Clinical Outcomes of RCTs and Registries

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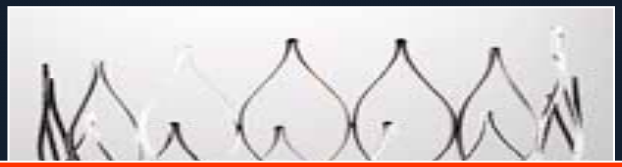
TAVR – A 10-Year Anniversary

TAVR Technologies

Current Generation Devices

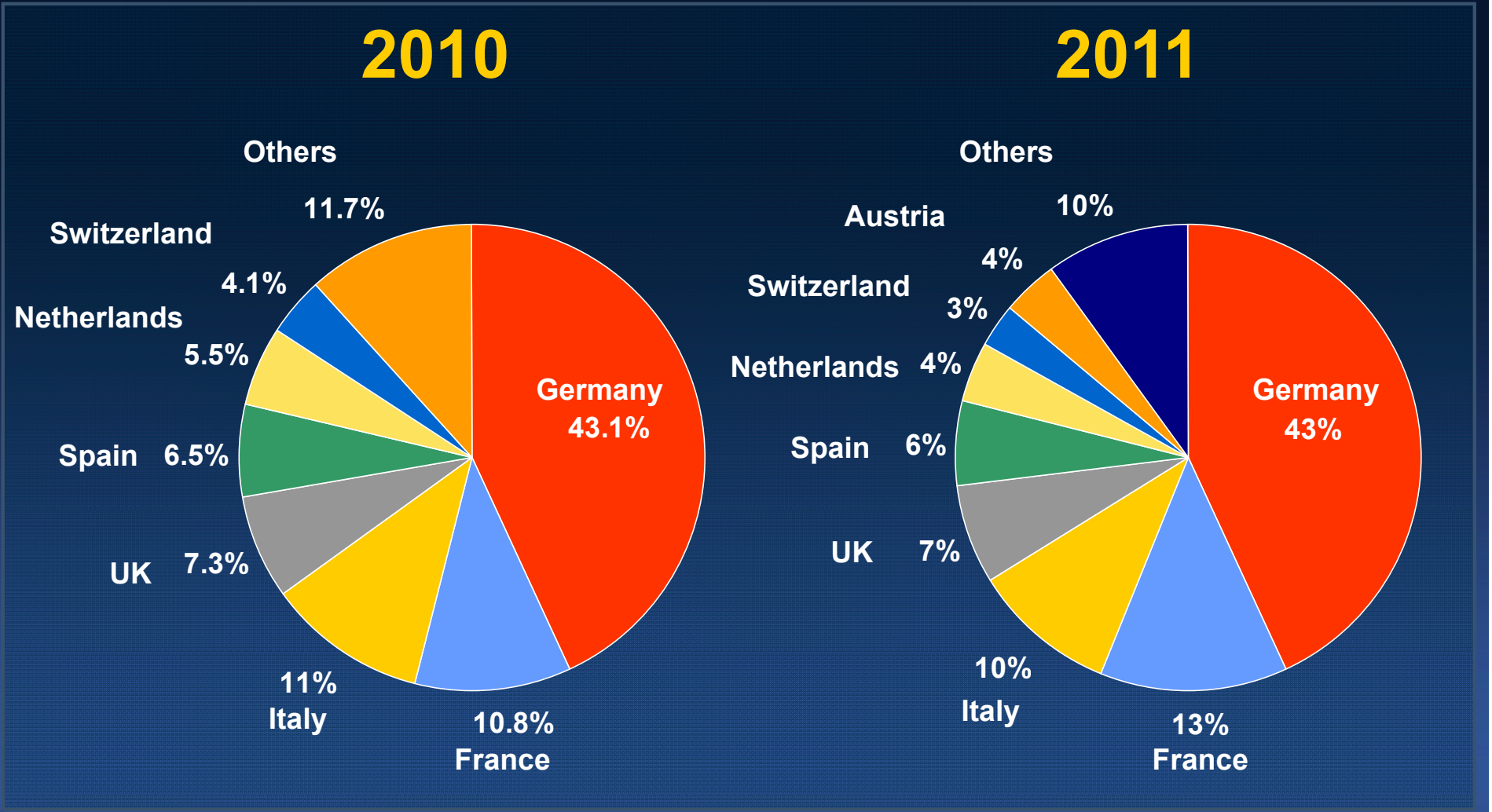


~ 50,000 patients treated thru 2011
in > 500 interventional centers
around the world !

Edwards Lifesciences

Medtronic CoreValve

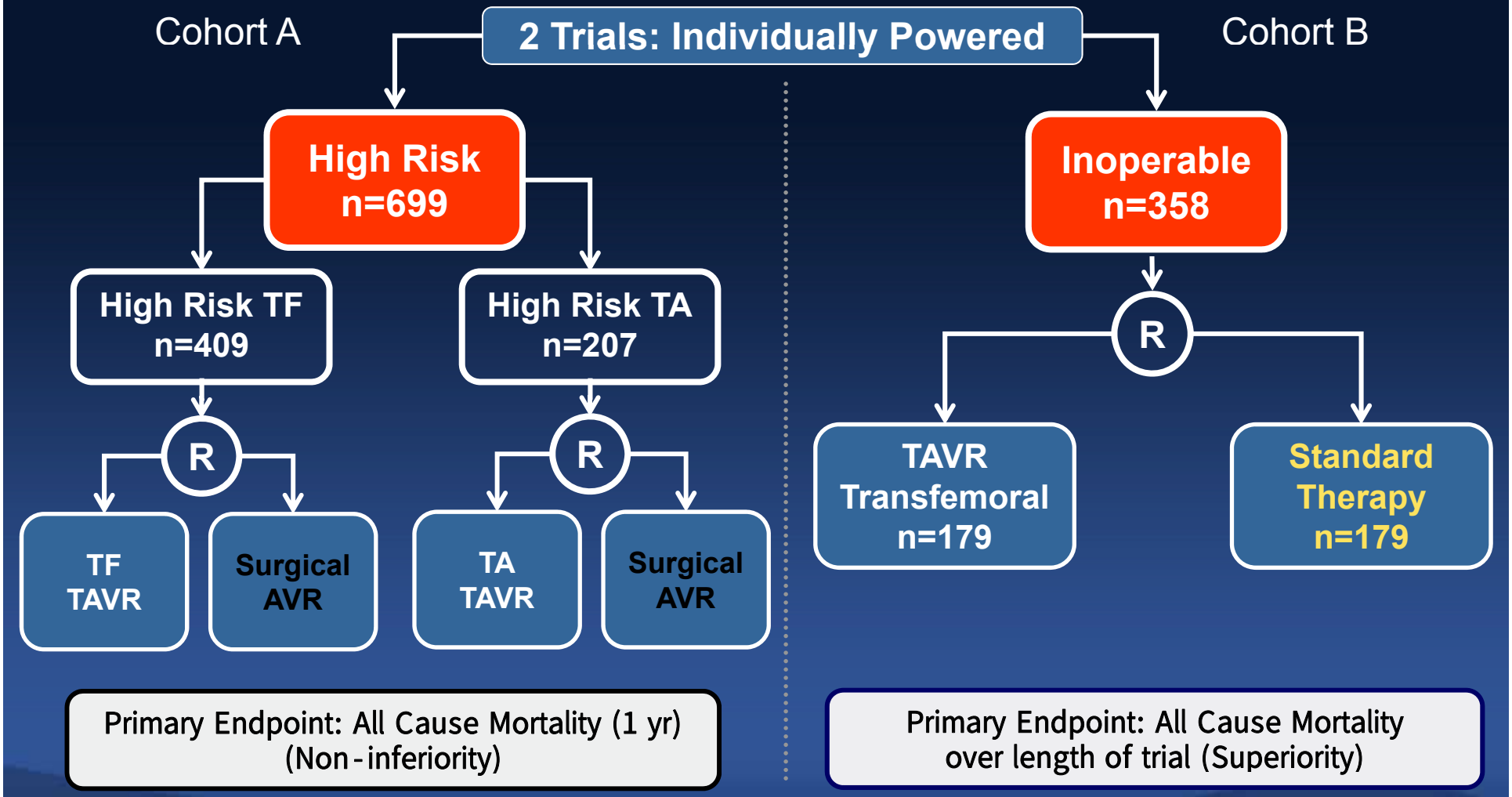
Market Share Across EU Countries



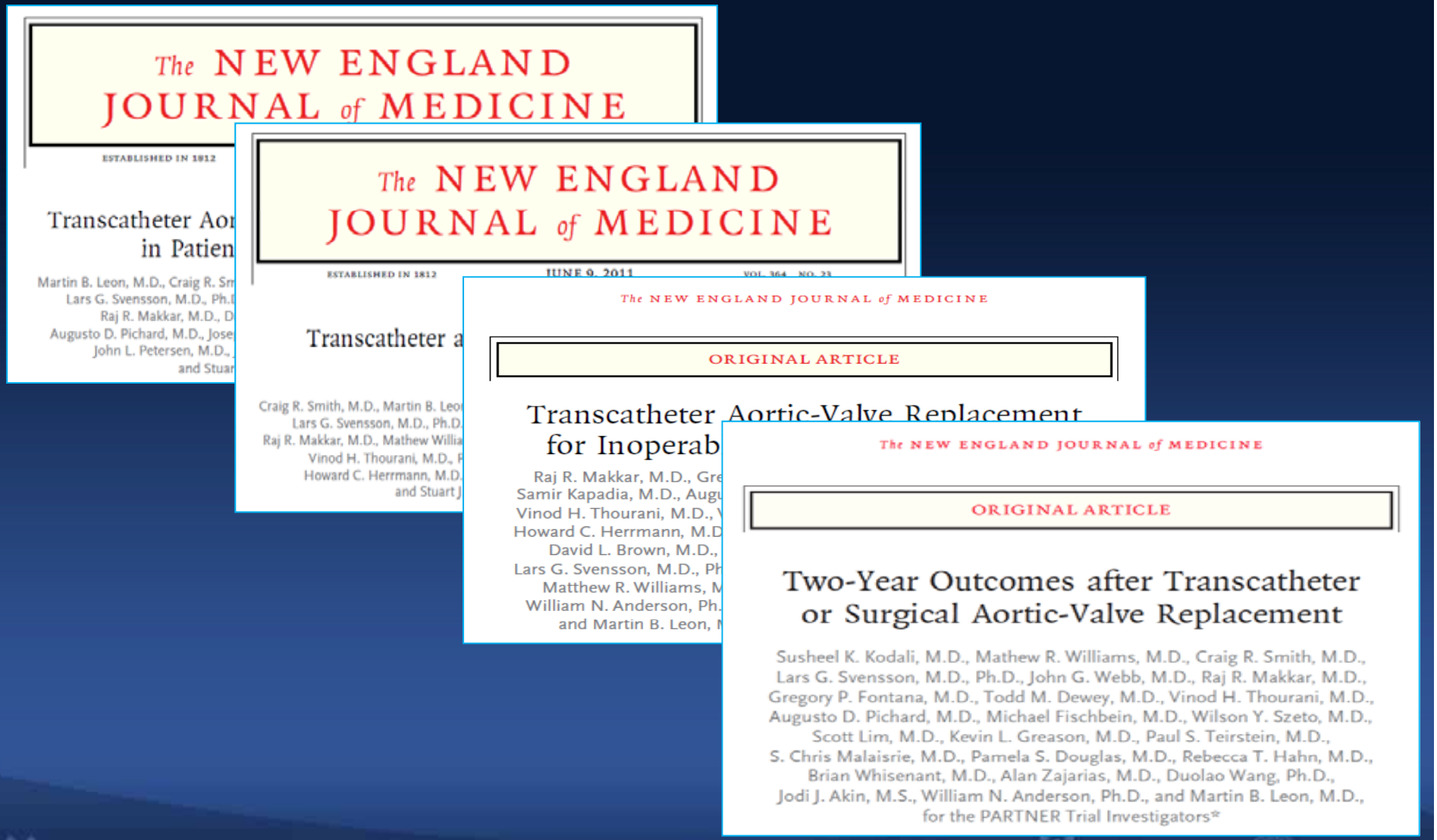
Source: BIBA Medical, UK-based provider of market analysis for the medical device industry

General Outcomes in RCT

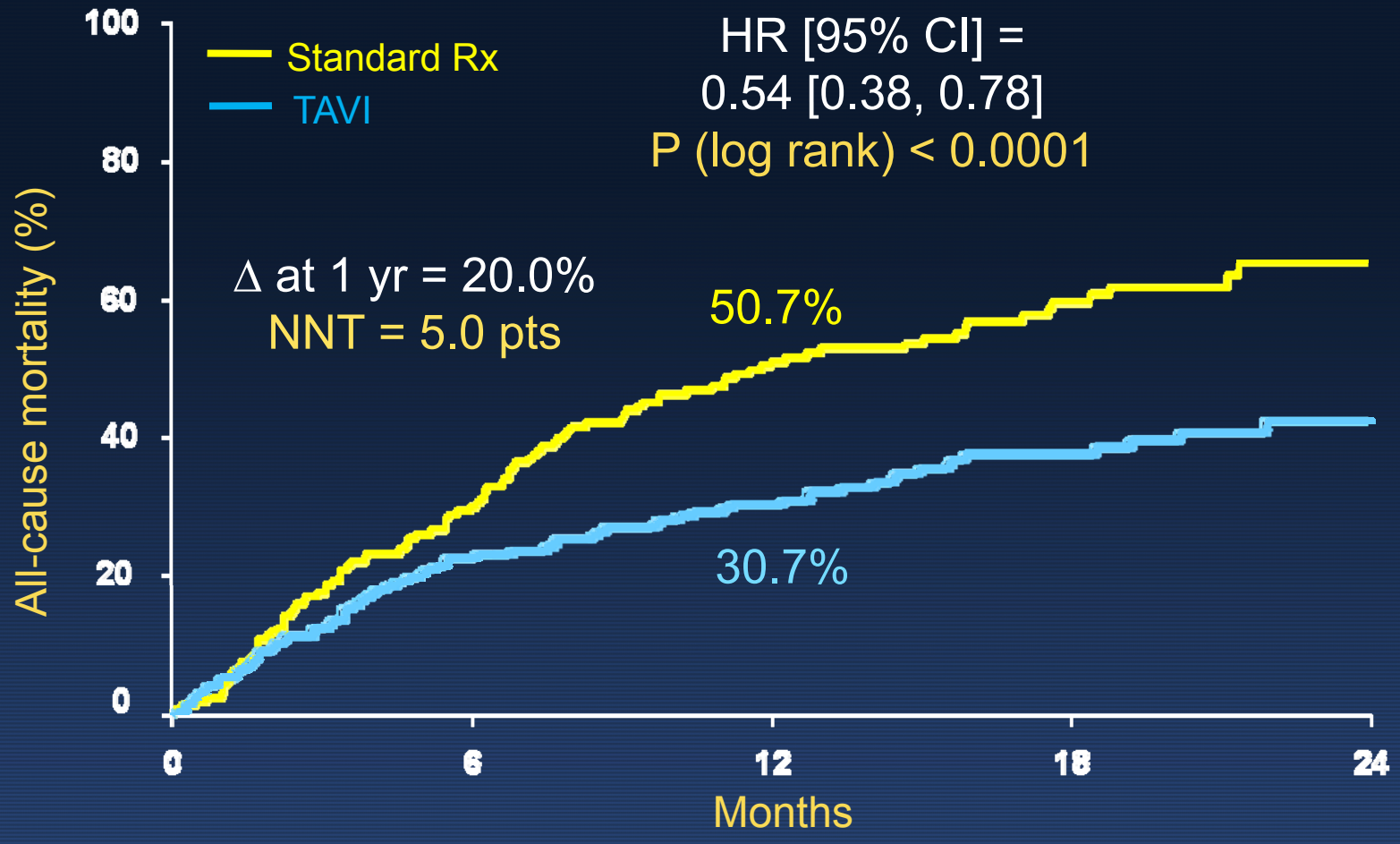
PARTNER Trial Design
Symptomatic Severe Aortic Stenosis



