FDA Executive Summary

Prepared for the February 13, 2024, Meeting of the
Circulatory System Devices Panel
to be held virtually

Premarket Application (PMA) for Pxxxxxx

TriClip G4 System

FDA Executive Summary

Pxxxxxx

Premarket Application for Abbott Medical's TriClip G4 System

1 Introduction

Abbott Medical submitted a Premarket Approval (PMA) application to the Center of Devices and Radiological Heath (CDRH) of the Food and Drug Administration (FDA) requesting approval to market the TriClip G4 System (TriClip) for improvement of health status in patients with symptomatic, severe tricuspid regurgitation (TR), whose symptoms and TR severity persist despite optimal medical therapy (OMT).

The PMA is primarily supported by clinical data from the TRILUMINATE pivotal trial, a prospective, open-label, multicenter, randomized (1:1), controlled clinical trial designed to test the superiority of TriClip plus OMT (device group) to OMT alone (control group). The study included symptomatic patients with severe TR at intermediate or greater surgical risk who were on stable optimized medical therapy for heart failure (HF). Patients with other cardiovascular conditions in need of interventional or surgical correction were excluded. In addition to the Randomized Cohort, the study included a Single-Arm Cohort for patients with a low likelihood of achieving TR reduction to moderate severity or lower, but a high likelihood of achieving TR reduction of at least one grade.

The primary endpoint of the Randomized Cohort was a hierarchical composite of all-cause mortality or tricuspid valve surgery, number of HF hospitalizations, and health status improvement by ≥15 points measured by the Kansas City Cardiomyopathy Questionnaire (KCCQ) overall summary score, assessed at 12-month follow-up. The primary endpoint of the Single-Arm Cohort was survival with a KCCQ summary score improvement of ≥10 points at 12 months compared to baseline.

FDA's Executive Summary reviews TR etiology, current standard of TR care, and the TRILUMINATE pivotal trial.

2 Background

2.1 Tricuspid Valve Anatomy and Tricuspid Regurgitation (TR)

The tricuspid valve apparatus is composed of an annulus, three leaflets (anterior, posterior and septal) in most cases, chordae tendineae, and papillary muscles. The leaflets insert into the tricuspid annulus and are attached to the right ventricle via chordae tendinea and papillary muscles. Tricuspid valve opening and closure depend on the proper function of all valve components. TR (or tricuspid insufficiency) occurs when the tricuspid valve leaflets do not close completely during systole resulting in regurgitation of blood from the right ventricle into the right atrium.

2.2 TR Severity Grading

Transthoracic echocardiography (TTE) is currently the gold standard for diagnosing TR and assessing its severity (Otto CM, et al. 2020). The current American Society of Echocardiography (ASE) parameters for grading chronic TR severity are shown in Table 1 (Zoghbi et al. 2017). The grading system incorporates qualitative, semiquantitative, and quantitative elements.

Table 1. Grading the Severity of Chronic TR by Echocardiography (Zoghbi et al. 2017).

Parameters	Mild TR	Moderate TR	Severe TR
Structural			
TV morphology	Normal or mildly abnormal leaflets	Moderately abnormal leaflets	Severe valve lesions (e.g., flail leaflet, severe retraction, large perforation)
RV and RA size	Usually normal	Normal or mild dilatation	Usually dilated*
IVC diameter	Normal <2 cm	Normal or mildly dilated 2.1-2.5 cm	Dilated >2.5 cm
Qualitative Doppler			
Color flow jet area†	Small, narrow, central	Moderate central	Large central jet or eccentric wall-impinging jet of variable size
Flow convergence zone	Not visible, transient, or small	Intermediate in size and duration	Large throughout systole
CWD jet	Faint/partial/parabolic	Dense, parabolic or triangular	Dense, often triangular
Semiquantitative			
Color flow jet area (cm^2)†	Not defined	Not defined	>10
VCW (cm)†	<0.3	0.3-0.69	≥0.7
PISA radius (cm)‡	≤0.5	0.6-0.9	>0.9
Hepatic vein flow§	Systolic dominance	Systolic blunting	Systolic flow reversal
Tricuspid inflow§	A-wave dominant	Variable	E-wave >1.0 m/sec
Quantitative			
EROA (cm^2)	<0.20	0.20-0.39‖	≥0.40
RVol (2D PISA, mL)	<30	30-44‖	≥45

TV: tricuspid valve; IVC: inferior vena cava; RV: right ventricle; RA: right atrium; CWD: continuous-wave Doppler; VCW: vena contracta width; PISA: proximal isovelocity surface area;

EROA: effective regurgitant orifice area; RVol: regurgitant volume.
*RV and RA size can be within the normal range in patients with acute severe TR.
†With Nyquist limit >50-70 cm/sec.
‡With baseline Nyquist limit shift of 28 cm/sec.
§Signs are nonspecific and are influenced by many other factors (RV diastolic function, atrial fibrillation, RA pressure).
‖There are little data to support further separation of these values.

To better characterize TR severity in patients treated with transcatheter devices, Hahn et al. (2017) proposed a modified grading scale, which further divides severe TR into severe TR, massive TR, and torrential TR. This grading scheme with additional diagnostic variables as described in Table 2 was used in the TRILUMINATE pivotal trial.

Table 2. Expanded 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.

2.3 Etiology

TR etiology can be grouped into 3 categories:

- Primary TR (also called degenerative, organic, or structural TR)
- Secondary TR (also called functional or non-structural TR)
- Cardiac implantable electronic device (CIED)-induced TR

In primary TR, regurgitation results from diseases affecting the integrity of any part of the tricuspid valve apparatus, such as rheumatic heart disease, tricuspid valve prolapse, endocarditis, or carcinoid heart valve disease. In secondary TR, regurgitation occurs in the absence of significant tricuspid valve structural abnormalities and is caused by tricuspid annular dilation secondary to right atrial enlargement, right ventricular enlargement (as a result of left-sided heart disease), or pulmonary hypertension (Topilsky et al, 2019). CIED-induced TR is caused by the interaction of a CIED lead with the valve leaflets.

The TRILUMINATE pivotal trial enrolled patients with all three TR etiologies but excluded patients with pacemaker or implantable cardioverter defibrillator (ICD) leads that could interfere with TriClip device placement.

2.4 Current TR Treatments

TR associated symptoms and signs include ascites, peripheral edema, liver dysfunction, decreased appetite, jugular vein distention, and abdominal fullness. TR symptoms are often not evident until the regurgitation is significant, by which time patients are often at high risk for cardiac surgery due to comorbidities or age. Survival is significantly worse in patients with moderate and severe TR vs. no or mild TR (Nath et al. 2004).

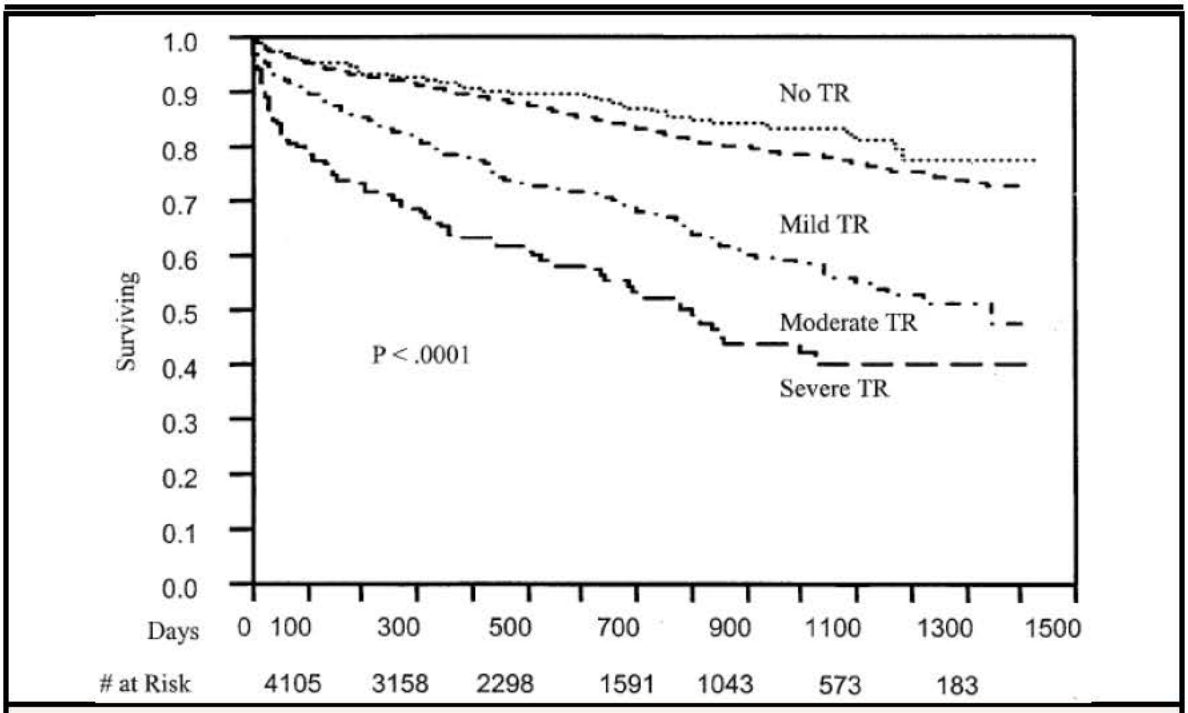


Figure 1. Kaplan-Meier Survival Curves for All Patients with TR (Nath et al. 2004).

TR treatment includes medical therapy and tricuspid valve surgery. Medical therapy mainly aims to manage volume overload via diuretics (a Class IIa recommendation). However, medical therapy with diuretics is frequently ineffective in alleviating symptoms, preventing hospitalization, or reducing morbidity or mortality, especially when patients develop diuretic

resistance secondary to worsening renal function (Beckhoff et al. 2018).

Per the 2020 American College of Cardiology (ACC)/American Heart Association (AHA) guidelines (Otto et al. 2020), tricuspid valve surgery is a Class I recommendation for patients with severe TR only if they are undergoing left-sided surgery (see Figure 2). Isolated tricuspid valve surgery is performed infrequently. Recent analyses of outcomes over a 10-year period show that although the frequency of TV surgery has increased, the majority (85%) were performed in conjunction with other cardiac surgery, and only 15% were performed as an isolated TV procedure (Zack CJ et al, 2017). Importantly, in-hospital mortality ranging from 8.1% to 10.9% has remained unchanged over the last decade. As a result, most patients with moderate or severe TR are not offered surgery.

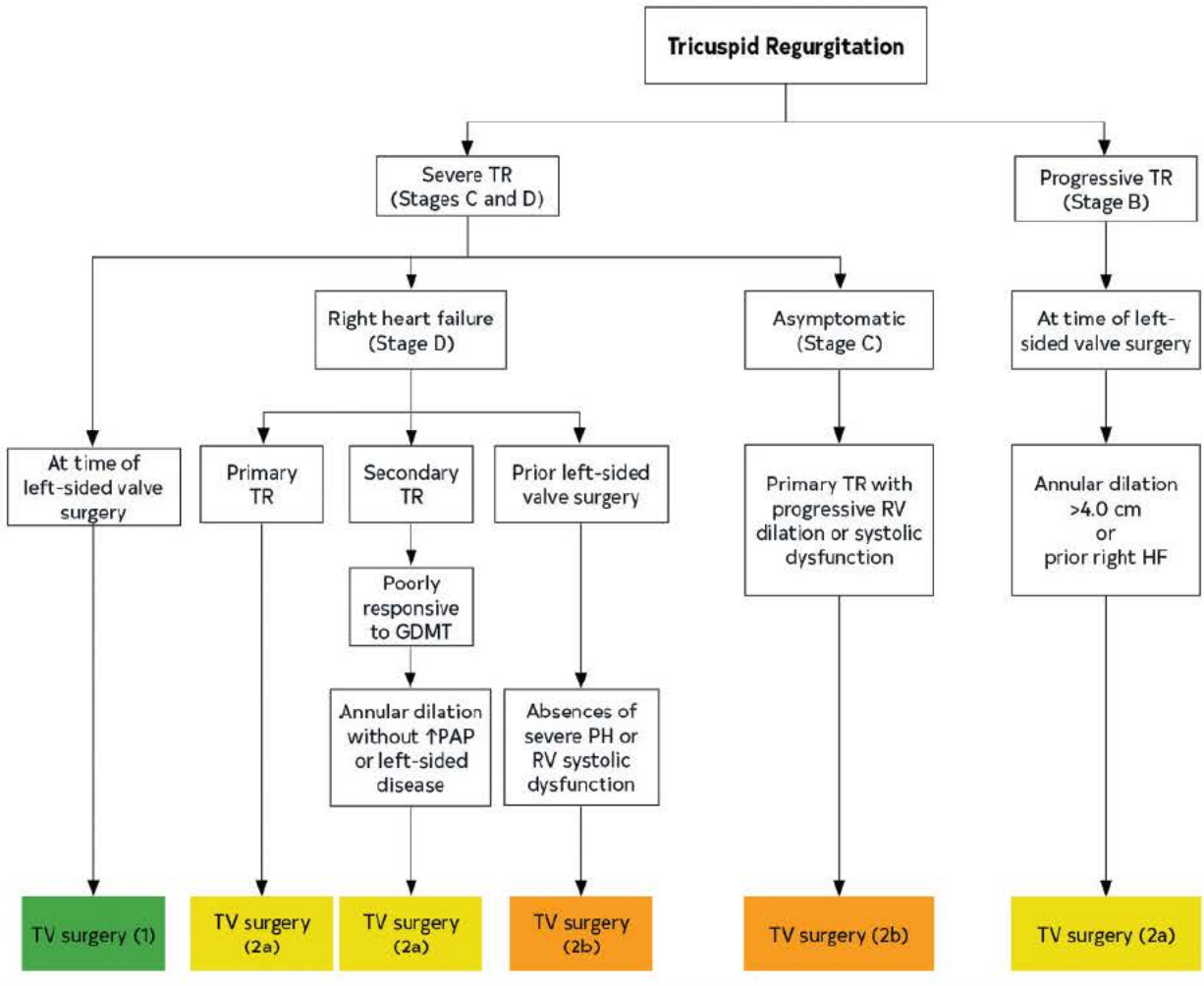


Figure 2. Indication for Surgery for Patients with TR (Otto et al. 2020).

2.5 Patient Reported Outcomes (PROs)

A PRO is any report that comes directly from the patient (i.e., study subject) about the status of their health condition, without amendment or interpretation of their response by a clinician or anyone else.

To provide guidance on the use of PROs for regulatory purposes, FDA issued a guidance document on PROs in 2009 (Food and Drug Administration 2009). The guidance document describes how FDA reviews and evaluates existing, modified, or newly created PRO instruments used to support claims in approved medical product labeling. Key guidance principles include:

- A PRO instrument used in a clinical trial can measure the effect of a medical intervention on one or more concepts (i.e., the thing being measured, such as a symptom or group of symptoms, effects on a particular function or group of functions, or a group of symptoms or functions shown to measure the severity of a health condition).
- A PRO can be measured in absolute terms (e.g., severity of a symptom, sign, or state of a disease) or as a change from a previous measure.
- Reliability, validity, and the ability to detect changes are considered in FDA's review of PRO instruments.

Commitment to partnering with patients was one of the CRDH's 2016-2017 strategic priorities (Food and Drug Administration). As part of the commitment, the Center encouraged increased use of PROs in regulatory decision making (Food and Drug Administration 2022).

2.5.1 Use of PRO Instruments in Blinded and Open-Label Clinical Trials

It is believed that study subject blinding to treatment assignment is important in drawing robust inferences from PRO data because a patient's knowledge on treatment assignment could impact their symptom perception and symptom severity grading. For example, it could be expected that patients randomized to the investigational group may report more optimistic subjective information than patients in the control group, who may be more pessimistic based on their treatment assignment, especially when the control group receives a nonpreferred treatment by the patients, such as no treatment or a more invasive treatment.

FDA's 2009 PRO guidance notes:

> "Suspicion of inadvertent unblinding can be a problematic review consideration for the FDA when assessing PRO endpoints" and
>
> "The effect of intentional unblinding is important to consider in the interpretation of clinical trial results. There are certain situations, such as in the evaluation of some medical devices or administration of identifiable treatment regimens, where blinding is not feasible…"

Although concerns regarding the validity of PRO data in open-label trials seem reasonable, there is very limited research in this area, mostly in the oncology literature, with no definitive conclusions regarding PRO outcomes bias (Anota et al. 2022; Lord-Bessen et al. 2023; Tack et al. 2023). Further, studies focused on blinded vs. open-label cardiac device interventions or specific

evaluation of the KCCQ are lacking. Even if one assumes that bias plays a role in open-label PRO outcomes, estimating the magnitude of the bias is challenging. One approach is to compare PRO outcomes from similar trials that differ in their design (i.e., blinded vs. open label). Another approach to help estimate potential bias in an open-label trial is to administer the PRO instrument prior to randomization and retest post-randomization but before the investigational intervention is administered. The durability of the treatment effect may help interpret PRO data, as it may be expected that the placebo effect of an ineffective therapy could wane over time. When comparing treatment and control groups in an open-label trial, responses in PRO domains that are proximal to the investigational product's mechanism of action may be more relevant than those in more distal domains, such as emotional function, social function, and global quality of life (Roydhouse et al. 2019). Thus, when considering a device that reduces TR severity, symptoms more closely associated with TR pathophysiology might be less prone to open-label bias vs. more general health status assessments. Lastly, unequal study patient withdrawal between treatment groups (e.g., a higher dropout rate in the control group vs. the test group) resulting in unequal or not-at-random missing PRO data can also introduce additional challenges in interpreting study results.

2.5.2 Kansas City Cardiomyopathy Questionnaire (KCCQ)

The KCCQ is a PRO instrument for measuring health status in patients with HF (Green et al. 2000). It is self-administered and includes 23 items across 7 domains: symptom frequency; symptom burden; symptom stability; physical limitations; social limitations; quality of life; and self-efficacy. Values for each domain and the summary scores range from 0 to 100, with higher scores indicating better health status. Clinical consensus suggested that a change of 5 points in the KCCQ overall summary score is a small but clinically important change, a change of 10 points represents a moderate to large improvement, and a change of 20 points is a large to very large improvement (Spertus et al. 2020).

KCCQ was qualified in 2020 by CDRH in the Medical Device Development Tools (MDDT) program (Food and Drug Administration 2020), which was launched in 2017 for the FDA to qualify tools that medical device manufacturers can choose to use in the development and evaluation of medical devices (Food and Drug Administration 2023). The KCCQ was qualified as a clinical outcome assessment PRO instrument for adults ≥18 years of age with symptomatic heart failure. The instrument can be used in feasibility and pivotal studies to evaluate treatment benefits for these patients (e.g., patients with stage C and D HF).

3 TriClip Device and Implant Procedure

The TriClip G4 System (Figure 3) is intended to reduce TR through tissue approximation. The device has the same form and function as the commercial MitraClip System used to treat mitral regurgitation. Only the delivery system was modified for access to the tricuspid valve. The TriClip G4 System includes the following components:

- TriClip Steerable Guide Catheter (TSGC), consisting of the Dilator, 25 Fr shaft, and Handle
- TriClip G4 Clip Delivery System (TCDS), consisting of the Delivery Catheter (DC), Steerable Sleeve (SS) and Clip
- TriClip G4 Clip pre-mounted on the distal end of the TCDS
- Accessories, consisting of the Stabilizer, Lift, Support Plate, Silicone Pad and Fasteners to

support and position the system during the procedure.

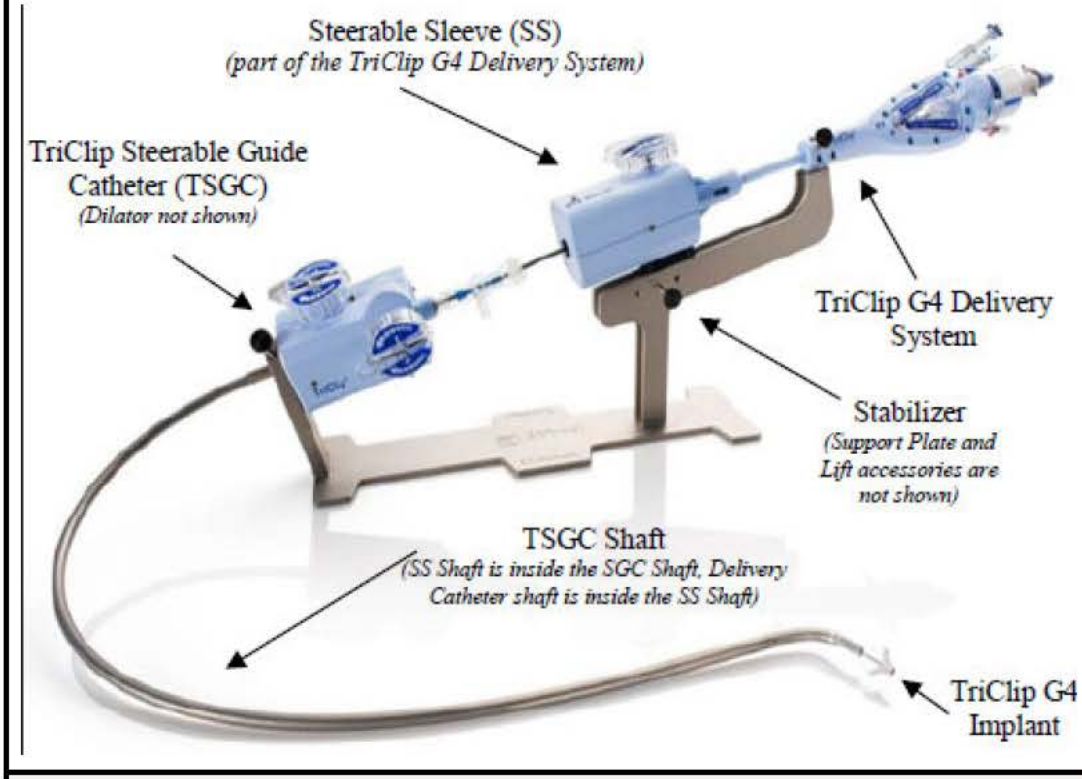
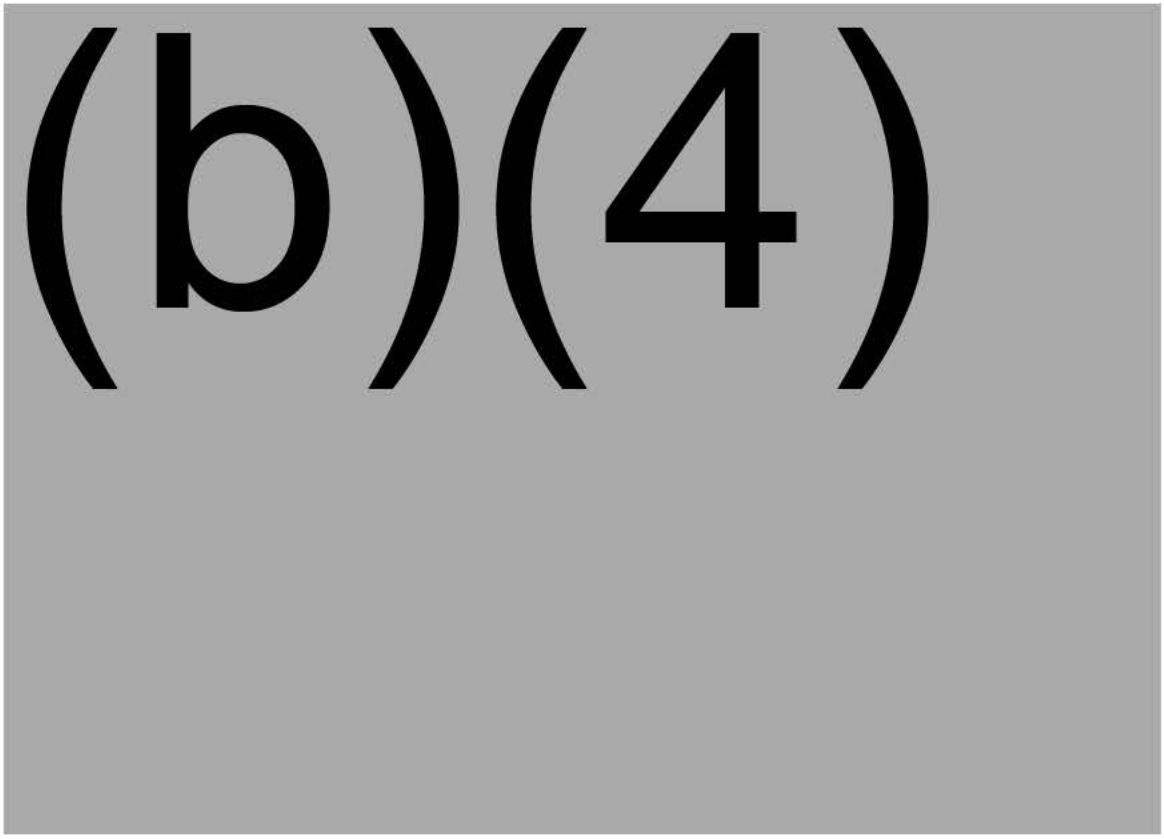


Figure 3. TriClip G4 System and Stabilizer Accessory.

