TAVI vs SAVR

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Edwards TAVI Clinical Program

From FIM To RCTs and Post-Market Registries

First In Man	Feasibility	Randomized Controlled	Post-Market
Procedural Success In Humans	Demonstrate "reasonable" safety and effectiveness	Effectiveness vs Control (AVR and medical therapy)	Evaluate transition to commercial use
RECAST **iREVIVE** **REVIVE I** **REVIVAL I** **TRAVERCE**	**REVIVE II** **REVIVAL II** **TRAVERCE** **PARTNER EU** **PREVAIL**	**PARTNER I** **PARTNER II**	**SOURCE** **SOURCE XT**

Balloon-Expandable Valves: Roadmap

1. **Edwards Sapien**
   PARTNER Cohorts B and A, PARTNER NRCA
2. **Edwards Sapien XT**
   PARTNER II Cohort B, CHOICE, SOURCE XT
3. **Edwards Sapien 3**
   FIM

Balloon-Expandable Valves: Roadmap

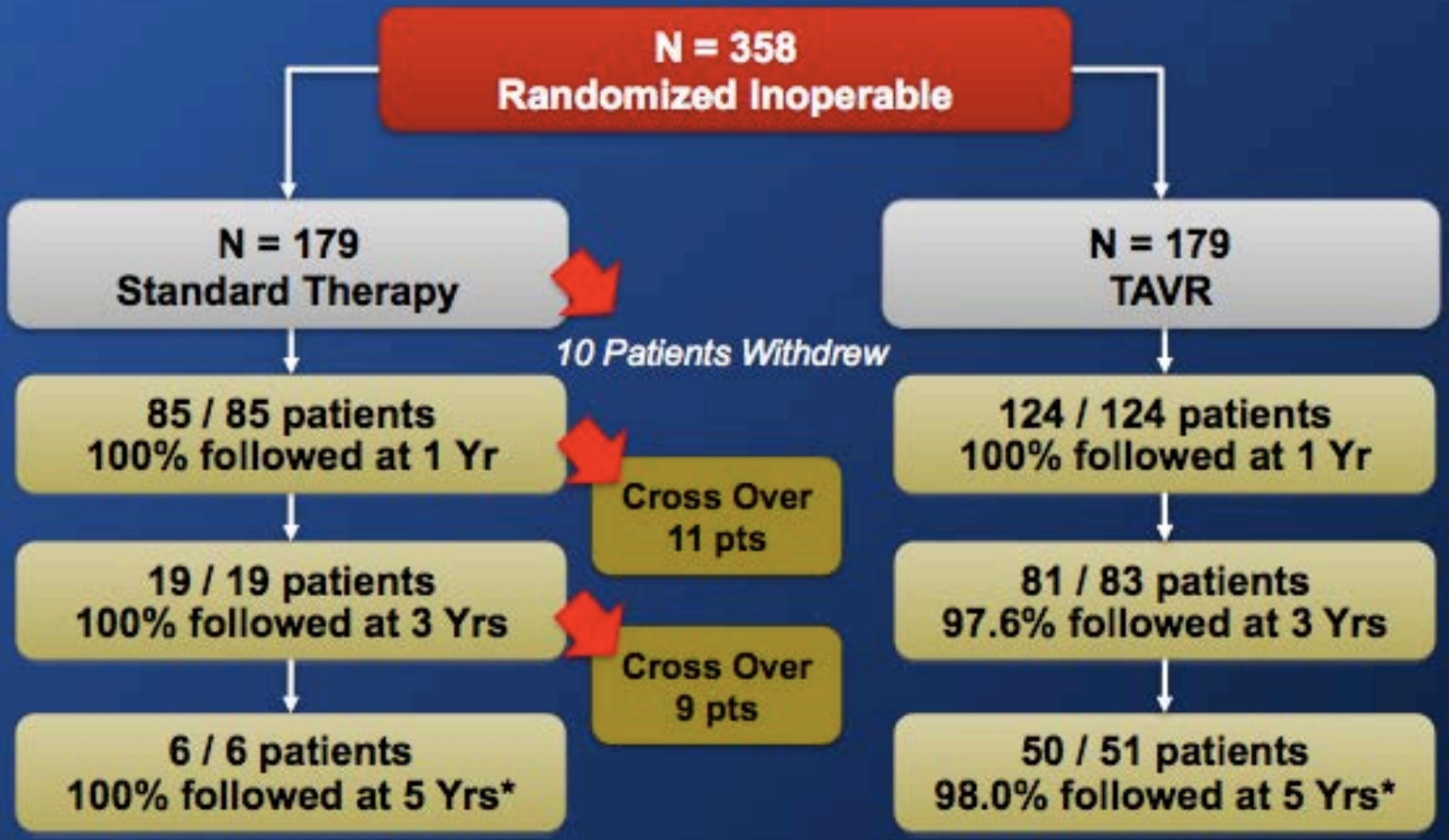
1

Edwards Sapien
PARTNER Cohorts B and A, PARTNER NRCA

Edwards Sapien XT
PARTNER II Cohort B, CHOICE, SOURCE XT

Edwards Sapien 3
FIM

Study Flow
Inoperable Cohort



** ± 2 months follow-up window*

S. Kapadia, TCT 2014

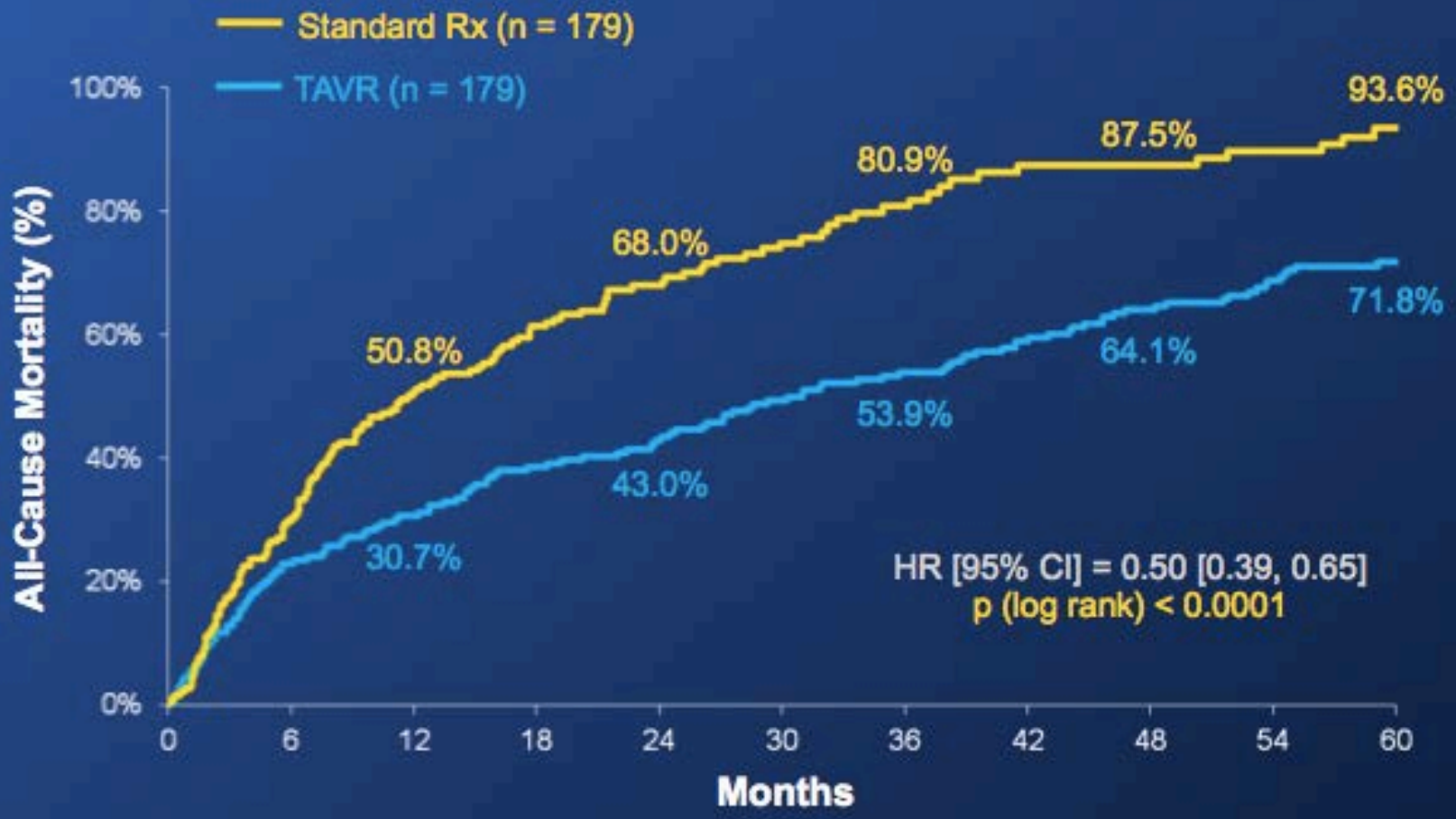
Patient Characteristics

Characteristic	TAVR N = 179	Standard Rx N = 179	p-value
Age – yr	83.1 ± 8.6	83.2 ± 8.3	0.95
Male sex (%)	45.8	46.9	0.92
STS Score	11.2 ± 5.8	12.1 ± 6.1	0.14
NYHA			
I or II (%)	7.8	6.1	0.68
III or IV (%)	92.2	93.9	0.68
CAD (%)	67.6	74.3	0.20
COPD			
Any (%)	41.3	52.5	0.04
O_2 dependent (%)	21.2	25.7	0.38
Creatinine > 2 mg/dL (%)	5.6	9.6	0.23
Frailty (%)	18.1	28.0	0.09
Porcelain aorta (%)	19.0	11.2	0.05
Chest wall radiation (%)	8.9	8.4	1.00

S. Kapadia, TCT 2014

All-Cause Mortality (ITT)
Crossover Patients Censored at Crossover

THE PARTNER TRIAL



** In an age and gender matched US population without comorbidities, the mortality at 5 years is 40.5%.*

S. Kapadia, TCT 2014

All-Cause Mortality (ITT)
Landmark Analysis

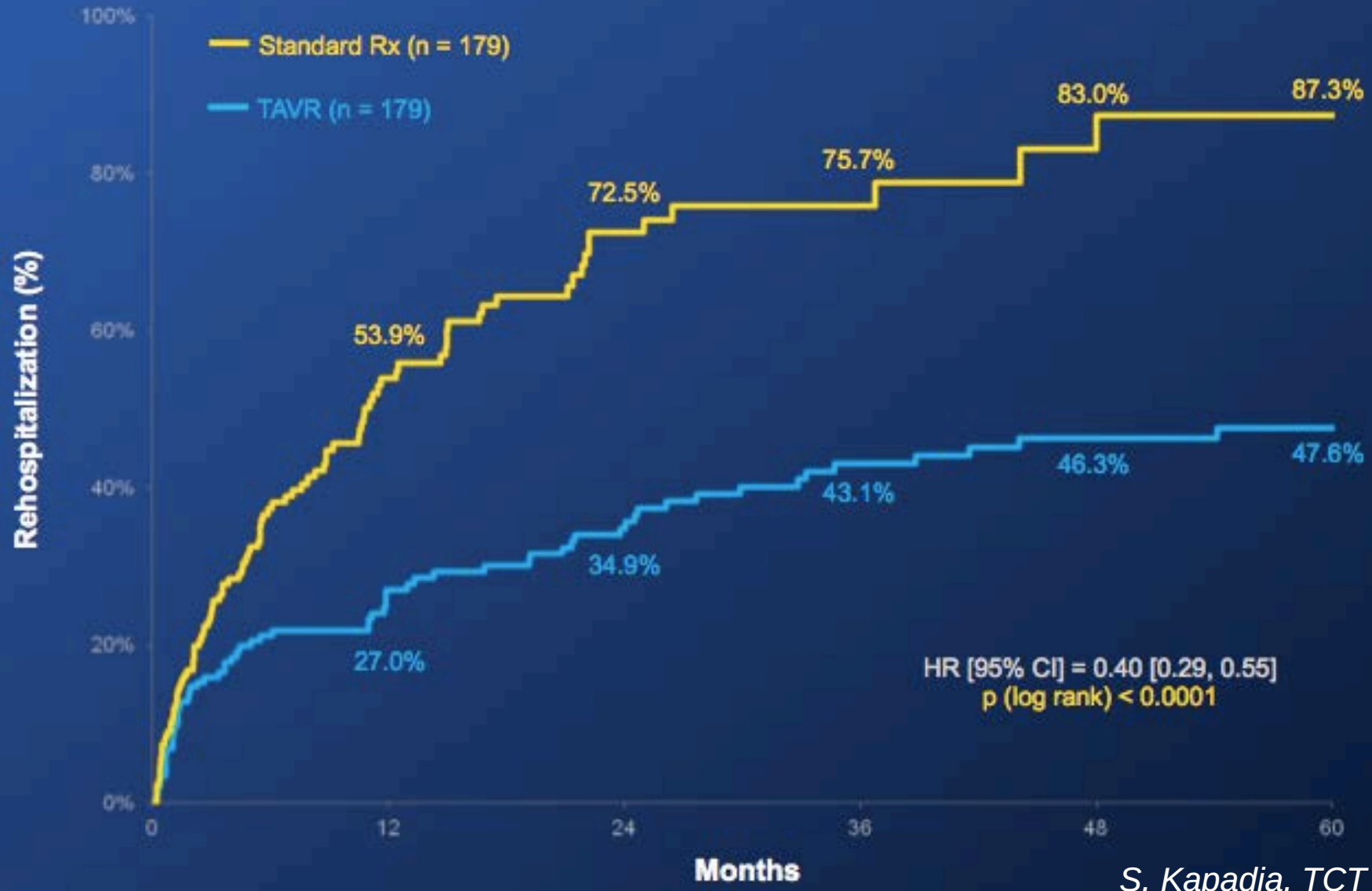
S. Kapadia, TCT 2014

All-Cause Mortality Stratified by STS Score (ITT)

THE PARTNER TRIAL

S. Kapadia, TCT 2014

Repeat Hospitalization (ITT)

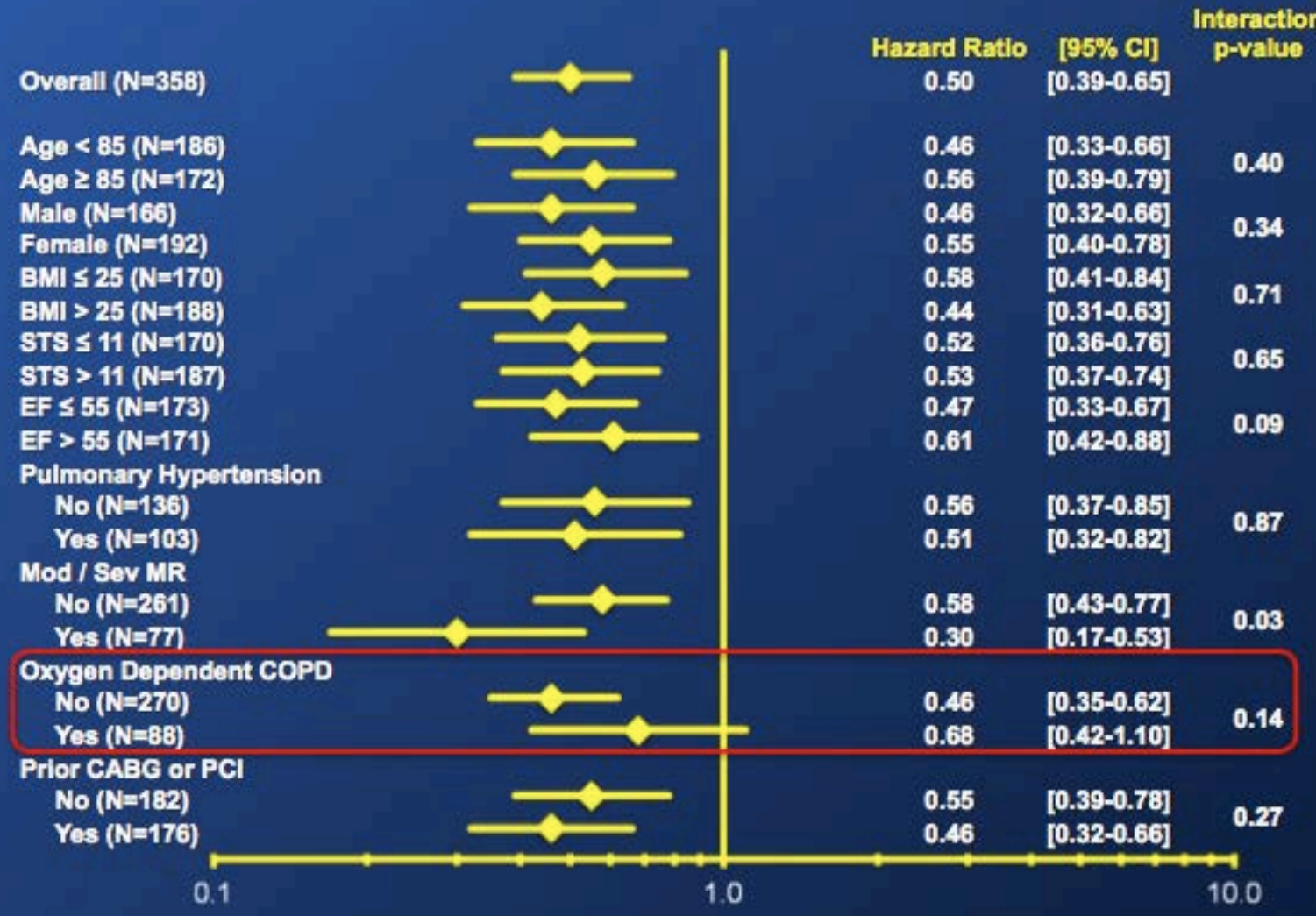


S. Kapadia, TCT 2014

Mean Gradient & Valve Area (AT)

