U.S. FOOD & DRUG ADMINISTRATION

Premarket Approval Application (PMA) for Abbott Medical's TriClip G4 System

Circulatory System Devices Advisory Committee Meeting

February 13, 2024

Introduction, Background, Clinical Study Design

Megan Naber, BS
General Engineer
Office of Cardiovascular Devices

Review Team

Lead Reviewer	Megan Naber, BS
Co-Lead Reviewer	Changfu Wu, PhD
Clinician (Surgical)	Bernard Vasseur, MD
Clinician (Interventional)	Mauro Moscucci, MD, MBA, MPH
Statistician	Xuan Ye, PhD
Team Lead, HVDT	Jennifer Bastijanic, PhD
Assistant Director, HVDT	Jaime Raben, PhD
Chief Medical Officer, OHT2	Andrew Farb, MD
Animal Studies	Natalie Miller, VMD, PhD
Biocompatibility	Girish Kumar, PhD
Sterility	Victoria Rodriguez, PhD

Outline

- Background
- Clinical Study Design
- Statistical Analysis
- Clinical Study Results
- Post-approval Study
- Conclusions

Tricuspid Regurgitation (TR)

- TR occurs when valve leaflets fail to close completely during systole resulting in regurgitation of blood from the right ventricle into the right atrium
- TR etiologies[1]
  - Primary TR (5-10% of cases)
  - Secondary TR (approximately 80% of cases)
  - Cardiac implantable electronic device (CIED)-induced TR (approximately 10-15% of cases)

[1]Hahn RT. Tricuspid Regurgitation. N Engl J Med 2023;388:1876-91. doi: 10.1056/NEJMra2216709

5-Grade Scale for TR Severity

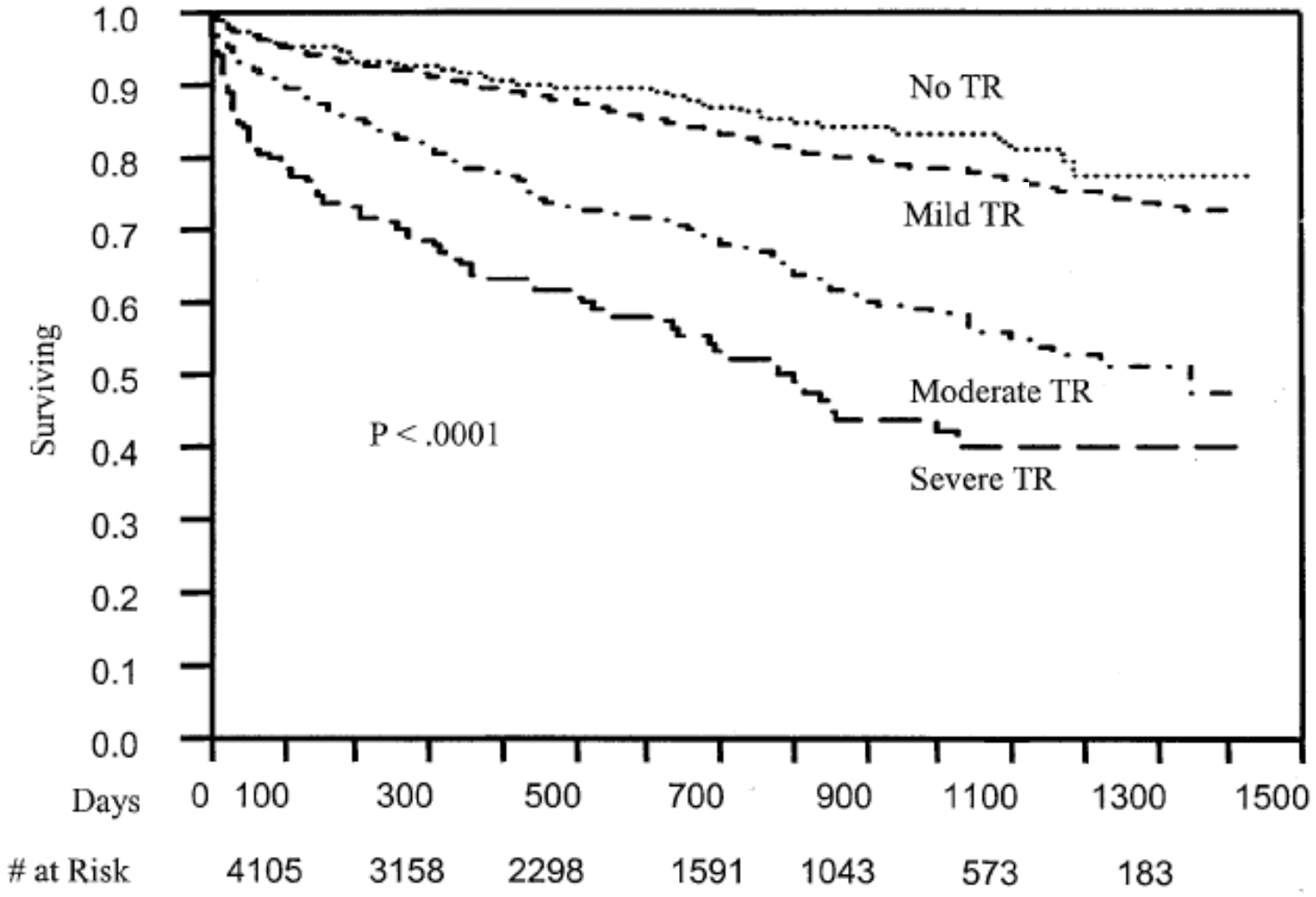
5-Grade Scale for Assessing TR Severity					
	Trace/Mild	**Moderate**	**Severe (Severe 3)**	**Massive (Severe 4)**	**Torrential (Severe 5)**
Vena contracta (biplane, mm)	<3	3–6.9	7–13	14–20	≥ 21
PISA radius (mm)	<6	6–9	>9	>9	>9
EROA (mm^2)	<20	20–39	40–59	60–79	≥80
Regurgitant volume (mL)	<15	15–44	45–59	60–74	≥75
3D VCA or quantitative EROA (mm^2)			75–94	95–114	≥115
IVC diameter (cm)	<2	2.1–2.5	>2.5	>2.5	>2.5
Hepatic flow	Systolic dominant	Systolic blunt	Systolic reversal	Systolic reversal	Systolic reversal

PISA: proximal isovelocity surface area; EROA: effective regurgitant orifice area; 3D VCA: three-dimensional vena contracta area; IVC: inferior vena cava

Hahn RT, Zamorano JL. The Need for a New Tricuspid Regurgitation Grading Scheme. Eur Heart J Cardiovasc Imaging 2017;18(12):1342-1343. doi:10.1093/ehjci/jex139

TR Signs/Symptoms & Mortality

- TR signs and symptoms
  - Ascites
  - Peripheral edema
  - Liver dysfunction
  - Decreased appetite
  - Jugular vein distention
  - Abdominal fullness
- Survival reduced in patients with moderate and severe TR



Kaplan-Meier Survival Curves for All Patients with TR[1]

[1]Nath J, Foster E, Heidenreich PA. Impact of tricuspid regurgitation on long-term survival. J Am Coll Cardiol 2004;43(3):405-9. doi:10.1016/j.jacc.2003.09.036

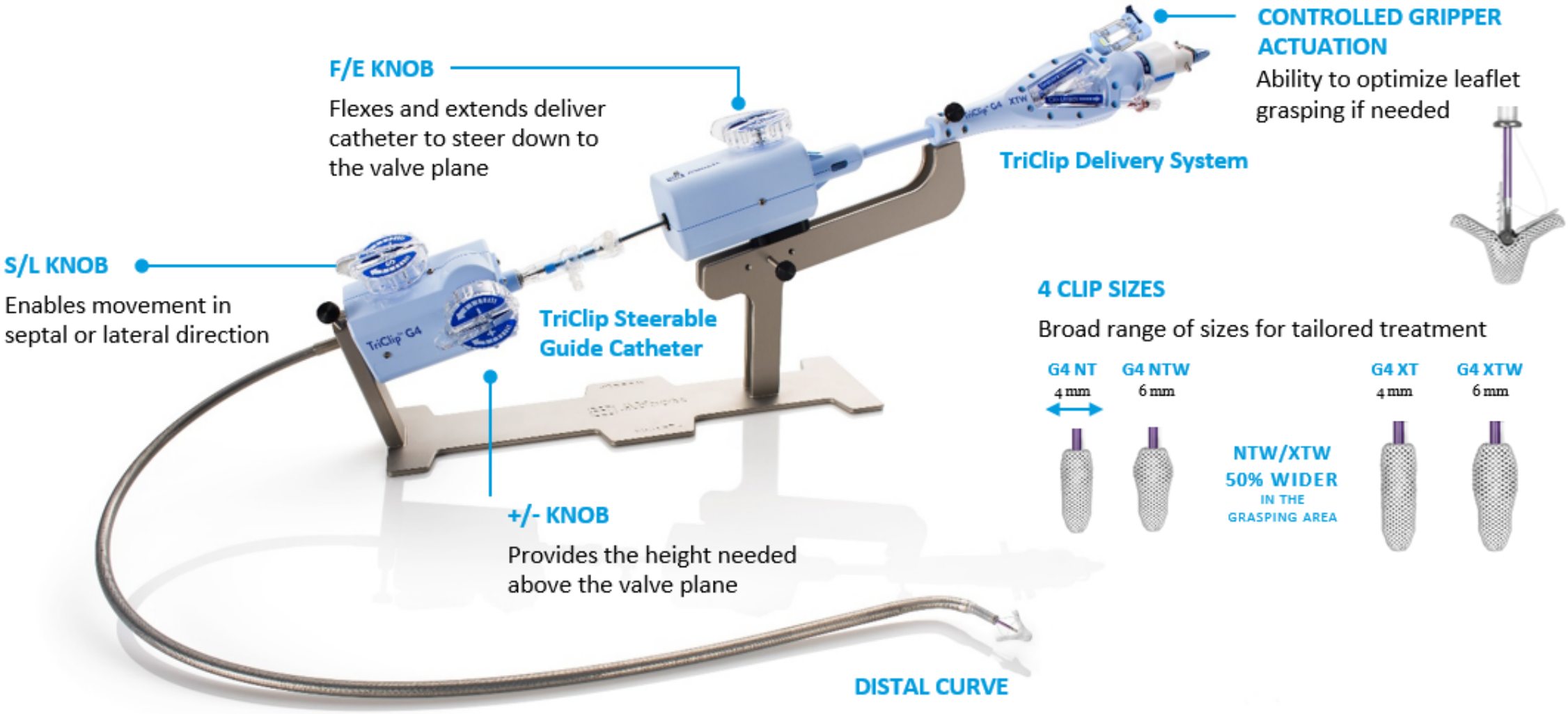
Current Severe TR Treatment

- Medical Therapy
  - Mainly diuretics to manage volume overload
    - Often ineffective, especially if diuretic resistance present
- Tricuspid Valve Surgery
  - Isolated TV surgery frequency has increased over the last decade, but only 15% of patients who underwent TV surgery had an isolated TV procedure[1]
  - In-hospital mortality ranges from 8.1% to 10.9% (unchanged over the last decade)

- **Most patients with moderate or severe TR are not offered surgery**
- **Isolated TV surgery uncommonly performed due to high operative mortality rate**

[1]Zack CJ, Fender EA, Chandrashekar P, et al. National Trends and Outcomes in Isolated Tricuspid Valve Surgery. J Am Coll Cardiol 2017;70:2953-2960. doi:10.1016/j.jacc.2017.10.039.

TriClip G4 System



Proposed Indications for Use

The TriClip G4 System is indicated for the **improvement of health status** in patients with symptomatic severe tricuspid regurgitation despite being treated optimally with medical therapy, who are at intermediate or greater risk for surgery, and in whom tricuspid valve edge-to-edge repair is appropriate **as determined by a heart team**.

Non-Clinical Testing

- Design verification & validation (including delivery system testing)
- Stability (shelf life, corrosion, FEA, fatigue, and particulate testing)
- Human factors
- MRI
- Packaging & sterilization
- GLP animal studies
- Biocompatibility

Non-clinical testing is complete and acceptable

Regulatory Timeline

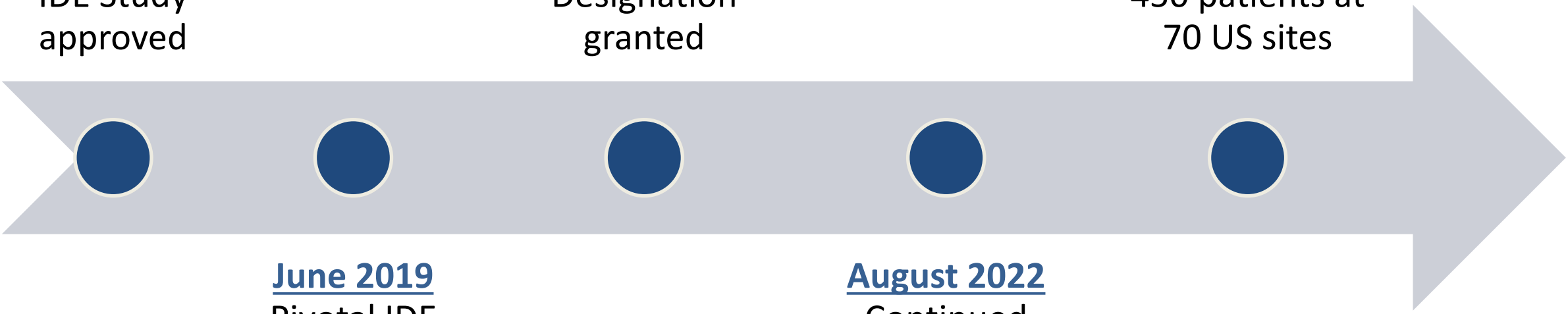
June 2017
Early Feasibility IDE Study approved

June 2019
Pivotal IDE Study approved

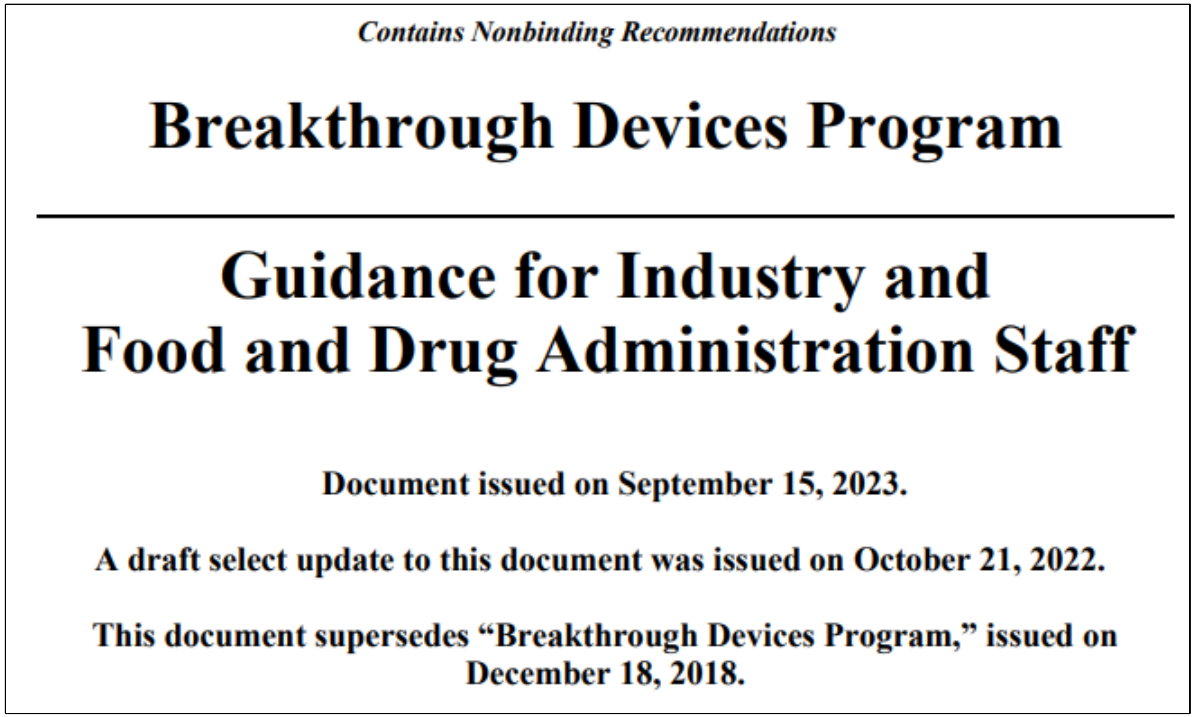
November 2020
Breakthrough Device Designation granted

August 2022
Continued Access Study (CAS) approved

September 2023
CAS expanded to 450 patients at 70 US sites



Breakthrough Devices Program



Contains Nonbinding Recommendations

Breakthrough Devices Program

Guidance for Industry and Food and Drug Administration Staff

Document issued on September 15, 2023.

A draft select update to this document was issued on October 21, 2022.

This document supersedes "Breakthrough Devices Program," issued on December 18, 2018.

- A breakthrough device has the potential to provide more effective treatment or diagnosis of a life-threatening or irreversibly debilitating disease vs. current available options
- The program is intended to provide patients with timely access to selected devices by expediting their development, assessment and review
- The TriClip System was granted breakthrough status in November 2020 for patients with severe symptomatic TR despite OMT

Breakthrough Devices Program

- Allows for:
  - Review team support
  - Enhanced timely interactions with FDA
  - Efficient and flexible clinical study design
  - Balanced pre/postmarket data collection
  - Priority review
- Does not alter or reduce the statutory requirement for premarket approval (a reasonable assurance of safety and effectiveness)

Pre/Postmarket Balance of Data Collection

- FDA may accept greater uncertainty for a premarket submission along with timely postmarket data collection if the uncertainty is sufficiently balanced and addressed
- Benefit/Risk considerations include:
  - Probable benefits from earlier access, vs.
  - Probable risk of harm should postmarket data show that the device is ineffective or unsafe

Patient Reported Outcomes (PROs)

Per FDA's 2009 Guidance, a PRO:[1]

- Is a status report of a patient's health condition directly from the patient without interpretation of the patient's response by a clinician or anyone else
- Can measure the effect of a medical intervention in a clinical trial
- Can be measured in absolute terms or as a change from a previous measure

[1]Food and Drug Administration. Guidance for Industry: Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims. December 2009. [Accessed January 6, 2024.] Available at: https://www.fda.gov/downloads/drugs/guidances/ucm193282.pdf

Patient Reported Outcomes (PROs)

- Reliability, validity, and the ability to detect changes are considered in FDA's review of PRO instruments
- Data captured by reliable PRO instruments in well-designed clinical studies can be used to support product labeling claims if the claim is consistent with the instrument's measurement capability

- **Partnering with patients is a CDRH strategic priority**
- **As part of this commitment, the Center encouraged increased use of PROs in regulatory decision making**

Kansas City Cardiomyopathy Questionnaire (KCCQ)

- A self-administered PRO instrument for measuring health status in HF patients[1]
- Includes 23 items across 7 domains
  - Symptom frequency, burden, & stability
  - Physical & social limitations
  - Social limitations
  - Quality of life
  - Self-efficacy
- CDRH-qualified in 2020 in the Medical Device Development Tools (MDDT) Program as a clinical outcome assessment PRO instrument for adults ≥18 years of age with symptomatic HF[2]

[1]Green CP, Porter CB, Bresnahan DR, Spertus JA. Development and Evaluation of the Kansas City Cardiomyopathy Questionnaire: a New Health Status Measure for Heart Failure. J Am Coll Cardiol 2000; 35:1245–1255. doi: 10.1016/s0735-1097(00)00531-3.
[2]Food and Drug Administration. Qualification of the Kansas City Cardiomyopathy Questionnaire Clinical Summary Score and its Component Scores: A Patient-Reported Outcome Instrument for Use in Clinical Investigations in Heart Failure. April 9, 2020. [Accessed January 6, 2024.] Available at: https://www.fda.gov/media/136862/download.

Use of PROs in Blinded Vs. Open-Label Trials

- Per the 2009 FDA Guidance[1]
  - The effect of intentional unblinding is important to consider in interpreting clinical trial results
  - In certain situations, such as in the evaluation of some medical devices or administration of identifiable treatments, blinding not feasible
- In open-label trials, PROs may be subject to bias/placebo effect
- Limited research available with no definitive conclusions regarding bias (and the potential magnitude of bias) in open-label studies

[1]Food and Drug Administration. Guidance for Industry: Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims. December 2009. [Accessed January 6, 2024.] Available at: https://www.fda.gov/downloads/drugs/guidances/ucm193282.pdf

Addressing Potential PRO Bias in Open-Label Trials

- Administer the PRO instrument prior to randomization and retest post-randomization but before the investigational intervention is performed
- Considerations in interpreting PRO data
  - Compare PRO outcomes from similar trials that differ in their design (i.e., blinded vs. open label)
  - Durability of treatment benefits
    - Placebo effects expected to wane over time (but duration generally not established)
  - Assess responses in specific PRO domains
    - PRO responses proximal to the device's mechanism of action (e.g., symptoms associated with severe TR and improvement following TR reduction) may be more relevant than more distal domains (such as emotional function, social function, and global quality of life)

The TRILUMINATE Pivotal Trial

- Prospective, open-label, multicenter, randomized (1:1), controlled clinical trial designed to test the superiority of TriClip device plus optimal medical therapy (OMT) to OMT alone
- Enrolled symptomatic severe TR patients at intermediate or greater surgical risk who were on stable optimized HF medical therapy

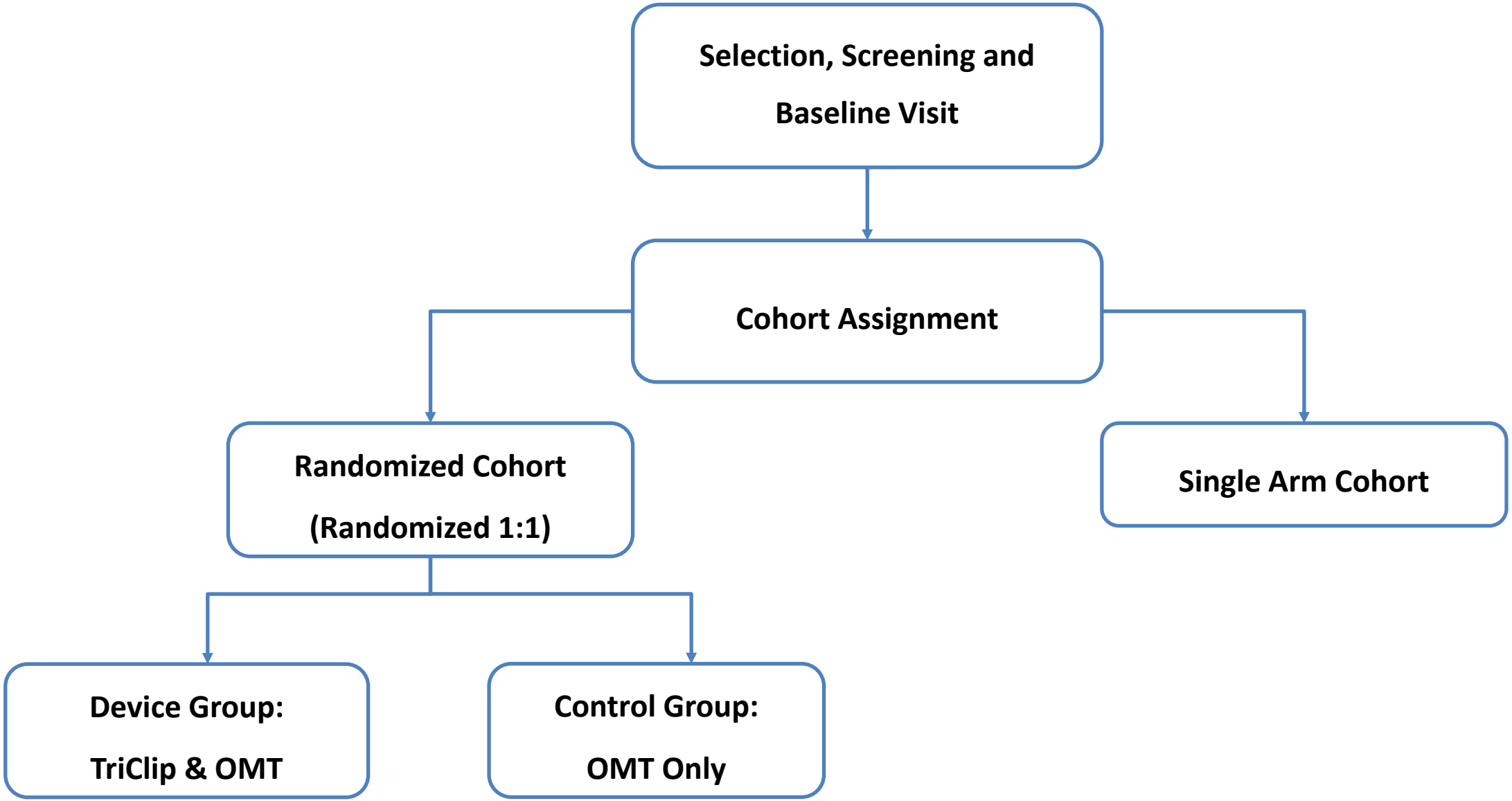
Primary Analysis Cohort N=350 Study Patients
Full Randomized Cohort N=572 Study Patients

The TRILUMINATE Single Arm Cohort

- Prospective, open-label, multicenter, nonrandomized controlled clinical trial designed to show that any reduction in TR provides health status benefit, even if TR severity was not reduced to moderate or less
- Enrolled symptomatic severe TR patients at intermediate or greater surgical risk who were on stable optimized HF medical therapy and who were determined by the Eligibility Committee to have a high likelihood of achieving at least 1 grade of TR reduction but a low likelihood of achieving moderate or less TR

N=100 Study Patients

Cohort Assignment



Key Inclusion Criteria

Randomized and Single Arm Cohorts

- Symptomatic with severe TR
- NYHA Functional Class II, III or ambulatory class IV
- Adequately treated as follows and stable for at least 30 days:
  - OMT for TR
  - Medical and/or device therapy for other cardiac conditions
- Intermediate or greater risk for TV surgery
- Femoral vein access was feasible and could accommodate a 25 Fr catheter

Key Exclusion Criteria

Randomized and Single Arm Cohorts

- Severe pulmonary hypertension
- Indication for other valve interventions in the prior 60 days.
- Prior TV procedure, or the presence of pacemaker or implantable ICD leads, which would interfere with placement of the TriClip device.
- Left ventricular ejection fraction ≤20%.
- Tricuspid valve anatomy which may preclude clip implantation, clip positioning, or sufficient TR reduction

Statistical Analysis

Xuan Ye, PhD
Statistician
Office of Clinical Evidence and Analysis

Randomized Cohort Primary Endpoint

- Primary endpoint: Hierarchical composite of 3 components at 12 months
  1. Time to all-cause death or tricuspid valve surgery
  2. Number of heart failure hospitalizations (HFH)
  3. Incidence of an improved KCCQ score ≥15 points vs. baseline
- Primary endpoint hypothesis tested using the Finkelstein-Schoenfeld method

H0: None of the components are different between the TriClip and the control group

H1: At least one component is different between the TriClip and the control group

Trial success would be declared if the primary endpoint for the Randomized Cohort was met

Randomized Cohort Adaptive Design & Interim Analysis

- Planned adaptive design
  - Minimum sample size n=350
  - Sample size re-estimation when the first 150 patients reach 12 months follow-up
  - Maximum sample size n=1000 after re-estimation
  - Type I error rate controlled using Cui, Hung, and Wang method*
- Interim analysis result
  - 572 patients already randomized at the time when the 150 patients reached 12 months follow-up
  - No sample size increase needed

- **Primary analysis cohort consisting of first 350 randomized patients**
- **Results from all 572 randomized patients also presented**

*Cui, L., Hung, H. J., & Wang, S. J. (1999). Modification of sample size in group sequential clinical trials. Biometrics, 55(3), 853-857.

