REDUCE-FMR: A Sham-Controlled Randomized Trial of Transcatheter Indirect Mitral Annuloplasty in Heart Failure Patients with Functional Mitral Regurgitation

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On behalf of the REDUCE-FMR Investigators
Financial Disclosures
Horst Sievert, MD

**Companies:**
4tech Cardio, Abbott, Ablative Solutions, Ancora Heart, Bavaria Medizin Technologie GmbH, Bioventrix, Boston Scientific, Carag, Cardiac Dimensions, Celonova, Cibiem, CGuard, Comed B.V., Contego, CVRx, Edwards, Endologix, Hemoteq, InspireMD, Lifetech, Maquet Getinge Group, Medtronic, Mitralign, Nuomao Medtech, Occlutech, pfm Medical, Recor, Renal Guard, Rox Medical, Terumo, Vascular Dynamics, Vivasure Medical, Venus, Veryan

**Relationships:** Consulting fees, travel expenses and study honoraria
REDUCE FMR – Background and Objective

- In patients with heart failure, FMR is associated with increased morbidity and mortality.
- Previous small studies with the Carillon device (AMADEUS\textsuperscript{1}, TITAN\textsuperscript{2}, and TITAN II\textsuperscript{3}) have shown evidence of reduced mitral regurgitation (MR) and left ventricle (LV) remodeling.
- The objective of REDUCE FMR was to demonstrate - in a sham-controlled randomized study - a decrease in quantitative MR with the Carillon device in heart failure patients with FMR.

\textsuperscript{1} Schofer et al. Circulation;120:326-333 \textsuperscript{2} Siminiak et al. EU J of Heart Failure (2012 14, 931-938. \textsuperscript{3} Lipiecki et al. Open Heart 2016;3:3000411
The Carillon Mitral Contour System – an Indirect Annuloplasty Device

Distal Anchor (in great cardiac vein)

Proximal Anchor (in coronary sinus)

Anchor sizes are individually selected for each patient

Trans-jugular Delivery System

Caution: Investigational device. Limited by Federal (U.S) law to investigational use.
Carillon Device Deployment and Cinching

- Distal Anchor Deployed
- Coronary Sinus Angiogram to Define the Landing Zone
- Tension Applied & Proximal Anchor Deployed
Case Example of MR Reduction after Carillon

Baseline: MR 3+*

At 12 Months: MR 1+*

*per core lab assessment
REDUCE FMR – Intended Randomization and Primary Endpoint

120 patients at 31 sites in Europe and Australia, and New Zealand

Sham-controlled randomized (3:1) 120 pts

- Treatment arm: 90 pts
- Control arm: 30 pts

Primary endpoint (ITT):
change in regurgitant volume (RV)
assessed by a blinded echo core lab at 1-year
Challenges Faced with the REDUCE FMR Study

- First blinded sham-controlled trial in the field of valve interventions
- Sham-controlled studies are typically difficult to enroll
- Very few prior valve trials have used a mechanistic endpoint utilizing echo based parameters
- We know from clinical experience:
  - The Carillon device usually reduces, but rarely eliminates MR
  - Acute results can be moderate with results improving over time (LV remodeling)

All these challenges worked against a positive outcome of this trial
REDUCE FMR – Study Administration

**Imaging Core Lab**
C5 Research
Cleveland Clinic Foundation
Cleveland, Ohio

**Data Safety Monitoring Board**
Prof. Martin Cowie
Prof. Emmanuel Lagarde
Prof. Keith Oldroyd

**Clinical Events Committee**
Prof. Andreas Baumbach
Dr. Robert Byrne
Dr. John Parissis

**Imaging Training and Standards:** Sonographer-focused technical training on echo quality and protocol requirements. Assessment of patient inclusion criteria was done site based

**Site Training:** Interventionists trained on device and protocol. Proctors were on-site for case support

**Core Lab Image Read Standards:** After initial quality review by core lab, the echo images were read in consensus format for MR grade and over-read for quantitative measures

**100% Source Data Monitoring:** All data monitored by independent CROs
REDUCE FMR – Investigator Sites
(Top enrollers in bold)

Australia
• Monash Health- R. Gooley and I. Meredith
• The Alfred Hospital- S. Duffy and D. Kaye
• Royal North Shore Hospital- R. Bhindi
• Royal Prince Alfred Hospital- M. Adams
• Flinders Medical Centre- C. De Pasquale
• The Prince Charles Hospital- C. Raffel and D. Walters

