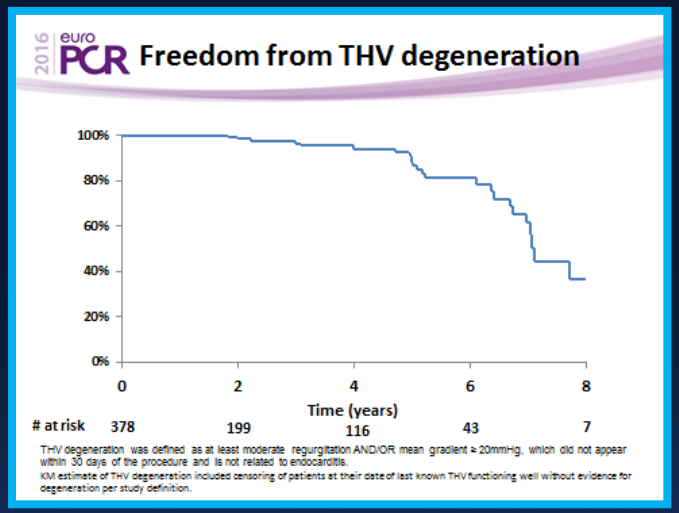
EuroPCR: Degenerated TAVR Not Uncommon by 10 Years
May 17, 2016 by Nicole Lou
MedPage

EuroPCR 2016: Study casts doubt on long-term TAVR durability
May 19, 2016 by Brad Perriello

Should We Worry about TAVR Durability?
Marie Thibault
May 19, 2016 by Marie Thibault
MDDI

Early Transcatheter Aortic-Valve Device Durability Comes Under Scrutiny
May 31, 2016 by Patrice Wendling
Medscape

TAVR Durability Issues



Some of the problems associated with this type of analysis…

- 2 center experience, ultra-sick patients, earliest versions of the Sapien THV
- Incorrect statistical methods - THV degeneration is a time-dependent "process", not a clinical "event"
- Competing risks of frequent deaths in these patients with multiple co-morbidities creates censoring problems
- Echo data are incomplete - ascertainment and interpretation, and definitions used were spurious - creates significant biases
- No. at risk after 5 years drops precipitously - tail shape unreliable
- *"Clinical" SVD - freedom from re-intervention - never discussed*

TAVR Durability Issues

The Gold Standards…

Hancock II

CE Perimount

Long-Term Durability of B
Valves: Implications From

Douglas R. Johnston, MD, Edward G. Soltesz
Jeeva
Nich
Euge

Departn
Researc

Very Long-Term Out
Carpentier-Edwards
Aortic Position

Thierry Bourguignon, MD, Anne-Lo
Alain Mirza, MD, Claudia Loardi,
Michel Marchand, MD, and Michel

Department of Cardiac Surgery, Tours University Hospital, France; and Department of Biostatistics, Edwards Lifesciences, Nyon, Switzerland

Hancock II Bioprosthesis for Aortic Valve Replacement: The Gold Standard of Bioprosthetic Valves Durability?

Tirone E. David, MD, Susan Armstrong, MS, and Manjula Maganti, MS

Division of Cardiovascular Surgery of Peter Munk Cardiac Centre, Toronto General Hospital and University of Toronto, Toronto, Ontario, Canada

Background. This study examined the long-term durability of the Hancock II bioprosthesis (Medtronic, Minneapolis, MN) in the aortic position.

Methods. From 1982 to 2004, 1134 patients underwent aortic valve replacement (AVR) with Hancock II bioprosthesis and were prospectively monitored. Mean patient age was 67 ± 11 years; 202 patients were younger than 60, 402 were 60 to 70, and 526 were older than 70. Median follow-up was 12.2 years and 99.2% complete. Valve function was assessed in 94% of patients. Freedom from adverse events was estimated by the Kaplan-Meier method.

Results. Survival at 20 and 25 years was 19.2% ± 2% and 6.7% ± 2.8%, respectively, with only 34 and 3 patients at risk. Survival at 20 years was 54.9% ± 6.4% in patients younger than 60 years, 22.7% ± 3.3% in those 60 to 70, and 2.4% ± 1.9% in those older than 70 ($p = 0.01$). Structural valve deterioration developed in 67 patients aged younger than 60, in 18 patients aged 60 to 70, and in 2 patients older than 70. The freedom from structural valve deterioration at 20 years was 63.4% ± 4.2% in the entire cohort, 29.2% ± 5.7% in patients younger than 60 years, 85.2% ± 3.7% in patients aged 60 to 70, and 99.8% ± 0.2% in patients older than 70 (truncated at 18 years). Repeat AVR was performed in 104 patients (74 for structural valve failure, 16 for endocarditis, and 14 for other reasons). At 20 years, the overall freedom from AVR was 65.1% ± 4% for any reason, 29.8% ± 5.4% in patients younger than 60 years, 86.8% ± 3.3% in patients 60 to 70, and 98.3% ± 0.6% in patients older than 70.