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



PARTNER Inoperable
Primary Endpoint: All-Cause Mortality

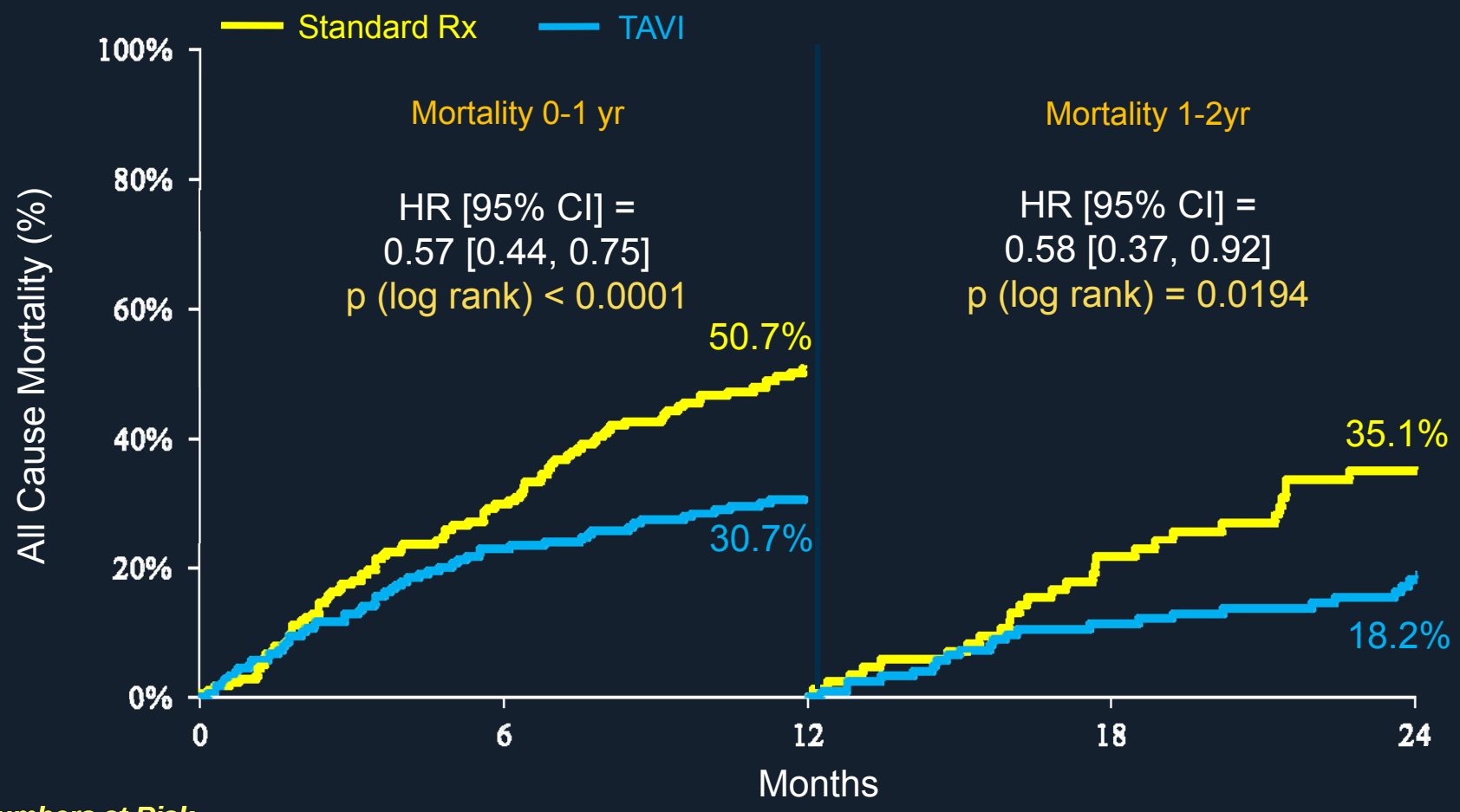


Numbers at Risk					
TAVI	179	138	122	67	26
Standard Rx	179	121	83	41	12

Leon et al, NEJM 2010; 363:1597-1607, Makkar et al, NEJM 2012;366:1696

PARTNER Inoperable

2-Y Mortality : Landmark Analysis

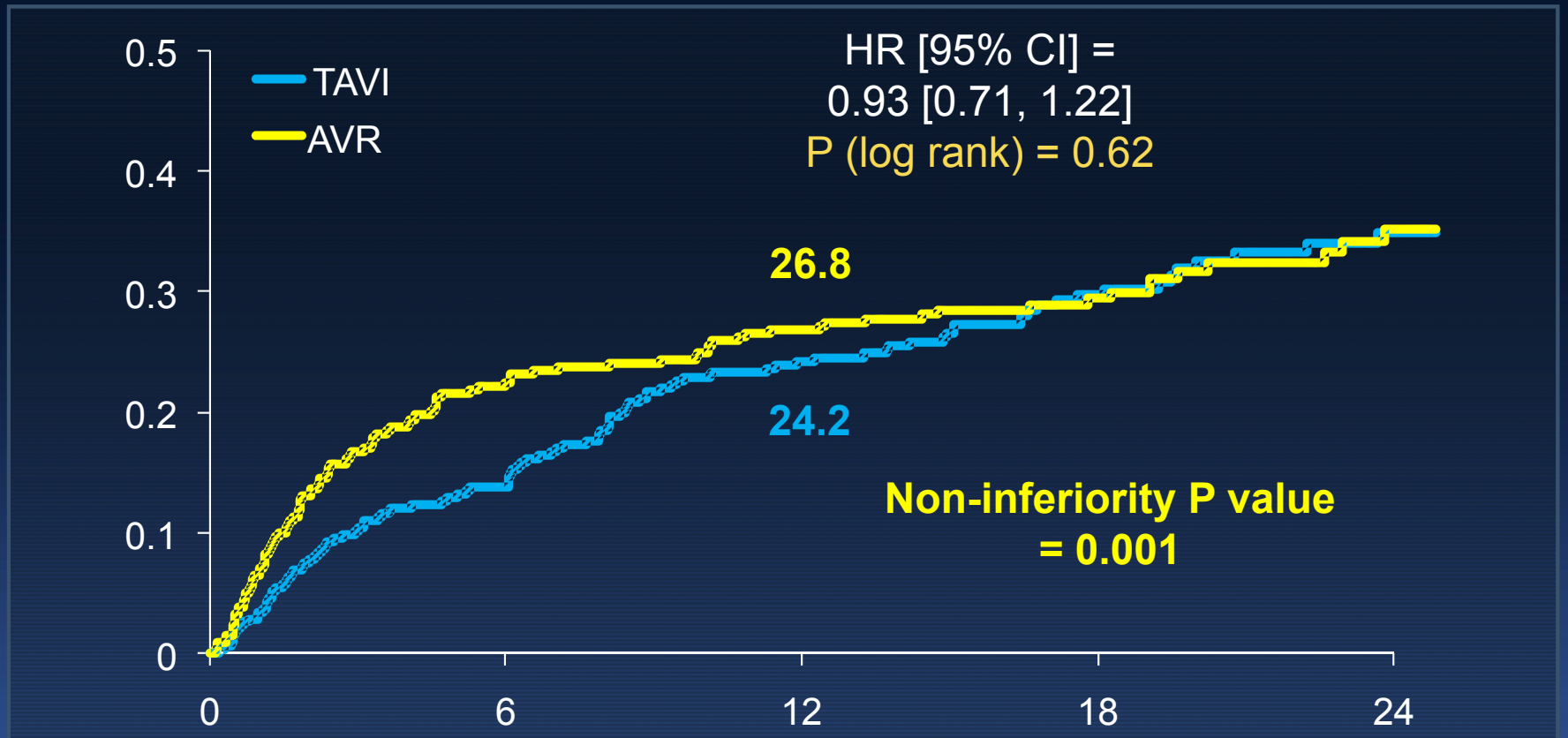


Numbers at Risk

TAVI	**179**	**138**	**124**	**110**	**83**
Standard Rx	**179**	**121**	**85**	**62**	**42**

Leon et al, NEJM 2010; 363:1597-1607, Makkar et al, NEJM 2012;366:1696

PARTNER High Risk
Primary Endpoint: All-Cause Mortality



Number at Risk

TAVI	348	298	260	147	67
AVR	351	252	236	139	65

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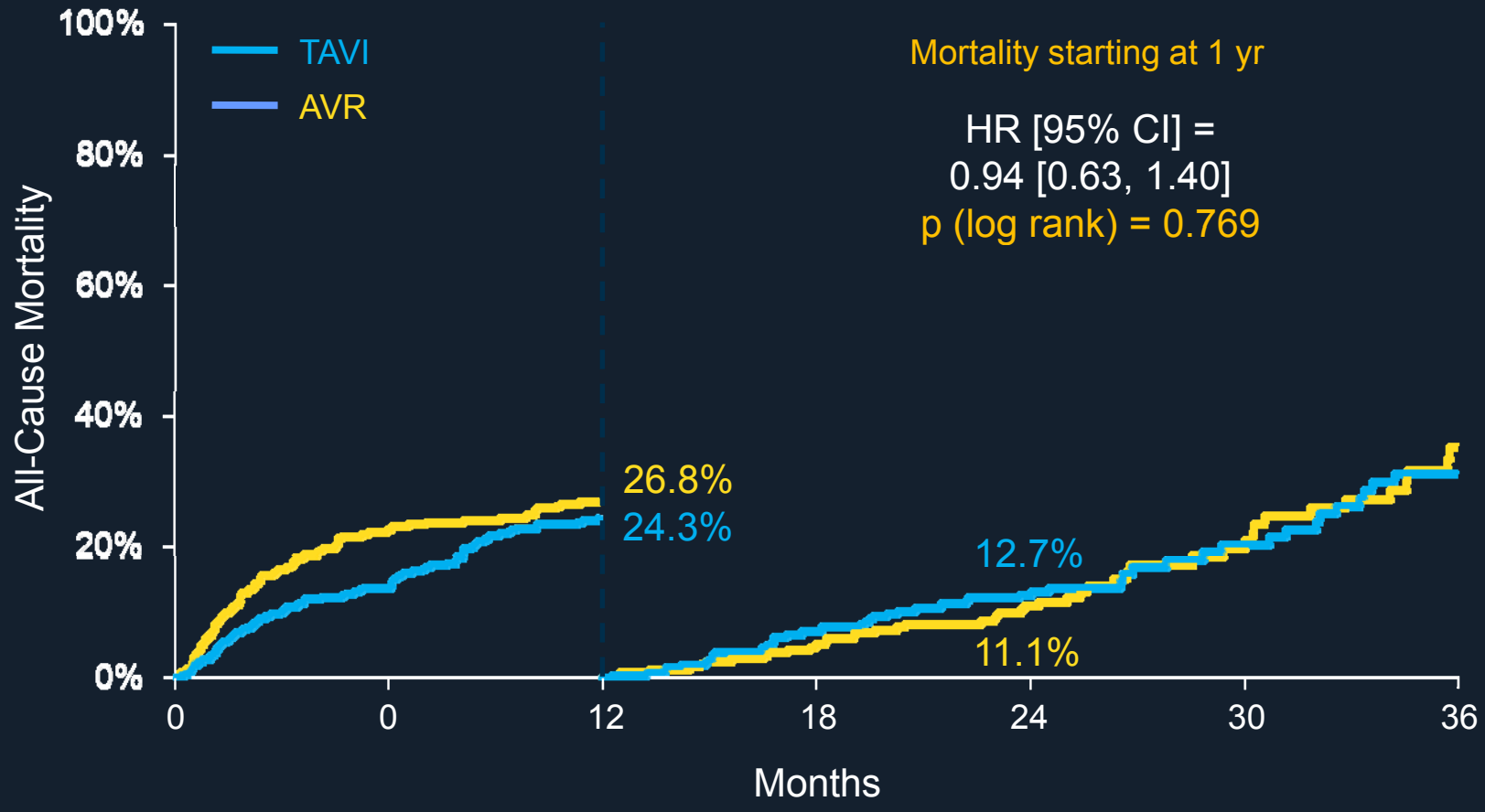
ASAN Medical Center

