Two-Year Outcomes With the Fully Repositionable and Retrievable Lotus™ Transcatheter Aortic Replacement Valve in 120 High-Risk Surgical Patients With Severe Aortic Stenosis: Results From the REPRISE II CE-Mark Study

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On behalf of the REPRISE II Investigators

Potential Conflicts of Interest

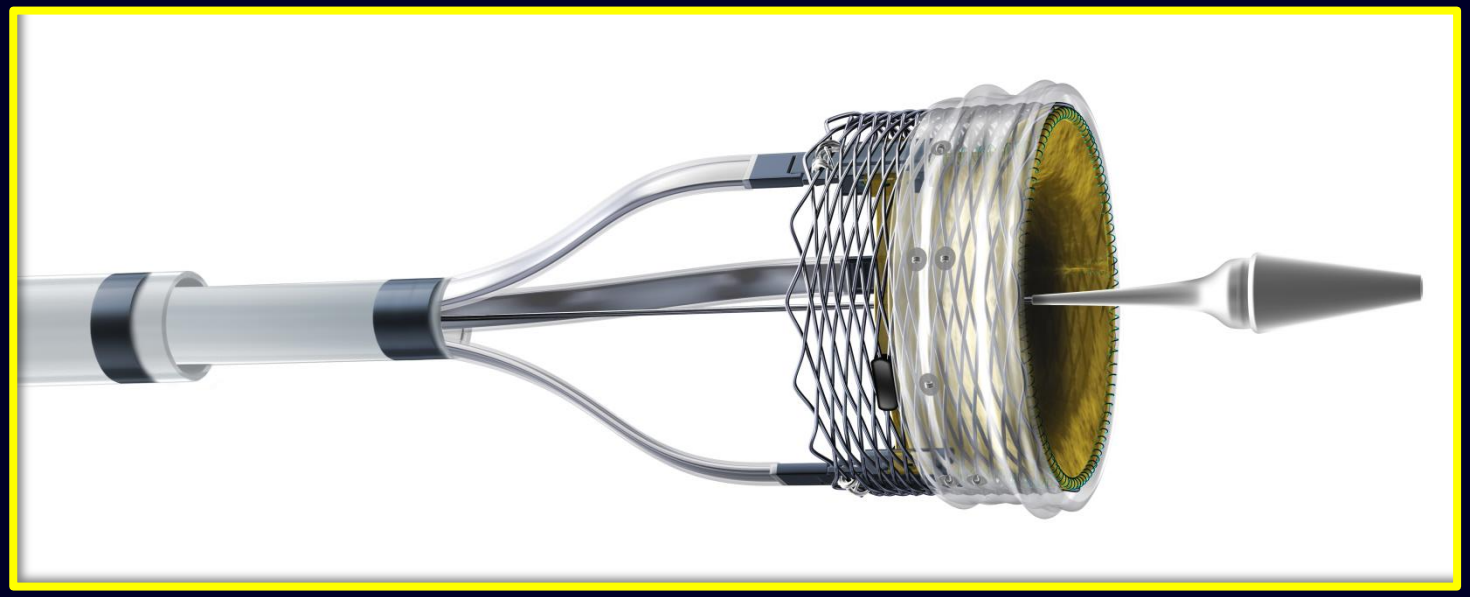
Speaker's name: Ian T. Meredith, AM

Consultant Fees/Honoraria/Speaker's Bureau:

Boston Scientific (Significant)

All faculty disclosures are available on the CRF Events App and online at www.crf.org/tct

Lotus Valve System Design Goals



- Pre-attached to catheter delivery system
- Bovine pericardial valve in woven nitinol frame
- Central radiopaque positioning marker to guide placement
- Valve functions early in deployment: hemodynamic stability
- Valve is fully repositionable & retrievable throughout entire deployment process
- Adaptive seal to minimize PVL

REPRISE II Study Design

Objective	Evaluate safety & performance of the Lotus Valve System for TAVR in symptomatic patients with severe calcific native aortic stenosis who are considered high risk for surgical valve replacement
Design	• Prospective, single-arm; multicenter trial • Follow-up at discharge/7 days, 30 days, 3 & 6 months, 1 year & annually through 5 years
Patients	• 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
Primary Endpoint (Device Performance)	Mean aortic valve pressure gradient at 30 days (Compared with a performance goal of 18mmHg)
Primary Endpoint (Safety)	All-cause mortality at 30 days

Additional REPRISE II Endpoints

VARC-2 Metrics

Safety

- 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.)

