REPRISE II: A Prospective Registry Study of Transcatheter Aortic Valve Replacement with a Repositionable Transcatheter Heart Valve in Patients with Severe Aortic Stenosis

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on behalf of the REPRISE II Investigators

31 October 2013 • San Francisco

Disclosures

Ian T. Meredith AM

- Consultant Fee / Honoraria / Speaker's Bureau:
  - Boston Scientific (Significant)
  - Medtronic (Modest)
- Proctor:
  - Boston Scientific (Significant)

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Early TAVI Devices for Severe Aortic Stenosis

Significant benefit for inoperable/high-risk patients, but…

Current devices have limitations

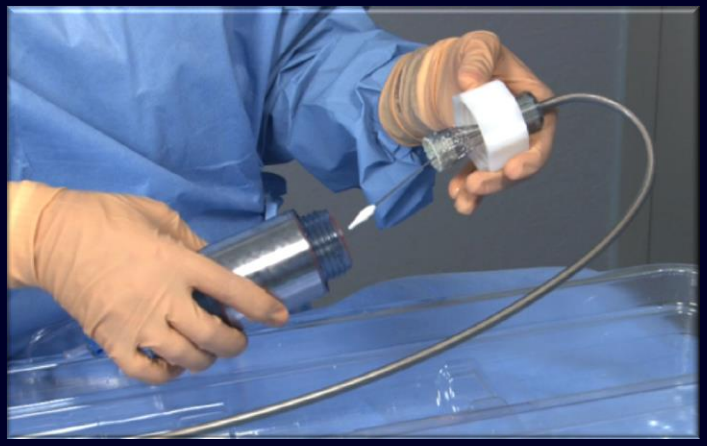
- Paravalvular regurgitation
  - Associated with increased mortality*
- Valve malpositioning
  - Valve migration, embolization, ectopic deployment, TAV-in-TAV
- Stroke

2nd generation devices should

- Reduce aortic regurgitation
- Have simple, precise & atraumatic aortic/ventricular repositioning
- Allow full atraumatic retrieval

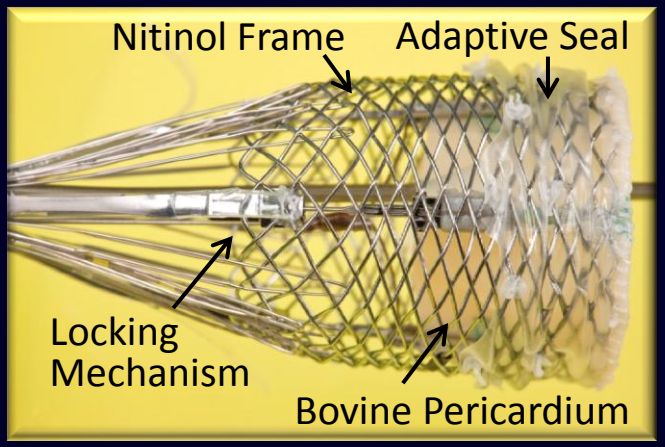
*Kodali, NEJM 2012;366:1685; Tamburino, Circ 2011;123:299; Abdel-Wahab, Heart 2011;97:899