Smith et al, NEJM 2011; 364:2187, Kodali et al, NEJM 2012;366:1686

PARTNER High Risk

2-Y Mortality : Landmark Analysis



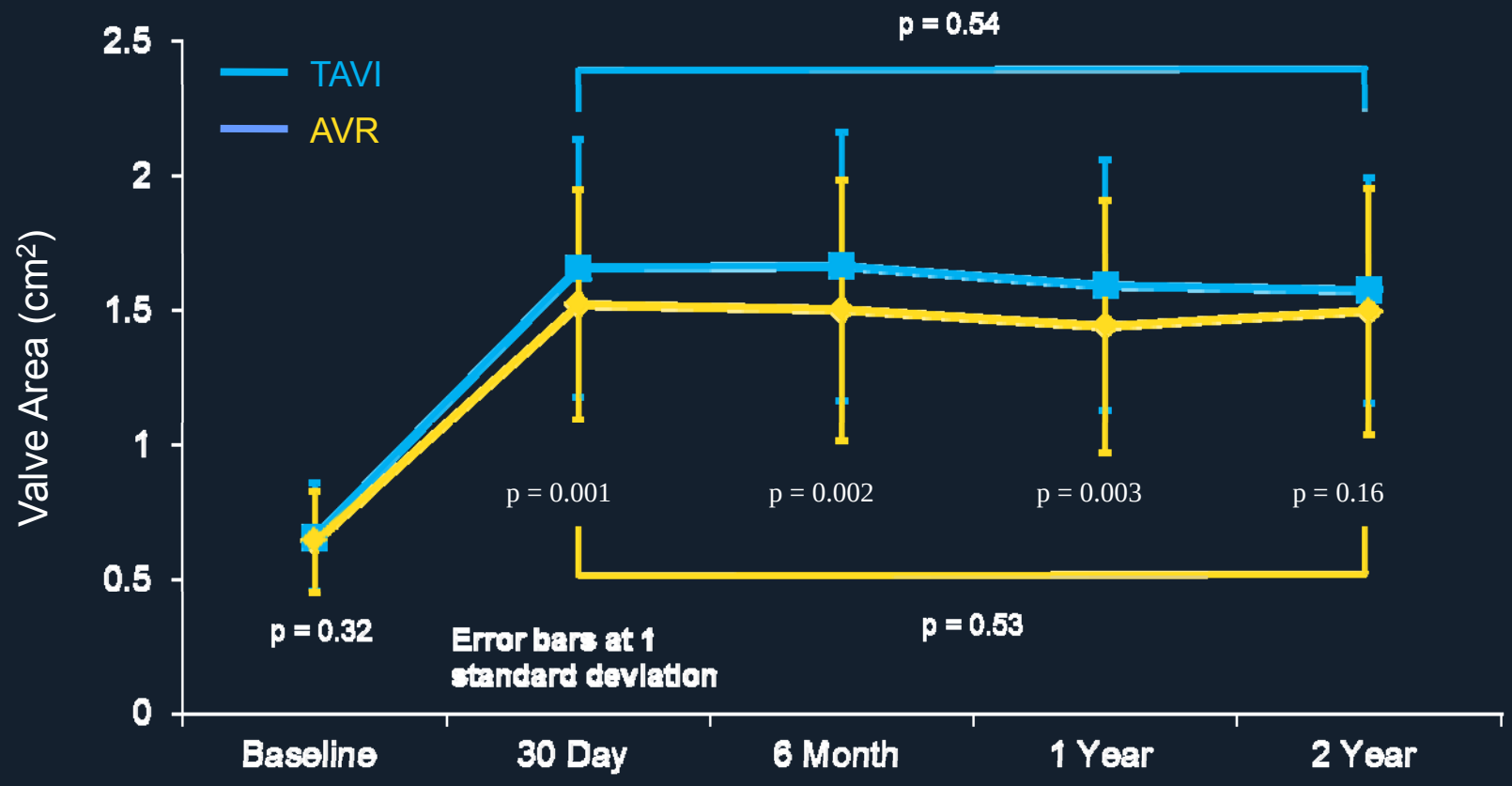
Numbers at Risk

TAVI	348	298	260	234	172	70	31
AVR	351	252	236	217	165	65	32

Smith et al, NEJM 2011; 364:2187, Kodali et al, NEJM 2012;366:1686

PARTNER High Risk

Valve Area to 2 Years



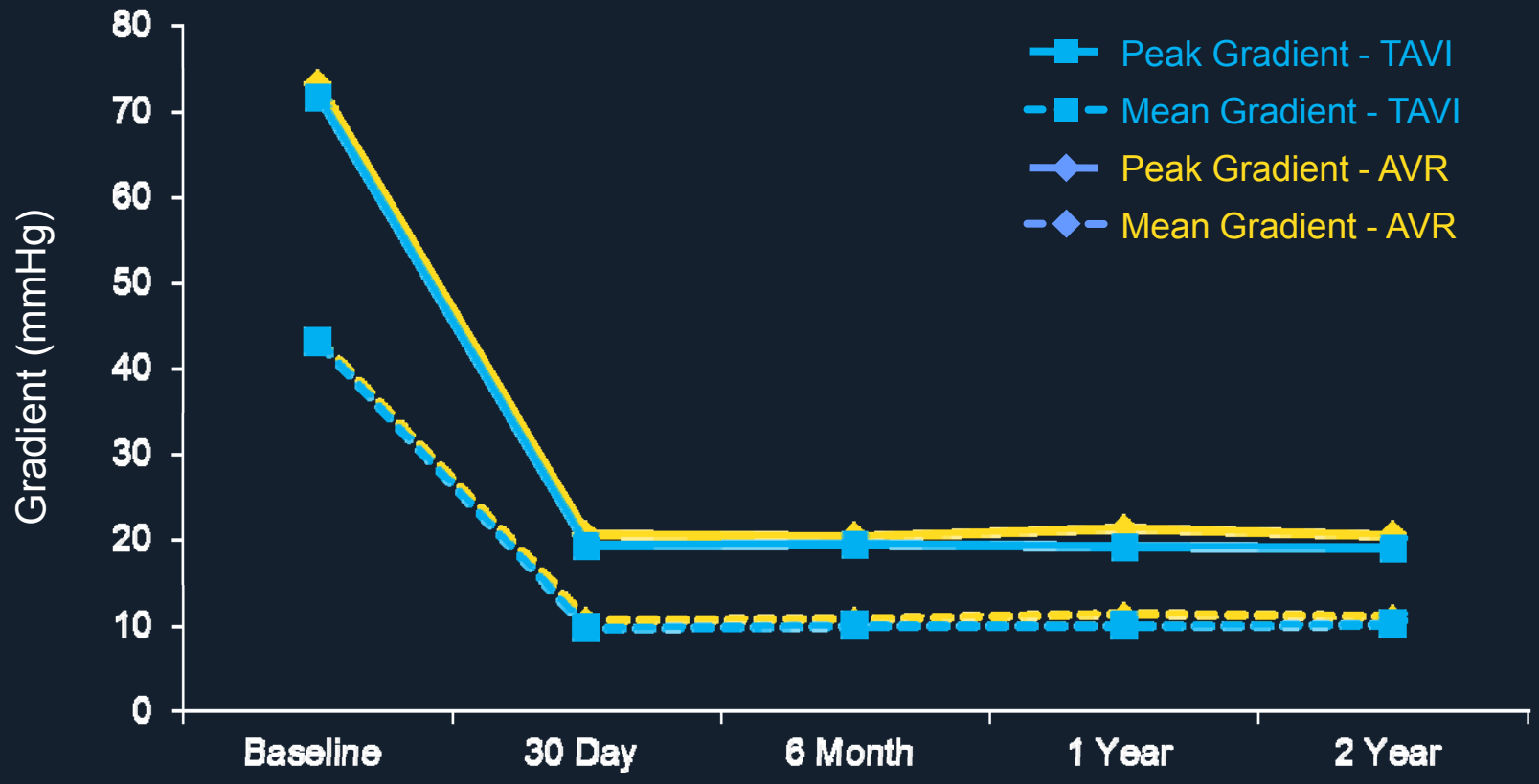
Numbers at Risk

TAVI	301	269	223	210	139
AVR	290	224	162	151	110

Smith et al, NEJM 2011; 364:2187, Kodali et al, NEJM 2012;366:1686

PARTNER High Risk

AV Pressure Gradient to 2 Years



Numbers at Risk

TAVI	307	275	233	218	144
AVR	295	228	168	155	112

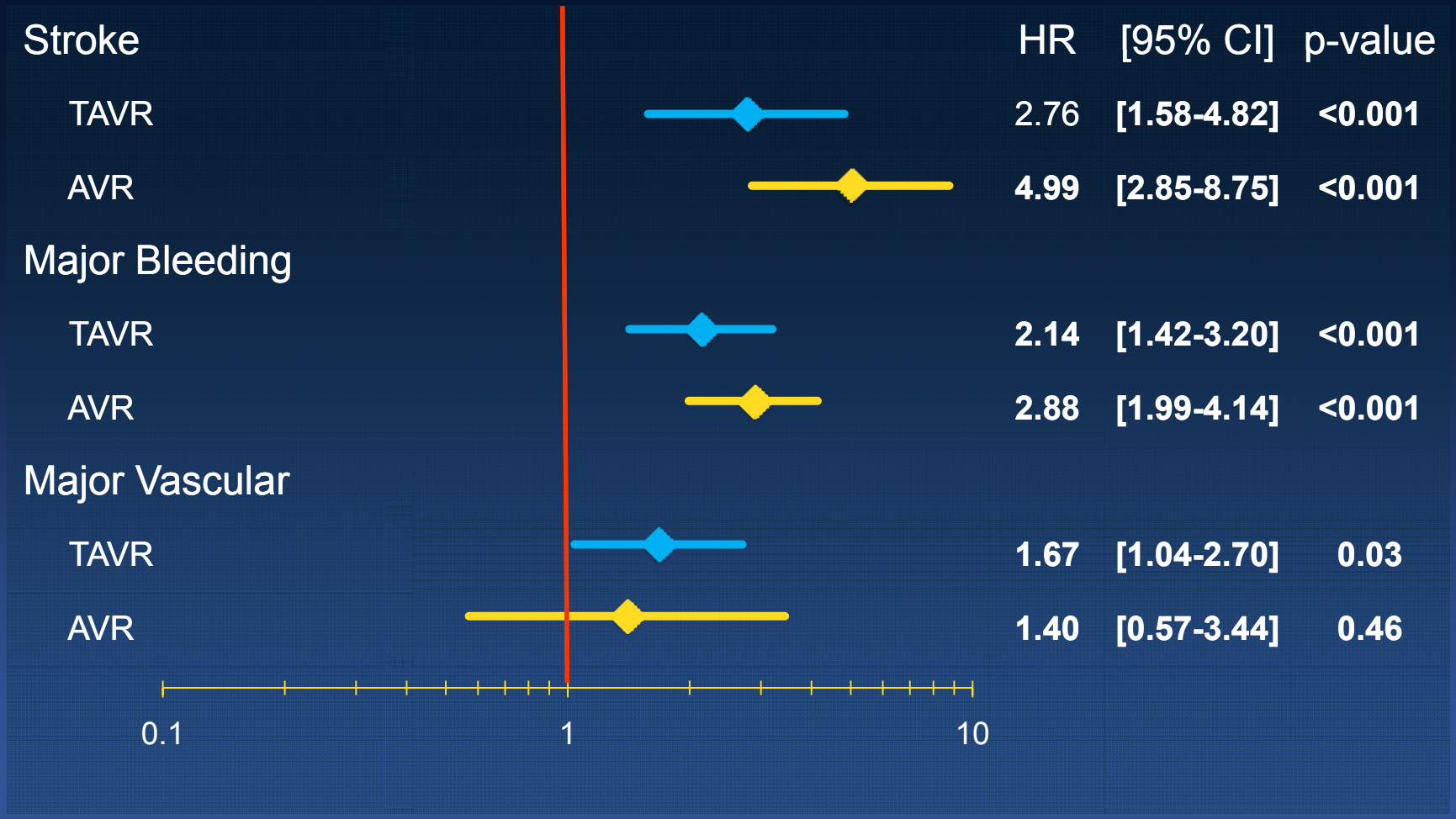
Smith et al, NEJM 2011; 364:2187, Kodali et al, NEJM 2012;366:1686

PARTNER High Risk
Event Rates for 2 Years

%	Surgery (N=351)	TAVI (N=348)	p
Death			
Overall	35.0	33.9	0.78
Cardiac	20.5	21.4	0.80
Repeat hospitalization	21.7	24.7	0.41
TIA	2.0	3.6	0.26
Stroke	4.9	7.7	0.17
MI	1.5	0	0.05
Major vascular complication	**3.8**	**11.6**	**< 0.001**
Major bleeding	**29.5**	**19.0**	**0.002**
Renal failure	6.9	6.2	0.75
New pacemaker	6.4	7.2	0.69