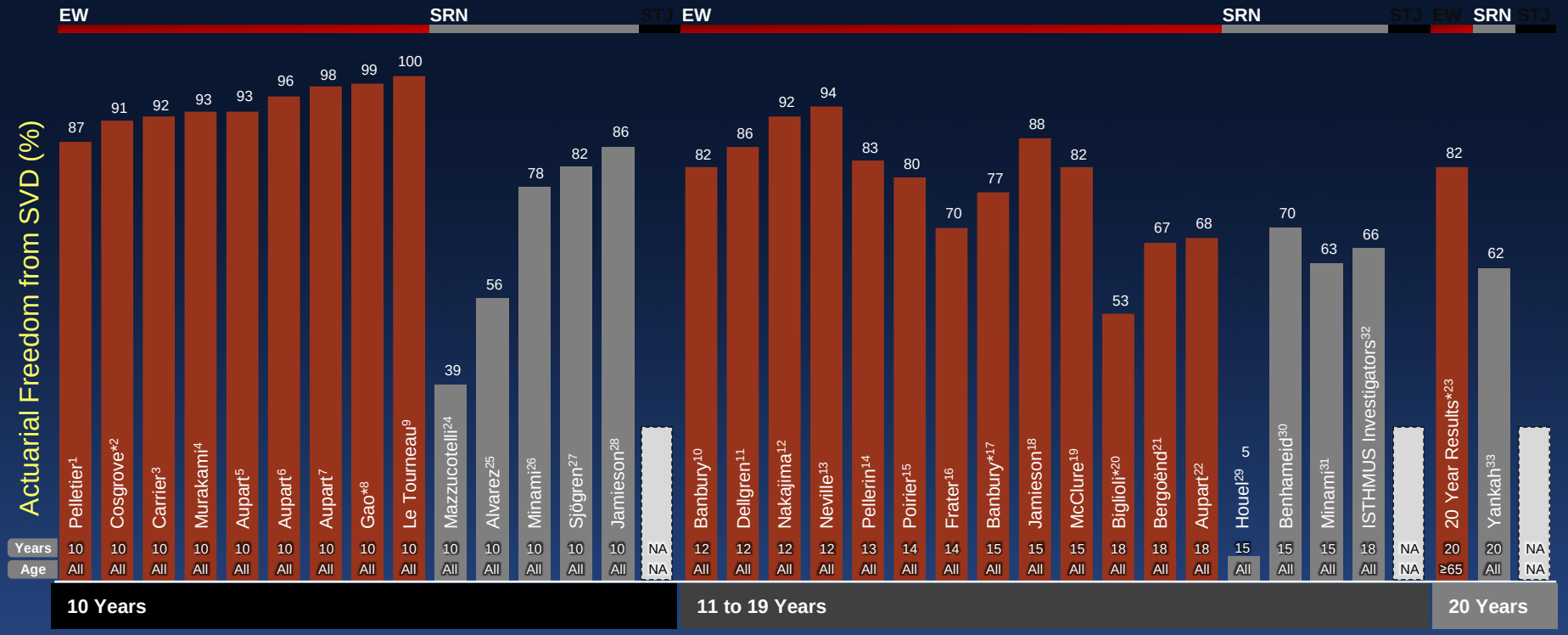
Conclusions: Hancock II bioprosthesis is a very durable valve in patients 60 years and older and is probably the gold standard of bioprosthetic valve durability in this patient population.

(Ann Thorac Surg 2010;90:775–81)

Freedom from Structural Valve Deterioration of Pericardial Aortic Bioprostheses

Actuarial Freedom from Structural Valve Deterioration

Pericardial Aortic Bioprostheses



* Freedom from explant / prosthesis replacement / reoperation due to SVD

Methodology: Comprehensive literature searches were conducted utilizing a combination of key words. See references section for key words, filters, and a search results summary.
Note: Patients and results are a subset of each study. See references section for total cohort size, patient mean age, and at risk population size.

TAVR Durability Issues

Early Failures of Surgical Valves…

Early stenosis of Medtronic Mosaic p
position

Jennifer S. Lawton, MD, Nader Moazami, MD, Michael K. Pasque, MI
St Louis, Mo

The third-generation Medtronic Mosaic porcine bioprosthesis (Medtronic Inc, Minneapolis, Minn) was introduced in 1994. The valve leaflets are fixed in glutaraldehyde at zero pressure (applying equal pressure to the inflow and outflow ends of the valve), the root is dilated to a pressure of 40 mm Hg (''physiologic fixation''), the fixed tissue is treated with α-aminooleic acid (a long-chain fatty acid that binds to the aldehyde fractions of the glutaraldehyde-preserved porcine tissue) to reduce calcification, and the tissue is mounted on a Hancock II (Medtronic Inc) flexible stent made of acetyl copolymer covered with Dacron fabric.[1,2]

than 60 years had aortic structural valve deterioration in this review. Freedom from structural valve deterioration in the aortic position at 8.5 years has been reported

re Trifecta
le previous
eplacement
18 years

previously, redo coronary artery bypass graft surgery 13 years previously, and repeat aortic valve replacement with a 21-mm Trifecta valve 4 years previously.

J Thorac Cardiovasc Surg 2014;147:e10-11
0022-5223/$36.00

http://dx.doi.org/10.1016/j.jtcvs.2013.07.053

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Original Article

Early Structural Valve Deterioration of Mitroflow Aortic Bioprosthesis: Mode, Incidence and Impact on Outcome in a Large Cohort of Patients

Thomas Sénage[1]; Thierry Le Tourneau[2]; Yohann Foucher[3]; Sabine Pattier[4]; Caroline Cueff[1]; Magali Michel[4]; Jean–Michel Serfaty[4]; Hubert François Carton[4]; Christian Perigaud[4]; Antoine Mugniot[4]; Ousama Al Habash[4]; Olivier Baron[4]; Jean Christian Roussel[1]*

