Repositionable Percutaneous Replacement of a Stenotic Aortic Valve through Implantation of the Lotus Valve System

30-day Outcomes for the First 60 Patients in the REPRISE II Study

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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 (Modest)
  - Medtronic (Modest)

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Early TAVI Devices for Severe Aortic Stenosis

Reprise

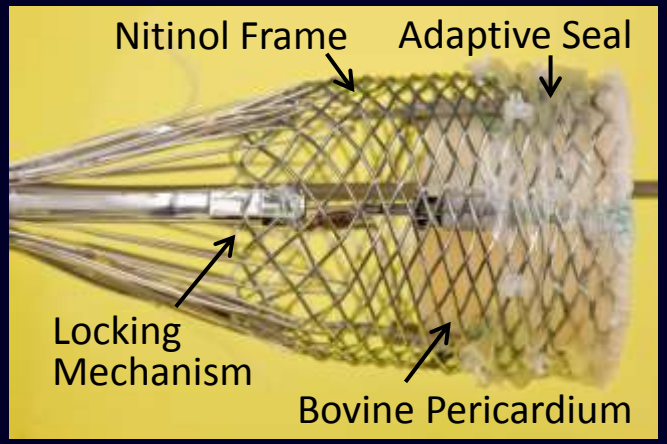
- Significant benefit for inoperable/high risk patients
- Shortcomings with current devices & clinical complications
  - Paravalvular leak
    - Association with increased mortality*
  - Valve malpositioning
    - Valve migration, embolization, ectopic deployment, TAV-in-TAV
  - Stroke
- Improvements needed to prevent undesirable outcomes
  - Reduce aortic regurgitation
  - Simple, precise & atraumatic aortic/ventricular repositioning
  - 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. Central radiopaque marker to aid precise positioning
4. Functions early enabling controlled deployment
5. Fully retrievable and repositionable
6. Adaptive seal designed to minimize paravalvular leak

Study Design

REPRISE II

- OBJECTIVE
  Evaluate safety & performance of the Lotus Valve System for TAVI in symptomatic patients with severe calcific aortic stenosis who are considered high risk for surgical valve replacement
- DESIGN
  Prospective; single-arm; multicentre; f/u at 7 days/discharge, 30 days, 3 & 6 months, 1 year & annually through 5 years
- PRIMARY ENDPOINT – DEVICE PERFORMANCE
  Mean aortic valve pressure gradient at 30 days compared to a performance goal of 18 mmHg
- PRIMARY ENDPOINT – SAFETY
  30-Day all-cause mortality

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 Key Inclusion Criteria

- Age ≥70 years
- Documented calcified native aortic stenosis
  - AVA <1.0 cm^2 (or AVA index <0.6 cm^2/m^2) plus either mean pressure gradient >40 mmHg or jet velocity >4 m/s (by echocardiography)
- High risk for surgical AVR
  - STS score ≥8% AND/OR documented heart team agreement of high risk due to frailty or comorbidities
- Symptomatic aortic valve stenosis with NYHA Class ≥II
- Aortic annulus size 19-27 mm
  - 23 mm & 27 mm valve sizes used

REPRISE II Key Exclusion Criteria

Anatomic

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

Clinical

- AMI within 30 days
- CVA or TIA within 6 months
- Dialysis dependent or Cr >3.0 mg/dL
- 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

REPRISE II Study Organization

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)