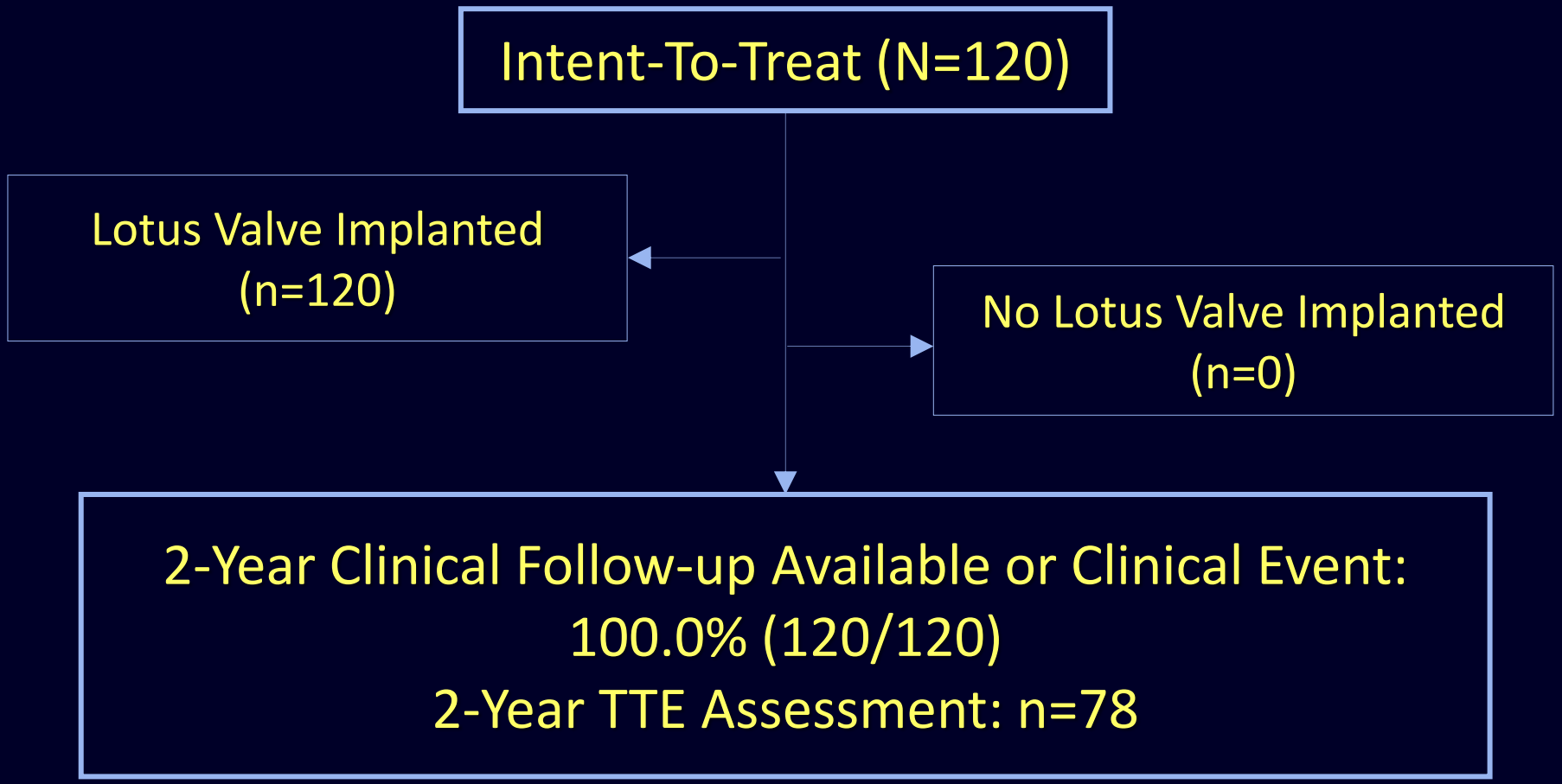
Effectiveness

- 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 Study Flow



Baseline Characteristics

REPRISE II (N=120)