Czech Republic
• University Hospital Olomouc- M. Táborský
• Na Homolce Hospital- P. Neužil
• Institute for Clinical and Experimental Medicine (IKEM)- J. Kautzner

France
• Clinique du Millénaire- C. Piot
• Pole Santé République- J. Lipiecki
• Hospital Georges Pompidou- C. Spaulding
• Hospital Charles Nicolle- E. Durand
• Clinique Saint Hilaire- J. Berland
• Rangueil University Teaching Hospital- D. Carrie
• Hopital Prive Saint Martin- J. Morelle

Germany
• CardioVascular Center Frankfurt- H. Sievert
• Sana Kliniken Lübeck- J. Weil
• Hospital Frankfurt Höchst- H. Hink
• Klinikum Lüdensheid- B. Lemke
• University Hospital Freiburg- J. Reinhöl
• Charité Universitätmedizin Berlin- U. Landmesser
• Augusta Kranken Anstalt gGmbH Bochum- M. Prull
• Elisabeth Krankenhaus Recklinghausen- T. Lawo
• Universitätsklinikum Frankfurt- S. Fichtlscherer

Netherlands
• University Hospital Maastricht- J. Vainer

New Zealand
• Auckland City Hospital- P. Ruygrok

Poland
• HCP Medical Center- T. Siminiak

United Kingdom
• Leeds Teaching Hospital NHS Trusts- C. Malkin and K Witte
• Harefield Hospital- M. Mason
• Freeman Hospital- M. Egred
# REDUCE FMR – Analysis Populations and Endpoints

## Intention to Treat (ITT): As randomized regardless of implantation status

## As-Treated (AT): All patients with device implants at end of procedure

## Per Protocol (PP): As-treated and patients who met inclusion and exclusion criteria

### Primary Endpoint (Efficacy)
- Change in regurgitant volume (RV) at 1-year assessed by the blinded echo core lab (ITT analysis)

### Secondary Endpoints
- **Efficacy**
  - Heart Failure Hospitalizations at 1-year
  - Change in regurgitant volume (RV) at 1-year (AT and PP analyses)
  - Change in LVEDV and LVESV (baseline to 1-year)
- **Safety**
  - Major Adverse Events at 1-month and 1-year, defined as: death, MI, device embolization, vessel perforation requiring intervention, PCI or surgery associated with device failure
REDUCE FMR – Sham Control and Study Blinding

• All patients were heavily sedated, blindfolded and received noise cancelation

• Randomization was done after coronary sinus angiogram (for study eligibility)

• Echo core lab was blinded to patient randomization as well as timing of echoes

• Patient questionnaires on blinding at each follow-up visit
  – patients indicated uncertainty of treatment 96% of the time

• Assessors were blinded to patient randomization through 1-year follow-up assessment
## Key Selection Criteria

### Inclusion

- Dilated ischemic or non-ischemic cardiomyopathy
- Functional mitral regurgitation moderate to severe defined as: 2+, 3+ or 4+
- NYHA II, III, or IV
- LVEF ≤ 50%
  - 40-50% LVEF must be MR3+/4+ AND NYHA III/IV
- LVEDD > 55mm, or LVEDD/BSA > 3.0 cm/m²
- Stable heart failure medication for at least 3-months

### Exclusion

- Hospitalization in past 3-months due to MI, CABG, or unstable angina
- Hospitalization in past 30 days for coronary angioplasty or stent placement
- Expected to require any cardiac surgery within 1-year
- **Presence of coronary artery stent** under the CS/GCV, in the implant target zone
- Severe **mitral annular calcification**
- Significant organic mitral valve pathology
135 Screened Patients

120 Patients Randomized

15 patients excluded (i.e. angiographic criteria or coronary sinus access)

Treatment
N=87

Sham Control
N=33

1 Month
N=33

6 Months
N=28

12 Months
N=24

2 deaths
3 withdrawals

2 deaths
3 withdrawals

3 deaths
1 missed
3 withdrawals

3 deaths
1 missed
3 withdrawals

Implanted
N=73

Non-Implanted*
N=14

1 Month
N=69

1 Month
N=14

6 Months
N=64

6 Months
N=12

12 Months
N=59

12 Months
N=11

2 withdrawals

1 death

* Non-implants
  8 compromised coronary flow
  2 coronary sinus vessel dissections
  2 anchor slippage
  1 no device size available
  1 no attempt made (randomization error)

