Efficacy and Safety of TAVR - 2016

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Columbia University Medical Center
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New York City

21st CardioVascular Summit
TCTAP 2016
April 26-29, 2016
Coex, Seoul, Korea

8 mins

April 28, 2016

Cardiovascular Research Foundation

Columbia University Medical Center
NewYork-Presbyterian

Disclosure Statement of Financial Interest
TCTAP 2016; Seoul, Korea; April 26-29, 2016

Martin B. Leon, MD

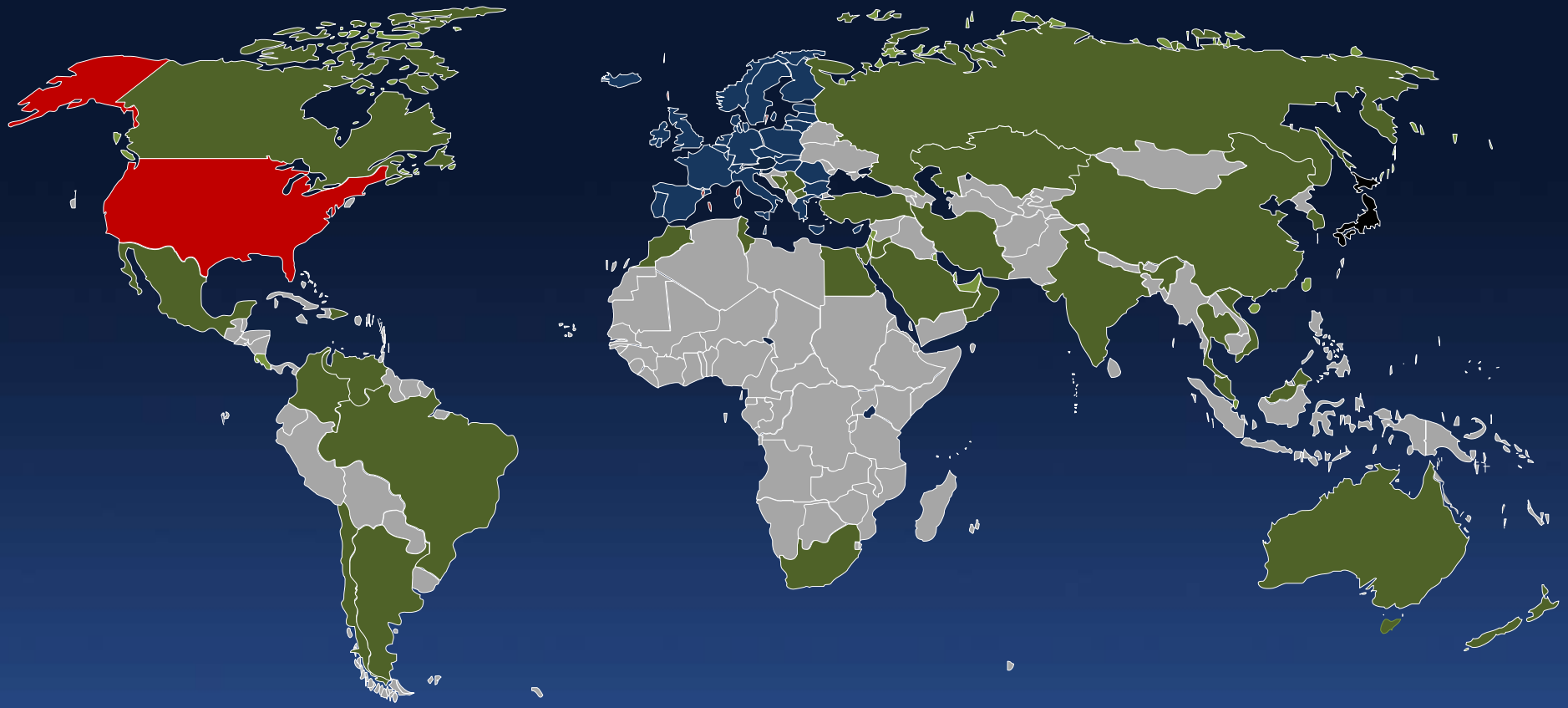
Within the past 12 months, I or my spouse/partner have had a financial interest/arrangement or affiliation with the organization(s) listed below.

Affiliation / Financial Relationship	Company
• Grant / Research Support	Abbott, Boston Scientific, Edwards Lifescience, Medtronic, St. Jude Medical
• Consulting Fees / Honoraria	Abbott, Boston Scientific, Medtronic, St. Jude Medical
• Shareholder / Equity	Claret, Coherex, Elixir, GDS, Medinol, Mitralign, Valve Medical

TAVR in 2016: *Landscape*

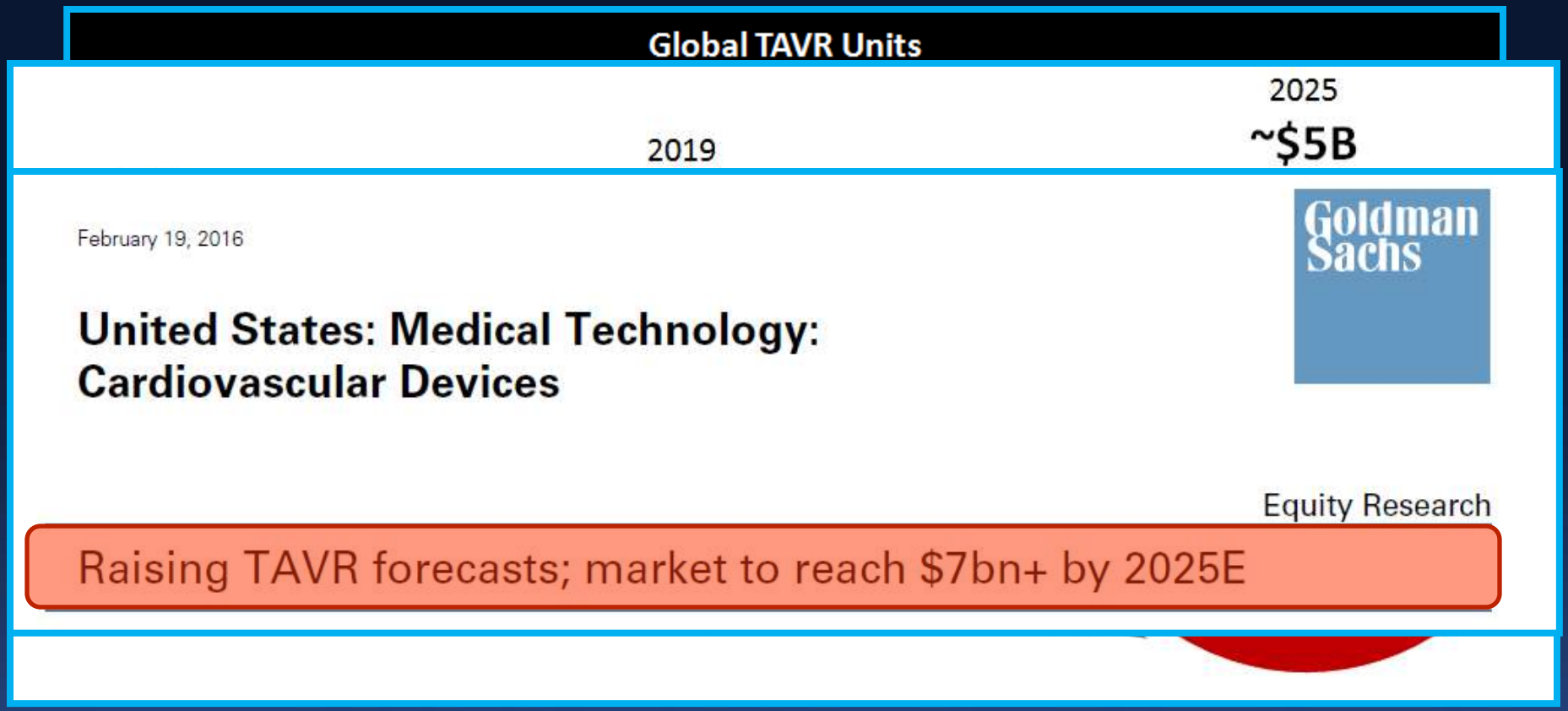
- ***TAVR is a "Breakthrough" Technology -*** Dramatic global growth and universal acceptance with seemingly unlimited future potential!

TAVR is Available in More Than 65 Countries Around the World



>250,000 total implants to date

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!

TAVR in 2015: *Landscape*

- ***TAVR is a "Breakthrough" Technology -*** Dramatic global growth and universal acceptance with seemingly unlimited future potential!
- ***TAVR growth has been fueled by:***
  - the multi-disciplinary heart team
  - commitment to evidence-based medicine
  - rapid technology enhancement
  - simplification of the procedure
  - striking reduction in complications

PARTNER THV Evolution

PI - 2007

Edwards SAPIEN™ THV
23 mm and 26 mm

PII - 2010

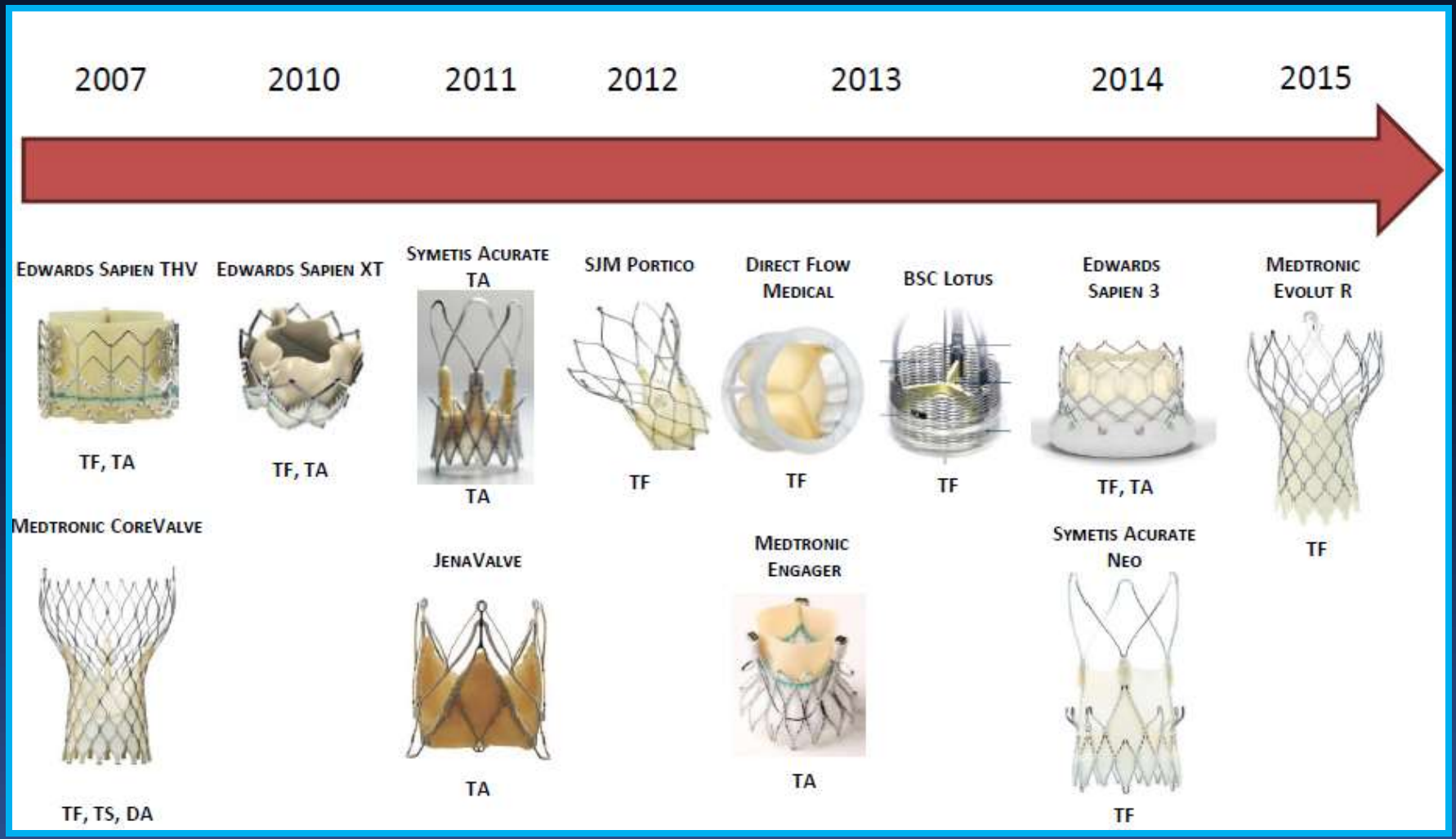
Edwards SAPIEN XT ™ THV
23 mm, 26 mm, and 29mm