Comorbidities & Baseline Scores

Age (Years)	84.4 ± 5.3 (120)	NYHA Class III or IV	75.8% (91)
Gender (Female)	56.7% (68)	euroSCORE 2011 (%)	6.9 ± 5.8 (120)
Diabetes, treated	22.5% (27)	STS Score (v 2.73; %)	7.1 ± 4.6 (120)
Prior Pacemaker	6.7% (8)	STS Plus Score (%)	11.8 ± 8.0 (120)

Echocardiographic Measurements*

AVA (cm^2)	0.7 ± 0.2 (97)	LVEF (%)	54.3 ± 10.7 (61)
MR (mod/severe)	11.6% (13)	Mean gradient (mmHg)	46.4 ± 15.0 (104)
AR (mod/severe)	15.2% (17)	Peak gradient (mmHg)	76.5 ± 23.6 (104)

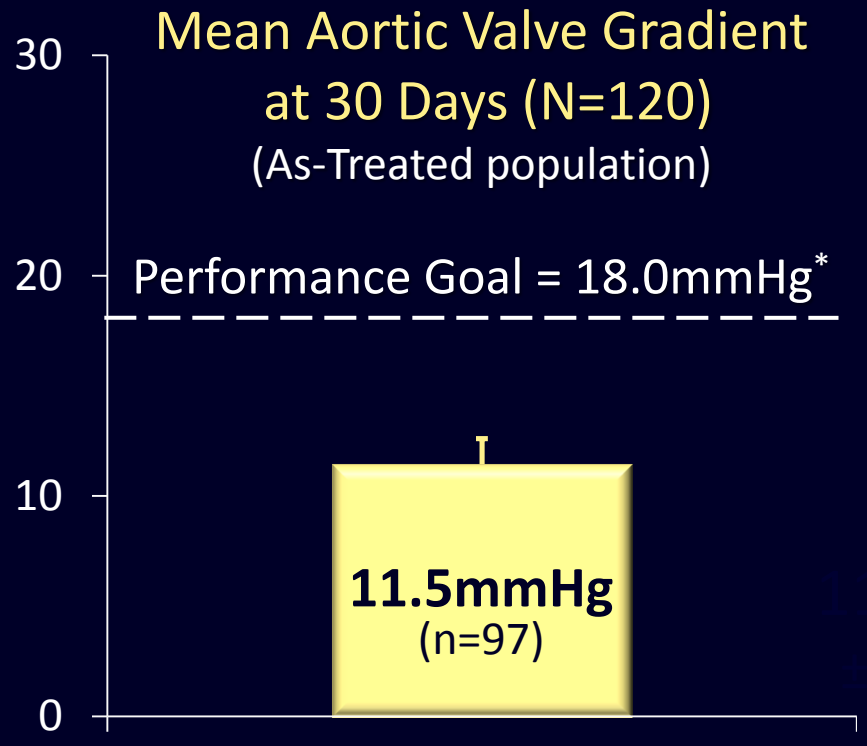
Frailty Indices

		Threshold
5 Meter gait speed (sec)	9.2 ± 6.7 (119)	> 6
Max grip strength average (kg)	20.1 ± 12.8 (120)	≤ 18
Katz Index	5.7 ± 0.9 (120)	< 6
Mini-Cognitive Assessment for Dementia	3.6 ± 1.4 (120)	< 4

Meredith, et al. *JACC*2014; 64:1339. * Independent Core Lab assessment

Primary Device Performance Endpoint

REPRISE II (N=120)