Bioprosthetic Surgical Valve Failure from VIVD Registry

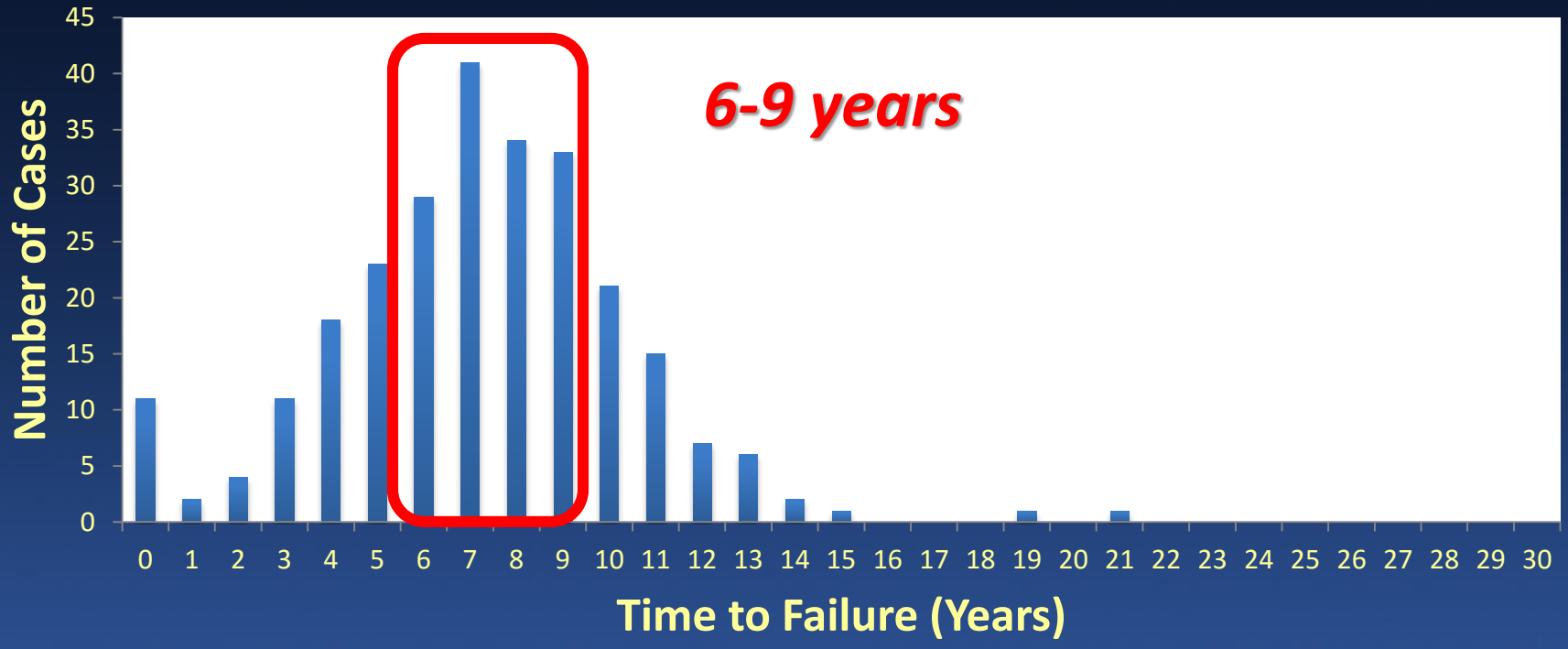
Valve-in-Valve International Data VIVID

Time to Failure - All VIVID Cases (n = 1304)

Bioprosthetic Surgical Valve Failure from VIVD Registry

Valve-in-Valve International Data VIVID

Time to Failure - Sorin Mitroflow (n = 261)



TAVR Durability Issues

General concepts…

Special Report

Considerations and Recommendations for the Introduction of Objective Performance Criteria for Transcatheter Aortic Heart Valve Device Approval

Stuart J. Head, MD, PhD; Darren Mylotte, MD; Michael J. Mack, MD; Nicolo Piazza, MD, PhD; Nicolas M. van Mieghem, MD, PhD; Martin B. Leon, MD; A. Pieter Kappetein, MD, PhD; David R. Holmes Jr, MD

Abstract—In the United States, new surgical heart valves can be approved on the basis of objective performance criteria (OPC). In contrast, the US Food and Drug Administration traditionally requires stricter criteria for transcatheter heart valve (THV) approval, including randomized, clinical trials. Recent US Food and Drug Administration approval of new-generation THVs based on single-arm studies has generated interest in alternative study approaches for THV device approval. This review evaluates whether THV device approval could follow a pathway analogous to that of surgical heart valves by incorporating OPC and provides several considerations and recommendations. Factors to be taken into account in the construction of OPC include the maturity of THV technology, variability in transcatheter aortic valve replacement practice, end points included as OPC, follow-up terms for specific OPC, patient populations to which these OPC apply, and (statistical) methods for OPC development. We recommend that approval of THV devices in the United States for low- and intermediate-risk patients or for new indications should provisionally rely on data from randomized, clinical trials. However, it is recommended that formal OPC be applied for approval of new-generation THVs for use in high- and extreme-risk patient populations. (***Circulation***. 2016;133:2086-2093. DOI: 10.1161/CIRCULATIONAHA.115.020493.)**

Key Words: aortic valve ■ aortic valve stenosis ■ device approval ■ heart valve prosthesis implantation ■ transcatheter aortic valve replacement

TAVR Journey - 2016

- **The Durability Controversy**

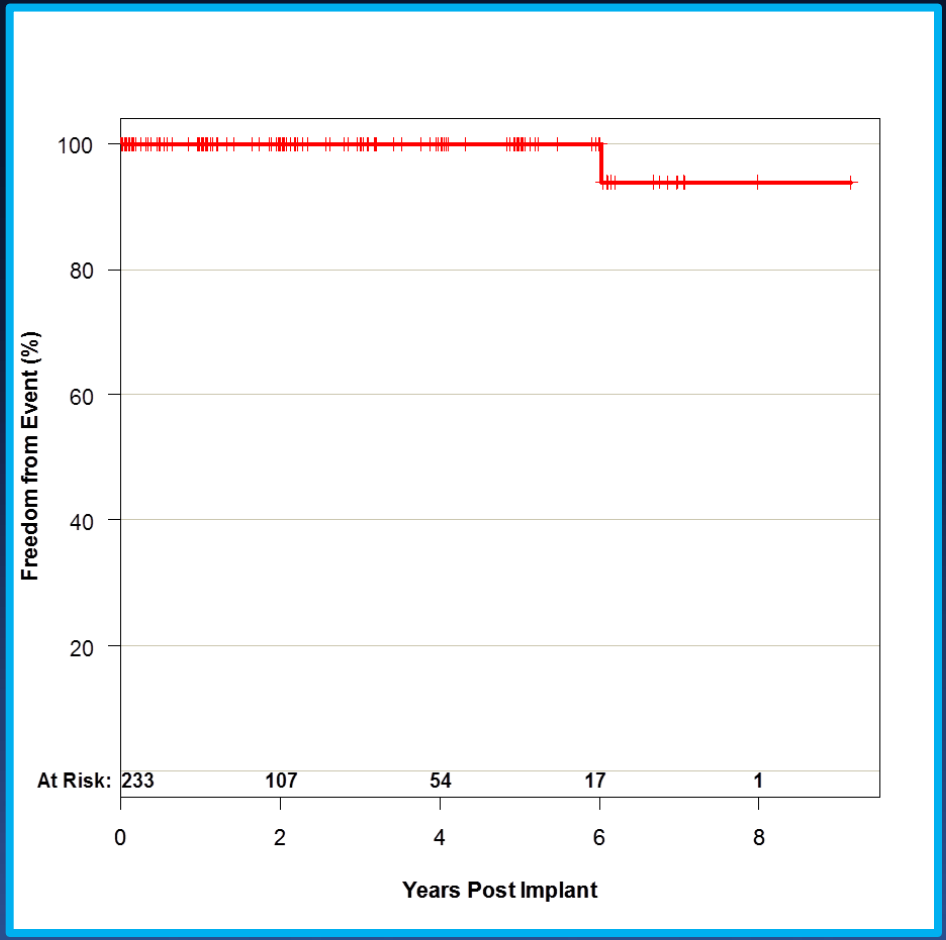
  Given the sensitivity of these long-term FU data, it's the responsibility of all TAVR investigators to carefully examine their late FU patients according to agreed-upon principles and definitions, including FDA studies like PARTNER, which will now extend clinical and echo FU to 10 years!