PII S3 - 2013

Edwards SAPIEN 3™ THV
20 mm, 23 mm, 26 mm, and 29mm

PARTNER enrolled >9,000 patients in FDA studies (including 4 RCTs) with 3 generations of TAVR systems in ~ 7 years!

TAVR Systems with CE-Approval (2007-15)



Courtesy of S. Windecker

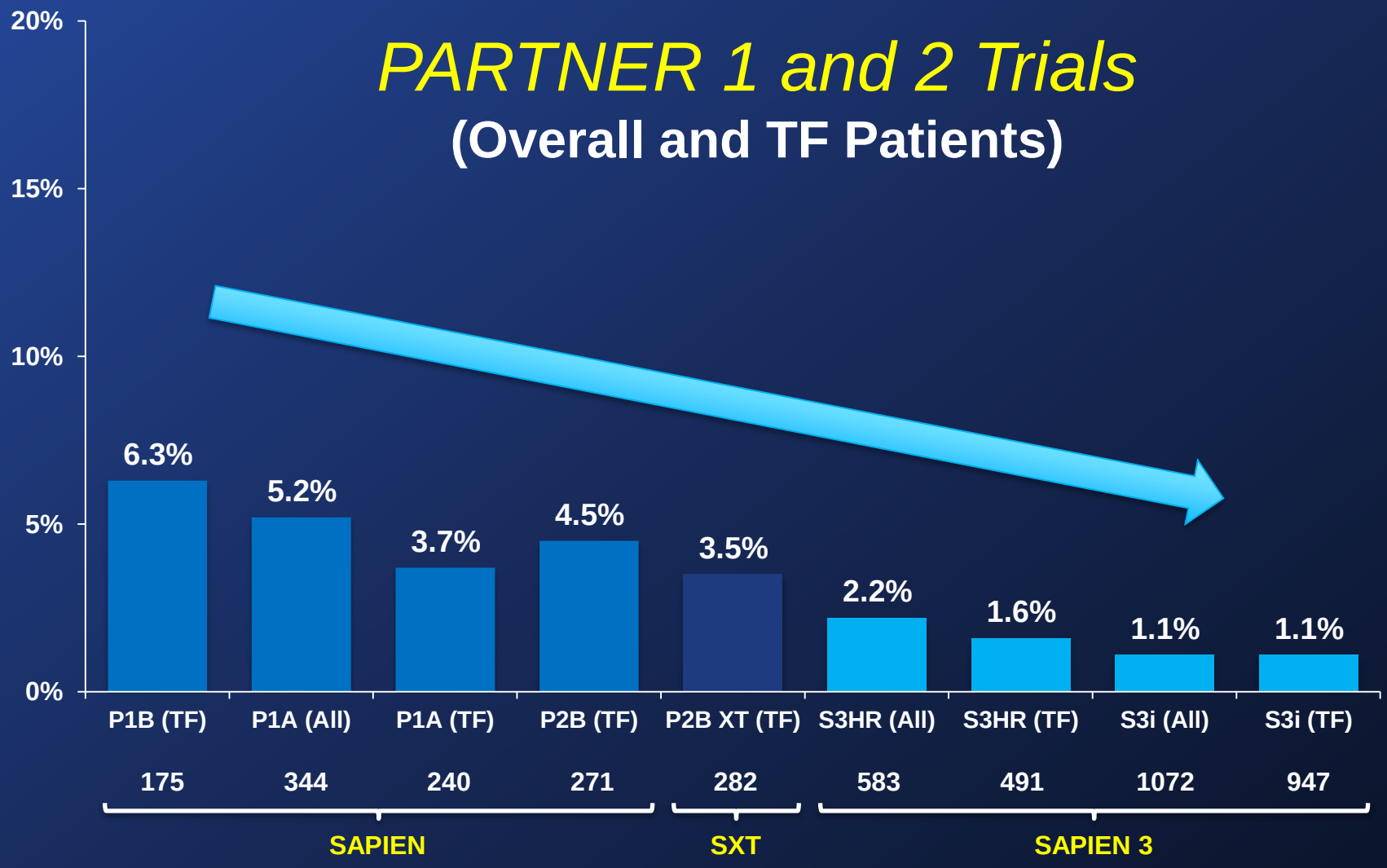
TAVR in 2016
Procedural Considerations

There is a strong trend (led by many physician thought leaders) to maximally simplify TAVR procedures!

- preferential percutaneous transfemoral access
- reduced use of general anesthesia
- less intra-procedural TEE
- eliminate pre-dilatation
- decreased use of complex and costly hybrid cath lab/OR environments
- early discharge programs

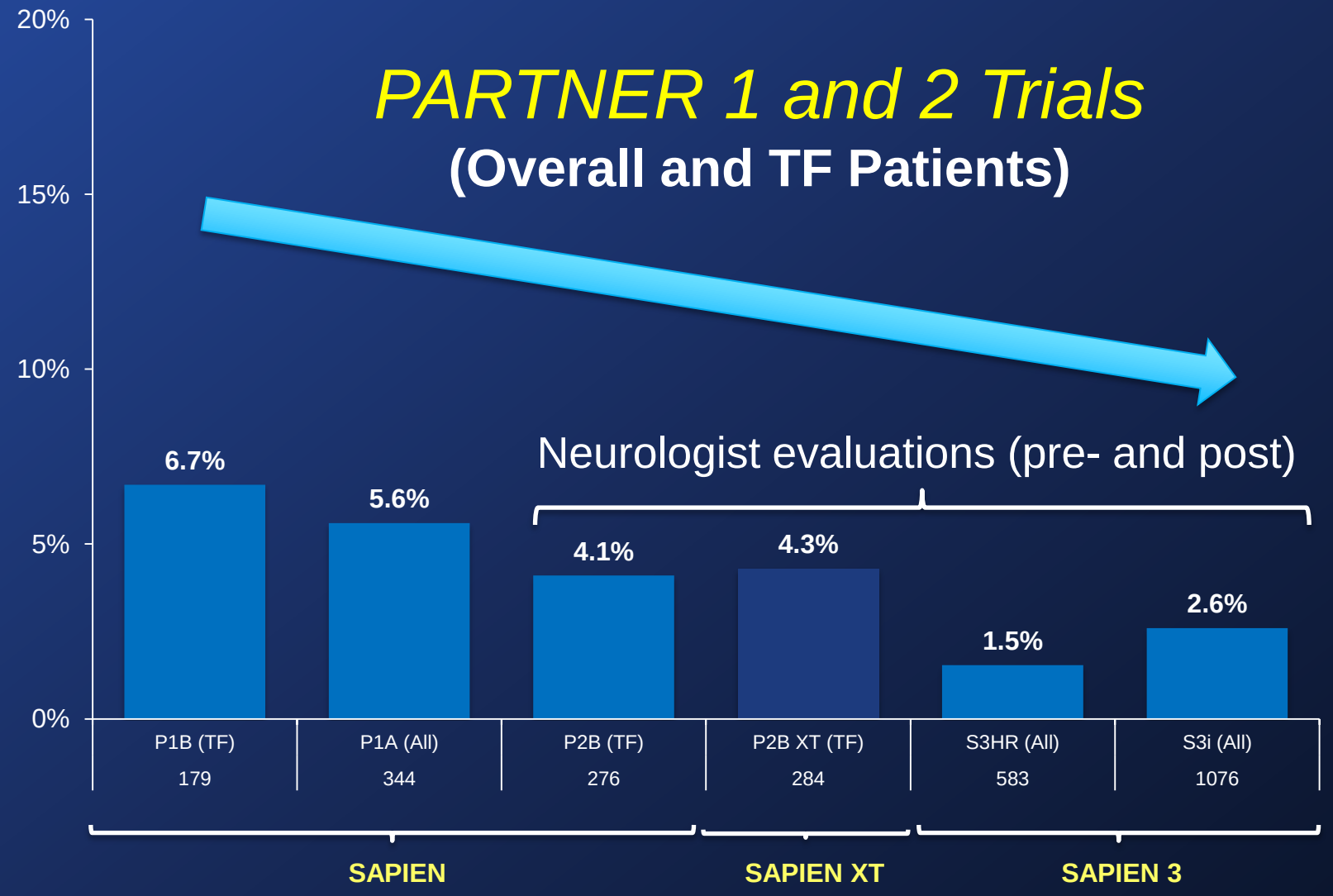
All-Cause Mortality at 30 Days

Edwards SAPIEN Valves (As Treated)