Lotus Valve System



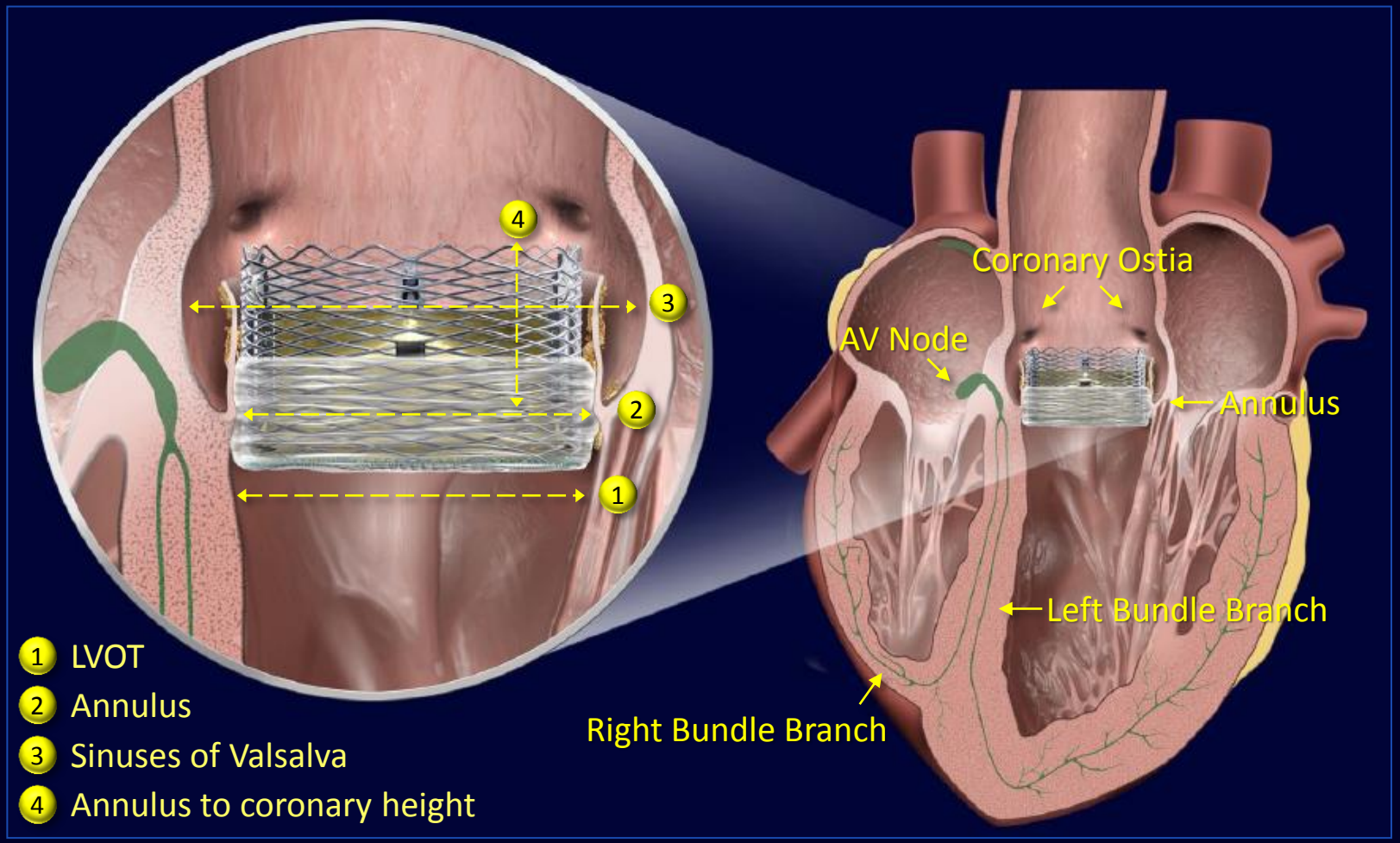
1. Preloaded delivery system

2. Simple handle design



3. Deployed via controlled mechanical expansion
4. Central radiopaque marker to aid precise positioning
5. Functions early, enabling controlled deployment
6. Fully repositionable and retrievable
7. Adaptive seal designed to minimize paravalvular leak

LOTUS Valve In Situ



REPRISE II Study

Objective	• Evaluate safety & performance of the LOTUS™ valve for TAVR in patients at high risk for surgery
Design	• Prospective, single-arm, multicentre trial; F/U at discharge/7d, 30d, 3m, 6m, yearly to 5 yrs
Primary Endpoints	• Performance: Mean aortic valve pressure gradient at 30 days (versus a performance goal of 18mmHg) • Safety: All-cause mortality at 30 days
Independent Data Assessments	• Clinical Events Committee • Core Labs: Angiography, ECG, Echocardiography, Pathology

REPRISE II Study Organization

PRINCIPAL INVESTIGATOR

Ian T. Meredith AM, MBBS, PhD, Monash Medical Centre, Clayton, Australia

CORE LABORATORIES

Angiography & CT/X-ray	Jeffrey J. Popma, MD (Director) Harvard Medical Faculty Physicians at Beth Israel Deaconess Medical Center, Boston, MA, USA
Echocardiography	Neil J. Weissman, MD (Director) MedStar Health Research Institute, Washington, DC, USA
Electrocardiography	Peter J. Zimetbaum, MD (Director) Harvard Clinical Research Institute, Boston, MA, USA
Pathology	Renu Virmani, MD (Director) CV Path Institute, Inc., Gaithersburg, MD, USA

CLINICAL EVENTS COMMITTEE

Sergio Waxman, MD (IC, Chair)

Carey Kimmelstiel, MD (IC)

Gregory Smaroff, MD (CT Surg)

Roberto Rodriguez, MD (CT Surg)

Viken Babikian, MD (Neurologist)

REPRISE II Key Inclusion Criteria

- Age ≥70 yrs
- NYHA Class ≥II
- AVA <1.0 cm^2 plus mean pressure gradient >40 mmHg or jet velocity >4 m/s, aortic annulus 19-27mm
- STS score ≥8% and/or high surgical risk due to frailty or comorbidities
- 2-Step patient review process: Heart Team & Case Review Committee

REPRISE II Exclusion Criteria

Key Clinical Exclusion Criteria

- AMI within 30 days
- CVA or TIA within 6 months
- Dialysis dep. or Cr >3.0 mg/dL (225.2 μmol/L)
- Cardiogenic shock or hemodynamic instability
- Any therapeutic invasive cardiac procedure within 30 days
- GI bleed within 3 months
- Life expectancy <12 months due to non-cardiac, co-morbid conditions

Key Anatomic Exclusion Criteria

- Unicuspid/bicuspid aortic valve, prosthetic valve or ring
- ≥3+ mitral or ≥3+ aortic regurgitation
- LVEF <30%
- Femoral artery lumen diameter
  - <6.0 mm (23mm valve)
  - <6.5 mm (27mm valve)

Additional REPRISE II Endpoints

VARC 2 Metrics

Safety

Included in VARC Safety Composite

- Cardiovascular mortality
- Stroke
- Life-threatening/disabling bleed
- Acute kidney injury (Stage 2/3)
- Coronary obstruction (periproc.)
- Major vascular complications
- Repeat procedure for valve dysfunction
- MI (periprocedural & spontaneous)
- Hospitalization for valve-related symptoms or CHF
- New permanent pacemaker
- New-onset atrial fibrillation
- Prosthetic valve endocarditis, thrombosis, migration, embolization
- Cardiac tamponade (periproc.)