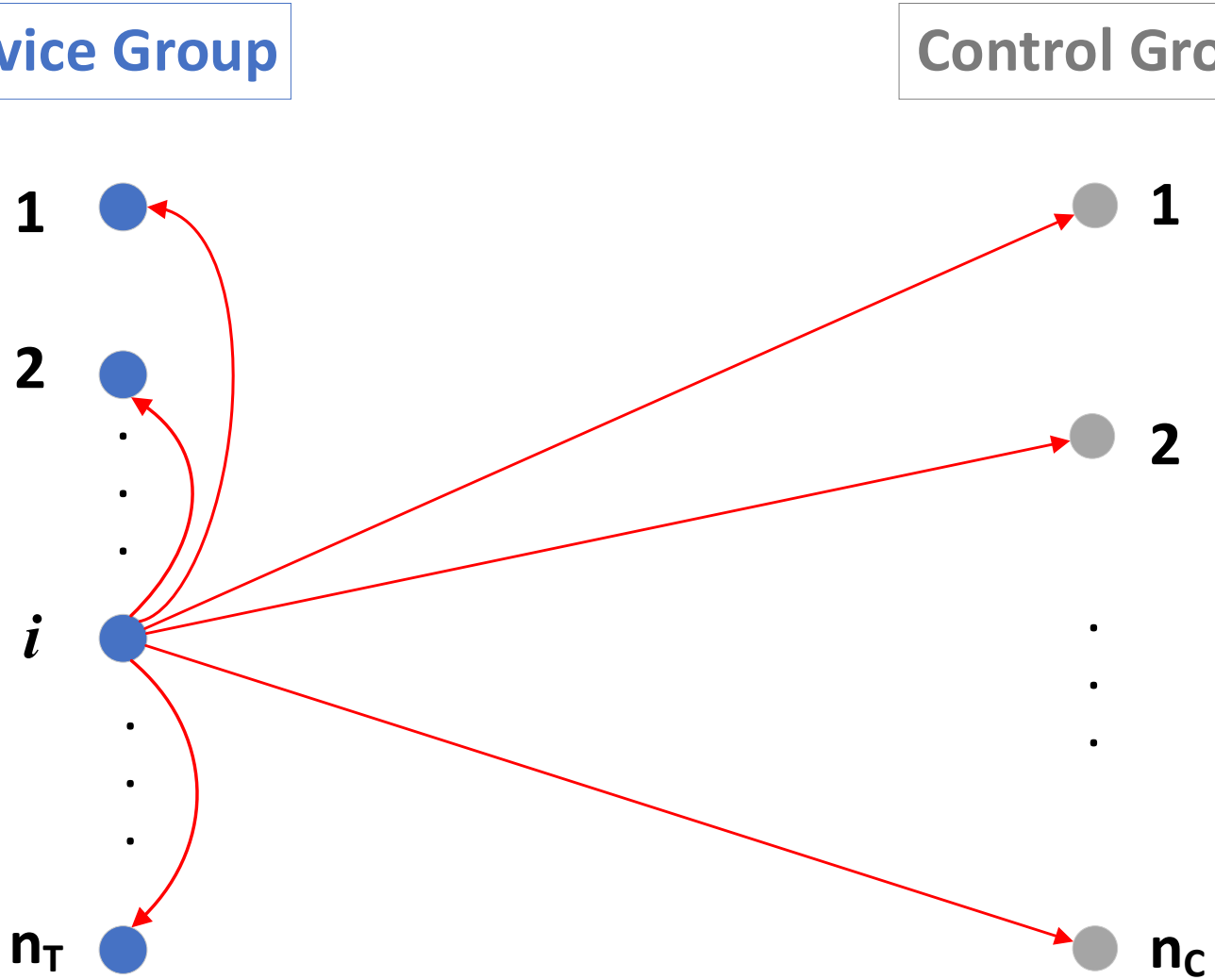
Finkelstein-Schoenfeld Test Method

- A nonparametric test based on a hierarchical pairwise comparison procedure that is a modification of the generalized Wilcoxon test
- Each patient is compared to every other patient
  - Patients in each pair are compared for the hierarchical components in sequence
- The patient who has better outcome is assigned a score of +1 while the other patient is assigned a score of -1
  - If not possible to determine which patient has a better outcome, a score of 0 is assigned to both patients
- The test statistic numerator is the sum of +1, -1, and 0 scores of all device group patients

Finkelstein-Schoenfeld hypothesis tested at a two-sided $\alpha = 0.05$

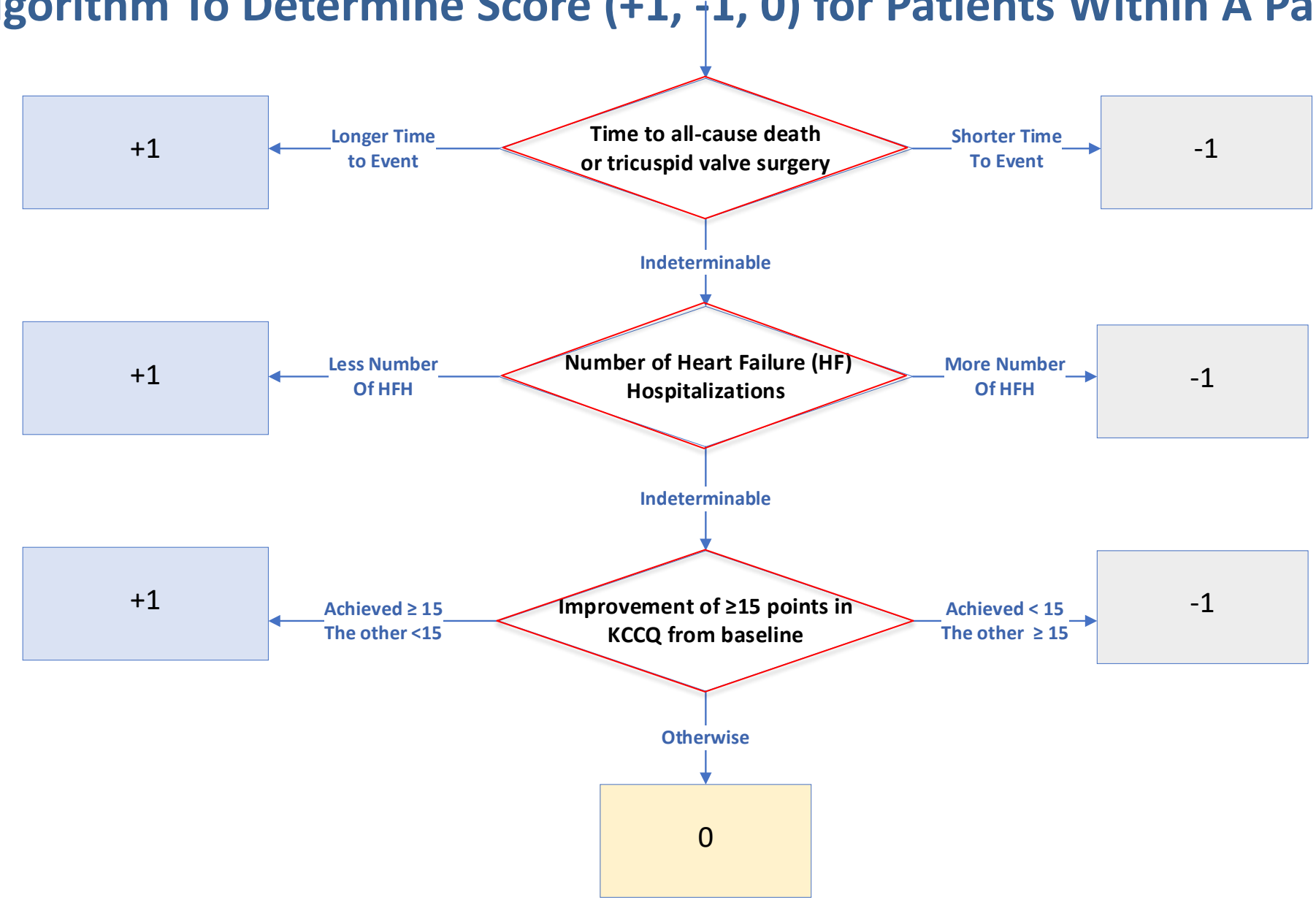
Finkelstein-Schoenfeld Test Method Example

One Device Group Patient Compared to All Other Patients



Finkelstein-Schoenfeld Method Example

Algorithm To Determine Score (+1, -1, 0) for Patients Within A Pair



Finkelstein-Schoenfeld Test Scores

		Device Group							Control Group							Score
		1	**2**	**…**	**i**	**…**	$\mathbf{n_T}$		**1**	**2**	**…**	**j**	**…**	$\mathbf{n_C}$		
Device Group	**1**	-	+1		-1		0		+1	-1		+1		+1		U_1
	2	-1	-		+1		+1									U_2
	…			-												…
	i	+1	-1		-		+1									U_i
	…					-										…
	$\mathbf{n_T}$	0	-1		-1		-									U_{n_T}
																$T=\sum U_i$

Finkelstein-Schoenfeld test statistic = $T/\sqrt{V}$

T is the sum of +1, -1, and 0 of all device group patients, $\sqrt{V}$ is the standard deviation of T

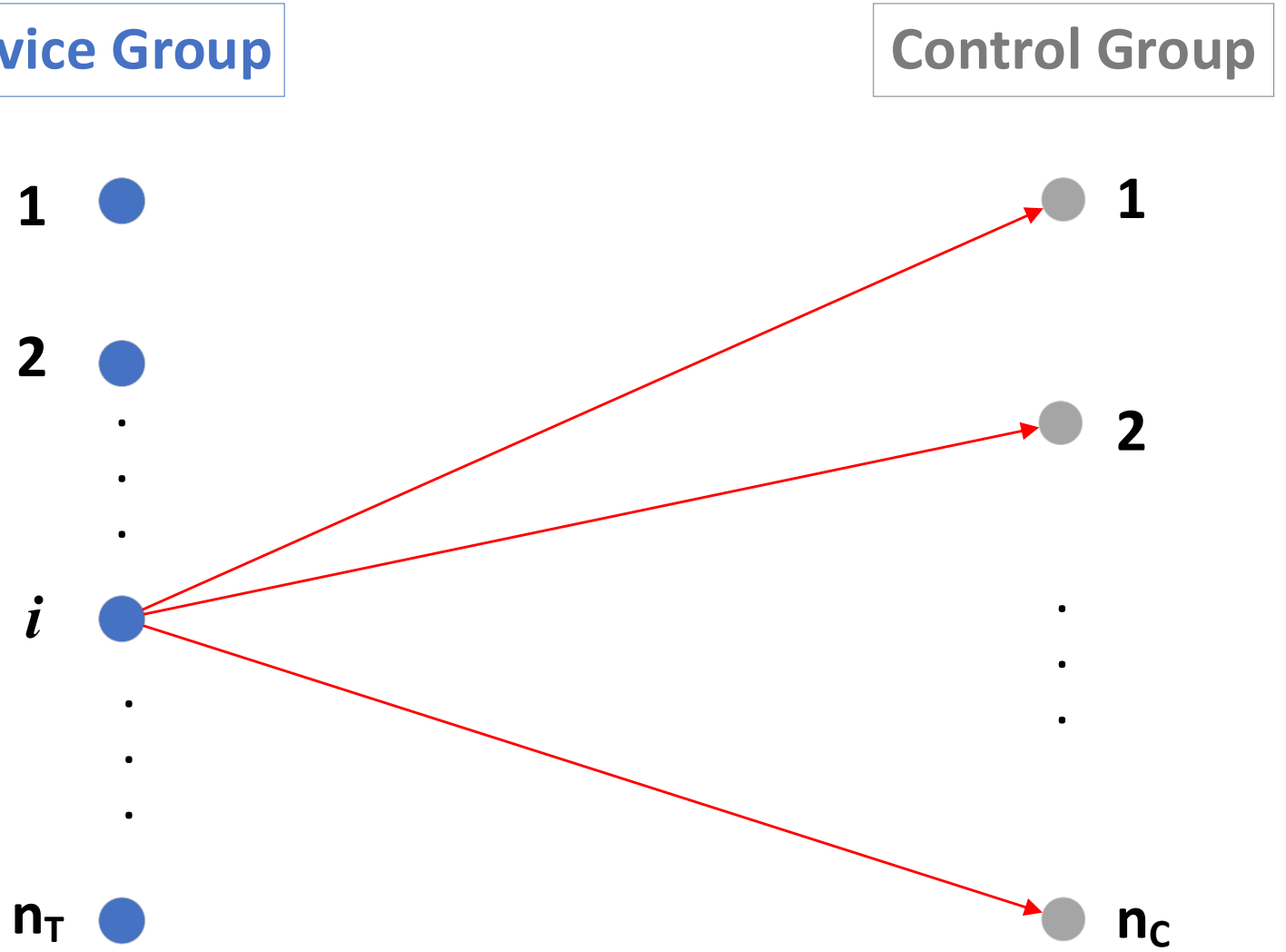
Supplementary Win Ratio Analysis

- Provides an estimate of the odds that the better outcome occurs in the treatment group patient
- Each device group patient is compared to each control group patient in the order of the hierarchical endpoint criteria
- Treatment or control patient with the better outcome = Winner
  - If not possible to determine a winner, a tie is declared, and the result is not used in the win ratio calculation
- Win ratio defined as the total number of wins in device group divided by the total number of wins in control group

$$Win\ ratio = \frac{\#\ of\ wins\ in\ Device}{\#\ of\ wins\ in\ Control}$$

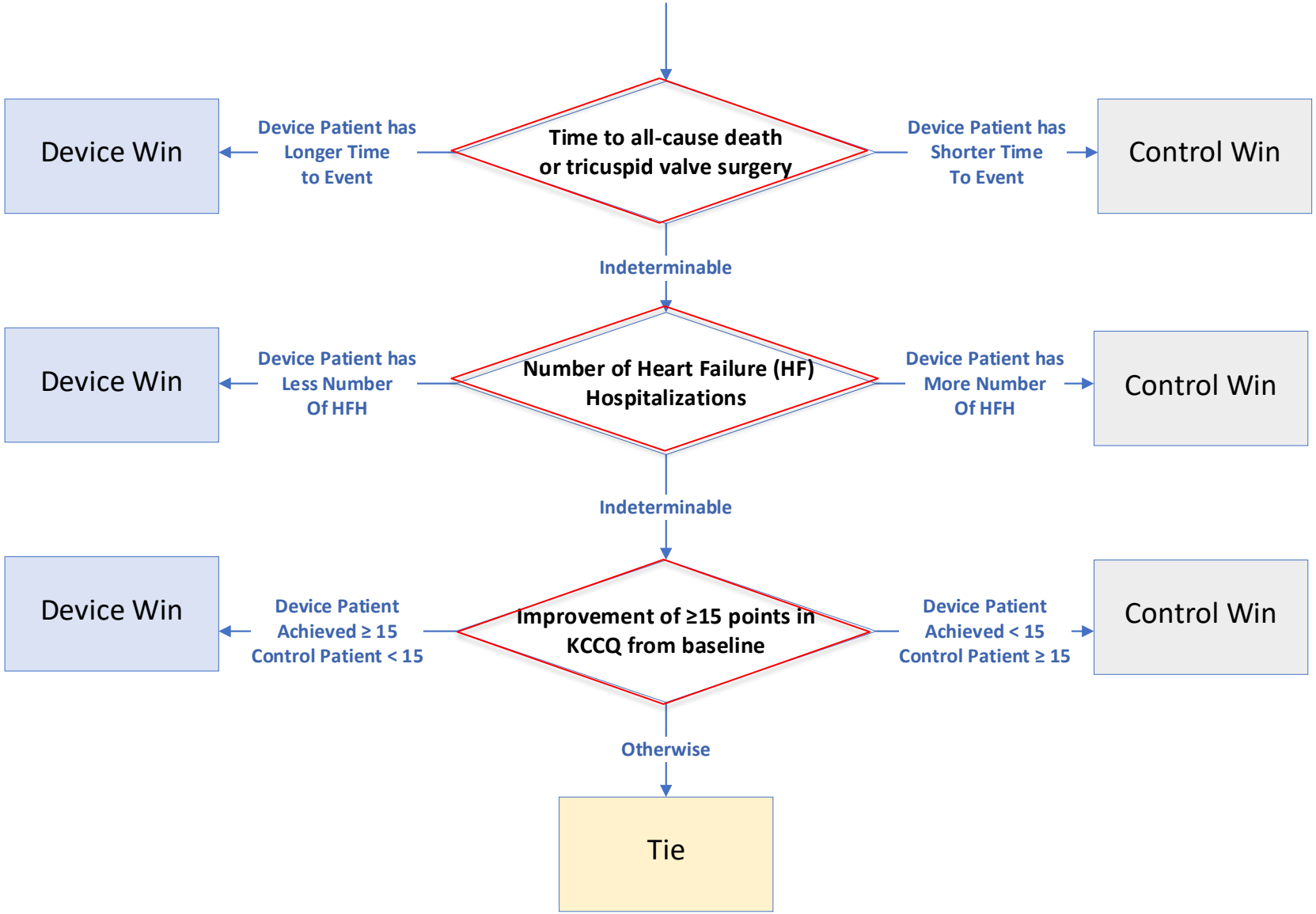
Win Ratio Analysis Method Example

One Device Group Patient Compared to All Control Patients



Win Ratio Method Example

Algorithm to Determine Winner within Each Device-Control Patient Pair



Win Ratio Analysis

	Control Group						
Device Group		1	2	…	j	…	n_C
	1	Device Win	Tie		Control Win		Tie
	2	Device Win	Control Win		Device Win		Control Win
	…	…					
	i						
	…						
	n_T						

Single-Arm Cohort Trial Primary Endpoint

- Survival and improvement in KCCQ score by ≥10 points vs. baseline at 12 months
- Primary endpoint test hypotheses

$$H_0\text{: } P(12M) \leq 30\%$$

$$H_1\text{: } P(12M) > 30\%$$

where P(12M) represents the proportion of patients who survive at 12 months and have at least 10-point improvement in KCCQ at 12 months

Single-Arm Cohort Trial Analysis Plan

Group Sequential Design

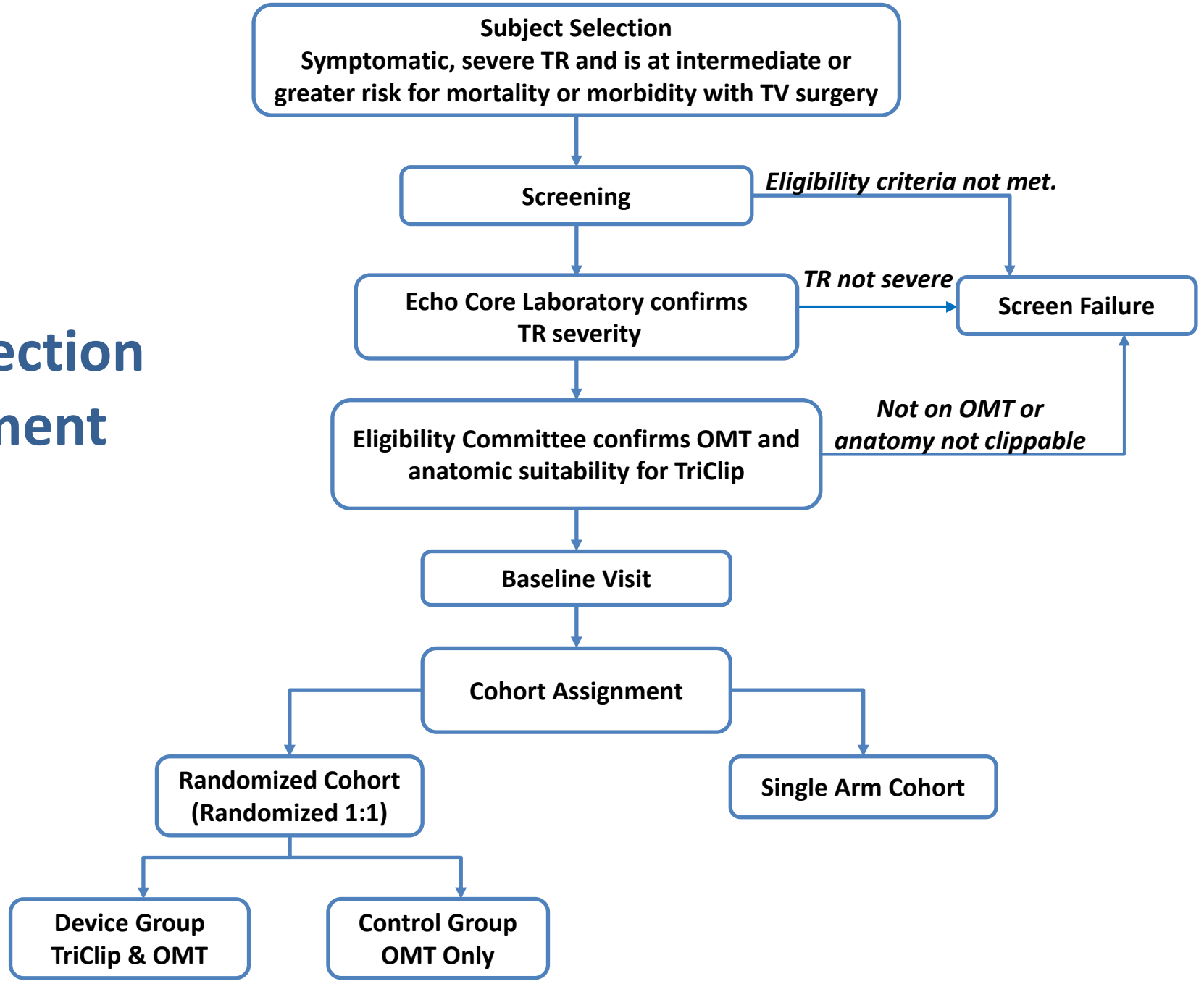
- Exact test for binomial distribution with overall one-sided $\alpha = 0.025$
- Planned interim analysis when the first 100 enrolled patients complete 12 months follow-up
  - Early success may be claimed if the test is successful at the interim analysis
  - Half of the α spent at the interim analysis
  - Final analysis at sample size n=200, if the test not successful at interim analysis

