OPTIONS FOR THE NO OPTION PATIENT
EVALUATION/TREATMENT OF REFRACTORY ANGINA

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The Carl and Edyth Lindner Family Distinguished Chair in Clinical Research
Director of Programmatic and Network Development

DISCLOSURES
**Refractory Angina**

- Increasing number of patients as CAD mortality decreases and population ages
- 10-12 million patients in the US with chronic angina
- 10-15% of card cath patients have myocardial ischemia with anatomy not ideal for CABG/PCI
- Chronic total occlusion, degenerated SVG, diffuse disease, poor distal targets, comorbidities and angina
- Angina in the COURAGE trial at 1 year: 42% for medical treatment vs. 34% for PCI (p<0.001)
- ISCHEMIA trial: Pts with weekly angina: Angina free at 3 months 45% vs 15%, 1 year +/- 60% vs 25%

**Current Challenges**

- Current terminology is confusing:
  - “No Option Patients”
  - Refractory Angina - Refractory Ischemia
  - Non-Revascularizable - Advanced CAD
- Limited natural history data
- No large national database or registry
- ? High morbidity and mortality

*Henry and Jolicoeur, Nature Reviews Cardiology 2014;11:78*

No Option Patients
Refractory angina/Advanced CAD/
Non-revascularizable/Refractory ischemia

Symptoms
Myocardial perfusion
Coronary anatomy
A) Improve quality of care for a unique and growing subset of patients

B) Define the long-term outcome, natural history, and predictors of adverse outcome

C) Provide unique treatment options to these patients including clinically available and novel research approaches
**Why Call it the OPTIMIST Clinic?**

- Would you rather send your mother to the NO-OPTION clinic?

**“No Option” Patients**

- Are these patients really out there?
- Are they high risk?
- Can you stratify the risk?
- Are they always no option?
“No Option” Patients
How Many?

- 500 consecutive coronary angiograms
  (Cleveland Clinic/Kaiser HMO 1998)
- 12% of patients: symptomatic, documented ischemia, poor revascularization candidate
- Predictors: Prior CABG, # of diseased vessels, CRF, LVEF
- 100,000 - 200,000 patients/year in the USA

Mukherjee D, Bhatt DL, Roe MT, Patel V, Ellis SG. Direct myocardial revascularization and angiogenesis—how many patients might be eligible? Am J Cardiol. 1999; 84:598-600

Clinical outcome of a cohort of patients eligible for therapeutic angiogenesis or transmyocardial revascularization

**Results** Fifty-nine patients of the 500 studied were identified who had refractory ischemia but were not candidates for traditional revascularization. The 59 patients ineligible for traditional methods of revascularization had a rehospitalization rate of 128% (76 total hospitalizations), a 25.5% rate of myocardial infarction (15 of 59), and a mortality rate of 16.9% (10 of 59).

**Conclusions** The prognosis of many patients eligible for newer methods of revascularization on maximal medical therapy is poor. [Am Heart J 2001;142:72-4]
Prevalence of “No Option” Patients

![Pie chart showing prevalence of different patient categories.]

- Normal: 15%
- CAD <70%: 19%
- Complete Revasc: 37%
- Partial Revasc: 13%
- Med tx: 9.3%
- No options: 6.7%

N = 493


3 Year Survival – Incomplete Revascularization

![Graph showing 3-year survival rates for different groups.]

- Groups 1-3
- Groups 4-6

P = 0.003

The OPTIONS In Myocardial Ischemic Syndrome Therapy (OPTIMIST) Program

- 1200 patients with 5.1 year f/u
- Current smoker 10%, DM 36%, CHF 32%, Previous MI 75%, CABG 72%, PCI 74%
- 17.4% mortality (64% cardiovascular)
- 16% subsequent revascularization, 16% EECP, 15% angiogenic therapy (protein, gene, stem cell), TMR 3%

Henry et al. Long-Term Survival in Patients with Refractory Angina. Eur Heart J. 2013 Sep;34(34):2683-8

MHI OPTIMIST PROGRAM
Long-Term Survival

96.1% at 1 year (95%CI 94.9-97.2)
72.7% at 9 years (95%CI 69.2-76.2)

Henry et al. Long-Term Survival in Patients with Refractory Angina. Eur Heart J. 2013 Sep;34(34):2683-8
Do “No Option” Patients Ever Need Revascularization?