Effectiveness

- NYHA class
- 5-meter gait speed (1 year vs. baseline)
- Quality of Life assessments
- Neurological assessments (NIHSS/mRS)

Valve Performance/Echocardiography

- Successful access, delivery, deployment, delivery system retrieval
- Success repositioning, if needed
- Successful valve retrieval, if needed
- Correct valve positioning
- Effective orifice area
- Mean & peak aortic valve gradients
- Peak aortic velocity
- Aortic valve regurgitation grade

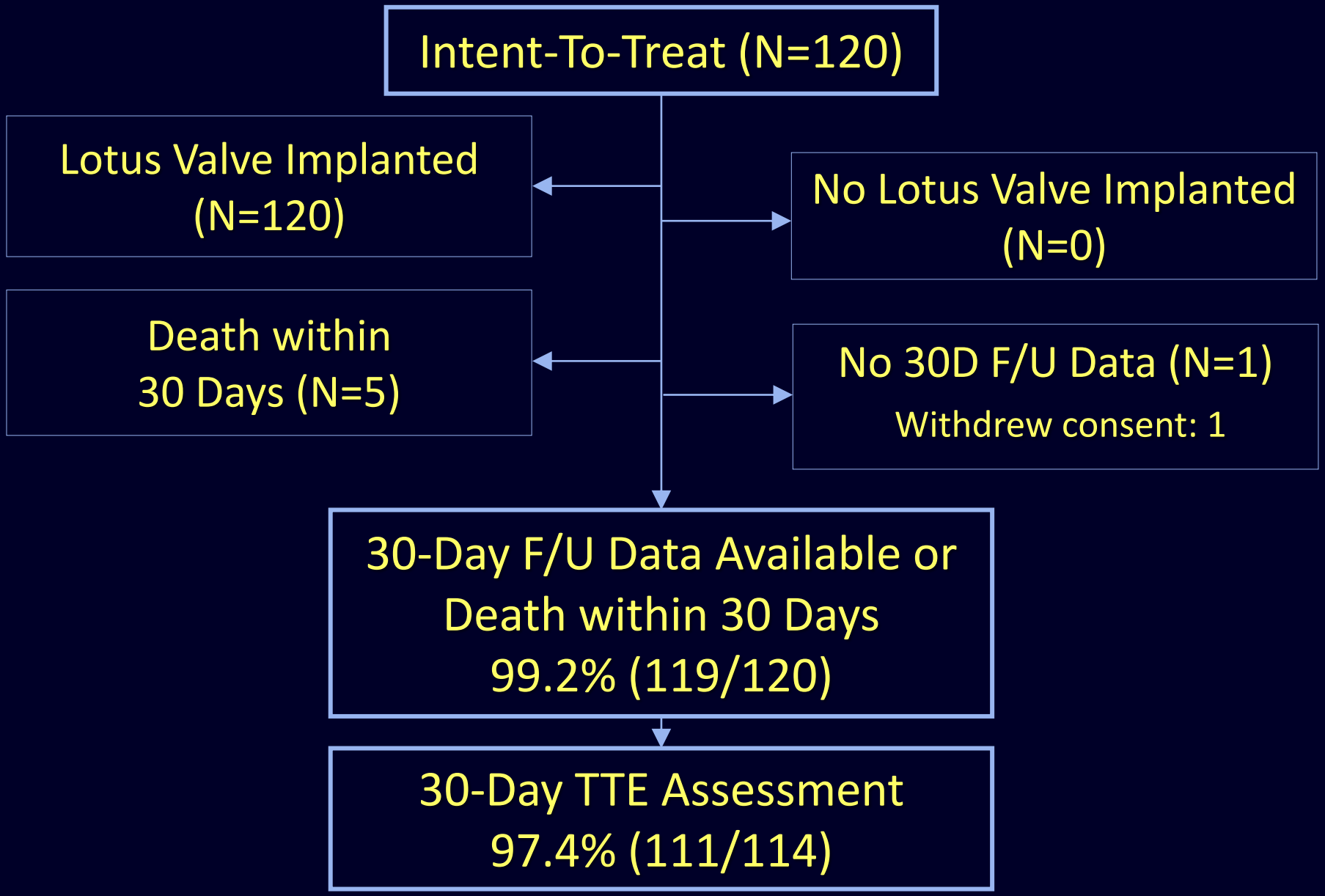
REPRISE II Enrollment

120 patients between Oct 2012 & Apr 2013 at 14 sites

	Patients
Ian Meredith Monash Medical Centre, Clayton, Australia	19
Darren Walters The Prince Charles Hospital, Brisbane, Australia	19
Nicolas Dumonteil Centre Hôpital Universitaire Rangueil , Toulouse, France	14
Stephen Worthley Royal Adelaide Hospital, Adelaide, Australia	13
Didier Tchétché Clinique Pasteur, Toulouse, France	12
Ganesh Manoharan Royal Victoria Hospital, Belfast, UK	8
Daniel Blackman The General Infirmary, Leeds, UK	8

	Patients
Gilles Rioufol Hôpital Cardiologique de Lyon, Bron, France	7
David Hildick-Smith Royal Sussex County Hospital, Brighton, UK	5
Robert Whitbourn St. Vincent's Hospital (Melbourne), Fitzroy, Australia	4
Thierry Lefèvre Institut Cardiovasculaire - Paris Sud, Massy, France	4
Rüdiger Lange Deutsches Herzzentrum Muenchen, Muenchen, Germany	4
Ralf Mueller HELIOS Klinikum Siegburg, Siegburg, Germany	2
Simon Redwood Guys and St. Thomas' NHS Foundation Trust, London, UK	1