Interim analysis result: Hypothesis test successful with sample size of n=100

Pivotal Clinical Study Results

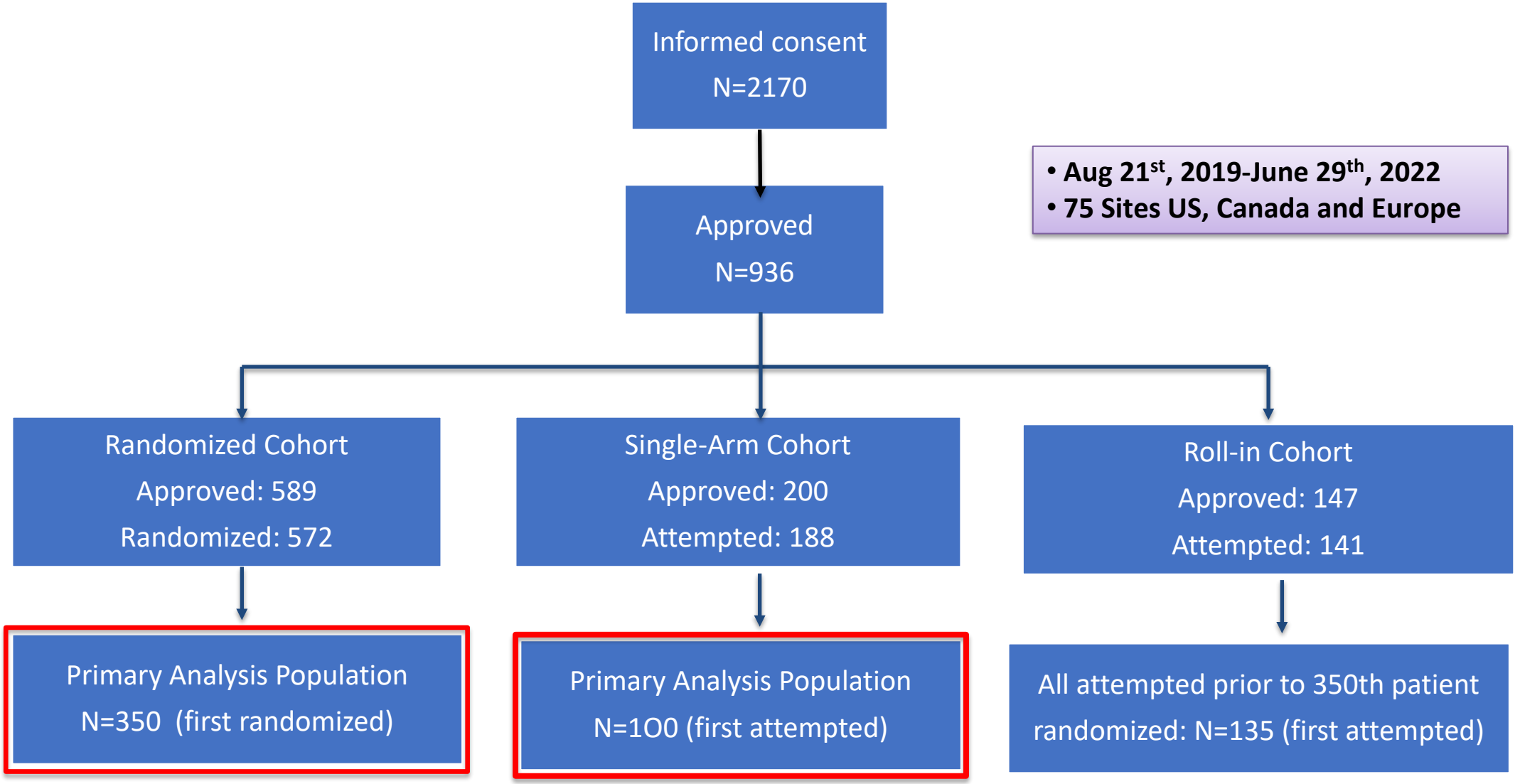
Mauro Moscucci, MD, MBA, MPH
Interventional Cardiologist
Medical Officer
Office of Cardiovascular Devices

Patient Selection & Assignment



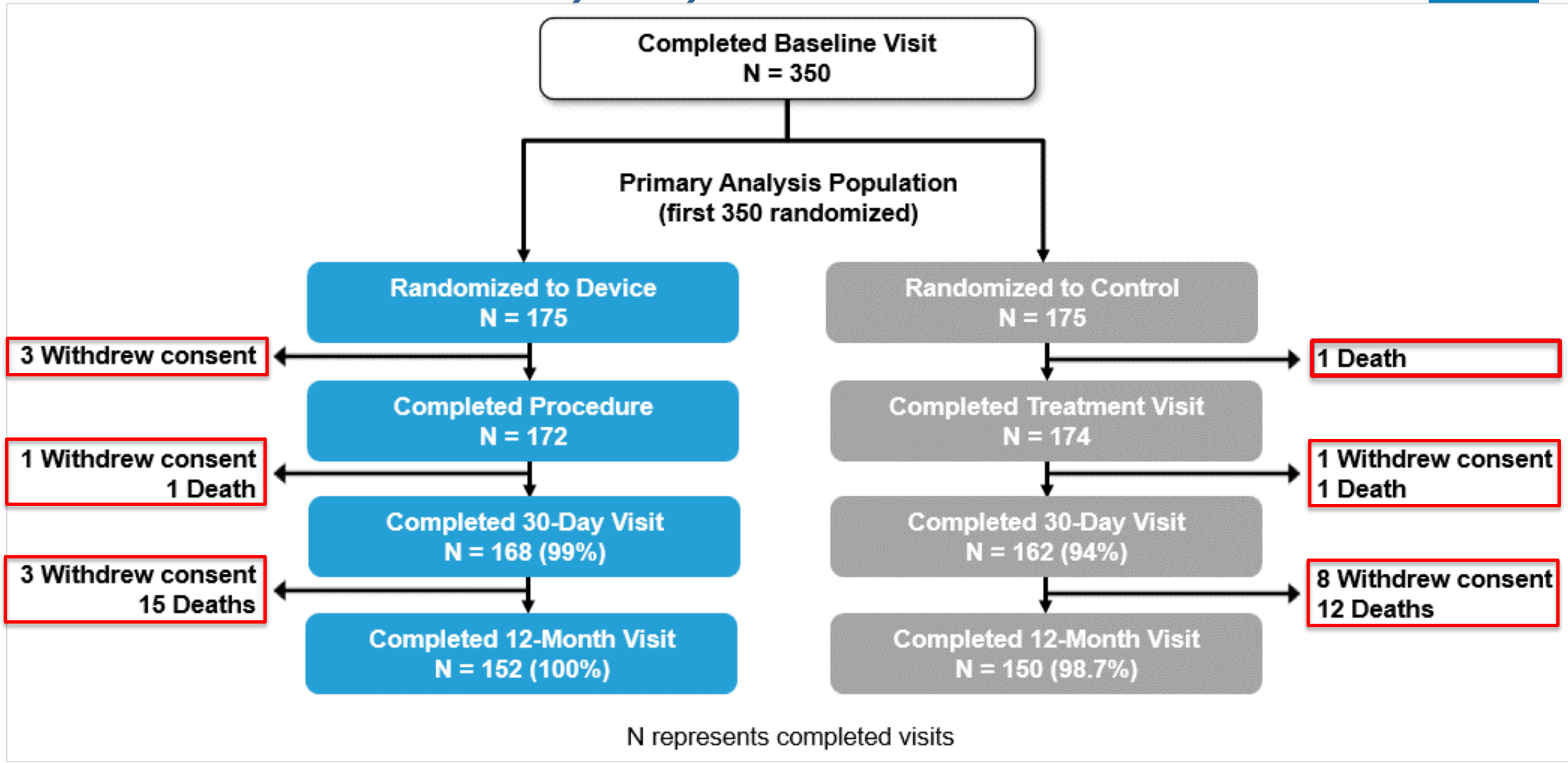
Patient Accountability

Randomized Cohort- Single Arm Cohort - Roll-in Cohort



Patient Disposition

Primary Analysis Randomized Cohort



Randomized Cohort Blinding

Unblinded to treatment group

- Study patients
- Investigators
- Sonographers
- Clinical Events Committee

Blinded to treatment group

Research staff administering

- KCCQ
- 6-minute walk test
- SF-36
- NYHA Class

Not assessed:

- **Research staff maintenance of blinding**
- **Study patients' awareness of follow-up echo results**

Primary Analysis Randomized & Single Arm Cohort Demographics

Demographics	Summary Statistic*		
	Randomized Cohort (N=350)		Single Arm Cohort (N=100)
	Device (N=175)	Control (N=175)	
Demographics			
Age	78.0 ± 7.4 (175)	77.8 ± 7.2 (175)	80.4 ± 6.2 (100)
Sex			
Male	44.0% (77/175)	46.3% (81/175)	47.0% (47/100)
Female	56.0% (98/175)	53.7% (94/175)	53.0% (53/100)
Race			
Caucasian	85.1% (149/175)	81.7% (143/175)	87.0% (87/100)
Black/African American	4.0% (7/175)	5.7% (10/175)	7.0% (7/100)
Asian	4.0% (7/175)	4.0% (7/175)	3.0% (3/100)
American Indian/Alaska Native	0.6% (1/175)	0.0% (0/175)	0.0% (0/100)
Native Hawaiian/Pacific Islander	0.0% (0/175)	0.0% (0/175)	0.0% (0/100)
Declined or unable to disclose	6.3% (11/175)	8.6% (15/175)	3.0% (3/100)
Ethnicity			
Hispanic or Latino	2.9% (5/175)	5.1% (9/175)	4.0% (4/100)
Not Hispanic or Latino	93.1% (163/175)	87.4% (153/175)	94.0% (94/100)
Declined/unknown	4.0% (7/175)	7.4% (13/175)	2.0% (2/100)

Primary Analysis Randomized & Single Arm Cohort Baseline Characteristics

Baseline Characteristics	Summary Statistic*		
	Randomized Cohort (N=350)		Single-Arm Cohort (N=100)
	Device (N=175)	Control (N=175)	
Atrial fibrillation	87.4% (153/175)	93.1% (163/175)	93.0% (93/100)
COPD	10.9% (19/175)	13.7% (24/175)	22.0% (22/100)
CRT/CRT-D/ICD/pacemaker	16.0% (28/175)	13.7% (24/175)	35.0% (35/100)
Liver disease	6.3% (11/175)	9.1% (16/175)	3.0% (3/100)
Renal disease	35.4% (62/175)	35.4% (62/175)	36.0% (36/100)
Peripheral vascular disease	9.1% (16/175)	10.3% (18/175)	11.0% (11/100)
Prior AV intervention	15.4% (27/175)	15.4% (27/175)	11.0% (11/100)
Prior MV intervention	25.7% (45/175)	24.0% (42/175)	36.0% (36/100)
KCCQ summary score	56.0 ± 23.4 (175)	54.1 ± 24.2 (174)	54.5 ± 22.6 (99)
6MWD (m)	240.5 ± 117.1 (164)	253.6 ± 129.1 (169)	237.7 ± 120.4 (97)
NYHA functional class			
Class I	0.0% (0/175)	0.0% (0/175)	0.0% (0/100)
Class II	40.6% (71/175)	44.6% (78/175)	41.0% (41/100)
Class III	57.1% (100/175)	52.0% (91/175)	53.0% (53/100
Class IV	2.3% (4/175)	3.4% (6/175)	6.0% (6/100)

Primary Analysis Randomized & Single Arm Cohort
Baseline TR Severity, TR Etiology, Coaptation Gap

TR Characteristics	Summary Statistic		
	Randomized Cohort (N=350)		Single-Arm Cohort (N=100)
	Device (N=175)	Control (N=175)	
TR severity			
Trace	0.0% (0/173)	0.0% (0/165)	0.0% (0/96)
Mild	0.0% (0/173)	0.0% (0/165)	0.0% (0/96)
Moderate	2.3% (4/173)	1.2% (2/165)	0.0% (0/96)
Severe grade 3 (severe)	25.4% (44/173)	29.7% (49/165)	9.4% (9/96)
Severe grade 4 (massive)	21.4% (37/173)	18.2% (30/165)	16.7% (16/96)
Severe grade 5 (torrential)	50.9% (88/173)	50.9% (84/165)	74.0% (71/96)
TR etiology			
Functional	94.8% (165/174)	92.9% (158/170)	85.9% (85/99)
Degenerative	2.3% (4/174)	1.2% (2/170)	5.1% (5/99)
Mixed	2.9% (5/174)	5.9% (10/170)	4.0% (4/99)
Pacer-related	0.0% (0/174)	0.0% (0/170)	5.1% (5/99)
Coaptation gap (mm)	5.5 ± 1.8 (137)	5.2 ± 1.7 (142)	7.4 ± 2.7 (75)

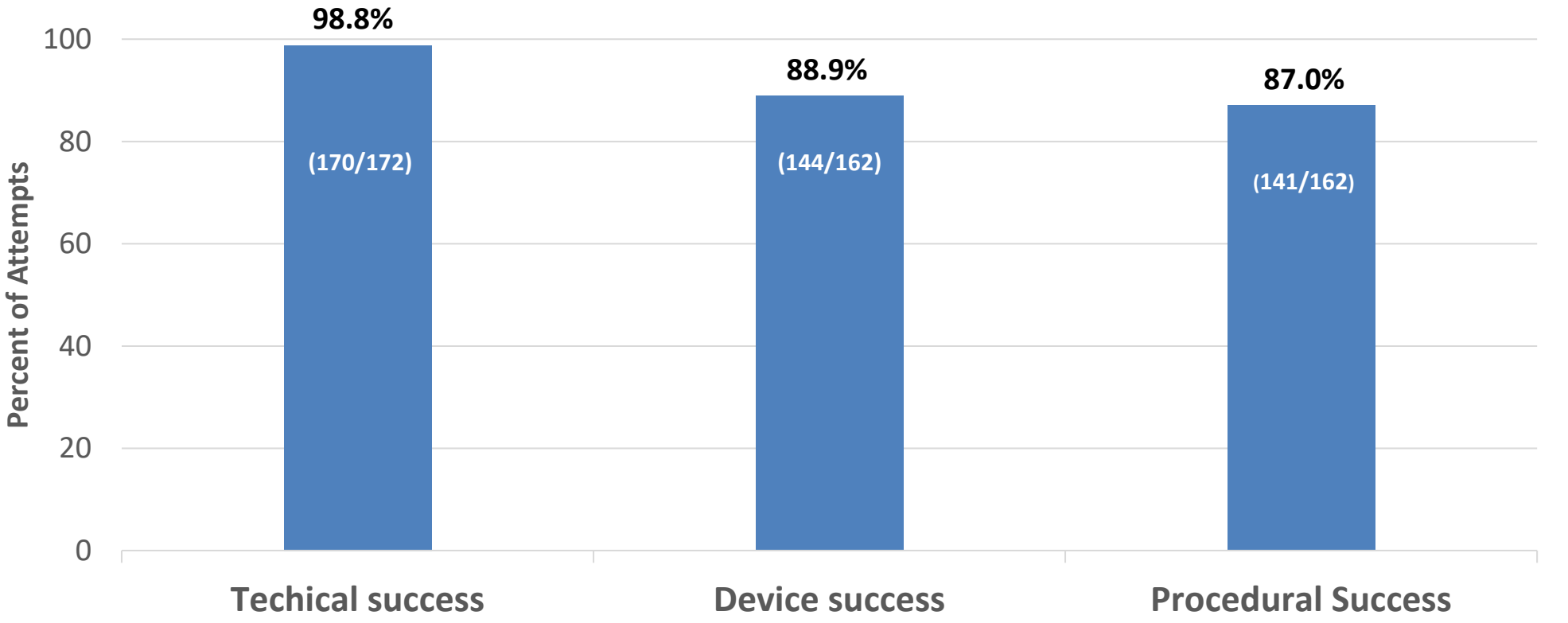
Select TriClip Procedure Data

Procedure Data	Summary Statistic	
	Randomized Cohort (Device Arm) (N=172)	Single-Arm Cohort (N=100)
Number of clips implanted	2.2 ± 0.7 (172)	2.2 ± 0.8 (100)
0 clips	1.2% (2/172)	2.0% (2/100)
1 clip	10.5% (18/172)	12.0% (12/100)
2 clips	61.0% (105/172)	49.0% (49/100)
3 clips	24.4% (42/172)	35.0% (35/100)
4 clips	2.9% (5/172)	2.0% (2/100)
Device used		
TriClip (first-generation)	47.1% (81/172)	67.0% (67/100)
TriClip G4	52.9% (91/172)	33.0% (33/100)
Total procedure time (min)	151.0 ± 71.7 (171)	153.5 ± 65.3 (100)
Device time (min)	89.7 ± 66.4 (168)	84.4 ± 58.8 (100)
Fluoroscopy exposure (min)	31.9 ± 23.5 (171)	33.0 ± 22.3 (99)

*Continuous measures: Mean ± SD (total no.); Categorical measures : % (no./total no.)

Procedure Outcomes

Technical, Device and Procedural Success



2 patients: Inability to successfully deploy the TriClip

- 10 Patients missing TR assessment
- 11 Patients Single leaflet attachment
- 3 Patients – no TR reduction
- 1 death within 30 days

- 18 Patients without device success
- 1 patient single leaflet attachment
- 1 Patient Rupture chordae
- 1 Patient access site complication

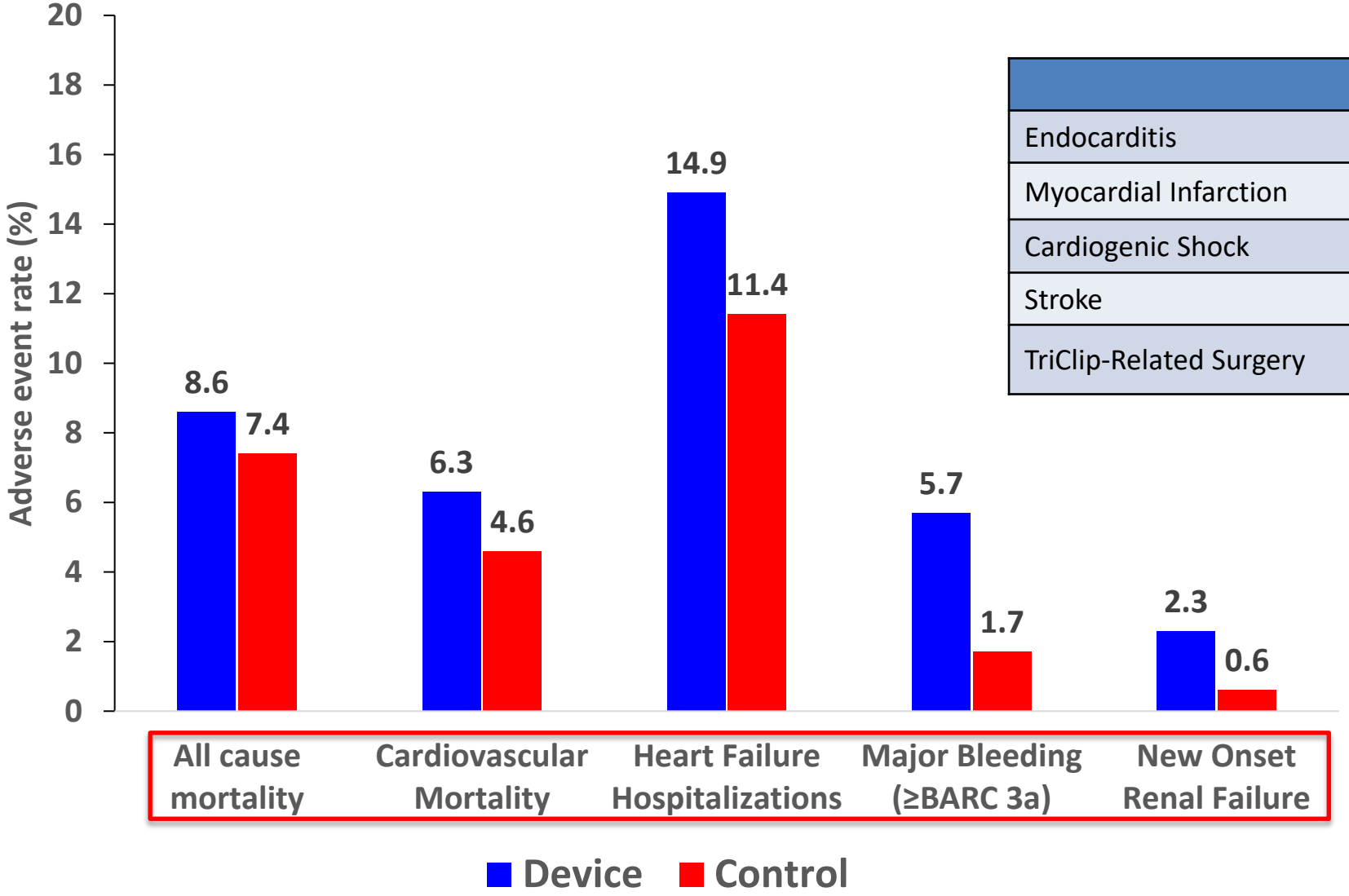
Major Adverse Events at 30 Days

Randomized Cohort Attempted TriClip Procedure Population

	Event Rate*
Cardiovascular mortality	0.6% (1/172)
New onset renal failure	1.2% (2/172)
Endocarditis requiring surgery	0% (0/172)
Non-elective cardiovascular surgery for TriClip device-related adverse events post-index procedure	0% (0/172)

*% (no./total no.)