- Despite their initial designation, the incidence of revascularization in the “No option” patient is 25.1% at a median duration of 1.6 years
  - 20.1% of Pts underwent subsequent PCI
    - 48% New lesions
    - 21% Restenosis
    - 31% Existing Lesions
  - Pts requiring revascularization have an annualized mortality rate of 2%/yr

Treatment Options

- Optimal medical management, risk factor modification, revascularization options
- Angiogenesis (protein, gene, cell)
- EECP
- Neurostimulation
- Novel drugs: Ranolazine, L-arginine, Ivrabadine, Nicorandil
- TMR
- Novel interventional techniques: CTO, coronary sinus occluder, ultrasonic therapy

Henry and Jolicoeur, Nature Reviews Cardiology 2014;11:78
Most common approved option in the US!!

The EECP Procedure

- Series of 3 cuffs wrapped around calves, lower thighs, upper thighs and buttocks
- Sequential distal to proximal compression upon diastole, and simultaneous release of pressure at end-diastole
- Increased diastolic pressure and retrograde aortic flow
- Increased venous return and...
- Systolic unloading, resulting in increased cardiac output
MUST-EECP: Exercise Results

Adjusted mean of change from baseline

MUST-EECP: % Change in Angina

**Required Treatment Regimens**

- A total of 35 hours is required
- Regimen: 1-2 hours daily
- At least 5 days per week for 4 to 7 weeks

It is recommended that 2 hours daily treatment sessions are separated by a 30 minutes rest interval.

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**TMR/PMR**

- Laser revascularization
  - Laser holes in the myocardium
  - Mechanism: Angiogenesis, Denervation
  - Increase morbidity and mortality

- DIRECT trial
  - Randomized, controlled study
  - No evidence for efficacy
12 Month Mortality in No Option Pts (Control and TMR)

- Schofield, et. al.
- Allen, et. al.
- Frazier, et. al.
- ATLANTIC

Control group vs Intervention group

Neurostimulation Devices
Percutaneous Leads
Theorized Mechanisms of Action

- Four mutually interacting mechanisms
  - Reduction of pain perception,
  - Decreased sympathetic tone,
  - Reduced myocardial oxygen demand,
  - Improved coronary microcirculatory blood flow (increased homogenization of myocardial blood flow)
- The interaction of these mechanisms results decreased myocardial ischemia

Latif O et al, Clin Cardiol 2001, 24: 533-41

Angina Pectoris

Typical Localisation

**SCS-Randomized Control Study**

**Symptoms**

- **Anginal attacks per day**
  - Baseline to 6 weeks (%):
    - Control group: -41
    - Treatment group: 33

- **Nitro consumption**
  - Control group: -48
  - Treatment group: 27


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**Treatment group**

- Selection, randomization
- SCS implantation

**Control group**

- Baseline tests
  - Week: 0-2

- Study period tests
  - Week: 6-8
  - Week: 12

- Follow-up tests
  - Week: 26, 52
Promising Pharmacology

- **Ranolazine**
  - Mechanism of action not entirely clear
  - Antianginal without the decreased blood pressure
  - Trials not really refractory angina

- **Larginine**
  - Precursor to nitric oxide
  - Suggestions of decreased angina and increased exercise time

- **Imbria**
  - Novel agent that decreases ischemia by shifting mitochondrial metabolism towards glucose oxidation (TRIMETAZIDINE-like)

L-arginine supplementation

**Beneficial Effects Reported in the Literature**

- ↑ EDNO production
- ↑ coronary blood flow in CAD
- ↓ ST segment depression in CAD
- ↑ work performed in CAD, claudication and heart failure
- ↑ erectile function
- ↓ pain of Raynaud’s Disease
- ↑ wound healing
- ↓ symptoms of cystitis
- ↓ symptoms of esophageal dysmotility

Maxwell AJ, Cooke JP. Nitric Oxide and the Cardiovascular System, 2000: 547-585
Mechanism of Action

