A Landmark Randomized Clinical Trial of Transcatheter Repair for Tricuspid Regurgitation

Paul Sorajja and David H. Adams
On behalf of the TRILUMINATE Pivotal investigators

March 4, 2023

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Disclosures

Paul Sorajja, MD

- Consulting or Advisory Board: 4C Medical, Abbott Structural, Anteris, Boston Scientific, Edwards Lifesciences, Foldax, Medtronic, Phillips, Siemens, Shifamed, VDyne, WL Gore, xDot
- Institutional Research: Abbott Structural, Boston Scientific, Edwards Lifesciences, Medtronic
- National P.I.: EXPAND II, Highlife (US), SUMMIT-MAC, SOAR-EFS, TRILUMINATE Pivotal, VISTA

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Tricuspid Regurgitation

- Tricuspid regurgitation is common, and associated with impaired survival and poor quality-of-life
- Diuretics is the main therapy, with surgery for selected patients and often at high operative risk
- Limited data exist in right-sided valvular disease, and knowledge is often inferred from left-sided understanding
- Transcatheter tricuspid therapies have recently emerged, but their benefit has not been studied in a randomized, controlled clinical trial

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Scientific Objective

The TRILUMINATE Pivotal Trial is designed to evaluate the safety and effectiveness of transcatheter tricuspid repair with the TriClip™ device in symptomatic patients with severe tricuspid regurgitation who are intermediate or greater estimated risk for mortality with tricuspid valve surgery

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Study Leadership

Steering Committee

David Adams	Mount Sinai Hospital
Jörg Hausleiter	Universität München
Patrick McCarthy	Northwestern University
Paul Sorajja	Minneapolis Heart Institute
Raj Makkar	Cedars-Sinai Medical Center
Ralph Stephan von Bardeleben	University Medicine of the Johannes Gutenberg University Mainz
Randolph Martin	Bay Labs, Inc.
Raymond Benza	Ohio State University
Rebecca Hahn	New York-Presbyterian/CUMC
Saibal Kar	Los Robles Medical Center
Scott Lim	University of Virginia Medical Center
Susheel Kodali	New York-Presbyterian/CUMC
Ulrich Jorde	Montefiore Medical Center
Vinod Thourani	Piedmont Hospital

Anatomic Eligibility Committee

Anita Asgar	Montreal Heart Institute
Brian Whisenant	Intermountain Medical Center
Gagan Singh	UC - Davis Medical Center
Gilbert Tang	Mount Sinai Hospital
Hursh Naik	Arizona CV Research Center
M. Azeem Latib	Montefiore Medical Center
Marta Sitges	Hospital Clinic Barcelona
Matthew Price	Scripps Health
Moody Makar	Cedars-Sinai Medical Center
Neil Fam	St. Michael's Hosital
Paul Sorajja	Minneapolis Heart Institute
Philipp Lurz	Universität Leipzig
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Saibal Kar	Los Robles Medical Center
Scott Lim	University of Virginia Medical Center
Susheel Kodali	New York-Presbyterian/CUMC
Tom Smith	UC Davis

Patient Management Eligibility Committee

Andrew Sauer	Saint Luke's Health System
Sandhya Murthy	Montefiore Medical Center
Raymond Benza	Ohio State University
Ulrich Jorde	Montefiore Medical Center

Echocardiographic Core Lab

Rebecca Hahn	Cardiovascular Research Foundation
Nadira Hamid	Cardiovascular Research Foundation

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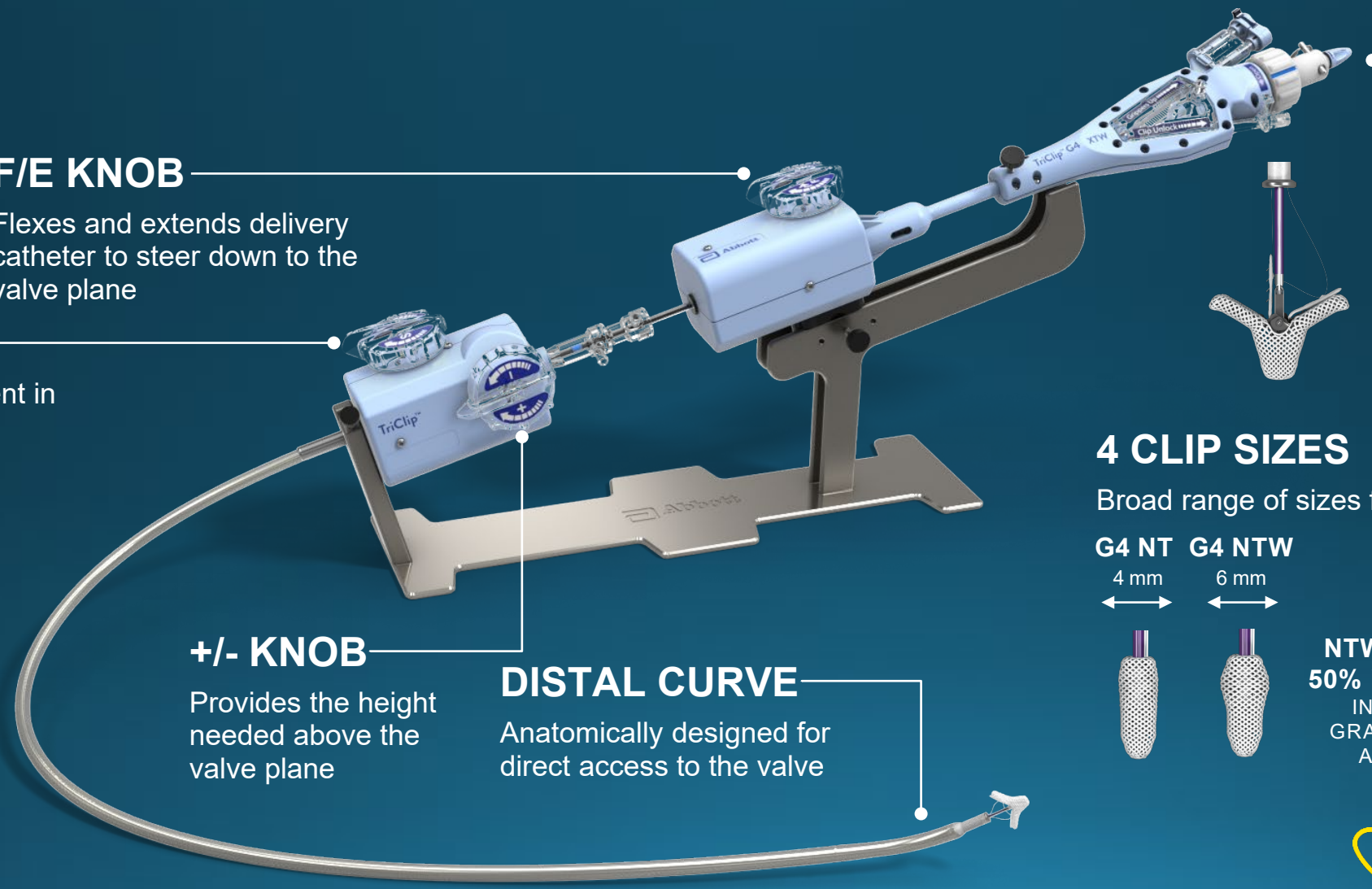
TriClip™ G4 Delivery System



