TAVR in Lower Risk Patients

Martin B. Leon, MD

Columbia University Medical Center
Cardiovascular Research Foundation
New York City

8 mins

April 26, 2016

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

Dr. Alain Cribier

First-in-Man PIONEER

April 16, 2002

In the Beginning, TAVR was…

- A niche procedure designed primarily to address the growing dilemma of *high surgical risk AS patients, esp. in the elderly*
- An “experimental” complex procedure with *frequent complications*
- A procedure with *unknown bioprosthetic valve durability*

In the Beginning, TAVR was…

Given these circumstances, it made sense to initially restrict TAVR to only those patients where surgery was either high-risk or could not reasonably be performed (usually in the elderly).

The severe AS-T

- Old…very old…
- Frail…very frail
- Lots of co-morbidi
  - Prior CABG (po
  - CKD
  - Severe COPD
  - PVD
  - Chronic AF
  - Cancer in remis

But still enjoying life !

Now, TAVR is…

- A *common procedure* with *low complications* which has become an effective and respected therapy for patients with AS
- The combination of better case selection, simplified procedural methods, and enhanced technology has resulted in *consistent clinical outcomes* across a wide range of operators and institutions
- A procedure with *known excellent mid-term valve durability*

Now, TAVR is…

Given these circumstances, it no longer makes sense to restrict TAVR based upon either age considerations or an imprecise and non-validated risk stratification algorithm!

My Primary Thesis…

TAVR should be the procedure of choice in *All-Comer* severe AS patients, *regardless of risk status!*

To Accept this Primary Thesis Requires…

1. *A "suspension of belief"* (uncoupling from the past)

2. *A reasonable body of evidence* (parity or superiority vs. surgery - mortality, strokes, QOL, valve performance, secondary benefits)

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!

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

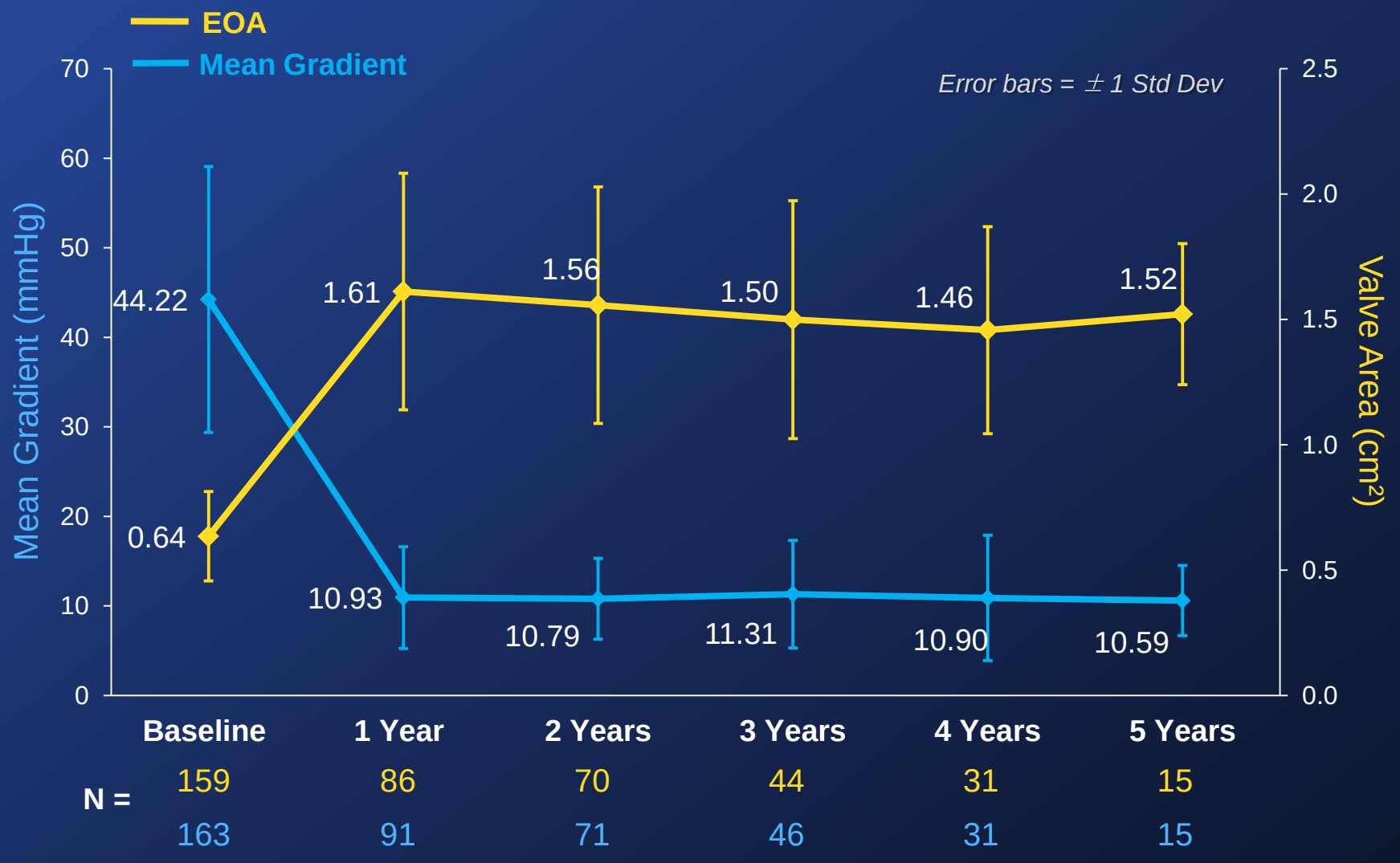
5-year outcomes of transcatheter aortic valve replacement compared with standard treatment for patients with inoperable aortic stenosis (PARTNER 1): a randomised controlled trial

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*

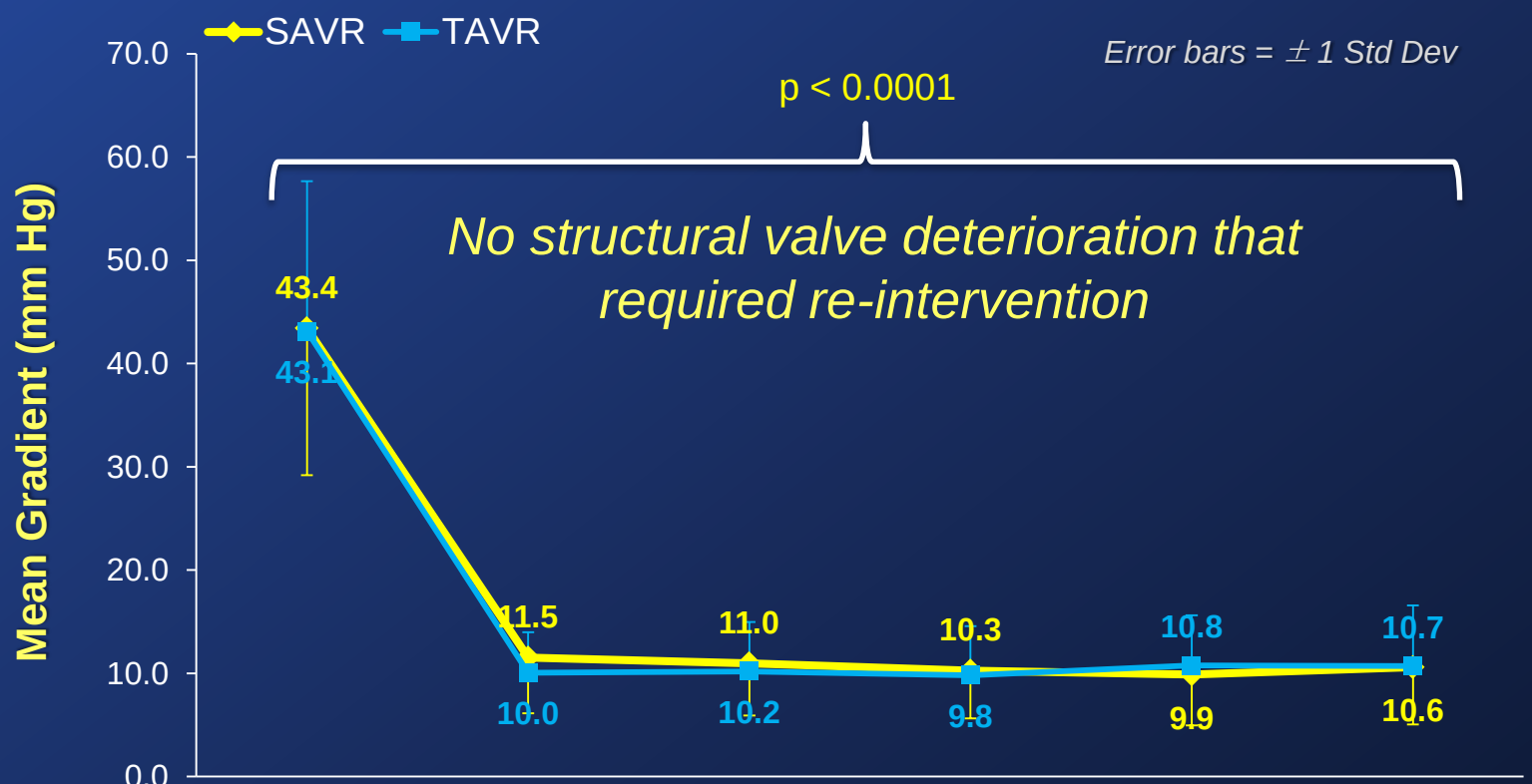
5-year outcomes of transcatheter aortic valve replacement or surgical aortic valve replacement for high surgical risk patients with aortic stenosis (PARTNER 1): a randomised controlled trial

