One-year outcomes with a fully repositionable and retrievable percutaneous aortic valve in 250 high surgical risk patients: Results from the REPRISE II trial extended cohort

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on behalf of the REPRISE II Investigators

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Disclosures

Ian T. Meredith AM

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

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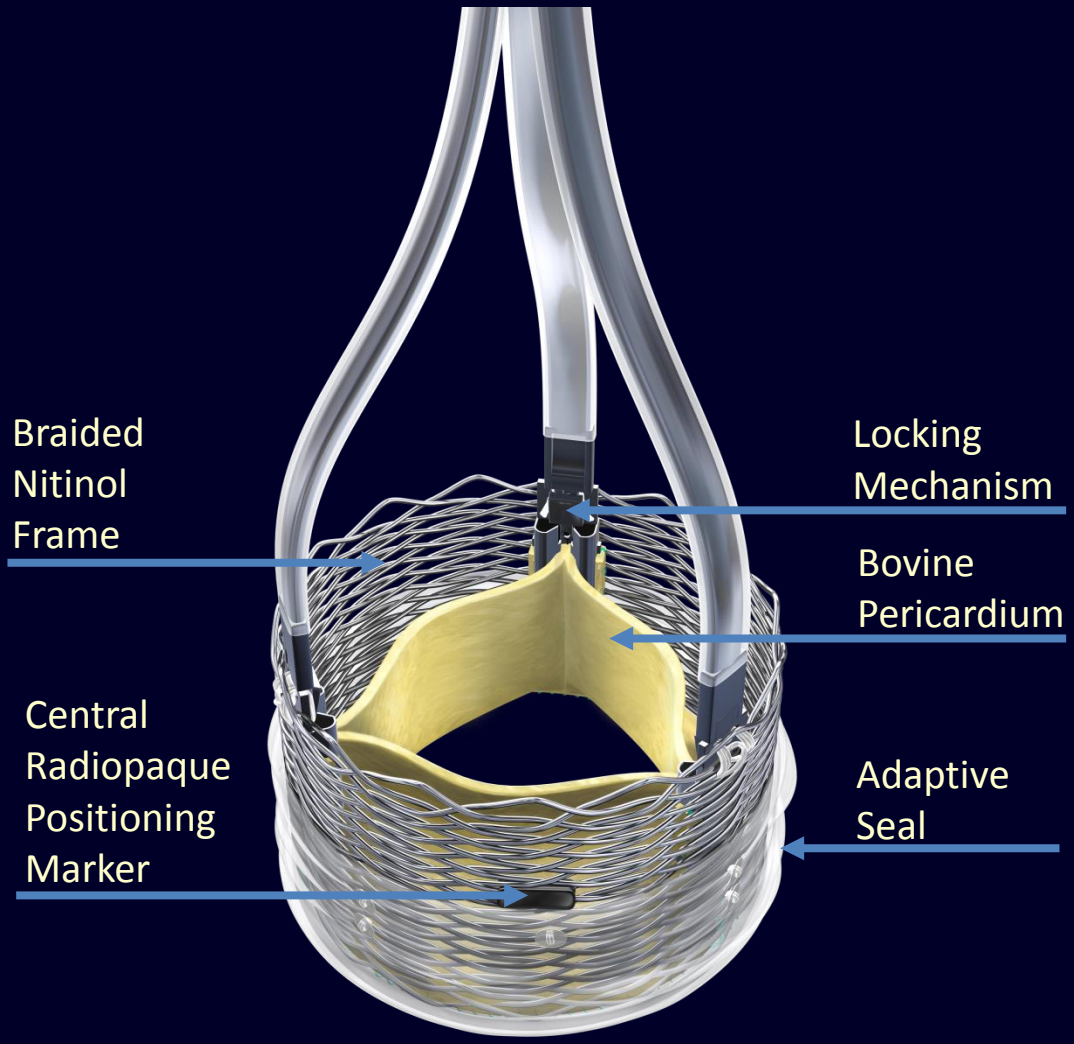
Lotus Valve Design Features



Lotus Valve Deployment

- Controlled mechanical expansion
- No rapid pacing
- Early valve function enables haemodynamic stability
- Complete repositionability & retrievability
- Adaptive seal designed to minimise PVL

REPRISE II Study with Extended Cohort

OBJECTIVE

- Evaluate safety & performance of the Lotus Valve System for TAVI in symptomatic patients with severe calcific aortic stenosis considered high risk for surgical valve replacement

DESIGN

- Prospective; single-arm; multicentre
- Available valve sizes: 23mm & 27mm
- F/U at 7 days/discharge, 30 days, 3 & 6 months, annually 1–5 years

INDEPENDENT DATA ASSESSMENTS

- Clinical Events Committee
- Core Labs: Angiography, ECG, Echocardiography, Pathology

REPRISE II Study Organisation

PRINCIPAL INVESTIGATOR

Ian T. Meredith, 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)