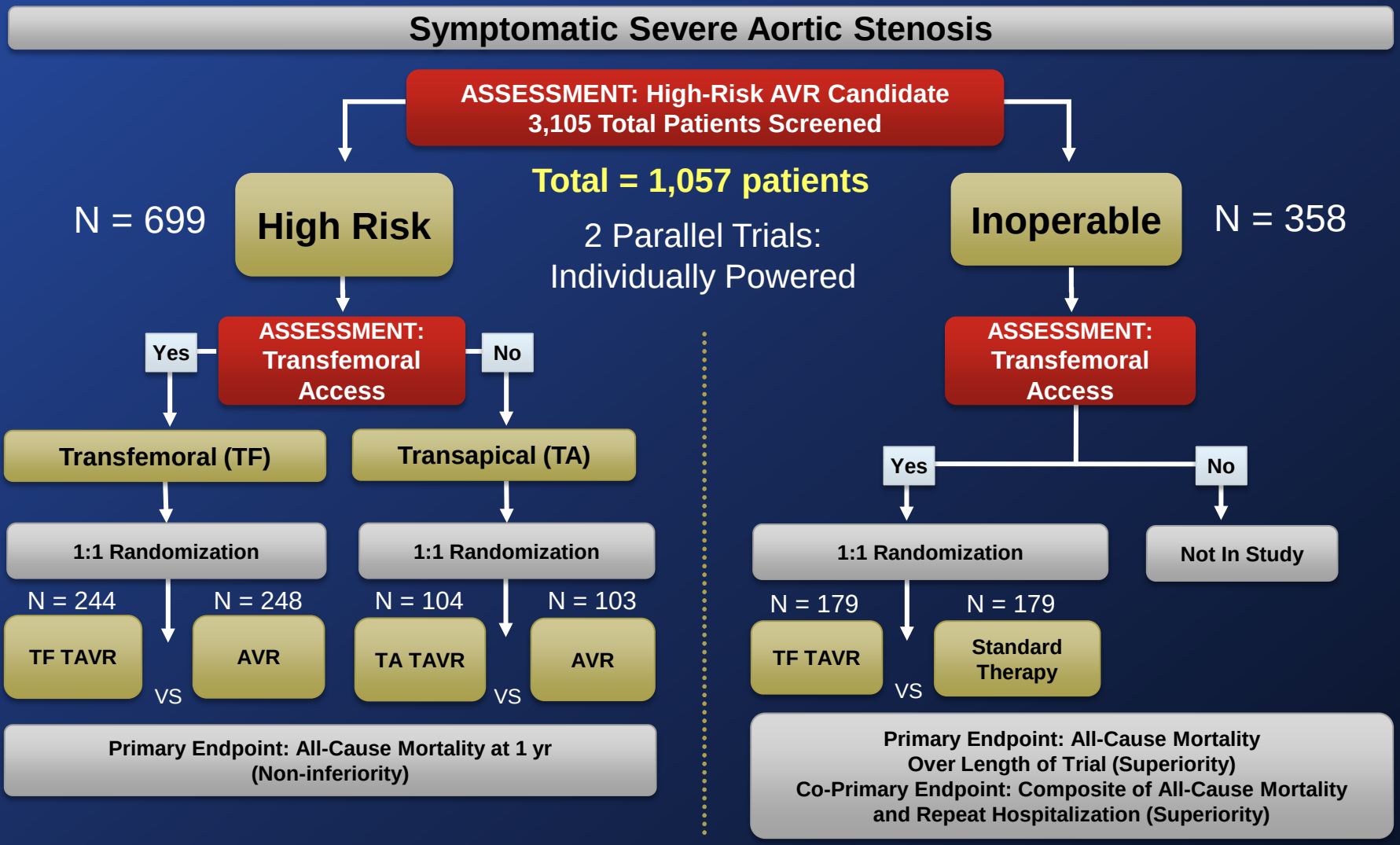
S. Kapadia, TCT 2014

Subgroup Analysis
All-Cause Mortality

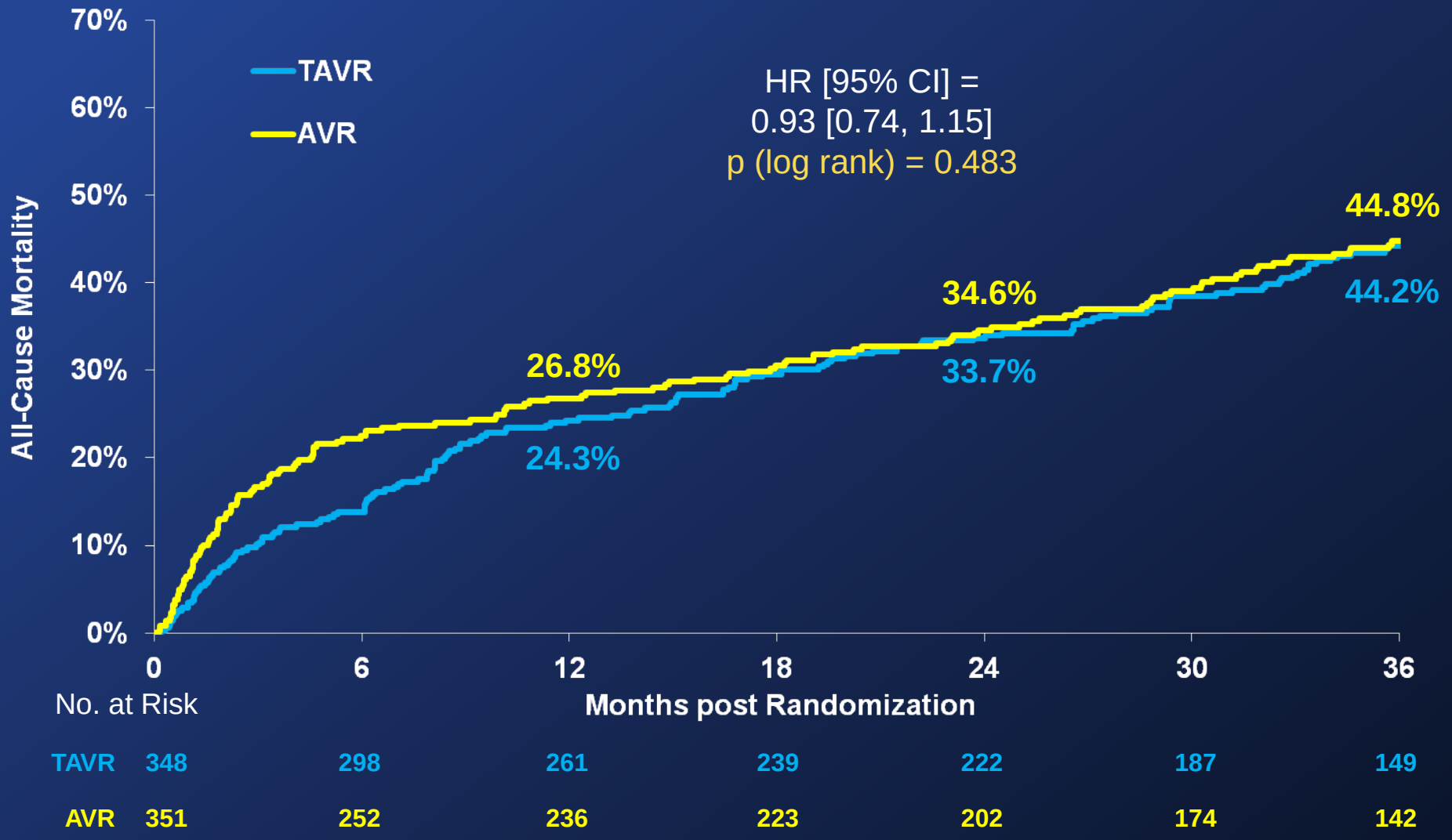


S. Kapadia, TCT 2014

PARTNER Study Design



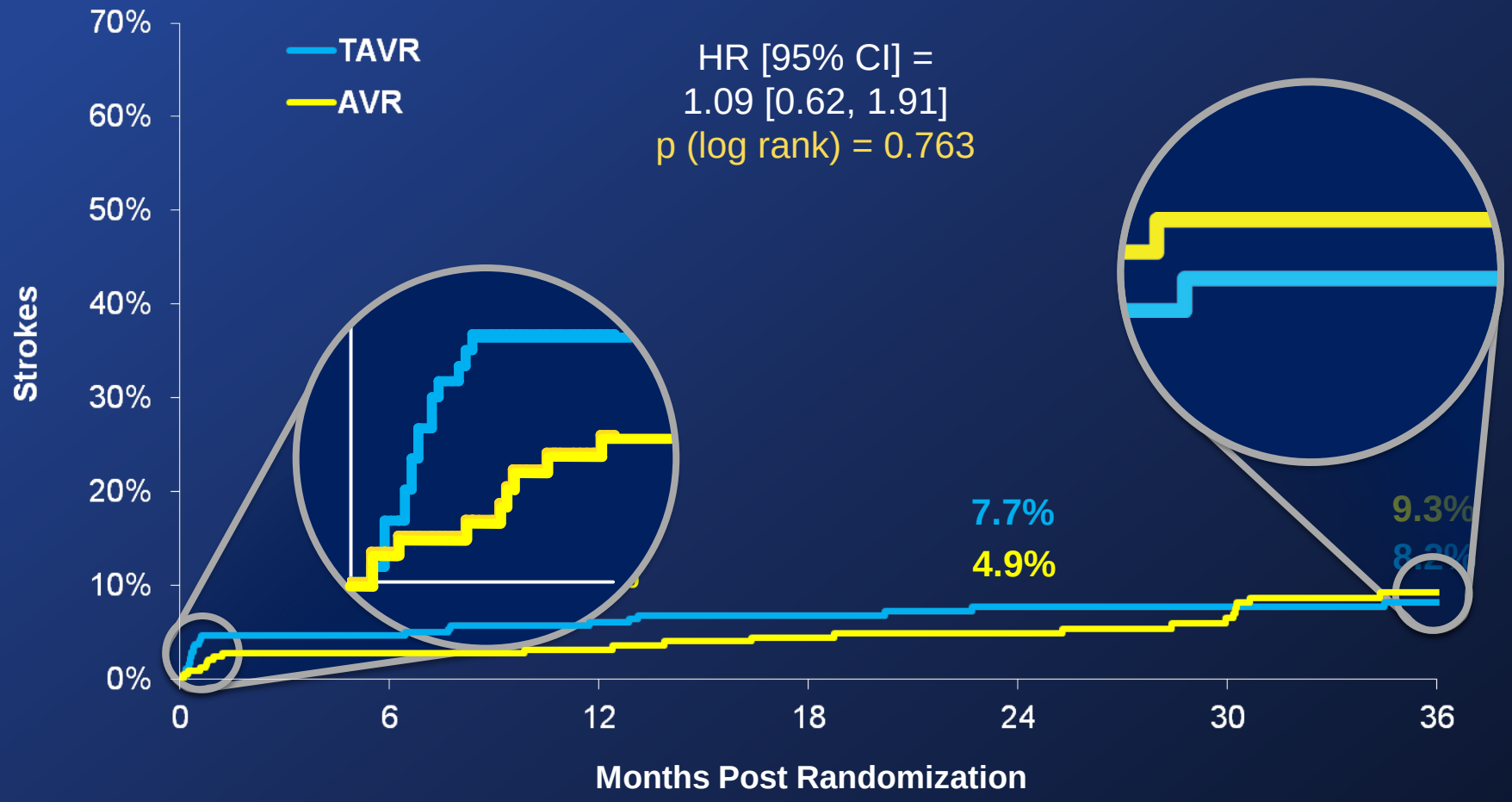
All-Cause Mortality (ITT)



No. at Risk

TAVR	348	298	261	239	222	187	149
AVR	351	252	236	223	202	174	142

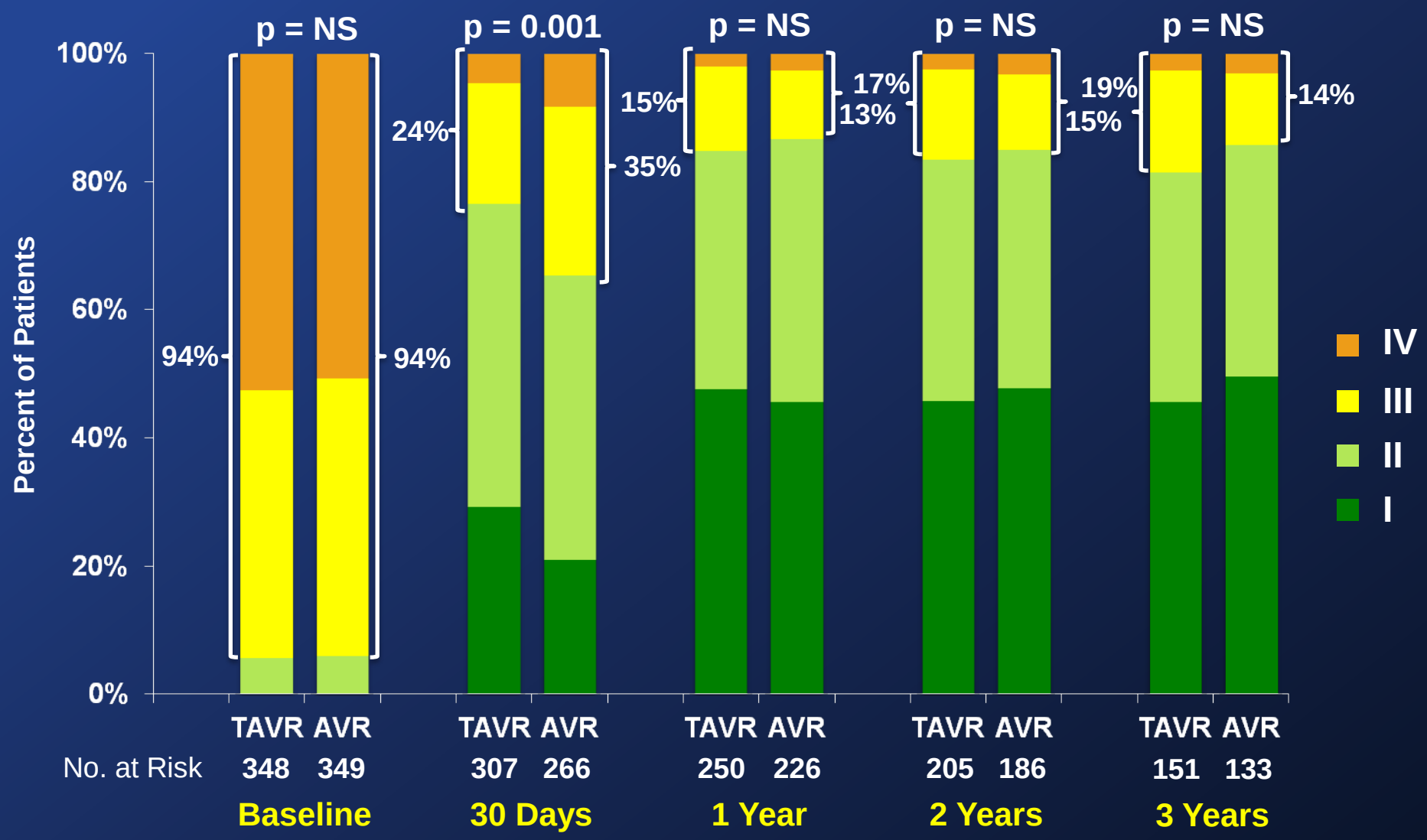
Strokes (ITT)