During the TriClip implant procedure, the operator advances the TSGC and Dilator over a commercially available guidewire to the right atrium. The user removes the Dilator and guidewire and inserts the TCDS through the TSGC, which serves as a conduit for positioning the TCDS into the right atrium. The TCDS is positioned by way of two knobs used to adjust the distal tip of the TSGC and one knob to adjust the tip of the TCDS. The user then manipulates the DS handle to position the Clip within the tricuspid valve. The DC handle includes adjustment knobs to open, close, and lock the Clip Arms to grasp the leaflets and secure the clip. The system allows for multiple grasping attempts prior to deployment, and the leaflets can be grasped simultaneously or independently. Once the valve leaflets have been adequately grasped, the DC Handle controls are used to disconnect the Clip from the DC, and all components (with the exception of the Clip) are removed from the body.

The TriClip G4 Clip (Figure 4) is composed of the Clip Arms, Clip Legs, Grippers, and a polyester fabric cover. The angle of the Clip Arms can be adjusted between fully opened (inverted) and fully closed while advancing and retracting the implant with the DC to position the implant and grasp the leaflets. Once the leaflets have been grasped by the Clip Arms, the operator lowers the Grippers to capture the leaflets and secure the Clip. The Grippers can be raised and lowered simultaneously or independently to capture the leaflets. If needed, the Clip can be fully opened to release the leaflets and reposition the implant prior to deployment. The Clip is available in four sizes: NT, NTW, XT, and XTW, with varying Clip length and width.



4 Breakthrough Device Designation

FDA's Breakthrough Devices Program is a voluntary program for devices that have the potential to provide more effective treatments or diagnoses than are currently available for life-threatening or irreversibly debilitating diseases or conditions. The program is intended to provide patients and health care providers with timely access to beneficial new medical devices by accelerating their development, assessment, and regulatory review. The statutory standard for PMA approval of a breakthrough device, however, is the same as a non-breakthrough device, that is, a reasonable assurance of safety and effectiveness.

The TriClip System received breakthrough device designation in November 2020, based on clinical data from the TRILUMINATE Early Feasibility Study (EFS). FDA determined that the TriClip System met breakthrough device criteria because it was a novel technology with the potential to provide more effective treatment of patients with severe symptomatic TR despite optimal medical management.

FDA Comment: Although the Breakthrough Device Program offers expanded opportunities to utilize efficient and flexible clinical study designs, a Breakthrough Device designation does not modify or reduce the statutory requirement for PMA approval. The totality of the data still needs to demonstrate that the device provides a reasonable assurance of safety and effectiveness for its intended population.

5 Proposed Indications for Use

Abbott Medical has proposed the following indications for use for the TriClip device:

> 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.

6 Pivotal Trial Overview

The TRILUMINATE pivotal trial was a randomized (1:1) controlled trial comparing transcatheter tricuspid repair using the TriClip device plus OMT vs. OMT alone in patients with severe, symptomatic TR who were determined by the site's local heart team to be at intermediate or greater risk for mortality or morbidity with open heart surgery. In addition to the Randomized Cohort, the trial also included a Single-Arm Cohort. After being enrolled into the trial, patients were assigned to a cohort by a centralized independent Eligibility Committee based on the following criteria:

- Randomized Cohort: High likelihood that the TriClip could reduce TR to moderate or less (i.e., less than or equal to grade 2).
- Single-Arm Cohort: High likelihood that the TriClip could reduce TR by at least 1 grade but a low likelihood that TR will be reduced to moderate or less.

The Eligibility Committee determined whether a patient was likely to achieve TR reduction to moderate or less based on multiple considerations, including but not limited to:

- Baseline TR severity
- The presence of CIED leads across the tricuspid valve
- The coaptation gap width

The trial was to enroll up to 550 patients in the Randomized Cohort and up to 200 patients in the Single-Arm Cohort. Up to 3 roll-in patients per implanter were to be enrolled at sites with implanters who did not have prior or recent experience using the TriClip device. The study flow chart is shown in Figure 5.

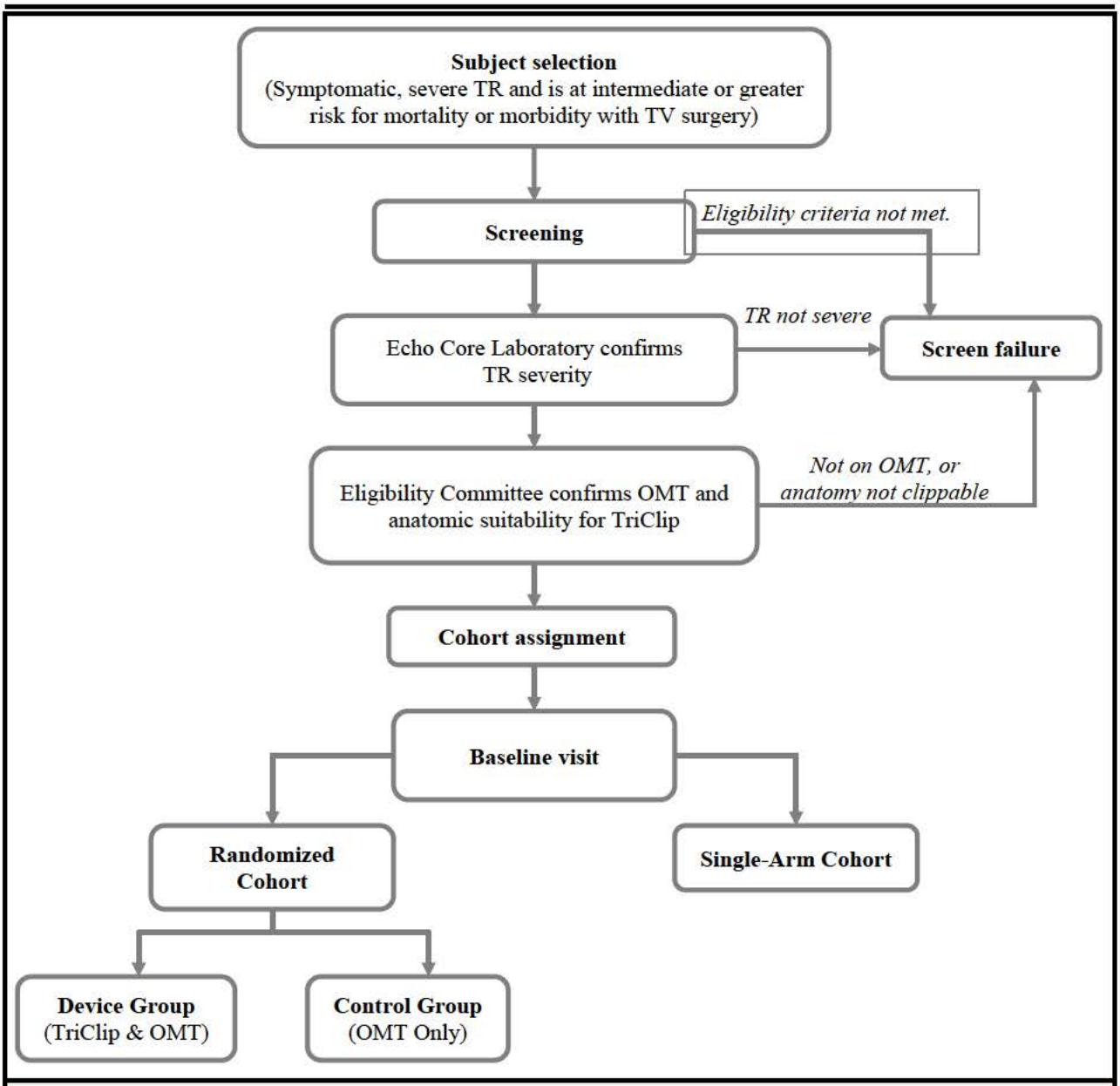


Figure 5. Study Flow Chart. TR: tricuspid regurgitation; OMT: optimal medical therapy.

6.1 Inclusion and Exclusion Criteria

6.1.1 Key Inclusion Criteria

Patients enrolled in the trial needed to meet all of the following criteria:

- In the judgment of the site local heart team, the patient was adequately treated per applicable standards (including medical management) and stable for at least 30 days as follows:

  - Optimized medical therapy for TR treatment (e.g., diuretics)
  - Medical and/or device therapy if needed for mitral regurgitation, atrial fibrillation, coronary artery disease and HF.

  The Eligibility Committee confirmed that the patient was adequately treated medically.
- Patient was symptomatic with severe TR despite optimal treatment as described above.
- TR severity was based on a qualifying TTE and confirmed by the echocardiography core laboratory (ECL). Note: If any cardiac procedure(s) occurred after eligibility was determined, TR severity was reassessed 30 days after the cardiac procedure(s).
- The cardiac surgeon on the site local heart team concurred that the patient was at intermediate or greater estimated risk for mortality or morbidity with tricuspid valve surgery.
- NYHA Functional Class II, III or ambulatory class IV.
- In the judgment of the TriClip implanting investigator, femoral vein access was feasible and could accommodate a 25 Fr catheter.
- Age ≥18 years at time of consent.
- Patient provided written informed consent prior to any trial related procedure.

6.1.2 Key Exclusion Criteria

Patients enrolled in the trial could not have any of the following criteria:

- Systolic pulmonary artery pressure (sPAP) >70 mmHg or fixed pre-capillary pulmonary hypertension assessed by right heart catheterization.
- Severe uncontrolled hypertension (systolic blood pressure ≥180 mmHg and/or diastolic blood pressure ≥110 mmHg).
- Prior tricuspid valve procedure that would interfere with placement of the TriClip device.
- Indication for left-sided cardiac intervention (e.g., severe aortic stenosis, severe mitral regurgitation) or pulmonary valve correction in the prior 60 days. Note: Patients with concomitant mitral and tricuspid valve disease had the option of mitral regurgitation treatment and waiting 60 days prior to TriClip trial eligibility reassessment.
- Pacemaker or implantable cardioverter defibrillator (ICD) leads that would prevent appropriate placement of the TriClip device.
- Tricuspid valve stenosis, defined as a tricuspid valve orifice ≤1.0 cm^2 and/or mean gradient ≥5 mmHg assessed by the ECL.
- Left ventricular ejection fraction (LVEF) ≤20%.
- Tricuspid valve leaflet anatomy which may preclude clip implantation, proper clip positioning on the leaflets, or sufficient reduction in TR. This may include:
  - Calcification in the grasping area
  - Severe coaptation defect (>2 cm) of the tricuspid leaflets
  - Severe leaflet defect(s) preventing proper device placement
  - Ebstein anomaly
- Tricuspid valve anatomy not evaluable by transthoracic echocardiogram (TTE) or transesophageal echocardiography (TEE).
- Active endocarditis, active rheumatic heart disease, or leaflets degenerated from rheumatic disease (i.e., noncompliant and perforated).
- Myocardial infarction (MI) or known unstable angina within 30 days.

- Percutaneous coronary intervention within 30 days.
- Hemodynamic instability defined as systolic blood pressure <90 mmHg with or without afterload reduction, cardiogenic shock, or the need for inotropic support or intra-aortic balloon pump or other hemodynamic support device.
- Cerebrovascular accident (CVA) within 90 days.
- Chronic hemodialysis.
- Bleeding disorders or hypercoagulable state.
- Active peptic ulcer or active gastrointestinal (GI) bleeding.
- Contraindication, allergy, or hypersensitivity to dual antiplatelet and anticoagulant therapy. Note: Contraindication to either antiplatelet or anticoagulant therapy (individually not both therapies) was not an exclusion criterion.
- Ongoing infection requiring current antibiotic therapy (if temporary illness). Note: Patients could enroll 30 days after discontinuation of antibiotics with no active infection.
- Known allergy or hypersensitivity to device materials.
- Evidence of intracardiac, inferior vena cava (IVC), or femoral venous mass, thrombus, or vegetation.
- Life expectancy <12 months.
- Pregnant or nursing subjects and those who plan pregnancy during the clinical investigation follow-up period. Female subjects of child-bearing potential were required to have a negative pregnancy test done within 7 days of the baseline visit. Female patients of childbearing potential instructed to use safe contraception.
- Presence of other anatomic or comorbid conditions, or other medical, social, or psychological conditions that, in the investigator's opinion, could limit the subject's ability to participate in the clinical investigation or to comply with follow-up requirements, or impact the scientific soundness of the clinical investigation results.

6.2 Follow-up Schedule

Patient follow-up schedule is shown in Table 3.

Table 3. Follow-up Schedule.

	Baseline	Procedure/ Treatment Visit (≤14 Days from Randomization)	Discharge (>16 Hours Post-procedure)	30 days (-3/+14 Days)	6 Month (±28 days)	12 and 18 Months & Annually Years 2-5 (±28 Days)
Physical exam and vital signs	X	X	X	X	X	X
Cardiovascular medications	X	X	X	X	X	X
Echocardiogram	X	X[#] (TEE only)	X (TTE Only)	X (TTE only)	X (TTE Only)	X[‡] (TTE only)

	(TTE only)					
CT*	X			X		X (1 year only)
MRI*	X			X		
CBC with differentials and platelet count	X		X	X	X	X
Gamma-GGT†, BNP or NT-proBNP, CK or CK-MB, BUN, serum creatinine, AST, ALT, INR (while on anticoagulation), bilirubin, serum sodium	X		X	X	X	X
KCCQ	X			X¶	X¶	X‡, ¶
SF-36	X			X¶		X (1 and 2 year only)¶
6-minute walk test	X				X¶	X‡, ¶
NYHA	X		X	X¶	X¶	X¶
12-lead ECG	X	X	X	X	X	X
Modified Rankin Scale[l]			X	X	X	X

CT: computed tomography; MRI: magnetic resonance imaging; CBC: complete blood count; GGT: gamma-glutamyl transferase; BNP: B-type natriuretic peptide; NT-proBNP: N-terminal pro B-type natriuretic peptide; CK: creatine kinase; CK-MB: creatine kinase myocardial band; BUN: blood urea nitrogen; AST: aspartate aminotransferase; ALT: alanine transaminase; INR: international normalized ratio; KCCQ: Kansas City Cardiomyopathy Questionnaire; SF-36: 36-Item Short Form Survey; NYHA: New York Heart Association; ECG: electrocardiogram; TTE: transthoracic echocardiogram; and TEE: transesophageal echocardiography.
*Only required for patients in the imaging sub-study.
†Only required for sites with capability.
‡Not required at 18 months.
[l]Only required at visit after onset of stroke, if stroke occurred.
¶These assessments were to be completed by blinded personnel.
#Not required for control patients.

6.3 Study Blinding (Randomized Cohort)

Study blinding for the Randomized Cohort was as follows:

- Investigators: Unblinded to treatment group.
- Research staff administering the KCCQ, 6-minute walk test, SF-36, and NYHA: Blinded to treatment group.
- Sonographers performing follow-up echocardiograms: Unblinded to treatment group as device is visible on TTE.
- Patients: Unblinded to treatment group. (Note: It is unknown if site echocardiographers discussed follow-up TR severity or other echocardiographic findings with patients).
- Clinical Events Committee (CEC): Unblinded to treatment group.

6.4 Statistical Analysis Populations

The analysis populations for the Randomized Cohort and Single-Arm Cohort are shown in Table 4.

Table 4. Statistical Analysis Populations

Analysis Population	Definition
Randomized Cohort	
Intent-to-Treat (ITT)	All patients randomized in the trial.
As-Treated (AT)	ITT patients grouped by treatment received.*
Per Protocol (PP)	ITT patients who received assigned randomized treatment according to protocol and followed all major study requirements.
Attempted Procedure (AP)	Patients randomized to the device group with an attempted TriClip procedure (i.e., femoral vein puncture performed).
Single-Arm Cohort	
Attempted Procedure (AP)	Patients with an attempted TriClip procedure (i.e., femoral vein puncture performed).

*Device patients who died or had heart failure hospitalization prior to the TriClip procedure are considered to be in the Control group regardless of randomization. Device patients who died or had heart failure hospitalization after (but not prior to) a TriClip procedure are considered to be in the device group regardless of randomization. Patients who did not experience death or heart failure hospitalization at any time during follow-up were assigned to the group that constituted >50% of their follow-up duration.

6.5 Randomized Cohort Endpoints

6.5.1 Primary Endpoint

The primary endpoint was a hierarchical composite of the following components at 12 months:

- Time to all-cause mortality or tricuspid valve surgery
- Number of HF hospitalizations
- Improvement of ≥15 points in KCCQ overall summary score (KCCQ score, hereafter) from baseline

HF hospitalization included any of the following:

- Hospitalization (≥24 hours) with the primary reason for admission being acute decompensated HF and administration of intravenous or mechanical HF therapies.
- An unscheduled or unplanned admission (≥24 hours) to the emergency department, hospital outpatient observation unit, or hospital inpatient unit, and intravenous administration of diuretic therapy. Overnight stays for intravenous administration of diuretic therapy at nursing home facilities, physical rehabilitation or extended care facilities, including hospice, are included in the definition of hospitalization if related to HF.
- Patient arrived in the emergency department with clinical presentation meeting the criteria of HF but died in the emergency department before hospital admission.

Elective HF "tune-ups" that occur following the TriClip procedure (i.e., administration of IV diuretics unrelated to a specific adverse event) and prolonged index hospitalization did not count as an HF hospitalization.

6.5.1.1 Statistical Analysis Plan

The null (H_0) and alternative (H_1) hypotheses for the primary endpoint were as follows:

H_0: None of the components is different between the TriClip and control groups
H_1: At least one component is different between the TriClip and control groups

The alternative hypothesis was that the TriClip group is superior to the control group, which was tested using the Finkelstein-Schoenfeld methodology (Finkelstein et al. 1999) at a two-sided significance level of 5%. The primary analysis population was the ITT population. A sample size of 350 randomized patients was simulated to provide approximately 83% power to reject the null hypothesis at a two-sided significance level of 5%.

As a supplementary analysis, the win-ratio approach (Pocock et al. 2012) was used to evaluate the treatment effect of the composite endpoint. In the analysis, each pair of patients from the device group and the control group were compared in the order of the hierarchy defined above; and the win ratio was defined as the number of winners divided by the number of losers in the device group (see appendix for details).

6.5.1.2 Interim Analysis: Sample Size Re-estimation

An adaptive design with sample size re-estimation was planned for when the first 150 randomized patients completed the 12-month follow-up visit. At that time, an independent statistician was to be unblinded to the interim data and calculate the conditional power for the primary endpoint. This would determine whether the primary endpoint could be assessed with the original 350-patient sample size, or an increased sample size would be needed. The randomized enrollment was to

continue until at least the re-estimated sample size was reached.

6.5.1.3 COVID-19 Censoring

In patients whose death or hospitalization was adjudicated by the CEC as COVID-19 related, these events and all subsequent primary endpoint outcomes (if any) were censored in the primary analysis.

6.5.2 Powered Secondary Endpoints

Four powered secondary endpoints were assessed hierarchically at 12 months (see Table 5).

Table 5. Ordered List of Secondary Endpoints for Hierarchical Testing – Randomized Cohort.

Order	Secondary Endpoint	Null and Alternative Hypotheses	Analysis Population	Significance Level
1	Freedom from MAEs at 30 days post-procedure	$H_0: P_D(MAEs) \leq 90\%$ $H_1: P_D(MAEs) > 90\%$	AP	2.5% (one-sided)
2	Change in KCCQ score at 12 months over baseline	$H_0: \mu_D(\Delta KCCQ) - \mu_C(\Delta KCCQ) = 0$ $H_1: \mu_D(\Delta KCCQ) - \mu_C(\Delta KCCQ) \neq 0$	ITT	5% (two-sided)
3	TR reduction to moderate or less at 30-day visit	$H_0: P_D(TR \leq 2) - P_C(TR \leq 2) = 0$ $H_1: P_D(TR \leq 2) - P_C(TR \leq 2) \neq 0$	ITT	5% (two-sided)
4	Change in 6MWD at 12 months over baseline	$H_0: \mu_D(\Delta 6MWD) - \mu_C(\Delta 6MWD) = 0$ $H_1: \mu_D(\Delta 6MWD) - \mu_C(\Delta 6MWD) \neq 0$	ITT	5% (two-sided)

MAEs: major adverse events, including cardiovascular mortality, new onset renal failure, endocarditis requiring surgery, and non-elective cardiovascular surgery for TriClip device-related adverse events post-index procedure; KCCQ: Kansas City Cardiomyopathy Questionnaire; 6MWD: 6-minute walk distance; AP: attempted procedure; ITT: intent-to-treat; H_0: null hypothesis; H_1: alternative hypothesis; P_D(MAEs): proportion of TriClip patients free from MAEs; μ_D(ΔKCCQ) and μ_C(ΔKCCQ): mean KCCQ score change in TriClip and control patients; P_D(TR≤2) and P_C(TR≤2): proportion of TriClip and control patients with ≤moderate TR; μ_D(Δ6MWD): mean 6MWD change in TriClip and control patients.

6.5.3 Descriptive Endpoints

The following descriptive endpoints were evaluated through 12 months in the Randomized Cohort:

- Technical success at exit from procedure room: Alive with successful access, delivery and retrieval of the device delivery system, and deployment and correct positioning of a TriClip, and no need for additional unplanned or emergency surgery or re-intervention related to the device or access procedure.
- Device success at 30 days post-procedure: Alive with original intended TriClip(s) in place, and no additional surgical or interventional procedures related to access or the device since completion of the original procedure and with intended performance of the TriClip(s), defined as ≥1 grade TR severity improvement with no embolization, single leaflet device attachment, or CEC-adjudicated device-related events.
- Procedural success at 30 days post-procedure: Device success and no device or procedure-related serious adverse events.
- Incidence of peripheral edema requiring hospitalization at 12 months and annually through 60 months.
- Incidence of ascites at 12 months, and annually through 60 months.
- Incidence of intravenous (IV) diuretic administration (including outpatient clinics) at 12 months and annually through 60 months.
- Change in KCCQ score from baseline through 30 days, 6 months, 12 months and annually through 60 months.
- SF-36 quality of life score at baseline and change from baseline at 30 days, 12 months and 24 months.
- Change in NYHA Functional Class from class III/IV to class I/II from baseline to 30 days, 6 months, 12 months and annually through 60 months.
- Change in 6-minute walk distance (6MWD) from baseline through 30 days, 6 months, 12 months and annually 60 months.
- Change in BNP/NT-proBNP from baseline through 30 days, 6 months, 12 months, and annually through months.
- Change in gamma-GGT from baseline through 30 days, 6 months, 12 months, and annually through 60 months.
- Change in patient weight from baseline through 30 days, 6 months, 12 months and annually through 60 months.
- Change in kidney function (assessed using eGFR) from baseline through 30 days, 6 months, 12 months and annually through 60 months.
- Change in liver function/MELD score from baseline through 30 days, 6 months, 12 months and annually through 60 months.
- Echocardiographic endpoints assessed from baseline through 30 days, 6 months, 12 months and annually through 60 months:
    - TR severity grade
    - Tricuspid valve annulus diameter
    - Effective regurgitant orifice area (EROA)
    - Regurgitant volume
    - Vena contracta width
    - Right ventricular end diastolic dimension (RVEDD)
    - Right ventricular fractional area change
    - Left ventricular end diastolic volume (LVEDV)
    - Left ventricular end systolic volume (LVESV)

- Tricuspid annular plane systolic excursion (TAPSE)
- Cardiac output
- Forward stroke volume (left ventricle)
- Inferior vena cava dimension

6.6 Single-Arm Cohort Endpoints

6.6.1 Primary Endpoint

The primary endpoint was survival at 12 months plus a KCCQ score improvement of ≥10 points compared to baseline.

6.6.1.1 Statistical Analysis Plan

The null (H_0) and alternative (H_1) hypotheses for primary endpoint were as follows:

$$H_0: P_D \leq 30\%$$
$$H_1: P_D > 30\%$$

where 30% was a performance goal based on the expected TriClip patient survival rate and the KCCQ result observed in the COAPT trial control group (NCT01626079; Stone et al. 2018). The alternative hypothesis was tested at a one-sided significance level of 2.5% in the AP population.

Assuming that the proportion of surviving patients with at least 10-point improvement in KCCQ score at 12 months from baseline was 50% and a 15% attrition rate, sample sizes of 100 and 200 patients were estimated to provide about 90% and 95% power, respectively, to reject the null hypothesis at a one-sided significance level of 2.5%.

6.6.1.2 Interim Analysis: Group Sequential Design

A group sequential design was implemented for the primary endpoint of the Single-Arm Cohort, which consisted of one interim analysis and one final analysis. The interim analysis was to be performed when the first 100 enrolled patients completed 12-months follow-up, with the p-value compared to a one-sided significance level of 1.25%. If the primary endpoint was not to be met at the interim analysis, it would be re-analyzed when 200 enrolled patients completed 12-month follow-up, with the p-value compared to a one-sided significance level of 1.68% to maintain an overall Type I error rate of 2.5%.

6.6.2 Powered Secondary Endpoints

Five powered secondary endpoints were assessed hierarchically at 12 months (see Table 6).

Table 6. Ordered List of Secondary Endpoints for Hierarchical Testing – Single-Arm Cohort.