Smith et al, NEJM 2011; 364:2187, Kodali et al, NEJM 2012;366:1686

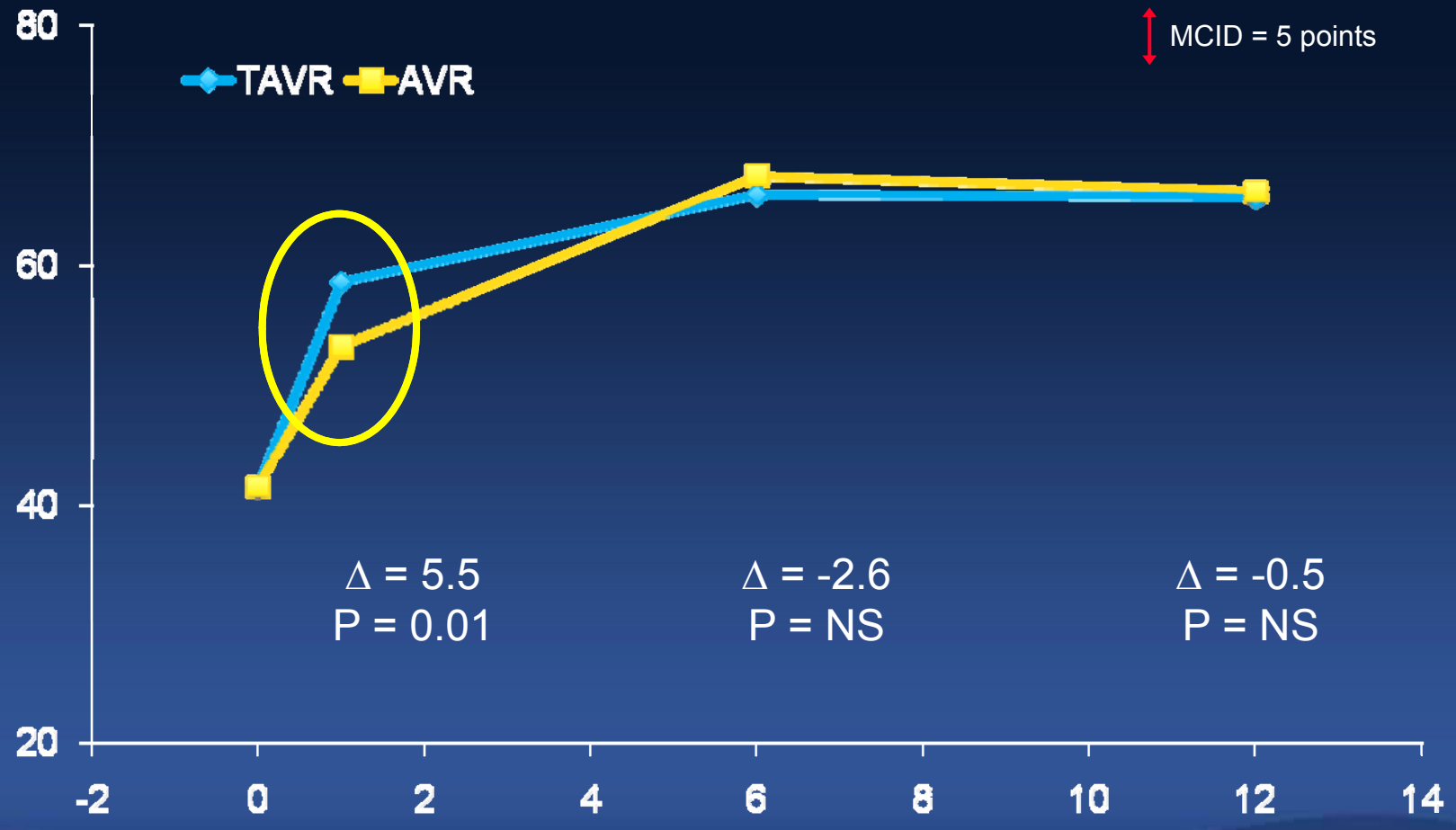
Procedural Predictors of Mortality



Primary Endpoint

KCCQ Overall Summary

Overall summary score can be derived from the physical function, symptom (frequency and severity), social function and quality of life domains.



Growth curve analysis; adjusted for baseline
MCID = minimum clinically important difference

Multivariate Baseline Predictors of Mortality - By Treatment Arm

TAVR	Hazard Ratio [95% CI]	p-value
Body Mass Index (kg/m^2)	0.93 [0.90-0.97]	<0.001
Mean Gradient (mmHg/10)	0.82 [0.72-0.94]	0.003
Baseline Creatinine	1.06 [1.00-1.13]	0.044
Prior Vascular Surgery or Stent	1.85 [1.01-3.39]	0.045
AVR		
Prior CABG	0.57 [0.40-0.82]	0.002
STS Risk Score	1.07 [1.02-1.12]	0.004
Liver Disease	2.59 [1.16-5.43]	0.020
Moderate/Severe MR	1.77 [1.17-2.68]	0.006

General Outcomes in Registry

Valve Academic Research Consortium

A Pooled Analysis by VARC-defined Event Rates

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CLINICAL RESEARCH — Valvular Medicine

Standardized Endpoint Definitions for Transcatheter Aortic Valve Implantation Clinical Trials

A Consensus Report From the Valve Academic Research Consortium

Martin B. Leon
Arie Pieter Kap
Marie-angéle M
Gerrit-Anne va

New York, New

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CLINICAL RESEARCH — Interventional Cardiology

Clinical Outcomes After Transcatheter Aortic Valve Replacement Using Valve Academic Research Consortium Definitions

A Weighted Meta-Analysis of 3,519 Patients From 16 Studies

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New York, New York; Montréal, Québec, Canada; and Rotterdam, the Netherlands

A Pooled Analysis
From Data Until 2011

First Author	N	Approach	Device	STS, %	EuroScore, %	Age, yrs	GR, mmHg	NYHA III/IV,%
D'Onofrio et al.	504	TA	SA	11.0	26.3	81.2	47.4	83
Buchanan et al.	305	TF/SC/TAo	Mix	8.6	24.2	79.4	–	67
Grube et al	186	TF	Co	–	23.4	81.4	47.1	78
Gurvitch et al.	310	TF/TA	SA	9.4	–	82.2	–	88
Hayashida et al.	127	TF	Mix	–	25.8	83.3	–	89
Lange et al.	412	TF,TA,SC,TAo	Mix	5.6	20.2	80.3	47.9	97
Mussardo et al.	120	TF	Mix	7.2	24.9	80.2	55.6	70
Nuis et al.	165	TF/SC	Co	4.6	13.1	81	46	79
Stahli et al.	130	TF/TA	Mix	–	22.7	83	49	72
Wenaweser et al.	256	TF/TA/SC	Mix	6.4	24.8	82.1	44.4	-
Ussia et al.	143	TF/SC	Mix	7.9	23.4	81.0	56.6	64
Bagur et al.	64	TF/TA	SA	7.5	21.0	80	43	100
Dehedin et al.	125	TF/SC	Mix	13.0	24.0	83	47	82
Gotzmann et al.	145	TF/SC	CO	–	21.0	79.1	47.8	96
Leon et al. (RCT)	179	TF	SA	11.2	26.4	83.1	44.5	92
Smith et al. (RCT)	348	TF/TA	SA	11.8	29.3	83.6	42.7	94
Pooled estimate rate (95% CI)	**3,519**	–	–	**8.7 (7.0-10.3)**	**22.8 (20.3-25.3)**	**81.5**	**47.6**	**82.0 (77.5-86.5)**

Généreux P et al. J Am Coll Cardiol 2012;59:2317

Patients - VARC Meta-Analysis
(16 studies; 3,519 patients)

Endpoint	*Pooled Estimate (%)*	*[95% CI]*
STS score	8.7	[7.0, 10.3]
Log Euroscore	22.8	[20.3, 25.3]
Age (years)	81.5	[80.8, 82.2]
Female	52.0	[46.3, 57.6]
NYHA 3 or 4	82.0	[77.5, 86.5]
AVA (cm^2)	0.61	[0.53, 0.68]
Mean gradient (mmHg)	47.6	[45.7, 49.5]

Généreux P et al. J Am Coll Cardiol 2012;59:2317

Mortality, Stroke - VARC Meta-Analysis
(16 studies; 3,519 patients)

Endpoint	*Pooled Estimate (%)*	*[95% CI]*
Mortality		
All at 30 days	7.8	[5.5, 11.1]
CV at 30 days	5.6	[3.7, 8.3]
All at 1 year	22.1	[17.9, 26.9]
CV at 1 year	14.4	10.6, 19.5
Strokes at 30 days		
Major	3.2	[2.1, 4.8]
Major + minor	4.0	[2.4, 6.3]
TIA	1.2	[0.0, 2.3]
All	5.7	[3.7, 8.9]

Généreux P et al. J Am Coll Cardiol 2012;59:2317

Vascular Cx- VARC Meta-Analysis
(16 studies; 3,519 patients)

Endpoint	*Pooled Estimate (%)*	*[95% CI]*
Vascular events at 30 days		
Major	11.9	[8.6, 16.4]
Minor	9.7	[6.7, 14.0]
All	18.8	[14.5, 24.3]
Bleeding at 30 days		
Life threatening	15.6	[11.7, 20.7]
Major	22.3	[17.8, 28.3]
Minor	9.9	[6.9, 14.3]
All	41.4	[35.5, 47.6]
Transfusion ≥ 1 unit	42.6	[19.8, 62.4]

Généreux P et al. J Am Coll Cardiol 2012;59:2317

Valve Performance - VARC Meta-Analysis
(16 studies; 3,519 patients)

Endpoint	*Pooled Estimate (%)*	*[95% CI]*
MI (peri-procedural)	1.1	[0.2, 2.0]
Valve performance at 30 days		
AVA ≤ 1.2 cm^2	4.8	[3.0, 6.6]
Mean gradient ≥ 20 mmHg	1.0	[0.0, 2.1]
AR ≥ moderate (PVL)	7.4	[4.6, 10.2]
Valve-in-valve	2.3	[1.3, 4.5]
Valve embolization	1.7	[0.2, 3.3]
Perm Pacemaker at 30 days		
Edwards	4.9	[3.9, 6.2]
Corevalve	28.9	[23.0, 36.0]

Généreux P et al. J Am Coll Cardiol 2012;59:2317

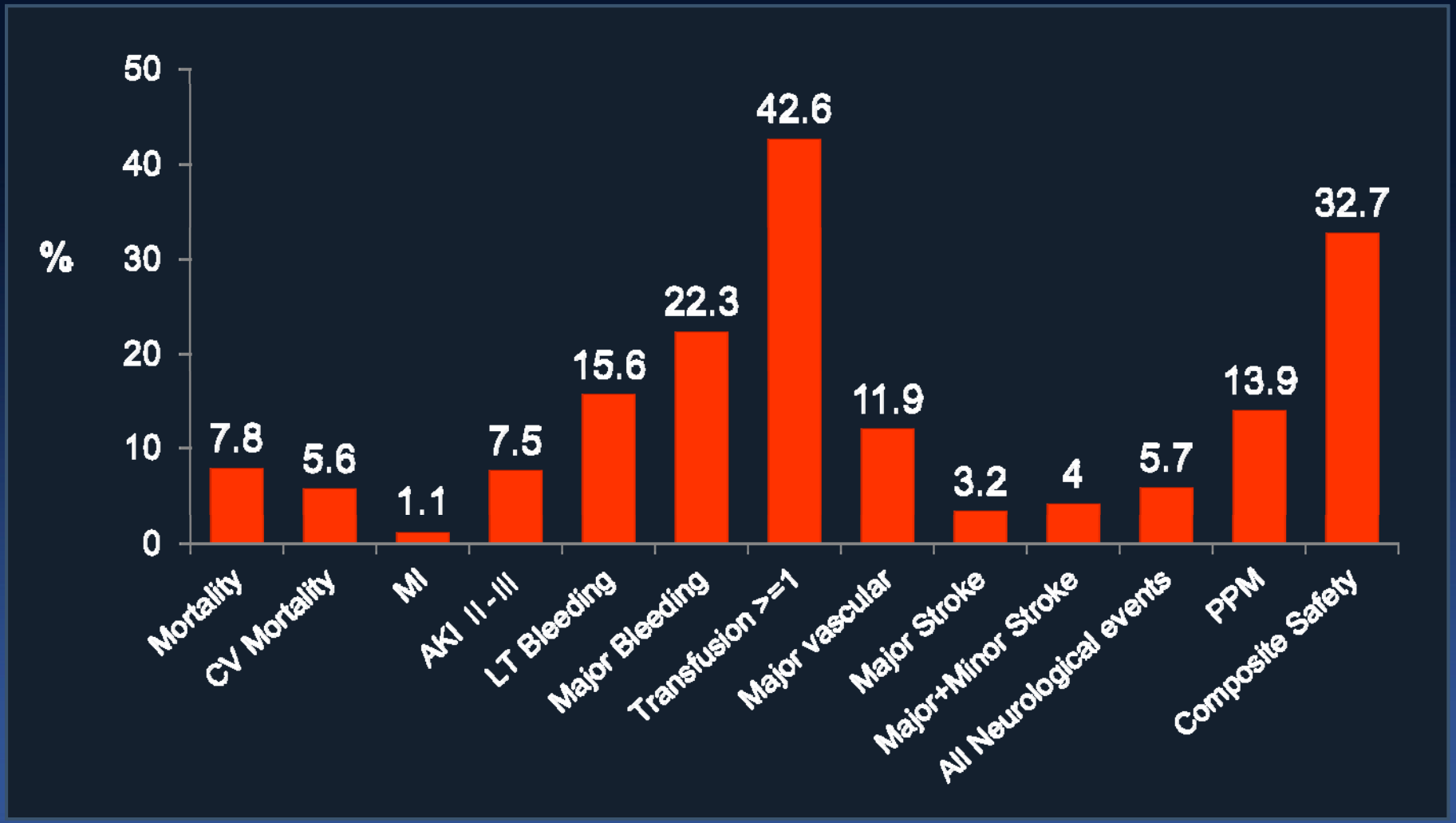
Procedural Cx - VARC Meta-Analysis
(16 studies; 3,519 patients)

Endpoint	*Pooled Estimate (%)*	*[95% CI]*
Endocarditis	0.6	[0.2, 1.4]
Coronary obstruction	0.7	[0.4, 1.1]
Tamponade	2.7	[1.7, 4.2]
LV perforation	0.4	[0.1, 1.5]
Conversion to surgery	1.3	[0.0, 2.6]
Unplanned CPB	1.3	[0.3, 2.2]
Annulus rupture	0.5	[0.2, 1.7]
Aortic rupture	0.9	[0.4, 2.2]
Aortic dissection	1.1	[0.4, 2.5]

Généreux P et al. J Am Coll Cardiol 2012;59:2317

30-Day Event Rates - VARC Meta-Analysis

(16 studies; 3,519 patients)



Composite safety: all-cause death, major stroke, left-threatening bleeding, AKI, peri-MI, major vascular Cx, repeated procedure due to valve-related dysfunction

Généreux P et al. J Am Coll Cardiol 2012;59:2317

FRANCE 2:

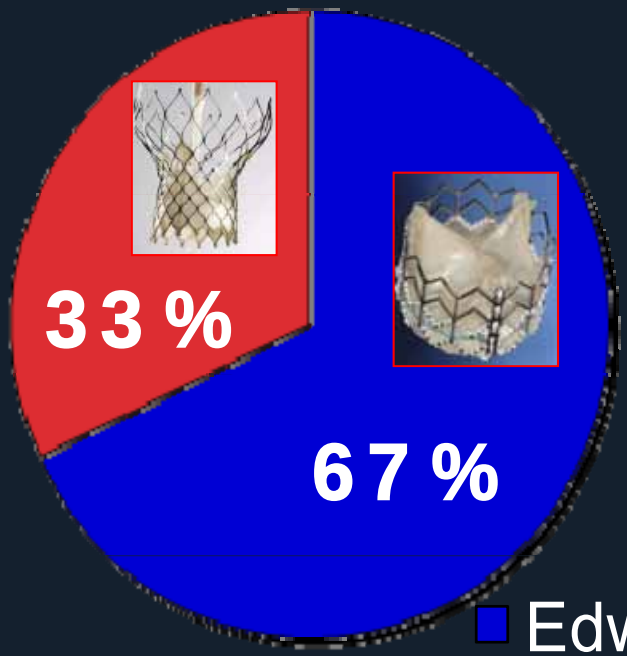
FRench Aortic National Corevalve and Edwards Registry