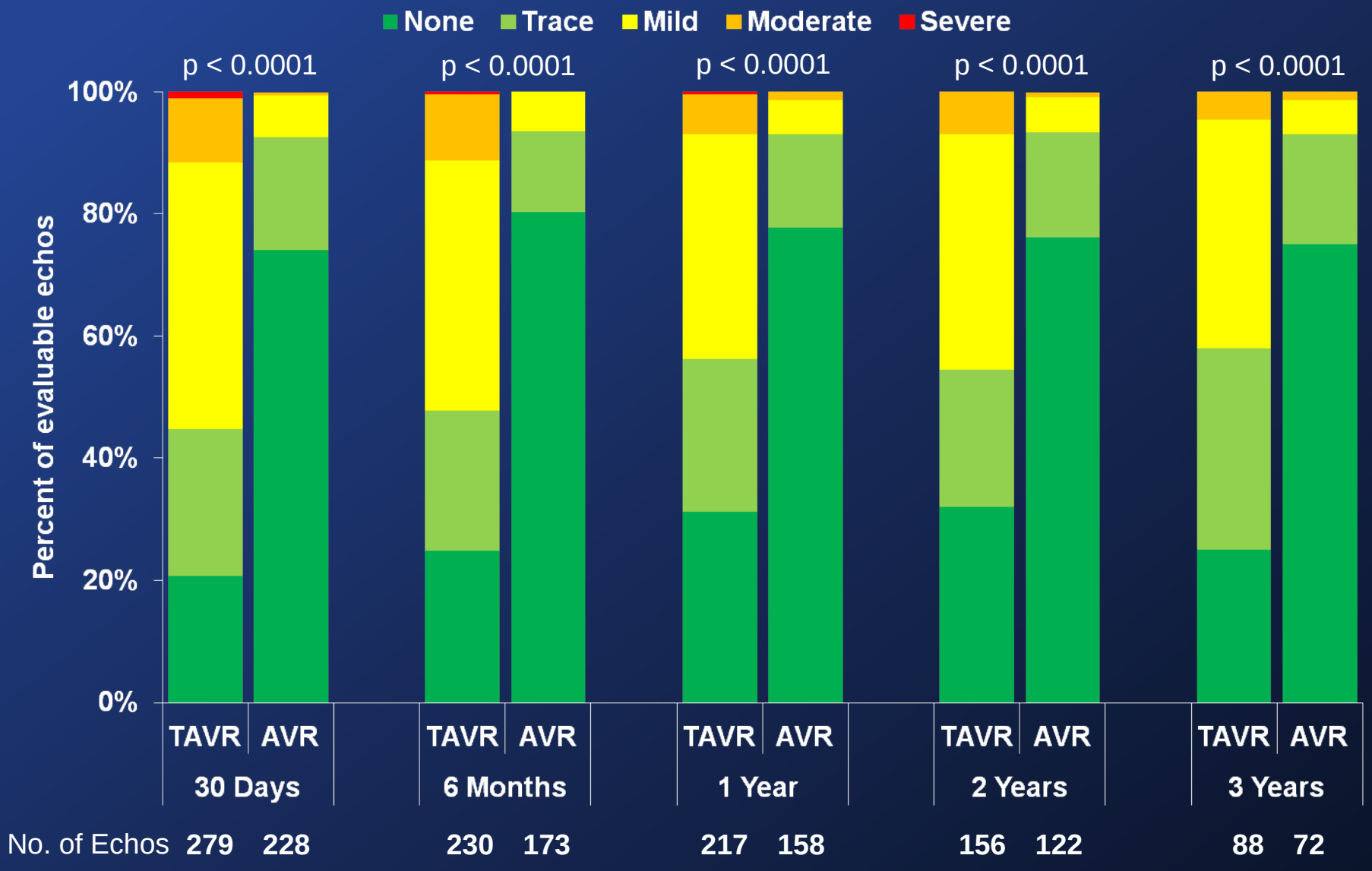
No. at Risk

TAVR	348	287	250	228	211	176	139
AVR	351	246	230	217	197	169	139

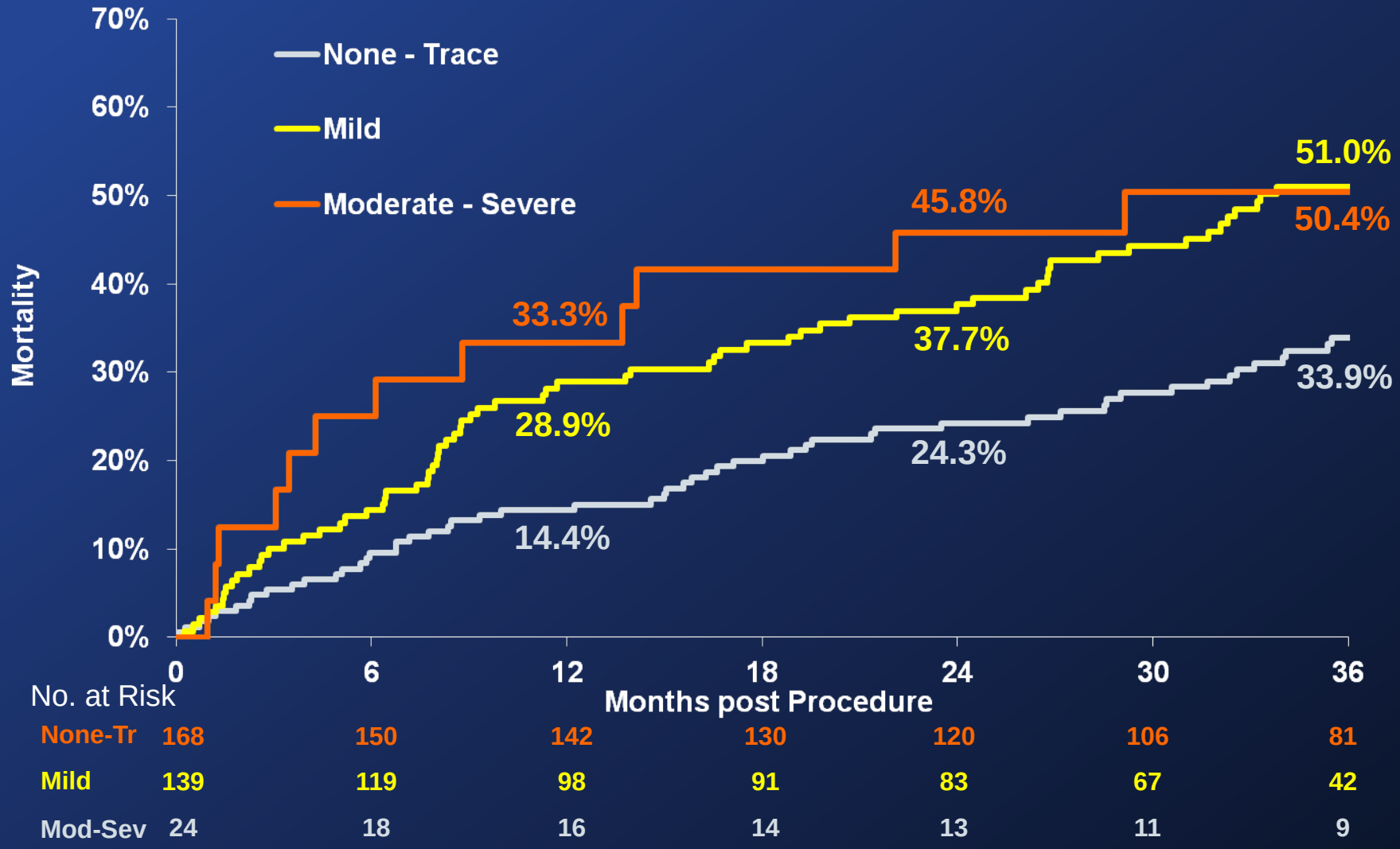
NYHA Class Survivors (ITT)



Paravalvular Aortic Regurgitation (AT)



Impact of Mild PVL on Mortality (AT)
TAVR Patients



No. at Risk

None-Tr	168	150	142	130	120	106	81
Mild	139	119	98	91	83	67	42
Mod-Sev	24	18	16	14	13	11	9

Comment

New born technique, learning centers vs well estabilished technique, experienced centers

First generation 23 Fr, TAVI model

Balloon-Expandable Valves: Roadmap

Edwards Sapien
PARTNER Cohorts B and A, PARTNER NRCA

2

Edwards Sapien XT
PARTNER II Cohort B, CHOICE, SOURCE XT

Edwards Sapien 3
FIM

Edwards SAPIEN vs SAPIEN XT Transcatheter Heart Valves

THE PARTNER II TRIAL

NEW FRAME GEOMETRY
- Less metal content
- Lower crimp profile

NEW FRAME MATERIAL
- Cobalt-chromium
- Greater tensile and yield strength

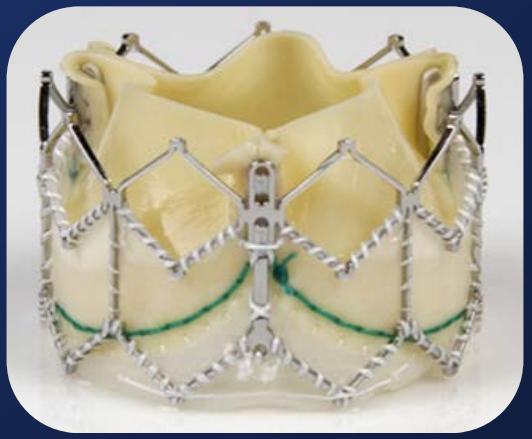
NEW LEAFLET GEOMETRY
- Partially closed

SAPIEN THV

Stainless Steel

SAPIEN XT THV

Cobalt-chromium



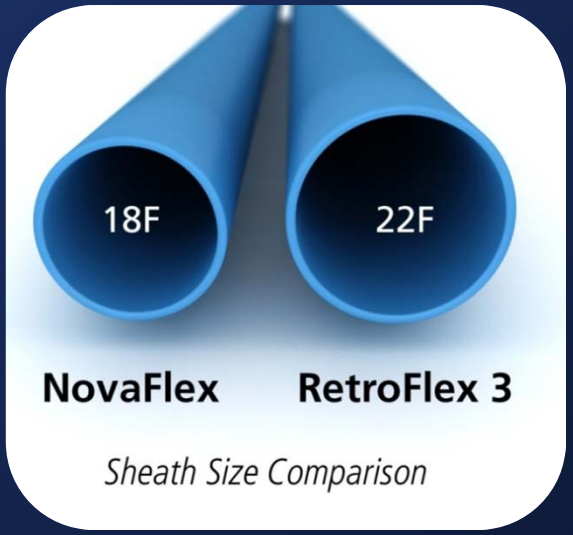
RetroFlex 3

NovaFlex

Sheath Size Comparison

THE PARTNER II TRIAL

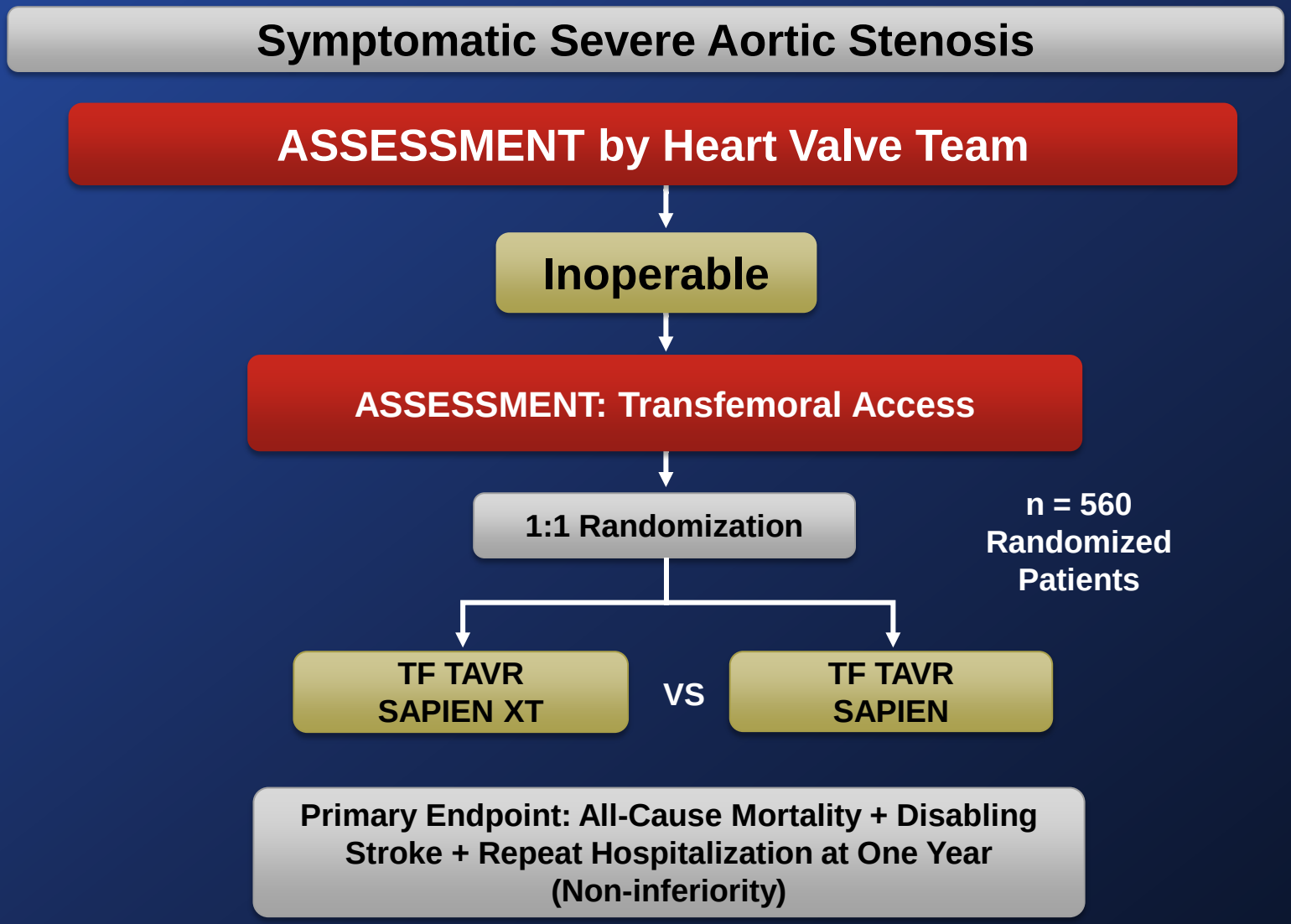
Valve	Valve Size	Sheath ID	Sheath OD	Minimum Vessel Diameter
SAPIEN THV	23mm	22F	25F (8.4mm)	7.0mm
SAPIEN XT THV	23mm	18F	22F (7.2mm)	6.0mm
SAPIEN THV	26mm	24F	28F (9.2mm)	8.0mm
SAPIEN XT THV	26mm	19F	23F (7.5mm)	6.5mm