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

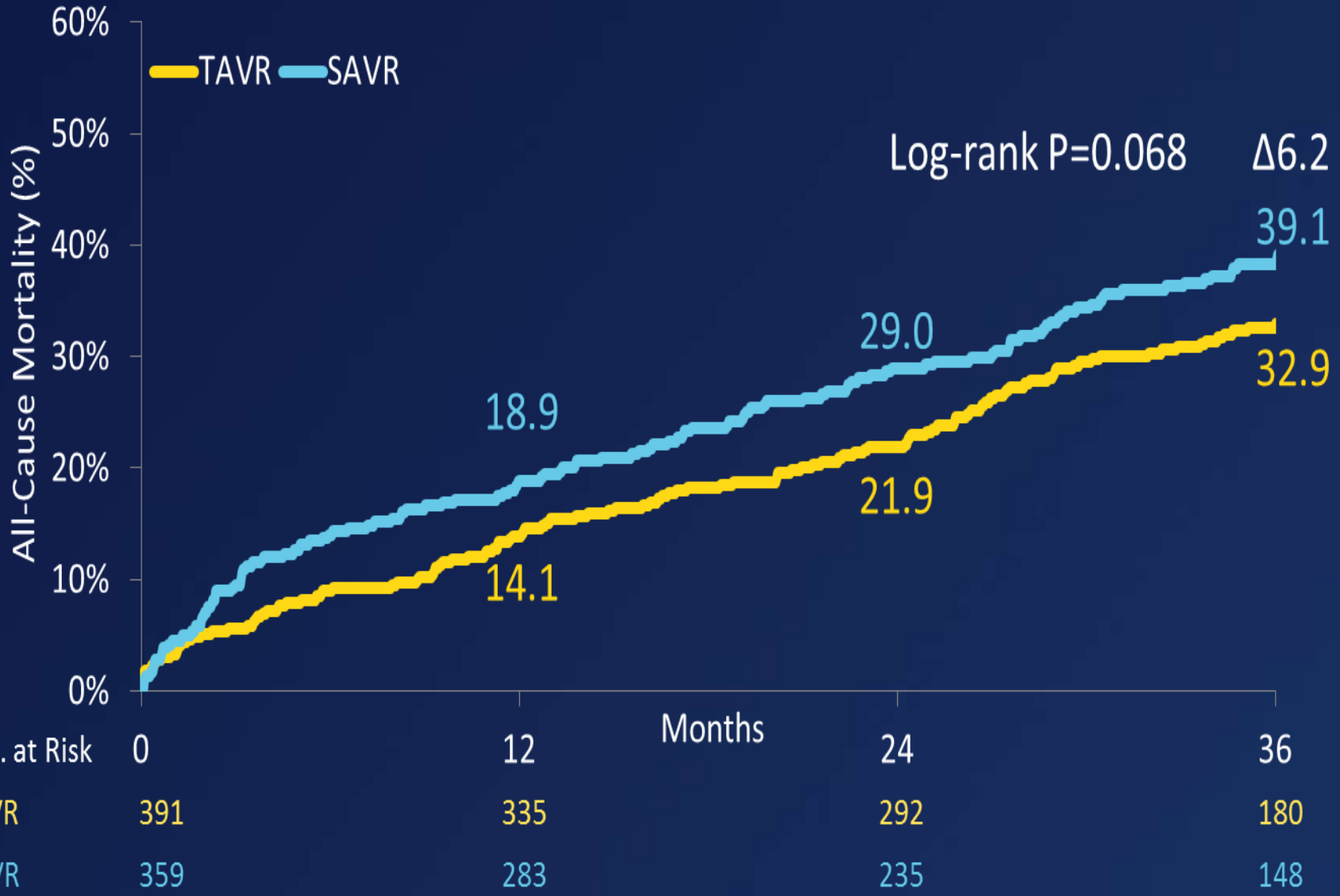


Aortic Valve Mean Area (AT)
P1A - All Patients

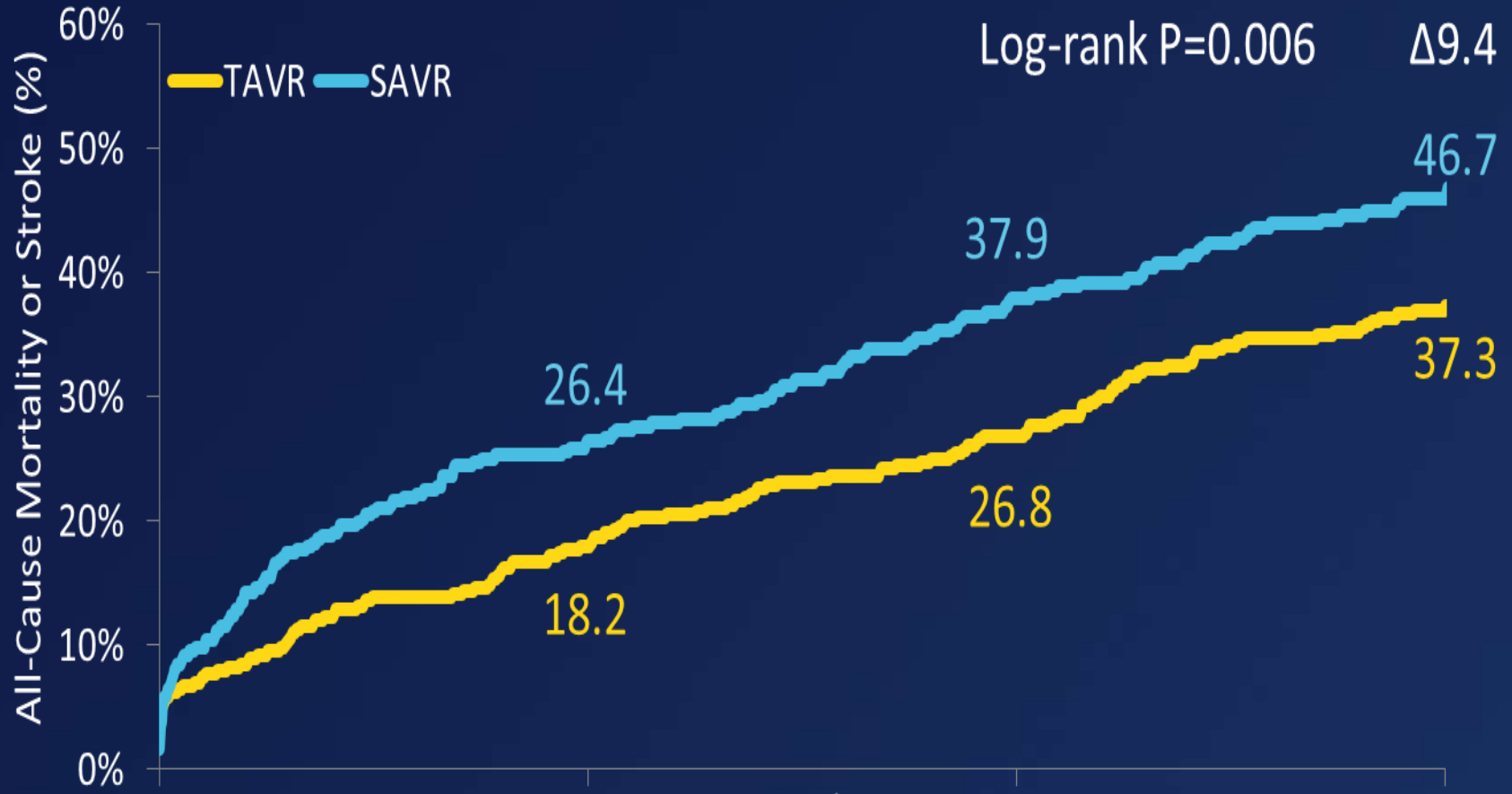


	Baseline	1 Year	2 Year	3 Year	4 Year	5 Year
TAVR	310	219	156	106	79	56
SAVR	299	158	123	86	61	48

All-Cause Mortality

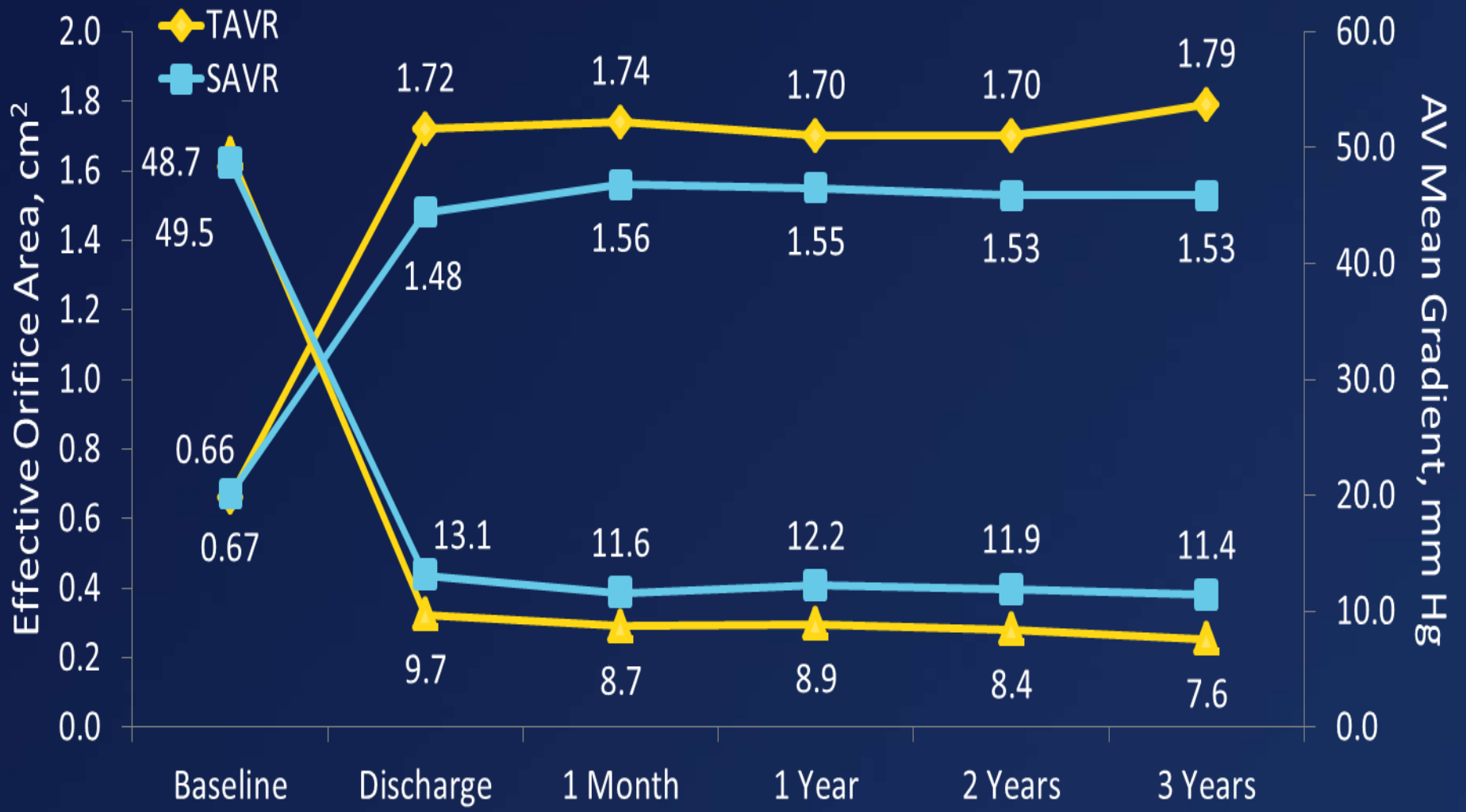


All-Cause Mortality or Stroke



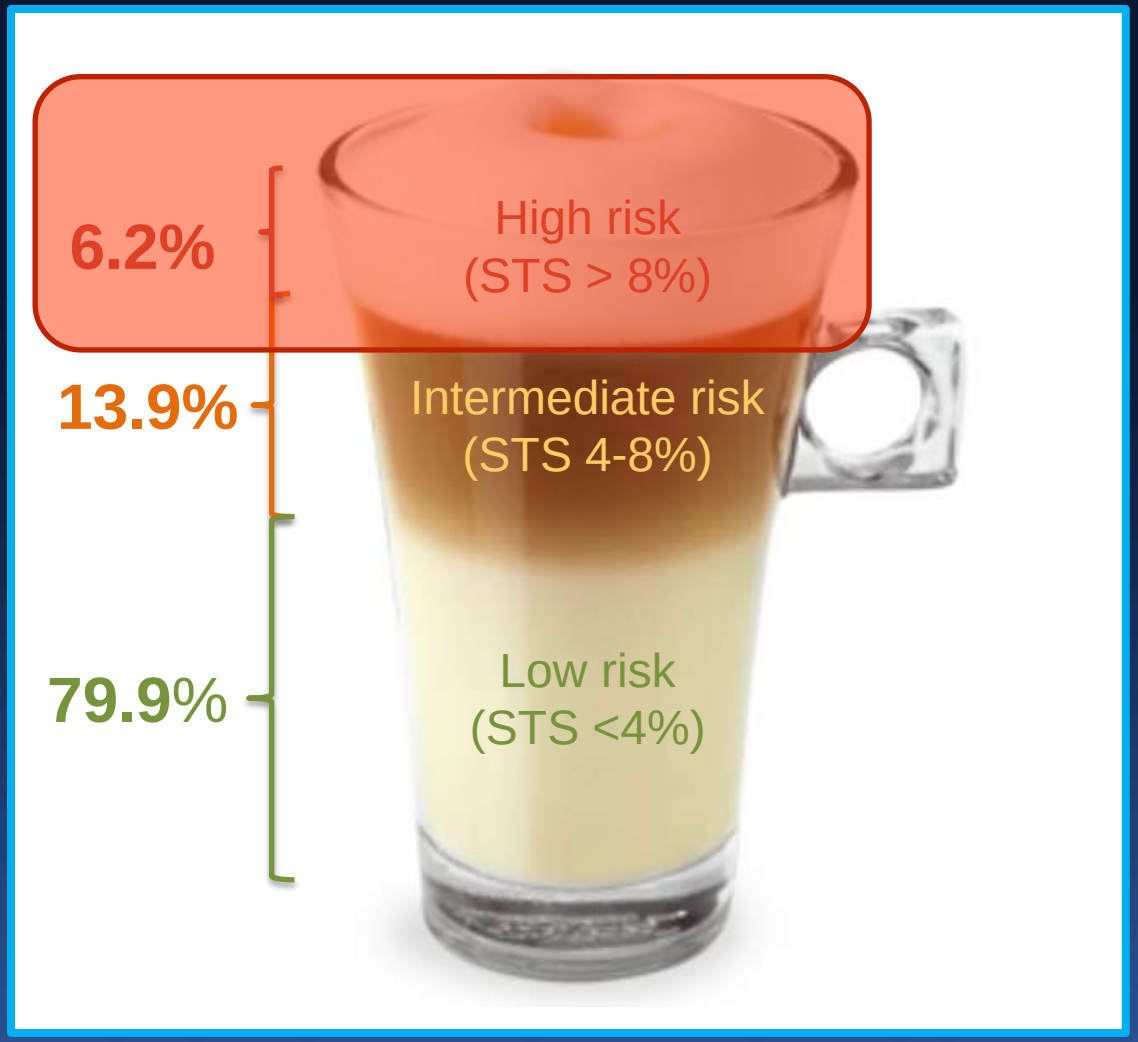
Valve Hemodynamics*

CoreValve had significantly better valve performance vs SAVR at all follow-ups (P<0.001)