REPRISE II Study Flow



Baseline Patient Characteristics

Comorbidities and Baseline Scores	*REPRISE II (N=120)*
Age (Years)	84.4 ± 5.3 (120)
Gender (Female)	56.7% (68)
STS Score (v 2.73) (%)	7.1 ± 4.6 (120)
STS Plus Score (%)	11.8 ± 8.0 (120)
euroSCORE 2011 (%)	6.9 ± 5.8 (120)
NYHA Class III or IV	75.8% (91)
Diabetes, treated	25.8% (31)
Atrial fibrillation, history	40.8% (49)

Frailty Indices	*REPRISE II (N=120)*	*Threshold*
5 Meter gait speed (sec)	9.2 ± 6.7	> 6
Max grip strength average (kg)	20.1 ± 12.8	≤ 18
Katz Index	5.7 ± 0.9	< 6
Mini-Cognitive Assessment for Dementia	3.6 ± 1.4	< 4

Baseline Echocardiographic Measurements

REPRISE II (N=120)

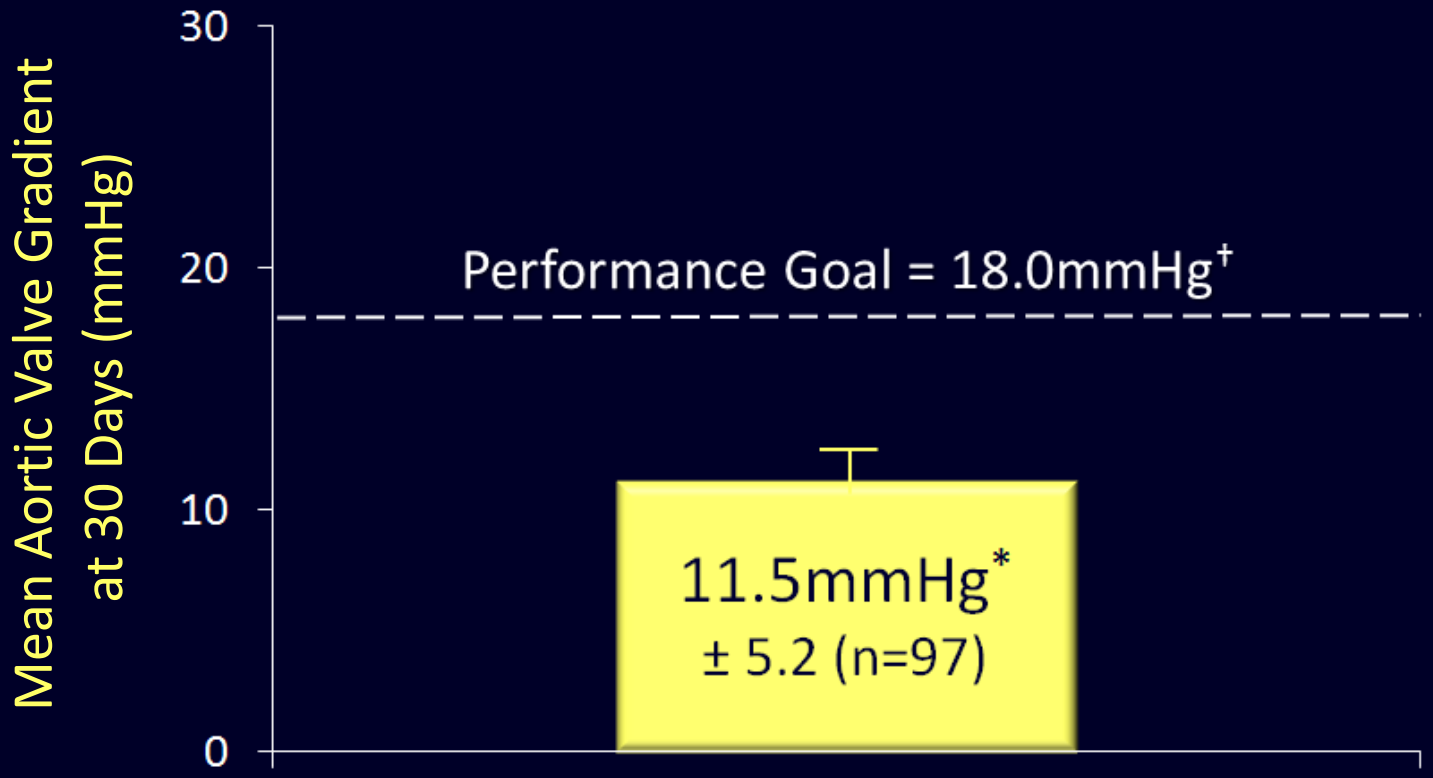
*Parameter**	*REPRISE II*
Aortic valve area (cm^2)	0.7 ± 0.2 (97)
Mean aortic gradient (mmHg)	46.4 ± 15.0 (104)
Peak aortic gradient (mmHg)	76.5 ± 23.6 (104)
LVEF (%)	54.3 ± 10.7 (61)
Mitral regurgitation (mod/severe)	11.6% (112)
Aortic regurgitation (mod/severe)	15.2% (112)

* All data are based on independent assessment from Core Laboratory

Data are mean ± SD (n)

Primary Device Performance Endpoint

REPRISE II (N=120)