F/E KNOB

Flexes and extends delivery catheter to steer down to the valve plane

S/L KNOB

Enables movement in septal or lateral direction

+/- KNOB

Provides the height needed above the valve plane

DISTAL CURVE

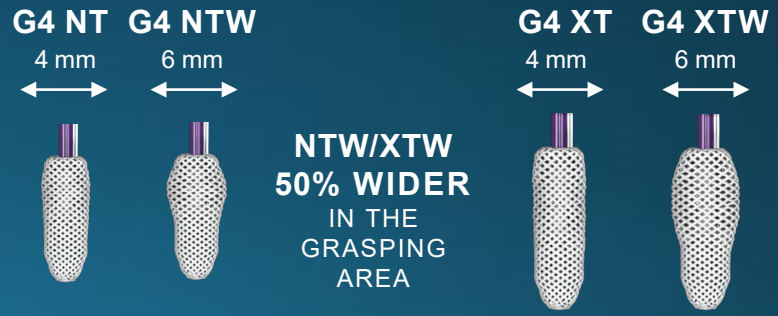
Anatomically designed for direct access to the valve

CONTROLLED GRIPPER ACTUATION

Ability to optimize leaflet grasping if needed

4 CLIP SIZES

Broad range of sizes for tailored treatment



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Study Enrollment Criteria

Key Inclusion Criteria

- Severe, symptomatic TR
- Stable GDMT and/or device therapy for heart failure for ≥ 30 days
- ≥ Intermediate risk of mortality/morbidity with tricuspid valve surgery

Key Exclusion Criteria

- Indication for other valve disease intervention
- Severe pulmonary HTN
- Left ventricular ejection fraction ≤20%
- Anatomy not suitable for TriClip therapy

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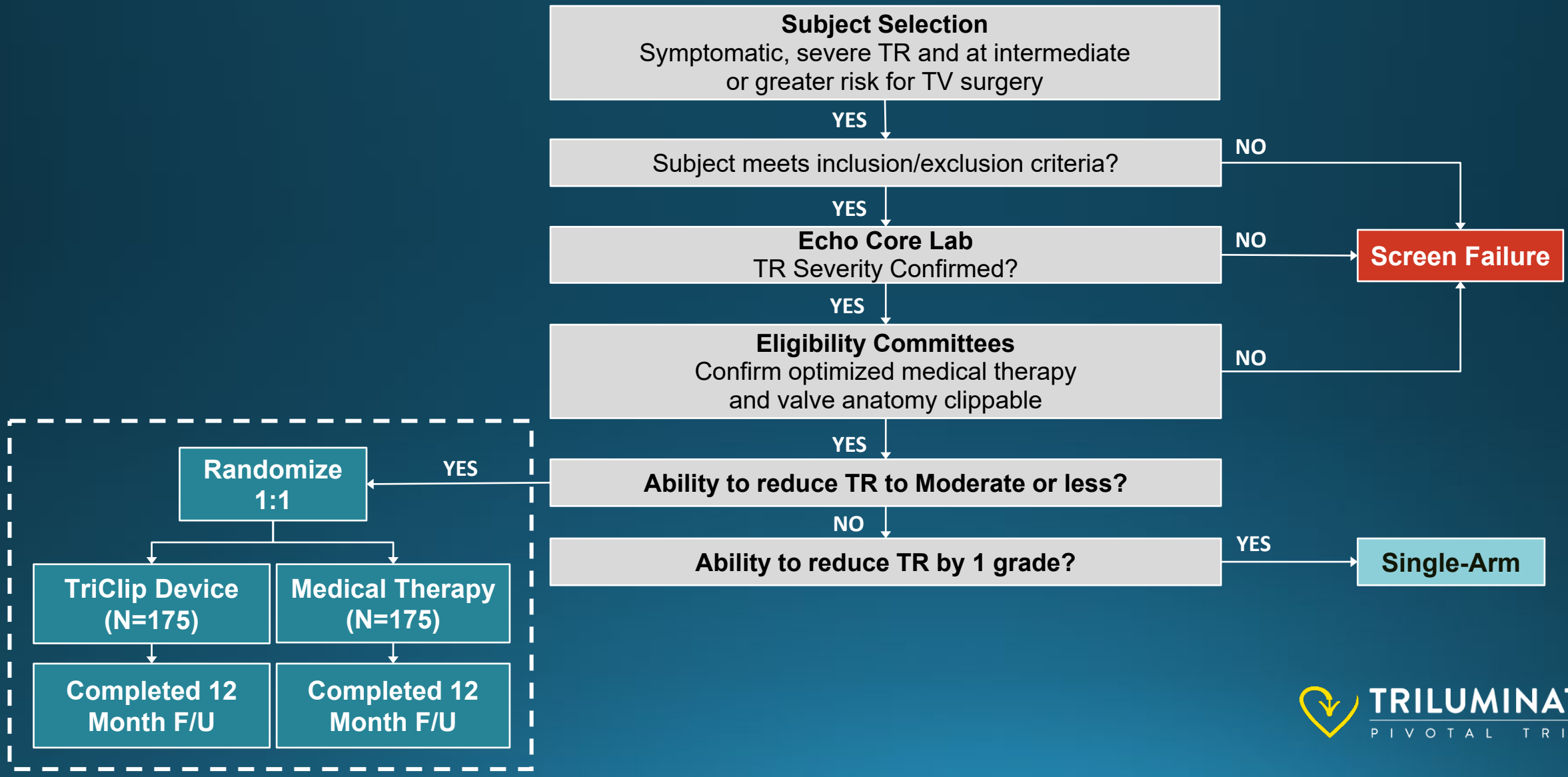
Enrollment and Treatment Pathway