*Site-reported

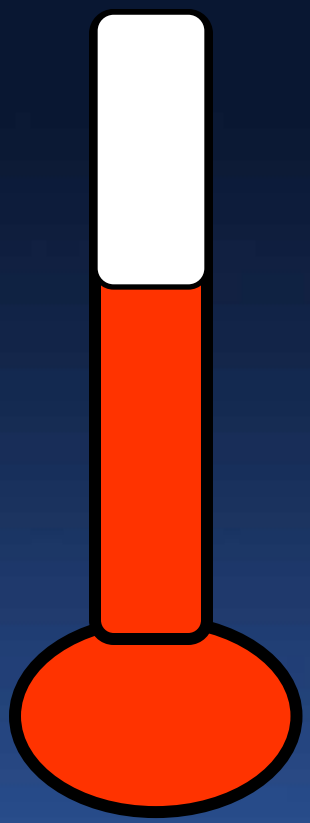
STS database 2002-2010 *(141,905 pts)*



Courtesy of N. Piazza

TAVR for Lower-Risk Patients

The "Modern" TAVR Era



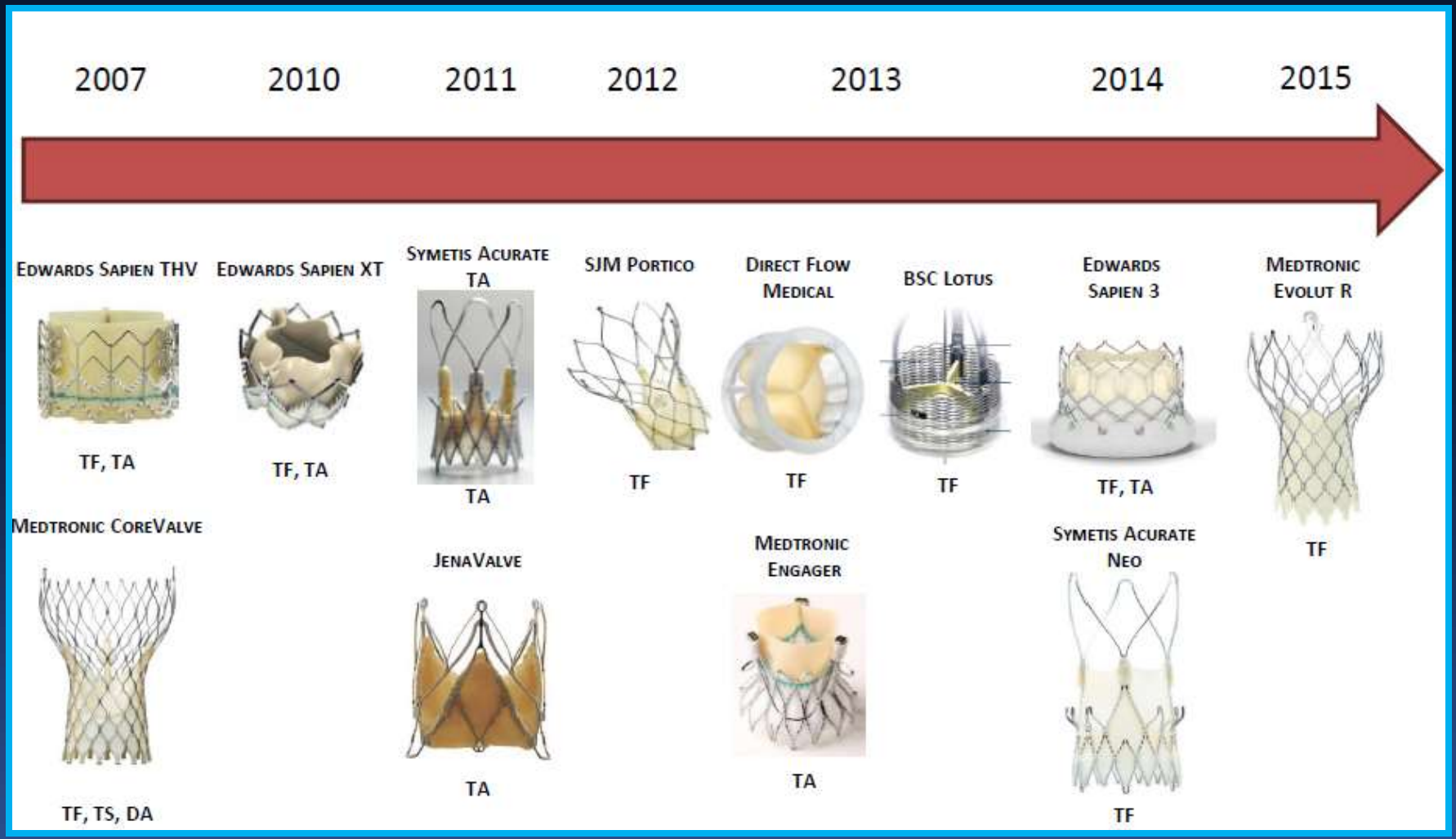
- Evidence-based outcomes (indications)
- Procedural considerations
- Technology evolution

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

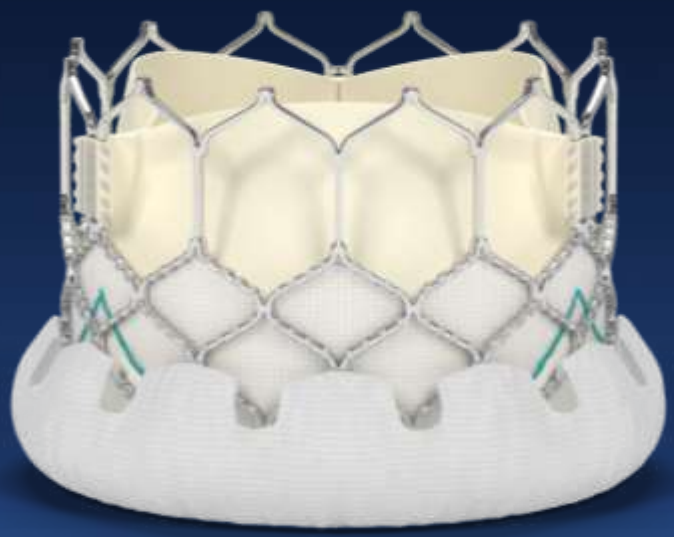
TAVR Systems with CE-Approval (2007-15)



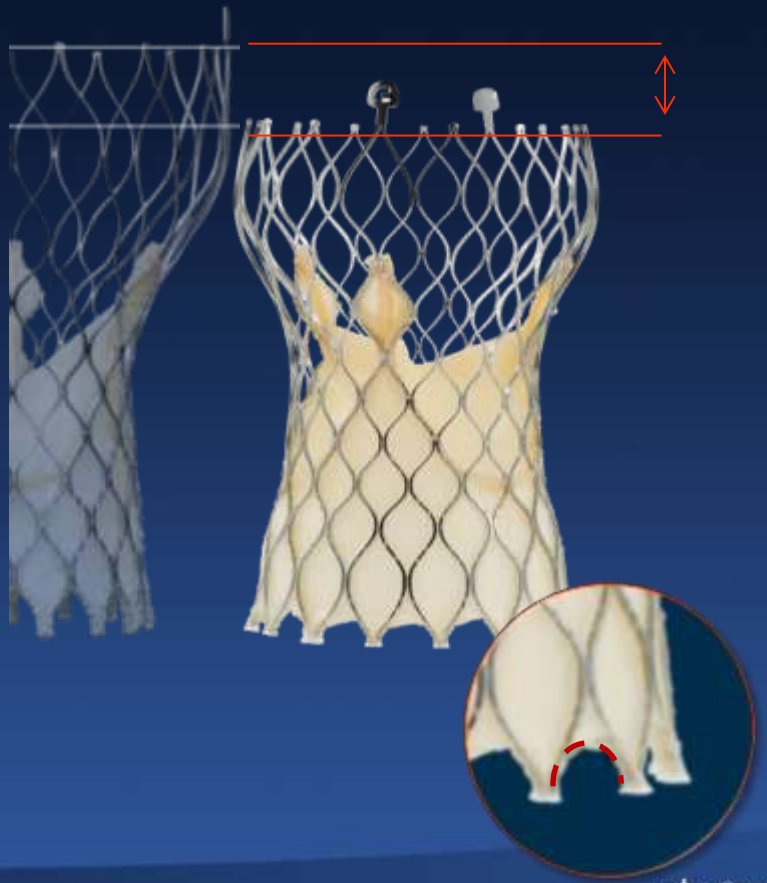
Courtesy of S. Windecker

Current "Standards" for TAVR

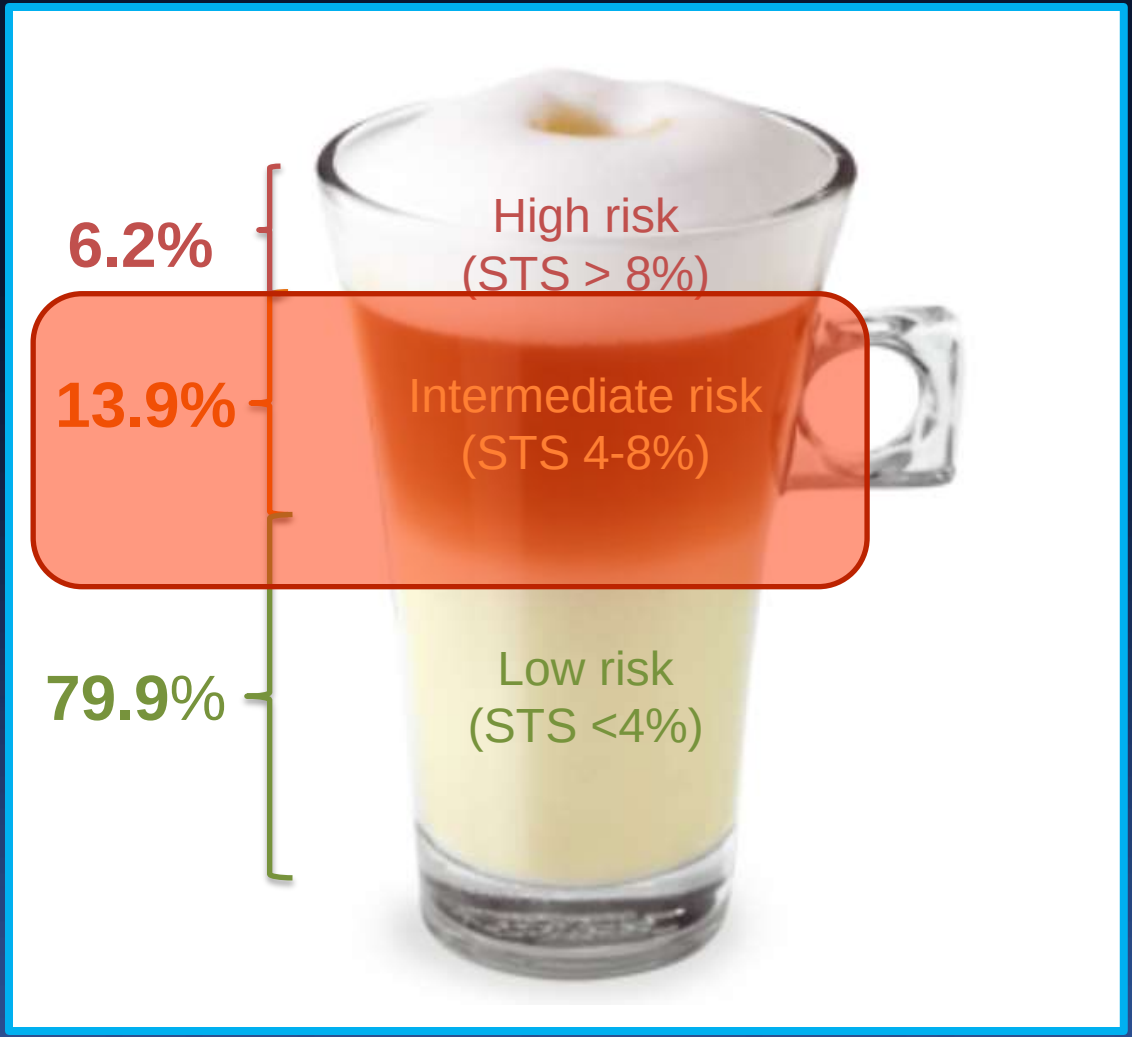
Edwards Sapien 3



MDT Evolut R



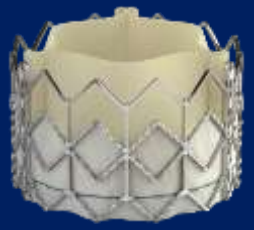
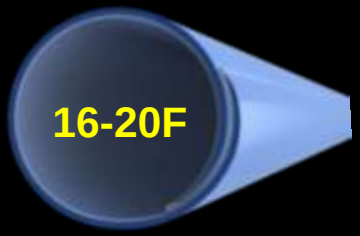
STS database 2002-2010 *(141,905 pts)*



