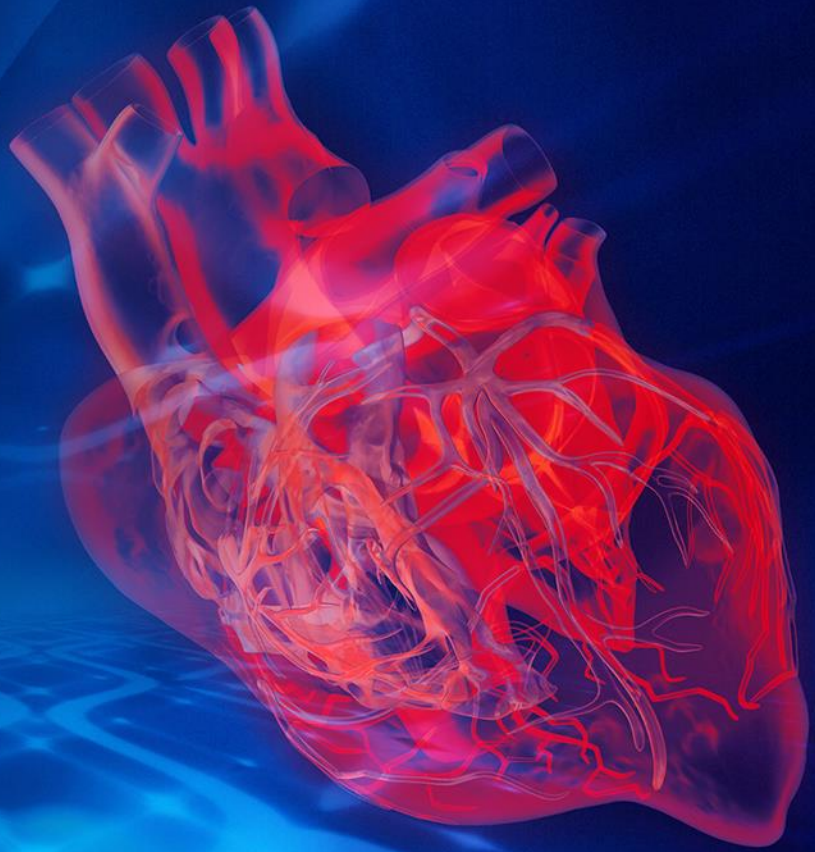
TRISCEND II Trial: A Randomized Trial of Transcatheter Tricuspid Valve Replacement in Patients with Severe Tricuspid Regurgitation



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Columbia University Irving Medical Center, New York, New York, USA

on behalf of the **TRISCEND II Trial** investigators

THE TRISCEND II PIVOTAL TRIAL

CRF TCT

Disclosure Statement of Financial Interest

Within the past 12 months, I or my spouse/partner have had a financial interest/arrangement or affiliation with the organization(s) listed below.

Affiliation/Financial Relationship	Company
Grant/Research Support	Edwards Lifesciences, Medtronic, Boston Scientific, Abbott Vascular, JenaValve
Consulting Fees/Honoraria	Anteris, Dura Biotech, Shifamed, Tricares, Phillips, Nyra Medical, Helix Valve Repair
Equity	Thubrikar Aortic Valve, Inc, Dura Biotech, Supira, MID, TriFlo, Adona, Tioga, Xdot, Moray Medical, Cardiomech

Background

- Although historically underappreciated, the importance of severe tricuspid regurgitation (TR) in leading to debilitating symptoms and poor outcomes is being increasingly recognized
- Treatment options for TR are limited, with medical therapy being suboptimal and surgery having high rates of morbidity and mortality
- There is an unmet need for transcatheter solutions that provide treatment options at lower risk and result in improved outcomes

EVOQUE Transcatheter Tricuspid Valve Replacement System

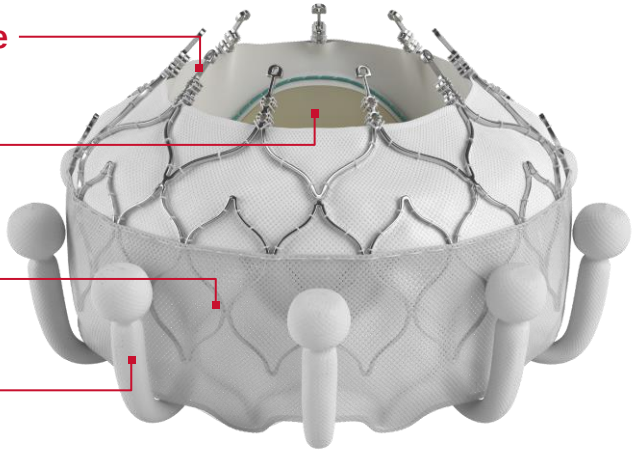
EVOQUE Valve

Nitinol self-expanding frame

Bovine pericardial tissue

Intra-annular sealing skirt

9 ventricular anchors



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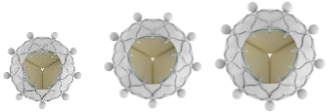


44 mm 48 mm 52 mm

EVOQUE Delivery System

Transfemoral

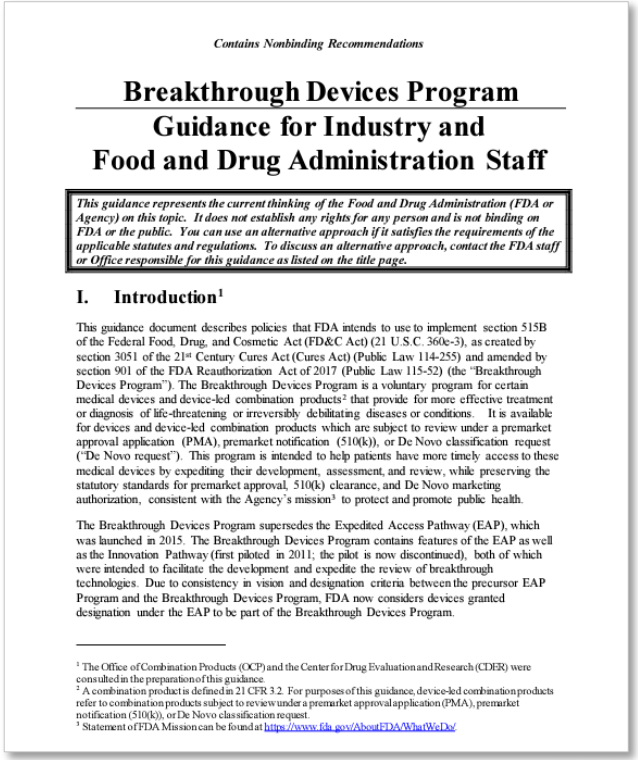
28 Fr outer diameter

3 planes of movement

EVOQUE Tricuspid Valve Replacement System Received FDA Breakthrough Designation

FDA Breakthrough Designation

- Designed to provide patients with timely access to new devices for life-threatening or irreversibly debilitating conditions
- May accept greater uncertainty if probable benefits outweigh probable risk of harm



Contains Nonbinding Recommendations

Breakthrough Devices Program
Guidance for Industry and
Food and Drug Administration Staff

This guidance represents the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff or Office responsible for this guidance as listed on the title page.