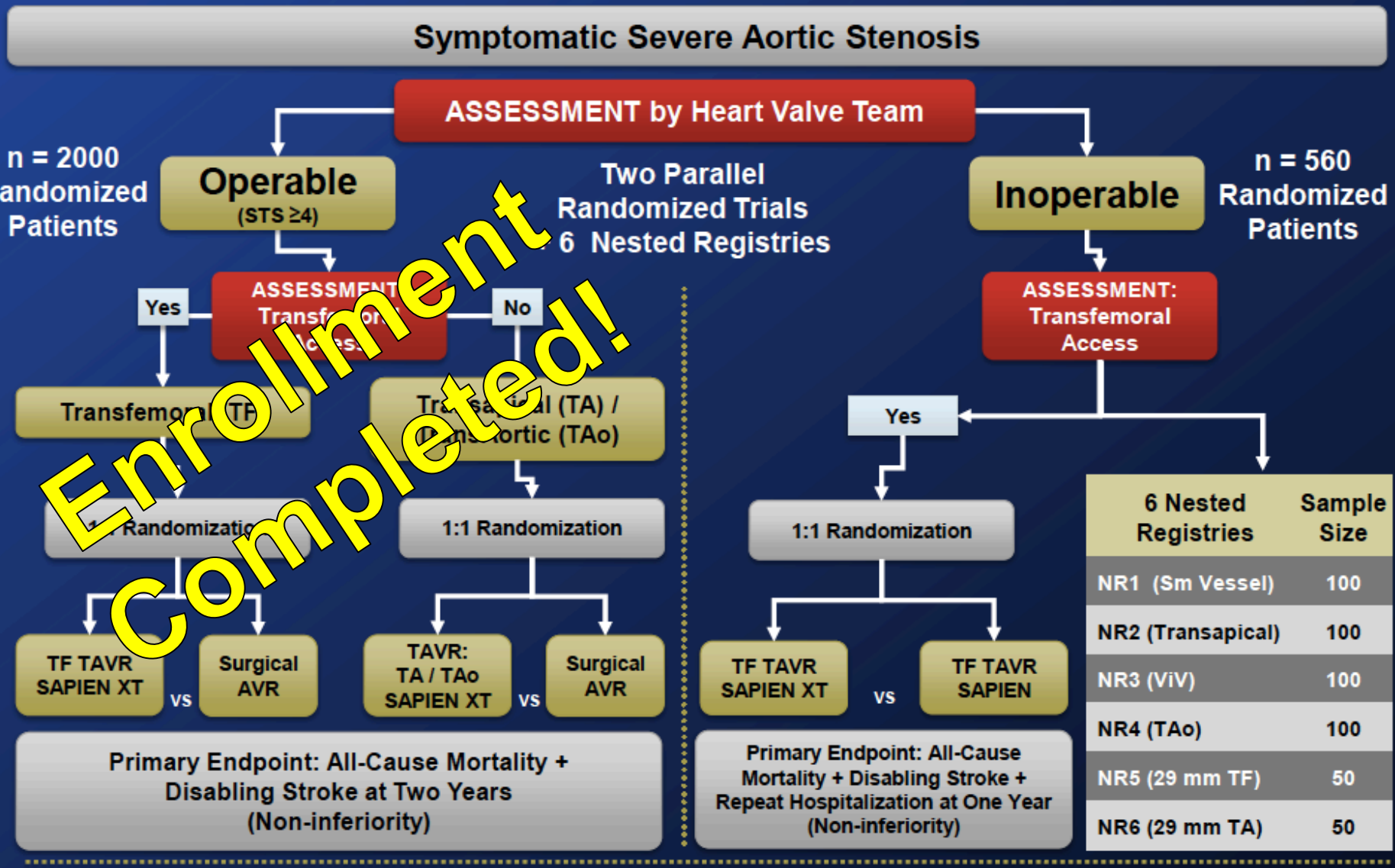
33% reduction in CSA

The PARTNER II Inoperable Cohort

Cohort B Study Design



The PARTNER II Trial
Study Design



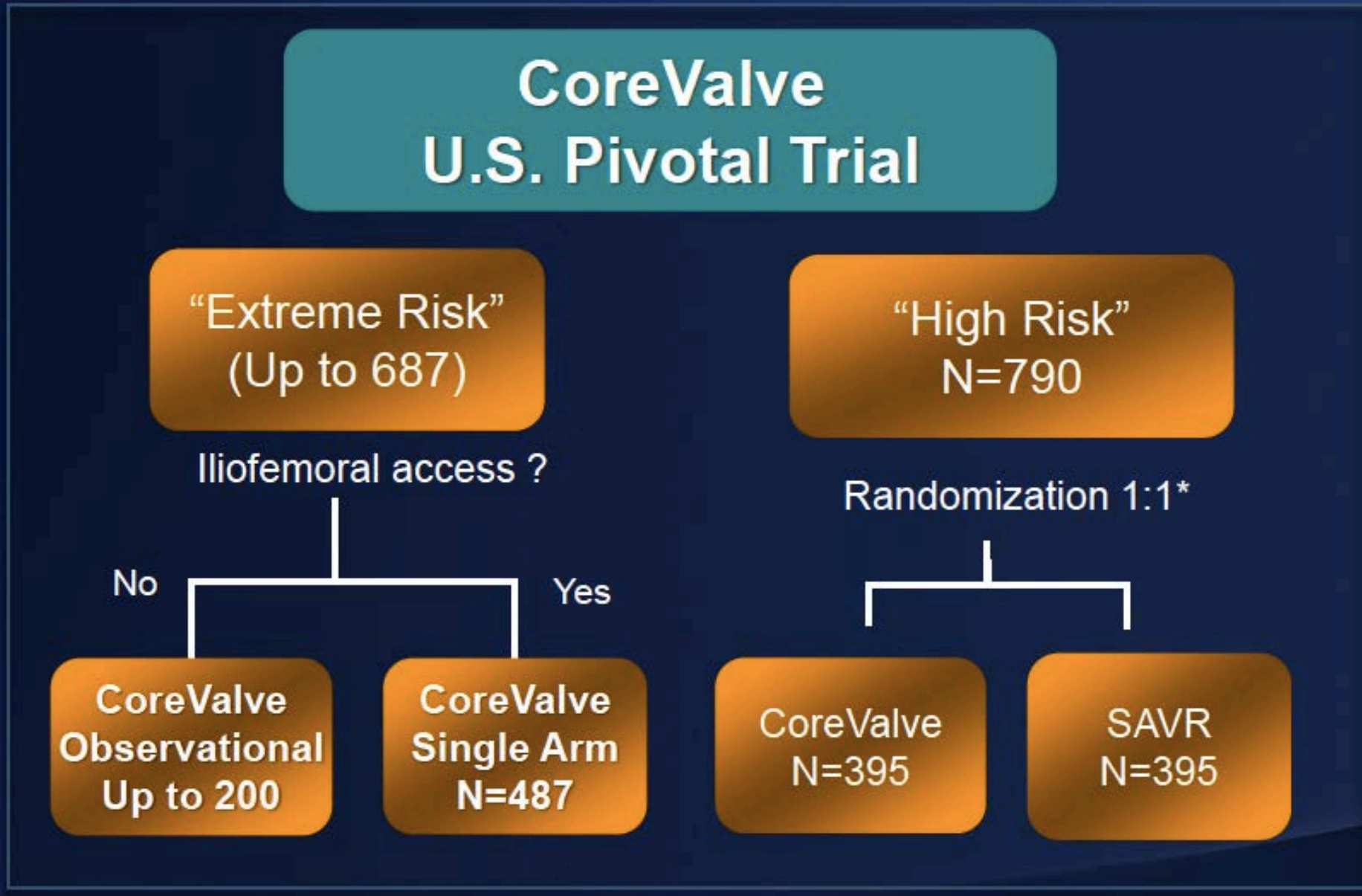
6 Nested Registries	Sample Size
NR1 (Sm Vessel)	100
NR2 (Transapical)	100
NR3 (ViV)	100
NR4 (TAo)	100
NR5 (29 mm TF)	50
NR6 (29 mm TA)	50

CoreValve TAVI Clinical Program

Medtronic CoreValve Clinical Research Portfolio

Foundational	Expansion	Confirmation
Confirm Efficacy and Optimize Practice	Expand Access to New Populations and Markets	Confirm Efficacy and Optimize Practice
CoreValve US Pivotal **CoreValve CE Pivotal**	**CoreValve ANZ** **CoreValve SURTAVI** **CoreValve Japan** **CoreValve Extended Use**	**ADVANCE** **Continued Access** **ADVANCE II** **ADVANCE DA**

CoreValve US Trial: Sample Sizes

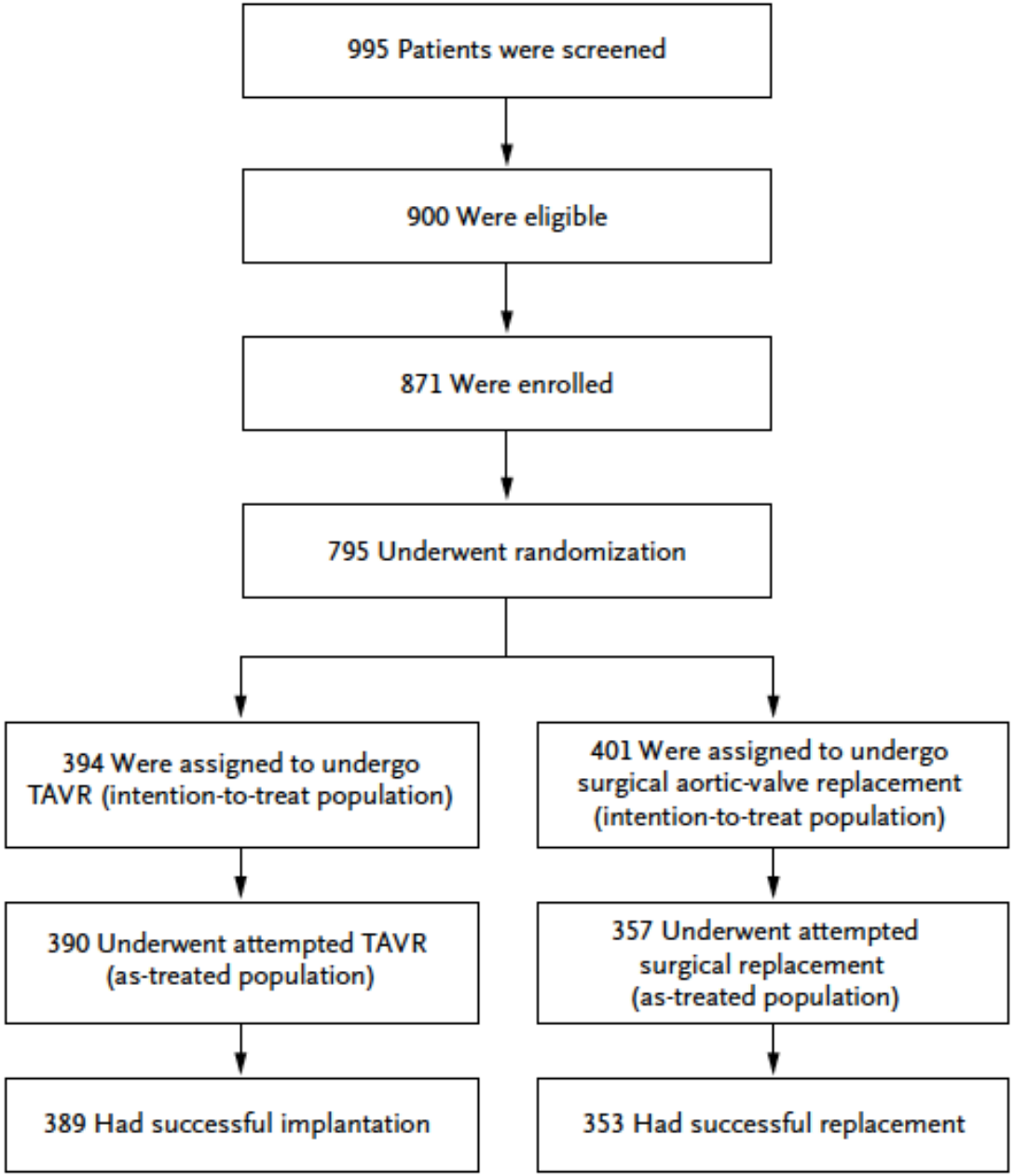


The NEW ENGLAND JOURNAL of MEDICINE

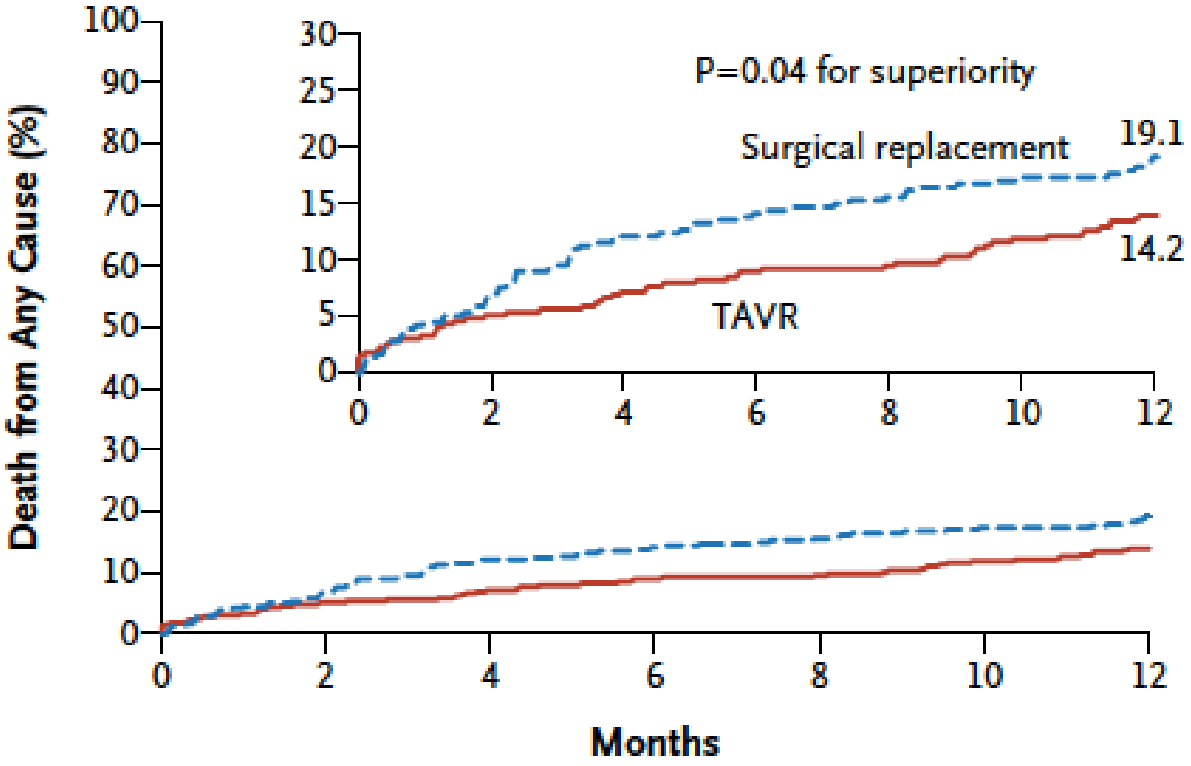
ORIGINAL ARTICLE

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*


995 Patients were screened
900 Were eligible
871 Were enrolled
795 Underwent randomization
394 Were assigned to undergo TAVR (intention-to-treat population)
401 Were assigned to undergo surgical aortic-valve replacement (intention-to-treat population)
390 Underwent attempted TAVR (as-treated population)
357 Underwent attempted surgical replacement (as-treated population)
389 Had successful implantation
353 Had successful replacement

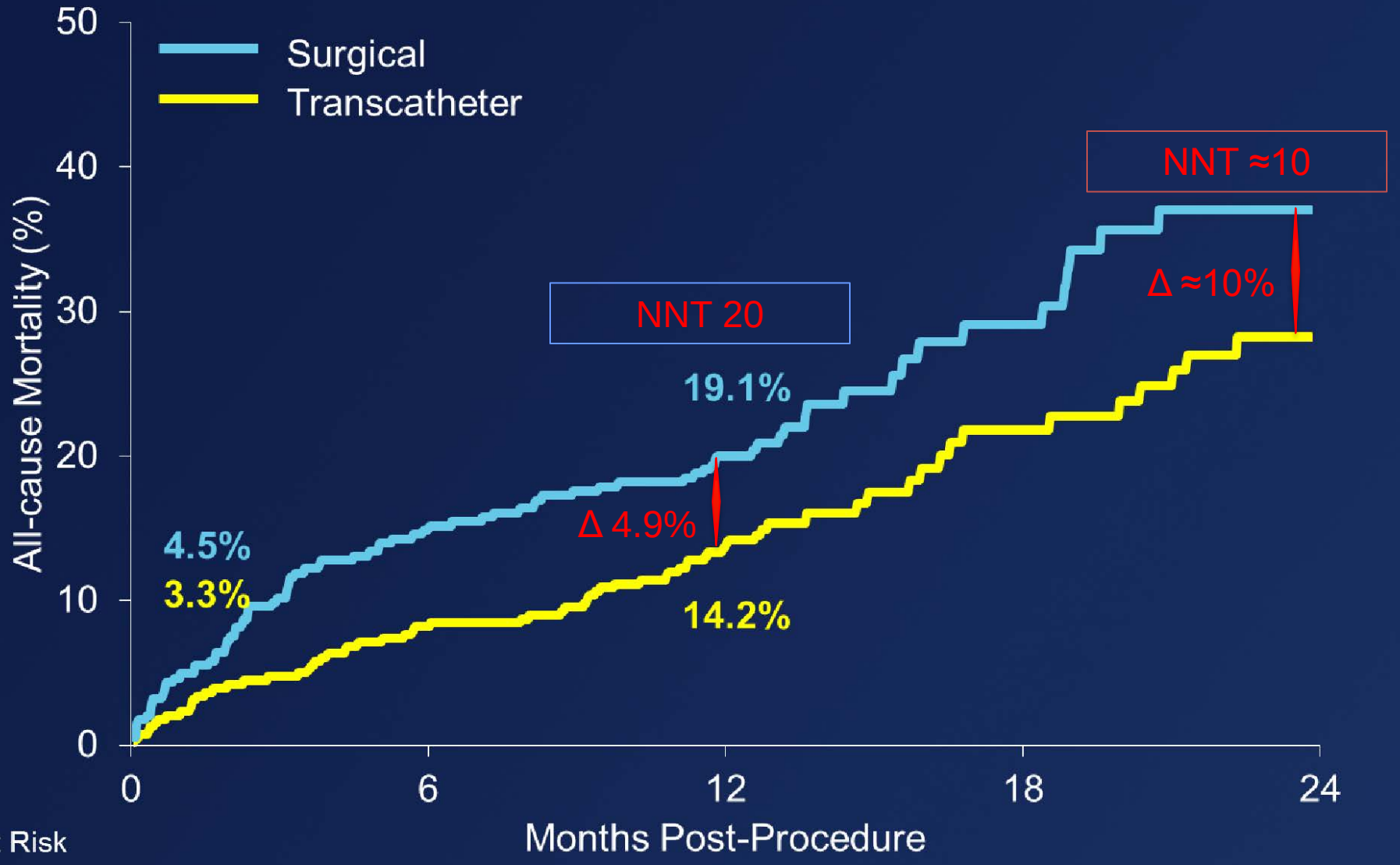
CoreValve U.S. Pivotal Trial
High-risk arm