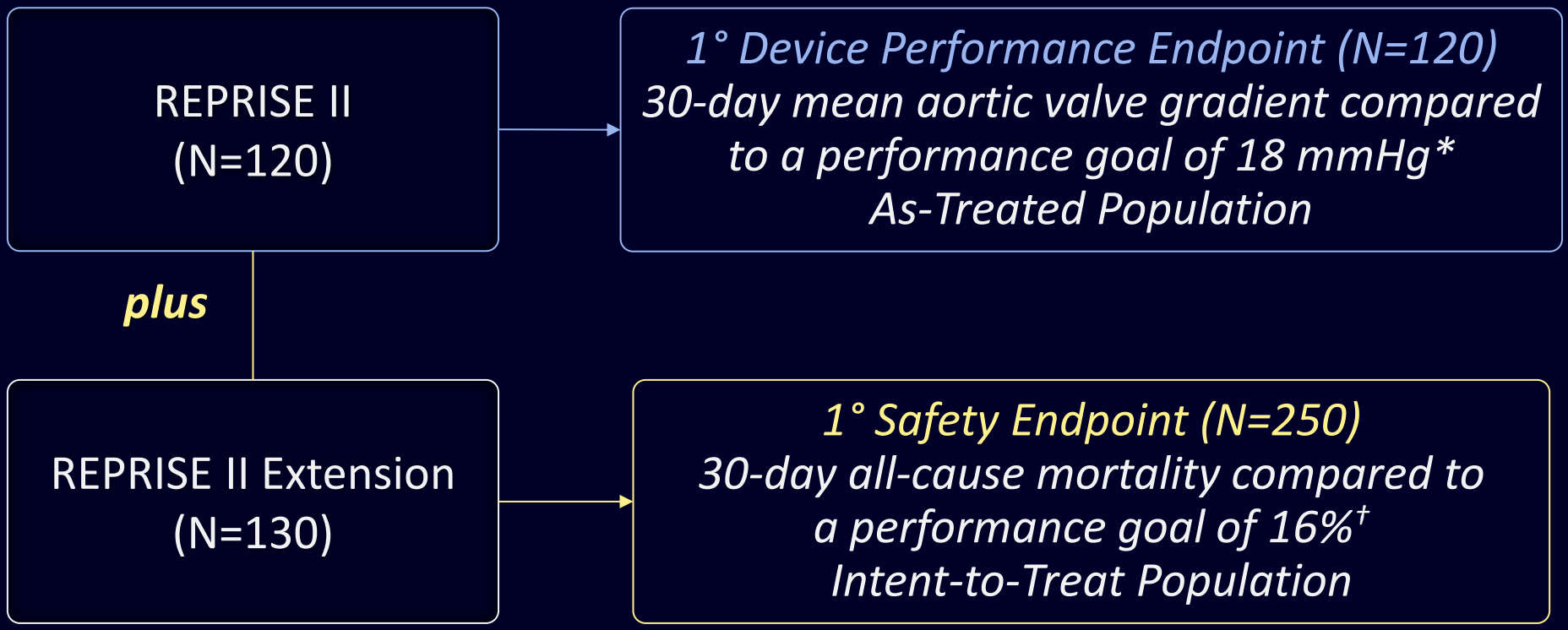
Gregory Smaroff, MD (CT Surg)

Roberto Rodriguez, MD (CT Surg)

Viken Babikian, MD (Neurologist)

REPRISE II Study with Extended Cohort

Preplanned Analysis of Pooled Data



* Meredith, et al. JACC 2014;64:1339

† Meredith, et al. PCR London Valves 2014

REPRISE II Key Enrollment Criteria

Inclusion

- Symptomatic calcified native aortic stenosis
- Age ≥70y; NYHA Class ≥II; aortic annulus 19-27mm
- STS score ≥8% and/or high surgical risk due to frailty or comorbidities

Exclusion – Clinical

- 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 (except PPM)
- GI bleed within 3 months
- Life expectancy <12 months due to non-cardiac, co-morbid conditions

Exclusion – Anatomic

- 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)

