What you should have read on interventional cardiology in the past year

- The Art trial
- The Evolut low risk trial
- The Partner 3 trial

S Pourbaix
CHR Citadelle , Liège
BWGIC meeting , 03/05/2019

The NEW ENGLAND JOURNAL of MEDICINE

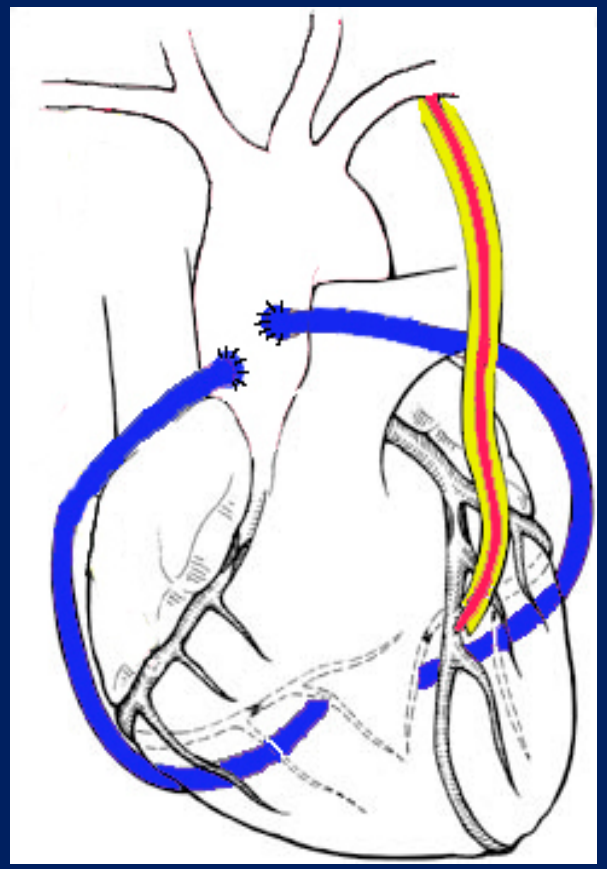
ORIGINAL ARTICLE

Bilateral versus Single Internal-Thoracic-Artery Grafts at 10 Years

David P. Taggart, M.D., Ph.D., Umberto Benedetto, M.D., Ph.D., Stephen Gerry, M.Sc., Douglas G. Altman, D.Sc.,* Alastair M. Gray, Ph.D., Belinda Lees, Ph.D., Mario Gaudino, M.D., Vipin Zamvar, M.S., F.R.C.S., Andrzej Bochenek, M.D., Brian Buxton, M.D., Cliff Choong, M.D., Stephen Clark, M.D., Marek Deja, M.D., Jatin Desai, M.D., Ragheb Hasan, M.D., Marek Jasinski, M.D., Peter O'Keefe, M.D., Fernando Moraes, M.D., John Pepper, M.D., Siven Seevanayagam, M.D., Catherine Sudarshan, M.D., Uday Trivedi, M.D., Stanislaw Wos, M.D., John Puskas, M.D., and Marcus Flather, M.B., B.S., for the Arterial Revascularization Trial Investigators†

David P. Taggart and all , NEJM 2019;380:437-446

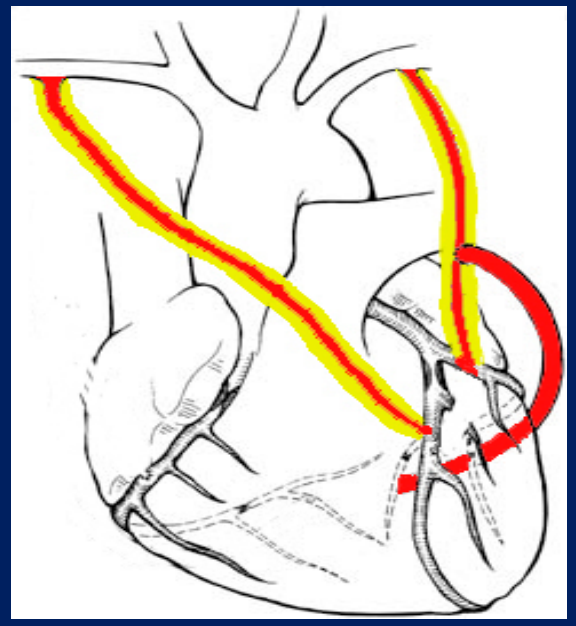
Art trial : ARterial revascularisation Trial

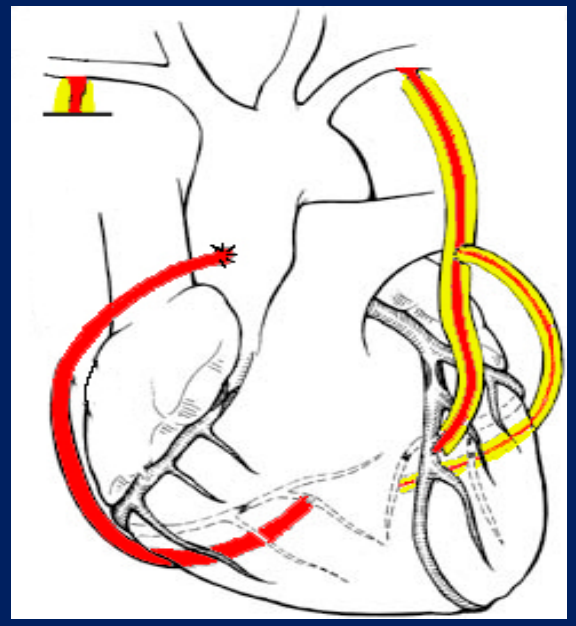


Coronary artery bypass grafting (CABG) is highly effective for symptoms and/or prognosis in multi-vessel and left main coronary artery disease *(Syntax , Precombat ,Best , Excel , Noble 2013-2016 ; Ahn and all JACC 2017; 10:1415-1424)*

Over 1 million CABG performed worldwide each year, standard operation is in >90% CABG x 3 (1 internal thoracic artery and 2 vein grafts)

Strong angiographic evidence of increasing failure of vein grafts over time (due to progressive atherosclerosis) that accelerates after 5 years and that increases **overall mortality and cardiac morbidity** *(Lopez RD ans all , Circ 2012 ;125 : 749-56 ; Yusuff S and all ,Lancet 1994 ;344:563-70)*





Strong angiographic evidence that ITA grafts have excellent long term patency rates (> 90% at 20 years) *(Cameron A , NEJM 1996;334: 216-19 ; Fitgibbon GM ,Jacc 1996 ; 28:616-626)*

Left ITA is established as the standard of care for grafting the left anterior descending (LAD) coronary artery during CABG

Numerous observational studies have estimated a 20% reduction in mortality with Bilateral versus Single ITA grafts over the long-term *(Lytle , JTC1999;117:855-872)*

Low use of Bilateral **ITA** (<10% in Europe, <5% in USA) due to 3 concerns

- increased technical complexity
- potentially increased mortality and morbidity ?
- lack of evidence from RCTs

Design and Outcome Measures

RCT of Bilateral ITA (plus vein grafts) versus Single ITA (plus vein grafts)

SAMPLE SIZE

- **Estimate**: that at 10 years, Bilateral **ITA** grafts will result in an absolute 5% reduction in mortality (i.e. from 25% to 20%) vs. Single **ITA** graft
- **Confirm**: with 90% power at p <0.05 requires 2928 patients
- **Aim**: to enrol >3000 patients (1500 in each arm) over 3-years

ART Endpoints

Primary outcome

Survival at 10 years

Secondary outcomes

composite outcomes of death from any cause , MI , stroke

rate of repeat revascularisation

safety outcomes : bleeding , sternal wound complications

QOL (SF-36 , ROSE and EuroqOL)

Cost effectiveness

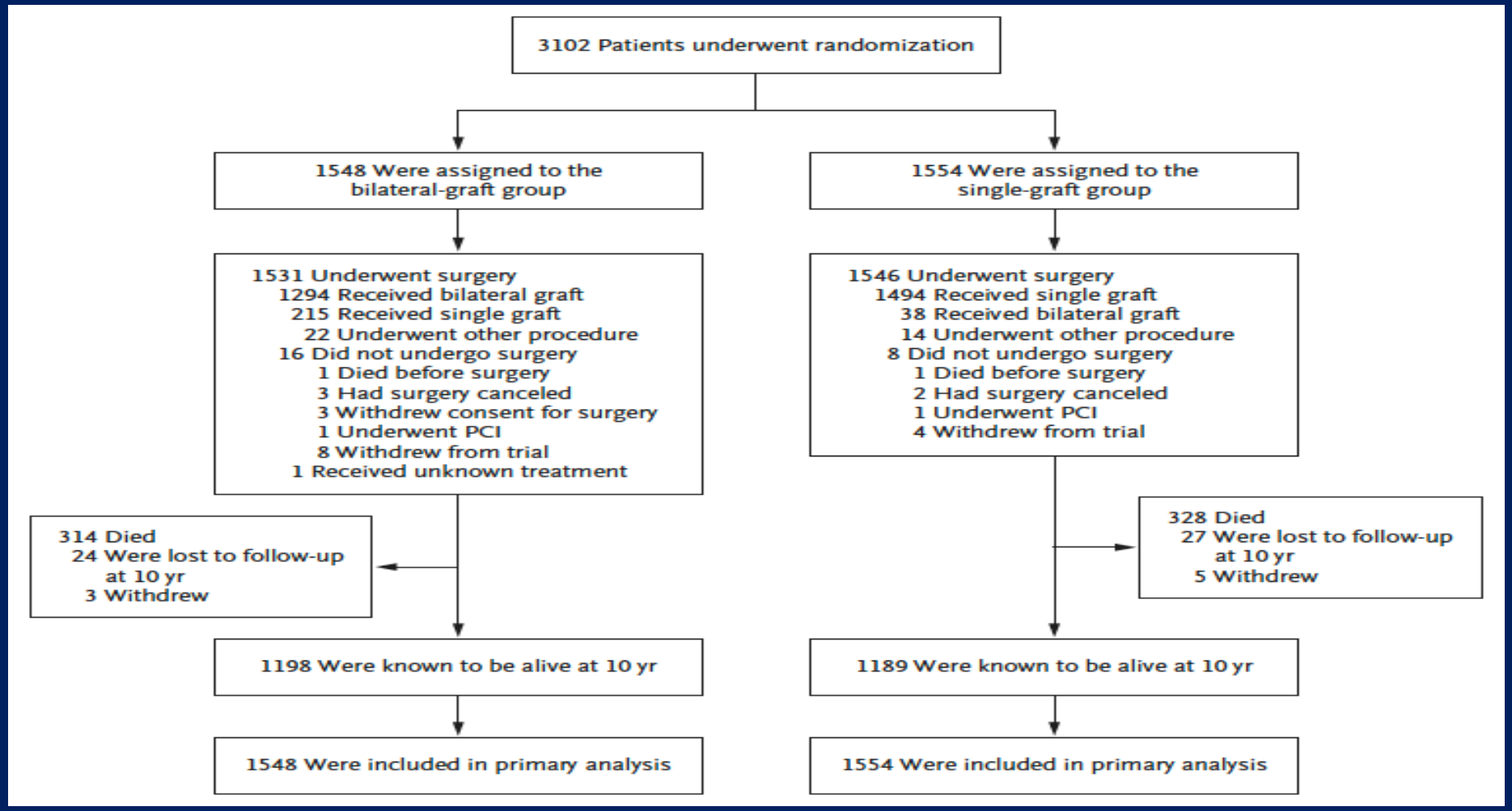
Art Endpoints

Subgroups analysis performed on the basis of baseline diagnosis of

- Diabetes
- Age (< 70 yrs , > 70 yrs)
- On vs off pump
- Radial artery versus vein grafts
- Number of grafts
- Impaired ventricular function

Per protocol analysis and as treated analysis

Enrolment : from June 2004 to December 2007



Inclusion criteria

CABG patients with multi-vessel +/- left main coronary artery disease

CABG for acute coronary syndrome (BUT not acute myocardial infarction)

CABG could be performed “on-pump” or “off-pump”

Exclusion criteria

Patients requiring single graft

Patients with evolving myocardial infarction

Patients requiring concomitant valve surgery

Patients requiring redo CABG

ART Patient characteristics

	SIMA (n=1554)	BIMA (n=1548)
Age: years mean (±SD)	63.5 (9.1)	63.7 (8.7)
Male	86%	85%
Diabetes	23.4%	24%
Urgent CABG	7.9%	7.6%
Prior myocardial infarction	43.8%	40%
Prior stenting	16%	15.6%
Prior CVA	3.1%	2.7%
Peripheral arterial disease	7.6%	6.6%

ART Surgery

		SIMA (n=1552)	BIMA (n=1542)	Δ
Off-Pump		40%	41.8%	
Grafts	1	0.7%	0.5%	
	2	17.7%	17.8%	
	3	48.5%	50.4%	
	4+	33.2%	31.3%	
	Radial artery graft	22%	19%	
Surgery length: mins mean (SD)		199 (58)	222 (61)	23 mins
Ventilation length: mins mean (SD)		863 (3293)	968 (3029)	105 mins
Duration ITU stay: hours mean (SD)		38 (106)	41 (94)	3 hours
Duration of post-op stay: days mean (SD)		7.5 (7.6)	8.0 (7.4)	0.5 days
Re-exploration for any cause		3.5%	4.3%	
Blood transfusion		12%	12%	
Intra Aortic Balloon Pump		3.7%	4.4%	
Renal support		4.4%	5.9%	

Art trial : results

- 98,4 % of patients with vital status

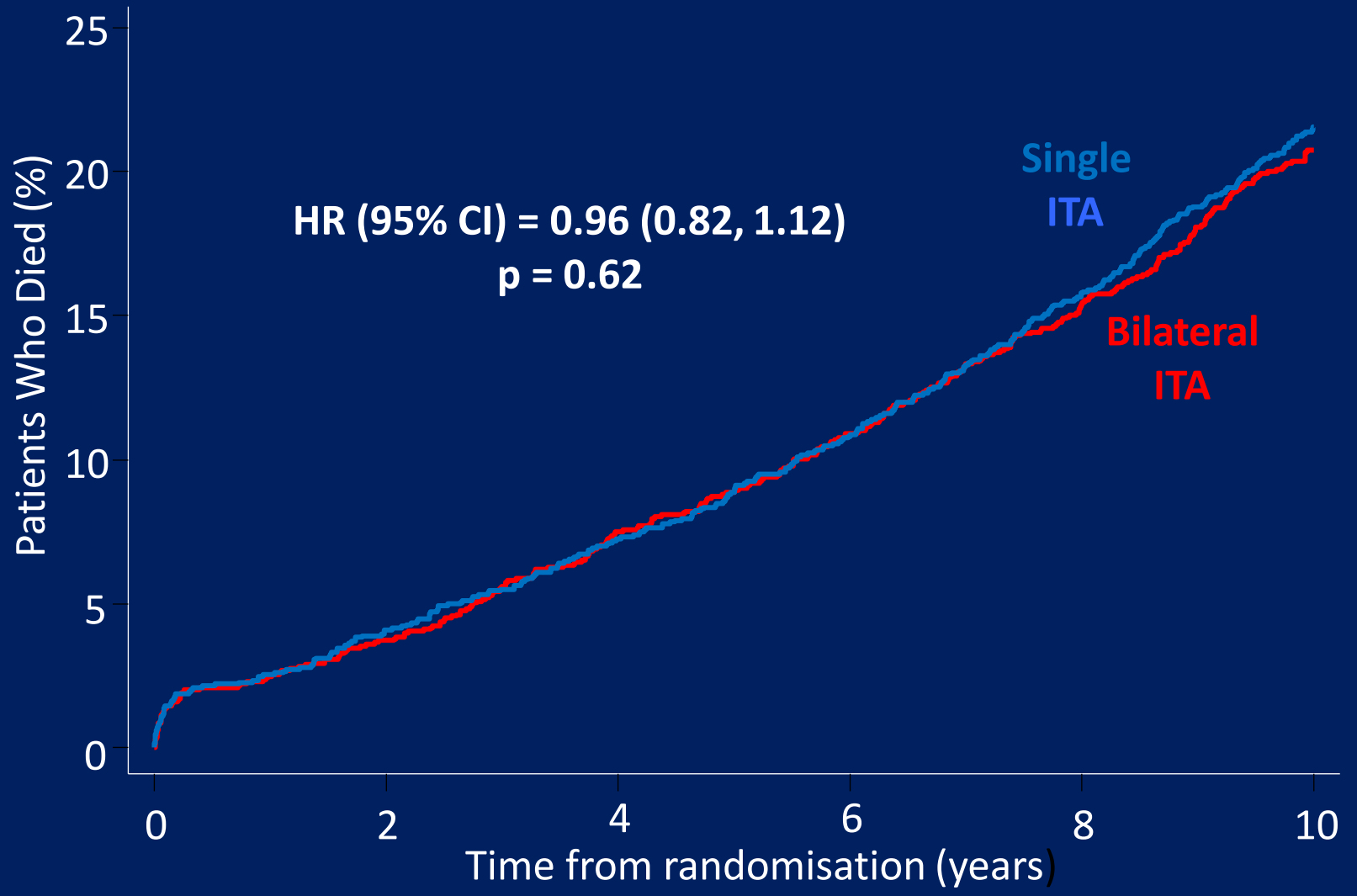
- Prespecified analysis of the PEP includes