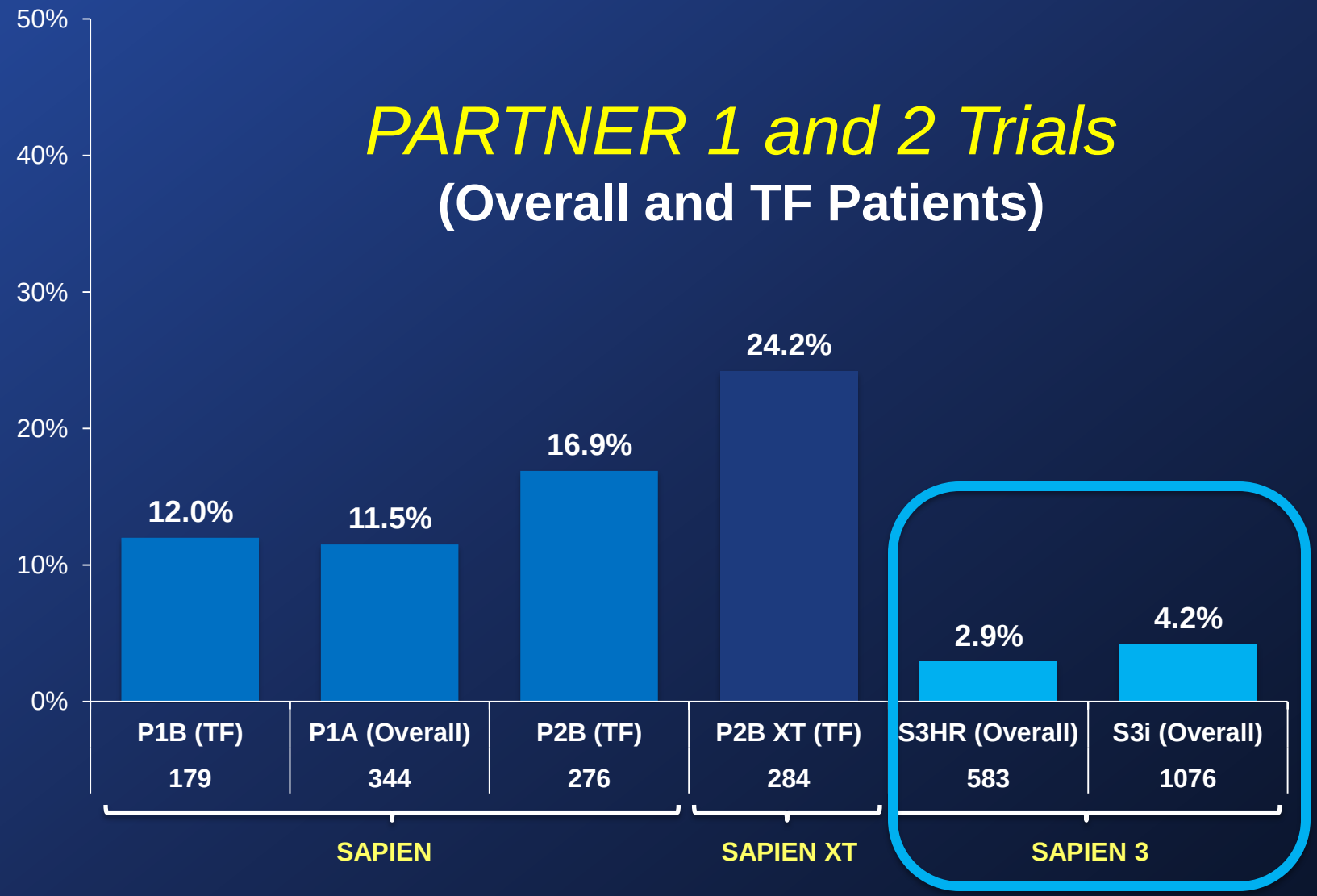


Strokes (All) at 30 Days

Edwards SAPIEN Valves



Moderate/Severe PVL at 30 Days
Edwards SAPIEN Valves

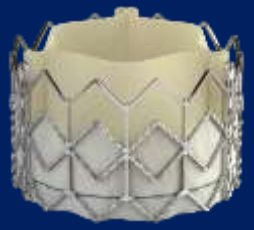
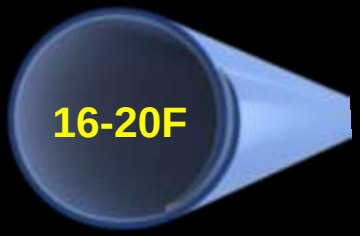


TAVR in 2015: *Landscape*

- ***TAVR has now "conquered" the intermediate-risk patient population (ie. STS 4-8%):***
  - "hard" endpoints of death and stroke (esp. the TF subgroup and the S3i propensity analysis)
  - multiple secondary endpoints cw surgery
  - reduced procedural complications
  - reduced length-of-stay
  - improved hemodynamics
  - reduced PVR

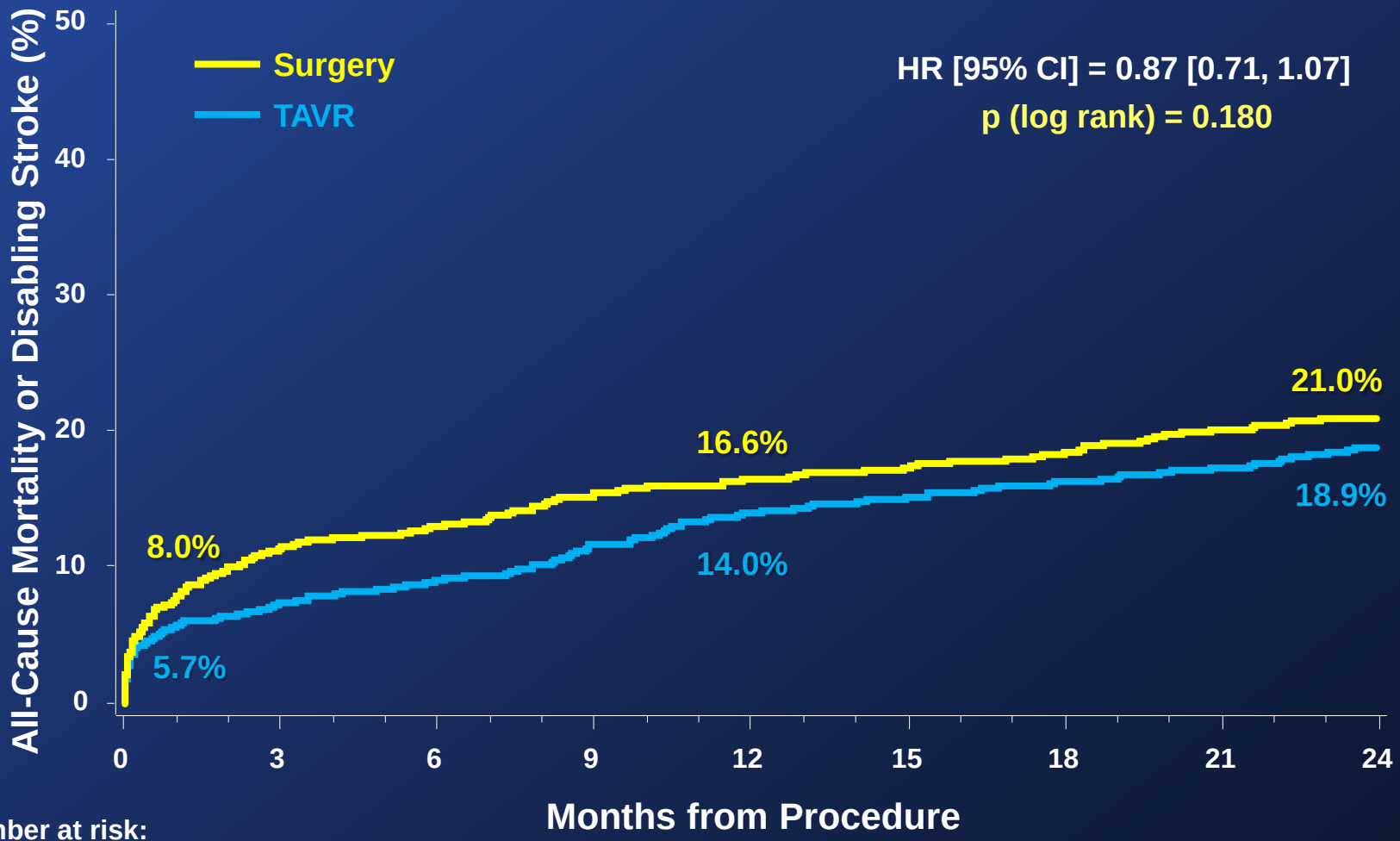
PARTNER SAPIEN Platforms
Device Evolution

THE PARTNER II TRIAL

	SAPIEN	SAPIEN XT	SAPIEN 3
Valve Technology			
Sheath Compatibility			
Available Valve Sizes	 23 mm 26 mm	 23mm 26mm 29mm 20 mm 23 mm 26 mm 29 mm	

Primary Endpoint (AT)
All-Cause Mortality or Disabling Stroke

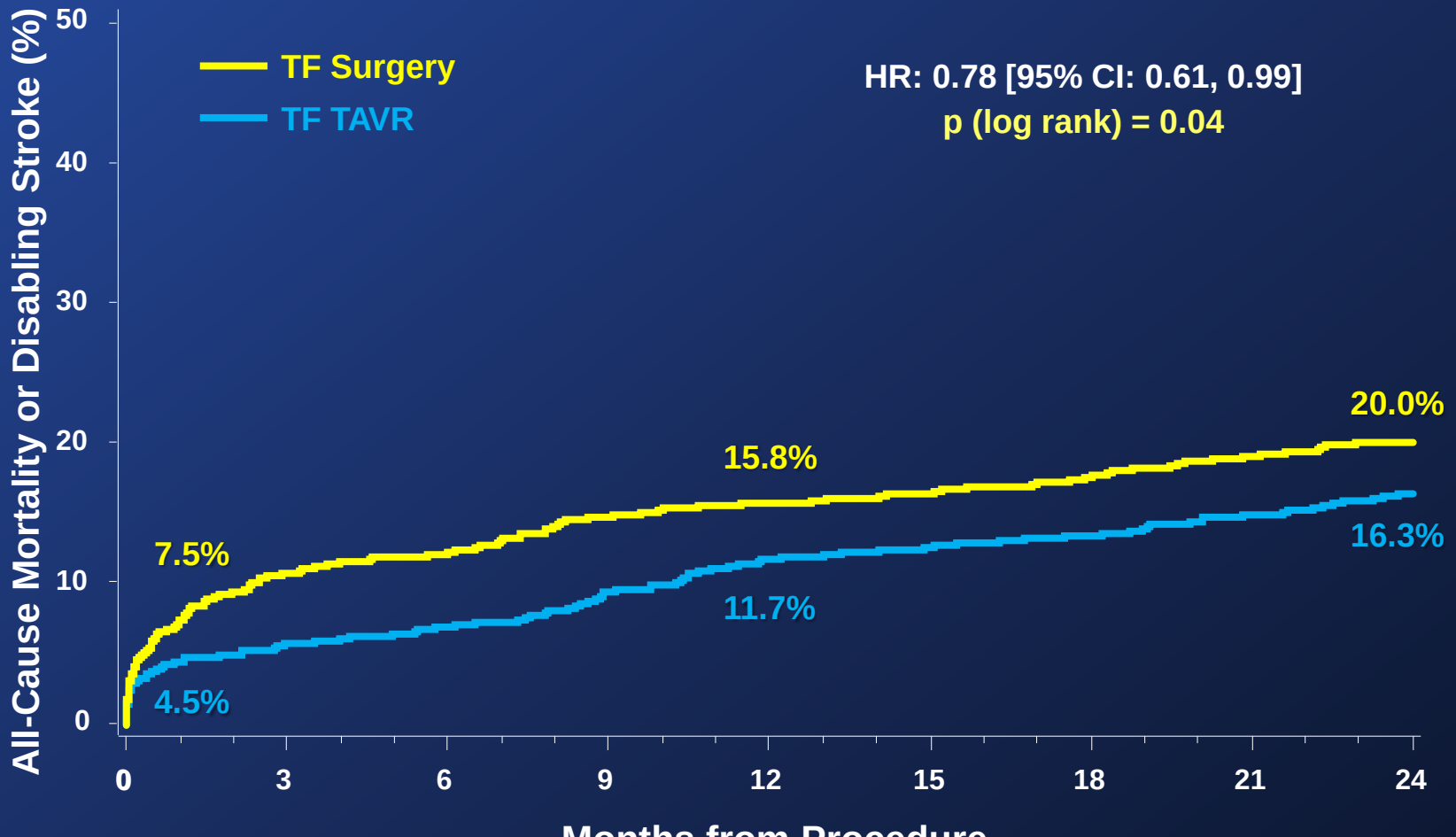
THE PARTNER II TRIAL



Number at risk:									
Surgery	944	826	807	779	766	743	731	715	694
TAVR	994	917	900	870	842	825	811	801	774

