Safety and Efficacy of the Coronary Sinus Reducer in Patients with Refractory Angina: the COSIRA Trial

(Coronary Sinus Reducer for Treatment of Refractory Angina)

Stefan Verheye, MD
Cardiovascular Center, ZNA Middelheim, Antwerp, Belgium
On Behalf of the COSIRA Investigators
The Problem: Refractory Angina

Patients with obstructive CAD and myocardial ischemia, who can not be treated with revascularization, and despite optimal medical therapy have:

- Significant disability
- Limited quality of life
- Multiple medications
- Frequent hospital admissions

The prevalence of RA continues to increase
The Reducer

- An hour-glass shaped stent implanted in the coronary sinus (CS)
- Creates controlled narrowing to modulate flow and elevate CS pressure
- CS pressure elevation increases endocardial perfusion providing relief of ischemia and angina
Angiographic view after Reducer Implantation

The narrowing created at the center of the Reducer
Reducer: Mechanism of Action

The Reducer creates a slight increase in CS pressure which results in dilatation of the capillaries and arterioles and improves perfusion of ischemic sub-endocardial myocardium.

In the setting of obstructive CAD – increased CS pressure can lead to:

- Redistribution of collateral blood flow from non-ischemic into ischemic territories of the myocardium
- Redistribution of arterial blood from sub-epicardial to sub-endocardial vessels, with normalization of the endocardial/epicardial blood flow ratio
- Redistribution of arterial blood significantly reducing myocardial ischemia
COSIRA Trial

(\textit{CO}ronary \textit{SI}inus Reducer for Treatment of Refractory \textit{A}ngina)

\textbf{Aim:}

To examine whether implantation of the Reducer could effectively and safely improve angina symptoms in patients with obstructive CAD, CCS class 3 or 4, having concomitant evidence of reversible myocardial ischemia and unsuitable for revascularization
COSIRA Methods

Study oversight:
- Prospective, phase-II, randomized, double-blind, sham-controlled, multi-center clinical trial to test the safety and efficacy of the Reducer
  - 11 clinical centers
  - 104 patients

Blinding:
- Patients and physician assessing CCS class and SAQ were blinded to treatment group throughout the study period
- DSE and ETT core labs were blinded to treatment group
# COSIRA Sites & Investigators

<table>
<thead>
<tr>
<th>Center</th>
<th>Location</th>
<th>Investigator(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antwerp Cardiovascular Center, ZNA Middelheim</td>
<td>Antwerp, Belgium</td>
<td>Stefan Verheye, Nathalie Meyten</td>
</tr>
<tr>
<td>Montreal Heart Institute, Montreal</td>
<td>Montreal, Canada</td>
<td>E. Marc Jolicoeur, Serge Doucet, Jean-Francois Tanguay</td>
</tr>
<tr>
<td>Royal Infirmary of Edinburgh</td>
<td>Edinburgh, UK</td>
<td>Miles Behan, Neal Uren</td>
</tr>
<tr>
<td>Kristianstad Central Hospital</td>
<td>Kristianstad, Sweden</td>
<td>Thomas Pettersson</td>
</tr>
<tr>
<td>Bradford Royal Infirmary</td>
<td>Bradford, UK</td>
<td>Paul Sainsbury, Steven Lindsay</td>
</tr>
<tr>
<td>Kings College Hospital</td>
<td>London, UK</td>
<td>Jonathan Hill</td>
</tr>
<tr>
<td>ZOL Hospital</td>
<td>Genk, Belgium</td>
<td>Mathias Vrolix</td>
</tr>
<tr>
<td>University Medical Center Utrecht</td>
<td>Utrecht, Netherlands</td>
<td>Pierfrancesco Agostoni</td>
</tr>
<tr>
<td>Rigshospitalet</td>
<td>Copenhagen, Denmark</td>
<td>Thomas Engstrom</td>
</tr>
<tr>
<td>Ottawa Heart Institute</td>
<td>Ottawa, Canada</td>
<td>Marino Labinaz</td>
</tr>
<tr>
<td>Royal Brompton Hospital</td>
<td>London, UK</td>
<td>Ranil de Silva</td>
</tr>
</tbody>
</table>
COSIRA: Enrollment Flow Chart

Assessed for Eligibility
N = 166

Screening failures N=59

Angiographic Screening
N = 107

Angiographic Screening failures N=3

Randomization
N = 104

Reducer Group
N = 52

Did not receive Reducer N=2

Control Group
N = 52

Followed Up
N = 52

Followed Up
N = 52

Analyzed
N = 52

Analyzed
N = 52
**Primary Efficacy Endpoint:**
An improvement in ≥2 CCS grades from baseline to 6-month evaluation.

