A Prospective, Randomised Investigation of a Novel Transcatheter Aortic Valve Implantation System: The REPRISE III Trial

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on behalf of the REPRISE III Investigators

16 May 2017 • Paris

Potential Conflicts of Interest

REPRISE III
Lotus™ Valve System

Speaker: Ted E. Feldman, MD

I have the following potential conflicts of interest to report:

- Institutional grant/research support: Abbott, Boston Scientific, Edwards Lifesciences
- Honoraria/consultation fees: Abbott, Boston Scientific, Edwards Lifesciences

The REPRISE III trial is sponsored and funded by Boston Scientific Corporation.

Background

REPRISE III
Lotus™ Valve System

- Transcatheter aortic valve implantation (TAVI): Well-established alternative to surgery for patients with severe aortic stenosis
- Current TAVI limitations include: Suboptimal deployment & paravalvular leak
- Lotus Valve System: Fully repositionable & retrievable TAVI device; Adaptive Seal to minimise PVL

Lotus Valve System

- Controlled mechanical expansion; rapid pacing not needed during deployment
- Early valve function; haemodynamic stability during implantation
- Complete assessment before release; reposition/retrieve if not acceptable

REPRISE III Trial Characteristics

DESIGN

- Global, prospective, multicentre, randomised, controlled, noninferiority trial to compare safety & effectiveness with the Lotus valve versus a self-expanding TAVI valve in patients at extreme or high surgical risk

PRIMARY / SECONDARY ENDPOINTS

- **Primary Safety:** Composite of all-cause mortality, stroke, life-threatening and major bleeding events, acute kidney injury (stage 2/3) and major vascular complications at 30 days
- **Primary Effectiveness:** Composite of all-cause mortality, disabling stroke, and moderate or greater paravalvular leak (core lab assessment) at 1 year
- **Secondary:** Moderate or greater PVL (core lab assessment) at 1 year

INDEPENDENT DATA ASSESSMENTS

- Clinical Events Committee
- Core Labs (Angiography & CT/X-ray, Echocardiography, ECG, Pathology)
- Independent Data Validation (primary, secondary & clinical endpoints)

REPRISE III Study Organization

PRINCIPAL INVESTIGATORS

Ted E. Feldman, MD, Evanston Hospital, Cardiology Division, Evanston, IL, USA

Michael J. Reardon, MD, Houston Methodist DeBakey Heart & Vascular Center, Houston, TX, USA

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), Baim Institute, Boston, MA, USA
Pathology	Renu Virmani, MD (Director), CV Path Institute, Inc., Gaithersburg, MD, USA

INDEPENDENT STUDY STATISTICIANS

Timothy Collier, MSc John Gregson, PhD	Department of Medical Statistics, London School of Hygiene & Tropical Medicine, London, UK

DATA MONITORING COMMITTEE

Stuart Pocock, PhD; Chair	Department of Medical Statistics, London School of Hygiene & Tropical Medicine, London, UK
David Faxon, MD	Brigham & Women's Hospital, Cardiovascular Division, Boston, MA, USA
Bernard Gersh, MB, ChB, DPhil	Mayo Clinic, Division of Cardiovascular Disease, Minneapolis, MN, USA
Steven Livesey, MD	Department of Cardiothoracic Surgery, Southampton General Hospital, Southampton, UK

CLINICAL EVENTS COMMITTEE

Sergio Waxman, MD (IC); Chair Gregory Smaroff, MD (CT Surg)	Lahey Clinic, Burlington, MA
Carey Kimmelstiel, MD (IC)	Tufts New England Medical Center, Boston, MA, USA
Roberto Rodriguez, MD (CT Surg)	Lankenau Hospital, Wynnewood, PA, USA
Viken Babikian, MD (Neurology)	Boston Medical Center, Boston, MA, USA

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REPRISE III Key Enrollment Criteria

REPRISE III
Lotus™ Valve System

Inclusion

- Symptomatic calcified native aortic stenosis
- NYHA Class ≥II; aortic annulus 20-27mm diameter
- STS score ≥8% and/or extreme or high surgical risk due to other specific criteria

Exclusion – Clinical

- AMI within 30 days
- Cerebrovascular accident or transient ischaemic attack within 6 months
- End-stage renal disease or GFR < 20 (based on Cockcroft-Gault formula)
- Cardiogenic shock or haemodynamic instability
- Any therapeutic invasive cardiac procedure within 30 days (except balloon aortic valvuloplasty or permanent pacemaker implantation)
- Untreated coronary artery disease requiring revascularisation
- 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
- 4+ aortic, mitral, or tricuspid regurgitation
- Femoral arterial access that is not acceptable for both test & control devices
- LVEF <20%

REPRISE III RCT Study Algorithm

Severe aortic stenosis; extreme or high operative risk
Annulus ≥20 mm and ≤27 mm; transfemoral access

Heart Team assessment → ← Case Review Committee confirmation

Randomised 2:1 (Lotus : CoreValve)
N=912

Neurologist examination‡ →

CoreValve† (26, 29 & 31mm)

Lotus Valve* (23, 25 & 27mm)

← *Neurologist examination*‡

- DAPT ≥1m *OR* warfarin + ASA or clopidogrel ≥1m (if anticoagulation needed)
- Clinical & echocardiographic follow-up: discharge or 7d, 30d, 6m, annually 1-5y

‡ Performed by a neurologist, neurology fellow, neurology physician assistant, or neurology nurse practitioner
† CoreValve platform (includes CoreValve Classic and Evolut R)
* Centres with no Lotus experience enrolled 2 roll-in patients before commencing enrollment of the evaluable cohort

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Enrollment

REPRISE III
Lotus™ Valve System

*912 patients between Sept 2014 & Dec 2015 at 55 centres**

Top 20	Patients		Patients
Vivek Rajagopal Piedmont Heart Institute, Atlanta, GA, USA	74	Gregory Mishkel St. John's Hospital, Springfield, IL, USA	25
Raj Makkar Cedars - Sinai Heart Institute, Los Angeles, CA, USA	66	David Rizik Scottsdale-Lincoln Health Network, Scottsdale, AZ, USA	22
Tanvir Bajwa Aurora St. Luke's Medical Center, Milwaukee, WI, USA	58	Vijay Iyer University at Buffalo/Gates Vascular Institute, Buffalo, NY, USA	20
Neal Kleiman Houston Methodist DeBakey Heart Center, Houston, TX, USA	54	Thomas Gleason University of Pittsburgh Medical Center, Pittsburgh, PA, USA	20
Axel Linke Herzzentrum Universität Leipzig, Leipzig, Germany	49	Didier Tchétché Clinique Pasteur, Toulouse, France	19
Dean Kereiakes The Christ Hospital Heart & Vascular Center, Cincinnati, OH, USA	43	Joshua Rovin Morton Plant Mease Healthcare System, Clearwater, FL, USA	19
Ted Feldman Evanston Hospital Cardiology Division, Evanston, IL, USA	38	John Giacomini Veteran's Administration Palo Alto Medical Cntr, Palo Alto, CA, USA	19
Ron Waksman Washington Hospital Center, Washington, D.C., USA	33	Robert Gooley Monash Medical Centre, Clayton, Victoria, Australia	17
Vinod Thourani Emory University Hospital, Atlanta, GA, USA	27	Didier Carrié Centre Hôpital Universitaire Rangueil, Toulouse, France	17
Robert Stoler Baylor Heart & Vascular Hospital, Dallas, TX, USA	26	Robert Bersin Swedish Medical Center, Seattle, WA, USA	17

