Clinical Considerations for Edwards Mitral and Tricuspid Transcatheter Therapies

Jeffrey J. Popma, MD
Professor of Medicine
Harvard Medical School
Director, Interventional Cardiology
Beth Israel Deaconess Medical Center
Boston, MA
Conflict of Interest Statement

Over the past year, I have received the following:

Institutional Grants: Medtronic, Boston Scientific, Abbott Vascular, Cook, Edwards

Medical Advisory Board: Boston Scientific
## Transcatheter Mitral Valve Therapies

<table>
<thead>
<tr>
<th>Annular Reduction</th>
<th>Individually Adjustable Clasps and Spacer</th>
<th>Valve Replacement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardioband</td>
<td>PASCAL</td>
<td>CardiAQ-Edwards</td>
</tr>
<tr>
<td>ACTIVE</td>
<td>CLASP</td>
<td>EFS RELIEF</td>
</tr>
<tr>
<td>FMR</td>
<td>DMR/FMR</td>
<td>DMR/FMR</td>
</tr>
</tbody>
</table>

Cardioband Mitral Repair System: Devices placed on the European market meeting the essential requirements referred to in Article 3 of the Medical Device Directive 93/42/EEC bear the CE marking of conformity. Manufactured by Valtech Cardio Ltd. Other: CAUTION: Non CE marked device. Not available for commercial use until validly CE marked. CAUTION: Exclusively for clinical investigations. To be used by qualified investigators only. Not available for commercial use until validly CE marked. Not approved for sale in any country.
Clinical Considerations

• Functional MR clinical studies performed on the background of guideline directed medical therapy (GDMT) and compared with GDMT alone (or surgery with GDMT)

• Core Lab echocardiographic/CT screening

• Patient functional status an important consideration
  - Not too sick (NYHA Class IV) or extreme risk
  - Not too healthy (NYHA Class II)
  - Need to suffer with MR to show benefit

• Clinical trial endpoints to include functional indices of benefit – i.e., re-hospitalization, 6MWT, QoL (measured as an improvement over baseline)
Edwards Cardioband Mitral Repair System

- Mitral annular repair by **transseptal** approach
- Allows for a **tailored approach for each patient**
- Delivers significant and consistent **MR reduction**

CE Mark Approval Received | The ACTIVE Trial Enrolling in the U.S.

Devices placed on the European market meeting the essential requirements referred to in Article 3 of the Medical Device Directive 93/42/EEC bear the CE marking of conformity. Manufactured by Valtech Cardio Ltd.
Annular reduCtion for Transcatheter Treatment of Insufficient Mitral ValvE (ACTIVE): Transcatheter Mitral Valve Repair with Edwards Cardioband System and GDMT vs. GDMT alone in Patients with FMR and Heart Failure

Study Chairman: Mark Reisman, MD University of Washington

Principal Investigators: Brian Whisenant, MD Intermountain Health
Vinod Thourani, MD Medstar

Study Device: Edwards Cardioband System

Study Design: Multicenter, randomized, parallel assignment
randomised 2:1 to Edwards Cardioband mitral with GDMT v. GDMT alone

Number Patients: 375 patients

Inclusion Criteria:
- Clinically significant functional MR
- NYHA Class II-IV symptoms
- Hospitalized in past year or elevated BNP

www.clinicaltrials.gov Identifier NCT03016975
Annular reduCtion for Transcatheter Treatment of Insufficient Mitral Valve (ACTIVE): Transcatheter Mitral Valve Replacement with Edwards Cardioband System and GMDT vs. GMDT alone in Patients with FMR and Heart Failure

Exclusion Criteria
- Degenerative MR
- Severe mitral annular calcification
- Other severe valve disorders
- Mitral valve anatomy which may preclude proper Edwards Cardioband deployment

Primary Endpoint
- Co Primary Endpoints
  - Prevalence of MR ≤ 2+ AND
  - Hierarchical comparison of device and control for the time to cardiovascular death, number of heart failure hospitalizations, improvement in 6 MWT (in meters) and KCCQ at one year

Status
- Enrolling

www.clinicaltrials.gov Identifier NCT03016975
Edwards PASCAL Mitral Repair System

- Transseptal mitral leaflet repair by using *individually adjustable clasps* to place a *spacer* between the native mitral valve leaflets
- Designed for *intuitive delivery* and *procedural simplicity*

