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Seoul, August 16th, 2017*

TAVR of High-Risk/Complex Patients: For Whom and With?

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Stanford University, Palo Alto, California, USA

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

Current Perspective in Transcatheter Valve Therapy

The tremendous momentum behind transcatheter valve therapies has continued to build with many major accomplishments, including:

- Regulatory approval for intermediate risk patients in Europe and the US
- Initiation of multiple randomized trials for the continued expansion of TAVR indications (Low Risk, Moderate AS with HF, Asymptomatic AS)
- Regulatory approval for iterative device designs (Lotus Edge, Evolut PRO, Evolut 34mm)
- Publication of new randomized data on cerebral embolic protection (SENTINEL)

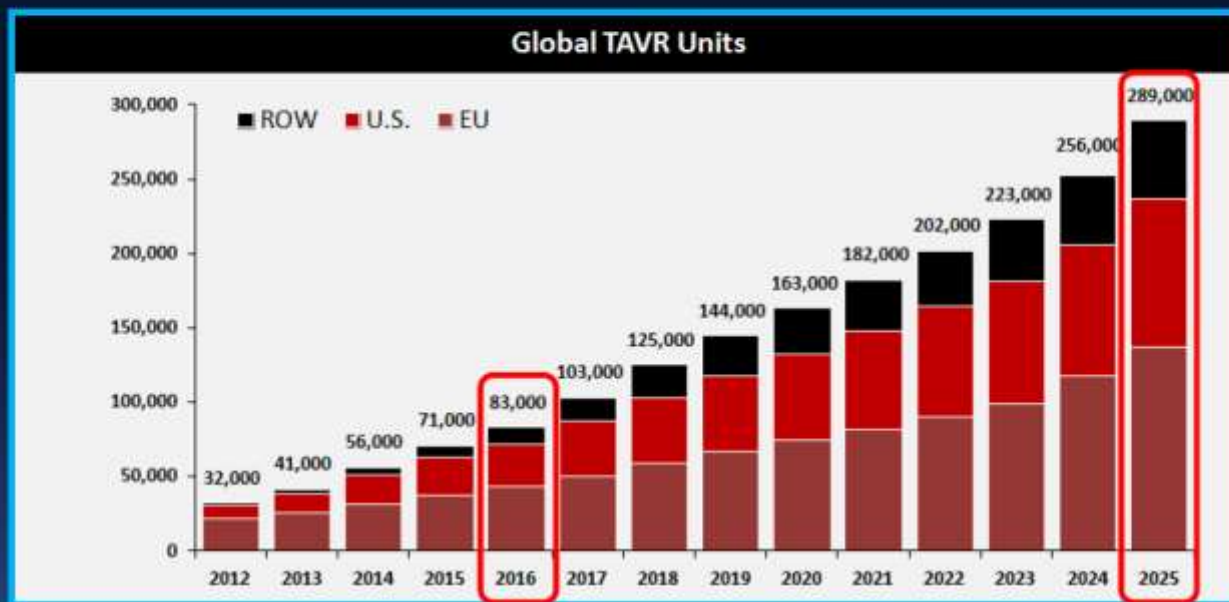
TAVR is clearly reaching new patient populations, and as this happens, both technology and technique continue to iterate and improve.

Treatment Trends

Future TAVR Growth

Annual TAVR volume is experiencing exponential growth. By the end of the calendar year ~ 400,000 procedures will have been done worldwide.

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

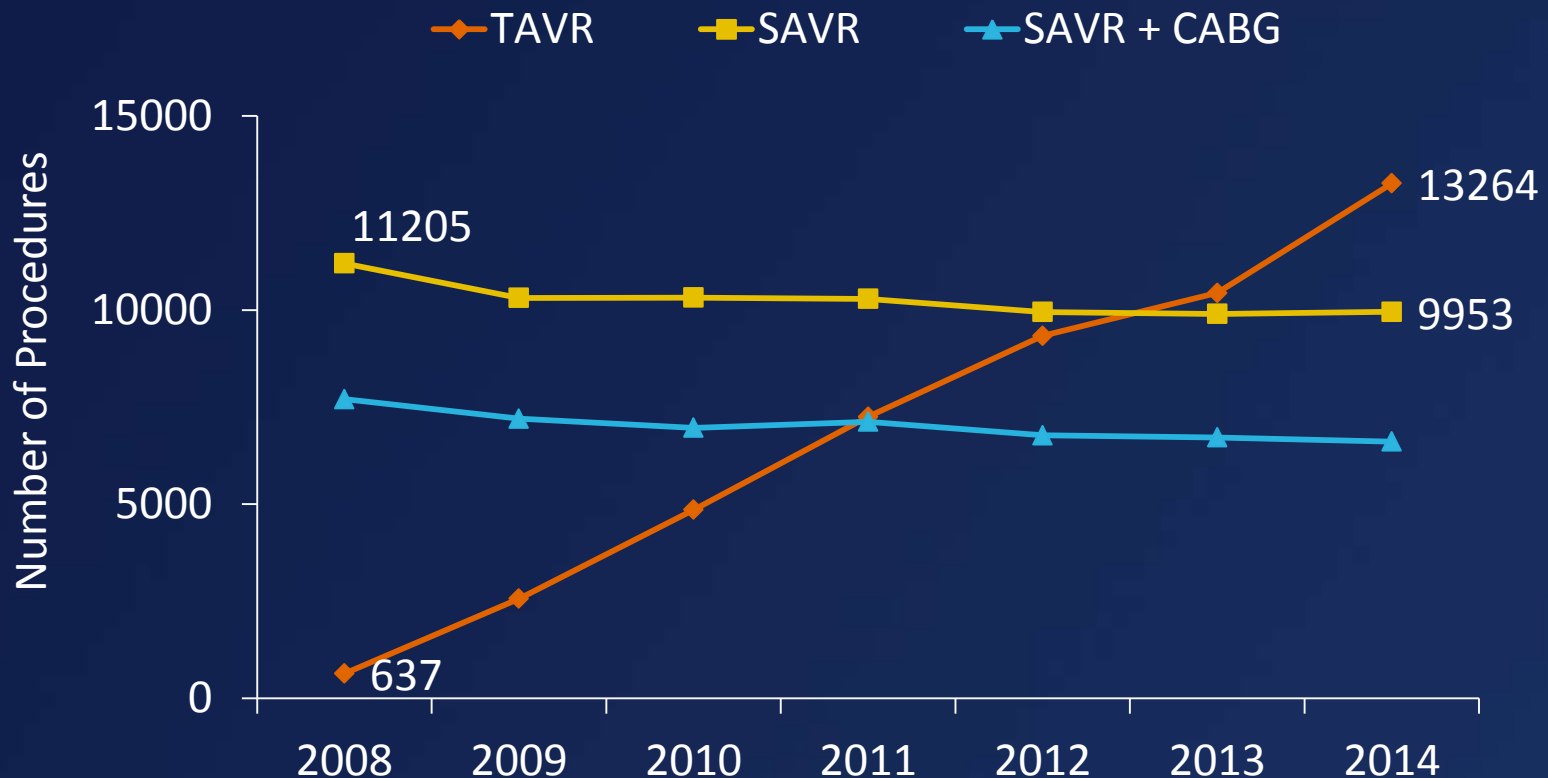
In the next 10 years, TAVR growth will increase X4!

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

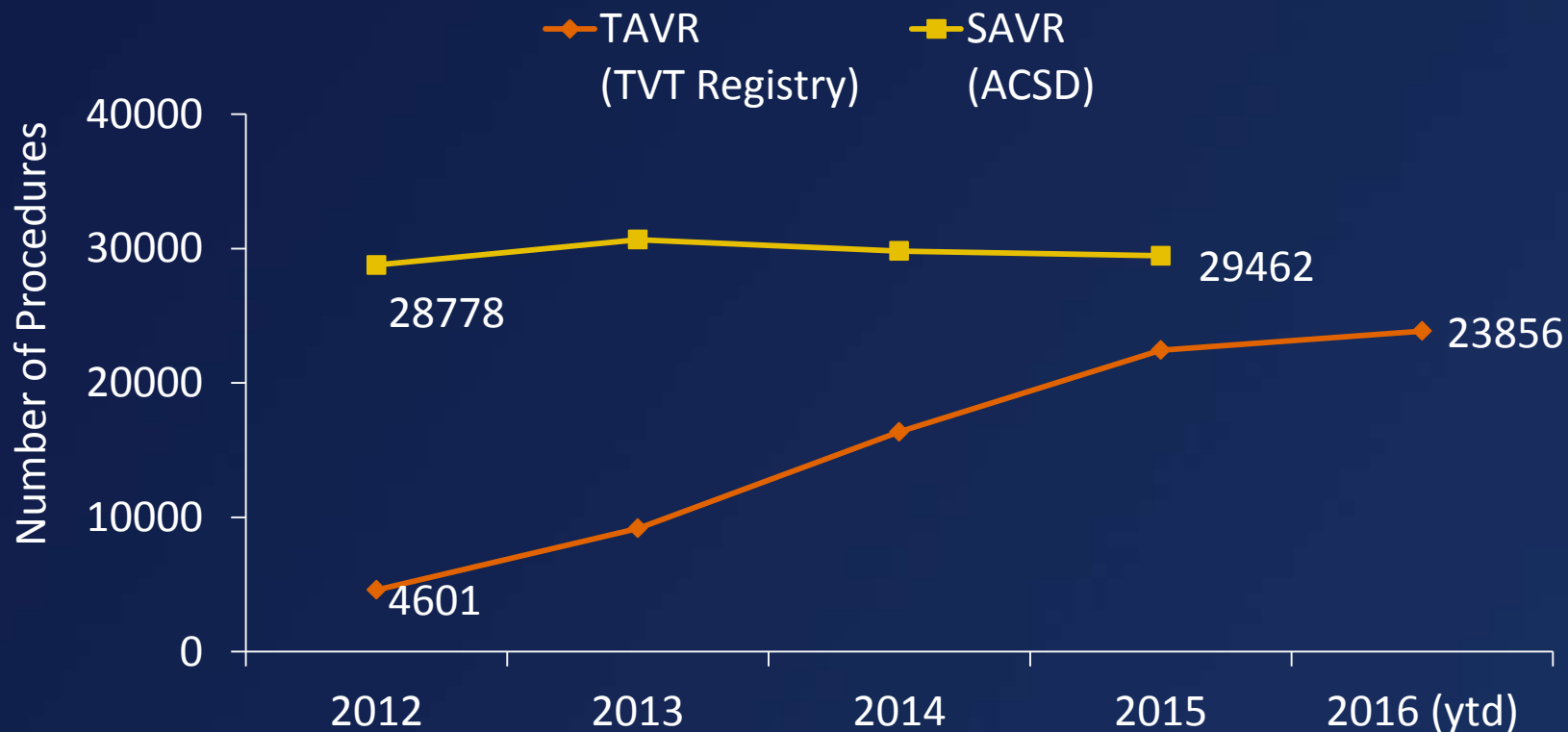


Treatment Trends



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



Transfemoral TAVR Devices

Current EU Commercial Landscape

- For the continued success of TAVR, complications specific to the therapy - such as paravalvular leak, vascular trauma and conduction disturbances - should be mitigated.
- Below are the current generation devices that are commercially approved and designed to achieve these goals.



