A Landmark Randomized Clinical Trial of Transcatheter Repair for Tricuspid Regurgitation

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

March 4, 2023
Disclosures
Paul Sorajja, MD

• Consulting or Advisory Board: 4C Medical, Abbott Structural, Anteris, Boston Scientific, Edwards Lifesciences, Foldax, Medtronic, Phillips, Siemens, Shifamed, VDyne, WL Gore, xDot

• Institutional Research: Abbott Structural, Boston Scientific, Edwards Lifesciences, Medtronic

• National P.I.: EXPAND II, Highlife (US), SUMMIT-MAC, SOAR-EFS, TRILUMINATE Pivotal, VISTA
Tricuspid Regurgitation

- Tricuspid regurgitation is common, and associated with impaired survival and poor quality-of-life
- Diuretics is the main therapy, with surgery for selected patients and often at high operative risk
- Limited data exist in right-sided valvular disease, and knowledge is often inferred from left-sided understanding
- Transcatheter tricuspid therapies have recently emerged, but their benefit has not been studied in a randomized, controlled clinical trial
The TRILUMINATE Pivotal Trial is designed to evaluate the safety and effectiveness of transcatheter tricuspid repair with the TriClip™ device in symptomatic patients with severe tricuspid regurgitation who are intermediate or greater estimated risk for mortality with tricuspid valve surgery.
## Study Leadership

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

### Anatomic Eligibility Committee
- **Anita Asgar**  
  Montreal Heart Institute
- **Brian Whisenant**  
  Intermountain Medical Center
- **Gagan Singh**  
  UC - Davis Medical Center
- **Gilbert Tang**  
  Mount Sinai Hospital
- **Hursh Naik**  
  Arizona CV Research Center
- **M. Azeem Latib**  
  Montefiore Medical Center
- **Marta Sitges**  
  Hospital Clinic Barcelona
- **Matthew Price**  
  Scripps Health
- **Moody Makar**  
  Cedars-Sinai Medical Center
- **Neil Fam**  
  St. Michael's Hospital
- **Paul Sorajja**  
  Minneapolis Heart Institute
- **Philipp Lurz**  
  Universität Leipzig
- **Ralph Stephan**  
  University Medicine of the Johannes Gutenberg University Mainz
- **von Bardeleben**  
  Gutenberg University Mainz
- **Rebecca Hahn**  
  New York-Presbyterian/CUMC
- **Richard Bae**  
  Minneapolis Heart Institute
- **Saibal Kar**  
  Los Robles Medical Center
- **Scott Lim**  
  University of Virginia Medical Center
- **Susheel Kodali**  
  New York-Presbyterian/CUMC
- **Tom Smith**  
  UC Davis

### Patient Management Eligibility Committee
- **Andrew Sauer**  
  Saint Luke's Health System
- **Sandhya Murthy**  
  Montefiore Medical Center
- **Raymond Benza**  
  Ohio State University
- **Ulrich Jorde**  
  Montefiore Medical Center

### Echocardiographic Core Lab
- **Rebecca Hahn**  
  Cardiovascular Research Foundation
- **Nadira Hamid**  
  Cardiovascular Research Foundation
TriClip™ G4 Delivery System

F/E KNOB
Flexes and extends delivery catheter to steer down to the valve plane

S/L KNOB
Enables movement in septal or lateral direction

+/- KNOB
Provides the height needed above the valve plane

DISTAL CURVE
Anatomically designed for direct access to the valve

CONTROLLED GRIPPER ACTUATION
Ability to optimize leaflet grasping if needed

4 CLIP SIZES
Broad range of sizes for tailored treatment

G4 NT
4 mm
G4 NTW
6 mm

G4 XT
4 mm
G4 XTW
6 mm

NTW/XTW 50% WIDER IN THE GRASPING AREA

G4 NTW
6 mm
G4 XTW
6 mm
Study Enrollment Criteria

**Key Inclusion Criteria**

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

**Key Exclusion Criteria**

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

**Subject Selection**
Symptomatic, severe TR and at intermediate or greater risk for TV surgery

- YES
  - Subject meets inclusion/exclusion criteria?
- NO
  - Screen Failure

**Echo Core Lab**
TR Severity Confirmed?

- YES
  - Eligibility Committees
    - Confirm optimized medical therapy and valve anatomy clippable
  - Ability to reduce TR by 1 grade?
    - YES
      - Single-Arm
    - NO
      - NO
- NO
  - Screen Failure