Compassionate Use FIH Experience | The CLASP Study Enrolling

CAUTION: EDWARDS PASCAL Mitral Repair System is a non CE marked device. Not available for commercial use until validly CE marked.
CAUTION: Exclusively for clinical investigations. To be used by qualified investigators only. Not available for commercial use until validly CE marked. Not approved for sale in any country.
Compassionate use of the PASCAL transcatheter mitral valve repair system for patients with severe mitral regurgitation: a multicentre, prospective, observational, first-in-man study

The CLASP Study: Edwards PASCAL Transcatheter Mitral Valve Repair System Study

Australia, Canada Investigators: Darren Walters, MD; Martin Ng, MD; John Webb, MD; Gideon Cohen, MD; Neil Fam, MD

US Principal Investigators: Ted Feldman, MD Northshore Medical Center; Robert Smith, MD Baylor Plano Medical Center

Study Device: Edwards PASCAL Transcatheter Mitral Valve Repair System

Study Design: Multicenter, prospective, single arm, non randomized

Inclusion Criteria:
- NYHA Class ≥ II or greater despite OMT
- Clinically significant MR (moderate-severe or severe) confirmed by TTE and TEE
- Patient able to perform 6 MWT
- Primary jet is non commissural, or insignificant
- MVA ≥ 2.0 cm² as measured by planimetry

www.clinicaltrials.gov Identifier NCT03170349
The CLASP Study: Edwards PASCAL Transcatheter Mitral Valve Repair System Study

<table>
<thead>
<tr>
<th>Primary Endpoint</th>
<th>Hierarchical composite of all-cause mortality or recurrent heart failure hospitalizations at 6 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Secondary Endpoints</td>
<td></td>
</tr>
<tr>
<td>• The hierarchical composite of all cause mortality or recurrent hospitalization at 30 days→1 year, annual</td>
<td></td>
</tr>
<tr>
<td>• MR reduction 30 days→1 year, annual</td>
<td></td>
</tr>
<tr>
<td>• All cause mortality at 30 days→1 year, annual</td>
<td></td>
</tr>
<tr>
<td>• Recurrent Hospitalization 30 days→1 year, annual</td>
<td></td>
</tr>
<tr>
<td>• $\Delta$ in 6 MWT distance at 30 days→1 year, annual</td>
<td></td>
</tr>
</tbody>
</table>

Status: Enrolling

www.clinicaltrials.gov Identifier NCT03170349
CardiAQ-Edwards TMVR System, Focused on Transseptal Delivery

- Mitral valve replacement by transcatheter approach
- Unique anchoring mechanism uses native valve anatomy
- Experience providing key learnings

US Early Feasibility Study Enrolling | The RELIEF Trial Enrolling

CAUTION: CardiAQ-EDWARDS Transcatheter Mitral Valve Replacement System is a non CE marked device. Not available for commercial use until validly CE marked. CAUTION: Exclusively for clinical investigations. To be used by qualified investigators only. Not available for commercial use until validly CE marked. Not approved for sale in any country.
The RELIEF Trial: REduction or eLimization of mItral rEgurgitation in Degenerative or Functional Mitral Regurgitation With the CardiAQ-Edwards™ Transcatheter Mitral Valve

Principal Investigators

Lars Sondergaard, MD; Jian Ye, MD; John Webb, MD; Dr. Mark Peterson, MD; Dr. Neil Fam, MD; Eric Horlick, MD; Mark Osten, MD; Francois Dagenais, MD; Eric Dumont, MD; Susanne Holme, MD; Ottavio Alfieri, MD; Antonio Colombo, MD; Gian Paolo Ussia, MD; Francesco Romeo, MD; Nico van Mieghem, MD; Arie Pieter Kappetein, MD; Thomas Modine, MD; Arnaud Sudre, MD; Thomas Walther, MD; Helge Möllmann, MD; Volkmar Falk, MD; Jörg Kempfert, MD; Hendrik Treede, MD; Ulrich Schäfer, MD; Stephan Baldus, MD; Thorsten Wahlers, MD; Stephan Windecker, MD; Thierry Carrel, MD

Study Device

CardiAQ-Edwards Transcatheter Mitral Valve Replacement System

Study Design

Multicenter, prospective, single arm, non randomized

www.clinicaltrials.gov Identifier NCT02722551
The RELIEF Trial: REduction or eLimination of mItral rEgurgitation in Degenerative or Functional Mitral Regurgitation With the CardiAQ-Edwards™ Transcatheter Mitral Valve

**Inclusion Criteria**
- NYHA ≥ II
- Moderate/severe or severe mitral regurgitation
- Prohibitive risk for open-heart surgery
- Meets anatomical criteria