Evolut PRO



SAPIEN 3



Lotus



CENTERA



Portico



ACURATE neo

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	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*

Imagery of TAVR Risk Strata

AS Patient Population Requiring Treatment



Imagery of TAVR Risk Strata

AS Patient Population Requiring Treatment



Guidelines: Heart Team

Recommendations for Choice of Intervention			
COR	LOE	Recommendations	Comment/Rationale
I	C	For patients in whom TAVR or high-risk surgical AVR is being considered, a heart valve team consisting of an integrated, multidisciplinary group of healthcare professionals with expertise in VHD, cardiac imaging, interventional cardiology, cardiac anesthesia, and cardiac surgery should collaborate to provide optimal patient care.	2014 recommendation remains current.

Patients at Extreme Surgical Risk

Foundational trials tested new TAVR therapy in patients without the option for a surgical aortic valve replacement

US CoreValve Pivotal Trial



CoreValve, N=489, STS 10.3%

PARTNER 1B



SAPIEN, N=179, STS 11.2%

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Transcatheter Aortic Valve Replacement Using a Self-Expanding Bioprosthesis in Patients With Severe Aortic Stenosis at Extreme Risk for Surgery

Jeffrey J. Popma, MD,¹ David H. Adams, MD,² Michael J. Reardon, MD,³ Steven J. Yakubov, MD,⁴ Neal S. Kleinman, MD,⁵ David Heimansohn, MD,⁶ James Hermiller, Jr, MD,⁷ G. Chai Hughes, MD,⁸ J. Kevin Harrison, MD,⁹ Joseph Coselli, MD,¹⁰ Jose Diaz, MD,¹¹ Ali Kaf, MD,¹² Theodore Schreiber, MD,¹³ Thomas G. Gleason, MD,¹⁴ John Conte, MD,¹⁵ Maurice Buchbinder, MD,¹⁶ G. Michael Deeb, MD,¹⁷ B  t   Carabello, MD,¹⁸ Patrick W. Serruys, MD, PhD,¹⁹ Stefan Chenoweth, MS,²⁰ Joe K. Oh, MD,²¹ for the CoreValve United States Clinical Investigators

Boston, Massachusetts; New York, New York; Houston, Texas; Columbus, Ohio; Indianapolis, Indiana; Durham, North Carolina; Detroit and Ann Arbor, Michigan; Pittsburgh, Pennsylvania; Baltimore, Maryland; Palo Alto, California; Rotterdam, the Netherlands; and Minneapolis and Rochester, Minnesota

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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*

Guidelines: TAVR in Patients at Extreme Surgical Risk

2017 Update

I	A	TAVR is recommended for symptomatic patients with severe AS (Stage D) and a prohibitive risk for surgical AVR who have a predicted post-TAVR survival greater than 12 months (58-61).	MODIFIED: LOE updated from B to A. Longer-term follow-up from RCTs and additional observational studies has demonstrated the benefit of TAVR in patients with a prohibitive surgical risk.
See Online Data Supplements 5 and 9 (Updated From 2014 VHD Guideline)			

Patients at High Surgical Risk

Trials randomizing high risk patients to either TAVR or SAVR soon followed

US CoreValve Pivotal Trial



CoreValve, N=390, STS 7.3% vs.
SAVR, N=357, STS 7.5%

PARTNER 1A



SAPIEN, N=348, STS 11.8% vs.
SAVR, N=351, STS 11.7%

ORIGINAL ARTICLE

Transcatheter Aortic-Valve Replacement with a Self-Expanding Prosthesis

David H. Adams, M.D., Jeffrey J. Popma, M.D., Michael J. Reardon, M.D., Steven J. Yakubov, M.D., Joseph S. Coselli, M.D., G. Michael Deeb, M.D., Thomas G. Gleason, M.D., Maurice Buchbinder, M.D., James Hermiller, Jr., M.D., Neal S. Kleiman, M.D., Stan Chetcuti, M.D., John Heiser, M.D., William Merhi, D.O., George Zorn, M.D., Peter Tadros, M.D., Newell Robinson, M.D., George Petrossian, M.D., G. Chad Hughes, M.D., J. Kevin Harrison, M.D., John Conte, M.D., Brijeshwar Maini, M.D., Mubashir Mumtaz, M.D., Sharla Chenoweth, M.S., and Jae K. Oh, M.D., for the U.S. CoreValve Clinical Investigators*

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JUNE 9, 2011

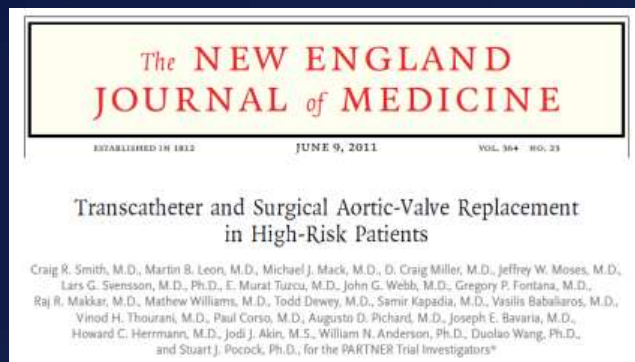
VOL. 364 NO. 23

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*

PARTNER 1A

The landmark study which randomized TAVI with SAPIEN to SAVR between 2007-2009, and demonstrated comparable outcomes between the treatments



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 Davidoff†, Lars G Svensson, for the PARTNER 1 trial investigators*

SAPIEN, N=348, STS 11.8% vs. SAVR, N=351, STS 11.7%

Guidelines: TAVR in Patients at High Surgical Risk

2017 Update

I	A	Surgical AVR or TAVR is recommended for symptomatic patients with severe AS (Stage D) and high risk for surgical AVR, depending on patient-specific procedural risks, values, and preferences (49-51).	MODIFIED: COR updated from IIa to I, LOE updated from B to A. Longer-term follow-up and additional RCTs have demonstrated that TAVR is equivalent to surgical AVR for severe symptomatic AS when surgical risk is high.
See Online Data Supplement 9 (Updated From 2014 VHD Guideline)			

High Risk and Inoperable Patients

Approved Devices



CoreValve
June 2014



SAPIEN XT
June 2014



Evolut R
June 2015



SAPIEN 3
June 2015



CoreValve
May 2007



SAPIEN XT
March 2010



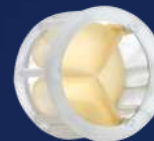
JenaValve TA
Sept 2011



Symetis
ACURATE TA
Sept 2011



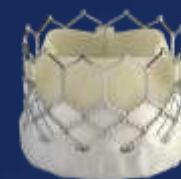
Portico
Nov 2012



Direct Flow
Jan 2013



Lotus
Oct 2013



SAPIEN 3
Jan 2014



Evolut R
Sept 2014




Symetis
ACURATE neo TF
Sept 2014

Patients at Intermediate Surgical Risk

Trials randomizing intermediate surgical risk patients to TAVR or SAVR

PARTNER IIA Trial



TAVR, N=1011, STS 5.8% vs
SAVR, N=1021, STS 5.8%

CoreValve SURTAVI Trial



TAVR, N=864, STS 4.4% vs SAVR,
N=796, STS 4.5%

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Transcatheter or Surgical Aortic-Valve Replacement in Intermediate-Risk Patients

Martin B. Leon, M.D., Craig R. Smith, M.D., Michael J. Mack, M.D., Raj R. Makkar, M.D., Lars G. Svensson, M.D., Ph.D., Susheel K. Kodali, M.D., Vinod H. Thourani, M.D., E. Murat Tuzcu, M.D., D. Craig Miller, M.D., Howard C. Herrmann, M.D., Darshan Doshi, M.D., David J. Cohen, M.D., Augusto D. Pichard, M.D., Samir Kapadia, M.D., Todd Dewey, M.D., Vasilis Babaliaros, M.D., Wilson Y. Szeto, M.D., Mathew R. Williams, M.D., Dean Kereiakes, M.D., Alan Zajarias, M.D., Kevin L. Greason, M.D., 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*



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ORIGINAL ARTICLE

Surgical or Transcatheter Aortic-Valve Replacement in Intermediate-Risk Patients

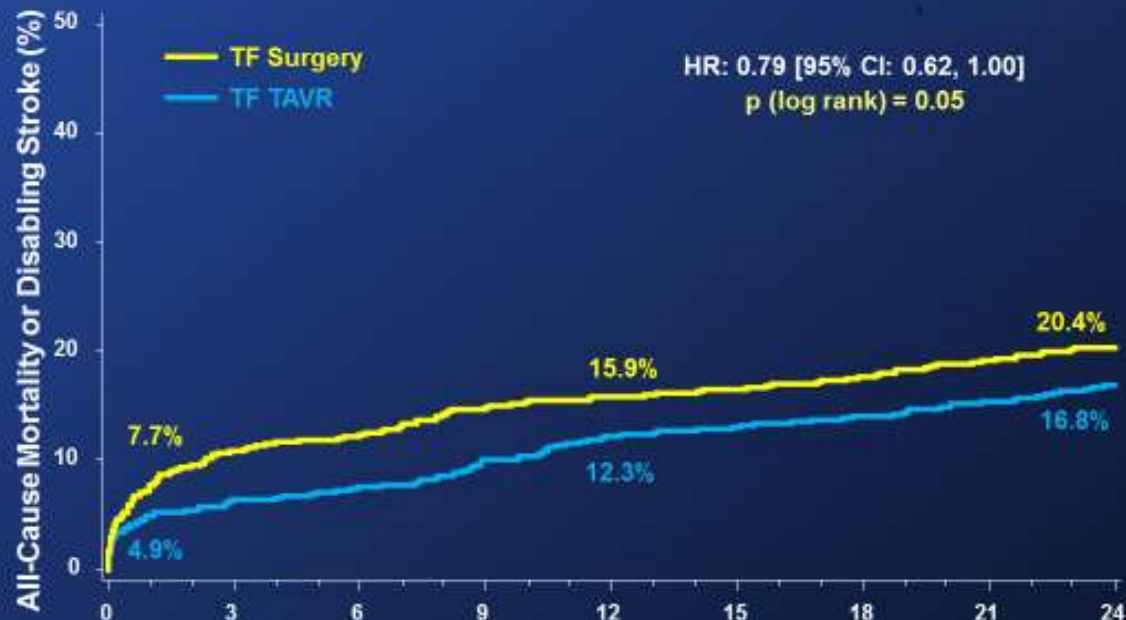
M.J. Reardon, N.M. Van Mieghem, J.J. Popma, N.S. Kleiman, L. Søndergaard, M. Mumtaz, D.H. Adams, G.M. Deeb, B. Maini, H. Gada, S. Chetcuti, T. Gleason, J. Heiser, R. Lange, W. Merhi, J.K. Oh, P.S. Olsen, N. Piazza, M. Williams, S. Windecker, S.J. Yakubov, E. Grube, R. Makkar, J.S. Lee, J. Conte, E. Yang, H. Nguyen, Y. Chang, A.S. Mugglin, P.W.J.C. Serruys, and A.P. Kappetein, for the SURTAVI Investigators*

PARTNER IIA Trial

The results from PARTNER IIA supported the use of TAVR as an alternative to surgery in intermediate risk patients.