Meredith, et al. JACC 2014;64:1339

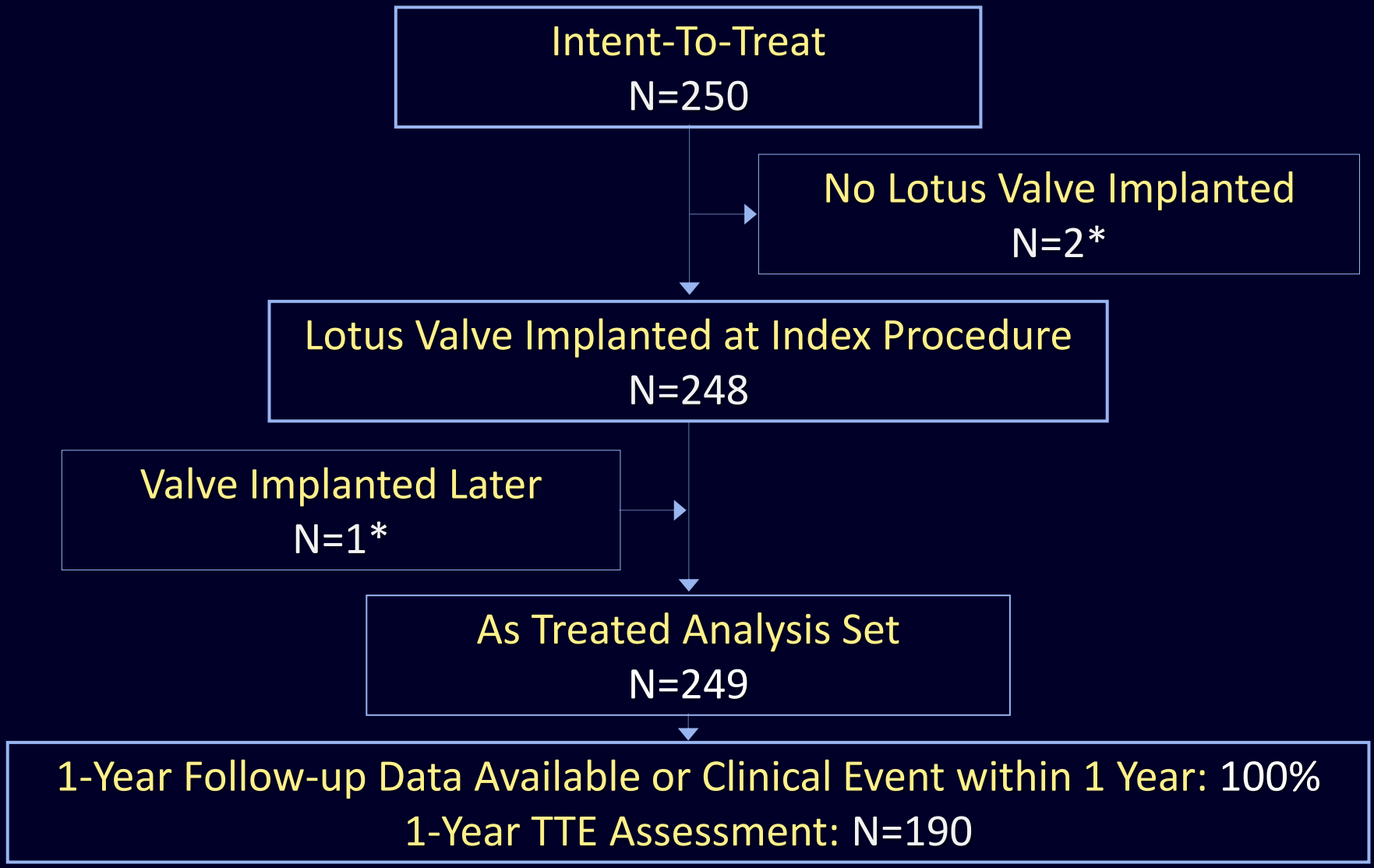
Enrollment – REPRISE II with Extended Cohort

250 patients between Oct 2012 & Apr 2014 at 20 sites

	Patients
Ian Meredith Monash Medical Centre, Clayton, Australia	38
Nicolas Dumonteil Centre Hôpital Universitaire Rangueil , Toulouse, France	29
Daniel Blackman The General Infirmary, Leeds, UK	22
Didier Tchétché Clinique Pasteur, Toulouse, France	21
David Hildick-Smith Royal Sussex County Hospital, Brighton, UK	19
Ganesh Manoharan Royal Victoria Hospital, Belfast, UK	19
Darren Walters The Prince Charles Hospital, Brisbane, Australia	19
Jan Harnek University Hospital of Lund, Lund, Sweden	16
Stephen Worthley Royal Adelaide Hospital, Adelaide, Australia	13
Gilles Rioufol Hôpital Cardiologique de Lyon, Bron, France	10

	Patients
Thierry Lefèvre Institut Cardiovasculaire - Paris Sud, Massy, France	9
Thomas Modine CHRU Lille - Hôpital Cardiologique, Lille, France	9
Nicolas Van Mieghem Erasmus Medical Center, Rotterdam, The Netherlands	8
Rüdiger Lange Deutsches Herzzentrum Muenchen, Muenchen, Germany	4
Robert Whitbourn St. Vincent's Hospital (Melbourne), Fitzroy, Australia	4
Simon Redwood Guys and St. Thomas' NHS Foundation Trust, London, UK	3
Corrado Tamburino Ospedale Ferrarotto, Catania, Italy	3
Ralf Müller HELIOS Klinikum Siegburg, Siegburg, Germany	2
Eulogio Garcia Hospital Clinico San Carlos, Madrid, Spain	1
Stephan Windecker Universitätsspital Bern, Bern, Switzerland	1

Study Flow – REPRISE II with Extended Cohort



* 2 patients had procedural complications prior to implantation; 1 procedural death prior to valve deployment and 1 vascular complication following valve retrieval. Lotus valve successfully implanted 42 days afterwards in this patient. This patient is included in the as-treated population set for 1-year outcomes but considered not implanted for device performance analysis on intention to treat.