Select CEC-Adjudicated Adverse Events through 12 Months *Primary Analysis Randomized Cohort (ITT)*

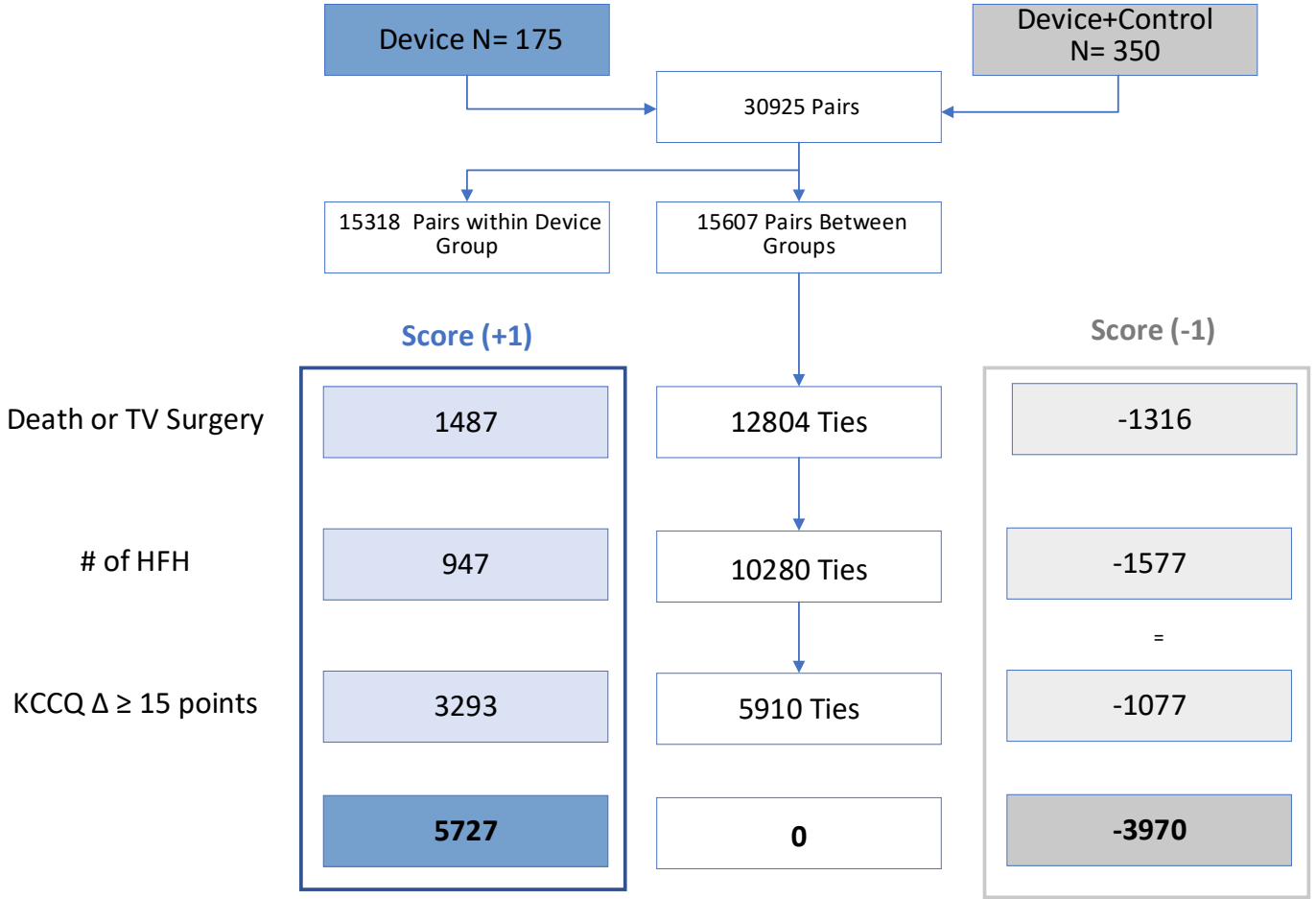


	Device	Control
Endocarditis	0	0
Myocardial Infarction	0	0
Cardiogenic Shock	0	0
Stroke	1.7%	1.7%
TriClip-Related Surgery	0	NA

Primary Endpoint Results

Primary Analysis Randomized Cohort (ITT)

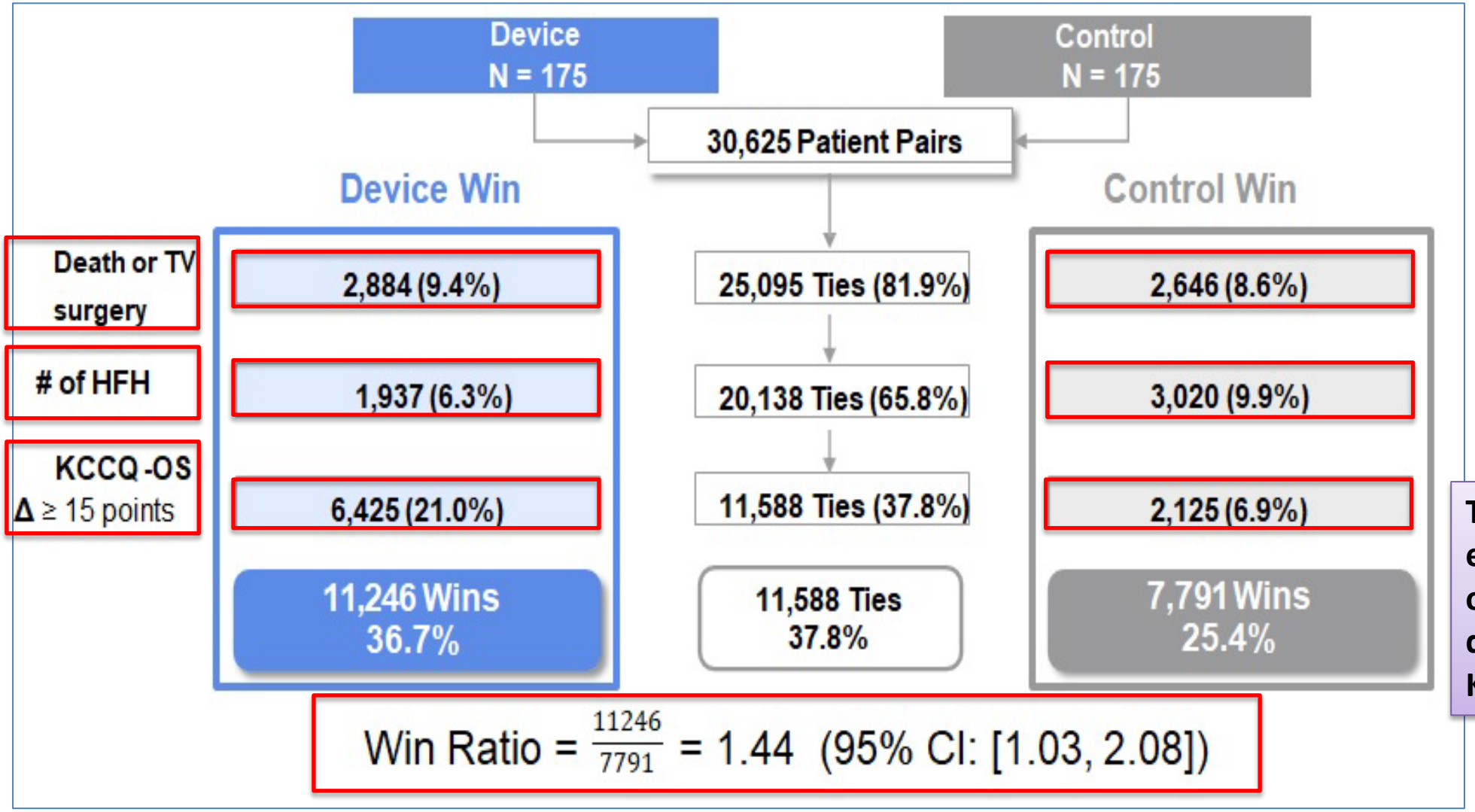
	Test Statistic	p-Value (2-sided)	Significance Level (2-sided)
Finkelstein-Schoenfeld analysis	2.16	0.0311	0.05



Primary endpoint met indicating the TriClip group superior to the control group

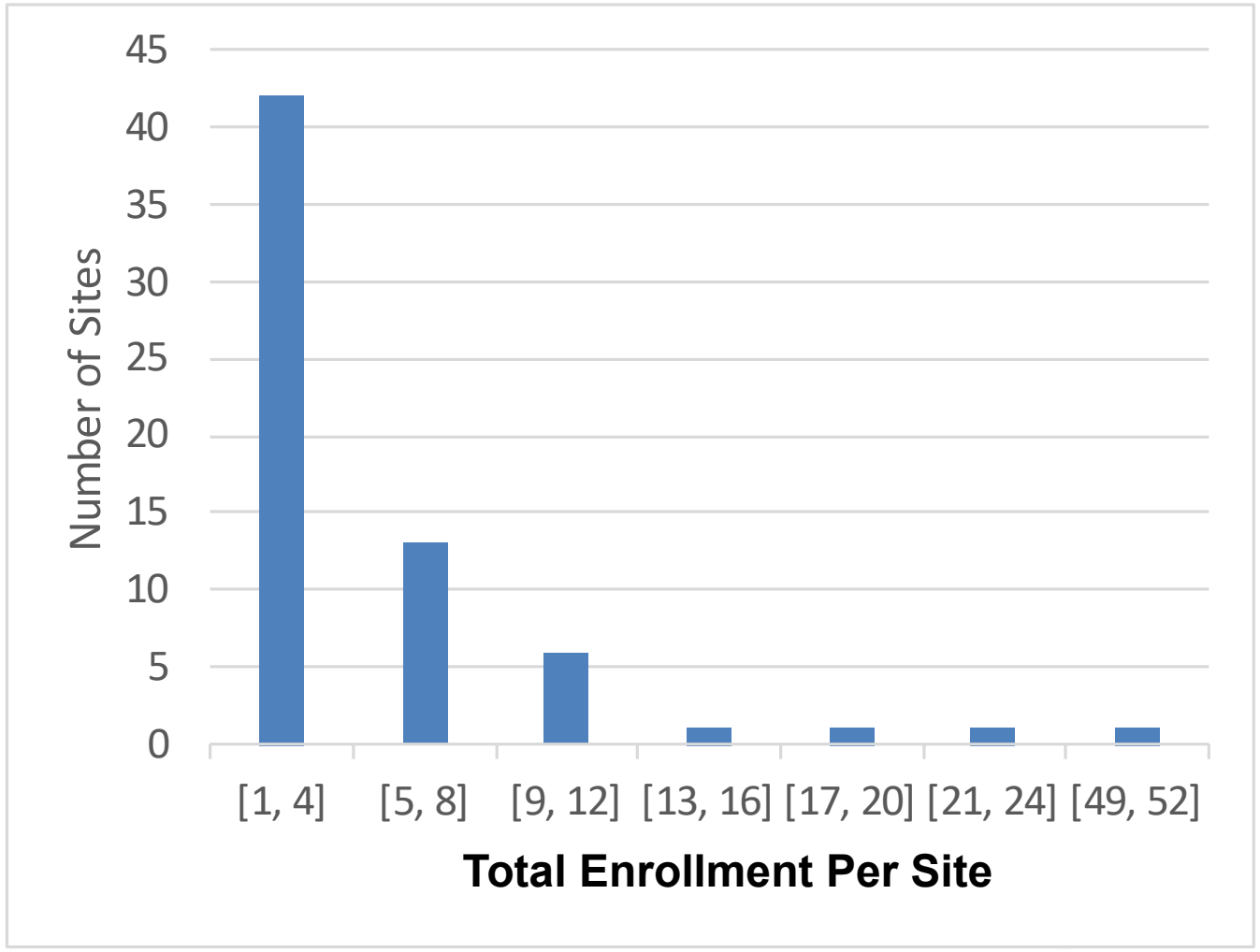
Win Ratio Results

Primary Analysis Randomized Cohort (ITT)



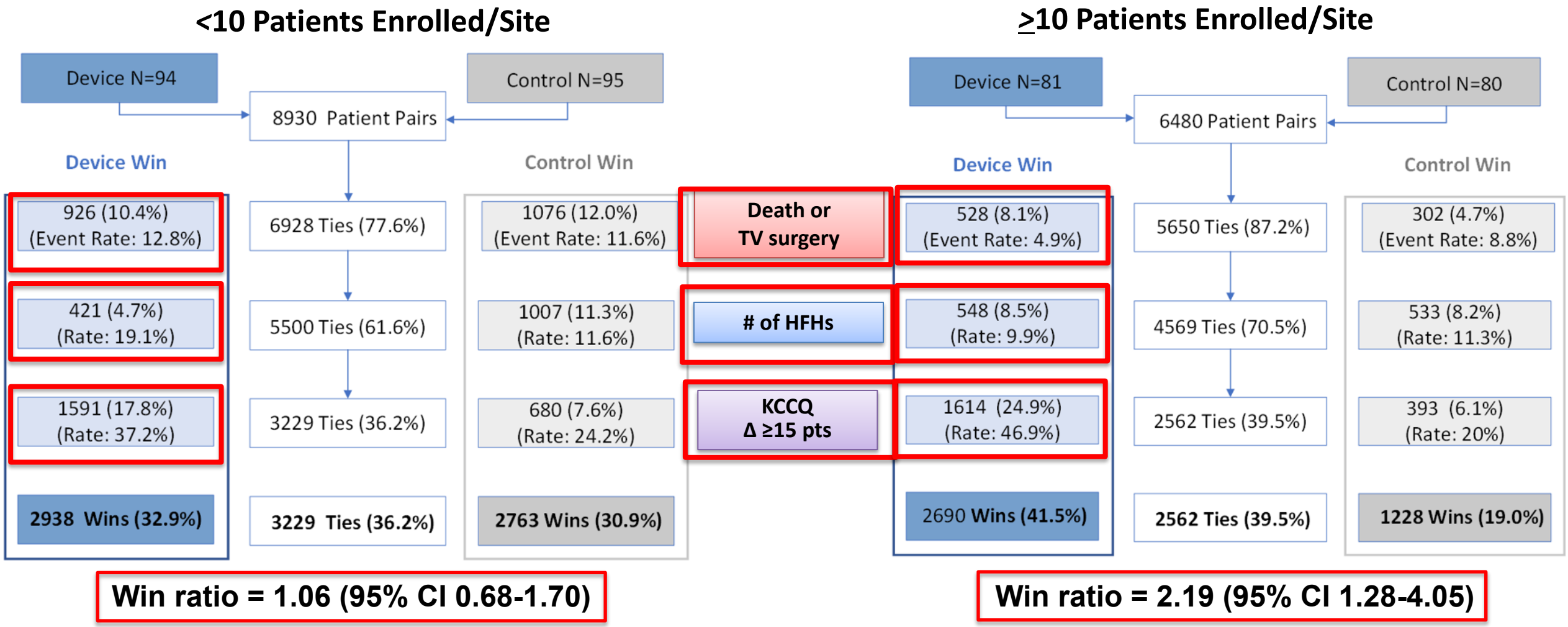
The win-ratio point estimate 1.44 in favor of the TriClip group, driven by improved KCCQ scores

Histogram of Patient Enrollment at Participating Sites
Primary Analysis Randomized Cohort (ITT)



<5 patients = 42 sites
5-9 patients = 14 sites
≥10 patients = 9 sites
51 patients = 1 site

Win Ratio Results by Site Enrollment Volume
Primary Analysis Randomized Cohort (ITT)



Powered Secondary Endpoint Results
Primary Analysis Randomized Cohort (ITT)

Order	Secondary Endpoint	Summary Statistics		p-Value	Result
		Device Arm	Control Arm		
1	Freedom from MAEs at 30 days post-procedure	98.3% [96.3%, 100%]*	-	<0.0001	Endpoint met
2	Change in KCCQ score at 12 months over baseline	12.0 ± 25.8 (155)†	1.0 ± 21.0 (155)†	<0.0001	Endpoint met
3	TR reduction to moderate or less at 30-day visit	87.0% (141/162)‡	5.4% (8/147)‡	<0.0001	Endpoint met
4	Change in 6MWD at 12 months over baseline (meters)	-5.1 ± 131.4 (131)	-28.1 ± 122.3 (136)	0.2482	**Endpoint not met**

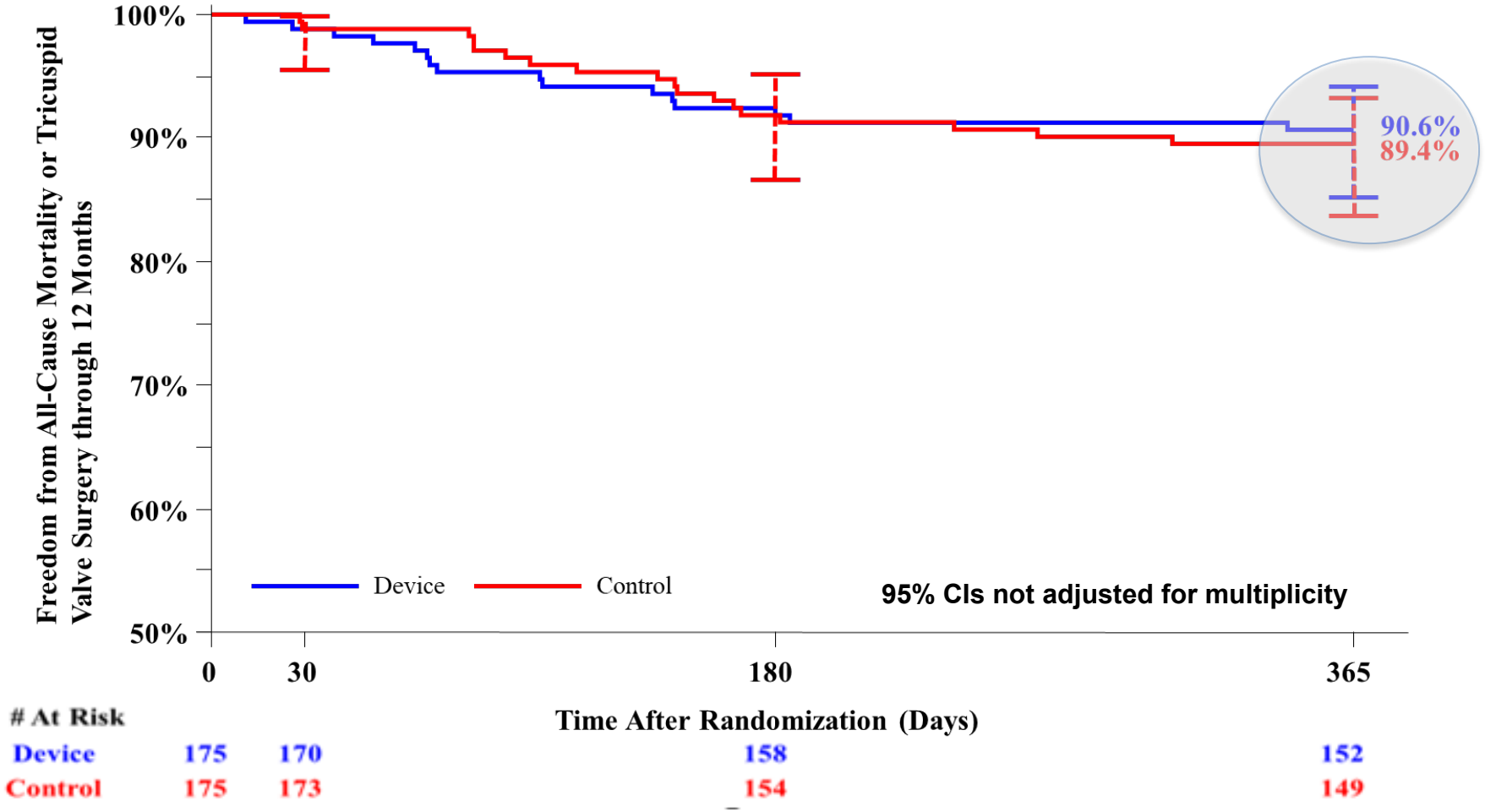
*Kaplan-Meier estimate [95% confidence interval]

†Least square means (standard error) from analysis of covariance (ANCOVA) model

‡% (no./total no.)

Freedom from Mortality or TV Surgery through 12 Months

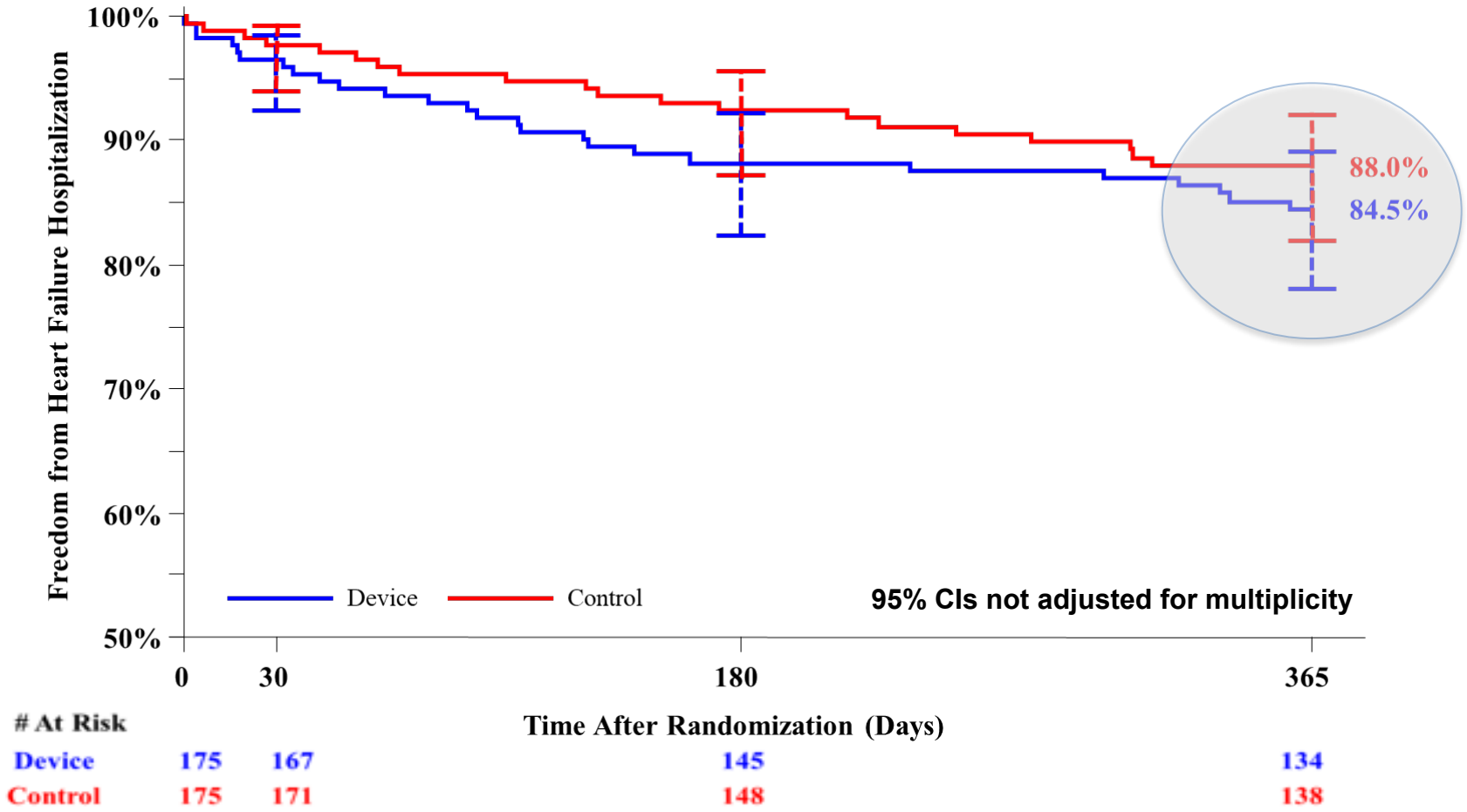
Primary Analysis Randomized Cohort (ITT)



Freedom from all-cause mortality or TV surgery through 12 months comparable between the TriClip and control groups.