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

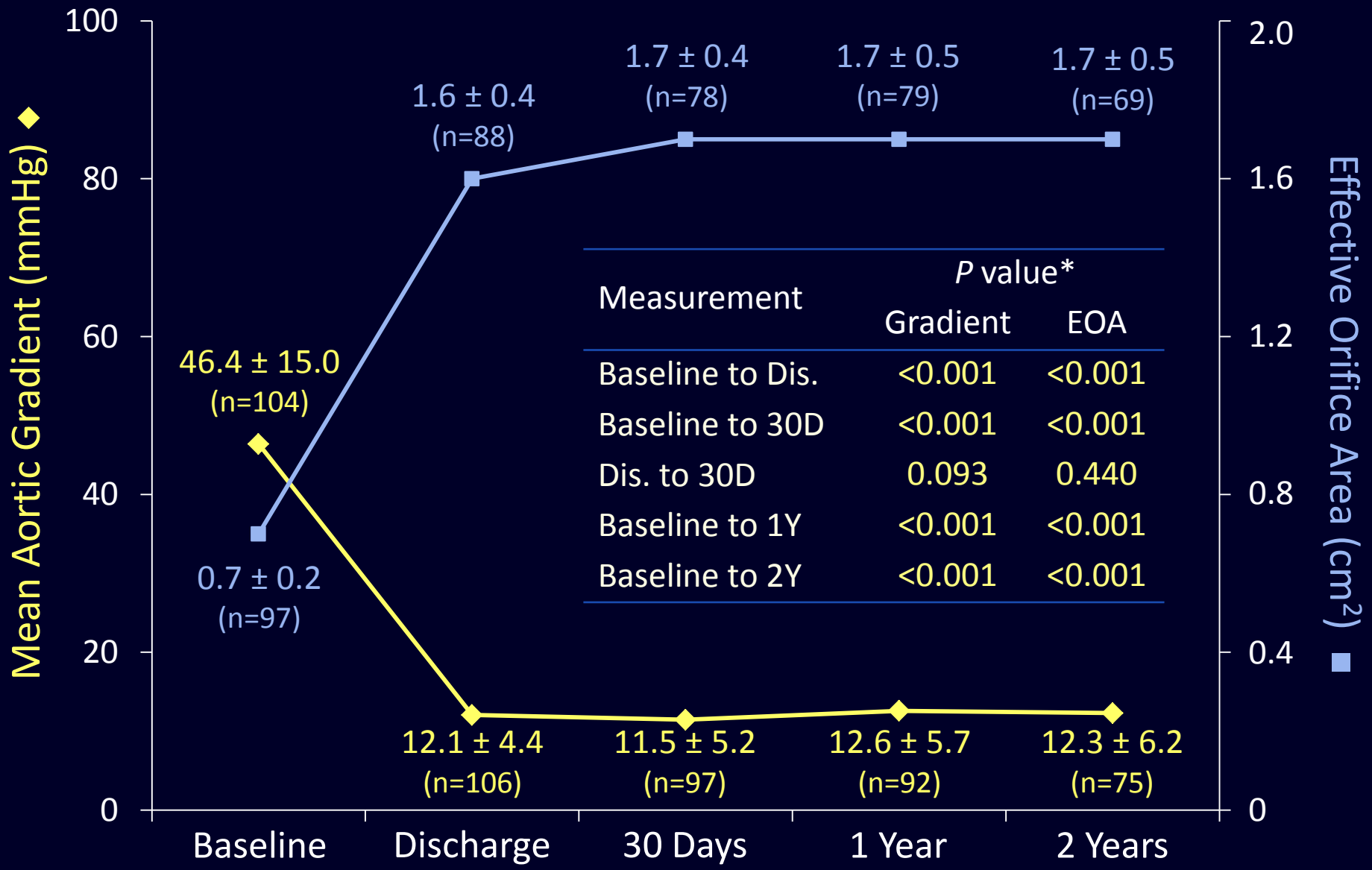
Successful access, delivery, deployment and system retrieval	100.0% (120/120)
Successful valve repositioning, if attempted (n=31)	100.0% (31/31)
Successful valve retrieval, if attempted (n=6)	100.0% (6/6)