**Primary Endpoints**
- Freedom from major adverse cardiac and cerebrovascular events MACCE at 30 days; all-cause mortality, myocardial infarction, stroke, renal failure, and conversion to surgery per MVARC definitions
- Freedom from individual adverse events at 30 days; % Freedom from individual adverse events

**Status**
- Enrolling

**www.clinicaltrials.gov**
Identifier NCT02722551
Early Feasibility Study of the CardiAQ Transcatheter Mitral Valve Implantation (TMVI) System (Transfemoral and Transapical Delivery Systems) for the Treatment of Moderate to Severe Mitral Regurgitation

Study Chairman
Howard Herrmann, MD University of Pennsylvania

Principal Investigators
Robert Guyton, MD Emory University
James Hermiller, MD St. Vincent Medical Center

Phase
Early Feasibility Study – 20 patients

Study Device
CardiAQ-Edwards TMVR System

Study Design
Multicenter, prospective, single arm, non randomized

Inclusion Criteria
• Clinically significant, symptomatic mitral regurgitation
• High Risk for open-heart surgery
• Meets anatomic criteria

Exclusion Criteria
• Unsuitable anatomy
• Prohibitively high risk

www.clinicaltrials.gov Identifier NCT02718001
Early Feasibility Study of the CardiAQ Transcatheter Mitral Valve Implantation (TMVI) System (Transfemoral and Transapical Delivery Systems) for the Treatment of Moderate to Severe Mitral Regurgitation

Primary Endpoint

Safety assessed by freedom from device or procedure-related adverse events at 30 days

Secondary Endpoints

• NYHA functional class 30 days, 1 year, annually
• Number of patients with improved NYHA Class
• 6 Minute walk test 30 days, 1 yr, annually measured by an increase in baseline, m
• Reduction of MR Grade 30 days, 1 yr, annually
• Number of patients with reduction in MR

Status

Enrolling

www.clinicaltrials.gov Identifier NCT02718001
## Transcatheter Tricuspid Valve Therapies

<table>
<thead>
<tr>
<th>Annular Reduction</th>
<th>Spacer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardioband</td>
<td>FORMA</td>
</tr>
<tr>
<td>TRI-REPAIR</td>
<td>EFS SPACER</td>
</tr>
<tr>
<td>FTR</td>
<td>FTR</td>
</tr>
</tbody>
</table>

Maisano TVT2017  

Praz TVT2017  

---

CAUTION: Non CE marked device. Not available for commercial use until validly CE marked. CAUTION: Exclusively for clinical investigations. To be used by qualified investigators only. Not available for commercial use until validly CE marked. Not approved for sale in any country.
Unique Challenges in Tricuspid Treatment

• Functional regurgitation in > 90% of patients resulting from annular dilation (> 40 mm) in the SL diameter

• Thin leaflets with complex chordal structure – septal chordae directly insert into septum

• Often associated with PA hypertension and RV dilation and RV failure → limited prognosis

• Proximity to the AV node in Triangle of Koch and right coronary artery

• Echocardiographic imaging more difficulty

• Complicated by the presence of prior PPM
Edwards Cardioband Tricuspid Repair System

- Tricuspid annular reduction based on tricuspid morphology
- Same concept and similar implant technique used with the Edwards Cardioband mitral repair system

CAUTION: EDWARDS Cardioband Tricuspid Repair System is a non CE marked device. Not available for commercial use until validly CE marked.
CAUTION: Exclusively for clinical investigations. To be used by qualified investigators only. Not available for commercial use until validly CE marked. Not approved for sale in any country.
TRI-REPAIR: Tricuspid Regurgitation RePAIr With Cardioband Transcatheter System (TRI-REPAIR)

European Investigators
Alec Vahanian, MD; George Nickenig, MD; K-H Kuck, MD; Joachim Schofer, MD; Stephan Baldus, MD; RS von Bardeleben, MD; Jorg Hausleiter, MD; Azeem Latib, MD

Number Patients
30

Study Device
Edwards Cardioband repair system

Study Design
Multicenter, prospective, single arm

Inclusion Criteria
- Chronic functional tricuspid regurgitation with an annular diameter ≥ 40 mm with a systolic pulmonary pressure ≤ 60 mm Hg
- NYHA Class II-IVa despite GDMT
- LVEF ≥ 30%

www.clinicaltrials.gov  Identifier NCT02981953
**Primary Endpoint**
- Rate of MSAE and SADE at 30 days
- Successful access, deployment and positioning of the Cardioband device
- Change in septolateral dimension at 30 days
- Septolateral dimension reduction at procedure