Order	Secondary Endpoint	Null and Alternative Hypotheses	Analysis Population	Significance Level
1	TR reduction by at least one grade at 30 days post-procedure	$H_0: P_D(\Delta TR \geq 1) \leq 50\%$ $H_1: P_D(\Delta TR \geq 1) > 50\%$	AP	2.5% (one-sided)
2	Freedom from MAEs at 30 days post-procedure	$H_0: P_D(MAEs) \leq 80\%$ $H_1: P_D(MAEs) > 80\%$	AP	2.5% (one-sided)
3	Change in 6MWD at 12 months over baseline	$H_0: \mu_D(\Delta 6MWD) \leq 0$ $H_1: \mu_D(\Delta 6MWD) > 0$	AP	2.5% (one-sided)
4	Freedom from all-cause mortality and tricuspid valve surgery at 12 months	$H_0: P_D(Survival) \leq 65\%$ $H_1: P_D(Survival) > 65\%$	AP	2.5% (one-sided)
5	Recurrent HF hospitalizations at 12 months	$H_0: \lambda_D(PRE) \leq \lambda_D(POST)$ $H_1: \lambda_D(PRE) > \lambda_D(POST)$	AP	2.5% (one-sided)

TR: tricuspid regurgitation; MAEs: major adverse events, including cardiovascular mortality, new onset renal failure, endocarditis requiring surgery, and non-elective cardiovascular surgery for TriClip device-related adverse events post-index procedure; 6MWD: 6-minute walk distance; AP: attempted procedure; HF: heart failure; H_0: null hypothesis; H_1: alternative hypothesis; $P_D(\Delta TR \geq 1)$: proportion of TriClip patients with TR reduction by at least 1 grade; $P_D(MAEs)$: probability of freedom from any MAE; $\mu_D(\Delta 6MWD)$: mean 6MWD change; $\lambda_D(PRE)$ and $\lambda_D(POST)$: annualized event rates for recurrent HF hospitalizations within 12 months pre- and post-procedure.

6.6.3 Descriptive Endpoints

The descriptive endpoints evaluated in the Randomized Cohort were also evaluated through 12 months in the Single-Arm Cohort.

7 Pivotal Trial Results

7.1 Patient Accountability

A total of 936 eligible patients were enrolled between August 21, 2019, and June 29, 2022, at 75 sites in the US, Canada, and Europe. Of these patients, 901 were approved by the Eligibility Committee and were randomized or had an attempted procedure, including 141 in the Roll-in

Cohort, 572 in the Randomized Cohort, and 188 in the Single-Arm Cohort. Patient accountability is shown in Figure 6. As planned, the primary endpoint analysis was performed on the first 350 patients (296 in the US, 38 in Canada, and 16 in Europe) in the Randomized Cohort and the first 100 patients with an attempted procedure in the Single-Arm Cohort.

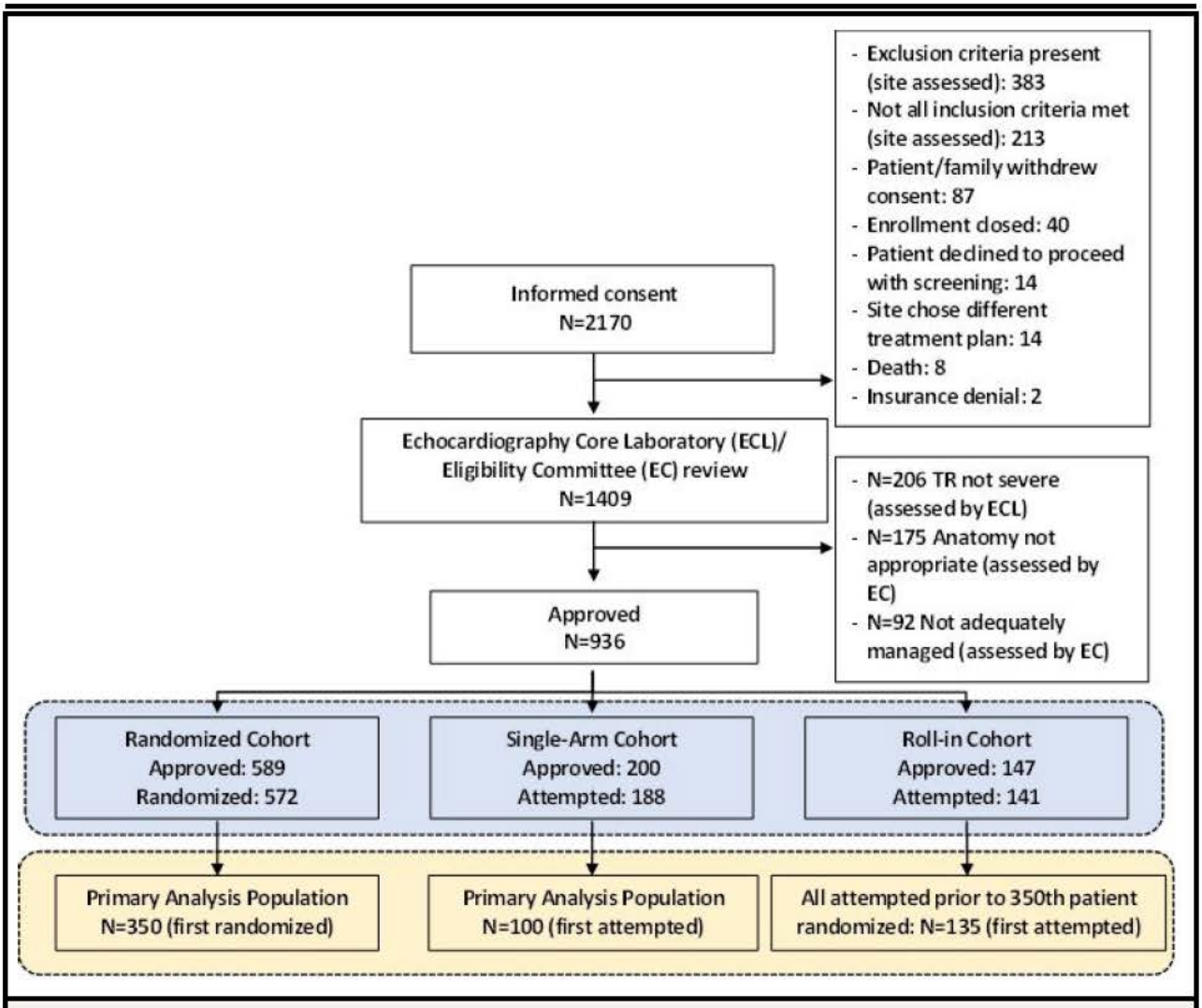


Figure 6. Patient Accountability.

7.2 Demographics and Baseline Characteristics

Patient demographics and baseline characteristics for the primary analysis population of the Randomized Cohort and Single-Arm Cohort are shown in Table 7.

Over 90% of Randomized Cohort patients had functional TR and atrial fibrillation. Torrential TR was present in approximately half of the patients in each group. No randomized patient had CIED-related TR. Medication use at baseline was similar between the two randomized groups. In all, demographics and baseline characteristics were similar between Randomized Cohort treatment

groups.

Approximately 86% of Single-Arm Cohort patients had functional TR and 93% had atrial fibrillation. A small proportion (5.1%) of Single-Arm Cohort had CIED-related TR. Compared to the Randomized Cohort, a higher proportion of Single-Arm Cohort patients had torrential TR (74.0% vs. 50.9%) and had a pacemaker or defibrillator. Patients in the Single-Arm Cohort had larger coaptation gaps than those in the Randomized Cohort. Baseline covariate differences were expected as TR severity and complex tricuspid anatomy were considered when assigning patients to the Randomized or Single-Arm Cohort.

Table 7. Demographics and Baseline Characteristics – Primary Analysis Population.

Demographics and Baseline Characteristics	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)
Body mass index (BMI, kg/m^2)	27.0 ± 5.8 (175)	26.9 ± 5.2 (175)	26.3 ± 5.3 (100)
Medical history			
Atrial fibrillation	87.4% (153/175)	93.1% (163/175)	93.0% (93/100)
Chronic obstructive pulmonary disease	10.9% (19/175)	13.7% (24/175)	22.0% (22/100)
CRT/CRT-D/ICD/permanent pacemaker	16.0% (28/175)	13.7% (24/175)	35.0% (35/100)
Dyslipidemia	66.9% (117/175)	52.6% (92/175)	64.0% (64/100)

Hypertension	81.1% (142/175)	80.6% (141/175)	83.0% (83/100)
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 aortic valve intervention	15.4% (27/175)	15.4% (27/175)	11.0% (11/100)
Prior mitral valve intervention	25.7% (45/175)	24.0% (42/175)	36.0% (36/100)
Echocardiography measurements			
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)
Health status			
KCCQ overall 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)
Medication use			
Beta-blockers	72.6% (127/175)	73.1% (128/175)	74.0% (74/100)
ACE-I or ARBs	42.3% (74/175)	45.1% (79/175)	41.0% (41/100)
Vasodilators	10.9% (19/175)	12.0% (21/175)	12.0% (12/100)
Diuretics	97.1% (170/175)	98.9% (173/175)	98.0% (98/100)

CRT: cardiac resynchronization therapy; CRT-D: cardiac resynchronization therapy defibrillator; ICD: implantable cardioverter-defibrillator; KCCQ: Kansas City Cardiomyopathy

Questionnaire; 6MWD: 6-minute walk distance; NYHA: New York Heart Association; ACE-I: angiotensin-converting enzyme 1; ARBs: angiotensin receptor blockers.
*Continuous measures – Mean ± standard deviation (total no.); Categorical measures - % (no./total no.)

FDA Comment: Key observations are as follows:

- A majority (53% to 55%) of enrolled patients were female.
- >80% were Caucasian.
- 87% to 93% had atrial fibrillation.
- Approximately 35% had renal disease.
- 97% had at least grade 3 TR and >50% had torrential TR.
- The average KCCQ score was in the mid-50s.
- The 6MWD was 240.5 ± 117.1 meters in randomized TriClip patients and 253.6 ± 129.1 meters in randomized control patients.
- Approximately 40% were NYHA Class II and 52% to 57% were Class III.

7.3 Procedural Information

The TriClip procedure was performed under general anesthesia with echocardiographic (TEE) and fluoroscopic guidance. Procedural data for the Randomized Cohort and Single-Arm Cohort AP Populations are shown in Table 8. TriClip was successfully implanted in 170 of the 172 (98.8%) patients with an attempted procedure in the Randomized Cohort and in 98 of the 100 patients with an attempted procedure in the Single-Arm Cohort, with approximately 85% of patients receiving two or three TriClip devices.

Table 8. Procedural Data – AP Population.

Procedural 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)

Table 8. Procedural Data – AP Population.		
Procedural Data	**Summary Statistic***	
	Randomized Cohort (Device Arm) (N=172)	**Single-Arm Cohort** (N=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 ± standard deviation (total no.); Categorical measures - % (no./total no.)

7.4 Randomized Cohort Results

7.4.1 Primary Endpoint

The Randomized Cohort primary endpoint analysis results are shown in Table 9. The Finkelstein-Schoenfeld test statistic result was 2.16 with a 2-sided p-value of 0.0311, which is less than the pre-specified two-sided significance level of 0.05. Thus, the primary endpoint was met indicating the TriClip group was superior to the control group.

Table 9. Primary Analysis Result – Randomized Cohort ITT Population.				
Primary Endpoint	**Test Statistic**	**p-Value (2-sided)**	**Significance Level (2-sided)**	**Result**
Finkelstein-Schoenfeld analysis	2.16	0.0311	0.05	Superiority endpoint met

The supplemental win ratio analysis is shown in Figure 7. The win ratio of the TriClip group vs. the control group was 1.44 (95% confidence interval of 1.03 - 2.08).

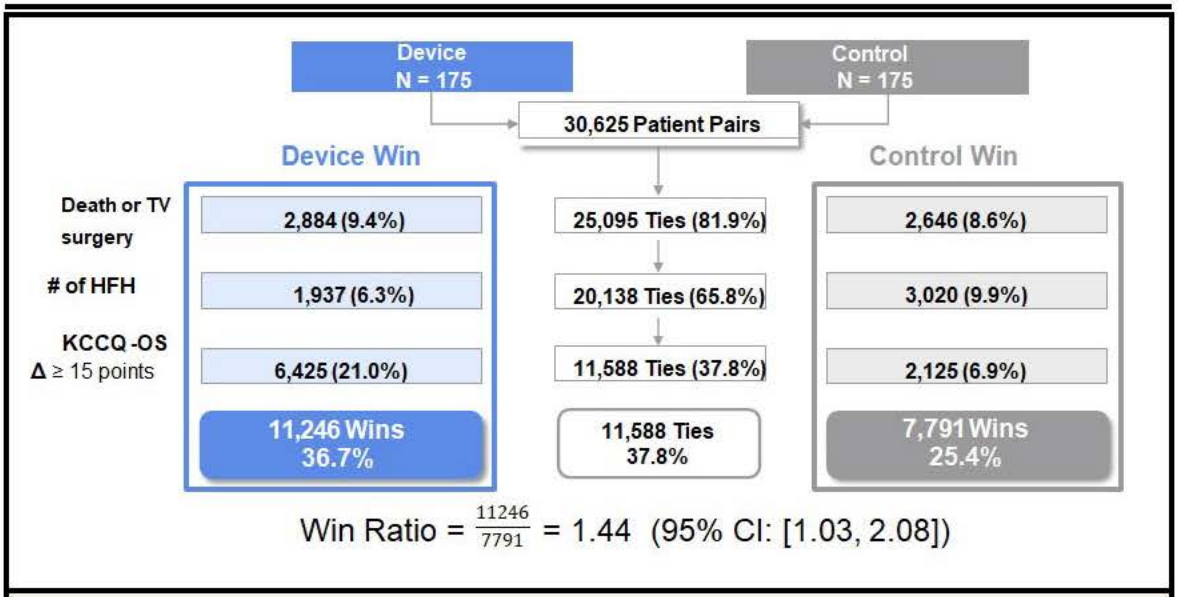


Figure 7. Win Ratio Analysis of the Randomized Cohort Primary Endpoint – ITT Population. TV: tricuspid valve; HFH: heart failure hospitalization; KCCQ-OQ: Kansas City Cardiomyopathy Questionnaire Overall Summary Score.

FDA Comment: The primary endpoint analysis showed superiority of the TriClip group vs. the control group for the hierarchical composite endpoint of death or tricuspid valve surgery, number of HF hospitalizations, and a ≥15-point KCCQ improvement tested using the Finkelstein-Schoenfeld method, and the win-ratio point estimate was 1.44 in favor of the TriClip group. The Panel will be asked to discuss the clinical significance of these results.

7.4.2 Sensitivity Analyses

Four planned sensitivity analyses were performed on the primary endpoint as follows:

- AT Population
- PP Population
- Four-component hierarchy: (1) death, (2) tricuspid valve surgery, (3) number of HF hospitalizations, and (4) ≥15-point KCCQ score improvement.
- COVID-19. COVID-19 related deaths or HF hospitalizations (including HF hospitalizations and KCCQ scores obtained subsequent to the initial HF hospitalization) included in the endpoint analysis.

The results of the four sensitivity analyses are shown in Table 10.

Table 10. Sensitivity Analyses of the Randomized Cohort Primary Endpoint.			
Sensitivity Analysis	**Finkelstein-Schoenfeld p-value (two-sided)**	**Win Ratio (95% CI)**	**Result**
AT Population	0.0126	1.55 [1.10, 2.24]	Endpoint met
PP Population	0.0652	1.39[0.97, 2.05]	**Endpoint not met**
Four-component hierarchy (ITT)	0.0362	1.44 [1.03, 2.08]	Endpoint met
COVID-19 inclusion (ITT)	0.0574	1.39 [0.99, 2.00]	**Endpoint not met**

AT: as-treated; PP: per protocol; ITT: intent-to-treat.

FDA Comment: The primary endpoint was met in the ITT and AT Populations but was not met in the PP Population. In addition, COVID-19 related deaths and HF hospitalizations as well as subsequent primary endpoint events, if any, were excluded from the primary analysis. When these events were included in the primary analysis, the primary endpoint was not met. The Panel will be asked to discuss the robustness of the superiority of the TriClip to control.

7.4.3 Results of Individual Components of the Primary Endpoint

The results of the individual components of the primary endpoint are shown as follows:

- There was no difference in time to all-cause mortality or tricuspid valve surgery between the TriClip and control groups through 12 months (Figure 8).
  - Kaplan-Meier estimates for freedom from all-cause mortality or tricuspid valve surgery were 90.6% and 89.4% at 12 months for the TriClip group and the control group, respectively.
- Freedom from HF hospitalization was numerically lower through 12 months in the device group compared to the control group (Figure 9).
  - Kaplan-Meier estimates for freedom from HF hospitalization at 12 months was 84.5% for the TriClip group and 88.0% for the control group.
  - Annualized HF hospitalization rates were 0.22 and 0.17 for the TriClip group and the control group, respectively.
- A significantly higher proportion of TriClip patients had a KCCQ score improvement of ≥15 points from baseline to 12 months compared to control patients (50% vs. 26%, respectively, Figure 10).

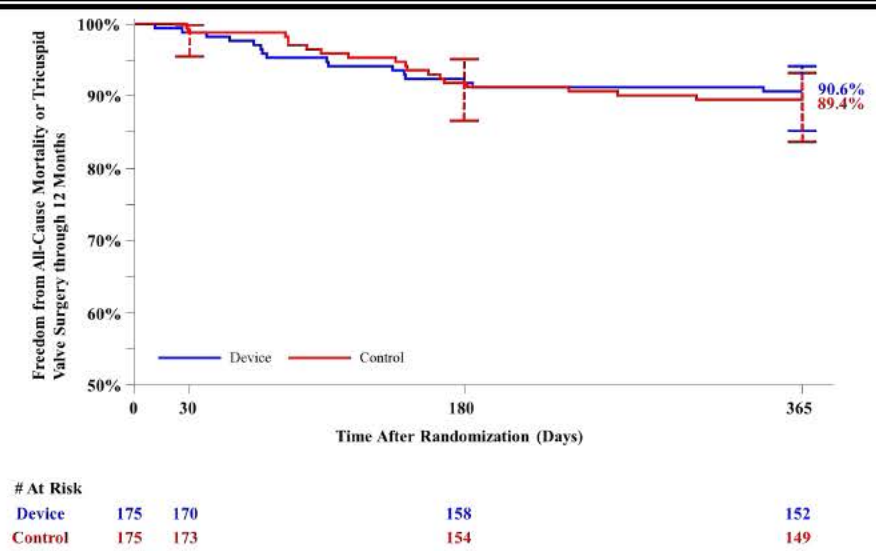


Figure 8. Freedom from All-Cause Mortality or Tricuspid Valve Surgery through 12 Months – Randomized Cohort ITT Population. The confidence intervals were calculated without multiplicity adjustment. The adjusted confidence intervals could be wider than presented here.

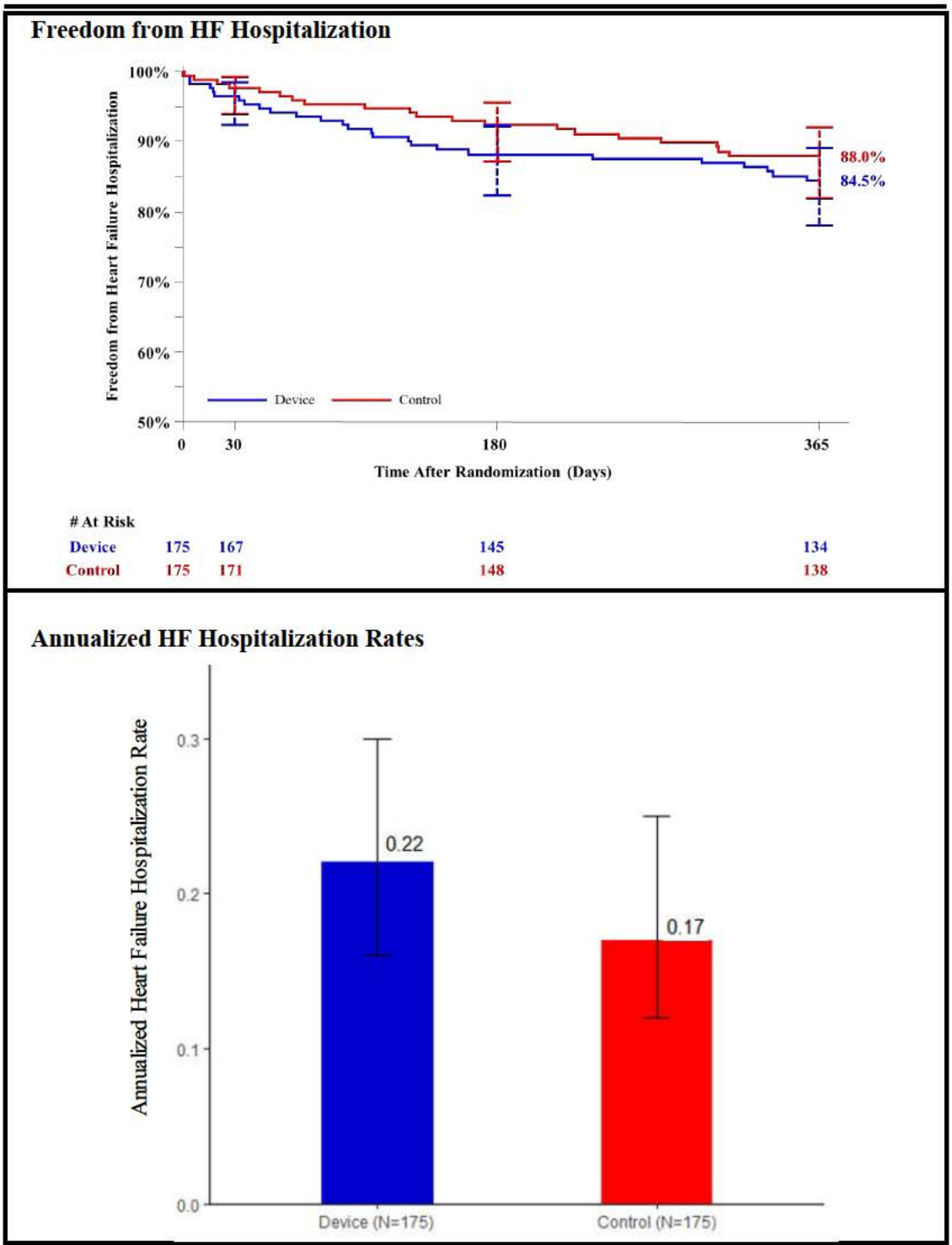


Figure 9. HF Hospitalizations through 12 Months – Randomized Cohort ITT Population. The confidence intervals were calculated without multiplicity adjustment. The adjusted confidence intervals could be wider than presented here.

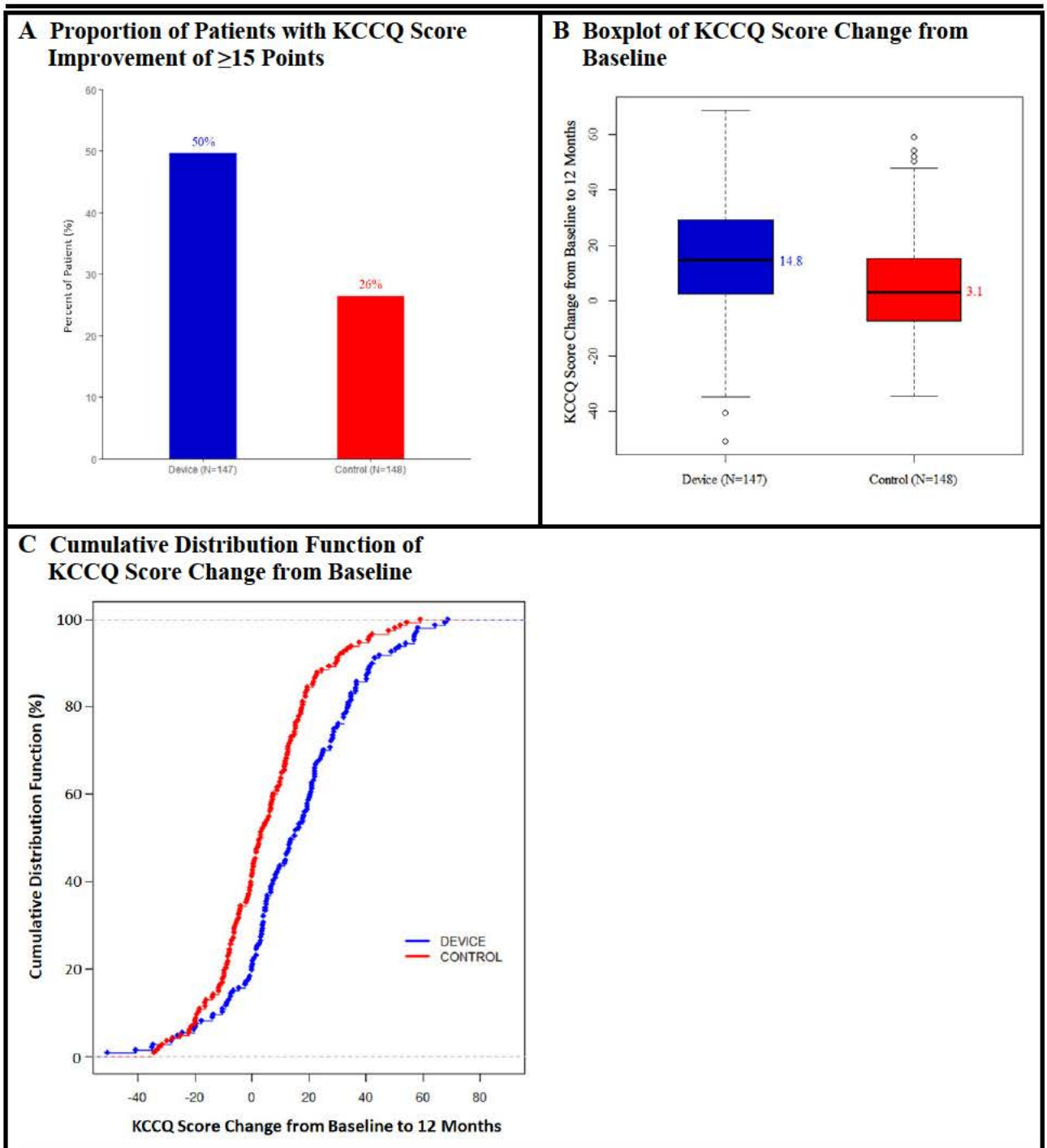


Figure 10. KCCQ Score Results at 12 Months – Randomized Cohort ITT Population.