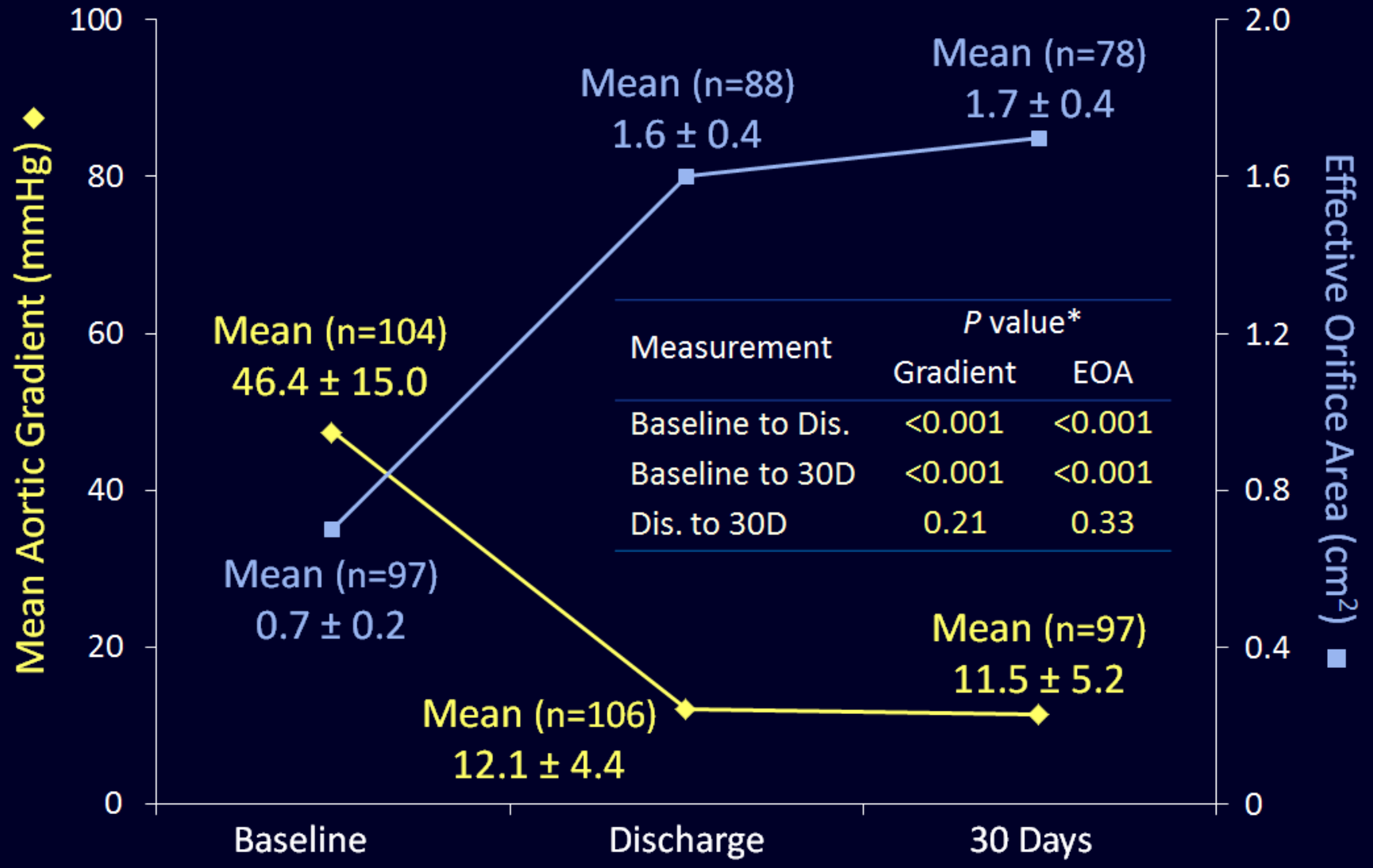


** Value of 11.5mmHg with a 98.7%‡ UCB of 12.6mmHg is significantly less than the performance goal (P <0.001)*

‡ Alpha-level adjustment for multiple analyses (final analysis)

† Based on an expected mean of ≤15 mmHg (literature review) plus a test margin of 3mmHg