**Secondary Efficacy Endpoints:**
Change in the following ischemia parameters from baseline to 6-month evaluation:

- An improvement in ≥1 CCS grade
- Dobutamine ECHO Wall Motion Score Index (WMSI)
- Seattle Angina Questionnaire (SAQ) Score
- Total Exercise Duration (min), Time to ST Segment Depression (min), and Maximal ST Segment Depression (mm) by Exercise Tolerance Test (ETT)
**Technical Success**
Successful delivery and deployment of the Reducer to the intended site as assessed by the investigator

**Major Adverse Events (MAEs)**
A composite of cardiac death, major stroke, and MI
- Peri-procedural through hospital discharge, at 30-day, 3-month, and 6-month post-procedural evaluations
Key eligibility criteria included:

1. Symptomatic CAD with chronic refractory angina pectoris classified as CCS grade 3 or 4 despite attempted optimal medical therapy for 30 days prior to screening

2. Documented evidence of reversible myocardial ischemia attributed to the LCA system as demonstrated by Dobutamine Stress Echocardiography

3. LVEF >25%

4. Only patients deemed unsuitable for coronary revascularization were eligible to participate in the study as decided by the heart team upon reviewing the recent coronary angiography
Key exclusion criteria included:

1. Recent revascularization procedure
2. Recent acute coronary syndrome
3. Patients with permanent leads in the right heart (pacemakers or defibrillators)
4. Patients with high (≥15 mmHg) mean RA pressure
5. Tortuous, or aberrant CS, or CS with a diameter >13 mm
## COSIRA: Baseline Clinic Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Sham Control</th>
<th>Reducer</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>66.04±9.81</td>
<td>69.58±8.66</td>
<td>0.054</td>
</tr>
<tr>
<td>Gender male, n (%)</td>
<td>40 (77)</td>
<td>44 (85)</td>
<td>0.46</td>
</tr>
<tr>
<td>Previous MI, n (%)</td>
<td>30 (58)</td>
<td>27 (52)</td>
<td>0.69</td>
</tr>
<tr>
<td>Previous CABG surgery, n (%)</td>
<td>38 (73)</td>
<td>42 (81)</td>
<td>0.49</td>
</tr>
<tr>
<td>Previous PCI, n (%)</td>
<td>40 (77)</td>
<td>36 (69)</td>
<td>0.51</td>
</tr>
<tr>
<td>Hypercholesterolemia, n (%)</td>
<td>46 (88)</td>
<td>50 (96)</td>
<td>0.27</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>25 (48)</td>
<td>21 (40)</td>
<td>0.55</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>41 (79)</td>
<td>42 (81)</td>
<td>0.81</td>
</tr>
</tbody>
</table>
COSIRA: Results

Primary endpoint: CCS ≥ 2 class Improvement

35% (18/52) of the patients in the Reducer group vs. 15% (8/52) of patients in the sham-control group improved by ≥2 CCS classes (p = 0.024)
71% (37/52) of the patients in the Reducer group vs. 42% (22/52) of patients in the sham-control group improved by ≥1 CCS classes (p =0.003)
COSIRA: Results

**CCS Class Improvement**

Mean CCS Class change from baseline to 6M F/U

P = 0.001

Baseline

Reducer

Baseline 3.19

6 months 2.13

Control

Baseline 3.13

6 months 2.65

P = 0.001
COSIRA: Results

CCS Class at baseline and at 6-months
## COSIRA: Results

### Secondary endpoints

**SAQ Scores**
\[ \Delta \text{ in baseline – 6M F/U} \]

<table>
<thead>
<tr>
<th></th>
<th>Reducer</th>
<th>Control</th>
<th>Fold improvement</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Quality of Life</strong></td>
<td>18.5 (44%)</td>
<td>7.5 (16%)</td>
<td>2.75</td>
<td>0.03</td>
</tr>
<tr>
<td><strong>Anginal Stability</strong></td>
<td>18.6 (33%)</td>
<td>6.8 (17%)</td>
<td>2.53</td>
<td>0.1</td>
</tr>
<tr>
<td><strong>Anginal Frequency</strong></td>
<td>15.5 (35%)</td>
<td>11 (24%)</td>
<td>1.5</td>
<td>0.4</td>
</tr>
</tbody>
</table>