FDA Comment: The TRILUMINATE pivotal trial was an unblinded (open-label) RCT. Patient reported outcomes such as the KCCQ score could be subject to the placebo effect in an unblinded trial. The primary endpoint of the TRILUMINATE pivotal trial was met, driven only by KCCQ score improvement in the device group; mortality or tricuspid valve surgery rates

were similar between treatment groups, and the HF hospitalization rate was numerically higher in the TriClip group vs. the control group. The Panel will be asked to discuss the strengths and limitations of the primary endpoint results considering potential placebo effects and the lack of reduced mortality or HF hospitalization rates through 12 months in the TriClip group vs. the control group.

7.4.4 Safety Results

CEC-adjudicated adverse events through 12 months (unless otherwise noted) are shown in Table 11 for the Randomized Cohort. Rates of HF hospitalizations, cardiovascular mortality, and tricuspid valve reintervention at 12 months as well as major bleeding and new onset renal failure at 30 days were numerically higher in the device group vs. the control group.

Table 11. CEC-Adjudicated Adverse Events through 12 Months – Randomized Cohort ITT Population.

Event	Summary Statistics	
	Device Arm* (N=175)	Control Arm† (N=175)
All-cause mortality	8.6% (15, 15, 0, 0, 1)	7.4% (13, 13, 0)
Cardiovascular (VARC II definition)	6.3% (11, 11, 0, 0, 0)	4.6% (8, 8, 0)
Heart failure-related	4.0% (7, 7, 0, 0, 0)	2.9% (5, 5, 0)
Non-heart failure-related	2.3% (4, 4, 0, 0, 0)	1.7% (3, 3, 0)
Non-cardiovascular (VARC II definition)	2.3% (4, 4, 0, 0, 1)	2.9% (5, 5, 0)
Hospitalization	36.0% (111, 63, 2, 7, 2)	34.3% (100, 60, 0)
Heart failure hospitalization	14.9% (35, 26, 1, 2, 0)	11.4% (8, 20, 0)
Other cardiovascular hospitalization	9.1% (17, 16, 1, 5, 0)	9.1% (21, 16, 0)
Non-cardiovascular hospitalization	21.7% (59, 38, 0, 0, 2)	21.1% (51, 37, 0)
Tricuspid valve surgery	1.7% (3, 3, 2, 2, 0)	3.4% (6, 6, 0)
Tricuspid valve intervention‡	2.3% (4, 4, 3, 4, 0)	1.7% (3, 3, 0)
Major bleeding (≥BARC 3a)‖	5.7% (10, 10, 0, 3, 0)	1.7% (3, 3, 0)
New onset renal failure‖	2.3% (4, 4, 0, 1, 0)	0.6% (1, 1, 0)
Transient ischemic attack (TIA)	0.6% (1, 1, 0, 0, 0)	0.0% (0, 0, 0)
Stroke (VARC II definition)	1.7% (3, 3, 0, 0, 0)	1.7% (4, 3, 0)
Myocardial infarction (VARC II definition)‖	0.0% (0, 0, 0, 0, 0)	0.0% (0, 0, 0)
Endocarditis requiring surgery‖	0.0% (0, 0, 0, 0, 0)	0.0% (0, 0, 0)

Non-elective cardiovascular surgery for TriClip-related adverse event post index procedure[I]	0.0% (0, 0, 0, 0, 0)	0.0% (0, 0, 0)
Cardiogenic shock	0.0% (0, 0, 0, 0, 0)	0.6% (1, 1, 0)

VARC: Valve Academic Research Consortium; BARC: Bleeding Academic Research Consortium; TIA: transient ischemic attack.
[*]Event rate (no. of events, no. of patients, no. of device-related events, number of procedure-related events, number of COVID-19-related events); event rate = no./total no. Number of COVID-19-related events includes related or possibly related events; this excludes events with unknown relatedness.
[†]Event rate (no. of events, no. of patients, number of COVID-19-related events).
[‡]Tricuspid valve intervention includes reintervention for device group and first intervention for control group.
[I]Per the study CEC charter, myocardial infarction, bleeding, new onset renal failure, endocarditis requiring surgery, and non-elective cardiovascular surgery for TriClip-related adverse event post index procedure were adjudicated up to 30 days post treatment visit for the device and control groups.

FDA Comment: At 12 months:

- Rates of all-cause mortality, cardiovascular mortality (HF and non-HF related), HF hospitalization, tricuspid valve intervention, major bleeding, and new onset renal failure were numerically higher in the TriClip group vs. the control group.
- The tricuspid valve surgery rate was numerically lower in the TriClip group vs. the control group.

The Panel will be asked to comment on the clinical significance of these outcomes.

7.4.5 Powered Secondary Endpoints

The results of the powered secondary endpoints are shown in Table 12. The endpoints of freedom from MAEs at 30 days post-procedure, change in KCCQ score at 12 months vs. baseline, and TR reduction to moderate or less at 30 days were met. There was a numerically smaller reduction in 6MWD at 12 months in the TriClip group vs. the control group (-8.12 vs. -25.17 meters), but the difference was not statistically significant, and standard deviations were large.

Table 12. Summary of Powered Secondary Endpoint Results – Randomized Cohort ITT Population (Paired).

Order	Secondary Endpoint	Summary Statistics		p-Value	Result
		Device Arm	Control Arm		
1	Freedom from	98.3%	-	< 0.0001	Endpoint met

	MAEs at 30 days post-procedure	[96.3%, 100%][*]			
2	Change in KCCQ score at 12 months over baseline	12.34 (1.75)[†]	0.61 (1.75)[†]	< 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[I] (meters)	-8.12 (10.50)[†]	-25.17 (10.31)[†]	0.2482	**Endpoint not met**

MAEs: major adverse events, including cardiovascular mortality, new onset renal failure, endocarditis requiring surgery, and non-elective cardiovascular surgery for TriClip device-related adverse events post-index procedure; TR: tricuspid regurgitation; KCCQ: Kansas City Cardiomyopathy Questionnaire; 6MWD: 6-minute walk distance.

[*]Kaplan-Meier estimate [95% confidence interval]

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

[‡]% (no./total no.)

[I]A KCCQ overall score of 0 and a 6MWD of 0 meter were imputed for patients who had a heart failure related cardiovascular death or tricuspid valve surgery prior to 12 months.

The individual MAE component rates are shown in Table 13. Of the MAEs, one case of new onset renal failure was adjudicated as procedure-related but not device-related. A second new onset renal failure case and the one cardiovascular mortality were adjudicated as neither procedure- nor device-related.

Table 13. Results of Individual MAE Components at 30 Days – Randomized Cohort AP Population.

MAE Component	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.)

7.4.6 Descriptive Endpoints

7.4.6.1 Procedural Endpoints

Technical success was achieved in 98.8% of TriClip patients, device success in 88.9%, and

procedural success in 87.0% (see Table 14).

Table 14. Results of Procedural Endpoints – Randomized Cohort AP Population.

Endpoints	Results
Technical success (at exit from procedure room)	98.8% (170/172)
Device success (at 30 days post-procedure)	88.9% (144/162)
Procedural success (at 30 days post-procedure)	87.0% (141/162)

- Technical success was not achieved in 2 patients due to inability to successfully deploy the TriClip device.
- Device success could not be evaluated in 10 patients due to missing TR grade assessment. In addition, device success was not achieved in 18 patients due to single leaflet device attachment (n=11), no reduction in TR (n=3), surgery/intervention within 30 days post procedure (n=3), and death within 30 days post procedure (n=1).
- Procedural success was not achieved in the same 18 patients in whom device success was not achieved and in 3 additional patients who experienced a device- or procedure-related site-reported serious adverse event: single leaflet device attachment (n=1; not confirmed by the ECL), ruptured chordae (n=1), and access site complication (n=1).

7.4.6.2 Peripheral Edema Requiring Hospitalizations, Ascites, and IV Diuretic Administration

Rates of peripheral edema requiring hospitalizations, ascites, and IV diuretic administration (including at outpatient clinics) through 12 months were generally low in both treatment groups (Table 15). The annualized rates of peripheral edema requiring hospitalizations and ascites were numerically lower in the TriClip group vs. the control group, and the annualized rate of IV diuretics use was numerically higher in the TriClip group.

Table 15: Peripheral Edema Requiring Hospitalizations, Ascites, and IV Diuretic Administration – Randomized Cohort ITT Population.

Endpoints	Device (N=175)	Control (N=175)	Difference [95% CI]*
Incidence of peripheral edema requiring hospitalizations at 12 months			
Number of events	4	18	-
Total follow-up (patient-years)†	160.4	161.5	-
Annualized rate [95% CI]‡	0.02 [0.01, 0.07]	0.11 [0.07, 0.18]	-
Percent of patients with events	1.7% (3/175)	7.4% (13/175)	-5.7% [-10.7%, -1.3%]
Incidence of ascites at 12 months			

Number of events	3	11	-
Total follow-up (patient-years)†	160.4	161.5	-
Annualized rate [95% CI]‡	0.02 [0.01, 0.06]	0.07 [0.04, 0.12]	-
Percent of patients with events	1.7% (3/175)	6.3% (11/175)	-4.6% [-9.3%, -0.4%]
IV diuretics usage (including outpatient clinics) at 12 months[I]			
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]	-
Percent of patients with events	14.9% (26/175)	13.1% (23/175)	1.71% [-5.64%, 9.07%]

CI: confidence interval. The CIs were calculated without multiplicity adjustment. The adjusted CIs could be wider than presented here.
*By the Newcombe score method.
†The total follow-up in patient-year is calculated as the sum of follow-up patient-years for each subject through the time period or end of study, whichever is earlier.
‡The annualized event rate is calculated as total number of events divided by total follow-up year through each time period.
[I]Administration of IV diuretics during the index procedure hospitalization or during the additional procedure hospitalization that was not due to an adverse event was excluded.

7.4.6.3 KCCQ Score through 12 Months

KCCQ scores and score changes through 12 months are shown in Figure 11 for the Randomized Cohort ITT Population. On average, the KCCQ score increased by 15.2 points in the device group vs. 4.8 points in the control group through 12 months.

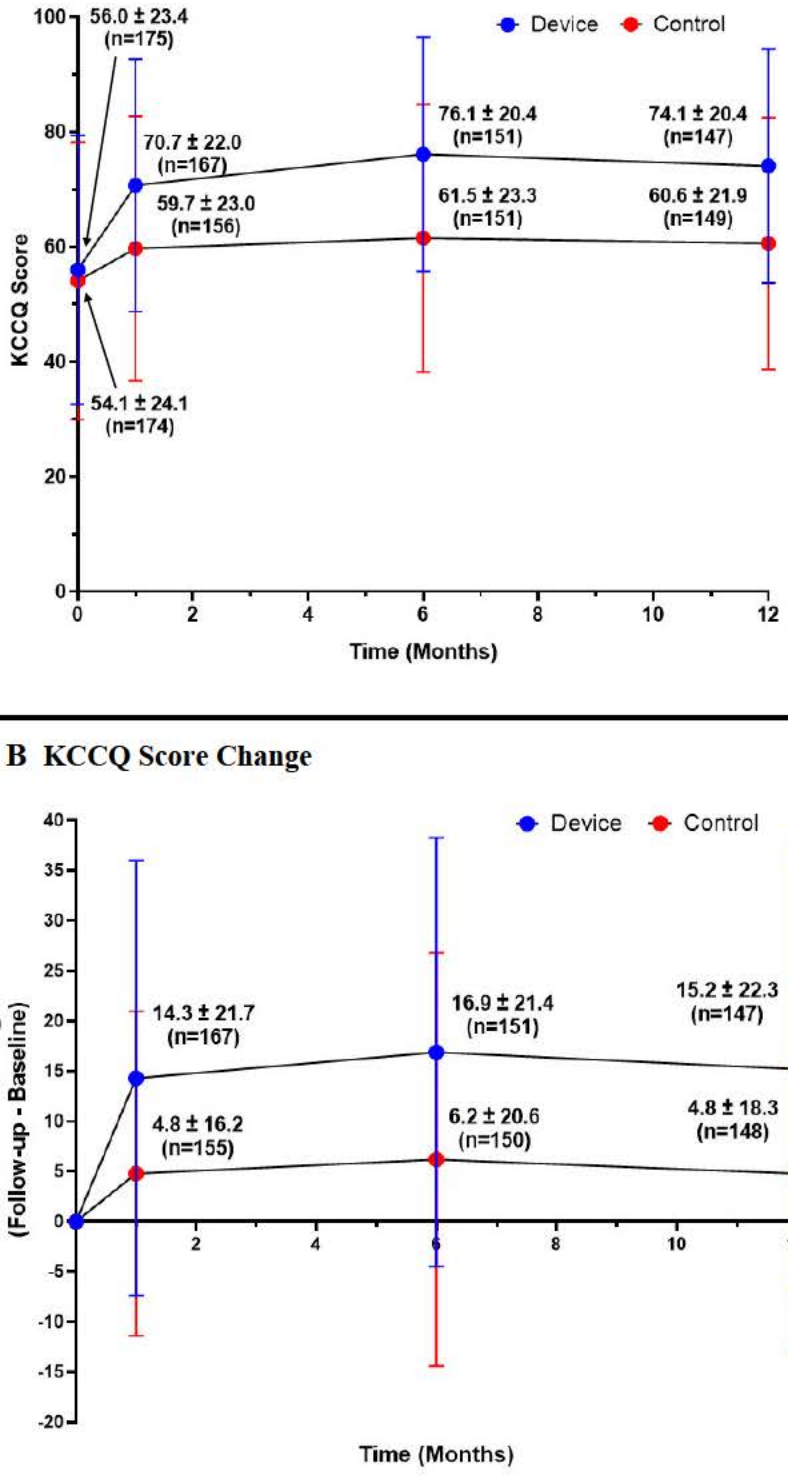


Figure 11. KCCQ Score by Visit – Randomized Cohort ITT Population (Unpaired). The error bars are standard deviations.

7.4.6.4 SF-36 Score through 12 Months

SF-36 scores through 12 months are shown in Figure 12 for the Randomized Cohort ITT Population. The mean physical component score increased by about 5 points through 12 months compared to the baseline in the TriClip group, while remaining mostly unchanged from baseline through 12 months in the control group. A similar trend was seen in the mental component score. The SF-36 score changes in the device group are considered clinically meaningful.

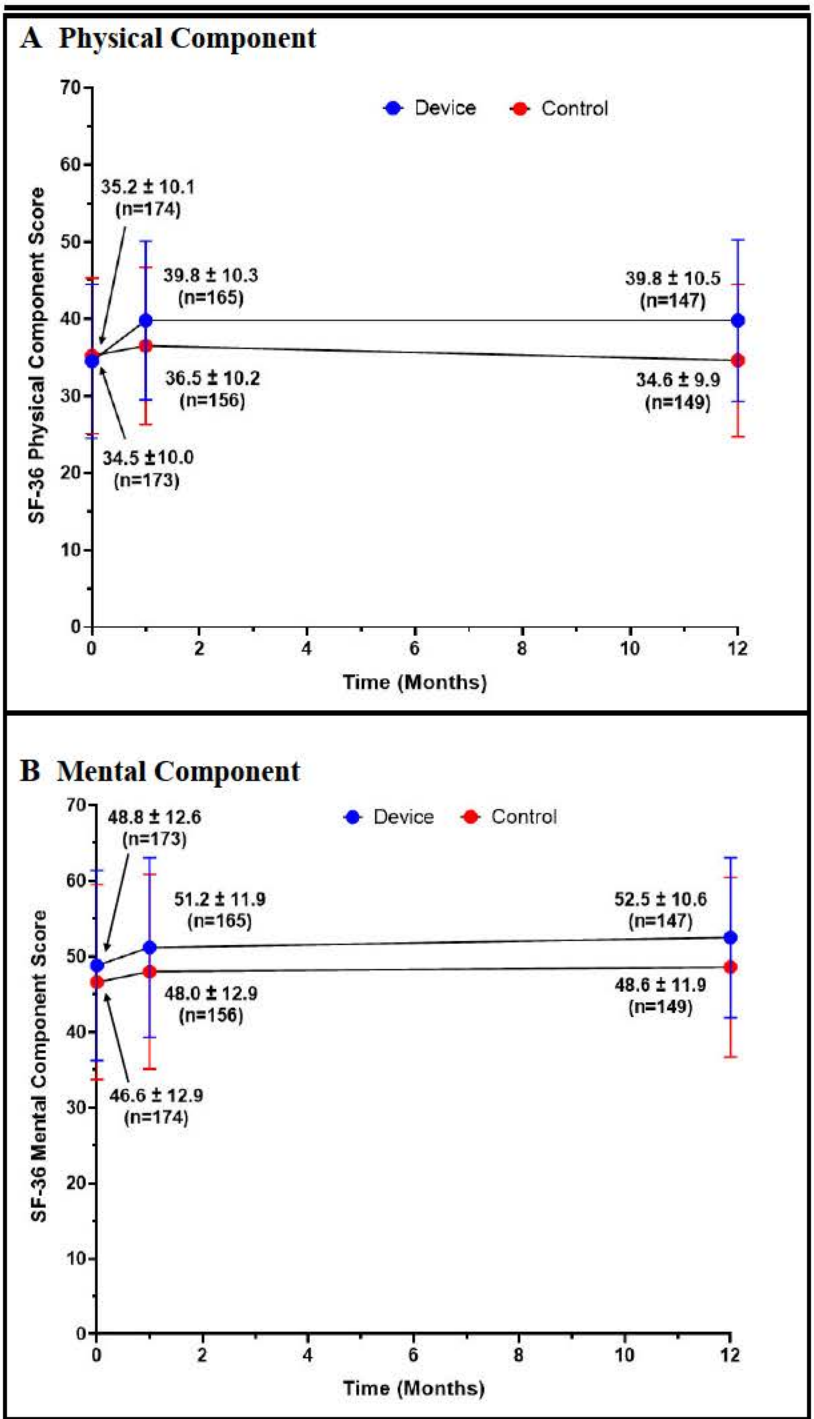


Figure 12. SF-36 Score by Visit – Randomized Cohort ITT Population (Unpaired). The error bars are standard deviations.

7.4.6.5 NYHA Functional Class through 12 Months

The results for NYHA classifications by visit are shown in Figure 13 for the Randomized Cohort

ITT Population. At baseline, 59% of patients in the TriClip group and 55% in the control group were in NYHA III/IV. At 12 months, fewer TriClip patients were in NYHA III/IV than the control patients (16% vs. 40%).

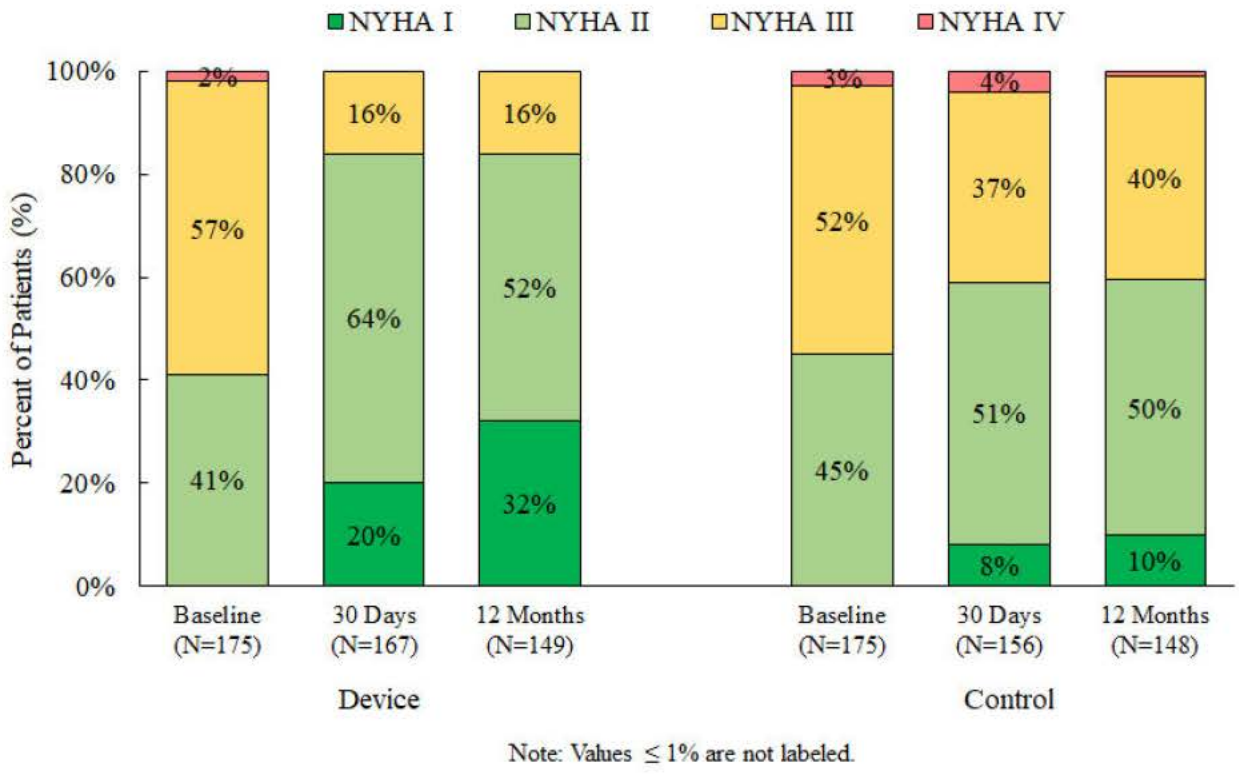


Figure 13. NYHA Functional Class by Visit – Randomized Cohort ITT Population (Unpaired).

7.4.6.6 6MWD through 12 Months

The unpaired results for 6MWD are shown in Figure 14 for the Randomized Cohort ITT Population. At 12 months, the 6MWD increased by about 28 meters from baseline in the device group, vs. about 13 meters in the control group.

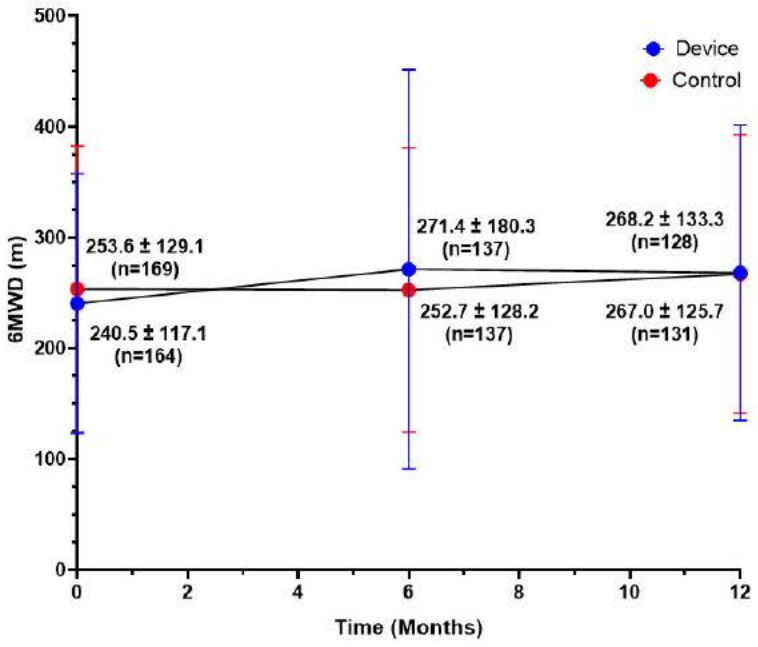


Figure 14. 6MWD by Visit – Randomized Cohort ITT Population (Unpaired). The error bars are standard deviations.

7.4.6.7 Renal Function, Hepatic Function, Natriuretic Peptides, and Body Weight Endpoints

Results of the laboratory test and body weight endpoints are shown in Table 16.

Table 16. Renal Function, Hepatic Function, Natriuretic Peptide, and Body Weight Endpoints – Randomized Cohort ITT Population.

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)	
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

Median (Q1, Q3)	184.0 (-223.0, 537.0)	-40.0 (-734.0, 195.0)	[-87.1, 1311.1]
Range (min, max)	(-4165.0, 6245.0)	(-12862.0, 4225.0)	
ΔBody weight (kg)			
Mean ± SD (n)	-0.5 ± 4.7 (148)	-1.0 ± 5.3 (147)	0.5 [-0.6, 1.7]
Median (Q1, Q3)	-0.2 (-2.3, 2.1)	-0.7 (-3.6, 2.0)	
Range (min, max)	(-17.5, 22.7)	(-22.0, 15.2)	
ΔKidney function assessed by 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)	
ΔLiver function assessed by MELD 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)	

CI: confidence interval; GGT: gamma-glutamyl transpeptidase; BNP: B-type natriuretic peptide; NT-proBNP: N-terminal pro b-type natriuretic peptide; eGFR: estimated glomerular filtration rate; MELD: model for end-stage liver disease.