Martine Gilard, MD
University of Brest, France

On behalf of the scientific committee and the investigators
M Laskar, P Donzeau-Gouge, K Chevreul, H Eltchaninoff, J Fajadet, B Iung, P Leprince, A Leguerrier, M Lievre, A Prat, E Teiger

FRANCE-2 Registry (N=3195)

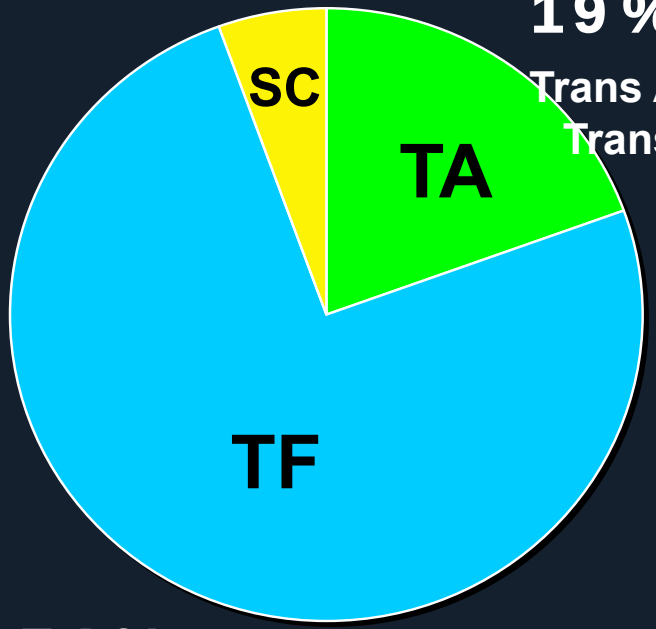
Valves



Edwards 74 %

CoreValve

Approach



Trans Apical 17.8%

Trans aortic 1.8%

Gilard M et al. N Engl J Med. 2012;366:1705

Sapien vs. Core : France-2

Characteristic	SAPIEN (N=2107)	Core (N=1043)
Age, yr	82.9 ± 7.2	82.3 ± 7.2
Male sex %	46.6	60.0
STS score %	15.6 ± 12.4	14.2 ± 11.2
Logistic EuroSCORE %	22.2 ± 14.3	21.3 ± 14.3
NYHA class III or IV %	75.5	76.1
Clinical history %		
CAD	48.7	46.2
Previous MI	17.0	15.4
Previous CABG	18.2	18.3
Cerebrovascular disease	10.0	9.9
PVD	21.8	18.6
COPD	25.3	26.2
Atrial fibrillation	25.2	29.6
Permanent pacemaker	13.5	15.5
Pulmonary hypertension	19.8	19.2
Mean Pr gradient (mmHg)	48.6 ± 16.5	47.1 ± 16.4

Gilard M et al. N Engl J Med 2012;366:1705-15.

Outcomes : France-2

%	Total N = 3195	Sapien N= 2107	Core N=1043
Procedural success	96.9	97.0	97.6
Hospital stay, days	11.1 ± 8.0	10.9 ± 7.5	11.3 ± 8.9
Total deaths			
30 days	9.7	9.6	9.4
1 year	24.0	24.0	23.7
Cardiac deaths at 1 yr	14.3	14.2	14.3
Implanting two devices	2.3	1.4	3.5
Conversion to surgery	0.4	0.4	0.4

Gilard M et al. N Engl J Med. 2012;366:1705

Major Complications : France-2

%	Total N = 3195	Sapien N= 2107	Core N=1043
Major Vascular complications	4.7	2.7	4.5
Myocardial Infarction	1.2	0.8	0.8
New Pacemaker	15.6	11.5	**24.2**
Bleeding (+ tamponade)	13.1	11.4	8.8
AR ≥ grade 2 at *30 days*	16.5	14.1	**21.5**
Stroke	4.1	3.8	4.3
Major	2.3	1.9	2.6

Gilard M et al. N Engl J Med. 2012;366:1705

FRANCE-2
Predictors of Mortality (late)

Multivarite Analysis

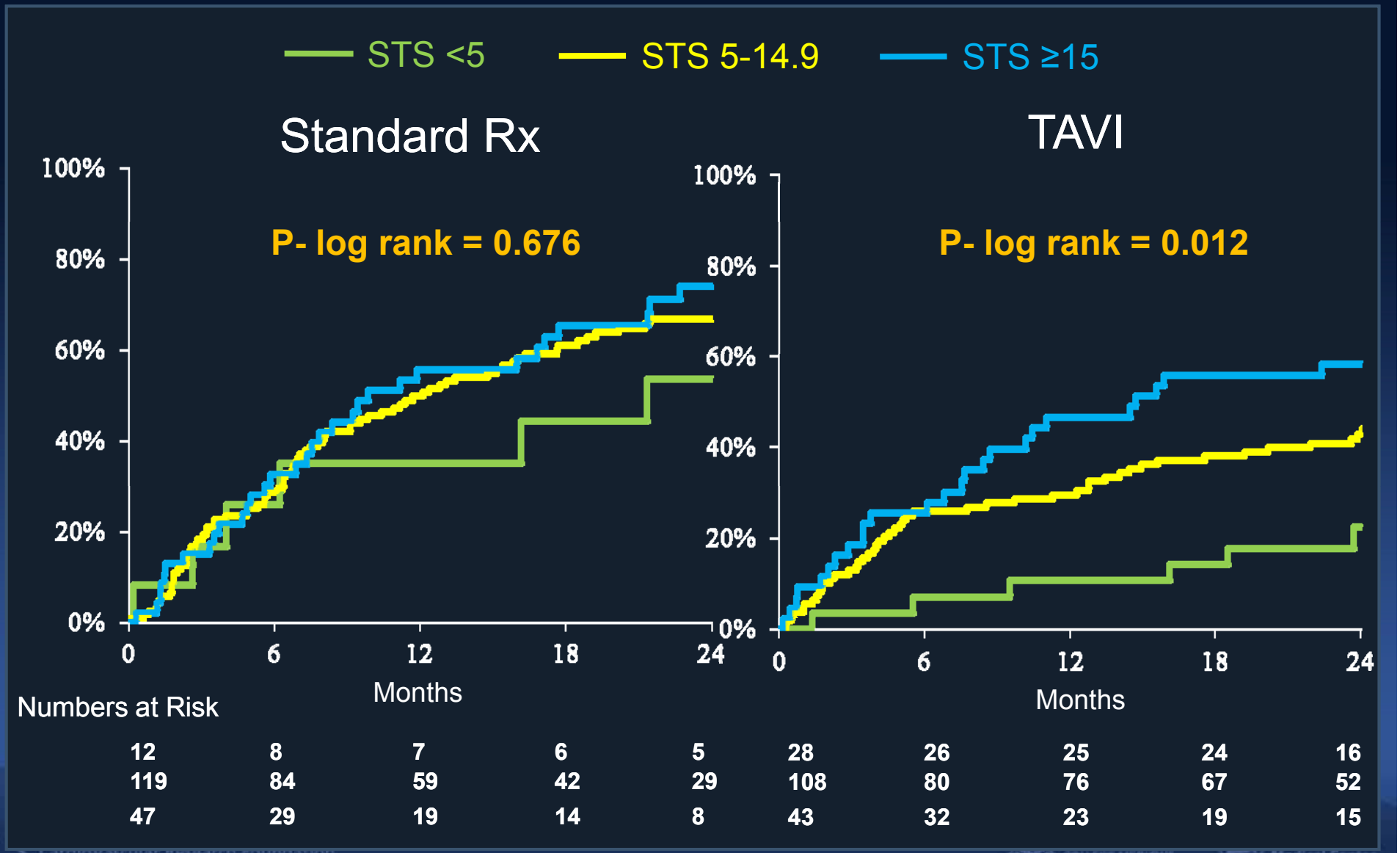
- Log EuroSCORE
- NYHA Class III/IV
- Transapical approach
- Peri-prosthetic AR

Gilard M et al. N Engl J Med. 2012;366:1705

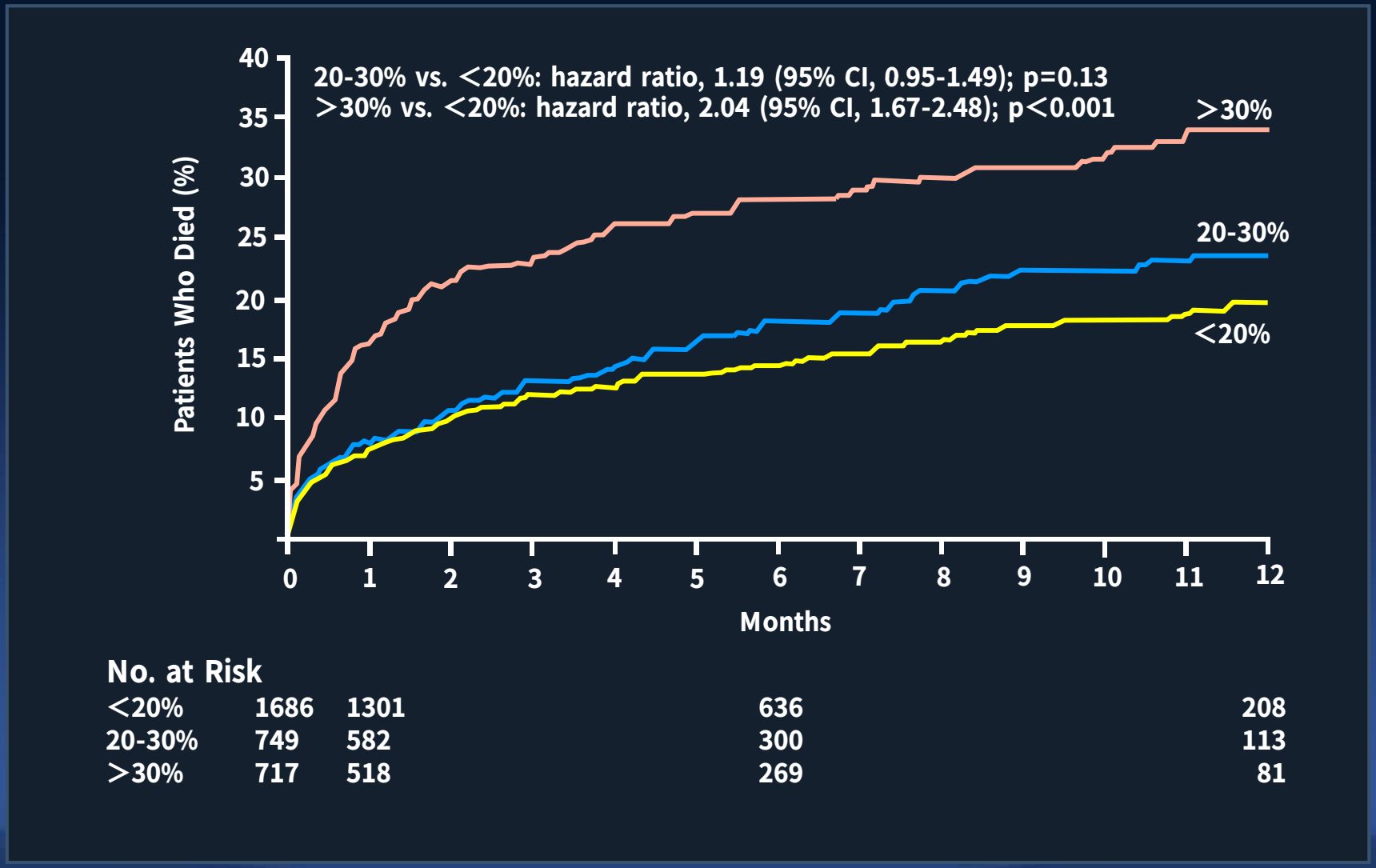
Outcomes
High vs. Low
Surgical-Risks

PARTNER Inoperable

Mortality Stratified by STS Score



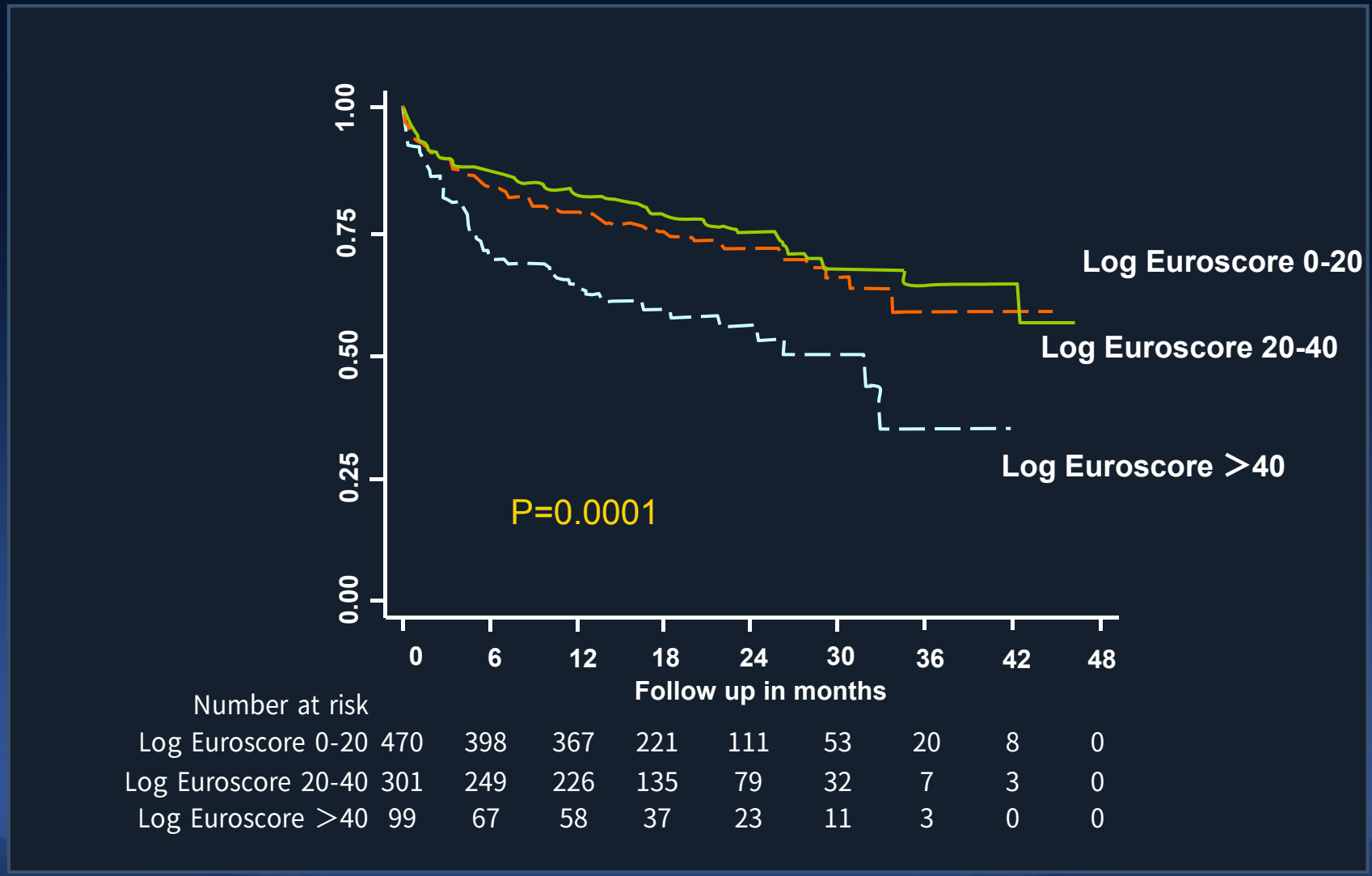
FRANCE-2 Registry
1-Y Survival According to EuroSCORE