No. at Risk				
TAVR	390	377	353	329
Surgical replacement	357	341	297	274

Adams DH. NEJM 2014

2-Year All-cause Mortality



No. at Risk					
Surgical	357	341	274	28	
Transcatheter	390	377	329	38	

Adams DH. NEJM 2014

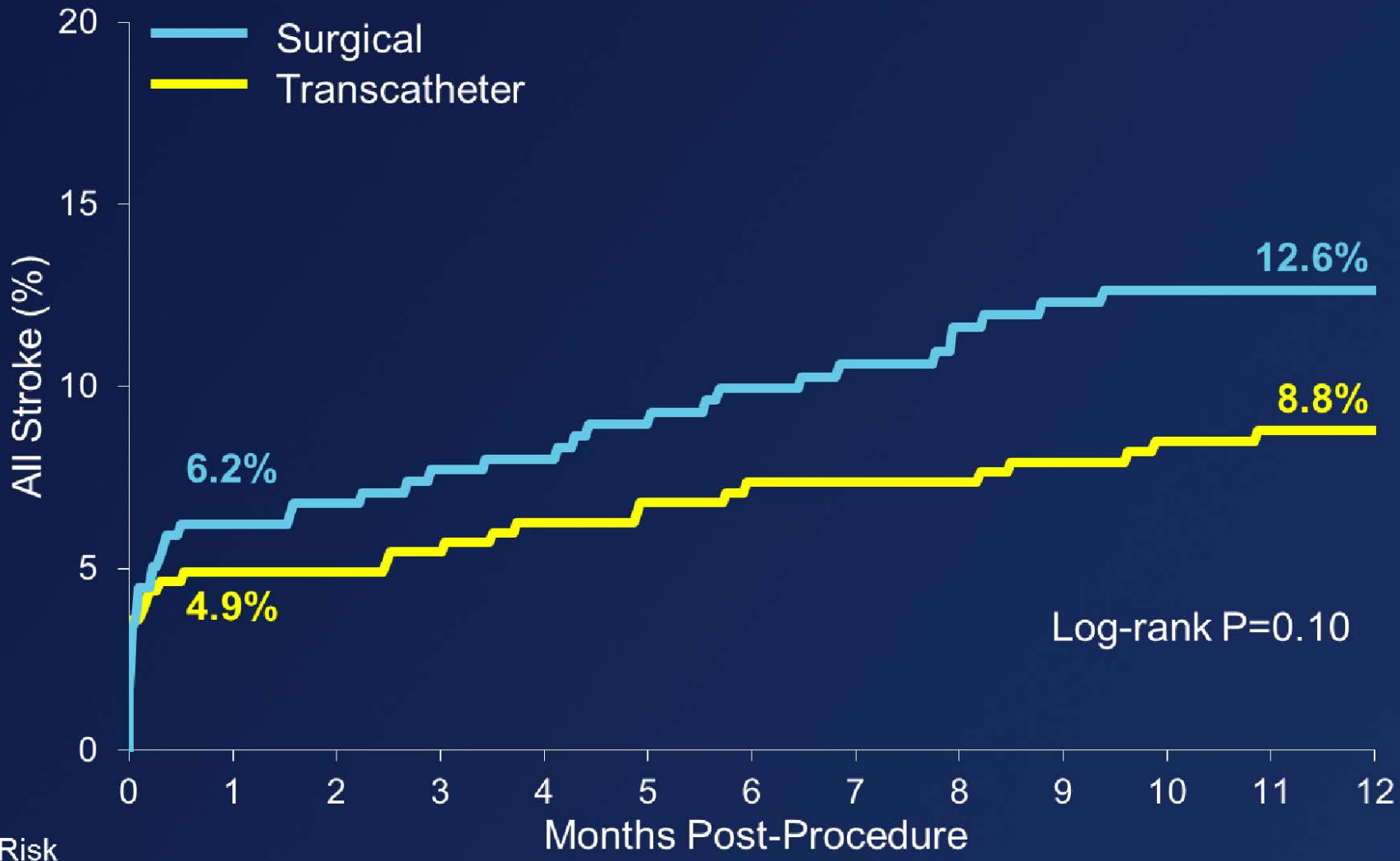
Other Endpoints

Events*	1 Month			1 Year		
	TAVR	SAVR	P Value	TAVR	SAVR	P Value
Vascular complications (major), %	5.9	1.7	0.003	6.2	2.0	0.004
Pacemaker implant, %	19.8	7.1	<0.001	22.3	11.3	<0.001
Bleeding (life threatening or disabling),%	13.6	35.0	<0.001	16.6	38.4	<0.001
New onset or worsening atrial fibrillation, %	11.7	30.5	<0.001	15.9	32.7	<0.001
Acute kidney injury, %	6.0	15.1	<0.001	6.0	15.1	<0.001

* Percentages reported are Kaplan-Meier estimates and log-rank P values

Adams DH. NEJM 2014

All Stroke



No. at Risk												
Surgical	357	322			274						249	
Transcatheter	390	363			334						314	

Adams DH. NEJM 2014

TAVR Randomized trials

PARTNER Cohort A Trial

Characteristic	Transcatheter Replacement (N=348)	Surgical Replacement (N=351)	P Value
Society of Thoracic Surgeons score†	11.8±3.3	11.7±3.5	0.61
Logistic EuroSCORE†	29.3±16.5	29.2±15.6	0.93

CoreValve U.S. Pivotal Trial

Characteristic	Intention-to-Treat Population		As-Treated Population	
	TAVR Group (N=394)	Surgical Group (N=401)	TAVR Group (N=390)	Surgical Group (N=357)
STS PROM estimate†				
Mean estimate — %	7.3±3.0	7.5±3.2	7.3±3.0	7.5±3.4
<4% — no. (%)	33 (8.4)	42 (10.5)	33 (8.5)	40 (11.2)
4–10% — no. (%)	308 (78.2)	288 (71.8)	304 (77.9)	251 (70.3)
>10% — no. (%)	53 (13.5)	71 (17.7)	53 (13.6)	66 (18.5)
Logistic EuroSCORE — %‡	17.6±13.0	18.4±12.8	17.7±13.1	18.6±13.0

Comparison of Complications and Outcomes to One Year of Transcatheter Aortic Valve Implantation Versus Surgical Aortic Valve Replacement in Patients With Severe Aortic Stenosis

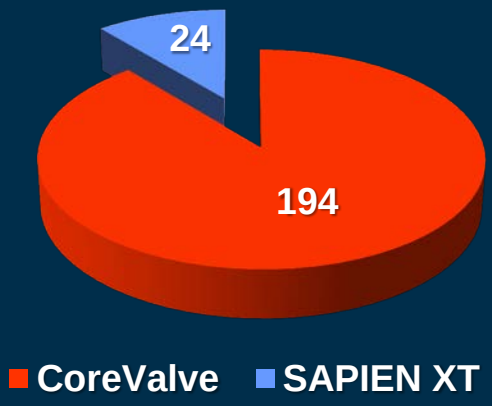
Corrado Tamburino, MD, PhD[a,c], Marco Barbanti, MD[a], Davide Capodanno, MD, PhD[a,c,*], Carmelo Mignosa, MD[b], Maurizio Gentile, MD[d], Patrizia Aruta, MD[a], Anna Maria Pistritto, MD[a], Claudio Bonanno, MD[a], Salvatore Bonura, MD[a], Alessandra Cadoni, MD[a], Simona Gulino, MD[a], Maria Concetta Di Pasqua, MD[a], Valeria Cammalleri, MD[a], Marilena Scarabelli, MD[a], Massimiliano Mulè, MD[a], Sebastiano Immè, MD[a], Giuliana Del Campo, MD[a], and Gian Paolo Ussia, MD[a]

Real world TAVI vs. SAVR

824 consecutive AS patients

606 patients undergoing SAVR

218 patients undergoing TAVI

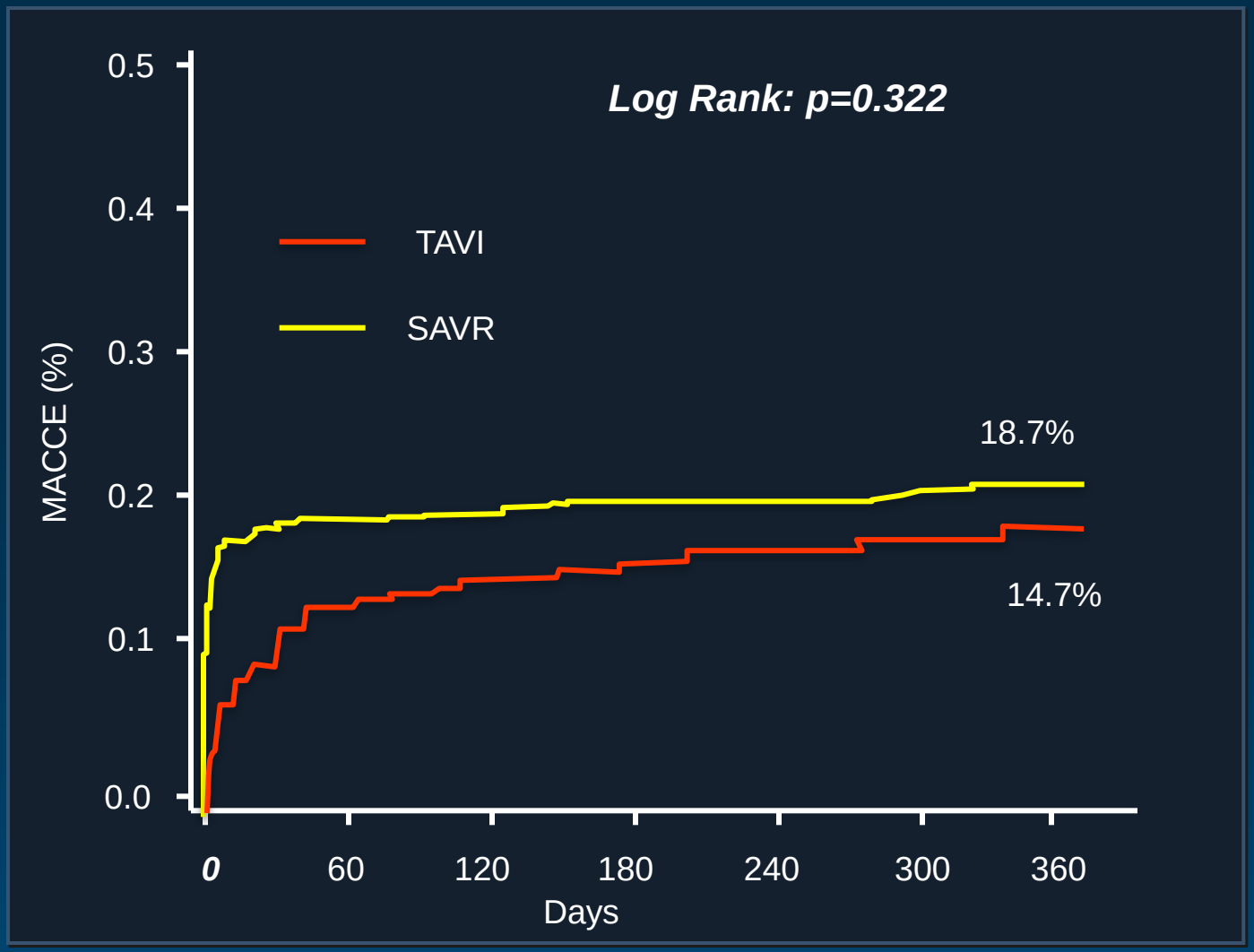


The “heart team” evaluated all the available clinical and imaging data and a consensus decision was obtained to determine the individual eligibility for TAVI

- Primary endpoint: MACCE at 1-year
- MACCE were defined as the composite of death from any cause, spontaneous myocardial infarction, and stroke, urgent or emergency conversion to surgery, or life-threatening/disabling bleeding.
- Clinical outcomes were defined according to the VARC

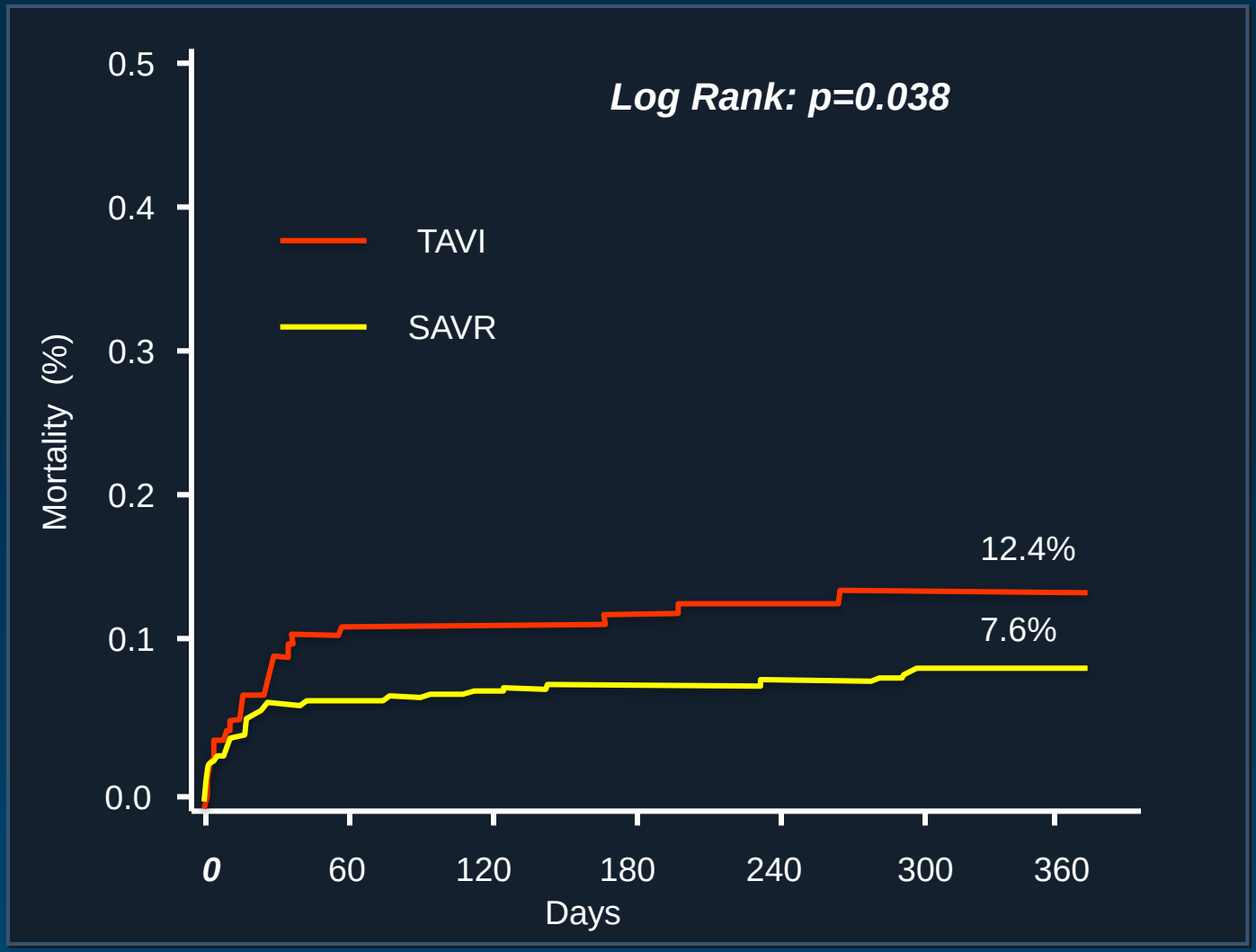
Tamburino C et al. AJC 2012

Real world TAVI vs. SAVR



Tamburino C et al. AJC 2012

Real world TAVI vs. SAVR



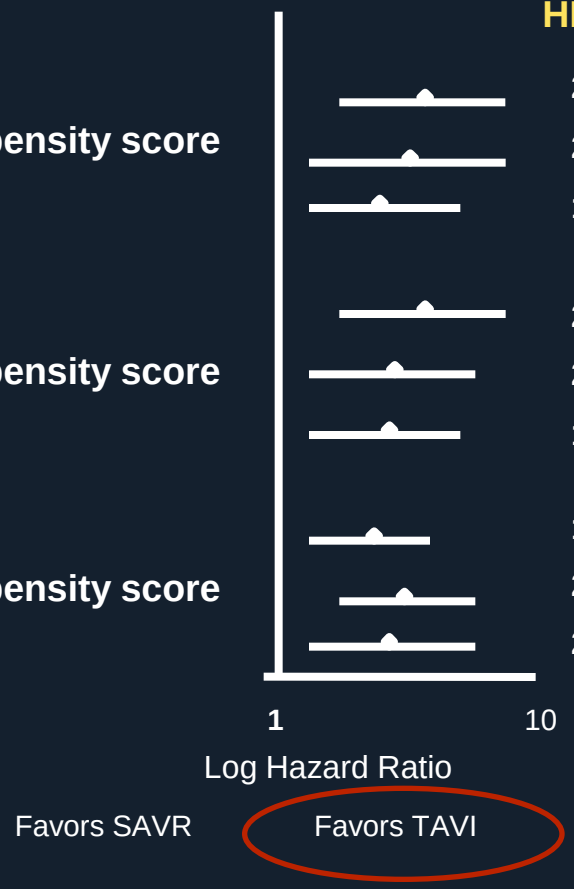
Tamburino C et al. AJC 2012

Real world TAVI vs. SAVR

30 days
- Adjusted with covariates
- Adjusted with covariates and propensity score
- Adjusted with propensity score