TF Primary Endpoint (ITT)

All-cause Mortality or Disabling Stroke



Number at risk:

	0	3	6	9	12	15	18	21	24
TF Surgery	775	643	628	604	595	577	569	557	538
TF TAVR	775	718	709	685	663	652	644	634	612

Intermediate Risk Patients

Regulatory Approvals

Recently, TAVR has been approved for use in patients at intermediate surgical risk in both Europe and the US

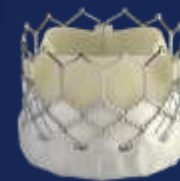


Aug 2016



Evolut R

Sept 2016



SAPIEN 3



August 2016



SAPIEN 3



SAPIEN XT

July 2017



Evolut PRO

The Low Risk Journey

TAVR Journey - 2017

Lower risk does not necessarily equals
younger patients !!

TAVR Journey - 2017

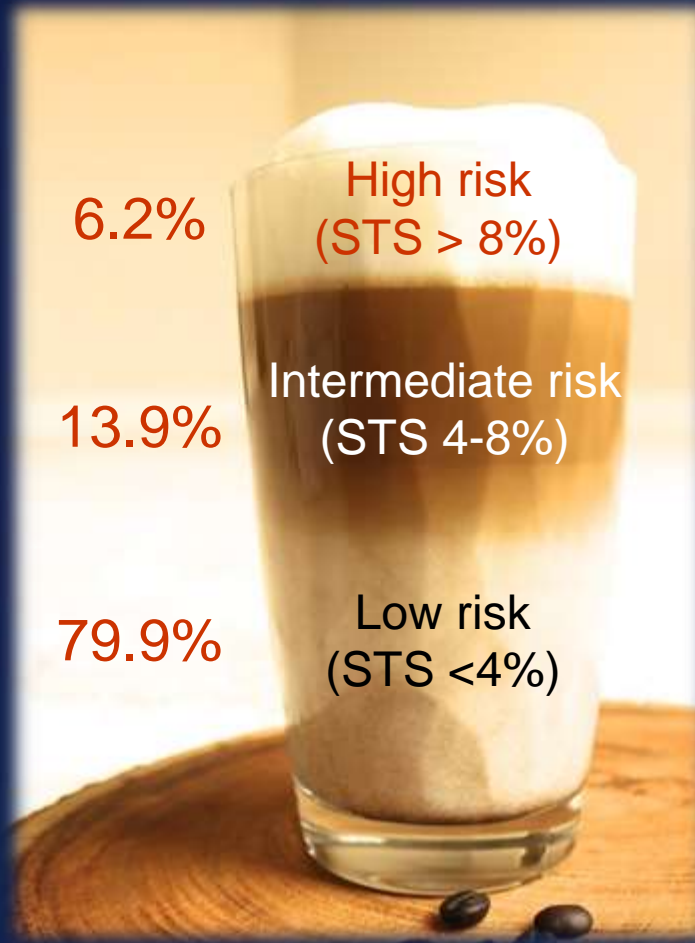
Why should we consider TAVR in Low Risk Patients?

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!

Lower surgical Risk

NOTION | The CoreValve Platform



The NOTION trial randomized all-comers at lower surgical risk between TAVR with CoreValve and SAVR

NOTION Trial | Select Baseline Characteristics

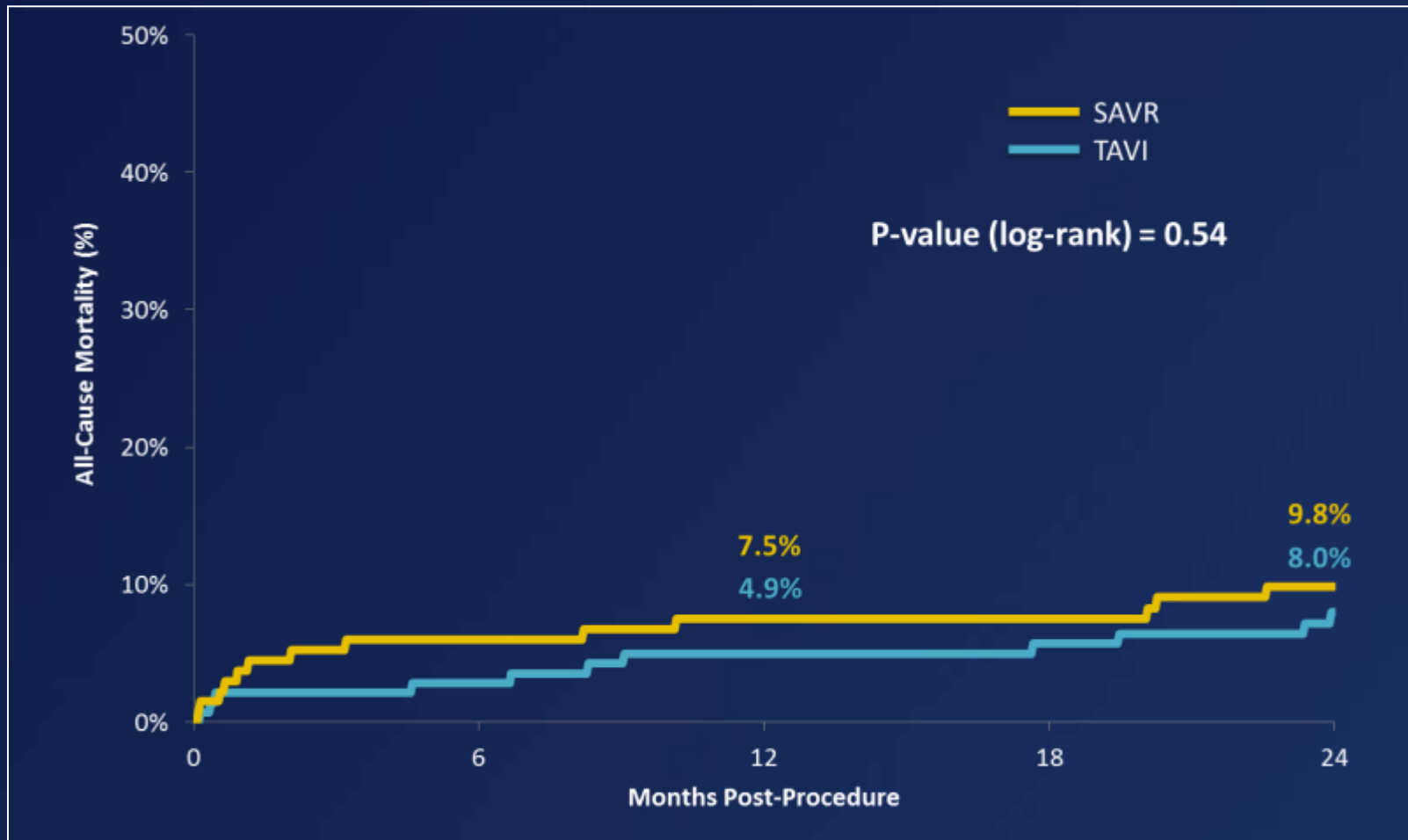
Characteristic, % or mean \pm SD	TAVR n=145	SAVR n=135	p-value
Age (yrs)	79.2 \pm 4.9	79.0 \pm 4.7	0.71
Male	53.8	52.6	0.84
STS Score	2.9 \pm 1.6	3.1 \pm 1.7	0.30
STS Score < 4%	83.4	80.0	0.46
NYHA class III or IV	48.6	45.5	0.61

Lower surgical Risk

NOTION | The CoreValve Platform



Though the study was likely under-powered, NOTION showed all-cause mortality with TAVR to be non-inferior to SAVR



Low Surgical Risk

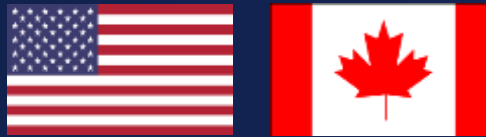
Active Trials Randomizing TAVR to SAVR

Medtronic Low Risk¹



N = ~1200
Up to 80 centers
Evolut R
Medtronic sponsored
10-year follow-up

PARTNER 3²



N = 1228
Up to 64 centers
SAPIEN 3, transfemoral
Edwards sponsored
10-year follow-up

UK TAVI³



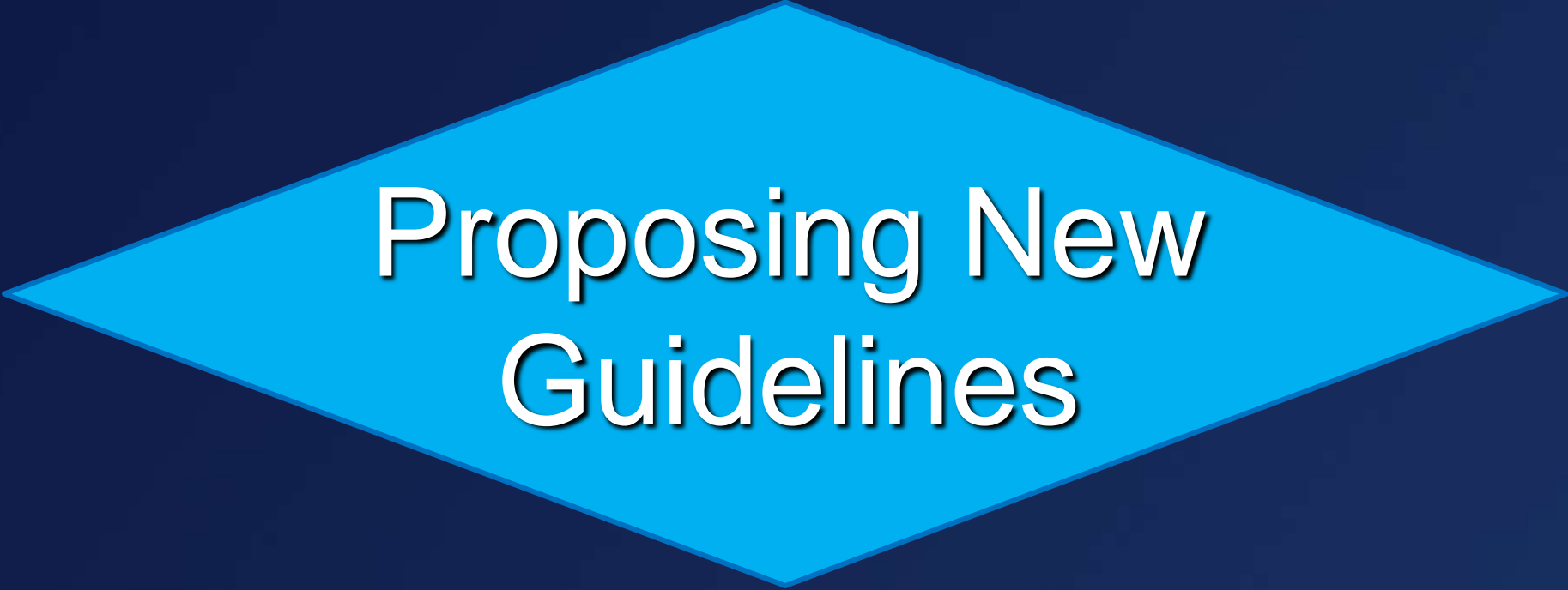
N = 808
All UK centers performing TAVI
All valves, all routes
Publically funded
5-year follow-up

TAVR Journey - 2017

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*

TAVR Journey - 2017



Proposing New Guidelines

TAVR Journey - 2017

Proposing New Guidelines

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

Therefore, we should consider introducing "clinical" guidelines to help the practicing TAVR community

TAVR Clinical Use in 2017

Class Ia (of course!)