No. at Risk				
<20%	1686	1301	636	208
20-30%	749	582	300	113
>30%	717	518	269	81

Gilard M et al. N Engl J Med. 2012;366:1705

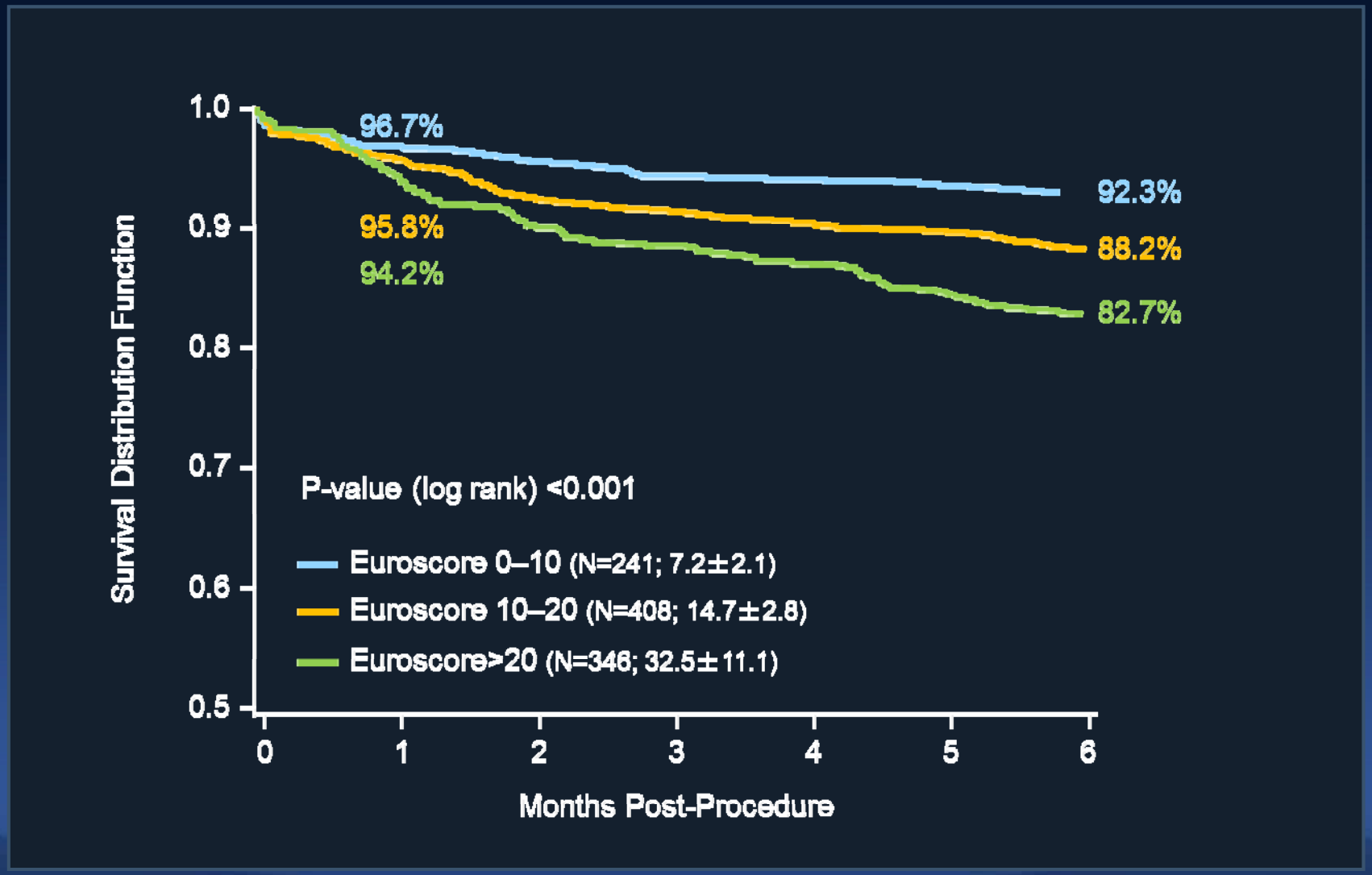
UK.TAVI Registry
2-Y Survival According to EuroSCORE