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Endpoints and Analysis

Trial Design	• Prospective, randomized, controlled, multi-center trial designed to test the superiority of TriClip™ therapy in addition to medical therapy (Device group) over medical therapy alone (Control group) • **450+** subjects enrolled at up to 80 sites in the US, Canada, Europe
Primary Endpoint	**To be assessed after the first 350 randomized subjects complete 12-month follow-up** A composite of mortality or tricuspid valve surgery, heart failure hospitalizations, and quality of life improvement ≥15 points assessed using the Kansas City Cardiomyopathy Questionnaire (KCCQ), evaluated at 12 months in a hierarchical fashion using the Finkelstein-Schoenfeld methodology
Secondary Endpoint	**Assessed hierarchically in the following order:** • Freedom from major adverse events (MAE) after procedure attempt (femoral vein puncture) at 30 days (Device group only) • Change in KCCQ at 12 months (superiority of Device vs. Control) • TR Reduction to moderate or less at 30-day post procedure (superiority of Device vs. Control) • Change in 6MWD at 12 months (superiority of Device vs. Control)

MAE defined as composite of Cardiovascular Mortality, New Onset Renal Failure, Endocarditis Requiring Surgery, and Non-Elective Cardiovascular Surgery for TriClip device-related AE post-index procedure.

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Broad Geographical Participation

 63  6  6

- Abbott Northwestern Hospital
- Allegheny General Hospital- ASRI
- Arizona Cardiovascular Research Center
- Aurora Medical Group
- Austin Heart
- Baptist Hospital of Miami
- Baylor Scott & White Heart & Vascular Hospital
- Beth Israel Deaconess Medical Center
- Brigham & Women's Hospital
- Buffalo General Hospital
- California Pacific Medical Center - Van Ness Campus
- Cardiovascular Institute of the South
- Cardiovascular Research Institute of Kansas
- Carolinas Medical Center
- Cedars-Sinai Medical Center
- Centennial Heart Cardiovascular Consultants
- Christ Hospital
- El Camino Hospital
- Hospital of the University of Pennsylvania
- Inova Fairfax Hospital
- Intermountain Medical Center
- JFK Medical Center
- Kansas University Medical Center
- Los Robles Regional Medical Center
- Manatee Memorial Hospital
- MedStar Health Research Institute
- Methodist Hospital of San Antonio
- Montefiore Medical Center - Moses Division
- Morton Plant Valve Clinic
- Mount Sinai Hospital
- New York-Presbyterian/Columbia University Medical Center
- North Shore University Hospital
- Northshore University HealthSystem
- Novant Health Heart and Vascular Research Institute
- Ohio Health Research Institute
- Phoenix Cardiovascular Research Group
- Piedmont Heart Institute
- Providence Heart & Vascular Institute
- Providence Medical Foundation
- Rush University Medical Center
- Scripps Health
- Sentara Norfolk General Hospital
- St. Thomas Hospital
- Sutter Medical Center, Sacramento
- Swedish Medical Center
- Tallahassee Research Institute
- The Cleveland Clinic Foundation
- The Methodist Hospital
- Tucson Medical Center
- University Hospital - Univ. of Alabama at Birmingham (UAB)
- University of California - Davis Medical Center
- University of Colorado Hospital
- University of Pittsburgh Medical Center
- University of Virginia Medical Center
- Yale New Haven Hospital
- Hamilton Health Science Centre
- Herzzentrum Leipzig GmbH
- Hospital Clínic de Barcelona
- Institut de Cardiologie de Montreal (Montreal Heart Inst.)
- Munchen Grosshadern
- Ospedale San Raffaele - Cardiac
- Ottawa Heart Institute
- St. Michael's Hospital
- St. Paul's Hospital
- Sunnybrook Health Sciences Centre
- Universitatsklinikum Bonn AdoR
- Universitatsmedizin der Johannes Gutenberg-Universitat Mainz

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Baseline Characteristics

	Device N=175 # (%)	Control N=175 # (%)
Age, Mean (years)	78.0 ± 7.4	77.8 ± 7.2
Sex (Female)	98 (56.0)	94 (53.7)
NYHA class III or IV	104 (59.4)	97 (55.4)
KCCQ Score, mean	56.0 ± 23.4	54.1 ± 24.2
Hypertension	142 (81.1)	141 (80.6)
Renal disease	62 (35.4)	62 (35.4)
Liver disease	11 (6.3)	16 (9.1)
Atrial fibrillation	153 (87.4)	162 (92.6)
Diabetes	28 (16.0)	27 (15.4)
COPD	19 (10.9)	24 (13.7)
CRT/CRT-D/ICD/PPM	28 (16.0)	24 (13.7)
Prior aortic intervention	27 (15.4)	27 (15.4)
Prior mitral intervention	45 (25.7)	42 (24.0)
Prior tricuspid intervention	1 (0.6)	0 (0.0)

	Device N=175 # (%)	Control N=175 # (%)
TR Severity		
Moderate	4 (2.3)	2 (1.2)
Severe	44 (25.4)	49 (29.7)
Massive	37 (21.4)	30 (18.2)
Torrential	88 (50.9)	84 (50.9)
Etiology (functional)	165 (94.8)	158 (92.9)
Coaptation Gap, Mean (mm)	5.5 ± 1.8	5.2 ± 1.7
Heart size/function, Mean		
RVEDD (base, cm)	5.0 ± 0.8	5.2 ± 0.8
TV annulus diameter (cm)	4.3 ± 0.7	4.5 ± 0.8
RV TAPSE (cm)	1.7 ± 0.4	1.6 ± 0.4
LVEF (%)	59.3 ± 9.3	58.7 ± 10.5
CO (L/min)	4.1 ± 1.2	4.2 ± 1.1