Freedom from Heart Failure Hospitalization through 12 Months

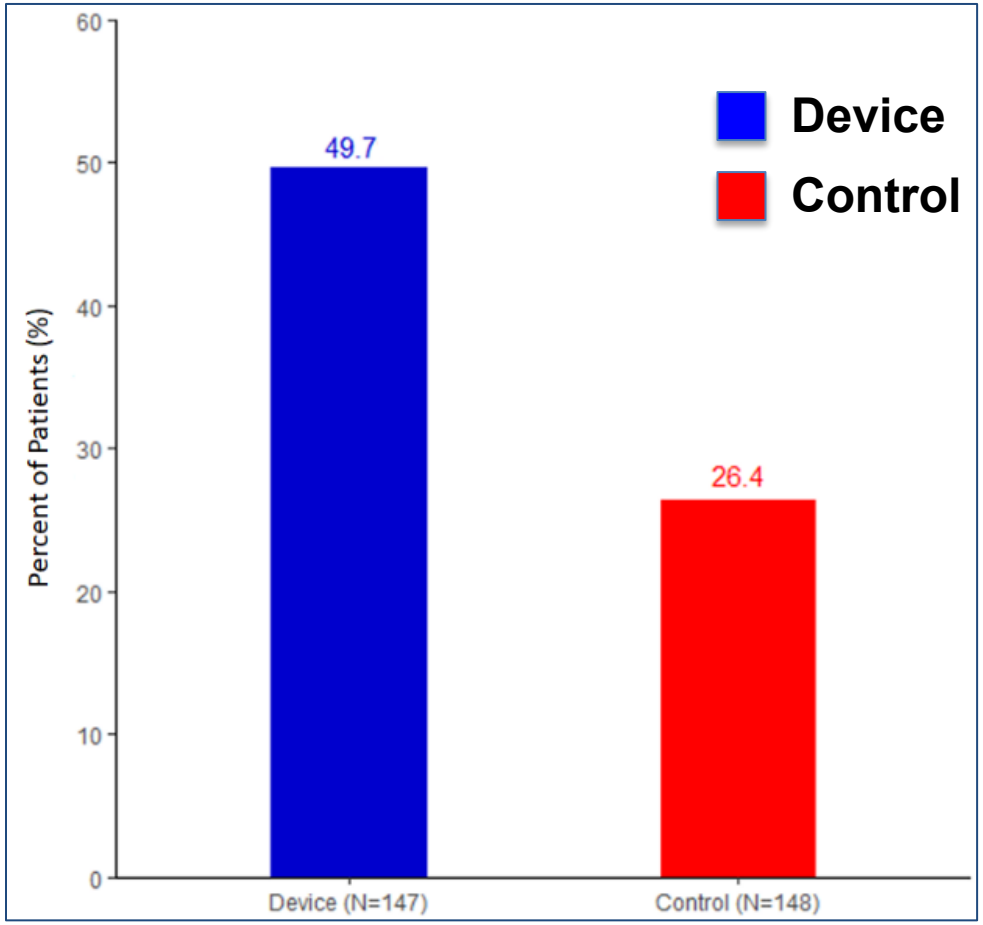
Primary Analysis Randomized Cohort (ITT)



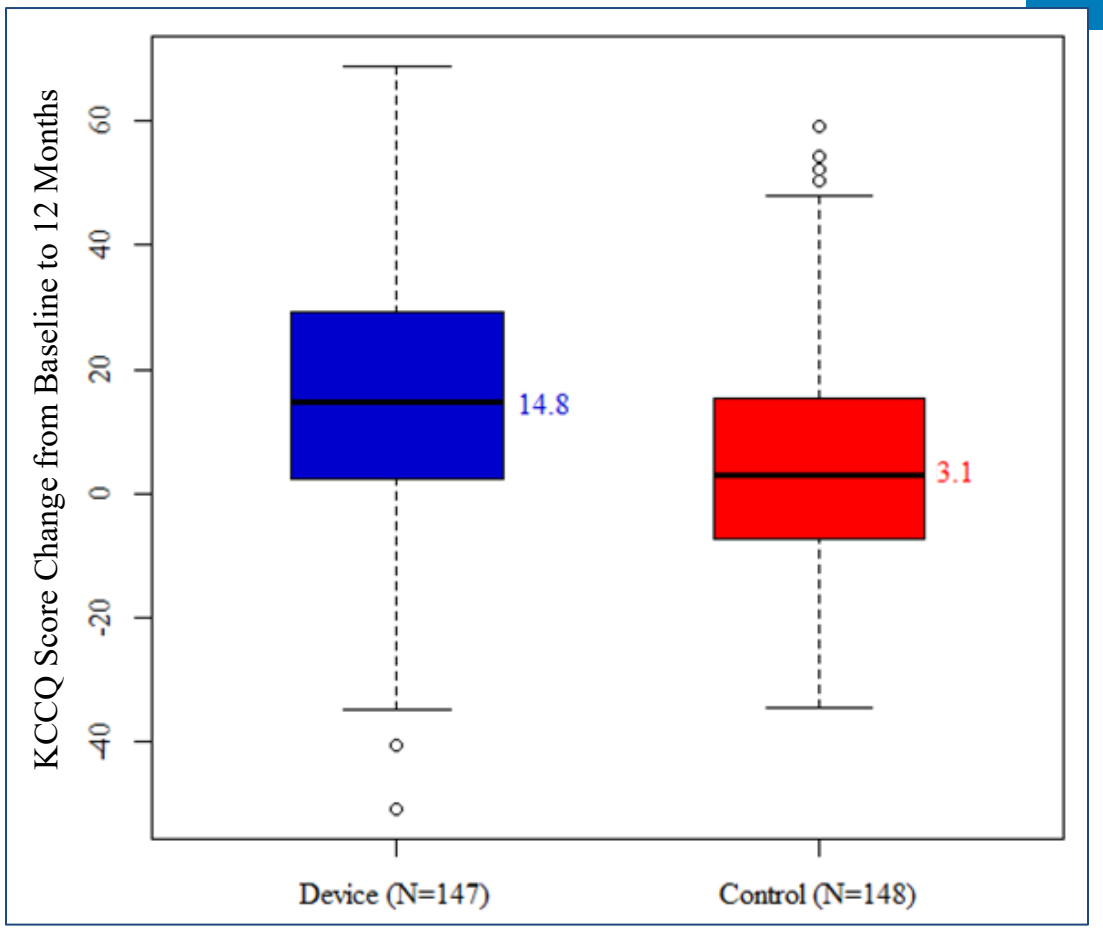
Freedom from heart failure hospitalization through 12 months numerically higher in the control group vs. the TriClip group

KCCQ Score at 12 Months

Primary Analysis Randomized Cohort (ITT)



Proportion of Patients with ≥15 Points KCCQ Score Improvement

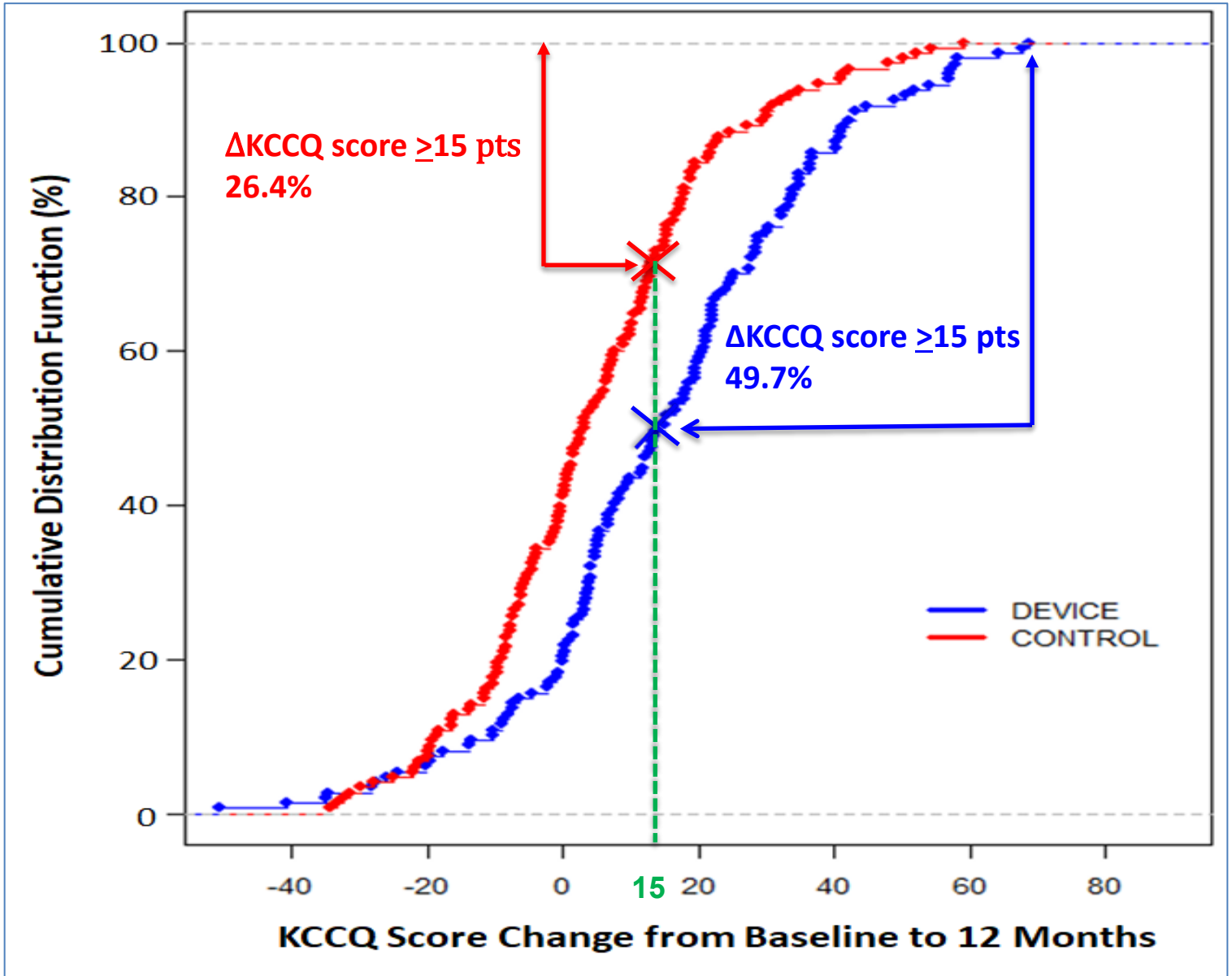


Boxplot of KCCQ Score Change from Baseline

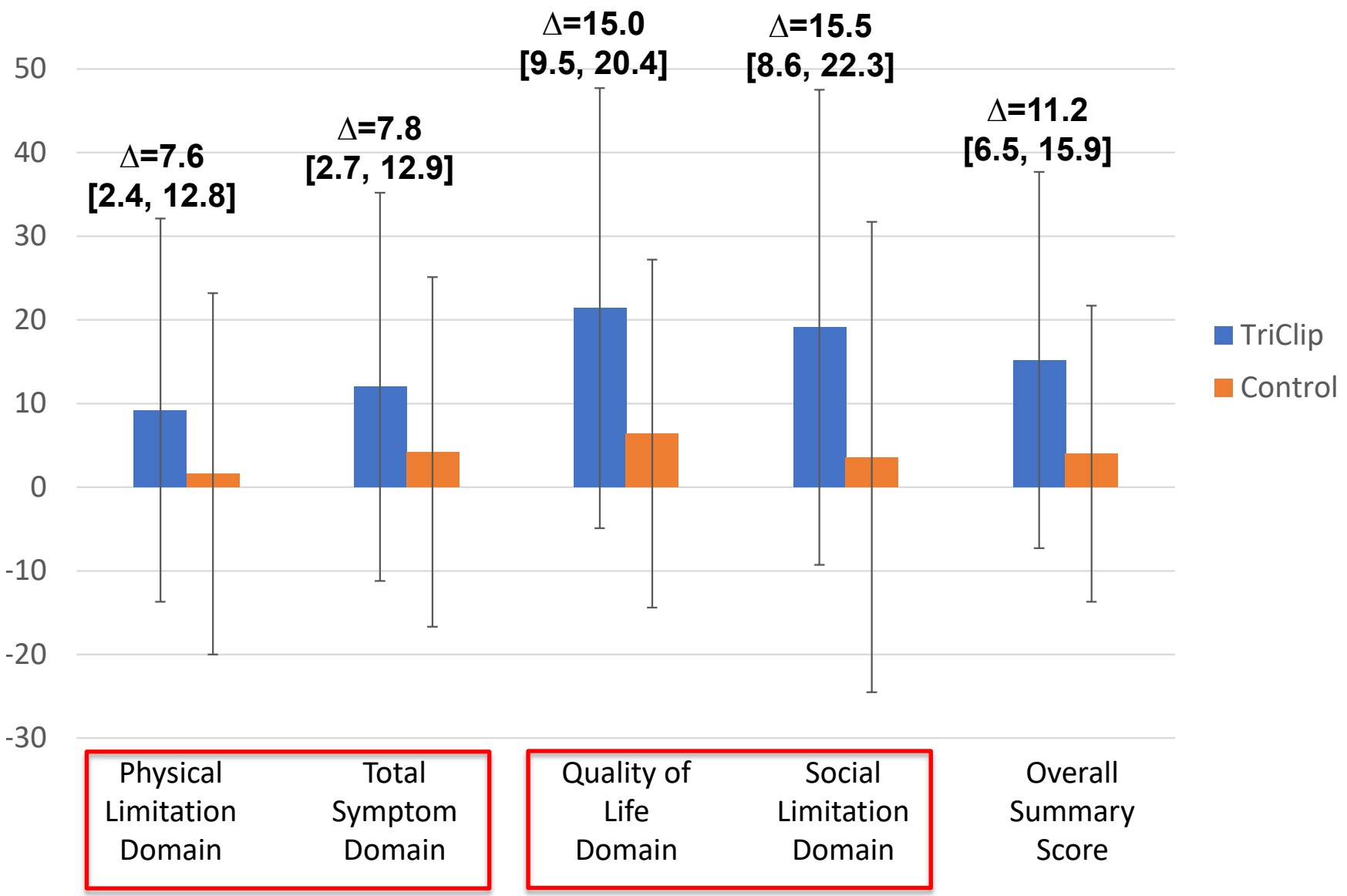
- **Proportion of patients with ≥15 points KCCQ score improvement higher in the TriClip group**
- **Median improvement from baseline in KCCQ score 14.8 in the TriClip group and 3.1 in the control group**

KCCQ Score Changes at 12 Months

Primary Analysis Randomized Cohort (ITT)



Changes in KCCQ Scores By Domain



KCCQ improvement difference between TriClip and control smaller in domains proximal to TR reduction:

- **Physical limitation**
- **Total symptoms**

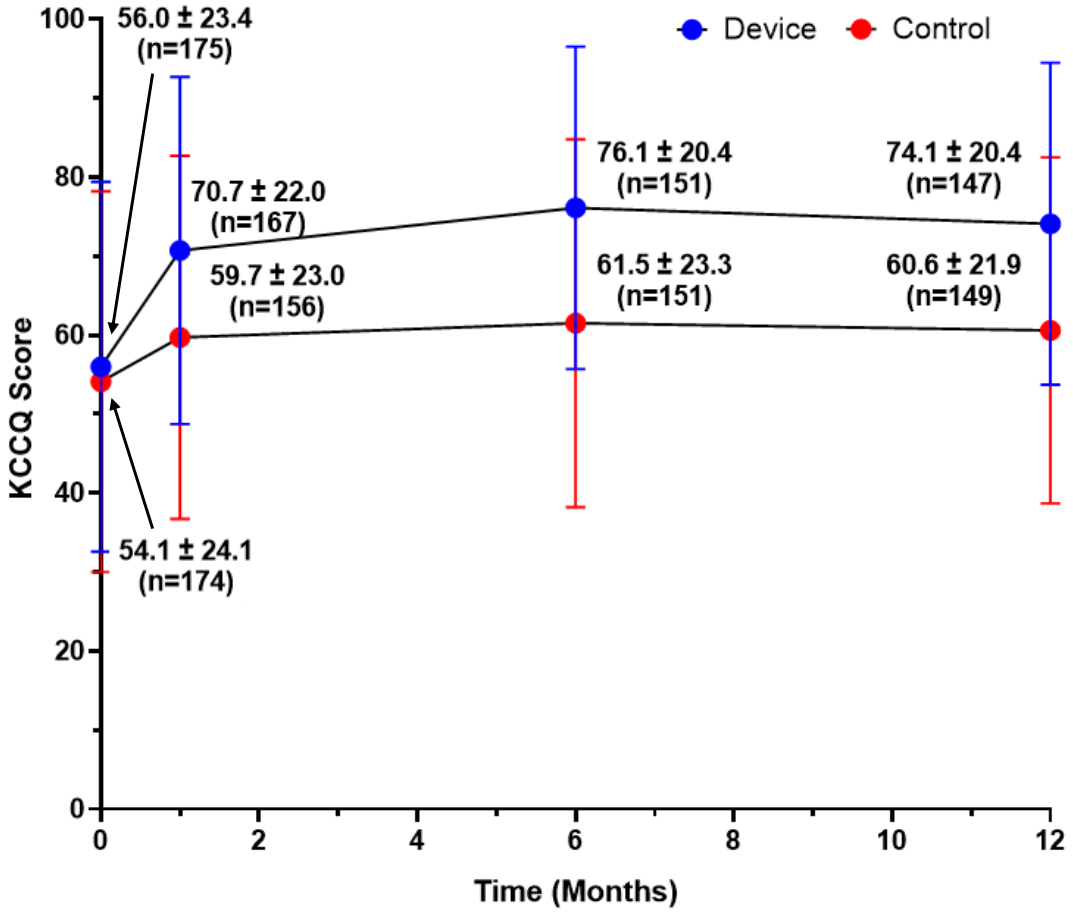
vs.

General health status domains:

- **Quality of life**
- **Social limitation**

KCCQ Scores at 1, 6, and 12 Months

Primary Analysis Randomized Cohort (ITT)

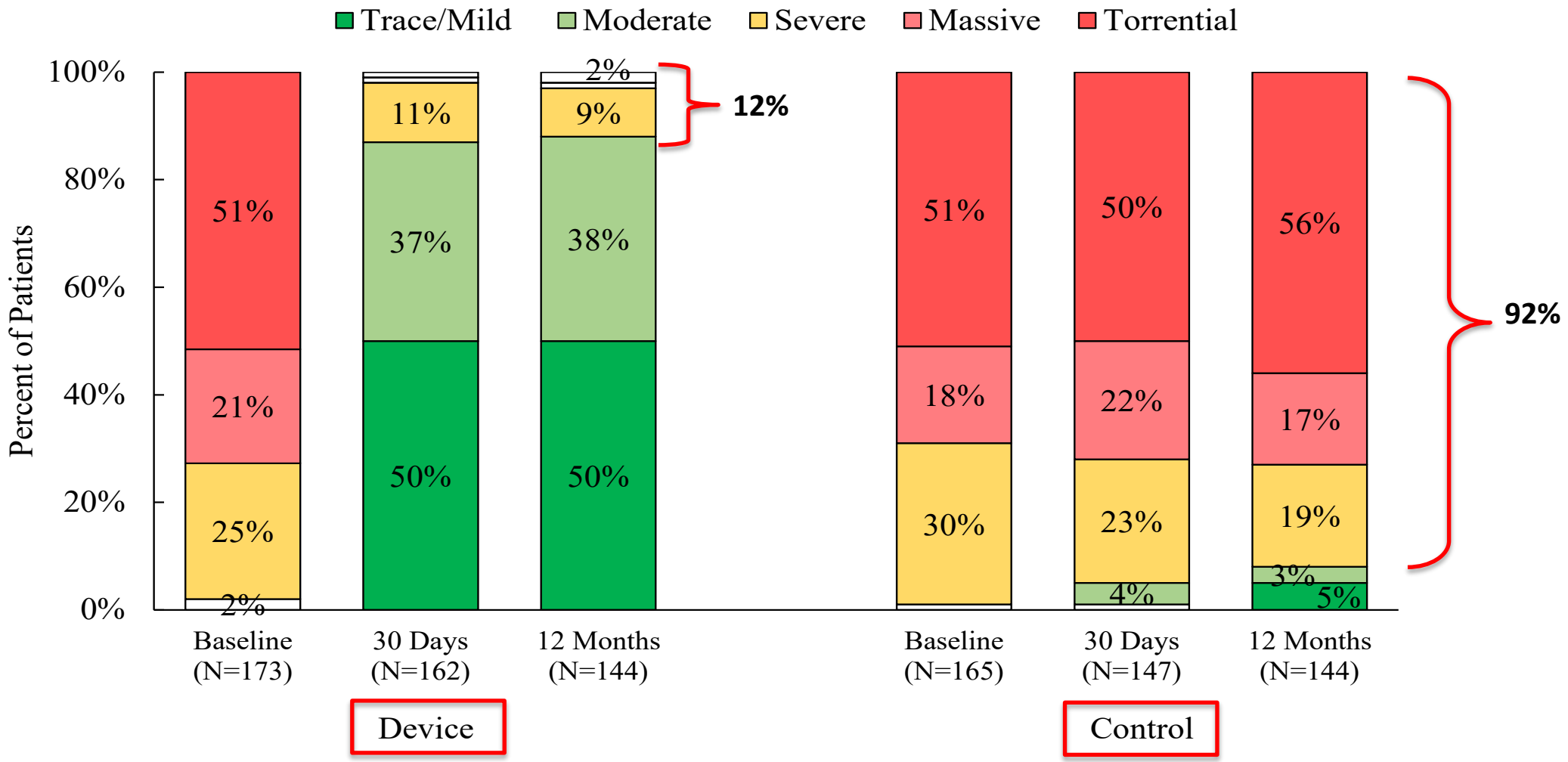


Randomized Cohort ITT Population (Unpaired). The error bars are standard deviations.

KCCQ score improvement in favor of the TriClip group observed at 1 month and sustained at 6-months and at 1-year

TR Severity at 30 Days and 12 Months

Primary Analysis Randomized Cohort (ITT, Unpaired)

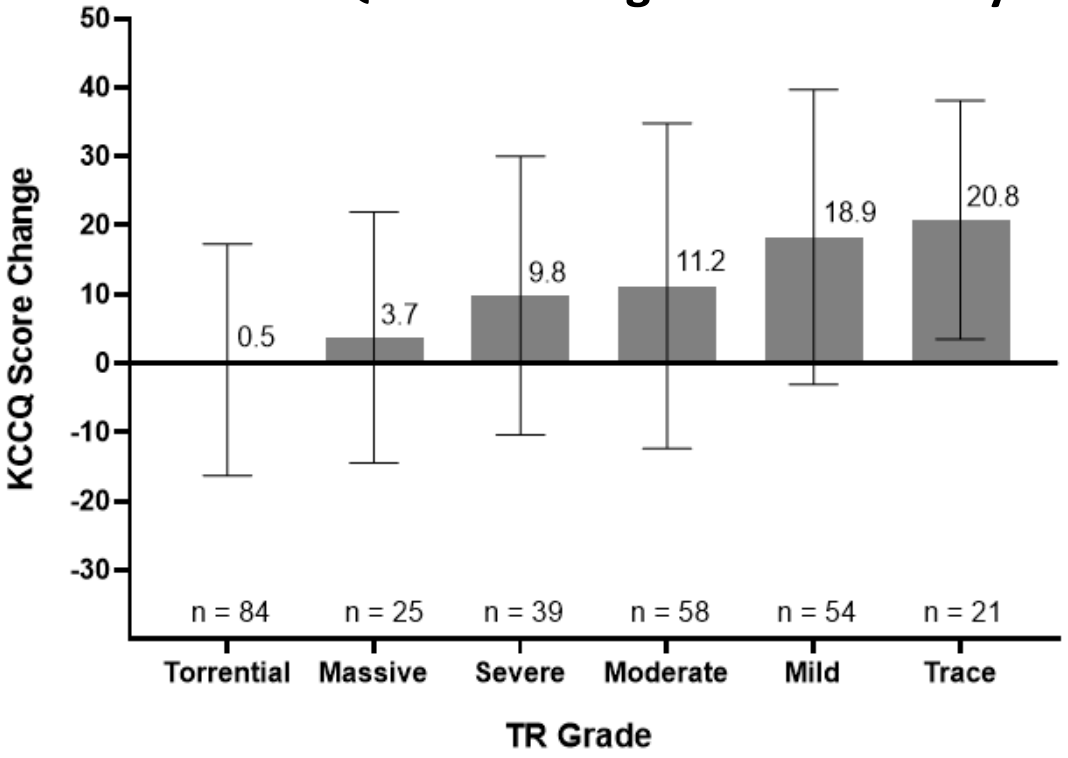


Values ≤1% not labeled

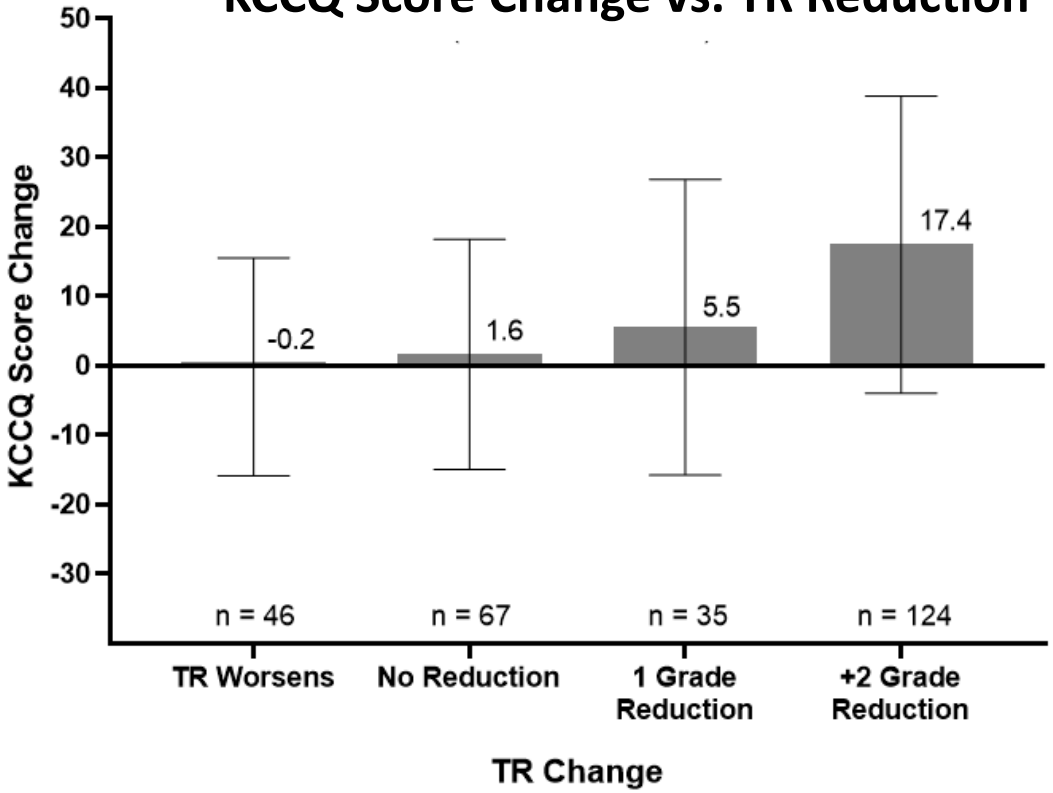
KCCQ Score and TR Severity at 12 Months

Primary Analysis Randomized Cohort (ITT)