CLASS I

Benefit >>>
Risk

SHOULD
be performed

- 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 PulmHyp

TAVR Clinical Use in 2017

Class Ib (enough already!)

CLASS I

Benefit >>>
Risk

SHOULD
be performed

- Intermediate-risk patients (esp. TF)
- ≥ 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 2017

Class IIa (strong preference!)

CLASS IIa

Benefit >>
Risk

IT IS
REASONABLE
to perform

- ≥ 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 2017

CLASS IIb

Benefit \geq
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 2017

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

Concerns and Still Unanswered Questions

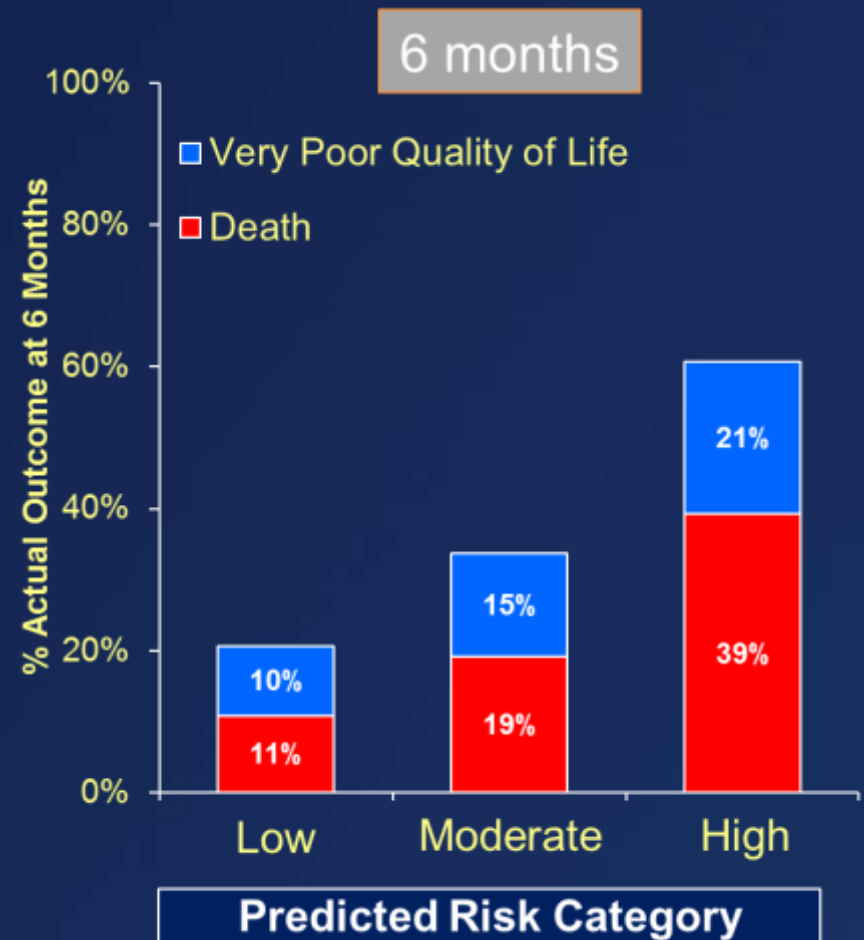
Patient Selection

Predicting Patients with Poor Outcome

- Certain patients don't improve after TAVR, and risk models are being developed to help prospectively identify these individuals.
- Providing these patients with palliative care may be a better treatment choice.

High Risk Features for Poor Outcome:

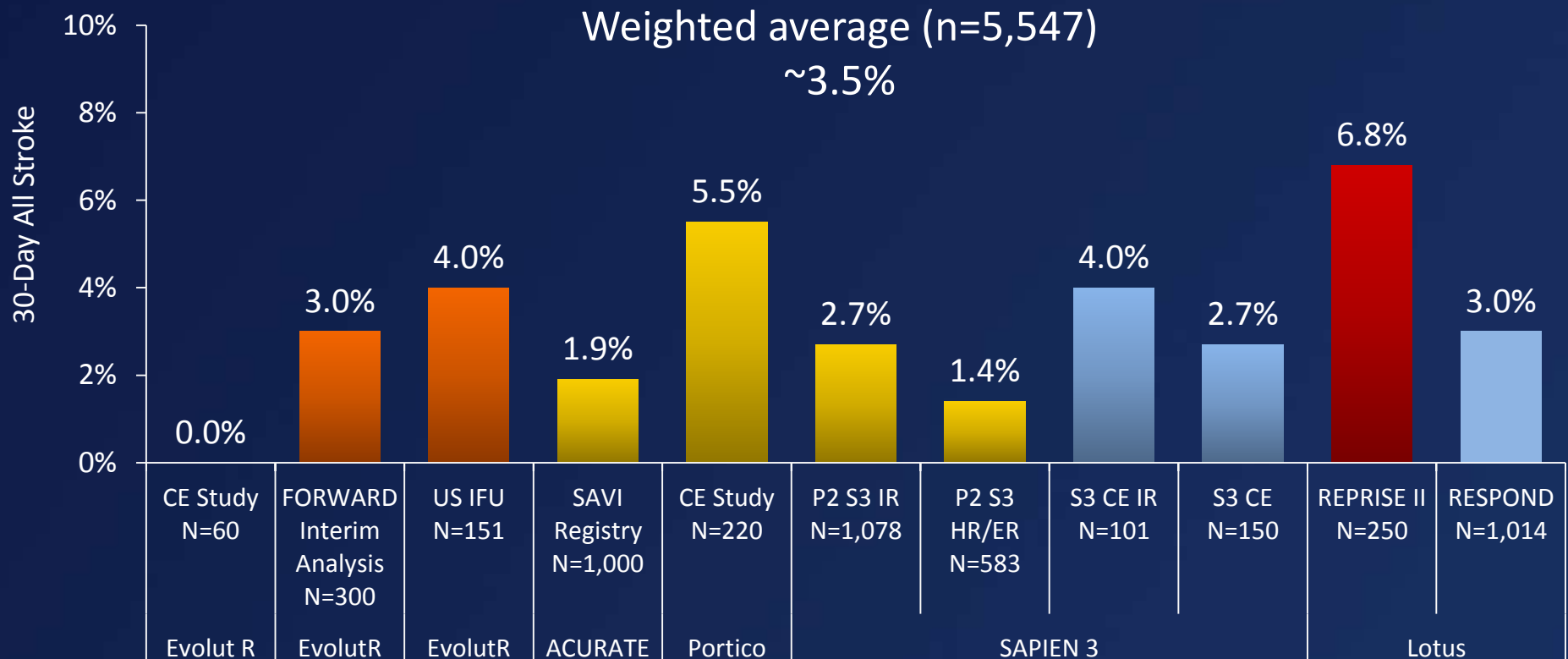
- Comorbidities:
 - Severe COPD and Home Oxygen
 - Kidney Disease (Dialysis)
- Disease Features
 - Low Aortic Gradient
- Functional Status / Frailty
 - Wheelchair Bound
 - Dementia
 - ADL Dependencies
 - Unintentional Weight Loss



TAVR Stroke

Rates with Contemporary Devices

- In contemporary practice, the overall stroke rate remains around 3.5%
- Smaller, more flexible delivery systems may be a contributing factor



¹Manoharan, et al., *J Am Coll Cardiol Interv* 2015; 8: 1359-67; ²Merlini, 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

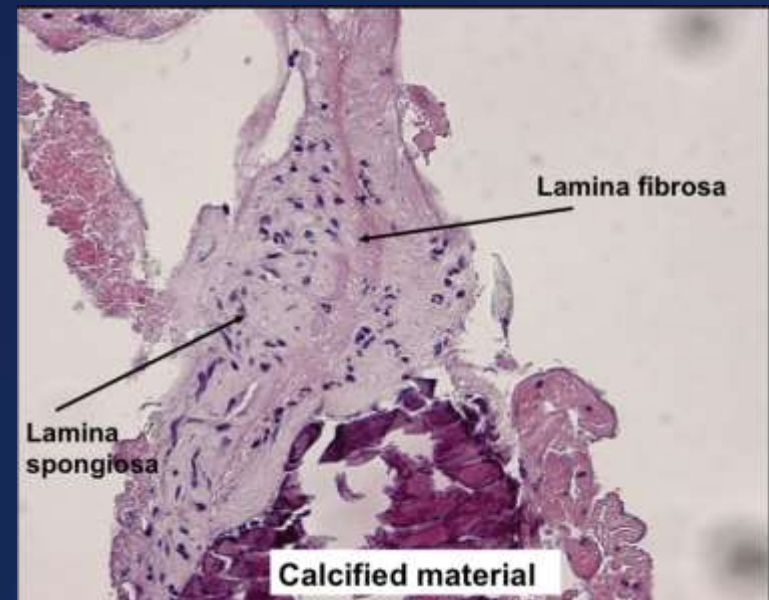
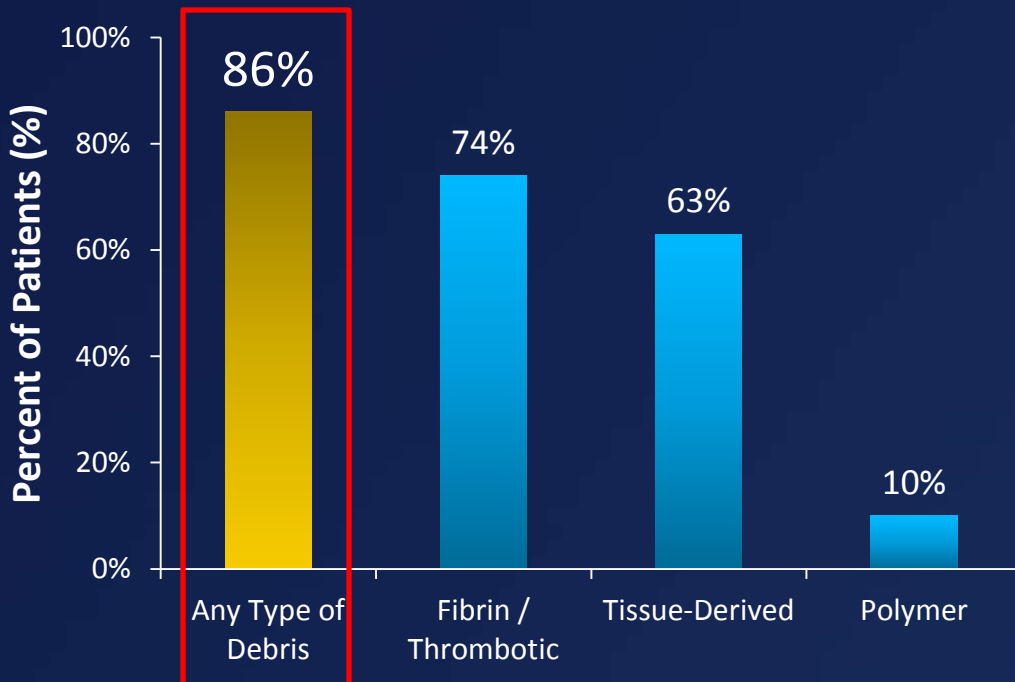
Neurologic Injury