I. Introduction[1]

This guidance document describes policies that FDA intends to use to implement section 515B of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 360e-3), as created by section 3051 of the 21st Century Cures Act (Cures Act) (Public Law 114-255) and amended by section 901 of the FDA Reauthorization Act of 2017 (Public Law 115-52) (the "Breakthrough Devices Program"). The Breakthrough Devices Program is a voluntary program for certain medical devices and device-led combination products[2] that provide for more effective treatment or diagnosis of life-threatening or irreversibly debilitating diseases or conditions. It is available for devices and device-led combination products which are subject to review under a premarket approval application (PMA), premarket notification (510(k)), or De Novo classification request ("De Novo request"). This program is intended to help patients have more timely access to these medical devices by expediting their development, assessment, and review, while preserving the statutory standards for premarket approval, 510(k) clearance, and De Novo marketing authorization, consistent with the Agency's mission[3] to protect and promote public health.

The Breakthrough Devices Program supersedes the Expedited Access Pathway (EAP), which was launched in 2015. The Breakthrough Devices Program contains features of the EAP as well as the Innovation Pathway (first piloted in 2011; the pilot is now discontinued), both of which were intended to facilitate the development and expedite the review of breakthrough technologies. Due to consistency in vision and designation criteria between the precursor EAP Program and the Breakthrough Devices Program, FDA now considers devices granted designation under the EAP to be part of the Breakthrough Devices Program.

[1] The Office of Combination Products (OCP) and the Center for Drug Evaluation and Research (CDER) were consulted in the preparation of this guidance.
[2] A combination product is defined in 21 CFR 3.2. For purposes of this guidance, device-led combination products refer to combination products subject to review under a premarket approval application (PMA), premarket notification (510(k)), or De Novo classification request.
[3] Statement of FDA Mission can be found at https://www.fda.gov/AboutFDA/WhatWeDo/

https://www.fda.gov/regulatory-information/search-fda-guidance-documents/breakthrough-devices-program

TRISCEND II: Two-Part Study Design Based on the Breakthrough Designation

THE TRISCEND II PIVOTAL TRIAL

‘First 150’
First 150 patients randomized and treated

Total Cohort
N = 400
All-randomized patients

Enrolled, follow-up ongoing

Primary Endpoints	First 150	Total Cohort
Safety (30 Days) • Composite MAE rate	✓	✓
Effectiveness (6 Months) • TR grade reduction • Hierarchical composite of KCCQ, NYHA and 6MWD	✓	✓
Hierarchical Composite (1 Year) 1. All-cause mortality 2. RVAD implant or heart transplant 3. TV surgery or intervention 4. Annualized heart failure hospitalization 5. KCCQ, NYHA, 6MWD		✓

✓✓ **Prespecified analysis**

6MWD, 6-minute walk distance; *KCCQ*, Kansas City Cardiomyopathy Questionnaire; *MAE*, major adverse event; *NYHA*, New York Heart Association; *RVAD*, right ventricular assist device; *TR*, tricuspid regurgitation; *TV*, tricuspid valve

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✓ **Prespecified analysis**

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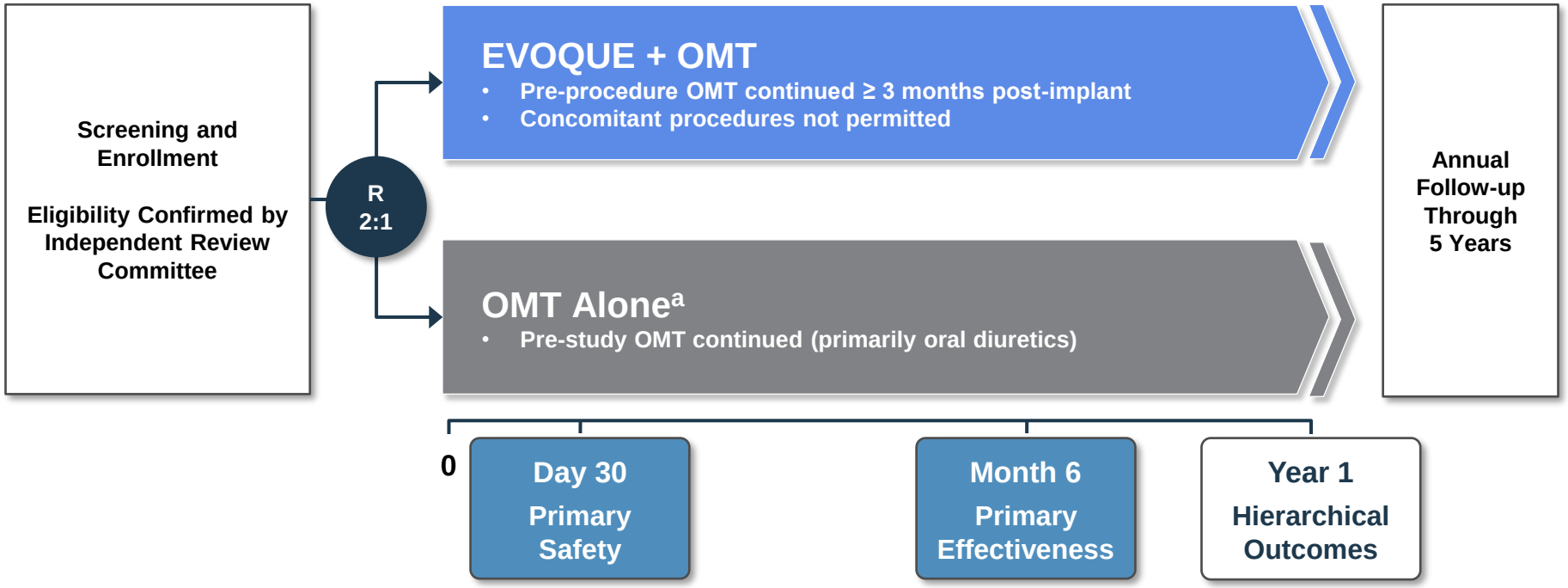
TRISCEND II Trial Design



[a]Patients randomized to OMT alone may be eligible for treatment with the EVOQUE system following 1- or 2-year follow-up visits.
OMT, optimal medical therapy; *R*, randomization

Trial Leadership & Oversight

THE TRISCEND II PIVOTAL TRIAL

TRICUSPID PROGRAM LEADERSHIP

Martin Leon, MD

Michael Mack, MD

GLOBAL PRINCIPAL INVESTIGATORS

Rebecca Hahn, MD

Susheel Kodali, MD

Philipp Lurz, MD, PhD

Vinod Thourani, MD

TRIAL OVERSIGHT

Steering Committee

- **Teresa De Marco, MD**
- **Jörg Hausleiter, MD**
- **Yoshi Kaneko, MD**
- **Mark Reisman, MD**
- **Tom Smith, MD**
- **Ralph Stephan von Bardeleben, MD, PhD**
- **Firas Zahr, MD**