**Eligibility Committees**

**Randomize 1:1**

- YES
  - TriClip Device (N=175)
    - Completed 12 Month F/U
  - Medical Therapy (N=175)
    - Completed 12 Month F/U
- NO
  - NO
  - NO
  - NO
## Endpoints and Analysis

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

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

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

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

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

Paired Analyses

Baseline

30-day

1-year

Device (n=173)

Control (n=165)

Device (n=161)

Control (n=146)

Device (n=136)

Control (n=125)

Device (n=136)

Control (n=125)

Device (n=136)

Control (n=125)

Trace/Mild

Moderate

Severe/Massive/Torrential

Baseline

30-day

1-year

87.0%

p<0.0001

88.9%

5.6%
Primary Endpoint

Finkelstein-Schoenfeld Analysis

Win ratio, 1.48 (1.06, 2.13), p=0.02

TriClip™ therapy demonstrated superiority to medical therapy driven by improvement in KCCQ

p<0.0001
Individual Component Analysis

1st Component:
Mortality or TV Surgery

2nd Component:
Heart Failure Hospitalization

Device 90.6%

Control 89.4%

Device 85.1%

Control 87.9%

p=0.75

p=0.41
Quality-of-life Improvement

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

![Bar chart showing proportion of patients improved by different KCCQ change levels.](chart.png)
Relationship between TR and Quality of Life

**Residual TR grade at 1-yr**

- Moderate or less (n=133) - 16
- Severe/Massive/Torrential (n=149) - 4

**TR severity change, baseline to 1-yr**

- Worsens (n=46) - 0
- No change (n=67) - 2
- 1 grade (n=35) - 6
- ≥2 grade (n=125) - 18
## Hierarchical Secondary Endpoints

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

<sup>1</sup> MAE Performance Goal 90%

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

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

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

†Attempted procedure population (3 subjects randomized to Device withdrew consent prior to index procedure)

#Defined as bleeding ≥ Type 3 based on a modified Bleeding Academic Research Consortium (BARC) definition

*SLDA and embolization evaluated through 30-day follow-up

^Assessed through adverse event reporting
Limitations

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

• TR was reduced by TriClip therapy to moderate or less in 87%, vs. only 4.8% for the control group, and reduction was sustained to 1-year follow-up

• The primary endpoint was met (p=0.02) demonstrating device superiority, driven mainly by significant improvement in QOL

• Degree of TR reduction was related to degree of improvement in QOL

• The 30-day MAE rate was only 1.7%, and death and pacemaker implant each occurred in 0.6%

• Survival free of mortality and TV surgery was high at 1 year in both groups (~90%)
Conclusions

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

Paul Sorajja, M.D., Brian Whisenant, M.D., Nadira Hamid, M.D., Hursh Naik, M.D., Raj Makkar, M.D., Peter Tadros, M.D., Matthew Price, M.D., Gagan Singh, M.D., Neil Fam, M.D., Saibal Kar, M.D., Jonathan G. Schwartz, M.D., Shamir Mehta, M.D., Richard Bae, M.D., Nishant Sekaran, M.D., Travis Warner, M.D., Moody Makar, M.D., George Zorn, M.D., Erin Spinner, Ph.D., Phillip M. Trusty, Ph.D., Raymond Benza, M.D., Ulrich Jorde, M.D., Patrick McCarthy, M.D., Vinod Thourani, M.D., Gilbert H.L. Tang, M.D., Rebecca Hahn, M.D., and David H. Adams, M.D., for the TRILUMINATE Investigators*