Aortic valve malpositioning	0%
Valve migration	0%
Valve embolization	0%
Ectopic valve deployment	0%
TAV-in-TAV deployment	0%

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

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

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	0.093	0.440
Baseline to 1Y	<0.001	<0.001
Baseline to 2Y	<0.001	<0.001

*Repeated measures and random effects ANOVA

Safety: Death & Stroke to 2 Years

REPRISE II (N=120)

KM Rates	*30 Days*	*1 Year*	*2 Years*
All-cause death	4.2% (5)	10.9% (13)	16.9% (20)
Cardiovascular death	4.2% (5)	6.7% (8)	10.4% (12)
Disabling stroke†	1.7% (2)	3.5% (4)	3.5% (4)
Non-disabling stroke†	4.2% (5)	6.0% (7)	6.0% (7)

Kaplan-Meier rates rates

Deaths between 1 &2 yrs: Non CV : peritonitis &septic shock (n=1), acute kidney injury (n=1), cancer (n=1),
CV Deaths : endocarditis and progressive heart failure (n=1), progressive heart failure (n=3).

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

Pacemaker Implantation at 2 Years

REPRISE II (N=120)

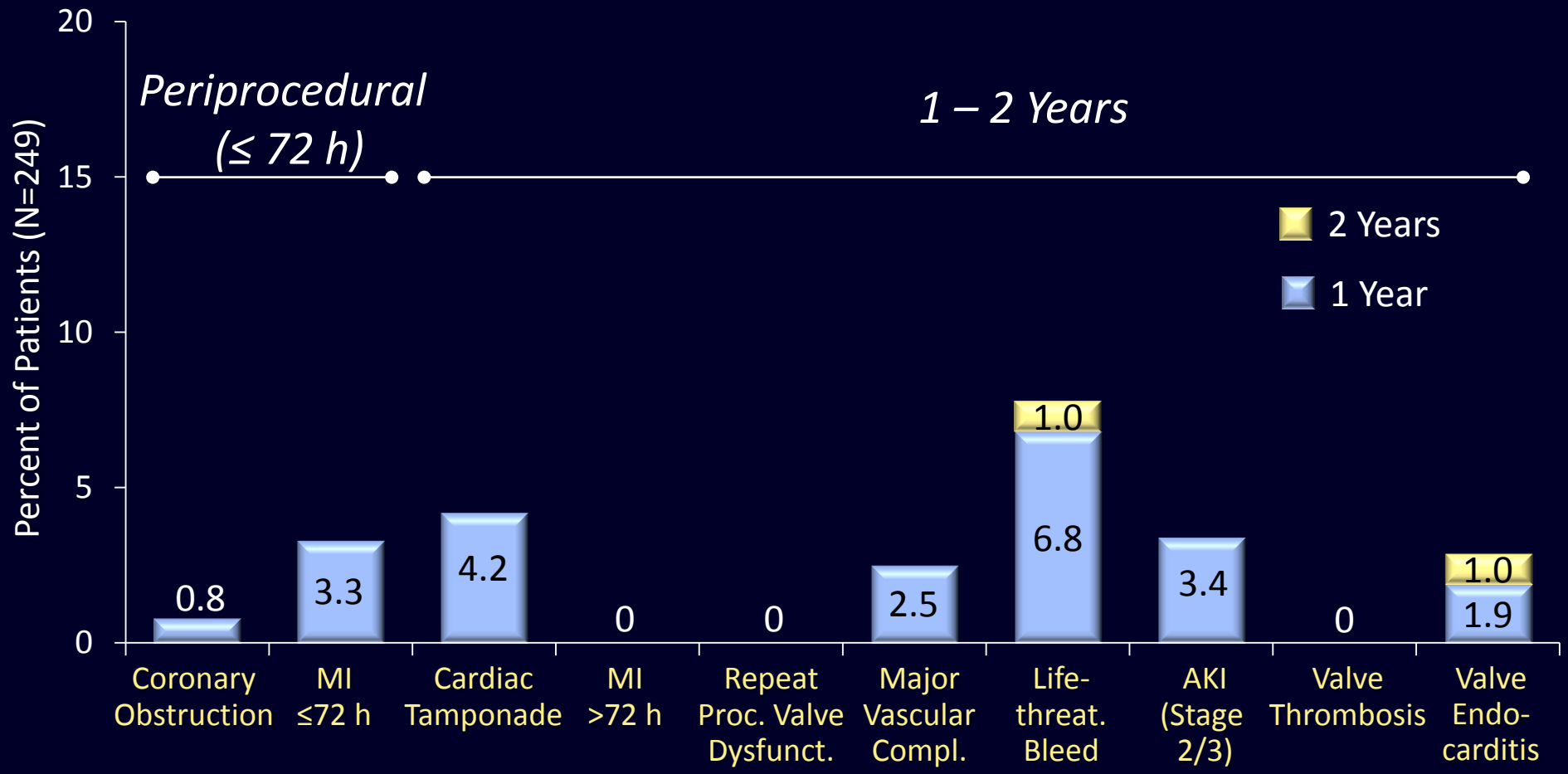
New Permanent Pacemaker (N=120)