Echocardiographic Core Laboratory, *Baylor Scott & White, Plano, TX, USA*

- **Paul Grayburn, MD**
- **Anna Sannino, MD, PhD**

Clinical Events Committee (CEC)

- **Carey D. Kimmelstiel, MD**, *Interventional Cardiologist*
- **Gregory Smaroff, MD**, *Cardiothoracic Surgeon*
- **Pablo A. Quintero Pinzon, MD**, *Cardiologist, Heart Failure*
- **David E. Thaler, MD, PhD**, *Neurologist*

Data Safety Monitoring Board (DSMB)

- **Eugene A. Grossi, MD**, *Cardiothoracic Surgery*
- **John Lopez, MD**, *Interventional Cardiology*
- **Michael M. Givertz, MD**, *Cardiology / Heart Failure*
- **Frederick S. K. Ling, MD**, *Interventional Cardiology / Cardiovascular Disease*
- **John Orav, PhD**, *Biostatistics*

Central Screening Committee (CSC)

Cardiac Surgery

- **S. Chris Malaisrie, MD**
- **Robert L. Smith, MD**
- **Howard K. Song, MD, PhD**

Heart Failure

- **Aasim Afzal, MD**
- **Shirin Jimenez, MD**
- **Johannes Steiner, MD**

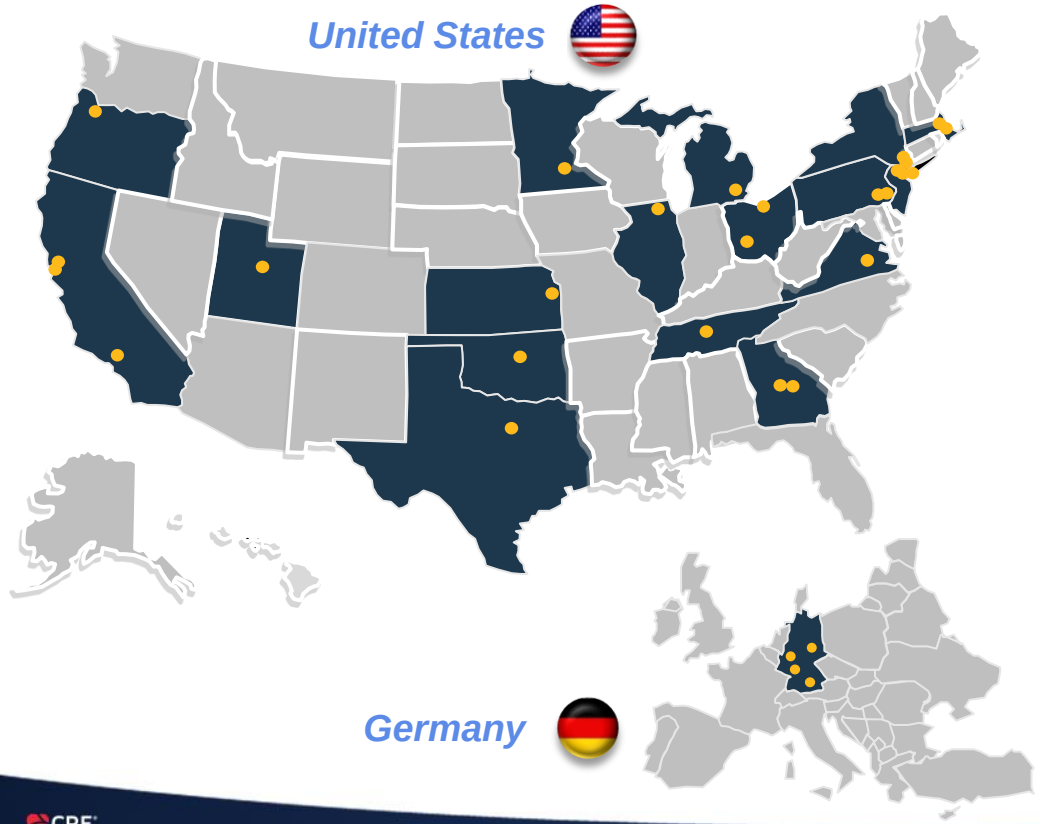
Echocardiography

- **Paul Grayburn, MD**
- **Anna Sannino, MD, PhD**
- **Thomas Smith, MD**

Interventional Cardiology

- **Colin Barker, MD**
- **Charles Davidson, MD**
- **Mackram Eleid, MD**
- **Sammy Elmariah, MD**
- **Marvin Eng, MD**
- **Neil Fam, MD**
- **Jörg Hausleiter, MD**
- **D. Scott Lim, MD**
- **Raj Makkar, MD**
- **Andrew Rassi, MD**
- **Mark Reisman, MD**
- **Volker Rudolph, MD**
- **Rahul Sharma, MD**
- **Brian Whisenant, MD**
- **Pradeep Yadav, MD**
- **Firas Zahr, MD**
- **Ralph Stephan von Bardeleben, MD, PhD**

30 Enrolling Sites



United States			
CA	• Cedars Sinai Medical Center • Kaiser Permanente San Francisco • Stanford University	NY	• Columbia University Irving Medical Ctr/NYPH • Montefiore Medical Center • NYU Langone Health
GA	• Emory University Hospital • Piedmont Heart Institute	OH	• The Christ Hospital • Cleveland Clinic
IL	• Northwestern Medical Center	OK	• Oklahoma Heart Institute
KS	• Cardiovascular Research Institute of Kansas	OR	• Oregon Health & Science University
MA	• Brigham and Women's Hospital • Massachusetts General Hospital	PA	• Lankenau Heart Institute • University of Pennsylvania
		TN	• Vanderbilt University Medical Center
MI	• Henry Ford Hospital	TX	• Baylor Heart Hospital Plano
MN	• Mayo Clinic	UT	• Intermountain Medical Center
NJ	• Morristown Medical Center • Rutgers Robert Wood Johnson Medical	VA	• University of Virginia Health System Hospital

Germany

- Herzzentrum Leipzig GmbH
- Herzzentrum Universitätsklinik Bonn
- Johannes Gutenberg-Universität Mainz
- Klinikum der Universität München - Großhadern

All enrolling sites for 'First 150' patients

Top Enrolling Sites

Rank	Principal Investigator | Site
1	**Raj Makkar, MD** | Cedars-Sinai Medical Center, Los Angeles, CA
2	**Charles J. Davidson, MD** | Northwestern University, Chicago, IL
3	**Rahul Sharma, MBBS** | Stanford University Medical Center, Palo Alto, CA
4	**Pradeep Yadav, MD; Vinod Thourani, MD** | Piedmont Heart Institute, Atlanta, GA
5	**Susheel K. Kodali, MD** | Columbia University Irving Medical Center, New York, NY
6	**Firas Zahr, MD** | Oregon Health & Science University, Portland, OR
7	**William W. O'Neill, MD** | Henry Ford Hospital, Detroit, MI
8	**Mackram F. Eleid, MD** | Mayo Clinic, Rochester, MN
9	**D. Scott Lim, MD** | University of Virginia Health System Hospital, Charlottesville, VA
10	**Colin Barker, MD** | Vanderbilt University Medical Center, Nashville, TN
11	**Jörg Hausleiter, MD** | Klinikum der Universität München, Munich, Germany
12	**Azeem Latib, MD** | Montefiore Medical Center, Bronx, NY
13	**Pinak B. Shah, MD** | Brigham and Women's Hospital, Boston, MA
14	**Ignacio Inglessis-Azuaje, MD** | Massachusetts General Hospital, Boston, MA
15	**Robert Kipperman, MD** | Morristown Medical Center, Morristown, NJ
16	**Ralph Stephan von Bardeleben, MD, PhD** | Johannes Gutenberg Universität Mainz, Mainz, Germany
17	**Philipp Lurz, MD, PhD** | Heart Center Leipzig at University of Leipzig, Leipzig, Germany
18	**Georg Nickenig, MD** | Universitätsklinikum Bonn, Bonn, Germany