TF Primary Endpoint (AT)
All-Cause Mortality or Disabling Stroke

THE PARTNER II TRIAL



Number at risk:									
TF Surgery	722	636	624	600	591	573	565	555	537
TF TAVR	762	717	708	685	663	652	644	634	612

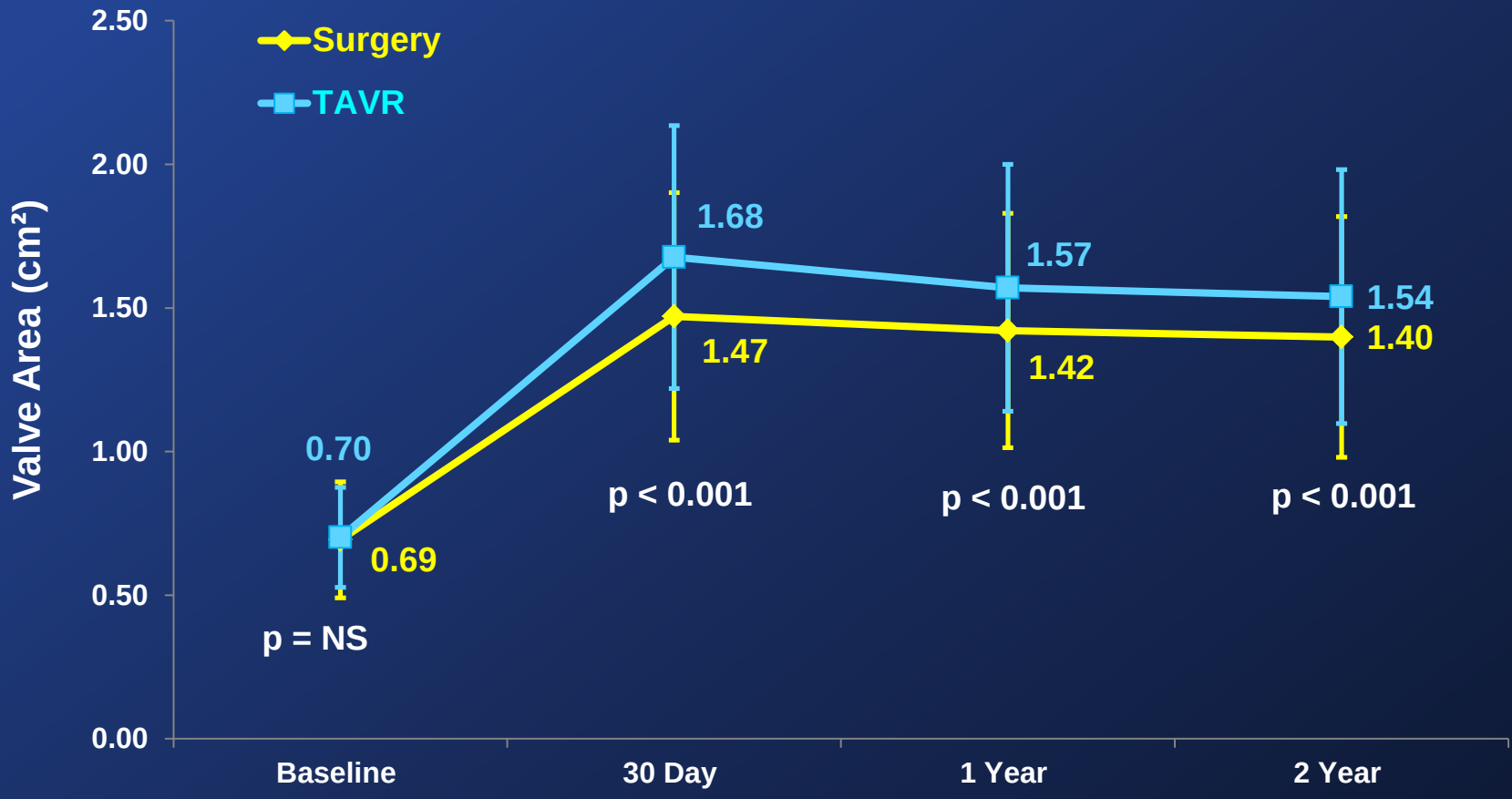
Other Clinical Endpoints (ITT)
At 30 Days and 2 Years

THE PARTNER II TRIAL

Events (%)	30 Days			2 Years		
	TAVR (n = 1011)	Surgery (n = 1021)	p-value*	TAVR (n = 1011)	Surgery (n = 1021)	p-value*
Rehospitalization	6.5	6.5	0.99	19.6	17.3	0.22
MI	1.2	1.9	0.22	3.6	4.1	0.56
Major Vascular Complications	7.9	5.0	0.008	8.6	5.5	0.006
Life-Threatening / Disabling Bleeding	10.4	43.4	<0.001	17.3	47.0	<0.001
AKI (Stage III)	1.3	3.1	0.006	3.8	6.2	0.02
New Atrial Fibrillation	9.1	26.4	<0.001	11.3	27.3	<0.001
New Permanent Pacemaker	8.5	6.9	0.17	11.8	10.3	0.29
Re-intervention	0.4	0.0	0.05	1.4	0.6	0.09
Endocarditis	0.0	0.0	NA	1.2	0.7	0.22

*Event rates are KM estimates, p-values are point in time

Echocardiography Findings (VI)
Aortic Valve Area



No. of Echos				
Surgery	861	727	590	488
TAVR	899	829	695	567

Error bars represent ± Standard Deviation

European Heart Journal Advance Access published March 31, 2016

European Heart Journal
doi:10.1093/eurheartj/ehw112

FASTTRACK CLINICAL RESEARCH
TAVI

Early clinical and echocardiographic outcomes after SAPIEN 3 transcatheter aortic valve replacement in inoperable, high-risk and intermediate-risk patients with aortic stenosis

Susheel Kodali[1*], Vinod H. Thourani[2], Jonathon White[1], S. Chris Malaisrie[3], Scott Lim[4], Kevin L. Greason[5], Mathew Williams[6], Mayra Guerrero[7], Andrew C. Eisenhauer[8,9], Samir Kapadia[10], Dean J. Kereiakes[11], Howard C. Herrmann[12], Vasilis Babaliaros[2], Wilson Y. Szeto[12], Rebecca T. Hahn[1], Philippe Pibarot[13], Neil J. Weissman[14], Jonathon Leipsic[15], Philipp Blanke[15], Brian K. Whisenant[16], Rakesh M. Suri[10], Raj R. Makkar[17], Girma M. Ayele[18], Lars G. Svensson[10], John G. Webb[15], Michael J. Mack[19], Craig R. Smith[1], and Martin B. Leon[1]

Susheel Kodali, MD
on behalf of The PARTNER Trial Investigators

ACC 2015 | San Diego | March 15, 2015

THE PARTNER II TRIAL

Baseline Patient Characteristics

S3i Patients (n=1076 at 51 sites)

THE PARTNER II TRIAL

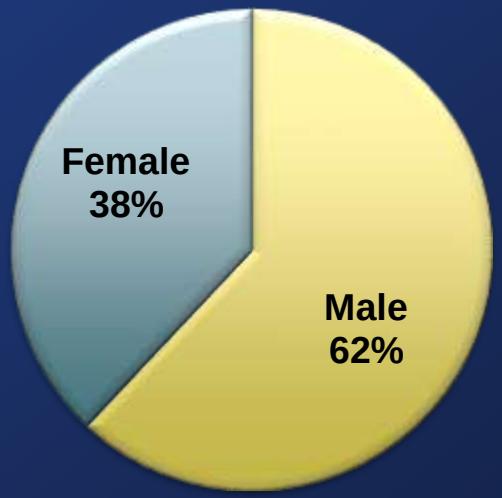
Average STS =

5.3%

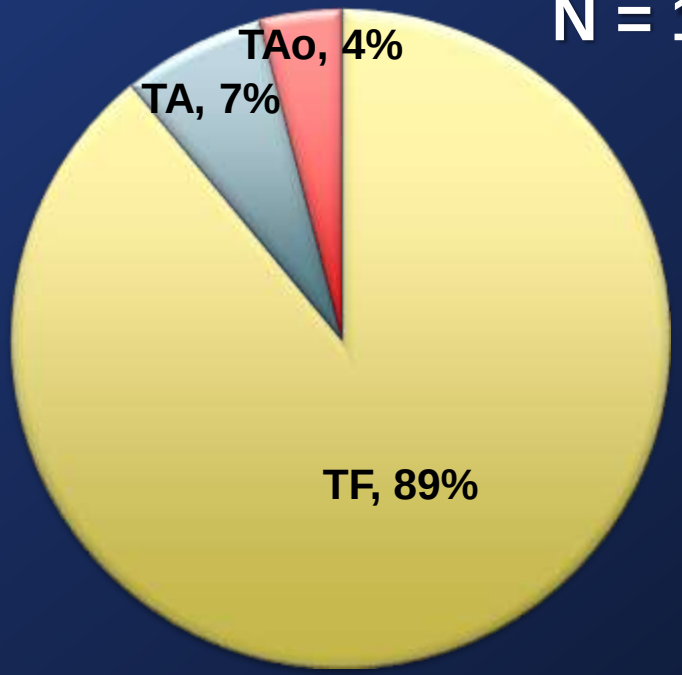
(Median 5.2%)