* United States (792), Germany (53), France (36), Australia (23), The Netherlands (6) & Canada (2)

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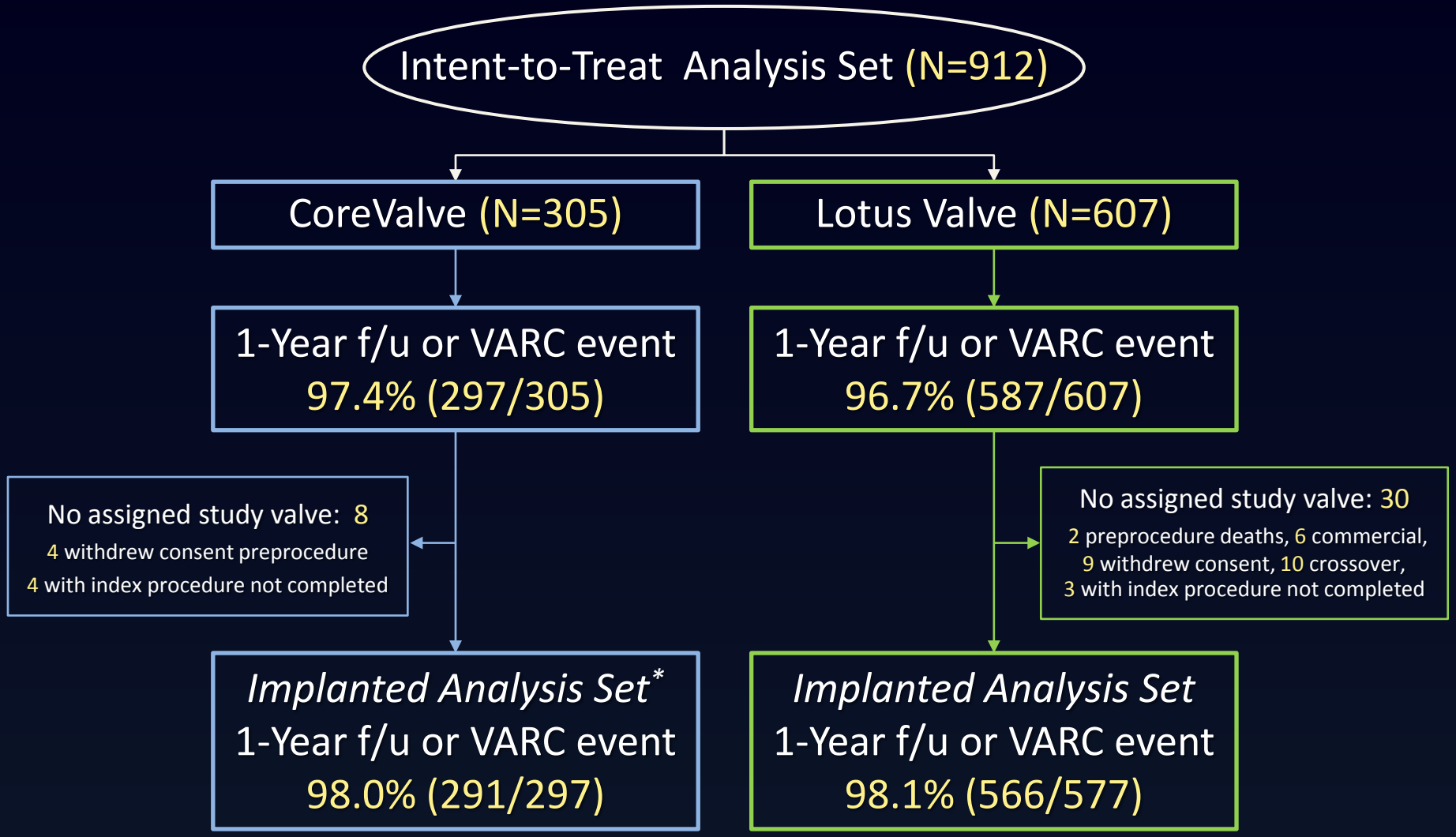
Patient Flow

REPRISE III
Lotus™ Valve System

55 Centres: United States, Germany, France, Australia, The Netherlands, Canada



*153 CoreValve Classic, 144 CoreValve Evolut R

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Baseline Characteristics

REPRISE III
Lotus™ Valve System

Demographics & Comorbidities – Intent-to-Treat

	CoreValve (N=305)	*Lotus (N=607)*	*P Value*
Age, years	82.9±7.6 (305)	82.8±7.1 (607)	0.71
Female sex, %	52.1 (159)	50.1 (304)	0.56
STS score, %	6.9±4.1 (305)	6.7±4.0 (607)	0.49
EuroSCORE II, %	6.4±5.5 (304)	6.4±5.5 (605)	1.00
Extreme surgical risk, %	21.6 (66)	23.1 (140)	0.63
Diabetes, treated, %	32.6 (99)	30.9 (187)	0.60
CAD, %	73.4 (224)	71.5 (433)	0.53
Prior PCI/CABG, %	43.9 (134)	44.6 (271)	0.84
Prior MI, %	19.0 (58)	18.3 (109)	0.78
Atrial fibrillation, %	31.6 (96)	35.1 (213)	0.28
Pacemaker, %	19.0 (58)	17.8 (108)	0.65
Prior stroke, %	14.5 (44)	11.3 (68)	0.17
PVD, %	25.7 (78)	31.1 (187)	0.09
COPD, %	30.7 (93)	31.9 (191)	0.72

Values are % (n) or mean±SD (n)

Baseline Characteristics

Additional Risk Assessments – Intent-to-Treat

REPRISE III
Lotus™ Valve System

Qualifying Risk Criterion	*CoreValve (N=305)*	*Lotus (N=607)*	*P Value*
STS Score ≥ 8, %	29.5 (90)	31.0 (188)	0.65
STS Score < 8, %	70.5 (215)	69.0 (419)	0.65
CABG – reoperation risk, %	20.0 (43)	16.0 (67)	0.21
Severe lung disease, %	14.0 (30)	15.3 (64)	0.66
Orthopaedic disease, %	12.6 (27)	18.6 (78)	0.05
Age ≥ 90 years, %	12.6 (27)	10.0 (42)	0.33
Severe pulmonary hypertension, %	8.4 (18)	8.1 (34)	0.91
Hostile chest, %	4.7 (10)	4.1 (17)	0.73
Prior chest radiation therapy, %	3.7 (8)	4.1 (17)	0.84
Porcelain aorta, %	3.3 (7)	4.5 (19)	0.44
Neuromuscular disease, %	2.3 (5)	1.4 (6)	0.52
Frailty*, %	70.7 (152)	72.6 (304)	0.62