6 months
- Adjusted with covariates
- Adjusted with covariates and propensity score
- Adjusted with propensity score

12 months
- Adjusted with covariates
- Adjusted with covariates and propensity score
- Adjusted with propensity score

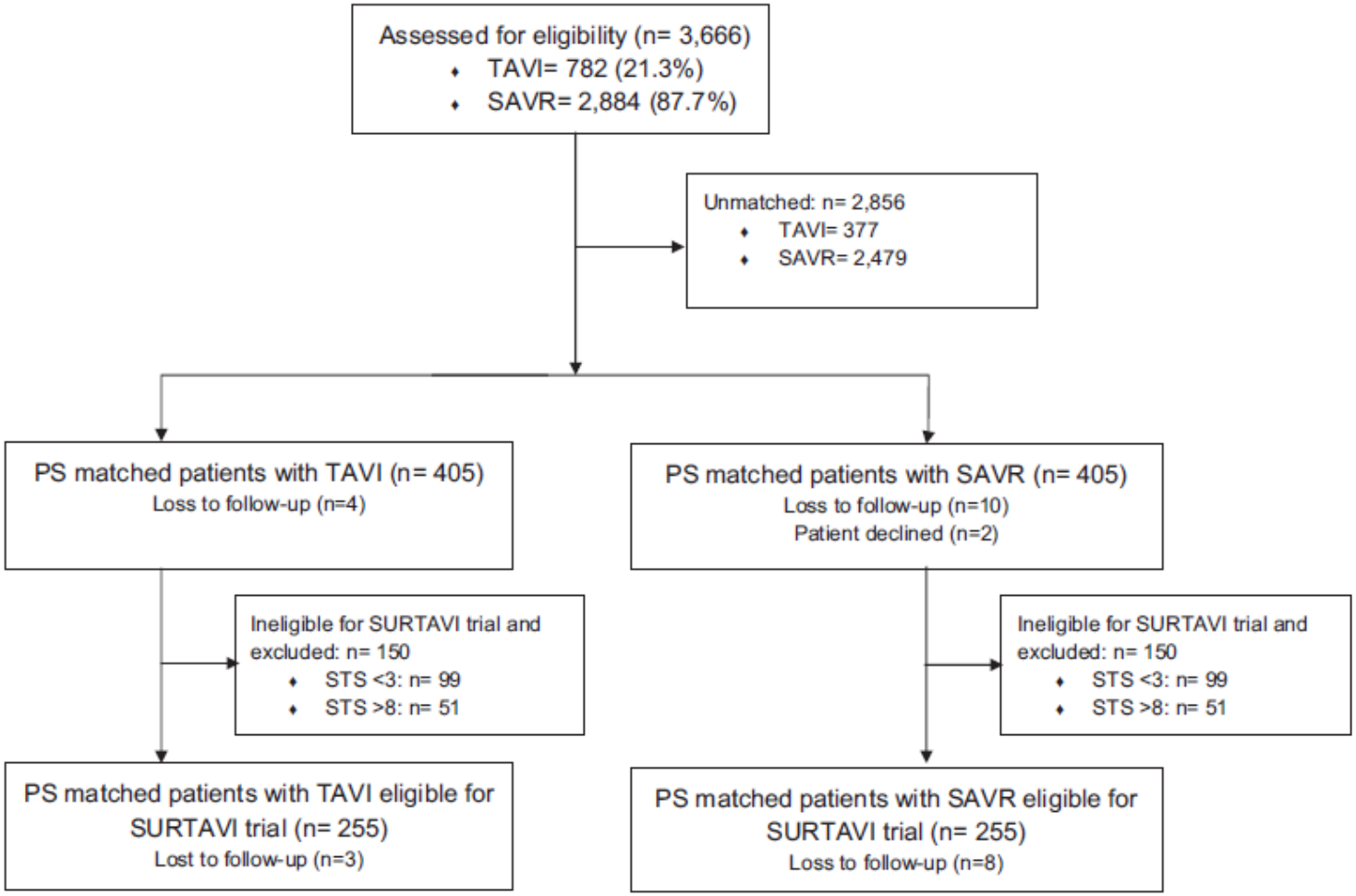


	HR/OR	LCL	UCL	p
	2.49	1.3	4.77	0.006
	2.28	1.2	4.31	0.012
	1.85	1.16	2.97	0.010
	2.29	1.26	4.15	0.006
	2.12	1.17	3.83	0.013
	1.81	1.16	2.83	0.009
	1.68	1.09	2.57	0.009
	2.30	1.52	3.6	0.014
	2.15	1.22	3.82	0.018

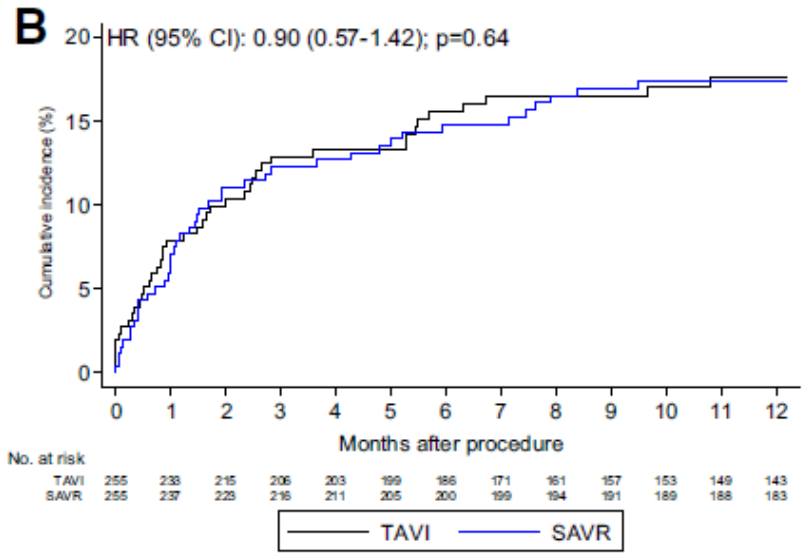
Tamburino C et al. AJC 2012

A 3-Center Comparison of 1-Year Mortality Outcomes Between Transcatheter Aortic Valve Implantation and Surgical Aortic Valve Replacement on the Basis of Propensity Score Matching Among Intermediate-Risk Surgical Patients

BERMUDA trial



BERMUDA trial



	TAVI, n (IR)	SAVR, n (IR)	HR (95% CI)	P Interaction
Overall	42 (17.5)	43 (17.3)	0.90 (0.57-1.42)	
Age				0.91
≤80	17 (17.5)	17 (17.0)	0.87 (0.41-1.82)	
>80	25 (17.5)	26 (17.6)	0.92 (0.51-1.63)	
Gender				0.024
Male	22 (23.9)	15 (15.7)	1.67 (0.81-3.41)	
Female	20 (13.6)	28 (18.4)	0.56 (0.30-1.04)	
Logistic EuroSCORE				0.91
≤20	26 (16.1)	27 (15.8)	0.88 (0.50-1.56)	
>20	16 (20.7)	16 (20.7)	0.93 (0.44-1.98)	
STS score				0.53
≤4.0	15 (17.9)	17 (18.9)	0.73 (0.34-1.60)	
>4.0	27 (17.4)	26 (16.5)	1.00 (0.57-1.76)	
Diabetes mellitus				0.22
No	32 (19.1)	29 (17.1)	1.08 (0.62-1.86)	
Yes	10 (14.0)	14 (18.0)	0.57 (0.24-1.36)	
Left ventricular function				0.20
<30%	6 (30.9)	2 (9.5)	2.50 (0.49-12.9)	
≥30%	36 (16.3)	41 (18.1)	0.82 (0.50-1.31)	
Cerebrovascular accident				0.93
No	35 (16.2)	35 (15.7)	0.91 (0.55-1.50)	
Yes	7 (30.6)	8 (33.0)	0.86 (0.29-2.55)	
Peripheral vascular disease				0.48
No	40 (17.9)	39 (16.9)	0.94 (0.59-1.52)	
Yes	2 (12.5)	4 (23.6)	0.50 (0.09-2.73)	
Pulmonary hypertension				0.42
No	33 (17.1)	36 (18.1)	0.89 (0.49-1.36)	
Yes	9 (18.1)	7 (14.4)	1.33 (0.46-3.84)	
Prior CABG				
No	40 (18.2)	40 (17.7)	0.92 (0.57-1.47)	0.74
Yes	2 (10.0)	3 (13.6)	0.67 (0.11-3.99)	

OBSERVANT

Italian OBservational Study of Effectiveness of AVR-TAVI procedures for severe Aortic steNosis Treatment

Ministero della Salute

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gise
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di Cardiologia Invasiva

ITACTA
ITALIAN ASSOCIATION OF CARDIOTHORACIC ANESTHESIOLOGISTS

Didactic Symposia: AORTIC VALVE THERAPIES Today and Tomorrow I
Session II. TAVR Clinical Indications 2014

One-Year Outcomes of Transfemoral Transcatheter Versus Surgical Aortic Valve Replacement in Patients with Intermediate Surgical Risk: *The Italian OBSERVANT Study*

on behalf of the Italian OBSERVANT Registry investigators

OBSERVANT - Methods

STUDY DESIGN

- Observational prospective multicenter cohort study
- Enrollment from December 2010 to June 2012
- Unique database for contemporary data collection on both procedures

STUDY POPULATION

- All adult patients admitted to hospitals with a diagnosis of severe symptomatic AS and requiring an interventional treatment (TAVI or AVR)

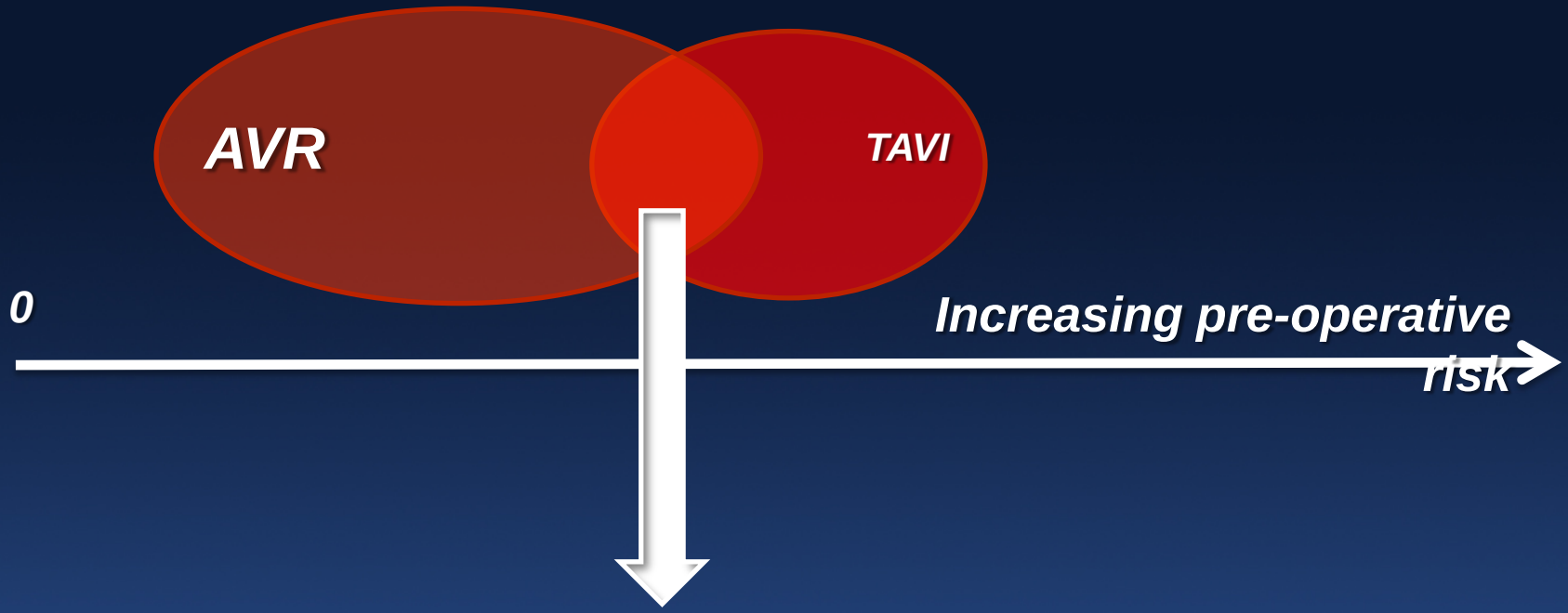
DATA COLLECTION

- Demographic characteristics
- Health status prior to intervention
- Standardized online data entry on a password-protected website

ENDPOINTS AND FOLLOW-UP

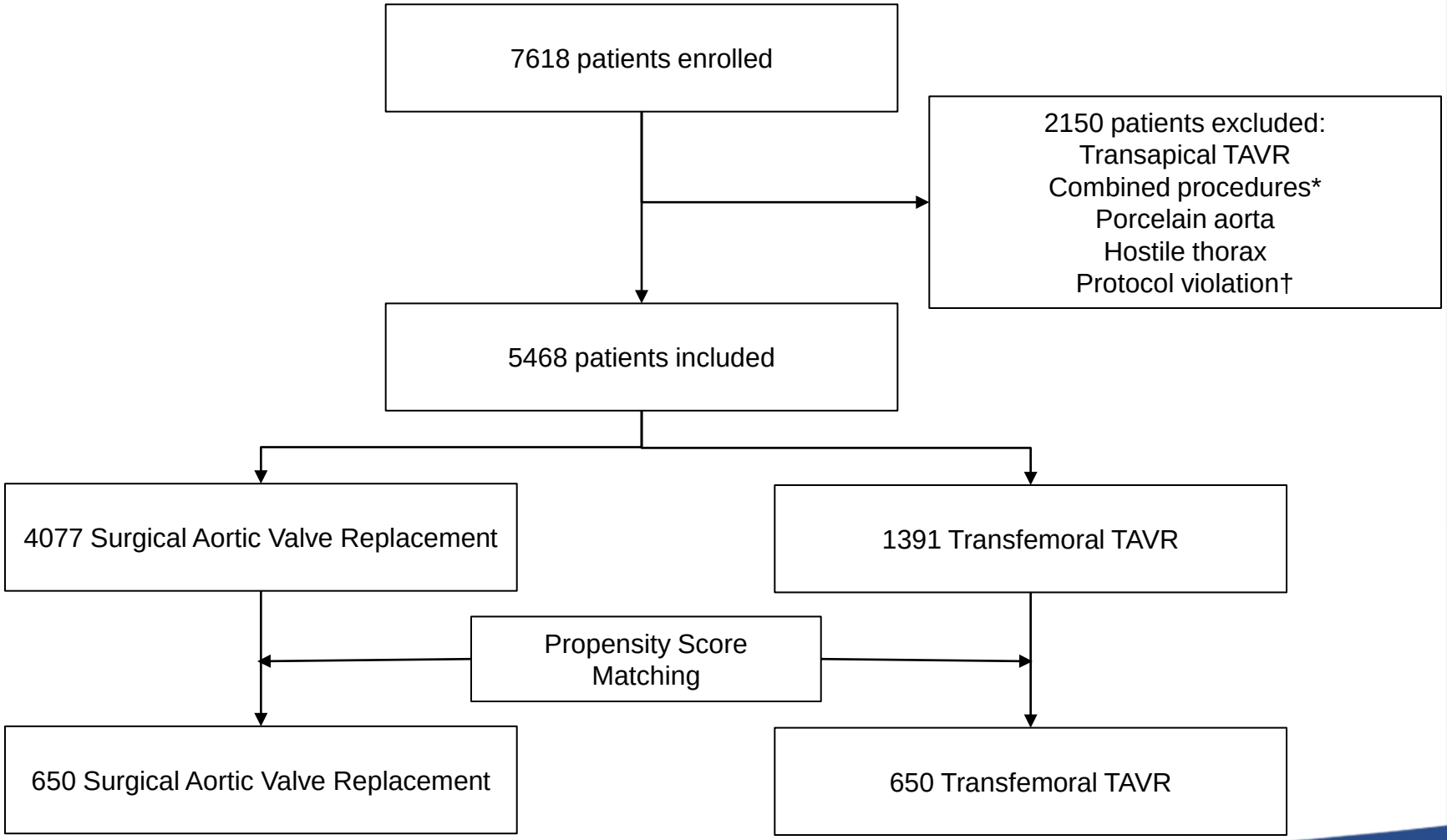
- Administrative follow-up through a record linkage with the HDR database linked with the Tax Register Information System