- Ranolazine will be a new class of antianginal drug in Canada
  - MOA of ranolazine’s antianginal effects has not been determined but these effects do not depend on reductions in heart rate or blood pressure
  - At therapeutic concentrations, ranolazine inhibits the late inward sodium current (I_{Na}) in cardiac myocytes
    - However, the relationship of this inhibition to treatment effects of anginal symptoms is unknown
  - Ranolazine also inhibits the delayed rectifier potassium channel (I_{K}) which prolongs the ventricular action potential
  - Ranolazine can prolong the QT interval in a concentration-dependent manner

Hasenfuss and Maier, 2007

ERICA: Study Design

Results: Effect of Ranolazine on Angina Episodes

Average Weekly Angina Over 6-Week Study Period

Results: Efficacy Stratified by Angina Severity

≤ 4.5 Angina Attacks per Week  > 4.5 Angina Attacks per Week

Angina Frequency  Nitroglycerin Use  Angina Frequency  Nitroglycerin Use

Placebo + Amlodipine  Ranolazine + Amlodipine
**MHIF Ranolazine Refractory Angina Registry Trial**

- 100 consecutive RA patients were enrolled as part of an extensive ongoing prospective RA registry
- Angina class, medications, MACE/death, myocardial infarction, and revascularization were obtained at 1, 6 and 12 months
- 57 of the 100 patients continued to use Ranolazine out to 1 year
- In the 43 patients who discontinued, reasons include: side effects (N=15), MACE (N=7), cost (N=5), ineffective (N=6), cost and ineffective (N=3), death (N=2), unknown (N=2).


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**Table 1. One Year Follow-Up Information**

<table>
<thead>
<tr>
<th>Angina Class Improvement</th>
<th>Continued Ranolazine</th>
<th>Discontinued Ranolazine</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Change, %</td>
<td>3 (5.3)</td>
<td>20 (48.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>One Class, %</td>
<td>22 (38.6)</td>
<td>11 (26.8)</td>
<td></td>
</tr>
<tr>
<td>Two Classes, %</td>
<td>26 (45.6)</td>
<td>9 (22.0)</td>
<td></td>
</tr>
<tr>
<td>Three Classes, %</td>
<td>6 (10.5)</td>
<td>1 (2.4)</td>
<td></td>
</tr>
</tbody>
</table>

| Death, %                 | 0 (0)                | 2 (5.0)                 | 0.16    |
| MI, %                    | 1 (1.7)              | 2 (5.0)                 | 0.57    |
| PCI/CABG, %              | 9 (15.5)             | 14 (35.0)               | 0.031   |
| Angina Hospitalization, %| 19 (32.8)            | 13 (32.5)               | 1.000   |

The Hope of Stem Cells

Can We Really Grow New Blood Vessels?
Angiogenesis Really, Really Works!

Chick Allantoic Membrane
Rabbit Cornea
Rabbit Hindlimb
Ameroid Pig Heart

Takeshita et al. JCI 93:662-670 2/94

Refractory Angina: Placebo-controlled Trials

- PROTEIN:
  - VIVA: n=178 IC VEGF-165
  - FIRST: n=337 IC FGF-2
  - FGF CABG: n=40 IM FGF-1 with LIMA
  - FGF BEAD: n=24 Perivascular with CABG

- GENE:
  - AGENT 1/2: n= 79 + 52 IC adFGF-4
  - AGENT 3: n= 415 IC adFGF-4
  - VEGF-2: n= 9 + 19 IM perc plVEGF-2
  - EUROINJECT: n= 76 IM perc plVEGF-A
  - NOTHERN: n=93 IM perc plVEGF-A

- CELL:
  - FOCUS: n=30 IM BM Cells
  - Ramshortst: n=50 IM BM Cells
  - FOCUS-2: n=38 IM BM Cells
  - ADVANCE: n=24 IM CD34+ Cells
  - ACT-34: n=162 IM CD34+Cells
  - PRECISE: n=27 IM Adipose derived Cells
**Placebo Results – Exercise Treadmill Time**

In order to detect a therapeutic effect, several biases and confounders must be taken into consideration by investigators testing novel therapies for refractory angina. These include: a) the fluctuating nature of angina; b) the regression to the mean; c) the Hawthorne effect; d) the placebo effect; and finally e) the therapeutic effect.