Enrollment

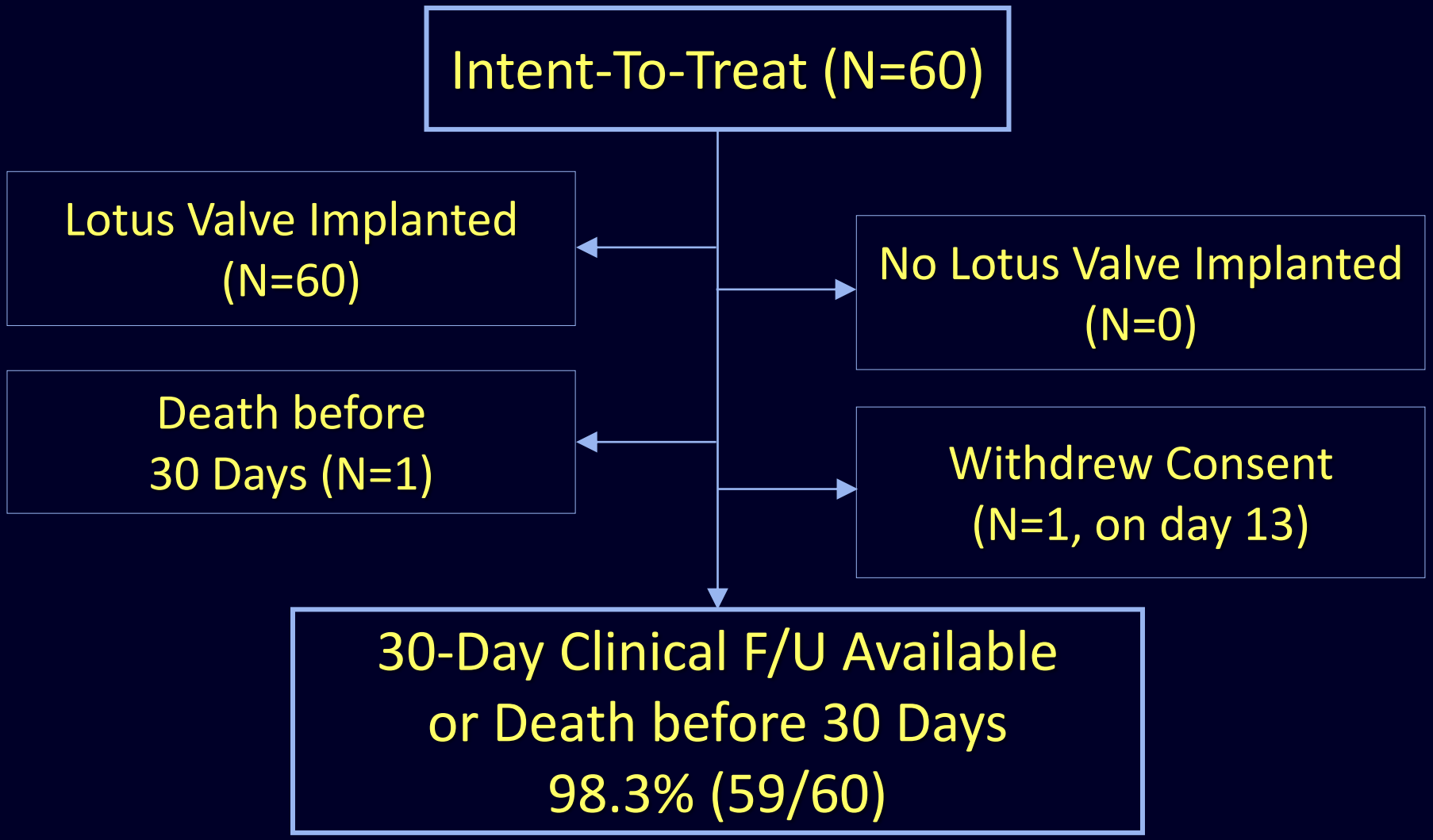
REPRISE II – First 60 Patients

Investigator	Patients*
Ian Meredith Monash Medical Centre, Clayton, Australia	19
Darren Walters The Prince Charles Hospital, Brisbane, Australia	18
Stephen Worthley Royal Adelaide Hospital, Adelaide, Australia	9
Didier Tchétché Clinique Pasteur, Toulouse, France	5
Robert Whitbourn St. Vincent's Hospital (Melbourne), Fitzroy, Australia	4
Nicolas Dumonteil Centre Hôpital Universitaire Rangueil , Toulouse, France	4
Gilles Rioufol Hôpital Cardiologique de Lyon, Bron, France	1

*Enrolled October 2012 through January 2013

Study Flow

Intent-To-Treat Population (First 60 Patients)



Baseline Demographics

REPRISE II – First 60 Patients

Parameter	Patients
Age (Years)	85.5±4.3 (60)
Gender (Female)	63.3% (38)
STS Score (v 2.73) (%)	6.4±3.0 (60)
euroSCORE 2011 (%)	6.7±5.1 (60)
NYHA Class III or IV	75.0% (45)
Diabetes, treated	25.0% (15)
Hypertension, history	85.0% (51)
Atrial fibrillation, history	38.3% (23)
Coronary artery disease	60.0% (36)
Cerebrovascular accident	5.0% (3)
COPD, mod/severe	11.7% (7)

Baseline Frailty, Disability, & Comorbidity

REPRISE II – First 60 Patients

Parameter	Patients	Frailty/Disability Threshold
Body Mass Index (kg/m^2)	27.3±5.9	< 19
5 Meter gait speed (sec)	8.5±4.1	> 6
Falls in the past 6 months	0.3±0.8	> 1
Max grip strength average (kg)	15.0±6.6	≤ 18
Katz Index	5.8±0.7	< 6
Charlson Comorbidity Index Score	2.2±1.6	> 3
Mini-Cognitive Assessment for Dementia	3.6±1.4	< 4