Treatment Group Attrition: 13% deaths (n=11) 5% withdrawals (n=4)

Control Group Attrition: 15% deaths (n=5) 12% withdrawals (n=4)
REDUCE FMR – Availability 1-Year Echoes

<table>
<thead>
<tr>
<th>Subject Status:</th>
<th>Implant N=73</th>
<th>Non-Implant N=14</th>
<th>Control N=33</th>
<th>Totals N=120</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>10 (14%)</td>
<td>1 (7%)</td>
<td>5 (15%)</td>
<td>16 (13%)</td>
</tr>
<tr>
<td>W/D Alt. – Therapy</td>
<td>1 (1%)</td>
<td>2 (14%)</td>
<td>4 (12%)</td>
<td>7 (6%)</td>
</tr>
<tr>
<td>W/D – Consent</td>
<td>3 (4%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>3 (3%)</td>
</tr>
<tr>
<td>Subjects Available for Echo</td>
<td>59 (81%)</td>
<td>11 (79%)</td>
<td>24 (73%)</td>
<td>94 (78%)</td>
</tr>
<tr>
<td>Unreadable Echo</td>
<td>10 (14%)</td>
<td>1 (7%)</td>
<td>7 (21%)</td>
<td>18 (15%)</td>
</tr>
<tr>
<td>Paired Echoes</td>
<td>49 (67%)</td>
<td>10 (71%)</td>
<td>17 (52%)</td>
<td>76 (63%)</td>
</tr>
<tr>
<td>RV Below Lower Quantification Limit*</td>
<td>4 (5%)</td>
<td>0 (0%)</td>
<td>4 (12%)</td>
<td>8 (7%)</td>
</tr>
<tr>
<td>Paired Echo for Analysis</td>
<td>45 (62%)</td>
<td>10 (71%)</td>
<td>13 (39%)</td>
<td>68 (57%)</td>
</tr>
</tbody>
</table>

- Paired echo analysis at 1-year available in 57% of patients
- Lower than expected, but comparable to recently published MITRA-FR Trial (43%)\(^1\) that encountered similar issues quantifying regurgitant volume in FMR\(^1\)

\(*\text{Quantitative assessments for patients with less than 30ml of regurgitant volume are difficult unless echoes are very precise.}\)

\(^1\) Obadia et al. New England Journal of Medicine, August 27, 2018 DOI: 10.1056/NEJMoa1805374
REDUCE FMR – Clinical Baseline Demographics (ITT)

<table>
<thead>
<tr>
<th></th>
<th>Treatment (N=87)</th>
<th>Control (N=33)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>70.1 ± 9.7</td>
<td>69.1 ± 8.9</td>
<td>0.59</td>
</tr>
<tr>
<td>Male</td>
<td>72.4% (63/87)</td>
<td>72.7% (24/33)</td>
<td>0.97</td>
</tr>
<tr>
<td>BMI</td>
<td>26.7 ± 5.3</td>
<td>28.1 ± 6.2</td>
<td>0.22</td>
</tr>
<tr>
<td>Etiology – Ischemic</td>
<td>67.8% (59/87)</td>
<td>63.6% (21/33)</td>
<td>0.67</td>
</tr>
<tr>
<td>Prior MI</td>
<td>49.4% (43/87)</td>
<td>51.5% (17/33)</td>
<td>0.84</td>
</tr>
<tr>
<td>NYHA Class</td>
<td></td>
<td></td>
<td>0.92</td>
</tr>
<tr>
<td>II</td>
<td>44.8% (39/87)</td>
<td>48.5% (16/33)</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>52.9% (46/87)</td>
<td>51.5% (17/33)</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>2.3% (2/87)</td>
<td>0.0% (0/33)</td>
<td></td>
</tr>
<tr>
<td>Median NT-BNP (IRQ) -ng/l</td>
<td>2505 (1085-4432)</td>
<td>2410 (1079-5283)</td>
<td>0.33</td>
</tr>
<tr>
<td>Atrial Fibrillation</td>
<td>58.6% (51/87)</td>
<td>60.6% (20/33)</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>Prior HFH in last year</td>
<td>44.8% (39/87)</td>
<td>45.5% (15/33)</td>
<td>&gt;0.99</td>
</tr>
</tbody>
</table>

