Efficacy of Coronary Sinus Reduction in Refractory Angina

Stefan Verheye MD PhD, E. Marc Jolicœur MD MSc MHS, Miles W Behan MD, Thomas Pettersson MD, Paul Sainsbury MD, Jonathan Hill MD, Mathias Vrolix MD, Pierfrancesco Agostoni MD, Thomas Engstrom MD, Marino Labinaz MD, Ranil de Silva MD, Marc Schwartz RCIS, Nathalie Meyten1 MD, Neal G Uren MD, Serge Doucet MD, Jean-Francois Tanguay MD, Steven Lindsay MD, Timothy D. Henry MD, Christopher J. White MD, Elazer R Edelman MD PhD, Shmuel Banai MD

SUPPLEMENTARY APPENDIX

Content Page

1. COSIRA Investigators:

Stefan Verheye, MD, PhD[1]; Nathalie Meyten, MD[1];
E. Marc Jolicœur, MD[2]; Serge Doucet, MD[2]; Jean-Francois Tanguay, MD[2]
Miles Behan, MD[3]; Neal Uren, MD[3]
Thomas Pettersson, MD[4]
Paul Sainsbury, MD[5]; Steven Lindsay, MD[5]
Jonathan Hill, MD[6]
Mathias Vrolix, MD[7]
Pierfrancesco Agostoni, MD[8]
Thomas Engstrom, MD[9]
Marino Labinaz, MD[10]
Ranil de Silva, MD[11]
Marc Schwartz, RCIS[12]
Timothy D. Henry, MD[13]
Christopher J. White, MD[14]
Elazer Edelman, MD, PhD[15]
Shmuel Banai, MD[16]

[1]Antwerp Cardiovascular Center, ZNA Middelheim, Antwerp, Belgium
[2]Montreal Heart Institute, Montreal, Canada
[3]Royal Infirmary of Edinburgh, Edinburgh, UK
[4]Kristianstad Central Hospital, Kristianstad, Sweden
[5]Bradford Royal Infirmary, Bradford, UK
[6]Kings College Hospital, London, UK
[7]ZOL Hospital, Genk, Belgium
[8]University Medical Center Utrecht, Utrecht, Netherlands
[9]Rigshospitalet, Copenhagen, Denmark
[10]Ottawa Heart Institute, Ottawa, Canada
[11]National Heart and Lung Institute, Imperial College London and NIHR Cardiovascular Biomedical Research Unit, Royal Brompton and Harefield NHS Foundation Trust. London, UK
[12]Neovasc, Inc. Richmond, BC, Canada
[13]Cedars- Sinai Medical Center, Los Angeles, CA
[14]The John Ochsner Heart & Vascular Institute, Ochsner Clinical School, University of Queensland, New Orleans, LA, USA
[15]Institute for Medical Engineering and Science, MIT, Cambridge, MA USA, and Cardiovascular Division Brigham and Women's Hospital, Harvard Medical School, Boston MA
[16]Tel Aviv Medical Center, The Tel Aviv University Medical School, Tel Aviv, Israel

2. COSIRA committees:

Clinical events committee (CEC)

Giovanni Amoroso, MD, PhD
Onze Lieve Vrouwe Gasthuis
Postbus 95500
1090 HM Amsterdam, Netherlands

Lieven Herbots, MD, PhD
Jessa Ziekenhuis
Stadsomvaart 11
3500 Hasselt, Belgium

Kees-Jan Royaards, MD
Maasstad Ziekenhuis
Groene Hilledijk 315
3075 Rotterdam, Netherlands

Data and safety monitoring board (DSMB)

Christophe Dubois, MD, PhD
UZ Leuven
Campus Gasthuisberg
Herestraat 49
B - 3000 Leuven, Belgium
Tel: 32 16 34 42 35

Kaatje Goetschalckx, MD
UZ Leuven
Campus Gasthuisberg
Herestraat 49
B - 3000 Leuven, Belgium
Tel: 32 16 34 42 35

A.J.J. IJsselmuiden, MD, PhD
Albert Schweitzer Hospital
Albert Schweitzerplaats 25
3318 AT Dordrecht, Netherlands
Tel: 31 78-6541111

Keith G. Oldroyd, MD
West of Scotland Regional Heart & Lung Centre
Golden Jubilee National Hospital
Agamemnon Street
Clydebank, Scotland G81 4DY
Tel: 44 141 951 5180

Steering Committee Members

Stefan Verheye, MD, PhD
ZNA Middelheim Hospital
Antwerp, Belgium
Tel: 32 49 6862375