Baseline Characteristics

REPRISE II with Extended Cohort (N=250; ITT)

Comorbidities & Baseline Scores

Age (Years)	84.0 ± 5.2 (250)	NYHA Class III or IV	77.2% (193)
Gender (Female)	52.4% (131)	euroSCORE 2011 (%)	6.4 ± 6.2 (250)
Diabetes, treated	24.0% (60)	STS Score (v 2.73; %)	6.5 ± 4.2 (250)
Atrial fibrillation	37.2% (93)	STS Plus Score (%)	10.6 ± 7.7 (250)

Echocardiographic Measurements*

AVA (cm^2)	0.7 ± 0.2 (197)	LVEF (%)	53.1 ± 10.5 (126)
MR (mod/severe)	10.6% (24)	Mean gradient (mmHg)	45.2 ± 13.6 (212)
AR (mod/severe)	13.3% (29)	Peak gradient (mmHg)	74.7 ± 21.1 (212)

Frailty Indices

		Threshold
5 Meter gait speed (sec)	8.6 ± 5.2 (236)	> 6
Max grip strength average (kg)	21.1 ± 11.5 (246)	≤ 18
Katz Index	5.7 ± 0.8 (247)	< 6
Mini-Cognitive Assessment for Dementia	3.5 ± 1.4 (244)	< 4

* Independent Core Lab assessment

Device Performance

REPRISE II with Extended Cohort (N=250; ITT)

Successful access, delivery, deployment & system retrieval	98.8%*
Successful valve repositioning, if attempted (n=85)	100.0%
Partial valve resheathing (n)	71
Full valve resheathing (n)	14
Successful valve retrieval, if attempted (n=13)	92.3%†
Aortic valve malpositioning	0.0%
Valve migration	0.0%
Valve embolisation	0.0%
Ectopic valve deployment	0.0%
TAV-in-TAV deployment	0.0%

*3 intra-procedural complications; two intra-procedural deaths (1 prior to valve deployment and 1 after valve deployment but prior to system retrieval), and *†1 vascular complication resulting from incomplete retraction into delivery catheter during retrieval but successfully implanted at day 42.

Procedural Device Success – VARC 2 Metrics

REPRISE II with Extended Cohort (N=250; ITT)

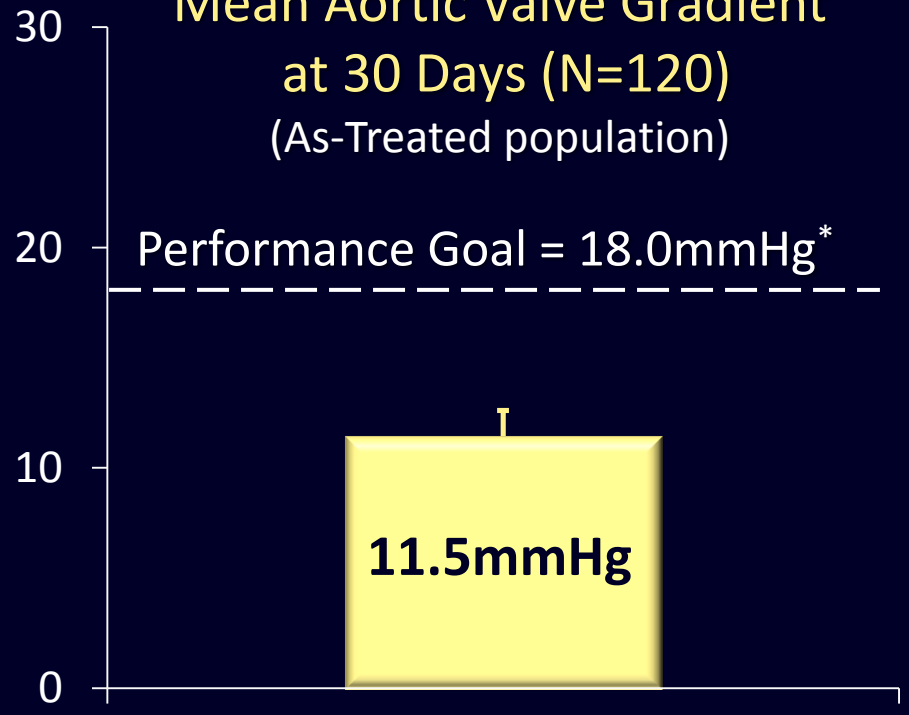
Core-lab adjudicated

No procedural mortality	98.4% (246/250)
Correct positioning of one valve in proper location	99.2% (248/250)
Mean aortic valve gradient <20 mmHg	95.0% (209/220)
Peak velocity <3 m/s	94.6% (209/221)
No moderate/severe prosthetic valve regurgitation	98.2% (215/219)