- **Intention to treat (ITT)**
- **As treated : non randomized**

-> 36% of Patients Received A ‘Different’ Treatment Strategy

- 14% of Bilateral **ITA** crossed to Single **ITA**
- 22% of Single **ITA** had a 2nd Arterial Graft (Radial Artery)

Mortality @ 10 years (Intention To Treat)

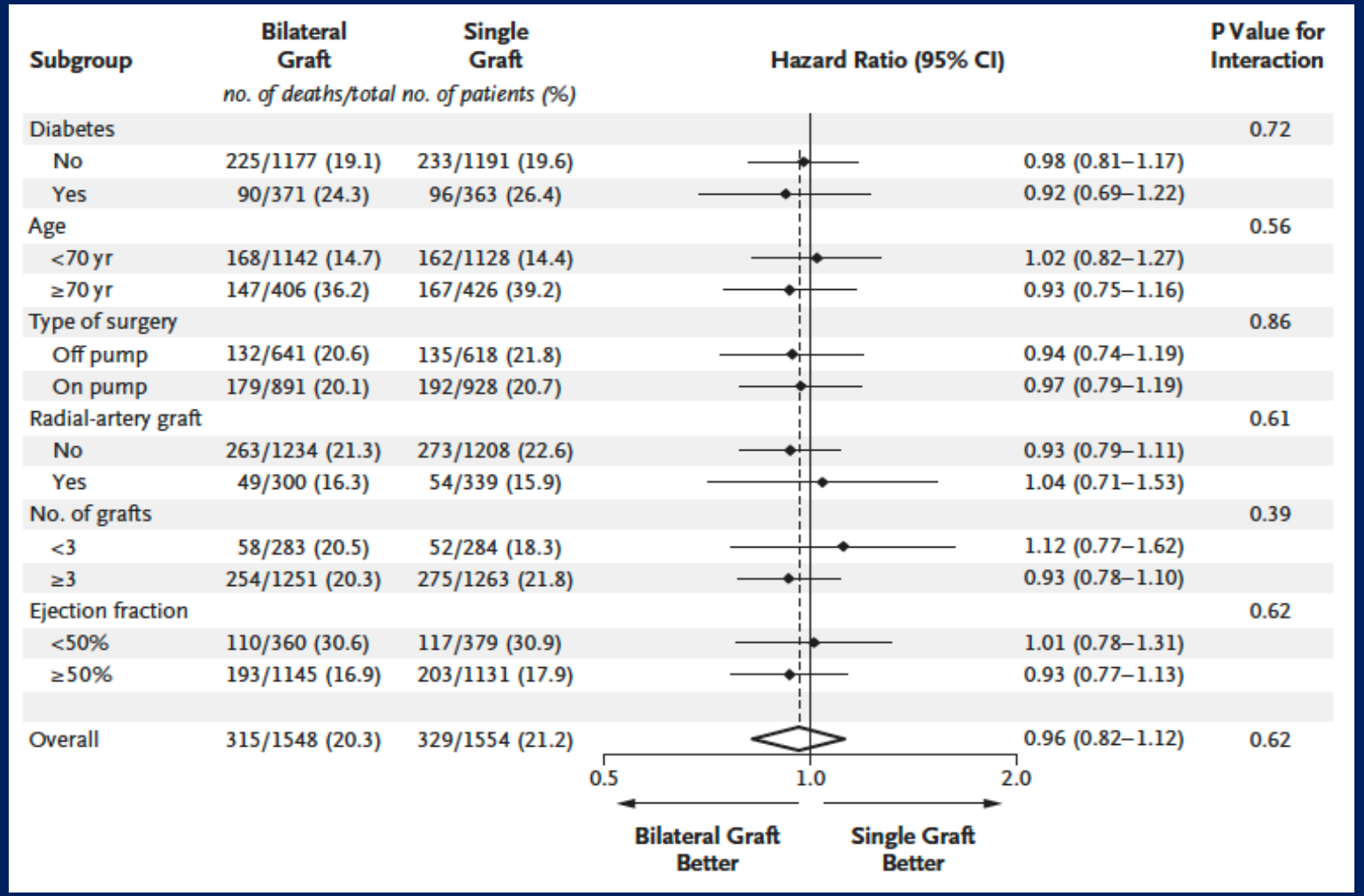


No. at risk						
Bilateral graft	1548	1481	1417	1359	1283	882
Single graft	1554	1484	1432	1370	1283	894

Clinical outcomes and adverse events @10 years (ITT)

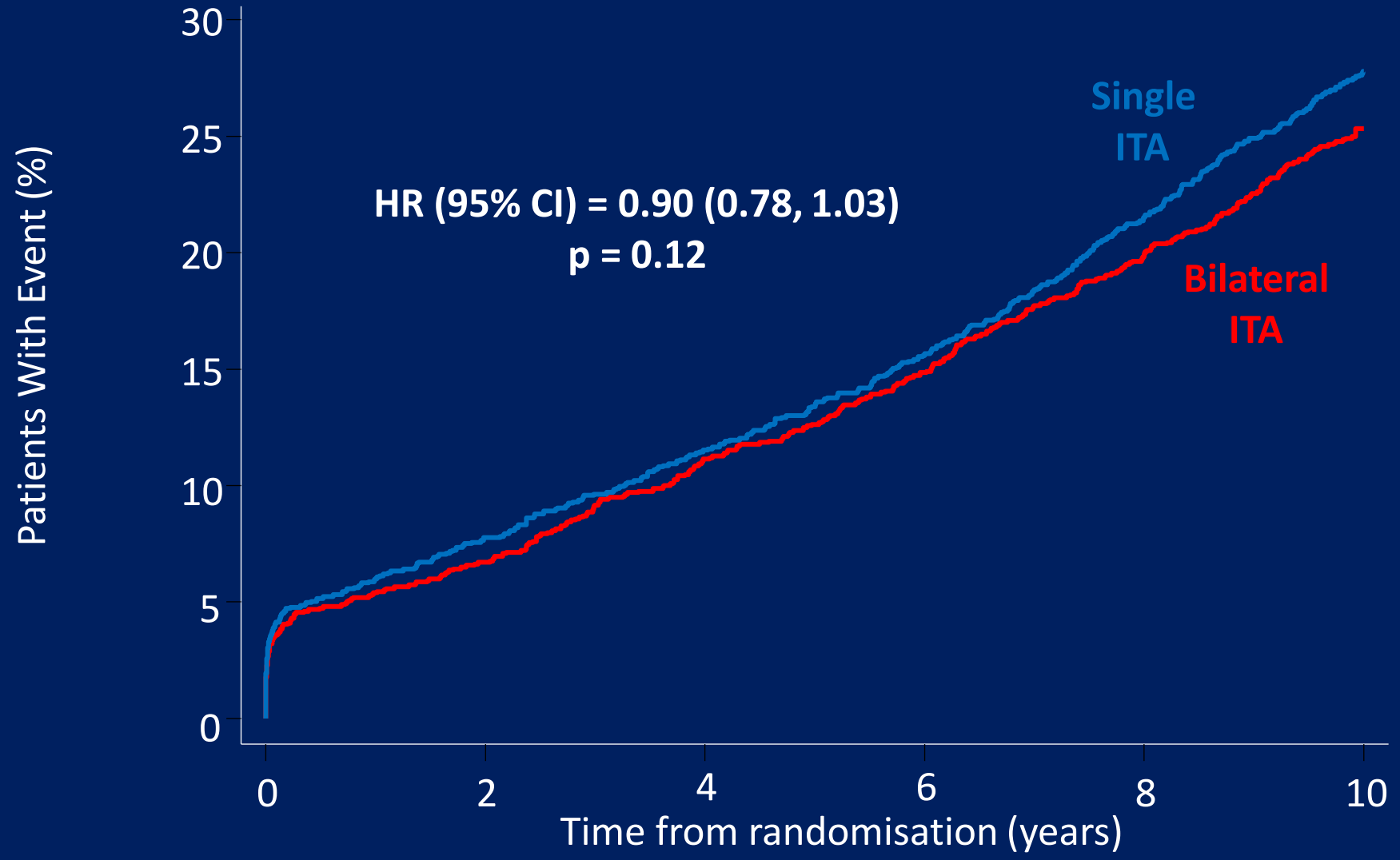
Variable	Bilateral-Graft Group (N=1548)	Single-Graft Group (N=1554)	Hazard Ratio or Relative Risk (95% CI)*	P Value
	number (percent)			
Clinical outcome				
Primary outcome: death from any cause	315 (20.3)	329 (21.2)	0.96 (0.82–1.12)	0.62
Composite of death, myocardial infarction, or stroke	385 (24.9)	425 (27.3)	0.90 (0.79–1.03)	—
Myocardial infarction†	71 (4.6)	78 (5.0)	0.92 (0.66–1.26)	—
Stroke†	57 (3.7)	76 (4.9)	0.75 (0.53–1.06)	—
Adverse event				
Repeat revascularization	159 (10.3)	156 (10.0)	1.02 (0.83–1.26)	—
Major bleeding‡	52 (3.4)	48 (3.1)	1.09 (0.74–1.61)	—
Sternal wound complication‡	54 (3.5)	30 (1.9)	1.81 (1.16–2.81)	—
Sternal wound reconstruction‡	31 (2.0)	10 (0.6)	3.11 (1.53–6.32)	—

Intention to treat of the PEP according to subgroup analysis



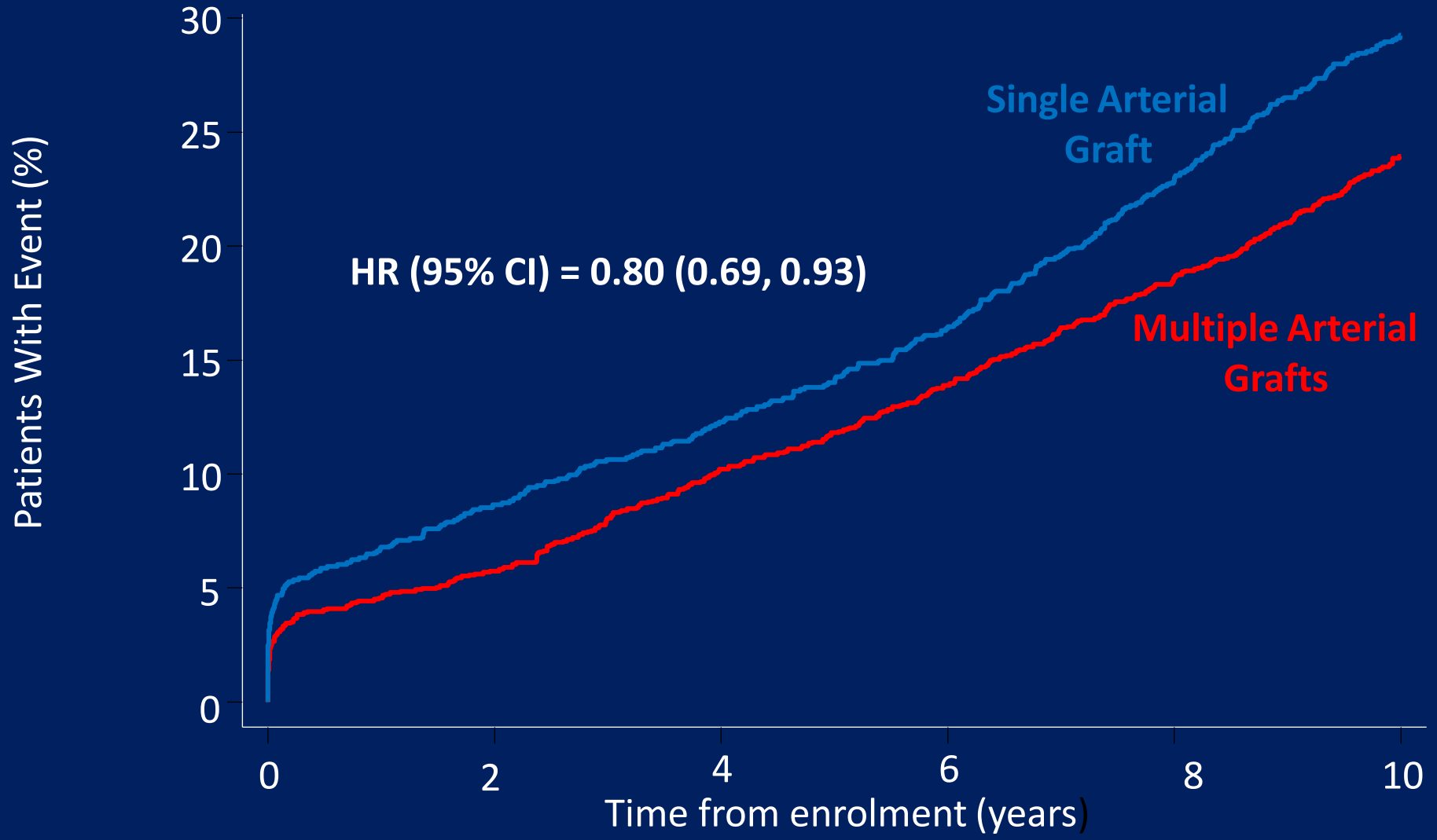
Subgroup	Bilateral Graft	Single Graft	Hazard Ratio (95% CI)	P Value for Interaction
	no. of deaths/total no. of patients (%)			
Diabetes				0.72
No	225/1177 (19.1)	233/1191 (19.6)	0.98 (0.81–1.17)	
Yes	90/371 (24.3)	96/363 (26.4)	0.92 (0.69–1.22)	
Age				0.56
<70 yr	168/1142 (14.7)	162/1128 (14.4)	1.02 (0.82–1.27)	
≥70 yr	147/406 (36.2)	167/426 (39.2)	0.93 (0.75–1.16)	
Type of surgery				0.86
Off pump	132/641 (20.6)	135/618 (21.8)	0.94 (0.74–1.19)	
On pump	179/891 (20.1)	192/928 (20.7)	0.97 (0.79–1.19)	
Radial-artery graft				0.61
No	263/1234 (21.3)	273/1208 (22.6)	0.93 (0.79–1.11)	
Yes	49/300 (16.3)	54/339 (15.9)	1.04 (0.71–1.53)	
No. of grafts				0.39
<3	58/283 (20.5)	52/284 (18.3)	1.12 (0.77–1.62)	
≥3	254/1251 (20.3)	275/1263 (21.8)	0.93 (0.78–1.10)	
Ejection fraction				0.62
<50%	110/360 (30.6)	117/379 (30.9)	1.01 (0.78–1.31)	
≥50%	193/1145 (16.9)	203/1131 (17.9)	0.93 (0.77–1.13)	
Overall	315/1548 (20.3)	329/1554 (21.2)	0.96 (0.82–1.12)	0.62

Mortality @ 10 years (As Treated)



No. at risk						
Bilateral graft	1548	1435	1362	1299	1214	830
Single graft	1554	1427	1366	1296	1194	821

Death, MI, stroke @ 10 years (As Treated)



No. at risk						
MAG	1690	1591	1510	1442	1353	934
SAG	1330	1212	1162	1101	1006	692

Why No Difference in Bilateral vs Single ITA Graft @ 10 years (Intention To Treat) ?