Key Inclusion and Exclusion Criteria Allowed for Identification of Patients with at Least Severe TR

THE TRISCEND II PIVOTAL TRIAL

Inclusion Criteria

- Age ≥ 18 years
- Signs / symptoms of TR or prior heart failure hospitalization
- Receiving OMT at the time of TR assessment
- Functional and/or degenerative TR graded as at least severe on a TTE
- Local Heart Team determines patient is appropriate for tricuspid valve replacement

Exclusion Criteria

- Anatomy precluding proper implant
- Life expectancy < 12 months (365 days)
- LVEF < 25%
- Evidence of severe right ventricular dysfunction
- Any of the following pulmonary pressure parameters
  - PASP > 60 mmHg by echo Doppler
  - PASP > 70 mmHg by RHC
  - PVR > 5 Wood units by RHC
- Previous tricuspid surgery or intervention
- Trans-tricuspid pacemaker or defibrillator lead
  - Implanted in RV within last 90 days
  - Pacemaker dependent without alternative option
  - Secondary prevention ICD with therapy delivered
- Severe aortic, mitral and/or pulmonic valve stenosis and/or regurgitation
- Unable to walk at least 100 m in a 6-minute walk test

ICD, implantable cardioverter defibrillator; *LVEF*, left ventricular ejection fraction; *OMT*, optimal medical therapy; *PASP*, pulmonary artery systolic pressure; *PVR*, pulmonary vascular resistance; *RHC*, right heart catheterization; *RV*, right ventricle; *TR*, tricuspid regurgitation; *TTE*, transthoracic echocardiogram

30-Day Primary Safety Composite Endpoint

THE TRISCEND II PIVOTAL TRIAL

Events Occurring ≤ 30 Days

- Cardiovascular mortality
- Myocardial infarction
- Stroke
- New need for renal replacement therapy
- Severe bleeding (fatal, life-threatening, extensive, or major)
- Non-elective TV re-intervention, percutaneous or surgical
- Major access site and vascular complications
- Major cardiac structural complications (access-related)
- Device-related pulmonary embolism
- Arrhythmia and conduction disorder requiring permanent pacing

All events adjudicated by independent clinical events committee

———

Composite MAE rate compared to pre-specified performance goal of **70%**

MAE, major adverse event; *TV*, tricuspid valve

Performance Goal Derived from MAE Rate in Isolated TV Replacement Surgery from Medicare FFS Claims

THE TRISCEND II PIVOTAL TRIAL

Stepwise hierarchical analysis based on level of severity

Patients with multiple MAEs counted once

30-Day MAE	%
Death	7.6
Cardiogenic shock	15.6
Myocardial infarction	1.2
Stroke	1.4
AKI with dialysis	3.0
Cardiac tamponade	1.1
Pulmonary embolism	8.0
Permanent pacemaker	12.3
Severe bleeding & transfusion	9.2
Prolonged ventilation	6.1
Pneumonia	4.4

Expected MAE Rate*: **43.8%**

95% CI: **41.6% - 46.0%**

*MAEs relevant for transcatheter treatment

MAEs from Medicare FFS Claims, Standard Analytic Files from 2011-2018 Isolated TV replacement surgery cohort, N=2036.
AKI, acute kidney injury; *CI*, confidence interval; *FFS*, fee-for-service; *MAE*, major adverse event; *TV*, tricuspid valve

6-Month Co-Primary Effectiveness Endpoints

THE TRISCEND II PIVOTAL TRIAL

1

TR Grade Reduction

- Proportion of patients with TR ≤ moderate

2

Hierarchical Composite Endpoint (pre-specified hierarchy)

1. KCCQ overall summary score improvement of ≥ 10 points
2. NYHA functional class improvement of ≥ 1 class
3. 6MWD improvement of ≥ 30 meters

6MWD, six-minute walk distance; *KCCQ*, Kansas City Cardiomyopathy Questionnaire; *NYHA*, New York Heart Association; *TR*, tricuspid regurgitation

Pre-Specified Analysis Methods for Co-Primary Effectiveness Endpoints

THE TRISCEND II PIVOTAL TRIAL

1

TR Grade Reduction

- Pooled 1-sided z-test

2

Hierarchical Composite Endpoint (pre-specified hierarchy)

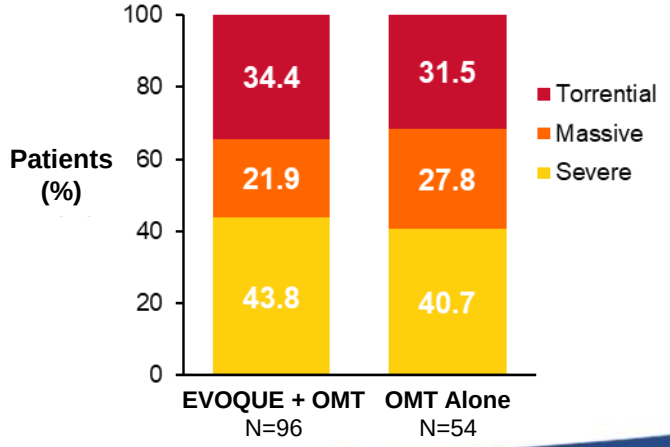
- **Finkelstein-Schoenfeld Method:**
  Compares all possible patient pairs between treatment groups for composite endpoint
  - **P-value:** Test of significance
  - **Win Ratio:** Assessment of the effect size

Baseline Characteristics

	EVOQUE + OMT N=96	OMT Alone N=54
Age, years	79.4 ± 7.7	78.2 ± 8.3
Female, %	82.3	75.9
NYHA class III-IV, %	79.2	70.4
KCCQ overall score, points	49.1 ± 21.5	49.7 ± 22.3
STS score, mitral valve replacement, %	10.2 ± 5.7	9.4 ± 4.5
Left ventricular ejection fraction, %	55.1 ± 8.6	52.4 ± 11.6
Atrial fibrillation, %	97.9	96.3
Hypertension,%	91.7	87.0
COPD, %	19.8	16.7
Stroke, %[a]	19.8	5.6
Renal disease, ≥ stage II, %	50.0	57.4
Ascites, %	15.6	20.4
HF hospitalization in past 12 months, %	31.3	31.5
Pacemaker/ICD, %	36.5	42.6
Prior valve surgery/intervention, %	31.3	31.5
Coronary artery bypass graft, %	10.4	24.1