REPRISE II Mean Aortic Gradient & EOA

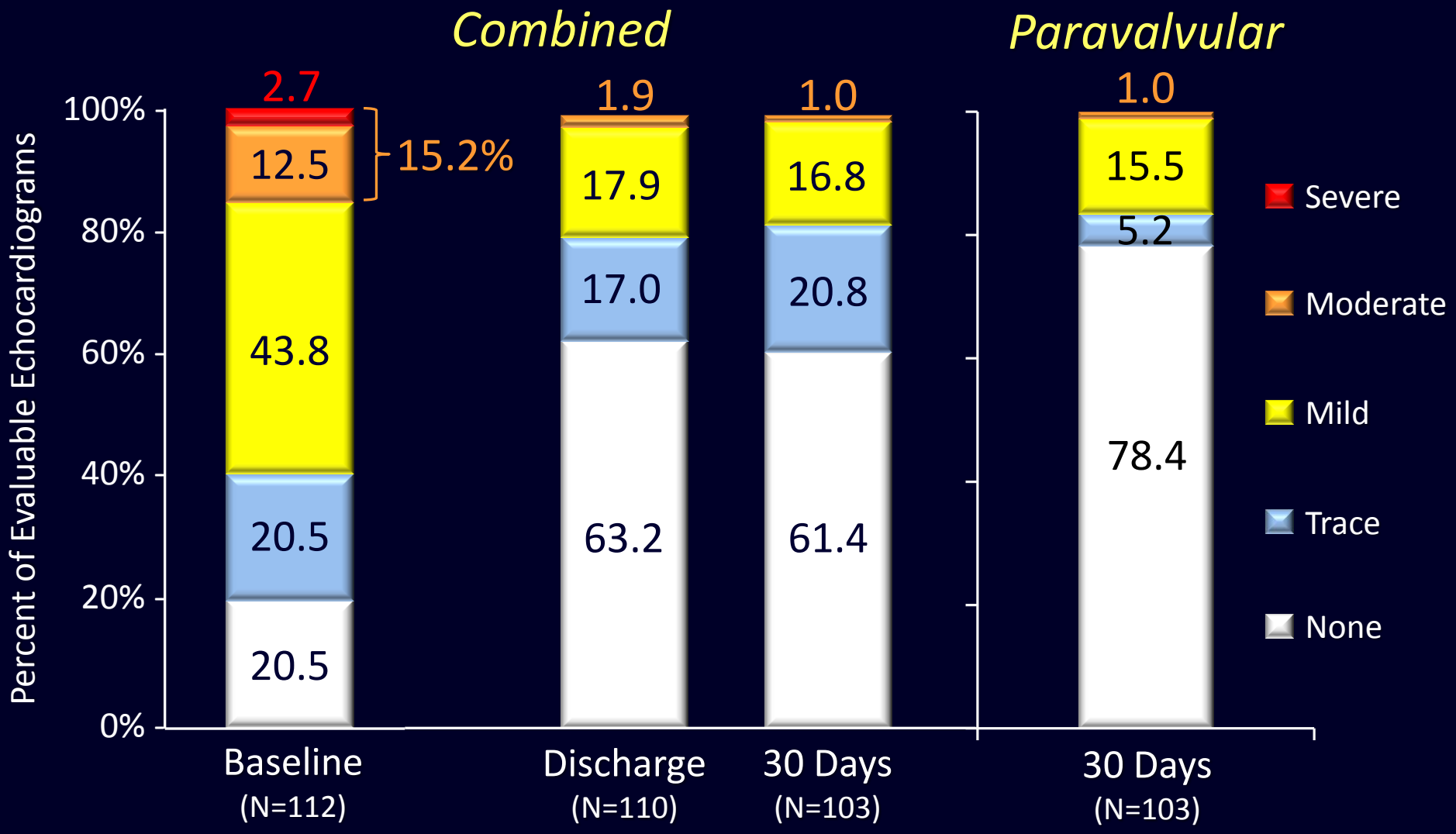


Measurement	*P* value*	
	Gradient	EOA
Baseline to Dis.	<0.001	<0.001
Baseline to 30D	<0.001	<0.001
Dis. to 30D	0.21	0.33

*Repeated measures and random effects ANOVA

REPRISE II Aortic Regurgitation Over Time

Core Lab Adjudicated Data



Post-dilation was not allowed per protocol and was not performed in any case.

Device Performance

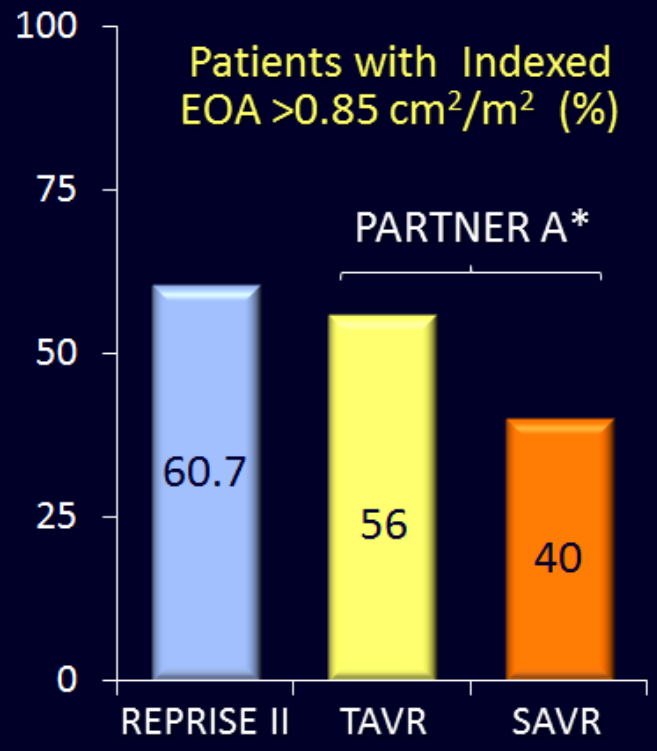
REPRISE II (N=120)

Successful access, delivery, deployment and system retrieval	100.0% (120/120)
Successful valve repositioning, if attempted (n=31)	100.0% (31/31)
Partial valve resheathing (n)	25
Full valve resheathing (n)	6
Successful valve retrieval, if attempted (n=6)	100.0% (6/6)

Aortic valve malpositioning	0.0% (0/120)
Valve migration	0.0% (0/120)
Valve embolization	0.0% (0/120)
Ectopic valve deployment	0.0% (0/120)
TAV-in-TAV deployment	0.0% (0/120)

REPRISE II Device Success – VARC 2

No procedural mortality	99.2% (119/120)
Correct positioning of one valve in proper location	100.0% (120/120)
Mean aortic valve gradient <20 mmHg	95.3% (101/106)
Peak velocity <3 m/s	94.3% (100/106)
No moderate/severe prosthetic valve regurgitation	98.1% (104/106)
Indexed EOA >0.85 cm^2/m^2 (>0.7 for BMI ≥30)	60.7% (51/84)