In this hypothetical scenario, the clinical status is depicted on a scale from worst to best against time. While these factors are not necessarily additive as depicted, they nonetheless affect real-world evidence, randomized trials, and economic analyses altogether.
AGENT 3

A Multicenter, Randomized, Double-Blind, Placebo Controlled Study to Evaluate the Efficacy and Safety of Ad5FGF-4 in Patients with Stable Angina

Henry et al. JACC 2007

Primary Endpoint
Change in Exercise Duration from Baseline (sec.)

Co-Primary 32% 31% 30%

Placebo
Ad5FGF-4, 10 vp
Ad5FGF-4, 10 vp

Median
≥2 Class Improvement in Angina

P=0.025
P=0.06
P=0.045
P=0.037

% of patients

Placebo
Ad5FGF-4, 10 vp
Ad5FGF-4, 10 vp

WK 12
MO 6
1 YR

P= Fishers exact test for distribution of angina class

Did you get Gene or Cell Therapy?
**CAPILLARY DENSITY**

*P<0.01

**P<0.005

Pre Tx

Post Tx

Injection sites

Autologous, Catheter-based, IM Transplantation of EPCs

Transplantation of EPC-Enriched (NA/CD31+) Fraction Attenuates Chronic Myocardial Ischemia in Swine

Viability

Wall Motion

Ischemic area (%)

P<0.05

Pre Post
Catheter-based Cell Transplantation

**Biosense Webster Injection Catheter**

| 1 x 10^5 CD34+ cells/kg (n = 55) | Placebo (n = 56) | 5 x 10^5 CD34+ cells/kg (n = 56) |

Endomyocardial Mapping and Injection with NOGA Isolex selected CD34+ cells / Placebo Rx

Follow-up Safety and Efficacy Assessments:
1 - 7 days, and 1, 3, 6, and 12 months; ETT at 3, 6, 12 months; MRI at 6 months, SPECT at 6 & 12 months

Losordo, Henry et al Circ Res 2011
**ACT-34 CMI: Reduction in Angina**

Anginal Episodes per Week
Change from baseline at 6 months

<table>
<thead>
<tr>
<th>Placebo</th>
<th>Low</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td>-8.6</td>
<td>-14.2</td>
<td>-13.7</td>
</tr>
</tbody>
</table>

P=0.04

Analysis of Variance (ANOVA)

Losordo, Henry et al Circ Res 2011

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**ACT-34 CMI: Exercise Time**

Total ETT Time
Change from baseline at 6 months

<table>
<thead>
<tr>
<th>Placebo</th>
<th>Low</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td>69</td>
<td>138</td>
<td>108</td>
</tr>
</tbody>
</table>

p=0.013

Losordo, Henry et al Circ Res 2011
Major Adverse Cardiac Events (24 Months)

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>$1 \times 10^5$ CD34+ cells/kg</th>
<th>$5 \times 10^5$ CD34+ cells/kg</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>7(12.5%)</td>
<td>1(1.8%)</td>
<td>2(3.6%)</td>
<td>0.081</td>
</tr>
<tr>
<td>MI</td>
<td>10(17.9%)</td>
<td>9(16.4%)</td>
<td>6(10.7%)</td>
<td>0.587</td>
</tr>
<tr>
<td>Death, MI</td>
<td>15(26.8%)</td>
<td>10(18.2%)</td>
<td>6(10.7%)</td>
<td>0.096</td>
</tr>
<tr>
<td>Death, MI, ACS Hospitalization</td>
<td>17(30.4%)</td>
<td>10(18.2%)</td>
<td>8(14.3%)</td>
<td>0.101</td>
</tr>
<tr>
<td>Death, MI, ACS or Worse CHF Hospitalization</td>
<td>19(33.9%)</td>
<td>12(21.8%)</td>
<td>9(16.1%)</td>
<td>0.078</td>
</tr>
</tbody>
</table>

Pts with MACE events from start of mobilization thru 12 mo in injected pts; *= Fisher’s Exact Test

Losordo, Henry et al Circ Res 2011

Refractory Angina Phase III
RENIEW Study Design

Subject population
- 21-80 yrs
- CCS class III or IV
- Angina
- Attempted “best” medical therapy
- Non-candidate for Surgical/Perc. revasc.
- Ischemia on SPECT or 3-10 min. mod. Bruce protocol with angina or anginal equivalent at baseline

Screening and Baseline Visits

Randomization

1 x $10^5$ CD34+ cells/kg (n = 200)
Active Control (n = 100)
Unblinded Standard of Care (n = 100)