SD: standard deviation; Q1: 1st quartile; Q3: 3rd quartile. CI: confidence interval; The CIs were calculated without multiplicity adjustment. The adjusted CIs could be wider than presented here.
*By normal approximation.

At 12 months:

- Mean gamma-glutamyl transpeptidase (GGT) level decreased by 13.2 U/L from baseline in the device group compared to 0.8 U/L in the control group.
- The average model for end-stage liver disease (MELD) score decreased by 0.6 in the device group vs. an increase of 0.7 in the control group.
- BNP levels decreased by 7.3 pg/mL in the TriClip group vs. an increase of 16.4 pg/mL in the control group.
- NT-ProBNP levels increased 209.3 pg/mL in the TriClip group vs. a decrease of 402.7 pg/mL in the control group.

7.4.6.8 Echocardiographic Endpoints

Echocardiographic endpoint results for the Randomized Cohort ITT Population are shown in Figure 15 (TR severity) and Table 17 (other echocardiographic endpoints). In the device group, the proportion of patients with greater than moderate TR was 97% at baseline, which decreased to 13% at 30 days and 12% at 12 months (Figure 15). In the control group, TR severity was greater than moderate in 99% of patients at baseline and remained greater than moderate in 95% of patients at 30 days and 92% at 12 months.

PISA EROA, PISA regurgitant volume, and vena contracta width all showed substantial decreases

from baseline to 12 months in the device group and were minimally changed in the control group (Table 17). There were no notable changes in cardiac size or function in either treatment group at 12 months. Right atrial volume, which would be expected to decrease as a result of reduced TR due to reverse remodeling, showed an unexpected small increase in the TriClip group.

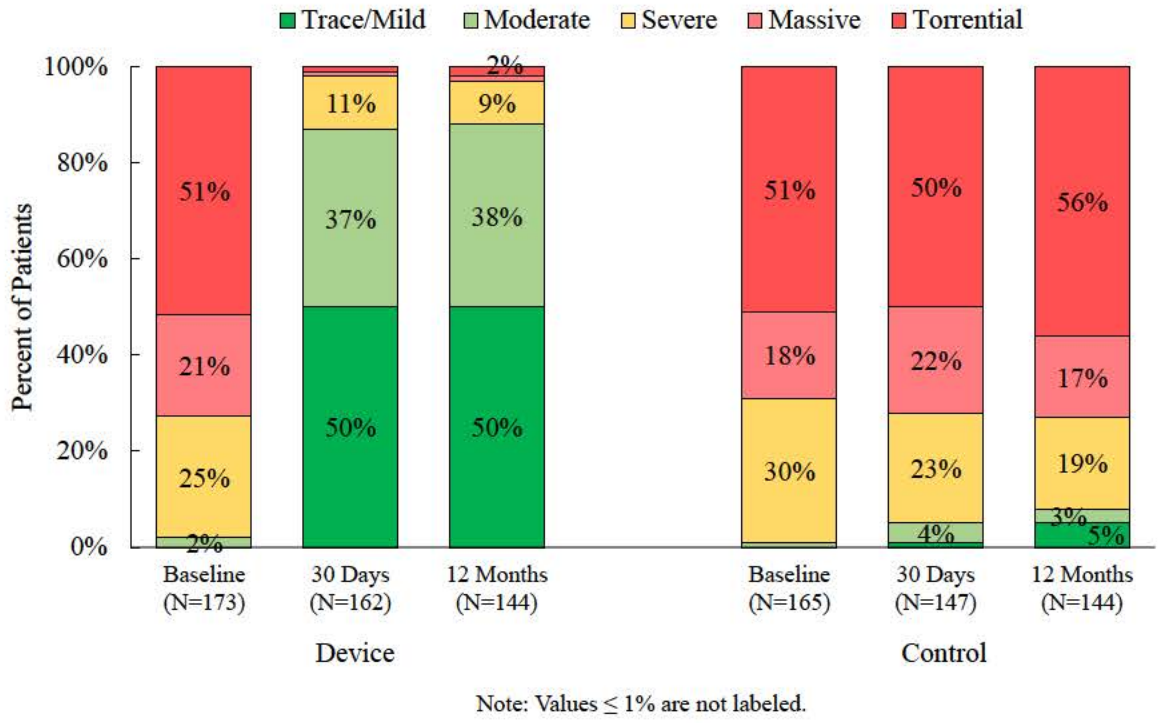


Figure 15. TR Severity Visit – Randomized Cohort ITT Population (Unpaired).

Table 17. Results of Echocardiographic Endpoints – Randomized Cohort ITT Population (Paired Analysis).

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 [-0.14, 0.19]
Median (Q1, Q3)	-0.10 (-0.50, 0.30)	-0.17 (-0.50, 0.30)	
Range (min, max)	(-1.46, 1.39)	(-3.90, 2.02)	
[95% CI]*	[-0.19, 0.02]	[-0.23, 0.02]	
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]
Range (min, max)	(-2.33, 0.25)	(-1.25, 0.80)	
[95% CI]*	[-0.50, -0.38]	[-0.09, 0.01]	
ΔPISA regurgitant volume calculation (mL)			
Mean ± SD (n)	-33.84 ± 20.48 (115)	-1.99 ± 23.56 (127)	-31.85 [-37.43, -26.28]
Median (Q1, Q3)	-33.20 (-44.90, -21.40)	-1.30 (-12.40, 10.21)	
Range (min, max)	(-105.20, 12.11)	(-115.90, 67.80)	
[95% CI]*	[-37.63, -30.06]	[-6.13, 2.15]	
ΔVena contracta width (SL, 4Ch view, cm)			
Mean ± SD (n)	-0.52 ± 0.48 (139)	0.03 ± 0.44 (136)	-0.54 [-0.65, -0.43]
Median (Q1, Q3)	-0.48 (-0.77, -0.26)	0.00 (-0.30, 0.32)	
Range (min, max)	(-3.00, 0.97)	(-1.10, 1.40)	
[95% CI]*	[-0.60, -0.44]	[-0.05, 0.10]	
ΔRV end diastolic diameter – mid (4Ch, cm)			
Mean ± SD (n)	-0.18 ± 0.73 (140)	-0.02 ± 0.85 (134)	-0.17 [-0.36, 0.02]
Median (Q1, Q3)	-0.20 (-0.60, 0.20)	0.10 (-0.50, 0.50)	
Range (min, max)	(-1.90, 2.80)	(-2.20, 2.90)	
[95% CI]*	[-0.31, -0.06]	[-0.16, 0.13]	
ΔRV end diastolic diameter – base (4Ch, cm)			
Mean ± SD (n)	-0.21 ± 0.71 (142)	-0.12 ± 0.76 (134)	-0.09 [-0.26, 0.08]
Median (Q1, Q3)	-0.15 (-0.70, 0.20)	-0.10 (-0.60, 0.40)	
Range (min, max)	(-2.40, 2.70)	(-2.00, 1.90)	
[95% CI]*	[-0.32, -0.09]	[-0.25, 0.01]	
ΔRight atrial volume (single plane Simpson's, mL)			
Mean ± SD (n)	7.78 ± 55.92 (140)	-2.13 ± 54.14 (136)	9.91 [-3.13, 22.95]
Median (Q1, Q3)	8.17 (-22.48, 28.25)	-4.35 (-29.90, 21.90)	
Range (min, max)	(-122.03, 276.20)	(-154.44, 181.20)	
[95% CI]*	[-1.56, 17.13]	[-11.31, 7.05]	
ΔRV fractional area change (%)			
Mean ± SD (n)	-0.73 ± 8.16 (133)	-0.52 ± 7.38 (125)	-0.21 [-2.12, 1.69]
Median (Q1, Q3)	-0.50 (-6.40, 3.90)	-1.00 (-5.80, 3.90)	
Range (min, max)	(-27.90, 21.22)	(-18.70, 23.00)	
[95% CI]*	[-2.13, 0.67]	[-1.83, 0.78]	
ΔLV end diastolic volume (mL)			
Mean ± SD (n)	3.91 ± 25.02 (129)	-4.80 ± 23.49 (114)	8.70

Median (Q1, Q3)	3.30 (-12.90, 16.30)	-4.98 (-16.80, 9.70)	[2.57, 14.84]
Range (min, max)	(-70.30, 94.50)	(-83.20, 52.70)	
[95% CI]*	[-0.45, 8.26]	[-9.16, -0.44]	
ΔLV end systolic volume (mL)			
Mean ± SD (n)	2.31 ± 15.28 (129)	-2.93 ± 12.52 (114)	5.24 [1.72, 8.75]
Median (Q1, Q3)	0.82 (-4.80, 8.80)	-2.95 (-9.50, 4.20)	
Range (min, max)	(-37.00, 85.50)	(-65.34, 23.80)	
[95% CI]*	[-0.35, 4.97]	[-5.25, -0.60]	
ΔRV TAPSE (cm)			
Mean ± SD (n)	-0.13 ± 0.45 (141)	0.00 ± 0.48 (132)	-0.13 [-0.24, -0.02]
Median (Q1, Q3)	-0.10 (-0.43, 0.10)	0.01 (-0.20, 0.30)	
Range (min, max)	(-1.40, 1.00)	(-2.27, 1.00)	
[95% CI]*	[-0.20, -0.06]	[-0.08, 0.08]	
ΔCardiac output (L/min)			
Mean ± SD (n)	-0.05 ± 1.89 (136)	0.03 ± 1.40 (131)	-0.07 [-0.47, 0.33]
Median (Q1, Q3)	-0.14 (-0.98, 0.63)	-0.04 (-0.88, 0.86)	
Range (min, max)	(-4.98, 14.95)	(-3.42, 4.10)	
[95% CI]*	[-0.37, 0.27]	[-0.21, 0.27]	
ΔLVOT Doppler stroke volume (mL)			
Mean ± SD (n)	-1.58 ± 17.62 (138)	-1.93 ± 16.48 (133)	0.35 [-3.73, 4.43]
Median (Q1, Q3)	-2.04 (-11.00, 7.80)	-1.50 (-11.73, 4.40)	
Range (min, max)	(-49.50, 65.00)	(-40.60, 51.70)	
[95% CI]*	[-4.55, 1.38]	[-4.76, 0.89]	
ΔInferior vena cava diameter (cm)			
Mean ± SD (n)	-0.09 ± 0.56 (135)	-0.01 ± 0.56 (136)	-0.08 [-0.21, 0.05]
Median (Q1, Q3)	-0.04 (-0.48, 0.34)	0.00 (-0.34, 0.32)	
Range (min, max)	(-1.80, 1.16)	(-1.90, 1.80)	
[95% CI]*	[-0.18, 0.01]	[-0.10, 0.09]	
ΔTricuspid valve diastolic mean gradient (CW, mmHg)			
Mean ± SD (n)	1.15 ± 1.28 (136)	0.07 ± 0.58 (126)	1.08 [0.84, 1.32]
Median (Q1, Q3)	0.86 (0.32, 1.89)	0.02 (-0.31, 0.43)	
Range (min, max)	(-2.80, 7.32)	(-1.11, 1.60)	
[95% CI]*	[0.93, 1.37]	[-0.04, 0.17]	

PISA: proximal isovelocity surface area (a method for estimating regurgitant volume); EROA: effective regurgitant orifice area; RV: right ventricular; LV: left ventricular: TAPSE: tricuspid annular plane systolic excursion (a measure of the RV apex to-base shortening and RV systolic

function); LVOT: left ventricular outflow tract.
SD: standard deviation; CI: confidence interval. The CIs were calculated without multiplicity adjustment. The adjusted CIs could be wider than presented here.
*By normal approximation.

FDA Comment: The key results of descriptive endpoints at 12 months are as follows:

- Similar to the change in KCCQ score, the changes in SF-36 score, NYHA functional class, and 6MWD numerically favored the TriClip group.
- Annualized rates of hospitalizations for peripheral edema and ascites numerically favored the TriClip group.
- The annualized rate of HF hospitalizations was numerically higher in the TriClip group (Figure 9B).
- Liver function assessments (GGT and MELD score) favored the TriClip group.
- BNP level (a HF biomarker) decreased in the TriClip group and increased in the control group.
- NT-proBNP level (another HF biomarker) increased in the TriClip group and decreased in the control group.
- Echocardiographic endpoints of PISA EROA, PISA regurgitant volume, and vena contracta width were substantially reduced in the device group, which is consistent with TR reduction. There was a small (0.18 cm) reduction in mid-RVEDD in the TriClip group. Unexpectedly, right atrial volume showed a small increase (7.78 mL) in the TriClip group.

The Panel will be asked to comment on the clinical significance of these outcomes.

7.5 Additional Data and Analyses

7.5.1 Association between KCCQ Score and TR

Post hoc analyses performed to investigate the associations between KCCQ score changes and TR severity and between KCCQ score changes and TR severity changes at 12 months. The associations are shown in Figure 16. Lower TR severity and greater TR severity reductions were generally associated with greater KCCQ score improvements.

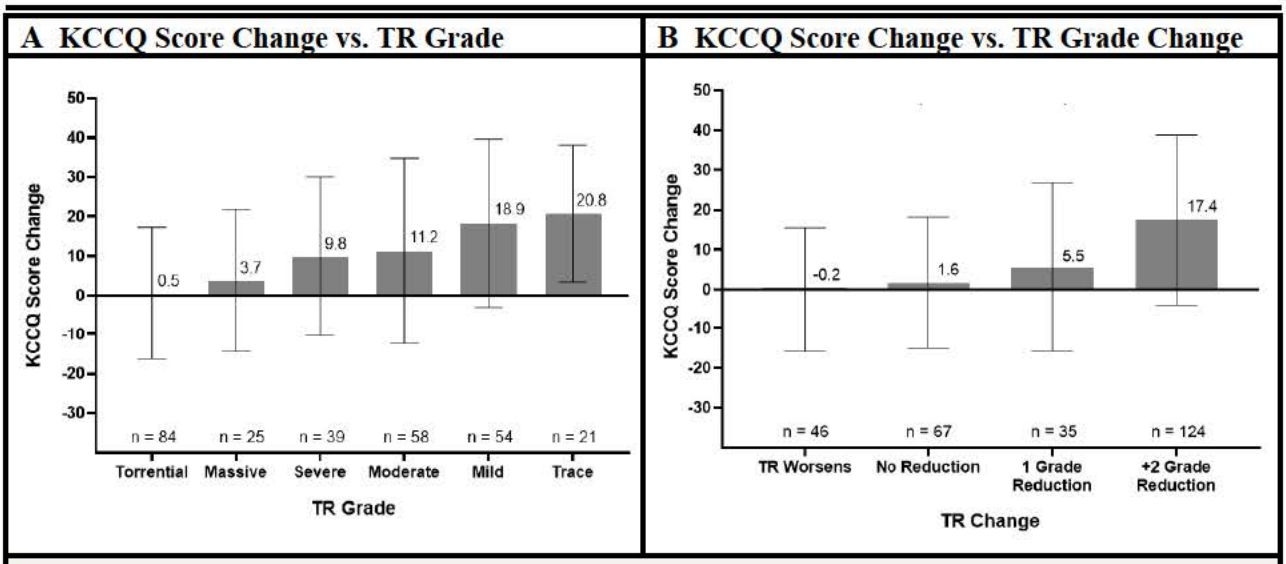


Figure 16. Association between KCCQ Score and TR at 12 Months. The error bars are standard deviations.

FDA Comment: Lower TR severity and greater TR severity reductions were associated with greater KCCQ score improvements. However, there were relatively wide standard deviations in KCCQ score changes at each TR severity level and at each TR severity change category. The Panel will be asked to discuss the impact of the association between TR severity and KCCQ data on addressing potential placebo effects in an open-label trial.

7.5.2 Medication Use

Oral medication uses through 12 months for diuretics, ACE inhibitors, angiotensin-receptor blockers (ARBs), beta-blockers, and vasodilators are shown in Table 18. Maximum daily doses were converted to equivalent doses between drugs within the same class. Changes in drug use were generally similar between treatment groups for all drug classes.

Table 18. Oral Medication Use Through 12 Months - Randomized Cohort ITT Population (Paired Analysis).

Change of Average Total Daily Equivalent Dosage (mg) Vs. Baseline	Summary Statistics*	
	Device (N=175)	Control (N=175)
Diuretics*		
Use through 12 months	96.0% (168/175)	99.4% (174/175)
Decrease use >50% or stop use	4.2% (7/168)	5.7% (10/174)

Stable use	85.7% (144/168)	87.4% (152/174)
Increase use >100% or new use	7.7% (13/168)	6.3% (11/174)
Angiotensin-converting enzyme inhibitors (ACE-I)*		
Use through 12 months	16.6% (29/175)	13.7% (24/175)
Decrease use >50% or stop use	20.7% (6/29)	4.2% (1/24)
Stable use	69.0% (20/29)	83.3% (20/24)
Increase use >100% or new use	10.3% (3/29)	8.3% (2/24)
Angiotensin-Receptor Blockers (ARBs)*		
Use through 12 months	28.0% (49/175)	34.9% (61/175)
Decrease use >50% or stop use	4.1% (2/49)	9.8% (6/61)
Stable use	85.7% (42/49)	83.6% (51/61)
Increase use >100% or new usage	4.1% (2/49)	6.6% (4/61)
Beta Blockers*		
Use through 12 months	75.4% (132/175)	77.1% (135/175)
Decrease use >50% or stop use	4.5% (6/132)	7.4% (10/135)
Stable use	88.6% (117/132)	86.7% (117/135)
Increase use >100% or new use	5.3% (7/132)	4.4% (6/135)
Vasodilators†		
Use through 12 months	10.3% (18/175)	12.0% (21/175)
Decrease use >50% or stop use	0.0% (0/18)	9.5% (2/21)
Stable use	77.8% (14/18)	81.0% (17/21)
Increase use >100% or new use	11.1% (2/18)	9.5% (2/21)

Note: (1) Drug equivalent dose is calculated by (daily dose/maximum total daily dose)* equivalent drug maximum total daily dose for each class; (2) the average total daily equivalent dosage during the period are calculated as the sum of the drug equivalent dose used during the period divided by days on drug for individual patients; (3) decrease >50% or stop of drug use is calculated as drug reduction >50% or stop using at least 30 consecutive days compared with use at baseline; (4) stable is defined as no more than a 100% increase or a 50% decrease in dose and maintained for at least 30 days and no new or stopped drug use; (5) increase >100% or new use is calculated as drug increase >100% or new use for at least 30 consecutive days compared with use at baseline; (6) if multiple states (defined as 30 consecutive days with no change in dosage) are present during a time period, the later state is taken; and (7) mineralocorticoid receptor antagonists (MRAs: spironolactone, eplerenone etc.) were categorized as diuretics and use and changes in these medications are included in the diuretics category.

*Proportion (no./total no.)

[1]Equivalent drugs for each class and their maximum total daily doses include: Furosemide 40 mg for diuretics, enalapril 40 mg for ACE Inhibitors and ARBs, and Carvedilol 100 mg for beta-blockers.
[2]Original dosage of Vasodilators are used in the analysis.

7.5.3 HF Hospitalization Pre- vs. Post-Procedure

HF hospitalization data pre- vs. post-procedure (pre- and post-randomization for control patients, hereafter) are shown in Table 19. The pre-procedure HF hospitalization rates were similar between the two groups. The device group and the control group both had lower HF hospitalization rates through 12 months post-procedure vs. 12 months pre-procedure, with the annualized HF hospitalization rate numerically higher in the device group than in the control group.

Table 19. HF Hospitalization Data Pre- vs. Post-Procedure – Randomized Cohort ITT Population.

	12 Months Pre-Procedure‡		12 Months Post-Procedure‡	
	Device (N=175)	**Control (N=175)**	**Device (N=175)**	**Control (N=175)**
Patients with HF hospitalization*	24.0% (42/175)	25.1% (44/175)	14.9% (26/175)	11.4% (20/175)
Number of HF hospitalization events	56	57	35	28
Total patient-years	175	175	160	161.5
Annualized rate†	0.32 [0.25, 0.42]	0.33 [0.25, 0.42]	0.22 [0.16, 0.30]	0.17 [0.12, 0.25]

HF: Heart failure
*Proportion (no./total no.)
†Rate [95% CI]. Annualized rate = number of HF hospitalization events / total patient-years.
‡Pre- and post-randomization for control patients.

7.5.4 Variability in Trial Enrollment and Results by Clinical Site

A histogram of patient enrollment at clinical sites is shown in Figure 17 for the Randomized Cohort ITT Population. Among the 65 sites that contributed to the primary analysis population, 56 sites enrolled <10 patients, of which 42 enrolled <5 patients; 9 sites enrolled ≥10 patients; and one site enrolled 51 patients.

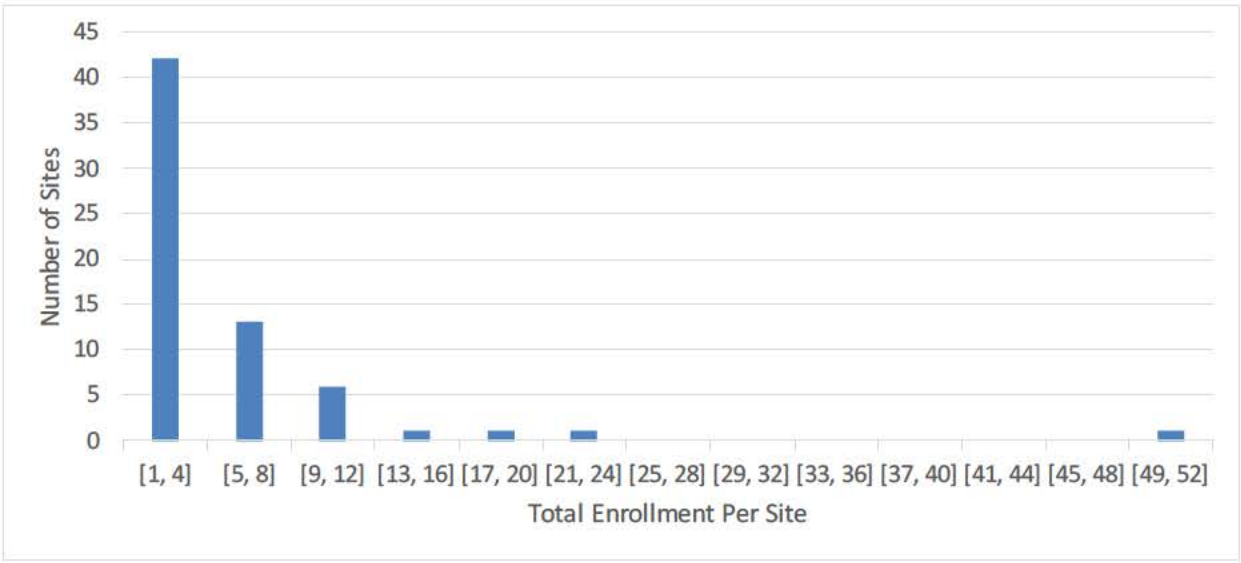


Figure 17. Histogram of Patient Enrollment at Participating Sites – Randomized Cohort ITT Population.

Post hoc win ratio analyses were performed to evaluate primary endpoint outcomes as a function of site enrollment variability for the following groups:

- Sites with ≥10 enrolled patients (Figure 18)
- Sites with <10 enrolled patients (Figure 19)

Sites that enrolled ≥10 patients had a higher win ratio point estimate than those that enrolled <10 patients (2.19 vs. 1.06, respectively).

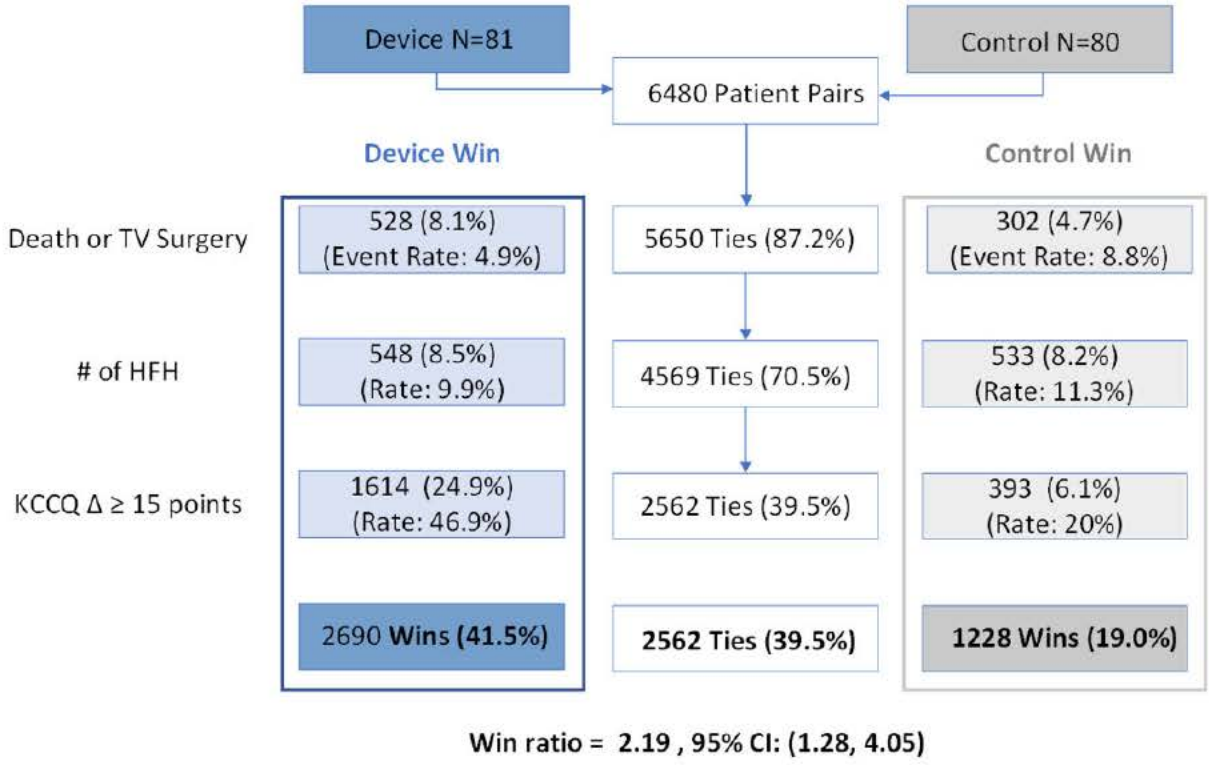


Figure 18. Win Ratio Analysis of Primary Endpoint for Sites that enrolled ≥10 Subjects - Randomized Cohort ITT Population. The confidence interval was calculated without multiplicity adjustment. The adjusted confidence interval could be wider than presented here.