CHU Rouen

239 pts from 2002-2011 (> 5 years FU)

Freedom from either reoperation, or if asymp, echo mean valve gradient >40 mmHg or severe AR (effective ROA > 0.3cm^2)

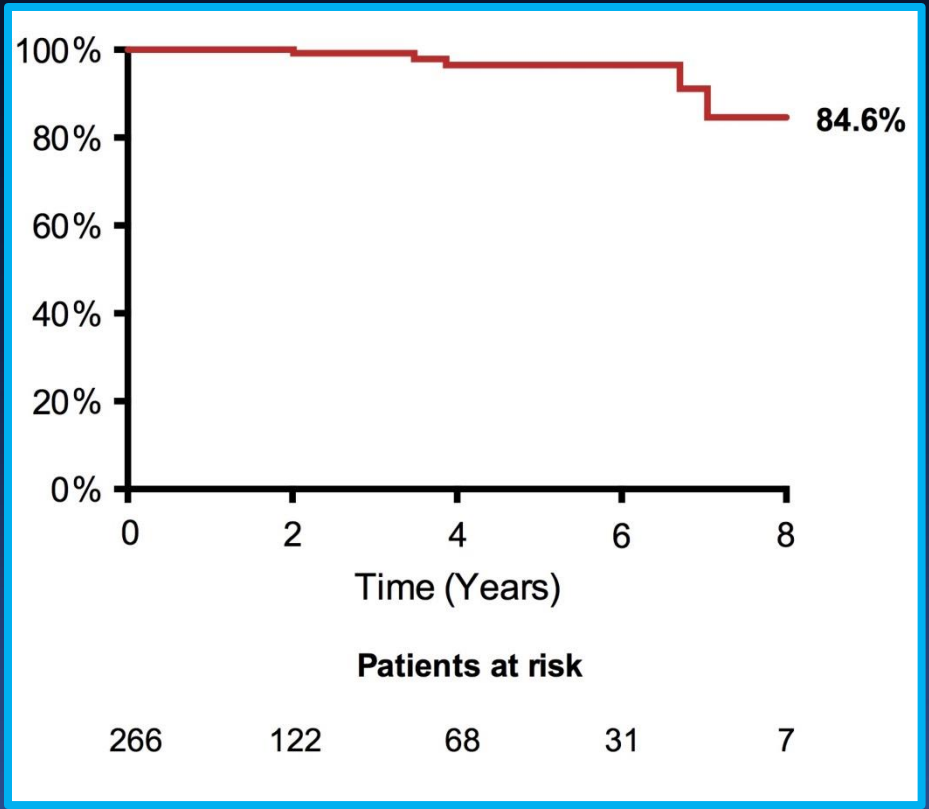
Among survivors, none with MG >40 and only 1 pt with severe AR resulting in ViV procedure



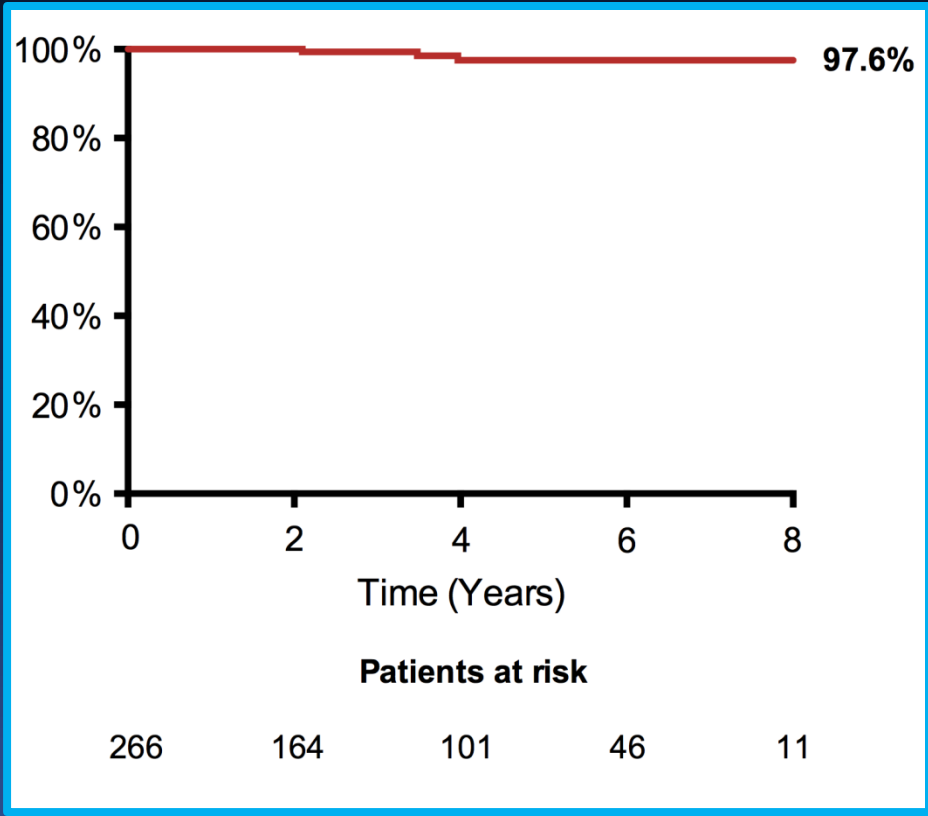
Vancouver

266 pts from before 2011 (> 5 years FU)