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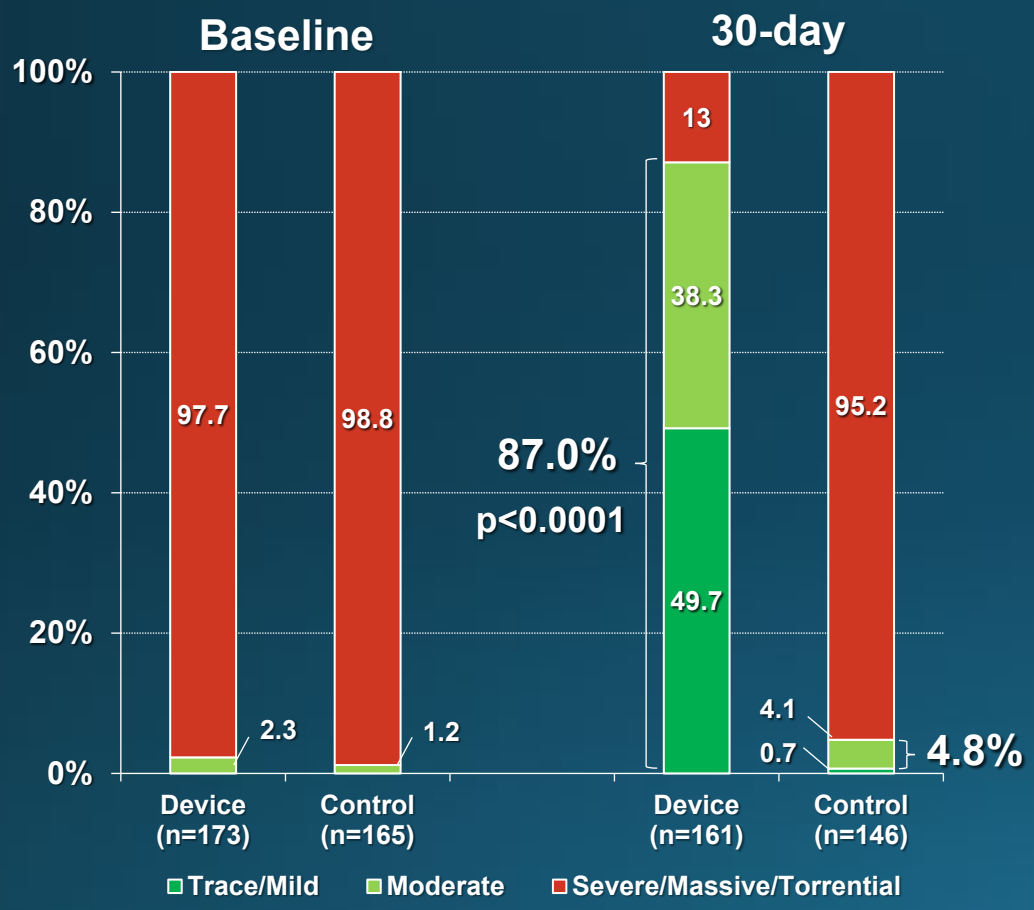
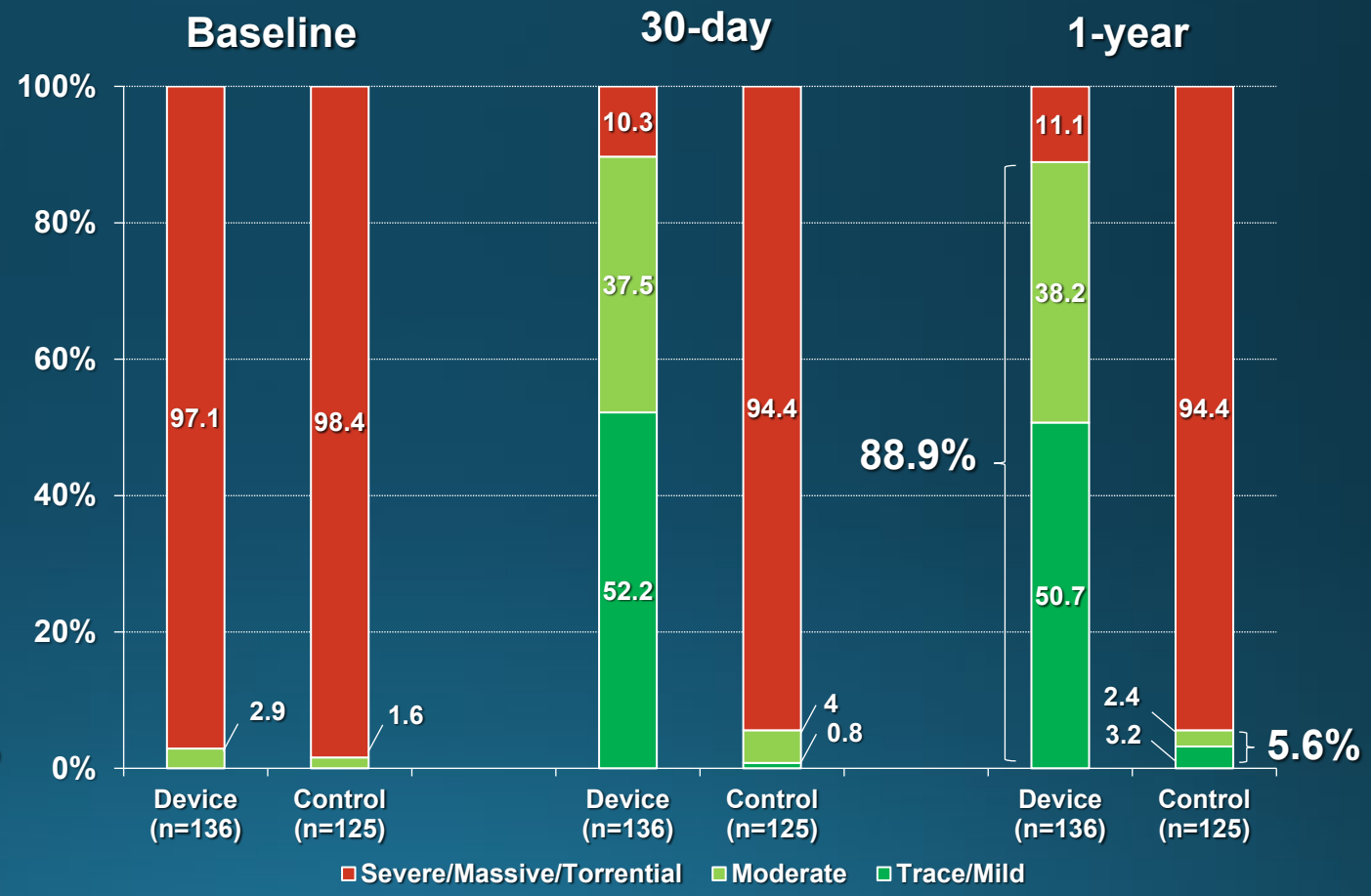
Reduction in TR Severity