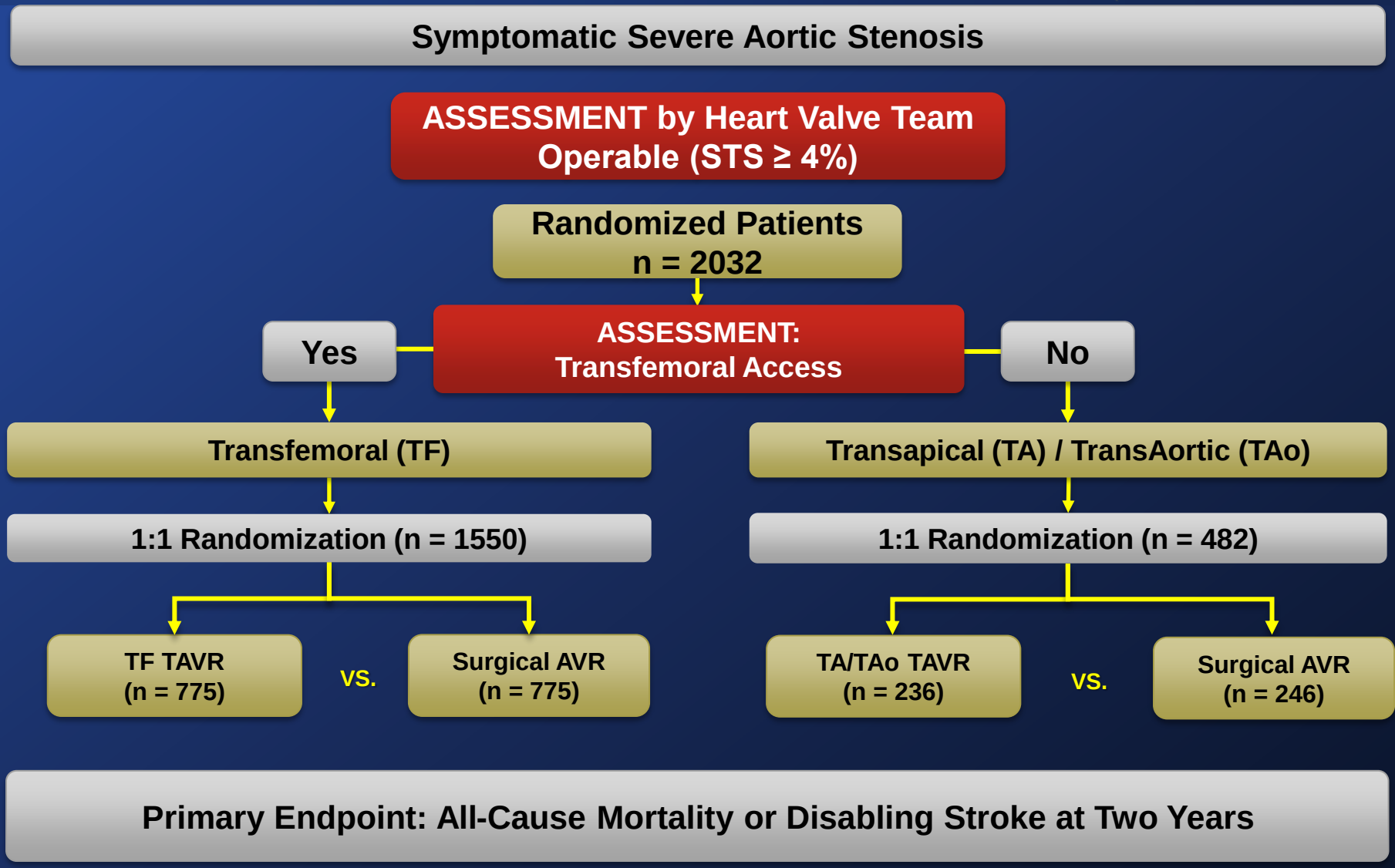
Courtesy of N. Piazza

PARTNER SAPIEN Platforms
Device Evolution

THE PARTNER II TRIAL

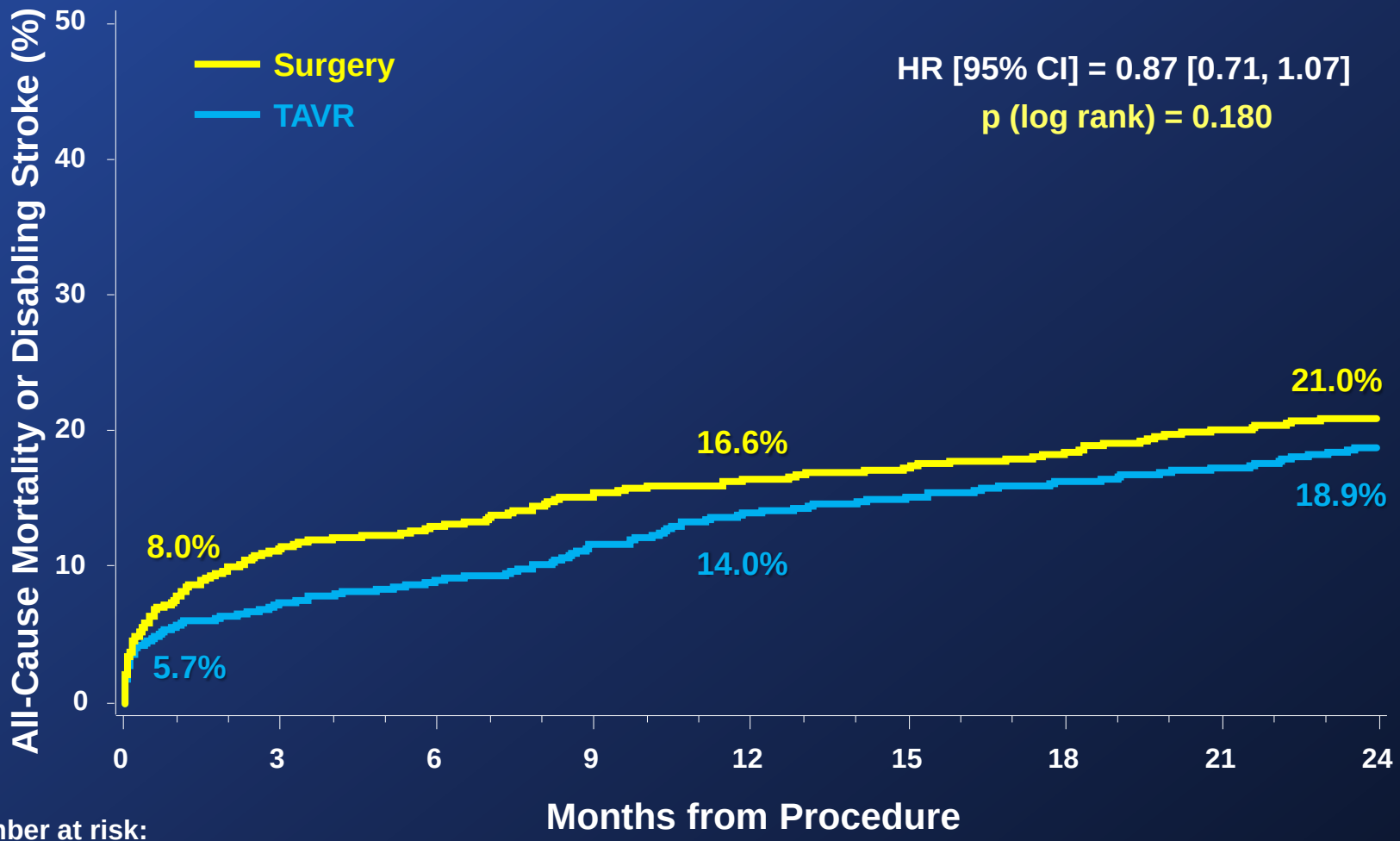
	SAPIEN	SAPIEN XT	SAPIEN 3
Valve Technology			
Sheath Compatibility			
Available Valve Sizes	 23 mm 26 mm	 23mm 26mm 29mm 20 mm 23 mm 26 mm 29 mm	

The PARTNER 2A Trial
Study Design



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

THE PARTNER II TRIAL

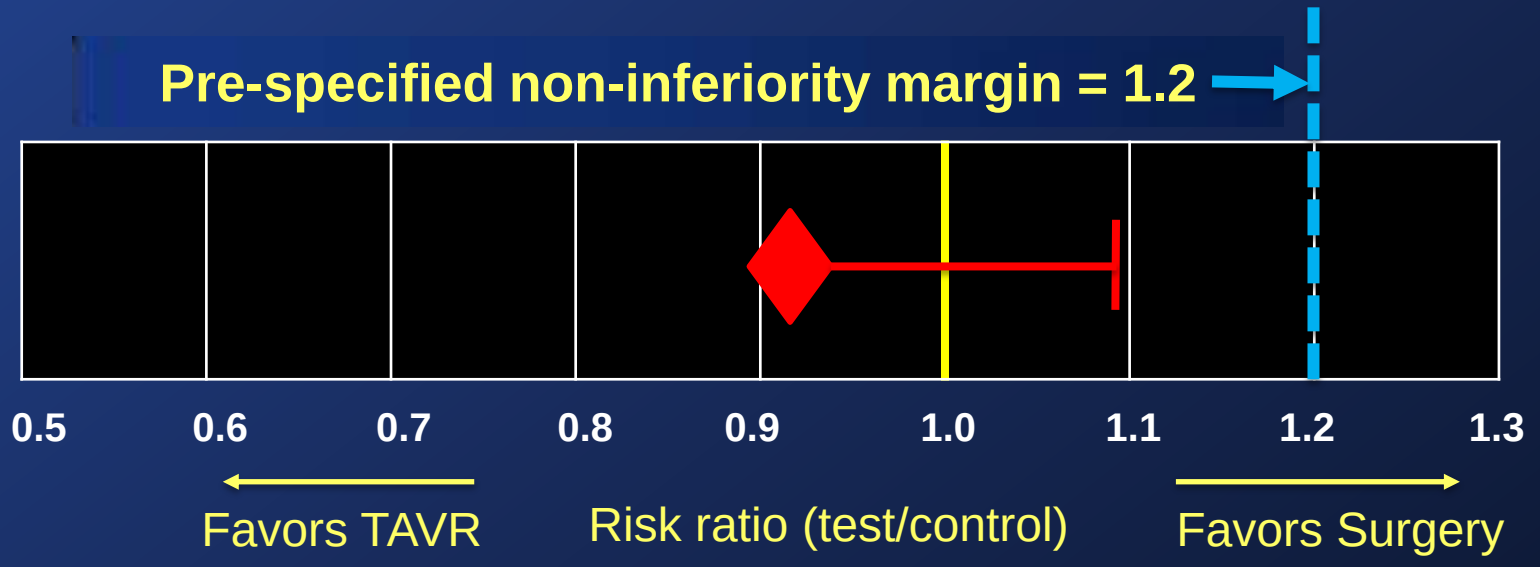


Number at risk:									
Surgery	944	826	807	779	766	743	731	715	694
TAVR	994	917	900	870	842	825	811	801	774