Primary Endpoints

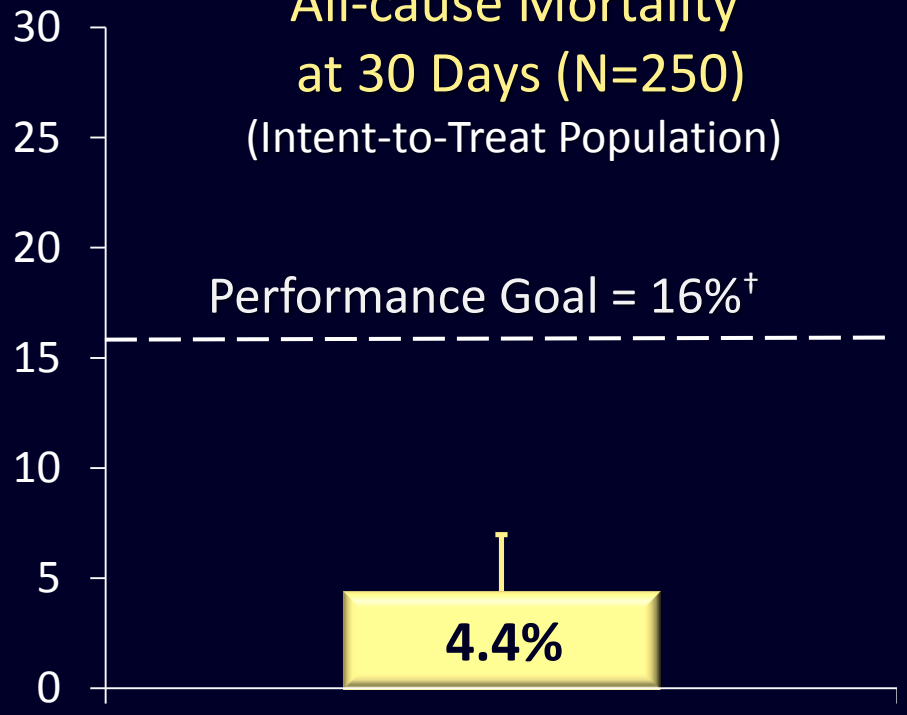
REPRISE II with Extended Cohort

Mean Aortic Valve Gradient at 30 Days (N=120)
(As-Treated population)



11.5mmHg ± UCB (12.6mmHg) is significantly below the performance goal (P<0.001)‡

All-cause Mortality at 30 Days (N=250)
(Intent-to-Treat Population)