Paired Analyses



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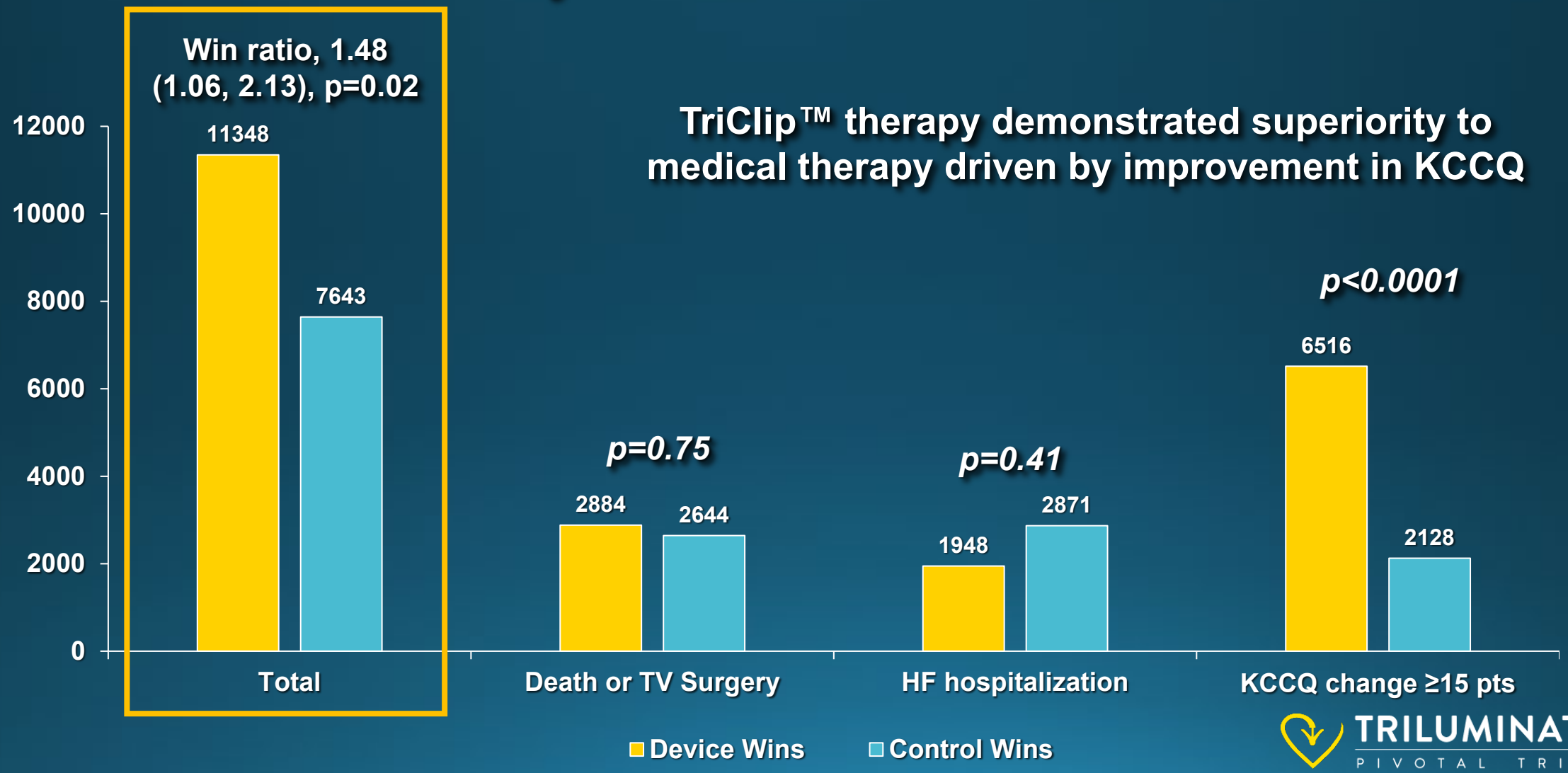
Primary Endpoint