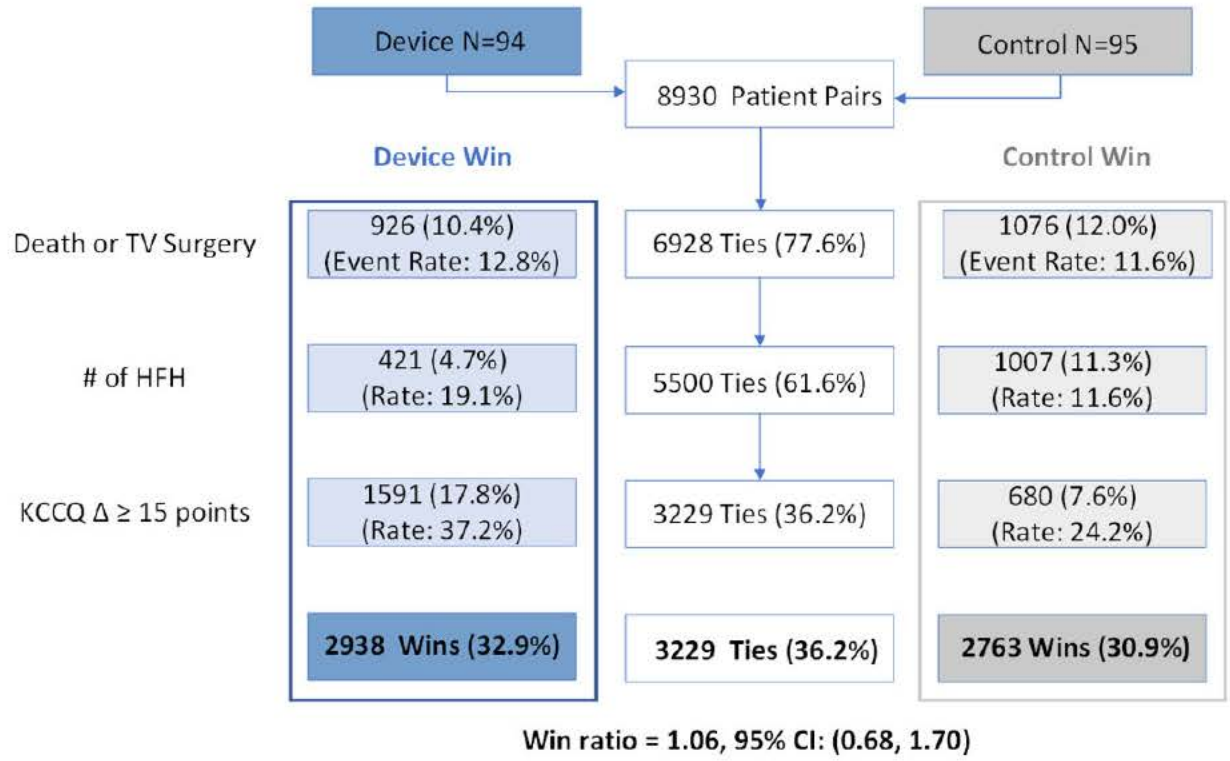


Figure 19. Win Ratio Analysis of Primary Endpoint for Sites that enrolled <10 Subjects - Randomized Cohort ITT Population. The confidence interval was calculated without multiplicity adjustment. The adjusted confidence interval could be wider than presented here.

FDA Comment: The win ratio result of the primary endpoint for the group of sites that enrolled ≥10 patients was more than two-fold higher vs. the group of sites that enrolled <10 patients. The Panel will be asked to discuss the win ratio outcome variability as a function of site enrollment and the generalizability of the primary endpoint results.

7.5.5 Pre-specified Subgroup Analyses

Analyses of the components of the primary endpoint were performed on the following subgroups (see Table 20):

- Sex (male vs. female)
- Baseline TR grade (severe vs. greater than severe)
- Baseline NYHA functional class (I/II vs. III/IV)
- TR etiology (primary TR vs. secondary TR)

Table 20. Pre-specified Subgroup Analyses - Randomized Cohort ITT Population.

		Components of Primary Endpoint at 12 Months					
		Tier 1 All-Cause Mortality or Tricuspid Valve Surgery		Tier 2 Heart Failure Hospitalization		Tier 3 KCCQ Score Improvement ≥15 Points	
		Kaplan-Meier Estimate*	Interaction p-value†	Kaplan-Meier Estimate*	Interaction p-value†	Proportion of patients	Interaction p-value†
Sex	Male (N=158)	Device: 12.0% Control: 14.9%	0.6676	Device: 19.1% Control: 15.7%	0.8200	Device: 40.0% Control: 16.7%	0.5793
	Female (N=192)	Device: 7.3% Control: 6.7%		Device: 12.8% Control: 8.9%		Device: 56.3% Control: 34.1%	
TR severity	Severe (N=93)	Device: 4.5% Control: 2.1%	0.4029	Device: 11.7% Control: 10.6%	0.7755	Device: 55.0% Control: 22.2%	0.4632
	Greater than Severe (N=239)	Device: 10.7% Control: 14.4%		Device: 17.7% Control: 13.8%		Device: 48.0% Control: 24.7%	
NYHA functional class	I/II (N=149)	Device: 7.0% Control: 9.0%	0.8346	Device: 8.6% Control: 11.7%	0.1351	Device: 33.8% Control: 17.1%	0.5996
	III/IV (N=201)	Device: 11.0% Control: 11.8%		Device: 20.4% Control: 12.4%		Device: 63.3% Control: 34.6%	
TR etiology†	Primary (N=21)	Device: 0.0% Control: 0.0%	0.9999	Device: 0.0% Control: 0.0%	0.9998	Device: 77.8% Control: 16.7%	0.0839
	Secondary (N=323)	Device: 9.9% Control: 11.7%		Device: 16.5% Control: 13.4%		Device: 47.4% Control: 26.0%	

TR: tricuspid regurgitation; KCCQ: Kansas City Cardiomyopathy Questionnaire; NYHA: New York Heart Association.

*The Cox regression model including the treatment, subgroup variable, and the interaction effect is used to

estimate the two-sided p-value.
[†]Due to the relatively small number of patients with primary TR, results from the primary TR subgroup may not be representative of this population.

Outcomes for each component of the primary endpoint were generally consistent across subgroups, with all interaction p-values being >0.15 (the traditional significance level for testing interactions). The only exception was KCCQ score change by TR etiology (p=0.0839); however, this is not considered a qualitative interaction, as the device group had a higher proportion of patients with a KCCQ improvement of ≥15 points vs. the control group for both the primary and secondary TR etiology subgroups.

7.5.6 *Post Hoc* Subgroup Analyses

Analyses of the components of the primary endpoint were performed on the following subgroups using an interaction test at a significance level of 15%:

- Atrial vs. ventricular secondary TR
- Age <80 vs. ≥80
- Baseline TR severity <5 vs. 5 (torrential)
- Baseline LVEF <50% vs. ≥50%
- Baseline TAPSE <1.6 vs. ≥1.6
- Pre-existing renal disease
- Pre-existing liver disease
- CIED lead(s) present

For atrial vs. ventricular secondary TR, the following two definitions were used:

- Definition #1 (based on Schlotter et al., 2022): Atrial secondary TR and isolated TR are considered to be a single category, and atrial secondary TR is based on an assessment of co-existing cardiac conditions (i.e., left ventricular dysfunction) rather than only the mechanism of TR (i.e., tethered leaflets vs. dilated atrium).
    - Atrial secondary TR:
        - Tenting height ≤ 10 mm
        - RVEDD (mid) ≤ 38 mm
        - LVEF ≥ 50%
    - Non-atrial secondary (ventricular secondary TR): Patients with tenting height, RVEDD (mid) and LVEF reported who do not meet all requirements for atrial secondary TR.

- Definition #2 (based on the definition of isolated TR from the ACC/AHA guidelines for the management of valvular heart disease; Otto et al. 2020): Isolated TR is considered equivalent to atrial secondary TR and is defined as TR associated with atrial fibrillation independent of left ventricular dysfunction, concomitant valve disease, and pulmonary hypertension.
    - Isolated (atrial) TR:
        - Atrial fibrillation present
        - LVEF >60%

- Pulmonary artery systolic pressure <50 mmHg
- No left-sided valve disease
- Normal appearing tricuspid valve leaflets

o Ventricular secondary TR: Patients who do not meet at least one of the above criteria.

The subgroup analyses for rate of all-cause mortality or tricuspid valve surgery are shown in Figure 20. While baseline LVEF, baseline TAPSE, and pacemaker leads have interaction p-values of <0.15, the corresponding 95% confidence intervals for the hazard ratios overlapped with 1, which indicate that there were no significant differences in time to all-cause mortality or tricuspid valve surgery between the device and control groups within each subgroup category.

Subgroup		N	Device (N = 175)	Control (N = 175)	HR [95% CI]	P-Value
Age	< 80	194	10.5% (10)	9.3% (9)	1.150 [0.467, 2.829]	0.4230
	≥ 80	156	7.9% (6)	12.1% (9)	0.654 [0.233, 1.839]	
Baseline TR Grade	< Grade 5	166	6.0% (5)	6.4% (5)	0.937 [0.271, 3.237]	0.8693
	Grade 5	172	11.8% (10)	14.6% (12)	0.827 [0.357, 1.915]	
Baseline LVEF	< 50	44	9.5% (2)	28.9% (6)	0.301 [0.061, 1.494]	0.0911
	≥ 50	275	10.1% (14)	6.9% (9)	1.496 [0.648, 3.456]	
Baseline TAPSE	< 1.6	161	13.0% (10)	9.0% (7)	1.504 [0.572, 3.950]	0.0980
	≥ 1.6	177	5.4% (5)	12.1% (10)	0.448 [0.153, 1.310]	
Pre-existing Renal Disease	No	226	4.5% (5)	9.0% (10)	0.505 [0.173, 1.478]	0.1503
	Yes	124	18.1% (11)	13.4% (8)	1.407 [0.566, 3.498]	
Pre-existing Liver Disease	No	323	9.3% (15)	10.4% (16)	0.913 [0.451, 1.846]	0.9313
	Yes	27	10.0% (1)	12.5% (2)	0.840 [0.076, 9.265]	
Pacemaker Leads at Baseline	No	298	10.4% (15)	9.5% (14)	1.126 [0.544, 2.333]	0.1445
	Yes	52	3.7% (1)	17.4% (4)	0.204 [0.023, 1.828]	
ATR vs VTR Definition#1	Atrial STR	137	11.9% (8)	10.3% (7)	1.178 [0.427, 3.250]	0.5102
	Ventricular STR	135	9.8% (7)	13.7% (8)	0.722 [0.262, 1.990]	
ATR vs VTR Definition#2	Atrial STR	76	12.8% (5)	11.4% (4)	1.123 [0.301, 4.184]	0.8420
	Ventricular STR	212	9.3% (10)	10.2% (10)	0.953 [0.397, 2.289]	

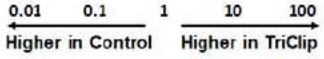


Figure 20. All-Cause Mortality or Tricuspid Valve Surgery *Post Hoc* Subgroup Analysis – Randomized Cohort ITT Population. TR: tricuspid regurgitation; LVEF: left ventricular

ejection fraction; TAPSE: tricuspid annular plane systolic excursion; ATR: atrial TR; VTR: ventricular TR. The percentages shown are Kaplan-Meier estimates of event rates; numbers in parentheses are number of patients with an event. The confidence intervals were calculated without multiplicity adjustment. The adjusted confidence intervals could be wider than presented here.

The subgroup analyses for HF hospitalization are shown in Figure 21. There were no significant differences in time to HF hospitalization between the subgroup categories.

Subgroup		N	Device (N = 175)	Control (N = 175)	HR [95% CI]	P-Value
Age	< 80	194	15.2% (14)	9.5% (9)	1.618 [0.700, 3.738]	0.5321
	≥ 80	156	15.8% (12)	15.5% (11)	1.114 [0.492, 2.525]	
Baseline TR Grade	< Grade 5	166	12.0% (10)	9.1% (7)	1.354 [0.515, 3.559]	0.8945
	Grade 5	172	19.5% (16)	16.2% (13)	1.256 [0.604, 2.611]	
Baseline LVEF	< 50	44	17.8% (4)	19.0% (4)	0.950 [0.237, 3.800]	0.7075
	≥ 50	275	14.9% (20)	12.6% (16)	1.223 [0.634, 2.360]	
Baseline TAPSE	< 1.6	161	15.9% (12)	13.2% (10)	1.296 [0.560, 2.999]	0.9977
	≥ 1.6	177	14.4% (13)	11.2% (9)	1.283 [0.548, 3.001]	
Pre-existing Renal Disease	No	226	13.7% (15)	6.5% (7)	2.193 [0.894, 5.380]	0.1368
	Yes	124	19.1% (11)	22.1% (13)	0.884 [0.396, 1.973]	
Pre-existing Liver Disease	No	323	15.3% (24)	10.0% (15)	1.592 [0.835, 3.035]	0.3280
	Yes	27	18.2% (2)	31.3% (5)	0.669 [0.130, 3.455]	
Pacemaker Leads at Baseline	No	298	15.6% (22)	9.9% (14)	1.693 [0.866, 3.309]	0.1039
	Yes	52	14.9% (4)	26.1% (6)	0.516 [0.145, 1.831]	
ATR vs VTR Definition#1	Atrial STR	137	14.1% (9)	9.0% (6)	1.604 [0.571, 4.508]	0.6071
	Ventricular STR	135	21.0% (15)	19.6% (11)	1.140 [0.524, 2.483]	
ATR vs VTR Definition#2	Atrial STR	76	19.4% (7)	8.6% (3)	2.175 [0.562, 8.412]	0.5064
	Ventricular STR	212	17.9% (19)	14.6% (14)	1.311 [0.658, 2.616]	

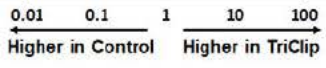


Figure 21. HF hospitalization *Post Hoc* Subgroup Analysis – Randomized Cohort ITT Population. TR: tricuspid regurgitation; LVEF: left ventricular ejection fraction; TAPSE: tricuspid annular plane systolic excursion; ATR: atrial TR; VTR: ventricular TR. The percentages shown are Kaplan-Meier estimates of event rates; numbers in parentheses are

number of patients with an event. The confidence intervals were calculated without multiplicity adjustment. The adjusted confidence intervals could be wider than presented here.

The subgroup analyses for percentage of patients with improvement of ≥15 points in KCCQ score at 12 months are shown in Figure 22. Only the age and atrial vs. ventricular secondary TR subgroups (definition #1) had interaction p-values <0.15, where the rate of KCCQ score improvement ≥15 points at 12 months was higher in the TriClip group in patients aged <80 years and in those with ventricular secondary TR (definition #1).

Subgroup		N	Device (N = 175)	Control (N = 175)	HR [95% CI]	P-Value
Age	< 80	194	54.8% (46/84)	23.9% (21/88)	3.86 [2.01, 7.41]	0.1160
	≥ 80	156	42.9% (27/63)	30.0% (18/60)	1.75 [0.83, 3.68]	
Baseline TR Grade	< Grade 5	166	46.8% (36/77)	21.4% (15/70)	3.22 [1.56, 6.65]	0.9672
	Grade 5	172	52.2% (36/69)	25.7% (18/70)	3.15 [1.54, 6.44]	
Baseline LVEF	< 50	44	63.2% (12/19)	28.6% (4/14)	4.29 [0.97, 18.97]	0.5053
	≥ 50	275	46.6% (55/118)	25.9% (30/116)	2.50 [1.44, 4.34]	
Baseline TAPSE	< 1.6	161	50.0% (32/64)	22.4% (15/67)	3.47 [1.63, 7.38]	0.6076
	≥ 1.6	177	48.8% (40/82)	26.4% (19/72)	2.66 [1.35, 5.24]	
Pre-existing Renal Disease	No	226	52.5% (53/101)	25.5% (25/98)	3.22 [1.77, 5.87]	0.3562
	Yes	124	43.5% (20/46)	28.0% (14/50)	1.98 [0.85, 4.62]	
Pre-existing Liver Disease	No	323	49.6% (69/139)	25.4% (34/134)	2.90 [1.74, 4.84]	0.6105
	Yes	27	50.0% (4/8)	35.7% (5/14)	1.80 [0.31, 10.52]	
Pacemaker Leads at Baseline	No	298	48.8% (60/123)	26.9% (35/130)	2.59 [1.53, 4.37]	0.5292
	Yes	52	54.2% (13/24)	22.2% (4/18)	4.14 [1.05, 16.29]	
ATR vs VTR Definition#1	Atrial STR	116	36.4% (20/55)	29.5% (18/61)	1.37 [0.63, 2.97]	0.0280
	Ventricular STR	108	57.4% (35/61)	21.3% (10/47)	4.98 [2.10, 11.81]	
ATR vs VTR Definition#2	Atrial STR	62	54.5% (18/33)	24.1% (7/29)	3.77 [1.27, 11.24]	0.4063
	Ventricular STR	177	46.2% (42/91)	27.9% (24/86)	2.21 [1.18, 4.14]	

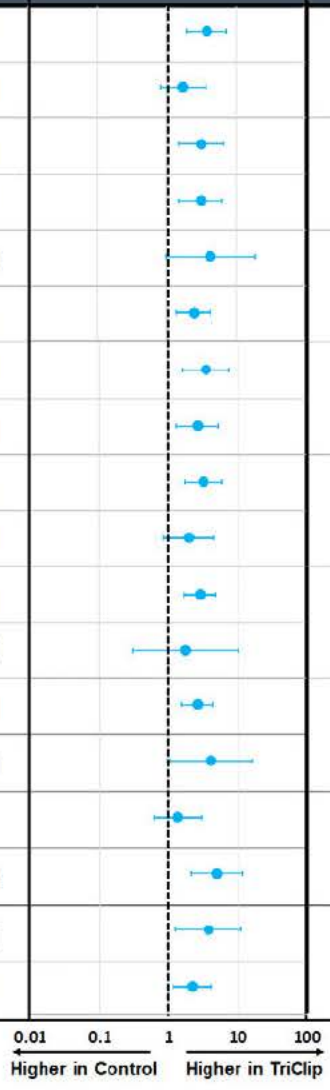


Figure 22. Percentage of Patients with KCCQ Score Improvement of ≥15 Points Post Hoc Subgroup Analysis – Randomized Cohort ITT Population. TR: tricuspid regurgitation; LVEF: left ventricular ejection fraction; TAPSE: tricuspid annular plane systolic excursion; ATR: atrial TR; VTR: ventricular TR. The confidence intervals were calculated without

multiplicity adjustment. The adjusted confidence intervals could be wider than presented here.

7.5.7 Primary Endpoint Result for All Available Patients

During FDA's PMA review, an additional 222 patients were randomized, resulting in a total of 572 randomized patients. Not all these 222 patients had completed the 12-month follow-up visit. The win ratio analysis result for all available randomized patients was 1.53 (Figure 23), which is slightly greater than the win- ratio result for the primary analysis cohort.

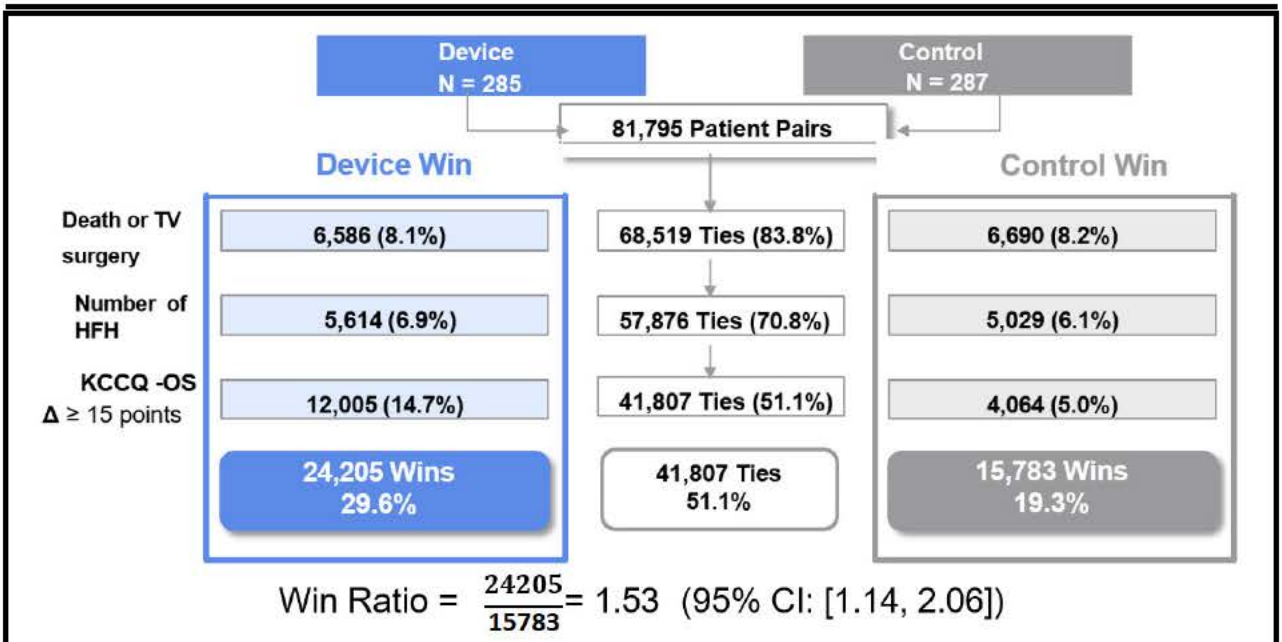


Figure 23. Win Ratio Analysis for All Available Patients – Randomized Cohort ITT Population. HFH: heart failure hospitalization; KCCQ-OS: Kansas City Cardiomyopathy Questionnaire overall summary score; CI: confidence interval. The CI was calculated without multiplicity adjustment. The adjusted CI could be wider than presented here.

7.5.8 2-Year Outcomes for Available Patients

Crossover from the control group to TriClip treatment was allowed if a patient had completed the 12-month follow-up visit, the patient had severe TR, and the patient's anatomy was suitable for treatment with TriClip. Of the 205 control patients who completed 1-year follow-up, 102 crossed over to TriClip.

Among 572 randomized patients, 106 completed the 2-year follow-up visit: 58 in the TriClip group and 48 in the control group, including 35 crossovers and 13 non-crossovers. The baseline characteristics for crossover and non-crossover control patients were generally similar. Comparisons in select 1-year outcomes between crossover and non-crossover control patients are

shown in Table 21. Compared to non-crossovers, crossovers had a higher proportion with torrential TR, were more symptomatic, had less improvement in KCCQ score and a larger decrease in 6MWD vs. baseline, and had nearly two times annualized rates of HF hospitalizations and edema requiring hospitalization at 12 months.

Table 2117. Outcomes for Crossovers and Non-crossovers at 12 Months Post-Randomization

	Crossover (N=102)	Non-crossover (N=103)
Torrential TR	69.6% (71/102)	44.6% (41/92)
NYHA III/IV	51.0% (52/102)	32.7% (33/101)
KCCQ change		
Mean ± SD (n)	-0.06 ± 18.29 (101)	8.42 ± 18.73 (102)
Median (Q1, Q3)	-1.04 (-11.72, 11.98)	5.86 (-1.45, 17.97)
Range (Min, Max)	(-34.38, 54.17)	(-35.15, 73.49)
6MWD change		
Mean ± SD (n)	-22.38 ± 110.15 (89)	-1.89 ± 92.70 (90)
Median (Q1, Q3)	-15.24 (-60.00, 20.00)	1.00 (-45.00, 45.00)
Range (Min, Max)	(-390.61, 268.60)	(-359.00, 260.00)
Incidence of heart failure hospitalizations		
Number of events	20	9
Total follow-up (patient-years)*	101.9	102.5
Annualized rate [95% CI]†	0.20 [0.13, 0.30]	0.09 [0.05, 0.17]
Number of patients with events	13.7% (14/102)	6.8% (7/103)
Incidence of peripheral edema requiring hospitalization		
Number of events	12	6
Total follow-up (patient-years)*	101.9	102.5
Annualized rate [95% CI]†	0.12 [0.07, 0.21]	0.06 [0.03, 0.13]
Number of patients with events	8.8% (9/102)	5.8% (6/103)

TR: tricuspid regurgitation; KCCQ: Kansas City Cardiomyopathy Questionnaire; NYHA: New York Heart Association; 6MWD: 6-minute walk distance.
SD: standard deviation; CI: confidence interval. The CIs were calculated without multiplicity adjustment. The adjusted CIs could be wider than presented here.
*The total follow-up in patient-year is calculated as the sum of follow-up patient-years for each subject through the time period or end of study, whichever is earlier.
†The annualized event rate is calculated as total number of events divided by total follow-up years through each time period.