**Secondary Endpoints**
- Change in TR grade, effective regurgitant orifice area (EROA) and regurgitant volume by echocardiography
- Changes in Tricuspid Annular Plane Systolic Excursion (TAPSE) over time
- Technical success
- Change in NYHA Class, 6 MWT, QOL, LVEF

www.clinicaltrials.gov Identifier NCT02981953
Edwards FORMA Tricuspid Repair System

Spacer
- Positioned within the regurgitant orifice
- Creates a platform for native leaflet coaptation
- Preserves underlying structure that reduces the gaps between leaflets

Rail
- Tracks Spacer into position
- Distally and proximally anchored

CAUTION: EDWARDS FORMA Tricuspid Repair System is a non CE marked device. Not available for commercial use until validly CE marked.
CAUTION: Exclusively for clinical investigations. To be used by qualified investigators only. Not available for commercial use until validly CE marked.
Not approved for sale in any country.
Early Feasibility Study of the Edwards FORMA Tricuspid Transcatheter Repair System

US Investigators

- Raj Makkar, MD
- Vasilis Babaliaros, MD
- Mackram Eleid, MD
- John Brown, MD
- Susheel Kodali, MD

Number Patients

- 30

Study Device

- Edwards FORMA tricuspid system

Study Design

- Multicenter, prospective, single arm

Inclusion Criteria

- Clinically significant, symptomatic NYHA Class II or greater
- Functional tricuspid regurgitation
- High risk for surgical tricuspid valve repair and risk/benefit favors use of an investigational device

www.clinicaltrials.gov

Identifier NCT02471807
Early Feasibility of the Edwards FORMA Tricuspid Transcatheter Repair System

Primary Endpoint
- Procedural Success at 30 days
- Device success and freedom from device or procedure related SAE

Secondary Endpoints
- Heart Failure Rehospitalization at 6 months, 1 yr
- Tricuspid Rehospitalization at 6 months, 1 yr
- Change in NYHA from baseline at 6 months, 1 yr
- Change in 6 MWT from baseline at 6 months, 1 yr
- Change in QOL from baseline at 6 months, 1 yr

www.clinicaltrials.gov Identifier NCT02471807
### Repair of Tricuspid Valve Regurgitation Using the Edwards Tricuspid Transcatheter Repair System (SPACER)

**Canada and EU Investigators**
- John Webb, MD; Eric Horlick, MD; Josep Rodes Cabau, MD; Thierry Lefèvre, MD; Helene Eltchaninoff, MD; Nicolas Dumontiel, MD; Franz-Josef Neumann, MD; Michael Laule, MD; Karl-Heinz Kuck, MD; Steffen Massberg, MD; Konstantinos Spargias, MD, PhD; Stephan Windecker, MD; Fabien Praz, MD

**Number Patients**
- 78

**Study Device**
- Edwards FORMA tricuspid system

**Study Design**
- Multicenter, prospective, single arm

**Inclusion Criteria**
- Clinically significant, symptomatic TR
- Functional TR
- NYHA Functional Class II or greater
- High surgical risk

**Identifier**
- NCT02787408

[www.clinicaltrials.gov](http://www.clinicaltrials.gov)
Primary Endpoint

- Mortality (cardiac) at 30 days compared to a literature derived Performance Goal based on high-risk surgical outcomes for tricuspid repair/replacement

Secondary Endpoints

- Heart Failure Rehospitalization at 6 months, 1 yr
- Tricuspid Rehospitalization at 6 months, 1 yr
- Change in NYHA from baseline at 6 months, 1 yr
- Change in 6 MWT from baseline at 6 months, 1 yr
- Change in QOL from baseline at 6 months, 1 yr

www.clinicaltrials.gov Identifier NCT02787408

Repair of Tricuspid Valve Regurgitation Using the Edwards TricuSPid TrAnsCatheter REpaiR System (SPACER)
Final Messages

• Rigorous transcatheter mitral and tricuspid clinical trial portfolio to expanded clinical evidence that includes assessments of patient oriented outcomes and functional status (e.g., re-hospitalization, 6MWT, QoL)

• Initial focus on symptomatic patients with moderate-severe or severe mitral or tricuspid regurgitation who are deemed to be at higher risk for surgery

• Gold standard for functional studies → GDMT

• (Evolving) morphology-based approach to device selection that will lead to patient-centered device selection to optimize long-term clinical outcomes