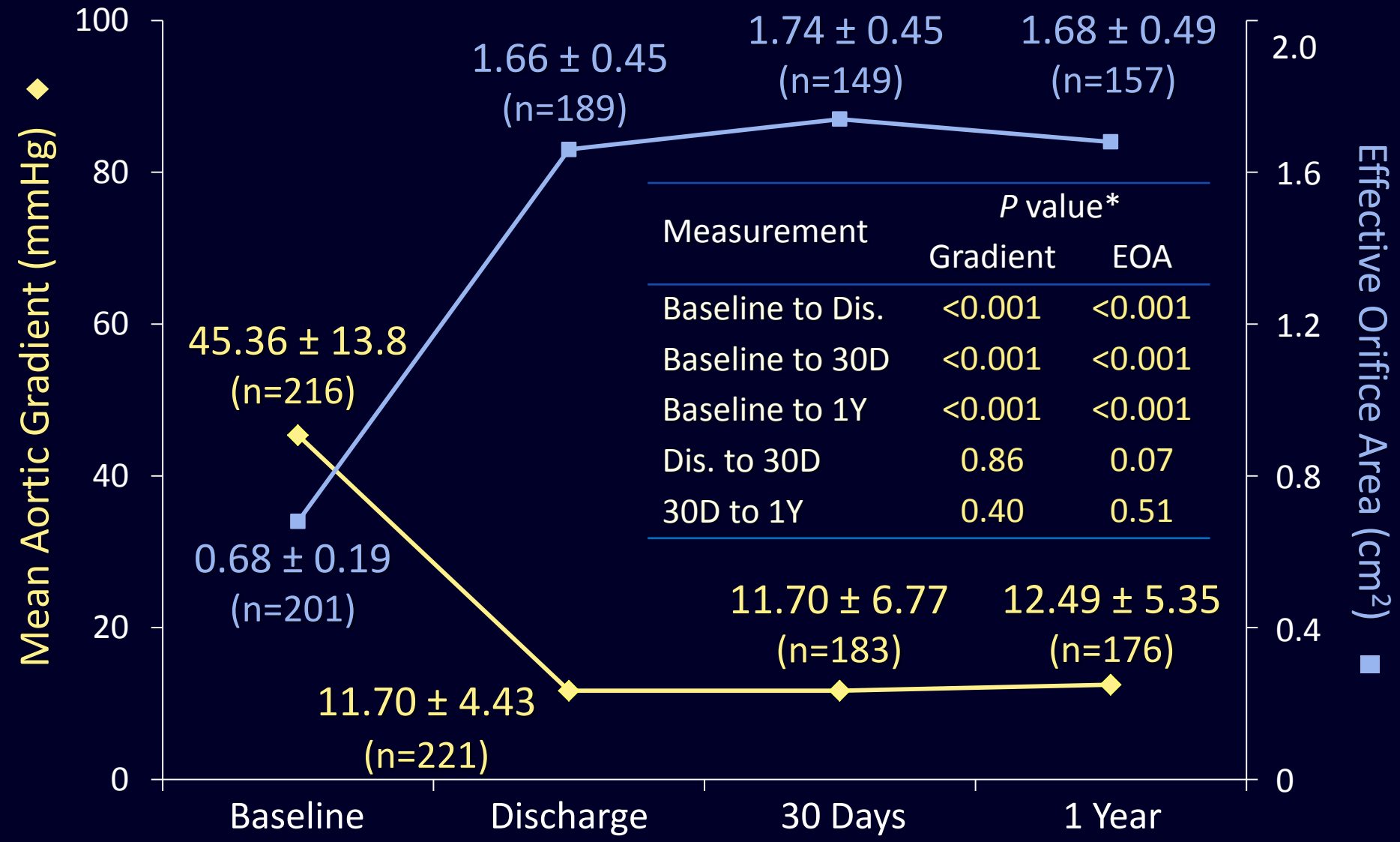


4.4% ± UCB (6.97%) is significantly below the performance goal (P<0.001)§

* Based on an expected mean of ≤15mmHg (literature review) plus a test margin of 3mmHg
† Based on an expected rate of 9.8% (literature review) plus a test margin of 6.2%
‡ Meredith, et al. *JACC* 2014; 64:1339.
§ Meredith, et al. PCR London Valves 2014.

Mean Aortic Gradient & EOA

REPRISE II with Extended Cohort (N=249; AT)

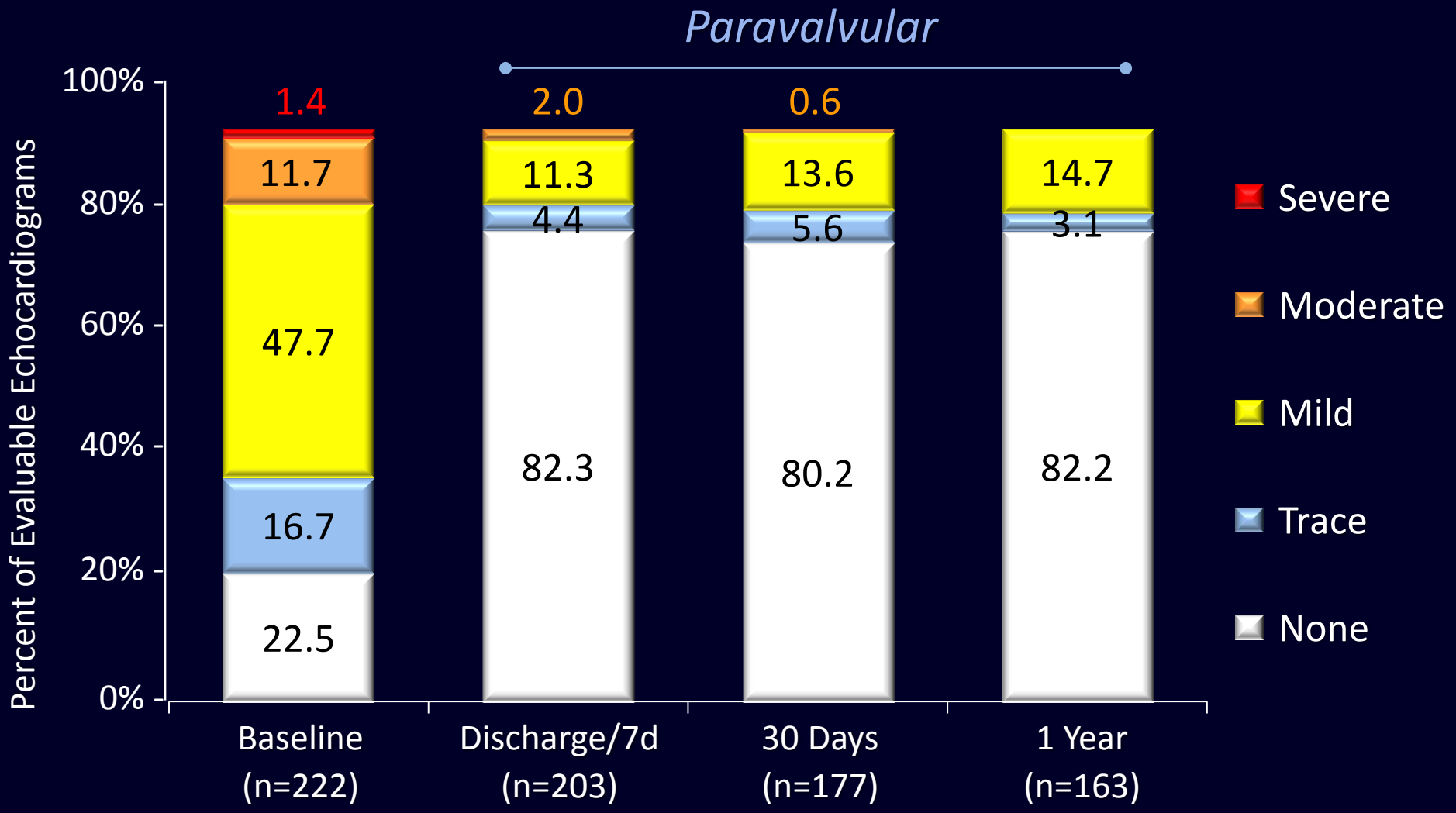


Measurement	*P* value*	
	Gradient	EOA
Baseline to Dis.	<0.001	<0.001
Baseline to 30D	<0.001	<0.001
Baseline to 1Y	<0.001	<0.001
Dis. to 30D	0.86	0.07
30D to 1Y	0.40	0.51

Values are mean ± standard deviations. As-treated population.