Values are % (n)

* Has at least one of the following: 5-metre walk >6 sec, Katz score of 3/6 or less, BMI <21, wheelchair bound, cannot live independently

Baseline Echocardiography
Core Lab Data – Intent-to-Treat

REPRISE III
Lotus™ Valve System

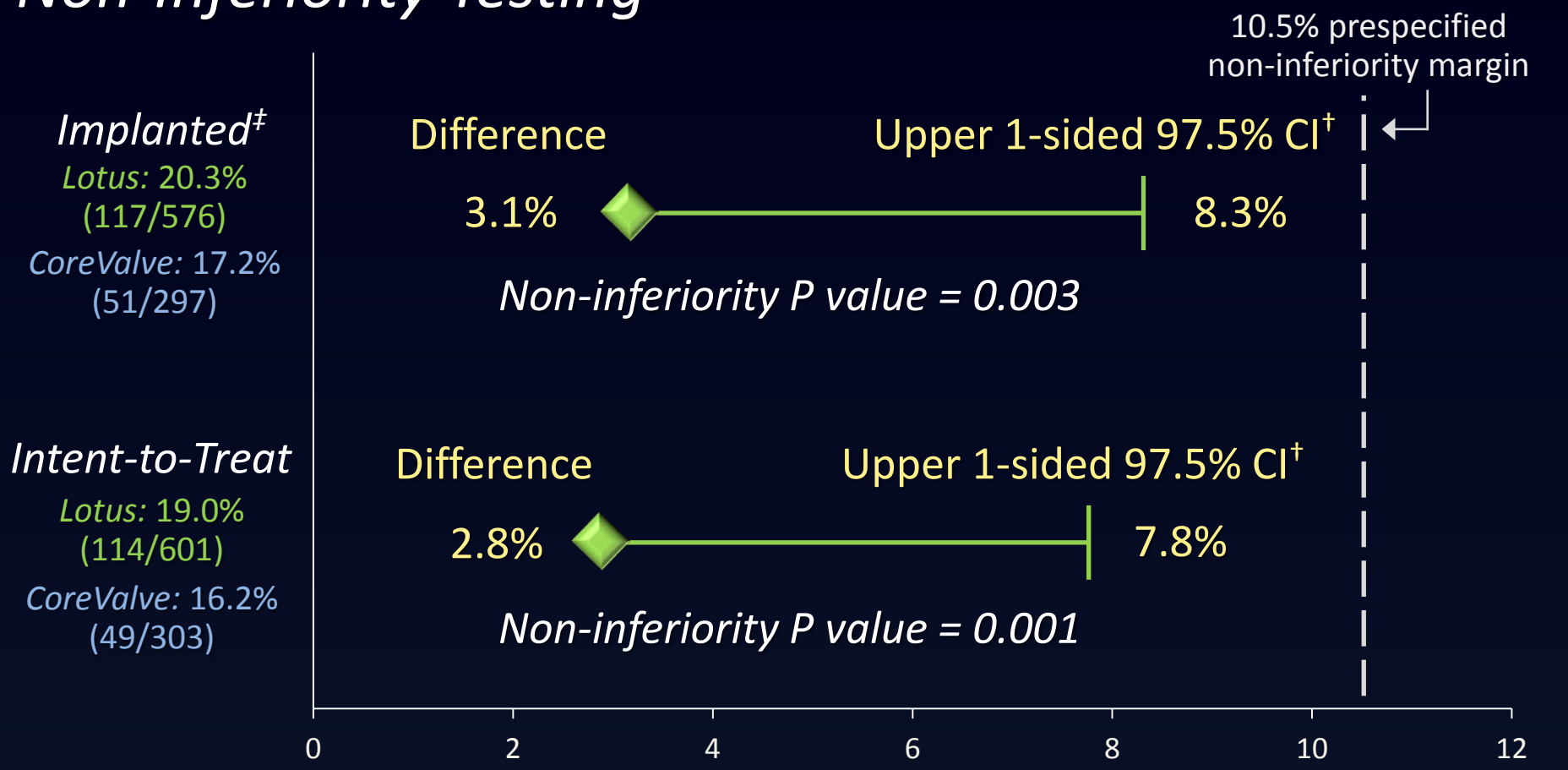
	CoreValve (N=305)	*Lotus (N=607)*	*P Value*
Aortic valve area (cm^2)	0.70±0.19 (280)	0.69±0.19 (541)	0.33
Aortic regurgitation (mod/sev), %	8.3 (24/290)	6.4 (36/562)	0.64
Mean aortic gradient (mmHg)	43.9±12.3 (294)	44.6±13.4 (575)	0.40
Peak aortic gradient (mmHg)	72.4±18.1 (294)	73.6±20.8 (575)	0.40
Mitral regurgitation (mod/sev), %	11.7 (33/283)	10.7 (59/554)	0.66
LVEF (%)	55.9±11.8 (254)	56.1±11.4 (485)	0.80
Doppler velocity index	0.23±0.05 (292)	0.22±0.05 (553)	0.01

Values are % (n/N) or mean±SD (n)

Primary Composite Safety Endpoint*

Non-Inferiority Testing

REPRISE III
Lotus™ Valve System



*All-cause mortality, stroke, life-threatening/major bleed, stage 2/3 AKI, major vascular complications at 30 days

→ *Non-inferiority criteria met for primary safety endpoint*

‡ Primary analysis set - enrolled patients implanted with the assigned valve
† Upper 1-sided CI and *P* value are derived from the Farrington-Manning test

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Primary Composite Safety Endpoint