TR Etiology by Core Lab[b]	EVOQUE + OMT N=96	OMT Alone N=54
Primary, %[c]	14.6	13.0
Secondary, %[d]	77.1	70.4
Mixed, %	7.3	14.8
Indeterminate, %	1.0	1.9

TR Severity by Core Lab[b]



Mean ±SD or %. Data from patients with available assessments. [a]Stroke: the only variable with significant difference, p=0.017. [b]Echocardiographic core lab: Baylor Scott & White The Heart Hospital Plano, Plano, TX, USA. [c]Degenerative, organic, structural or pacer-related. [d]Functional or nonstructural. *COPD*, chronic obstructive pulmonary disease; *HF*, heart failure; *ICD*, implantable cardioverter-defibrillator; *KCCQ*, Kansas City Cardiomyopathy Questionnaire; *NYHA*, New York Heart Association; *OMT*, optimal medical therapy; *STS*, Society of Thoracic Surgeons; *TR*, tricuspid regurgitation

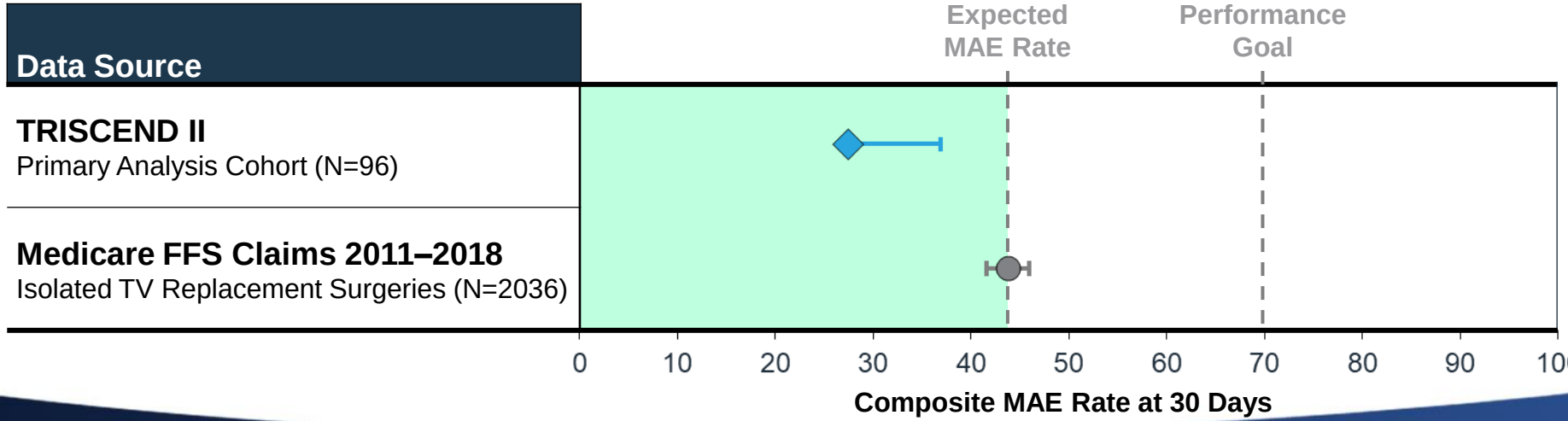
EVOQUE System Procedure Characteristics

	EVOQUE + OMT N=96
Patients with study valve implanted	95.8%[a]
Procedure time (minutes)	115.2 ± 48.5
Device time (minutes)	65.0 ± 29.6
Percutaneous access Right femoral vein Left femoral vein	100% 83.3% 16.7%
Conversion to surgery	2.1%[b]
Length of hospital stay (days)	4.0 [2.0, 8.0]
Discharged to home	90.6%

%, mean ± SD, median [IQR]. [a]Four procedures aborted due to challenging imaging or anatomy. [b]Two patients required open surgery to repair right ventricular perforation and were discharged with EVOQUE valve in place.

TRISCEND II Met Primary Safety Endpoint

	Total Events (N)	EVOQUE + OMT Patients (%) N=96[a]	One-Sided 97.5% Upper Confidence Bound
Composite MAE at 30 days	**36**	**26 (27.4%)**	**36.9%**



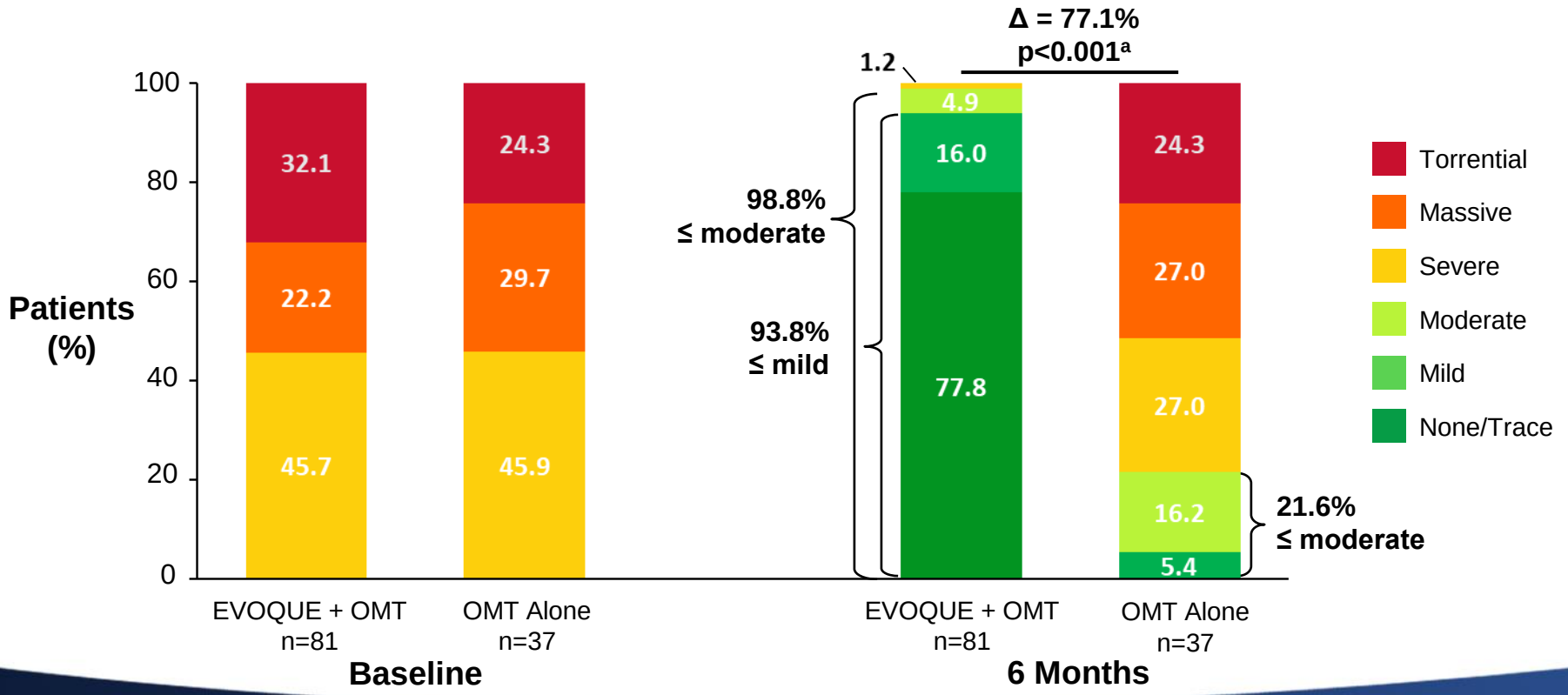
Error bars show 95% CI. [a]One patient had aborted procedure and withdrew from trial without experiencing an MAE, excluded from primary safety endpoint analysis.
FFS, fee-for-service; *MAE*, major adverse event; *OMT*, optimal medical therapy; *TV*, tricuspid valve