*Pibarot, JACC 2013;61:E1865

Safety: Death & Stroke at 30 Days

REPRISE II (N=120)

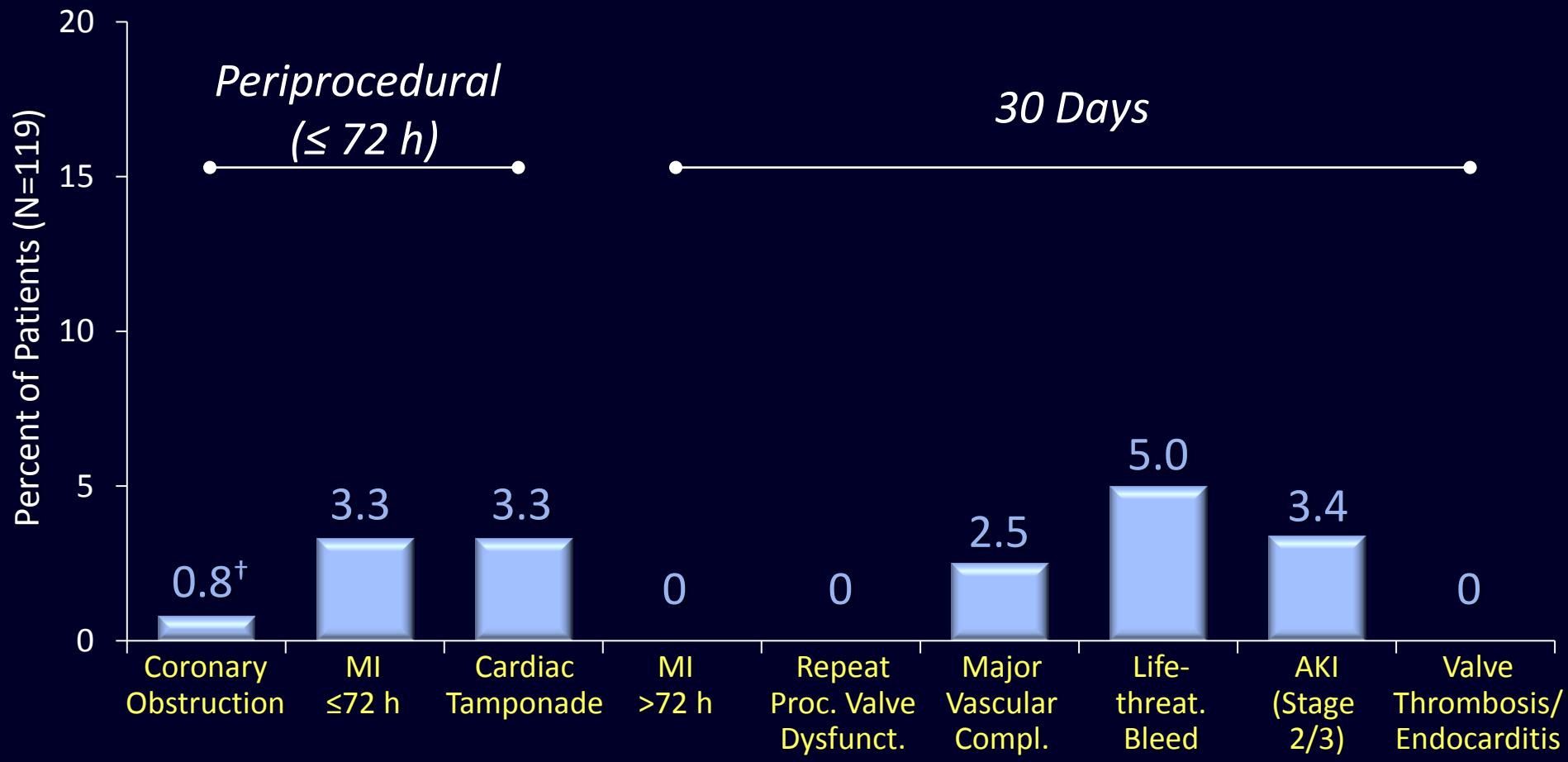
Event	*Patients (N=119)**
All-cause mortality (primary safety endpoint)	4.2% (5)
Cardiovascular mortality	4.2% (5)
All stroke†	5.9% (7)
Disabling stroke	1.7% (2)
Non-disabling stroke	4.2% (5)

† All patients were assessed by a neurologist before and after TAVR

* One patient withdrew consent

Additional VARC 2 Safety Endpoints

REPRISE II (N=120)



† Stent thrombosis in LAD (implanted >30d previous) with rescue PCI performed after BAV