Moat NE et al. J Am Coll Cardiol 2011;58:2130

ADVACE EU Core Registry

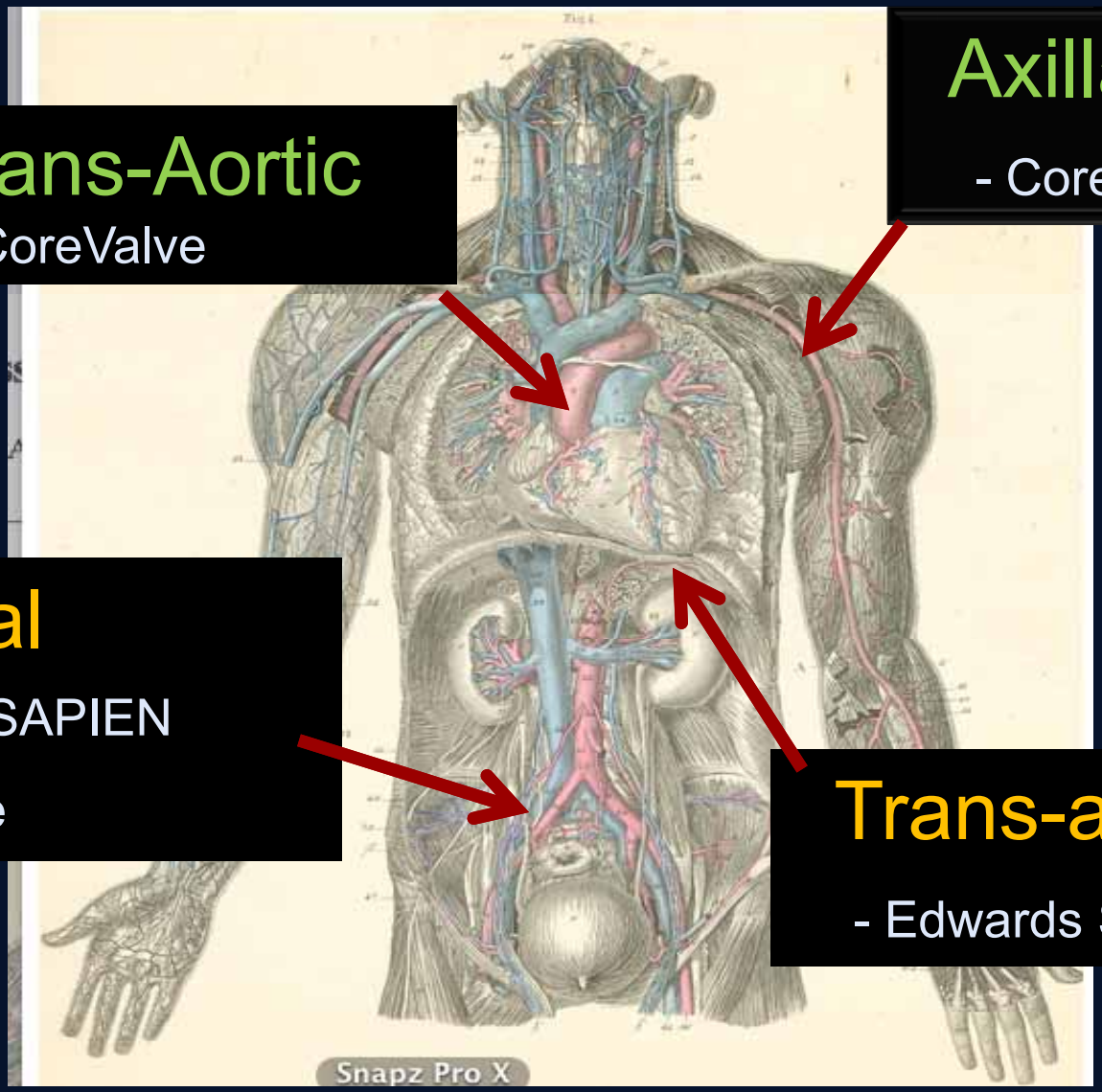
6-M Survival According to EuroSCORE



Linke A et al. PCR 2011

Outcomes
TF vs. TA

Access Routes For TAVI



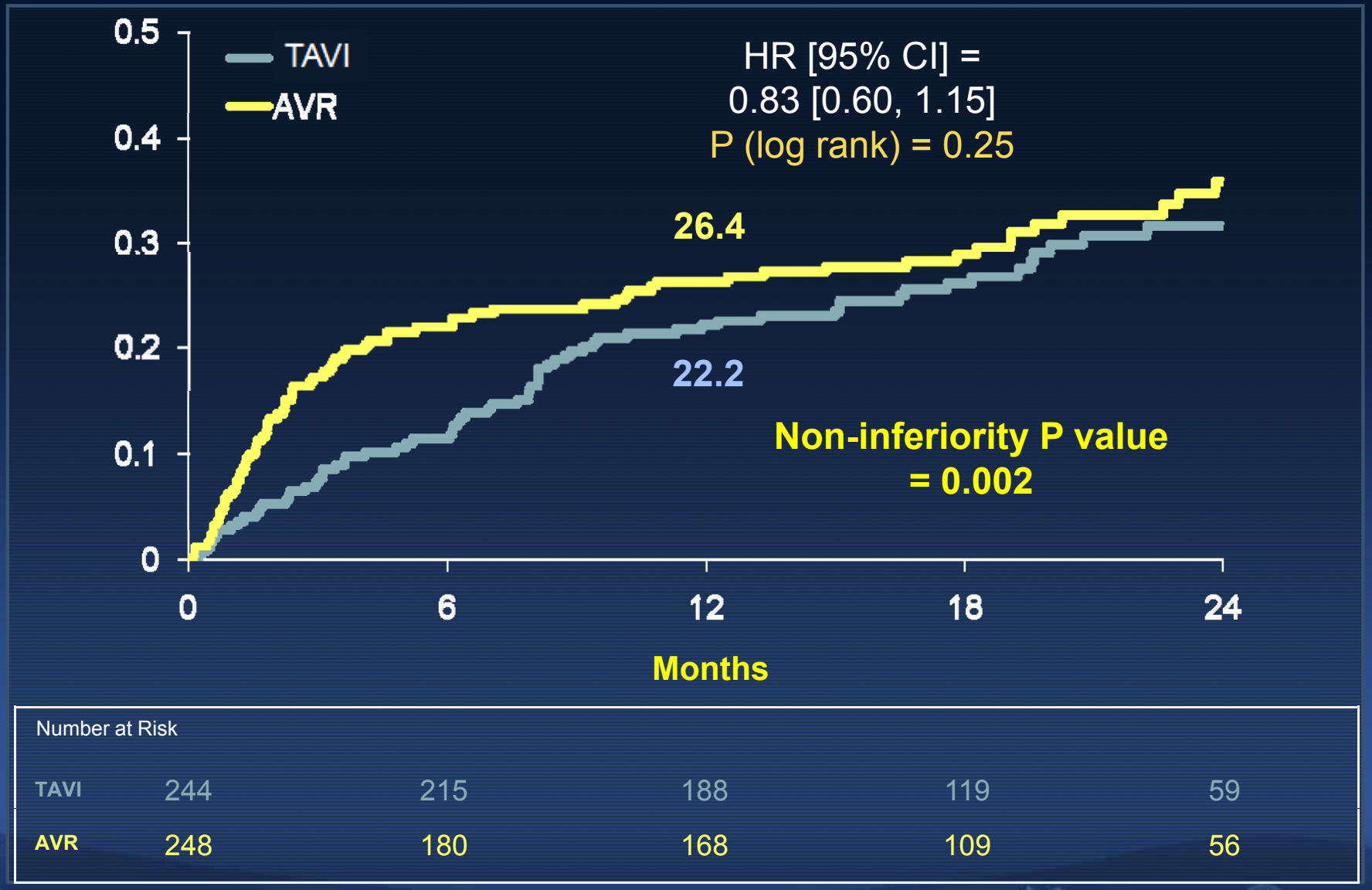
Trans-Aortic
- CoreValve

Axillary
- CoreValve

Femoral
- Edwards SAPIEN
- CoreValve

Trans-apical
- Edwards SAPIEN

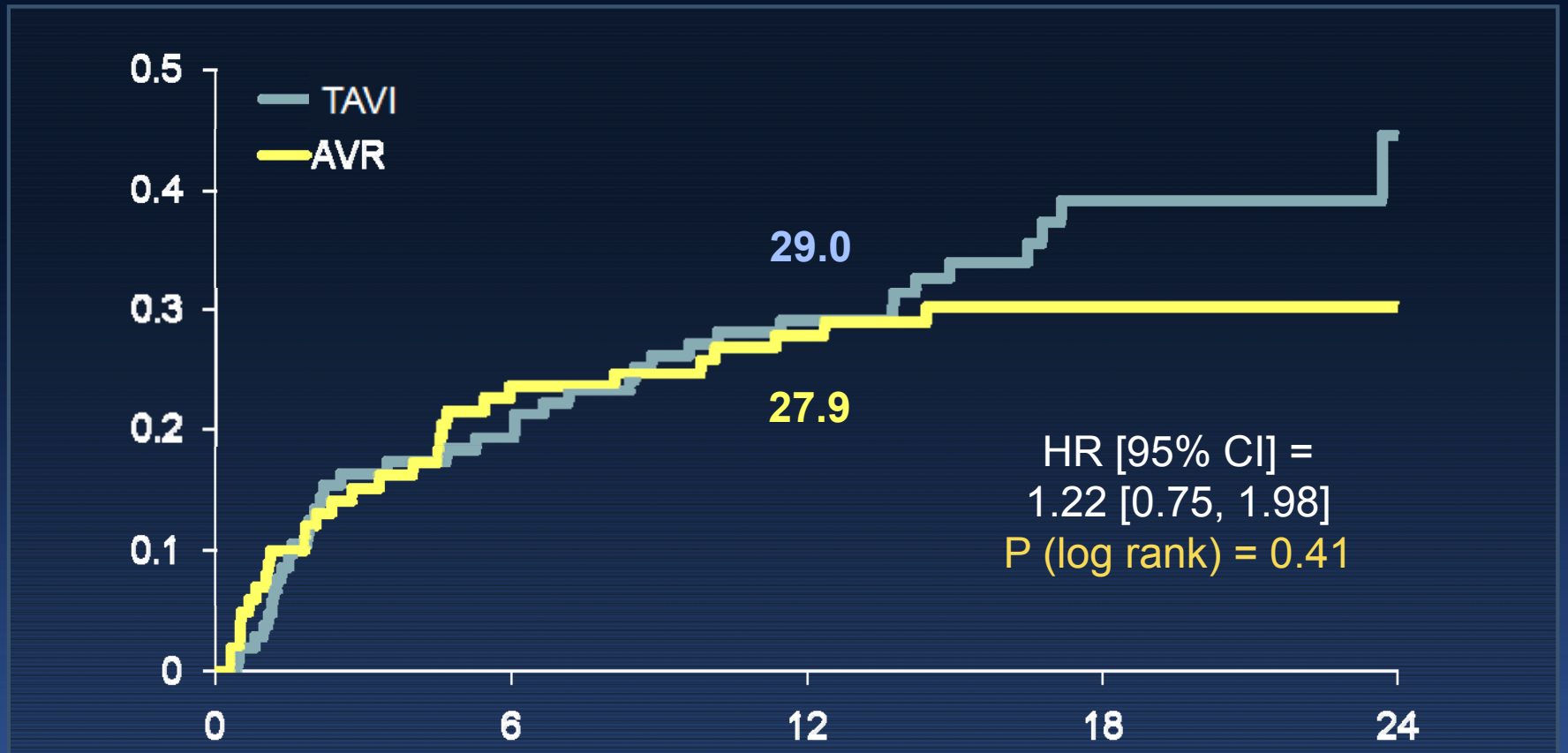
PARTNER High Risk, TF with Sapien (N=492)
All-Cause Mortality



Number at Risk					
TAVI	244	215	188	119	59
AVR	248	180	168	109	56

Kodali et al, NEJM 2012; 366:1686

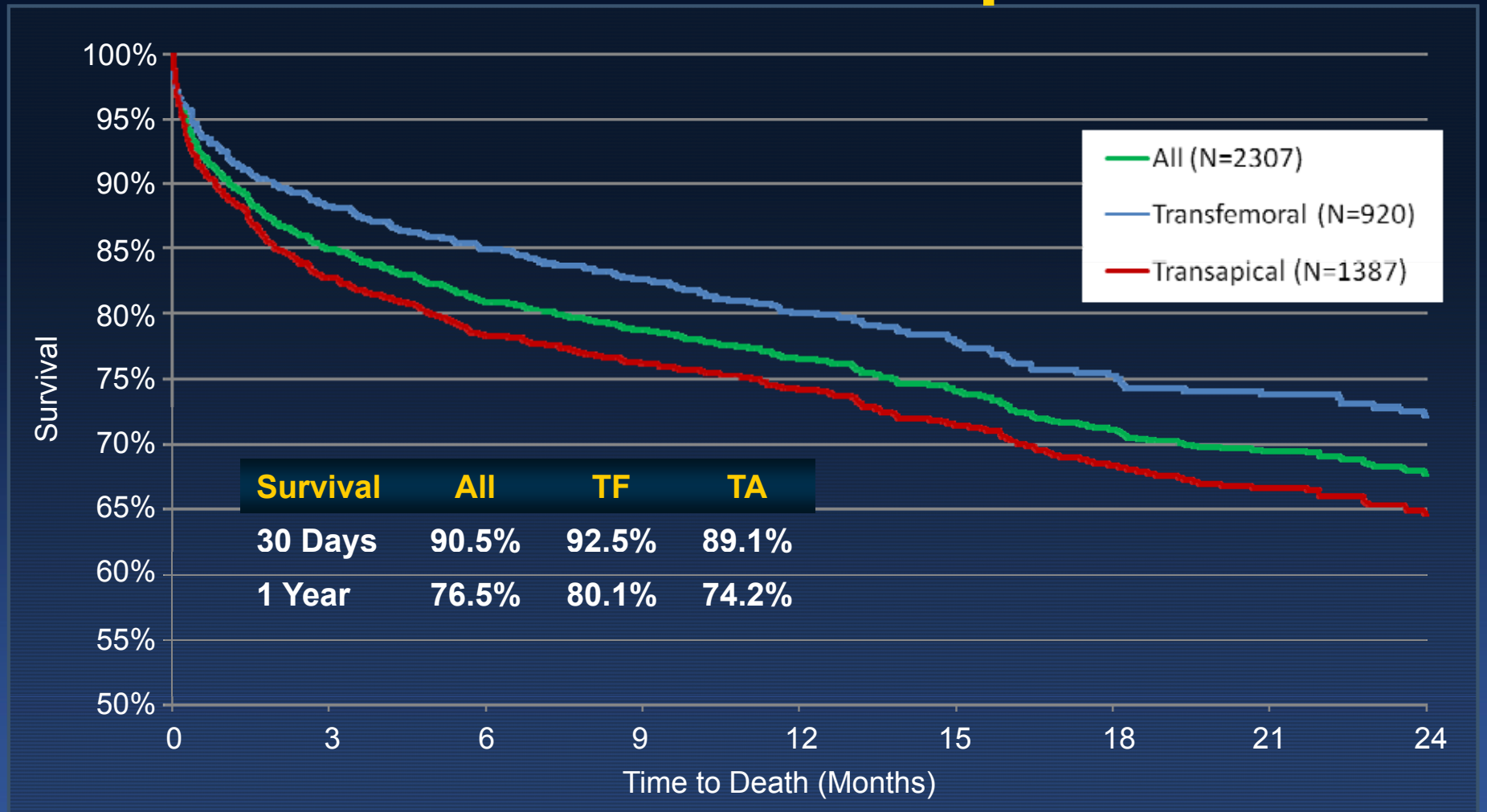
PARTNER High Risk, TA with Sapien (N=207)
All-Cause Mortality



Number at Risk					
TAVR	104	83	72	28	8
AVR	103	72	68	30	9

Kodali et al, NEJM 2012; 366:1686

2-Y Mortality in SOURCE Registry
TF vs. TA with Sapien



Survival	All	TF	TA
30 Days	90.5%	92.5%	89.1%
1 Year	76.5%	80.1%	74.2%

N at Risk	30 Days	1 Year	2 Years
All (N=2307)	2080	1506	487

CardioVascular Research Foundation

Thomas M et al. Circulation. 2011;124:425

University of Ulsan College Medicine · Asan Medical Center

TF vs. TA, SC : France-2 Registry

Characteristic	Transfemoral (N=2326)	Transapical (N=567)	Subclavian (N=184)	P value
Age, yr	83.0 ± 7.2	81.5 ± 7.2	82.2 ± 7.2	< 0.001
Male sex %	47.4	58.6	71.2	< 0.001
STS score %	14.5 ± 11.9	15.1 ± 13.8	16.6 ± 13.4	0.15
Logistic EuroSCORE %	**21.2 ± 14.7**	**24.8 ± 14.7**	**20.3 ± 15.2**	< 0.001
NYHA class III or IV %	77.8	70.0	71.4	< 0.001
Clinical history %				
CAD	44.4	59.4	58.4	< 0.001
Previous MI	14.5	25.0	18.5	< 0.001
Previous CABG	15.2	30.0	24.2	< 0.001
CVA	9.6	11.0	11.2	0.50
PVD	12.5	48.1	41.6	< 0.001
COPD	25.3	22.7	35.4	0.003
Atrial fibrillation	27.9	21.0	31.5	0.002
Pul. hypertension	20.0	16.8	23.5	0.16

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Outcomes : France-2

%	TF (N=2326)	TA (N=567)	SC (N=184)	P value
Procedural success	97.1	95.9	96.7	0.35
Hospital stay, days	10.5 ± 8.1	13.3 ± 7.8	11.6 ± 6.0	< 0.001
Total deaths				
30 days	8.5	13.9	10.1	< 0.001
1 year	21.7	32.3	25.1	< 0.001
Cardiac deaths at 1 yr	12.7	19.8	14.4	0.79
Implanting two devices	2.0	2.9	2.8	0.46
Conversion to surgery	0.7	0.7	0	0.84

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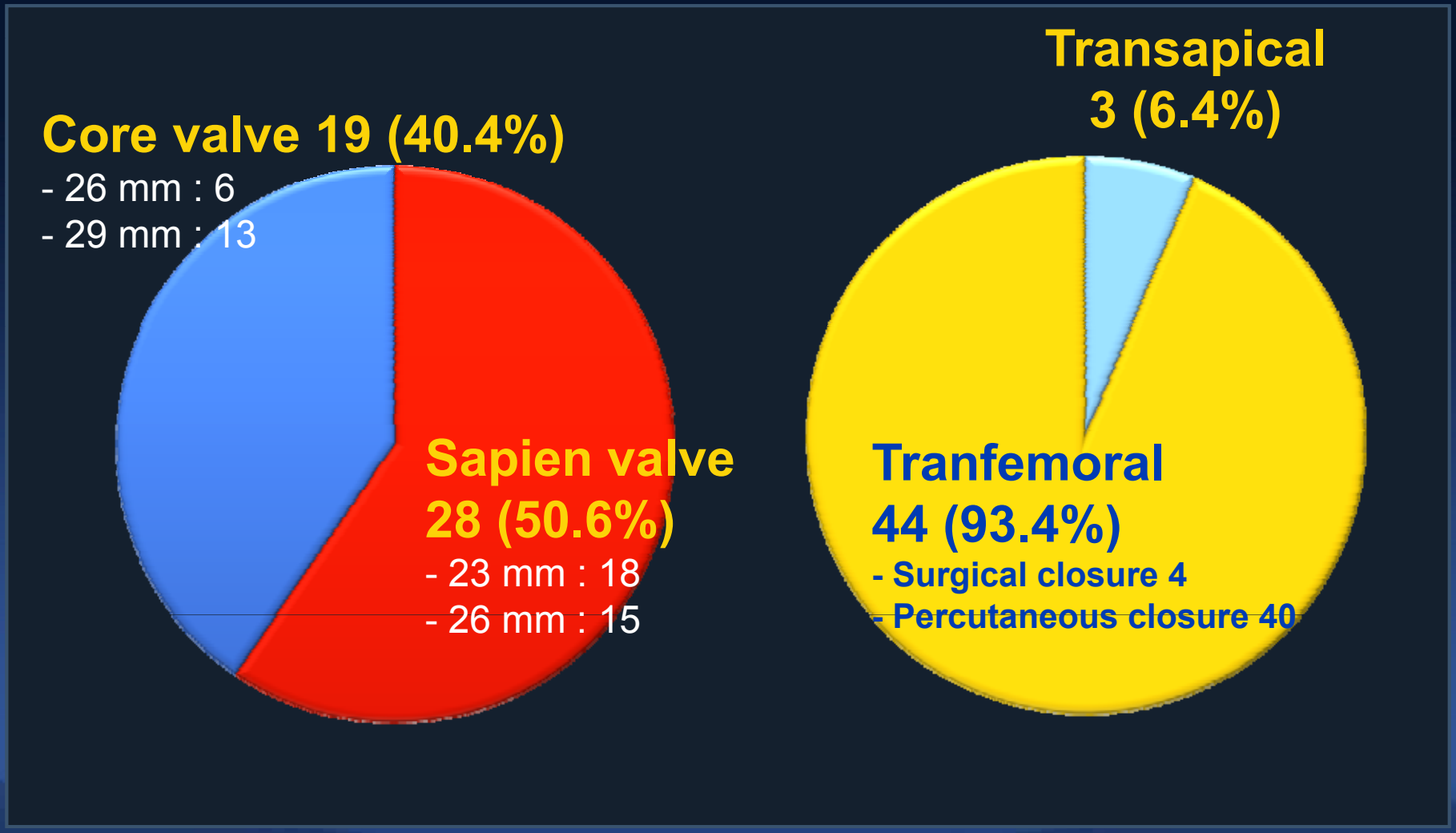
Major Complications : France-2

%	TF (N=2326)	TA (N=567)	SC (N=184)	P value
Major Vascular complications	5.5	1.9	4.3	0.002
Myocardial Infarction	0.8	1.8	3.3	0.004
New Pacemaker	15.2	13.6	25.5	< 0.001
Major bleeding	1.5	3.4	3.3	< 0.001
AR ≥ grade 2 at *30 D*	18.6	9.0	15.2	0.09
Major stroke	2.2	2.1	2.7	0.88
Valve migration	1.2	1.4	1.1	0.91