Finkelstein-Schoenfeld Analysis



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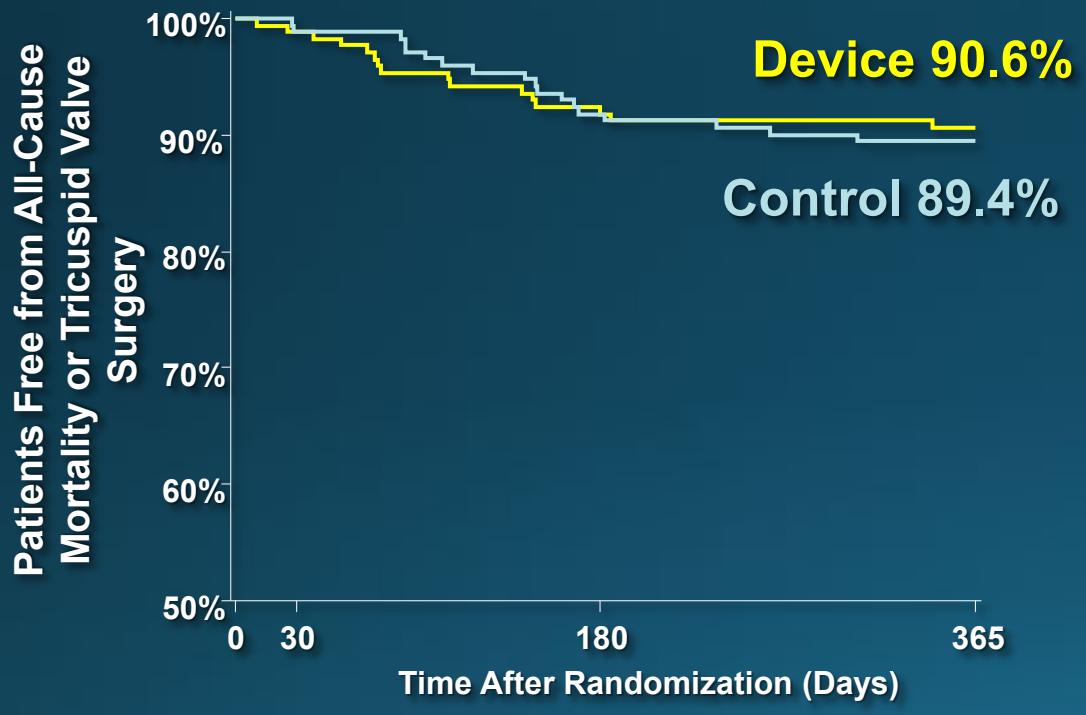
Individual Component Analysis