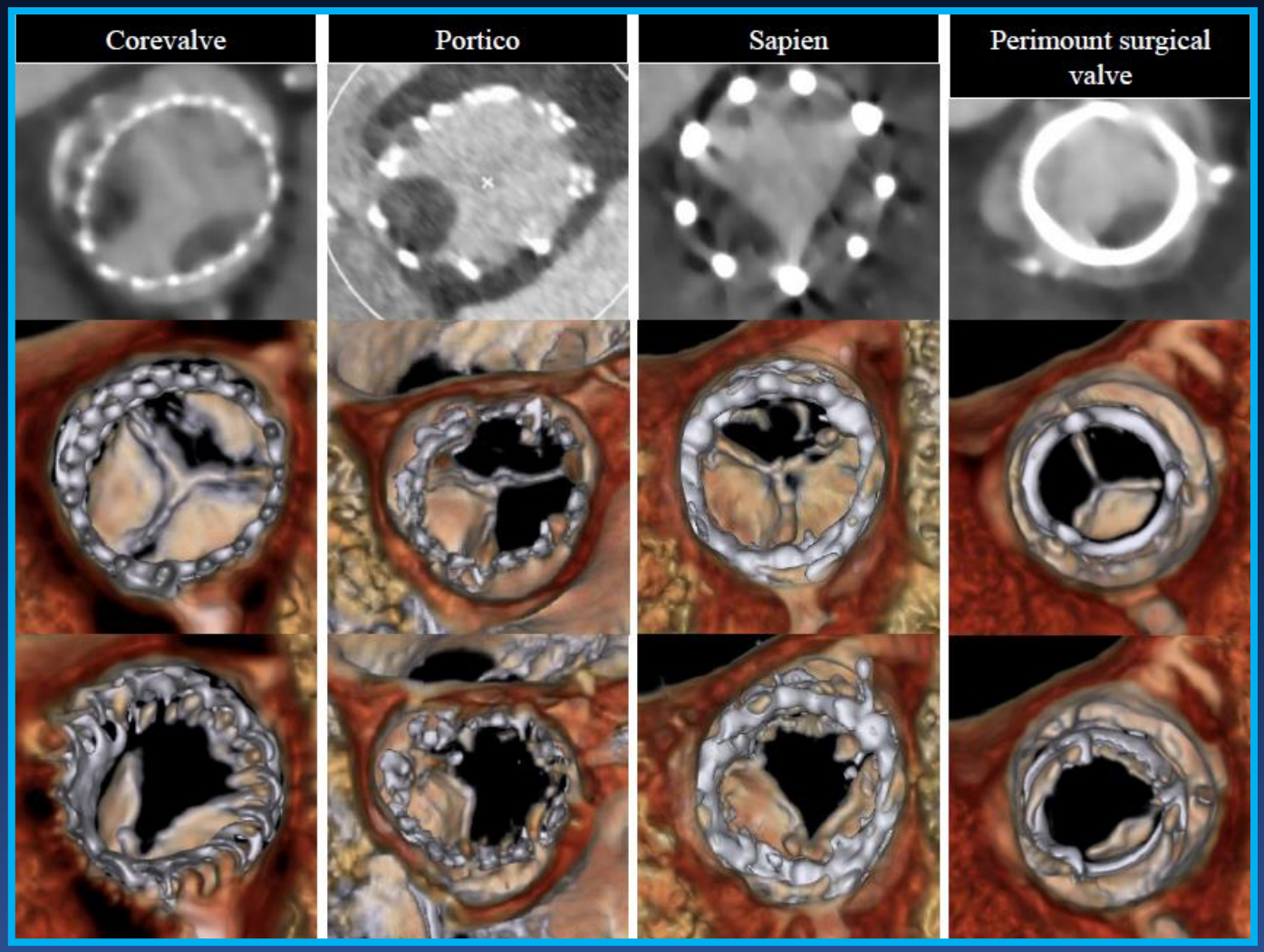
Freedom from Severe Failure



Freedom from Reintervention



Valve Leaflet Abnormalities



Makkar, et al. 2015

TAVR Journey - 2016

- **The Durability Controversy**

  An ancillary concern has been valve leaflet thickening/thrombosis - incidence and clinical implications - multiple ongoing 4D CTA studies (>2,000 pts)…

  - RESOLVE (400 pts, target = 1,000 pts) and SAVORY (120 pts)
  - GALILEO Substudy (300 pts)
  - PORTICO Substudy (200 pts), PARTNER 3 LR and Evolut LR studies (400 pts each)

TAVR Journey - 2016

- **Mission Central = Next Steps to Further Enhance TAVR Value**
  - *Continued expansion of clinical indications (test the outer limits)!*

TAVR - UNLOAD Trial Design

Moderate AS + HF

(600 patients, 1:1 randomized)

TAVR UNLOAD Trial

International Multicenter Randomized

Heart Failure
LVEF < 50%
NYHA ≥ 2
Optimal HF therapy (OHFT)
Moderate AS

R

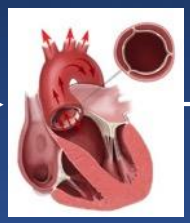
TAVR + OHFT

OHFT Alone

Follow-up:
1 month
6 months
1 year

Clinical endpoints
Symptoms
Echo
QoL

Primary Endpoint
Hierarchical occurrence of:
- **All-cause death**
- **Disabling stroke**
- **Hospitalizations for HF, aortic valve disease**
- **Change in KCCQ**



Reduced AFTERLOAD
Improved LV systolic and diastolic function

TAVR Journey - 2016

- **Mission Central = Next Steps to Further Enhance TAVR Value**
  - *Continued expansion of clinical indications (test the outer limits)!*
  - *Continued reduction of TAVR-related complications (strokes, PVL, and PM)*

SENTINEL Study Design
(TAVR RCT)

US Co-PIs:
Samir Kapadia
Susheel Kodali
German Co-PI:
Axel Linke

Population: Subjects with severe AS with clinical indications for TAVR with the Edwards Sapien THV/XT/S3 or Medtronic CoreValve/Evolut-R
N=296 subjects randomized 1:1:1
at sites in the U.S and Germany.