1 Year – Intent-to-Treat

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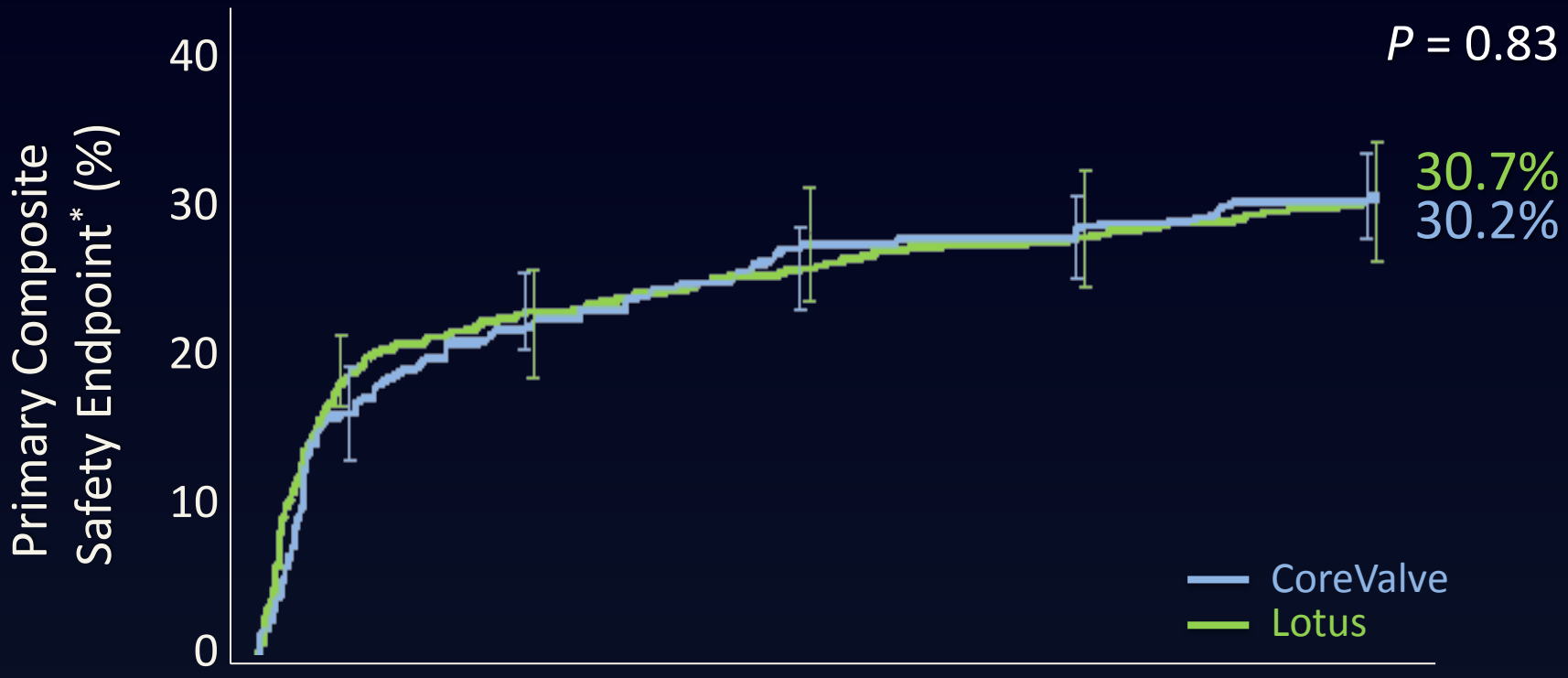
Lotus™ Valve System



No. at risk	0	30	90	180	270	365	Days
CoreValve	305	253	233	215	207	165	
Lotus	607	485	456	438	419	334	

*All-cause mortality, stroke, life-threatening/major bleed, stage 2/3 AKI, major vascular complications

ITT; KM Event Rate ± 1.5 SE; log-rank *P* value

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Outcomes – 30 Days
Intent-to-Treat

REPRISE III
Lotus™ Valve System

		CoreValve (N=305)	Lotus (N=607)	P Value
Primary Composite Safety Endpoint	All-cause mortality, %	2.3 (7)	2.5 (15)	0.86
	Stroke, %	4.3 (13)	4.8 (29)	0.72
	Disabling, %	3.3 (10)	2.0 (12)	0.23
	Life threatening bleeding, %	5.0 (15)	8.0 (48)	0.09
	Major bleeding, %	5.9 (18)	4.8 (29)	0.48
	Major vascular complications, %	5.3 (16)	7.0 (42)	0.32
	AKI (Stage 2/3 ≤7d), %	3.6 (11)	2.5 (15)	0.34
	New pacemaker, %	15.8 (48)	29.1 (175)	<0.001
	With no prior pacemaker, %	19.6 (48)	35.5 (175)	<0.001
	TAV-in-TAV deployment*, %	3.0 (9)	0.0 (0)	<0.001
	Aortic valve malpositioning*, %	2.6 (8)	0.0 (0)	<0.001

*Procedural; includes valve migration, valve embolization & ectopic valve deployment to discharge/7 days

Values are % (n); binary event rates

Primary Effectiveness–Non-inferiority

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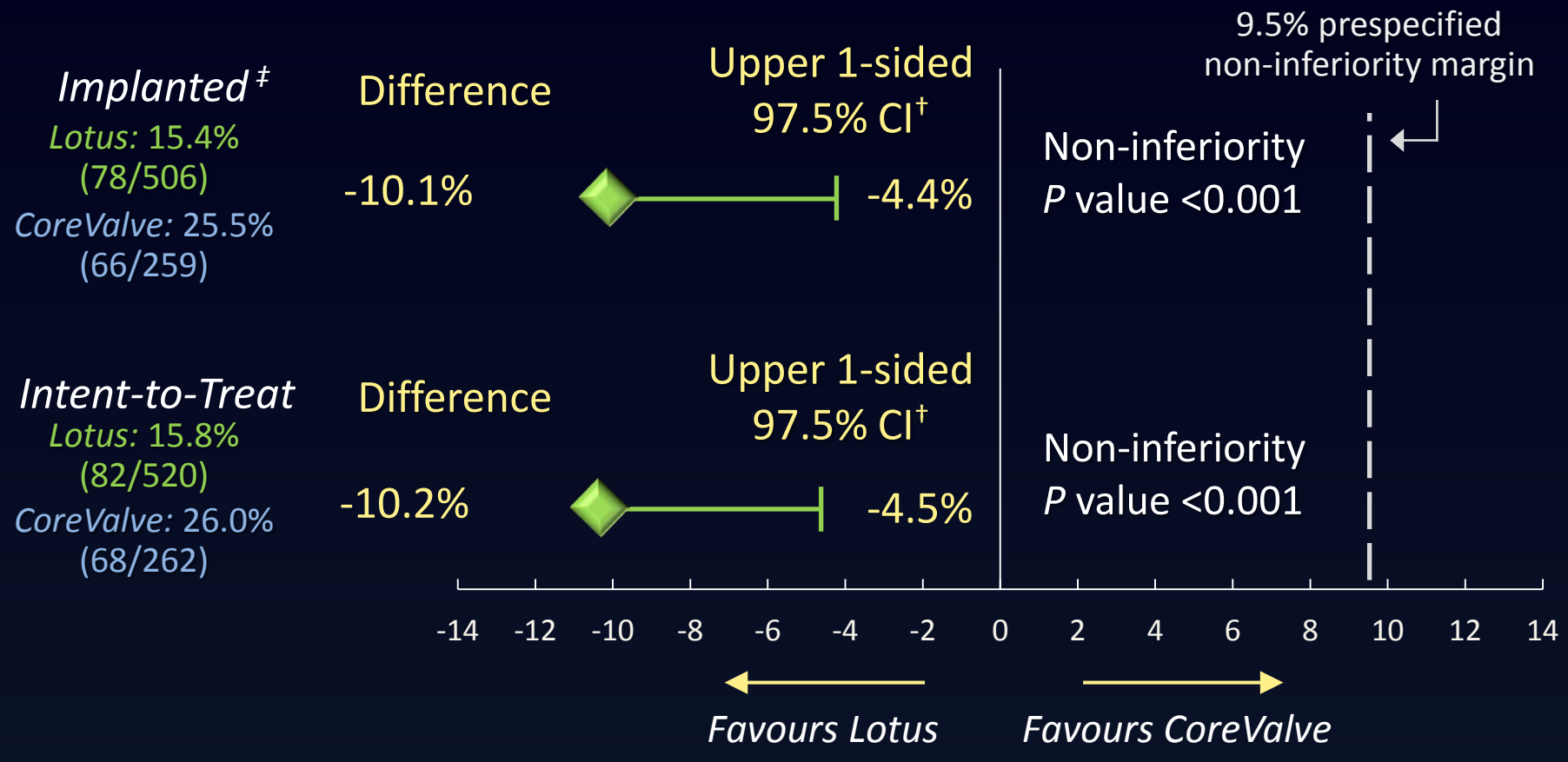
Lotus™ Valve System