Methods – Propensity Score

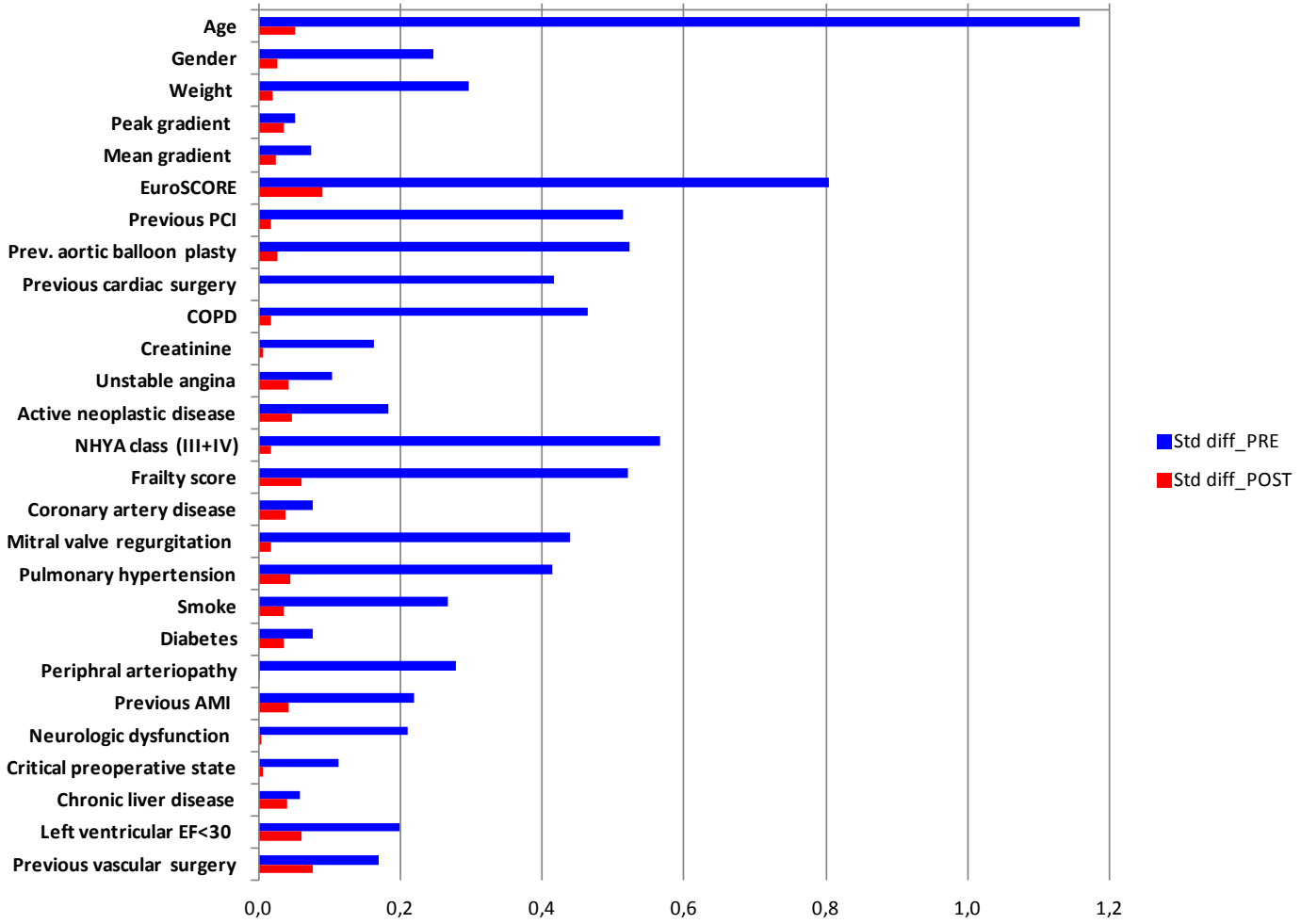


This area represents the subgroup of patients potentially eligible to both procedures

Results – Patients' flow chart



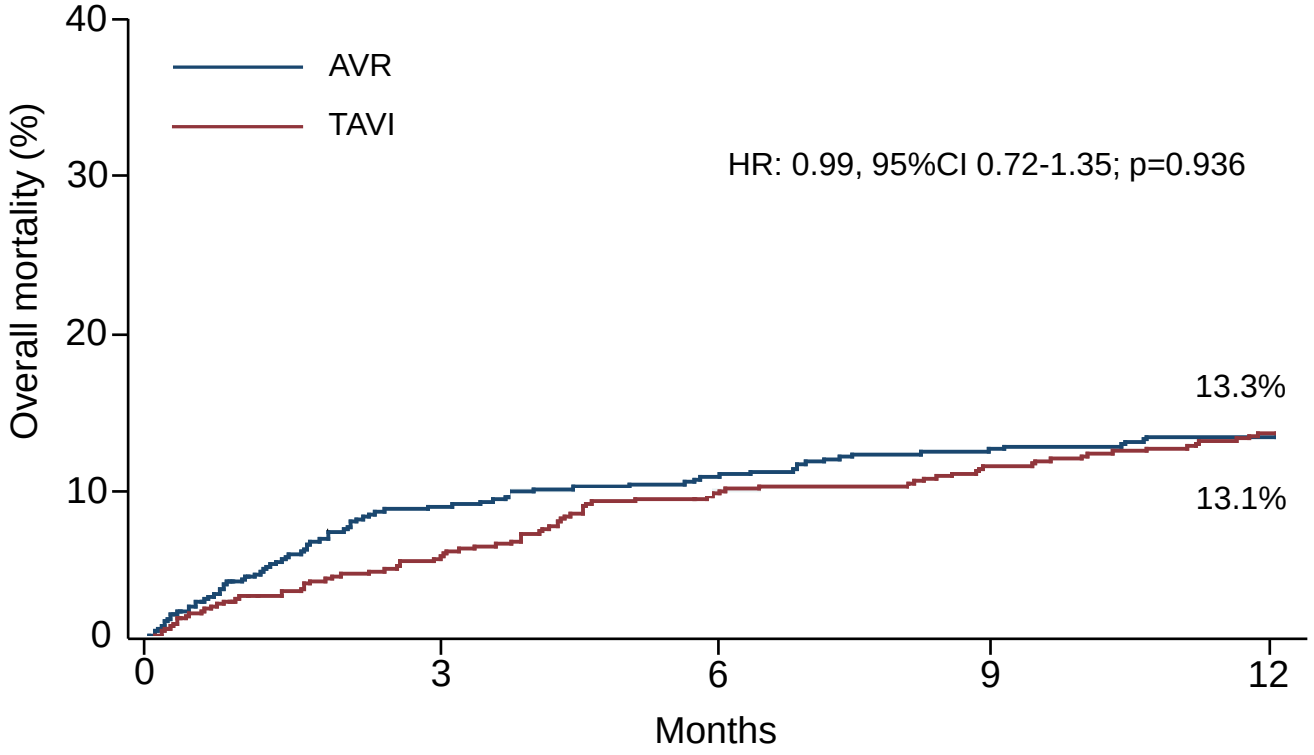
Results – Propensity matching



In-hospital Outcomes & 30-day mortality

	SAVR N=650	TAVI N=650	P value
Renal failure, n (%)	64 (10.9)	36 (6.1)	0.004
New PPM, n (%)	23 (3.6)	98 (15.5)	<0.001
AMI, n (%)	5 (0.8)	3 (0.5)	0.479
Stroke, n (%)	14 (2.2)	8 (1.3)	0.180
Infection			
Wound, n (%)	10 (1.6)	6 (1.0)	
Lung or other organs, n (%)	24 (3.9)	29 (4.7)	0.191
Sepsis, n (%)	11 (1.8)	4 (0.6)	
RBC Transfusions: number of units	3.6±3.6	2.3±2.2	0.002
ICU stay (days)	3.8±7.7	3.2±4.7	0.077
Total hospital stay (days)	12.6±1.34	8.8±8.5	<0.001
Death (30 days), n (%)	24 (3.8)	20 (3.2)	0.546

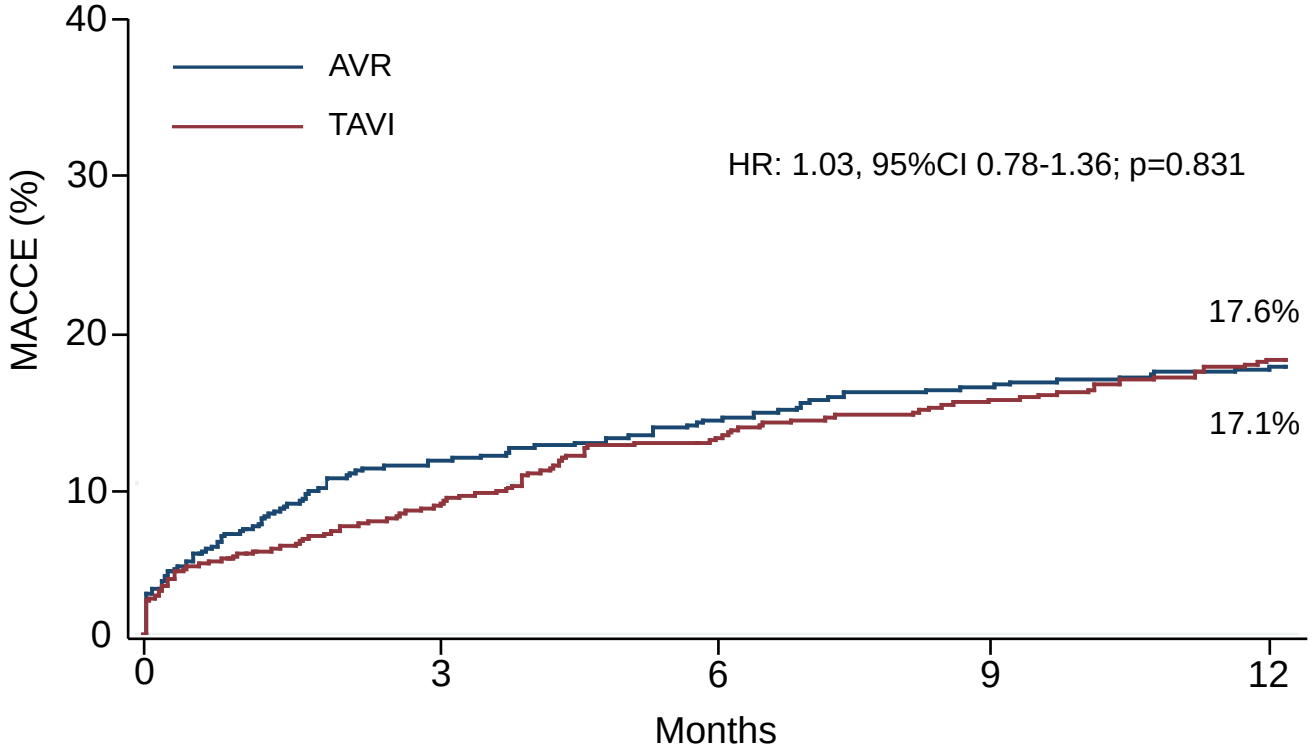
Overall mortality



No. at risk:

AVR	650	549	535	525	519
TAVI	650	569	543	531	517

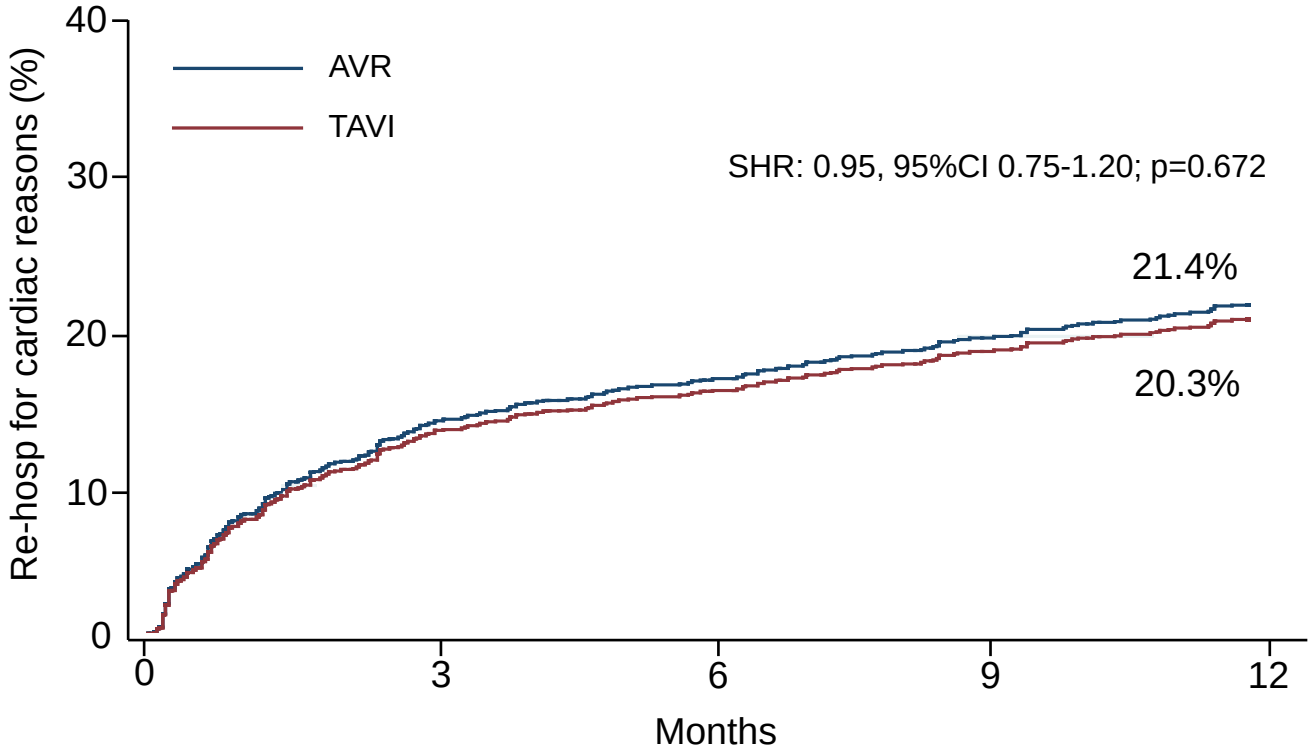
MACCE



No. at risk:

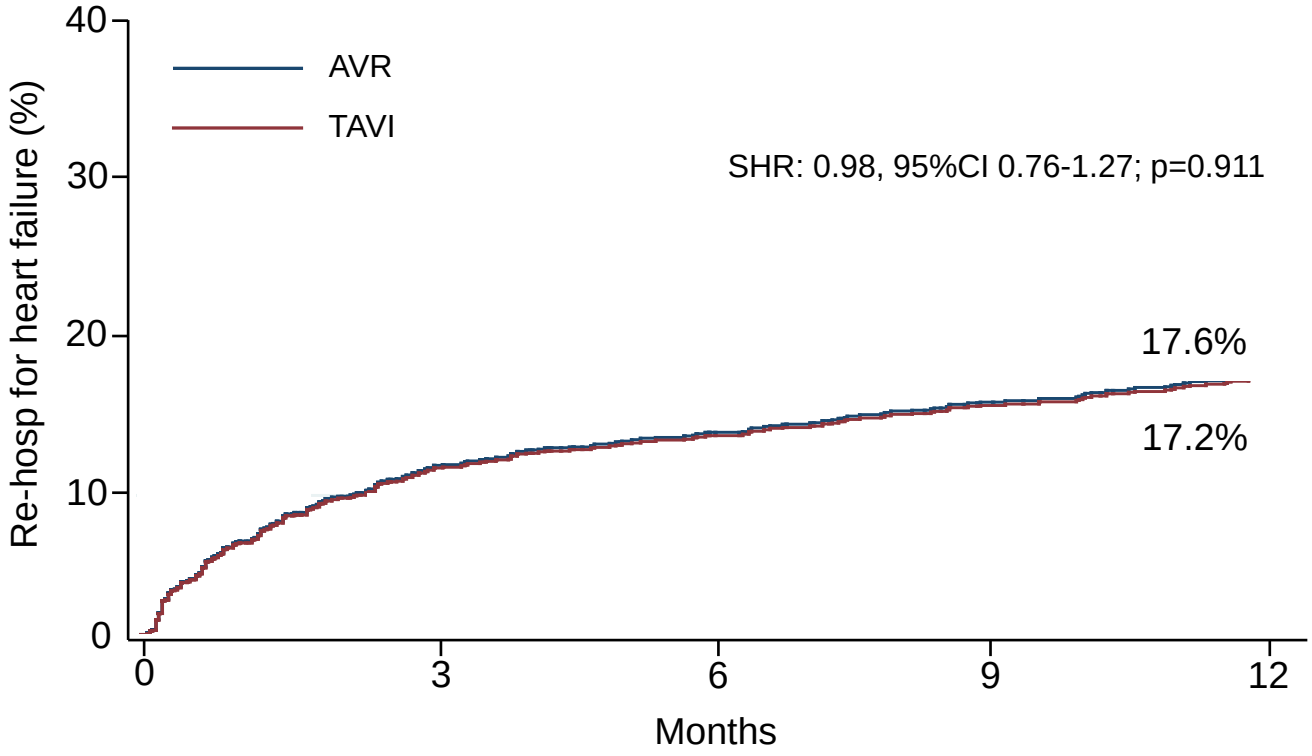
AVR	650	534	515	502	495
TAVI	650	552	525	509	492