Shmuel Banai, MD
Tel Aviv Medical Center
6 Weitzman St
Tel Aviv, 64239 Israel
Tel: 972 3 697 3395

E. Marc Jolicoeur, MD, MSc, MHS
Montreal Heart Institute
5000 Bélanger Street
Montréal, QC H1T 1C8
Tel: (514) 376-3330 x 3249

Marc Schwartz, RCIS
Neovasc Inc.
13700 Mayfield Place, Suite 2135
Richmond, BC V6V 2E4
Tel: (847) 494-0660

Elazer Edelman, MD, PhD
Brigham and Women's Hospital
75 Francis Street
Boston, MA 02115
Tel: (617) 471-2003

Christopher White, MD
Ochsner Medical Center
1514 Jefferson Highway
New Orleans, LA 70121
Tel: (504) 842-3717

Timothy Henry, MD
Cedars-Sinai Medical Center
127 S San Vicente Boulevard, SuiteA-3100
Los Angeles, CA 90048
Tel: (310) 423-3300

Michael Jaff, DO
Massachusetts General Hospital
55 Fruit Street, Suite 5B
Boston, MA 02114
Tel: (617) 726-3784

3. Inclusion and Exclusion criteria for COSIRA

A. Inclusion criteria

1. Patient > 18 years of age
2. Symptomatic CAD with chronic refractory angina pectoris classified as CCS class III or IV despite attempted optimal medical therapy for 30 days prior to screening
3. Patient has limited treatment options for revascularization by CABG or PCI
4. Evidence of reversible ischemia that is attributable to the left coronary arterial system
5. Left ventricular ejection fraction > 25%
6. Male or non-pregnant female (NB: Females of child bearing potential must have a negative pregnancy test)
7. Patient understands the nature of the procedure and provides written informed consent prior to enrollment
8. Patient is willing to comply with specified follow-up evaluation and can be contacted by telephone

B. Exclusion criteria

Clinical

1. Recent (< 3 months) acute coronary syndrome
2. Recent (<6 months) successful PCI or CABG
3. Recent (< 1 month) unstable angina (recent onset, crescendo, or rest angina with ECG changes)
4. De-compensated CHF or hospitalization due to CHF during the 3 months prior to screening
5. Patient with pacemaker or defibrillator electrode in the right atrium, right ventricle, or coronary sinus
6. Life-threatening rhythm disorders or any rhythm disorders requiring an internal defibrillator and or pacemaker
7. Severe COPD as indicated by a forced expiratory volume in one second < 55% of the predicted value
8. Patient cannot undergo exercise tolerance test (bicycle) for reasons other than refractory angina
9. Severe valvular heart disease
10. Patient having undergone tricuspid valve replacement or repair
11. Chronic renal failure (serum creatinine >2 mg/dL), including patients on chronic hemodyalisis
12. Moribund patients, or patients with comorbidities limiting life expectancy < 1 year
13. Contraindication to required study medications that cannot be adequately controlled with pre-medication
14. Known allergy to stainless steel or nickel
15. Currently enrolled in another investigational device or drug trial that has not completed the primary endpoint or that clinically interferes with the current study endpoints

Anatomical

16. Mean right atrial pressure ≥ 15 mmHg
17. Patient with anomalous or abnormal CS as demonstrated by angiographic abnormalities defined either:
    a. Abnormal CS anatomy (*e.g.*, tortuosity, aberrant branch, persistent left SVC) and/or;

    b. CS diameter at the site of planned Reducer implantation < 9.5 mm or > 13 mm

4. **Details of the study outcome assessments**:

Outcomes: At baseline all participants underwent 1) a clinical interview to determine the CCS class, 2) physical examination, 3) symptom-limited stress test, 4) dobutamine stress echocardiogram, and 5) Seattle Angina Questionnaire (SAQ).

CCS Class: Participants were assessed for CCS grade at discharge, 30-days, 3 and 6-months. To maintain blinding, clinical follow-up was done by investigators blinded to the treatment allocation.

Safety: Adverse or serious adverse device-related events were monitored peri-procedurally, prior to hospital discharge, and at the 6-month follow-up. Procedural success was defined as successful delivery and deployment of the Reducer at the intended site in the absence of adverse or serious adverse device-related events. Major adverse events were defined as a composite of death, myocardial infarction (MI), cardiac tamponade, life-threatening arrhythmias (ventricular tachycardia or fibrillation), and respiratory failure 30-days and 6-month post-procedure, as adjudicated by the CEC.

Stress testing: A bicycle ergometry stress-test adapted from the ACIP protocol[13] was selected because the incremental increases in exercise workload are more gradual (≤ 1.5 METS/stage) compared to the larger work demands inherent in Bruce protocol treadmill testing.[1] Baseline and 6-month results were compared.