Primary Endpoint (ITT)
All-cause Mortality or Disabling Stroke

THE PARTNER II TRIAL

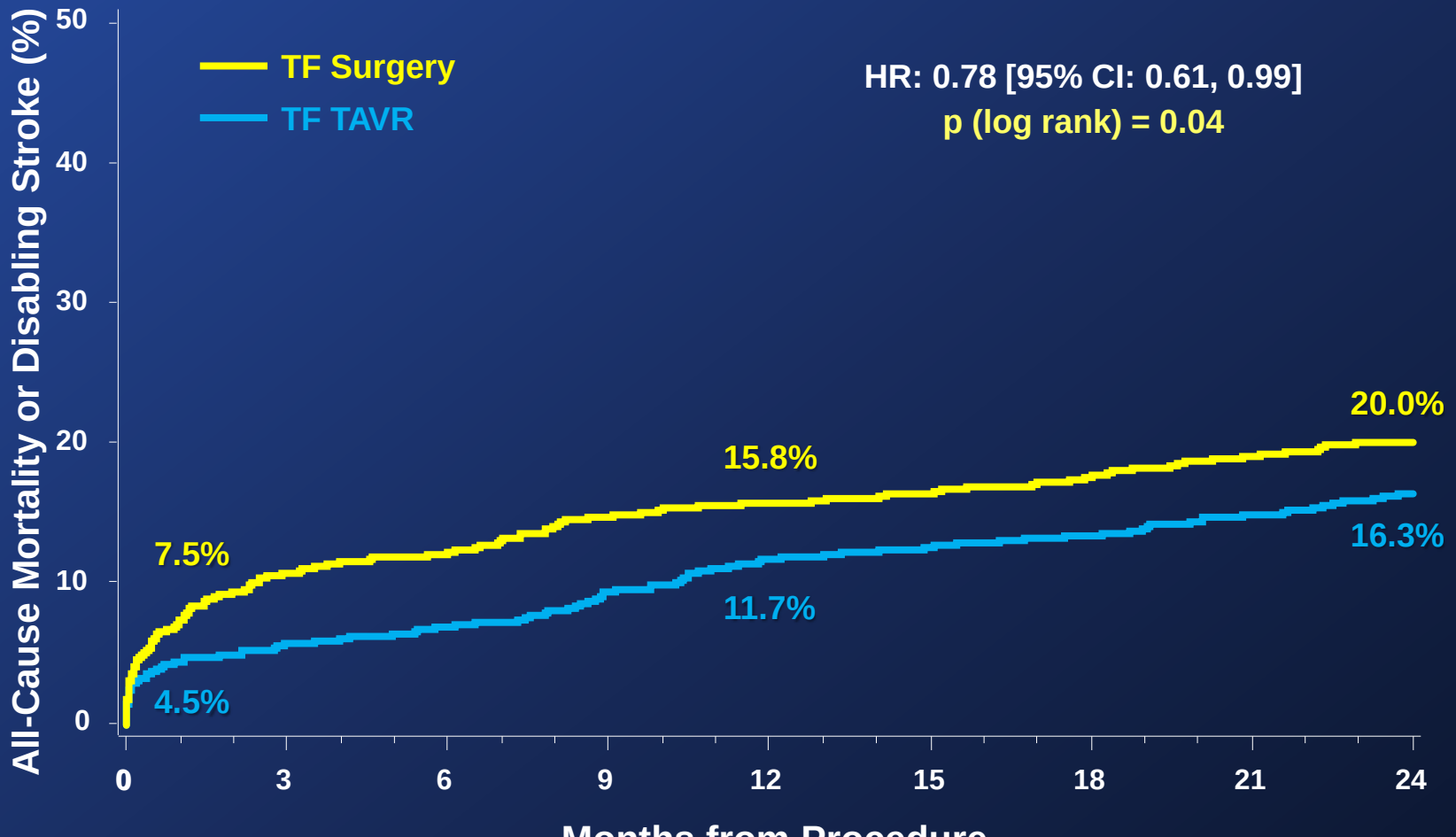
TAVR	SAVR		
n = 1011	n = 1021	Relative Risk Ratio 0.92	Non-Inferiority
19.3%	21.1%	Upper 1-sided 97.5%CI 1.09	p-value = 0.001



Primary Non-Inferiority Endpoint Met

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

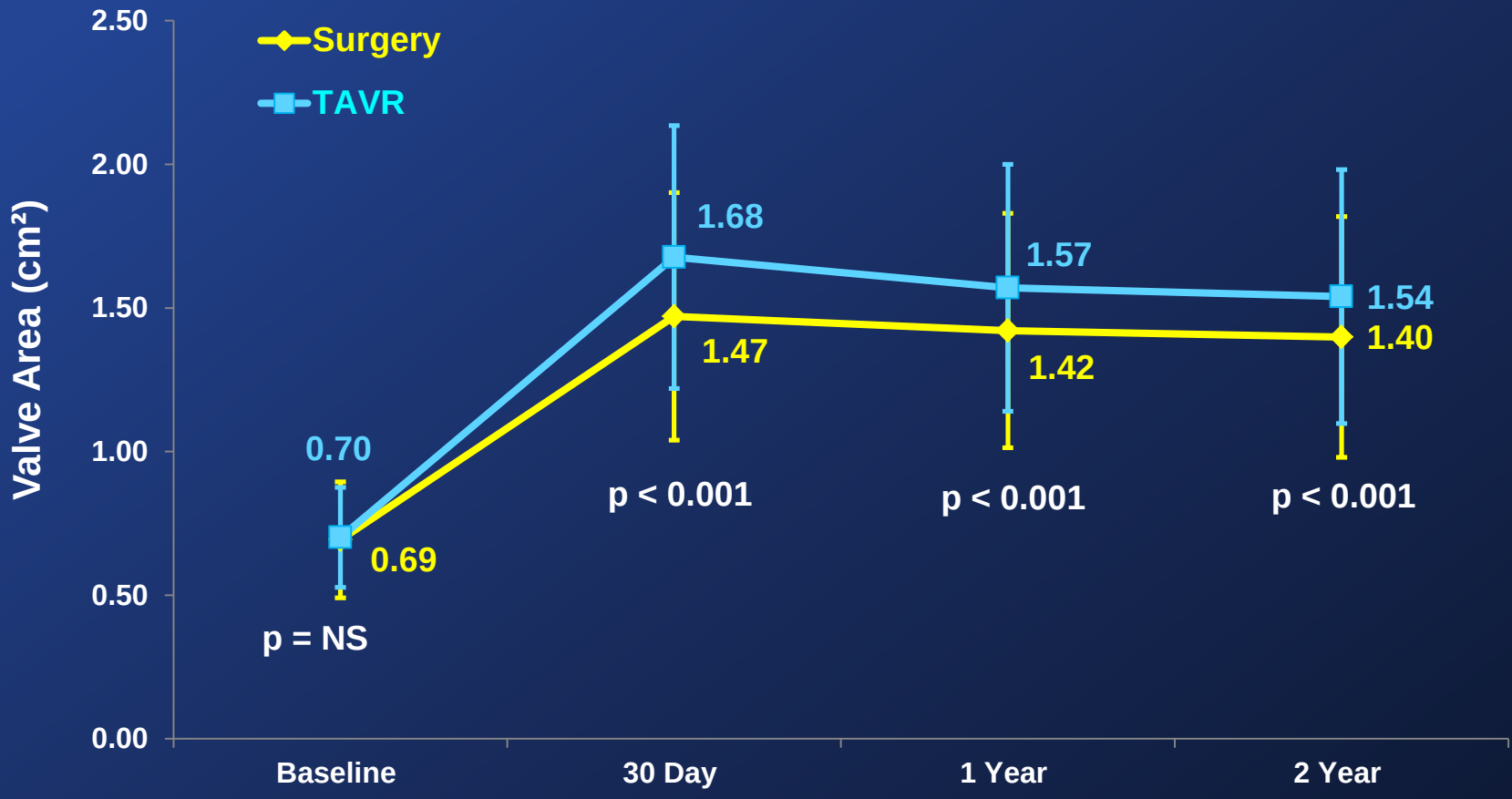
Other Clinical Endpoints (ITT)
At 30 Days and 2 Years

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

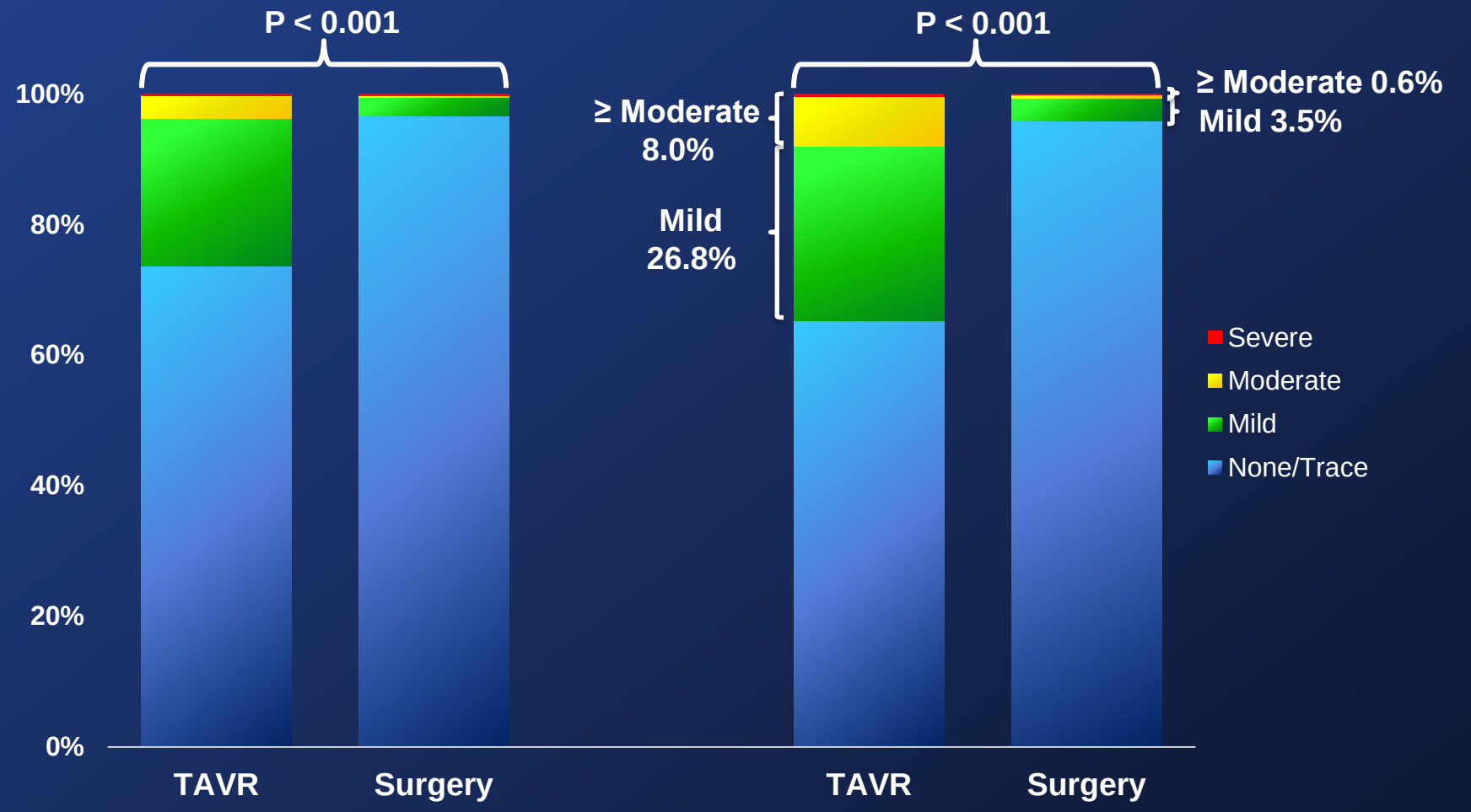


No. of Echos				
Surgery	861	727	590	488
TAVR	899	829	695	567

Error bars represent ± Standard Deviation

Paravalvular Regurgitation (VI)
3-Class Grading Scheme

THE PARTNER II TRIAL



No. of echos	30 Days	2 Years
TAVR	872	600
Surgery	757	514

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

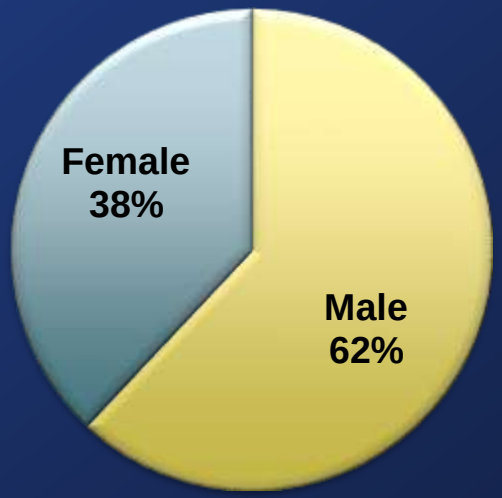
Average STS =

5.3%

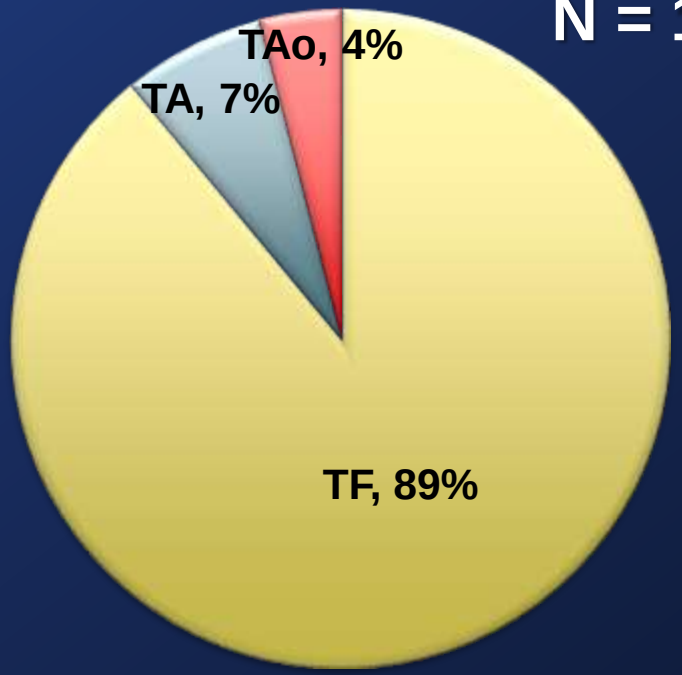
(Median 5.2%)