- Most patients were NYHA III
- Almost half of the patients were NYHA II – less sick than in most other heart failure trials
<table>
<thead>
<tr>
<th></th>
<th>Treatment (N=87)</th>
<th>Control (N=33)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEF (%)</td>
<td>33.5 ± 8.9</td>
<td>37.1 ± 8.7</td>
<td>0.09</td>
</tr>
<tr>
<td>LVEDD (cm)</td>
<td>6.4 ± 0.9</td>
<td>6.4 ± 0.9</td>
<td>0.92</td>
</tr>
<tr>
<td>EROA (- m²)</td>
<td>25 ± 15</td>
<td>24 ± 14</td>
<td>0.56</td>
</tr>
<tr>
<td>Regurgitant Volume (ml)</td>
<td>39.4 ± 23.5</td>
<td>39.3± 23.7</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>MR Grade</td>
<td></td>
<td></td>
<td>0.54</td>
</tr>
<tr>
<td>1</td>
<td>28.7% (25/87)</td>
<td>32.3% (10/31)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>39.1% (34/87)</td>
<td>25.8% (8/31)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>26.4% (23/87)</td>
<td>35.5% (11/31)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>5.7% (5/87)</td>
<td>6.5% (2/31)</td>
<td></td>
</tr>
</tbody>
</table>

- MR was less severe than planned: baseline RV was 39 ml, 30% had MR 1+
- Less sick patient population than in most other heart failure trials
## REDUCE FMR – Baseline HF Medications (ITT)

<table>
<thead>
<tr>
<th></th>
<th>Treatment (N=87)</th>
<th>Control (N=33)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE/ARB</td>
<td>78.2% (68/87)</td>
<td>81.8% (27/33)</td>
<td>0.66</td>
</tr>
<tr>
<td>ARNi</td>
<td>6.9% (6/87)</td>
<td>6.1% (2/33)</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>Beta Blockers</td>
<td>85.1% (74/87)</td>
<td>93.9% (31/33)</td>
<td>0.19</td>
</tr>
<tr>
<td>Any Diuretics</td>
<td>93.1% (81/87)</td>
<td>97.0% (32/33)</td>
<td>0.67</td>
</tr>
<tr>
<td>MRA- Diuretic</td>
<td>58.6% (51/87)</td>
<td>57.6% (19/33)</td>
<td>0.92</td>
</tr>
<tr>
<td>Loop- Diuretic</td>
<td>92.0% (80/87)</td>
<td>93.9% (31/33)</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>Anticoagulant (VKA or Xa inhibitors)</td>
<td>43.7% (38/87)</td>
<td>39.4% (13/33)</td>
<td>0.84</td>
</tr>
</tbody>
</table>

Patients had to be on a stable medication regimen for at least 3 months
## REDUCE FMR – Safety (MAE) at 1-Year (ITT)

<table>
<thead>
<tr>
<th></th>
<th>Treatment (N=87)</th>
<th>Control (N=33)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>30 Days</td>
<td>1-Year</td>
</tr>
<tr>
<td></td>
<td>Device Related</td>
<td>Procedure Related</td>
</tr>
<tr>
<td>Death</td>
<td>0% (0)</td>
<td>2.3% (2)*</td>
</tr>
<tr>
<td>MI</td>
<td>1.1% (1)</td>
<td>3.5% (3)*</td>
</tr>
<tr>
<td>Cardiac Perforation**</td>
<td>0% (0)</td>
<td>0% (0)</td>
</tr>
<tr>
<td>Device Embolism</td>
<td>0% (0)</td>
<td>0% (0)</td>
</tr>
<tr>
<td>Surgery or PCI related to device</td>
<td>0% (0)</td>
<td>0% (0)</td>
</tr>
</tbody>
</table>

**Cumulative MAE Rate**  
- Treatment: 16.1% (14)  
- Control: 18.2% (6)

* One death and two procedural MIs adjudicated as “possibly” related to device, however definitive relationship could not be established
** Of a cardiac structure (heart, artery and/or vein) leading to hemopericardium and requiring percutaneous or surgical intervention
Details of 30 day events

• 2 procedure related deaths within 30 days (2.3%)
  - Heart failure and renal failure
  - Troponin elevations but no device compression of a coronary artery
    • Both patients had baseline occluded circumflex arteries

• 3 myocardial infarctions (3.5%)
  - 1 with a device compression of an atrioventricular branch artery
    • no further sequelae and not heart failure hospitalizations over 12 months
  - 2 patients without coronary artery compression
    • significant troponin elevation
    • but no Q-wave infarctions
  - All 3 MI patients with complete 1 year follow-up. No significant change in EF