SAFETY ARM
TAVR with Sentinel

TEST ARM
TAVR with Sentinel

RCT

CONTROL ARM
TAVR only

Histopathology

Safety Follow-up

Safety Follow-up

MRI Assessments

Neurological and Neurocognitive Tests

Primary (superiority) Efficacy Endpoint: Reduction in median total new lesion volume assessed by 3T DW-MR by baseline subtraction (3-7 days)

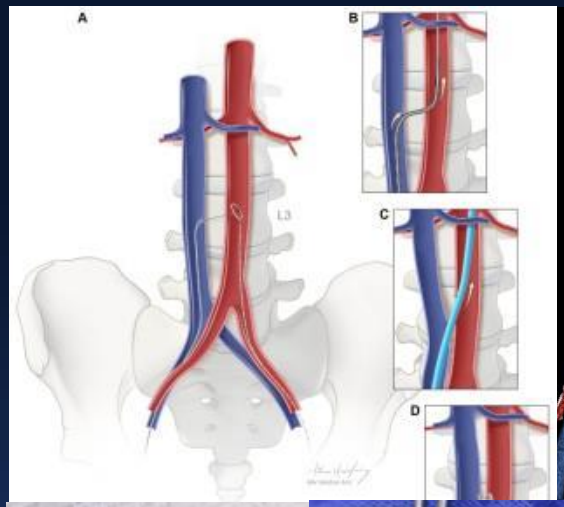
Primary (non-inferiority) Safety Endpoint: Occurrence of all MACCE at 30 days

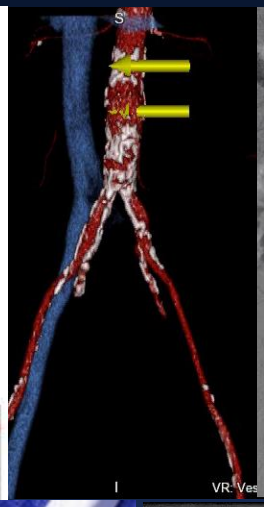
TAVR Journey - 2016

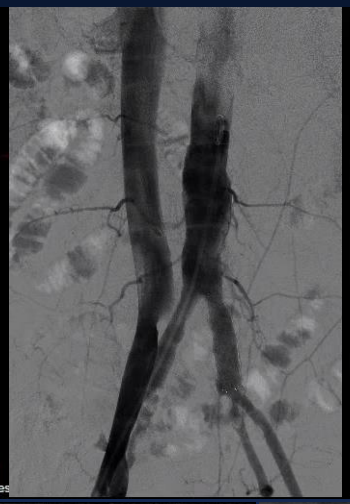
- **Mission Central = Next Steps to Further Enhance TAVR Value**
  - *Continued expansion of clinical indications (test the outer limits)!*
  - *Continued reduction of TAVR-related complications (strokes, PVL, and PM)*
  - *Elimination of trans-thoracic access in non-TF cases*

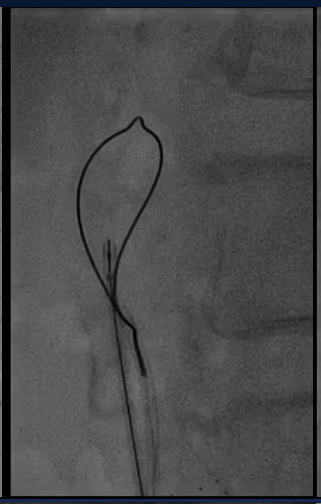
Trans-Caval Access for TAVR

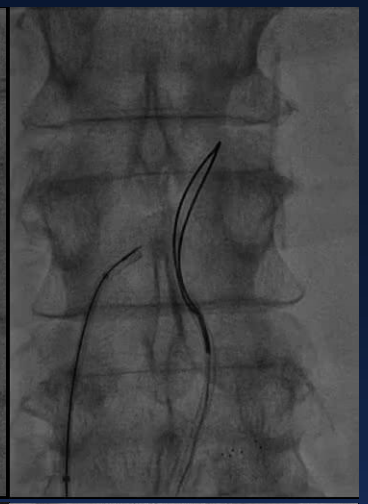
(202 pts in 28 centers - 5/14/16)