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



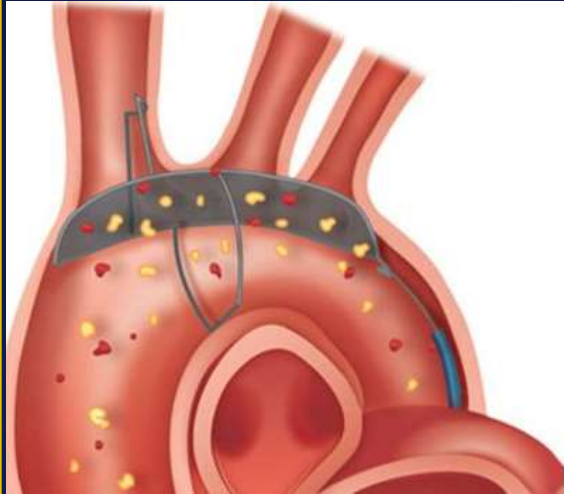
Fragments of aortic valve leaflet

Neurologic Injury

Embolic Protection Devices

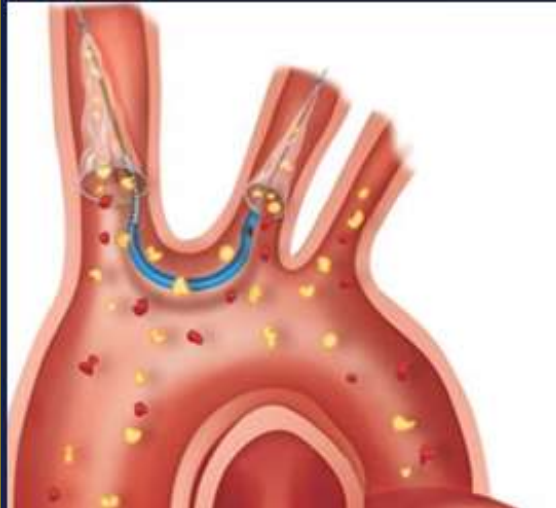
Embolic protection devices provide a key therapeutic strategy to mitigate complications caused by procedural embolic debris

TriGuard Embolic Deflection Device (Keystone Heart)¹



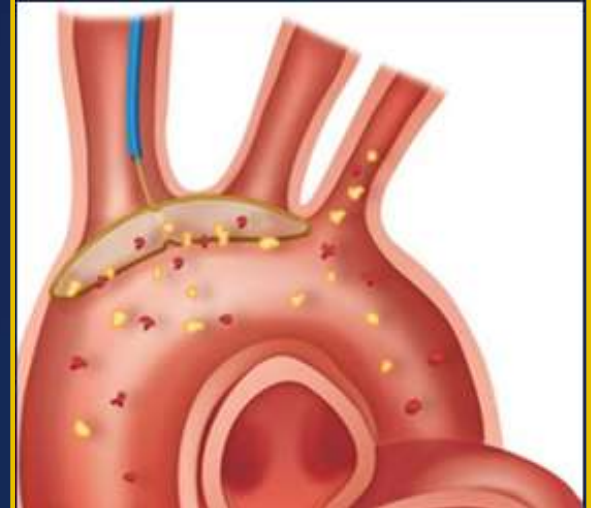
- ✓ Pore Size: 130 μm
- ✓ Delivery Sheath: 9F
- ✓ Access: Transfemoral
- ✓ Coverage: Brachiocephalic, left common carotid, left subclavian

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

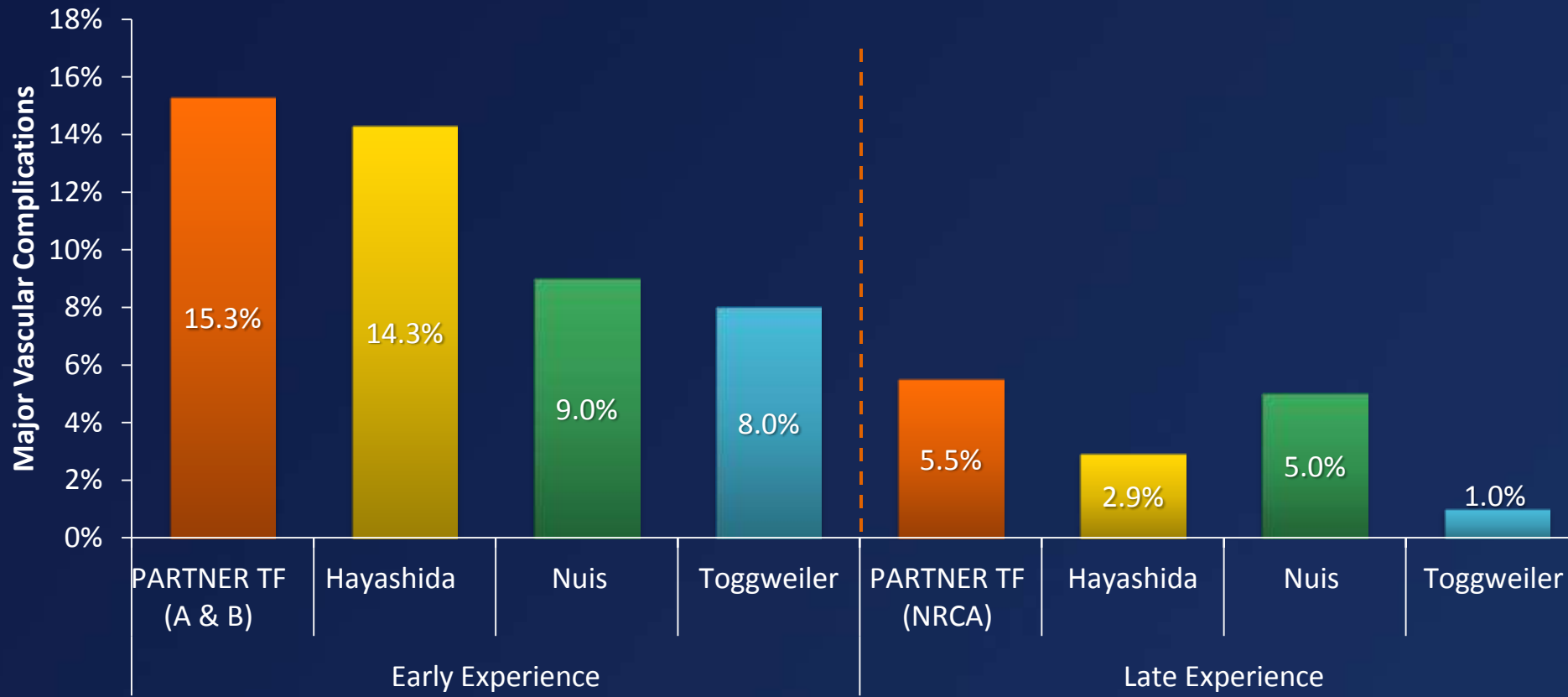


- ✓ Pore Size: 100 μm
- ✓ Delivery Sheath: 6F
- ✓ Access: Brachial
- ✓ Coverage: Brachiocephalic, left common carotid

Vascular Complications

Impact of Learning Curve

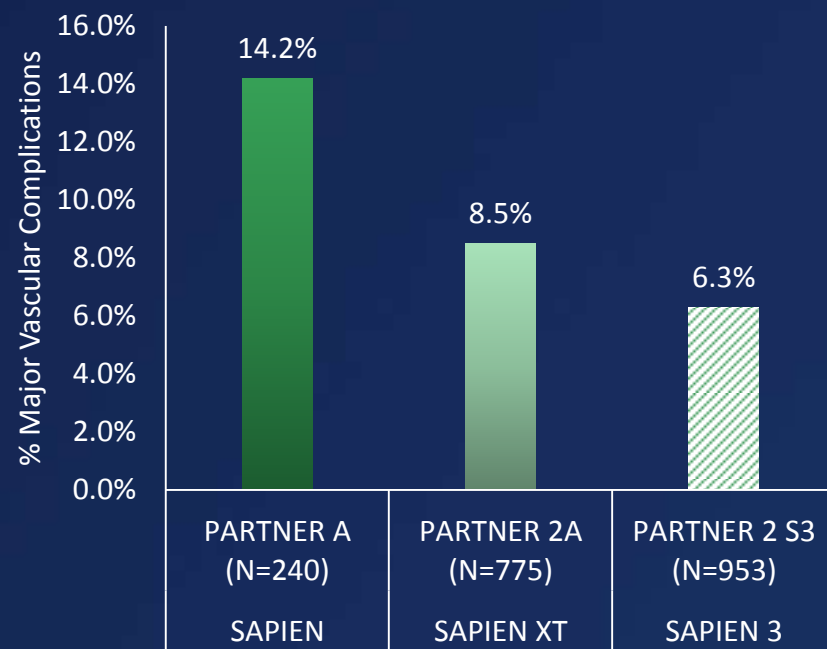
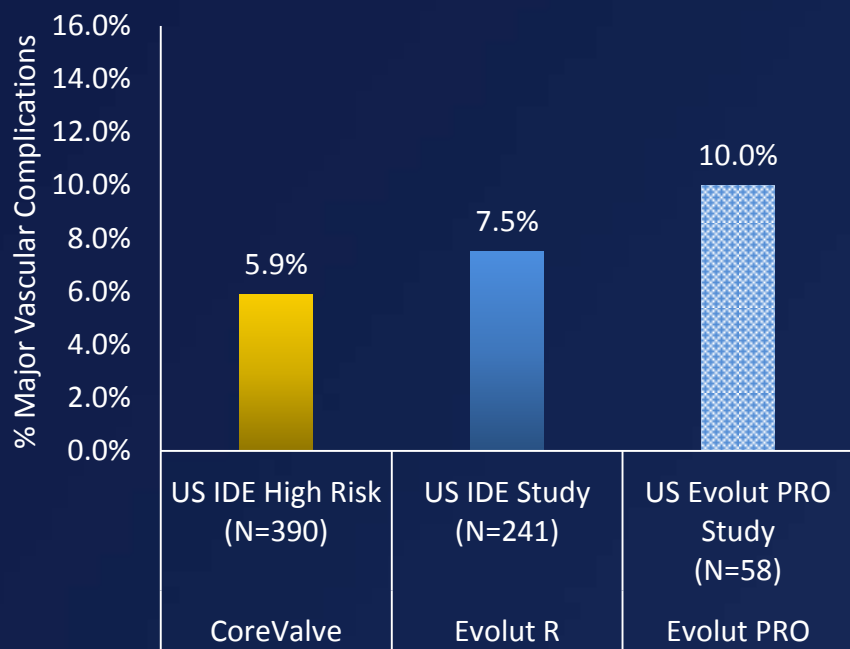
The impact of learning curve on vascular complications has been demonstrated in other clinical scenarios as well, including the PARTNER trial and single-center studies