Primary Safety Endpoint at 30 Days

CEC-Adjudicated Major Adverse Events	EVOQUE + OMT N=95 % (n)
Cardiovascular mortality	3.2 (3)
Myocardial infarction	1.1 (1)
Stroke	0.0 (0)
New need for renal replacement therapy	1.1 (1)
Severe bleeding[a]	10.5 (10)
Non-elective TV re-intervention	0.0 (0)
Major access site and vascular complication	3.2 (3)
Major cardiac structural complication	2.1 (2)
Device-related pulmonary embolism	1.1 (1)
Arrhythmia and conduction disorder requiring permanent pacing	14.7 (14)
Composite MAE Rate[b]	**27.4 (26)**

[a]Severe bleeding as defined by the Mitral Valve Academic Research Consortium. [b]Patients may have had more than 1 event. *CEC*, clinical events committee; *MAE*, major adverse event; *OMT*, optimal medical therapy; *TV,* tricuspid valve

Significant Reductions in TR Grade with EVOQUE System at 6 Months



Graph shows paired data. Echocardiographic core lab: Baylor Scott & White The Heart Hospital Plano, Plano, TX, USA. [a]Pooled Z-Test with continuity correction to be compared with one-sided significance level of 0.025. *OMT*, optimal medical therapy; *TR*, tricuspid regurgitation

Superior QoL and Functional Outcomes With EVOQUE System Compared to OMT

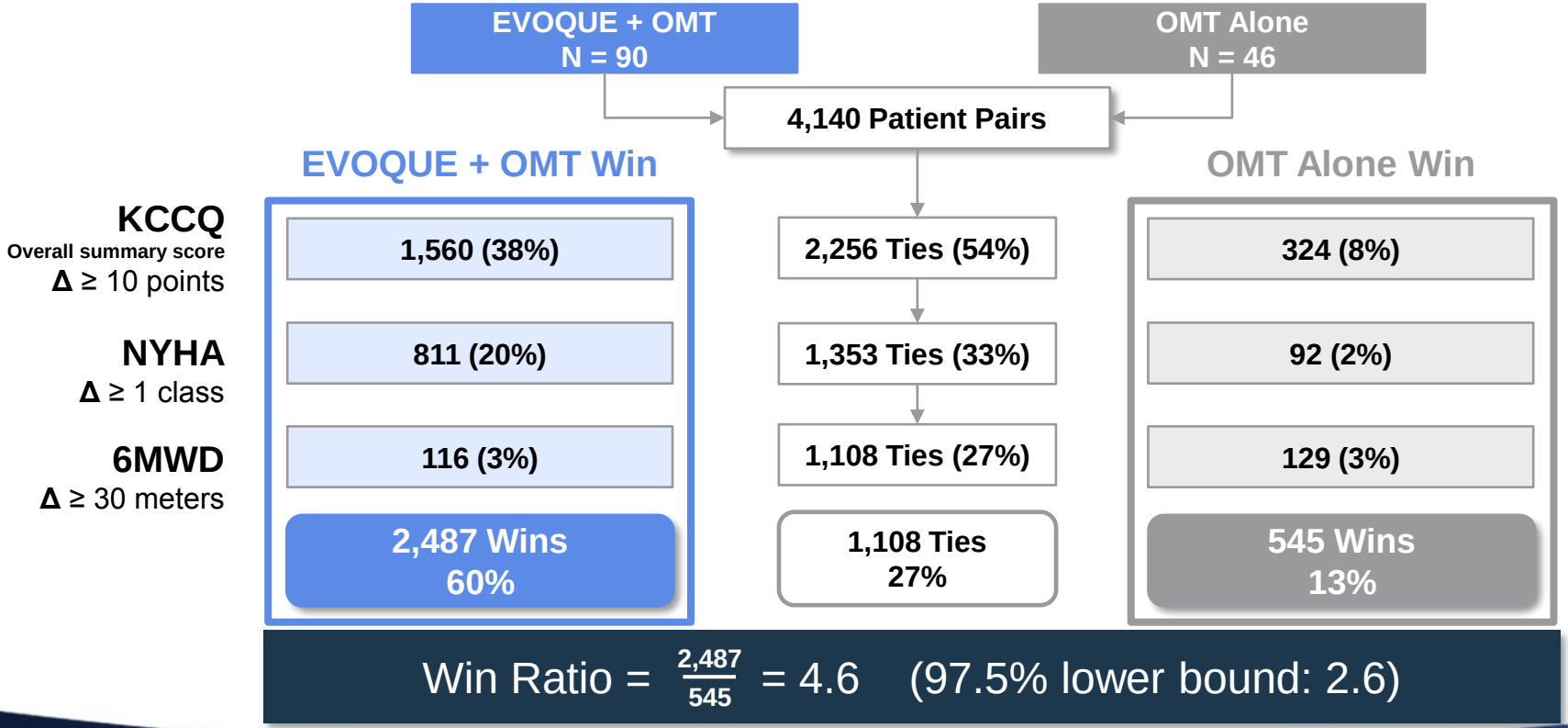
P-value[a]	Trial Result
< 0.001	SUCCESS

- Pairwise comparisons across all possible combinations of patients for each component in hierarchical order
  1. KCCQ: Δ Summary score ≥ 10-point improvement
  2. NYHA: ≥ 1 class reduction
  3. 6MWD: ≥ 30-meter improvement
- Summary score for each patient used to compare treatment groups

[a]P-value calculated using Finkelstein-Schoenfeld method with one-sided significance level of 0.025. *6MWD*, 6-minute walk distance; *KCCQ*, Kansas City Cardiomyopathy Questionnaire; *NYHA*, New York Heart Association; *OMT*, optimal medical therapy, *QoL*, quality of life