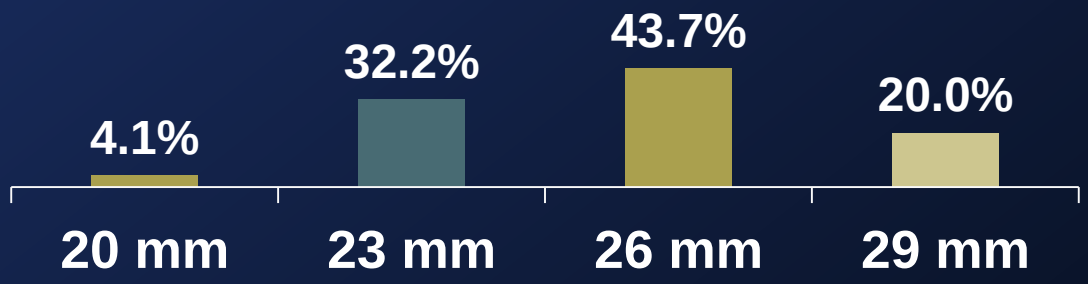
Average Age =

81.9yrs



N = 1076



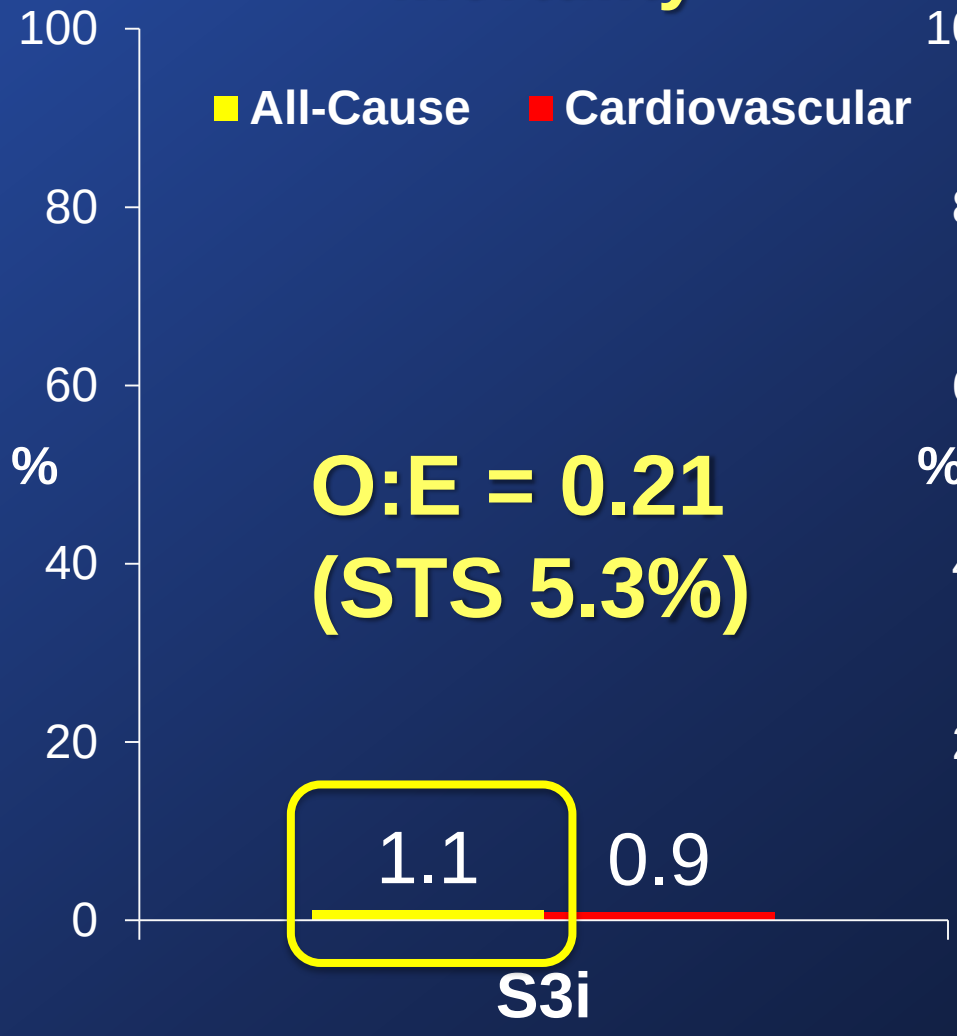


Mortality and Stroke: S3i

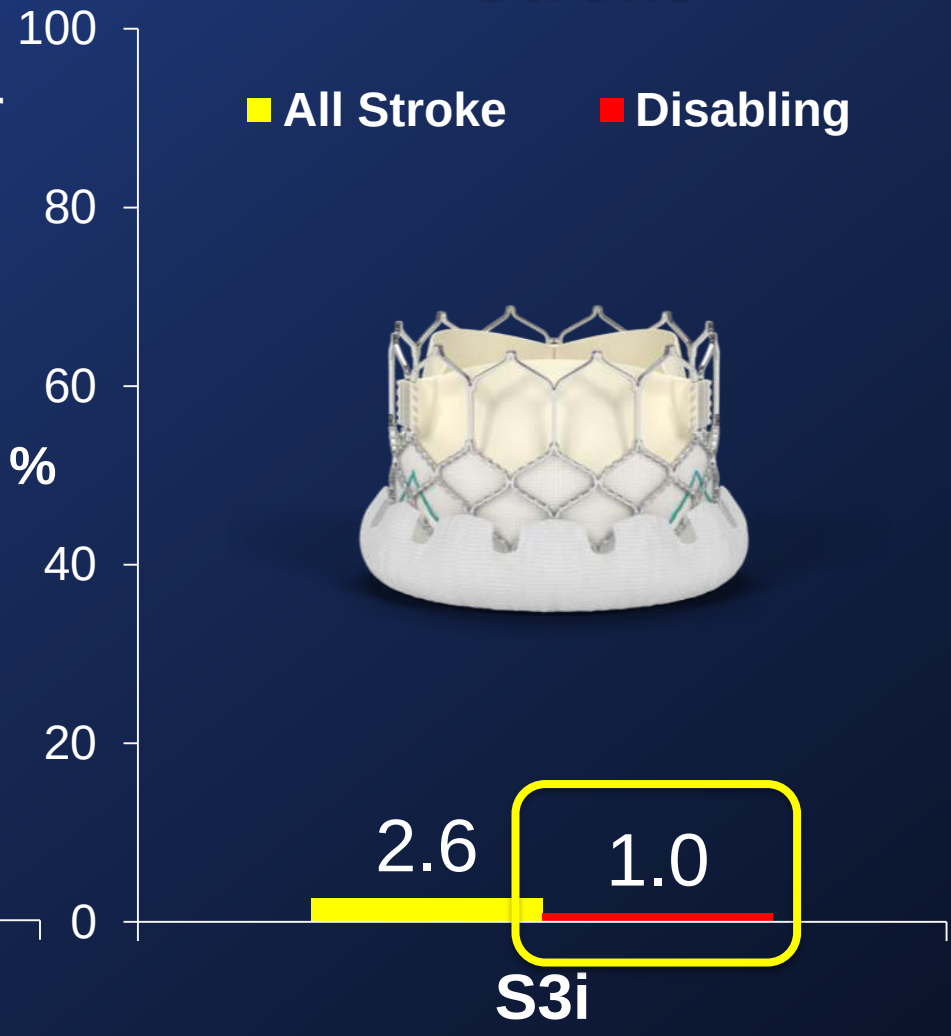
At 30 Days (As Treated Patients)

THE PARTNER II TRIAL

Mortality



Stroke

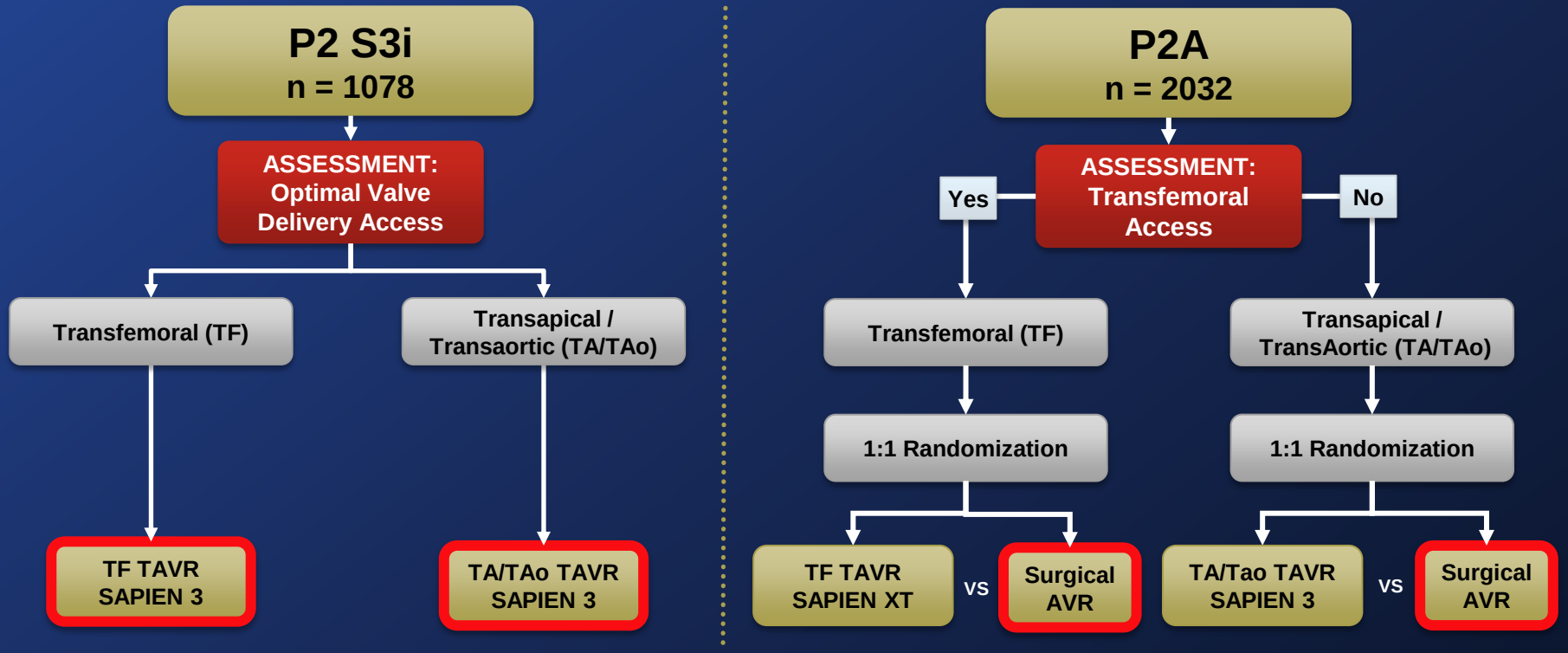


The PARTNER 2A and S3i Trials
Study Design

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)