The Kaplan-Meier estimates of freedom from all-cause mortality or tricuspid valve surgery at 2

years were 76.9%, 75.1%, and 70.7% for the device, control, and control (censored) groups, respectively, where the device and control groups refer to the original randomly assigned treatment groups and the control (censored) group refers to the original control group with all crossovers being censored (Figure 24). Given the limited data at 2 years, no definitive conclusions can be drawn regarding outcome differences among the three groups.

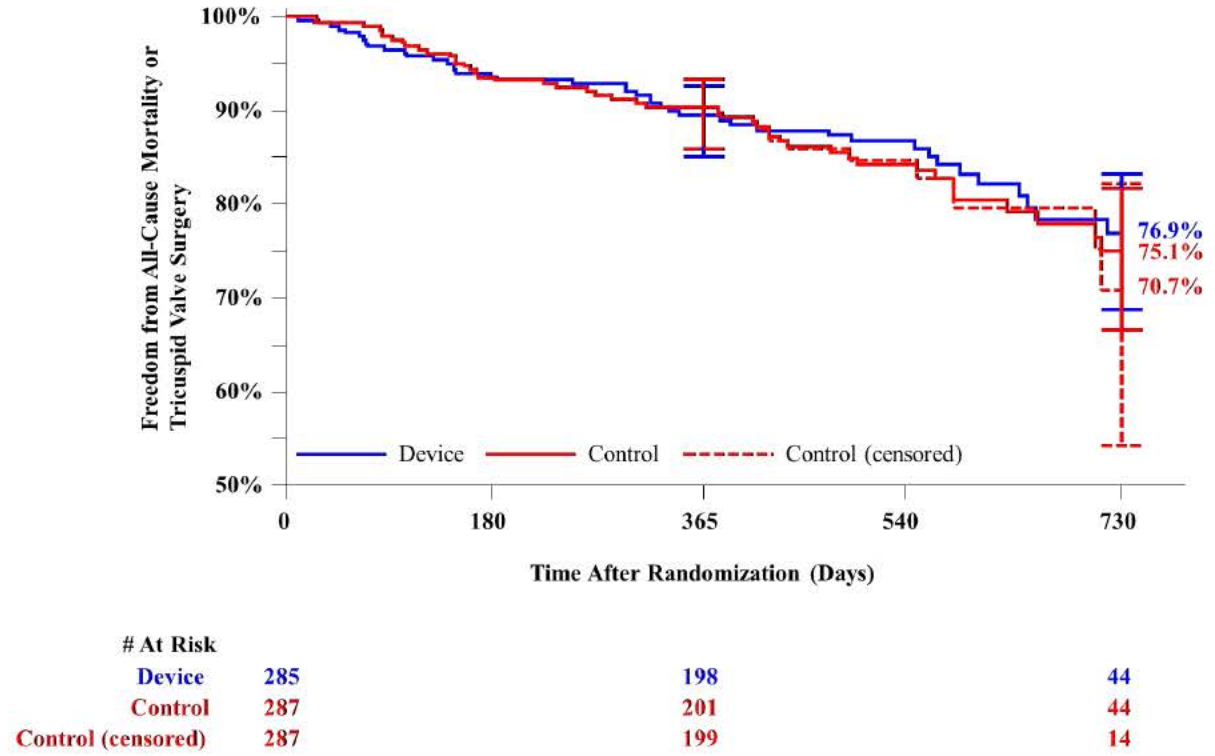


Figure 24. Freedom from All-Cause Mortality or Tricuspid Valve Surgery through 2 Years – Randomized Cohort ITT Population. The confidence intervals were calculated without multiplicity adjustment. The adjusted confidence intervals could be wider than presented here.

The Kaplan-Meier estimates of freedom from HF hospitalization at 2 years were 79.2%, 69.4%, and 63.0% for the device, control, and control (censored) groups, respectively (Figure 25). The annualized rates of HF hospitalization were 0.18, 0.26, and 0.24 events/patient-year for the three groups, respectively (Figure 26). Although the TriClip group had a numerically higher freedom from HF hospitalization rate and lower annualized HF hospitalization rate than the control and control (censored) groups at 2 years, no definitive conclusions can be drawn regarding comparative results among the three groups due to limited data at 2 years.

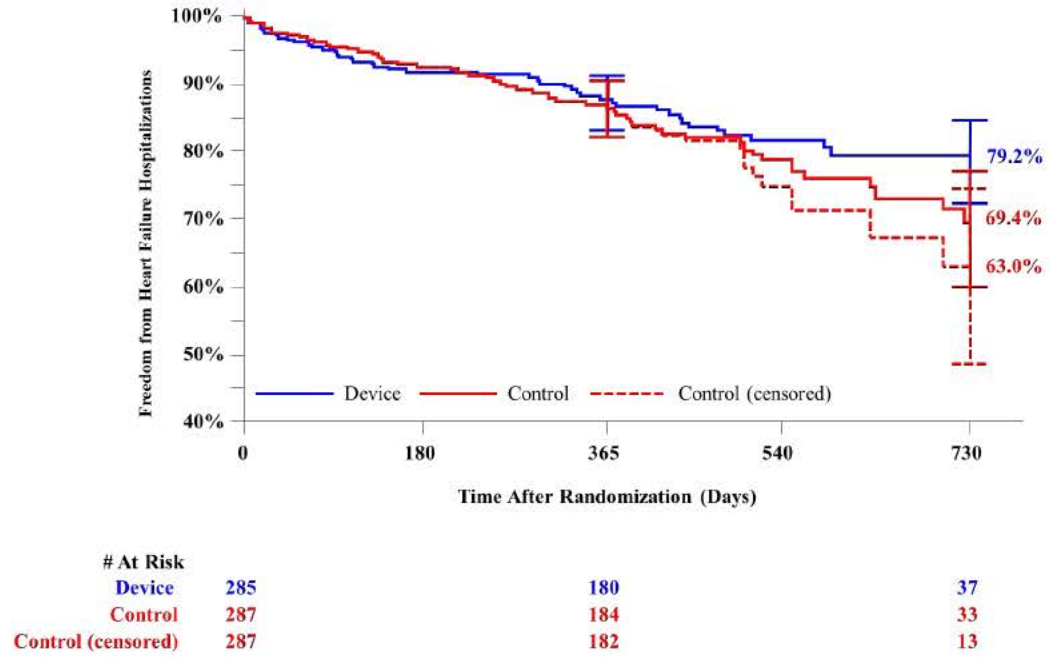


Figure 25. Freedom from HF Hospitalization through 2 Years – Randomized Cohort ITT Population. The confidence intervals were calculated without multiplicity adjustment. The adjusted confidence intervals could be wider than presented here.

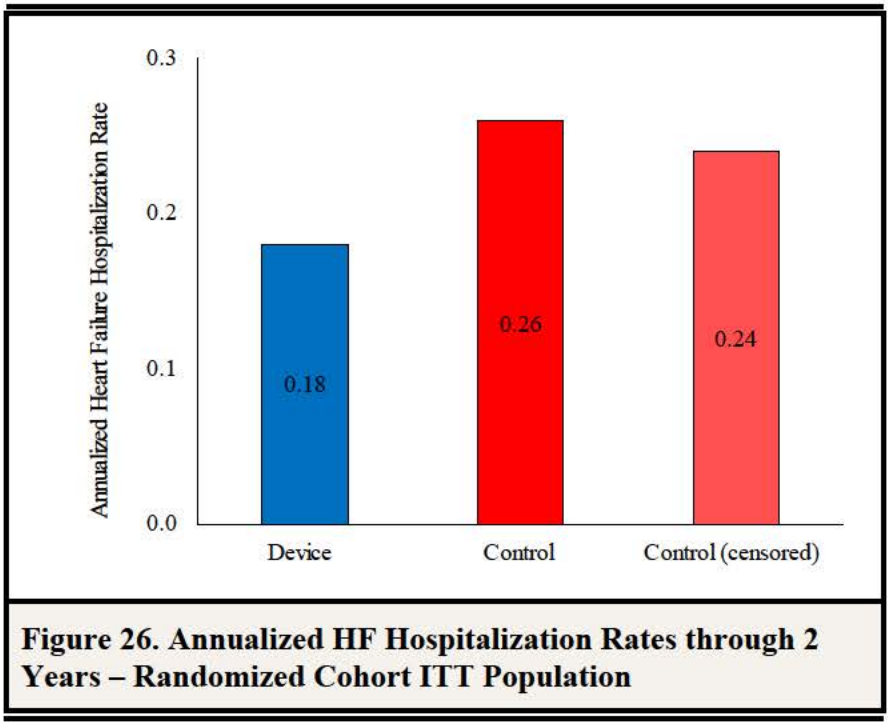


Figure 26. Annualized HF Hospitalization Rates through 2 Years – Randomized Cohort ITT Population

Changes in KCCQ score through 2 years are shown in Figure 27. The results suggest that the KCCQ score improvement observed in the TriClip group at 30 days (16.1±21.0) was sustained through 2 years (15.6±27.4).

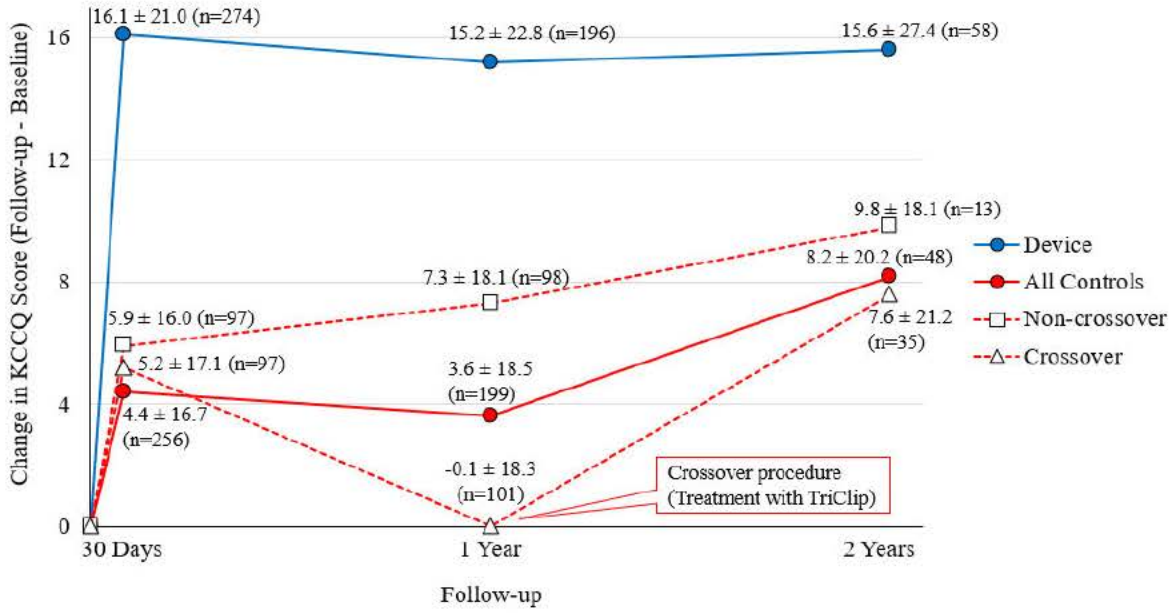


Figure 27. Change in KCCQ Score from Baseline through 2 Years.

7.6 Single-Arm Cohort Results

7.6.1 Primary Endpoint

There were 100 patients with an attempted TriClip procedure in the Single-Arm Cohort. The primary analysis was performed on 91 patients, which excluded patients who withdrew (n=1), died or were hospitalized due to COVID-19 (n=2), or missed the 12-month visit or did not complete the 12-month KCCQ assessment (n=6). The results of the primary analysis are shown in Table 22. Fifteen (15) patients died prior to 12 months, 34 had a KCCQ score improvement of <10 points, and 42 survived with a KCCQ score improvement of at ≥10 points at 12 months. The proportion of patients who survived and experienced at least a 10-point improvement in KCCQ score at 12 months from baseline was 46.2%, with a lower 98.75% confidence limit of 34.3%, which exceeded the performance goal of 30%. Thus, the primary endpoint was met.

Table 2218. Primary Analysis Results – Single-Arm Cohort.					
Primary Endpoint	**Rate**	**Lower 98.75% Confidence Limit**	**Performance Goal**	**P-value**	**Result**
Survival with ≥10 point improvement vs. baseline in KCCQ score at 12 months	46.2% (42/91)	34.3%	30%	0.008	Endpoint Met

7.6.2 Safety Results

CEC-adjudicated adverse event rates through 12 months are shown in Table 23. The rates of all-cause mortality, cardiovascular mortality, and heart failure hospitalization were approximately two-fold higher in the Single-Arm Cohort than in the TriClip group of the Randomized Cohort. Other event rates were comparable to the TriClip group of the Randomized Cohort.

Table 2319. CEC-Adjudicated Adverse Events through 12 Months – Single-Arm Cohort AP Population.	
Event	**Summary Statistics* N=100**
All-cause mortality	15% (15, 15, 0, 0, 1)
Cardiovascular (VARC II definition)	11% (11, 11, 0, 0, 0)
Heart failure-related	10% (10, 10, 0, 0, 0)
Non-heart failure-related	1% (1, 1, 0, 0, 0)
Non-cardiovascular (VARC II definition)	4% (4, 4, 0, 0, 1)
Hospitalization	50% (85, 50, 5, 4, 1)
Heart failure hospitalization	24% (33, 24, 1, 0, 0)
Other cardiovascular hospitalization	14% (17,14, 4, 3, 0)
Non-cardiovascular hospitalization	26% (35, 26, 0, 1, 1)
Tricuspid valve surgery	2% (2, 2, 1, 0, 0)
Tricuspid valve intervention	7% (7, 7, 5, 4, 0)
Major bleeding (greater than BARC 3a)[I]	5% (5, 5, 0, 1, 0)
New onset renal failure[I]	0% (0, 0, 0, 0, 0)
Transient ischemic attack (TIA)	1% (1, 1, 0, 0, 0)
Stroke (VARC II)	0% (0, 0, 0, 0, 0)

Myocardial infarction (VARC II definition)[I]	0% (0, 0, 0, 0, 0)
Endocarditis requiring surgery[I]	0% (0, 0, 0, 0, 0)
Non-elective cardiovascular surgery for TriClip-related adverse event post index procedure[I]	0% (0, 0, 0, 0, 0)
Cardiogenic shock	1% (1, 1, 0, 1, 0)

VARC: Valve Academic Research Consortium; BARC: Bleeding Academic Research Consortium; TIA: transient ischemic attack.
[*]Event rate (no. of events, no. of patients, no. of device-related events, number of procedure-related events, number of COVID-19-related events); event rate = no./total no. Number of COVID-19-related events includes related or possibly related events; this excludes events with unknown relatedness.
[I]Per the study CEC charter, myocardial infarction, bleeding, new onset renal failure, endocarditis requiring surgery, and non-elective cardiovascular surgery for TriClip-related adverse event post index procedure were adjudicated up to 30 days post treatment visit for the device and control groups.

7.6.3 Powered Secondary Endpoints

The results of the powered secondary endpoints for the Single-Arm Cohort are summarized in Table 24. TR reduction by at least one grade at 30 days post-procedure occurred in 98.9% of patients, and freedom from MAEs at 30 days post-procedure occurred in 100% of patients; these endpoints were met. However, the improvement in 6MWD at 12 months from baseline (13.7±92.7) did not meet the performance goal, so the endpoint was not met. As a result, the subsequent endpoints in the pre-defined hierarchy (freedom from all-cause mortality or tricuspid valve surgery and recurrent HF hospitalizations at 12 months post-procedure) were not hypothesis-tested. Descriptively, the annualized HF hospitalization rates pre- and post-TriClip procedure were generally similar.

Table 2420. Summary of Powered Secondary Endpoints – Single-Arm Cohort AP Population.

Order	Secondary Endpoint	Summary Statistics	p-Value	Result
1	TR reduction by at least one grade at 30 days post-procedure	98.9% (87/88)[*]	< 0.0001	Endpoint met
2	Freedom from MAEs at 30 days post-procedure	100% (99/99)[*]	<0.0001	Endpoint met
3	Change in 6MWD at 12 months from baseline (m)	13.7±92.7 (71)[†] 95% CI: [-8.3, 35.6]	0.1090	**Endpoint not met**
4	Freedom from all-cause mortality and tricuspid valve	83.7% (3.7%)[‡]	-	Not tested

	surgery at 12 months			
5	Recurrent HF hospitalizations at 12 months (events/patient-year)	Pre-procedure: 0.33 [0.23, 0.46][I] Post-procedure: 0.36 [0.26, 0.51][I]	-	Not tested

TR: tricuspid regurgitation; MAEs: major adverse events, including cardiovascular mortality, new onset renal failure, endocarditis requiring surgery, and non-elective cardiovascular surgery for TriClip device-related adverse events post-index procedure; 6MWD: 6-minute walk distance; HF: heart failure.
CI: confidence interval. The CIs were calculated without multiplicity adjustment. The adjusted CIs could be wider than presented here.
[*]% (no./total no.)
[†]Mean ± standard deviation (total no.)
[‡]Kaplan-Meier estimate (standard error)
[I]Annualized event rate [95% CI].

7.6.4 Descriptive Endpoints

7.6.4.1 Procedural Endpoints

Technical success, device success, and procedural success were achieved in 98%, 90%, and 86.7% of patients, respectively (see Table 25). Technical success was not achieved in 2 patients due to failure to implant a TriClip device. Device success was not achieved in 9 patients: 7 due to single leaflet device attachment and 2 due to failure to implant a TriClip device. Procedural success was not achieved in the same 9 patients in whom device success was not achieved plus in 3 additional patients who experienced a site-reported serious adverse event: hypotension (n=1), urinary retention (n=1), and lingual hematoma (n=1).

Table 2521. Results of Procedural Endpoints – Single-Arm Cohort AP Population.

Endpoint	Result
Technical success (at exit from procedure room)	98% (98/100)
Device success (at 30 days post-procedure)	90% (81/90)
Procedural success (at 30 days post-procedure)	86.7% (78/90)

7.6.4.2 Health Status Endpoints

Health status endpoint results are shown in Table 26. Clinically meaningful improvements at 12 months were observed in the KCCQ score, SF-36 score physical and mental components, and the proportion of patients that improved from NYHA III/IV at baseline to NYHA I/II. The 6MWD improvement is not considered to be clinically meaningful.

Table 2622. Results of Health Status Endpoints – Single-Arm Cohort AP Population.	
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)

KCCQ: Kansas City Cardiomyopathy Questionnaire; SF-36: 36-Item Short Form Health Survey; NYHA: New York Heart Association; 6MWD: 6-minute walk distance.
SD: standard deviation; Q1: 1st quartile; Q3: 3rd quartile.

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

The annualized rates of peripheral edema requiring hospitalization, ascites, and IV diuretic use are shown in Table 27.

Table 2723. Peripheral Edema Requiring Hospitalization, Ascites, and IV Diuretic Use at 12 Months – Single-Arm Cohort AP Population.	
Endpoint	**Results**
Incidence of peripheral edema requiring hospitalization at 12 months	
Number of events	15
Total follow up (patient-years)	90.8

Annualized rate [95% CI]	0.17 [0.10, 0.27]
Number of patients with events	11.0% (11/100)
Incidence of ascites at 12 months	
Number of events	4
Total follow up (patient-years)	90.8
Annualized rate [95% CI]	0.04 [0.02, 0.12]
Number of patients with events	3.0% (3/100)
IV diuretic use (including at outpatient clinics) at 12 months	
Number of days	174
Total follow-up (patient-years)	90.8
Annualized rate [95% CI]	1.92 [1.65, 2.22]
Number of patients with events	27.0% (27/100)

CI: confidence interval. The CIs were calculated without multiplicity adjustment. The adjusted CIs could be wider than presented here.

7.6.4.4 Renal Function, Hepatic Function, Natriuretic Peptide, and Body Weight Endpoints

The results of laboratory and body weight endpoints are shown in Table 28. There was no clinically meaningful change through 12 months for renal function, hepatic function, natriuretic peptides, and body weight. However, similar to the finding in the Randomized Cohort, the mean NT-proBNP level increased.

Table 2824. Renal Function, Hepatic Function, Natriuretic Peptide, and Body Weight – Single-Arm Cohort AP Population.

Endpoint Change from Baseline to 12 Months	Results
ΔGGT (U/L)	
Mean ± SD (n)	-4.1 ± 30.2 (60)
Median (Q1, Q3)	-5.0 (-15.0, 8.0)
Range (mix, max)	(-80.0, 62.0)
ΔBNP (pg/mL)	
Mean ± SD (n)	0.1 ± 266.4 (34)
Median (Q1, Q3)	-16.5 (-126.0, 36.0)
Range (mix, max)	(-367.0, 934.0)
ΔNT-proBNP (pg/mL)	
Mean ± SD (n)	221.4 ± 1360.8 (29)
Median (Q1, Q3)	64.0 (-374.0, 328.0)
Range (mix, max)	(-1538.0, 4977.0)
ΔPatient weight (kg)	

Mean ± SD (n)	-1.2 ± 5.2 (81)
Median (Q1, Q3)	-0.7 (-3.6, 1.7)
Range (mix, max)	(-23.5, 9.0)
ΔKidney function assessed by eGFR (ml/min/1.73 m^2)	
Mean ± SD (n) Median (Q1, Q3) Range (mix, max)	-1.4 ± 13.2 (76) -0.7 (-8.4, 6.1) (-32.0, 36.9)
ΔLiver Function assessed by MELD score	
Mean ± SD (n)	0.4 ± 5.3 (60)
Median (Q1, Q3)	0.0 (-2.4, 2.7)
Range (mix, max)	(-11.0, 16.7)

GGT: gamma-glutamyl transpeptidase; BNP: B-type natriuretic peptide; NT-proBNP: N-terminal pro b-type natriuretic peptide; eGFR: estimated glomerular filtration rate; MELD: Model for End-Stage Liver Disease.

SD: standard deviation; Q1: 1st quartile; Q3: 3rd quartile .

7.6.4.5 Echocardiographic Endpoints

Changes in TR severity and other echocardiographic parameters at 12 months are shown in Figure 28 and Table 29. The proportion of patients with greater than moderate TR decreased from 100% at baseline to 21% at 12 months. The PISA EROA, PISA regurgitant volume, and vena contracta width decreased substantially from baseline to 12 months. No substantial changes in cardiac size and function through 12 months were observed.

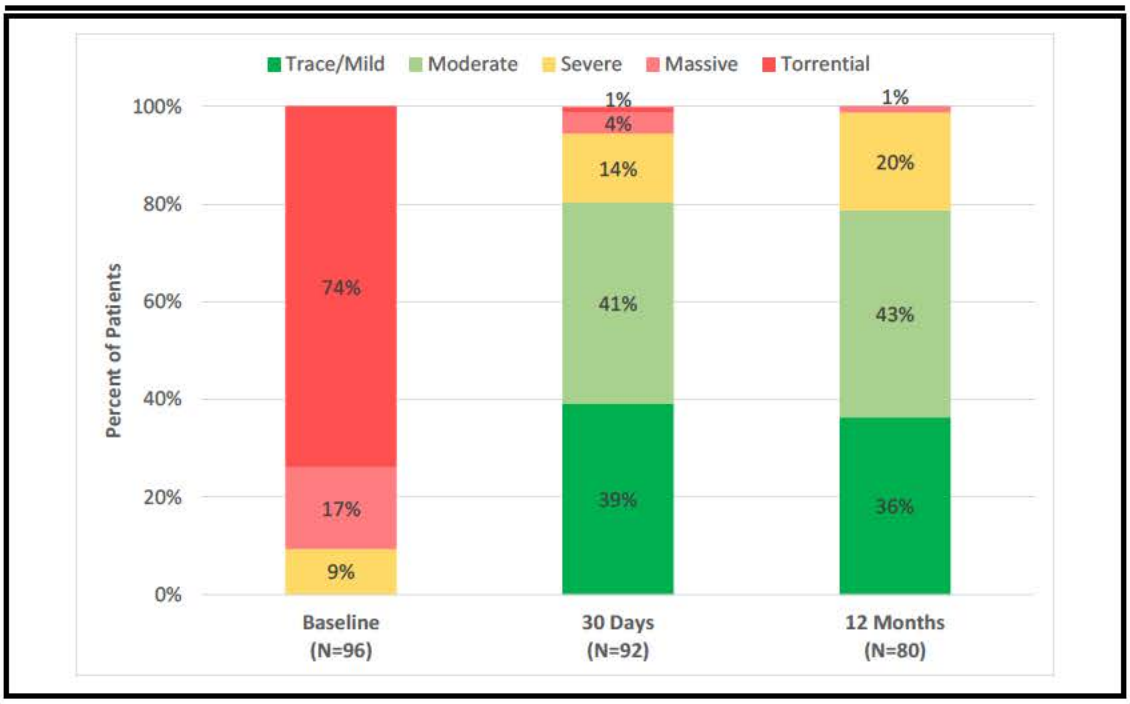


Figure 28. TR Severity at Baseline, 30 Days, and 12 Months– Single-Arm Cohort AP Population (Unpaired).