Conflicting results with data from previous non randomized studies

- Clinical FU >< angiographic FU
- Clinical impact of veinous graft failure on survival ?
- Guideline Based Medical Therapy: in > 80% (slows vein graft failure
- Radial Artery Use

  22% of Single **ITA** , 19% in the double **ITA**
- Differential X-over

  14% of Bilateral **ITA** → Single **ITA**; 4% Single **ITA** → Bilateral **ITA**
- Surgeon Experience

  Individual Surgeon X-over from Bilateral **ITA** to Single **ITA** : 0%-100%

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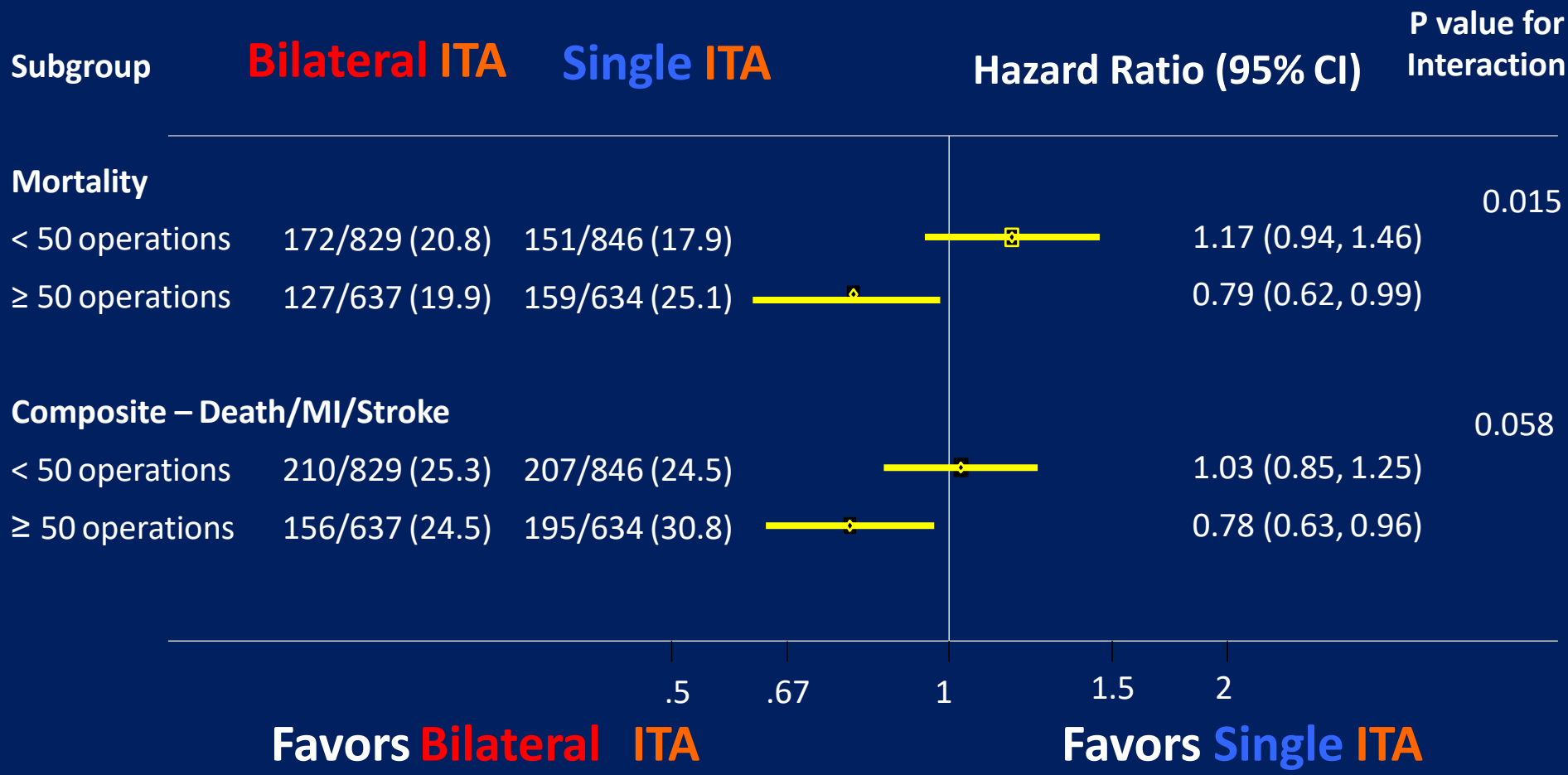
Radial-Artery or Saphenous-Vein Grafts in Coronary-Artery Bypass Surgery

Mario Gaudino, M.D., Umberto Benedetto, M.D., Stephen Fremes, M.D., Giuseppe Biondi-Zoccai, M.D., M.Stat., Art Sedrakyan, M.D., Ph.D., John D. Puskas, M.D., Gianni D. Angelini, M.D., Brian Buxton, M.D., Giacomo Frati, M.D., David L. Hare, M.D., Philip Hayward, M.D., Giuseppe Nasso, M.D., Neil Moat, M.D., Miodrag Peric, M.D., Kyung J. Yoo, M.D., Giuseppe Speziale, M.D., Leonard N. Girardi, M.D., and David P. Taggart, M.D., for the RADIAL Investigators*

Table 3. Main Outcomes.*

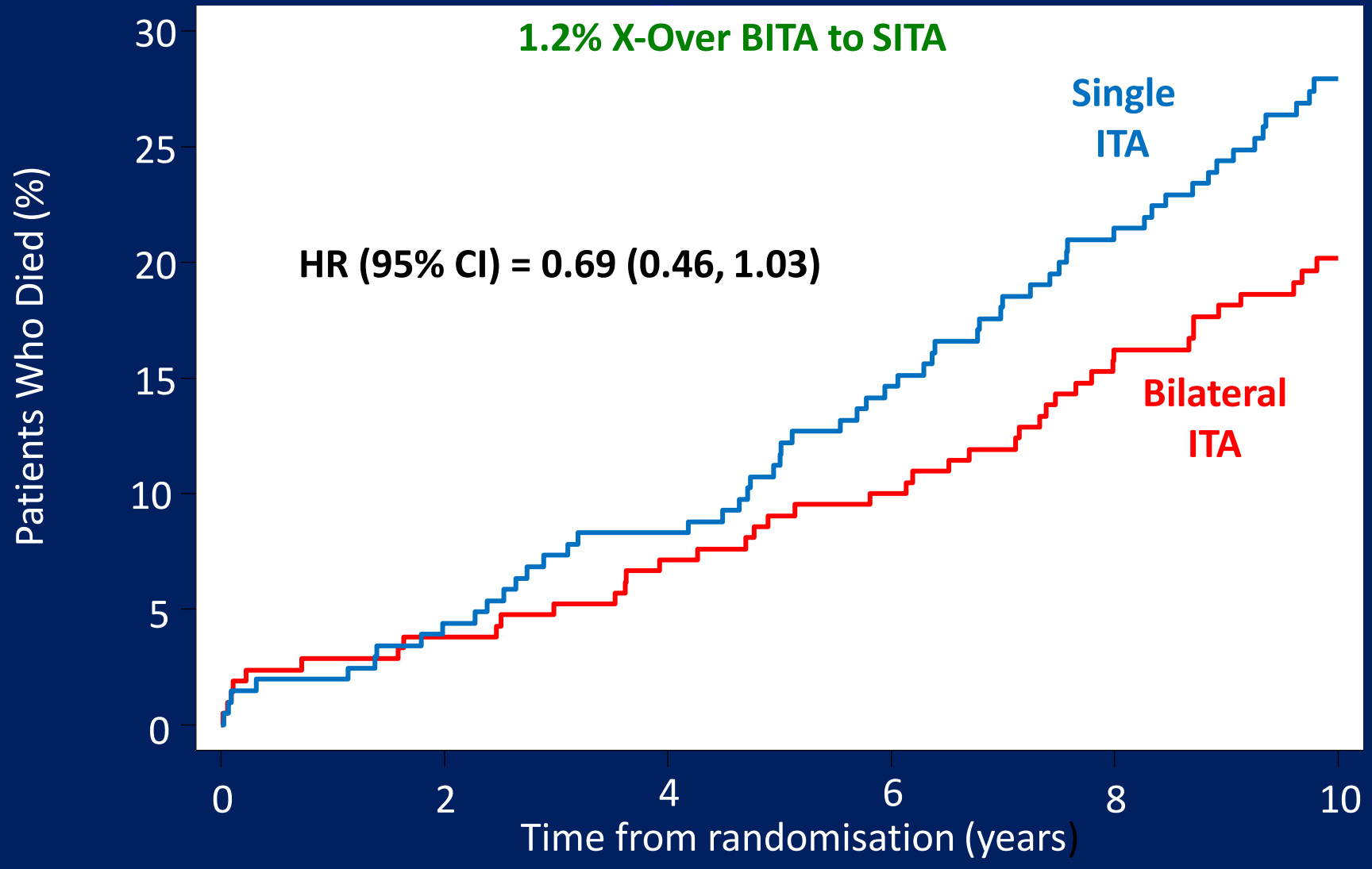
Outcome	Radial-Artery Group (N=534)		Saphenous-Vein Group (N=502)		Treatment Effect†	
	No. of Events (%)	Events per 1000 Patient-Yr‡	No. of Events (%)	Events per 1000 Patient-Yr‡	Hazard Ratio (95% CI)	P Value
Death, myocardial infarction, or repeat revascularization	67 (12.5)	25	94 (18.7)	39	0.67 (0.49–0.90)	0.01
Death	40 (7.5)	15	42 (8.4)	17	0.90 (0.59–1.41)	0.68
Myocardial infarction	16 (3.0)	6	21 (4.2)	9	0.72 (0.53–0.99)	0.04
Repeat revascularization	23 (4.3)	9	43 (8.6)	17	0.50 (0.40–0.63)	<0.001
Graft occlusion§	28/345 (8.1)	19	61/307 (19.9)	46	0.44 (0.28–0.70)	<0.001

Effects of Surgeon Volume in ART Intention To Treat Analysis



Intention to Treat

10-Year mortality for highest volume (n=416) surgeon in ART



No. at risk						
Bilateral graft	211	202	195	188	175	122
Single graft	205	196	188	175	161	114

Conclusions : Ten Year Analysis of the ART trial

ART is the largest CABG trial with long term follow-up (>98% @ 10 yrs)

Excellent 10 year outcomes for CABG in both groups

14% allocated to Bilateral **ITA** actually received Single **ITA**, and 22% of single ITA received additional radial artery graft

Intention To Treat: Confirms safety of Bilateral **ITA** grafts @ 10 years

Intention To Treat: No significant differences in all cause mortality or composite of mortality, myocardial infarction or stroke

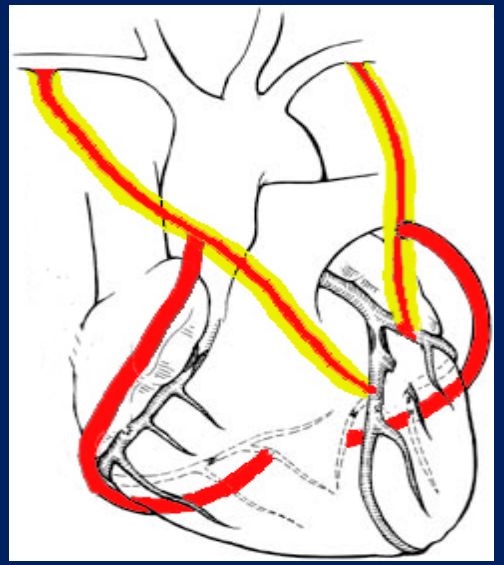
Conclusions : Ten Year Analysis of the ART trial

As Treated (Non randomized) group: Potential for multiple arterial grafts to provide superior outcomes

Surgeon experience appears to be a crucial factor for outcomes with Bilateral **ITA** grafts

Need for further trials of Single vs Multiple arterial grafts by appropriately experienced surgeons

Roma trial : Randomized comparison of the clinical Outcome of single versus Multiple Arterial grafts (European journal of cardiothoracic surgery 2017 ; 52: 1031-40)



TAVR in low risk patients

Slides with the courtesy of TCTMD

Background

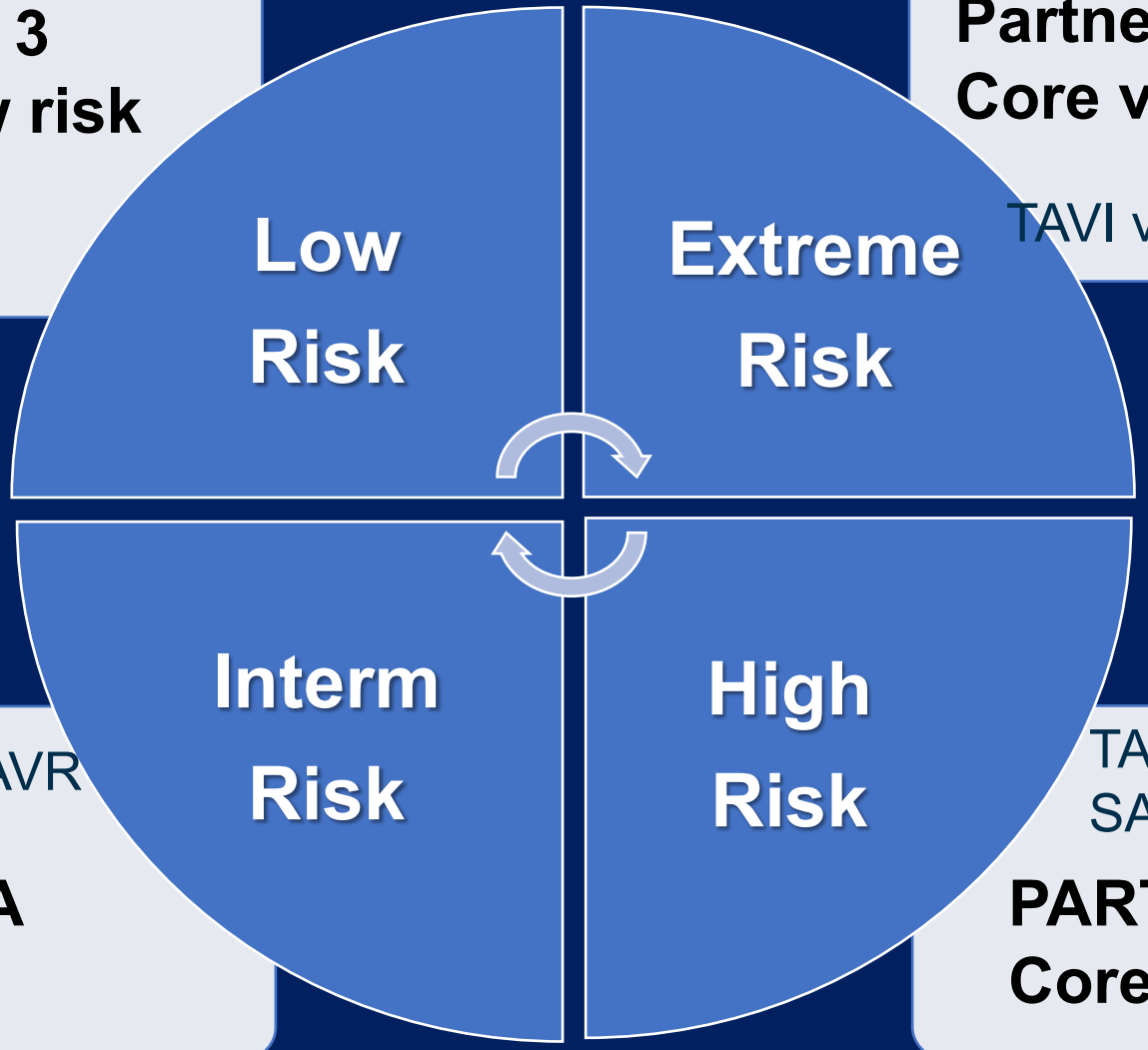
- Previous PARTNER and Core valve (Core valve high risk , Surtavi) studies have shown that TAVR was superior to standard therapy in extreme-risk patients and non-inferior to surgery in high- and intermediate-risk patients.
- Over the past decade, technology enhancements and procedural refinements have reduced complications and improved clinical outcomes after TAVR.
- The majority of AS patients treated with surgery have low surgical risk profiles and TAVR vs. surgery in such patients has not been investigated in rigorous clinical trials.