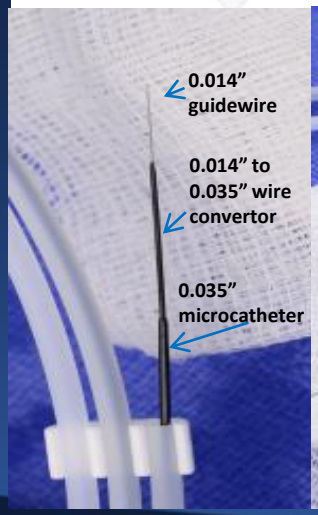


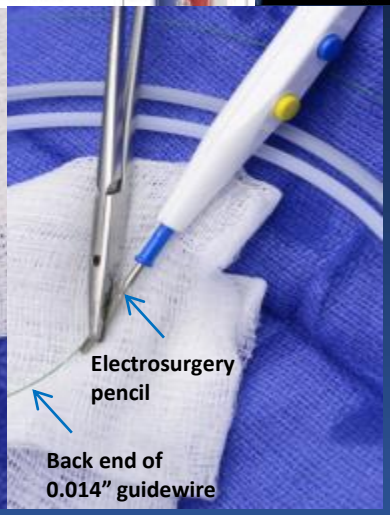


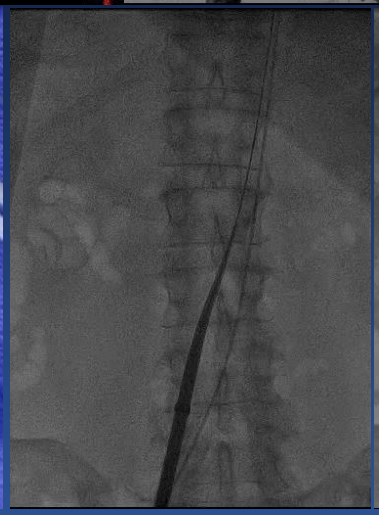


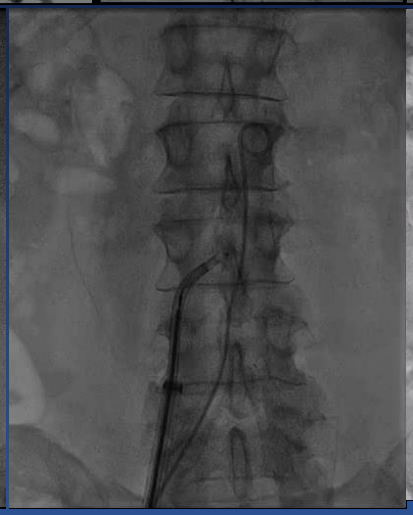


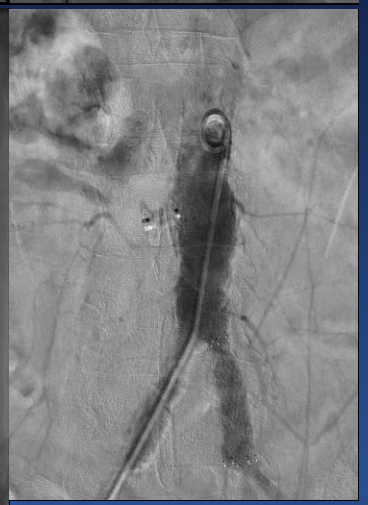




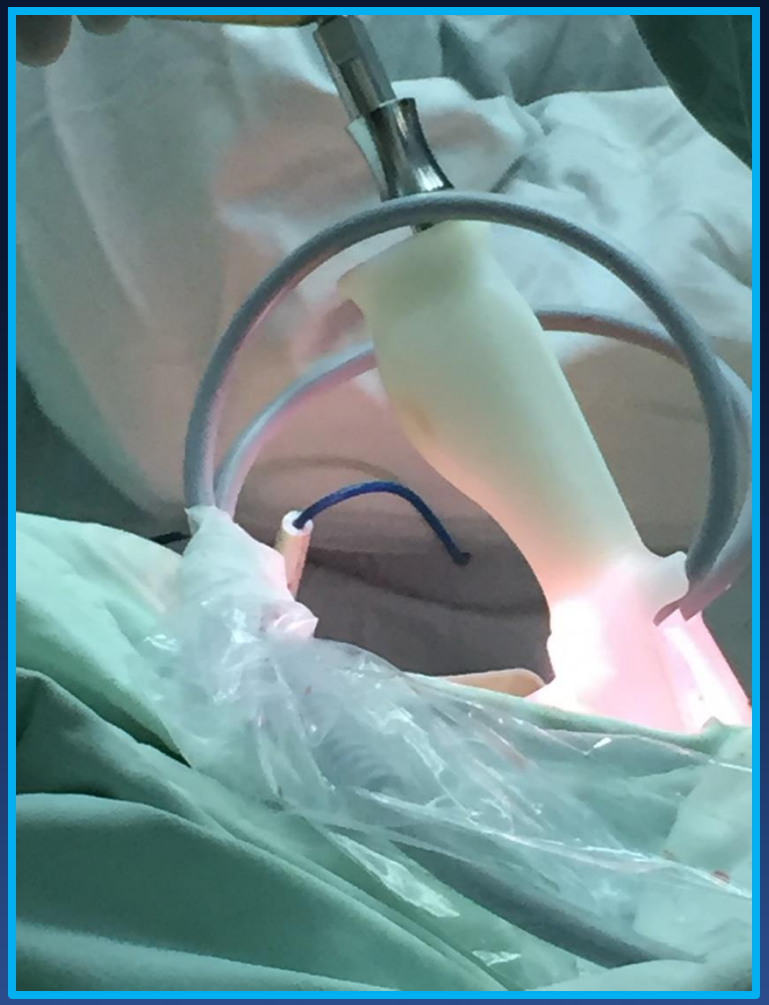


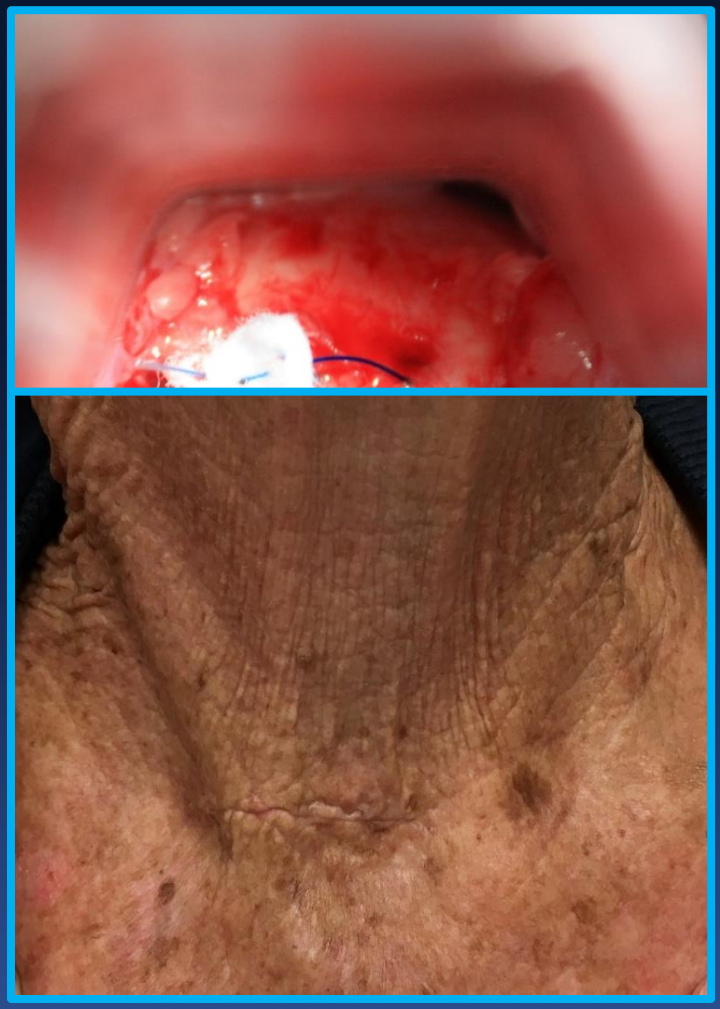






Direct Mediastinal Access for TAVR





TAVR Journey - 2016

- **Mission Central = Next Steps to Further Enhance TAVR Value**
  - *Continued expansion of clinical indications (test the outer limits)!*
  - *Continued reduction of TAVR-related complications (strokes, PVL, and PM)*
  - *Elimination of trans-thoracic access in non-TF cases*
  - *Rational and properly studied adjunctive pharmacotherapy regimens*