Cell Mobilization (G-CSF 5 μg/kg/d x 4d)
Apheresis on Day 5

Intramyocardial Mapping and Injection with NOGA
ISOLEX selected CD34+ cells / Placebo

Efficacy Assessments during 12 month follow-up: ETT, angina frequency, and QoL (SF-36)
Safety Assessments during 24 month follow-up: AEs, SAEs, MACE

Safety Assessments during 24 month follow-up: AEs, SAEs, MACE
**RENEW: PRIMARY ENDPOINT AS TREATED**

**Mean**

**Median**

![Graph showing change in mean TET (s) and change in median exercise time (s) over time (Baseline, 3-months, 6-months, 12-months).]

Povsic et al. JACC Card Int 2016;9(15):1576-1585

**RENEW: ANGINA FREQUENCY**

6 months Relative Risk

- **As Treated**: 0.63 P=0.05
- **ITT**: 0.58 P=0.02

Povsic et al. JACC Card Int 2016;9(15):1576-1585
RENEW RESULTS: 2-YEAR MACE

<table>
<thead>
<tr>
<th></th>
<th>Standard of Care (n=28)</th>
<th>Active Control (n=28)</th>
<th>CD34+ Cell Tilt (n=50)</th>
<th>Started Mobilization but Not Injected (n=6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with MACE</td>
<td>19 (67.9%)</td>
<td>12 (42.9%)</td>
<td>23 (46.0%)</td>
<td>2 (33.3%)</td>
</tr>
<tr>
<td>Death</td>
<td>2 (7.1%)</td>
<td>3 (10.7%)</td>
<td>2 (4.0%)</td>
<td>0</td>
</tr>
<tr>
<td>MI</td>
<td>2 (7.1%)</td>
<td>3 (10.7%)</td>
<td>5 (10.0%)</td>
<td>2 (33.3%)</td>
</tr>
<tr>
<td>Perforation</td>
<td>0</td>
<td>0</td>
<td>2 (4.0%)</td>
<td>1* (16.7%)</td>
</tr>
<tr>
<td>Stroke</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>CV hospitalization</td>
<td>18 (64.3%)</td>
<td>9 (32.1%)</td>
<td>21 (42.0%)</td>
<td>2 (33.3%)</td>
</tr>
<tr>
<td>Ventricular arrhythmias</td>
<td>1 (3.6%)</td>
<td>2 (7.1%)</td>
<td>1 (2.0%)</td>
<td>-</td>
</tr>
<tr>
<td>MACE &lt;2 weeks</td>
<td>0</td>
<td>0</td>
<td>3 (6.0%)</td>
<td>2 (33.3%)</td>
</tr>
<tr>
<td>MACE during follow-up</td>
<td>19 (67.9%)</td>
<td>12 (42.9%)</td>
<td>21 (42.0%)</td>
<td>2 (33.3%)</td>
</tr>
</tbody>
</table>

Povsic et al. JACC Card Int 2016;9(15):1576-1585

OPPORTUNITY LOST!!

"Oh, Lord! Here come circumstances beyond our control."
CD34+ Cell Therapy for Patients with Refractory Angina

- Improvement in exercise time, angina, and mortality compared to placebo
- Improved total exercise time throughout the 3-12 month period on treadmill stress test
- Lower relative frequency of angina throughout the 3-12 month period
- Significant decrease in all-cause mortality at 24 months
- CD34+ delivery in ischemic myocardium

Henry et al. Eur Heart J 2018;39(23):2208-2216

Placebo Controlled Trials which have shown improvement in Ex Time for Patients with Refractory Angina

- Myocardial Angiogenesis (Protein, Gene) = 0
- EECP = 0
- TMR/PMR = 0
- Neurostimulation = 0
- Novel Drugs = 0
Conclusions

- We believe that this type of cell therapy for refractory angina is particularly promising and may improve both functional status and mortality.
- It is important to explore methods to bring this therapy to patients.

*“I go home today. They cured me using this new miracle drug. I’m afraid it’ll be years before it’s approved for humans.”*

Bone Marrow Stem Cell Treatment for Ischemic Heart Disease in Patients with No Option of Revascularization: A Systematic Review and Meta-Analysis

Sheila A. Fisher1,2, Carolyn Doree1,2, Susan J. Brunskill1,2, Anthony Mathur3, Enca Martin-Rendon2,4.