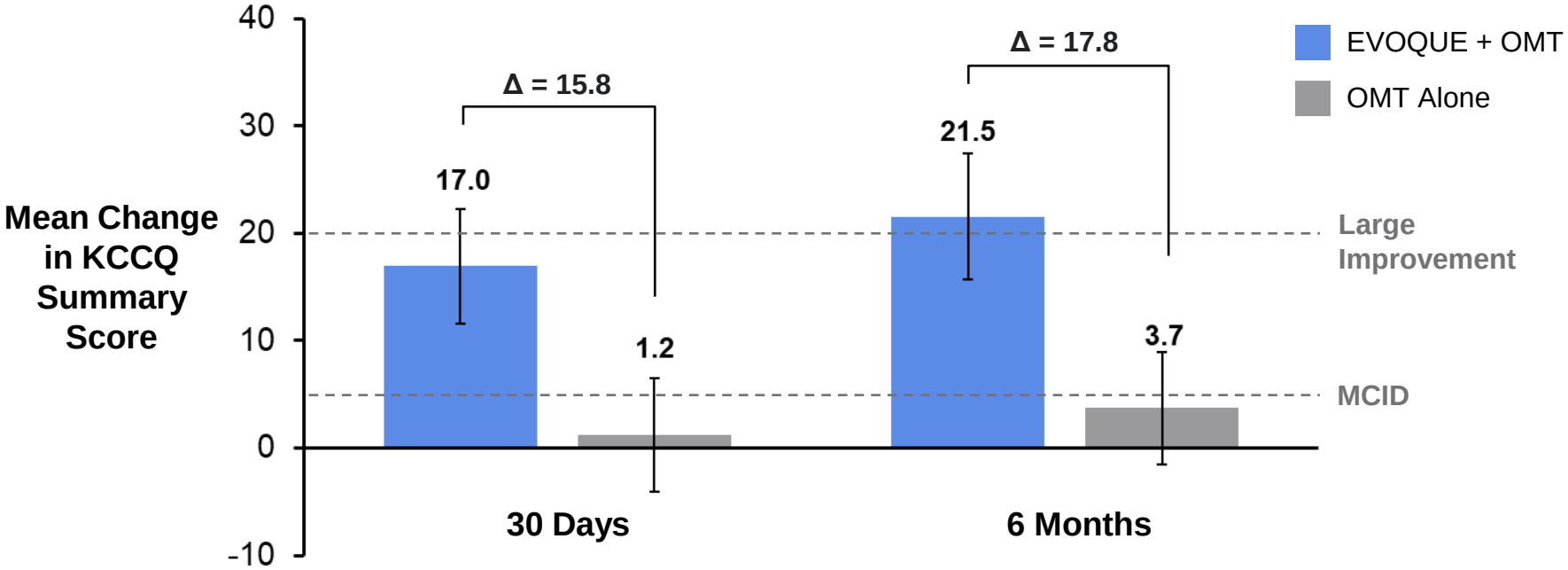
Superior QoL Outcomes with EVOQUE System Compared to OMT

THE TRISCEND II PIVOTAL TRIAL



6MWD, six-minute walk distance; *KCCQ*, Kansas City Cardiomyopathy Questionnaire; *NYHA*, New York Heart Association; *OMT*, optimal medical therapy; *QoL*, quality of life; *TR*, tricuspid regurgitation