KCCQ Score Change vs. TR Severity



KCCQ Score Change vs. TR Reduction

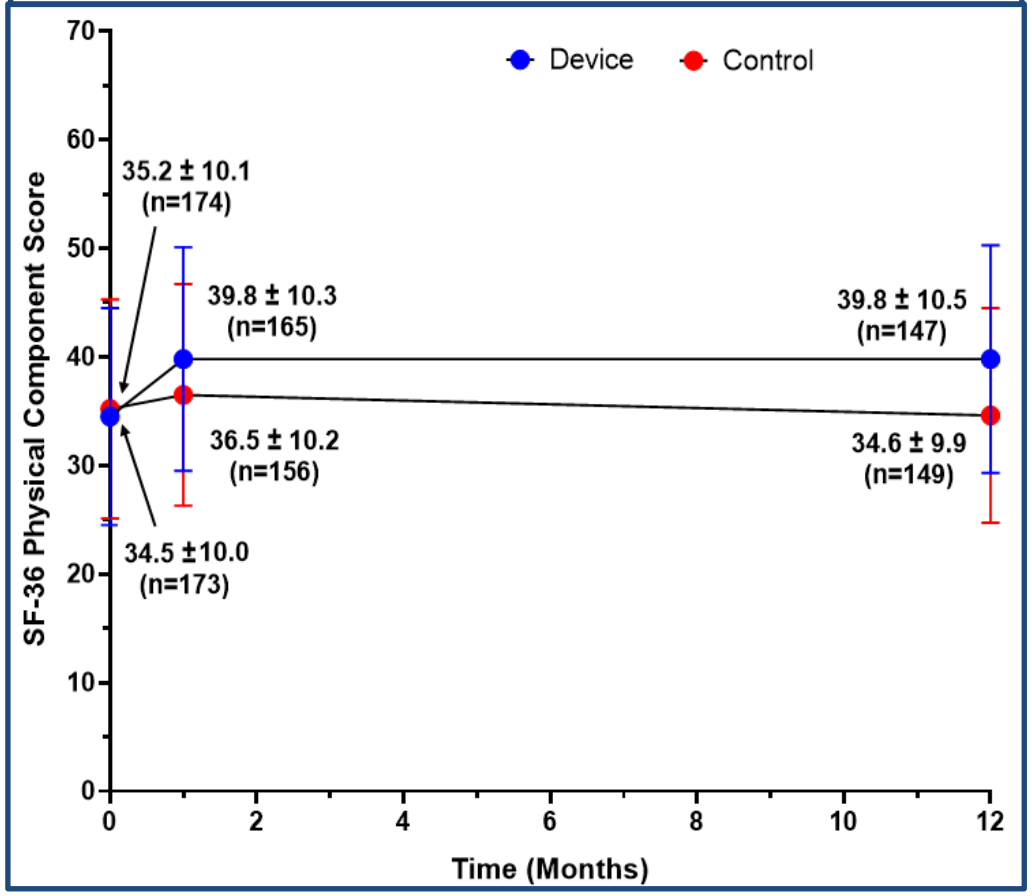


Lower TR severity and greater TR severity reductions associated with greater KCCQ score improvements

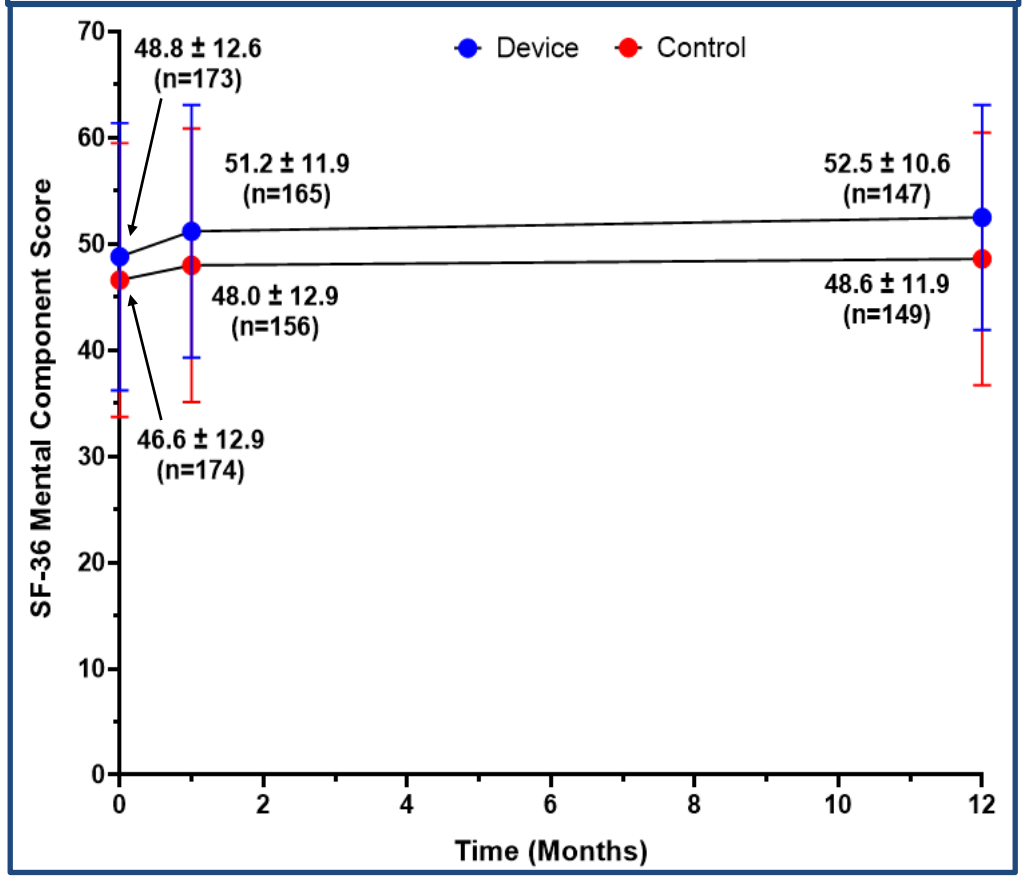
SF-36 Score at 1, 6, and 12 Months

Primary Analysis Randomized Cohort (ITT, Unpaired)

SF-36 Physical Component

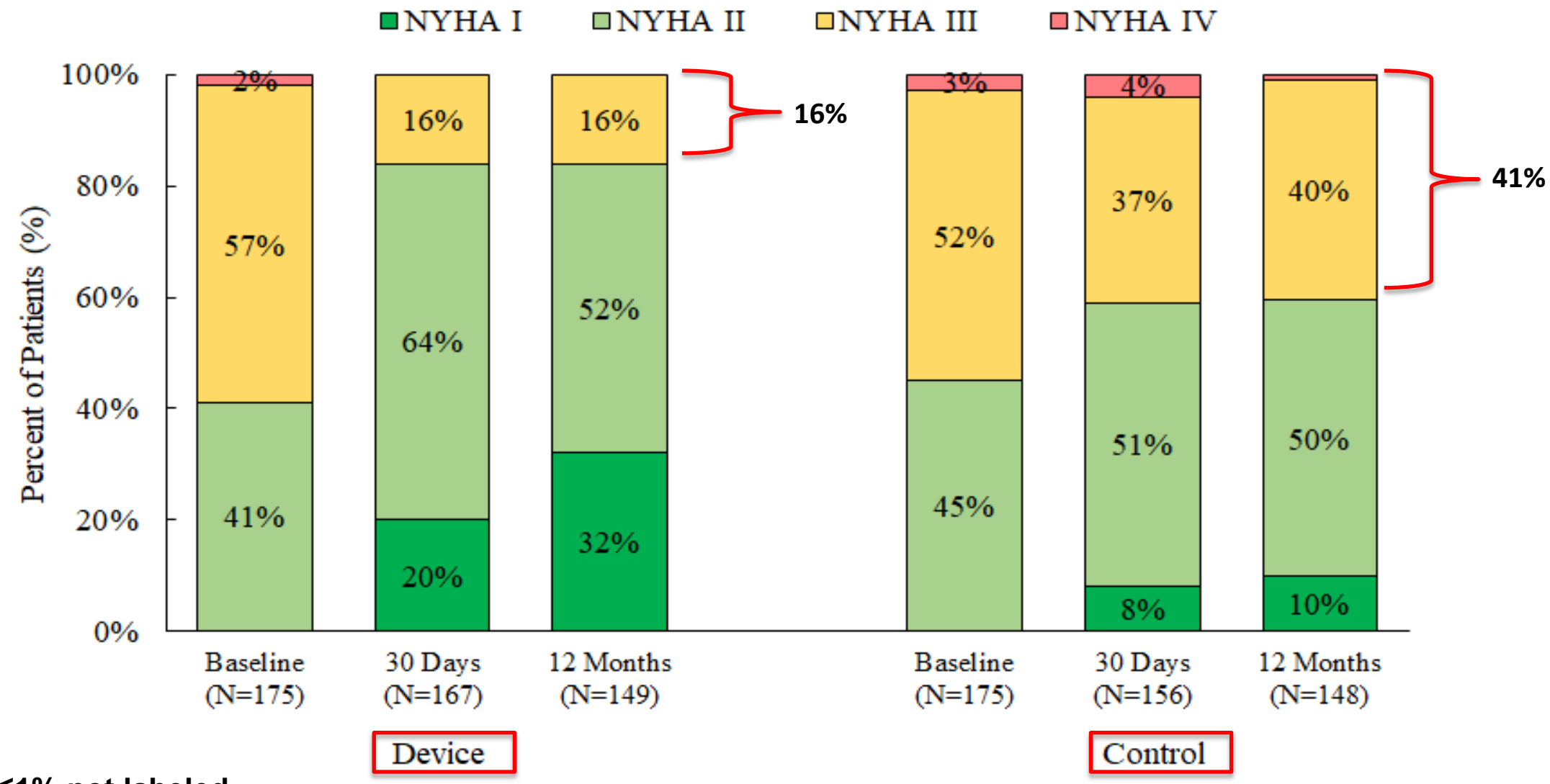


SF-36 Mental Component



NYHA Functional Class at Baseline, 30 Days and 12 Months

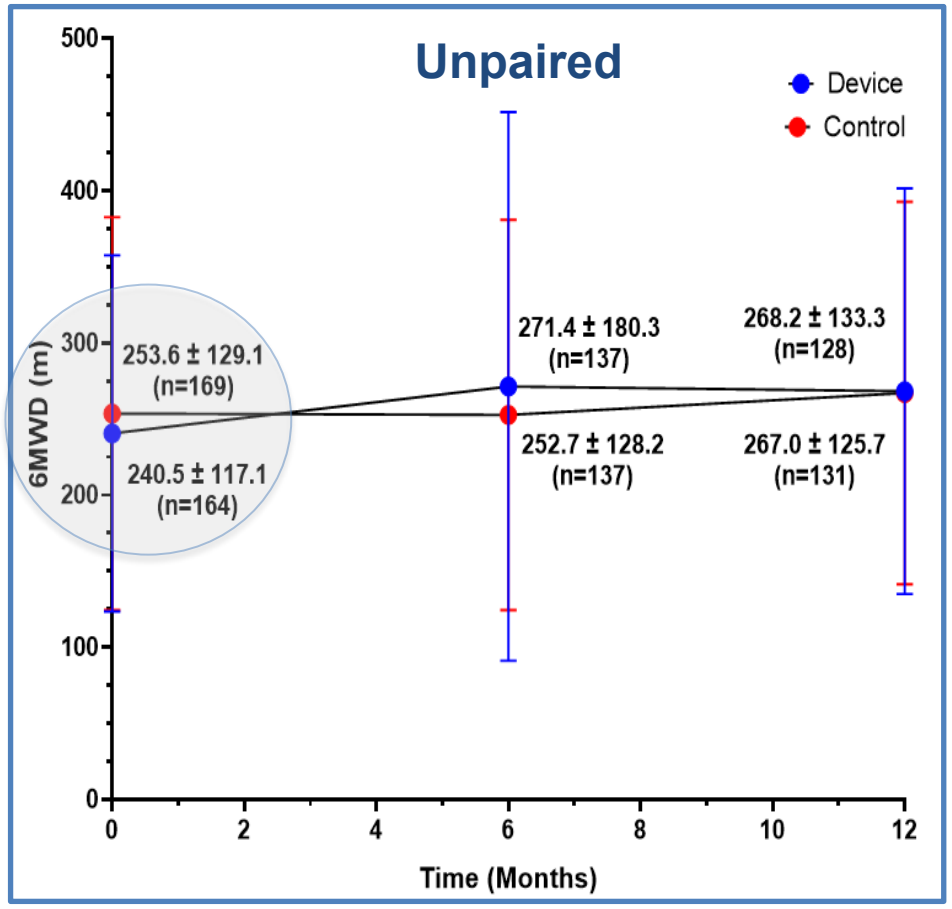
Primary Analysis Randomized Cohort (ITT, Unpaired)

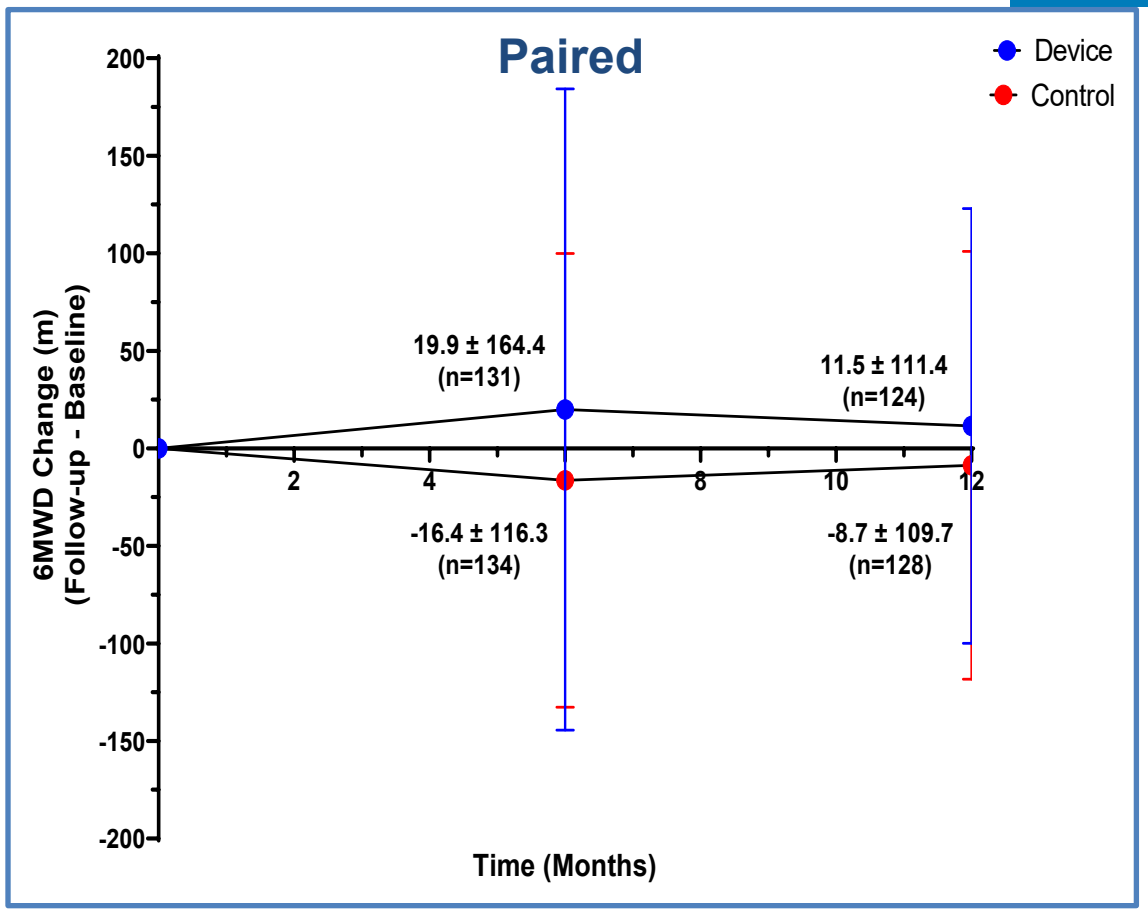


Values ≤1% not labeled

6MWD at 6 and 12 Months

Primary Analysis Randomized Cohort (ITT)





6MWD Change (m) Baseline to 12 Months (Paired)	Device (N=175)	Control (N=175)	Difference [95% CI]
Mean ± SD (n)	11.5 ± 111.4 (124)	-8.7 ± 109.7 (128)	20.3 [-7.2, 47.7]
Median (Q1, Q3)	0.0 (-37.3, 60.0)	-6.0 (-51.9, 35.2)	

Peripheral Edema Requiring Hospitalizations, Ascites, & IV Diuretic Administration

Primary Analysis Randomized Cohort (ITT)

Endpoints	Device (N=175)	Control (N=175)	Difference [95% CI]
Incidence of peripheral edema requiring hospitalizations at 12 months			
Number of events	7	18	
Total follow-up (patient-years)[†]	160.4	161.5	
Annualized rate [95% CI][‡]	0.04 [0.02, 0.09]	0.11 [0.07, 0.18]	
Proportion of patients with events	3.4% (6/175)	7.4% (13/175)	-4.00% [-9.20%, 0.90%]
Incidence of ascites at 12 months			
Number of events	5	11	
Total follow-up (patient-years)[†]	160.4	161.5	
Annualized rate [95% CI][‡]	0.03 [0.01, 0.07]	0.07 [0.04, 0.12]	
Proportion of patients with events	2.9% (5/175)	6.3% (11/175)	-3.43% [-8.33%, 1.14%]
IV diuretics usage (including outpatient clinics) at 12 months[‖]			
Number of days	191	159	
Total follow-up (patient-years)[†]	160.4	161.5	
Annualized rate [95% CI][‡]	1.19 [1.03, 1.37]	0.98 [0.84, 1.15]	
Proportion of patients with events	14.9% (26/175)	13.1% (23/175)	1.71% [-5.64%, 9.07%]

Organ Function and Biomarkers Endpoints
Primary Analysis Randomized Cohort (ITT)

Endpoint Change from Baseline to 12 Months	Device Group (N=175)	Control Group (N=175)	Difference [95% CI]*
ΔGGT (U/L)			
Mean ± SD (n)	-13.2 ± 73.9 (87)	-0.8 ± 56.0 (90)	-12.4 [-31.9, 7.1]
Median (Q1, Q3)	-7.0 (-22.0, 2.0)	-2.5 (-17.0, 12.0)	
Range (min, max)	(-547.0, 259.2)	(-129.0, 302.4)	
ΔMELD score			
Mean ± SD (n)	-0.6 ± 4.6 (114)	0.7 ± 4.4 (106)	-1.2 [-2.4, -0.0]
Median (Q1, Q3)	0.0 (-2.0, 2.0)	0.5 (-1.0, 3.0)	
Range (min, max)	(-22.0, 10.3)	(-25.3, 12.2)	
Δ eGFR (ml/min/1.73 m^2)			
Mean ± SD (n)	0.1 ± 13.3 (138)	-1.8 ± 11.9 (134)	2.0 [-1.0, 5.0]
Median (Q1, Q3)	-0.4 (-7.5, 7.6)	-1.8 (-8.9, 5.5)	
Range (min, max)	(-34.0, 60.0)	(-27.9, 35.2)	
ΔBNP (pg/mL)			
Mean ± SD (n)	-7.3 ± 233.1 (68)	16.4 ± 273.6 (66)	-23.7 [-110.7, 63.3]
Median (Q1, Q3)	6.2 (-72.5, 77.5)	-10.5 (-73.0, 68.0)	
Range (min, max)	(-1005.0, 655.0)	(-501.0, 1759.0)	
ΔNT-proBNP (pg/mL)			
Mean ± SD (n)	209.3 ± 1354.5 (51)	-402.7 ± 2114.3 (51)	612.0 [-87.1, 1311.1]
Median (Q1, Q3)	184.0 (-223.0, 537.0)	-40.0 (-734.0, 195.0)	
Range (min, max)	(-4165.0, 6245.0)	(-12862.0, 4225.0)	

Echocardiographic Endpoints
Primary Analysis Randomized Cohort (ITT)

Echocardiographic Endpoint Change from Baseline to 12 Months	Device Arm (N=175)	Control Arm (N=175)	Difference [95% CI]*
ΔTricuspid annulus diameter (end-diastole, apical 4Ch, cm)			
Mean ± SD (n)	-0.09 ± 0.64 (140)	-0.11 ± 0.74 (135)	0.02
Median (Q1, Q3)	-0.10 (-0.50, 0.30)	-0.17 (-0.50, 0.30)	[-0.14, 0.19]
ΔPISA EROA (cm^2)			
Mean ± SD (n)	-0.44 ± 0.33 (115)	-0.04 ± 0.31 (127)	-0.40
Median (Q1, Q3)	-0.42 (-0.56, -0.26)	0.00 (-0.16, 0.12)	[-0.48, -0.32]
ΔPISA regurgitant volume calculation (mL)			
Mean ± SD (n)	-33.84 ± 20.48 (115)	-1.99 ± 23.56 (127)	-31.85
Median (Q1, Q3)	-33.20 (-44.90, -21.40)	-1.30 (-12.40, 10.21)	[-37.43, -26.28]
ΔVena contracta width (SL, 4Ch view, cm)			
Mean ± SD (n)	-0.52 ± 0.48 (139)	0.03 ± 0.44 (136)	-0.54
Median (Q1, Q3)	-0.48 (-0.77, -0.26)	0.00 (-0.30, 0.32)	[-0.65, -0.43]
ΔTricuspid valve diastolic mean gradient (CW, mmHg)			
Mean ± SD (n)	1.15 ± 1.28 (136)	0.07 ± 0.58 (126)	1.08
Median (Q1, Q3)	0.86 (0.32, 1.89)	0.02 (-0.31, 0.43)	[0.84, 1.32]

Quantitative & semiquantitative TR measurements consistent with marked TR reduction in the device group (with a small increase in TV diastolic gradient)

Echocardiographic Endpoints (RA/RV dimensions)

Primary Analysis Randomized Cohort (ITT)

Echocardiographic Endpoint Change from Baseline to 12 Months	Device Arm (N=175)	Control Arm (N=175)	Difference [95% CI]*
ΔRV end diastolic diameter – mid (4Ch, cm)			
Mean ± SD (n)	-0.18 ± 0.73 (140)	-0.02 ± 0.85 (134)	-0.17
Median (Q1, Q3)	-0.20 (-0.60, 0.20)	0.10 (-0.50, 0.50)	[-0.36, 0.02]
ΔRV end diastolic diameter – base (4Ch, cm)			
Mean ± SD (n)	-0.21 ± 0.71 (142)	-0.12 ± 0.76 (134)	-0.09
Median (Q1, Q3)	-0.15 (-0.70, 0.20)	-0.10 (-0.60, 0.40)	[-0.26, 0.08]
ΔRight atrial volume (single plane Simpson's, mL)			
Mean ± SD (n)	7.78 ± 55.92 (140)	-2.13 ± 54.14 (136)	9.91
Median (Q1, Q3)	8.17 (-22.48, 28.25)	-4.35 (-29.90, 21.90)	[-3.13, 22.95]
ΔRV fractional area change (%)			
Mean ± SD (n)	-0.73 ± 8.16 (133)	-0.52 ± 7.38 (125)	-0.21
Median (Q1, Q3)	-0.50 (-6.40, 3.90)	-1.00 (-5.80, 3.90)	[-2.12, 1.69]
ΔRV TAPSE (cm)			
Mean ± SD (n)	-0.13 ± 0.45 (141)	0.00 ± 0.48 (132)	-0.13
Median (Q1, Q3)	-0.10 (-0.43, 0.10)	0.01 (-0.20, 0.30)	[-0.24, -0.02]
ΔInferior vena cava diameter (cm)			
Mean ± SD (n)	-0.09 ± 0.56 (135)	-0.01 ± 0.56 (136)	-0.08
Median (Q1, Q3)	-0.04 (-0.48, 0.34)	0.00 (-0.34, 0.32)	[-0.21, 0.05]