### Mortality

[Table and chart showing mortality data]

*PLoS One 2013 Jun 19;8(6):e64669*

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### Martin-Rendon Meta-analysis

#### Angina Class

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>BMSC Mean SD</th>
<th>Control Mean SD</th>
<th>Total Mean SD</th>
<th>Weight</th>
<th>Mean Difference IV Fixed, 95% CI</th>
<th>Mean Difference IV Fixed, 95% CI</th>
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</thead>
<tbody>
<tr>
<td>Losordo 2007</td>
<td>-1.4 1</td>
<td>18 0.4</td>
<td>18 0.4</td>
<td>17</td>
<td>6.97 [0.67, 3.85]</td>
<td>6.97 [0.67, 3.85]</td>
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<tr>
<td>Pern 2011</td>
<td>-1.2 1.2</td>
<td>20 0.8</td>
<td>20 0.8</td>
<td>19</td>
<td>10.25 [3.57, 16.93]</td>
<td>10.25 [3.57, 16.93]</td>
</tr>
<tr>
<td>Pokushalov 2010</td>
<td>-1.5 3.2</td>
<td>49 11.2</td>
<td>49 11.2</td>
<td>48</td>
<td>11.1 [5.23, 16.95]</td>
<td>11.1 [5.23, 16.95]</td>
</tr>
<tr>
<td>van Ramshorst 2009</td>
<td>-0.79 0.73</td>
<td>24 -0.39</td>
<td>24 -0.39</td>
<td>23</td>
<td>25.61 [-0.97, 0.11]</td>
<td>25.61 [-0.97, 0.11]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td></td>
<td>130 100.0%</td>
<td></td>
<td></td>
<td>2.17 [-0.55, 4.81]</td>
<td>2.17 [-0.55, 4.81]</td>
</tr>
<tr>
<td></td>
<td>Heterogeneity: CH² = 1.05, df = 4 (P = 0.90), P = 0% Test for overall effect: Z = 2.41 (P = 0.02)</td>
<td></td>
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</table>

*PLoS One 2013 Jun 19;8(6):e64669*

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#### Angina Frequency

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>BMSC Mean SD</th>
<th>Control Mean SD</th>
<th>Total Mean SD</th>
<th>Weight</th>
<th>Mean Difference IV Fixed, 95% CI</th>
<th>Mean Difference IV Fixed, 95% CI</th>
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</thead>
<tbody>
<tr>
<td>Losordo 2007</td>
<td>0.6 10.3</td>
<td>18 16.3</td>
<td>18 16.3</td>
<td>17</td>
<td>6.71 [2.55, 10.87]</td>
<td>6.71 [2.55, 10.87]</td>
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<tr>
<td>Losordo 2011 LD</td>
<td>7.2 7.3</td>
<td>53 11.8</td>
<td>53 11.8</td>
<td>52</td>
<td>44.8 [8.89, 80.78]</td>
<td>44.8 [8.89, 80.78]</td>
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<tr>
<td>Losordo 2011 SD</td>
<td>6.3 8.7</td>
<td>53 11.8</td>
<td>53 11.8</td>
<td>52</td>
<td>40.4 [8.02, 72.82]</td>
<td>40.4 [8.02, 72.82]</td>
</tr>
<tr>
<td>Pokushalov 2010</td>
<td>4.2 8.4</td>
<td>49 18.6</td>
<td>49 18.6</td>
<td>48</td>
<td>42.9 [5.49, 80.35]</td>
<td>42.9 [5.49, 80.35]</td>
</tr>
<tr>
<td>Wang 2010</td>
<td>5.6 15.7</td>
<td>56 15.4</td>
<td>56 15.4</td>
<td>55</td>
<td>7.6 [3.37, 11.87]</td>
<td>7.6 [3.37, 11.87]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td></td>
<td>229 100.0%</td>
<td></td>
<td></td>
<td>5.21 [-7.35, 17.78]</td>
<td>5.21 [-7.35, 17.78]</td>
</tr>
<tr>
<td></td>
<td>Heterogeneity: CH² = 6.11, df = 4 (P = 0.19), P = 34% Test for overall effect: Z = 2.76 (P = 0.006)</td>
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*PLoS One 2013 Jun 19;8(6):e64669*
In Summary: The Case for Refractory Angina

- Defined Patient Population with an unmet clinical need
- The Problem is inadequate myocardial perfusion
- CD34+ stem cell is an endothelial progenitor with well documented clinical implications
- Small and Large animal models which confirm the mechanism
- Double blind Placebo controlled Phase 1, Phase 2 and Phase 3 trials which demonstrate consistent benefit including improved exercise tolerance, reduction in angina and improvement in mortality
- Multiple metaanalysis which demonstrate consistent results with other angiogenic cells
- SAFE!!!
- Limited treatment options
Why is this not available for our Patients?