Background

PARTNER 3
Evolut low risk

Partner 1 B
Core valve extreme risk

TAVI versus medical



TAVR versus SAVR

PARTNER 2A
SURTAVI

TAVR versus SAVR

PARTNER 1A
Core valve high risk

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ORIGINAL ARTICLE

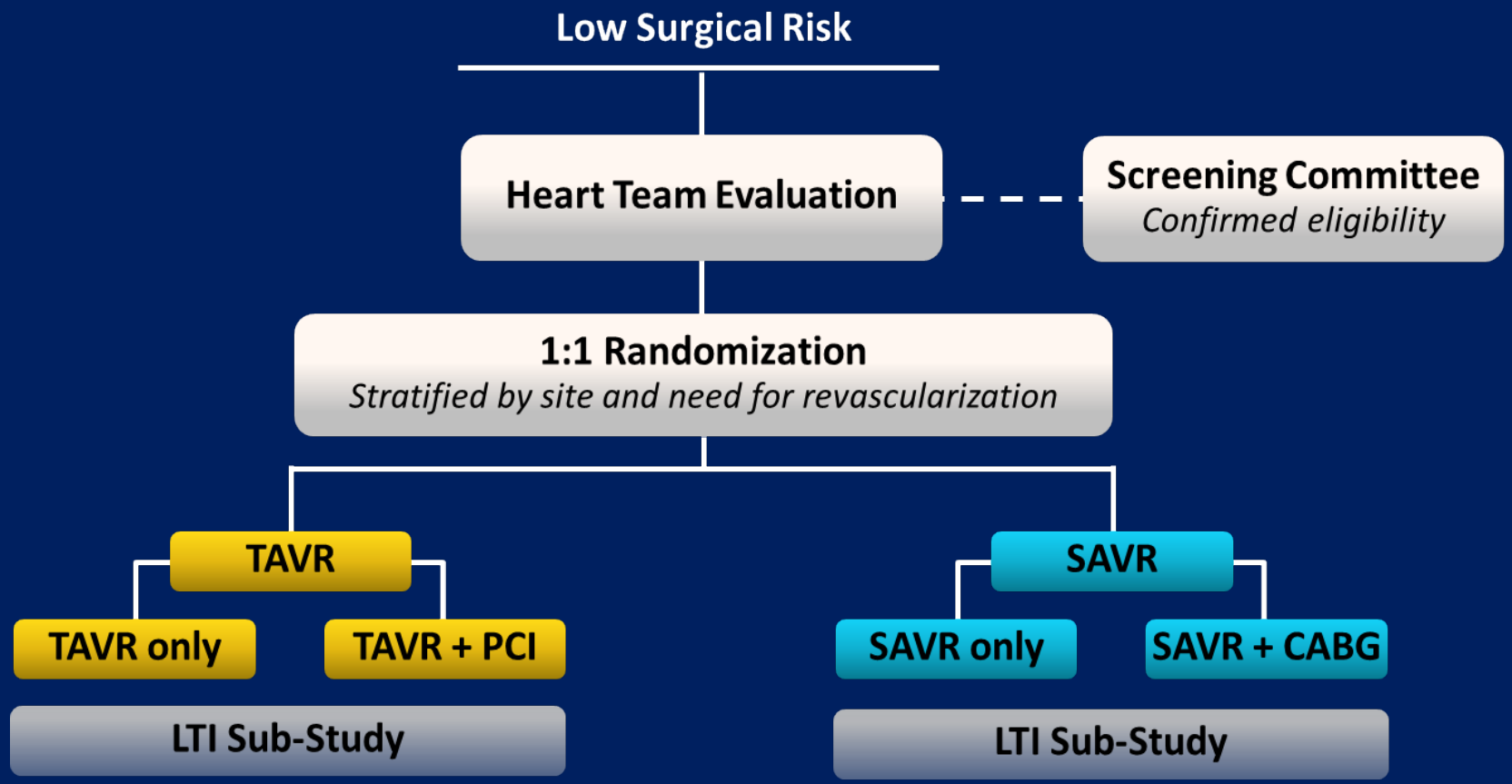
Transcatheter Aortic-Valve Replacement with a Self-Expanding Valve in Low-Risk Patients

Jeffrey J. Popma, M.D., G. Michael Deeb, M.D., Steven J. Yakubov, M.D., Mubashir Mumtaz, M.D., Hemal Gada, M.D., Daniel O'Hair, M.D., Tanvir Bajwa, M.D., John C. Heiser, M.D., William Merhi, D.O., Neal S. Kleiman, M.D., Judah Askew, M.D., Paul Sorajja, M.D., Joshua Rovin, M.D., Stanley J. Chetcuti, M.D., David H. Adams, M.D., Paul S. Teirstein, M.D., George L. Zorn III, M.D., John K. Forrest, M.D., Didier Tchétché, M.D., Jon Resar, M.D., Antony Walton, M.D., Nicolo Piazza, M.D., Ph.D., Basel Ramlawi, M.D., Newell Robinson, M.D., George Petrossian, M.D., Thomas G. Gleason, M.D., Jae K. Oh, M.D., Michael J. Boulware, Ph.D., Hongyan Qiao, Ph.D., Andrew S. Mugglin, Ph.D., and Michael J. Reardon, M.D., for the Evolut Low Risk Trial Investigators*

NEJM , March 17, 2019

Evolut low risk trial

Objective : To assess the safety and efficacy of TAVR with the Evolut self-expanding supra-annular valve compared with surgical AVR in patients with a low predicted risk of 30-day surgical mortality (non inferiority clinical trial)



Study Endpoints

Primary Safety and Effectiveness Endpoint

All-cause mortality or disabling stroke at 2 years

Hierarchical Powered Secondary Endpoints

<u>Noninferiority</u>

- Mean gradient at 1 year
- EOA at 1 year
- Change in NYHA class from baseline to 1 year
- Change in KCCQ score from baseline to 1 year

<u>Superiority</u>

- Mean gradient at 1 year
- EOA at 1 year
- Change in KCCQ score from baseline to 30 days

Other Secondary Endpoints

- 30-day safety composite of
  - All-cause mortality
  - Disabling stroke
  - Life-threatening bleeding
  - Major vascular complications
  - Stage 2 or 3 acute kidney injury
- New pacemaker implantation at 30 days
- Heart failure , rehospitalizations at 1 year
- Aortic-valve reintervention at 1 year
- Moderate/severe AR at 1 year
- All stroke at 1 year
- Life-threatening bleeding at 1 year

Key Inclusion Criteria

Symptomatic severe AS[1]:

- Aortic valve area ≤1.0 cm^2 (or aortic valve area index <0.6 cm^2/m^2), **OR** mean gradient ≥40 mmHg **OR** Vmax ≥4 m/sec at rest

Asymptomatic very severe AS[1]:

- Aortic valve area ≤1.0 cm^2 (or aortic valve area index <0.6 cm^2/m^2), **AND** Vmax ≥5 m/sec or mean gradient ≥ 60 mmHg at rest
- Aortic valve area of ≤1.0 cm^2 (or aortic valve area index of ≤0.6 cm^2/m^2), **AND** a mean gradient ≥40 mmHg or Vmax ≥4.0 m/sec by transthoracic echocardiography at rest, **AND** an exercise tolerance test that demonstrates limited exercise capacity, abnormal BP response, or arrhythmia
- Aortic valve area of ≤1.0 cm^2 (or aortic valve area index of ≤0.6 cm^2/m^2), **AND** mean gradient ≥40 mmHg, **OR** Vmax ≥4.0 m/sec by transthoracic echocardiography at rest, **AND** LVEF<50%.

A predicted risk of 30-day mortality <3% per multidisciplinary local heart team assessment.

Key Exclusion Criteria

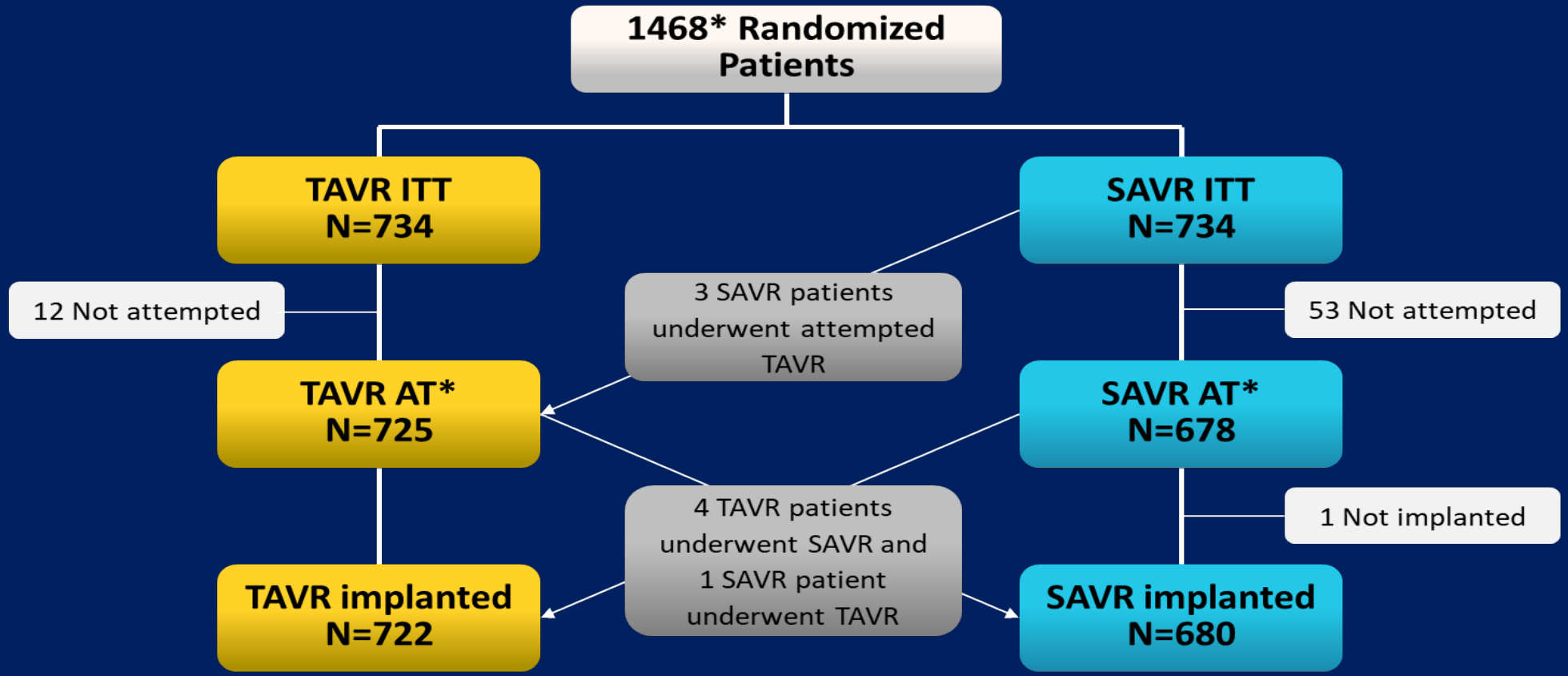
Anatomic

- Multivessel coronary artery disease with SYNTAX score >22
- Bicuspid aortic valve verified by imaging
- Unsuitable anatomy including native aortic annulus <18 mm or >30 mm
- Severe mitral or tricuspid regurgitation

Clinical

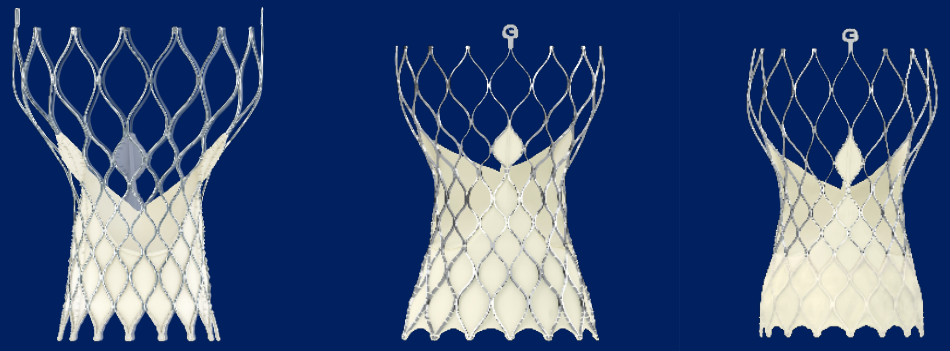
- Hypersensitivity or contraindication to all anticoagulation/ antiplatelet regimens
- Any PCI or peripheral intervention within 30 days prior to randomization
- Symptomatic carotid or vertebral artery disease or successful treatment of carotid stenosis within 10 weeks of Heart Team assessment
- Recent (within 2 months) cerebrovascular accident or transient ischemic attack
- Acute MI within 30 days
- Severe liver, lung or renal disease

Patient Flow



Mars 2016 -> November 2018

Study Timeline and Valves Studied



CoreValve 31 = 3.6%	Evolut R = 74.1%	Evolut PRO = 22.3%

Vascular access
- 99% transfemoral
- 0.6% subclavian
- 0.4% direct aortic

*For this analysis

Baseline Characteristics

Mean ± SD or %	TAVR (N=725)	SAVR (N=678)
Age, years	74.1 ± 5.8	73.6 ± 5.9
Female sex	36.0	33.8
Body surface area, m^2	2.0 ± 0.2	2.0 ± 0.2
STS PROM, %	1.9 ± 0.7	1.9 ± 0.7
NYHA Class III or IV	25.1	28.5
Hypertension	84.8	82.6
Chronic lung disease (COPD)	15.0	18.0
Cerebrovascular disease	10.2	11.8
Peripheral arterial disease	7.5	8.3

There are no significant differences between groups.

Baseline Cardiac Risk Factors

Mean ± SD or %	TAVR (N=725)	SAVR (N=678)
SYNTAX Score	1.9 ± 3.7	2.1 ± 3.9
Permanent pacemaker, CRT or ICD	3.2	3.8
Prior CABG	2.5	2.1
Previous PCI	14.2	12.8
Previous myocardial infarction	6.6	4.9
Atrial fibrillation/flutter	15.4	14.5
Aortic valve gradient, mm Hg	47.0 ± 12.1	46.6 ± 12.2
Aortic Valve area, cm^2	0.8 ± 0.2	0.8 ± 0.2
Left ventricular ejection fraction, %	61.7 ± 7.9	61.9 ± 7.7

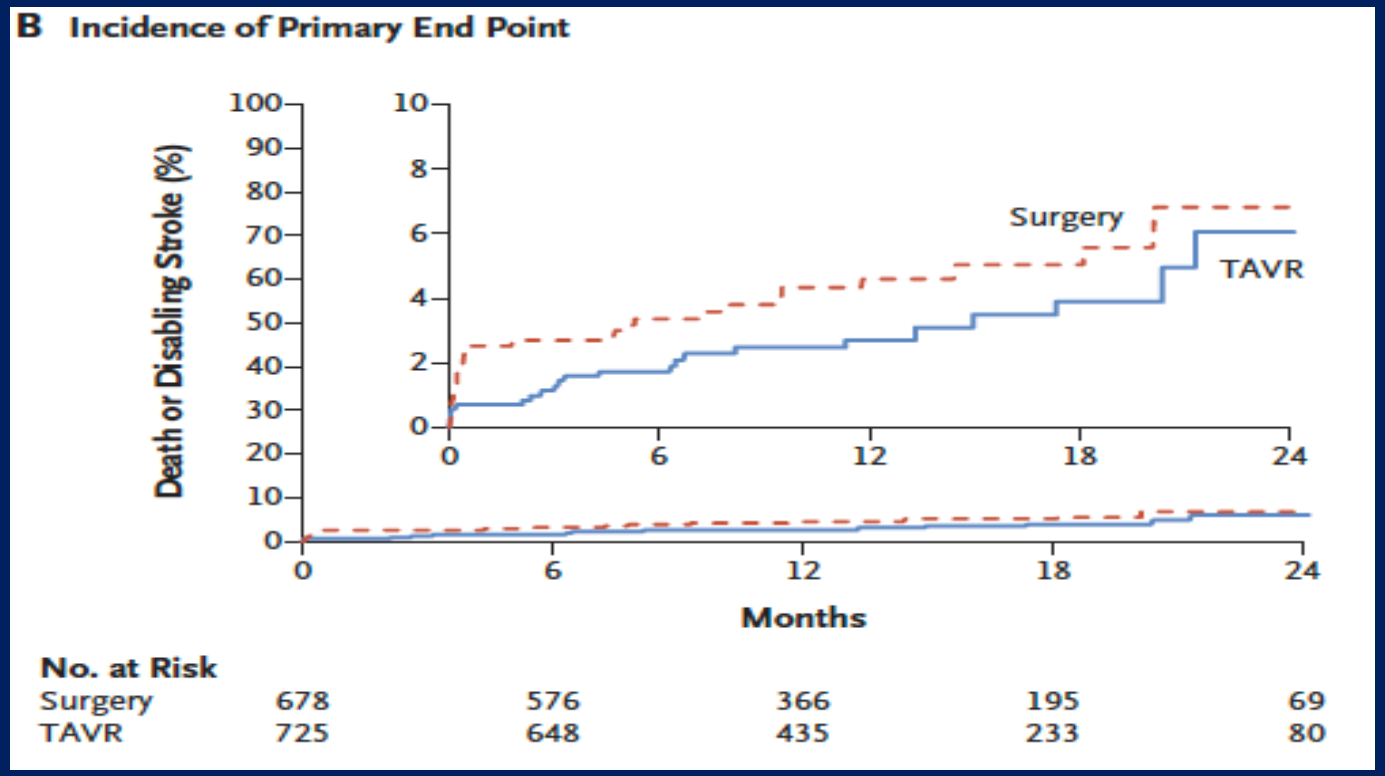
There are no significant differences between groups.