• There were no late myocardial infarctions in the device arm
REDUCE FMR – Primary Endpoint
Change in Regurgitant Volume (RV) at 1-year (ITT)

- 22% reduction in treatment group
- 8% increase in control group
- Absolute difference 10.4 ml

Primary Endpoint Met

P = 0.03

Mean RV Change – Paired data (ml)
REDUCE FMR – Primary Endpoint
Mean Regurgitant Volume (RV) at 1-year (ITT)

- All data, unpaired, at a noted follow-up point
- Separation between groups trends positively over time
- 10.6 ml separation between treatment and control at 1-year
REDUCE FMR – Predefined Secondary Analysis
Change in Regurgitant Volume RV at 1-Year (As Treated)

- As treated analysis excludes the 14 patients who were not implanted with the device
- The same statistical significance is observed
- Treatment effects are amplified when the non-implanted patients are removed from the treatment cohort
- MR 1+ patients remain in treatment group and negatively influenced overall improvements

Mean RV Change – Paired data (ml)

<table>
<thead>
<tr>
<th></th>
<th>Treatment</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=45</td>
<td>-7.5</td>
<td></td>
</tr>
<tr>
<td>N=13</td>
<td>3.3</td>
<td></td>
</tr>
</tbody>
</table>

P = 0.02
REDUCE FMR – Predefined Secondary Analysis
Change in Regurgitant Volume (RV) at 1-Year (Per Protocol)

- Per protocol analysis excludes all patients who did not meet protocol criteria (i.e. MR 1+, anatomical criteria, etc.)
- The same trending is observed between groups
- Treatment effects are highly amplified when there is adherence to the study design
- Due to smaller numbers statistical significance not quite met

P = 0.06
REDUCE FMR – Secondary Endpoint Analysis
Change in LVEDV and LVESV 1-Year (AT – As Treated)

- Secondary endpoints included change in LVEDV and LVESV at 1-year
- A volume reduction at 6-months and 12-months was observed in the treatment group
- The control group showed increased volumes at 6-months with further increased volumes at 1-year
REDUCE FMR – Secondary Endpoint Analysis
HF Hospitalizations (AT – As Treated)

**Freedom from 1st HF Hospitalization**

- The rate of recurrent HFH in the treatment group was approximately half that of the control group.
- At 1 year, almost 1-month benefit in total days alive without a HF related hospitalization was achieved.

<table>
<thead>
<tr>
<th></th>
<th>Treatment (n=73)</th>
<th>Control (n=33)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrent HFH (n/N)</td>
<td>11.0% (8/73)</td>
<td>21.2% (7/33)</td>
<td>0.23</td>
</tr>
<tr>
<td>Rate of total HF admissions per patient-year (with 95% confidence limits)</td>
<td>0.57 (0.39, 0.74)</td>
<td>0.73 (0.44, 1.03)</td>
<td>0.35</td>
</tr>
<tr>
<td>Days alive and without HF related hospitalization (mean days, range)</td>
<td>321 (10, 365)</td>
<td>292 (23, 365)</td>
<td>0.28</td>
</tr>
</tbody>
</table>
REDUCE FMR: Limitations

• The sample size of this sham-controlled randomized trial is too small to draw definitive conclusions on treatment effects of the secondary clinical endpoints (e.g. death, QoL and 6MWD)

• The frequency of MR 1+ (30%) in the ITT analysis population was unintended and negatively influenced overall improvements in regurgitant volumes in the treatment arm

• Echo follow-up assessments of quantitative MR proved to be difficult – further influencing treatment results
REDUCE FMR – Conclusions (1)

- Despite all the limitations, the primary endpoint, reduction in regurgitant volume (RV) at 1-year, was met.
- The reduction in RV was amplified in patients in whom the device was implanted (AT), and in the ‘intended’ patient population (PP).
- Safety was similar in the treatment vs. sham-controlled groups with a MAE at 1 year of 16.1% in the treatment group vs. 18.2% in the control group.
- Echo indicators of positive remodeling from LVESV and LVEDV were also observed in the as treated group (AT).
This sham-controlled study in FMR patients should inform future clinical research:

- Sham-controlled trials in valve therapy can be performed
- Careful echo pre-screening of patients by a core lab is necessary

The ongoing CARILLON FDA pivotal randomized FMR trial is sham-controlled, with echo pre-screening of MR severity, and is powered to a hierarchical endpoint which includes clinical endpoints.
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On behalf of the REDUCE-FMR Investigators