Paravalvular Aortic Regurgitation

REPRISE II With Extended Cohort (N=249; AT)



No moderate or severe paravalvular aortic regurgitation at 1 year

Core-lab adjudicated data. As-treated population.

Safety: Death & Stroke to 1 Year

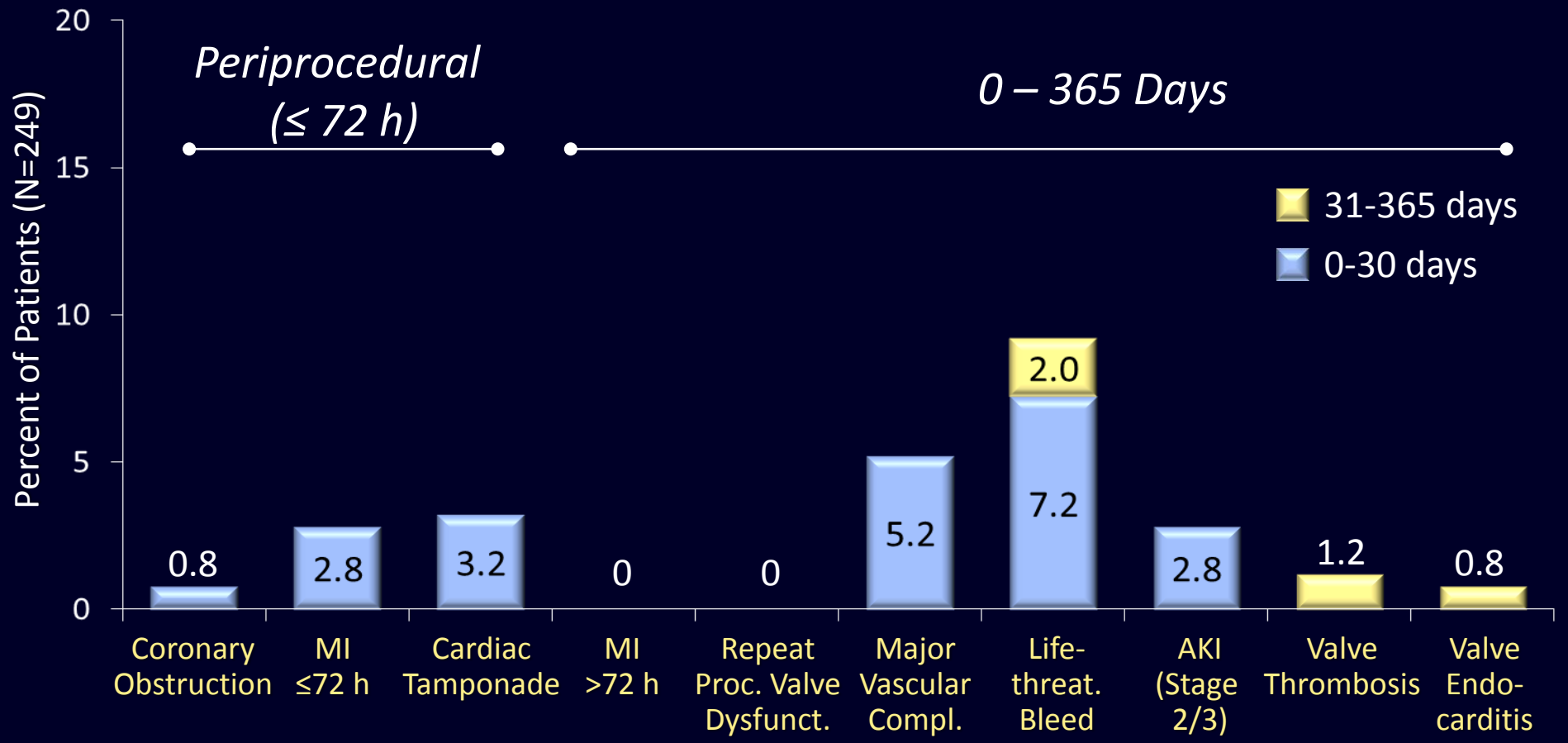
REPRISE II with Extended Cohort (N=249; AT)

Event	*30 Days*	*1 Year*
All-cause death	4.0% (10/249)	11.6% (29/249)
Cardiovascular death	3.6% (9/249)	7.6% (19/249)
Disabling stroke	2.8% (7/249)	3.6% (9/249)
Non-disabling stroke	4.0% (10/249)	4.8% (12/249)

All REPRISE II patients (n=120) were assessed by a neurologist before and after TAVI.

Additional VARC 2 Safety Endpoints

REPRISE II with Extended Cohort (N=249; AT)



5 bleeding events: intraocular bleed on day 43, haemorrhagic strokes on days 123 and 245, traumatic subdural hematoma resulting from fall on day 276, post-operative anemia following hip surgery on day 301.

2 cases of valve endocarditis successfully treated with antibiotics without sequelae.

3 cases of valve thrombosis successfully resolved with anticoagulant therapy without sequelae.