TAVR Procedural Data

%	TAVR (N=724)
General anesthesia	56.9
Iliofemoral access	99.0
Embolic protection device used	1.2
Pre-TAVR balloon dilation	34.9
Post-TAVR balloon dilation	31.3
More than 1 valve used	1.2
Partial or complete repositioning of the valve (Evolut/PRO only)	37.3
Staged or concomitant PCI performed	6.9

Primary Endpoint

All-Cause Mortality or Disabling Stroke at 2 Years



Incidence of death or disabling stroke @ 2 years : 5,3 % in the TAVR and 6,7 % in the SAVR group

Primary Endpoint Met : TAVR is noninferior to SAVR

Clinical Outcomes at 30 Days

Bayesian rates as %	TAVR (N=725)	SAVR (N=678)	(95% BCI for Difference)
30-Day composite safety endpoint*	5.3	10.7	(-8.3, -2.6)
All-cause mortality	0.5	1.3	(-1.9, 0.2)
Disabling stroke*	0.5	1.7	(-2.4, -0.2)
Life-threatening or disabling bleeding*	2.4	7.5	(-7.5, -2.9)
Acute kidney injury, stage 2-3*	0.9	2.8	(-3.4, -0.5)
Major vascular complication	3.8	3.2	(-1.4, 2.5)
Atrial fibrillation*	7.7	35.4	(-31.8, -23.6)
Permanent pacemaker implant*	17.4	6.1	(8.0, 14.7)
All-cause mortality or disabling stroke*	0.8	2.6	(-3.2, -0.5)
All stroke	3.4	3.4	(-1.9, 1.9)
Aortic valve reintervention	0.4	0.4	(-0.8, 0.7)

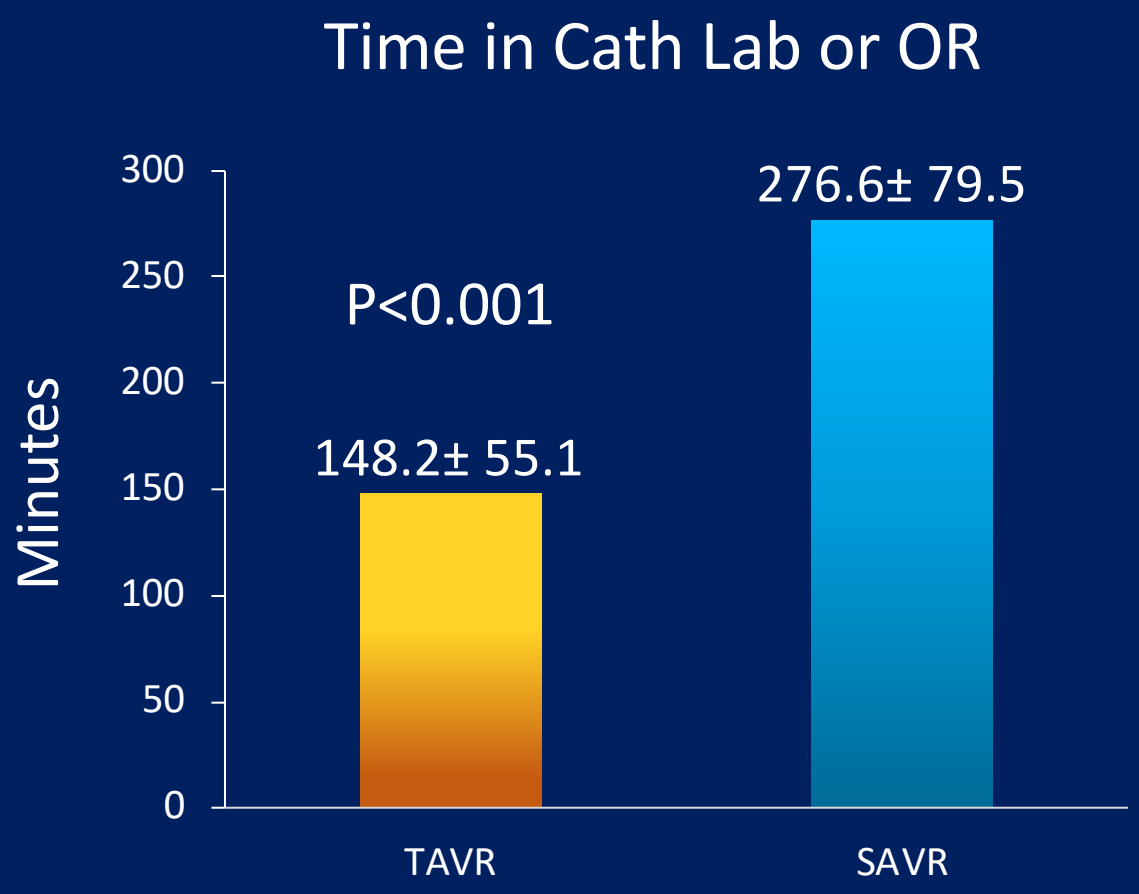
* Significantly favors TAVR; * Significantly favors SAVR

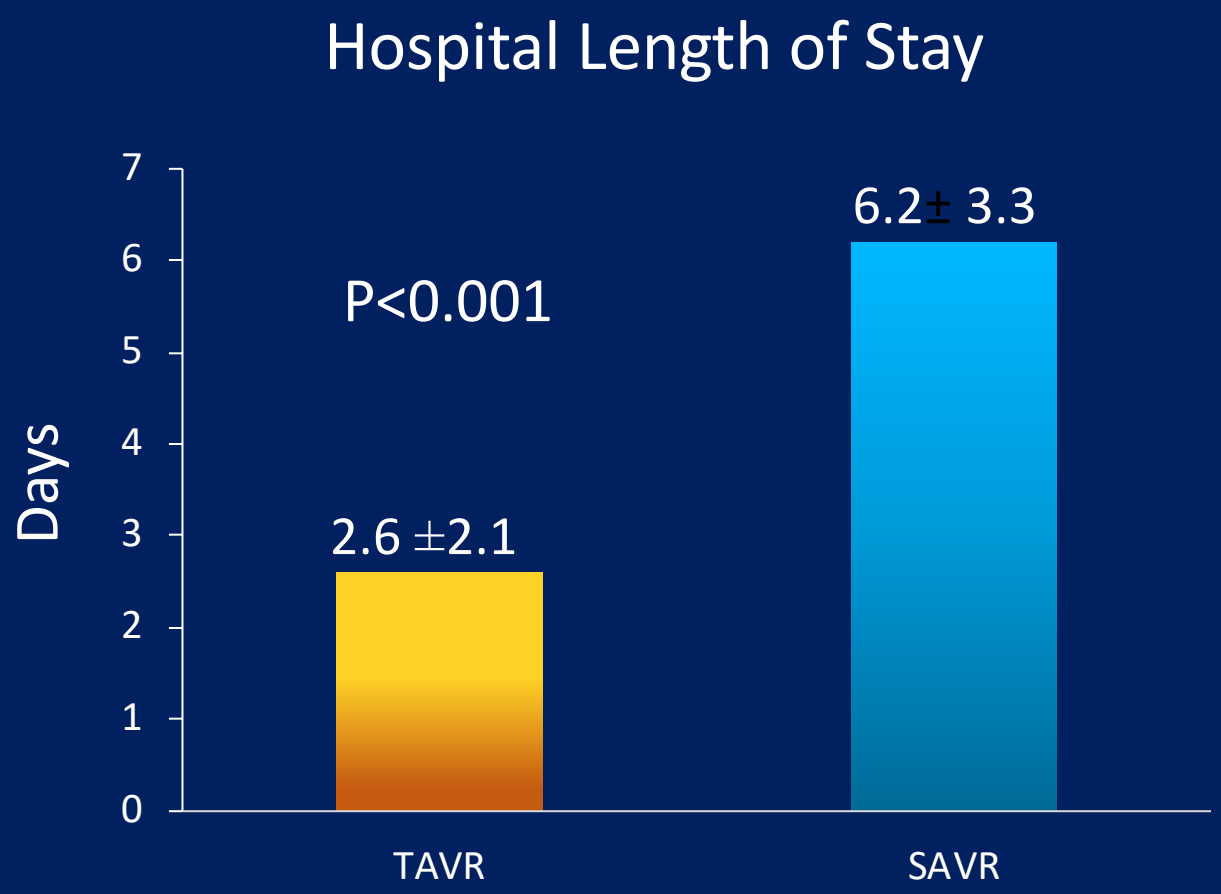
Clinical Outcomes at 1 Year

Bayesian rates as %	TAVR (N=725)	SAVR (N=678)	(95% BCI for Difference)
All-cause mortality or disabling stroke	2.9	4.6	(-4.0, 0.4)
All-cause mortality	2.4	3.0	(-2.6, 1.3)
Cardiovascular mortality	1.7	2.6	(-2.7, 0.7)
All stroke	4.1	4.3	(-2.4, 1.9)
Disabling stroke*	0.8	2.4	(-3.1, -0.3)
Transient ischemia attack	1.7	1.8	(-1.6, 1.3)
Myocardial infarction	1.7	1.6	(-1.3, 1.5)
Endocarditis	0.2	0.4	(-0.9, 0.5)
Valve thrombosis	0.2	0.3	(-0.9, 0.5)
Aortic valve reintervention	0.7	0.6	(-1.0, 0.9)
Heart failure hospitalization*	3.2	6.5	(-5.9, -1.0)