Vascular Complications

Transfemoral Patients

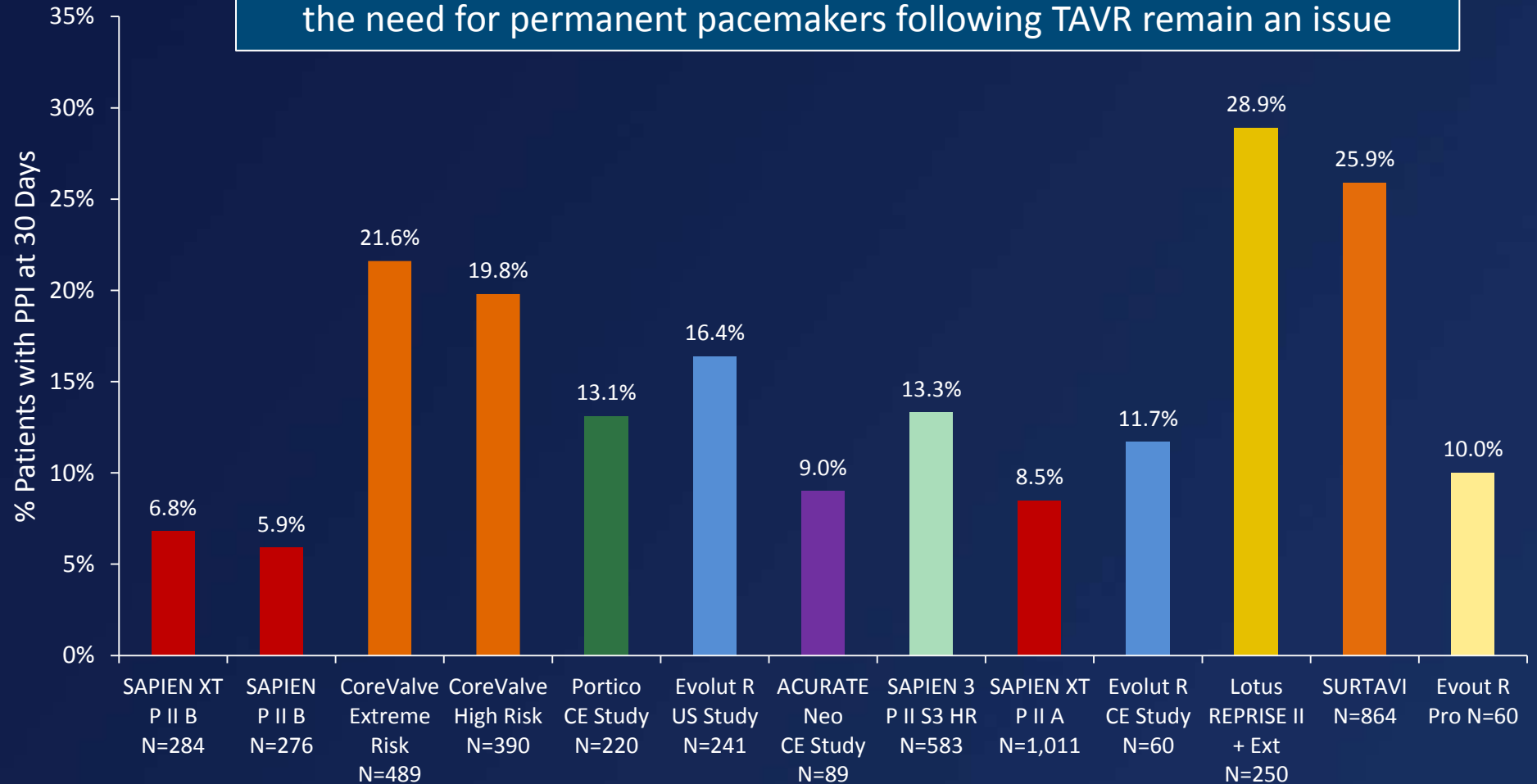
Contemporary rates of major vascular complications hover between 5 – 10% as more patients with smaller vessels have the transfemoral approach



Permanent Pacemakers

Rates at 30 Days

Despite new technological advances, new conduction disturbances and the need for permanent pacemakers following TAVR remain an issue

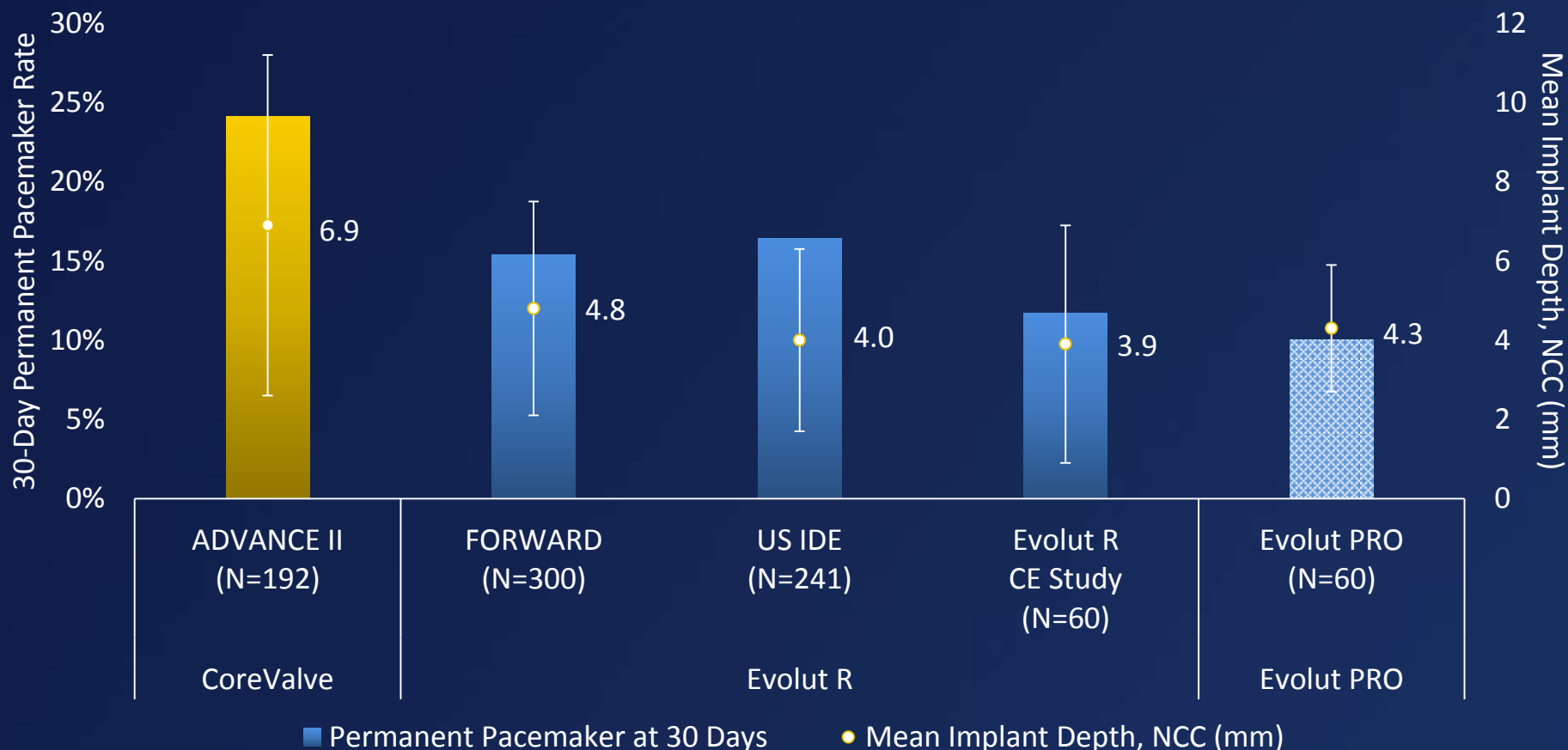


¹Webb, et. al. *J Am Coll Cardiol Interv* 2015; 8: 1797-806; ²Popma, et al., *J Am Coll Cardiol* 2014; 63: 1972-81; ³Adams, et al., *N Engl J Med* 2014; 370: 1790-8; ⁴Linke, et. al. presented at PCR London Valves 2015; ⁵Williams, et al., presented at ACC 2016; ⁶Abizaid, et al., presented at CRT 2015; ⁷Kodali, et al., *Eur Heart J* 2016; doi:10.1093/eurheartj/ehw112; ⁸Leon, et al., *N Engl J Med* 2016 Apr 2 [E-pub ahead of print]; ⁹Manoharan, et al., *J Am Coll Cardiol Interv* 2015; 8: 1359-67; ¹⁰Lefevre, et al., *J Am Coll Cardiol Interv* 2016; 9: 68-75; ¹¹Meredith, et al., presented at PCR London Valves 2014; ¹²Reardon et al. presented at ACC 2017; ¹³Forrest et al. presented at ACC 2017

Permanent Pacemaker Rate

Medtronic Cohorts with Measured Implant Depths

The recapturability of Evolut R and Evolut PRO may be driving improvements in implant depth, which in turn leads to lower rates of new permanent pacemakers



Permanent Pacemakers

Clinical Impact

Studies out to 3 years have demonstrated no impact of pacemakers on mortality, but this needs to be monitored over the long term, especially in patients with fewer competing comorbidities

Study	Valve Type (n)	30 Day PPM Rate	Follow-Up	Mortality Impact
De Carlo ¹	CoreValve (n=275)	25.5%	1 year	None (p=0.90)
Buellesfeld ²	CoreValve (n=319)	27.8%	1 year	None (p=0.77)
	Edwards (n=34)			
Pereira ³	CoreValve (n=65)	32.8%	1 year	None (p=0.11)
Nazif ⁸	SAPIEN (n=1973)	8.8%	1 year	None (p=0.08)
SURTAVI ⁹	CoreValve (n=864)	25.9%	2 years	None (p=0.32)
CoreValve ANZ ⁴	CoreValve (n=476)	31.1%	2 years	None (p=0.32)
Extreme Risk US Trial ⁵	CoreValve (n=489)	21.6%	3 years	None (p=0.62)
ADVANCE ⁷	CoreValve (n=1015)	26.3%	3 years	None (p=0.70)
Urena ⁶	CoreValve (n=698)	15.4%	3 years	None (p=0.15)
	Edwards (n=858)			