Table 2925. Echocardiographic Endpoints - Single-Arm Cohort AP Population.	
Echocardiographic Endpoint Change from Baseline to 12 Months	**Results**
ΔTricuspid annulus diameter (end-diastole, apical 4Ch, cm)	
Mean ± SD (n)	-0.08 ± 0.71 (78)
Median (Q1, Q3)	-0.10 (-0.70, 0.48)
Range (min, max)	(-1.60, 1.60)
[95% CI]	[-0.24, 0.08]
ΔPISA EROA (cm^2)	
Mean ± SD (n)	-0.55 ± 0.30 (65)
Median (Q1, Q3)	-0.52 (-0.68, -0.36)
Range (min, max)	(-1.53, -0.02)
[95% CI]	[-0.62, -0.47]
ΔPISA regurgitant volume calculation (mL)	
Mean ± SD (n)	-37.52 ± 17.04 (65)
Median (Q1, Q3)	-37.30 (-47.30, -28.40)
Range (min, max)	(-73.18, 2.85)
[95% CI]	[-41.75, -33.30]
ΔVena contracta width (SL, 4Ch view, cm)	
Mean ± SD (n)	-0.60 ± 0.46 (78)
Median (Q1, Q3)	-0.63 (-0.82, -0.33)
Range (min, max)	(-1.80, 1.00)
[95% CI]	[-0.70, -0.49]
ΔRV end diastolic diameter – mid (4Ch, cm)	
Mean ± SD (n)	-0.11 ± 0.75 (77)
Median (Q1, Q3)	-0.20 (-0.50, 0.40)
Range (min, max)	(-2.10, 2.00)
[95% CI]	[-0.28, 0.06]
ΔRV end diastolic diameter – base (4Ch, cm)	
Mean ± SD (n)	-0.24 ± 0.72 (77)
Median (Q1, Q3)	-0.30 (-0.80, 0.40)
Range (min, max)	(-2.40, 1.10)
[95% CI]	[-0.40, -0.07]
ΔRight atrial volume (single plane Simpson's, mL)	
Mean ± SD (n)	8.30 ± 72.98 (78)

Median (Q1, Q3)	-3.70 (-33.28, 26.70)
Range (min, max)	(-118.80, 313.50)
[95% CI]	[-8.15, 24.76]
ΔRV fractional area change (%)	
Mean ± SD (n)	-2.19 ± 10.34 (74)
Median (Q1, Q3)	-2.25 (-9.90, 3.83)
Range (min, max)	(-33.10, 31.80)
[95% CI]	[-4.58, 0.21]
ΔLV end diastolic volume (mL)	
Mean ± SD (n)	3.15 ± 23.06 (73)
Median (Q1, Q3)	0.70 (-11.10, 15.29)
Range (min, max)	(-37.30, 69.92)
[95% CI]	[-2.23, 8.53]
ΔLV end systolic volume (mL)	
Mean ± SD (n)	1.78 ± 11.55 (73)
Median (Q1, Q3)	2.90 (-6.40, 7.00)
Range (min, max)	(-19.35, 35.92)
[95% CI]	[-0.91, 4.48]
ΔRV TAPSE (cm)	
Mean ± SD (n)	-0.06 ± 0.50 (77)
Median (Q1, Q3)	-0.16 (-0.40, 0.28)
Range (min, max)	(-0.98, 1.53)
[95% CI]	[-0.17, 0.05]
ΔCardiac output (L/min)	
Mean ± SD (n)	0.04 ± 1.49 (76)
Median (Q1, Q3)	-0.05 (-0.91, 0.89)
Range (min, max)	(-3.33, 5.22)
[95% CI]	[-0.30, 0.38]
ΔLVOT Doppler stroke volume (mL)	
Mean ± SD (n)	-0.08 ± 17.73 (77)
Median (Q1, Q3)	-0.63 (-7.56, 10.20)
Range (min, max)	(-61.20, 57.50)
[95% CI]	[-4.11, 3.94]
ΔInferior vena cava diameter (cm)	
Mean ± SD (n)	-0.22 ± 0.61 (74)
Median (Q1, Q3)	-0.20 (-0.58, 0.10)
Range (min, max)	(-1.49, 1.30)
[95% CI]	[-0.36, -0.07]
ΔTricuspid valve diastolic mean gradient (CW, mmHg)	
Mean ± SD (n)	0.73 ± 0.77 (70)
Median (Q1, Q3)	0.64 (0.23, 1.21)

Range (min, max)	(-0.67, 2.96)
[95% CI]	[0.55, 0.92]

PISA: proximal isovelocity surface area (a method for estimating regurgitant volume); EROA: effective regurgitant orifice area; RV: right ventricular; LV: left ventricular; TAPSE: tricuspid annular plane systolic excursion (a measure of the RV apex to-base shortening and RV systolic function); LVOT: left ventricular outflow tract.

SD: standard deviation; Q1: 1st quartile; Q3: 3rd quartile; CI: confidence interval. The CIs were calculated without multiplicity adjustment. The adjusted CIs could be wider than presented here.

FDA Comment: Patients in the Single-Arm Cohort met the same enrollment criteria as the Randomized Cohort except that patients were assigned to the Single-Arm Cohort if the Eligibility Committee determined that there was a high likelihood that TR would be reduced by ≥1 grade with the TriClip device, but a low likelihood that TR would be reduced to moderate or less (≤2 grades). The Single-Arm Cohort was intended to show that any reduction in TR provides health status benefit, even if TR severity was not reduced to moderate or less. TR reduction by at least 1 grade at 30 days was achieved in 98.9% (87/88) of patients (Table 22), and TR reduction to moderate or less was achieved in 80% of patients. The Panel will be asked to discuss the clinical significance of the Single-Arm Cohort outcomes, their value-added to the Randomized Cohort results, and their implications on defining the TriClip intended use population.

7.7 Imaging Sub-study

A pre-planned exploratory imaging sub-study was conducted on a subset of patients to further investigate changes in TR, right ventricular size, and right ventricular function and to gain additional insights into cardiac reverse remodeling. Ten (10) sites participated, and site selection was based on MRI/CT imaging expertise, adequate imaging equipment, and study enrollment. The imaging sub-study was to enroll 100 patients. A total of 82 patients enrolled and completed baseline imaging as of July 3, 2023, with 44 patients enrolled at a single site. Patient accountability is shown in Figure 29. The number of patients in each cohort who reached 30-day and 12-month follow-ups as of July 3, 2023, is shown in Table 30.

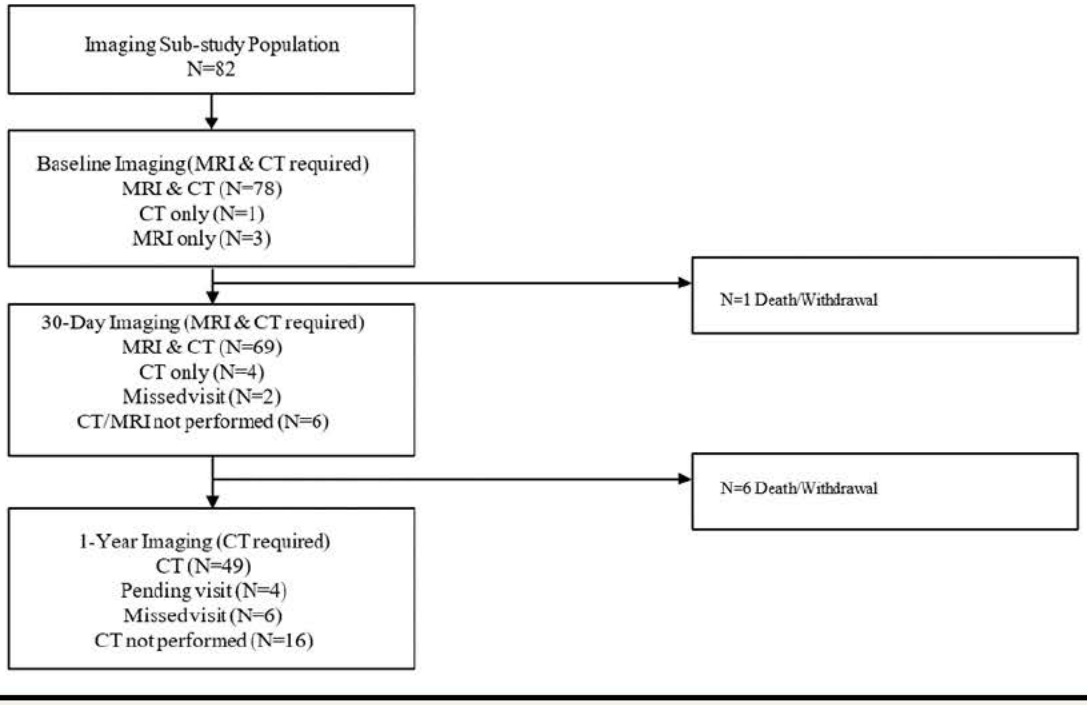


Figure 29. Imaging Sub-Study Patient Accountability.

Table 3026. Imaging Sub-Study Patient Follow-up Status.

	Randomized	Single-Arm	Roll-In	Total
Patients with 30-day follow-up	67	13	1	81
Patients with 12-month follow-up	58	12	1	71

MRI and CT were performed at baseline and 30 days, and CT was performed at 12 months. TR parameters were only assessed with MRI. The 30-day cardiac MRI results (Table 31) showed TR reduction in TriClip patients consistent with the echocardiogram results. In addition, there were general trends in right ventricular reverse remodeling in TriClip patients. However, the sample sizes were relatively small and there was large patient-to-patient variability in the results. The long-term prognostic values of the observed changes are unknown.

Table 3127. 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)	
ΔTR volume (mL)			
Mean ± SD (n)	-34.1 ± 28.2 (27)	3.2 ± 22.1 (24)	-39.0 ± 16.3 (10)

Median (Q1, Q3)	-28.0 (-52.0, -10.0)	2.0 (-13.0, 11.5)	-43.0 (-46.0, -28.0)
Range (min, max)	(-100.0, 4.0)	(-20.0, 84.0)	(-62.0, -9.0)
[95% CI]	[-45.3, -23.0]	[-6.2, 12.5]	[-50.6, -27.4]
ΔTR fraction (%)			
Mean ± SD (n)	-27.8 ± 16.0 (27)	-2.3 ± 21.2 (24)	-29.1 ± 14.6 (10)
Median (Q1, Q3)	-28.0 (-45.0, -13.8)	0.5 (-8.4, 6.0)	-29.5 (-37.0, -18.0)
Range (min, max)	(-52.9, 9.4)	(-66.4, 60.2)	(-56.3, -9.0)
[95% CI]	[-34.1, -21.4]	[-11.3, 6.6]	[-39.5, -18.7]
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)
Range (min, max)	(-64.0, 37.0)	(-113.0, 63.0)	(-83.0, -2.0)
[95% CI]	[-17.8, 0.4]	[-19.5, 11.6]	[-47.2, -11.9]
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)
Range (min, max)	(-16.0, 4.0)	(-13.0, 10.0)	(-32.0, -1.0)
[95% CI]	[-6.8, -2.7]	[-2.5, 2.5]	[-13.0, -1.3]
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)
Range (min, max)	(-17.0, 5.0)	(-15.0, 17.0)	(-16.0, 2.0)
[95% CI]	[-8.2, -3.0]	[-1.9, 3.2]	[-13.0, -5.4]
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)
Range (min, max)	(-8.2, 20.3)	(-12.0, 8.8)	(-10.9, 18.5)
[95% CI]	[5.4, 11.4]	[-2.1, 1.7]	[0.4, 13.7]
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)
Range (min, max)	(-12.0, 6.0)	(-8.0, 16.0)	(-12.0, 3.0)
[95% CI]	[-3.7, -0.2]	[-1.4, 3.7]	[-6.1, 0.7]
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)
Range (min, max)	(-19.0, 41.0)	(-22.0, 19.0)	(-79.0, 29.0)
[95% CI]	[0.0, 10.3]	[-3.5, 4.2]	[-20.3, 16.7]

CI: confidence interval. The CIs was calculated without multiplicity adjustment. The adjusted CIs could be wider than presented here.

*Corrected RVEF: provides a more accurate measurement of forward flow by subtracting

regurgitant volume from the total stroke volume for a regurgitant valve.

The 30-day and 12-month cardiac CT results are shown in Table 32 and Table 33, respectively. Similar to the cardiac MRI results, general trends of right ventricular reverse remodeling were observed in TriClip patients. However, sample sizes were relatively small, and there was large patient-to-patient variability in the results. The long-term prognostic values of the observed changes are unknown.

Table 3228. Imaging Sub-Study: 30-Day Cardiac CT Results.

Endpoint Change from Baseline to 30 Days	Randomized Cohort		Single Arm & Roll-In Cohort (N=14)
	Device Arm (N=27)	Control Arm (N=29)	
ΔRight atrial end diastolic volume (RAEDV, mL)			
Mean ± SD (n)	-20.3 ± 31.6 (26)	-4.9 ± 43.0 (29)	-4.3 ± 21.8 (14)
Median (Q1, Q3)	-21.5 (-32.0, -1.0)	-10.0 (-30.0, 15.0)	-7.0 (-22.0, 10.0)
Range (min, max)	(-106.0, 34.0)	(-81.0, 156.0)	(-40.0, 39.0)
[95% CI]	[-33.1, -7.6]	[-21.2, 11.4]	[-16.9, 8.3]
ΔTricuspid valve annular area (mm^2)			
Mean ± SD (n)	-201.2 ± 177.0 (26)	-49.3 ± 147.1 (29)	-105.0 ± 308.8 (14)
Median (Q1, Q3)	-195.0 (-290.0, -80.0)	-70.0 (-120.0, 80.0)	-85.0 (-300.0, 10.0)
Range (min, max)	(-640.0, 160.0)	(-430.0, 160.0)	(-520.0, 630.0)
[95% CI]	[-272.6, -129.7]	[-105.3, 6.6]	[-283.3, 73.3]
ΔRight ventricular end diastolic volume (RVEDV, mL)			
Mean ± SD (n)	-34.2 ± 32.8 (26)	-1.8 ± 30.3 (29)	-21.4 ± 37.8 (14)
Median (Q1, Q3)	-36.5 (-60.0, -9.0)	-6.0 (-25.0, 16.0)	-10.0 (-47.0, 7.0)
Range (min, max)	(-109.0, 23.0)	(-54.0, 69.0)	(-93.0, 30.0)
[95% CI]	[-47.5, -21.0]	[-13.4, 9.7]	[-43.2, 0.5]
ΔRight ventricular mass (g)			
Mean ± SD (n)	-4.8 ± 7.4 (26)	0.3 ± 5.3 (29)	-0.1 ± 6.0 (14)
Median (Q1, Q3)	-3.0 (-7.0, -1.0)	0.0 (-2.0, 4.0)	-0.5 (-5.0, 3.0)
Range (min, max)	(-27.0, 4.0)	(-9.0, 10.0)	(-10.0, 12.0)
[95% CI]	[-7.9, -1.8]	[-1.7, 2.3]	[-3.5, 3.4]
ΔRight ventricular ejection fraction (%)			
Mean ± SD (n)	-5.0 ± 6.4 (26)	-0.1 ± 6.8 (29)	-6.6 ± 5.2 (14)
Median (Q1, Q3)	-6.5 (-10.0, 1.0)	0.0 (-4.0, 4.0)	-6.0 (-10.0, -2.0)
Range (min, max)	(-14.0, 7.0)	(-17.0, 14.0)	(-18.0, 2.0)
[95% CI]	[-7.6, -2.4]	[-2.7, 2.5]	[-9.6, -3.7]
ΔRight ventricular free wall strain (%)			
Mean ± SD (n)	-1.3 ± 5.9 (22)	-0.5 ± 4.1 (26)	-2.5 ± 5.5 (12)
Median (Q1, Q3)	-2.5 (-6.0, 2.0)	-0.5 (-4.0, 2.0)	-1.5 (-6.5, 2.0)
Range (min, max)	(-11.0, 11.0)	(-8.0, 8.0)	(-12.0, 5.0)

[95% CI]	[-3.9, 1.3]	[-2.1, 1.2]	[-6.0, 1.0]

SD: standard deviation; CI: confidence interval. The CIs were calculated without multiplicity adjustment. The adjusted CIs could be wider than presented here.

Table 33. Imaging Sub-Study: 12-Month 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)
Range (min, max)	(-83.0, 45.0)	(-70.0, 99.0)	(-33.0, 23.0)
[95% CI]	[-35.4, -3.5]	[-12.3, 21.0]	[-25.1, 18.6]
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)
Range (min, max)	(-690.0, 90.0)	(-240.0, 390.0)	(-360.0, 0.0)
[95% CI]	[-287.3, -102.7]	[-69.8, 63.8]	[-305.0, -83.6]
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)
Range (min, max)	(-74.0, 8.0)	(-61.0, 68.0)	(-103.0, 0.0)
[95% CI]	[-48.1, -23.5]	[-18.8, 16.9]	[-73.4, -11.4]
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)
Range (min, max)	(-16.0, 2.0)	(-10.0, 13.0)	(-10.0, 8.0)
[95% CI]	[-6.9, -2.4]	[-1.6, 4.4]	[-8.8, 1.7]
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)
Range (min, max)	(-16.0, 5.0)	(-10.0, 11.0)	(-11.0, 7.0)
[95% CI]	[-9.8, -4.0]	[-1.6, 3.3]	[-8.6, 4.3]
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)
Range (min, max)	(-20.0, 5.0)	(-14.0, 10.0)	(-13.0, 4.0)
[95% CI]	[-7.8, -0.7]	[-3.9, 1.3]	[-7.3, 4.7]

SD: standard deviation; CI: confidence interval. The CIs were calculated without multiplicity adjustment. The adjusted CIs could be wider than presented here.

8 Postmarket Studies

Patients enrolled under the TriClip IDE, including those enrolled under the Continued Access Protocol (enrollment limited to 450 patients, 360 enrolled as of January 5, 2024, no study results yet available), will be followed through 5 years. Additionally, Abbott Medical proposes to conduct registry-based postmarket surveillance of the TriClip device through the Society of Thoracic Surgeons (STS)/ACC Transcatheter Valve Therapy (TVT) Registry, including linkage of the TVT Registry with the Centers for Medicare and Medicaid Services (CMS) claims data. Patient outcomes will be analyzed annually through 5 years post-procedure. Patient demographics and baseline characteristics and outcomes during the first year post-procedure (including assessments performed at the index procedure, discharge, 30 days, and 12 months) will be collected through the TVT Registry. For years 2 through 5 post-procedure, outcomes (including mortality, repeat procedure for tricuspid valve-related dysfunction, and hospitalization) will be collected from the CMS claims data.

9 Conclusions

This executive summary provides background on TR and current treatment options, a description of the TriClip device, and a review of the TRILUMINATE pivotal trial results. Based on the information provided, Abbott Medical is requesting that the TriClip device be approved and indicated for the improvement of health status in patients with symptomatic severe TR despite being treated with OMT, who are at intermediate or greater risk for surgery, and in whom tricuspid valve edge-to-edge repair is deemed appropriate by a heart team.

The TRILUMINATE pivotal trial was an open-label randomized controlled trial comparing treatments with the TriClip device plus OMT vs. OMT alone. The trial included a Randomized Cohort and a Single-Arm Cohort. Both cohorts met their 12-month primary endpoints. The Randomized Cohort primary endpoint success was driven by improvement in KCCQ score, which is a patient reported outcome that could be subject to the placebo effect in an unblinded trial. There was no signal of reduced mortality or HF hospitalization associated with TriClip device implantation through 12 months post-procedure.

The TRILUMINATE pivotal trial Randomized Cohort also showed a 30-day freedom from MAEs rate of 98.3% with a lower 95% confidence limit of 96.3%, which met the prespecified performance goal of 90%. In addition, there were no occurrences of device thrombus or device embolization.

The TriClip was designated a breakthrough device by FDA. Because of the importance of HF associated with TR and FDA's mission to bring novel beneficial treatments to patients, we are seeking the Panel's input on the benefits and risks of the TriClip device and whether the information provided demonstrates a reasonable assurance of device safety and effectiveness as defined in 21 CFR 860.7(d)(l) and (e)(l). The evidence must show that when using the device properly, the evidence supports that in a significant portion of the target population, there is an

absence of unreasonable risks (safety) and that there are clinically significant benefits (effectiveness).

10 References

Anota A, Pozet A, Lemasson H, et al. Impact of open-label versus blinded study design on patient-reported outcomes data in randomized clinical trials of immunotherapy in advanced or metastatic cancer patients: A systematic review. Qual Life Res 2022;31:645-657. doi: 10.1007/s11136-021-02945-8.

Beckhoff F, Alushi B, Jung C, et al. Tricuspid Regurgitation - Medical Management and Evolving Interventional Concepts. Front Cardiovasc Med 2018;5:49. doi:10.3389/fcvm.2018.00049

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

Food and Drug Administration. Center for Devices and Radiological Health 2016-2017 Strategic Priorities. [Accessed January 6, 2024.] Available at: https://www.fda.gov/media/95317/download.

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.

Food and Drug Administration. Guidance for Industry and Food and Drug Administration Staff, and Other Stakeholders: Principles for Selecting, Developing, Modifying, and Adapting Patient-Reported Outcome Instruments for Use in Medical Device Evaluation. January 26, 2022. [Accessed January 6, 2024.] Available at: https://www.fda.gov/media/141565/download.

Food and Drug Administration. Qualification of Medical Device Development Tools - Guidance for Industry, Tool Developers, and Food and Drug Administration Staff. July 17, 2023. [Accessed January 6, 2024.] Available at: https://www.fda.gov/media/87134/download.

Finkelstein DM and Schoenfeld DA. Combining Mortality and Longitudinal Measures in Clinical Trials. Stat Med 1999;18:1341-54. doi: 10.1002/(sici)1097-0258(19990615)18:11<1341::aid-sim129>3.0.co;2-7.

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.

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

Lord-Bessen J, Signorovitch J, Yang M, Georgieva M, et al. Assessing the impact of open-label designs in patient-reported outcomes: Investigation in oncology clinical trials. JNCI Cancer Spectr 2023;7:pkad002. doi:10.1093/jncics/pkad002.

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

Otto, CM, Nishimura RA, Bonow RO et al. 2020 ACC/AHA Guideline for the Management of Patients with Valvular Heart Disease: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation 2021; 143(5): e72-e227. doi:10.1161/CIR.0000000000000923.

Pocock SJ, Ariti CA, Collieret TJ, et al. The Win Ratio: a New Approach to the Analysis of Composite Endpoints in Clinical Trials Based on Clinical priorities. Eur Heart J 2012;33:176-82. doi: 10.1093/eurheartj/ehr352.

Roydhouse JK, Fiero MH, Kluetz PG. Investigating Potential Bias in Patient-Reported Outcomes in Open-label Cancer Trials. JAMA Oncol 2019;5:457-458. doi: 10.1001/jamaoncol.2018.6205.

Schlotter F, Dietz MF, Stolz L. Atrial Functional Tricuspid Regurgitation: Novel Definition and Impact on Prognosis. Circ Cardiovasc Interv 2022;15:e011958. doi: 10.1161/CIRCINTERVENTIONS.122.011958.

Spertus JA, Jones PG, Sandhu AT, et al. Interpreting the Kansas City Cardiomyopathy Questionnaire in Clinical Trials and Clinical Care: JACC State-of-the-Art Review. J Am Coll Cardiol 2020;76:2379-2390. doi: 10.1016/j.jacc.2020.09.542.

Stone GW, Lindenfeld J, Abraham WT, et al. Transcatheter Mitral-Valve Repair in Patients with Heart Failure. N Engl J Med 2018; 379:2307-2318. doi: 10.1056/NEJMoa1806640

Tack M. Problems with the MetaBLIND study: An examination of data on blinding patients in trials with patient-reported outcomes. J Health Psychol 2023; 28:861-881. doi: 10.1177/13591053211059391.

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.

Zoghbi WA, Adams D, Bonow RO, et al. Recommendations for Noninvasive Evaluation of Native Valvular Regurgitation: A Report from the American Society of Echocardiography Developed in Collaboration with the Society for Cardiovascular Magnetic Resonance. J Am Soc Echocardiogr 2017;30(4):303-371. doi:10.1016/j.echo.2017.01.007

11 Appendix

Win-Ratio Analysis

In the win-ratio analysis of the primary endpoint, each patient from the device group was compared with each patient from the control group in the hierarchy of the primary endpoint composite. The pairwise comparison will move to the next hierarchy level (if any left), only when it is a tie at the current hierarchy level. The outcome of each pairwise comparison can be classified into one of the following categories:

(1) The TriClip patient had tricuspid valve surgery or died first.
(2) The control patient had tricuspid valve surgery or died first.
(3) The TriClip patient experienced more HF hospitalizations.
(4) The control patient experienced more HF hospitalizations.
(5) The TriClip patient, but not the control patient, had an improvement of ≥15 points in KCCQ score from baseline.
(6) The control patient, but not the TriClip patient, had an improvement of ≥15 points in KCCQ score from baseline.
(7) None of the above (i.e., a tie).

Let N_1, N_2, N_3, N_4, N_5, N_6, N_7 be the number of pairs in categories (1), (2), (3), (4), (5), (6), and (7), respectively. The total number of "winners" for the device group is: $N_W = N_2 + N_4 + N_5$, and the total number of "losers" for the device group is: $N_L = N_1 + N_3 + N_6$. The "win ratio" is defined as the total number of "winners" divided by the total number of "losers," i.e., $R_W = N_W/N_L$.