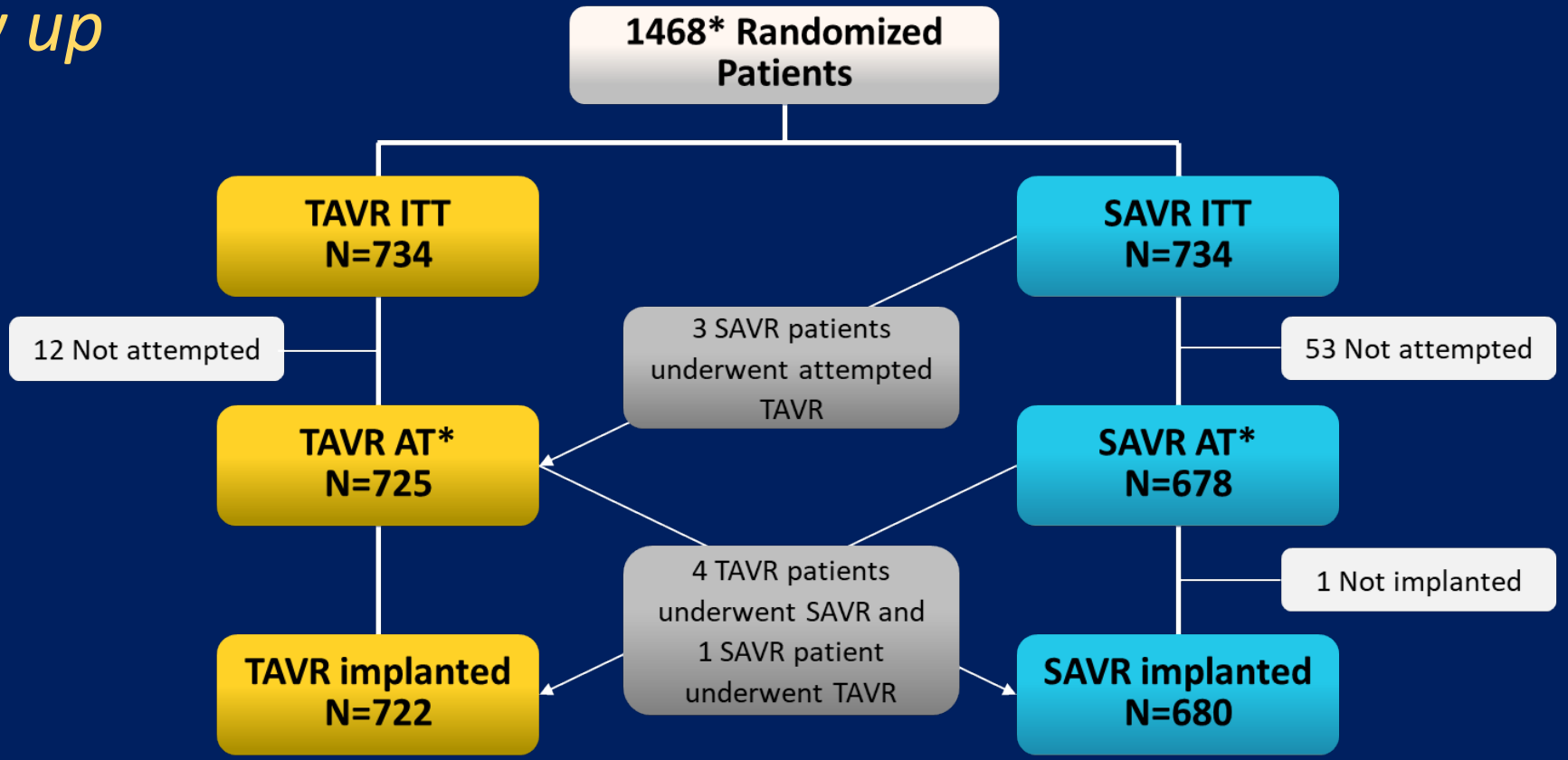
* Significantly favors TAVR

Procedural Time and Length of Stay





Follow up

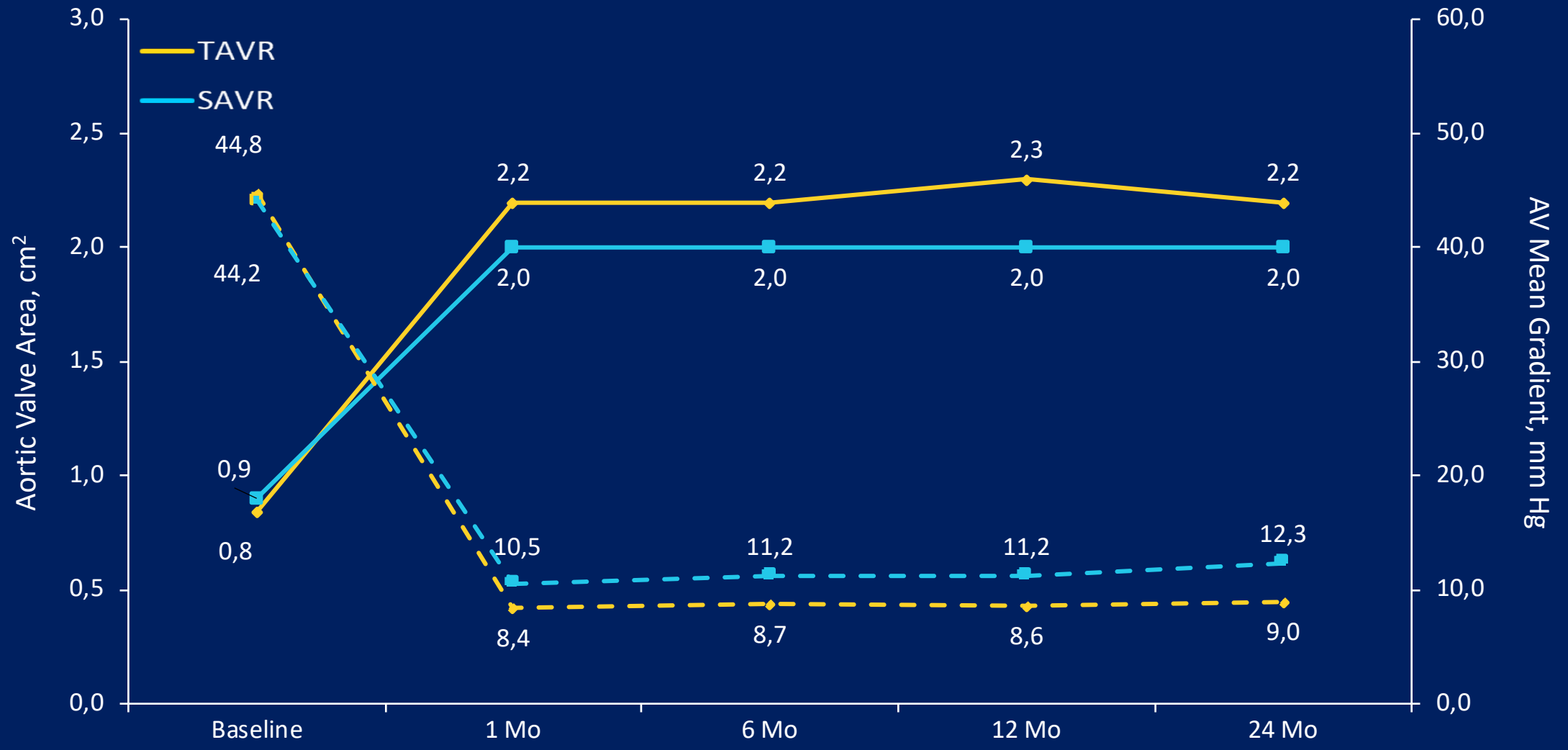


12 month follow up
TAVR group : 432
SAVR group : 352

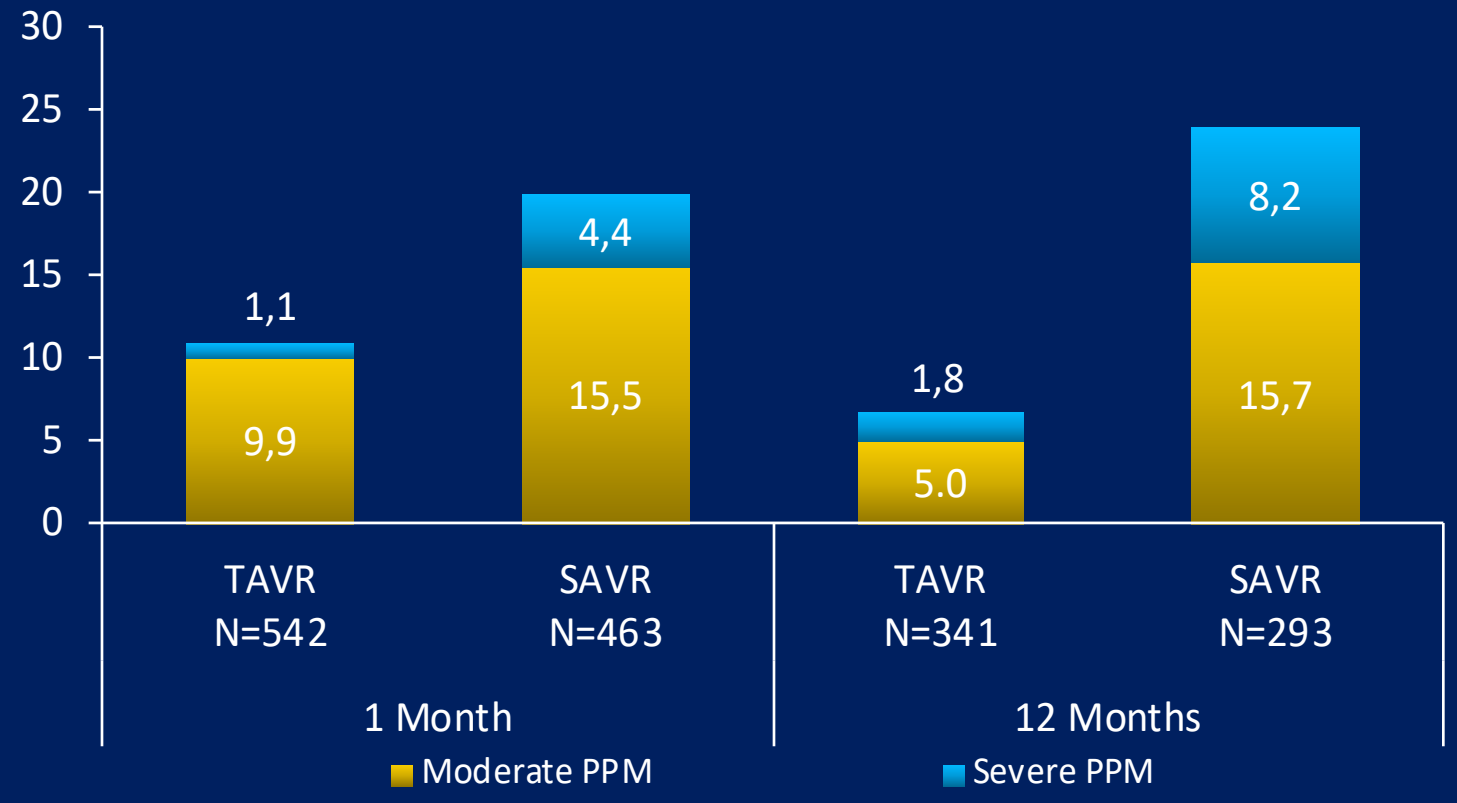
24 month follow up
TAVR group : 72
SAVR group : 65

Complete 24 M FU of the entire cohort has not been reached
Median follow up in each group 12,2 months

Aortic valve hemodynamics



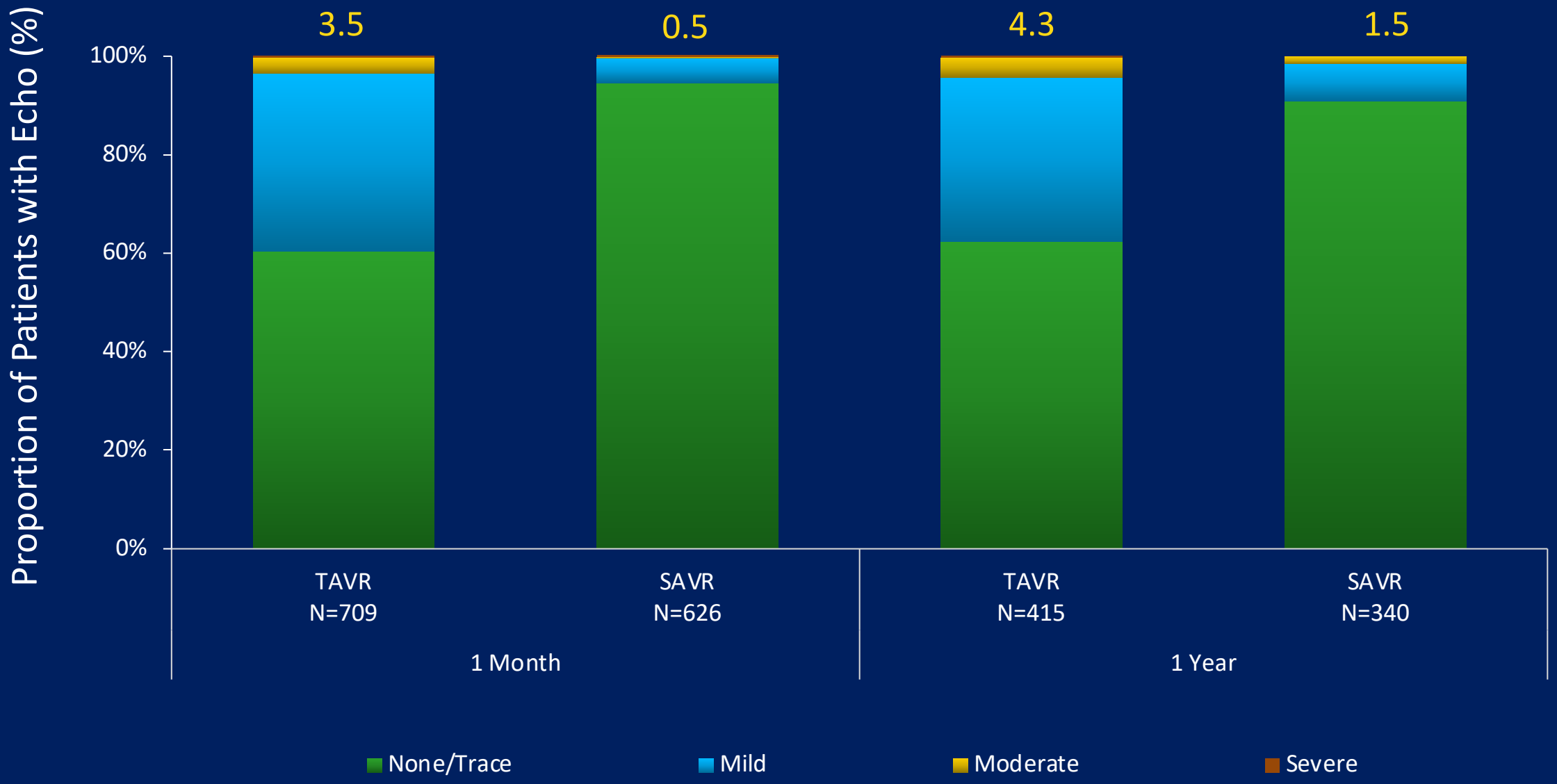
Prosthesis-Patient Mismatch



P<0.001

P<0.001

Total Aortic Valve Regurgitation



Conclusions

- TAVR with self-expanding supra-annular valves was noninferior to surgery for the primary endpoint of death or disabling stroke at 2 years in patients with severe aortic stenosis at low surgical risk.
- At 30 days, TAVR showed a better safety and recovery profile than surgery, with less death or disabling stroke, less disabling stroke, shorter length of stay and better QOL while SAVR had fewer pacemakers implanted and less residual AR.
- At 1 year, both groups had excellent survival. TAVR showed fewer disabling strokes and heart failure rehospitalizations with superior hemodynamics manifest by lower gradients, larger EOAs and less PPM.

LIMITATIONS

- Prespecified analysis occured when 850 patients had reached 12 months FU and complete 24 FU of the entire cohort has not been reached
- Conclusions regarding the advantages and disadvantages of TAVR compared to surgery await long term follow up (10 years)
- Exclusion of patients with anatomical contraindications (bicuspid valve ..) and those who were candidates for mechanical valves
- The last generation , Evolut pro , was used in only 22 ,3 % of the patients who received TAVR

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Transcatheter Aortic-Valve Replacement with a Balloon-Expandable Valve in Low-Risk Patients

M.J. Mack, M.B. Leon, V.H. Thourani, R. Makkar, S.K. Kodali, M. Russo, S.R. Kapadia, S.C. Malaisrie, D.J. Cohen, P. Pibarot, J. Leipsic, R.T. Hahn, P. Blanke, M.R. Williams, J.M. McCabe, D.L. Brown, V. Babaliaros, S. Goldman, W.Y. Szeto, P. Genereux, A. Pershad, S.J. Pocock, M.C. Alu, J.G. Webb, and C.R. Smith, for the PARTNER 3 Investigators*

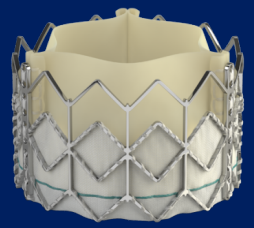
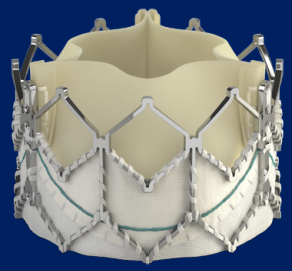
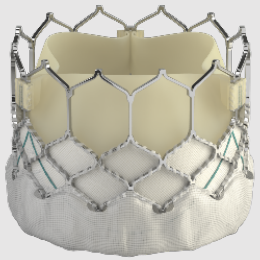
NEJM , March 17, 2019
Partner 3 trial

Purpose

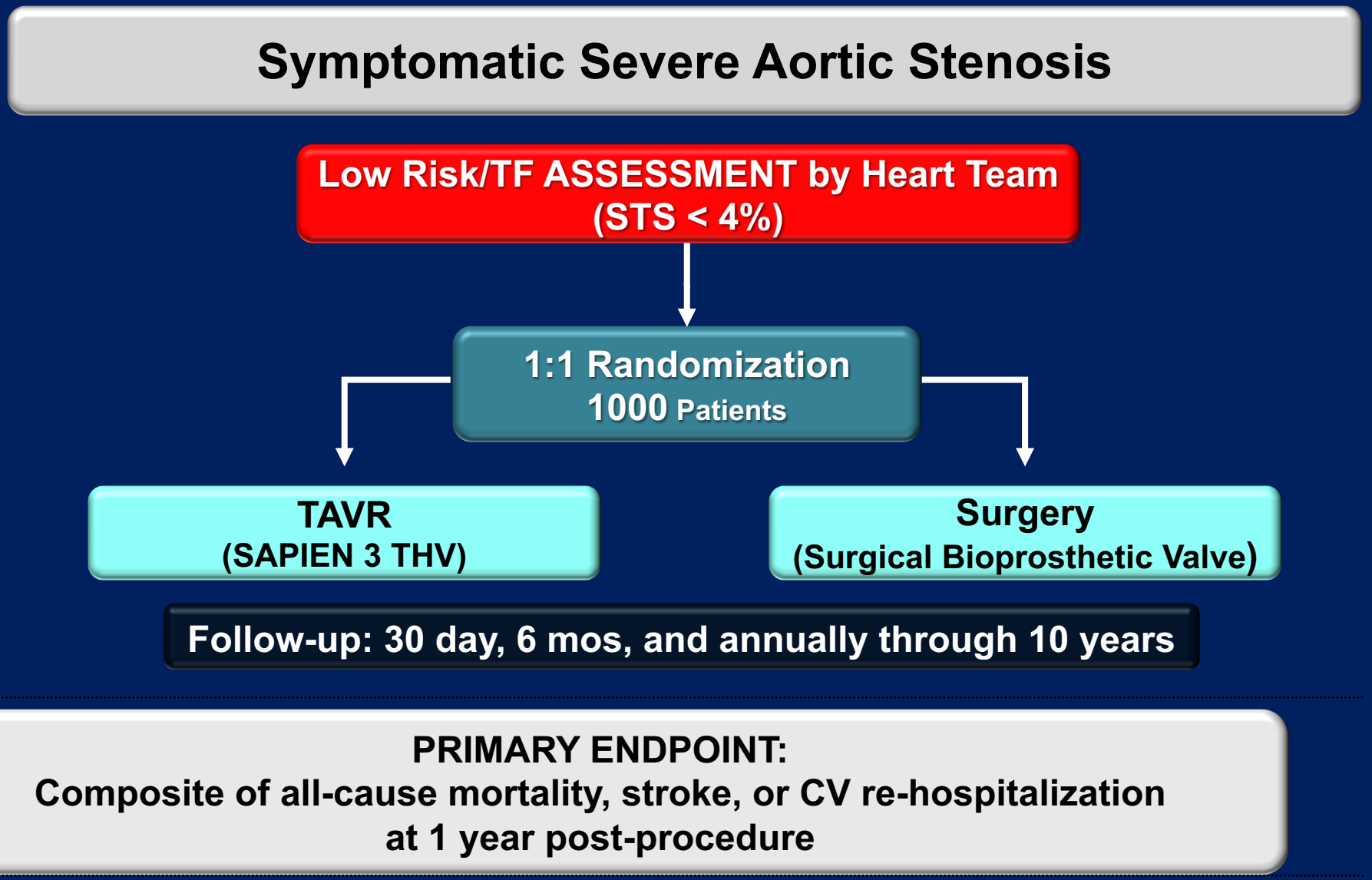
To compare the safety and effectiveness of the SAPIEN 3 TAVR system versus conventional surgery in patients with severe symptomatic aortic stenosis who are at *low surgical risk*.