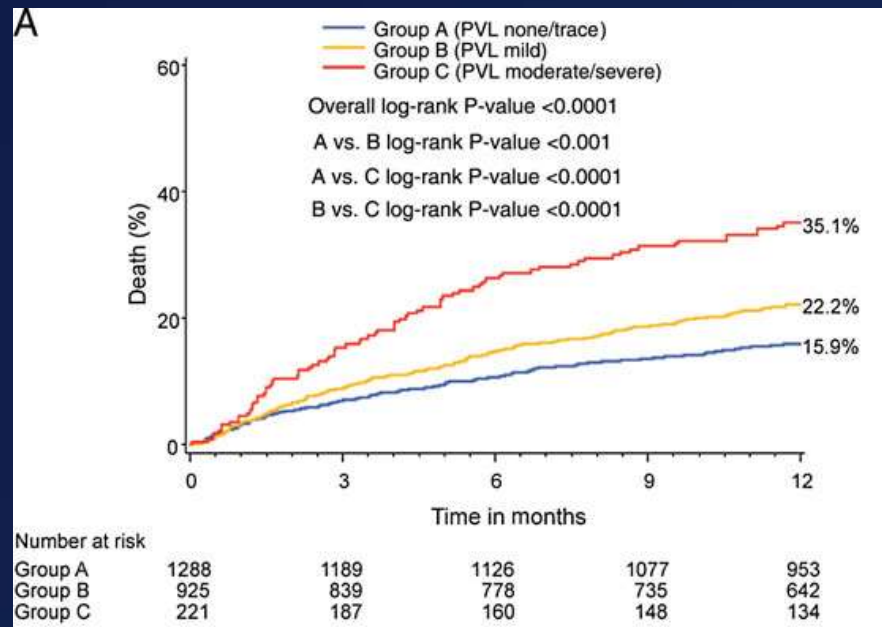
¹De Carlo M, et al., *Am Heart J* 2012; 163: 492-9; ²Buellesfeld L, et al., *J Am Coll Cardiol* 2012; 60(6): 493-501; ³Pereira E, et al., *PACE* 2013; 36(5): 559-69; ⁴Muller D, et al., presented at EuroPCR 2013; ⁵Popma J, et al., *J Am Coll Cardiol* 2014; 63(10): 1972-81; ⁶Urena M, et al., *Circulation* 2014; 129: 1233-1243; ⁷Piazza N, et al., presented at TVT 2015; ⁸Nazif T, et al., *J Am Coll Cardiol Interv* 2015; 8: 60-9; ⁹Reardon et al. presented at ACC 2017

Paravalvular Leak

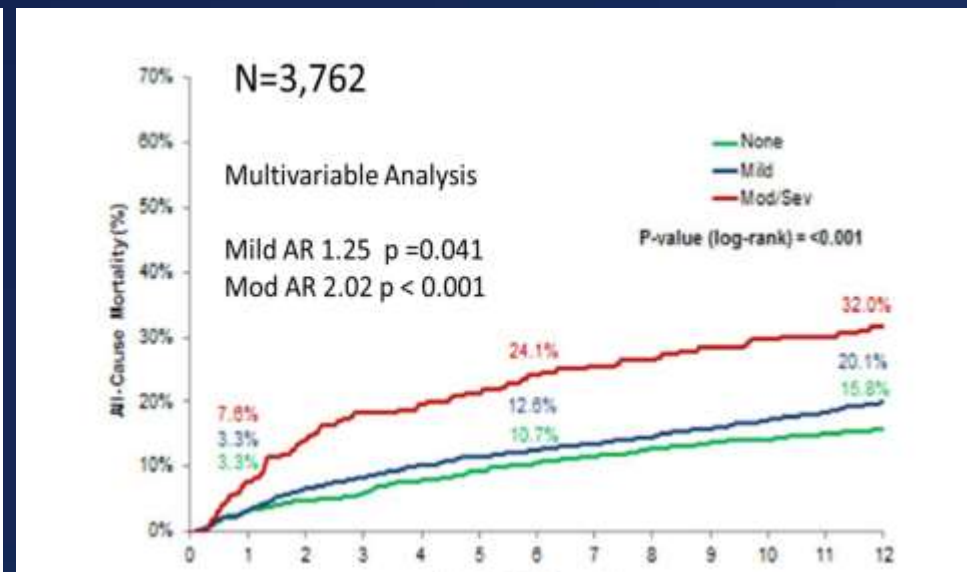
Clinical Impact

- Moderate / severe PVL is a multivariable predictor of all-cause mortality in multiple studies with various valve types, increasing the risk of death by 2x at 1 year.
- Mild PVL may also have a clinical impact in certain patients. Iterative technology and precise implant position are the most likely ways to diminish the risk of PVL.

PARTNER



US CoreValve Pivotal Trial



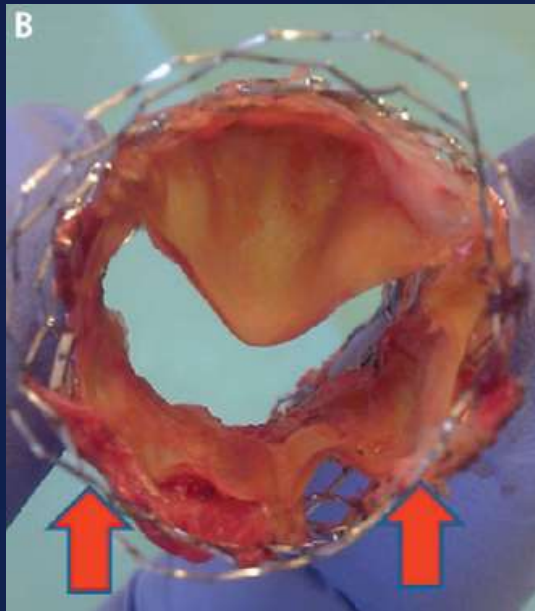
Lifetime Management

Key Concerns

As TAVR is applied to younger patients, evidence-based recommendations 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