Death, Disabling Stroke, ≥ Moderate PVL at 1 Year



Non-inferiority criteria met for primary effectiveness endpoint

‡ Primary analysis set - enrolled patients implanted with the assigned valve

† Upper 1-sided CI and *P* value are derived from the Farrington-Manning test

Moderate or greater PVL is based on core lab assessment

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Primary Effectiveness – Superiority

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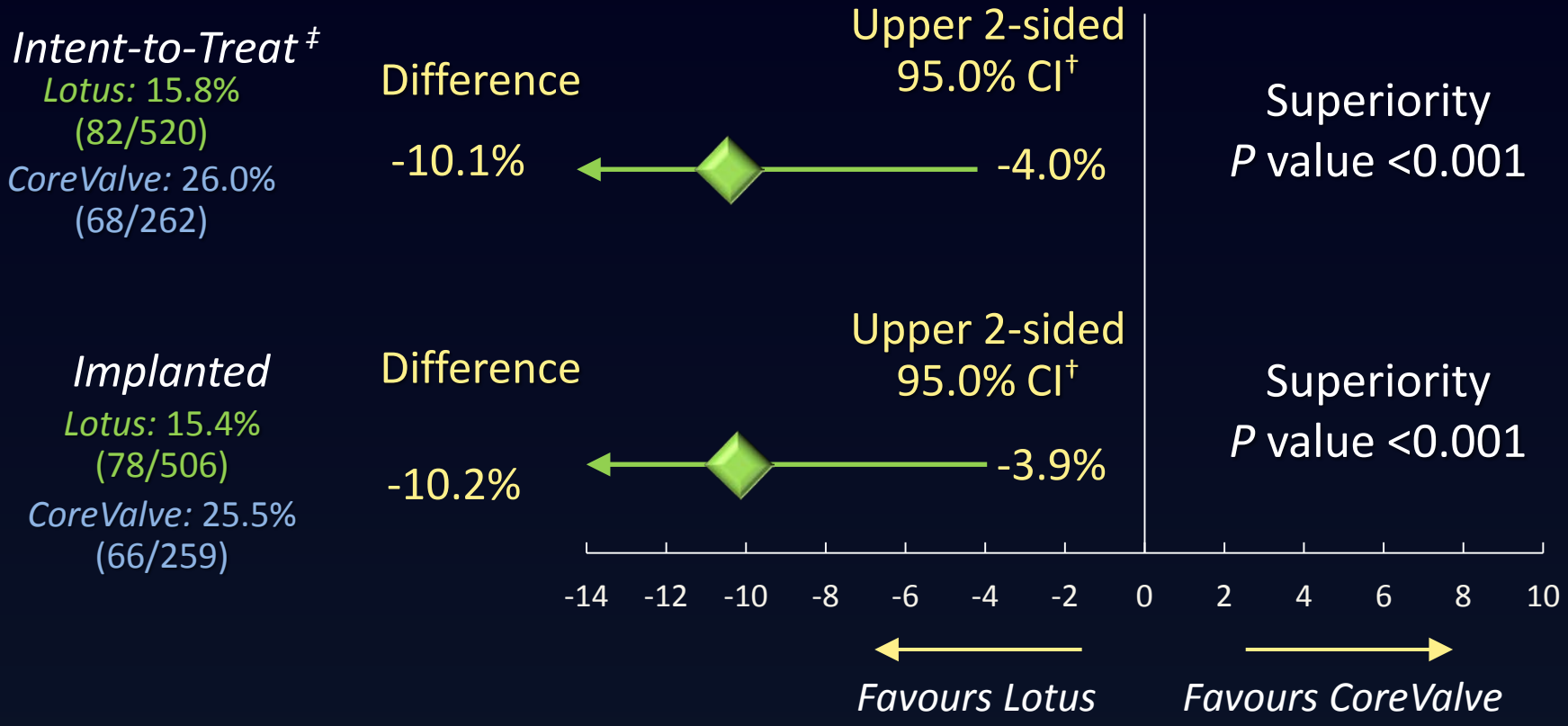
Lotus™ Valve System

Death, Disabling Stroke, ≥ Moderate PVL at 1 Year



Superiority achieved for primary effectiveness endpoint

‡ Primary analysis set

† Superiority *P* value and 95% CI are derived from the Chi-square test

Primary Effectiveness Endpoint
Components at 1 Year – Intent-to-Treat

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Lotus™ Valve System

	CoreValve (N=305)	*Lotus (N=607)*	*P Value*
All-cause mortality*	13.5% (40/297)	11.9% (70/587)	0.51
Cardiac death	9.8% (29/297)	7.7% (45/587)	0.29
Stroke†	9.4% (28/297)	7.0% (41/587)	0.20
Disabling*	7.1% (21/297)	3.6% (21/587)	0.02
Moderate or greater PVL*	6.9% (15/216)	0.9% (4/452)	<0.001

* Component of the primary effectiveness endpoint

† All patients had a neurological examination conducted by a neurology professional at baseline, discharge, 1 year, and after any suspected stroke. All patients also had NIHSS at discharge and 1 year and mRS at baseline and all f/u time points.