SAPIEN Valve Evolution

Transfémoral access
No embolic protection device

	SAPIEN	SAPIEN XT	SAPIEN 3
Valve Technology			
Sheath Compatibility			
Available Valve Sizes	 23 mm 26 mm	 23 mm 26 mm 29 mm	 20 mm 23 mm 26 mm 29 mm
	PARTNER 1 2011	**PARTNER 2** 2014	**PARTNER 3** 2015

PARTNER 3 Study Design



PRIMARY ENDPOINT:
Composite of all-cause mortality, stroke, or CV re-hospitalization at 1 year post-procedure

Secondary endpoints

- Stroke
- Composite of death and stroke
- New onset of Afib
- Length of hospitalization
- Poor treatment outcome (NYHA , 6 min test , KCCQ score)

Key Inclusion Criteria

Severe Aortic Stenosis

- AVA ≤ 1.0 cm^2 or AVA index ≤ 0.6 cm^2/m^2
- Jet velocity ≥ 4.0 m/s or mean gradient ≥ 40 mmHg, AND
  - NYHA Functional Class ≥ 2, OR
  - Abnormal exercise test with severe SOB, abnormal BP response, or arrhythmia, OR
  - Asymptomatic with LVEF < 50%

Low Surgical Risk

- Determined by multi-disciplinary heart team
- STS < 4%
- Adjudicated by case review board

Key Exclusion Criteria

Anatomic

- Aortic annulus diameter < 16 mm or > 28 mm (3D imaging)
- Bicuspid valve (CT imaging)
- Severe AR (> 3+) or MR (> 3+)
- Severe LV dysfunction (LVEF < 30%)
- Severe calcification of aortic valvar complex (esp. LVOT)
- Vascular anatomy not suitable for safe femoral access
- Complex CAD: ULM, Syntax score > 32, or not amenable for PCI
- Low coronary takeoff (high risk for obstruction)

Clinical

- Acute MI within 1 month
- Stroke or TIA within 90 days
- Renal insufficiency (eGFR < 30 ml/min) and/or renal replacement Rx
- Hemodynamic or respiratory instability
- Frailty (objective assessment; > 2/4+ metrics)

Study Flow and Follow-Up

1520 patients with severe symptomatic AS at low surgical risk consented between March 25, 2016 and October 26, 2017 at 71 sites in the US, Canada, Japan, ANZ

Excluded from Randomization N=520

- Anatomic exclusions (n=308)
- Clinical exclusions (n=89)
- Other exclusions (n=38)
- Incomplete screening (n=85)

Eligible for Enrollment and Randomized N=1000 at 71 sites

TAVR N=503

Surgery N=497

98.4% Follow-up for Primary Endpoint

Baseline Patient Characteristics

Demographics & Vascular Disease	TAVR (N=496)	Surgery (N=454)	Other Co-Morbidities	TAVR (N=496)	Surgery (N=454)
Age (years)	73.3 ± 5.8	73.6 ± 6.1	Diabetes	31.3%	30.2%
Male	67.5%	71.1%	COPD (any)	5.1%	6.2%
BMI – kg/m^2	30.7 ± 5.5	30.3 ± 5.1	Pulmonary Hypertension	4.6%	5.3%
STS Score	1.9 ± 0.7	1.9 ± 0.6	Creatinine > 2mg/dL	0.2%	0.2%
NYHA Class III or IV*	31.3%	23.8%	Frailty (overall; > 2/4+)	0	0
Coronary Disease	27.7%	28.0%	Atrial Fibrillation (h/o)	15.7%	18.8%
Prior CABG	3.0%	1.8%	Permanent Pacemaker	2.4%	2.9%
Prior CVA	3.4%	5.1%	Left Bundle Branch Block	3.0%	3.3%
Peripheral Vascular Disease	6.9%	7.3%	Right Bundle Branch Block	10.3%	13.7%

Procedural & Hospital Findings

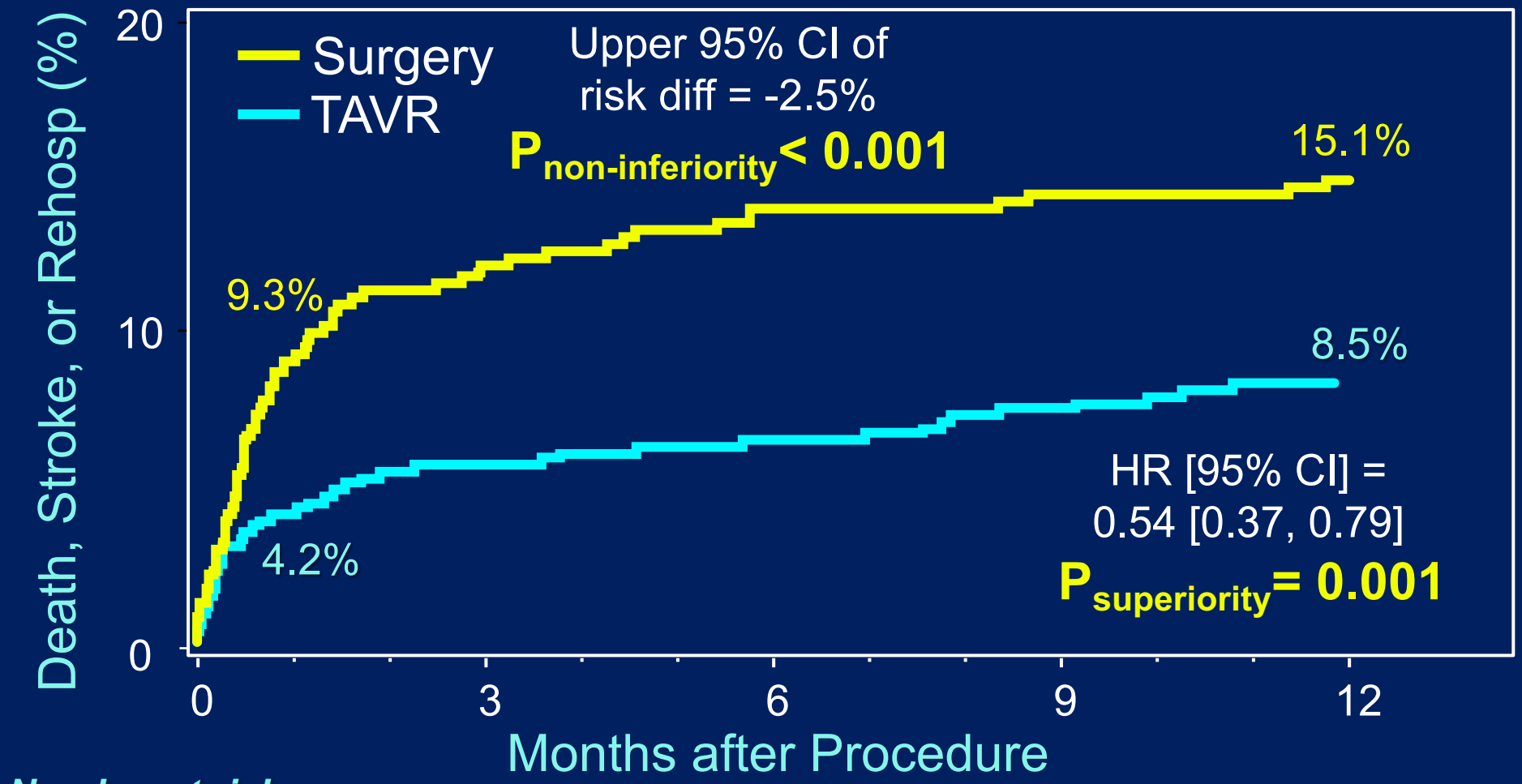
Variable	TAVR (N=496)	Surgery (N=454)	P-value
Conscious Sedation	65.1%	NA	NA
Procedure Time (min)	58.6 ± 36.5	208.3 ± 62.2	<0.001
Fluoroscopy Time (min)	13.9 ± 7.1	NA	NA
Aortic Cross-Clamp Time (min)	NA	74.3 ± 27.8	NA
Total CPB Time (min)	NA	97.7 ± 33.8	NA
Median ICU Stay (days)	2.0	3.0	<0.001
Median Total LOS (days)	3.0	7.0	<0.001
Discharge to Home/Self-care	96.0%	73.1%	<0.001
Concomitant Procedures	7.9%	26.4%	<0.001

Procedural Complications
In-Hospital

Complication	TAVR (N=496)	Surgery (N=454)	P-value
In-hospital Death	0.4% (2)	0.9% (4)	0.43
≥ 2 Transcatheter Valves Implanted*	0.2% (1)	NA	NA
Valve Embolization	0	NA	NA
Aortic Dissection	0	NA	NA
Annular Rupture	0.2% (1)	NA	NA
Ventricular Perforation	0.2% (1)	0.4% (2)	0.61
Coronary Obstruction	0.2% (1)	0.4% (2)	0.61
Access Site Infections	0.4% (2)	1.3% (6)	0.16

*Valve-in-valve

Results
all cause mortality , stroke or CV re-hospitalization @ 1 year

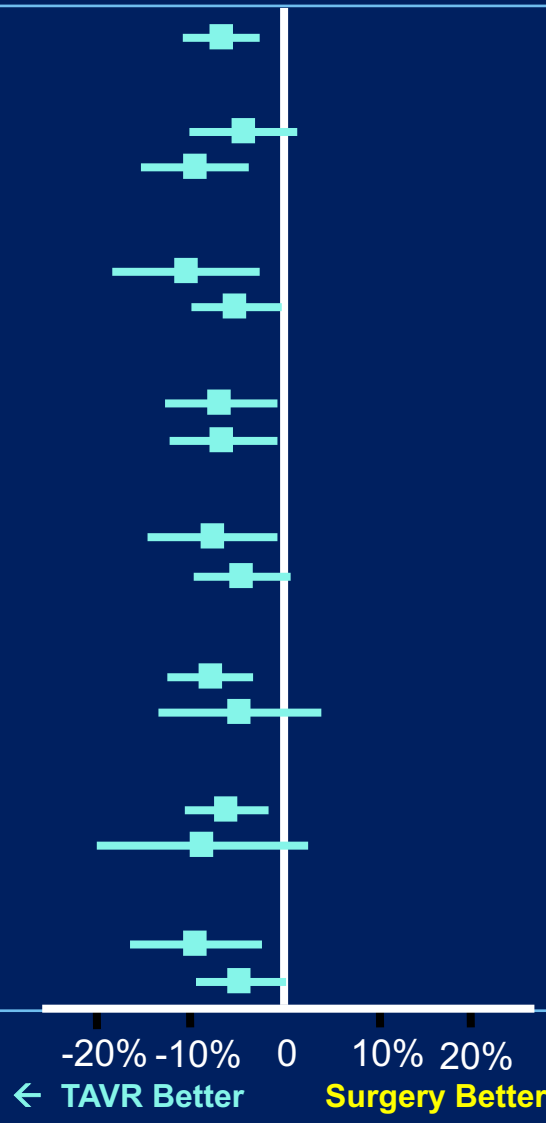


Number at risk:

Surgery	**454**	**408**	**390**	**381**	**377**	**374**
TAVR	**496**	**475**	**467**	**462**	**456**	**451**

Primary Endpoint - Subgroup Analysis

Subgroup	TAVR	Surgery	Diff [95% CI]	P-value*
Overall	**8.5**	**15.1**	**-6.6 [-10.8, -2.5]**	
Age				
≤ 74 (n=516)	10.6	14.9	-4.3 [-10.1, 1.5]	**0.21**
> 74 (n=434)	5.8	15.3	-9.5 [-15.3, -3.7]	
Sex				
Female (n=292)	8.1	18.5	-10.4 [-18.3, -2.5]	**0.27**
Male (n=658)	8.7	13.8	-5.1 [-9.9, -0.3]	
STS Score				
≤ 1.8 (n=464)	9.1	15.7	-6.7 [-12.6, -0.7]	**0.98**
> 1.8 (n=486)	8.0	14.5	-6.5 [-12.2, -0.8]	
LV Ejection Fraction				
≤ 65 (n=384)	9.6	17.2	-7.6 [-14.5, -0.7]	**0.48**
> 65 (n=524)	8.0	12.4	-4.4 [-9.6, 0.7]	
NYHA Class				
I/II (n=687)	6.8	14.5	-7.8 [-12.4, -3.2]	**0.54**
III/IV (n=263)	12.3	16.9	-4.7 [-13.5, 4.1]	
Atrial Fibrillation				
No (n=786)	7.9	14.0	-6.1 [-10.5, -1.7]	**0.67**
Yes (n=163)	11.6	20.3	-8.7 [-19.9, 2.5]	
KCCQ Overall Summary Score				
≤ 70 (n=407)	10.5	19.9	-9.4 [-16.5, -2.4]	**0.27**
> 70 (n=536)	6.5	11.2	-4.6 [-9.4, 0.2]	



Event rates are KM estimates (%)

* P-value is for interaction

Pre-specified Secondary Endpoints

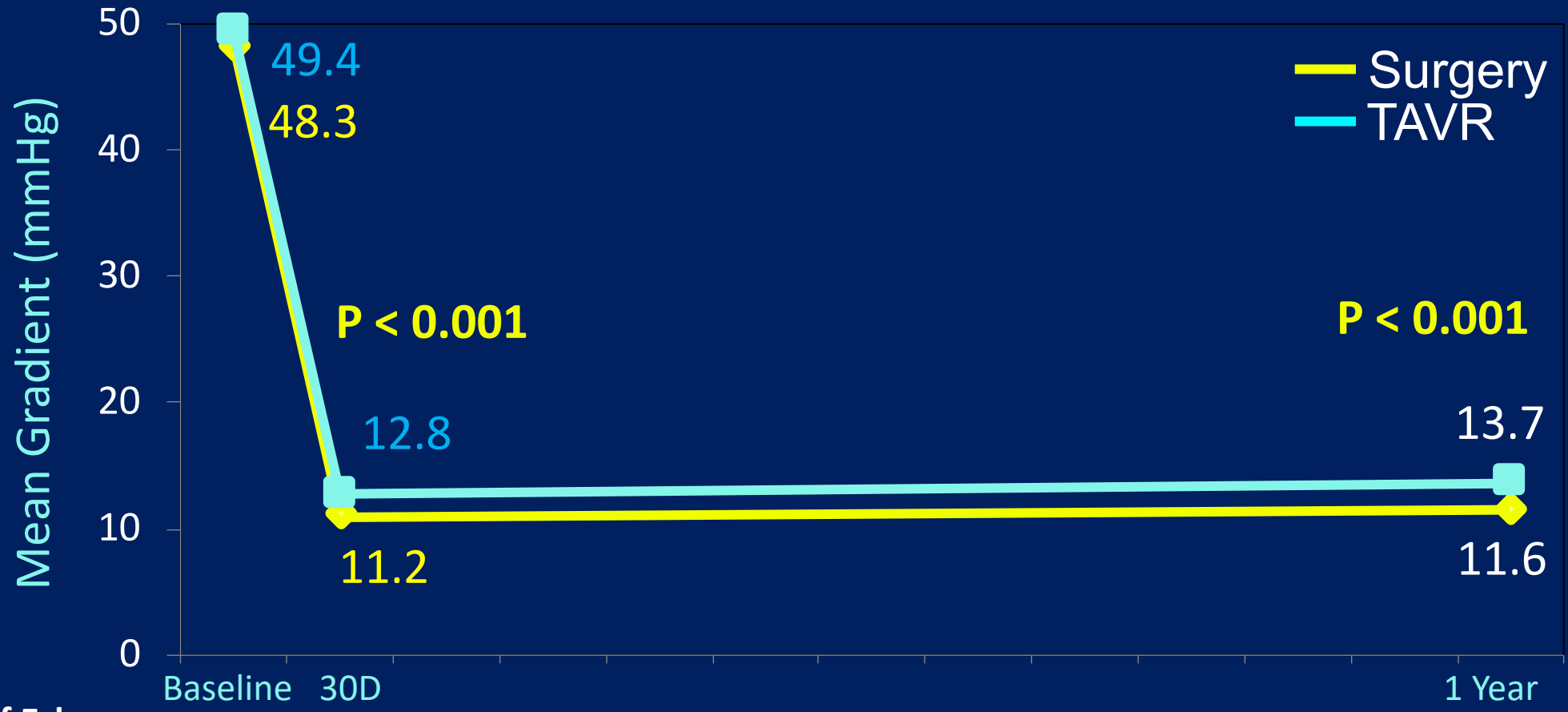
Order of Testing	Endpoint	TAVR (N=496)	Surgery (N=454)	Treatment Effect [95% CI]	P-value
1	New onset atrial fibrillation at 30 days	5.0%	39.5%	0.10 [0.06, 0.16]	<0.001
2	Length of index hospitalization (days)	3.0 (2.0, 3.0)	7.0 (6.0, 8.0)	-4.0 [-4.0, -3.0]	<0.001
3	All-cause death, all stroke, or rehospitalizations at 1 year	8.5%	15.1%	0.54 [0.37, 0.79]	0.001
4	Death, KCCQ < 45 or KCCQ decrease from baseline ≥ 10 points at 30 days	3.9%	30.6%	-26.7% [-31.4%, -22.1%]	<0.001
5	Death or all stroke at 30 days	1.0%	3.3%	0.30 [0.11, 0.83]	0.01
6	All stroke at 30 days	0.6%	2.4%	0.25 [0.07, 0.88]	0.02

Other Secondary Endpoints

Outcomes	30 Days			1 Year		
	TAVR (N=496)	Surgery (N=454)	P-value	TAVR (N=496)	Surgery (N=454)	P-value
Bleeding - Life-threat/Major	3.6% (18)	24.5% (111)	<0.001	7.7% (38)	25.9% (117)	<0.001
Major Vascular Complics	2.2% (11)	1.5% (7)	0.45	2.8% (14)	1.5% (7)	0.19
AKI - stage 2 or 3*	0.4% (2)	1.8% (8)	0.05	0.4% (2)	1.8% (8)	0.05
New PPM (incl baseline)	6.5% (32)	4.0% (18)	0.09	7.3% (36)	5.4% (24)	0.21
New LBBB	22.0% (106)	8.0% (35)	<0.001	23.7% (114)	8.0% (35)	<0.001
Coronary Obstruction	0.2% (1)	0.7% (3)	0.28	0.2% (1)	0.7% (3)	0.28
AV Re-intervention	0% (0)	0% (0)	NA	0.6% (3)	0.5% (2)	0.76
Endocarditis	0% (0)	0.2% (1)	0.29	0.2% (1)	0.5% (2)	0.49
Asymp Valve Thrombosis	0.2% (1)	0% (0)	0.34	1.0% (5)	0.2% (1)	0.13