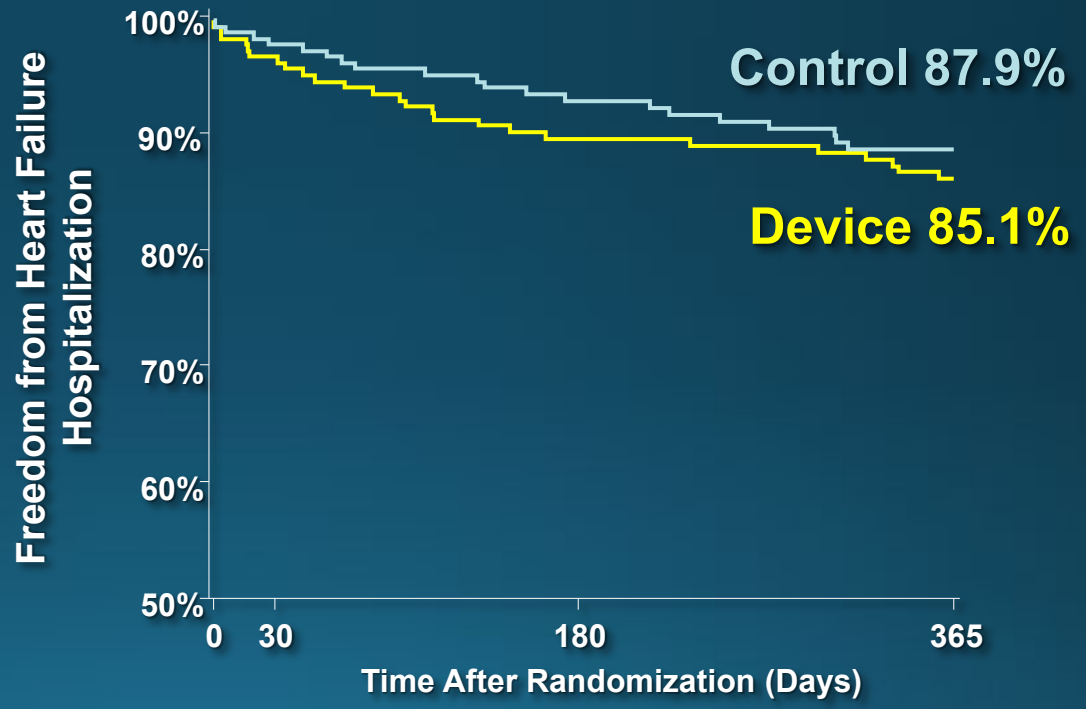
1st Component: Mortality or TV Surgery

p=0.75



2nd Component: Heart Failure Hospitalization

p=0.41



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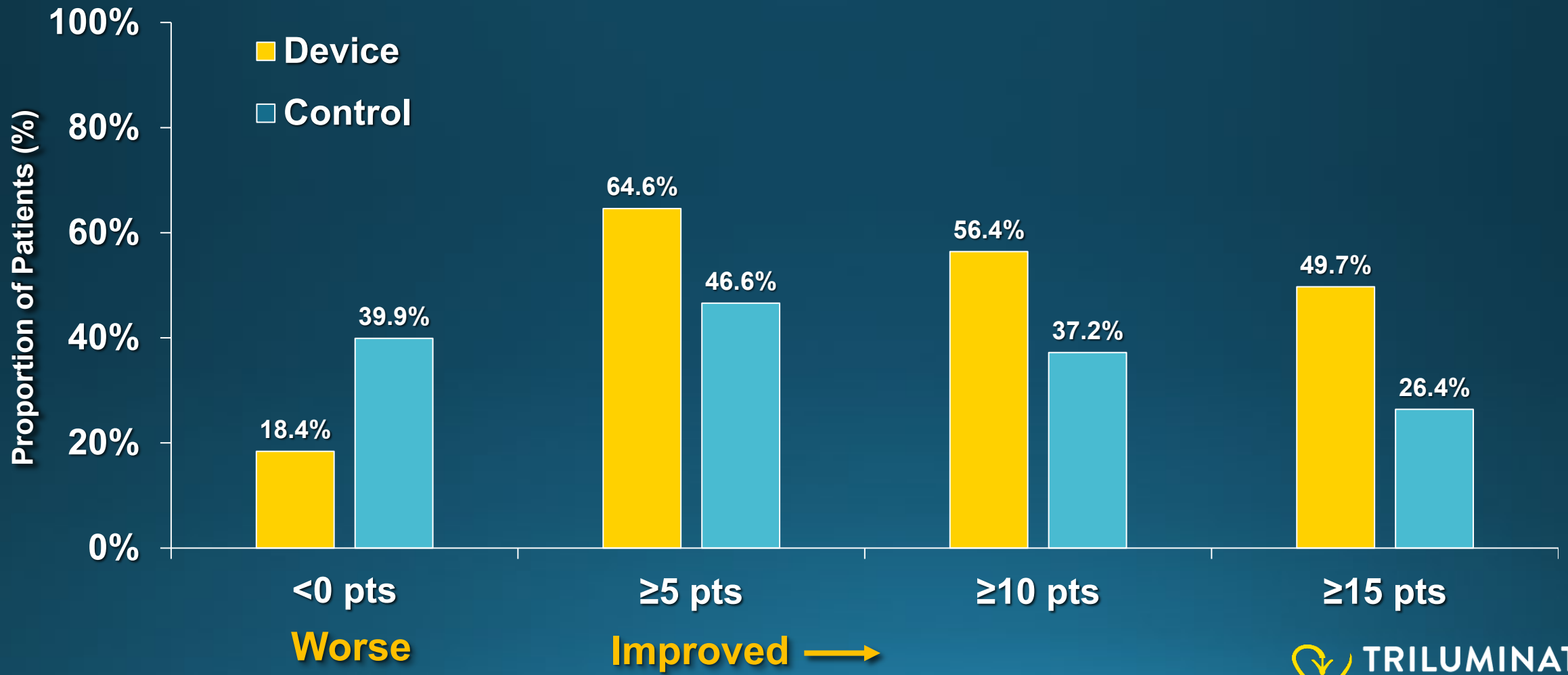
Quality-of-life Improvement

3rd Component, KCCQ change ≥15 pts, baseline to 1-yr



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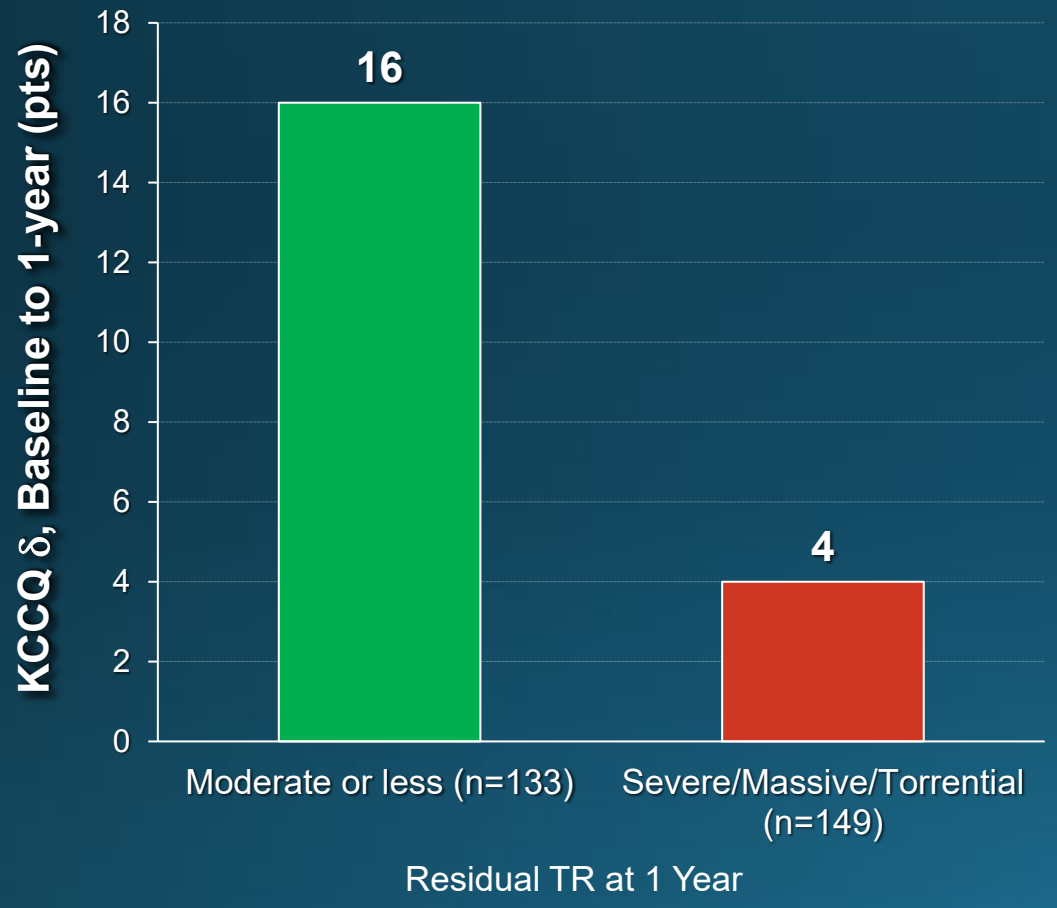
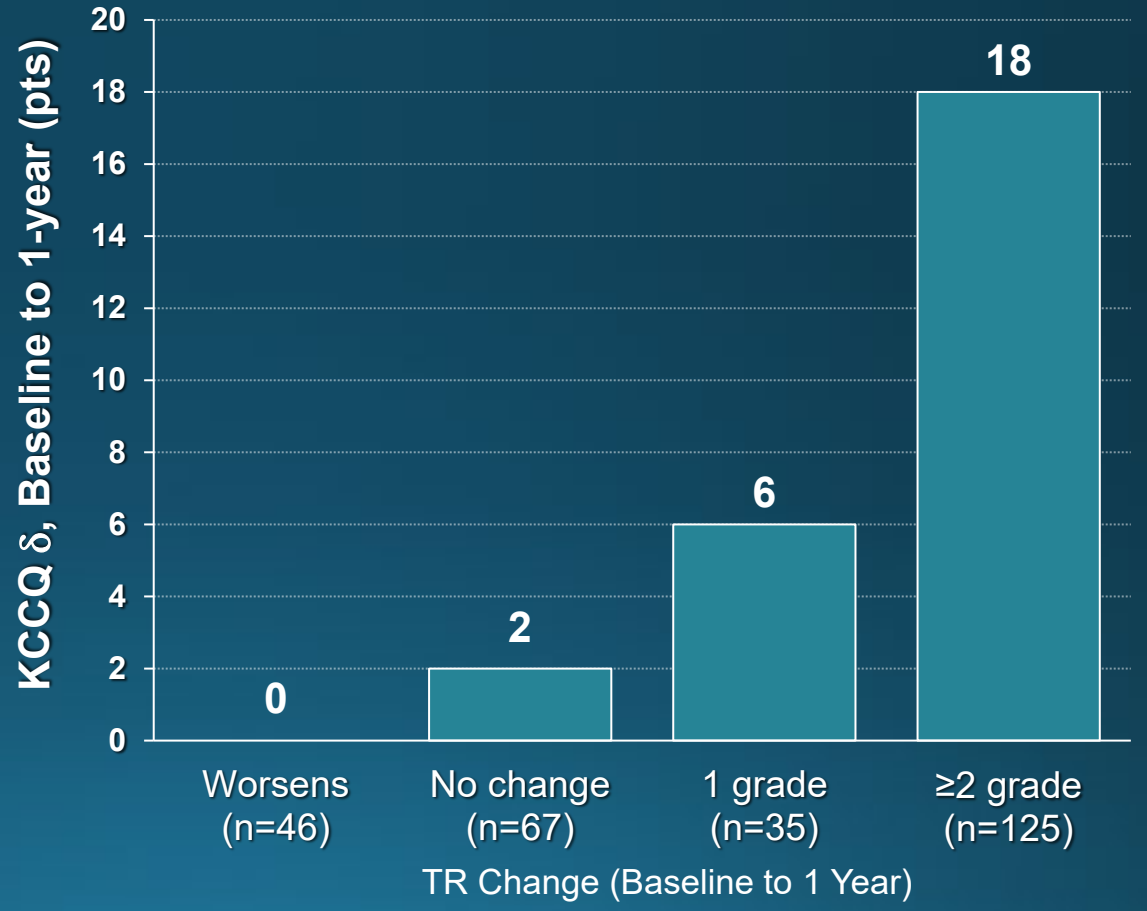
Relationship between TR and Quality of Life