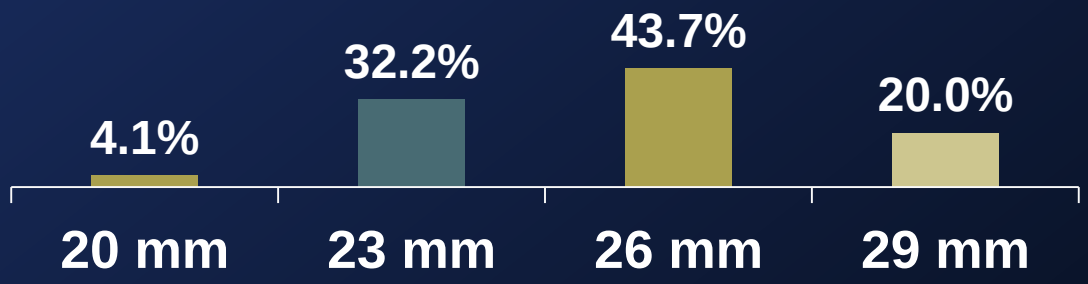
Average Age =

81.9yrs



N = 1076



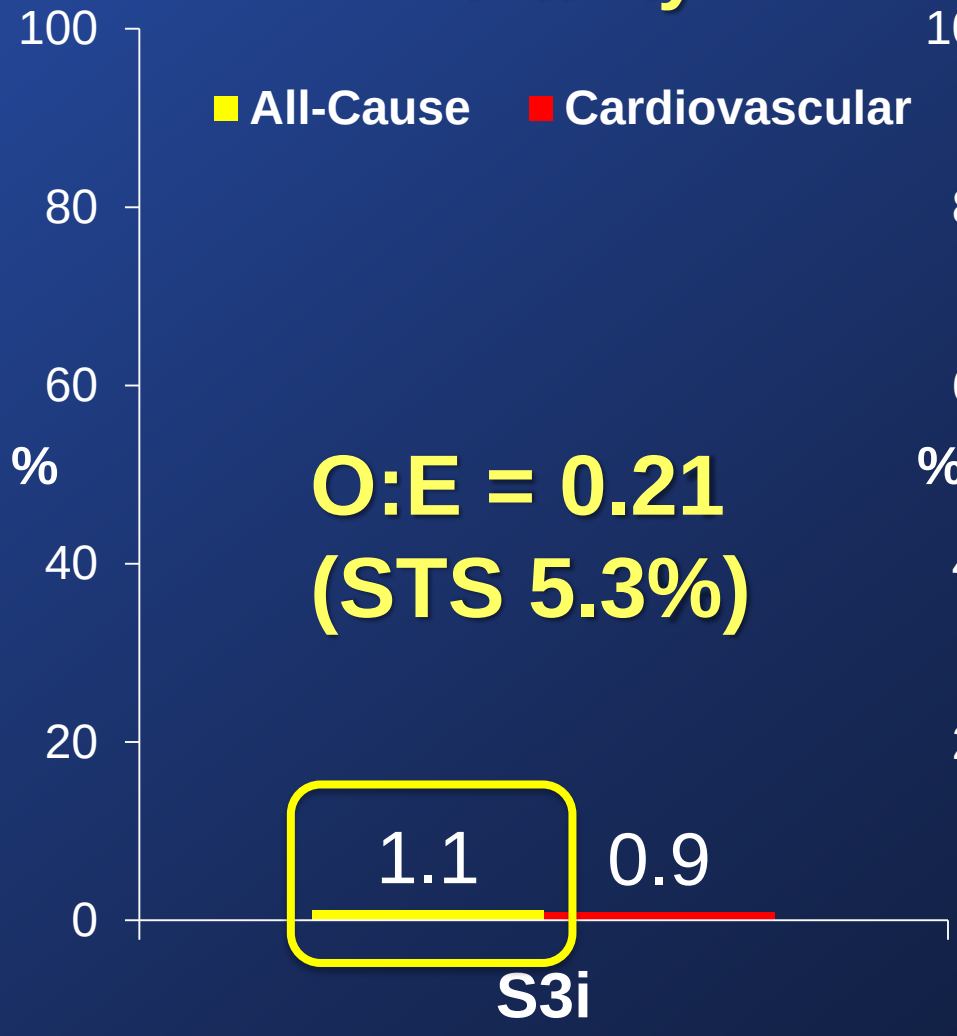


Mortality and Stroke: S3i

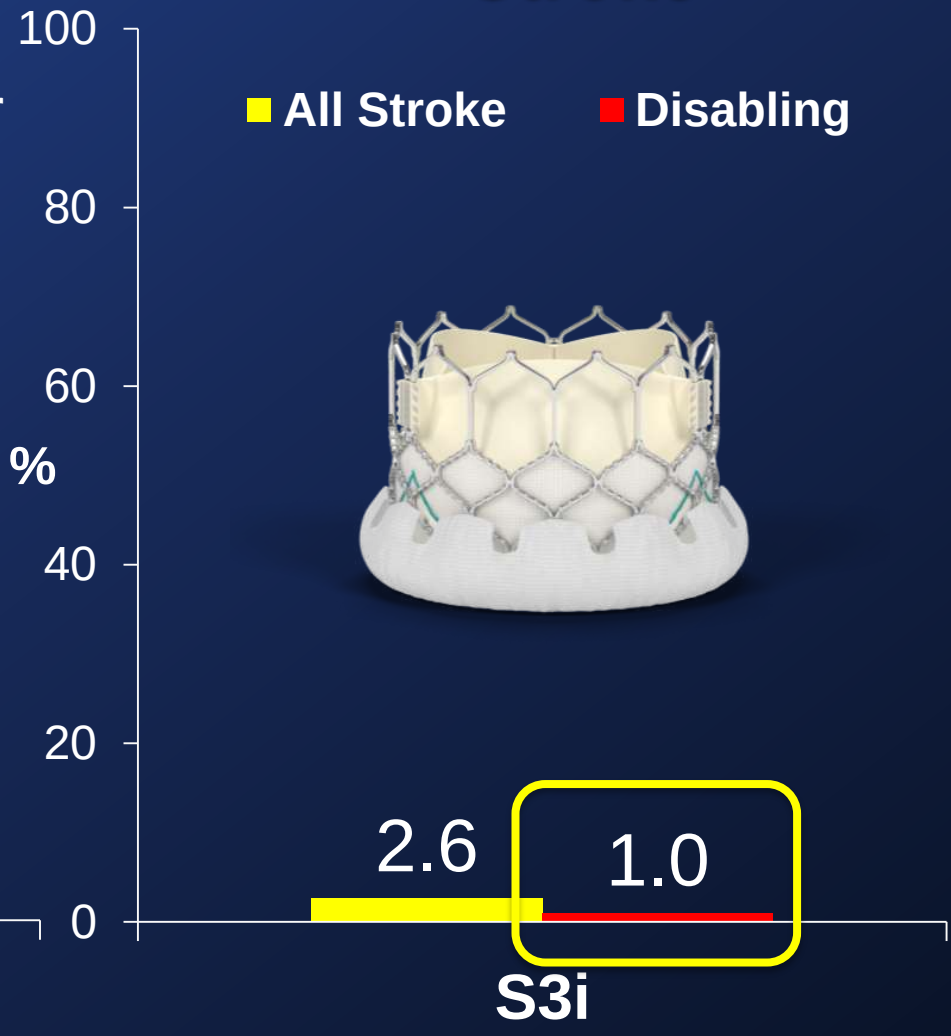
At 30 Days (As Treated Patients)

THE PARTNER II TRIAL

Mortality



Stroke

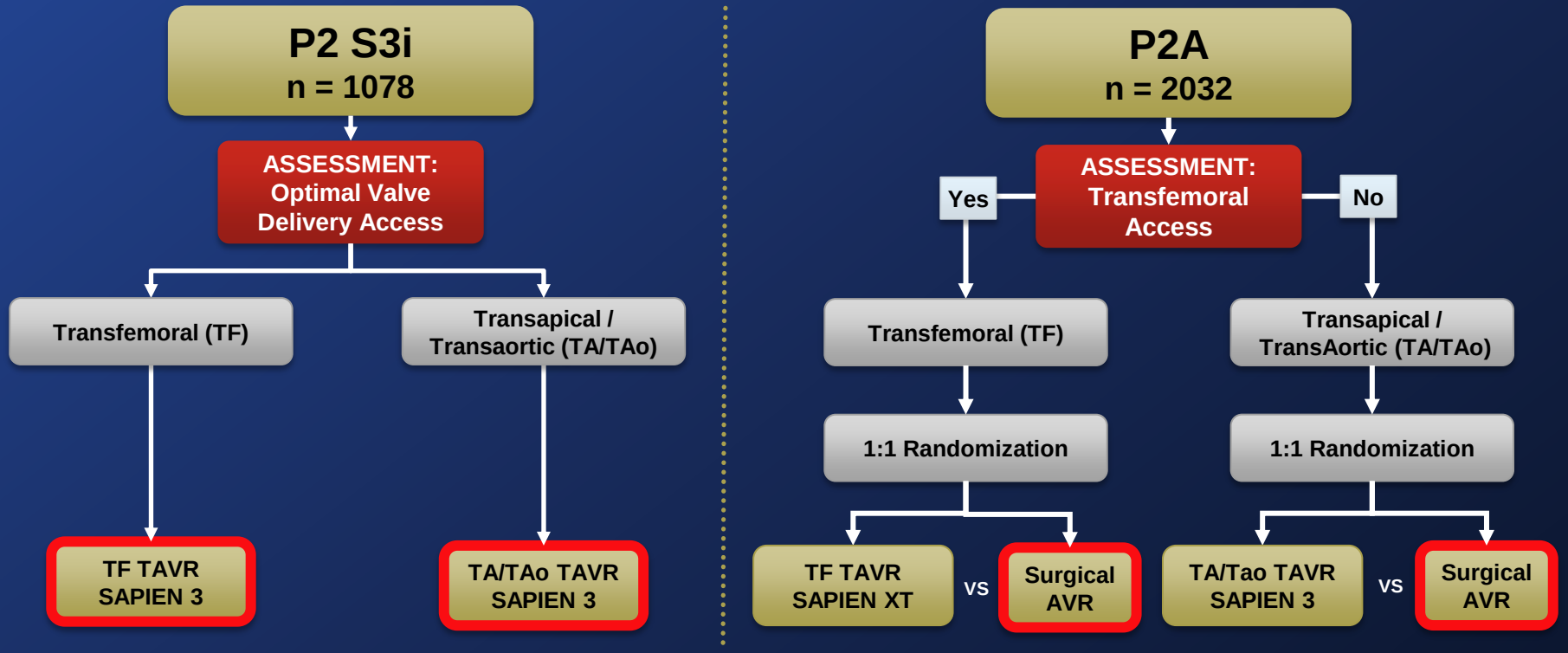


The PARTNER 2A and S3i Trials
Study Design

THE PARTNER II TRIAL

Intermediate Risk Symptomatic Severe Aortic Stenosis

Intermediate Risk ASSESSMENT by Heart Valve Team



Primary Endpoint: All-Cause Mortality, All Stroke, or Mod/Sev AR at One Year (Non-inferiority Propensity Score Analysis)