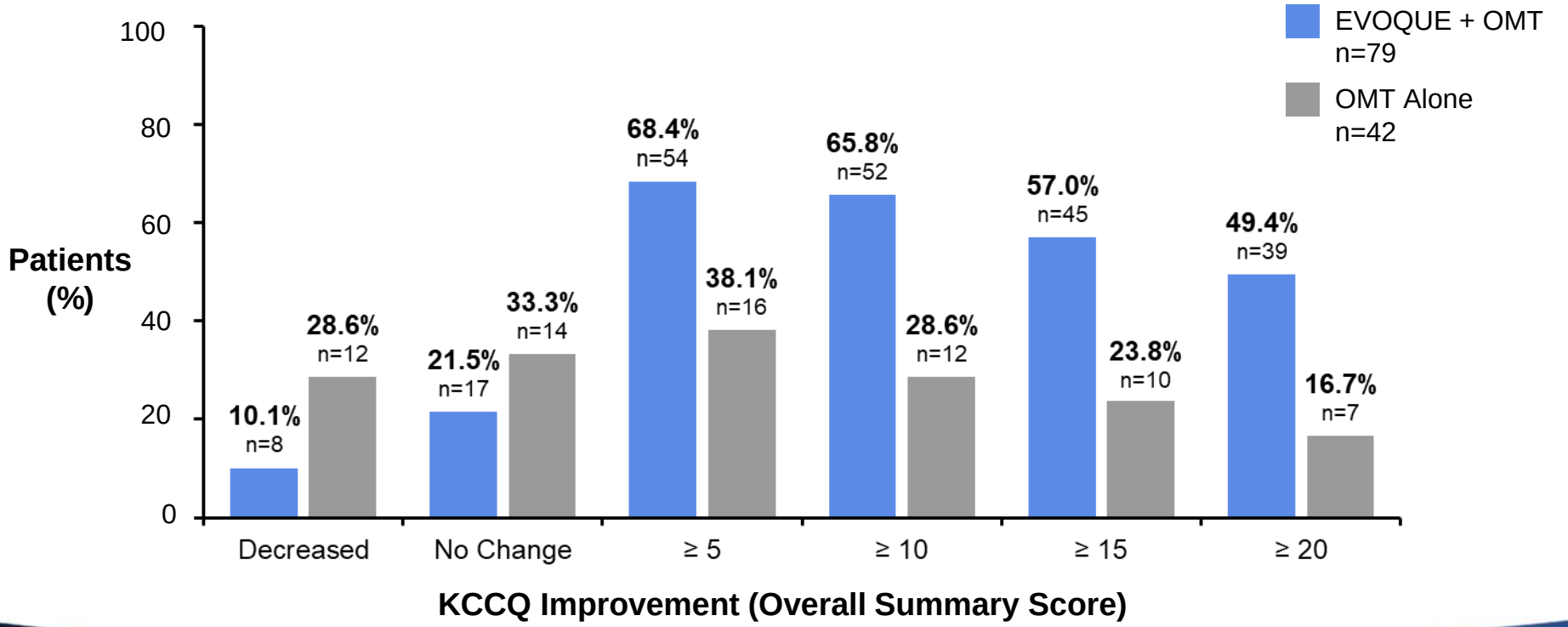
Changes in KCCQ at 30 Days and 6 Months



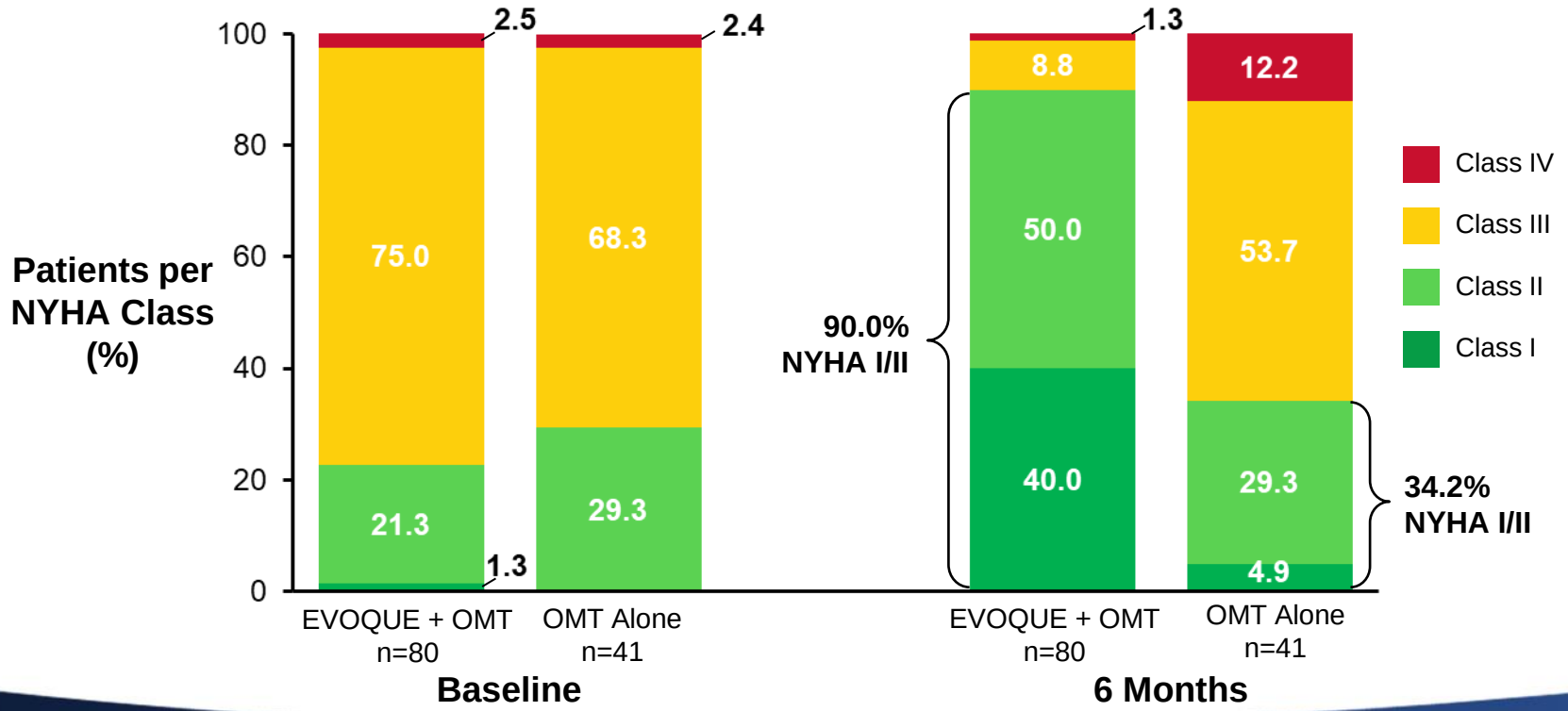
	30 Days		6 Months	
Baseline Mean KCCQ Score	50.6 n=82	48.0 n=45	50.7 n=79	51.2 n=42

Graphs show paired analysis. Error bars show 95% CI. *KCCQ*, Kansas City Cardiomyopathy Questionnaire; *MCID*, Minimal Clinically Important Difference; *OMT*, optimal medical therapy

Differences in Magnitude of KCCQ Improvement at 6 Months between EVOQUE and OMT Groups

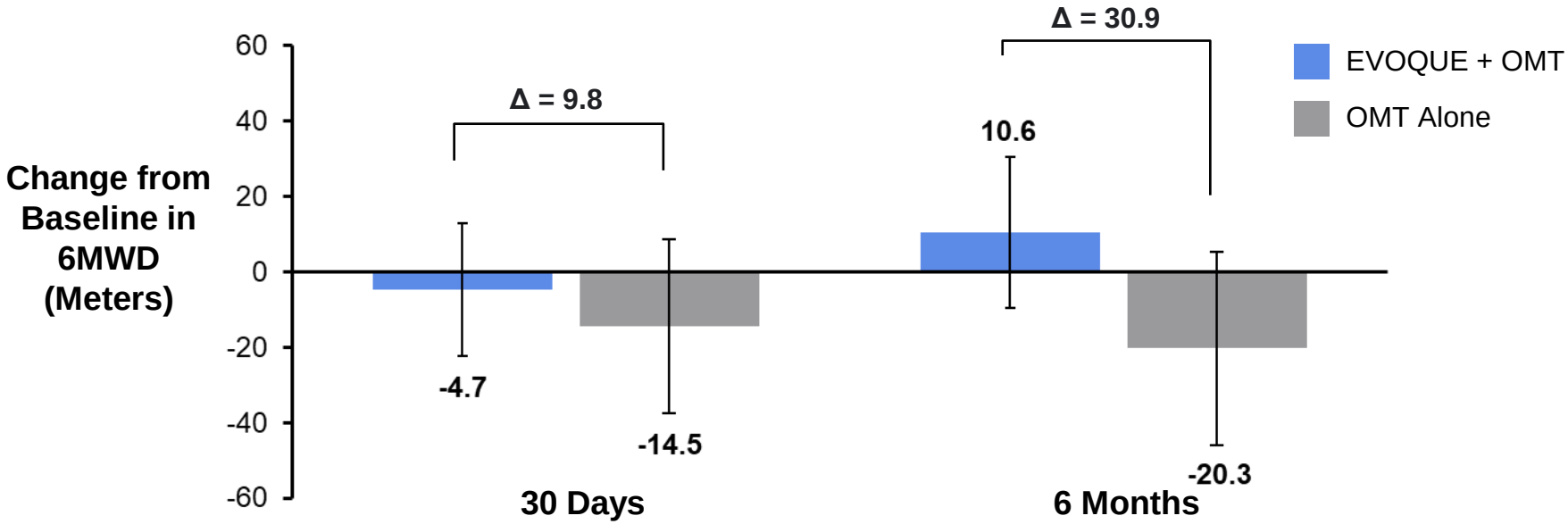


Changes in NYHA Class at 6 months between EVOQUE and OMT Groups



Graphs show paired analysis. *NYHA*, New York Heart Association; *OMT*, optimal medical therapy

Changes in 6MWD at 6 months between EVOQUE and OMT Groups



Baseline mean 6MWD (meters)	243.0 n=81	253.5 n=39	247.0 n=73	265.4 n=34

Graphs show paired analysis. Error bars show 95% CI. *6MWD*, six-minute walk distance; *OMT*, optimal medical therapy

Conclusions

- TRISCEND II has demonstrated that transcatheter tricuspid valve replacement (TTVR) with the EVOQUE system is feasible with an acceptable safety profile in a highly comorbid patient population
  - MAE rate of 27.4% is less than the expected MAE rate of 43.8%
- TTVR with the EVOQUE system effectively eliminates TR in a vast majority of patients despite the presence of massive or torrential at baseline in more than 50% of population
  - Mild or less in 93.8%
  - None/trace in 77.8%
- Treatment of severe TR with the EVOQUE system resulted in meaningful improvements in functional status and symptoms at 6 months

Final Thoughts

- The unique trial design of TRISCEND II, based on FDA breakthrough designation, provides an early look at the safety and effectiveness of the EVOQUE system in the first 150 patients
- Important clinical and echocardiographic endpoints including mortality and heart failure hospitalization from the full cohort of 400 patients will be presented in the future