0 days to 1 Year	38 (32.2%)
1 Year to 2 Years	2 (2.0%)
3rd degree AV block on day 432	1
Symptomatic bradycardia on day 673	1
0 Days to 2 Years	40 (34.2%)

Kaplan-Meier rates

Additional VARC 2 Safety Endpoints

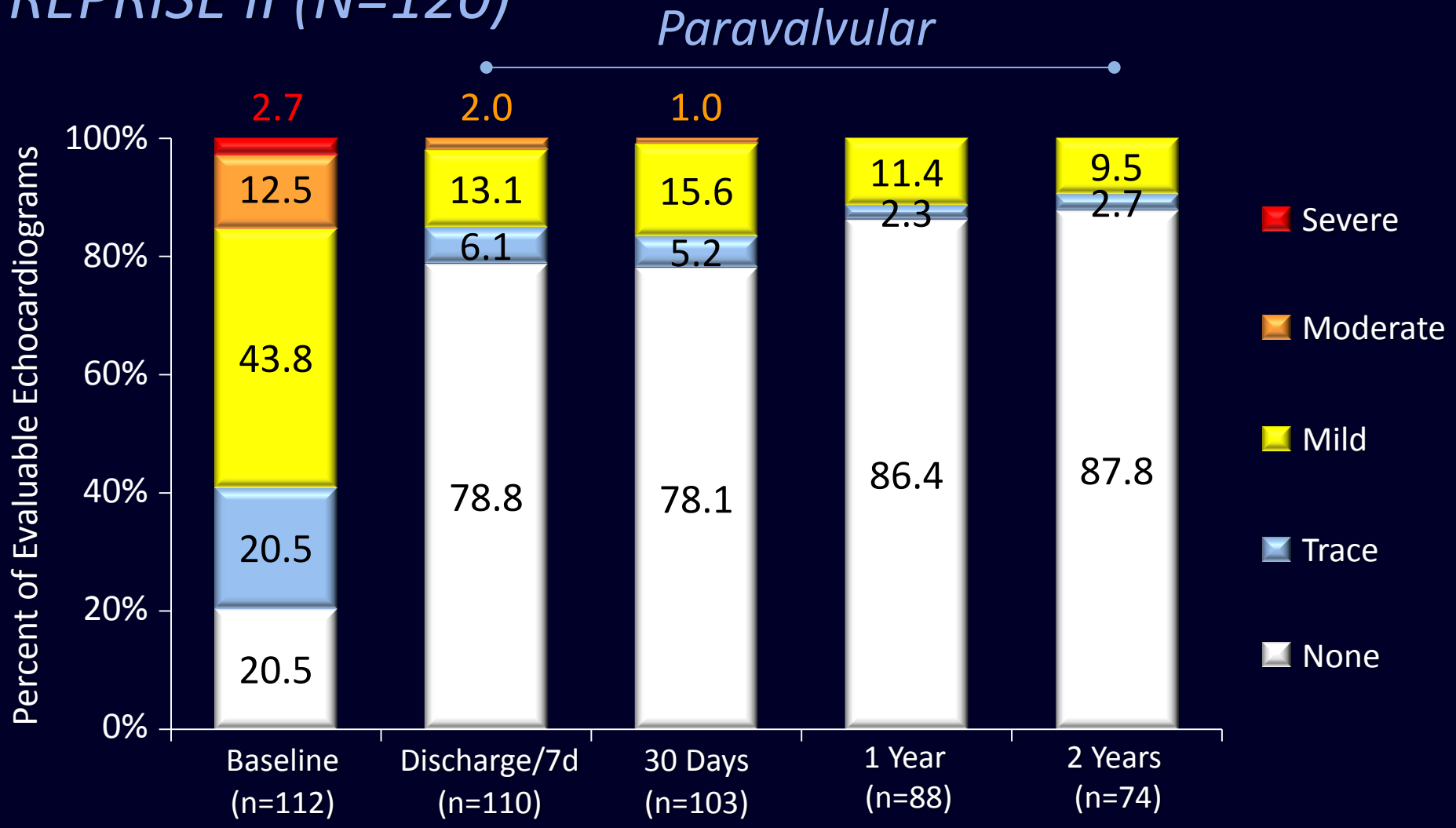
REPRISE II (N=120)