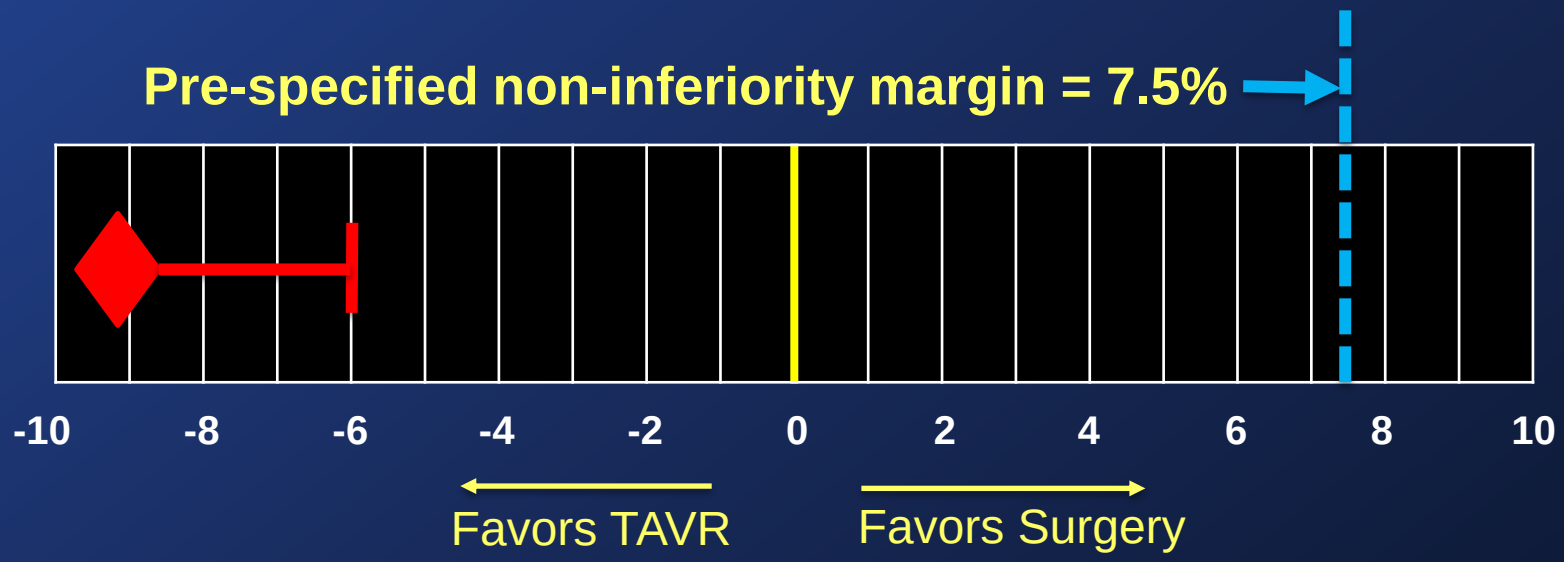
Primary Endpoint - Non-inferiority

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

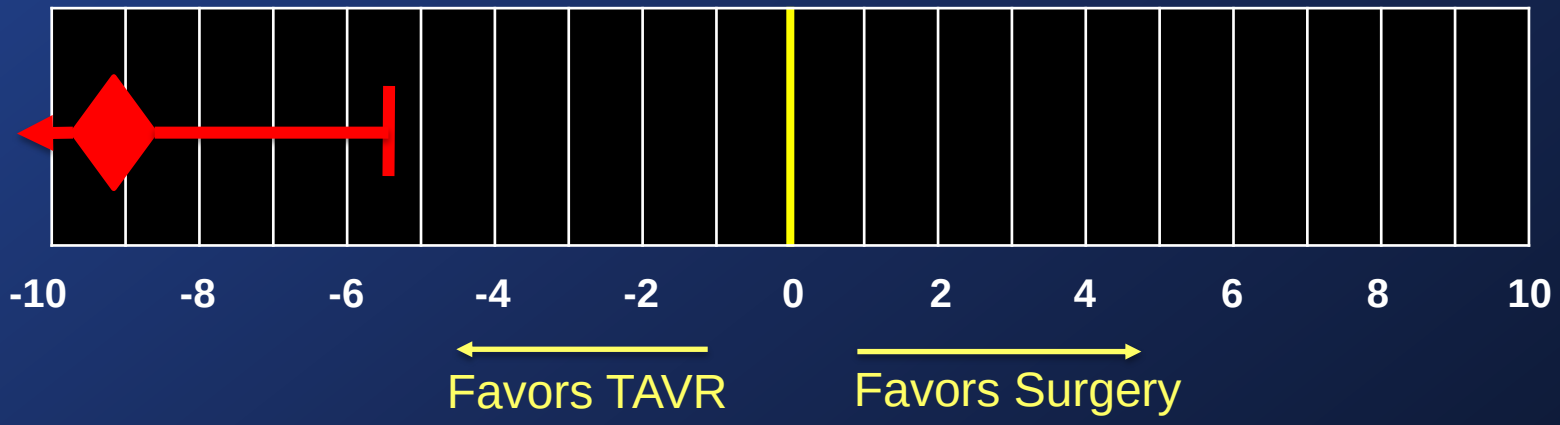
Primary Endpoint - Superiority

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

THE PARTNER II TRIAL

Weighted Difference	**-9.2%**
Upper 2-sided 95.0% CI	**-5.4%**

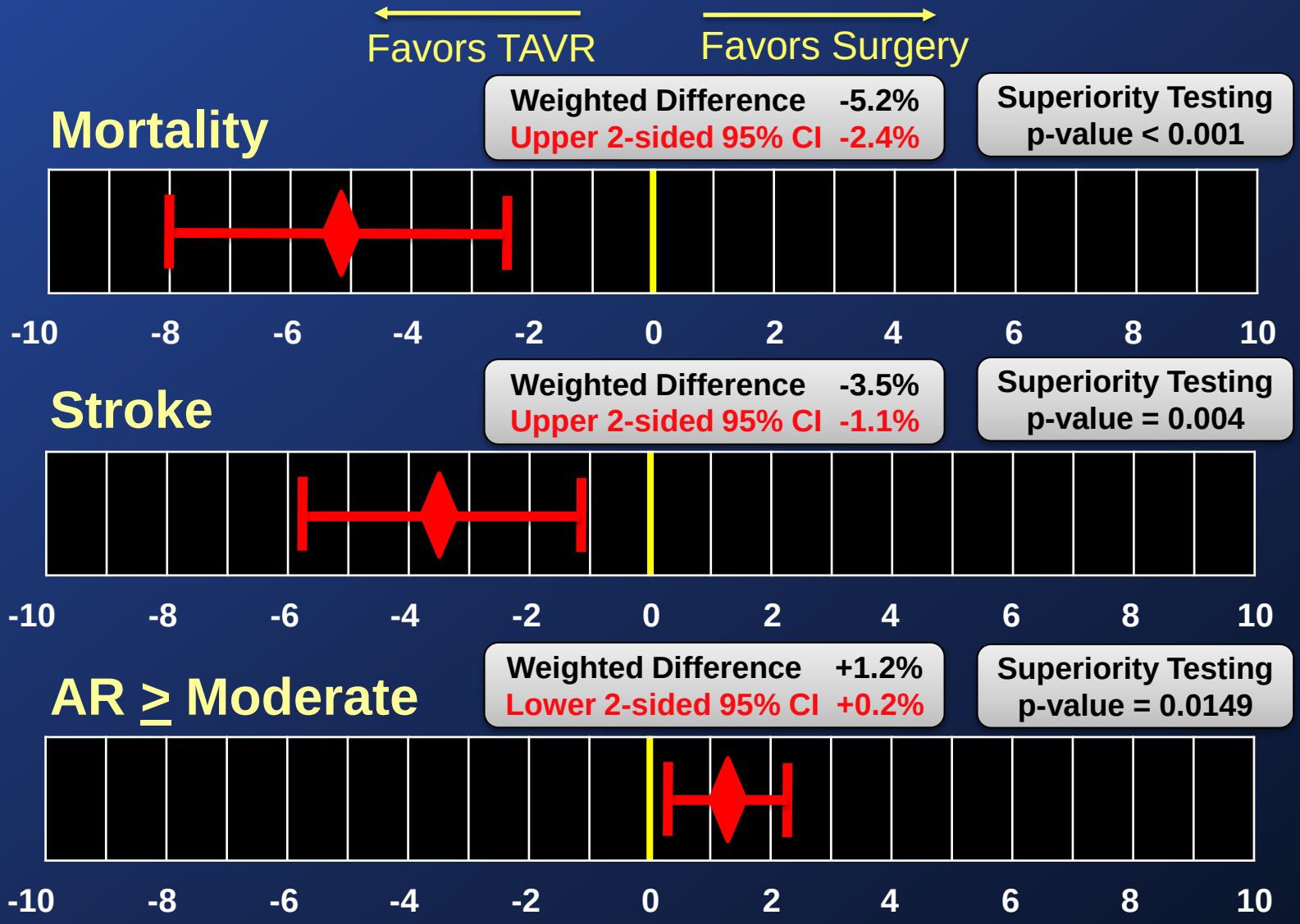
Superiority Testing
p-value < 0.001



Superiority Achieved

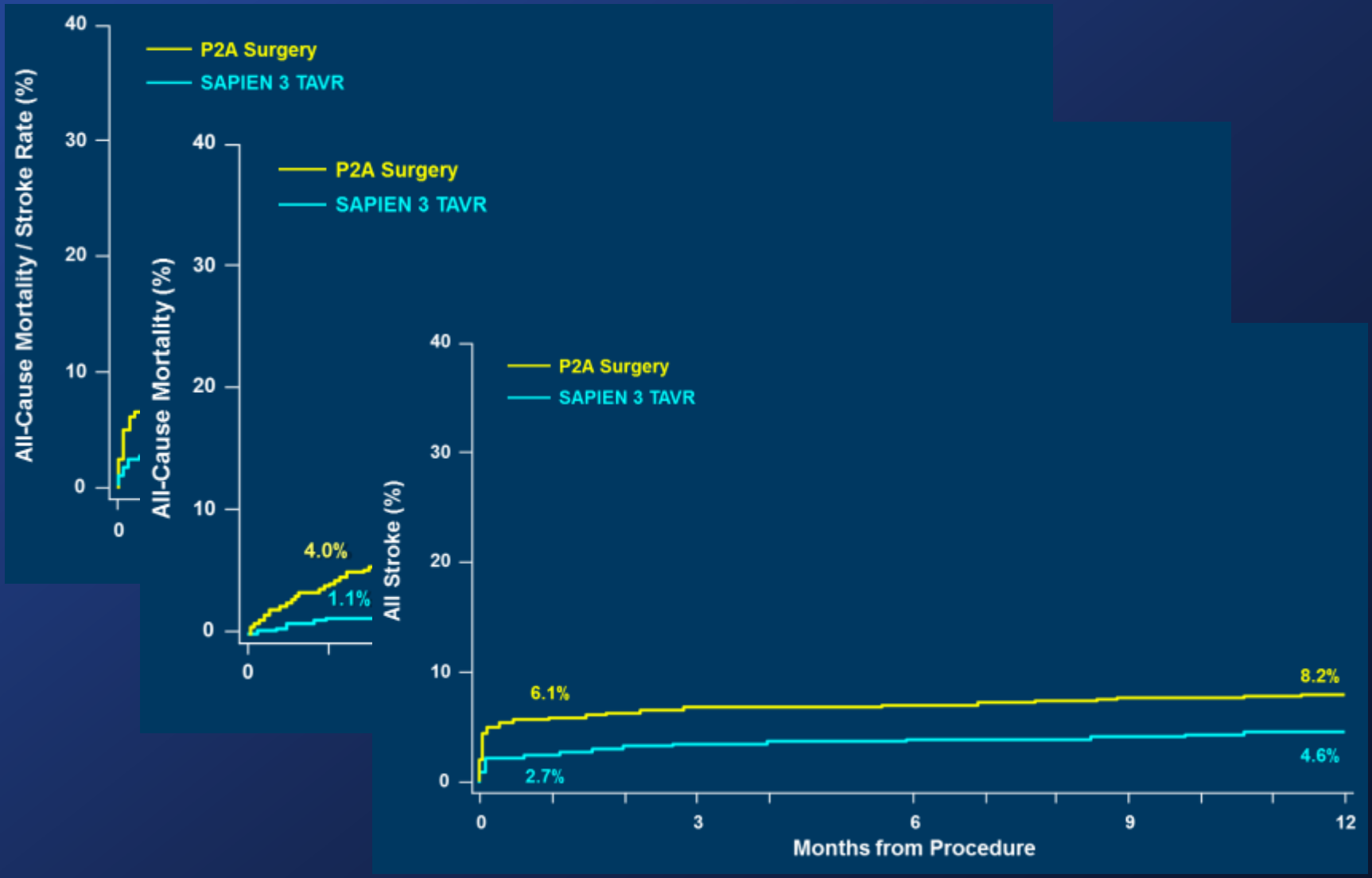
Superiority Analysis
Components of Primary Endpoint (VI)