All-cause Mortality

1 Year – Intent-to-Treat

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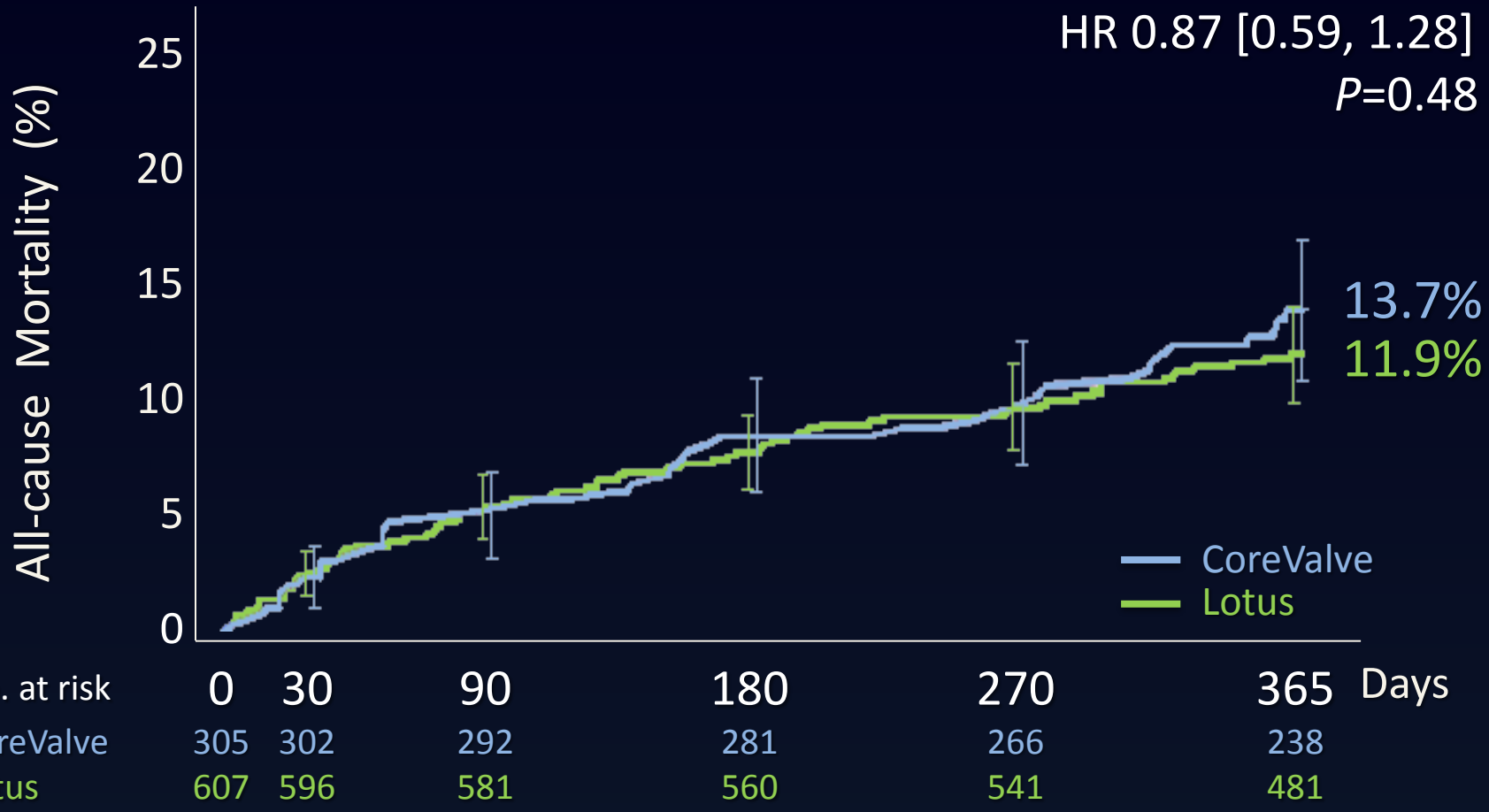
Lotus™ Valve System



ITT; KM Event Rate ± 1.5 SE; log-rank *P* value

All-Cause Mortality/Disabling Stroke

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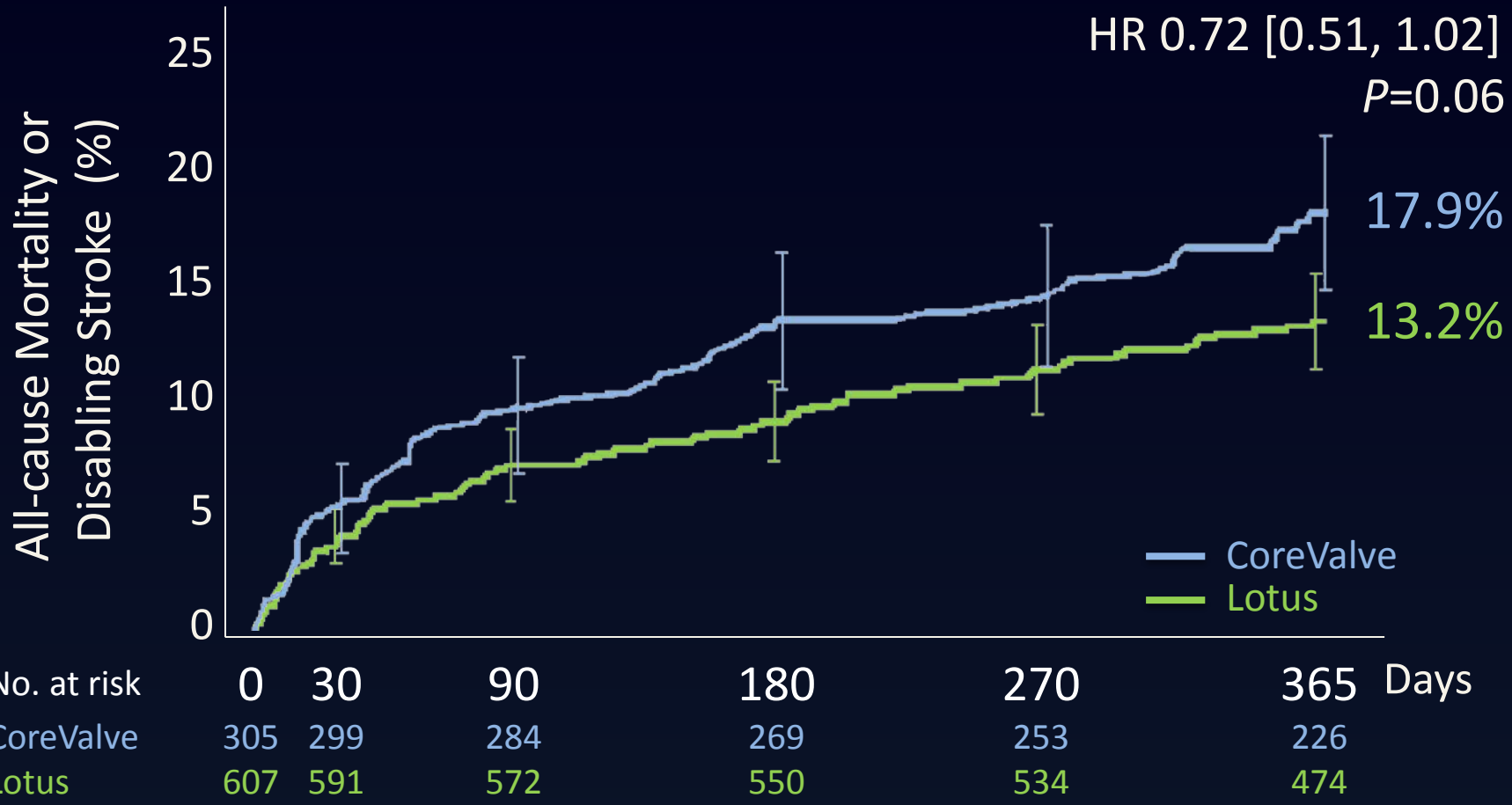
Lotus™ Valve System