Gilard M et al. N Engl J Med. 2012;366:1705

Outcomes in AMC

AMC Since 2011 (n=47)
Used Devices and Approach



Patients

Characteristic	Sapien	Core
Age, yr	76.3 ± 5.0	80.2 ± 5.5
Male sex %	39.3	31.6
Logistic EuroSCORE %	25.4 ± 6.0	25.8 ± 13.5
NYHA class III or IV %	87.8	80.0
Mean LVEF, %	58.8 ± 9.6	61.7 ± 7.0
Clinical history %		
CAD	69.6	59.6
Previous MI	14.5	25.0
Previous CABG	15.2	30.0
CVA	9.6	11.0
PVD	73.9	63.9
COPD	87	87
Atrial fibrillation	27.9	21.0
Aortic Valve Area, cm^2	0.67 ± 0.13	0.64 ± 0.17
Mean Pr gr. (mmHg)	59.6 ± 21.2	69.7 ± 23.1

Outcomes to 1 Year

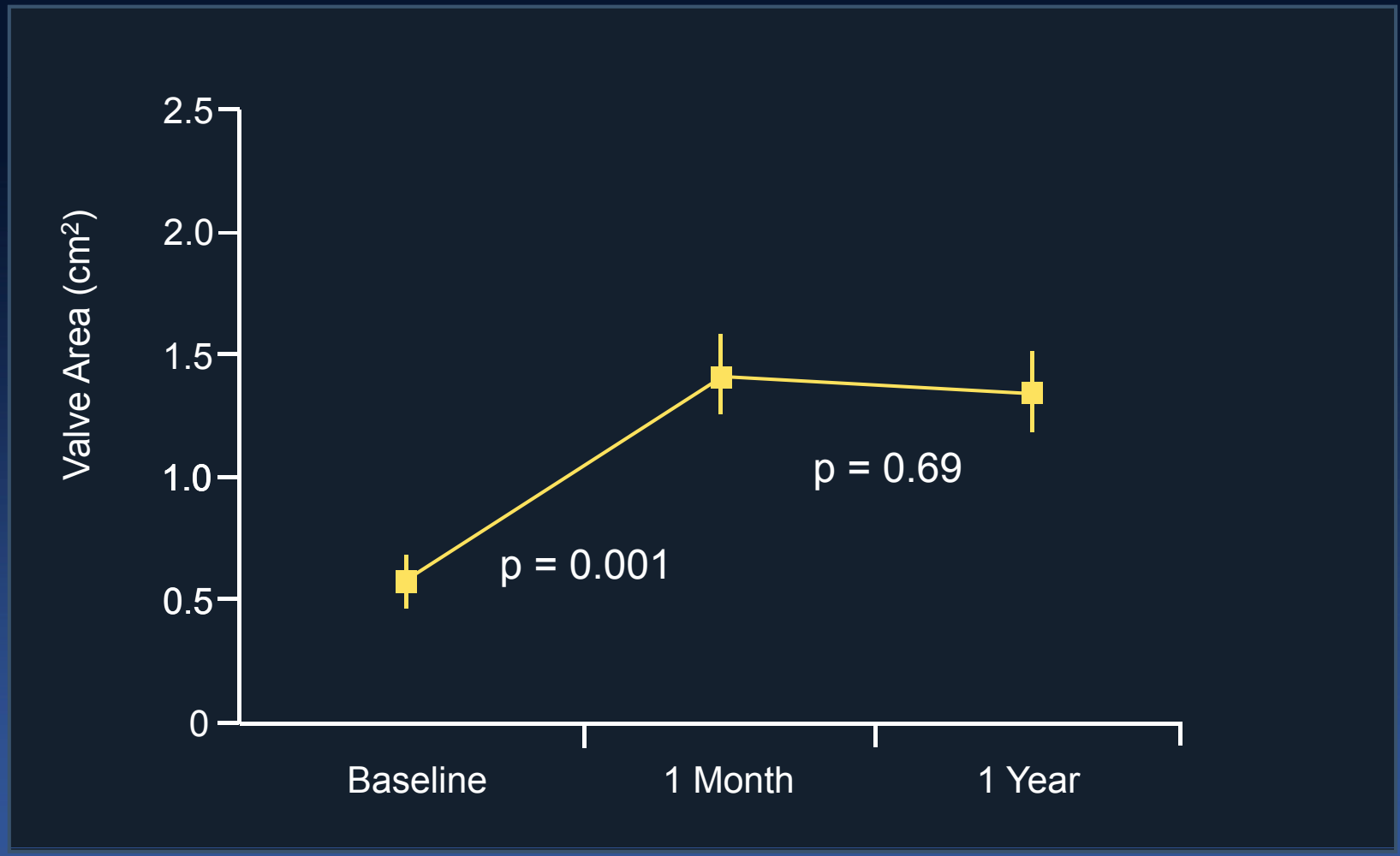
	N=47
Successful valve implantation	45 (95.7%)
Death	0
MI	0
Stroke	1 (2.1%)
Conversion to open surgery	3 (6.4%)
Valve in failed valve	1 (2.1%) *
Valve embolization	3 (6.4%)
Vascular complication	2 (4.3%)
Cardiac tamponade	1 (2.1%)
Permanent pacemaker	5 (11%) *

* All core valves

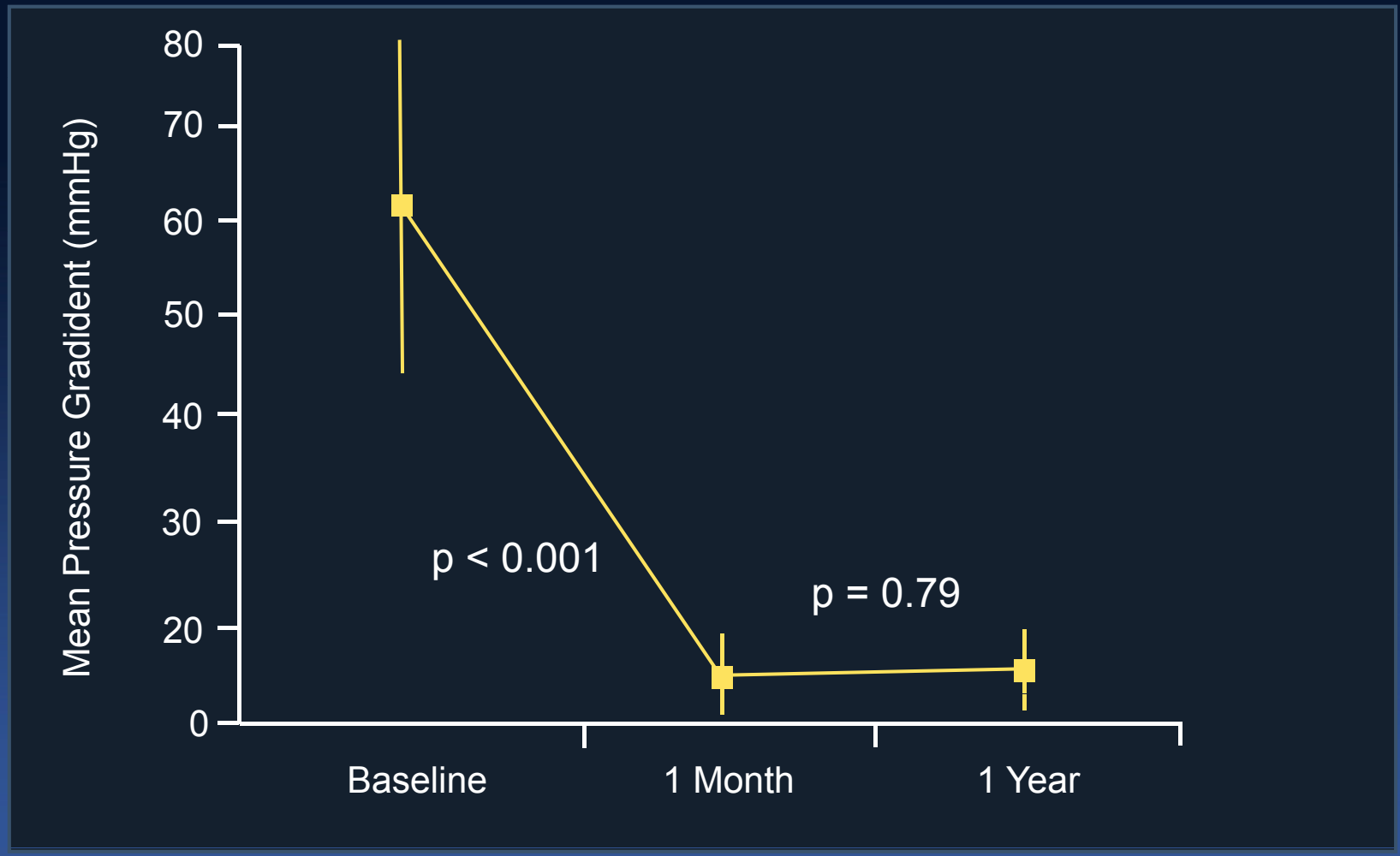
Echocardiographic Findings

	Baseline (N=47)	Post-procedure (N=47)	9 months (N=27)
LVEF, %	59.5±8.8	64.4±7.0	63.0±3.8
AV area, cm2	0.68±0.14	1.45±0.33	1.35±0.4
Mean PG, mmHg	59.4±22.4	16.6±5.7	15.6±7.1
Peak PG, mmHg	98.7±34.5	30.5±9.5	29.1±11.9
Moderate to severe AR	0	0	0
Paravalvular leak	NA	All mild	All mild
Moderate to severe MR	0	0	0
Moderate to severe pul HTN	0	0	0

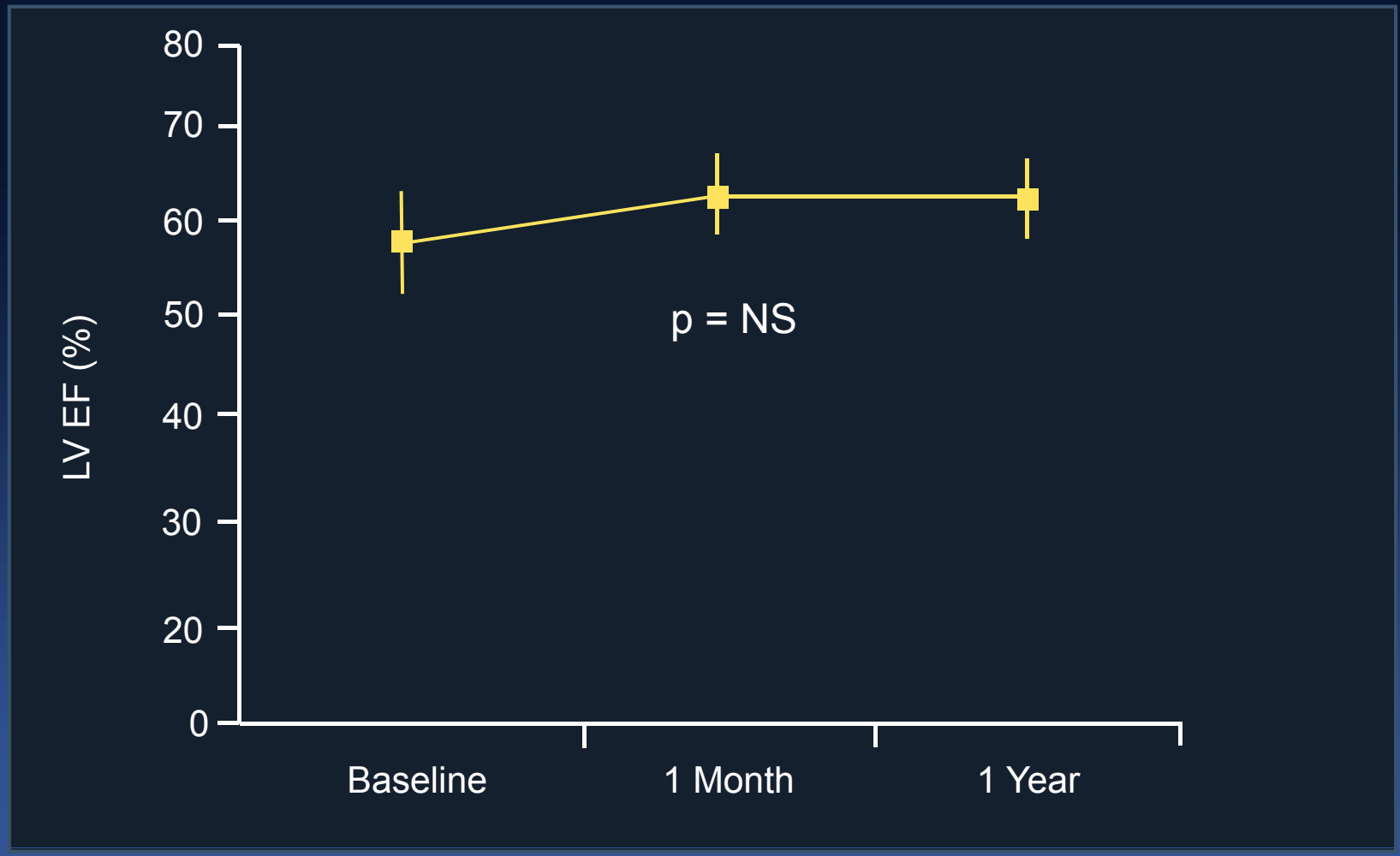
Aortic Valve Area to 1 Year



AV Pressure Gradient to 1 Year



LV Ejection Fraction to 1 Year



AMC
Improved Safety with New Devices

	RF I or III N=9	NovaFlex N=16
Procedural success	8 (88.9%)	16 (100%)
Mortality	0	0
Stroke	0	1 (6%)
Permanent pacemaker	0	0
Vascular complication		
Access site	1 (11.1%)	0
Iliac artery perforation	1 (11.1%)	0
Device embolization	2 (22.2%)	1 (6%)

Data on TAVI until 2012,

- With the dramatic continued growth in practices and researches, TAVI procedure leads to a feasible alternative to surgical AVR in the treatment of high-risk AS patients.
- Both Edward Sapien and Core valves obtained similar outcomes in terms of the incidences of procedural success, death, MI, stroke, vascular complication and bleeding.
- However, patients treated with Core valve had a higher chance to receive permanent pacemaker after procedure.
- In the non-randomized observational studies, TF approach showed comparable or better prognosis than TA or SC approach.

Data on TAVI until 2012,

- Procedural and long-term outcomes of TAVI procedure is closely related with the patient's surgical risk.
- Mid-term outcome after TAVI using the available two devices is comparable to surgical AVR.
- In the Asian Pacific countries, the TAVI program is recently introduced and rapidly propagated to most countries.
- Further randomized and registry studies using current and new TAVI devices are warranted to improve safety and efficacy of this complex procedure.