Aortic valve hemodynamic

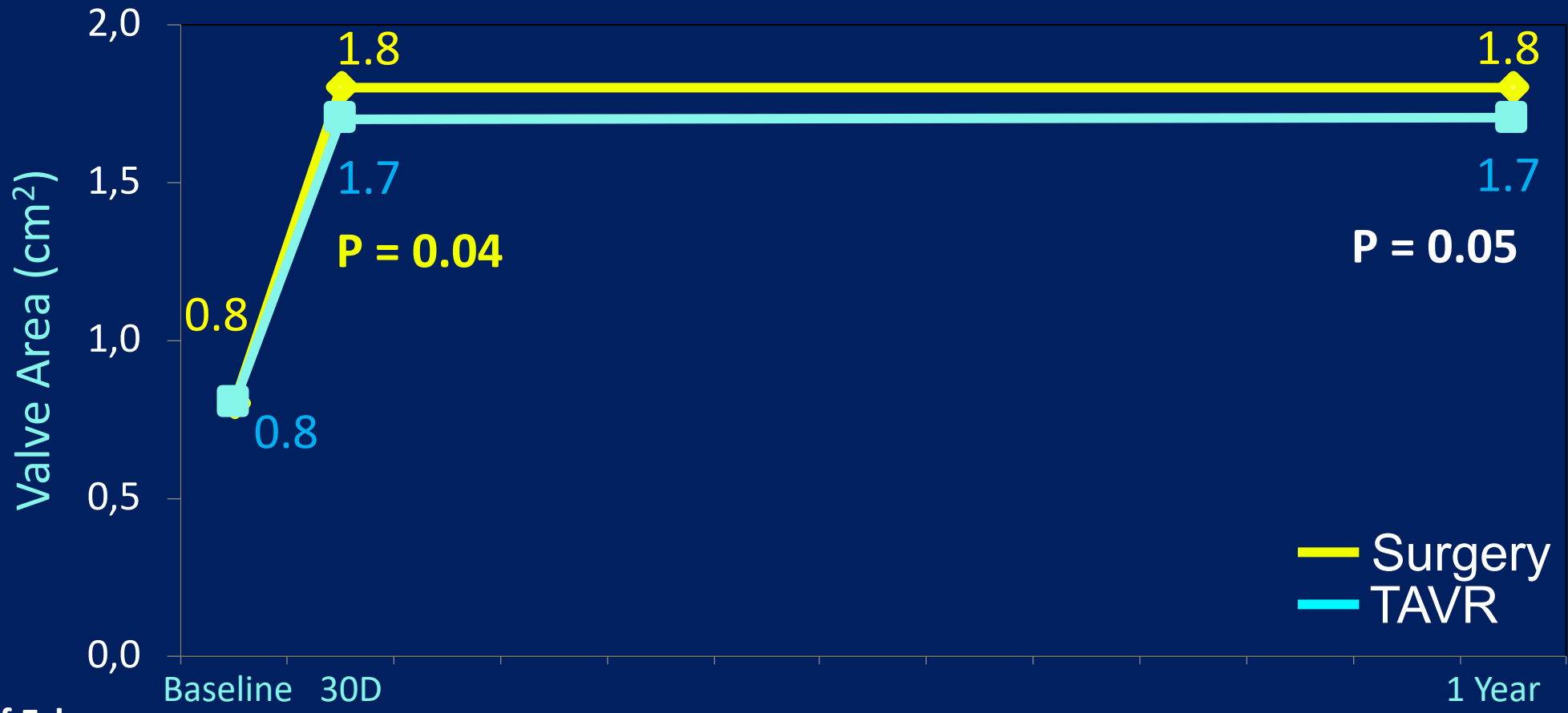
Mean Gradient



No. of Echos			
Surgery	441	426	390
TAVR	483	490	469

Echocardiography Findings

Aortic Valve Area

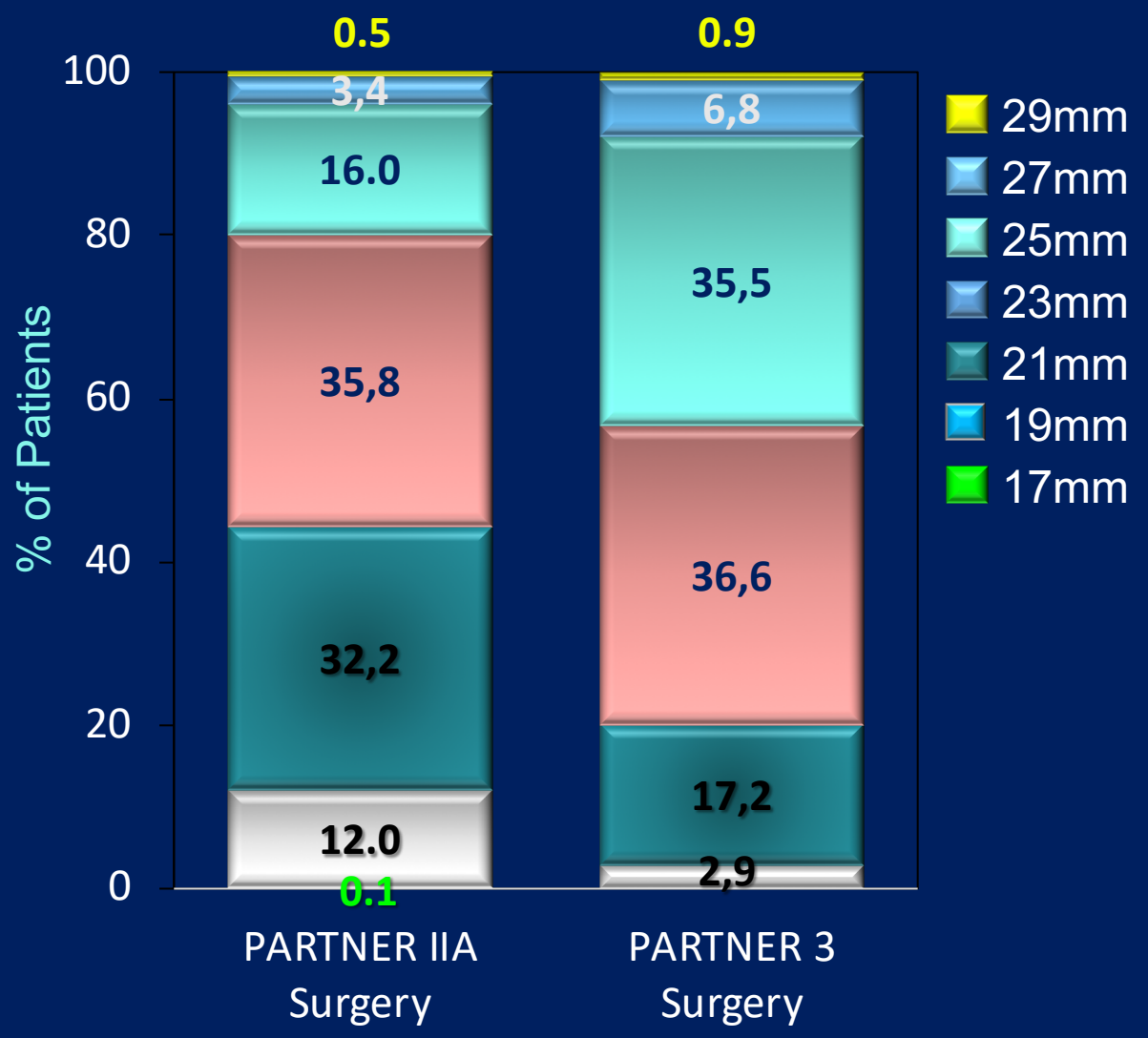


No. of Echos			
Surgery	**423**	**395**	**371**
TAVR	**458**	**470**	**446**

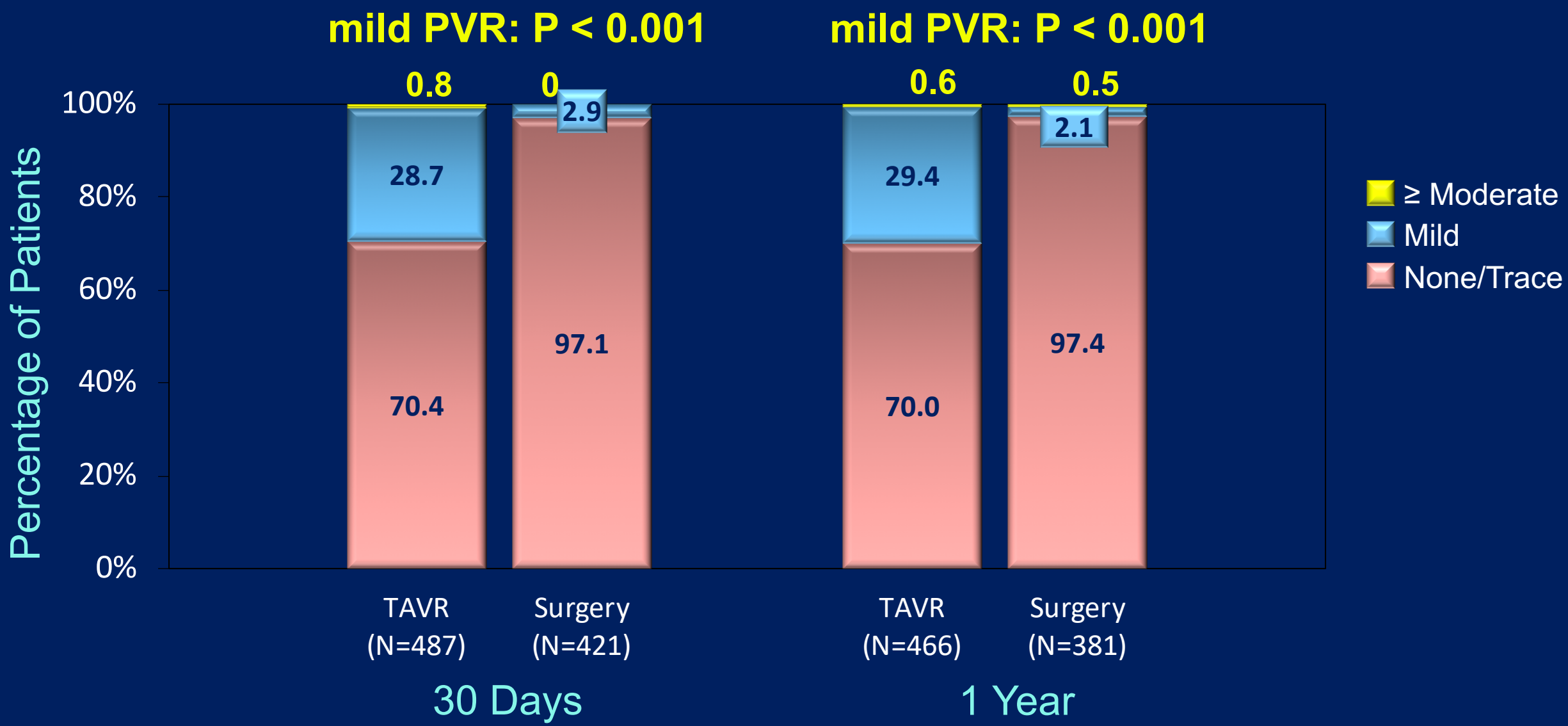
P-values are based on the ANCOVA for TAVR vs Surgery adjusted by baseline.

The PARTNER Trials

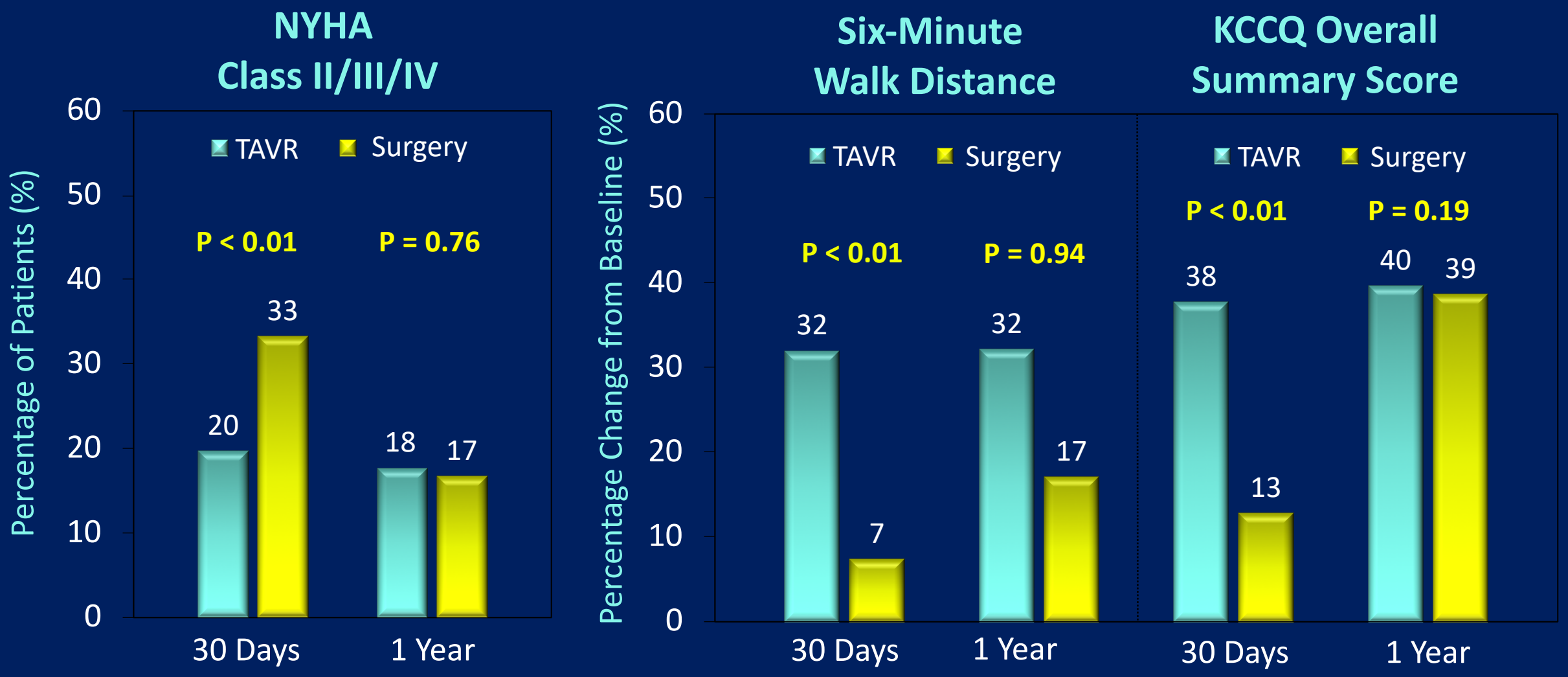
Valve Size Distribution



Paravalvular Regurgitation



Functional Assessments



The PARTNER 3 Trial
Conclusions

In a population of severe symptomatic aortic stenosis patients who were at low surgical risk, TAVR (using the SAPIEN 3 valve) compared to surgery:

- Significantly reduced the primary endpoint of death, stroke, or rehospitalization by 46% at 1-year.
- Secondary endpoints adjusted for multiple comparisons indicated that TAVR reduced new-onset AF, index hospitalization days, and a measure of poor treatment outcome (death or low KCCQ score at 30 days).
- Other secondary endpoint analyses also showed reduced bleeding after TAVR and no differences in the need for new permanent pacemakers, major vascular complications.
- Some secondary endpoints favored surgery, including reduced new LBBB, reduced mild PVR, and lower aortic valve gradients.

The PARTNER 3 Trial
Study Limitations

- Results only reflect 1-year outcomes, long-term assessment of structural valve deterioration is required
  - 10-year clinical and echocardiographic FU planned in all patients
- Results only apply to the enrolled AS population (e.g. bicuspid aortic valves, non-suitable for TF, and complex CAD excluded)
- Findings cannot be extrapolated to TAVR performed with other systems , less experienced operators

Thank you