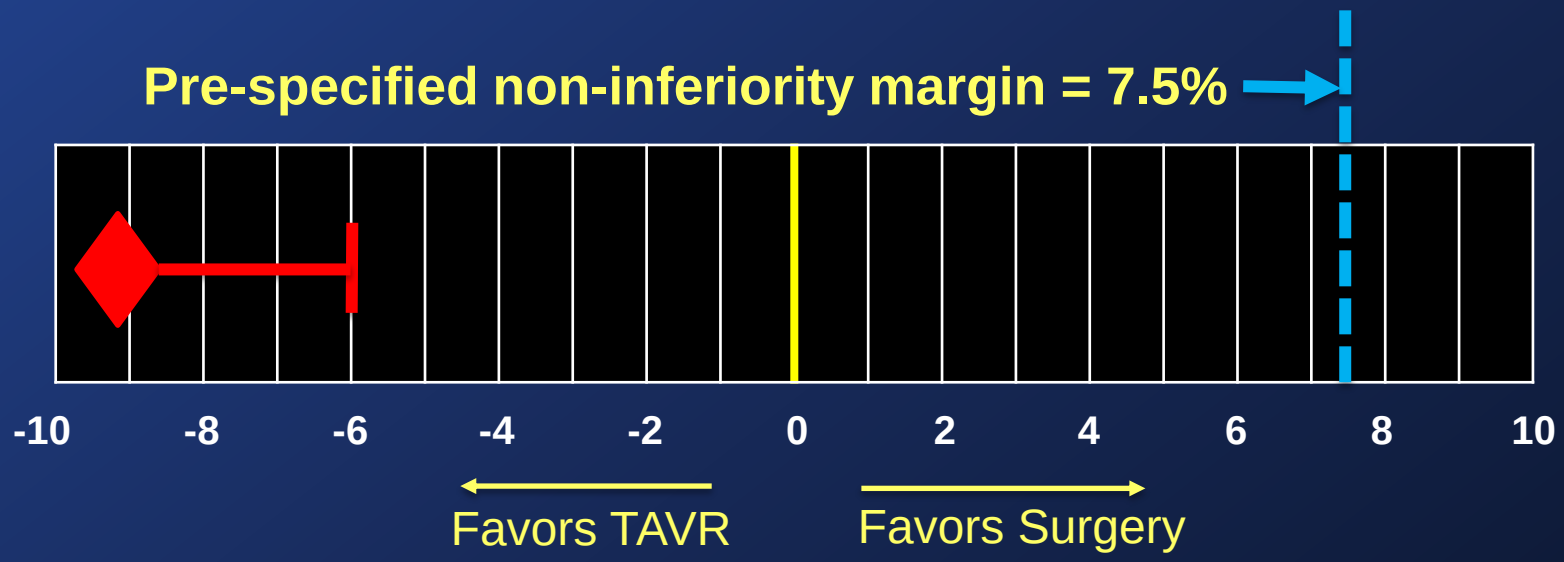
Primary Endpoint - Non-inferiority

Death, Stroke, or AR ≥ Mod at 1 Year (VI)

THE PARTNER II TRIAL

Weighted Difference **-9.2%**
Upper 1-sided 95% CI **-6.0%**

Non-Inferiority
p-value < 0.001



Primary Non-Inferiority Endpoint Met

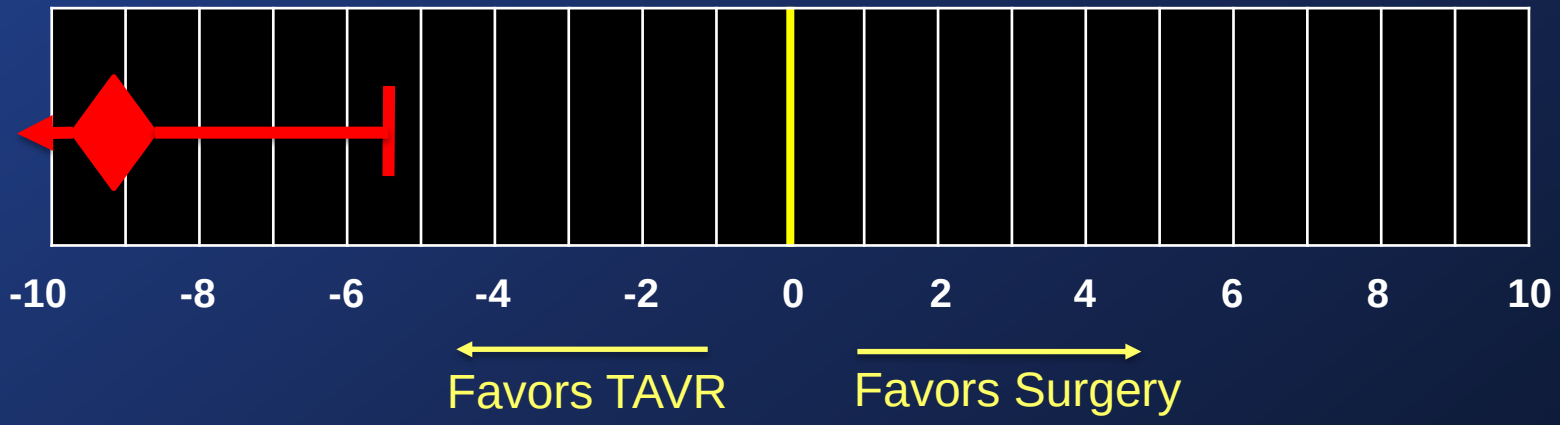
Primary Endpoint - Superiority

Death, Stroke, or AR ≥ Mod at 1 Year (VI)