Kaplan-Meier rates. Individual values may not sum to cumulative values due to rounding.

Paravalvular Aortic Regurgitation

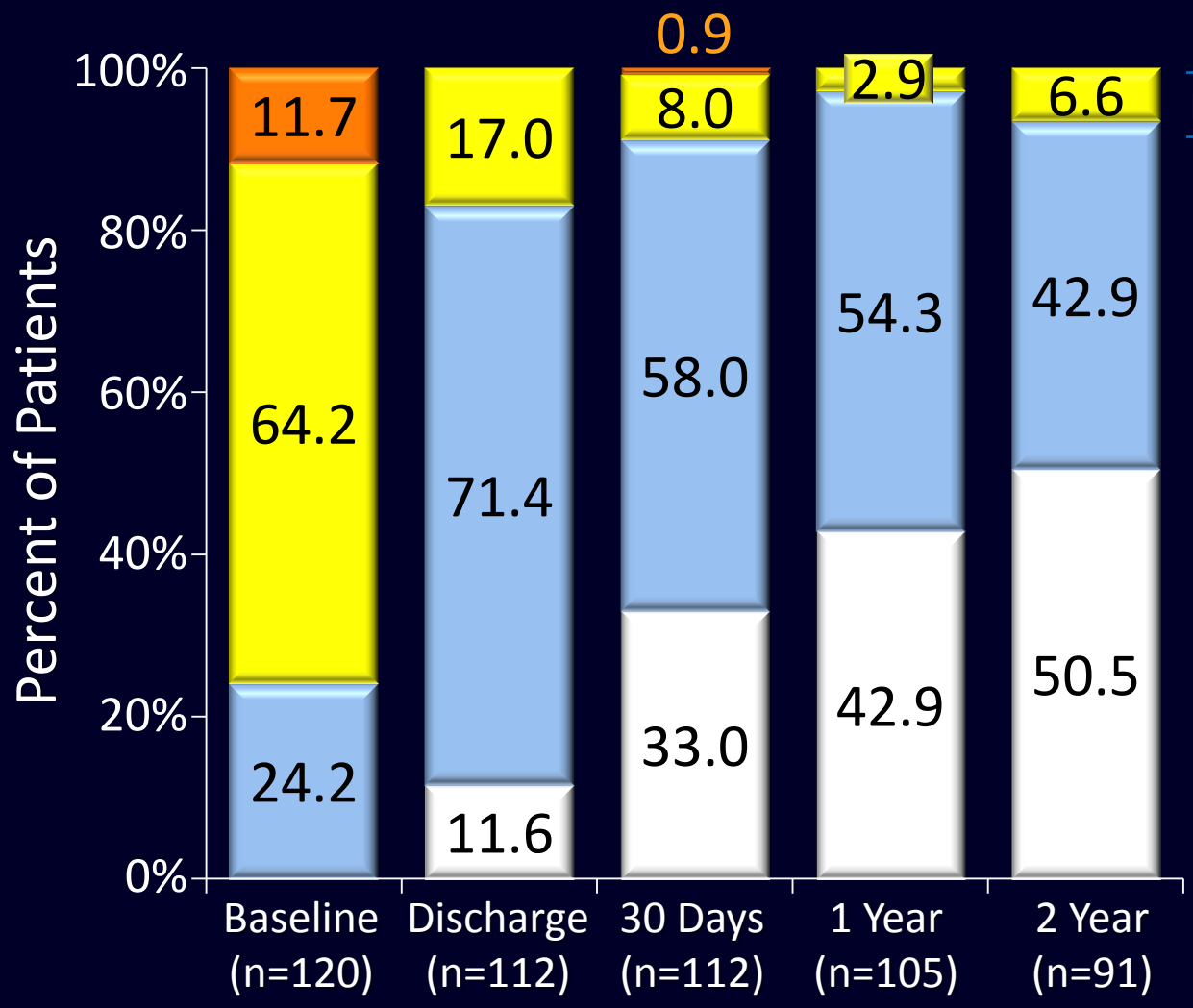
REPRISE II (N=120)