1 Year – Intent-to-Treat



ITT; KM Event Rate ± 1.5 SE; log-rank *P* value

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Disabling Stroke

1 Year – Intent-to-Treat

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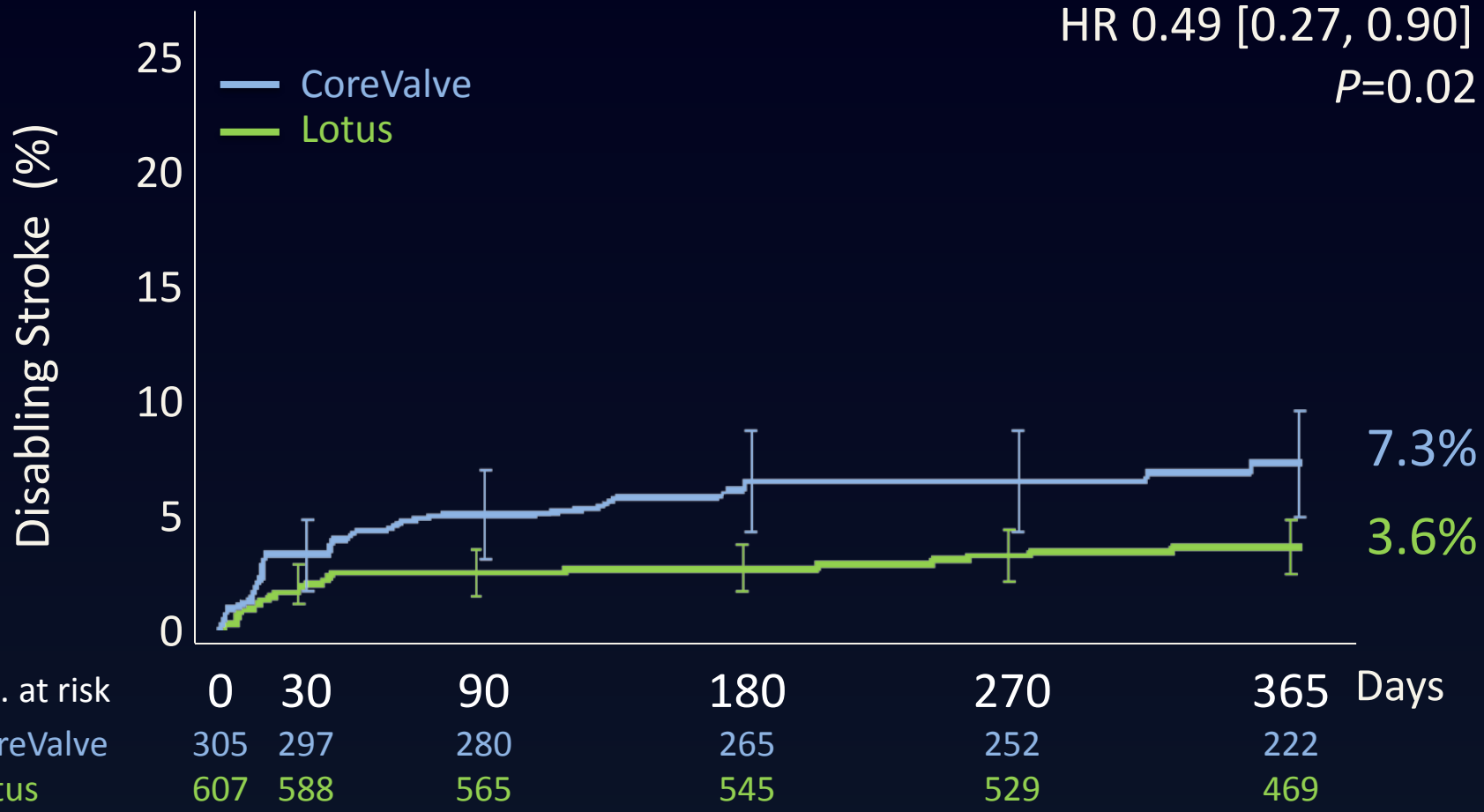
Lotus™ Valve System



ITT; KM Event Rate ± 1.5 SE; log-rank *P* value

Additional VARC Events at 1 Year
Intent-to-Treat

REPRISE III
Lotus™ Valve System

	CoreValve (N=305)	*Lotus (N=607)*	*P Value*
Myocardial infarction, %	4.4 (13)	3.2 (19)	0.39
Life threatening bleeding, %	9.8 (29)	9.9 (58)	0.96
Major bleeding, %	8.4 (25)	8.3 (49)	0.97
New onset atrial fibrillation, %	4.7 (14)	6.6 (39)	0.25
Hospitalisation*, %	13.8 (41)	11.2 (66)	0.27
Endocarditis, %	0.0 (0)	0.7 (4)	0.31
Valve thrombosis, %	0.0 (0)	1.5 (9)	0.03
Repeat procedure†, %	2.0 (6)	0.2 (1)	0.007

* Hospitalisation for valve-related symptoms or worsening congestive heart failure (NYHA class III or IV)
† Repeat procedure for valve-related dysfunction
Values are % (n); binary event rates