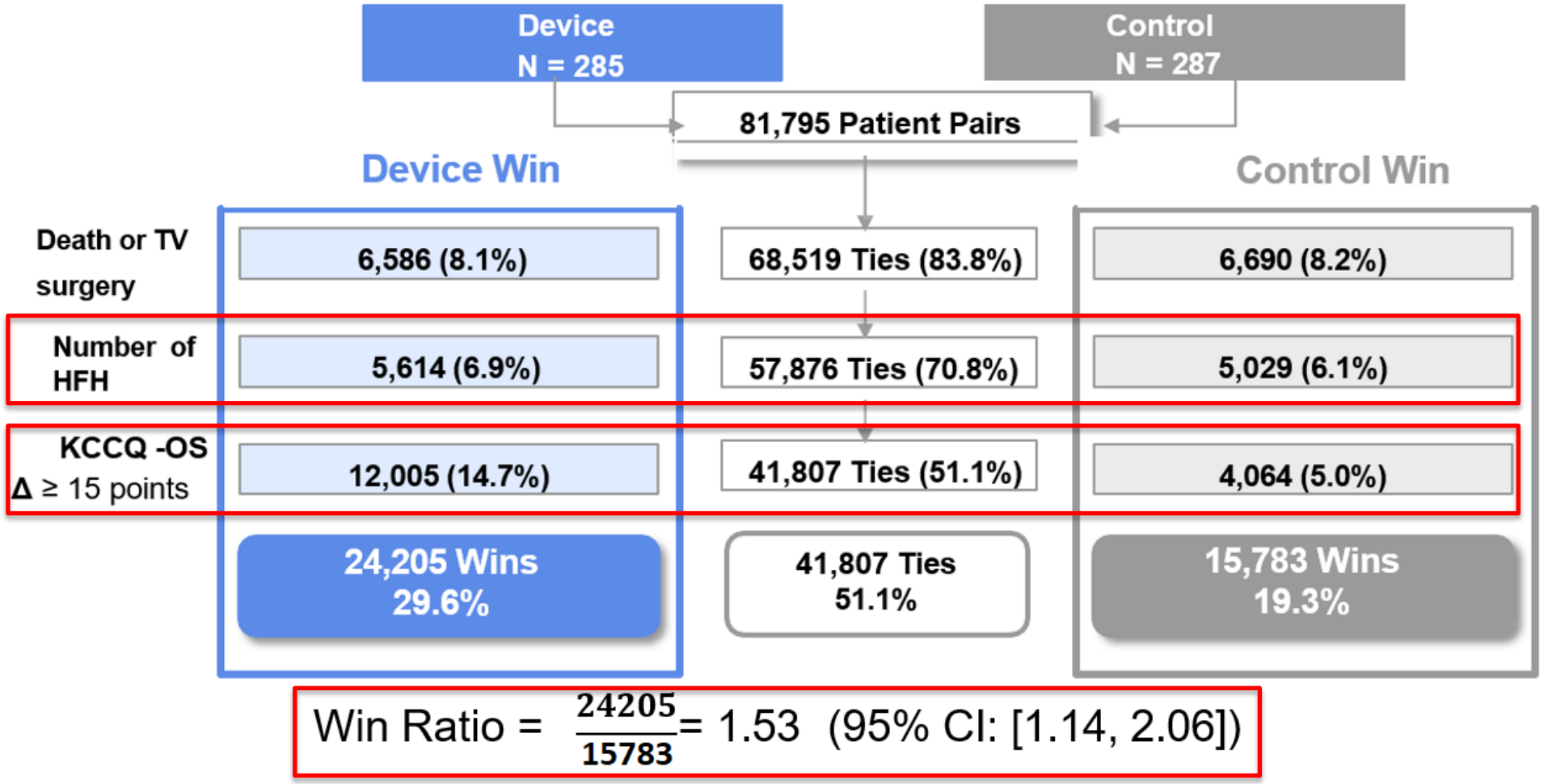
- **Small reduction in RVEDD in the device group**
- **Small increase in RA volume in the device group**
- **Small reduction in %FA and TAPSE in the device group**

Full Randomized Cohort
572 patients

Primary Endpoint Result

Full Randomized Cohort (n=572)

During FDA's PMA review, an additional 222 patients reached 12-month follow-up resulting in a total of 572 randomized patients

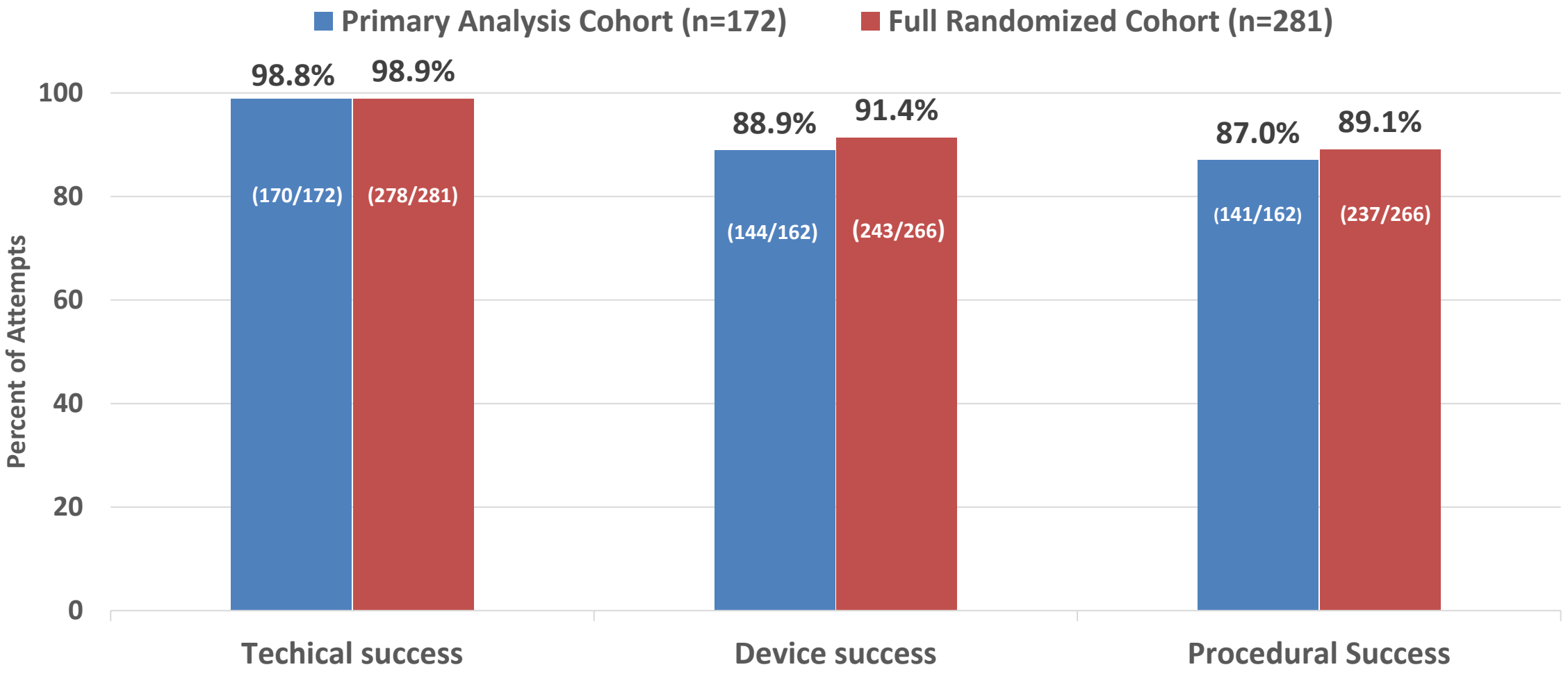


95% CI not adjusted for multiplicity

Procedure Outcomes

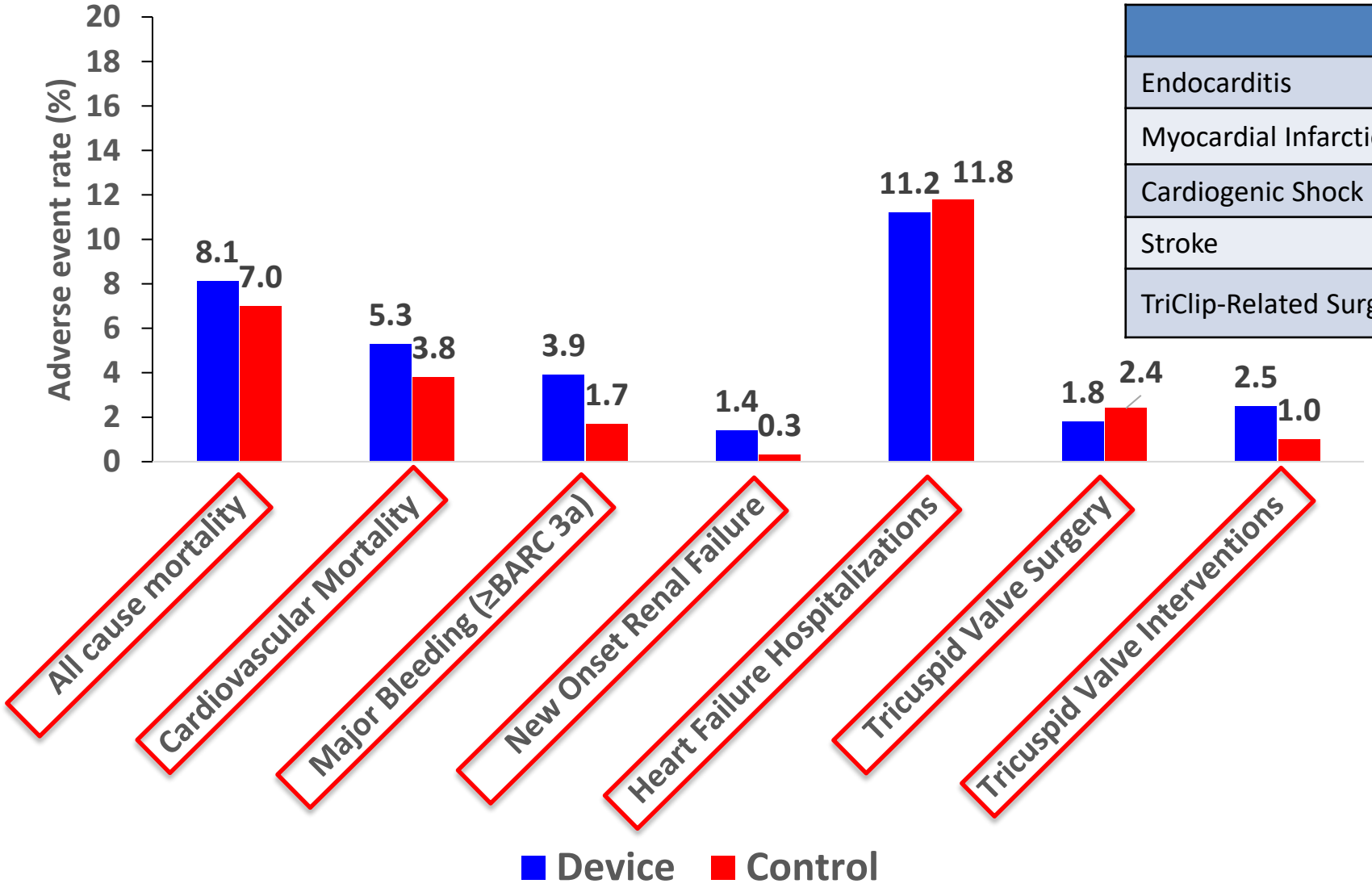
Technical, Device and Procedural Success

Primary Analysis Cohort Versus Full Randomized Cohort



Selected CEC-Adjudicated Adverse Events through 12 Months

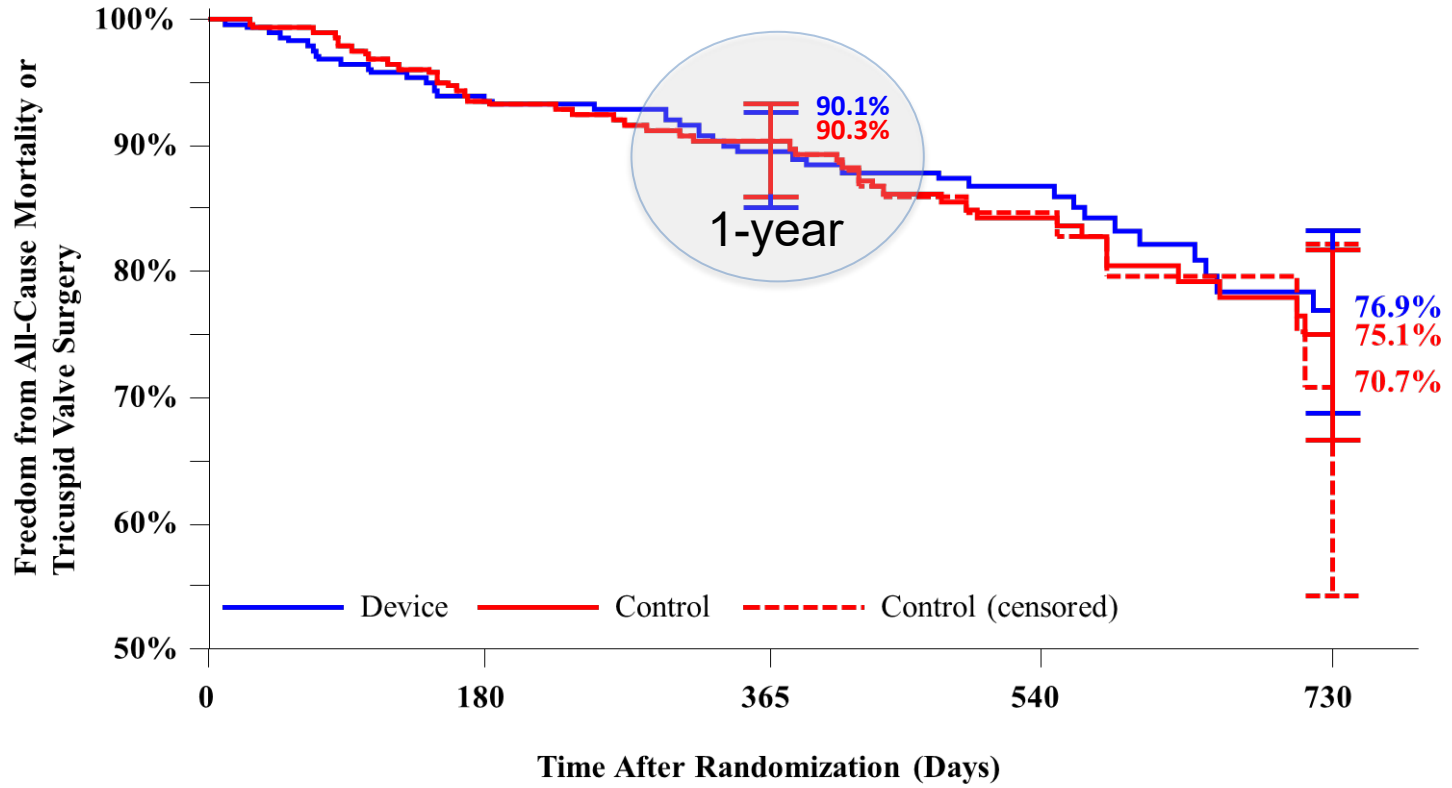
Full Randomized Cohort (ITT, n 572)



	Device	Control
Endocarditis	0	0
Myocardial Infarction	0	0
Cardiogenic Shock	0	0.3%
Stroke	1.1%	1.0%
TriClip-Related Surgery	0	NA

1 and 2-Year Freedom from All Cause Mortality or TV surgery

Full Randomized Cohort (n=572)

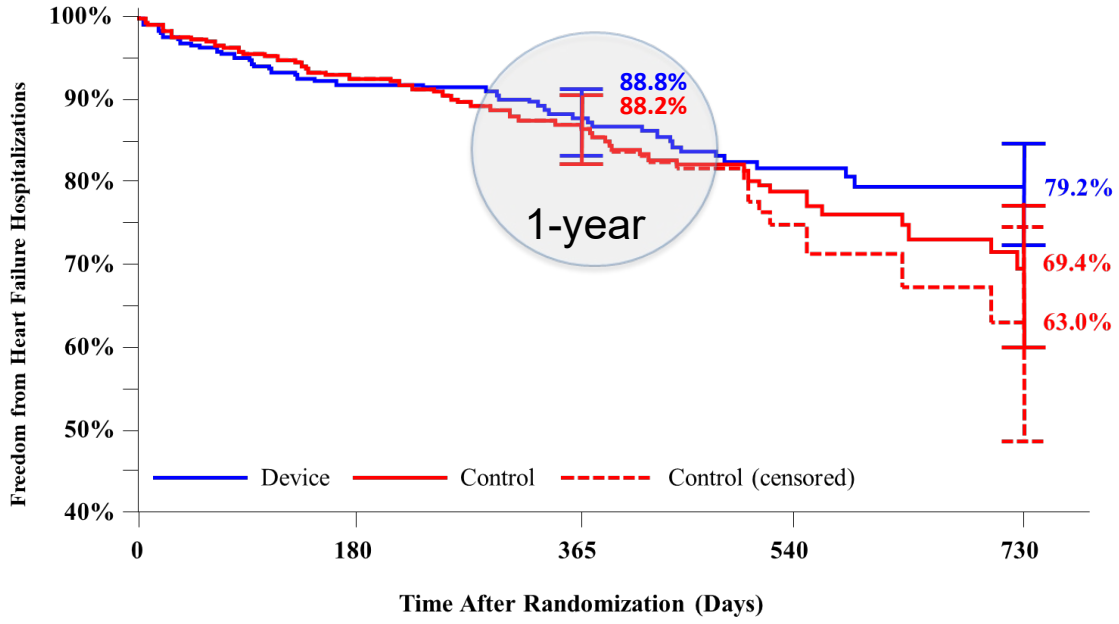


# At Risk			
Device	285	198	44
Control	287	201	44
Control (censored)	287	199	14

95% CIs not adjusted for multiplicity

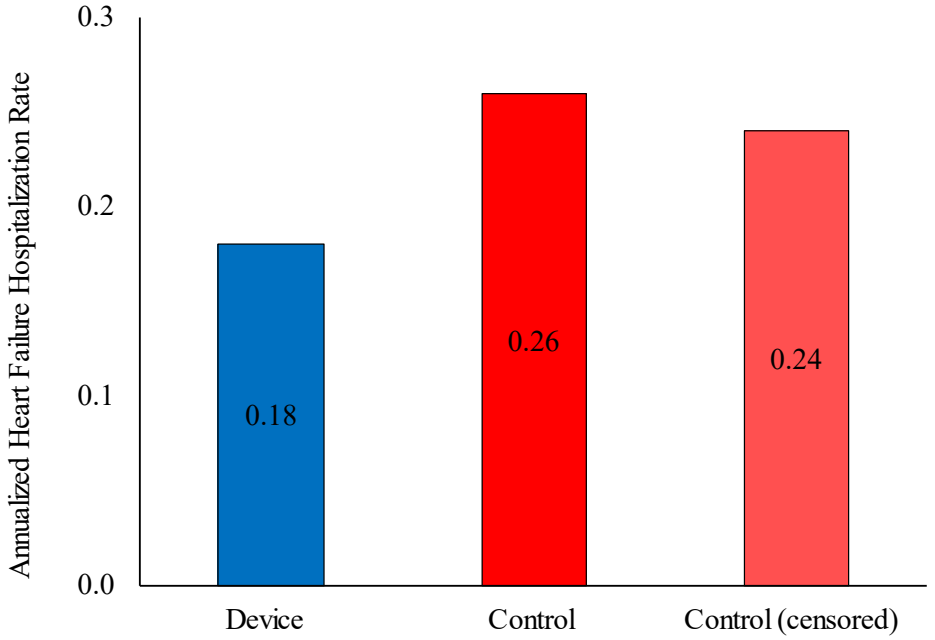
1 and 2-Year Heart Failure Hospitalization
Full Randomized Cohort (n=572)

Freedom from Heart Failure Hospitalization



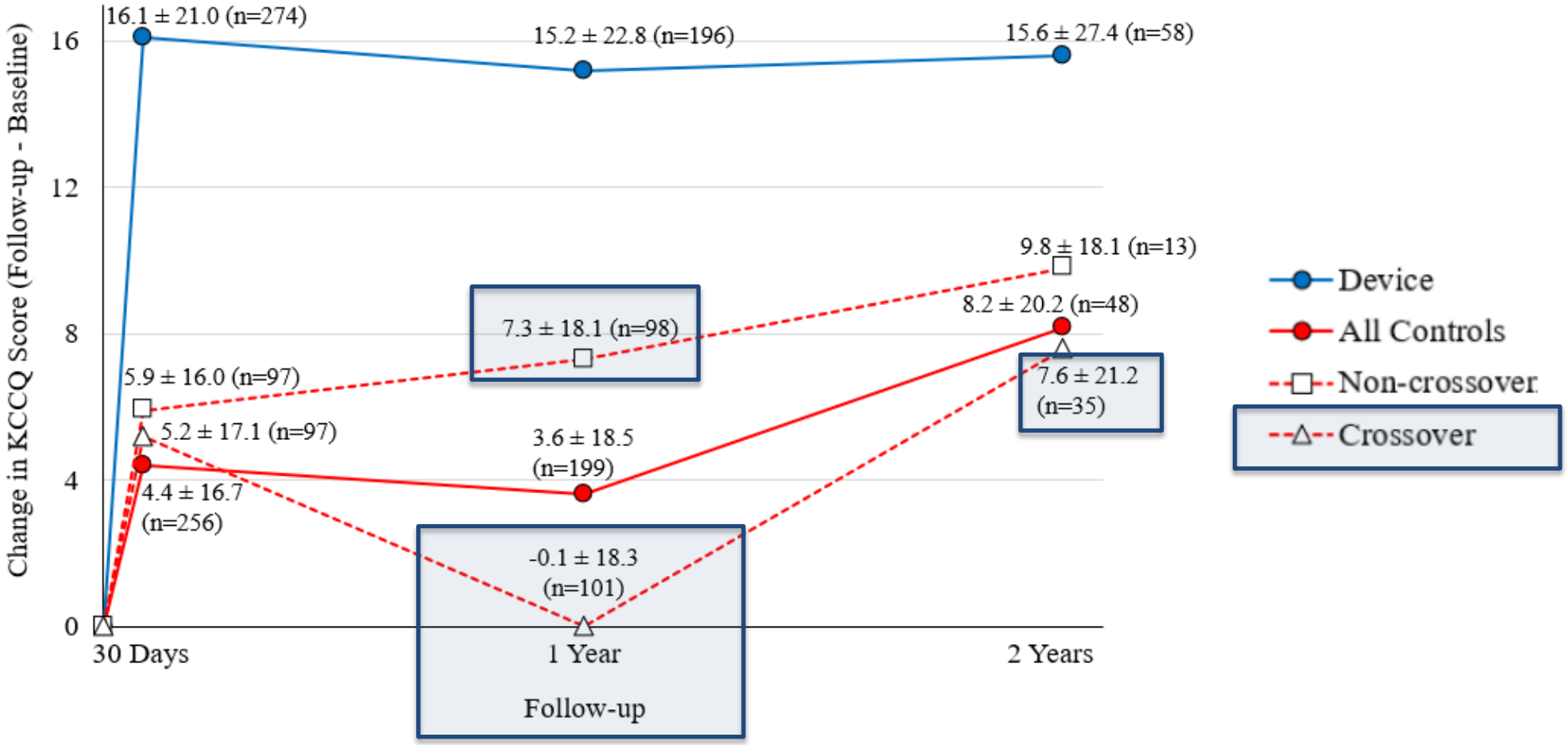
# At Risk			
Device	285	180	37
Control	287	184	33
Control (censored)	287	182	13