THE PARTNER II TRIAL

Weighted Difference -9.2%
Upper 2-sided 95% CI -5.4%

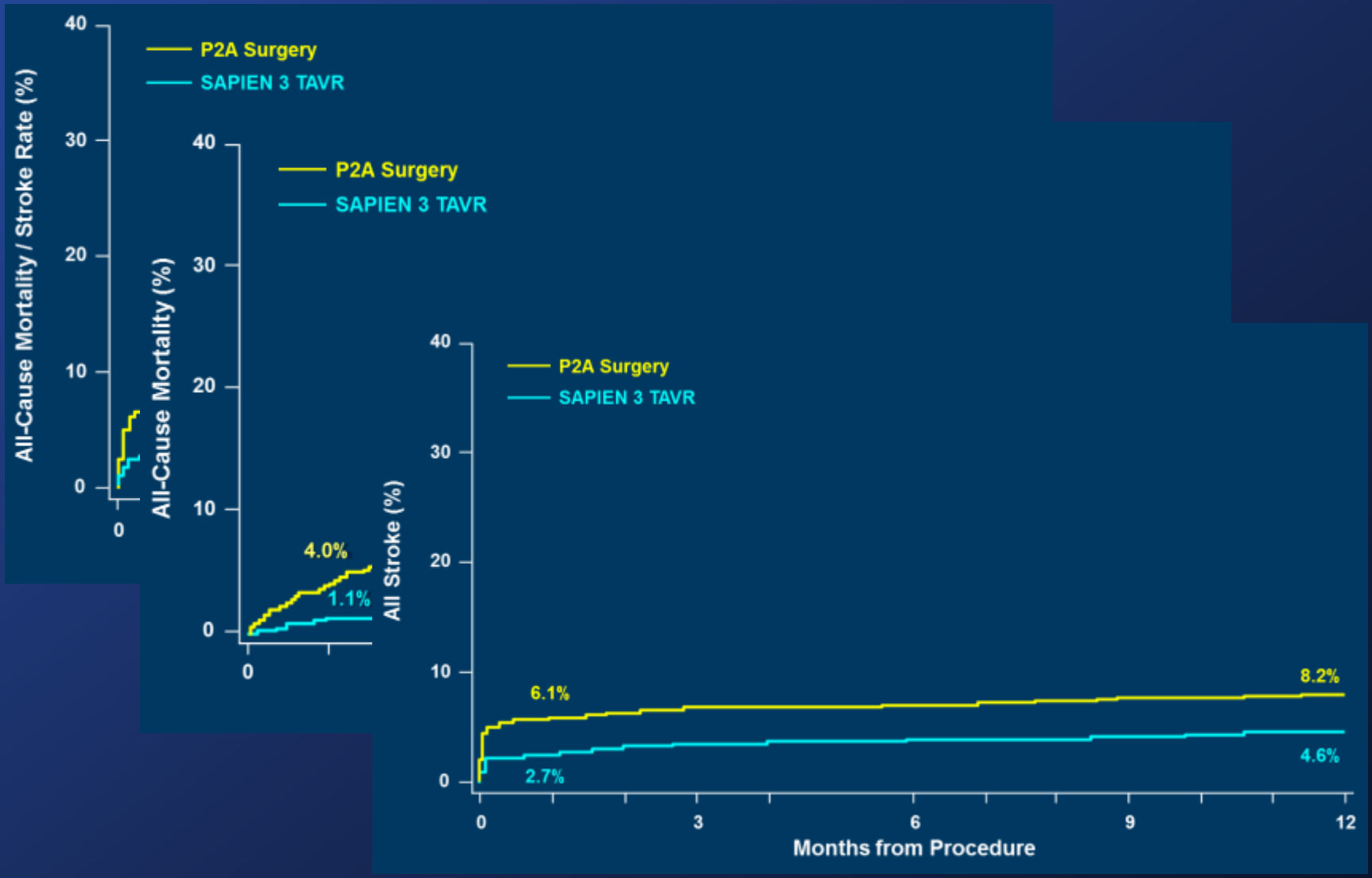
Superiority Testing
p-value < 0.001



Superiority Achieved

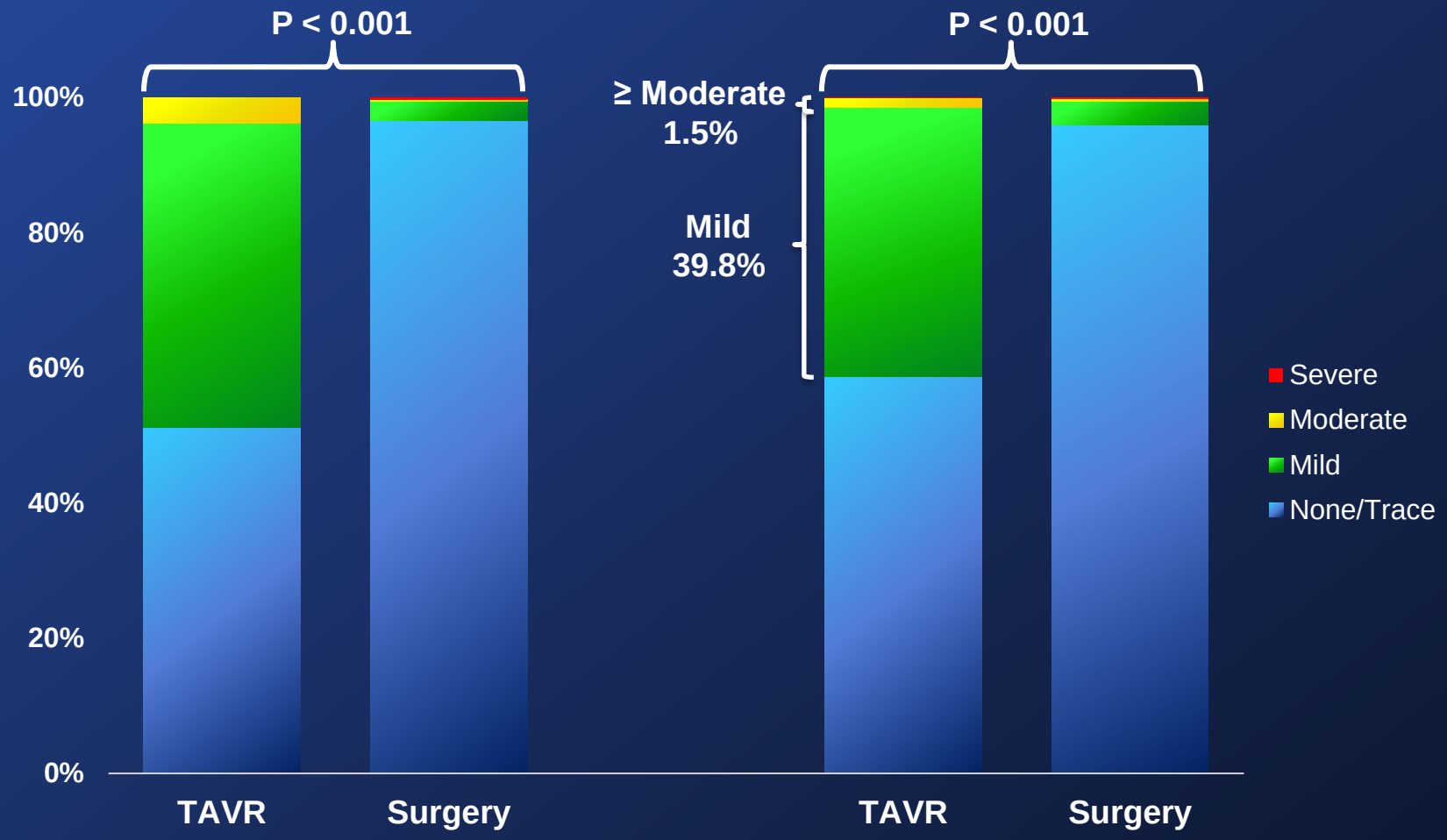
Unadjusted Time-to-Event Analysis
All-Cause Mortality and All Stroke (AT)

THE PARTNER II TRIAL



Paravalvular Regurgitation
3-Class Grading Scheme (VI)

THE PARTNER II TRIAL



No. of echos	30 Days	1 Year
P2A Surgery	755	610
S3i TAVR	992	875

The PARTNER 2A and S3i Trial
Clinical Implications

- The results from the PARTNER 2A randomized trial and the S3i propensity score analysis in > 3,100 intermediate-risk patients with severe aortic stenosis, provide strong evidence that SAPIEN 3 TAVR when compared with surgery *improves clinical outcomes and is the preferred therapy!*

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

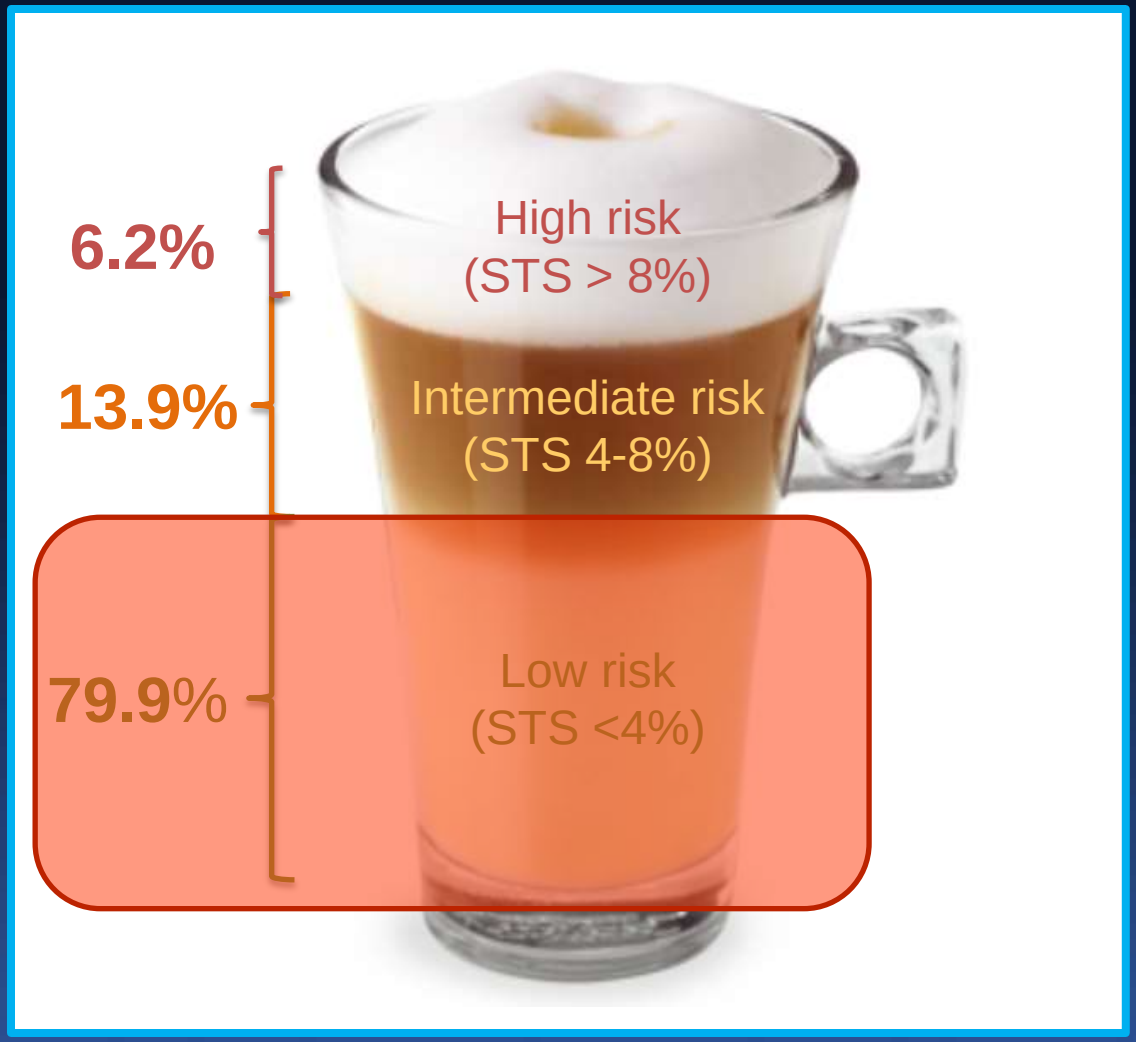
Vinod H Thourani, Susheel Kodali, Raj R Makkar, Howard C Herrmann, Mathew Williams, Vasilis Babaliaros, Richard Smalling, Scott Lim, S Chris Malaisrie, Samir Kapadia, Wilson Y Szeto, Kevin L Greason, Dean Kereiakes, Gorav Ailawadi, Brian K Whisenant, Chandan Devireddy, Jonathon Leipsic, Rebecca T Hahn, 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*

TAVR in 2016: *Future*

- ***TAVR will continue to expand to lower-risk patients and other clinical indications -*** Due to relentless evidence-based clinical research with multiple ongoing and planned clinical trials!

STS database 2002-2010 *(141,905 pts)*



Courtesy of N. Piazza

PARTNER 3 Low Risk Trial

Symptomatic Low-Risk Severe AS Patients

Heart Team determination of risk eligibility (STS < 4)

n=1300

1:1 Randomization

~ 650 pts

~ 650 pts

TAVR (SAPIEN 3)

Surgery (Bioprosthesis)

CT Imaging Sub-Study (n=200)

CT Imaging Sub-Study (n=200)

Primary Endpoint: Composite of all-cause mortality, all strokes, or re-hospitalization at 1 year (non-inferiority)

Expanding Clinical Indications
A TAVR Crossroads?

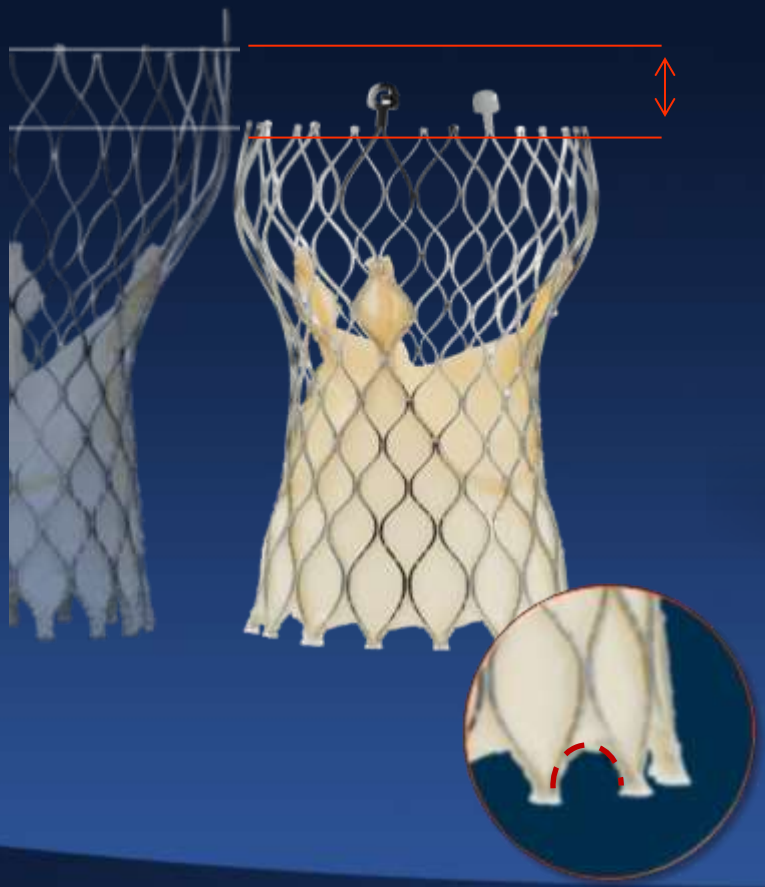
- Bioprosthetic valve failure (aortic and mitral)
- Intermediate and low-risk patients
- Low-flow, low-gradient AS
- Bicuspid AV disease
- AS + concomitant disease (CAD, MR, AF)
- Severe asymptomatic AS
- Moderate AS + CHF
- High-risk AR