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Paravalvular Leak at 1 Year

Core Lab Assessment – Intent-to-Treat

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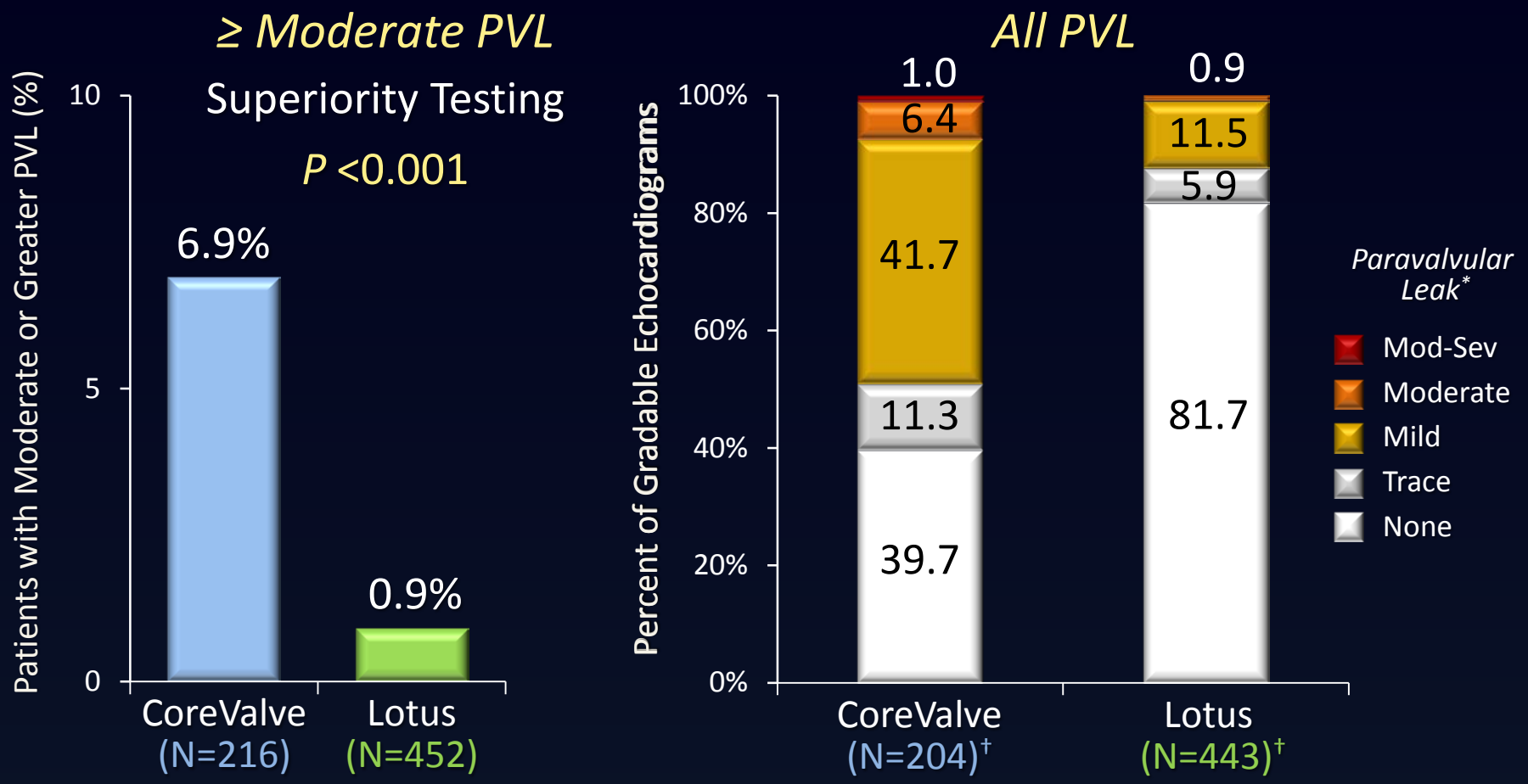
Lotus™ Valve System



→ *Superiority achieved for secondary endpoint*

* There were no cases of severe PVL (grading per Pibarot, et al. , *JACC Cardiovasc Imaging* 2015;8:340)

† For superiority testing, echocardiograms with less than moderate total aortic regurgitation and visible PVL that was not gradable were included in the group with less than moderate PVL. For reporting of all PVL, only echocardiograms with gradable PVL were included.

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Haemodynamics
Core Lab Data

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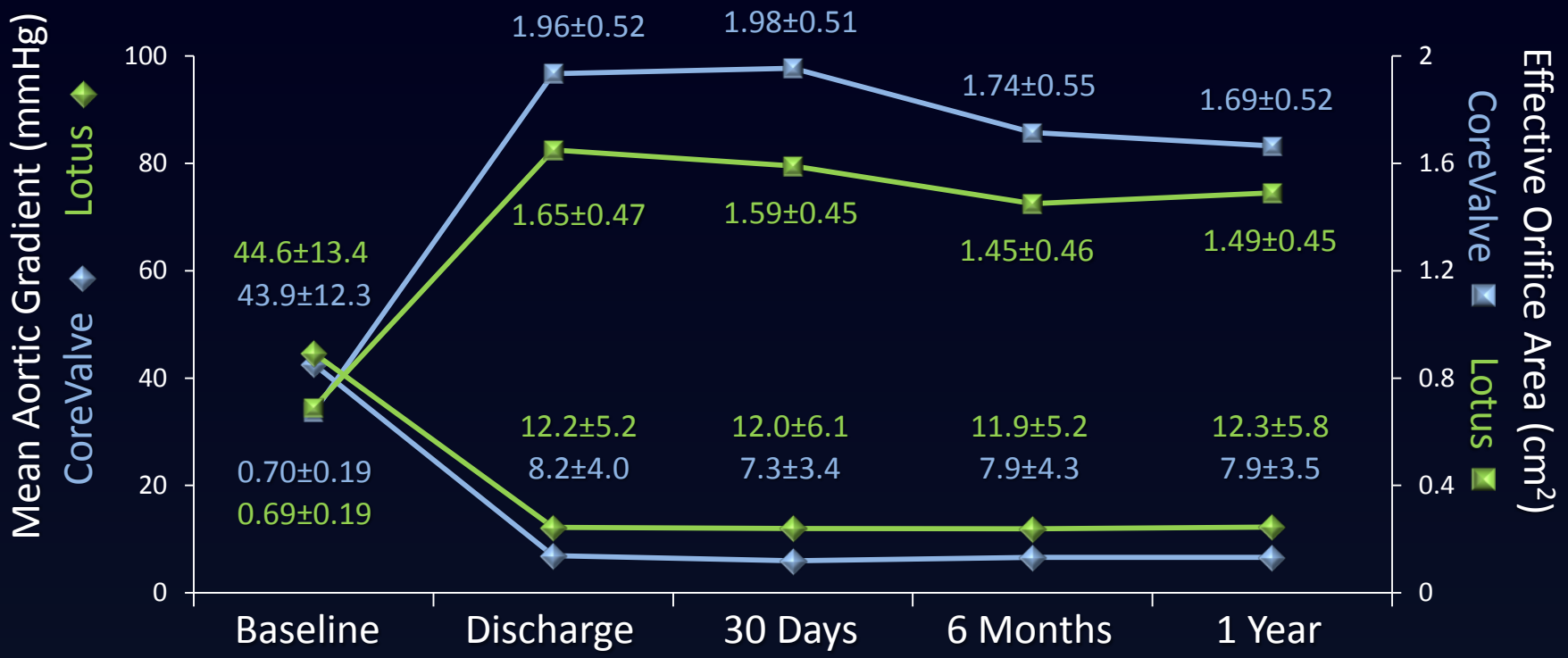
Lotus™ Valve System



Mean Aortic Gradient (mmHg)	294	281	261	233	219	CoreValve (N)
	575	564	543	484	461	Lotus (N)
Effective Orifice Area (cm^2)	280	247	238	209	199	CoreValve (N)
	541	510	505	439	419	Lotus (N)

Lotus vs CoreValve: *P* <0.001 at discharge and later time points

Values are mean±SD; intent-to-treat analysis set

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Summary

REPRISE III
Lotus™ Valve System

In this large global randomised trial comparing Lotus to CoreValve the Lotus Valve demonstrated:

- Noninferiority for the 30-day primary safety endpoint†
  - † All-cause mortality, stroke, life-threatening/major bleeding, stage 2/3 AKI and major vascular complications
- Superiority for the 1-year primary effectiveness endpoint‡
  - ‡ All-cause mortality, disabling stroke and moderate or greater PVL
- Less moderate or greater paravalvular leak
- Fewer disabling strokes
- Fewer repeat procedures
- More valve thrombosis
- More new pacemaker implantations
- Smaller valve areas and higher gradients
- Less TAV-in-TAV deployment and less valve malpositioning