Annualized HF Hospitalization Rates (2-Years Data)



- At 1-year follow-up, from heart failure hospitalization was similar between the device and the control group
- Interpretation of 2-year data limited by the small sample size and crossover of control patients to TriClip treatment

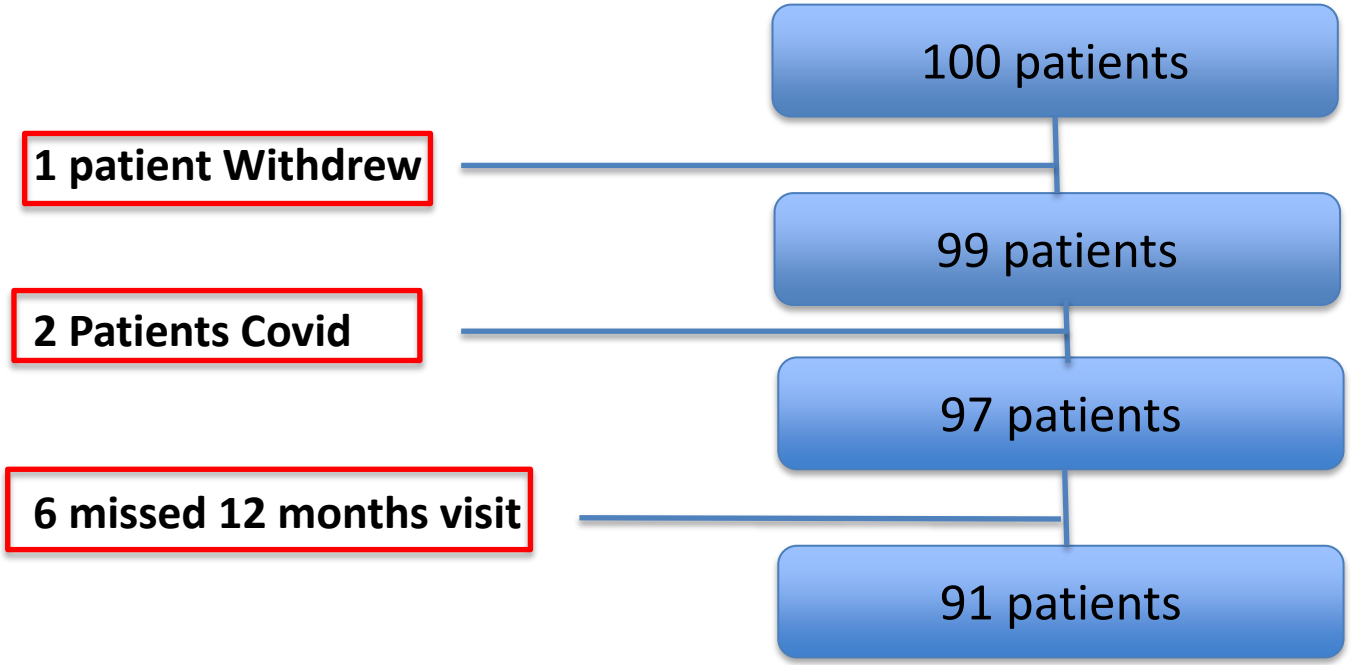
KCCQ Score Changes Through 2 Years
Full Randomized Cohort Including Crossovers



The KCCQ score improvement observed in the device group at 30 days was sustained through 2 years

Single Arm Cohort
100 patients

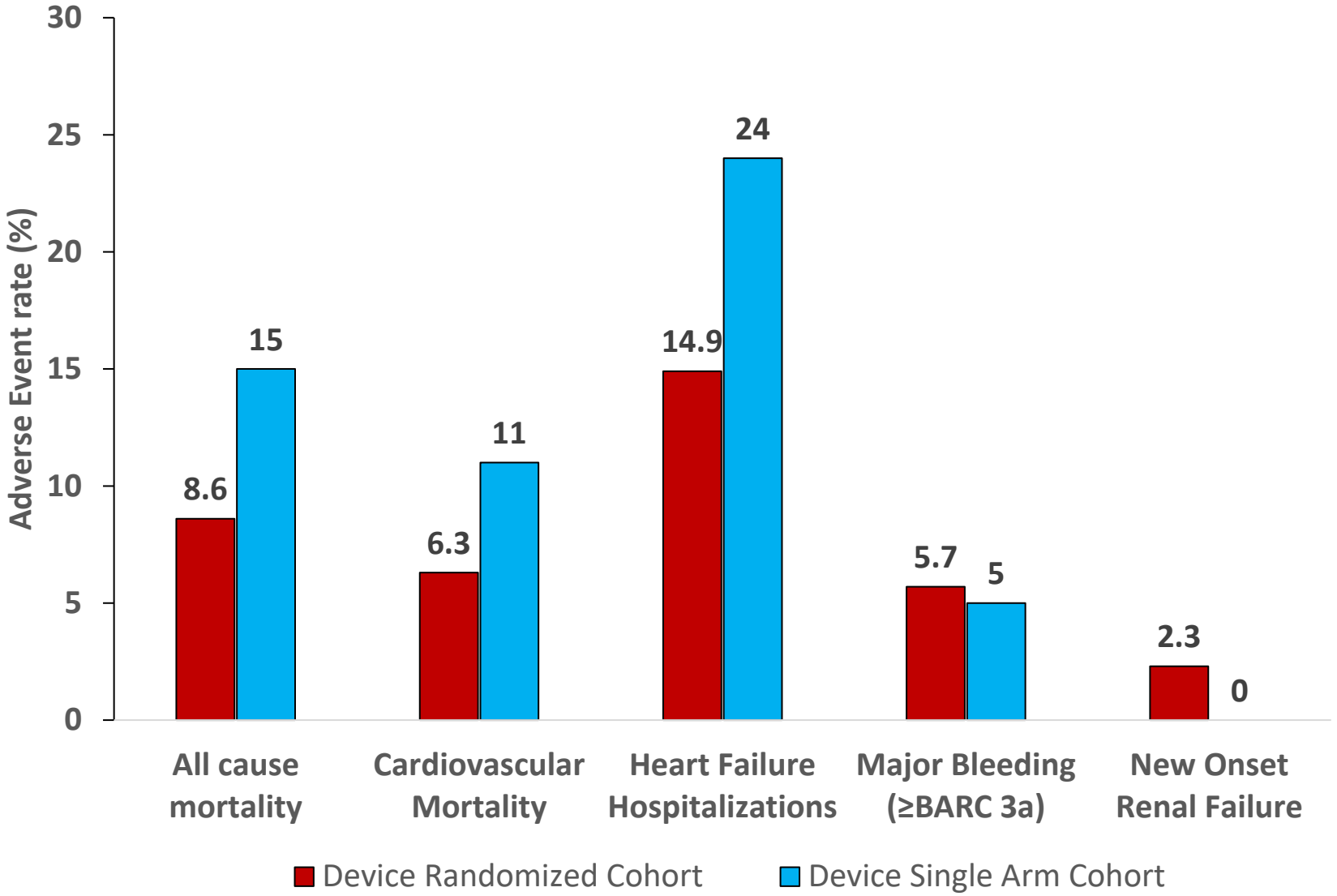
Single-Arm Cohort AP Population
Primary Analysis Results



Primary Endpoint	Rate	Lower 98.75% CI	Performance Goal	P-value	Result
Survival with ≥10 points KCCQ score improvement vs. baseline at 12 months	46.2% (42/91)	34.3%	30%	0.008	**Endpoint Met**

Select CEC-Adjudicated Adverse Events Through 12 months

Device Randomized Cohort and Single-Arm Cohort

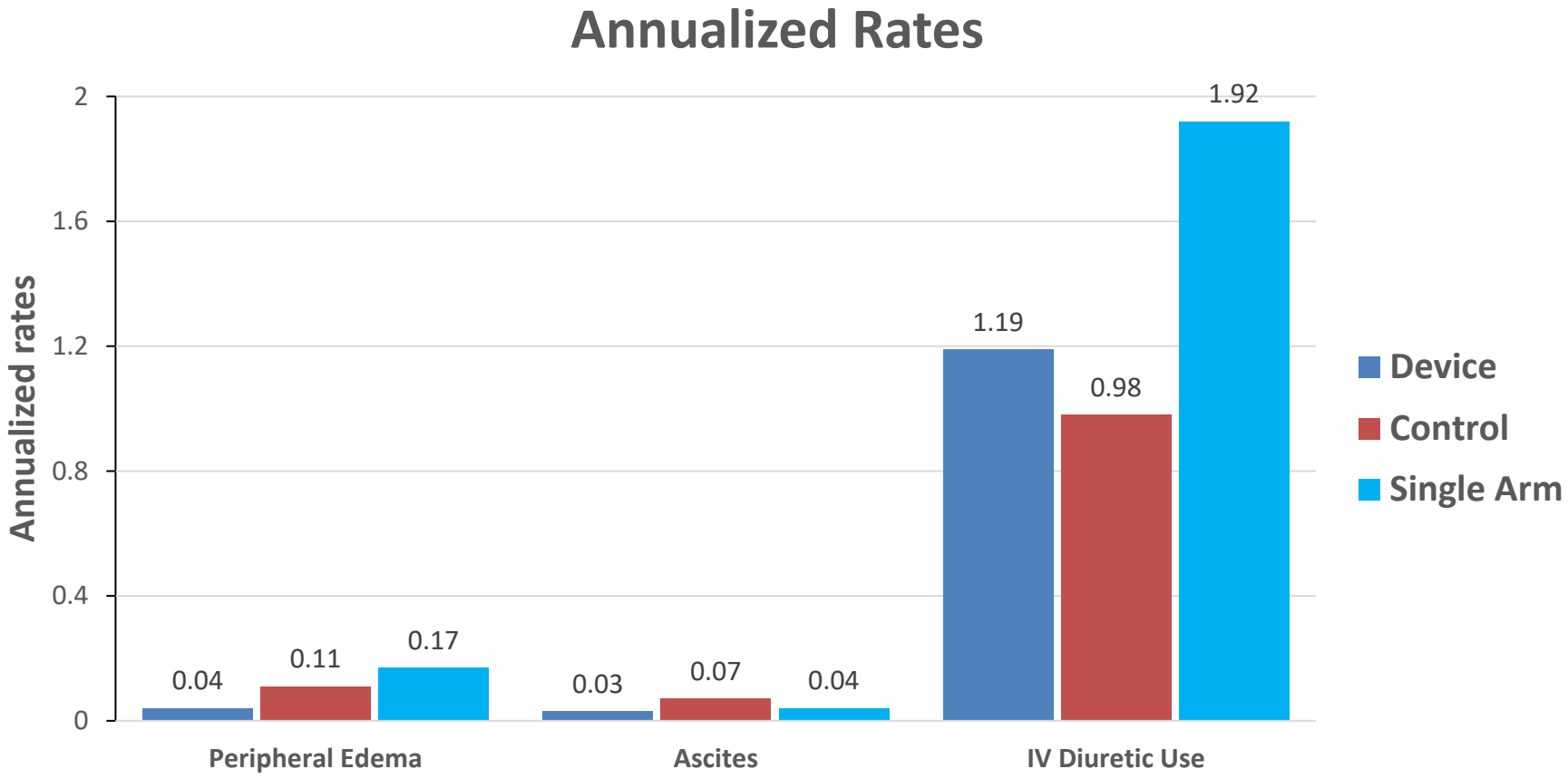


Single-Arm Cohort AP Population
Health Status Endpoints

Endpoint Change from Baseline to 12 Months	Results
ΔKCCQ overall summary score	
Mean ± SD (n)	14.5 ± 20.0 (78)
Median (Q1, Q3)	10.9 (2.9, 27.1)
Range (min, max)	(-47.5, 58.9)
ΔSF-36 physical component score	
Mean ± SD (n)	3.4 ± 7.5 (77)
Median (Q1, Q3)	3.0 (-0.5, 7.6)
Range (min, max)	(-17.4, 19.7)
ΔSF-36 mental component score	
Mean ± SD (n)	3.4 ± 12.2 (77)
Median (Q1, Q3)	3.3 (-2.7, 9.9)
Range (min, max)	(-33.3, 45.3)
ΔNYHA from III/IV to I/II	
% (no./total no)	41.8% (33/79)
Δ6MWD (m)	
Mean ± SD (n)	13.7 ± 92.7 (71)
Median (Q1, Q3)	6.0 (-40.0, 72.5)
Range (min, max)	(-231.1, 207.3)

Peripheral Edema Requiring Hospitalization, Ascites, & IV Diuretic Use at 12 Months

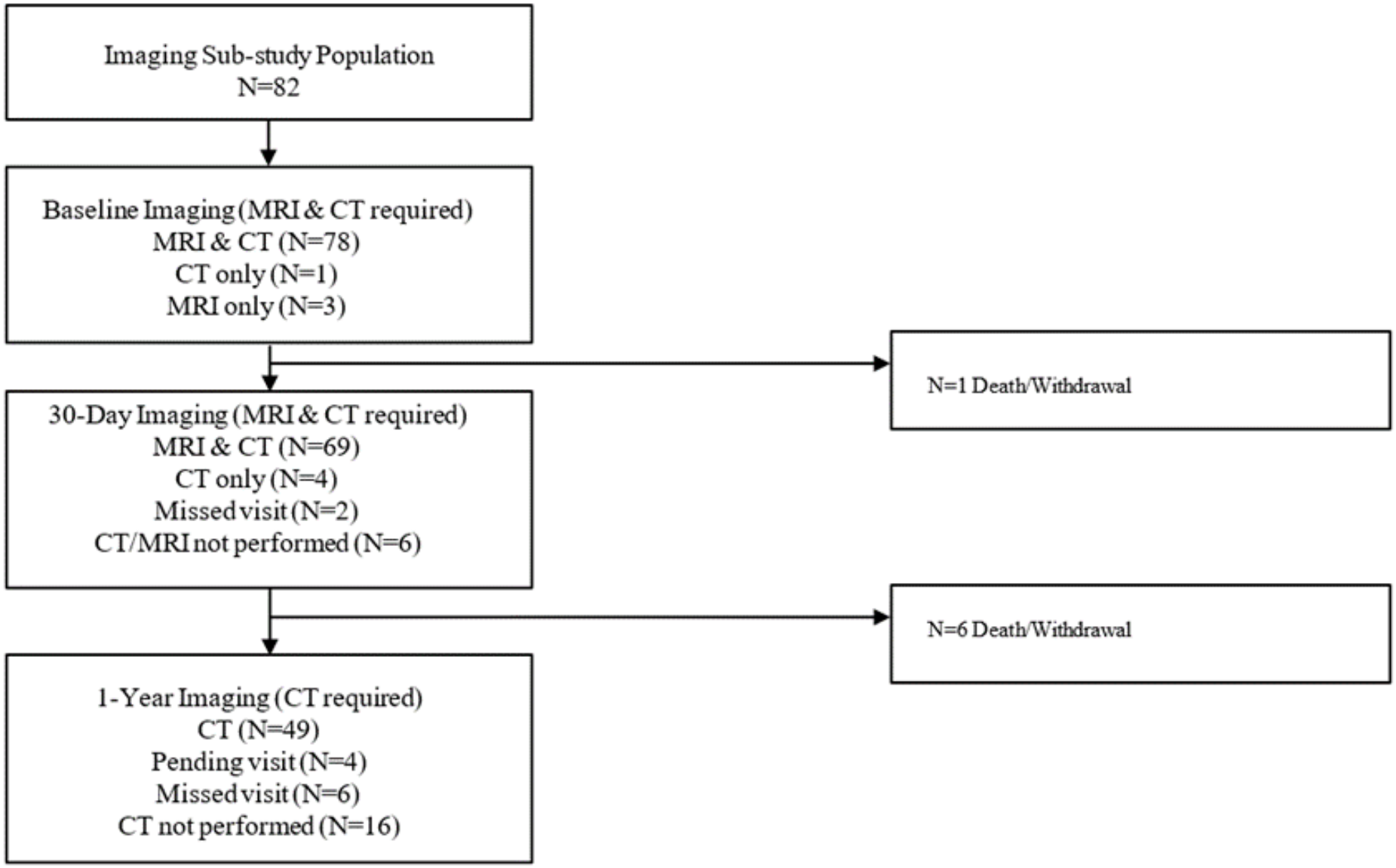
Primary Analysis Randomized Cohort and Single-Arm Cohort



Interpretation of annualized rates in the Single Arm Cohort is limited by different baseline characteristics and suitability for TriClip compared with the Randomized Cohort

Imaging Sub-Study

Pre-Planned Exploratory Imaging Sub-study



Imaging Sub-Study
30-Day Cardiac MRI Results

Endpoint Change from Baseline to 30 Days	Randomized Cohort		Single-Arm & Roll-in Cohorts (N=12)
	Device Arm (N=27)	Control Arm (N=26)	
ΔRight atrial end diastolic volume (RAEDV, mL)			
Mean ± SD (n)	-8.7 ± 23.1 (27)	-4.0 ± 38.5 (26)	-29.6 ± 27.8 (12)
Median (Q1, Q3)	-9.0 (-21.0, 8.0)	-3.0 (-16.0, 22.0)	-17.5 (-51.0, -5.5)
ΔRight ventricular mass (g)			
Mean ± SD (n)	-4.7 ± 5.2 (27)	0.0 ± 6.0 (25)	-7.2 ± 8.7 (11)
Median (Q1, Q3)	-5.0 (-9.0, 0.0)	1.0 (-4.0, 5.0)	-5.0 (-9.0, -1.0)
ΔRight ventricular ejection fraction (RVEF, %)			
Mean ± SD (n)	-5.6 ± 6.6 (27)	0.6 ± 6.1 (25)	-9.2 ± 5.6 (11)
Median (Q1, Q3)	-6.0 (-11.0, 1.0)	1.0 (-1.0, 2.0)	-10.0 (-15.0, -6.0)
ΔCorrected RVEF (%)*			
Mean ± SD (n)	8.4 ± 7.6 (27)	-0.2 ± 4.5 (24)	7.1 ± 9.3 (10)
Median (Q1, Q3)	8.1 (4.0, 15.0)	0.0 (-2.6, 2.5)	8.5 (-1.0, 14.0)
ΔRight ventricular free wall strain (%)			
Mean ± SD (n)	-2.0 ± 4.5 (27)	1.2 ± 6.1 (25)	-2.7 ± 4.8 (10)
Median (Q1, Q3)	-1.0 (-5.0, 1.0)	0.0 (-3.0, 3.0)	-2.0 (-6.0, 2.0)
ΔPulmonary forward flow (mL)			
Mean ± SD (n)	5.2 ± 13.0 (27)	0.3 ± 9.1 (24)	-1.8 ± 27.5 (11)
Median (Q1, Q3)	5.0 (-4.0, 14.0)	1.0 (-4.0, 5.0)	4.0 (-5.0, 10.0)

**** Corrected RVEF: Measurement of forward flow = total stroke volume-regurgitant volume for a regurgitant valve***

Imaging Sub-Study
12-Months Cardiac CT Results

Endpoint Change from Baseline to 12 Months	Randomized Cohort		Single-Arm & Roll-In Cohorts (N=7)
	Device Group (N=20)	Control Group (N=20)	
ΔRight atrial end diastolic volume (RAEDV, mL)			
Mean ± SD (n)	-19.5 ± 34.2 (20)	4.4 ± 35.5 (20)	-3.3 ± 23.6 (7)
Median (Q1, Q3)	-18.0 (-31.5, -4.0)	5.0 (-14.0, 23.0)	4.0 (-28.0, 21.0)
ΔTricuspid valve annular area (mm^2)			
Mean ± SD (n)	-195.0 ± 197.1 (20)	-3.0 ± 142.8 (20)	-194.3 ± 119.7 (7)
Median (Q1, Q3)	-205.0 (-305.0, -60.0)	-20.0 (-70.0, 60.0)	-160.0 (-300.0, -130.0)
ΔRight ventricular end diastolic volume (RVEDV, mL)			
Mean ± SD (n)	-35.8 ± 26.4 (20)	-1.0 ± 38.1 (20)	-42.4 ± 33.5 (7)
Median (Q1, Q3)	-38.0 (-58.5, -18.5)	-3.5 (-22.5, 12.5)	-37.0 (-56.0, -16.0)
ΔRight ventricular mass (g)			
Mean ± SD (n)	-4.7 ± 4.9 (20)	1.4 ± 6.5 (20)	-3.6 ± 5.7 (7)
Median (Q1, Q3)	-3.5 (-6.5, -1.0)	1.5 (-4.5, 5.0)	-5.0 (-7.0, -2.0)
ΔRight ventricular ejection fraction (%)			
Mean ± SD (n)	-6.9 ± 6.2 (20)	0.9 ± 5.2 (20)	-2.1 ± 7.0 (7)
Median (Q1, Q3)	-9.0 (-11.0, -2.0)	0.5 (-2.0, 4.0)	-2.0 (-8.0, 7.0)
ΔRight ventricular free wall strain (%)			
Mean ± SD (n)	-4.2 ± 7.2 (18)	-1.3 ± 5.4 (19)	-1.3 ± 6.5 (7)
Median (Q1, Q3)	-3.5 (-8.0, 2.0)	-2.0 (-5.0, 3.0)	2.0 (-8.0, 3.0)

Clinical Summary
Primary Analysis Randomized Cohort (ITT)

- TriClip technical success >98%
- Significant TR reduction through 12 months
- The primary effectiveness endpoint met, driven by improved KCCQ scores, which were sustained at 12 months
  - KCCQ improvement correlated with TR reduction
  - All cause mortality or TV surgery comparable among the 2 groups
  - Freedom from HF hospitalization numerically higher in the control group
- Favorable changes in the TriClip group for SF-36 scores, NYHA functional class, and liver function tests
- Open-label trial design introduces uncertainty into strength of device benefit

Clinical Summary
Full Randomized Cohort (ITT)

- Win ratio at 12 months favored the TriClip group driven by improved KCCQ scores
  - Kaplan-Meier estimates for all cause mortality or tricuspid valve surgery similar between the device and control groups
  - Kaplan-Meier estimates of freedom from heart failure hospitalization similar between the device and control groups
- Interpretation of 2-year data limited by the small sample size and crossover of control patients to TriClip treatment

Clinical Summary
Single Arm Cohort

- Primary endpoint of the proportion of patients who survived and had a ≥10-point improvement in KCCQ score at 12 months met

Clinical Summary
MRI and CT Imaging Sub-Studies

TriClip device use associated with:

- Favorable right atrial (RA) and right ventricular (RV) volume changes, supporting favorable RA and RV remodeling
- Favorable changes in corrected RV ejection fraction and pulmonary forward flow
- Small changes in other parameters of RV systolic performance, including uncorrected RV ejection fraction and RV free wall longitudinal strain of unclear significance

Study limitations

- **Small sample size**
- **Long-term prognostic implications not known**

Proposed Post-Approval Study and FDA Conclusions

Megan Naber, BS
General Engineer
Office of Cardiovascular Devices

Proposed Post-Approval Study

- TRILUMINATE study and Continued Access Study (CAS) patients followed through 5 years
- New Registry-based new enrollment study with 5-year follow-up
  - TVT Registry will collect patient demographics, baseline characteristics, and outcomes at 30 days and 1 year
  - CMS linkage will provide survival and hospitalization data for years 2-5
  - Objectives
    - Provide real-world procedural success and adverse event rates
    - Expand data to include additional patients, sites, and operators
    - Assess generalizability of premarket data
    - Evaluate learning curves/training program

Conclusions

- TRILUMINATE Randomized Cohort primary analysis
  - Primary endpoint (driven by KCCQ improvement) and safety endpoint met
  - Mortality or TV surgery rates similar between device and control groups at 12 months
  - HF hospitalization rate numerically higher in the device group
- TRILUMINATE Full Randomized Cohort
  - Win ratio favored device group (driven by KCCQ improvement)
  - Mortality or TV surgery and HF hospitalization rates similar between device and control groups at 12 months
  - Limited 2-year data
- TRILUMINATE Single-Arm Cohort
  - Primary endpoint and safety endpoint met

Conclusions

TRILUMINATE Study

- Strengths
  - Low major adverse event rate at 30 days
  - High technical/device success rates at 30 days
  - Sustained TR reduction and KCCQ improvement
- Limitations
  - Open label design
  - Randomized Cohort primary endpoint success driven by KCCQ score improvement
  - Difference in win ratio results seen between high enrolling and low enrolling sites