* Not powered for statistical significance
COSIRA: Results

Secondary endpoints

ETT Stress Test*

<table>
<thead>
<tr>
<th>Total Exercise Duration (sec)</th>
<th>Reducer</th>
<th>Control</th>
<th>Fold improvement</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>441</td>
<td>464</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6M F/U</td>
<td>500</td>
<td>467</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Improvement</td>
<td>59 (13%)</td>
<td>3 (1%)</td>
<td>13</td>
<td>0.07</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Time to 1mm ST depression</th>
<th>Reducer</th>
<th>Control</th>
<th>Fold improvement</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>385</td>
<td>437</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6M F/U</td>
<td>433</td>
<td>455</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Improvement</td>
<td>48 (13%)</td>
<td>18 (4%)</td>
<td>3.1</td>
<td>0.4</td>
</tr>
</tbody>
</table>

* Not powered for statistical significance
## COSIRA: Results

### Secondary endpoints

<table>
<thead>
<tr>
<th></th>
<th>Reducer</th>
<th>Control</th>
<th>Fold improvement</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stress WMSI</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>1.55</td>
<td>1.44</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6M F/U</td>
<td>1.34</td>
<td>1.32</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Improvement</td>
<td>0.21 (14%)</td>
<td>0.012 (8%)</td>
<td>1.7</td>
<td>0.2</td>
</tr>
<tr>
<td><strong>Stress Modified LCA WMSI</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>1.50</td>
<td>1.30</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6M F/U</td>
<td>1.31</td>
<td>1.27</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Improvement</td>
<td>48 (13%)</td>
<td>0.03 (2.3%)</td>
<td>5.6</td>
<td>0.06</td>
</tr>
</tbody>
</table>

* Not powered for statistical significance
COSIRA: Results

Safety

Technical success rate: 96.2%
Procedural success rate: 100%

<table>
<thead>
<tr>
<th>Major Adverse Events</th>
<th>Reducer</th>
<th>Sham-Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac Death</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>MI</td>
<td>2*</td>
<td>3</td>
</tr>
</tbody>
</table>

*All MAEs with the exception of one periprocedural NSTEMI were adjudicated by the CEC as not related to the device or the index procedure.

The 1 peri-procedural NSTEMI was adjudicated as possibly related due to the timing of the procedure and event (1 day post implantation). Further investigation showed that the patient had progression of a LCx lesion leading to the NSTEMI.
The COSIRA trial evaluated the CS Reducer as a new therapy for patients with refractory angina

Reducer implantation was significantly better than a sham intervention to improve angina symptoms in patients with advanced coronary artery disease unsuitable for revascularization and treated with optimal medical therapy

The improvement of ≥2 angina CCS classes (the primary end point) occurred 2.3 times more frequently in the Reducer group, demonstrating a clinically meaningful difference (P =0.024)
Although underpowered for the pre-specified secondary outcomes, we observed concordant improvements from baseline to 6 month follow-up in the Reducer group in:

- ≥1 angina CCS class
- change in quality of life, anginal stability and anginal frequency scores by SAQ
- change in total exercise duration
- change in time-to-1 mm ST segment depression
- and change in LV wall motion score index
Conclusions and clinical implications

Among patients suffering from severe disabling angina pectoris, this double-blinded, randomized, sham-controlled trial demonstrated safety and efficacy of the Reducer in improving symptoms of angina and improving quality of life

Based on these findings, we believe that percutaneous transvenous implantation of the CS Reducer is a safe and effective treatment for patients with refractory angina who are not suitable for coronary revascularization despite maximally tolerated therapy.
THANK YOU
Back up Slides
Normal Perfusion of the Myocardium

Endocardium

Epicardium

Left Ventricular Cavity

Endo/Epi blood flow ratio = 1.2
Ischemic Myocardium

LVEDP

Endo/Epi blood flow ratio = 0.5
Ischemic Myocardium with elevated CS pressure

Endo/Epi blood flow ratio = 1.2

CS Pressure Elevation