TAVR Adjunct Pharmacology

Customized Patient-Based Therapy

BEFORE	DURING	AFTER
Acetylsalicylic acid (ASA)	UNFRACTIONATED HEPARIN: target ACT ≥300”	ASA + CLOPIDOGREL
	Bivalirudin: BRAVO (BivalRudin and Aortic Valve intervention Outcomes)	Acetylsalicylic acid (ASA) ARTE trial
	Low Molecular Weight Heparin	Non anti-VKA Oral Anticoagulant ± ASA: Atlantis, Action, GALILEO

TAVR Journey - 2016

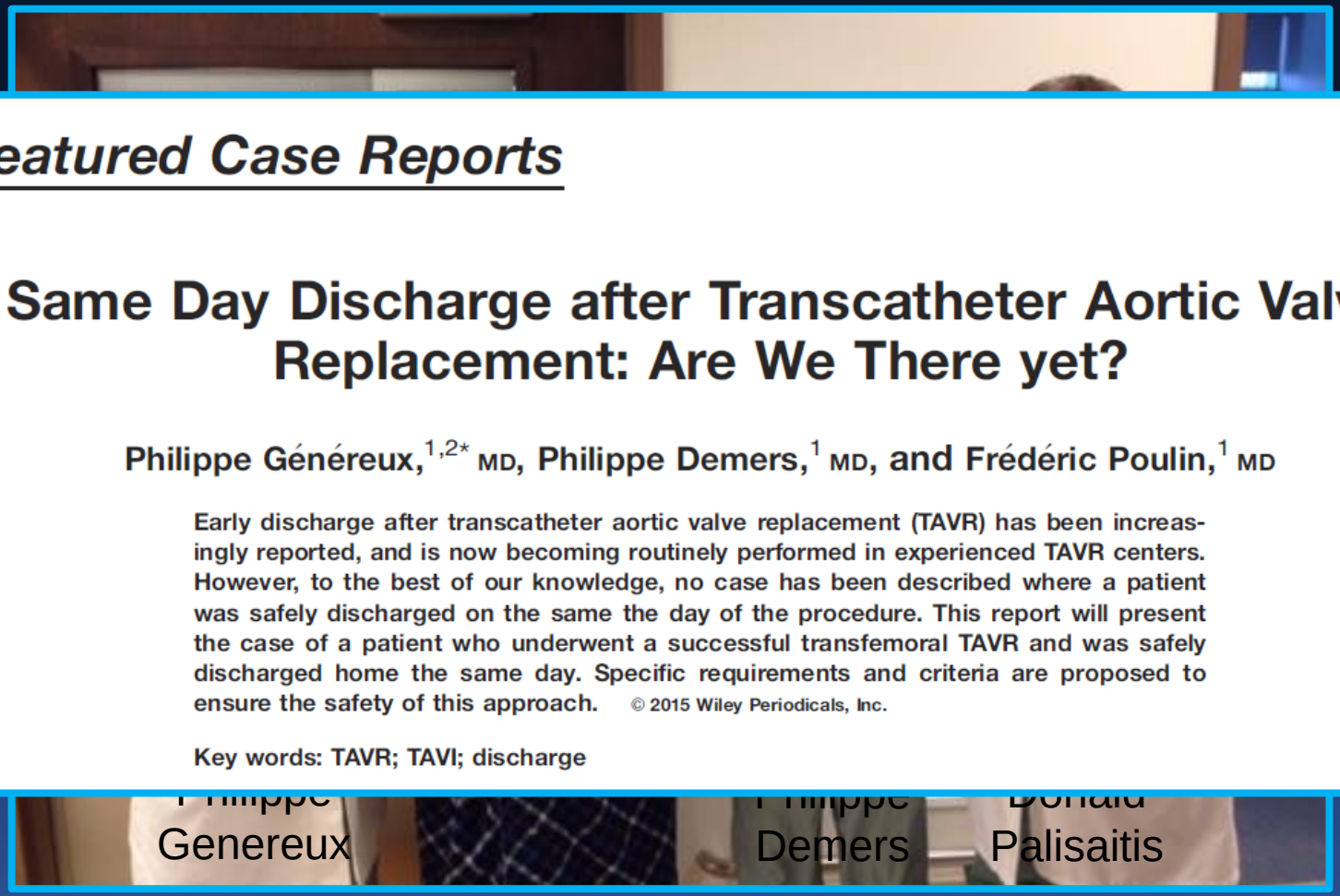
- **Final Thoughts…**

Are We There Yet?

The ultimate role of TAVR is yet to be determined. But we can foresee a future time when the use of TAVR (vs. surgery) will be a risk-benefit assessment based upon clinical and anatomic factors, and not an imprecise risk stratification model!

“Outpatient” Same-Day TAVR

Sacre-Coeur Hospital; Montreal, CN



Featured Case Reports

Same Day Discharge after Transcatheter Aortic Valve Replacement: Are We There yet?

Philippe Généreux,[1,2*] MD, Philippe Demers,[1] MD, and Frédéric Poulin,[1] MD

Early discharge after transcatheter aortic valve replacement (TAVR) has been increasingly reported, and is now becoming routinely performed in experienced TAVR centers. However, to the best of our knowledge, no case has been described where a patient was safely discharged on the same the day of the procedure. This report will present the case of a patient who underwent a successful transfemoral TAVR and was safely discharged home the same day. Specific requirements and criteria are proposed to ensure the safety of this approach.

Key words: TAVR; TAVI; discharge

Genereux Demers Palisaitis