THE PARTNER II TRIAL



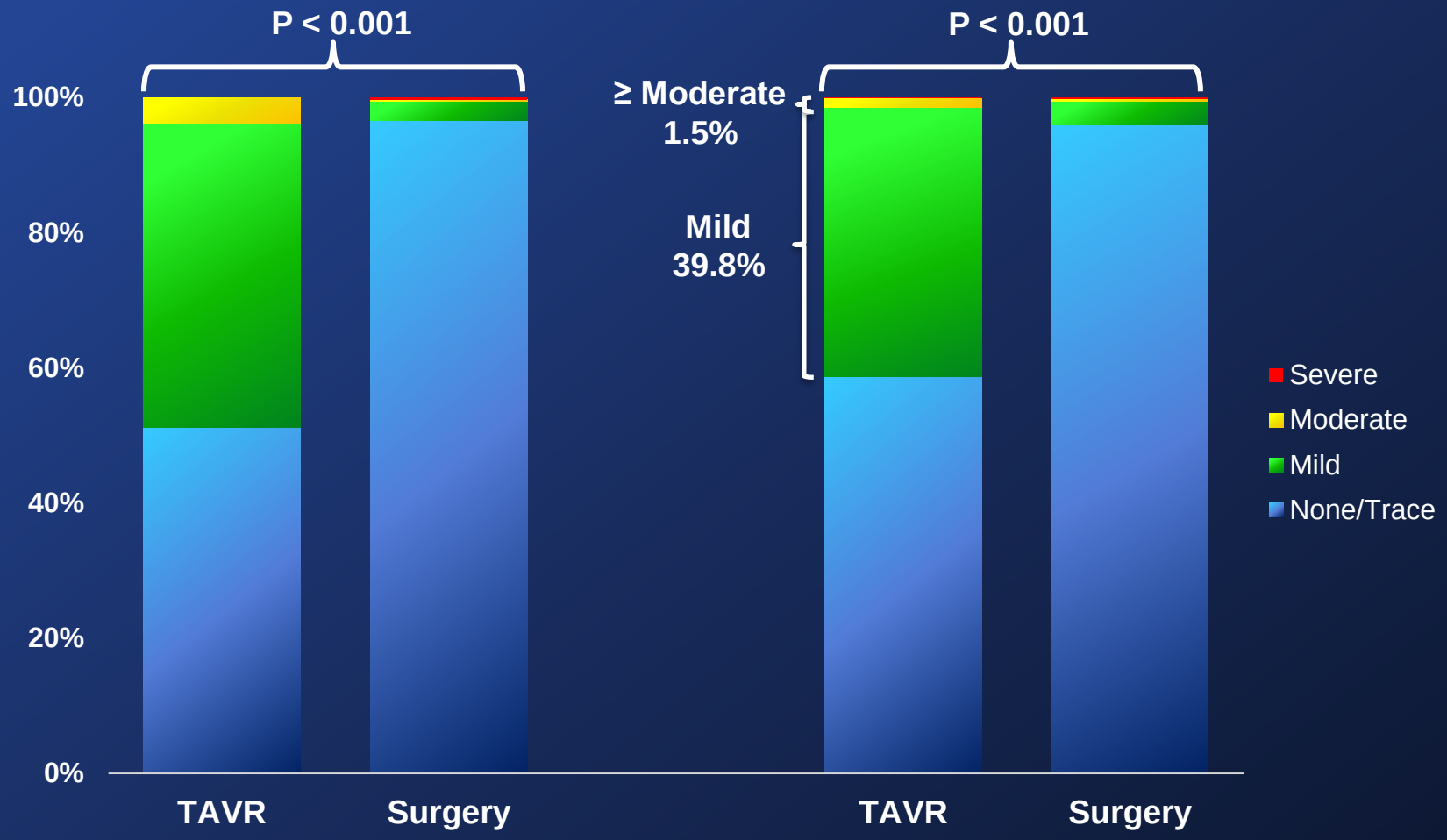
Unadjusted Time-to-Event Analysis
All-Cause Mortality and All Stroke (AT)

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

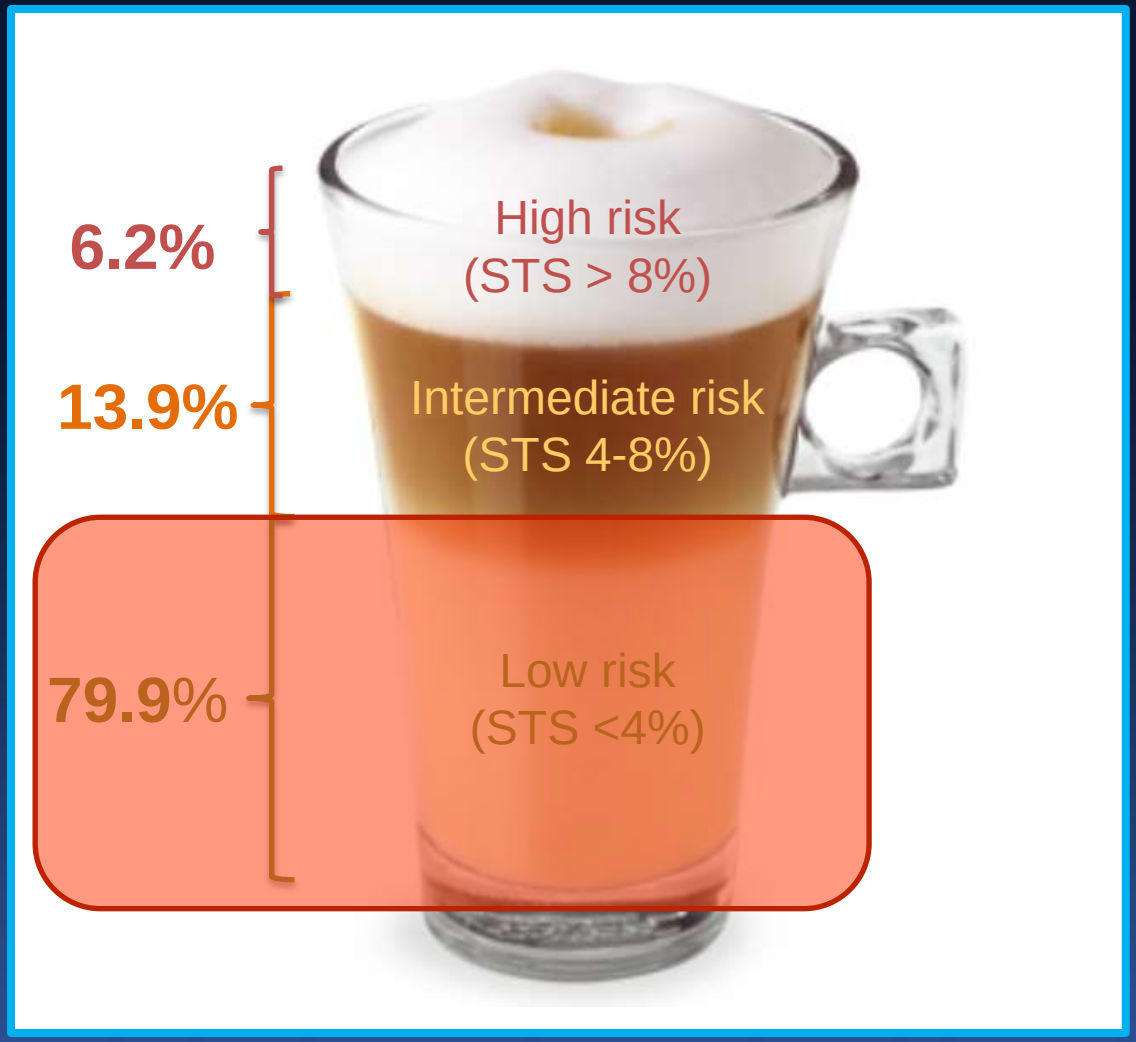
ORIGINAL ARTICLE

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*

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)

Who does not qualify for TAVR?

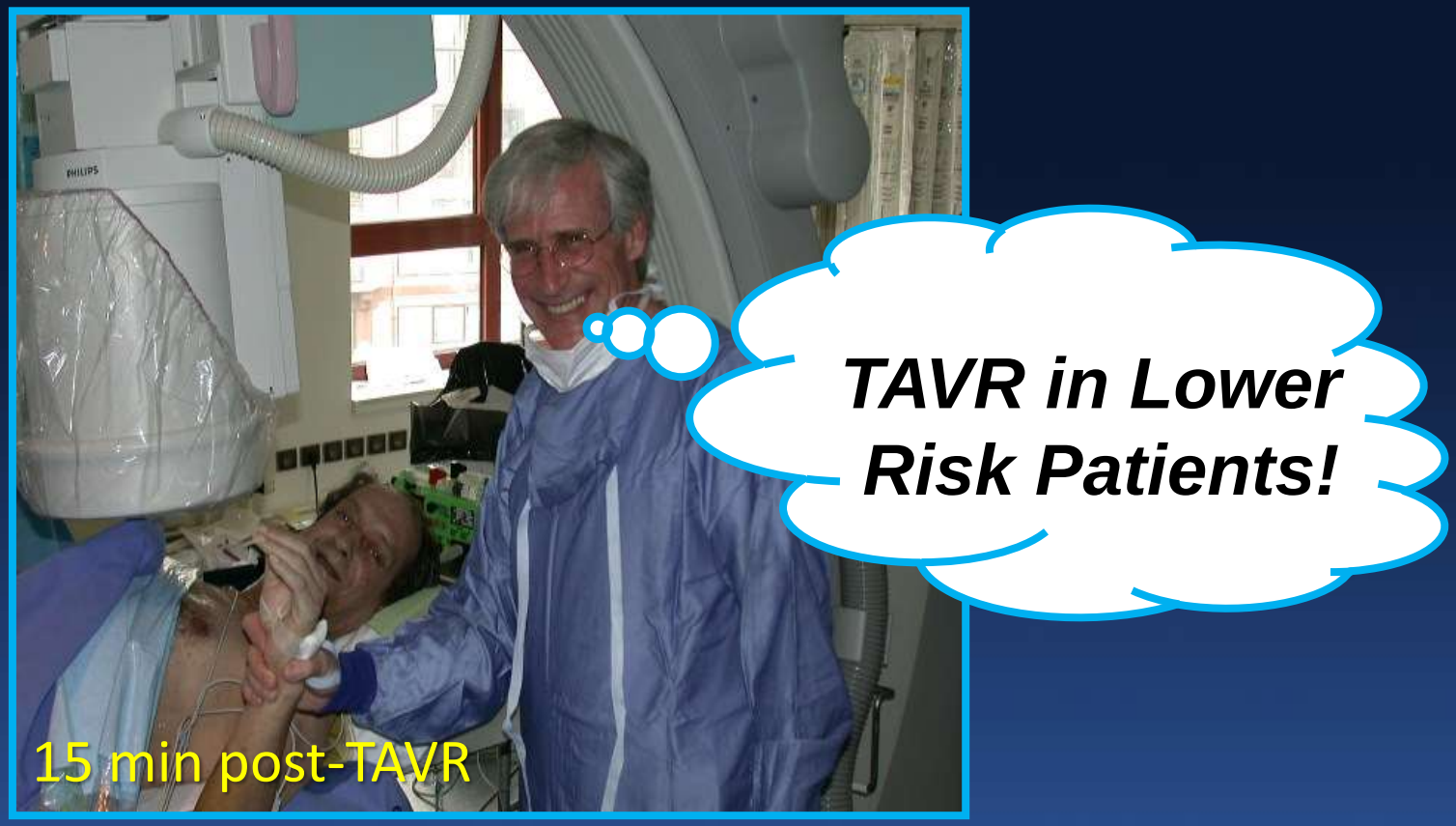
surgery?

Who are Lower-Risk Patients Considered for TAVR?

- Often “younger” = 65 - 80 yo
- Low surgical risk patients with few co-morbidities (so-called intermediate or low-risk categories)
- *Must be good candidates for TAVR – favorable anatomic considerations*
- Usually are appropriate for minimalist procedure and early discharge strategies

Dr. Alain Cribier

First-in-Man PIONEER



April 16, 2002