PHASE 1 GENE THERAPY TRIAL: XYLOCOR

Dose dependent improvements in PET and Angina
CIRC CARD INTERVENTIONS: In Press

Baseline and 6 Month Polar Maps From Subject with Extensive Inferoseptal Ischemia

PHASE 1 SAFETY: No SAEs determined by investigator or IDMC to be related to study drug

Source: 2022 AATS presentation
Pivotal CardiAMP Autologous Cell Therapy Trial for Chronic Myocardial Ischemia and Refractory

CellAMP Therapy

1. Cell Collection
2. Cell Processing
3. Cell Delivery

Pre-procedure Screening

Post-procedure

Proliferation of Stem Cell Clinics

Federal Regulatory Oversight of US Clinics
Marketing, Adverse Events, and Clinical Trials: Insights from 3 New FDA Draft Guidance Documents
PCI Options

› Facilitated Antegrade Steering Technique (FAST–CTO)
  ◦ Bridgepoint System (3 parts)

› Retrograde
  ◦ Find true Lumen using collaterals

Results

BEFORE

A

E

AFTER
What you see...
The tip of the iceberg
Resolution >500 µm

What you don’t see...
The hidden side of the iceberg
Resolution <500 µm

JAMA 1955,159 (13):1264-1271

SCIENTIFIC BASIS FOR THE SURGICAL TREATMENT OF CORONARY ARTERY DISEASE

Claude S. Beck, M.D.
and
David S. Leighton, M.D., Cleveland

Fig. 10.—Partial ligation of the coronary sinus. The ligature is tied on a stilet 3 mm. in diameter, as in A, B, and C, and the stilet is removed after the ligature is tied, as in D.
Generation II Reducer System

Reducer Implantation

One size fits all – by choosing position in the coronary sinus and compliance chart. RBP = 6 atm

2-3 atm

4 atm (nominal)

Crimped

Inflated

Delivery System

79

80

Neovasc Reducer: final result
Results: efficacy

Improvement in Angina score (CCS):

Average CCS:
Baseline- 3.07 ± 0.47
follow-up- 1.64 ± 0.84
(p<0.0001, n=14)

CCS class was lower after 6 m in 12 of the 14 patients

Efficacy of a Device to Narrow the Coronary Sinus in Refractory Angina

Stefan Verhey, M.D., Ph.D., E. Marc Jolicœur, M.D., Miles W. Behan, M.D.,
Thomas Pettersson, M.D., Paul Sainsbury, M.D., Jonathan Hill, M.D.,
Mathias Vrolix, M.D., Pierfrancesco Agostoni, M.D., Thomas Engstrom, M.D.,
Marino Labinaz, M.D., Ranil de Silva, M.D., Marc Schwartz, R.C.I.S.,
Nathalie Meyten, M.D., Neal G. Uren, M.D., Serge Doucet, M.D.,
Jean-François Tanguay, M.D., Steven Lindsay, M.D., Timothy D. Henry, M.D.,
Christopher J. White, M.D., Elazer R. Edelman, M.D., Ph.D., and Shmuel Banai, M.D.
COSIRA trial design

Key Inclusion criteria:
- Stable CCS III-IV angina
- Myocardial ischemia in the left circulation
- Limited revasc. option
- Optimal medical tx
- LEVF > 25%

Prospective, randomized, double-blind, sham-controlled, clinical trial
11 clinical centers
104 patients


Panel A
- The proportion of patients with improvement of ≥2 CCS angina classes (primary end point) was significantly higher in the Reducer group, P=0.02
- The proportion with improvement of ≥1 CCS class was significantly higher in the Reducer group, P=0.003

Panel B
- The mean (±SD) CCS class was reduced from 3.2±0.4 at baseline to 2.1±1.0 at 6 months of follow-up in the Reducer group, as compared with a reduction from 3.1±0.3 to 2.6±0.9 in the control group, P=0.001

Representative CT Angiogram of the Device in the Coronary Sinus at 6 Months


Shockwave Therapy

Burkhart et al, Cardiovasc Ultrasound. 2017 Apr 12;15(1)
Just for the Record!