Baseline Echocardiographic Measurements

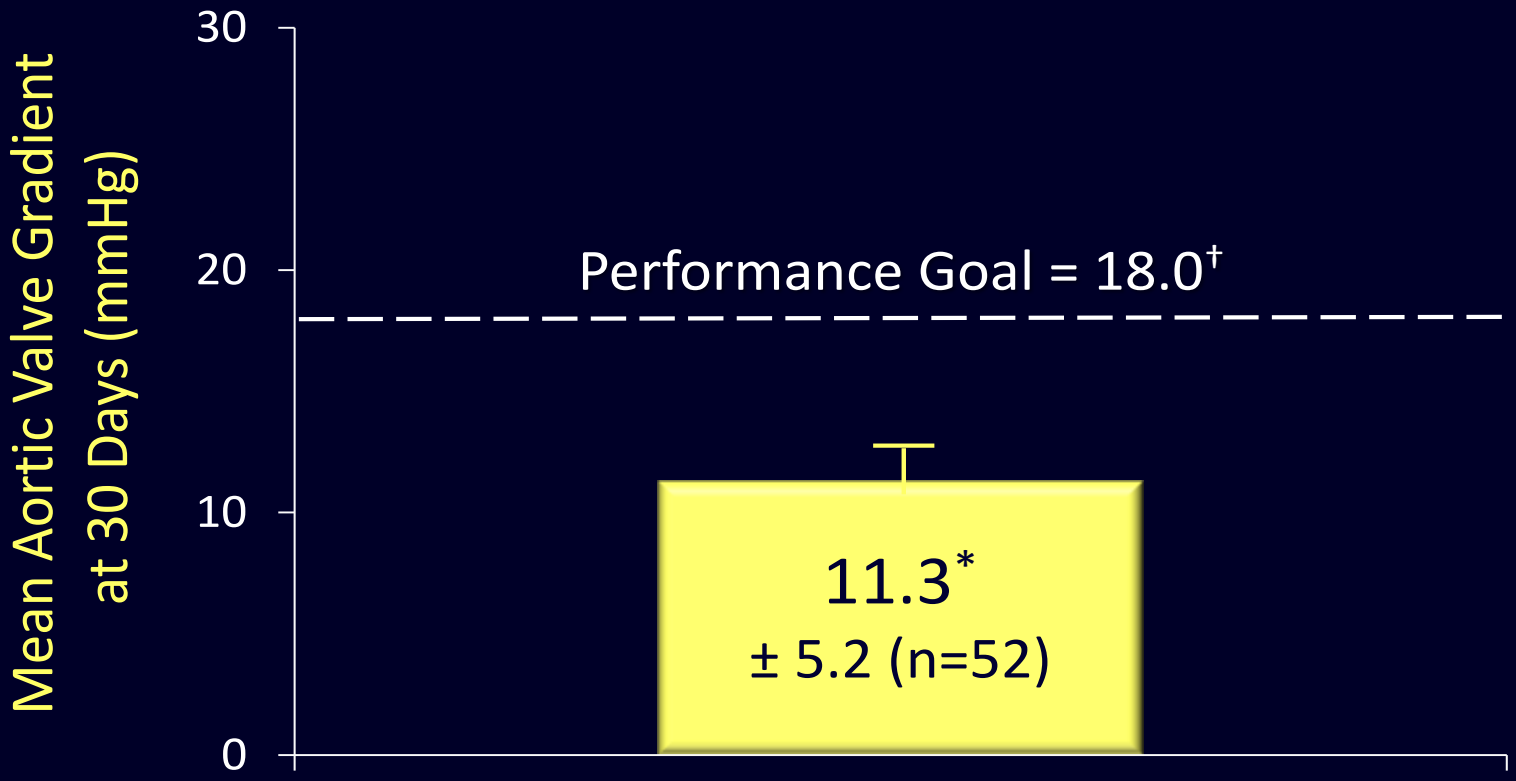
REPRISE II – First 60 Patients

Parameter*	Patients
Aortic valve area (cm^2)	0.6 ± 0.2 (52)
Mean aortic gradient (mmHg)	47.5 ± 17.2 (57)
Peak aortic gradient (mmHg)	78.0 ± 27.5 (57)
LVEF (%)	54.2 ± 8.5 (35)
Mitral regurgitation (mod/severe)	16.7% (10)
Aortic regurgitation (mod/severe)	18.3% (11)