Pacemaker Implantation

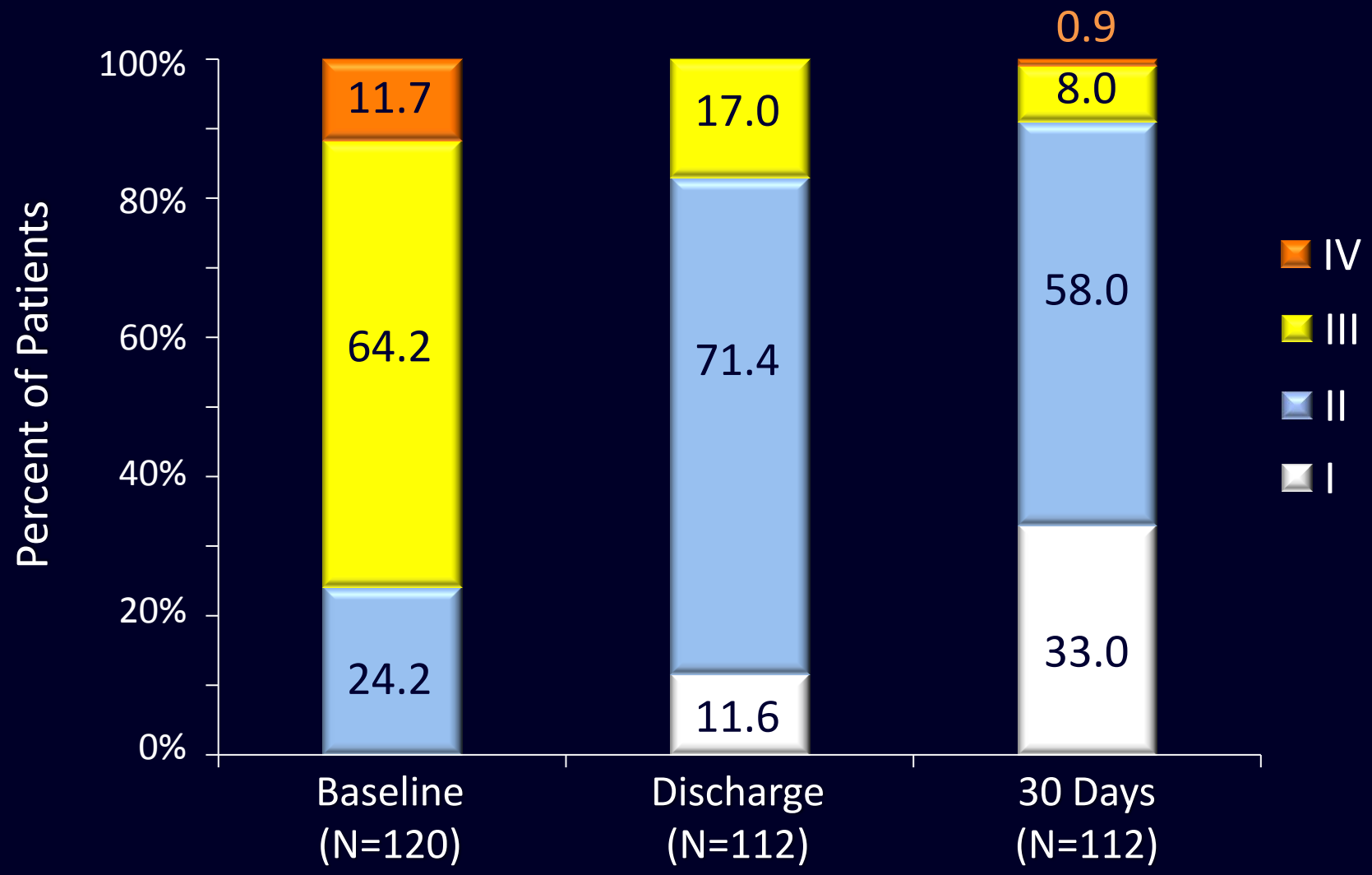
REPRISE II (N=120)

Variable	*Patients*
Newly implanted pacemaker	28.6% (34/119)
Baseline RBBB	17.6% (6/34)
New conduction disturbance post valvuloplasty	41.2% (14/34)
LVOT overstretch ≥10%	55.9% (19/34)
Annulus overstretch ≥10%	41.2% (14/34)
Paced rhythm at 30 days	47.1% (16/34)

Indication	*Patients*
3rd degree AV block	30
New LBBB, symptomatic bradycardia	1
LBBB, EP study showing severe infranodal disease	2
Trifascicular block	1

NYHA Class Changes Over Time

REPRISE II (N=120)



Summary & Conclusions

REPRISE II – Lotus Valve System

- Successful valve implantation and positioning in all 120 patients
- Primary device performance endpoint met
- Low mortality (4.2%) & disabling stroke (1.7%) at 30 days
- No embolization, ectopic valve deployment, or TAV-in-TAV
- Negligible aortic regurgitation
- Clinical event rates consistent with those reported for other valves

Results suggest the differentiated 2nd generation Lotus TAVR device will be a valuable addition for treatment of severe aortic stenosis

LOTUS Valve Clinical Program

REPRISE I	Feasibility Study; Acute Safety & Performance (Extreme/High Risk) N=11; single arm; 23mm valve size Primary Endpoint: Device success (VARC-1) without MACCE 12-month follow-up reported
REPRISE II	CE Mark Study; Safety & Performance (Extreme/High Risk) N=120; single arm; 23 & 27mm valve sizes Primary Device Performance Endpoint: Mean pressure gradient at 30d 30-day follow-up reported
REPRISE II Extension	Safety & Performance Study (Extreme/High Risk) N=130; single arm; 23 & 27mm valve sizes Primary Safety Endpoint: All-cause mortality at 30d Enrolling
RESPOND	Post Market Safety & Performance Study (Real World) N=1000; single arm; 23, 25* & 27mm valve sizes Primary Endpoint: All-cause mortality at 30d & 1y Anticipated start: 1Q 2014
REPRISE III	FDA Approval Study; Safety & Efficacy (Extreme/High Risk) N~1000; Global RCT vs. EDW; 23, 25 & 27mm valve sizes Primary Endpoint: All-cause mortality & disabling stroke at 12m Anticipated start: Mid-2014

* Upon approval