Dobutamine echocardiography*:* Wall motion of each of 16-segments at rest and during peak dobutamine infusion was quantified (1-normal, 2-hypokinetic, 3-akinetic, 4-dyskinetic, 5-aneurysmal),[2] and the summed wall motion scores of myocardial segments divided by the number of segments to provide a Wall-Motion-Score Index (WMSI). Baseline and 6-month WMSI at rest and stress were compared. A modified LCA WMSI was also computed using 11-segments attributed to the LCA territory. Stress test and dobutamine echo data were interpreted by an independent core laboratory blinded to treatment assignment.

SAQ Score: a brief 19-item self-administered questionnaire that captures five perspectives: physical limitation, angina stability, angina frequency, treatment satisfaction, and disease perception was used to assess quality of life. The SAQ was repeated at 30-days, 3 and 6-months.[3]

Computed Tomography Angiography (CTA): In patients assigned to the Reducer, CTA was performed at 6-months to document the patency of the Reducer in the CS. To limit radiation exposure, this test was only performed in patients assigned to the Reducer and performed after the final CCS class assessment has been fulfilled to maintain blinding.

5. Supplementary tables

Quality of life assessed by Seattle Angina Questionnaire (SAQ) shows a statistically significant change from baseline to 6-month follow-up for the Reducer group (17.6 ± 26.2) compared with the Control group (7.6 ± 23.3, p = 0.048). Additionally, there were strong trends favouring the Reducer group in: anginal stability and anginal frequency as measured by SAQ; time to 1 mm ST segment depression and total exercise duration by ETT; and stress modified left coronary artery WMSI by DSE. The percentage changes in the endpoints of interest in the intent-to-treat population are summarized in the tables 3, 4 and 5.

Table S1: Seattle Angina Questionnaire (SAQ): (Changes from Baseline to 6 months follow up – Intent-to-Treat)

Physical Limitations			
SAQ – Physical Limitations	**Reducer N=51**	**Control N=47**	**All Patients N=98**
Baseline – mean (SD)	47.4 (24.7)	45.4 (24.5)	46.4 (24.5)
6-month follow-up – mean (SD)	56.5 (27.1)	52.8 (26.7)	54.7 (26.9)
Δ (baseline to 6MFU) – mean (SD)	9.2 (20.2)	7.4 (22.1)	8.3 (21.0)
% Δ (baseline to 6MFU)	**19.41%**	**16.30%**	**17.89%**
t-Test: Δ in Baseline to 6MFU Control vs. Reducer group	**p = 0.675***		**–**
Anginal Stability			
SAQ – Anginal Stability	**Reducer N=51**	**Control N=48**	**All Patients N=99**
Baseline – mean (SD)	43.1 (22.4)	39.1 (25.7)	41.2 (24.0)
6-month follow-up – mean (SD)	61.3 (27.5)	47.4 (25.9)	54.5 (27.5)
Δ (baseline to 6MFU) – mean (SD)	18.1 (32.4)	8.3 (37.3)	13.4 (35.0)
% Δ (baseline to 6MFU)	**42.00%**	**21.23%**	**32.52%**
t-Test: Δ in Baseline to 6MFU Control vs. Reducer group	**p = 0.165***		**–**
Anginal Frequency			
SAQ – Anginal Frequency	**Reducer N=51**	**Control N=48**	**All Patients N=99**
Baseline – mean (SD)	43.7 (25.9)	46.7 (28.8)	45.2 (27.3)
6-month follow-up – mean (SD)	59.0 (29.3)	57.7 (29.1)	58.4 (29.1)
Δ (baseline to 6MFU) – mean (SD)	15.3 (28.9)	11.0 (24.9)	13.2 (27.0)
% Δ (baseline to 6MFU)	**35.01%**	**23.55%**	**29.20%**
t-Test: Δ in Baseline to 6MFU Control vs. Reducer group	**p = 0.436***		**–**