* All data based on independent assessment from Core Laboratory

Primary Device Performance Endpoint

REPRISE II – First 60 Patients



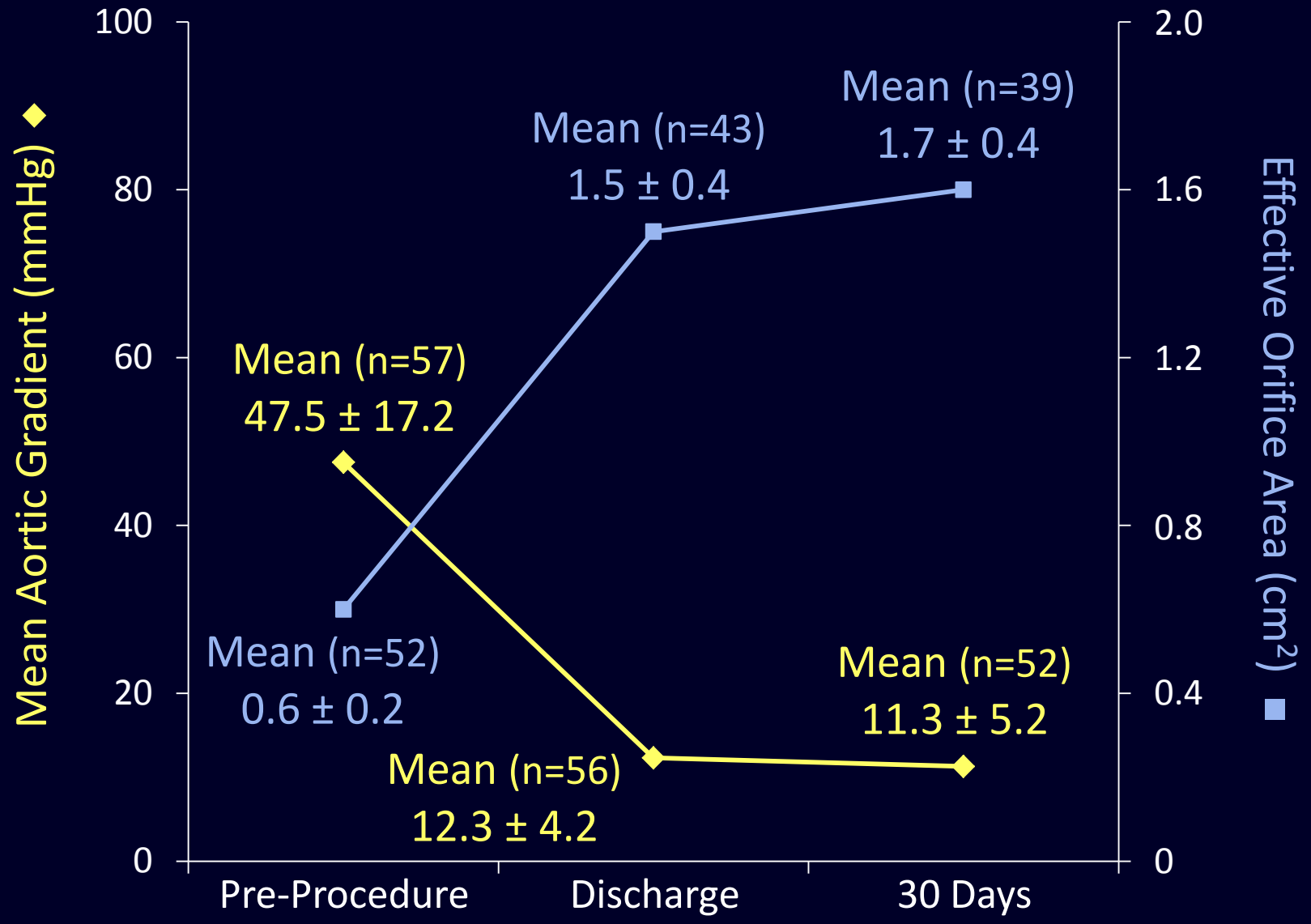
** Value of 11.3 with a 99.2%‡ UCB of 13.1 is significantly less than the performance goal (P<0.001)*

‡ Alpha-level adjustment for interim analysis

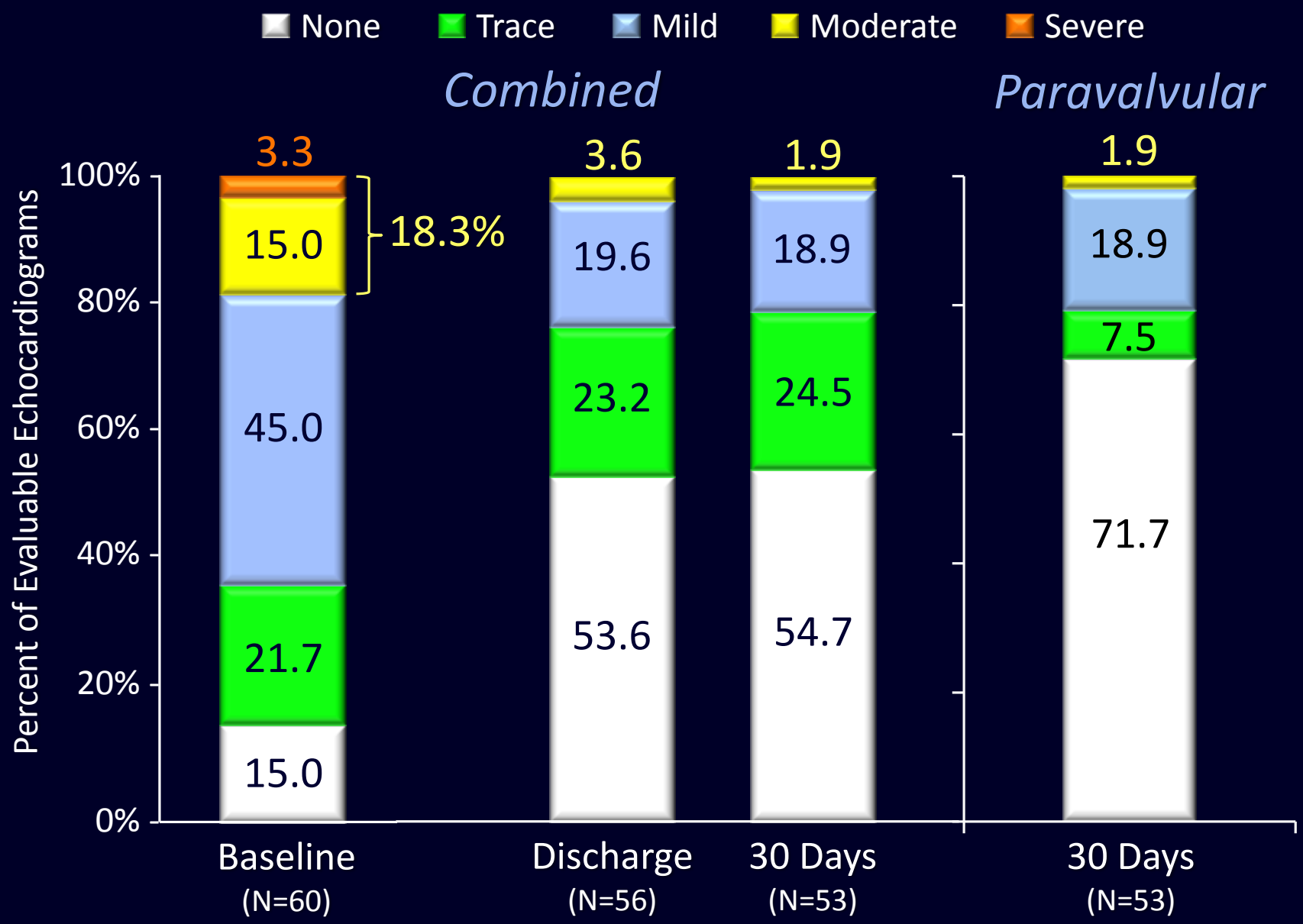
† Based on an expected mean of ≤15 mmHg (literature review) plus a test margin of 3 mmHg