Re-hospitalization for cardiac reasons
Competing risk regression*



**Fine and Gray method*

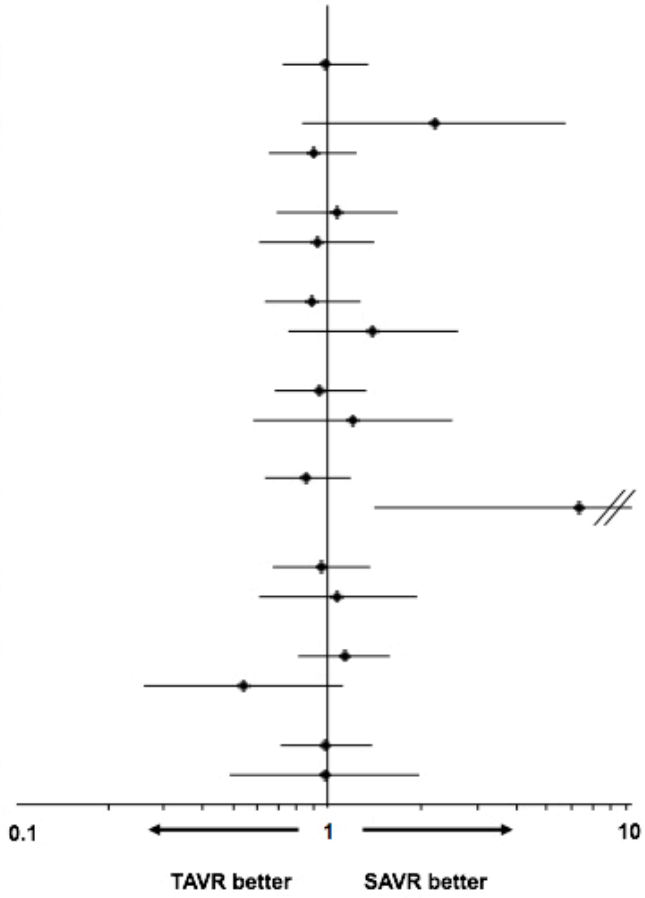
Re-hospitalization for heart failure
Competing risk regression*



**Fine and Gray method*

Primary End Point – Subgroups Analysis

Subgroups	Death from any cause		Risk ratio (95% CI)	P value for interaction
	SAVR	TAVR		
	n (%)			
Overall	82 (13.6)	83 (13.8)	0.99 (0.72-1.35)	
Age				0.09
≤75	6 (6.3)	13 (13.7)	2.19 (0.83-5.76)	
>75	76 (14.9)	70 (13.8)	0.90 (0.65-1.24)	
Gender				0.66
Male	37 (14.9)	40 (16.1)	1.07 (0.69-1.68)	
Female	44 (12.6)	43 (12.1)	0.93 (0.61-1.42)	
Diabetes mellitus				0.22
No	65 (14.3)	59 (13.0)	0.89 (0.63-1.27)	
Yes	17 (11.3)	24 (16.1)	1.39 (0.75-2.60)	
Pulmonary hypertension				0.56
No	69 (13.0)	67 (12.7)	0.95 (0.68-1.33)	
Yes	13 (17.2)	16 (21.3)	1.21 (0.58-2.52)	
NYHA class 4				0.01
No	80 (14.5)	71 (13.0)	0.86 (0.63-1.19)	
Yes	2 (3.7)	2 (21.6)	2.00 (1.42-28.47)	
Moderate/severe MR				0.72
No	60 (13.3)	59 (13.1)	0.96 (0.67-1.38)	
Yes	22 (14.4)	24 (15.8)	1.08 (0.61-1.93)	
Coronary artery disease				0.07
No	63 (12.3)	72 (14.8)	1.14 (0.81-1.59)	
Yes	19 (16.3)	11 (9.5)	0.54 (0.26-1.13)	
Logistic Euroscore				0.99
≤5%	66 (13.6)	67 (13.8)	0.99 (0.71-1.40)	
>5%	16 (13.5)	16 (13.6)	0.99 (0.49-1.97)	



Limitations

- **OBSERVANT is not a randomized trial**
- **Outcomes were not defined according to Valve Academic Research Consortium (VARC)**
- **No echo corelab**
- **Transapical procedures were excluded**

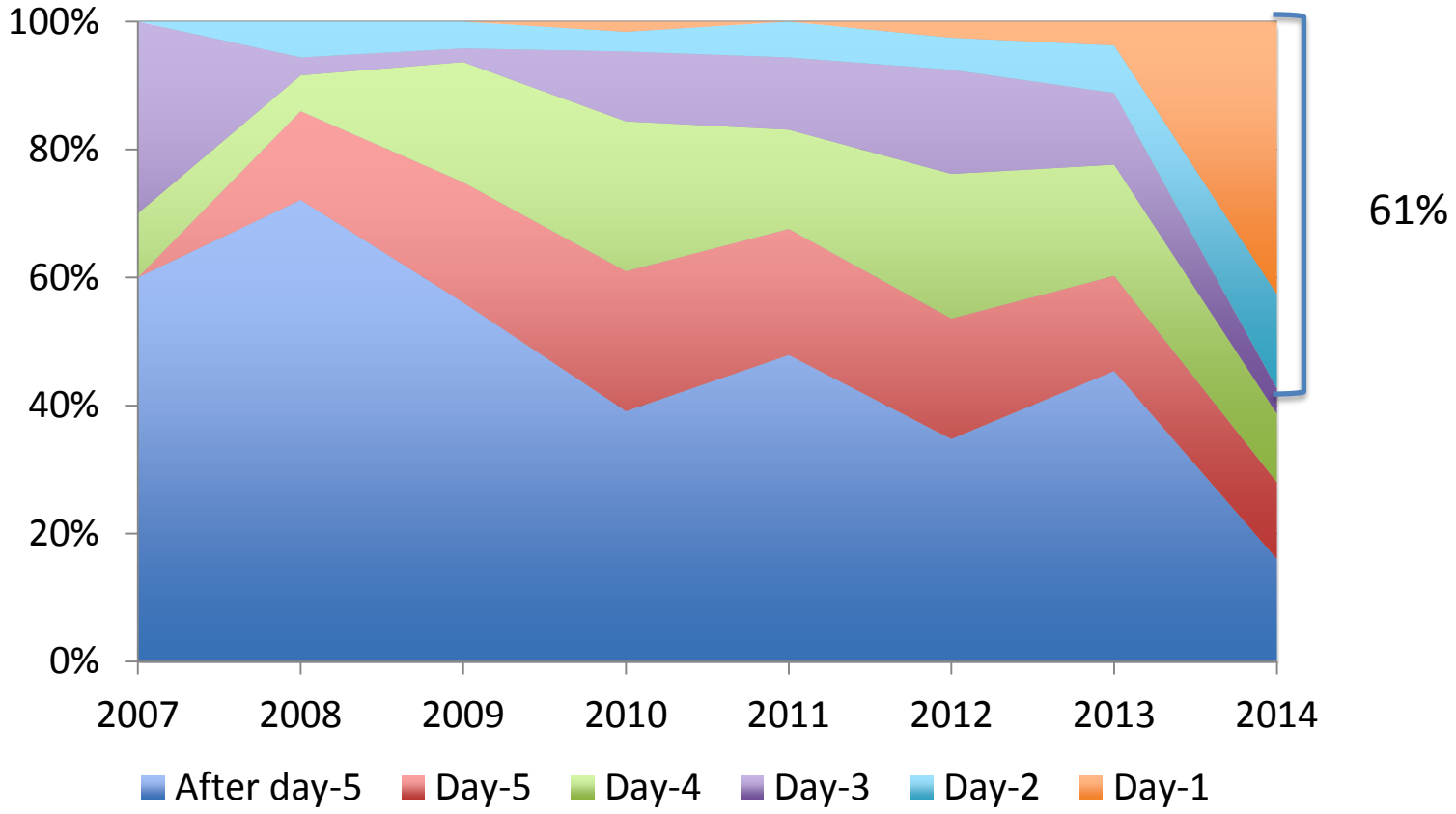
Final Comment

- No surgical valve ever tested in RCT
- TAVI is well beyond the “proof of concept”
- Long-term durability and peformance tested
- Comparative RCTs and Registries with first percutaneous models showed similar or better results with TAVI vs SAVR
- PPM, PVL markedly reduced with new models and appropriate sizing and implant

Early discharge after transfemoral TAVI

Proof of concept – Ferrarotto Experience

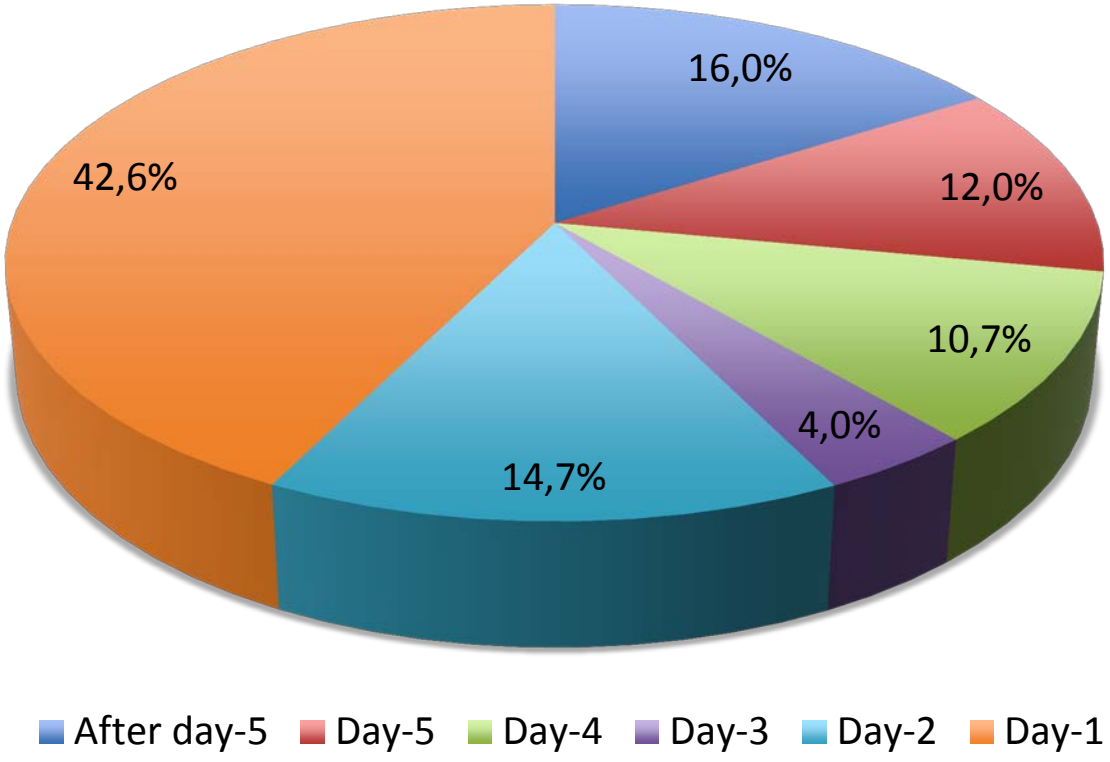
N=465 patients



Early discharge after transfemoral TAVI

Proof of concept – Ferrarotto Experience

- Jan 2014- Aug 2014
- N=74 pts (n=45, 61.3%, discharged within 3 days)
- Early discharge group: 30-day post discharge PPM: n=1, 2.8%



Early discharge after transfemoral TAVI

Proof of concept – Ferrarotto Experience

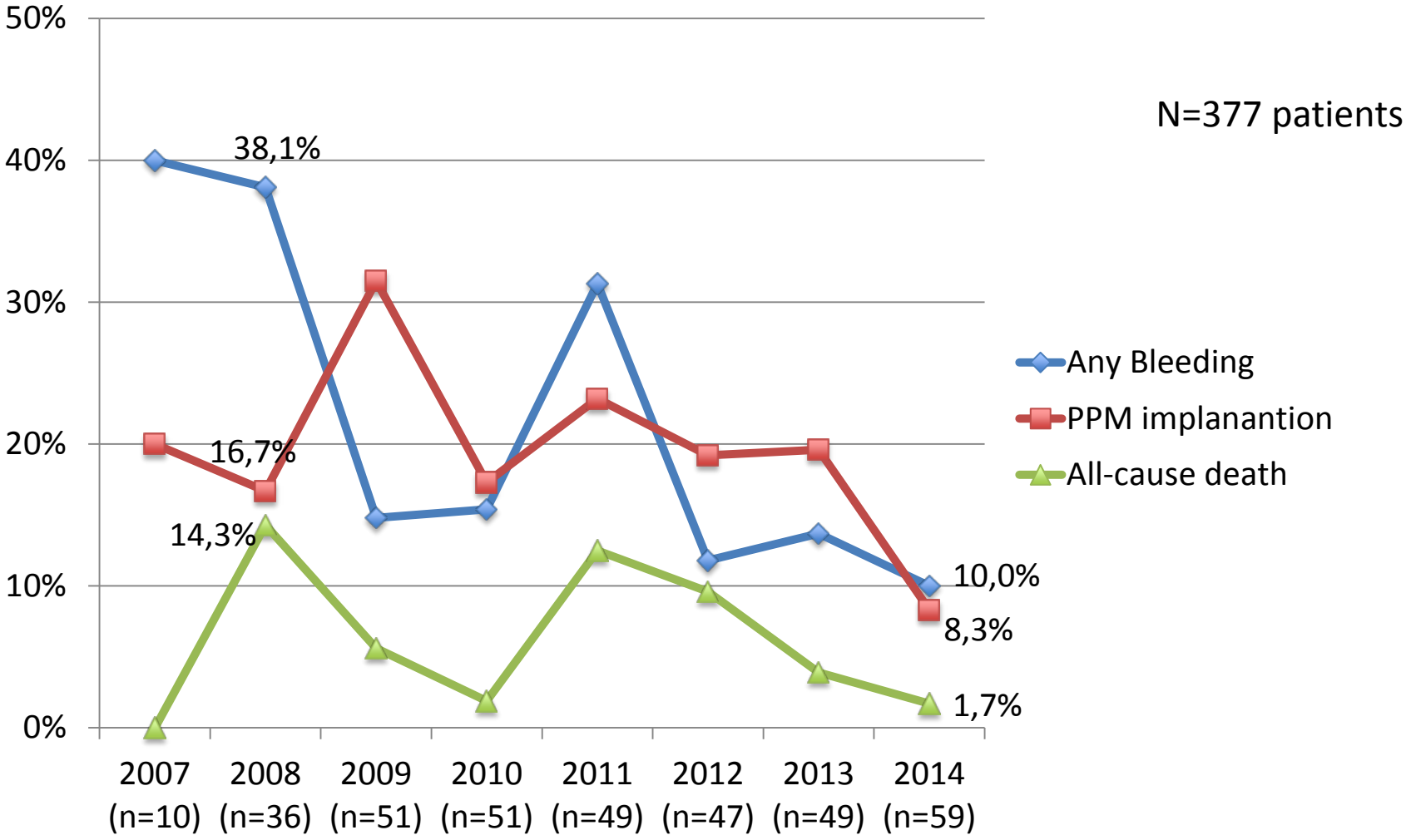
30-day outcomes post-discharge

	Before matching			After matching		
	Early discharge (n=107)	**Late discharge (n=358)**	**P value**	**Early discharge (n=89)**	**Late discharge (n=178)**	**P value**
Death	2 (1.9)	6 (1.7)	0.583	2 (2.2)	3 (1.7)	0.540
New PPM	0 (0.0)	2 (0.6)	0.592	0 (0.0)	2 (1.1)	0.444
Any bleeding	1 (0.9)	0 (0.0)	0.230	1 (1.1)	0 (0.0)	0.333
Re-hosp	1 (0.9)	3 (0.8)	0.650	1 (1.1)	2 (1.1)	1.000
Composite safety endpoint	3 (2.8)	8 (2.2)	0.483	3 (3.4)	5 (2.8)	0.533

Barbanti M et al, submitted

Transcatheter Aortic Valve Implantation

CoreValve Ferrarotto Experience (June 2007-October 2014)



My crystal ball