Change in KCCQ vs Residual TR at 1-yr



Change in KCCQ vs Change in TR severity



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Hierarchical Secondary Endpoints

	Device Group (N=175)	Control Group (N=175)	Difference (95% CI)	p-value
Freedom from MAE through 30 Days post procedure – Kaplan-Meier estimate of event-free rate (lower 97.5% CI)[1]	98.3	-	-	<0.001
Change in KCCQ from baseline to 12 months (pts)[2]				
Endpoint analysis	12.3	0.6	11.7	<0.001
Non-imputed data	15.2	4.8	10.4	-
TR Severity ≤ Moderate at 30 Days – no./total no (%)	87.0	4.8	-	<0.001
Change in 6-min walk test distance from baseline to 12 months (m)[2]				
Endpoint analysis	-8.1	-25.2	17.1	0.25
Non-imputed data	11.5	-8.7	20.3	-

[1] MAE Performance Goal 90%

[2] Subjects who experienced a heart failure related cardiovascular death or received tricuspid valve surgery had KCCQ score and 6MWT distance imputed as 0 at 12 months. 6MWT also imputed as 0 for subjects unable to exercise due to cardiac reasons.

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Safety Profile

Major Adverse Event (MAE) Through 30 Days Post-Procedure – no.(%)	Device N=172†
Total	**3 (1.7%)**
Cardiovascular mortality	1 (0.6%)
Endocarditis requiring surgery	0 (0%)
New-onset renal failure	2 (1.2%)
Non-elective CV Surgery, TVRS for device-related AE	0 (0%)

Other Clinical Safety Endpoints Through 30 Days Post-Procedure– no.(%)	Device N=172†
Any-cause mortality	1 (0.6%)
Tricuspid valve surgery	1 (0.6%)
Tricuspid valve re-intervention	3 (1.7%)
Major bleeding#	8 (4.7%)
Tricuspid mean gradient ≥ 5mmHg	8 (4.7%)
Single leaflet device attachment (SLDA)*	12 (7.0%)
Stroke	1 (0.6%)
Myocardial Infarction	0 (0%)
Embolization*	0 (0%)
Thrombosis	0 (0%)
New CRT/CRT-D/ICD/perm. pacemaker^	1 (0.6%)

†Attempted procedure population (3 subjects randomized to Device withdrew consent prior to index procedure)
#Defined as bleeding ≥ Type 3 based on a modified Bleeding Academic Research Consortium (BARC) definition
*SLDA and embolization evaluated through 30-day follow-up
^Assessed through adverse event reporting

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Limitations

- Since patients were not blinded, a Hawthorne effect may have played a role in outcomes in both groups
- The trial was conducted almost entirely during the COVID-19 pandemic, which may have affected clinical outcomes

Summary

- TR was reduced by TriClip therapy to moderate or less in 87%, vs. only 4.8% for the control group, and reduction was sustained to 1-year follow-up
- The primary endpoint was met (p=0.02) demonstrating device superiority, driven mainly by significant improvement in QOL
- Degree of TR reduction was related to degree of improvement in QOL
- The 30-day MAE rate was only 1.7%, and death and pacemaker implant each occurred in 0.6%
- Survival free of mortality and TV surgery was high at 1 year in both groups (~90%)

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Conclusions

- TRILUMINATE Pivotal is a pioneering study as the first RCT in this unique population of patients with severe TR
- The TriClip device was highly effective in reducing TR and led to significant improvements in quality of life at one year, without the high procedural risk often associated with tricuspid surgery.
- These results are very meaningful for a highly symptomatic population whose quality of life is impacted by TR
- With the excellent benefit-to-risk profile of the TriClip system, a historically untreated population will have a treatment option to improve their quality of life

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The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Transcatheter Repair for Patients with Tricuspid Regurgitation

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