Mean Aortic Gradient & EOA

REPRISE II – First 60 Patients

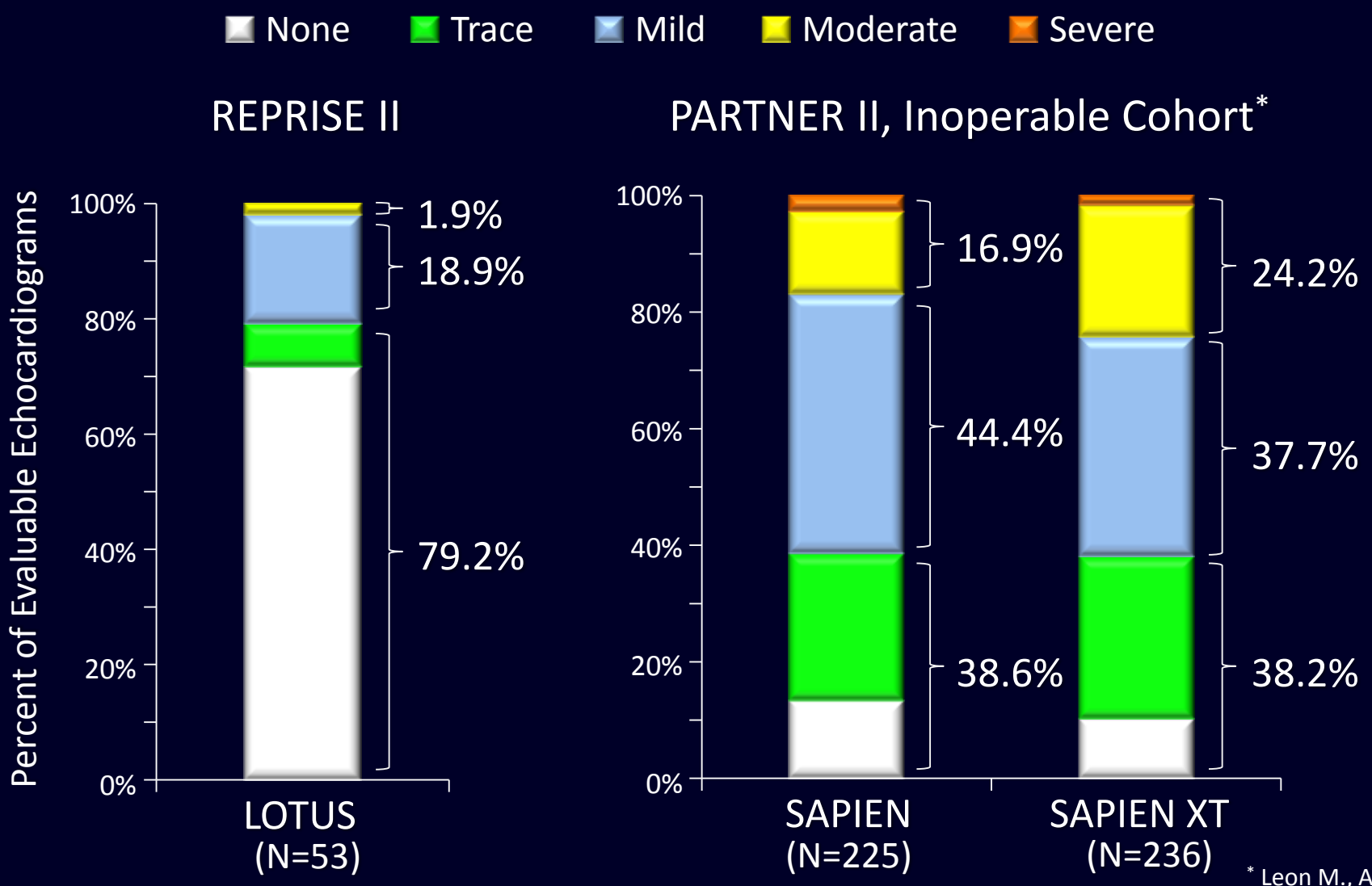


REPRISE II Aortic Regurgitation Over Time



Paravalvular Aortic Regurgitation-30 Days

REPRISE II Comparison with Edwards Valves



* Leon M., ACC 2013

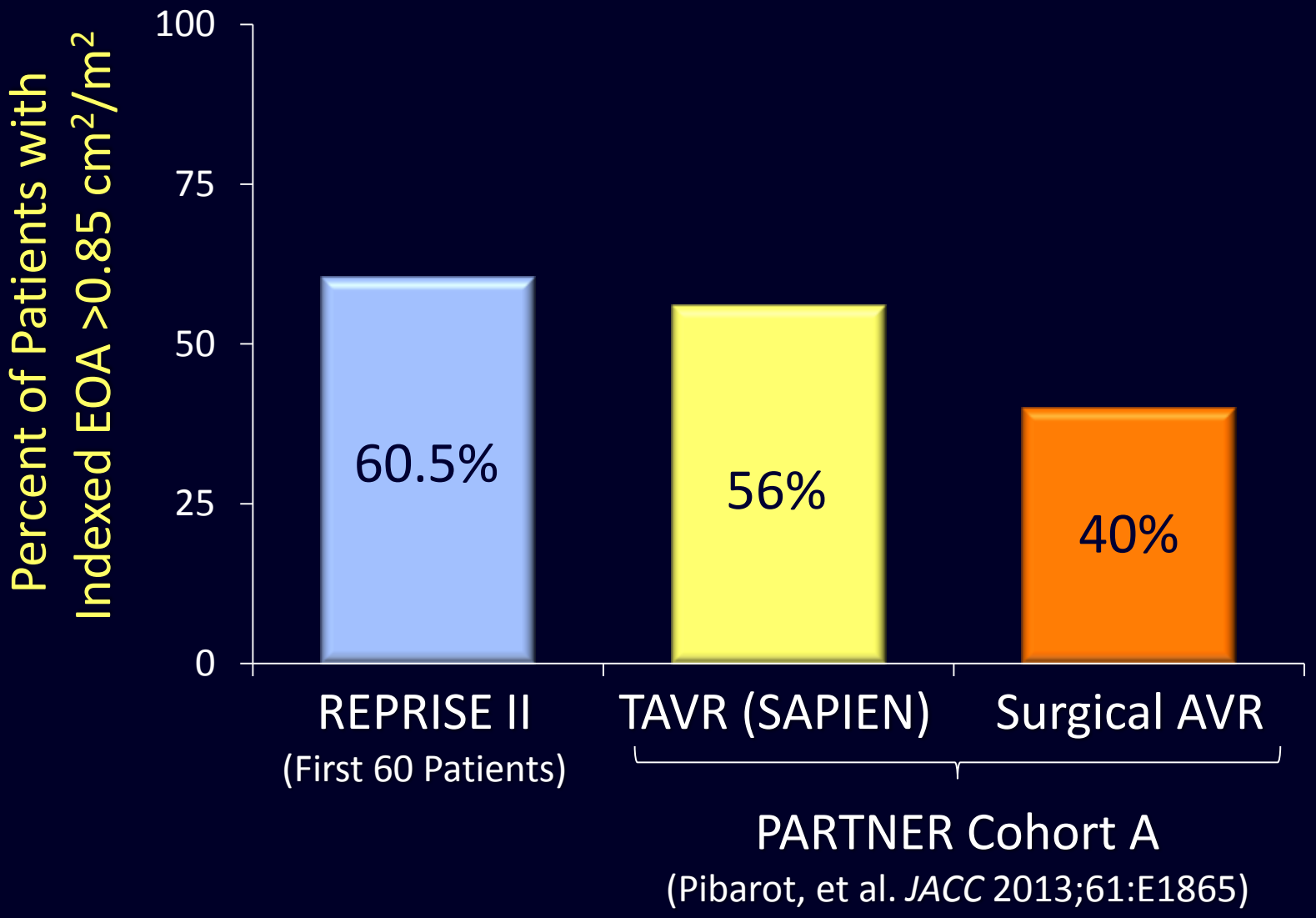
Valve Performance/Success

REPRISE II (First 60 Patients) - Procedure/Discharge

Device Performance – VARC 2	
Access, delivery, deployment, system retrieval	100.0% (60/60)
Valve repositioning, if attempted (n=16)	100.0% (16/16)
Valve retrieval, if attempted (n=4)	100.0% (4/4)
Device Success – VARC 2	
Absence of procedural mortality	98.3% (59/60)
Correct positioning of one valve in proper location	100.0% (60/60)
Intended performance (based on discharge echo)	
Mean aortic valve gradient <20 mmHg	94.6% (53/56)
Peak velocity <3 m/s	94.6% (53/56)
No moderate/severe prosthetic valve regurgitation	96.4% (54/56)
Indexed EOA >0.85 cm^2/m^2 (>0.7 for BMI ≥30)	60.5% (26/43)