Treatment Satisfaction			
SAQ – Treatment Satisfaction	**Reducer N=51**	**Control N=48**	**All Patients N=99**
Baseline – mean (SD)	79.7 (18.6)	77.6 (18.1)	78.6 (18.3)
6-month follow-up – mean (SD)	82.6 (17.6)	80.4 (19.3)	81.5 (18.4)
Δ (baseline to 6MFU) – mean (SD)	2.9 (16.6)	2.9 (15.8)	2.9 (16.2)
% Δ (baseline to 6MFU)	**3.64%**	**3.74%**	**3.69%**
t-Test: Δ in Baseline to 6MFU Control vs. Reducer group	**p = 0.981***		**–**
Quality of Life			
SAQ – Quality of Life	**Reducer N=51**	**Control N=48**	**All Patients N=99**
Baseline – mean (SD)	42.3 (19.7)	46.9 (20.6)	44.5 (20.2)
6-month follow-up – mean (SD)	60.0 (23.7)	54.5 (27.0)	57.3 (25.4)
Δ (baseline to 6MFU) – mean (SD)	17.6 (26.2)	7.6 (23.3)	12.8 (25.2)
% Δ (baseline to 6MFU)	**41.61%**	**16.20%**	**28.76%**
t-Test: Δ in Baseline to 6MFU Control vs. Reducer group	**p = 0.048***		**–**

* Student's t-test

Table S2: Exercise Tolerance Test (Changes from Baseline to 6 months follow up – Intent-to-Treat)

Total Exercise Duration			
Exercise Duration (seconds)	**Reducer N=42**	**Control N=48**	**All Patients N=90**
Baseline – mean (SD)	441.29 (193.74)	463.67 (256.84)	453.22 (228.59)
6-month follow-up – mean (SD)	499.81 (194.32)	467.25 (245.68)	482.44 (222.57)
Δ (baseline to 6MFU) – mean (SD)	58.52 (161.26)	3.58 (125.81)	29.22 (145.26)
% Δ (baseline to 6MFU)	**13.26%**	**0.77%**	**6.45%**
t-Test: Δ in Baseline to 6MFU Control vs. Reducer group	**p = 0.073***		**–**
Time to 1 mm ST Segment Depression			
Time to 1 mm ST Segment Depression	**Reducer N=11**	**Control N=11**	**All Patients N=22**
Baseline – mean (SD)	384.82 (137.23)	437.09 (154.14)	410.95 (144.90)
6-month follow-up – mean (SD)	433.36 (184.98)	455.55 (180.40)	444.45 (178.66)
Δ (baseline to 6MFU) – mean (SD)	48.55 (79.83)	18.45 (87.21)	33.50 (83.03)
% Δ (baseline to 6MFU)	**12.62%**	**4.22%**	**8.15%**
t-Test: Δ in Baseline to 6MFU Control vs. Reducer group	**p = 0.409***		**–**
Maximal ST Segment Depression			
Maximal ST Segment Depression (mm)	**Reducer N=19**	**Control N=18**	**All Patients N=37**
Baseline – mean (SD)	-1.14 (0.54)	-1.01 (0.82)	-1.08 (0.69)
6-month follow-up – mean (SD)	-1.16 (0.62)	-0.77 (1.27)	-0.97 (1.00)
Δ (baseline to 6MFU) – mean (SD)	-0.02 (0.48)	0.23 (0.82)	0.11 (0.67)
% Δ (baseline to 6MFU)	**1.40%**	**-22.77%**	**-10.19%**
t-Test: Δ in Baseline to 6MFU Control vs. Reducer group	**p = 0.266***		**–**
METs			
METs	**Reducer N=31**	**Control N=34**	**All Patients N=65**
Baseline – mean (SD)	3.54 (0.99)	3.61 (1.22)	3.57 (1.11)
6-month follow-up – mean (SD)	3.64 (1.03)	3.77 (1.16)	3.71 (1.09)
Δ (baseline to 6MFU) – mean (SD)	0.10 (0.66)	0.17 (1.10)	0.13 (0.91)
% Δ (baseline to 6MFU)	**2.82%**	**4.71%**	**3.64%**
t-Test: Δ in Baseline to 6MFU Control vs. Reducer group	**p = 0.783***		**–**
Double product			
Double product	**Reducer N=34**	**Control N=35**	**All Patients N=69**

Baseline – mean (SD)	18362.59 (5873.43)	17904.31 (3964.24)	18130.13 (4965.09)
6-month follow-up – mean (SD)	17932.26 (5131.72)	17159.31 (5373.22)	17540.19 (5231.37)
Δ (baseline to 6MFU) – mean (SD)	-430.32 (4641.79)	-745.00 (4042.84)	-589.94 (4318.99)
% Δ (baseline to 6MFU)	**-2.34%**	**-4.16%**	**-3.25%**
t-Test: Δ in Baseline to 6MFU Control vs. Reducer group	**p = 0.765***		**–**

* Student's t-test

Table S3: Dobutamine stress echocardiography (DSE) wall motion score index (WMSI) and modified left coronary artery (LCA) stress wall-motion score index (Changes from Baseline to 6 months follow up – Intent-to-Treat)