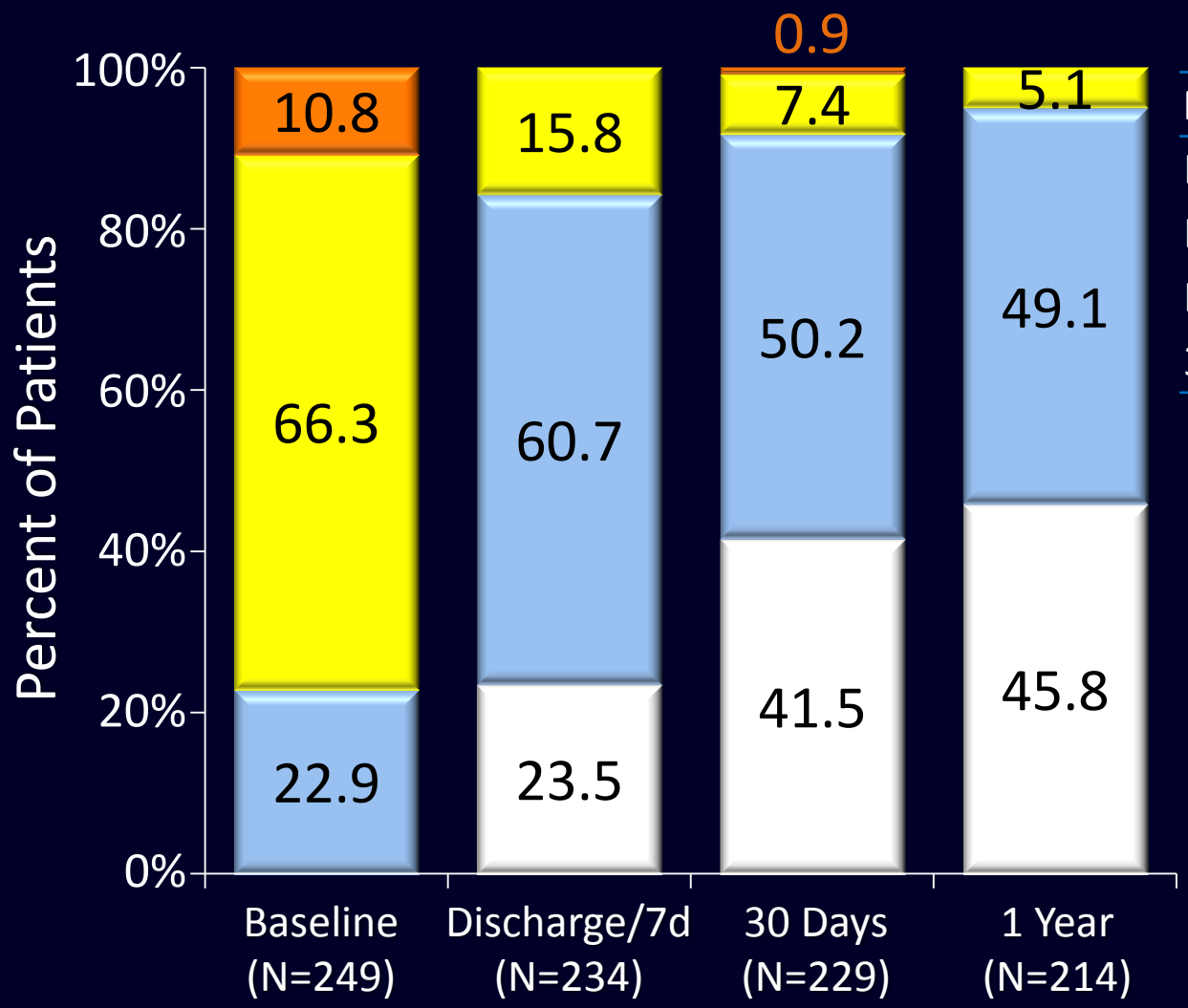
Pacemaker Implantation at 1 Year

REPRISE II with Extended Cohort (N=249; AT)

New Permanent Pacemaker	
0 to 30 days	72 (28.9%)
31 Days to 1 Year	9 (3.6%)
Complete heart block	1
Symptomatic bradycardia	1
LBBB/symptomatic bradycardia	3
AF/LAFB/bradycardia	1
Sick sinus syndrome	2
LBBB with prolonged HV interval	1
0 Days to 1 Year	81 (32.5%)

NYHA Class Changes Over Time

REPRISE II with Extended Cohort (N=249; AT)



Measurement	*P* value
Baseline to Discharge	<0.001
Baseline to 1 Year	<0.001
Discharge to 30 Days	<0.001
30 Days to 1 Year	0.26

P values calculated from paired Wilcoxon signed-rank test. As-treated population.

Conclusions

REPRISE II with Extended Cohort (N=250)

- At 1 year
  - Sustained and excellent safety and efficacy
  - Conserved valve haemodynamics
  - No moderate or severe PVL
    - >85% of patients had no/trace PVL
  - Significant and sustained improvement in NYHA functional class (~95% of patients NYHA Class I or Class II)
  - Adverse event rates consistent with those reported for other valves
- These findings are consistent with those reported for the REPRISE II main cohort, and support the use of the Lotus Valve for the treatment of aortic stenosis in high-risk surgical patients.