Indexed Effective Orifice Area Post Implant

REPRISE II Comparison with PARTNER Cohort A



Valve Malpositioning/Other Complications

REPRISE II – First 60 Patients

Parameter	Patients
Aortic valve malpositioning	0.0% (0)
Valve migration	0.0% (0)
Valve embolization	0.0% (0)
Ectopic valve deployment	0.0% (0)
TAV-in-TAV deployment	0.0% (0)
Aortic valve endocarditis	0.0% (0)
Aortic valve thrombosis	0.0% (0)

Safety: Death & Stroke at 30 Days

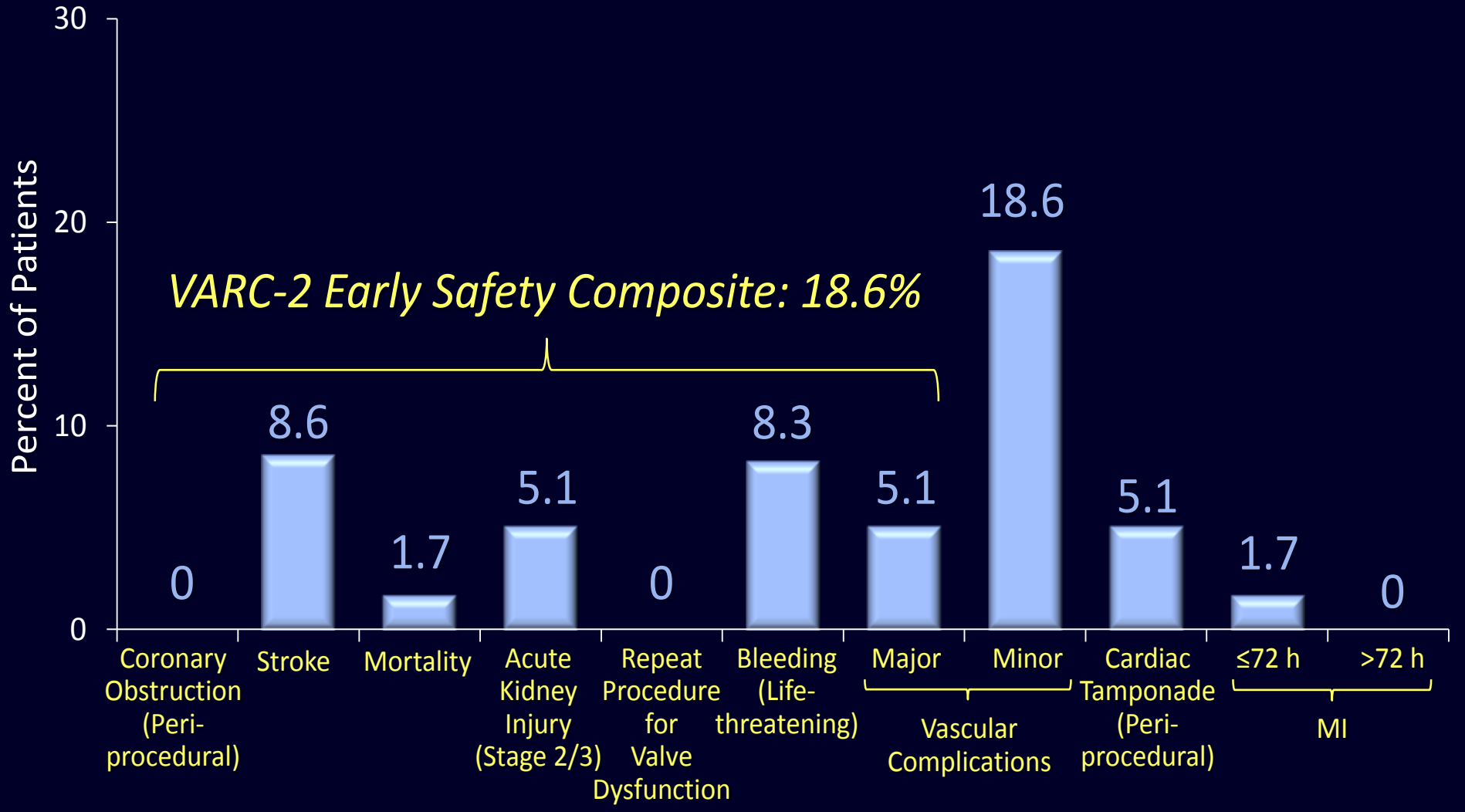
REPRISE II – First 60 Patients

Event	Patients
All-cause mortality (primary safety endpoint)*	1.7% (1)
Cardiovascular mortality	1.7% (1)
All stroke*	8.6% (5)
Disabling stroke	3.4% (2)
Non-disabling stroke	5.2% (3)