TAVR in 2016: *Future*

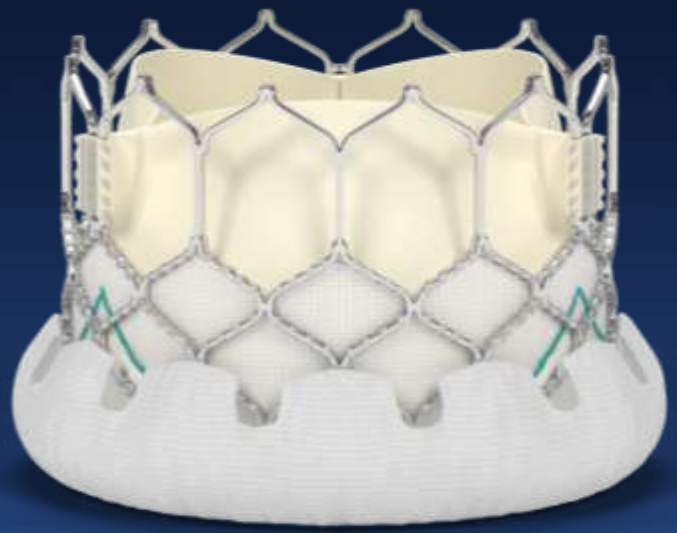
- ***TAVR will continue to expand to lower-risk patients and other clinical indications -*** Due to relentless evidence-based clinical research – multiple ongoing and planned clinical trials!
- ***TAVR associated technology advances will continue to favorably impact clinical outcomes and help to simplify procedures***
  - new TAVR systems
  - accessory technologies
  - advanced imaging systems

Current "Standards" for TAVR

MDT Evolut R



Edwards Sapien 3



TAVR Systems

Global Inventory (#23)

Currently In Patients

- Sapien 3
- Evolut R
- Sy
- E gager
- Portico
- Centera

Future Contenders?

- Venus A
- Shanghai Valve
- Trin ty
- Co
- Va
- MyVal
- HLT
- NVT (Germany)
- Zurich TEHV

Claret Sentinel
Cerebral Protection System (CPS)

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 in 2016: *Future*

- ***TAVR growth will be highly dependent upon strategies to manage high-cost technologies in constrained healthcare systems and a healthy dose of "humility" (recognizing and addressing "gap" areas)***
  - site management; operational and economic efficiencies
  - emphasize the multi-disciplinary heart team
  - known unknowns and new imponderables (subclinical valve thrombosis, valve durability, and optimal pharmacotherapy)

TAVR in 2016: *Economic Considerations*

Warning: Medicare May Be Bad for Your Heart

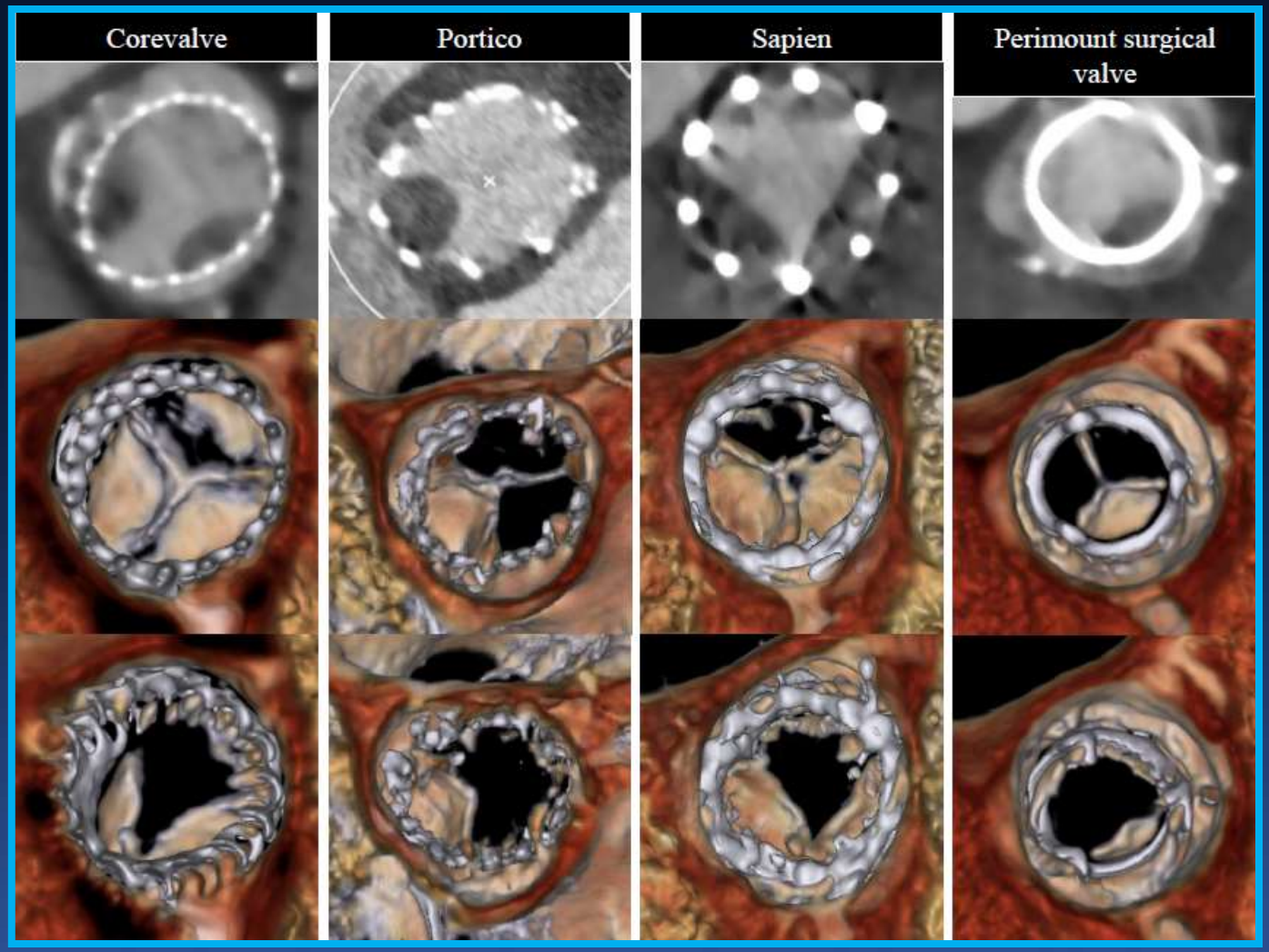
Aortic valve replacements are superior to open-heart surgery and less risky. So why are they hard to get?

By
SCOTT GOTTLIEB
April 11, 2016 7:14 p.m. ET
324 COMMENTS

Wall Street Journal
April 11, 2016

Can we afford to use the best therapies for our patients?

Valve Leaflet Abnormalities



Makkar, et al. NEJM 2015

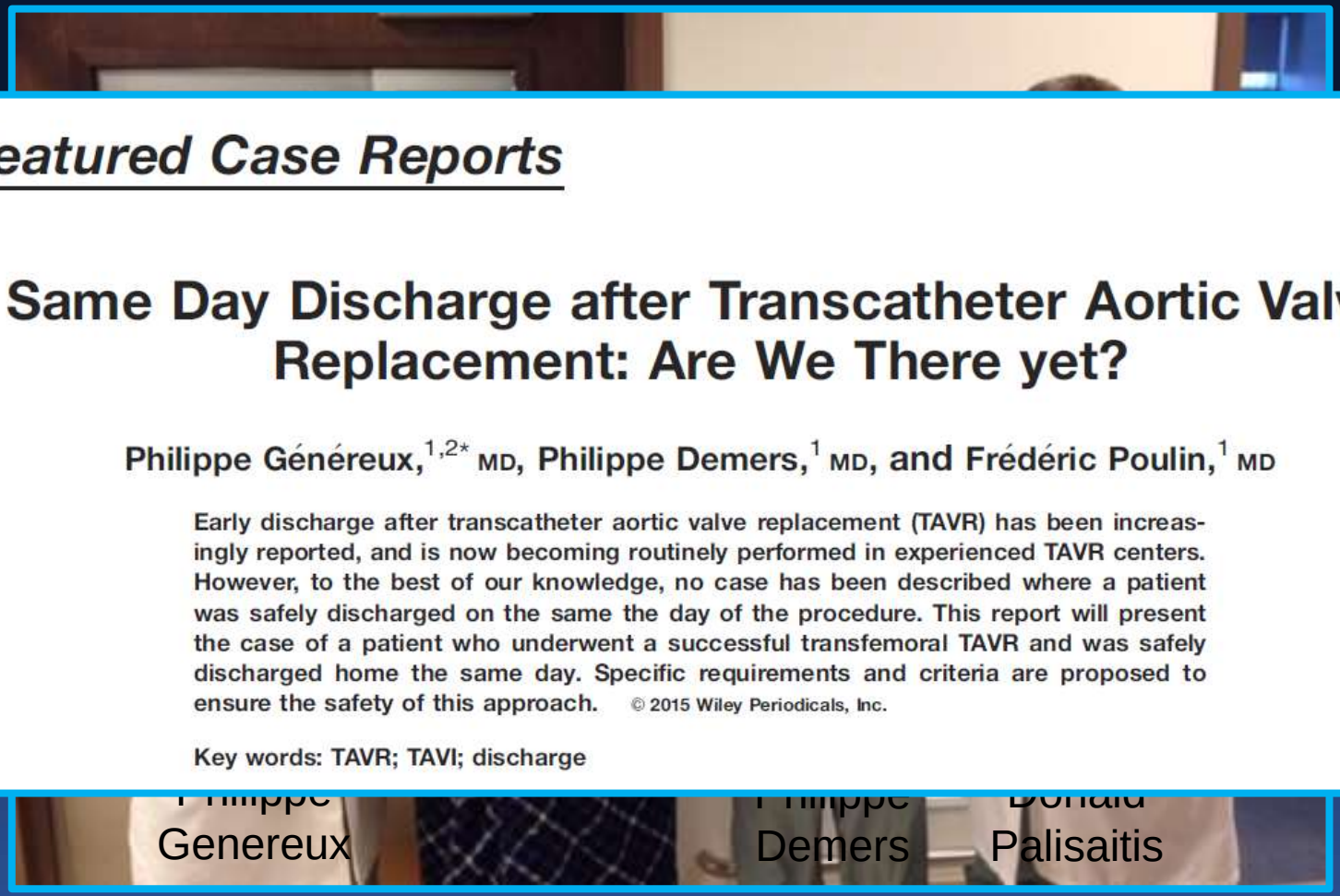
TAVR Adjunct Pharmacology

Customized Patient-Based Therapy

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

"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

Expanded TAVR Clinical Indications

A Transformative Technology at the Crossroads?