- CABG did not work!
- PCI did not work!
- Medical therapy did not work!
- TLC did not work!

Current Trials

- Xylocor: Triple gene for VEGF
- Imbria: novel metabolic inhibitor
- Stem Cell: CD34+ and BMC Selected
- Coronary Sinus Reducer: COSIRA-2
INOCA (ISCHEMIA & NON-OBSTRUCTIVE CORONARY ARTERY DISEASE) & CORONARY MICROVASCULAR DYSFUNCTION (CMD)

- INOCA is increasingly recognized
- Estimated prevalence of 3 to 4 million
- Women make up about 70% of INOCA population in the US
- CMD is present in ~50% INOCA

Non-endothelial Dependent CMD predicts MACE
Step 1: Coronary angiography & LVEDP

Normal
- No stenosis

Mild
- 1 to 50%

Moderate
- 50 to 80%

Step 2: Diagnostic guidewire and Adenosine test

<table>
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<tr>
<th>FFR + CFR + IMR*</th>
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<tr>
<td>FFR &gt; 0.8</td>
</tr>
<tr>
<td>CFR &gt; 2.0</td>
</tr>
<tr>
<td>IMR &lt; 25</td>
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</table>

- No Coronary Microvascular Dysfunction Present
- Coronary Microvascular Dysfunction Present

Step 3: Vasoreactivity (Acetylcholine test)

1. No or <90% diameter reduction
2. No angiography
3. No ischaemic ECG changes

- Non cardiac pain

INQCA ENDOTYPES

INQCA ENDOTYPES

Intracoronary BMC Administration Normalizes Coronary Flow Reserve

**MEASURE w/F**

(intact vessel normalized to reference vessel)

Placebo

BMC

n = 28

n = 26

p = 0.021

0.8

0.6

0.4

0.2

0.0

0.11

0.0

Sims et al., Circulation 2007

Erbs et al., Circulation 2007
AUTOLOGOUS CD34 CELL THERAPY FOR TREATMENT OF CORONARY MICROVASCULAR DYSFUNCTION IN PATIENTS WITH ANGINA AND NON-OBSTRUCTIVE CORONARY ARTERIES (ESCAPE-CMD)

Timothy D. Henry, MD, FACC, MSCAI
Medical Director, The Carl and Edyth Lindner Center for Research and Education
The Christ Hospital, Cincinnati, OH


ESCAPE-CMD INCREASES CFR AT 6 MONTHS IN CMD

96
ESCAPE-CMD DECREASES ANGINA FREQUENCY AT 6 MONTHS

ESCAPE-CMD IMPROVES ANGINA CLASS AT 6 MONTHS

Figure 3. CCS angina class changes from baseline to month 6.
ESCAPE-CMD IMPROVES SEATTLE ANGINA QUESTIONNAIRE SCORES AT 6 MONTHS

The Effect of Coronary Sinus Narrowing on Coronary Microvascular Function

Preliminary Results Intern analysis of the first 10 patients out of 50

Invasive Coronary Blood Flow Physiology Evaluation

Tel Aviv Medical Center single center study
N=10
The Effect of CS Narrowing on functional capacity and angina severity in ANOCA patients

- Preliminary Results
  - Interim analysis of the first 10 patients out of 30

### Functional capacity and QOL

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<tr>
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<th>BL</th>
<th>NY</th>
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<tbody>
<tr>
<td>6MWT</td>
<td>240</td>
<td>370</td>
</tr>
<tr>
<td>CCS Class</td>
<td>2.50</td>
<td>1.90</td>
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</tbody>
</table>

Tel Aviv Medical Center single center study
N=10

### Current Microvascular Angina Trials

- CD34+ stem cell (Phase 2)
- Imbria: novel metabolic inhibitor
- WARRIOR trial
- ?Coronary Sinus Reducer
We still need better Options!!