No moderate or severe paravalvular aortic regurgitation at 2 years

NYHA Class Changes Over Time

REPRISE II (N=120)



Measurement	*P* value
Baseline to Discharge	<0.001
Baseline to 2 Years	<0.001
Discharge to 30 Days	<0.001
1 Year to 2 Years	0.713

P values calculated from paired Wilcoxon signed-rank test

REPRISE II at 2 Years

Summary/Conclusions

At 2 years in the main 120-patient cohort:

- Sustained and excellent valve hemodynamic results
- >87% of patients without any paravalvular regurgitation
- No moderate or severe PVL in any patient
- Significant and sustained improvement in NYHA class functional status
- Adverse event rates consistent with those reported for other transcatheter valves

LOTUS Clinical Program

Reprise

✓REPRISE I	**Feasibility (Acute Safety, High Risk)** N=11; single arm; 23mm valve size 1° Endpoint: Device success (VARC) without MACCE	**3-yr f/u** **TCT 2015**
✓REPRISE II	**CE Mark Study (Safety & Performance, High Risk)** N=120; single arm; 23 & 27mm valve sizes 1° Endpts: 30-day mean pressure gradient & 30-day mortality	**2-yr f/u** **TCT 2015**
✓REPRISE II Extension	**Safety/Performance (High Risk)** N=130; single arm 23 & 27mm valve sizes → **REPRISE II Extended Cohort** N=250 1° Safety Endpt: 30-day mortality	**1-yr f/u** **PCR LV 2015**
RESPOND	**Post Market Study (Safety & Performance, All Comers)** N=1000; single arm; 23, 25, & 27mm valve sizes 1° Safety Endpoint: Mortality at 30 days & 1 year	**Enrolling Q2 2014**
REPRISE III	**FDA Approval (Safety & Effectiveness, High Risk & InOp)** N=1032; Global RCT; Lotus (23, 25, & 27mm) vs. CoreValve (26, 29, & 31mm) 1° Safety Endpoint: 30-day mortality, stroke, LT/major bleed, AKIN stage 2/3 or major vascular complications 1° Effectiveness Endpoint: 1-year mortality, stroke, LT bleed, disabling stroke or mod/severe PVL	**Enrolling Q3 2014**
REPRISE Japan	**PMDA Approval (Safety & Effectiveness, High Risk & InOp)** N=50; single arm; 23, 25, & 27mm valve sizes 1° Endpoint similar to REPRISE III; safety at 30d, effectiveness at 6 months	**Enrolling Q2 2015**