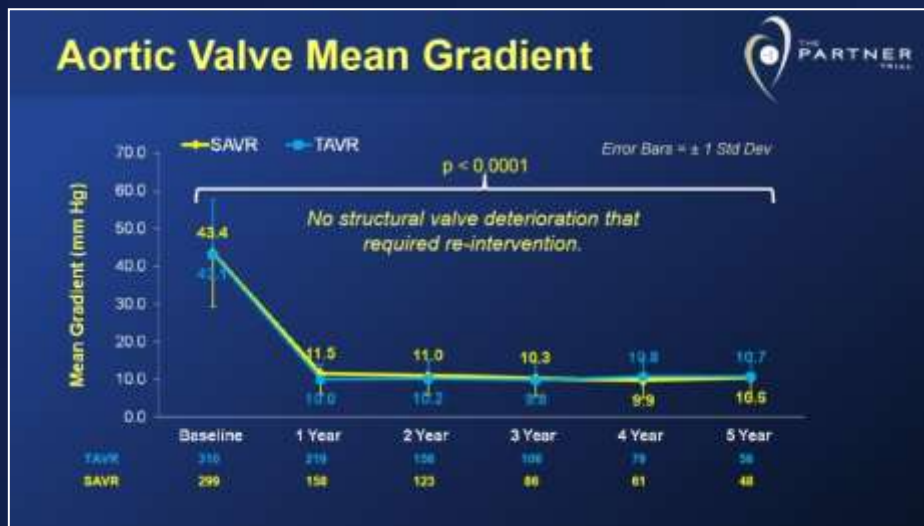


Durability

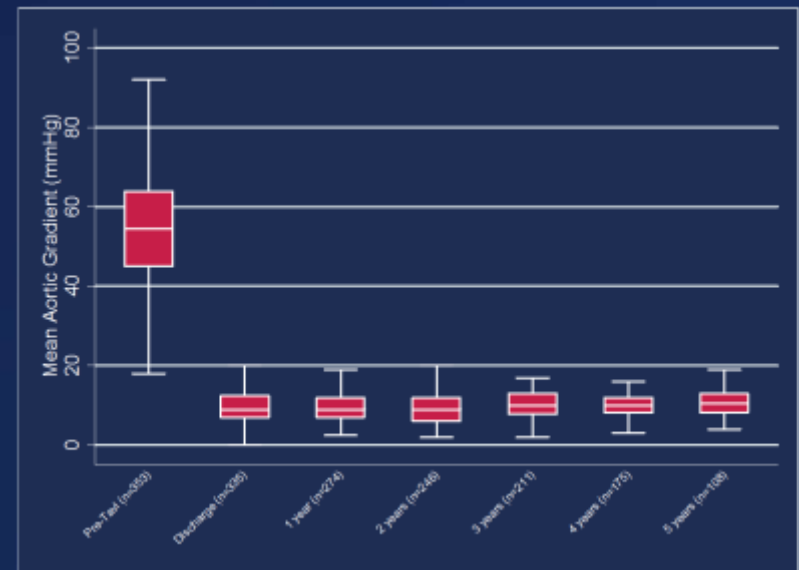
Long-term Follow-up

- 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



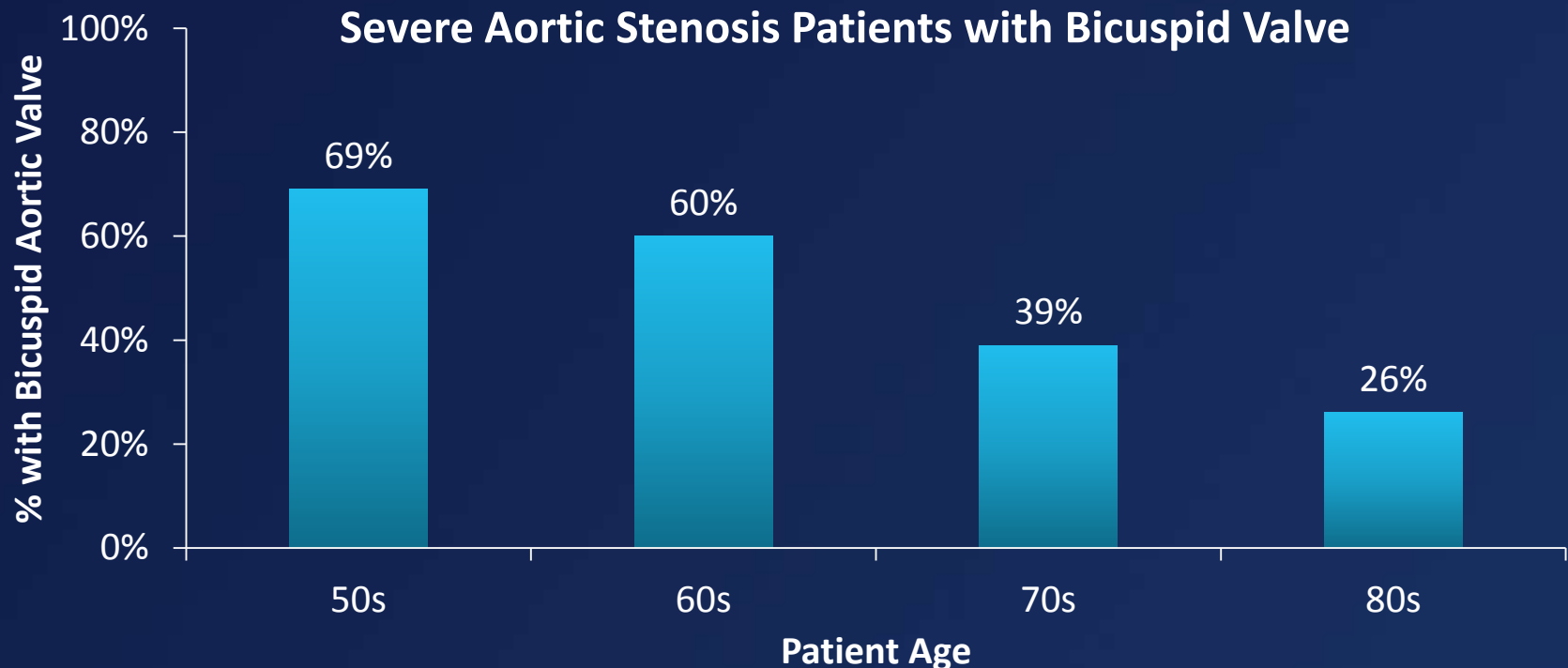
Italian Registry | CoreValve



Special Anatomy

Bicuspid Valve

- Bicuspid aortic valves become more frequent in younger patients with severe AS
- When TAVR is applied to “all-comers,” this anatomy becomes an important issue
- Significantly more work needs to be done to learn optimal implant techniques and device designs for this anatomical variation



Earlier Intervention

Earlier Intervention

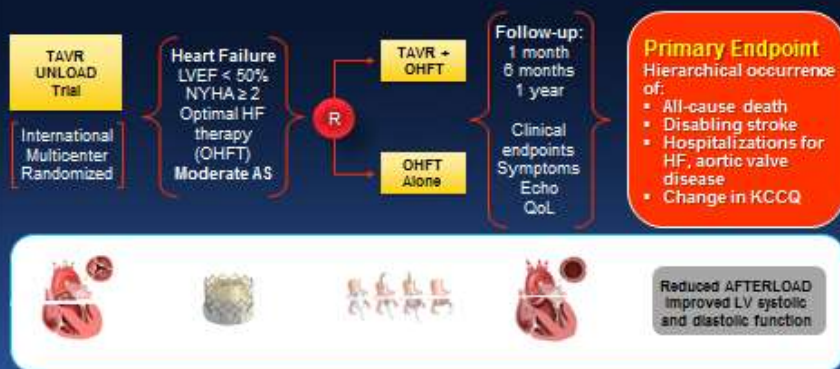
Active Trials

There is interest in using TAVR to intervene earlier in the AS disease process to prevent inevitable myocardial damage and functional decline

TAVR UNLOAD

TAVR will be compared to medical therapy in patients with moderate AS, symptoms of heart failure, and reduced EF

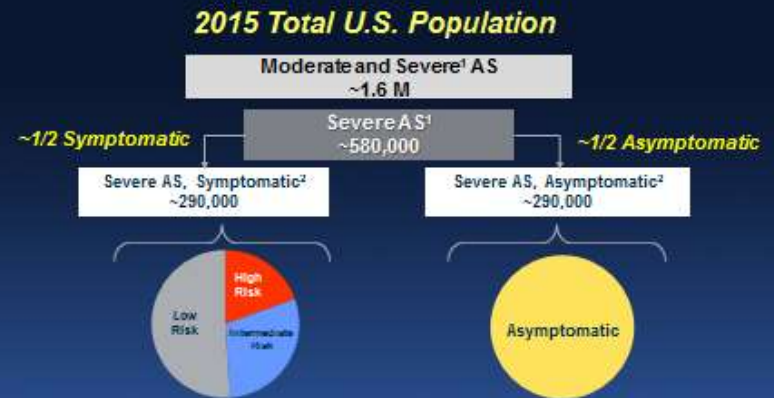
TAVR UNLOAD Trial Study Design (600 patients, 1:1 Randomized)



EARLY TAVR

TAVR will be applied to asymptomatic patients with severe AS

Severe AS in Asymptomatic Patients EARLY TAVR Trial



New Valves on the Horizon

Venus A-Valve System

- Self-expanding frame
- Porcine pericardial valve
- Supra-annular leaflets
- 23, 26, 29 and 32mm
- Higher radial force



Venibri

- Preloaded in the delivery system, reduced profile

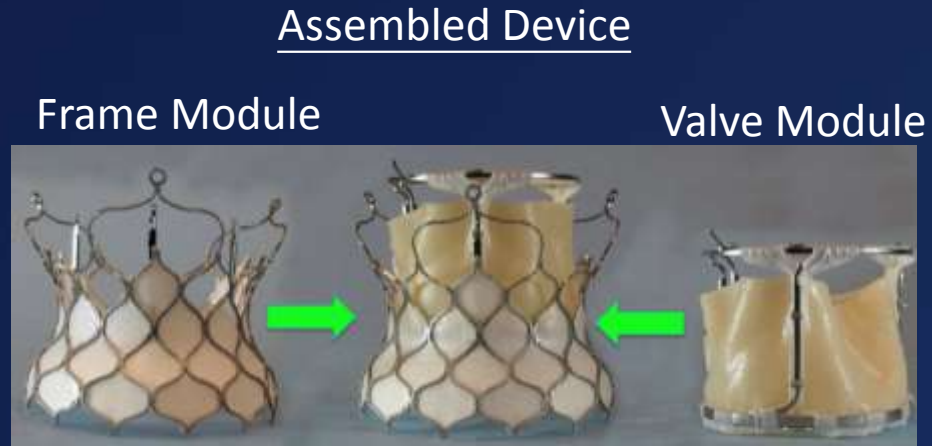


- Reduce aldehyde residue, decrease tissue calcification
- Dry tissue, half of the thickness as the fresh tissue
- Total recovery in 20s
- The new version will be retrievable



Valve Medical

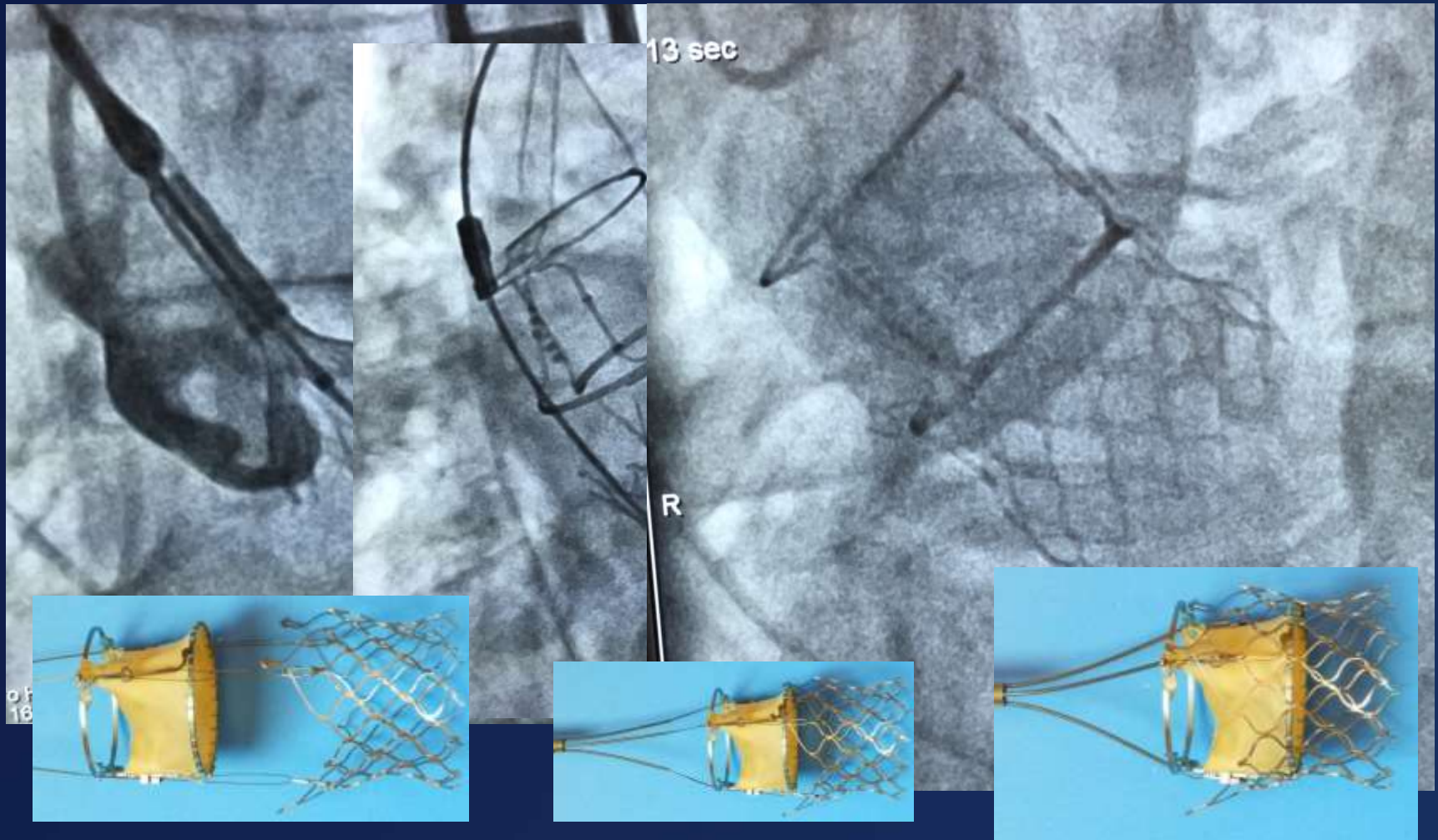
- Frame and leaflets are introduced separately
- *In-situ* docking (valve to frame in ascending Ao)
- 12 Fr delivery
- Bovine pericardium
- Not crimped



Frame and Valve
Module Docking
and Locking



First Successful 12 French Valve Medical TAVR Modular Implant



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

Xeltis

Endogenous Tissue Restoration (ERT)



- Synthetic matrix made of biodegradable polymers
- Polymer leaflets mounted on nitinol self-expanding frame



*Valve after
bioabsorption*

- Regrowth of endogenous tissue coincident with bioabsorption of polymer implant

Final Thoughts

- TAVR is now proven in patients at intermediate surgical risk, which represents the culmination of many years of rigorous study.
- Currently there is significant clinical investment in applying this technology to younger patients at low surgical risk.
- Careful study is an absolute requirement because certain TAVR-specific complications remain a concern.
- However, the survival advantage and quick recovery to improved quality of life which was achieved with transfemoral TAVR versus SAVR in the high risk and intermediate risk trials provides a highly encouraging signal.

Thank you for your kind Attention