Stress WMSI (SWMSI)			
DSE – SWMSI	**Reducer N=48**	**Control N=44**	**All Patients N=92**
Baseline – mean (SD)	1.54 (0.47)	1.44 (0.39)	1.49 (0.43)
6-month follow-up – mean (SD)	1.33 (0.39)	1.32 (0.40)	1.33 (0.39)
Δ (baseline to 6MFU) – mean (SD)	-0.21 (0.38)	-0.12 (0.32)	-0.17 (0.35)
% Δ (baseline to 6MFU)	**-13.64%**	**-8.33%**	**-11.41%**
t-Test: Δ in Baseline to 6MFU Control vs. Reducer group	**p = 0.202***		–
Stress Modified LCA (SMLCA)-WMSI			
DSE – SMLCA-WMSI	**Reducer N=48**	**Control N=46**	**All Patients N=94**
Baseline – mean (SD)	1.50 (0.53)	1.30 (0.43)	1.40 (0.49)
6-month follow-up – mean (SD)	1.31 (0.46)	1.26 (0.44)	1.29 (0.45)
Δ (baseline to 6MFU) – mean (SD)	-0.19 (0.41)	-0.04 (0.35)	-0.12 (0.39)
% Δ (baseline to 6MFU)	**-12.67%**	**-3.23%**	**-8.57%**
t-Test: Δ in Baseline to 6MFU Control vs. Reducer group	**p = 0.064***		–

* Student's t-test

Periprocedural Serious Adverse Events (SAE):

In the Reducer group, defined as a composite of death, myocardial infarction (MI), cardiac tamponade, clinically-driven re-dilation of a failed Reducer, life-threatening arrhythmias (ventricular tachycardia [VT] or ventricular fibrillation [VF]), and respiratory failure through 30 days postprocedure, as adjudicated by the CEC. In the Control group, defined as a composite of death, MI, cardiac tamponade, life-threatening arrhythmias (VT or VF), and respiratory failure through 30 days post-procedure, as adjudicated by the CEC.

Table S4: Periprocedural Serious Adverse Events

Adverse Event	Reducer N=50	Control N=54	All Patients N=104
Death	0 (0%)	0 (0%)	0 (0%)
Myocardial infarction – NSTEMI	1 (2.0%)	0 (0%)	1 (1.0%)
Cardiac tamponade	0 (0%)	0 (0%)	0 (0%)
Re-dilation of failed Reducer	0 (0%)	0 (0%)	0 (0%)
Life-threatening arrhythmias	0 (0%)	0 (0%)	0 (0%)
Respiratory failure	0 (0%)	0 (0%)	0 (0%)

Other SAEs up to 30 days follow-up

Total SAEs

	Reducer N=76	Control N=93	All Patients N=169
Serious adverse events – n (%)	3 (3.9)	2 (2.2)	5 (3.0)

Breakdown:

Reducer	Control
Unstable Angina (n=1)	Unstable Angina (n=1)
Acute Myocardial infarction (n=1)	Epigastric pain (n=1)
Crohn's disease (n=1)	

Serious Adverse Events are summarized by patients in the table below. There were 34 SAEs in total (10 Reducer, 24 Control) in 17 patients (6 Reducer, 11 Control). The majority of the SAEs were categorized as cardiac disorders, as would be expected for this patient population. Overall, fewer Reducer patients (12.0%) experienced an SAE than control (20.0%). The most commonly reported SAEs were unstable angina (2.0% Reducer, 7.4% Control), angina pectoris (2.0% Reducer, 5.6% Control) and chest pain (2.0% Reducer, 5.6% Control).

Table S5: Serious adverse events

Sham Control	**Reducer**
Atypical chest pain (n = 6)	Atypical chest pain (n = 1)
Stable angina (n = 5)	Stable angina (n = 1)
Unstable angina (n = 4)	Unstable Angina (n = 1)
Acute coronary syndrome (n = 2)	Acute myocardial infarction (n=1)
Myocardial infarction (n =1)	Myocardial infarction (n=1)
Arrhythmia (n = 1)	Decompensated heart failure (n=1)
Multi-system failure (n = 1)	Gastrointestinal bleeding (n=1)
Pulmonary edema (n = 1)	Injury (n=1)
COPD (n = 1)	COPD (n = 1)
Epigastric pain (n = 1)	Crohn's disease (n=1)
Cough (n = 1)	

References:

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3. Spertus JA, Winder JA, Dewhurst TA, Deyo RA, Prodzinski J, McDonnell M, Fihn SD. Development and evaluation of the Seattle Angina questionnaire: A new functional status measure for coronary artery disease. *Journal of the American College of Cardiology* 1995;25(2):333-341.