* Component of VARC-2 safety composite; all strokes were ischaemic

VARC Safety Composite & Other Endpoints

REPRISE II – First 60 Patients at 30 Days



Pacemaker Implantation

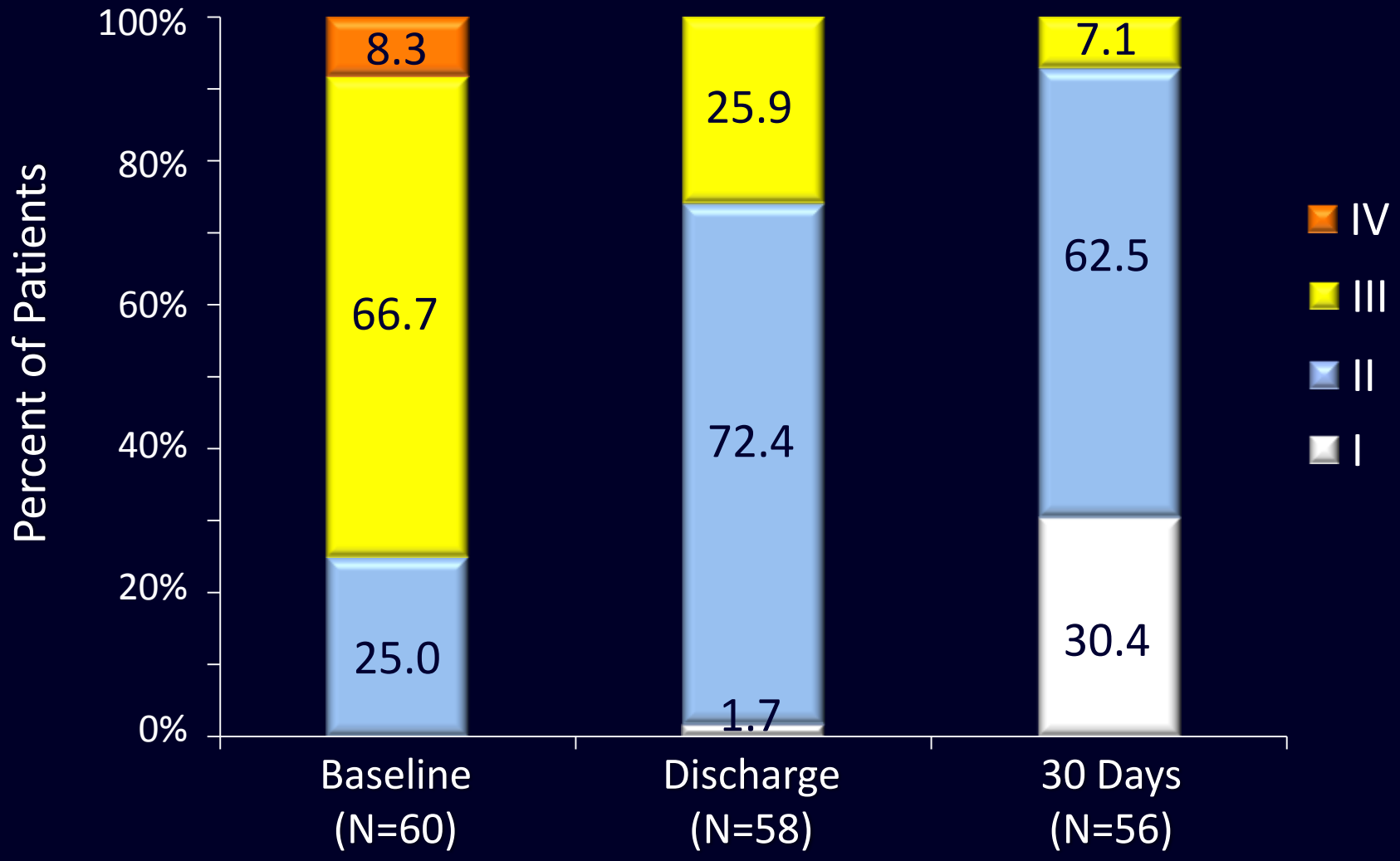
REPRISE II – First 60 Patients

Variable	Patients
Newly implanted pacemaker	29.3% (17/58)
Baseline PR prolongation	41.2% (7/17)
Baseline RBBB	23.5% (4/17)
Baseline LBBB	0.0% (0/17)
New conduction disturbance post valvuloplasty	58.8% (10/17)
Paced rhythm at 30 days	64.7% (11/17)

Indication	Patients
3rd degree AV block	15
1st degree AV block, RBBB, LAFB	1
Atrial fibrillation with slow ventricular rate	1

NYHA Class Changes Over Time

REPRISE II – First 60 Patients



Summary & Conclusions

REPRISE II – First 60 Patients

- Successful valve implantation in all 60 patients
- Primary device performance endpoint met
- Low mortality rate at 30 days (1.7%)
- Valve repositioning/retrieval was performed as needed
- No embolization, ectopic valve deployment, or TAV-in-TAV
- Negligible aortic regurgitation
- Clinical event rates consistent with those reported for other valves
- One of the first studies to report outcomes based on VARC-2 metrics

Results suggest the Lotus Valve, a differentiated, 2nd generation TAVI device, may be a valuable addition to the armamentarium for treatment of severe aortic stenosis